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Design, Synthesis, and Structure−Activity Relationship of 7-Propanamide Benzoxaboroles as Potent Anticancer Agents

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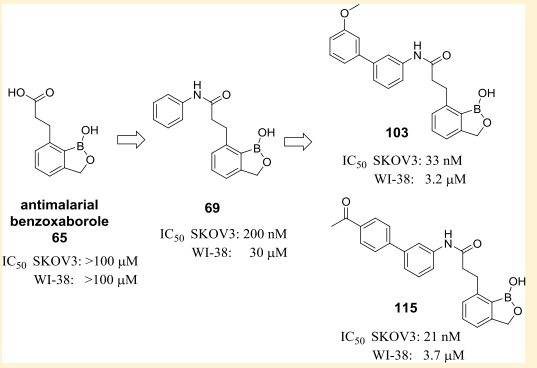
Supporting Information

ABSTRACT: Benzoxaboroles, as a novel class of bioactive molecules with unique physicochemical properties, have been shown to possess excellent antimicrobial activities with tavaborole approved in 2014 as an antifungal drug. Although urgently needed, the investigation of benzoxaboroles as anticancer agents has been lacking so far. In this study, we report the design, synthesis, and anticancer structure−activity relationship of a series of 7-propanamide benzoxaboroles. Compounds **103** and **115** showed potent activity against ovarian cancer cells with IC_{50} values of 33 and 21 nM, respectively. Apoptosis was induced by these compounds and colony formation was effectively inhibited. Furthermore, they also showed excellent efficacy in ovarian tumor xenograft mouse model.



INTRODUCTION

In the past 15 years, boron-containing compounds have gradually emerged as a novel class of useful structures that possess fascinating chemical properties and unique biological activitites.[1−3] Due to the rare existence of boron-containing organic compounds in nature and the historical lack of experience in the development of boron-containing drugs, they are largely ignored in drug discovery with assumed concerns on their toxicity and lack of druglikeness. In 2003, the first approved boron-containing drug, i.e., bortezomib (Velcade) (Figure 1), a boronic acid-based proteasome inhibitor, was

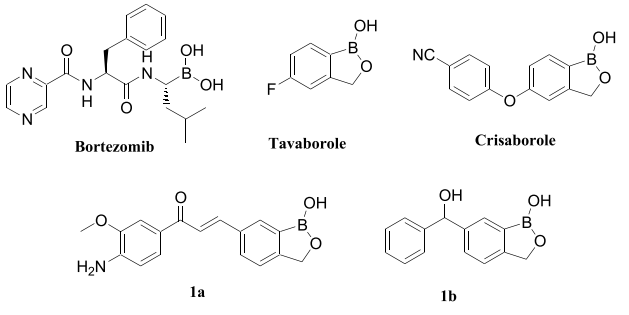


Figure 1. Chemical structures of bortezomib, tavaborole, crisaborole, and compounds **1a** and **1b**.

used for the treatment of multiple myeloma.[4] Interestingly, although benzoxaboroles, a class of cyclic boronic acids, were first synthesized and studied in the 1950s,[5,6] their medical use had remained literally unknown for 50 years until tavaborole (**tb**, Kerydin) (Figure 1) was approved in 2014 as a topical treatment of fungal infection of the toenails.[7,8] As the second benzoxaborole drug, crisaborole (Eucrisa) was approved in 2016 as a nonsteroidal topical treatment of atopic dermatitis.[9] There are also a number of compounds in the pipelines as well, including acoziborole for trypanosomiasis, GSK656 for tuberculosis, and AN13762 for malaria.[10−12] We have reported a number of potent antiparasitic and antibacterial benzoxaboroles such as compounds **1a** and **1b** in the past.[13−17] At the same time, antiviral and anti-inflammatory properties have also been reported by researchers.[18,19]

Today, cancer still remains one of the major causes of human death despite efforts and progress in the past decades. About 2.8 and 0.6 million cancer deaths occurred in 2015 alone in China[20] and the United States,[21] respectively. While chemotherapy remains the main treatment, clinically used anticancer drugs are generally limited by toxicity, side effects, and resistance.[22,23] Thus, it remains urgent to develop novel anticancer agents.

Benzoxaboroles have unique physicochemical properties that are distinct from any previously known drug classes.[1−3] In light of their recently proven druglikeness and success in anti-infective application, it is imperative and urgent to explore the potential of benzoxaboroles as anticancer agents. However, an investigation of their anticancer activity has been lacking to date. Although several preliminary efforts toward this goal have been reported, the anticancer activity of benzoxaboroles has not been convincingly defined in those studies.[24,25,29] We have previously reported a small group of chalcone−benzoxaborole hybrids as preliminary anticancer agents.[26] Here, we report the design, synthesis, and structure−activity relationship of a series of 7-propanamide benzoxaboroles with potent anticancer activity. Compounds **103** and **115** showed inhibitory activity

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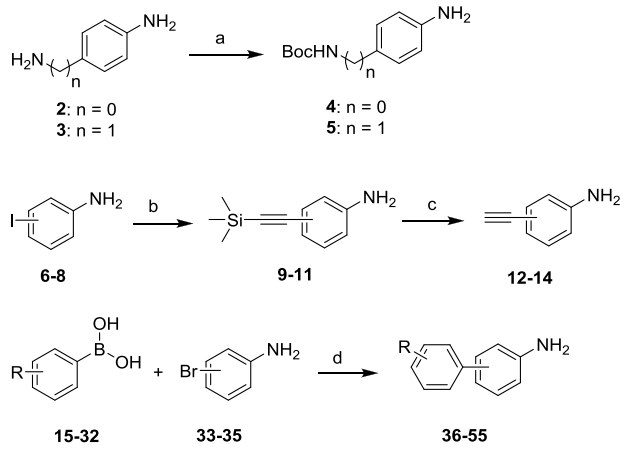
against ovarian cancer cells with IC_{50} values of 33 and 21 nM, respectively, and excellent selectivity between cancerous and normal cells. They effectively induced cancer cell apoptosis and inhibited colony formation. Furthermore, they demonstrated satisfactory efficacy and safety in ovarian tumor xenograft mouse model.

RESULTS AND DISCUSSION

Chemistry. Various amines were synthesized following the procedure shown in Scheme 1. Analines **4** and **5** were prepared by *tert*-butyloxycarbonyl (Boc) protection of the corresponding aminoalkylated analines **2** and **3**. The acetylenylanalines **12**−**14** were prepared from iodoanilines **6**−**8** by installation of the trimethylsilylacetylenyl group under the conditions of $Pd(PPh_3)_2Cl_2$, CuI, and triethylamine (TEA) followed by removal of the trimethylsilyl group by KOH. Phenylanalines **36**−**55** were prepared by the Suzuki−Miyaura coupling reaction of arylboronic acids **15**−**32** and bromoanilines **33**−**35**.

Scheme 1. Synthesis of Various Amine Intermediates[a]

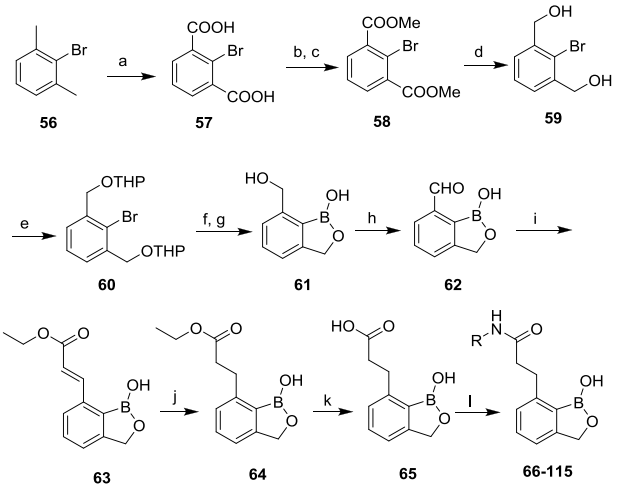


[a]Reagents and conditions: (a) Boc_2O, tetrahydrofuran (THF); (b) trimethylsilylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, THF, TEA; (c) KOH, MeOH; (d) $Pd(PPh_3)_2Cl_2$, sat. aqueous (aq) Na_2CO_3, EtOH, toluene.

The 7-propanamide benzoxaborole derivatives **66**−**115** were prepared following the procedures shown in Scheme 2. The key aldehyde intermediate **62** was prepared as we previously reported.[27] Aldehyde **62** was converted to ester **63** by the Wittig reaction. Compound **63** underwent reduction by Pd/C and H_2 and hydrolysis under alkaline condition, to give carboxylic acid **65**. Subsequent condensation with various amines under the conditions of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) gave the 7-propanamide benzoxaboroles **66**−**115**.

As shown in Scheme 3, acrylate **63** was hydrolyzed to acrylic acid **126**, which was subsequently coupled with analine to give acrylamide **127**. Compounds **129**−**132** were prepared by the condensation of hydrocinnamic acid and corresponding amines. Meanwhile, three nonboron analogues **145**−**147** were synthesized as shown in Scheme 3C. First, the diol **59** was converted to mono-methoxymethyl (MOM)-protected compound **133**, which was oxidized by PCC to give aldehyde **134**. Ester **135** was obtained by the Wittig reaction and then reduced to **136**. Next, a vinyl group was introduced by the Stille reaction to give compound **137**, which was subsequently

Scheme 2. Synthesis of 7-Propanamide Benzoxaboroles[a]



[a]Reagents and conditions: (a) $KMnO_4$, *t*-BuOH, H_2O; (b) $SOCl_2$; (c) MeOH, Et_3N; (d) $LiBH_4$, MeOH, THF; (e) dihydropyran, *p*-TsOH−H_2O, dimethylformamide (DMF); (f) *n*-BuLi, B(*i*-PrO)$_3$, THF; (g) 6 M HCl, MeOH; (h) pyridinium chlorochromate (PCC), Celite, dichloromethane (DCM); (i) ethyl (triphenylphosphoranylidene)acetate, toluene; (j) Pd/C, H_2, EtOH; (k) NaOH, MeOH, H_2O; (l) RNH_2, EDCI, DCM.

hydrolyzed under alkaline condition. Next, condensation with various amines gave compounds **139**−**141**, which was followed by oxidation of the vinyl group to give aldehydes **142**−**144**. Finally, compounds **142**−**144** were hydrolyzed, which was followed by cyclization under the acidic condition to provide lactols **145**−**147**.

