A Potent and Highly Efficacious Bcl-2/Bcl-xL Inhibitor
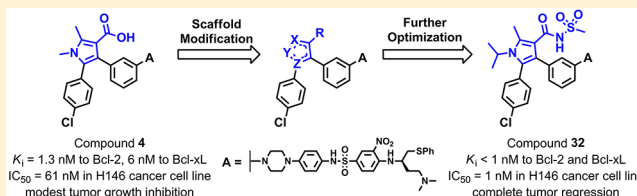
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ABSTRACT: Our previously reported Bcl-2/Bcl-xL inhibitor, **4**, effectively inhibited tumor growth but failed to achieve complete regression in vivo. We have now performed extensive modifications on its pyrrole core structure, which has culminated in the discovery of **32** (BM-1074). Compound **32** binds to Bcl-2 and Bcl-xL proteins with K_i values of <1 nM and inhibits cancer cell growth with IC$_{50}$ values of 1–2 nM in four small-cell lung cancer cell lines sensitive to potent and specific Bcl-2/Bcl-xL inhibitors. Compound **32** is capable of achieving rapid, complete, and durable tumor regression in vivo at a well-tolerated dose schedule. Compound **32** is the most potent and efficacious Bcl-2/Bcl-xL inhibitor reported to date.

INTRODUCTION

A common feature in many different types of human tumors is overexpression of the pro-survival Bcl-2 family members Bcl-2 and Bcl-xL,[1−4] which make tumor cells resistant to conventional cancer therapeutic agents. Therefore, it has been proposed that small-molecule inhibitors of Bcl-2 and Bcl-xL may have a promising therapeutic potential for the treatment of human cancer.[3]

Compounds **1**[5] and **2**[6] represent two highly potent and specific Bcl-2/Bcl-xL inhibitors. Preclinical studies have shown that **1** and **2** are effective as single agents against lymphomas, chronic lymphoid leukemia (CLL), and a subset of small-cell lung cancer (SCLC) models and can enhance the antitumor activity of conventional anticancer drugs and γ-irradiation in preclinical models of diverse tumor types.[3] Compound **2** is currently in phase I/II clinical trials, where it has shown promising single-agent activity in patients with CLL and B-cell lymphomas.

Because design of Bcl-2 and Bcl-xL inhibitors involves targeting the interaction of Bcl-2/Bcl-xL proteins with their proapoptotic binding partners such as BAD and BIM proteins, a challenging task in drug discovery, very few new, potent, specific, and bona fide small-molecule inhibitors of this interaction have been reported, even after the discovery of **1** and **2**. Recently, we reported the structure-based design of a family of new, highly potent, and specific Bcl-2/Bcl-xL inhibitors (Figure 1).[7−9] Our initial lead compound **3** binds to Bcl-2 and Bcl-xL with high affinities and potently inhibits cell growth in cancer cell lines that are sensitive to **1** and **2**, but it lacks chemical stability and fails to achieve significant in vivo antitumor activity.[7] Subsequent structure-based design and optimization of **3** led to compounds **4** and **5**, which have excellent chemical stability, bind to Bcl-2 and Bcl-xL with K_i values of <1 nM, and inhibit cancer cell growth with low nanomolar activity.[8] While **5** effectively inhibits tumor growth and in fact induces tumor regression in the H146 small-cell

lung cancer model at its maximum tolerated dose (MTD), the tumor regression it caused was transient,[8] suggesting further optimization was needed toward our goal of developing a new class of Bcl-2/Bcl-xL inhibitors for cancer treatment. Very recently, we have reported further structure-based optimization of compound **5**, with a focus on two regions in the molecule, which led to the successful discovery of a superior compound, **6** (BM-957).[9] Compound **6** binds to Bcl-2 and Bcl-xL with K_i values <1 nM and inhibits tumor cell growth with IC$_{50}$ values of 21−22 nM against H146 and H1417 small-cell cancer cell lines.[9] Significantly, **6** achieved tumor regression in an animal model of human cancer.[9]

In the previous study, which yielded compound **6**, we focused our modifications on the nitro group and the soluble "tail" containing the N,N-dimethylamino group in compound **4**. In the present study, we report our further optimization of **4**, with a focus on its 1H-pyrrole-3-carboxylic acid core structure. Our efforts have culminated in the discovery of **32** (BM-1074), which, based upon its cellular activity and in vivo efficacy, is arguably the most potent and efficacious Bcl-2/Bcl-xL inhibitor discovered to date.

RESULTS AND DISCUSSION

Previously, we have shown that removal of the acid group from the pyrrole carboxylic acid of **4**, yielding compound **7**, resulted in a >50-fold decrease in binding affinity to Bcl-2 and a modest decrease in binding affinity to Bcl-xL.[8] Compound **7**, at concentrations as high as 10 μM, was found to be completely inactive in inhibition of cell growth in the H146 cancer cell line (Table 1), suggesting that very high binding affinity to Bcl-2/Bcl-xL is clearly needed in order for small-molecule inhibitors to effectively inhibit cancer cell growth.[8] Converting this acid group into a methylamide (compound **8**) has a modest negative
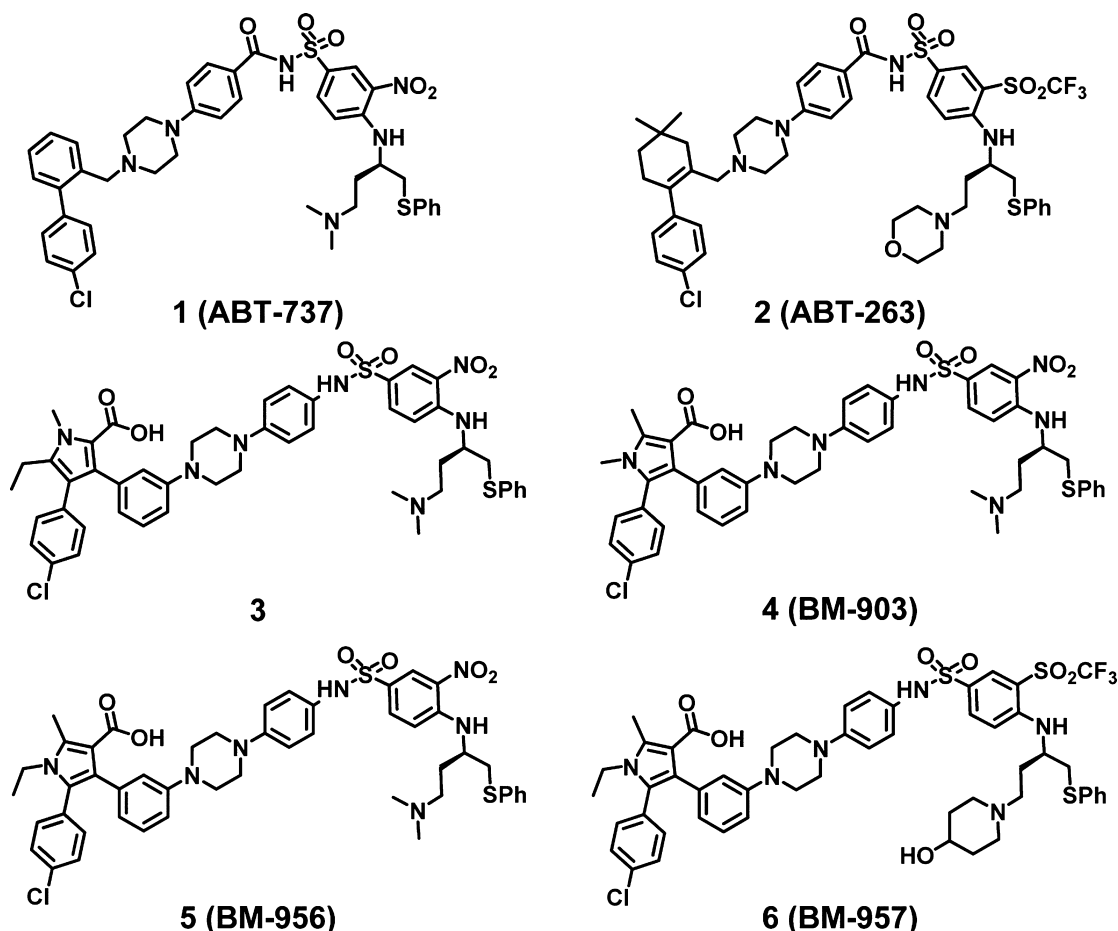
Figure 1. Chemical structures of **1** (ABT-737),[5] **2** (ABT-263),[6] and our recently reported potent and specific Bcl-2/Bcl-xL inhibitors.

effect on binding to Bcl-2 but has no effect on binding to Bcl-xL (Table 1). Interestingly, compound **8** has an IC_{50} value of 36 nM in the H146 cell line (Table 1) and is thus slightly more potent than compound **4**, suggesting that compound **8** has superior cell permeability compared to compound **4**. These binding and cellular data showed that modifications of the acid group of **4** can have a significant negative or positive effect on binding to Bcl-2/Bcl-xL and on cellular activity. Accordingly, we have made additional modifications at this position in order to further explore the structure−activity relationships and to identify promising new compounds. All the designed and synthesized new compounds were tested with our standard fluorescence-polarization (FP) assays[7] for their binding affinities to Bcl-2 and Bcl-xL proteins and for their cell growth inhibitory activity in the H146 small-cell lung cancer cell line, which is sensitive to potent and bona fide Bcl-2/Bcl-xL inhibitors such as compounds **1−6**,[7] and the results are presented in Table 1.
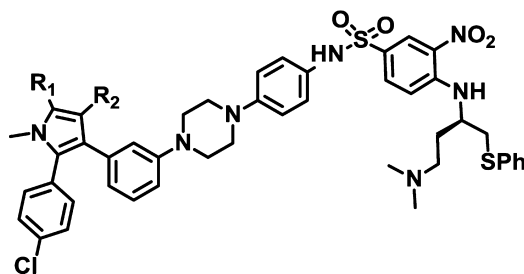
First, changing the *N*-methylamide in compound **8** to an amide group resulted in compound **9**, which is 4 and 2 times less potent than **8**, respectively, in binding to Bcl-2 and Bcl-xL. Compound **9** has an IC_{50} value of 245 nM in the H146 cell line and is thus 6 times less potent than **8** in this cell line. Replacement of the methyl group in the *N*-methylamide of compound **8** with a *cis*-3-hydroxy-3-methylcyclobutyl group or a 3-methylazetidine-3-ol group resulted in compounds **10** and **11**, respectively. Compounds **10** and **11** bind to Bcl-2 with affinities similar to that of compound **8**, but both compounds are slightly less potent than **8** in binding to Bcl-xL. While
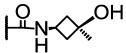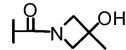
compounds **10** and **11** have very similar affinities to Bcl-2 and Bcl-xL proteins, their activity in inhibition of cell growth in the H146 cell line differs by a factor of 6, further indicating that modifications of this site can have a significantly different effect on binding affinities to Bcl-2/Bcl-xL and cellular activity for this class of compounds.

In the cocrystal structure of **4** in complex with Bcl-xL (Figure 2), the acid group in **4** forms a hydrogen bond/salt bridge with Arg132 in Bcl-xL,[8] and we synthesized compound **12** to test if the methylsulfonylamide, a bioisostere of the carboxylic acid, can replace the acid group in **4** and achieve high binding affinities to Bcl-2 and Bcl-xL and potent cellular activity in the H146 cell line. Compound **12** is as potent as **4** in binding to both Bcl-2 and Bcl-xL proteins and has an IC_{50} value of 38 nM in the H146 cell line, thus being twice as potent as **4**. These results show that the methylsulfonylamide group can indeed effectively replace the acid group, achieving not only high binding affinities to Bcl-2/Bcl-xL but also potent cellular activity.

In addition to their ability to form hydrogen bonds and salt bridges, acid and methyl-sulfonylamide groups have strong electron-withdrawing properties. To further define the contributions of these groups for binding to Bcl-2 and Bcl-xL and cellular activity in compounds **4** and **12**, we synthesized compounds **13−15** to investigate if other electron-withdrawing groups, such as Cl, CF3, and CN, can effectively replace the acid group in compound **4** to achieve high binding affinities to Bcl-2 and Bcl-xL and potent cellular activity. Although compound **13** with Cl and compound **14** with CF3 have similar potencies to

Table 1. Structure–Activity Relationship Studies on the Pyrrole Ring of Lead Compound 4

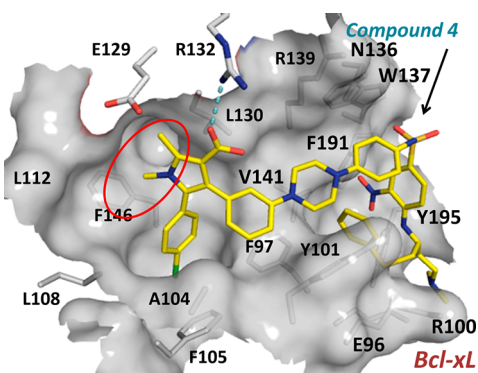| Compound ID	R_1	R_2	(IC$_{50}$ ± SD, nM)		
			Binding Affinities		Cell growth inhibition
			Bcl-2	Bcl-xL	H-146 Cell Line
4	-CH$_3$	-CO$_2$H	1.3 ± 0.2	6 ± 1	61 ± 39
7	-CH$_3$	-H	99 ± 5	11 ± 6	>1,000
8	-CH$_3$	-CONHCH$_3$	5 ± 1	6 ± 3	36 ± 26
9	-CH$_3$	-CONH$_2$	19 ± 5	14 ± 5	245 ± 17
10	-CH$_3$	(structure with O, N-H, OH)	7.5 ± 1.2	15 ± 1	12 ± 2
11	-CH$_3$	(structure with O, N, OH)	5.6 ± 0.6	9.4 ± 0.6	66 ± 4
12	-CH$_3$	-CONHSO$_2$CH$_3$	0.9 ± 0.2	5 ± 1	38 ± 22
13	-CH$_3$	-Cl	260 ± 93	12 ± 8	>1,000
14	-CH$_3$	-CF$_3$	271 ± 74	13 ± 2	>1,000
15	-CH$_3$	-CN	17 ± 6	4.5 ± 1.3	491 ± 160
16	-CF$_3$	-CO$_2$H	1.1 ± 0.6	6 ± 2	496 ± 59
17	-Cl	-CO$_2$H	1.5 ± 0.9	4.7 ± 1.5	100 ± 17

Figure 2. Crystal structure of **4** (yellow) in a complex with Bcl-xL (gray) (PDB entry: 3SP7).[8] The red oval highlights space available for further modifications around the pyrrole ring. The hydrogen bond/salt bridge of the acid group to Arg132 is indicated by a dashed cyan line.
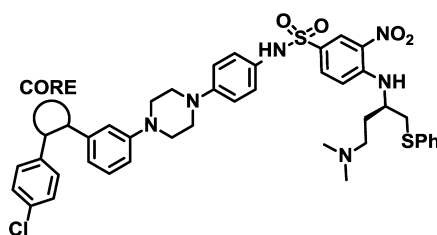
Bcl-xL as compared to **4**, both compounds are 100 times less potent than **4** in binding to Bcl-2. Compounds **13** and **14** are also >100 times less potent than **4** in inhibition of cell growth in the H146 cancer cell line. Compound **15**, in which the acid group in **4** has been replaced by a nitrile, is >10 times less potent than **4** in binding to Bcl-2 but has a similar binding affinity to Bcl-xL, as compared to **4**. Compound **15** has an IC$_{50}$

value of 496 nM in the H146 cell line and is thus 8 times less potent than **4**.

In our cocrystal structure of **4** in complex with Bcl-xL (Figure 2), the methyl group in **4** (R$_1$ = CH$_3$) is in close contact with the hydrophobic portion of the Glu129 side chain in Bcl-xL. We thus synthesized compounds **16** and **17** to determine whether the methyl group can be replaced by other small hydrophobic groups such as CF$_3$ and Cl groups to achieve high binding affinities to Bcl-2/Bcl-xL. As suggested by the cocrystal structure for compound **4**, both **16** and **17** bind to Bcl-2 and Bcl-xL with the same high affinities as compared to compound **4** (Table 1). In the H146 cell line, compound **17** is slightly less potent than **4**, but **16** is 8 times less potent than **4**.

In all the synthesized compounds described here, the pyrrole was retained as the core structure. We next designed and synthesized five classes of compounds to investigate if other five-membered heteroaromatic groups can effectively replace the pyrrole moiety in compound **4** and achieve high binding affinities to Bcl-2/Bcl-xL and potent cellular activity. Since our data showed that removal of the carboxylic acid in **4** greatly decreases its binding to Bcl-2 and cellular activity while replacement of the carboxylic acid with a methylsulfonylamide group can effectively maintain both high binding affinities to Bcl-2/Bcl-xL and potent cellular activity, we have synthesized several new compounds possessing or lacking an acid or a methylsulfonylamide group in each class of compounds. The

Table 2. Structure−Activity Relationships for Compounds in Which Other Five-Membered Heteroaromatic Rings Were Used To Replace the Pyrrole in the Initial Lead Compound 4

Compound ID	Core	Binding Affinities (IC$_{50}$ ± SD, nM)		Cell growth inhibition (IC$_{50}$ ± SD, nM)	Compound ID	Core	Binding Affinities (IC$_{50}$ ± SD, nM)		Cell growth inhibition (IC$_{50}$ ± SD, nM)
		Bcl-2	Bcl-xL	H-146			Bcl-2	Bcl-xL	H-146
7		99 ± 5	11 ± 6	>10,000	4		1.3 ± 0.2	6 ± 1	61 ± 39
					12		0.9 ± 0.2	5 ± 1	38 ± 22
18		46 ± 10	18 ± 1	>10,000	23		3.8 ± 1.1	8.3 ± 0.7	>1,000
19		110 ± 4	32 ± 9	>10,000	24		5.4 ± 1.1	5 ± 2	>1,000
20		210 ± 28	15 ± 1	>10,000	25		7.1 ± 1.6	6.1 ± 2.2	>1,000
21		140 ± 53	26 ± 3	>10,000	26		3.7 ± 0.6	5.9 ± 1.7	541 ± 76
22		350 ± 146	22 ± 7	>10,000	27		3.8 ± 1.0	4.7 ± 0.2	199 ± 46

Table 3. Structure−Activity Relationship of Analogues of Compounds 4 and 12

compound	R$_1$	R$_2$	binding affinities (IC$_{50}$ ± SD, nM)			cell growth inhibition (IC$_{50}$ ± SD, nM)
			Bcl-2	Bcl-X$_L$	Mcl-1	H-146
5	OH	Et	2 ± 1.6	6.6 ± 2.3	NT[a]	8.1 ± 3.5
28	OH	iPr-	1.4 ± 0.5	4.8 ± 0.1	NT	3 ± 2.4
29	OH	Pr	10 ± 4	8.2 ± 2.2	NT	42 ± 5
30	OH	Bu	23 ± 2	16 ± 2	NT	67 ± 5
31 (BM-1075)	NHSO$_2$CH$_3$	Et	1.8 ± 0.3	7.0 ± 1.8	>2000	4.8 ± 0.9
32 (BM-1074)	NHSO$_2$CH$_3$	iPr-	1.8 ± 0.2	6.9 ± 1.8	>2000	1.3 ± 0.3

[a]NT = not tested.

binding and cellular data for these compounds are summarized in Table 2.