Discovery of Initial Hit Compound 69. To explore the therapeutic value of benzoxaborole derivatives with high efficiency, we have previously developed a type of versatile formyl benzoxaborole intermediates that could be obtained in large scale and rapidly derivatized into benzoxaboroles bearing a variety of functional groups at the 4-, 5-, 6-, or 7-position of the phenyl ring.[27] The 7-propionic acid derivative **65** was consequently obtained and found to possess potent antimalarial activity.[28] However, it did not show any antiproliferation activity on cancer cells. To explore the anticancer potential of benzoxaboroles, the amide analogues **66**−**72** were synthesized. As shown in Table 1, compounds **66**−**68** with aliphatic chains showed no inhibitory activity on cancer cell proliferation. Interestingly, the phenyl compound **69** gave submicromolar inhibitory potency on the three cancer cell lines tested (SKOV3: ovarian carcinoma; MDA-MB231: breast cancer; HCT116: colon colorectal carcinoma), while toxicity was low on normal cells (WI-38: human lung fibroblast). However, when the phenyl group was spaced by one or two carbons from the amide bond (compounds **70** and **71**), the anticancer potency was abolished. The thiazolyl substitution in compound **72** also gave abolished activity.

Modification on Phenyl Group of Compound 69 Did Not Improve Antiproliferation Potency. We explored the effect of various substitutions of the phenyl ring of compound **69** on its anticancer activity, as shown in Table 2. First, the para-substituted phenyl groups (compounds **73**−**84**) were explored. The fluoro compound **73** gave submicromolar activity that was slightly weaker than the unsubstituted compound **69**. When the larger halogen atoms were introduced, the inhibitory activity gradually decreased from

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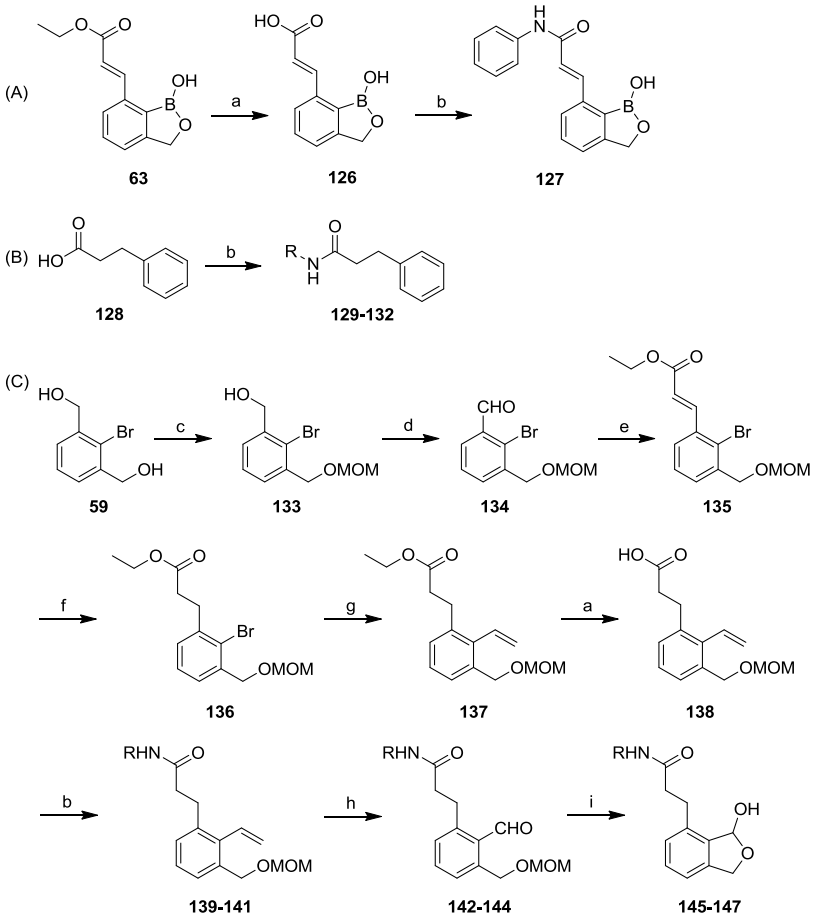
Scheme 3. Synthesis of Analogue Compounds[a]



[a]Reagents and conditions: (a) NaOH, MeOH, H_2O; (b) RNH_2, EDCI, DCM; (c) methoxymethyl chloride (MOMCl), *N*,*N*-diisopropylethylamine (DIPEA), THF; (d) PCC, Celite, DCM; (e) ethyl (triphenylphosphoranylidene)acetate, toluene; (f) $NaBH_4$, $NiCl_2 \cdot 6H_2O$; (g) tributyl(vinyl)tin, $Pd(PPh_3)_4$, DMF; (h) $NaIO_4$, K_2OsO_4, THF, H_2O; (i) 4 M aqueous HCl, THF.

chloro compound **74** to iodo compound **76** that showed near-100-fold decreased activity compared to the fluoro compound **73**. Analogues **77**−**84** also showed a similar tendency of lower activity associated with bulkier substituents. The methyl and methoxy compounds **77** and **80** gave submicromolar activity, while larger substituents in compounds **78**, **79**, **81**, **83**, and **84** all gave significantly diminished activity. However, an exception is compound **82** with a bulky Boc group that showed significantly higher activity than its shorter analogue **81**, which may be due to the flexibility of alkyl chain by addition of an extra carbon atom. Next, we investigated the effect of moving the substituents from para- to meta- and ortho-positions. The *m*-bromo analogue **85** showed improved potency compared to the *p*-bromo compound **75**. The *m*-iodo compound **86** also showed similar tendency. This observation implied that the meta-position may be a favorable spot for further optimization. Therefore, larger groups such as isopropyl and acetylenyl were introduced into the meta-position in compounds **87** and **88**, which both showed submicromolar activity. Interestingly, the ortho-substituted analogues **89** and **90** also showed good activity. The disubstituted and trisubstituted analogues showed diminished activity as shown by compounds **92** and **93**. However, the m,p-disubstituted analogue **91** gave good inhibitory activity. Thus, the simple halogen or alkyl modifications on the phenyl ring only achieved inhibitory activity comparable to the unsubstituted compound **69**. This series of compounds implied that bulky groups may be tolerated as demonstrated by compound **82**, and substitutions at the ortho- and meta-position of the phenyl ring are more favorable than the para-substitution. At the same time, it was demonstrated that selectivity between cancerous and normal cells is tunable depending on the substitution patterns. For example, compound **82** showed nearly no selectivity while compound **77** showed good selectivity, although these two compounds possess similar antiproliferative potency. Thus, it proved feasible to fine-tune the structure−activity relationship to obtain good selectivity between cancerous and normal cells while retaining the antiproliferative potency. These observations led to the design and synthesis of the naphthyl and biphenyl compounds in Table 3 to improve the potency.

Discovery of Biphenyl Compounds with Significantly Improved Antiproliferation Potency. As shown in Table 3, the 1-naphthyl compound **94** showed antiproliferation activity comparable to the phenyl compound **69**, but its selectivity between cancer cells and normal cells was low. The 2-naphthyl analogue **95** showed a 10-fold decrease of potency. Next, biphenyl compounds **96**−**98** were explored. The biphenyl-2-yl and 4-yl compounds **96** and **98** only showed moderate activity; however, the 3-yl compound **97** showed submicromolar potency and good selectivity between cancerous and normal cells. Based on this observation and the chemical accessibility

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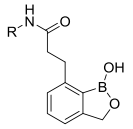
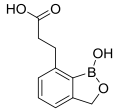
Table 1. Inhibitory Effect of Compounds 65−72 on Cancerous and Normal Cell Proliferation



	Structure	[a]IC_{50} (μM)			
		SKOV3	MDA-MB231	HCT116	WI-38
65		>100	>100	>100	>100
66		>100	>100	>100	>100
67		>100	>100	>100	>100
68		>100	>100	>100	>100
69		0.20	0.23	0.35	30
70		>100	>100	>100	>100
71		>100	>100	>100	>100
72		>100	>100	>100	>100
	Doxorubicin	0.032	0.0069	0.023	0.59

[a]IC_{50} indicates compound concentration required to inhibit cell viability by 50%. Values are expressed as the mean of triplicate experiments.

of various biphenyls, we took compound **97** for further structural modification. Introduction of a fluoro atom at the 4′-position gave compound **100**, which is the first compound with IC_{50} value below 100 nM in this work. It also showed good selectivity (ca. 44-fold) between SKOV3 and normal cells. However, the 3′-fluoro compound **99** and the chloro compounds **101** and **102** only gave slightly diminished potency. When the hydrogen-bond acceptor group, methoxy, was installed in compounds **103**−**105**, the potency was further improved for all three compounds. The most potent compound **103** gave an IC_{50} value as low as 33 nM, which is the most active compound so far in this study. At the same time, it also showed good selectivity between cancerous and normal cells (ca. 100-fold selectivity: SKOV3 vs WI-38 cells). When the methoxy group was replaced by the electronegative trifluoromethyl group (compounds **106** and **107**), they showed more than 10-fold decrease of activity. The thioether, trifluoromethyl, and cyano derivatives **108**−**113** all showed submicromolar activity that is comparable to the unsubstituted compound **97**, but no improvement of potency. When acetyl group, which is a hydrogen-bond acceptor, was introduced in compounds **114** and **115**, the potency was significantly improved. Especially in compound **115**, an IC_{50} value of 21 nM on SKOV3 cells was achieved, which represents the highest potency in this study. It also showed good selectivity between cancerous and normal cells (ca. 180-fold selectivity: SKOV3 vs WI-38 cells), which is better than the low-potency compounds such as the phenyl compound **69** (ca. 150-fold selectivity: SKOV3 vs WI-38 cells). We believe with a further elucidation of the intracellular targets, there is sufficient space to further improve the selectivity by rational design.

Both Oxaborole Ring and 7-Propanamide Substitution Are Essential for Antiproliferation Potency. To evaluate the essentiality of the oxaborole moiety and the 7-propanamide substitution, a number of control compounds were synthesized and tested as shown in Table 4. In compounds **103**, **105**, and **115**, when the substituting position on the phenyl was changed from 7- to 4-, 5-, and 6- as in compounds **116**−**124**, the antiproliferation activity was significantly diminished. Furthermore, the parent benzoxaborole **125** and the antifungal drug tavaborole (**tb**) did not show any antiproliferation activity at all, which suggests that the 7-propanamide substitution is essential for the antiproliferation activity. Compound **127** with a double bond showed abolished activity compared to its saturated counterpart **69**, which suggests that the saturated chain is favorable owing to its conformational flexibility. When the oxaborole ring was removed as in compounds **129**−**132** or when the boron was replaced by carbon as in lactols **145**−**147**, they showed either completely abolished activity or significantly diminished activity compared to their corresponding benzoxaboroles **69**, **103**, **105**, and **115**. This observation suggests that the oxaborole moiety is essential for the antiproliferation activity. Thus, both the oxaborole ring and the 7-propanamide substitution are essential for the potent antiproliferation activity of the compounds in this study.