For each of these five different classes, compounds **23−27**, containing either an acid or a methylsulfonylamide group, show high binding affinities to both Bcl-2 and Bcl-xL proteins with IC$_{50}$ values of 3−7 nM. However, these compounds have a significantly weaker activity in cellular assays than compounds **4** and **12**. While compounds **26** and **27** have IC$_{50}$ values of 541

and 199 nM, respectively, compounds **23**, **24**, and **25** have minimal activity at 1 μM.

In comparison, analogues **18−22** without either an acid or a methylsulfonylamide group show at least a 10-fold weaker binding affinity to Bcl-2 than their corresponding analogues **23−27**. Compounds **18−22** are also 5−10 times less potent in their binding to Bcl-xL than compounds **23−27**. Consistent with their weaker affinities to both Bcl-2 and Bcl-xL, compounds **18−22** have IC$_{50}$ values of >10 μM in the H146 cell line in the cell growth inhibition assay, further emphasizing that very high binding affinities are needed in order for small molecule inhibitors of Bcl-2 and Bcl-xL to achieve potent cellular activity.

Judged by the binding affinities to Bcl-2 and Bcl-xL and the cellular activity in the H146 cell line, compounds **4** and **12** are two of the most potent and promising compounds, and accordingly, we focused on these two compounds in our further optimization.

Upon the basis of the cocrystal structure of compound **4** complexed with Bcl-xL (Figure 2), the *N*-methyl group in **4** inserts into a hydrophobic pocket in Bcl-xL, which can, however, accommodate a hydrophobic group larger than methyl. Indeed, our previous study showed that replacement of the *N*-methyl group in **4** (R$_2$ = CH$_3$, Table 3) with either an *N*-ethyl or *N*-isopropyl group yielded analogues **5** and **28** with high binding affinities to Bcl-2/Bcl-xL and significantly improved cellular activity (Table 3).[8] In fact, compounds **5** and **28** are 8 and 20 times more potent than compound **4** in inhibition of cell growth in the H146 cell line.

To probe this site further and to identify the optimal group for binding to Bcl-2/Bcl-xL and cellular activity, we designed and synthesized compounds **29** and **30**, in which the *N*-methyl group in compound **4** was replaced by either an *N*-*n*-propyl or *N*-*n*-butyl group, respectively. Although both **29** and **30** have high binding affinities to Bcl-2 and Bcl-xL, they are several times less potent than compounds **5** and **28** in their binding to Bcl-2. Consistent with their weaker affinities to Bcl-2, compounds **29** and **30** are >5 and >10 times less potent than compounds **5** and **28**, respectively, in inhibition of cell growth in the H146 cell line. Our data therefore showed that the *N*-ethyl and *N*-isopropyl groups at this site in compounds **5** and **28** are most optimal for achieving high binding affinities to Bcl-2 and Bcl-xL and potent cell growth inhibition of the H146 cell line.

Since the methylsulfonylamide group can effectively replace the acid group in compound **4** and retain high binding affinities to Bcl-2/Bcl-xL and potent cellular activity, we next synthesized compounds **31** and **32** in which the acid group in compounds **5** and **28** was replaced by a methylsulfonylamide group (Table 3). As shown in Table 3, compounds **31** and **32** show high binding affinities to both Bcl-2 and Bcl-xL proteins, are very potent in inhibition of cell growth in the H146 cell line, and achieve IC$_{50}$ values of 4.8 and 1.3 nM, respectively. To assess their binding specificity, we tested compounds **31** and **32** for their binding affinity to Mcl-1 in our optimized FP assay (Table 3).[7] Our data showed that compounds **31** and **32** have no appreciable binding to Mcl-1 at concentrations as high as 2 μM. Hence, compounds **31** and **32** are potent and specific Bcl-2 and Bcl-xL inhibitors.

Upon the basis of their high binding affinities to Bcl-2 and Bcl-xL and potent cell growth inhibitory activity in the H146 cell line, **31** and **32** represent promising new lead compounds for further in vivo evaluation for their therapeutic potential.

First, we evaluated the maximum tolerated dose (MTD) of both compounds in severe combined immunodeficient (SCID) mice. Both compounds administered intravenously (iv) in mice at 15 mg/kg, daily, 5 days a week for 2 weeks were found to be well-tolerated and did not cause significant weight loss (<5%) or other signs of toxicity during and after the treatment. However, at 25 mg/kg, both compounds caused significant weight loss (~10%) and, therefore, we concluded that 15 mg/kg dosed intravenously is the MTD for both drugs in SCID mice.

We next tested compounds **31** and **32** for their ability to induce apoptosis at the MTD in H146 xenograft tumors in SCID mice. A single dose of either compound at 15 mg/kg was administered iv to SCID mice bearing the H146 xenograft tumors. Animals were sacrificed at 3, 6, and 24 h time points, and tumor tissues were removed for Western blot analysis for cleavage of poly ADP ribose polymerase (PARP) and caspase-3, two critical biochemical apoptosis markers. The data in Figure 3 showed that both compounds induce robust cleavage of PARP and caspase-3 at both 3 and 6 h time points in H146 tumor tissues, indicative of strong apoptosis induction in vivo.
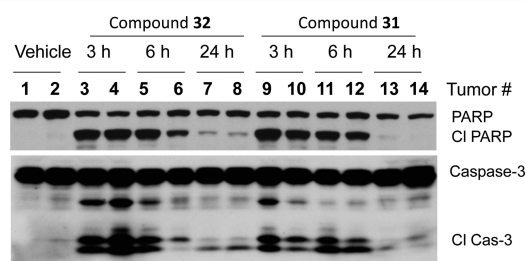

Figure 3. Western blot analysis of tumor tissues for cleavage of PARP and caspase-3. Mice were treated with a single dose of compound **31** or **32** (15 mg/kg, iv) and sacrificed at 3, 6, and 24 h time points, and tumors were removed for Western blot analysis. Key: Cl PARP, cleaved PARP; Cl Cas-3, cleaved caspase-3.

Upon the basis of the strong apoptosis induction in vivo observed for both **31** and **32**, we evaluated their antitumor efficacy in the H-146 xenograft tumor model, and the results are shown in Figure 4. Both compounds **31** and **32** show strong antitumor activity. While compound **31** achieves only partial tumor regression, **32** is capable of achieving rapid, complete, and persistent tumor regression. At day 62, 18 days after the treatment was ended, none of the eight mice treated with **32** had measurable tumors, and at day 117, 74 days after the end of the treatment with **32**, four mice (50%) did not have measurable tumors. The average tumor size for the eight mice was 47 mm^3 at day 117, as compared to 130 mm^3 at the start of the treatment (day 33). Furthermore, all the mice treated with compound **32** suffered no significant weight loss (<5%) and did not show other signs of toxicity during or after the treatment. In our previous study, we had tested compound **5** for its antitumor activity in the H146 xenograft model and found that while **5** effectively inhibited tumor growth at 25 mg/kg, iv, 5 days per week for 2 weeks, it failed to achieve long-lasting tumor regression.[8] Hence, compound **32** at 15 mg/kg is considerably more effective than compound **5** at 25 mg/kg in inducing complete and persistent tumor regression in the H146 xenograft model.

To further define their anticancer activity, we next tested compounds **31** and **32** in three additional small-cell lung cancer cell lines, known to be sensitive to **1** and **2**, and the data are
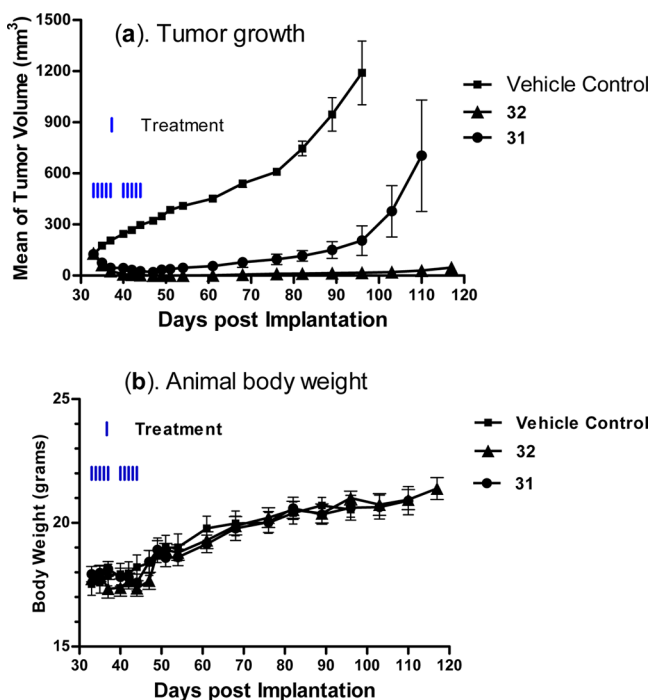
Figure 4. Antitumor activity of compounds **31** and **32** in the H146 small-cell lung cancer xenograft model in SCID mice. Tumors were grown to an average size of 126 mm³ and compound **31** or **32** was administered at 15 mg/kg intravenously, daily, 5 days a week for 2 weeks. (a) Tumor growth. (b) Animal body weight.

summarized in Table 4. While all four compounds effectively inhibit cell growth in these three cancer cell lines, compound

Table 4. Cell Growth Inhibitory Activity of Compounds 31, 32, 1, and 2 in Three Small-Cell Lung Cancer Cell Lines

cell lines	$IC_{50} \pm SD$ (nM)			
	1	**2**	**31**	**32**
H1963	54.0 ± 28.2	26.6 ± 7.9	8.2 ± 4.9	1.0 ± 0.5
H187	137.7 ± 71.3	38.4 ± 26.8	7.9 ± 3.9	1.4 ± 1.3
H1417	173.4 ± 122.1	54.2 ± 11.1	11.1 ± 2.0	2.3 ± 0.2

32 is the most potent of the compounds. Compound **32** has IC_{50} values of 1.0, 1.4, and 2.3 nM in these three cancer cell lines and is >10 times more potent than **2** and >50 times more potent than **1** against each of these three cell lines, on the basis of their IC_{50} values.

■ CHEMISTRY

Initially, we employed a convergent synthesis[7] (method A, Scheme 1) for the preparation of the target molecules. The piperazine **38**, embedded in our target molecules, was prepared in three steps starting with the reaction of the aniline (**33**) and 4-fluoro-3-nitrobenzene-1-sulfonyl chloride (**34**), forming the sulfonamide (**35**).[7] Displacement of the activated fluorine in **35** with (R)-N¹,N¹-dimethyl-4-(phenylthio)butane-1,3-diamine (**36**) and acid removal of the Boc protecting group generated **38**. The second fragment was designed as a variable scaffold, in which diversity could be built upon to develop compounds for SAR. These scaffolds consisted of various five-membered heteroaromatic rings with a 4-chlorophenyl and as a synthetic handle, an adjacent 3-iodophenyl group, to which **38** could be attached. Accordingly, in this methodology, **38** was subjected to

Buchwald−Hartwig coupling[7,10] with the synthesized scaffolds **9a** and **18a−21a** furnishing **9** and **18−21**, respectively. However, this synthetic route was complicated by poor yields of the target molecules, especially when the scaffolds contained a carboxylic acid or bioisosteres, and ultimately, this precluded further use of this methodology for further studies.
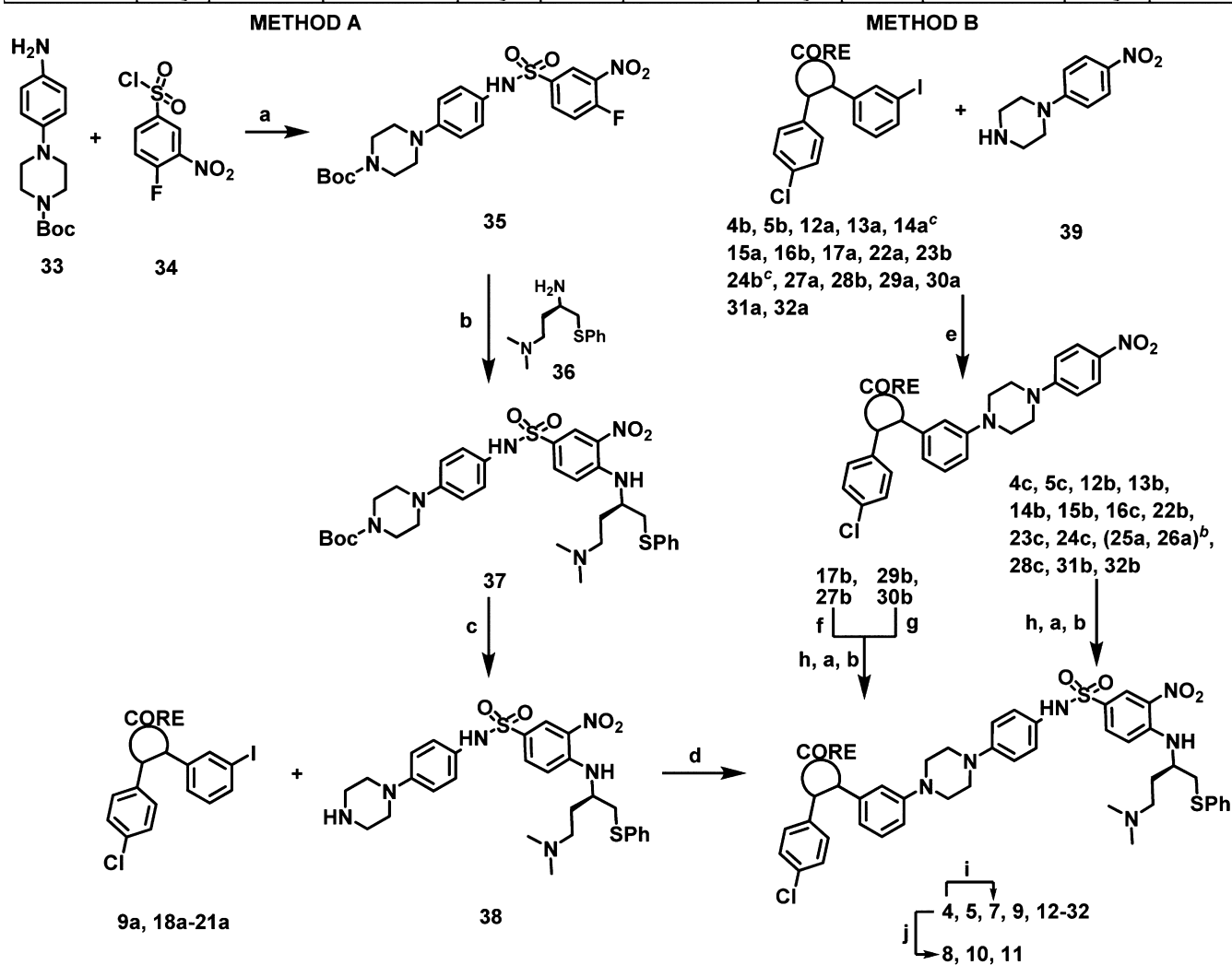
Consequently, a stepwise synthesis[7,8] (method B, Scheme 1) applicable to all scaffolds was carried out. In this methodology, (4-nitrophenyl)piperazine (**39**) was subjected to Ullman coupling[11] with the synthetic scaffolds **4b**, **5b**, **12a**, **13a**, **14a**, **15a**, **16b**, **17a**, **22a**, **23b**, **24b**, **27a**, **28b**, **29a**, **30a**, **31a**, and **32a** producing intermediates **4c**, **5c**, **12b**, **13b**, **14b**, **15b**, **16c**, **17b**, **22b**, **23c**, **24c**, **27b**, **28c**, **29b**, **30b**, **31b**, and **32b**, respectively. Intermediates **25a** and **26a** were obtained using the method described in Scheme 6. Base hydrolysis of ethyl ester intermediates **17b** and **27b** or low temperature acid hydrolysis of the tert-butyl ester intermediates **29b** and **30b** gave the corresponding carboxylic acids. Reduction of the nitro groups in these intermediates (**17b**-carboxylic acid, **27b**-carboxylic acid, **29b**-carboxylic acid, **30b**-carboxylic acid, **4c**, **5c**, **12b**, **13b**, **14b**, **15b**, **16c**, **22b**, **23c**, **24c**, **25a**, **26a**, **28c**, **31b**, and **32b**) by catalytic hydrogenation led to aniline intermediates that were subjected to the same synthetic strategy used for the preparation of **37**, generating the target compounds **4**, **5**, **12−17**, and **22−32**. Decarboxylation of **4** by acid treatment generated target compound **7**. Target compounds **8**, **10**, and **11** were obtained by EDCI-mediated coupling to carboxylic acid **4** of methylamine, (1s,3s)-3-amino-1-methylcyclobutanol, and 3-methylazetidine-3-ol, respectively.

Preparation of the 2-methylfuran scaffold **27a**, and the variously substituted 1H-pyrrole scaffolds **4b**, **5b**, **9a**, **12a**, **13a**, **14a**, **15a**, **16b**, **28b**, **29a**, **30a**, **31a**, **32a** is outlined in Scheme 2. Intermediates **44a−d** were prepared using an established synthetic strategy[8] in which condensation of the β-keto esters **40a−c** with 3-iodobenzaldehyde (**41a**) produced intermediates **42a−c**, respectively, and the bromo analogue (**42d**) was prepared by the condensation of β-keto ester (**40a**) with 3-bromobenzaldehyde (**41b**). Compounds **42a−d** were subjected to a Stetter reaction with 4-chlorobenzaldehyde, furnishing **44a−d**.[8,12] The furan intermediate (**27a**) was prepared by heating **44a** with HCl, and AcOH in EtOH. The 2-trifluoromethyl-1H-pyrrole intermediate (**16a**) was prepared by condensation of intermediate (**44b**) with methylamine. Paal−Knorr cyclization of **44a** with methylamine, of **44d** with methylamine, and **44c** with ethylamine, n-propylamine, n-butylamine, or isopropylamine furnished pyrroles **4a**, **46**, **5a**, **28a**, **29a**, and **30a**, respectively.[13] Base hydrolysis of the ethyl ester intermediates **4a** and **16a** or low temperature acid hydrolysis of the tert-butyl ester intermediates **5a** and **28a** furnished the corresponding 1H-pyrrole-3-carboxylic acid scaffolds **4b** and **16b**, and **5b** and **28b**, respectively.[8]
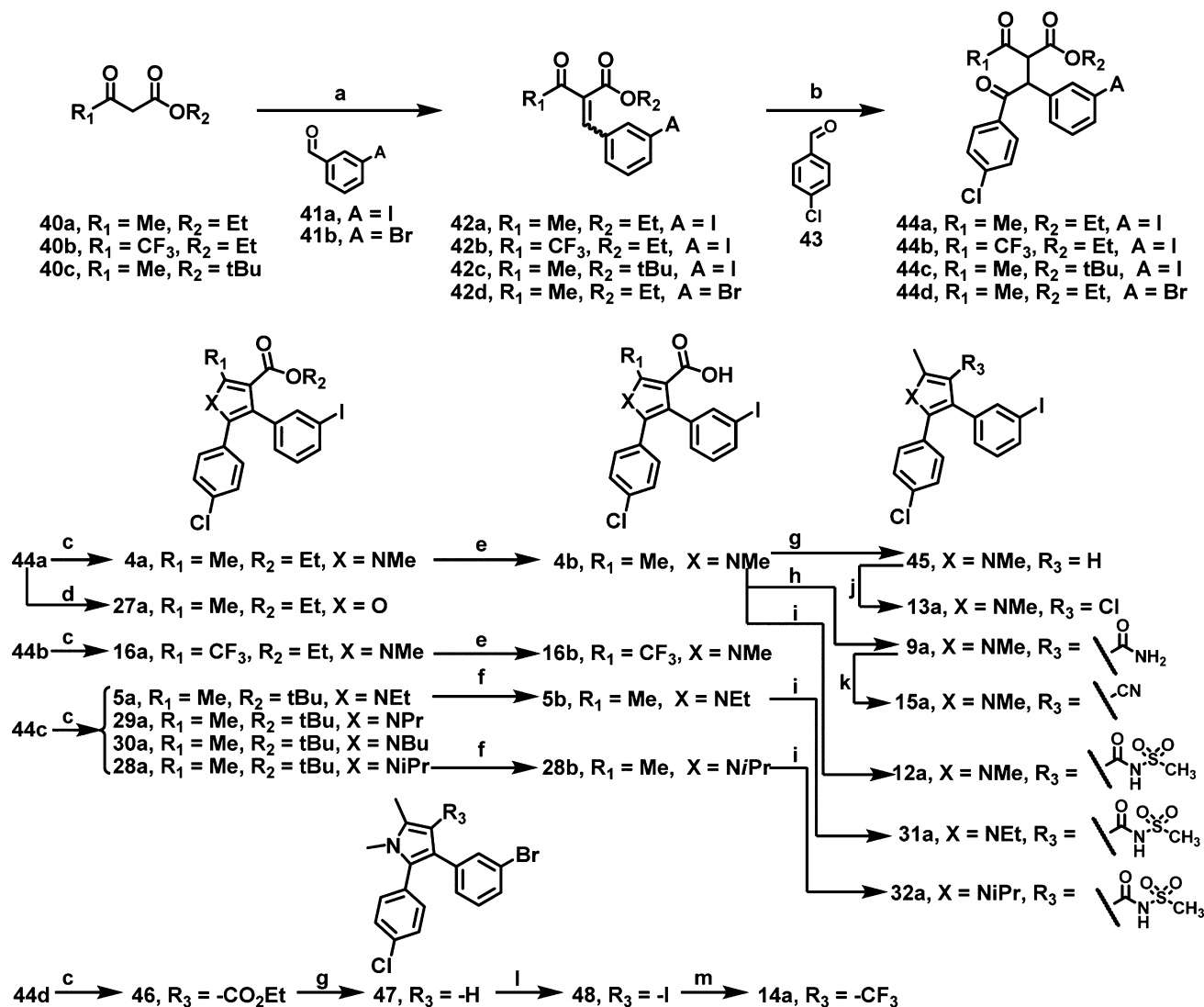
EDCI-catalyzed coupling of ammonia to the carboxylic acid **4b** furnished the 1H-pyrrole-3-carboxamide scaffold **9a**, but the same conditions failed to produce the N-(methylsulfonyl)-carboxamide (**12a**), which was instead prepared by formation of the acid chloride of **4b** and heating it with excess methanesulfonamide. In a similar manner used for the preparation of **12a**, **31a** and **32a** were prepared from **5b** and **28b**, respectively. Scaffold **13a** was prepared in two steps starting with the acid-mediated decarboxylation of **4b** followed by chlorination at the 3-position with N-chlorosuccinamide (NCS). The 3-trifluoromethyl-1H-pyrrole scaffold **14a** was prepared from **46** in three steps.[7] Acid-mediated decarboxylation

Scheme 1. Convergent Method A and Stepwise Method B for the Preparation of 4, 5, and 7–32[d]

ID	Core	R	ID	Core	R	ID	Core	R	ID	Core	R
4b, 4c, 4 [a]		OH (C=O)	14a, 14b, 14		–CF₃	21a, 21		–H	5b, 5c, 5 [a]	Et-N	OH (C=O)
7 [a]		–H	15a, 15b, 15		–CN	22a, 22b, 22		–H	28b, 28c, 28[a]		OH (C=O)
8 [a]		NHCH₃ (C=O)	16b, 16c, 16		OH (C=O)	23b, 23c, 23		NSCH₃ HO	29a, 29b	Pr-N	OtBu (C=O)
9a, 9		NH₂ (C=O)	17a, 17b		OEt (C=O)	24b, 24c, 24		NSCH₃ HO	29	Pr-N	OH (C=O)
10		N OH (C=O)	17		OH (C=O)	25a, 25		OH (C=O)	30a, 30b	Bu-N	OtBu (C=O)
11		N OH (C=O)	18a, 18		–H	26a, 26		OH (C=O)	30	Bu-N	OH (C=O)
12a, 12b, 12		NSCH₃ HO (C=O)	19a, 19		–H	27a, 27b		OEt (C=O)	31a, 31b, 31	Et-N	N SCH₃ (C=O,C=O)
13a, 13b, 13		–Cl	20a, 20		–H	27		OH (C=O)	32a, 32b, 32		N SCH₃ (C=O,C=O)

METHOD A / **METHOD B**

4b, 5b, 12a, 13a, 14a[c]
15a, 16b, 17a, 22a, 23b
24b[c], 27a, 28b, 29a, 30a
31a, 32a

4c, 5c, 12b, 13b,
14b, 15b, 16c, 22b,
23c, 24c, (25a, 26a)[b],
28c, 31b, 32b

17b, 29b,
27b 30b

35, **36**, **37**, **38**, **39**

9a, 18a-21a

4, 5, 7, 9, 12-32
8, 10, 11

[a]Previously reported.[8] [b]Synthesis described in Scheme 6. [c]I = Br. [d]Reagents and conditions: (a) pyridine, **34**, 0 °C, 15 min; (b) DMF, **36**, DIEA, overnight; (c) DCM, TFA, rt; (d) 2:1 toluene:DMF, Pd(dba)₂, NaOtBu, P(tBu)₃; (e) CuI, L-proline, K₂CO₃, DMSO, 90 °C, overnight; (f) NaOH, 1:1:1 1,4-dioxane:EtOH:H₂O, reflux (g) (1) DCM, H₂SO₄ (concd), 0 °C, 10 min, (2) satd NaHCO₃; (h) 10% Pd–C/H₂, MeOH, 1 atm, 15 min; (i) TFA, 10 min; (j) amine, EDCI, HOBt, DIEA, DCM, rt, overnight.

Scheme 2. Synthesis of Variously Substituted 1H-Pyrroles and 2-Methylfuran Scaffolds[a]

[a]Reagents and conditions: (a) piperidine, **41a** or **41b**, AcOH, toluene reflux; (b) **43**, thiazolium catalyst, Et₃N, 70 °C, 5 h; (c) (i) primary amine, MeOH, overnight (ii) 2 N HCl, 5 min; (d) AcOH, HCl (concd), EtOH, 70 °C, 4 h; (e) NaOH, 1:1:1 1,4-dioxane:EtOH:H₂O, reflux; (f) (1) DCM, H₂SO₄ (concd), 0 °C, 10 min, (2) satd NaHCO₃; (g) TFA, DCM, rt, overnight; (h) ammonia (0.5 M in 1,4-dioxane), EDCI, HOBt, DIEA, DCM, rt, overnight; (i) (1) (COCl)₂, DCM, cat. DMF, reflux, 1 h (2) methanesulfonamide, DMAP, ClCH₂CH₂Cl, reflux, overnight; (j) NCS, DMF, rt, overnight; (k) pyridine, TFAA, 1,4-dioxane, 0 °C, 3 h, rt; (l) NIS, DMF, rt, overnight; (m) methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, CuI, DMF, 100 °C, overnight.
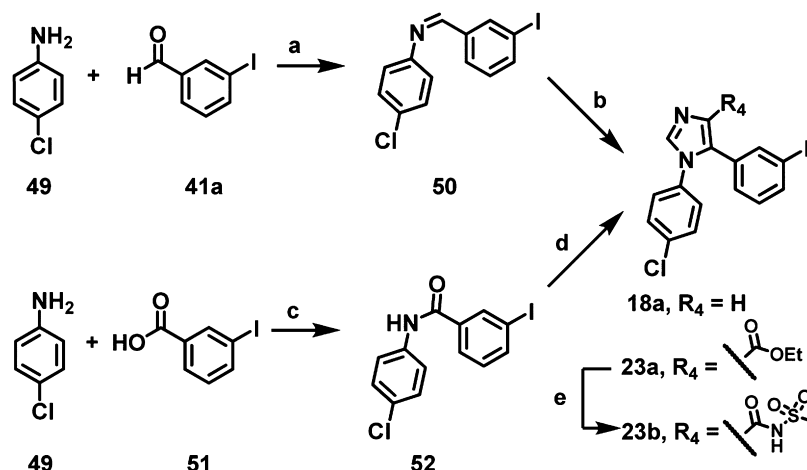
of **46** generated intermediate **47**, which was iodinated at the 3-position with *N*-iodosuccinamide (NIS), producing **48**. A trifluoromethyl group was selectively installed at the 3-position of the iodopyrrole by Cu(I)-catalyzed coupling with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate, producing **14a**.[14] The 1*H*-pyrrole-3-carbonitrile scaffold **15a** was prepared by dehydration of pyrrole-3-carboxamide **9a**.[15]

Imidazole scaffolds **18a** and **23b** were prepared as outlined in Scheme 3. The imidazole **18a** was synthesized by a two-step 1,3-dipolar addition of toluenesulfonylmethyl isocyanide (TosMIC) with imine **50**.[16] Compound **50** was prepared by reaction of 4-chloroaniline (**49**) with **41a** under Dean−Stark conditions.[16] The imidazole (**23b**) was prepared using a procedure described by Yang et al. for the construction of imidazol[1,5-*a*][1,4]benzodiazapines.[17] EDCI coupling of **49** with 3-iodobenzoic acid (**51**) generated the amide **52**, which was treated with diethyl chlorophosphate to generate the
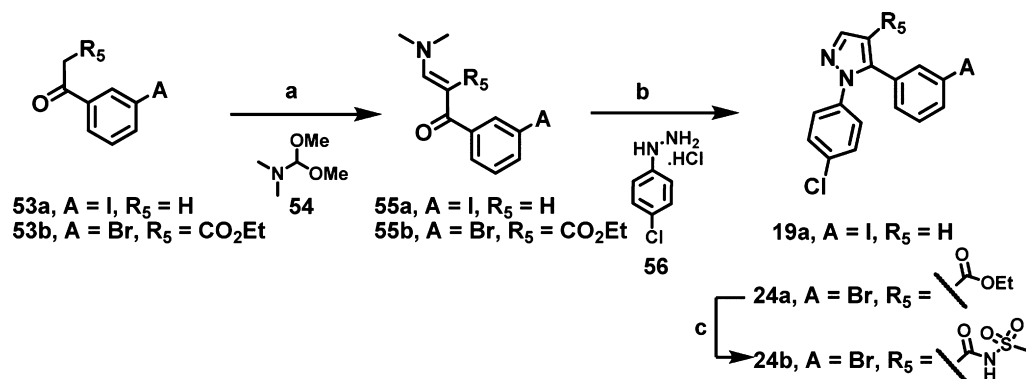
unstable iminophosphate, which was condensed under basic conditions with ethyl isocyanoacetate to produce the imidazole **23a**.[17] Base hydrolysis of the ethyl ester (**23a**) produced its corresponding acid that was converted to its acid chloride and reacted with methanesulfonamide to generate the imidazole scaffold (**23b**).

The pyrazole scaffolds (**19a** and **24b**) were prepared using a previously established method.[18] Treatment of **53a** or **53b** with *N,N*-dimethylformamide dimethylacetal (**54**) generated the enaminones (**55a** and **55b**) which, when condensed with 4-chlorophenylhydrazine (**56**), produced the pyrazoles (**19a** and **24a**), respectively.[18] Base hydrolysis of the ethyl ester (**24a**) produced the corresponding carboxylic acid that was converted to its acid chloride and reacted with methanesulfonamide to produce the pyrazole scaffold **24b**.

The pyrazoles **20a** and **21a** and the isoxazole **22a** were prepared from a common intermediate, enaminone **59**. 3-

Scheme 3. Synthesis of Imidazole Scaffolds 18a and 23b[a]

[a]Reagents and conditions: (a) toluene, reflux; (b) TosMIC, K$_2$CO$_3$, MeOH, DME; (c) EDCI, HOBt, DIEA, DCM, rt, overnight; (d) (i) KOt-Bu, THF, ClPO(OEt)$_2$, (ii) ethyl isocyanoacetate, KOt-Bu; (e) (i) NaOH, 1:1:1 1,4-dioxane:EtOH:H$_2$O, reflux, (ii) (1) SOCl$_2$, reflux, 3 h (2) methanesulfonamide, DMAP, ClCH$_2$CH$_2$Cl, reflux, overnight.

Scheme 4. Synthesis of Pyrazole Scaffolds 19a and 24b[a]

[a]Reagents and conditions: (a) toluene, 54, reflux; (b) 56, EtOH, reflux; (c) (i) NaOH, 1,4-dioxane:EtOH:H$_2$O (1:1:1 v/v/v), reflux, (ii) (1) SOCl$_2$, reflux, 3 h (2) methanesulfonamide, DMAP, ClCH$_2$CH$_2$Cl, reflux, overnight.

Iodophenylacetic acid (**57**) was converted to its acid chloride by refluxing in thionyl chloride. Friedel−Craft acylation of chlorobenzene with 3-iodophenylacetyl chloride, using a standard method,[19] resulted in removal of the iodine atom from **58**, and to avoid this problem, the reaction was diluted and carried out at 0 °C, producing compound **58** as the major product. Treatment of ketone **58** with **54** produced the enaminone (**59**). Condensation of methyl hydrazine with **59** produced a mixture of two regioisomers that were separated to give the pyrazoles (**20a** and **21a**).[20] Condensation of **59** with hydroxylamine produced only one isoxazole (**22a**).[21]
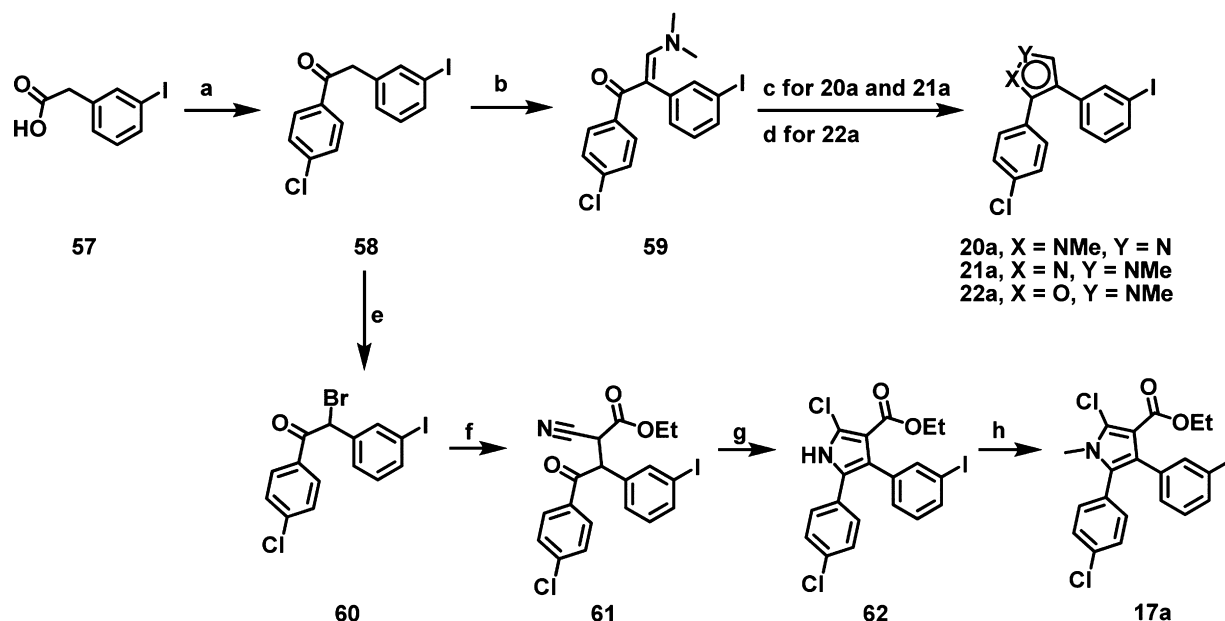
The 2-chloropyrrole (**17a**) was prepared in four steps starting from intermediate **58**. Compound **58** was treated with Br$_2$ in AcOH to produce the α-bromo ketone (**60**), which reacted with ethyl 2-cyanoacetate under basic conditions to produce compound **61**.[22] Treatment of **61** with 4 M HCl in 1,4-dioxane formed the 2-chloropyrrole (**62**), which was methylated with CH$_3$I under basic conditions to give the ethyl ester (**17a**).[22]

The pyrazole acids (**25a** and **26a**) were synthesized following the procedure outlined in Scheme 6. Condensation of **63** with methylhydrazine produced two regioisomers, (**64a** and **64b**),[23] which were separated and treated separately with NIS,
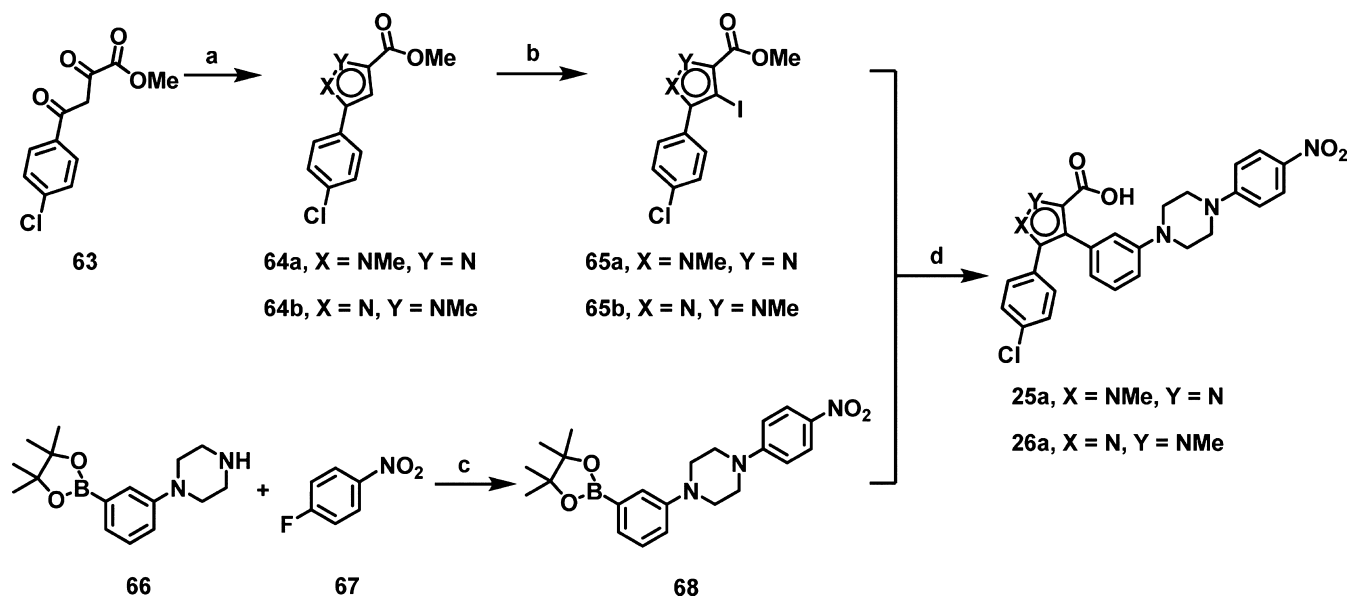
producing **65a** and **65b**.[24] In parallel, the pinacol boronic ester (**68**) was prepared by displacement of the activated fluorine in 4-fluoronitrobenzene (**67**) with the piperazine (**66**). This boronic ester was subjected to Suzuki coupling with **65a** or **65b**.[24] The Suzuki coupling condition also resulted in hydrolysis of the methyl ester and furnished the pyrazole acids **25a** and **26a**.