Membrane Permeability and Pharmacokinetic (PK) Profile of Compounds 103 and 115. Compounds **103** and **115** were evaluated for their membrane permeability and pharmacokinetic properties. Compound **103** showed high permeability in the caco-2 assay with a high P_{app} (A → B 19.5 and B → A 26.5 × 10^{-6} cm/s) and a low efflux ratio of 1.36. Compound **115** showed a medium permeability with a moderate P_{app} (A → B 3.95 and B → A 2.23 × 10^{-6} cm/s) and a low efflux ratio of 0.56. In the PK study as shown in Table 5, when dosed orally at 10 mg/kg, compound **103** showed an oral (po) bioavailability of 19.5% and a half-life ($T_{1/2}$) of 2.2 h, while compound **115** has a very low bioavailability of 4.6%, which may be ascribed to its relatively low permeability and a half-life ($T_{1/2}$) of 2.0 h. Both compounds showed reasonable peak plasma concentration (C_{max}) (434 and 373 ng/mL) and area under the curve (AUC) values of 551 and 1920 h ng/mL, respectively.

Apoptosis Was Induced by Compound 103. To determine whether the proliferative inhibition induced by compound **103** was attributed to apoptosis, SKOV3 cells were treated with vehicle and compound **103** at different concentrations (1, 3, or 10 μM) for 48 h and then stained with annexin V−fluorescein isothiocyanate (FITC) and propidium iodide (PI). As shown in Figure 2, the percentages of apoptotic SKOV3 cells were determined by flow cytometry.

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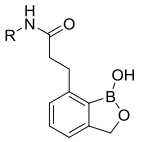
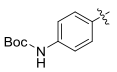
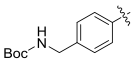
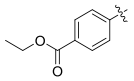
Table 2. Inhibitory Effect of Compounds 73−93 on Cancerous and Normal Cell Proliferation



	Structure	[a]IC$_{50}$ (μM)			
		SKOV3	MDA-MB231	HCT116	WI-38
73		0.72	0.44	0.65	12
74		5.0	3.6	12	>100
75		9.2	5.3	46	42
76		51	33	50	49
77		0.86	1.1	4.5	>100
78		6.3	6.6	45	>100
79		4.2	33	19	55
80		0.90	0.85	1.7	>100
81		>100	29	24	>100
82		2.0	1.3	2.3	4.8
83		>100	>100	>100	>100
84		83	36	>100	>100
85		0.54	0.72	1.4	20
86		0.63	5.3	2.3	71
87		0.51	1.6	1.6	22
88		0.98	1.6	3.6	>100
89		0.20	0.93	0.43	1.6
90		0.82	1.3	1.4	18
91		0.60	0.87	1.2	15
92		>100	>100	>100	>100
93		19	71	64	74

[a]IC$_{50}$ indicates compound concentration required to inhibit cell viability by 50%. Values are expressed as the mean of triplicate experiments.

Compound **103** induced apoptosis in a concentration-dependent manner, resulting in 28.2, 31.6, and 51.3% of apoptotic cells (early and late apoptosis) at 1, 3, and 10 μM, respectively.

Cleavage of Poly(ADP-ribose) Polymerase (PARP) and Caspase 3/9 Was Induced by Compound 103. To further elucidate the potential mechanisms of apoptosis induced by compound **103**, cleaved PARP and caspase 3/9 were determined by Western blotting as the markers of apoptosis. As shown in Figure 3, treatment of H460 cells with compound **103** triggered cleavage of PARP and caspase 3/9 at low concentrations, which indicated that compound **103** induced the apoptosis at least partially through the cleavage of caspase 3/9 and PARP.

Colony Formation Was Inhibited by Compound 103. The ability of compound **103** to inhibit the colony formation of SKOV3 cells was tested. As shown in Figure 4, the exposure of SKOV3 cells to low concentrations of compound **103** resulted in a significant inhibition of colony formation. The cancer cell growth was completely abolished at the concentration of 500 nM and above.

Tumor Growth in Xenograft Mouse Model Was Reduced. Finally, we evaluated the in vivo efficacy of compounds **103** and **115** in SKOV3 xenograft mouse model. Six BALB/c mice per group were administered via intraperitoneal injection with vehicle, compounds **103** and **115**, at a dosage of 2 and 10 mg/kg, respectively, once a day for 33 days. As shown in Figure 5, compounds **103** and **115** both

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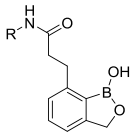
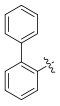
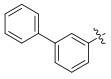
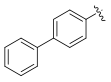
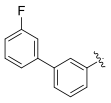
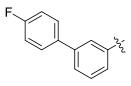
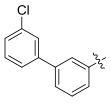
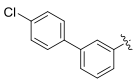
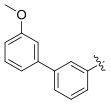
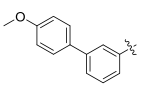
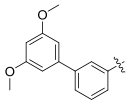
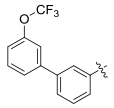
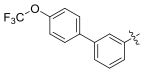
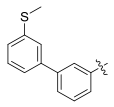
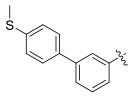
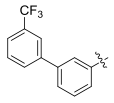
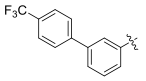
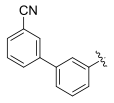
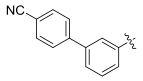
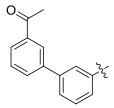
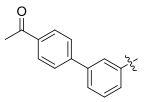
Table 3. Inhibitory Effect of Compounds 94−115 on Cancerous and Normal Cell Proliferation



	Structure	[a]IC_{50} (μM)			
		SKOV3	MDA-MB231	HCT 116	WI-38
94		0.17	0.15	0.20	1.2
95		1.4	1.8	1.7	>100
96		26	18	23	77
97		0.25	0.22	0.89	12
98		48	8.8	13	32
99		0.48	0.57	0.46	37
100		0.093	0.25	0.55	4.1
101		0.30	0.25	0.35	58
102		0.22	0.26	0.38	9.8
103		0.033	0.037	0.26	3.2
104		0.048	0.088	0.16	1.4
105		0.044	0.040	0.053	1.7
106		0.46	0.46	0.31	9.8
107		0.56	0.64	0.73	25
108		0.15	0.15	0.11	2.0
109		0.14	0.14	0.18	3.8
110		0.39	0.41	0.58	23
111		0.50	0.51	0.55	26
112		0.12	0.11	0.14	7.3
113		0.34	0.38	0.41	12
114		0.068	0.052	0.086	2.2
115		0.021	0.056	0.11	3.7

[a]IC_{50} indicates compound concentration required to inhibit cell viability by 50%. Values are expressed as the mean of triplicate experiments.

significantly inhibited tumor growth in a dose-dependent manner as measured by tumor volume and weight. At the same time, the body weight of the treated mice did not show any significant decrease, which implied that the two compounds

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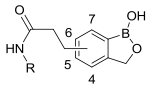
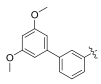
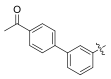
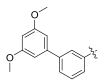
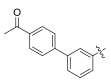
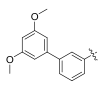
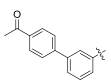
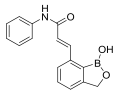
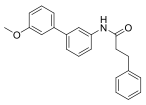
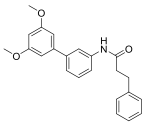
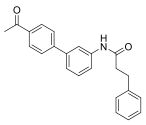
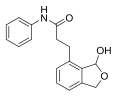
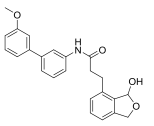
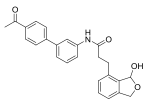
Table 4. Inhibitory Effect of Compounds 116−147 on Cancer Cell Proliferation



		Structure	[a]IC_{50} (μM) SKOV3	MDA-MB231	HCT 116	WI-38
116	6-		62	49	21	>100
117	6-		29	21	3.7	>100
118	6-		>100	59	19	>100
119	5-		>100	90	81	>100
120	5-		93	77	56	>100
121	5-		79	66	63	>100
122	4-		78	76	46	>100
123	4-		88	93	50	>100
124	4-		57	41	48	>100
125			>100	>100	>100	58
tb			>100	>100	65	32
127			>100	>100	>100	>100
129			>100	>100	>100	>100
130			24	25	40	>100
131			>100	87	>100	>100
132			3.2	2.7	4.0	13
145			78	12	22	42
146			61	52	49	93
147			41	29	18	>100

[a]IC_{50} indicates compound concentration required to inhibit cell viability by 50%. Values are expressed as the mean of triplicate experiments.

Table 5. Oral (po) and Intravenous (iv) Pharmacokinetic (PK) Parameters[a] of Compounds 103 and 115 in SD Rats

		dose (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (h ng/mL)	CL (mL/(h kg))	V_{ss} (mL/kg)	$T_{1/2}$ (h)	F (%)
103	iv	2	NA	NA	551	3750	7630	1.4	NA
	po	10	0.2	434	547	NA	NA	2.2	19.5
115	iv	2	NA	NA	1920	1050	882	0.6	NA
	po	10	0.25	373	459	NA	NA	2.0	4.6

[a]PK parameters were based on mean plasma concentration−time profiles of three animals per time points. PK parameters were calculated by noncompartmental analysis using DAS 2.0.

may have desired toxicity properties, but further comprehensive toxicity evaluation is needed.

CONCLUSIONS

Benzoxaboroles, as a novel class of bioactive molecules with unique chemical properties, have been shown to possess excellent antimicrobial activities with tavaborole approved in 2014 as an antifungal drug. Although urgently needed, the investigation of benzoxaboroles as anticancer agents has been lacking to date. In this work, based on an antimalarial benzoxaborole **65**, which does not show any anticancer activity, a series of 7-propanamide derivatives were designed and synthesized to give an initial hit compound **69**, which

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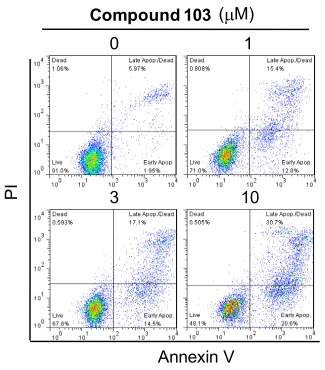

Figure 2. Induction of apoptosis on SKOV3 cells by compound **103**: flow cytometry analysis of apoptotic SKOV3 cells induced by compound **103** at different concentrations. Cells were treated with vehicle or compound **103** at 1.0, 3.0, and 10 μM for 48 h.

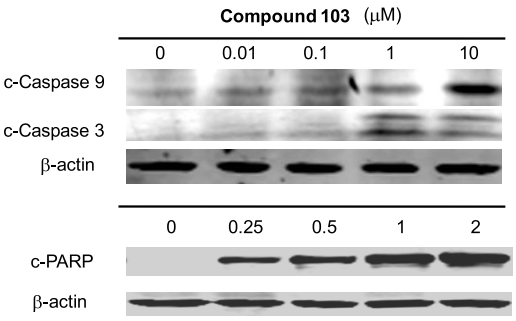

Figure 3. Western blot analysis of biological markers for apoptosis induction by compound **103** on H460 cells for 48 h.

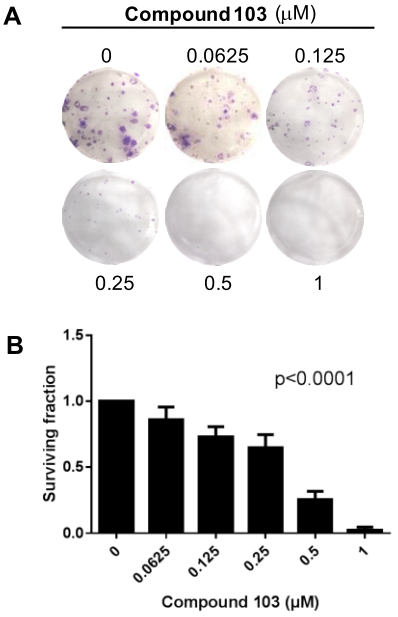

Figure 4. Inhibitory effects of compound **103** on colony formation of SKOV3 cells. (A) Cells were treated with compound **103** at various concentrations. Digital image was taken and all visible colonies were counted. (B) Data were normalized to untreated control. The error bars represent standard deviations from triplicates. The statistical significance was obtained with one-way analysis of variance (ANOVA) ($P < 0.0001$).

showed submicromolar antiproliferation activity on three cancer cell lines. Further structure−activity relationship studies found that replacement of the phenyl by biphenyl and installation of hydrogen-bond acceptor group were critical for the significant improvement of antiproliferation potency. Both the benzoxaborole moiety and the 7-propanamide modifications are essential for the anticancer activity. Thus, it led to the identification of a series of potent anticancer compounds. Among them, the most potent compound **115** showed an IC_{50} value of 21 nM on ovarian cancer cells and near-200-fold selectivity versus normal cells. More importantly, it also demonstrated in vivo efficacy and low toxicity on tumor xenograft mouse model at a dosage of 2 and 10 mg/kg.

This work is the first to show that benzoxaboroles may serve as potent and efficacious anticancer agents. Although there are existing reports commenting on their anticancer activity, the reported potency at cellular level was not ideal and in vivo efficacy was not reported.[30] However, the intracellular target of our benzxoaboroles remains to be elucidated. They were demonstrated to effectively induce cancer cell apoptosis through the caspase 3/9 and PARP pathways and inhibited colony formation. In previous reports, the biological activities of benzoxaboroles were mainly assessed by phenotypic screening while the cellular targets largely remained unknown. Although leucyl-tRNA synthetases (LeuRS) have been identified as the cellular target of the antifungal benzoxaborole tavaborole,[8] compounds **103** and **115** did not inhibit human LeuRS, which is consistent with our previously reported observation that the eukaryotic helix blocked the 7-position of the benzoxaborole.[16] Tavaborole did not show any anticancer activity, either. At the same time, benzoxaborole has been used as a novel chemotype in the development of enzyme inhibitors. An interesting example was the carbonic anhydrase inhibitors reported by Winum and Simone et al.[31,32] As a continuous development, we are currently making efforts to decipher the cellular targets of the anticancer benzoxaboroles reported herein.

EXPERIMENTAL SECTION

Chemistry: General Procedures. All solvents and reagents were purchased from commercial suppliers and used without further purification if not indicated. Column chromatography was performed using Huanghai silica gel (48−75 μm). NMR spectra were recorded on AVANCE 400 (Bruker). Chemical shifts (δ) are expressed in parts per million (ppm) relative to residual solvent as an internal reference. High-resolution mass spectroscopy (HRMS) images were obtained on an Agilent 6530 accurate-mass quadrupole time-of-flight LC/MS. High-performance liquid chromatography (HPLC) analysis was performed on an Agilent 1200 with a flow rate of 1 mL/min and a gradient of 10% MeCN/90% H_2O to 100% MeCN in 20 min using a diode array detector. An Agilent Eclipse XDB-C18 column (4.6 mm × 150 mm, 5 μm) was used. Purity was based on the integrated UV chromatogram (220 nm). All compounds used for biological evaluation have purity of ≥95%. Melting points were measured on a SGWX-4 melting point apparatus.

***t*-Butyl (4-Aminophenyl)carbamate (4).** To a solution of *p*-aminoanaline (3.24 g, 30 mmol) and K_2CO_3 (1.52 g, 11 mmol) in THF (30 mL) was added Boc_2O (2.18 g, 10 mmol) dropwise over 0.5 h. After stirred overnight at room temperature (rt), the mixture was diluted with H_2O (70 mL) and extracted with DCM (50 mL × 3). The organic phase was combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuum followed by purification on silica gel column chromatography (petroleum ether/EtOAc = 2:1) to give compound **4** (2.02 g, 100%) as a yellow solid. ^1H NMR (400 MHz, dimethyl sulfoxide (DMSO)-d_6): δ 8.77 (s, 1H), 7.06 (d, J = 8.2 Hz, 2H), 6.46 (d, J = 8.2 Hz, 2H), 4.72 (s, 2H), 1.44

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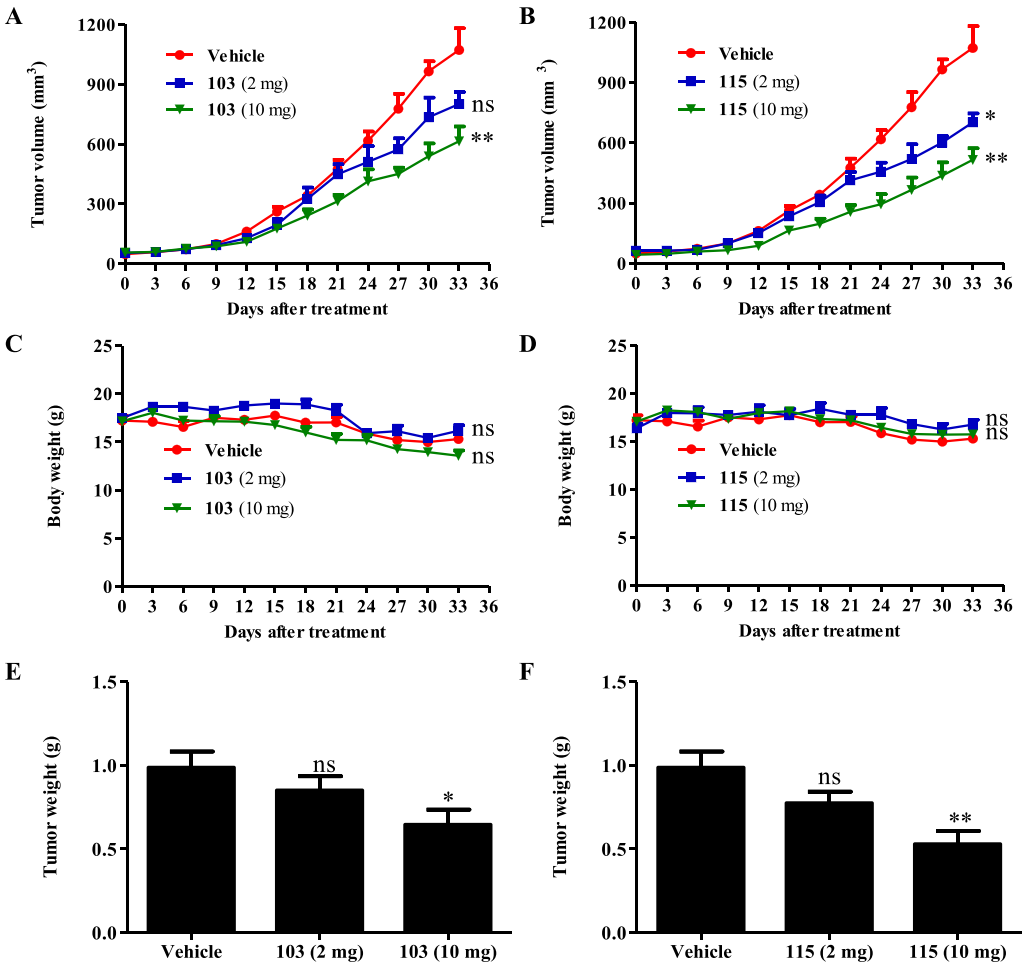

Figure 5. In vivo anticancer activity of compounds **103** and **115** on SKOV3 xenograft mouse model. Female nude BALB/c mice were administered by intraperitoneal injection with vehicle, compounds **103** and **115**, at a dosage of 2 and 10 mg/kg, respectively (n = 6 each group), once a day for 33 days. Average tumor volume (A, B), average body weight (C, D), and average tumor weight (E, F) were measured every 3 days. Data are expressed as the mean ± standard error (n = 6). * indicates $P < 0.05$ and ** indicates $P < 0.01$ vs control.

(s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 143.8, 128.4, 120.1, 113.8, 78.0, 28.1 ppm.

***t*-Butyl (4-Aminobenzyl)carbamate (5).** Compound **5** (0.97 g, 53.4%) was prepared following a similar procedure to compound **4** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, J = 8.2 Hz, 2H), 6.64 (d, J = 8.2 Hz, 2H), 4.70 (s, 1H), 4.18 (d, J = 5.2 Hz, 2H), 3.64 (s, 2H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 145.6, 128.8, 128.7, 115.1, 79.2, 44.3, 28.4 ppm.