■ SUMMARY

In the present study, we have optimized compound **4**, which is a potent Bcl-2/Bcl-xL inhibitor but was unable to achieve tumor regression in animal models of human cancer. In contrast to our previous study,[9] in which our modifications were focused on the nitro group and the soluble thiophenyl-containing "tail" group in compound **4**, the present study was centered on the pyrrole core structure, which has a significant effect on binding affinities to Bcl-2/Bcl-xL and cellular activity in cancer cells. Our optimization efforts have yielded compound **32**, which binds to Bcl-2 and Bcl-xL with K_i values <1 nM. Similar to other initial lead compounds, compound **32** does not show any appreciable binding to Mcl-1 protein at concentrations as high as 2 μM. Compound **32** potently inhibits cancer cell growth in the H146 small-cell lung cancer

Scheme 5. Synthesis of Pyrazoles 20a and 21a, Isoxazole 22a, and 2-Chloropyrrole 17a[a]

20a, X = NMe, Y = N
21a, X = N, Y = NMe
22a, X = O, Y = NMe

17a

[a]Reagents and conditions: (a) (i) SOCl$_2$, reflux, 2 h, (ii) AlCl$_3$, chlorobenzene, 0 °C, 2 h; (b) **54**, toluene, reflux, 2 h; (c) NH$_2$NHCH$_3$, EtOH, reflux; (d) NH$_2$OH·HCl, Na$_2$CO$_3$, 2:1 MeOH:H$_2$O, AcOH, reflux; (e) AcOH, Br$_2$, DCM; (f) ethyl 2-cyanoacetate, K$_2$CO$_3$, acetone; (g) 4 M HCl in 1,4-dioxane; (h) MeI, K$_2$CO$_3$, DMF.

Scheme 6. Synthesis of Pyrazole Acid Intermediates 25a and 26a[a]

63

64a, X = NMe, Y = N
64b, X = N, Y = NMe

65a, X = NMe, Y = N
65b, X = N, Y = NMe

25a, X = NMe, Y = N
26a, X = N, Y = NMe

66   67   68

[a]Reagents and conditions: (a) NH$_2$NHCH$_3$, AcOH, EtOH; (b) NIS, CAN, CH$_3$CN, 70 °C; (c) K$_2$CO$_3$, DMSO, rt, overnight; (d) Pd(PPh$_3$)$_4$, K$_2$CO$_3$, 2:1 DME/H$_2$O reflux, 2 h.

cell line and achieves an IC$_{50}$ value of 1.3 nM. Compound **32** also potently inhibits cell growth, with IC$_{50}$ values of 1.0−2.3 nM, in three other small-cell lung cancer cell lines that were known to be sensitive to **1** and **2**. In direct comparison, compound **32** is >10 and >50 times more potent than **2** and **1**, respectively, against these cancer cell lines. Significantly, compound **32** achieves rapid, complete, and persistent tumor regression in the H146 xenograft tumor model in mice at a well-tolerated dose schedule. Taken together, these data show that compound **32** is arguably the most potent and efficacious Bcl-2/Bcl-xL inhibitor reported to date and warrants extensive

evaluation as a potential clinical development candidate for the treatment of human cancer.

■ EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were performed under a nitrogen atmosphere in dry solvents under anhydrous conditions, and all commercial reagents were used as supplied without further purification. NMR spectra were obtained on a Bruker 300 UltraShield spectrometer at a ^{1}H frequency of 300 MHz and ^{13}C frequency of 75 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to an internal standard. The final

products were purified by a C18 reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in CH$_3$CN) as eluents. All final compounds have purity ≥95% as determined by Waters ACQUITY UPLC. Syntheses of compounds **4, 5, 7, 8, 28**, and their intermediates were reported previously.[8]

Ethyl 2-Acetyl-4-(4-chlorophenyl)-3-(3-iodophenyl)-4-oxobutanoate (44a).[8] Ethyl acetoacetate (**40a**, 2.27 g, 17.4 mmol), 3-iodobenzaldehyde (**41a**, 4.04 g, 17.4 mmol), piperidine (70 μL), and acetic acid (200 μL) were dissolved in toluene (10 mL) and refluxed with azeotropic removal of water using a Dean−Stark apparatus. After reaction overnight, the solution was cooled; diluted with EtOAc; washed sequentially with 1.0 M HCl, saturated sodium bicarbonate, and brine; and then dried over sodium sulfate. Purification by column chromatography (9:1 hexane:EtOAc) provided 5.3 g of the product **42a** as a mixture of isomers. Triethylamine (1.55 mL) was added to a slurry of **42a** (5.3 g, 15.4 mmol), 4-chlorobenzaldehyde (**43**, 2.16 g, 15.4 mmol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.583 g, 2.3 mmol), and the mixture was stirred with heating at 70 °C until **42a** was consumed. After cooling to room temperature, the mixture was diluted with EtOAc; washed sequentially with 1.0 M HCl, saturated sodium bicarbonate, and brine; and dried over sodium sulfate. The EtOAc was removed in vacuo and provided 7.5 g of crude **44a**, which was used without further purification.

Ethyl 5-(4-Chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate (4a).[8] A 2.0 M solution of methylamine in MeOH (35 mL, 70 mmol) was added to compound **44a** (7.5 g, 15.4 mmol) dissolved in 5 mL of MeOH. After 24 h the solution was acidified with 1.0 M HCl and the compound was extracted with EtOAc. The EtOAc solution was washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide crude **4a**. Purification by column chromatography (5:1 hexane:EtOAc) provided 4.9 g (59% after three steps) of **4a**.

Ethyl 5-(4-Chlorophenyl)-4-(3-iodophenyl)-2-methylfuran-3-carboxylate (27a). Concentrated HCl (25 mL) and glacial acetic acid (5 mL) were added to a solution of **44a** (1.0 g, 2.06 mmol) in EtOH (25 mL), and the mixture was heated to 70 °C. After 4 h, the reaction was quenched with saturated sodium bicarbonate, extracted with EtOAc, washed with brine, dried over sodium sulfate, and filtered, and the EtOAc was removed in vacuo to produce crude **27a**. Purification by column chromatography provided 834 mg (96% yield) of **27a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.74−7.65 (m, 2H), 7.29−7.17 (m, 5H), 7.11 (t, J = 7.74 Hz, 1H), 4.09 (q, J = 7.13 Hz, 2H), 2.68 (s, 3H), 1.06 (t, J = 7.15 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.83, 159.06, 146.84, 139.22, 136.78, 135.95, 133.65, 130.11, 129.63, 128.88(2C), 128.59, 126.93 (2C), 121.23, 115.78, 94.03, 60.22, 14.39, 14.08.

Ethyl 2-(2-(4-Chlorophenyl)-1-(3-iodophenyl)-2-oxoethyl)-4,4,4-trifluoro-3-oxobutanoate (44b). Starting with the ethyl trifluoroacetoacetate (**40b**), compound **44b** was prepared according to the procedure described for the preparation of compound **44a**.

Ethyl 5-(4-Chlorophenyl)-4-(3-iodophenyl)-1-methyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxylate (16a). Starting with **44b**, compound **16a** was prepared in a similar manner as that described for the preparation of compound **4a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.54−7.45 (m, 2H), 7.35 (d, J = 8.51 Hz, 2H), 7.10 (d, J = 8.50 Hz, 2H), 7.01−6.85 (m, 2H), 4.22 (q, J = 7.14 Hz, 2H), 3.58 (s, 3H), 1.18 (t, J = 7.13 Hz, 3H); ESI-MS m/z 533.83 (M + H)$^+$.

tert-Butyl 2-Acetyl-4-(4-chlorophenyl)-3-(3-iodophenyl)-4-oxobutanoate (44c). Starting with tert-butyl acetoacetate (**40c**), compound **44c** was prepared according to the procedure described for the preparation of compound **44a**.

tert-Butyl 5-(4-Chlorophenyl)-1-ethyl-4-(3-iodophenyl)-2-methyl-1H-pyrrole-3-carboxylate (5a). Ethylamine (11.7 mL, 2.0 M in MeOH, 23.40 mmol) was added to a solution of compound **44c** (3.0 g, 5.85 mmol) in MeOH (20 mL). After 24 h, the solution was acidified with 1.0 M HCl and stirred briefly, and the compound was extracted with EtOAc. The EtOAc solution was washed sequentially with saturated NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to provide crude **5a**. Purification by column chromatography (using a gradient of hexane and DCM, the product

eluted at 100% DCM) provided 1.30 g (43% yield) of **5a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.53 (t, J = 1.63 Hz, 1H), 7.44 (dt, J = 1.39, 7.76 Hz, 1H), 7.26 (d, J = 8.50 Hz, 2H), 7.07 (d, J = 8.49 Hz, 2H), 6.93 (dt, J = 1.34, 7.66 Hz, 1H), 6.84 (t, J = 7.72 Hz, 1H), 3.80 (q, J = 7.18 Hz, 2H), 2.61 (s, 3H), 1.27 (s, 9H), 1.14 (t, J = 7.18 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.26, 140.07, 138.85, 135.37, 134.70, 134.12, 132.78 (2C), 130.50, 129.73, 129.66, 129.16, 128.75 (2C), 122.64, 113.05, 93.37, 79.83, 39.18, 28.26 (3C), 16.25, 11.47.

tert-Butyl 5-(4-Chlorophenyl)-4-(3-iodophenyl)-1-isopropyl-2-methyl-1H-pyrrole-3-carboxylate (28a). Starting with isopropylamine and **44c**, compound **28a** was prepared according to the procedure described for the preparation of compound **5a** (In this case, the reaction was heated in a sealed tube.): ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.50 (t, J = 1.39 Hz, 1H), 7.42 (dt, J = 1.30, 7.67 Hz, 1H), 7.25 (d, J = 8.41 Hz, 2H), 7.05 (d, J = 8.39 Hz, 2H), 6.92−6.87 (m, 1H), 6.82 (t, J = 7.69 Hz, 1H), 4.33 (sept, J = 7.07 Hz, 1H), 2.69 (s, 3H), 1.41 (d, J = 7.09 Hz, 6H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.35, 139.97, 139.05, 135.17, 134.57, 134.14, 133.16 (2C), 131.21, 130.26, 129.53, 129.11, 128.56 (2C), 122.48, 113.91, 93.34, 79.83, 48.81, 28.18 (3C), 22.48 (2C), 13.06.

tert-Butyl 5-(4-Chlorophenyl)-4-(3-iodophenyl)-2-methyl-1-propyl-1H-pyrrole-3-carboxylate (29a). Starting with n-propylamine and **44c**, compound **29a** was prepared according to the procedure described for the preparation of compound **5a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.53 (t, J = 1.56 Hz, 1H), 7.46−7.41 (m, 1H), 7.25 (d, J = 8.48 Hz, 2H), 7.05 (d, J = 8.49 Hz, 2H), 6.94−6.89 (m, 1H), 6.84 (t, J = 7.69 Hz, 1H), 3.75−3.66 (m, 2H), 2.59 (s, 3H), 1.51 (sex, J = 7.69 Hz, 2H), 1.27 (s, 9H), 0.75 (t, J = 7.42 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.28, 140.07, 138.86, 135.71, 134.66, 133.99, 132.76 (2C), 130.55, 130.00, 129.65, 129.15, 128.71 (2C), 122.53, 112.94, 93.37, 79.81, 45.96, 28.23 (3C), 24.24, 11.67, 11.28.

tert-Butyl 1-Butyl-5-(4-chlorophenyl)-4-(3-iodophenyl)-2-methyl-1H-pyrrole-3-carboxylate (30a). Starting with n-butylamine and **44c**, compound **30a** was prepared according to the procedure described for the preparation of compound **5a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.53 (s, 1H), 7.43 (d, J = 7.75 Hz, 1H), 7.25 (d, J = 8.38 Hz, 2H), 7.05 (d, J = 8.40 Hz, 2H), 6.92 (d, J = 7.60 Hz, 1H), 6.84 (t, J = 7.70 Hz, 1H), 3.79−3.69 (m, 2H), 2.60 (s, 3H), 1.47 (quin, J = 7.68 Hz, 2H), 1.27 (s, 9H), 1.14 (sex., J = 7.28 Hz, 2H), 0.78 (t, J = 7.31 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.27, 140.07, 138.87, 135.66, 134.65, 133.98, 132.78 (2C), 130.53, 129.97, 129.65, 129.13, 128.68 (2C), 122.53, 112.95, 93.35, 79.79, 44.15, 32.98, 28.23 (3C), 19.97, 13.71, 11.66.

Ethyl 2-Acetyl-3-(3-bromophenyl)-4-(4-chlorophenyl)-4-oxobutanoate (44d). Starting with 3-bromobenzaldehyde (**41b**) and ethyl acetoacetate (**40a**), compound **44d** was prepared according to the procedure described for the preparation of compound **44a**.

Ethyl 4-(3-Bromophenyl)-5-(4-chlorophenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate (46). Starting with **44d**, compound **46** was prepared in the manner described for the preparation of compound **4a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.31 (s, 1H), 7.29−7.20 (m, 3H), 7.07−6.90 (m, 4H), 4.07 (q, J = 7.1 Hz, 2H), 3.39 (s, 3H), 2.61 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.55, 138.25, 136.80, 134.06, 133.84, 132.45 (2C), 130.55, 129.96, 129.39, 128.93, 128.80, 128.68 (2C), 122.51, 121.17, 111.21, 59.39, 31.92, 14.02, 11.87.

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylic Acid (4b).[8] NaOH (8.2 g, 204.3 mmol) was added to a solution of **4a** (4.9 g, 10.2 mmol) in 300 mL of 1:1:1 dioxane:EtOH:H$_2$O, and the solution was heated at reflux until no compound **4a** was observed by TLC. After cooling, the reaction was slowly neutralized with 1 M HCl and the compound was extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to produce compound **4b** as a pale solid that was not further purified.

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1-methyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxylic Acid (16b). Compound **16b** was prepared according to the procedure described for the preparation of **4b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.55−7.41 (m, 2H), 7.35 (d,

J = 8.46 Hz, 2H), 7.09 (d, J = 8.42 Hz, 2H), 7.06−6.99 (m, 1H), 6.92 (t, J = 7.76 Hz, 1H), 3.59 (s, 3H); ESI-MS m/z 505.83 (M + H)$^+$.

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide (9a). Ammonia (1.5 mL, 0.5 M in 1,4-dioxane, 0.73 mmol) was added to a solution of **4b** (164 mg, 0.36 mmol), EDCI (104 mg, 0.54 mmol), HOBt (70 mg, 0.54 mmol), and DIEA (188 μL, 1.08 mmol) in 4 mL of DCM. After stirring overnight, the solvent was removed in vacuo and the crude was purified by column chromatography (the compound eluted at a 5:1 to 1:1 ratio of DCM:EtOAc) to give 145 mg (90% yield) of **9a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.60−7.51 (m, 2H), 7.27 (d, J = 8.49 Hz, 2H), 7.13−7.07 (m, 1H), 7.03 (d, J = 8.50 Hz, 1H), 6.96 (t, J = 7.72 Hz, 1H), 5.40−4.91 (m, 2H), 3.40 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 167.64, 139.85, 137.42, 136.19, 135.65, 134.10, 132.47 (2C), 130.37, 130.24, 130.20, 129.98, 128.84 (2C), 120.07, 113.60, 94.38, 31.89, 11.82; ESI-MS m/z 451.25 (M + H)$^+$.

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-N-(methylsulfonyl)-1H-pyrrole-3-carboxamide (12a). Oxalyl chloride (40 μL, 0.44 mmol) followed by DMF (catalytic) was added to a solution of the carboxylic acid **4b** (100 mg, 0.22 mmol) in DCM (4 mL) and heated under reflux for 30 min. After cooling, DCM and excess oxalyl chloride were removed in vacuo to produce the corresponding acid chloride. The resulting solid was redissolved in 1,2-DCE (5 mL), then methanesulfonamide (104 mg, 1.1 mmol) and DMAP (13 mg, 0.11 mmol) were added, and the solution was heated at reflux overnight. Then the solvent was removed in vacuo and the crude was purified by column chromatography. The compound eluted between a 1:1 ratio of hexanes:EtOAc to 100% EtOAc) to give 91 mg (79% yield) of **12a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.63 (dt, J = 1.44, 7.73 Hz, 1H), 7.54 (t, J = 1.57 Hz, 1H), 7.30 (d, J = 8.49 Hz, 2H), 7.20 (bs, 1H), 7.12 (dt, J = 1.41, 7.62 Hz, 1H), 7.09−7.00 (m, 3H), 3.42 (s, 3H), 3.27 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.09, 139.80, 138.67, 137.28, 135.82, 134.65, 132.38 (2C), 131.16, 130.83, 130.06, 129.11, 129.03 (2C), 119.86, 111.60, 94.91, 42.03, 32.10, 12.04; ESI-MS m/z 528.92 (M + H)$^+$.