2-((Trimethylsilyl)ethynyl)aniline (9). To a solution of 2-iodoaniline (1.1 g, 5.0 mmol), $Pd(PPh_3)_2Cl_2$ (105.3 mg, 0.15 mmol), and CuI (19.0 mg, 0.1 mmol) in a mixture of dry THF (10 mL) and TEA (3 mL) was added trimethylsilylacetylene (915 μL, 7.0 mmol) dropwise over 1 h. After stirred overnight at rt, the mixture was evaporated in vacuum and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 50:1) to obtain compound **9** as a yellow oil (797 mg, 83.9%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.0, 7.6 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 5.28 (s, 2H), 0.24 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.7, 131.6, 129.9, 115.7, 113.7, 105.4, 102.6, 98.6, 0.0 ppm.

3-((Trimethylsilyl)ethynyl)aniline (10). Compound **10** (888 mg, 93.4%) was prepared following a similar procedure to compound **9** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.99 (t, J = 7.8 Hz, 1H), 6.63 (s, 1H), 6.57 (t, J = 7.8 Hz, 2H), 5.20 (s, 2H), 0.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 129.6, 122.9, 119.4, 117.0, 115.3, 106.8, 92.7, 0.5 ppm.

4-((Trimethylsilyl)ethynyl)aniline (11). Compound **11** (565 mg, 59.4%) was prepared following a similar procedure to compound **9** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 5.53 (s, 2H), 0.18 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.1, 137.5, 133.3, 117.0, 113.9, 108.6, 107.9, 90.5, 0.7 ppm.

2-Ethynylaniline (12). To a solution of KOH (4.46 g, 32.3 mmol) in MeOH (20 mL) was added a solution of **9** (612 mg, 3.23 mmol) in DCM (20 mL). After stirred at rt for 3 h, the reaction mixture was filtered. The filtrate was concentrated and purified by silica gel column chromatography (petroleum ether/EtOAc = 10:1) to obtain compound **12** as a yellow oil (210 mg, 55.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 7.6 Hz, 1H), 7.15 (dd, J = 8.0, 7.6 Hz, 1H), 6.71−6.66 (m, 2H), 4.24 (s, 2H), 3.38 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 132.6, 130.1, 117.8, 114.3, 106.6, 82.4, 80.6 ppm.

3-Ethynylaniline (13). Compound **13** (208 mg, 43.1%) was prepared following a similar procedure to compound **12** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00 (t, J = 7.8 Hz, 1H), 6.64 (s, 1H), 6.59−6.57 (m, 2H), 5.20 (s, 2H), 3.96 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 129.6, 122.4, 119.5, 117.0, 115.2, 84.9, 79.5 ppm.

4-Ethynylaniline (14). Compound **14** (267 mg, 64.4%) was prepared following a similar procedure to compound **12** as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.11 (d, J = 8.6 Hz, 2H), 6.50 (d, J = 8.6 Hz, 2H), 5.49 (s, 2H), 3.76 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.4, 132.7, 113.4, 107.6, 85.0, 77.1 ppm.

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1,1′-Biphenyl-2-amine (36). To a solution of 2-bromoaniline (1.0 g, 5.8 mmol) in a mixture of toluene (25 mL) and EtOH (9 mL) were added $Pd(PPh_3)_2Cl_2$ (203.5 mg, 0.29 mmol), phenylboronic acid (708 mg, 5.8 mmol), and sat aq Na_2CO_3 (3 mL). The reaction mixture was refluxed overnight under nitrogen atmosphere. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL × 3). The organic phase was combined, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 25:1) to obtain compound **36** as a white solid (837 mg, 85.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46−7.40 (m, 4H), 7.33 (t, J = 7.0 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.63 (t, J = 7.4 Hz, 1H), 4.75 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.9, 139.6, 129.9, 128.7, 128.5, 128.1, 126.7, 125.7, 116.7, 115.2 ppm.

1,1′-Biphenyl-3-amine (37). Compound **37** (338.7 mg, 68.9%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.56 (m, 2H), 7.44−7.40 (m, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 4.24 (s, 2H), 3.71 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 142.4, 141.3, 129.6, 128.6, 127.2, 127.1, 117.6, 114.0, 113.8 ppm.

1,1′-Biphenyl-4-amine (38). Compound **38** (195.2 mg, 39.7%) was prepared following a similar procedure to compound **36** as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.53 (m, 2H), 7.43−7.38 (m, 4H), 7.27 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 3.74 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 141.1, 131.6, 128.6, 128.0, 126.4, 126.2, 115.4 ppm.

3′-Fluoro-1,1′-biphenyl-3-amine (39). Compound **39** (493.4 mg, 90.7%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46 (dd, J = 10.8, 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 10.8 Hz, 1H), 7.17−7.12 (m, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.87 (s, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 5.19 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5 (d, J = 241.8 Hz), 149.1, 143.5 (d, J = 7.6 Hz), 139.4 (d, J = 2.1 Hz), 130.6 (d, J = 8.6 Hz), 129.5, 122.4, 114.4, 113.7, 113.6 (d, J = 20.8 Hz), 113.9 (d, J = 21.6 Hz), 112.1 ppm.

4′-Fluoro-1,1′-biphenyl-3-amine (40). Compound **40** (407.8 mg, 75.1%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, J = 8.8, 5.4 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 8.8 Hz, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.85 (t, J = 2.0 Hz, 1H), 6.67 (dd, J = 7.8, 2.0 Hz, 1H), 3.71 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (d, J = 244.4 Hz), 146.7, 141.4, 137.4 (d, J = 3.3 Hz), 129.7, 128.5 (d, J = 7.9 Hz), 117.4, 115.4 (d, J = 21.3 Hz), 114.0, 113.6 ppm.

3′-Chloro-1,1′-biphenyl-3-amine (41). Compound **41** (481.1 mg, 81.3%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.85 (s, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 5.19 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.1, 143.2, 139.2, 133.4, 130.5, 129.5, 126.8, 126.0, 125.0, 114.2, 113.7, 112.0 ppm.

4′-Chloro-1,1′-biphenyl-3-amine (42). Compound **42** (564.0 mg, 95.3%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.10 (t, J = 7.8 Hz, 1H), 6.82 (s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 5.18 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 139.8, 139.5, 131.9, 129.5, 128.7, 128.2, 114.3, 113.5, 112.0 ppm.

3′-Methoxy-1,1′-biphenyl-3-amine (43). Compound **43** (465.0 mg, 70.9%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (t, J = 8.0 Hz, 1H), 7.12−7.05 (m, 3H), 6.89 (dd, J = 8.0, 2.0 Hz, 1H), 6.83 (t, J = 2.0 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.56 (dd, J = 8.0, 1.5 Hz, 1H), 5.13 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.5, 149.0, 142.6, 140.7, 129.7, 129.3, 118.8, 114.4, 113.2, 112.6, 112.1, 111.9, 55.0 ppm.

4′-Methoxy-1,1′-biphenyl-3-amine (44). Compound **44** (347.5 mg, 60.1%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.97−6.94 (m, 3H), 6.87 (t, J = 2.0 Hz, 1H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 146.7, 142.0, 133.9, 129.6, 128.1, 117.3, 114.0, 113.5, 113.4, 55.3 ppm.

3′,5′-Methoxy-1,1′-biphenyl-3-amine (45). Compound **45** (425.0 mg, 79.7%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08 (t, J = 7.8 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 2.2 Hz, 2H), 6.57 (dd, J = 7.8, 1.2 Hz, 1H), 6.47 (t, J = 2.2 Hz, 1H), 5.14 (s, 2H), 3.85 (s, 3H), 3.79 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 148.9, 143.3, 140.8, 129.2, 114.4, 113.3, 112.2, 104.6, 98.9, 55.1 ppm.

3′-Trifluoromethoxy-1,1′-biphenyl-3-amine (46). Compound **46** (674.9 mg, 91.7%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (dt, J = 8.0, 1.4 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.48 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.23 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 148.8, 143.4, 139.1, 130.6, 129.5, 125.5, 120.1 (q, J = 254.7 Hz), 119.3, 118.7, 114.3, 113.8, 112.0, ppm.

4′-Trifluoromethoxy-1,1′-biphenyl-3-amine (47). Compound **47** (553.0 mg, 75.1%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.86 (s, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.21 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 147.5, 140.3, 139.4, 129.5, 128.1, 121.2, 120.1 (q, J = 254.5 Hz), 114.3, 113.5, 112.1 ppm.

3′-Methylthio-1,1′-biphenyl-3-amine (48). Compound **48** (355.2 mg, 56.9%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.35 (m, 2H), 7.31 (dt, J = 7.8, 1.4 Hz, 1H), 7.22 (dt, J = 7.6, 1.4 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.84 (t, J = 1.8 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.56 (dd, J = 7.8, 1.4 Hz, 1H), 5.16 (s, 2H), 2.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.0, 141.7, 140.3, 138.5, 129.3, 129.2, 124.5, 123.6, 123.0, 114.3, 113.3, 112.0, 14.6 ppm.

4′-Methylthio-1,1′-biphenyl-3-amine (49). Compound **49** (456.0 mg, 73.1%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 (t, J = 7.8 Hz, 1H), 6.83 (s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 5.14 (s, 2H), 3.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.0, 140.1, 137.5, 136.8, 129.3, 126.8, 126.2, 113.9, 113.0, 111.6, 14.6 ppm.

3′-Trifluoromethyl-1,1′-biphenyl-3-amine (50). Compound **50** (619.3 mg, 89.8%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85−7.84 (m, 2H), 7.65−7.59 (m, 2H), 7.16 (t, J = 7.8 Hz, 1H), 6.99 (s, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.27 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.3, 142.1, 139.3, 130.4, 129.9, 129.7, 129.6, 129.5, 125.6, 123.5 (t, J = 3.8 Hz), 122.9, 122.7 (t, J = 3.9 Hz), 114.5, 114.0, 112.3 ppm.

4′-Trifluoromethyl-1,1′-biphenyl-3-amine (51). Compound **51** (561.0 mg, 81.4%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (s, 4H), 7.14 (dd, J = 8.0, 7.6 Hz, 1H), 6.90 (s, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 5.25 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 145.0, 139.2, 129.6, 127.1, 125.6 (t, J = 3.8 Hz), 114.4, 114.0, 112.1 ppm.

3′-Cyano-1,1′-biphenyl-3-amine (52). Compound **52** (507.1 mg, 89.8%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (t, J = 1.6 Hz, 1H), 7.89 (dt, J = 7.8, 1.6 Hz, 1H), 7.78 (dt, J = 7.8, 1.2 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.87 (t, J = 1.6 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.62 (dd, J = 7.8, 1.6 Hz, 1H), 5.22 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 142.1, 138.6,

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131.2, 130.6, 129.9, 129.8, 129.6, 118.8, 114.3, 113.9, 112.0, 111.8 ppm.