5-(4-Chlorophenyl)-1-ethyl-4-(3-iodophenyl)-2-methyl-N-(methylsulfonyl)-1H-pyrrole-3-carboxamide (31a). Concentrated H$_2$SO$_4$ (2 mL) was added to a cooled (0 °C) solution of **5a** (620 mg, 1.19 mmol) in a mixture of DCM (5 mL) and THF (2 mL). After 10 min, the reaction was slowly quenched with saturated NaHCO$_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to produce 569 mg of its carboxylic acid **5b** as a white solid. Oxalyl chloride (222 μL, 2.44 mmol), followed by DMF (catalytic amount, ~10 drops), was added to a solution of the carboxylic acid (569 mg, 1.22 mmol) in DCM (7 mL) and heated to reflux for 30 min. After cooling, DCM and excess oxalyl chloride were removed in vacuo to produce the corresponding acid chloride. The resulting solid was redissolved in 1,2-DCE (10 mL), then methanesulfonamide (580 mg, 6.1 mmol) and DMAP (75 mg, 0.61 mmol) were added, and the solution was heated under reflux overnight. After this time, the solvent was removed in vacuo and the crude was purified by column chromatography (the compound eluted between a 1:1 ratio of hexanes:EtOAc to 100% EtOAc) to give 526 mg (82% yield, three steps) of **31a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.60 (dt, J = 1.42, 7.82 Hz, 1H), 7.55 (t, J = 1.52 Hz, 1H), 7.31 (d, J = 8.44 Hz, 2H), 7.22 (bs, 1H), 7.14−6.99 (m, 4H), 3.83 (q, J = 7.18 Hz, 2H), 3.27 (s, 3H), 2.65 (s, 3H), 1.17 (t, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.17, 139.74, 137.64, 137.13, 135.74, 134.78, 132.59 (2C), 130.72, 130.61, 129.96, 129.37, 128.99 (2C), 120.20, 111.67, 94.81, 41.99, 39.44, 16.08, 11.77.

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1-isopropyl-2-methyl-N-(methylsulfonyl)-1H-pyrrole-3-carboxamide (32a). Starting with **28a**, compound **32a** was prepared according to the procedure described for the preparation of compound **31a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.58 (d, J = 7.70 Hz, 1H), 7.52 (s, 1H), 7.29 (d, J = 8.37 Hz, 2H), 7.18 (bs, 1H), 7.11−7.04 (m, 3H), 7.01 (t, J = 7.68 Hz, 1H), 4.35 (sept, J = 7.02 Hz, 1H), 3.25 (s, 3H), 2.73 (s, 3H), 1.44 (d, J = 7.09 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.28, 139.66, 137.34, 136.93, 135.87, 134.76, 132.94 (2C), 131.08, 130.62, 130.13,

129.83, 128.79 (2C), 120.16, 112.50, 94.69, 49.26, 41.87, 22.33 (2C), 13.29.

2-(4-Chlorophenyl)-3-(3-iodophenyl)-1,5-dimethyl-1H-pyrrole (45). Trifluoroacetic acid (3 mL) was added to a solution of **4b** (500 mg, 1.11 mmol) in DCM (2 mL). After standing overnight at room temperature, the reaction was slowly quenched with saturated NaHCO$_3$ and extracted with EtOAc. The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to give crude **45**. Purification by column chromatography (using a gradient of hexanes:EtOAc) produced 223 mg (49% yield) of **45**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.56 (t, J = 1.6 Hz, 1H), 7.40−7.30 (m, 3H), 7.16 (d, J = 8.5 Hz, 2H), 6.99−6.93 (m, 1H), 6.82 (t, J = 7.8 Hz, 1H), 6.12 (s, 1H), 3.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 139.02, 136.75, 134.04, 133.76, 132.52 (2C), 131.61, 130.18, 129.90, 129.05 (2C), 127.02, 120.59, 106.85, 94.51, 31.60, 12.68.

3-Chloro-5-(4-chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-1H-pyrrole (13a). N-Chlorosuccinamide (91 mg, 0.68 mmol) was added to a solution of **45** (213 mg, 0.52 mmol) in DMF (3 mL). After overnight at room temperature, water was added and the mixture was extracted with EtOAc. The combined EtOAc layer was washed with brine, dried over Na$_2$SO$_4$, and filtered, and the solvent was removed in vacuo to give crude **13a**. Purification by column chromatography (using a gradient of hexanes:EtOAc) produced 145 mg (63% yield) of **13a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.58 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.11−7.01 (m, 3H), 6.91 (t, J = 7.8 Hz, 1H), 3.39 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 139.05, 136.16, 135.09, 133.92, 132.41 (2C), 130.28, 129.77, 129.47, 129.01, 128.96 (2C), 126.35, 118.83, 108.99, 93.98, 32.35, 10.28.

3-(3-Bromophenyl)-2-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrole (47). Starting with **46** (300 mg, 0.69 mmol), 181 mg (72%) of compound **47** was obtained according to the procedure described for the preparation of **45**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.37−7.28 (m, 3H), 7.20−7.11 (m, 3H), 6.98−6.90 (m, 2H), 6.12 (s, 1H), 3.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 138.94, 133.75, 132.51 (2C), 131.60, 130.64, 130.18, 129.72, 129.05 (2C), 128.03, 126.38, 122.44, 120.69, 106.87, 31.56, 12.66.

3-(3-Bromophenyl)-2-(4-chlorophenyl)-4-iodo-1,5-dimethyl-1H-pyrrole (48). Starting with NIS (129 mg, 0.58 mmol) and **47** (173 mg, 0.48 mmol), 174 mg (75% yield) of compound **48** was obtained according to the procedure described for the preparation of **13a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.37−7.22 (m, 4H), 7.11−6.95 (m, 4H), 3.46 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 138.17, 133.83, 133.55, 132.27 (2C), 132.02, 130.91, 130.49, 129.51, 129.39, 129.37, 128.85 (2C), 124.02, 121.90, 33.27, 14.00.

3-(3-Bromophenyl)-2-(4-chlorophenyl)-1,5-dimethyl-4-(trifluoromethyl)-1H-pyrrole (14a). Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (785 μL, 6.2 mmol) and copper(I) iodide (142 mg, 0.74 mmol) were added to a solution of **48** (300 mg, 0.62 mmol) in DMF (3 mL). The solution was placed under vacuum, flushed with nitrogen three times, and then heated to 100 °C overnight. After cooling to room temperature, the reaction was slowly quenched with saturated ammonium chloride and then extracted with diethyl ether. The extracted solution was washed with water and brine, dried over Na$_2$SO$_4$, filtered, and concentrated to give crude **14a**. Purification by column chromatography (using a gradient of hexanes:EtOAc) provided 152 mg (57% yield) of **14a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.32−7.22 (m, 4H), 7.08−6.97 (m, 4H), 3.40 (s, 3H), 2.43 (d, J = 1.4 Hz, 3H).

5-(4-Chlorophenyl)-4-(3-iodophenyl)-1,2-dimethyl-1H-pyrrole-3-carbonitrile (15a). To a solution of **9a** (86 mg, 0.19 mmol) and pyridine (31 μL, 0.38 mmol) in 1,4-dioxane (2 mL) at 0 °C was added trifluoroacetic anhydride (TFAA) (30 μL, 0.21 mmol) dropwise. After 3 h at room temperature, the reaction was quenched with water and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to provide crude **15a**. Purification by column chromatography (gradient of hexanes:EtOAc) provided 65 mg (79%) of **15a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.56−7.46 (m, 2H), 7.36 (d, J = 8.39 Hz, 2H), 7.17−7.07 (m, 3H), 6.95 (t, J = 7.91 Hz, 1H), 3.40 (s, 3H), 2.47 (s, 3H); ^{13}C

NMR (75 MHz, CDCl$_3$) δ ppm 139.18, 137.82, 135.83, 135.21, 134.87, 132.43, 130.42, 130.22, 129.29, 129.20, 128.28, 122.29, 116.88, 94.36, 91.91, 32.43, 12.09.

4-Chloro-*N*-(3-iodobenzylidene)aniline (50). A solution of 3-iodobenzaldehyde (4.1 g, 17.7 mmol) and 4-chloroaniline (2.25 g, 17.7 mmol) in toluene (70 mL) was heated to reflux in a Dean–Stark apparatus. After reaction overnight, the solvent was removed in vacuo and the crude product was used in the following reaction. ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.31 (d, J = 16.03 Hz, 2H), 7.81 (d, J = 7.71 Hz, 2H), 7.36 (d, J = 7.08 Hz, 2H), 7.24–7.09 (m, 3H).

1-(4-Chlorophenyl)-5-(3-iodophenyl)-1*H*-imidazole (18a). A solution of **50** (6.05 g, 17.7 mmol), toluenesulfonylmethyl isocyanide (5.2 g, 26.6 mmol), potassium carbonate (4.9 g, 35.4 mmol) in 120 mL of MeOH, and 50 mL of DME was refluxed for 2 h. After cooling to room temperature, the reaction was quenched with water and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to provide crude **18a**. Purification by column chromatography (the compound eluted between 1:1 and 1:2 hexanes:EtOAc) provided 3.95 g (59%, two steps) of **18a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.68 (d, J = 1.04 Hz, 1H), 7.63–7.58 (m, 2H), 7.40 (d, J = 8.80 Hz, 2H), 7.28 (d, J = 1.06 Hz, 1H), 7.13 (d, J = 8.80 Hz, 2H), 7.01–6.96 (m, 2H).

N-(4-Chlorophenyl)-3-iodobenzamide (52). 4-Chloroaniline (2.06 g, 16.13 mmol) was added to a solution of 3-iodobenzoic acid (**51**, 2.0 g, 8.06 mmol), EDCI (2.32 g, 12.09 mmol), HOBt (1.56 g, 12.09 mmol), and DIEA (4.2 mL, 24.18 mmol) in 130 mL of DCM. After stirring overnight, the solvent was removed in vacuo and the crude was purified by column chromatography to give 2.4 g (83%) of **52**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.69 (s, 1H), 7.65 (d, J = 8.00 Hz, 1H), 7.40–7.24 (m, 5H), 7.07 (d, J = 7.74 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 206.32, 144.03, 137.70, 137.59, 135.22, 134.86, 130.52, 129.26, 128.13, 127.69, 94.74.

Ethyl 1-(4-Chlorophenyl)-5-(3-iodophenyl)-1*H*-imidazole-4-carboxylate (23a). Potassium *tert*-butoxide (0.516 g, 4.61 mmol) was added to a solution of **52** (1.5 g, 4.19 mmol), at 0 °C, in THF. After 20 min at 0 °C, the reaction was cooled to −35 °C and diethyl chlorophosphate (783 μL, 5.45 mmol) was added slowly. After 30 min at 0 °C, the reaction was cooled to −35 °C, then ethyl isocyanoacetate (504 μL, 4.61 mmol) and *t*-BuOK (0.516, 4.61 mmol) were added, and the reaction was allowed to warm to room temperature. After 4 h, the reaction was quenched with saturated sodium bicarbonate and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to provide crude **23a**. Purification by column chromatography (the compound eluted between 1:1 and 1:2 hexanes:EtOAc) provided 1.15 g (61%) of **23a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.76 (s, 1H), 7.69–7.63 (m, 2H), 7.34 (d, J = 8.68 Hz, 2H) 7.15 (d, J = 7.83 Hz, 1H), 7.10–6.98 (m, 3H), 4.28 (q, J = 7.12 Hz, 2H), 1.28 (t, J = 7.13 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 162.37, 139.53, 137.81, 137.73, 135.86, 134.77, 133.65, 131.09, 129.97, 129.80, 129.74(2C), 129.48, 126.98 (2C), 93.33, 60.56, 14.17; ESI-MS m/z 453.50 (M + H)$^+$.

1-(4-Chlorophenyl)-5-(3-iodophenyl)-*N*-(methylsulfonyl)-1*H*-imidazole-4-carboxamide (23b). Compound **23a** was converted to its corresponding carboxylic acid in the manner described for the preparation of **4b**. A solution of this carboxylic acid (300 mg, 0.71 mmol) in 3 mL of thionyl chloride was heated at reflux for 2 h. After cooling, thionyl chloride was removed in vacuo to produce the corresponding acid chloride. The resulting solid was redissolved in 10 mL of 1,2-DCE, followed by the addition of methanesulfonamide (337 mg, 3.55 mmol) and DMAP (43 mg, 0.355 mmol), and the solution was heated at reflux overnight. After this time, the reaction was cooled, water was added, and the mixture was extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to provide crude **23b**. Purification by column chromatography provided 195 mg (55% yield) of **23b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 9.57 (s, 1H), 7.69 (d, J = 7.92 Hz, 1H), 7.66 (s, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.70 Hz, 2H), 7.11–6.99 (m, 3H), 3.35 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 160.19, 139.39, 138.67, 137.39, 136.27, 135.61, 133.53, 130.69, 130.23 (2C), 130.17, 129.97, 128.81, 127.19 (2C), 93.75, 42.00; ESI-MS m/z 502.67 (M + H)$^+$.

1-(4-Chlorophenyl)-5-(3-iodophenyl)-1*H*-pyrazole (19a). A solution of 3-iodoacetophenone **53a** (5.0 g, 20.3 mmol) and *N,N*-dimethylformamide dimethylacetal (41 mL, 304.8 mmol) in 200 mL of toluene was refluxed with azeotropic removal of water using a Dean–Stark apparatus. After 3 h, the solvent was removed in vacuo to give **55a** as an oil. A solution of crude **55a** (20.3 mmol) and 4-chlorophenylhydrazine hydrochloride (**56**) (4.0 g, 22.3 mmol) in ethanol was heated to reflux for 4 h. After cooling, EtOH was removed and the residue redissolved in EtOAc. The EtOAc solution was washed with H$_2$O and then brine, dried over Na$_2$SO$_4$, filtered, and concentrated to give crude **19a**. Purification by column chromatography (hexanes:EtOAc) provided 6.48 g (84%, two steps) of **19a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.75–7.60 (m, 3H), 7.33 (d, J = 8.57 Hz, 2H), 7.23 (d, J = 8.61 Hz, 2H), 7.12–6.97 (m, 2H), 6.51 (d, J = 1.28 Hz, 1H).

Ethyl 5-(3-Bromophenyl)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carboxylate (24a). Starting with ethyl 3-(3-bromophenyl)-3-oxopropanoate (**53b**, 1.0 g, 3.69 mmol), 0.67 g (44%, two steps) of compound **24a** was prepared according to the procedure described for the preparation of **19a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.18 (s, 1H), 7.56–7.50 (m, 2H), 7.29 (d, J = 8.84 Hz, 2H), 7.22 (t, J = 7.68 Hz, 1H), 7.18–7.10 (m, 3H), 4.22 (q, J = 7.14 Hz, 2H), 1.23 (t, J = 7.14 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 162.70, 143.66, 142.89, 137.56, 134.18, 133.65, 132.56, 130.80, 129.82, 129.38, 129.19, 126.53, 122.21, 114.78, 60.51, 14.28.

5-(3-Bromophenyl)-1-(4-chlorophenyl)-*N*-(methylsulfonyl)-1*H*-pyrazole-4-carboxamide (24b). Starting with **24a**, compound **24b** was obtained according to the procedure described for the preparation of **23b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.17 (s, 1H), 7.64 (ddd, J = 1.24, 1.85, 7.91 Hz, 1H), 7.48 (t, J = 1.68 Hz, 1H), 7.38–7.27 (m, 4H), 7.14 (d, J = 8.88 Hz, 2H), 3.34 (s, 3H).

1-(4-Chlorophenyl)-2-(3-iodophenyl)ethanone (58). A solution of 3-iodophenylacetic acid (**57**) (2.0 g, 7.63 mmol) and thionyl chloride (3 mL) was refluxed for 2 h. After cooling to room temperature, excess thionyl chloride was removed in vacuo, producing 3-iodophenylacetyl chloride as a brown solid. The crude 3-iodophenylacetyl chloride was dissolved in chlorobenzene (10 mL) and added to a 0 °C solution of aluminum chloride (1.73 g, 12.97 mmol) and chlorobenzene (50 mL). After 2 h at 0 °C, the reaction was poured into ice and extracted with DCM. The DCM solution was washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide crude **58**. Purification by column chromatography (the compound eluted at 19:1 hexanes:EtOAc) provided 2.03 g (75%) of **58**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.93 (d, J = 8.68 Hz, 2H), 7.66–7.56 (m, 2H), 7.45 (d, J = 8.68 Hz, 2H), 7.21 (d, J = 7.82 Hz, 1H), 7.07 (t, J = 8.23 Hz, 1H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 195.82, 140.14, 138.55, 136.57, 136.39, 134.81, 130.57, 130.15, 129.31, 128.99, 94.82, 44.94.

1-(4-Chlorophenyl)-3-(dimethylamino)-2-(3-iodophenyl)-prop-2-en-1-one (59). A solution of **58** (1.5 g, 4.21 mmol), and *N,N*-dimethylformamide dimethylacetal (**54**, 8.4 mL, 63.1 mmol) in 70 mL of toluene was heated to reflux with azeotropic removal of water using a Dean–Stark apparatus. After 3 h, the solvent was removed in vacuo to give **59** as an oil that was used without purification in the following reactions.

3-(4-Chlorophenyl)-4-(3-iodophenyl)-1-methyl-1*H*-pyrazole (21a) and 5-(4-Chlorophenyl)-4-(3-iodophenyl)-1-methyl-1*H*-pyrazole (20a). A solution of **59** (1.1 g, 2.67 mmol), methylhydrazine (210 μL, 4.01 mmol), and EtOH (80 mL) was refluxed for 4 h. After cooling, EtOH was removed and the residue redissolved in EtOAc. The EtOAc solution was washed with water and then brine, dried over Na$_2$SO$_4$, filtered, and concentrated to give a crude mixture of **21a** and **20a**. Purification by column chromatography (the compounds eluted between a solvent mixture of 4:4:0.1 and 4:4:0.2 DCM:hexanes:ethyl ether) eluted **21a** first, followed by **20a**. **21a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.66 (s, 1H), 7.59 (d, J = 7.87 Hz, 1H), 7.46 (s, 1H), 7.41 (d, J = 8.36 Hz, 2H), 7.29 (d, J = 8.48 Hz, 2H), 7.16 (d, J = 7.80 Hz, 1H), 7.01 (t, J = 7.74 Hz, 1H), 3.97 (s, 3H). **20a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.70 (s, 1H), 7.58 (s, 1H), 7.49 (d, J = 7.74 Hz,

1H), 7.44 (d, J = 8.33 Hz, 2H), 7.23 (d, J = 8.44 Hz, 2H), 7.01 (d, J = 7.82 Hz, 1H), 6.92 (t, J = 7.75 Hz, 1H), 3.77 (s, 3H).

5-(4-Chlorophenyl)-4-(3-iodophenyl)isoxazole (22a). A solution of **59** (300 mg, 0.73 mmol), hydroxylamine hydrochloride (56 mg, 0.801 mmol), sodium carbonate (108 mg, 1.02 mmol), MeOH (50 mL), H_2O (25 mL), and AcOH (1 mL) was heated to reflux for 4 h. After cooling to room temperature, H_2O was added and the mixture was extracted with EtOAc. The EtOAc solution was washed with sodium bicarbonate and then brine, dried over Na_2SO_4, filtered, and concentrated to give crude **22a**. Purification by column chromatography (hexanes:EtOAc) provided 247 mg (89%) of **22a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.33 (s, 1H), 7.79−7.67 (m, 2H), 7.54 (d, J = 8.58 Hz, 2H), 7.36 (d, J = 8.59 Hz, 2H), 7.32 (d, J = 7.78 Hz, 1H), 7.13 (t, J = 7.77 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.43, 151.71, 137.44, 137.42, 136.59, 132.10, 130.84, 129.40, 128.63, 128.01, 125.75, 115.13, 94.98.

2-Bromo-1-(4-chlorophenyl)-2-(3-iodophenyl)ethanone (60). A solution of bromine (86 μL, 1.68 mmol) in acetic acid (4 mL) was added to a solution of **58** (500 mg, 1.40 mmol) in DCM (4 mL). After 3 h at room temperature, H_2O was added and the mixture was extracted with DCM. The extracted solution was washed sequentially with sodium bicarbonate, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated to give crude **60**. Purification by column chromatography (hexanes:EtOAc) provided 220 mg (36%) of **60**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.91 (d, J = 8.55 Hz, 2H), 7.87 (s, 1H), 7.63 (d, J = 7.91 Hz, 1H), 7.48 (d, J = 7.80 Hz, 1H), 7.40 (d, J = 8.53 Hz, 2H), 7.08 (t, J = 7.85 Hz, 1H), 6.21 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 189.53, 140.55, 138.32, 137.96, 137.60, 132.17, 130.66, 130.61, 129.33, 128.66, 94.62, 48.74.

Ethyl 4-(4-Chlorophenyl)-2-cyano-3-(3-iodophenyl)-4-oxobutanoate (61). A mixture of potassium carbonate (636 mg, 4.60 mmol) and ethyl cyanoacetate (1.71 mL, 16.07 mmol) was heated at 45 °C. After 45 min, the mixture was allowed to cool to room temperature and then a solution of **60** (1.0g, 2.30 mmol) in 5 mL of Me$_2$CO was added dropwise. After stirring overnight, H_2O was added and the solution was extracted with EtOAc. The extracted solution was sequentially washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated to give crude **61**. Purification by column chromatography (hexanes:EtOAc) provided 1.01 g (94%) of **61**.

Ethyl 2-Chloro-5-(4-chlorophenyl)-4-(3-iodophenyl)-1H-pyrrole-3-carboxylate (62). To **61** (500 mg, 1.07 mmol) was added 6 mL of 4 M HCl in 1,4-dioxane. After 4 h, the reaction was slowly quenched with saturated sodium bicarbonate and the solution extracted with EtOAc. The extracted solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude **62**. Purification by column chromatography (the compound eluted with 100% DCM) provided 323 mg (62%) of **62**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 9.10 (s, 1H), 7.67−7.53 (m, 2H), 7.18 (d, J = 8.43 Hz, 2H), 7.13 (d, J = 7.67 Hz, 1H), 7.06−6.93 (m, 3H), 4.11 (q, 7.10 Hz, 2H), 1.08 (t, J = 7.11 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.72, 139.73, 136.97, 136.18, 133.57, 130.06, 129.72, 129.27, 129.09, 128.51, 127.64, 122.19, 121.89, 112.37, 93.73, 60.40, 14.11.

Ethyl 2-Chloro-5-(4-chlorophenyl)-4-(3-iodophenyl)-1-methyl-1H-pyrrole-3-carboxylate (17a). Potassium carbonate (274 mg, 1.98 mmol) was added to a solution of **62** (323 mg, 0.66 mmol) in DMF (3 mL). After 10 min at room temperature, iodomethane (86 μL, 1.33 mmol) was added and the mixture stirred overnight. The reaction was slowly quenched with saturated ammonium chloride and extracted with EtOAc. The extracted solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude **17a**. Purification by column chromatography (the compound eluted at a solvent mixture between 1:1 to 3:1 of DCM:hexanes) provided a quantitative yield of **17a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.58−7.45 (m, 2H), 7.28 (d, J = 8.44 Hz, 2H), 7.05 (d, J = 8.42 Hz, 2H), 6.98 (d, J = 7.70 Hz, 1H), 6.88 (t, J = 7.67 Hz, 1H), 4.13 (q, J = 7.12 Hz, 2H), 3.49 (s, 3H), 1.08 (t, J = 7.13 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.43, 139.87, 136.91, 135.49, 134.53, 132.38, 130.84, 129.94, 129.20, 129.02, 128.93, 123.51, 122.76, 110.84, 93.24, 60.05, 32.64, 14.14.

Methyl 3-(4-Chlorophenyl)-1-methyl-1H-pyrazole-5-carboxylate (64b) and Methyl 5-(4-Chlorophenyl)-1-methyl-1H-pyrazole-3-carboxylate (64a). Methyl hydrazine (0.656 mL, 12.47 mmol) was added, dropwise, to a solution of methyl 4-(4-chlorophenyl)-2,4-dioxobutanoate (**63**, 2.0 g, 8.31 mmol), AcOH (2.4 mL), and EtOH (40 mL). After 3 h of stirring at room temperature, H_2O was added and the mixture extracted with EtOAc. The extracted solution was washed with saturated sodium bicarbonate and then brine, dried over Na_2SO_4, filtered, and concentrated to give a crude mixture of **64a** and **64b**. Purification by column chromatography (using a gradient of hexanes:EtOAc where **64b** eluted at 9:1 and **64a** eluted between 4:1 to 1:1) provided 0.824 g (40%) of **64b** and 0.974 g (47%) of **64a**. **64b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.71 (d, J = 8.57 Hz, 2H), 7.36 (d, J = 8.56 Hz, 2H), 7.07 (s, 1H), 4.21 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 160.32, 148.88, 133.96, 133.77, 131.24, 129.06 (2C), 126.91 (2C), 108.03, 52.17, 39.83. **64a**: 7.46 (d, J = 8.58 Hz, 2H), 7.37 (d, J = 8.59 Hz, 2H), 6.85 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 162.52, 143.87, 142.35, 135.23, 130.01 (2C), 129.11 (2C), 127.90, 108.92, 51.95, 38.27.

Methyl 3-(4-Chlorophenyl)-4-iodo-1-methyl-1H-pyrazole-5-carboxylate (65b). N-Iodosuccinamide (903 mg, 4.01 mmol), followed by ceric ammonium nitrate (17 mg, 0.0308 mmol), was added to a solution of **64b** (774 mg, 3.08 mmol) in MeCN (30 mL), and the mixture was heated at 70 °C overnight. After cooling to room temperature, the solvent was removed in vacuo and the residue redissolved in EtOAc. The EtOAc solution was washed with H_2O and then brine, dried over Na_2SO_4, filtered, and concentrated to give crude **65b**. Purification by column chromatography (using a gradient of hexanes:EtOAc) provided 1.03 g (89% yield) of **65b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.71 (d, J = 8.61 Hz, 2H), 7.41 (d, J = 8.61 Hz, 2H), 4.23 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 159.73, 151.89, 135.04, 134.73, 131.05, 130.23 (2C), 128.64 (2C), 64.17, 52.31, 41.57.

Methyl 5-(4-Chlorophenyl)-4-iodo-1-methyl-1H-pyrazole-3-carboxylate (65a). Starting with **64a** (974 mg, 3.89 mmol), compound **65a** (337 mg, 23% yield) was obtained according to the procedure described for the preparation of compound **65b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 7.52 (d, J = 8.34 Hz, 2H), 7.33 (d, J = 8.39 Hz, 2H), 3.97 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 161.80, 146.46, 142.35, 136.30, 131.68 (2C), 129.41 (2C), 127.37, 63.65, 52.31, 39.28.

1-(4-Nitrophenyl)-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (68). Potassium carbonate (361 mg, 2.61 mmol) was added to a solution of 3-piperazinylphenylboronic acid pinacol ester (**66**, 500 mg, 1.74 mmol) and 1-fluoro-4-nitrobenzene (**67**, 269 mg, 1.91 mmol) in DMSO (5 mL). After stirring overnight, the reaction was quenched with 2 N HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to produce crude **68**. Column chromatography, using a gradient of DCM:EtOAc, produced 238 mg (33% yield) of pure **68** as an orange oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.11 (d, J = 9.35 Hz, 2H), 7.45−7.27 (m, 3H), 7.09−7.02 (m, 1H), 6.82 (d, J = 9.41 Hz, 2H), 3.60−3.50 (m, 4H), 3.41−3.30 (m, 4H), 1.35 (s, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 154.75, 150.17, 138.54, 128.82, 126.98, 126.00 (2C), 122.44, 119.45, 112.76 (2C), 83.90 (2C), 48.97 (2C), 47.06 (2C), 24.95 (4C); ESI-MS m/z 410.42 (M + H)$^+$.

5-(4-Chlorophenyl)-1-methyl-4-(3-(4-(4-nitrophenyl)-piperazin-1-yl)phenyl)-1H-pyrazole-3-carboxylic Acid (25a). Pd(PPh$_3$)$_4$ (10 mg) was added to a solution of **65a** (30 mg, 0.08 mmol), boronic ester **68** (65 mg, 0.16 mmol), and potassium carbonate (44 mg, 0.32 mmol) in DME/H_2O (9 mL, 2:1). The mixture was placed under vacuum, flushed with nitrogen twice, and heated to 90 °C overnight. After cooling to room temperature, saturated NH$_4$Cl was added and the mixture was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over Na_2SO_4, and filtered through a plug of Celite, and the solvent was removed in vacuo to give crude **25a**. Purification by reverse phase HPLC provided pure **25a**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD)

δ ppm 8.15 (d, *J* = 9.17 Hz, 2H), 7.38 (d, *J* = 8.32 Hz, 2H), 7.22−7.12 (m, 3H), 6.96−6.82 (m, 4H), 6.78 (d, *J* = 7.54 Hz, 1H), 3.89 (s, 3H), 3.64−3.51 (m, 4H), 3.30−3.19 (m, 4H); ESI-MS *m/z* 518.50 (M + H)⁺.

3-(4-Chlorophenyl)-1-methyl-4-(3-(4-(4-nitrophenyl)-piperazin-1-yl)phenyl)-1*H*-pyrazole-5-carboxylic Acid (26a). Starting with **65b**, compound **26a** was prepared according to the procedure described for the preparation of compound **25a**: ¹H NMR (300 MHz, 10:1 CDCl₃:CD₃OD) δ ppm 8.14 (d, *J* = 9.35 Hz, 2H), 7.33−7.16 (m, 5H), 6.97−6.77 (m, 5H), 4.23 (s, 3H), 3.62−3.50 (m, 4H), 3.32−3.21 (m, 4H); ESI-MS *m/z* 518.33 (M + H)⁺.

5-(4-Chlorophenyl)-1,2-dimethyl-*N*-(methylsulfonyl)-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carboxa-mide (12b). A mixture of **12a** (585 mg, 1.1 mmol), 1-(4-nitrophenyl)piperazine (916 mg, 4.43 mmol), copper(I) iodide (105 mg, 0.55 mmol), L-proline (127 mg, 1.1 mmol), and potassium carbonate (612 mg, 4.43 mmol) was placed under vacuum and then flushed with N₂ three times. To this mixture was added DMSO (13 mL), and the solution was placed under vacuum, flushed with N₂ three times, and then heated to 100 °C overnight. After cooling to room temperature, the reaction was slowly quenched with saturated ammonium chloride and stirred for 10 min. The solution was then extracted with DCM, and the extracted solution was washed with saturated ammonium chloride, 2 M hydrochloric acid, and brine; dried over Na₂SO₄; filtered; and concentrated to give crude **12b**. Purification by column chromatography (using a gradient of DCM:EtOAc) provided 491 mg (74%) of **12b** as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.15 (d, *J* = 9.36 Hz, 2H), 7.53 (bs, 1H), 7.32−7.21 (m, 3H), 7.07 (d, *J* = 8.40 Hz, 2H), 6.93 (dd, *J* = 2.21, 8.16 Hz, 1H), 6.88−6.78 (m, 3H), 6.70 (d, *J* = 7.49 Hz, 1H), 3.62−3.52 (m, 4H), 3.45 (s, 3H), 3.39−3.29 (m, 4H), 3.24 (s, 3H), 2.67 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 163.39, 154.76, 150.58, 139.05, 139.02, 134.66, 134.36, 132.38 (2C), 130.91, 130.42, 129.64, 128.91 (2C), 126.19 (2C), 123.20, 121.84, 119.16, 116.34, 113.05 (2C), 111.38, 48.96 (2C), 46.83 (2C), 42.24, 32.13, 12.20; ESI-MS *m/z* 608.50 (M + H)⁺.

1-(3-(4-Chloro-2-(4-chlorophenyl)-1,5-dimethyl-1*H*-pyrrol-3-yl)phenyl)-4-(4-nitrophenyl)piperazine (13b). Starting with **13a** (123 mg, 0.28 mmol), 95 mg (65% yield) of compound **13b** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.11 (d, *J* = 9.3 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.18−7.07 (m, 3H), 6.81 (d, *J* = 9.4 Hz, 2H), 6.77−6.68 (m, 3H), 3.54−3.44 (m, 4H), 3.42 (s, 3H), 3.23−3.11 (m, 4H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 154.86, 150.18, 138.67, 134.69, 133.55, 132.52 (2C), 130.92, 128.90, 128.80 (2C), 128.70, 126.22, 126.10 (2C), 122.32, 120.36, 118.60, 114.18, 112.81 (2C), 108.96, 48.86 (2C), 46.98 (2C), 32.29, 10.25; ESI-MS *m/z* 521.67 (M + H)⁺.

1-(3-(2-(4-Chlorophenyl)-1,5-dimethyl-4-(trifluoromethyl)-1*H*-pyrrol-3-yl)phenyl)-4-(4-nitrophenyl)piperazine (14b). Starting with **14a** (152 mg, 0.36 mmol), 68 mg (34% yield) of compound **14b** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.14 (d, *J* = 9.3 Hz, 2H), 7.30−7.20 (m, 2H), 7.16−7.02 (m, 3H), 6.84 (d, *J* = 9.3 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.73−6.63 (m, 2H), 3.56−3.46 (m, 4H), 3.43 (s, 3H), 3.25−3.13 (m, 4H), 2.45 (s, 3H); ESI-MS *m/z* 555.17 (M + H)⁺.

5-(4-Chlorophenyl)-1,2-dimethyl-4-(3-(4-(4-nitrophenyl)-piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carbonitrile (15b). Starting with **15a** (216 mg, 0.50 mmol), 150 mg (59%) of compound **15b** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.14 (d, *J* = 9.36 Hz, 2H), 7.37 (d, *J* = 8.42 Hz, 2H), 7.22−7.08 (m, 3H), 6.91−6.79 (m, 3H), 7.76 (dd, *J* = 2.00, 8.14 Hz, 1H), 6.66 (d, *J* = 7.67 Hz, 1H), 3.58−3.47 (m, 4H), 3.42 (s, 3H), 3.29−3.17 (m, 4H), 2.49 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 154.89, 150.60, 139.03, 138.80, 134.67, 133.87, 132.67 (2C), 130.07, 130.03, 129.45, 129.28 (2C), 126.17 (2C), 124.18, 120.96, 117.46, 117.23, 114.74, 112.88 (2C), 91.98, 48.82 (2C), 47.06 (2C), 32.36, 12.08; ESI-MS *m/z* 512.33 (M + H)⁺.

5-(4-Chlorophenyl)-1-methyl-4-(3-(4-(4-nitrophenyl)-piperazin-1-yl)phenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-car-boxylic Acid (16c). Starting with **16b** (484 mg, 0.96 mmol), 150 mg (27%) of compound **16c** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.10 (d, *J* = 9.36 Hz, 2H), 7.34 (d, *J* = 8.42 Hz, 2H), 7.13 (d, *J* = 8.43 Hz, 2H), 7.06 (t, *J* = 7.83 Hz, 1H), 6.88−6.68 (m, 4H), 6.55 (d, *J* = 7.65 Hz, 1H), 3.60 (s, 3H), 3.51−3.41 (m, 4H), 3.24−3.07 (m, 4H); ESI-MS *m/z* 585.42 (M + H)⁺.

Ethyl 2-Chloro-5-(4-chlorophenyl)-1-methyl-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carboxylate (17b). Starting with **17a** (353 mg, 0.71 mmol), 199 mg (51%, two steps) of compound **17b** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.12 (d, *J* = 9.33 Hz, 2H), 7.27 (d, *J* = 8.46 Hz, 2H), 7.16−7.04 (m, 3H), 6.84 (d, *J* = 9.41 Hz, 2H), 6.77 (dd, *J* = 1.76, 8.18 Hz, 1H), 6.71−6.60 (m, 2H), 4.13 (q, *J* = 7.17 Hz, 2H), 3.51 (s, 3H), 3.58−3.43 (m, 4H), 3.22−3.10 (m, 4H), 1.10 (t, *J* = 7.11 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 163.74, 154.81, 149.83, 138.62, 135.31, 134.17, 132.41 (2C), 130.58, 129.65, 128.77 (2C), 128.32, 126.06 (2C), 124.57, 123.25, 122.91, 119.24, 114.72, 112.80 (2C), 111.01, 59.98, 48.99 (2C), 46.96 (2C), 32.61, 14.13.