4′-Cyano-1,1′-biphenyl-3-amine (53). Compound **53** (438.8 mg, 77.7%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 6.89 (s, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.64 (dd, J =7.8, 1.6 Hz, 1H), 5.26 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.3, 145.5, 138.9, 132.6, 129.6, 127.2, 118.9, 114.4, 114.3, 112.1, 109.5 ppm.

3′-Acetyl-1,1′-biphenyl-3-amine (54). Compound **54** (544.8 mg, 88.7%) was prepared following a similar procedure to compound **36** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (t, J = 1.6 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7. 57 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.93 (t, J = 1.6 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.63 (dd, J = 7.8, 1.6 Hz, 1H), 5.22 (s, 2H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.9, 149.2, 141.4, 139.9, 137.2, 131.0, 129.5, 129.1, 126.9, 125.8, 114.4, 113.5, 112.1, 26.8 ppm.

4′-Acetyl-1,1′-biphenyl-3-amine (55). Compound **55** (523.3 mg, 85.4%) was prepared following a similar procedure to compound **36** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.6 Hz, 2H), 7.25 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.93 (t, J = 1.8 Hz, 1H), 6.73 (dd, J = 7.8, 1.8 Hz, 1H), 3.79 (s, 2H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 146.9, 146.0, 141.0, 135.7, 129.8, 128.8, 127.1, 117.6, 114.9, 113.7, 26.6 ppm.

Ethyl (*E*)-3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-acrylate (63). To a solution of aldehyde **62** (1.68 g, 10.4 mmol) in toluene (150 mL) was added ethyl (triphenylphosphoranylidene)-acetate (4.34 g, 12.4 mmol). After stirred overnight at rt, the reaction mixture was evaporated in vacuum followed by purification on silica gel column chromatography (petroleum ether/EtOAc = 2:1) to obtain compound **63** as a white solid (1.6 g, 66.7%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.10 (d, J = 16.2 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 16.2 Hz, 1H), 5.02 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 154.5, 143.0, 137.2, 131.1, 125.0, 123.0, 119.1, 69.6, 59.9, 14.1 ppm.

Ethyl 3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-propanoate (64). To a solution of compound **63** (1.3 g, 5.6 mmol) in EtOH (120 mL) was added 10% Pd/C (592 mg). After stirred overnight under hydrogen atmosphere at rt, the reaction mixture was filtered and the filtrate was evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 2:1) to obtain compound **64** as a white solid (1.2 g, 93.2%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.30 (t, J = 7.8 Hz, 2H), 2.26 (t, J = 7.8 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 154.1, 144.6, 130.8, 126.7, 119.1, 69.7, 59.6, 35.4, 29.2, 14.0 ppm.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)propanoic Acid (65). To a solution of compound **64** (1.51 g, 6.45 mmol) in MeOH (66 mL) was added 1 M NaOH aq solution (33 mL). After stirred overnight at rt, the reaction mixture was acidified with conc. HCl to pH = 3. Then, the mixture was filtered to obtain compound **65** (1.23 g, 92.9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.96 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 2.99 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 154.1, 145.0, 130.8, 126.6, 119.0, 69.7, 35.5, 29.2 ppm; HRMS [electrospray ionization (ESI)]: $[M + H]^+$ $C_{10}H_{12}BO_4$ calcd 207.0829, found 207.0827; mp: 159−162 °C; HPLC: purity 99.1%, retention time 3.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-ethyl-propanamide (66). Compound **65** (200 mg, 0.97 mmol) was dissolved in $SOCl_2$ (4 mL). After refluxed for 2 h, the mixture was evaporated in vacuo and the residue was dissolved in DCM (12 mL). To the mixture were added ethylamine hydrochloride (238 mg, 2.9 mmol) and TEA (324 mg, 3.2 mmol). After stirred at room temperature overnight, the mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 150:1) to obtain compound **66** as a white solid (81 mg, 35.8%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.73 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 4.95 (s, 2H), 3.05−2.97 (m, 4H), 2.36 (t, J = 7.6 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1, 154.0, 145.6, 130.6, 126.5, 118.7, 69.5, 37.2, 33.1, 29.6, 14.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{12}H_{17}BNO_3$ calcd 234.1301, found 234.1304; mp: 121−125 °C; HPLC: purity 96.4%, retention time 7.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(*tert*-butyl)propanamide (67). Compound **67** (90 mg, 27.5%) was prepared following a similar procedure to compound **66** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.31 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 4.95 (s, 2H), 2.97 (d, J = 7.6 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.1, 153.9, 145.8, 130.5, 126.5, 118.7, 69.5, 49.7, 37.9, 29.7, 28.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{14}H_{21}BNO_3$ calcd 262.1614, found 262.1635; mp: 151−157 °C; HPLC: purity 96.0%, retention time 11.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-cyclo-hexylpropanamide (68). To a solution of compound **65** (60 mg, 0.29 mmol) in dry DCM (10 mL) were added aminocyclohexane (30 mg, 0.30 mmol) and EDCI (220 mg, 0.58 mmol). After stirred overnight at rt, the reaction mixture was evaporated in vacuum. The residue was purified by silica gel column chromatography (DCM/MeOH = 150:1) to obtain compound **68** as a white solid (32.7 mg, 39.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 4.95 (s, 2H), 3.53−3.46 (m, 1H), 2.98 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 1.68−1.62 (m, 4H), 1.53 (d, J = 11.9 Hz, 1H), 1.24−1.18 (m, 2H), 1.11−1.02 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 154.0, 145.7, 130.6, 126.6, 118.8, 69.6, 47.2, 37.3, 32.4, 29.7, 25.2, 24.5 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{23}BNO_3$ calcd 288.1771, found 288.1779; mp: 221−224 °C; HPLC: purity 97.9%, retention time 11.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-phenylpropanamide (69). Compound **69** (192 mg, 70.5%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.99 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.27 (dd, J = 8.0, 7.4 Hz, 2H), 7.21 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 4.97 (s, 2H), 3.10 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 154.1, 145.4, 139.2, 130.7, 128.5, 126.6, 122.8, 118.9, 118.8, 69.6, 38.1, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{17}BNO_3$ calcd 282.1301, found 282.1299; mp: 197−199 °C; HPLC: purity 95.6%, retention time 11.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-benzyl-propanamide (70). Compound **70** (25.4 mg, 35.5%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.25 (t, J = 5.9 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 7.2 Hz, 2H), 7.15−7.11 (m, 3H), 4.95 (s, 2H), 4.24 (d, J = 5.9 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 2.47 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 154.0, 145.5, 139.5, 130.7, 128.1, 127.0, 126.7, 126.5, 118.8, 69.6, 41.8, 37.1, 29.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{19}BNO_3$ calcd 296.1458, found 296.1462; mp: 158−162 °C; HPLC: purity 96.5%, retention time 10.1 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-phene-thylpropanamide (71). Compound **71** (28.4 mg, 37.9%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.85 (t, J = 5.6 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.2 Hz, 2H), 7.21−7.18 (m, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.10 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 3.26−3.21 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.47 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 154.0, 145.6, 139.4, 130.7, 128.5, 128.2, 126.5, 125.9, 118.8,

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69.6, 37.2, 35.1, 29.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{21}BNO_3$ calcd 310.1614, found 310.1611; mp: 145−149 °C; HPLC: purity 99.4%, retention time 11.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(thiazol-2-yl)propanamide (72). Compound **72** (34.5 mg, 32.9%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.98 (s, 1H), 7.43 (d, J = 3.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.10 (t, J = 7.8 Hz, 2H), 2.76 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 157.8, 154.0, 144.8, 137.4, 126.4, 119.0, 113.0, 69.6, 36.6, 28.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{13}H_{14}BN_2O_3S$ calcd 289.0818, found 289.0823; mp: 204−206 °C; HPLC: purity 98.8%, retention time 9.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-fluorophenyl)propanamide (73). Compound **73** (46.1 mg, 63.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.49−7.45 (m, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 8.8 Hz, 2H), 5.05 (s, 2H), 3.16 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 154.1, 145.4, 135.6, 130.8, 126.6, 120.6 (d, J = 7.8 Hz), 119.0, 115.1 (d, J = 22.0 Hz), 69.7, 38.1, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BFNO_3$ calcd 300.1207, found 300.1210; mp: 234−237 °C; HPLC: purity 98.0%, retention time 11.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-chlorophenyl)propanamide (74). Compound **74** (46.0 mg, 57.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.48 (s, 1H), 5.04 (s, 2H), 3.16 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 154.0, 145.2, 138.0, 130.6, 128.4, 126.5, 120.4, 118.9, 69.6, 38.0, 29.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BClNO_3$ calcd 316.0912, found 316.0909; mp: 216−219 °C; HPLC: purity 97.2%, retention time 13.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-bromophenyl)propanamide (75). Compound **75** (53.8 mg, 51.3%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 8.99 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 4.96 (s, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.3, 138.5, 131.4, 130.7, 126.6, 120.8, 119.0, 114.4, 69.7, 38.1, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BBrNO_3$ calcd 360.0407, found 360.0402; mp: 232−235 °C; HPLC: purity 95.7%, retention time 13.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-iodo-phenyl)propanamide (76). Compound **76** (32.6 mg, 27.5%) was prepared following a similar procedure to compound **68** as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.59 (d, J = 8.6 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 3.15 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 173.9, 155.7, 146.4, 139.9, 138.9, 132.3, 128.2, 123.1, 120.1, 72.2, 40.1, 31.5 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BINO_3$ calcd 408.0268, found 408.0268; mp: 228−231 °C; HPLC: purity 95.6%, retention time 13.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-methylphenyl)propanamide (77). Compound **77** (49.5 mg, 57.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 8.99 (s, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 8.2 Hz, 2H), 4.96 (s, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 154.6, 146.0, 137.2, 132.2, 131.3, 129.5, 127.1, 119.5, 119.4, 70.2, 38.7, 30.0, 20.9 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{19}BNO_3$ calcd 296.1458, found 296.1460; mp: 179−182 °C; HPLC: purity 96.2%, retention time 12.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-ethynylphenyl)propanamide (78). Compound **78** (14.5 mg, 12.2%) was prepared following a similar procedure to compound **68** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 9.00 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 4.06 (s, 1H), 3.09 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.3, 139.7, 132.2, 130.7, 126.6, 119.0, 118.7, 115.7, 83.5, 79.6, 69.7, 38.2, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{17}BNO_3$ calcd 306.1301, found 306.1305; mp: 193−196 °C; HPLC: purity 95.2%, retention time 11.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-*t*-butylphenyl)propanamide (79). Compound **79** (30.9 mg, 38.2%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H), 8.99 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.25 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 154.1, 145.5, 145.1, 136.6, 130.7, 126.6, 125.1, 118.9, 118.8, 69.6, 38.1, 33.9, 31.1, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{20}H_{25}BNO_3$ calcd 338.1927, found 338.1927; mp: 145−147 °C; HPLC: purity 99.1%, retention time 15.2 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-methoxylphenyl)propanamide (80). Compound **80** (51.3 mg, 40.5%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (s, 1H), 8.99 (s, 1H), 7.47 (d, J = 8.9 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.97 (s, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 155.2, 154.3, 145.6, 132.4, 131.0, 126.8, 120.8, 119.2, 113.9, 69.8, 55.2, 38.2, 29.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{19}BNO_4$ calcd 312.1407, found 312.1403; mp: 200−203 °C; HPLC: purity 95.5%, retention time 10.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-(*t*-butoxycarbonylamino)phenyl)propanamide (81). Compound **81** (36.5 mg, 37.9%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.71 (s, 1H), 9.22 (s, 1H), 9.00 (s, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.39−7.33 (m, 3H), 7.21 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 4.97 (s, 2H), 3.09 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 154.2, 152.9, 145.5, 134.7, 133.7, 130.8, 126.7, 119.6, 119.0, 118.5, 78.9, 69.7, 38.1, 29.5, 28.1 ppm; HRMS (ESI): $[M + H]^+$ $C_{21}H_{26}BN_2O_5$ calcd 397.1935, found 397.1931; mp: >270 °C; HPLC: purity 99.6%, retention time 12.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-((*tert*-butoxycarbonyl)aminomethyl)-phenyl)propanamide (82). Compound **82** (338.2 mg, 84.9%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (s, 1H), 8.98 (s, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 5.8 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.16−7.12 (m, 3H), 4.96 (s, 2H), 4.04 (d, J = 5.8 Hz, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.38 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 155.6, 154.1, 145.4, 137.7, 134.6, 130.7, 127.2, 126.6, 118.9, 77.6, 69.6, 42.9, 38.1, 29.4, 28.1 ppm; HRMS (ESI): $[M + Na]^+$ $C_{22}H_{27}BN_2NaO_5$ calcd 433.1911, found 433.1911; mp: 171−174 °C; HPLC: purity 99.1%, retention time 12.7 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-ethoxycarbonylphenyl)propanamide (83). Compound **83** (90.3 mg, 26.3%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 9.02 (s, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 4.26 (q, J = 7.0 Hz, 2H), 3.10 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 165.3, 154.2, 145.3, 143.5, 130.8, 130.2, 126.7, 123.9, 119.1, 118.3, 69.7, 60.4, 38.3, 29.3, 14.2 ppm; HRMS