5-(4-Chlorophenyl)-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)-phenyl)isoxazole (22b). Starting with **22a** (100 mg, 0.24 mmol), 43 mg (39%) of compound **22b** was obtained according to a modified procedure described for the preparation of **12b**; i.e., for this scaffold the reaction is not heated but instead is run at room temperature: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.35 (s, 1H), 8.15 (d, *J* = 9.33 Hz, 2H), 7.61 (d, *J* = 8.57 Hz, 2H), 7.41−7.29 (m, 3H), 7.03−6.80 (m, 5H), 3.65−3.52 (m, 4H), 3.41−3.30 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 163.07, 154.79, 152.18, 151.36, 139.10, 136.36, 131.11, 130.33, 129.31 (2C), 128.72 (2C), 126.32, 126.19 (2C), 120.63, 117.02, 116.29, 116.07, 113.05 (2C), 48.67 (2C), 47.16 (2C); ESI-MS *m/z* 461.83 (M + H)⁺.

1-(4-Chlorophenyl)-*N*-(methylsulfonyl)-5-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-imidazole-4-carboxa-mide (23c). Starting with **23b**, compound **23c** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.15 (d, *J* = 9.28 Hz, 2H), 7.38 (d, *J* = 7.05 Hz, 2H), 7.22 (t, *J* = 7.63 Hz, 1H), 7.16−7.01 (m, 2H), 7.01−6.89 (m, 2H), 6.86 (d, *J* = 9.32 Hz, 2H), 6.70 (d, *J* = 7.04 Hz, 1H), 3.61−3.50 (m, 4H), 3.35 (s, 3H), 3.32−3.22 (m, 4H); ESI-MS *m/z* 581.92 (M + H)⁺.

1-(4-Chlorophenyl)-*N*-(methylsulfonyl)-5-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrazole-4-carboxa-mide (24c). Starting with **24b**, compound **24c** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.26 (s, 1H), 8.13 (d, *J* = 9.19 Hz, 2H), 8.02 (bs, 1H), 7.37 (t, *J* = 7.94 Hz, 1H), 7.29 (d, *J* = 8.72 Hz, 2H), 7.18 (d, *J* = 8.68 Hz, 2H), 7.04 (d, *J* = 8.41 Hz, 1H), 6.93−6.78 (m, 3H), 6.74 (d, *J* = 7.39 Hz, 1H), 3.66−3.53 (m, 4H), 3.45−3.35 (m, 4H), 3.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 160.36, 154.62, 151.32, 143.95, 142.48, 138.93, 137.47, 134.41, 130.97, 129.40(2C), 128.34, 126.28 (2C), 126.16 (2C), 120.87, 117.81, 116.90, 115.42, 112.88 (2C), 47.92 (2C), 46.72 (2C), 42.30; ESI-MS *m/z* 581.58 (M + H)⁺.

Ethyl 5-(4-Chlorophenyl)-2-methyl-4-(3-(4-(4-nitrophenyl)-piperazin-1-yl)phenyl)furan-3-carboxylate (27b). Starting with **27a** (400 mg, 0.95 mmol), 132 mg (27%, two steps) of compound **27b** was obtained according to the procedure described for the preparation of **12b**: ¹H NMR (300 MHz, CDCl₃) δ ppm 8.10 (d, *J* = 9.38 Hz, 2H), 7.36−7.24 (m, 3H), 7.16 (d, *J* = 8.73 Hz, 2H), 6.98 (dd, *J* = 2.00, 8.19 Hz, 1H), 6.92−6.77 (m, 4H), 4.10 (q, *J* = 7.12 Hz, 2H), 3.63−3.48 (m, 4H), 3.39−3.26 (m, 4H), 2.68 (s, 3H), 1.07 (t, *J* = 7.13 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 163.86, 158.48, 154.74, 150.63, 146.43, 138.73, 134.53, 133.14, 129.34, 128.90, 128.63 (2C), 126.70 (2C), 126.05 (2C), 123.11, 122.40, 118.17, 115.96, 115.67, 112.84 (2C), 60.01, 49.02 (2C), 47.02 (2C), 14.39, 14.06; ESI-MS *m/z* 546.42 (M + H)⁺.

***tert*-Butyl 5-(4-Chlorophenyl)-2-methyl-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1-propyl-1*H*-pyrrole-3-car-**

boxylate (29b). Starting with **29a** (390 mg, 0.81 mmol), 242 mg (53%) of compound **29b** was obtained according to the procedure described for the preparation of **12b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.14 (d, *J* = 9.36 Hz, 2H), 7.24 (d, *J* = 8.42 Hz, 2H), 7.13–7.03 (m, 3H), 6.85 (d, *J* = 9.42 Hz, 2H), 6.77–6.60 (m, 3H), 3.79–3.68 (m, 2H), 3.55–3.43 (m, 4H), 3.22–3.09 (m, 4H), 2.59 (s, 3H), 1.53 (sex., *J* = 7.66 Hz, 2H), 1.28 (s, 9H), 0.76 (t, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.53, 154.96, 149.82, 138.80, 137.20, 135.10, 133.66, 132.79 (2C), 131.16, 129.77, 128.56 (2C), 128.18, 126.14 (2C), 124.35, 123.53, 119.27, 114.25, 113.16, 112.92 (2C), 79.57, 49.25 (2C), 47.11 (2C), 45.99, 28.22 (3C), 24.28, 11.70, 11.29; ESI-MS *m/z* 615.00 (M + H)[+].

***tert*-Butyl 1-Butyl-5-(4-chlorophenyl)-2-methyl-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carboxylate (30b).** Starting with **30a** (400 mg, 0.81 mmol), 227 mg (49%) of compound **30b** was obtained according to the procedure described for the preparation of **12b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.14 (d, *J* = 9.36 Hz, 2H), 7.24 (d, *J* = 8.42 Hz, 2H), 7.14–7.04 (m, 3H), 6.85 (d, *J* = 9.36 Hz, 2H), 6.76–6.58 (m, 3H), 3.83–3.70 (m, 2H), 3.55–3.44 (m, 4H), 3.23–3.12 (m, 4H), 2.59 (s, 3H), 1.49 (p, *J* = 7.94 Hz, 2H), 1.28 (s, 9H), 1.16 (sex., *J* = 7.45 Hz, 2H), 0.79 (t, *J* = 7.31 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 165.53, 154.96, 149.83, 138.82, 137.22, 135.06, 133.67, 132.82 (2C), 131.16, 129.75, 128.55 (2C), 128.18, 126.14 (2C), 124.36, 123.55, 119.29, 114.25, 113.17, 112.93 (2C), 79.57, 49.26 (2C), 47.12 (2C), 44.16, 33.04, 28.23 (3C), 19.99, 13.72, 11.71; ESI-MS *m/z* 629.42 (M + H)[+].

5-(4-Chlorophenyl)-1-ethyl-2-methyl-*N*-(methylsulfonyl)-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carboxamide (31b). Starting with **31a**, compound **31b** was prepared according to the procedure described for the preparation of compound **12b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.14 (d, *J* = 9.34 Hz, 2H), 7.59 (bs, 1H), 7.32–7.18 (m, 3H), 7.11 (d, *J* = 8.40 Hz, 2H), 6.88–6.79 (m, 3H), 6.73 (s, 1H), 6.65 (d, *J* = 7.33 Hz, 1H), 3.86 (q, *J* = 7.02 Hz, 2H), 3.58–3.47 (m, 4H), 3.36–3.26 (m, 4H), 3.23 (s, 3H), 2.69 (s, 3H), 1.19 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.46, 154.54, 151.10, 138.84, 138.00, 134.46, 132.60 (2C), 130.29, 130.21, 130.00, 128.86 (2C), 126.17 (2C), 122.40, 122.35, 118.75, 115.87, 112.89 (2C), 111.44, 48.51, 46.90, 42.18, 39.42, 16.13, 11.99; ESI-MS *m/z* 622.17 (M + H)[+].

5-(4-Chlorophenyl)-1-isopropyl-2-methyl-*N*-(methylsulfonyl)-4-(3-(4-(4-nitrophenyl)piperazin-1-yl)phenyl)-1*H*-pyrrole-3-carboxamide (32b). Starting with **32a**, compound **32b** was prepared according to the procedure described for the preparation of compound **12b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.12 (d, *J* = 9.34 Hz, 2H), 7.55 (bs, 1H), 7.30–7.14 (m, 3H), 7.10 (d, *J* = 8.38 Hz, 2H), 6.88–6.78 (m, 3H), 6.70 (s, 1H), 6.63 (d, *J* = 7.52 Hz, 1H), 4.39 (sept, *J* = 6.96 Hz, 1H), 3.60–3.47 (m, 4H), 3.33–3.24 (m, 4H), 3.23 (s, 3H), 2.77 (s, 3H), 1.46 (d, *J* = 7.08 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 163.63, 154.81, 150.99, 138.69, 137.87, 134.57, 134.44, 132.96 (2C), 130.85, 130.71, 130.08, 128.66 (2C), 126.14 (2C), 122.31, 121.03, 118.68, 115.74, 112.82 (2C), 112.08, 49.23, 48.45, 46.81, 42.05, 22.37, 13.54.

(R)-*tert*-Butyl 4-(4-(4-(4-(Dimethylamino)-1-(phenylthio)-butan-2-ylamino)-3-nitrophenylsulfonamido)phenyl)-piperazine-1-carboxylate (37). To a cooled (0 °C) solution of *tert*-butyl 4-(4-aminophenyl)piperazine-1-carboxylate (**33**, 2 g, 7.21 mmol) in pyridine (30 mL) was added 4-fluoro-3-nitrobenzene-1-sulfonyl chloride (**34**, 2.25 g, 9.37 mmol). After 30 min, pyridine was removed in vacuo and the oil was purified by column chromatography to give 1.82 g (53% yield) of intermediate **35**. Intermediate **35** (1.82 g, 3.79 mmol) was redissolved in DMF (10 mL), and then (R)-*N*[1],*N*[1]-dimethyl-4-(phenylthio)butane-1,3-diamine **36** (1.02 g, 4.55 mmol) and DIEA (2 mL, 11.37 mmol) were added. After stirring overnight, the solvent was removed in vacuo and the crude was purified by column chromatography (using a gradient of DCM:EtOAc) to produce 2.14 g (82% yield) of **37** as a yellow solid: ^{1}H NMR (300 MHz, CDCl$_3$) δ ppm 8.99 (d, *J* = 8.24 Hz, 1H), 8.49 (d, *J* = 2.21 Hz, 1H), 7.48 (dd, *J* = 1.83, 9.14 Hz, 1H), 7.35–7.28 (m, 2H), 7.25–7.16 (m, 3H), 7.02 (d, *J* = 8.82 Hz, 2H), 6.80 (d, *J* = 8.93 Hz, 2H), 6.61 (d, *J* = 9.34 Hz, 1H), 4.03–3.88 (m, 1H), 3.60–3.48 (m, 4H), 3.11 (d, *J* = 6.07 Hz, 2H), 3.09–3.01 (m, 4H), 2.53–2.40 (m, 1H), 2.35–2.24 (m,

1H), 2.20 (s, 6H), 2.11–1.94 (m, 1H), 1.90–1.74 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ppm 154.86, 149.70, 146.82, 134.95, 133.56, 131.11 (2C), 130.93, 129.32 (2C), 128.42, 127.84, 127.37, 125.34, 124.89 (2C), 117.18 (2C), 114.52, 80.18, 55.34, 51.55, 49.38 (2C), 45.54 (2C), 38.57, 30.59, 28.59 (3C); ESI-MS *m/z* 685.33 (M + H)[+].

(R)-4-(4-(Dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitro-*N*-(4-(piperazin-1-yl)phenyl)benzenesulfonamide (38). Trifluoroacetic acid (5 mL) was added to a solution of **37** (2.14 g, 3.12 mmol) in DCM (3 mL). After 5 h at room temperature, the reaction was slowly quenched with saturated NaHCO$_3$ and extracted with EtOAc, and solid NaCl was added to salt out the product. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to give quantitative yield of **38** as an orange solid: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.30 (d, *J* = 2.11 Hz, 1H), 7.53 (dd, *J* = 2.09, 9.16 Hz, 1H), 7.24–7.15 (m, 2H), 7.10–6.97 (m, 5H), 6.92–6.82 (m, 3H), 4.13–3.99 (m, 1H), 3.37–3.31 (m, 1H), 3.18 (d, *J* = 5.87 Hz, 1H), 3.15–3.07 (m, 4H), 3.07–2.95 (m, 4H), 2.57–2.33 (m, 2H), 2.25 (s, 6H), 2.13–1.78 (m, 2H); ^{13}C NMR (75 MHz, CD$_3$OD) δ ppm 150.43, 148.03, 136.52, 134.31, 131.70, 131.59 (2C), 131.05, 130.04 (2C), 128.04, 127.74, 126.90, 124.80 (2C), 118.12 (2C), 116.18, 56.62, 52.77, 50.11 (2C), 45.90 (2C), 45.32 (2C), 39.47, 32.18; ESI-MS *m/z* 585.92 (M + H)[+].

(R)-*N*-(4-(4-(3-(1-(4-Chlorophenyl)-1*H*-imidazol-5-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (18) (Method A). A round-bottom flask containing a solution of imidazole **18a** (20 mg, 0.051 mmol), piperazine **38** (60 mg, 0.103 mmol), Pd(dba)$_2$ (5.8 mg, 0.01 mmol), P(*t*Bu)$_3$ (50 μL), sodium *tert*-butoxide (10 mg, 0.103 mmol), toluene (2 mL), and DMF (1 mL) was placed under vacuum briefly and then flushed with N$_2$ three times. The solution, under nitrogen, was heated to 90 °C overnight. After cooling, the reaction was filtered through Celite and then through a plug of silica. The crude was dissolved in MeOH, 4.0 M HCl in dioxane was added, and after 5 min the solvent was removed. The residue was redissolved in 3:1 MeOH/water and purified by reverse phase HPLC to give 12 mg (28% yield) of **18** as a yellow powder: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 9.23 (s, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 7.83 (s, 1H), 7.60 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.30-7.15 (m, 3H), 7.12–7.00 (m, 6H), 7.00–6.90 (m, 3H), 6.80–6.71 (m, 2H), 4.19–4.04 (m, 1H), 3.28–3.12 (m, 12H), 2.87 (s, 6H), 2.35–2.09 (m, 2H); ESI-MS *m/z* 837.50 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)phenyl)piperazin-1-yl)phenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (9). Starting with **9a**, compound **9** was obtained according to the procedure described for the preparation of **18**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, *J* = 2.2 Hz, 1H), 7.63 (dd, *J* = 2.3, 9.1 Hz, 1H), 7.29–7.21 (m, 4H), 7.20–7.11 (m, 4H), 7.10–7.03 (m, 4H), 6.97–6.85 (m, 3H), 6.80–6.74 (m, 3H), 4.13–4.05 (m, 1H), 3.43 (s, 3H), 3.31–3.20 (m, 9H), 3.19–3.09 (m, 3H), 2.82 (s, 6H), 2.62 (s, 3H), 2.40–2.05 (m, 2H); ESI-MS *m/z* 907.67 (M + H)[+].

(R)-*N*-(4-(4-(3-(1-(4-Chlorophenyl)-1*H*-pyrazol-5-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (19). Starting with **19a**, compound **19** was obtained according to the procedure described for the preparation of **18**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.35 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.59 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.32–7.23 (m, 3H), 7.22–7.16 (m, 2H), 7.12–6.87 (m, 9H), 6.80–6.73 (m, 2H), 6.60 (d, *J* = 1.9 Hz, 1H), 4.16–4.02 (m, 1H), 3.29–3.12 (m, 11H), 2.87 (s, 6H), 2.31–2.09 (m, 2H); ESI-MS *m/z* 837.50 (M + H)[+].

(R)-*N*-(4-(4-(3-(5-(4-Chlorophenyl)-1-methyl-1*H*-pyrazol-4-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (20). Starting with **20a**, compound **20** was obtained according to the procedure described for the preparation of **18**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.44 (d, *J* = 1.9 Hz, 1H), 7.74 (s, 1H), 7.64 (dd, *J* = 1.8, 9.1 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.31–7.23 (m, 4H), 7.23–7.09 (m, 6H), 7.08–7.00 (m, 2H), 6.94 (d, *J* = 8.30 Hz, 1H), 6.89–6.74 (m, 3H), 4.19–4.04 (m, 1H), 3.78 (s, 3H), 3.49–3.09

(m, 12H), 2.82 (s, 6H), 2.40−2.07 (m, 2H); ESI-MS m/z 851.33 (M + H)$^+$.

(R)-N-(4-(4-(3-(3-(4-Chlorophenyl)-1-methyl-1H-pyrazol-4-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfonamide (21). Starting with **21a**, compound **21** was obtained according to the procedure described for the preparation of **18**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 2.2, 9.1 Hz, 1H), 7.52 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.31−7.19 (m, 5H), 7.18−7.10 (m, 3H), 7.07 (d, J = 8.9 Hz, 2H), 6.94−6.71 (m, 6H), 4.11−4.02 (m, 1H), 3.97 (s, 3H), 3.31−3.06 (m, 12H), 2.82 (s, 6H), 2.38−2.08 (m, 2H); ESI-MS m/z 851.58 (M + H)$^+$.

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide (8).[8] To a solution of **4** (50 mg, 0.055 mmol), EDCI (16 mg, 0.083 mmol), HOBt (11 mg, 0.083 mmol), and DIEA (28 μL, 0.165 mmol) in 5 mL of DCM was added methylamine (138 μL of 2 M in THF, 0.275 mmol). After stirring overnight, the solvent was removed in vacuo, the crude was redissolved in MeOH and 4.0 M HCl in dioxane was added, and after 5 min the solvent was removed. The residue was redissolved in 3:1 MeOH/H$_2$O and purified by reverse phase HPLC to give 34 mg (68%) of **8** as a yellow powder.

5-(4-Chlorophenyl)-4-(3-(4-(4-(4-((R)-4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-N-((1s,3s)-3-hydroxy-3-methyl-cyclobutyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide (10). Starting with (1s,3s)-3-amino-1-methylcyclobutanol and **4**, compound **10** was obtained according to the procedure described for the preparation of **8**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.37 (d, J = 2.1 Hz, 1H), 7.55 (dd, J = 2.1, 9.1 Hz, 1H), 7.21−7.15 (m, 4H), 7.14−7.05 (m, 4H), 7.03−6.95 (m, 4H), 6.86−6.77 (m, 3H), 6.71−6.59 (m, 3H), 4.06−3.96 (m, 1H), 3.80 (p, 7.9 Hz, 1H), 3.34 (s, 3H), 3.20−3.00 (m, 12H), 2.73 (s, 6H), 2.49 (s, 3H), 2.30−2.00 (m, 4H), 1.48−1.37 (m, 2H), 1.18 (s, 3H); ESI-MS m/z 991.42 (M + H)$^+$.

(R)-N-(4-(4-(3-(2-(4-Chlorophenyl)-4-(3-hydroxy-3-methyla-zetidine-1-carbonyl)-1,5-dimethyl-1H-pyrrol-3-yl)phenyl)-piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)-butan-2-ylamino)-3-nitrobenzenesulfonamide (11). Starting with 3-methylazetidin-3-ol and **4**, compound **11** was obtained according to the procedure described for the preparation of **8**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.2 Hz, 1H), 7.63 (dd, J = 2.2, 9.1 Hz, 1H), 7.34−7.22 (m, 4H), 7.19−7.03 (m, 8H), 6.89 (d, J = 9.0 Hz, 2H), 6.83−6.73 (m, 2H), 6.67 (br s, 1H), 6.61 (d, J = 7.6 Hz, 1H), 4.13−4.05 (m, 1H), 3.83 (q, 10 Hz, 2H), 3.40 (s, 3H), 3.30−3.10 (m, 13H), 2.82 (s, 6H), 2.39 (s, 3H), 2.36−2.10 (m, 2H), 1.11 (s, 3H); ESI-MS m/z 977.17 (M + H)$^+$.

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1,2-dimethyl-N-(methylsulfon-yl)-1H-pyrrole-3-carboxamide (12). A round-bottom flask containing a solution of compound **12b** (100 mg, 0.16 mmol) in MeOH (10 mL) was placed under vacuum briefly and then flushed with N$_2$ atmosphere three times. Pd−C (10%, 50 mg) was added to this solution, which was then purged again. The N$_2$ was removed in vacuum and a balloon of H$_2$ gas was connected to the flask. After 15 min, the reaction was filtered through Celite, and the solvent was removed in vacuo to produce the aniline intermediate that was used without further purification. To a cooled (0 °C) solution of the aniline intermediate in pyridine (6 mL) was added 4-fluoro-3-nitrobenzene-1-sulfonyl chloride **34** (50 mg, 0.21 mmol). After 30 min, pyridine was removed in vacuo and the oil was purified by column chromatography to give 79 mg of an oily red intermediate. The resulting oil (79 mg, 0.10 mmol) was redissolved in DMF (2 mL), and then (R)-N^1,N^1-dimethyl-4-(phenylthio)butane-1,3-diamine (**36**, 45 mg, 0.20 mmol) and DIEA (0.1 mL) were added. After standing overnight, the solvent was removed in vacuo and the crude was purified by column chromatography to produce **12** as a yellow solid. The solid was dissolved in MeOH, 4.0 M HCl in dioxane was added, and after 5 min the solvent was removed. The residue was redissolved in 3:1 MeOH/H$_2$O and purified by reverse-phase HPLC to give 92 mg (58%, three

steps) of **12** as a yellow powder: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 1.81 Hz, 1H), 7.61 (dd, J = 1.61, 8.84 Hz, 1H), 7.32−7.00 (m, 13H), 6.94−6.82 (m, 3H), 6.79−6.63 (m, 3H), 4.14−4.00 (m, 1H), 3.45 (s, 3H), 3.31−3.07 (m, 15H), 2.82 (s, 6H), 2.65 (s, 3H), 2.37−2.05 (m, 2H); ESI-MS m/z 985.67 (M + H)$^+$.

(R)-N-(4-(4-(3-(4-Chloro-2-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrol-3-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylami-no)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfona-mide (13). Starting with **13b**, compound **13** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 2.3, 9.1 Hz, 1H), 7.31−7.23 (m, 4H), 7.18−7.02 (m, 8H), 6.90−6.72 (m, 6H), 4.17−4.07 (m, 1H), 3.43 (s, 3H), 3.29−3.06 (m, 12H), 2.81 (s, 6H), 2.33 (s, 3H), 2.40−2.10 (m, 2H); ESI-MS m/z 900.17 (M + H)$^+$.

(R)-N-(4-(4-(3-(2-(4-Chlorophenyl)-1,5-dimethyl-4-(trifluoro-methyl)-1H-pyrrol-3-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(di-methylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrobenze-nesulfonamide (14). Starting with **14b**, compound **14** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.46 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 2.2, 9.1 Hz, 1H), 7.29−7.23 (m, 4H), 7.18−7.10 (m, 4H), 7.09−7.02 (m, 4H), 6.90−6.67 (m, 6H), 4.12−4.04 (m, 1H), 3.44 (s, 3H), 3.28−3.08 (m, 12H), 2.82 (s, 6H), 2.45 (d, J = 1.4 Hz, 3H), 2.37−2.08 (m, 2H); ESI-MS m/z 932.42 (M + H)$^+$.

(R)-N-(4-(4-(3-(2-(4-Chlorophenyl)-4-cyano-1,5-dimethyl-1H-pyrrol-3-yl)phenyl)piperazin-1-yl)phenyl)-4-(4-(dimethylami-no)-1-(phenylthio)butan-2-ylamino)-3-nitrobenzenesulfona-mide (15). Starting with **15b**, compound **15** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.46 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 2.2, 9.1 Hz, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.28−7.22 (m, 2H), 7.20−7.08 (m, 6H), 7.05 (d, H = 8.9 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.83−6.67 (m, 4H), 4.12−4.02 (m, 1H), 3.43 (s, 3H), 3.30−3.08 (m, 12H), 2.82 (s, 6H), 2.49 (s, 3H), 2.39−2.09 (m, 2H); ESI-MS m/z 889.33 (M + H)$^+$.

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1-methyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxylic acid (16). Starting with **16c**, compound **16** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 1.7 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.38−7.29 (m, 2H), 7.28−7.23 (m, 2H), 7.20−7.01 (m, 8H), 6.91−6.57 (m, 6H), 4.12−4.04 (m, 1H), 3.58 (s, 3H), 3.27−3.02 (m, 12H), 2.81 (s, 6H), 2.36−2.07 (m, 2H); ESI-MS m/z 962.58 (M + H)$^+$.

(R)-N-(4-(4-(3-(5-(4-Chlorophenyl)isoxazol-4-yl)phenyl)-piperazin-1-yl)phenyl)-4-(4-(dimethylamino)-1-(phenylthio)-butan-2-ylamino)-3-nitrobenzenesulfonamide (22). Starting with **22b**, compound **22** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.2 Hz, 1H), 8.38 (s, 1H), 7.64 (dd, J = 2.3, 9.1 Hz, 1H), 7.61−7.58 (m, 2H), 7.39−7.31 (m, 3H), 7.28−7.23 (m, 2H), 7.17−7.09 (m, 5H), 7.52−7.00 (m, 3H), 6.99−6.90 (m, 2H), 6.78 (d, J = 9.4 Hz, 1H), 4.14−4.07 (m, 1H), 3.43−3.09 (m, 12H) 2.82 (s, 6H), 2.37−2.09 (m, 2H); ESI-MS m/z 838.33 (M + H)$^+$.

(R)-1-(4-Chlorophenyl)-5-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-N-(methylsulfonyl)-1H-imida-zole-4-carboxamide (23). Starting with **23c**, compound **23** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.2 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, J = 2.1, 9.1 Hz, 1H), 7.36 (d, J = 9.0, 2H), 7.29−7.05 (m, 10H), 7.00−6.91 (m, 4H), 6.77 (d, J = 9.3 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 4.14−4.05 (m, 1H), 3.32 (s, 3H), 3.30−3.05 (m, 12H), 2.81 (s, 6H), 2.36−2.08 (m, 2H); ESI-MS m/z 959.42 (M + H)$^+$.

**(R)-1-(4-Chlorophenyl)-5-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-N-(methylsulfonyl)-1H-pyra-

zole-4-carboxamide (24). Starting with **24c**, compound **24** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.1 Hz, 1H), 8.24 (s, 1H), 7.63 (dd, J = 2.0, 9.1 Hz, 1H), 7.32−7.22 (m, 5H), 7.20−7.00 (m, 8H), 6.99−6.89 (m, 3H), 6.79−6.70 (m, 2H), 4.15−4.05 (m, 1H), 3.35−3.04 (m, 15H), 2.81 (s, 6H), 2.37−2.08 (m, 2H); ESI-MS m/z 958.42 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1-methyl-1H-pyrazole-3-carboxylic Acid (25). Starting with **25a**, compound **25** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.31 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 2.3, 9.2 Hz, 1H), 7.38−7.35 (m, 2H), 7.26−6.90 (m, 15H), 6.85 (d, J = 7.6 Hz, 1H), 4.11−4.07 (m, 1H), 3.82 (s, 3H), 3.45−3.33 (m, 9H), 3.21−3.14 (m, 3H), 2.84 (s, 6H), 2.25−2.15 (m, 2H); ESI-MS m/z 895.75 (M + H)[+].

(R)-3-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1-methyl-1H-pyrazole-5-carboxylic Acid (26). Starting with **26a**, compound **26** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.32 (d, J = 2.3 Hz, 1H), 7.58 (dd, J = 2.3, 9.2 Hz, 1H), 7.30−7.25 (m, 3H), 7.20−7.14 (m, 4H), 7.09−6.96 (m, 9H), 6.90 (d, J = 10.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.18 (s, 3H), 4.10−4.06 (m, 1H), 3.37−3.31 (m, 9H), 3.21−3.15 (m, 3H), 2.84 (s, 6H), 2.24−2.13 (m, 2H); ESI-MS m/z 895.50 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-2-methylfuran-3-carboxylic Acid (27). To a solution of **27b** (260 mg, 0.48 mmol) in 60 mL of 1:1:1 dioxane:EtOH:H$_2$O was added NaOH (190 mg, 4.8 mmol), and the solution was refluxed until no compound **27b** was observed by TLC. After cooling, the reaction was slowly neutralized with 1 M HCl and the compound was extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to produce 97 mg of the acid intermediate as a yellow solid. Starting with this acid, compound **27** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.32 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 2.3, 9.2 Hz, 1H), 7.35−6.97 (m, 16H), 6.91−6.88 (m, 2H), 4.09−4.07 (m, 1H), 3.34−3.31 (m, 9H), 3.21−3.15 (m, 3H), 2.84 (s, 6H), 2.65 (s, 3H), 2.25−2.15 (m, 2H); ESI-MS m/z 895.92 (M + H)[+].

(R)-2-Chloro-5-(4-chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)phenyl)piperazin-1-yl)phenyl)-1-methyl-1H-pyrrole-3-carboxylic Acid (17). Starting with **17b**, compound **17** was obtained according to the procedure described for the preparation of **27**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 2.3, 9.1 Hz, 1H), 7.31−7.23 (m, 4H), 7.19−7.11 (m, 4H), 7.10−7.02 (m, 4H), 6.94−6.85 (m, 3H), 6.84−6.80 (m, 1H), 6.76 (d, J = 9.2 Hz, 2H), 4.13−4.04 (m, 1H), 3.51 (s, 3H), 3.31−3.07 (m, 12H), 2.81 (s, 6H), 2.35−2.08 (m, 2H); ESI-MS m/z 928.42 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-2-methyl-1-propyl-1H-pyrrole-3-carboxylic Acid (29). Concentrated H$_2$SO$_4$ (2 mL) was added to a cooled (0 °C) solution of **29b** (92 mg, 0.15 mmol) in a mixture of DCM (2 mL) and THF (0.5 mL). After 10 min the reaction was slowly quenched with saturated NaHCO$_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to produce 68 mg of its carboxylic acid as a yellow solid. Starting with this acid, compound **29** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.17 Hz, 1H), 7.62 (dd, J = 2.16, 9.10 Hz, 1H), 7.30−7.22 (m, 4H), 7.18−7.10 (m, 4H), 7.10−7.03 (m, 4H), 6.94−6.73 (m, 6H), 4.14−4.02 (m, 1H), 3.79−3.69 (m, 2H), 3.34−3.19 (m, 9H), 3.19−3.07 (m, 3H), 2.81 (s, 6H), 2.62 (s, 3H), 2.37−2.06 (m, 2H), 1.54 (sex., J =

7.62 Hz, 2H), 0.77 (t, J = 7.39 Hz, 3H); ESI-MS m/z 936.83 (M + H)[+].

(R)-1-Butyl-5-(4-chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)phenyl)piperazin-1-yl)phenyl)-2-methyl-1H-pyrrole-3-carboxylic Acid (30). Starting with **30b**, compound **30** was obtained according to the procedure described for the preparation of **29**: ^{1}H NMR (300 MHz, 10:1 CDCl$_3$:CD$_3$OD) δ ppm 8.45 (d, J = 2.11 Hz, 1H), 7.63 (dd, J = 1.92, 9.10 Hz, 1H), 7.31−7.20 (m, 4H), 7.20−7.04 (m, 8H), 7.04−6.85 (m, 5H), 6.78 (d, J = 9.24 Hz, 1H), 4.16−4.01 (m, 1H), 3.85−3.73 (m, 2H), 3.44−3.07 (m, 12H), 2.81 (s, 6H), 2.63 (s, 3H), 2.38−2.03 (m, 2H), 1.48 (sex., J = 6.87 Hz, 2H), 1.29−1.08 (m, 2H), 0.79 (t, J = 7.31 Hz, 3H); ESI-MS m/z 950.67 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1-ethyl-2-methyl-N-(methylsulfonyl)-1H-pyrrole-3-carboxamide (31). Starting with **31b**, compound **31** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.35 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 2.1, 9.1 Hz, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.23−6.93 (m, 15H), 6.80 (d, J = 7.6 Hz, 1H), 4.19−4.08 (m, 1H), 3.89 (q, J = 7.0 Hz, 2H), 3.46−3.33 (m, 9H), 3.26−3.16 (m, 7H), 2.87 (s, 6H), 2.70 (s, 1H), 2.55 (s, 3H), 2.34−2.11 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); ESI-MS m/z 999.83 (M + H)[+].

(R)-5-(4-Chlorophenyl)-4-(3-(4-(4-(4-(4-(dimethylamino)-1-(phenylthio)butan-2-ylamino)-3-nitrophenylsulfonamido)-phenyl)piperazin-1-yl)phenyl)-1-isopropyl-2-methyl-N-(methylsulfonyl)-1H-pyrrole-3-carboxamide (32). Starting with **32b**, compound **32** was obtained according to the procedure described for the preparation of **12**: ^{1}H NMR (300 MHz, CD$_3$OD) δ ppm 8.34 (d, J = 2.2 Hz, 1H), 7.65 (dd, J = 2.1, 9.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.27−6.98 (m, 15H), 6.90 (d, J = 7.3 Hz, 1H), 4.40 (h, J = 7.0 Hz, 1H), 4.21−4.10 (m, 1H), 3.62−3.34 (m, 9H), 3.27−3.15 (m, 6H), 2.99 (s, 1H), 2.87 (s, 7H), 2.61 (s, 3H), 2.34−2.10 (m, 2H), 1.42 (d, J = 7.0 Hz, 6H); ESI-MS m/z 1013.83 (M + H)[+].

Fluorescence Polarization (FP) Based Binding Assays. Binding affinities of our synthesized compounds to Bcl-2, Bcl-xL, and Mcl-1 were determined using an FP-based competitive binding assay described previously.[7] Briefly, preincubated protein/probe complex (1.5 and 1 nM for the Bcl-2 assay, 10 and 2 nM for the Bcl-xL assay, and 20 and 2 nM for the Mcl-1 assay, respectively) and serial dilutions of the inhibitors were incubated at room temperature for 2 h with gentle shaking. Millipolarization (mP) values were measured and plotted over total compound concentrations, nonlinear regression fitting to the binding curves generated the IC$_{50}$ values, and the K_i values were calculated using the equation described previously.[25]

Cell Growth Inhibition Assay. This assay was performed as previously reported.[7] Human small cell lung cancer cell lines H146, H1963, H187, and H1417 were purchased from American Type Culture Collection (ATCC) and were maintained in RPMI-1640 medium containing 10% FBS. Various concentrations of compounds were incubated for 4 days in 96-well flat bottom cell culture plates that were seeded at a density of 1×10^{14} cells/well. At the end of incubation, the effect of compounds on cell growth was evaluated by WST assay. In this assay, 20 μL of WST-8 dye was added to each well and incubated for an additional 1−2 h, and then the absorbance was measured, at 450 nm, in a microplate reader (Molecular Devices). Using the GraphPad Prism software (GraphPad Software, La Jolla, CA), the IC$_{50}$ values were calculated by comparing absorbance in the untreated cells and the cells treated with the compounds. The standard deviation for each compound was obtained by performing a minimum of three independent experiments in each cell line.

In Vivo Pharmacodynamic (PD) and Efficacy Studies in the H146 Xenograft Model. We employed a similar procedure to that used in our previous studies.[7,8] An H146 small-cell lung cancer xenograft model was used for our in vivo PD and efficacy studies. Xenograft tumors (one tumor per mouse) were developed by injection of 5×10^6 H146 cancer cells with Matrigel, subcutaneously, on the dorsal side of the SCID mice (from Charles River).

For the PD studies, mice bearing tumors approximately 100 mm^3 in volume were given a single dose of **31**, **32** (15 mg/kg), or vehicle. The tumor tissues were harvested at 3, 6, or 24 h, followed by Western blot analysis to determine levels of PARP and caspase-3, as well as cleaved PARP and caspase-3.

For the efficacy studies, mice with tumor volumes between 100 and 150 mm^3 were randomized into different groups (eight mice per group) with mean tumor volume of 126 mm^3. Each group of mice was treated intravenously with either vehicle control or **31** or **32** at 15 mg/kg, daily, 5 days/week for 2 weeks. Tumor sizes and animal weights were measured 3 times per week during the treatment and twice per week after the treatment. Data are presented as mean tumor volumes ± SEM. Statistical analyses were performed using two-way ANOVA and unpaired two-tailed t test, using Prism (version 4.0, GraphPad, La Jolla, CA). $P < 0.05$ was considered statistically significant. The efficacy experiment was performed under the guidelines of the University of Michigan Committee for Use and Care of Animals.

■ ASSOCIATED CONTENT

Accession Codes

Coordinates for compound **4** complexed with Bcl-xL were deposited into the Protein Data Bank under Accession Number 3SP7.

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Author Contributions

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Notes

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■ ABBREVIATIONS USED

AcOH, acetic acid; DIEA, *N,N*-diisopropylethylamine; EDCI, 1-ethyl-(3-dimethylaminopropyl)carbodiimide; Et$_3$N, triethylamine; EtOAc, ethyl acetate; EtOH, ethanol; FBS, fetal bovine serum; FP, fluorescence polarization; HOBt, hydroxybenzotriazole; MeOH, methanol; mP, millipolarization; NIS, *N*-iodosuccinamide; PARP, poly ADP ribose polymerase; Pd-(dba)$_2$, Bis(dibenzylidene-acetone)palladium(0); SCID, severe combined immunodeficient; TosMIC, toluenesulfonylmethyl isocyanide.

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