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(ESI): $[M + H]^+$ $C_{19}H_{21}BNO_5$ calcd 354.1513, found 354.1515; mp: 155−157 °C; HPLC: purity 98.9%, retention time 11.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4-nitrophenyl)propanamide (84). Compound **84** (19.9 mg, 12.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.18 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 4.56 (s, 1H), 3.17 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 174.3, 155.8, 146.3, 146.2, 144.6, 132.3, 128.3, 125.7, 120.4, 120.2, 72.2, 40.1, 32.8, 31.3, 23.7, 14.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BN_2O_5$ calcd 327.1152, found 327.1148; mp: 243−247 °C; HPLC: purity 98.5%, retention time 12.4 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3-bromophenyl)propanamide (85). Compound **85** (37.8 mg, 36.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.0 (s, 1H), 9.00 (s, 1H), 7.94 (s, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.26−7.19 (m, 3H), 7.15 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.09 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.4, 154.7, 145.8, 141.3, 131.3, 131.1, 127.2, 126.0, 122.0, 121.8, 119.5, 118.2, 70.2, 38.7, 29.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BBrNO_3$ calcd 360.0407, found 360.0405; mp: 188−192 °C; HPLC: purity 97.7%, retention time 13.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3-iodophenyl)propanamide (86). Compound **86** (44.0 mg, 37.1%) was prepared following a similar procedure to compound **68** as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 8.98 (s, 1H), 8.08 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 4.97 (s, 2H), 3.08 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.2, 140.5, 131.3, 130.7, 130.6, 127.1, 126.5, 118.9, 118.1, 94.4, 69.6, 38.1, 29.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{16}H_{16}BINO_3$ calcd 408.0268, found 408.0272; mp: 199−202 °C; HPLC: purity 96.7%, retention time 13.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3-*i*-propylphenyl)propanamide (87). Compound **87** (33.0 mg, 42.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (s, 1H), 9.00 (s, 1H), 7.43−7.40 (m, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.20 (m, 3H), 6.89 (d, J = 7.6 Hz, 1H), 4.97 (s, 2H), 3.09 (t, J = 7.7 Hz, 2H), 2.85−2.78 (m, 1H), 2.63 (t, J = 7.7 Hz, 2H), 1.17 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 154.1, 148.8, 145.5, 139.2, 130.8, 128.4, 126.6, 121.0, 118.9, 116.9, 116.6, 69.7, 38.1, 33.4, 29.4, 23.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{23}BNO_3$ calcd 324.1771, found 324.1775; mp: 117−120 °C; HPLC: purity 99.4%, retention time 14.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3-ethynylphenyl)propanamide (88). Compound **88** (43.7 mg, 36.9%) was prepared following a similar procedure to compound **68** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.00 (s, 1H), 7.77 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 4.97 (s, 2H), 4.16 (s, 1H), 3.09 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.3, 139.3, 130.7, 129.0, 126.5, 126.1, 121.8, 121.7, 119.5, 118.9, 83.3, 80.3, 69.6, 38.1, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{17}BNO_3$ calcd 306.1301, found 306.1306; mp: 177−179 °C; HPLC: purity 98.8%, retention time 12.4 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(2-methoxylphenyl)propanamide (89). Compound **89** (18.5 mg, 24.5%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.22−7.17 (m, 2H), 7.08 (dd, J = 8.0, 7.5 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (dd, J = 7.8, 7.5 Hz, 1H), 5.06 (s, 2H), 3.84 (s, 3H), 3.16 (t, J = 7.8 Hz, 2H), 2.73 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 173.9, 155.8, 151.4, 146.4, 132.3, 128.2, 126.1, 123.3, 121.5, 120.2, 111.8, 72.2, 56.3, 40.3, 32.0 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{19}BNO_4$ calcd 312.1407, found 312.1412; mp: 158−162 °C; HPLC: purity 98.0%, retention time 12.0 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(2-ethynylphenyl)propanamide (90). Compound **90** (9.7 mg, 8.2%) was prepared following a similar procedure to compound **68** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 8.98 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.40−7.35 (m, 2H), 7.21 (t, J = 8.2 Hz, 2H), 7.12 (d, J = 7.6 Hz, 1H), 4.97 (s, 2H), 4.43 (s, 1H), 3.11 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 155.0, 145.2, 139.4, 132.2, 131.5, 130.3, 127.4, 123.6, 119.8, 119.4, 110.8, 84.2, 79.3, 70.8, 40.5, 31.0 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{17}BNO_3$ calcd 306.1301, found 306.1296; mp: 182−185 °C; HPLC: purity 97.6%, retention time 12.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3-bromo-4-methylphenyl)propanamide (91). Compound **91** (51.2 mg, 47.0%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 9.00 (s, 1H), 7.94 (s, 1H), 7.38−7.34 (m, 2H), 7.24 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 3.08 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 154.1, 145.3, 138.3, 131.2, 130.8, 130.7, 126.6, 123.6, 122.0, 119.0, 118.1, 69.7, 38.1, 29.3, 21.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{17}H_{18}BBrNO_3$ calcd 374.0563, found 374.0564; mp: 174−177 °C; HPLC: purity 98.6%, retention time 14.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3,4-dimethoxylphenyl)propanamide (92). Compound **92** (27.4 mg, 33.1%) was prepared following a similar procedure to compound **68** as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.36 (t, J = 7.5 Hz, 1H), 7.23−7.16 (m, 3H), 6.94 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 5.05 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.16 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 173.7, 155.7, 150.4, 147.2, 146.5, 133.6, 132.2, 128.3, 120.1, 113.8, 113.3, 106.9, 72.2, 56.8, 56.4, 40.0, 31.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{18}H_{21}BNO_5$ calcd 342.1513, found 342.1512; mp: 201−204 °C; HPLC: purity 98.1%, retention time 10.1 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(2,4,6-trimethylphenyl)propanamide (93). Compound **93** (17.3 mg, 7.4%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.37 (t, J = 7.5 Hz, 1H), 7.22−7.19 (m, 2H), 6.85 (s, 2H), 5.06 (s, 2H), 4.57 (s, 1H), 3.19 (t, J = 7.6 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.23 (s, 3H), 2.01 (s, 6H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 174.5, 155.8, 146.5, 138.0, 136.6, 133.0, 132.3, 129.6, 128.5, 120.2, 72.2, 38.9, 31.7, 21.0, 18.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{19}H_{23}BNO_3$ calcd 324.1771, found 310.1776; mp: 262−266 °C; HPLC: purity 95.1%, retention time 10.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(naphthalene-1-yl)propanamide (94). Compound **94** (22.2 mg, 27.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.81 (s, 1H), 9.02 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.52−7.46 (m, 3H), 7.39 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 4.99 (s, 2H), 3.17 (t, J = 7.5 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.3, 154.2, 145.4, 133.6, 133.5, 130.8, 128.0, 127.8, 126.8, 125.9, 125.6, 125.5, 125.1, 122.8, 121.8, 119.0, 69.7, 37.8, 29.8 ppm; HRMS (ESI): $[M + H]^+$ $C_{20}H_{19}BNO_3$ calcd 332.1458, found 332.1456; mp: 172−175 °C; HPLC: purity 96.2%, retention time 11.8 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(naphthalene-2-yl)propanamide (95). Compound **95** (36.0 mg, 37.3%) was prepared following a similar procedure to compound **68** as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.04 (s, 1H), 9.02 (s, 1H), 8.29 (s, 1H), 7.84−7.78 (m, 3H), 7.55 (dd, J = 8.8, 2.0 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.40−7.35 (m, 2H), 7.20 (t, J = 7.6 Hz, 2H), 4.98 (s, 2H), 3.14 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.4, 136.7,

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133.3, 130.7, 129.5, 128.1, 127.3, 127.1, 126.6, 126.2, 124.3, 119.8, 118.9, 114.9, 69.6, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{20}H_{19}BNO_3$ calcd 332.1458, found 332.1462; mp: 230−233 °C; HPLC: purity 95.2%, retention time 13.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(1,1′-biphenyl-2-yl)propanamide (96). Compound **96** (12.3 mg, 11.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.48 (d, J = 7.6 Hz, 1H), 7.37−7.26 (m, 9H), 7.21 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 5.05 (s, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 174.5, 155.7, 146.4, 140.4, 138.5, 135.5, 132.3, 131.5, 130.1, 129.5, 129.0, 128.5, 128.3, 127.6, 127.5, 120.2, 72.2, 39.5, 31.5 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{21}BNO_3$ calcd 358.1614, found 358.1620; mp: 161−164 °C; HPLC: purity 98.4%, retention time 13.4 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(1,1′-biphenyl-3-yl)propanamide (97). Compound **97** (52.4 mg, 50.4%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 9.01 (s, 1H), 7.90 (s, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 3H), 7.30 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 154.1, 145.4, 140.6, 140.1, 139.7, 130.7, 129.2, 128.9, 127.4, 126.6, 126.5, 121.3, 118.9, 118.0, 117.2, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{21}BNO_3$ calcd 358.1614, found 358.1619; mp: 146−149 °C; HPLC: purity 98.8%, retention time 14.7 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(1,1′-biphenyl-4-yl)propanamide (98). Compound **98** (51.6 mg, 49.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.00 (s, 1H), 7.68−7.59 (m, 6H), 7.43 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 154.1, 145.4, 139.7, 138.6, 134.5, 130.7, 128.8, 126.8, 126.7, 126.6, 126.1, 119.3, 118.9, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{21}BNO_3$ calcd 358.1614, found 358.1612; mp: 272−274 °C; HPLC: purity 95.0%, retention time 14.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-fluoro-1,1′-biphenyl-3-yl)propanamide (99). Compound **99** (58.8 mg, 53.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 9.02 (s, 1H), 7.92 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.54−7.49 (m, 1H), 7.46−7.34 (m, 5H), 7.22−7.17 (m, 3H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 162.6 (d, J = 242.0 Hz), 154.1, 145.4, 142.6 (d, J = 7.7 Hz), 139.8, 139.2, 130.9 (d, J = 8.6 Hz), 130.8, 129.4, 126.6, 122.6, 121.4, 119.0, 118.6, 117.3, 114.3 (d, J = 20.9 Hz), 113.2 (d, J = 21.9 Hz), 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{20}BFNO_3$ calcd 376.1520, found 376.1514; mp: 140−143 °C; HPLC: purity 97.9%, retention time 14.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-fluoro-1,1′-biphenyl-3-yl)propanamide (100). Compound **100** (48.3 mg, 44.2%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.01 (s, 1H), 7.88 (s, 1H), 7.63 (dd, J = 8.6, 5.5 Hz, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 8.6 Hz, 3H), 7.21 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 4.97 (s, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 154.1, 145.4, 139.7, 139.6, 130.7, 129.2, 128.5 (d, J = 8.1 Hz), 126.6, 121.2, 118.9, 118.0, 117.2, 115.6 (d, J = 21.3 Hz), 69.6, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{20}BFNO_3$ calcd 376.1520, found 376.1522; mp: 158−160 °C; HPLC: purity 97.7%, retention time 14.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-chloro-1,1′-biphenyl-3-yl)propanamide (101). Compound **101** (44.8 mg, 39.3%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 9.02 (s, 1H), 7.91 (s, 1H), 7.62 (s, 1H), 7.60−7.57 (m, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.41−7.33 (m, 3H), 7.21 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.4, 142.3, 139.8, 139.0, 133.6, 130.8, 129.4, 127.3, 126.6, 126.2, 125.2, 121.4, 119.0, 118.6, 117.3, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{20}BClNO_3$ calcd 392.1225, found 392.1234; mp: 122−125 °C; HPLC: purity 98.8%, retention time 15.2 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-chloro-1,1′-biphenyl-3-yl)propanamide (102). Compound **102** (52.6 mg, 46.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 9.01 (s, 1H), 7.91 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.57−7.52 (m, 3H), 7.40−7.35 (m, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.4, 139.8, 139.2, 138.9, 132.3, 130.8, 129.3, 128.9, 128.3, 126.6, 121.2, 119.0, 118.3, 117.1, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{22}H_{20}BClNO_3$ calcd 392.1225, found 392.1220; mp: 184−187 °C; HPLC: purity 97.2%, retention time 15.9 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (103). Compound **103** (33.0 mg, 35.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.01 (s, 1H), 7.86 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.40−7.34 (m, 3H), 7.31 (d, J = 8.0 Hz, 1H), 7.22−7.15 (m, 3H), 7.11 (s, 1H), 6.94 (dd, J = 8.2, 2.2 Hz, 1H), 4.97 (s, 2H), 3.82 (s, 3H), 3.11 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 159.6, 154.1, 145.4, 141.6, 140.5, 139.7, 130.7, 129.9, 129.1, 126.6, 121.4, 118.9, 118.8, 118.1, 117.3, 113.0, 112.0, 69.7, 55.0, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{23}BNO_4$ calcd 388.1720, found 388.1718; mp: 133−136 °C; HPLC: purity 99.2%, retention time 14.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-methoxy-1,1′-biphenyl-3-yl)propanamide (104). Compound **104** (59.6 mg, 52.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 9.01 (s, 1H), 7.84 (s, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 4.97 (s, 2H), 3.80 (s, 3H), 3.11 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 158.8, 154.1, 145.4, 140.2, 139.7, 132.4, 130.7, 129.1, 127.6, 126.6, 120.8, 118.9, 117.3, 116.8, 114.3, 69.7, 55.1, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{23}BNO_4$ calcd 388.1720, found 388.1718; mp: 170−172 °C; HPLC: purity 99.6%, retention time 14.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′,5′-dimethoxy-1,1′-biphenyl-3-yl)propanamide (105). Compound **105** (35.3 mg, 29.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 9.01 (s, 1H), 7.82 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.39−7.29 (m, 3H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 6.70 (d, J = 2.2 Hz, 2H), 6.51 (t, J = 2.2 Hz, 1H), 4.97 (s, 2H), 3.80 (s, 6H), 3.11 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 160.8, 154.2, 145.4, 142.4, 140.6, 139.6, 130.8, 129.2, 126.7, 121.5, 119.0, 118.4, 117.4, 104.7, 99.3, 69.7, 55.2, 38.3, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{24}H_{25}BNO_5$ calcd 418.1826, found 418.1826; mp: 161−164 °C; HPLC: purity 98.2%, retention time 14.4 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-trifluoromethoxy-1,1′-biphenyl-3-yl)propanamide (106). Compound **106** (66.5 mg, 51.8%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.02 (s, 1H), 7.91 (s, 1H), 7.67−7.59 (m, 3H), 7.53 (s, 1H), 7.42−7.35 (m, 4H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1,

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148.8, 145.3, 142.4, 139.8, 138.8, 130.8, 130.7, 129.4, 126.5, 125.6, 121.4, 119.8, 118.9, 118.7, 117.3, 69.6, 38.2, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BF_3NO_4$ calcd 442.1437, found 442.1432; mp: 129−132 °C; HPLC: purity 97.4%, retention time 16.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-trifluoromethoxy-1,1′-biphenyl-3-yl)propanamide (107). Compound **107** (46.5 mg, 36.2%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 9.02 (s, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.4, 139.8, 139.4, 139.1, 130.8, 129.3, 128.4, 126.6, 121.4, 119.0, 118.4, 117.3, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BF_3NO_4$ calcd 442.1437, found 442.1438; mp: 174−177 °C; HPLC: purity 96.6%, retention time 16.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-methylthio-1,1′-biphenyl-3-yl)propanamide (108). Compound **108** (42.8 mg, 36.4%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, acetone-d_6): δ 9.22 (s, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.40−7.32 (m, 5H), 7.29−7.26 (m, 1H), 7.22 (d, J = 7.5 Hz, 2H), 4.99 (s, 2H), 3.25 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, acetone-d_6): δ 172.9, 156.9, 147.8, 143.6, 143.0, 141.9, 141.8, 141.4, 132.9, 131.2, 131.1, 129.0, 127.2, 126.6, 125.5, 123.7, 121.0, 120.4, 119.7, 72.1, 41.2, 32.2, 16.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{23}BNO_3S$ calcd 404.1492, found 404.1497; mp: 152−154 °C; HPLC: purity 95.7%, retention time 14.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-methylthio-1,1′-biphenyl-3-yl)propanamide (109). Compound **109** (60.1 mg, 51.1%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.93 (s, 1H), 9.01 (s, 1H), 7.88 (s, 1H), 7.56−7.53 (m, 3H), 7.39−7.34 (m, 4H), 7.29 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.11 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.51 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 154.1, 145.4, 139.9, 139.8, 137.5, 136.5, 130.7, 129.2, 126.9, 126.6, 126.3, 120.9, 118.9, 117.9, 116.8, 69.7, 38.2, 29.4, 14.6 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{23}BNO_3S$ calcd 404.1492, found 404.1491; mp: 158−162 °C; HPLC: purity 95.5%, retention time 15.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-trifluoromethyl-1,1′-biphenyl-3-yl)propanamide (110). Compound **110** (52.5 mg, 42.4%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.01 (s, 1H), 7.94−7.92 (m, 2H), 7.87 (s, 1H), 7.76−7.70 (m, 2H), 7.64 (dt, J = 7.0, 2.0 Hz, 1H), 7.44−7.40 (m, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.3, 141.1, 139.9, 138.9, 130.7, 130.6, 130.0, 129.4, 126.5, 125.4, 124.0 (d, J = 3.8 Hz), 122.8 (d, J = 4.1 Hz), 121.5, 118.9, 118.7, 117.3, 69.6, 38.2, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BF_3NO_3$ calcd 426.1488, found 426.1485; mp: 149−152 °C; HPLC: purity 98.7%, retention time 16.2 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-trifluoromethyl-1,1′-biphenyl-3-yl)propanamide (111). Compound **111** (56.5 mg, 45.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 9.02 (s, 1H), 7.99 (s, 1H), 7.83 (s, 4H), 7.60 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 154.9, 146.2, 144.9, 140.7, 139.8, 131.6, 130.3, 128.1, 127.4, 126.6 (d, J = 3.6 Hz), 122.4, 119.8, 118.3, 70.5, 39.1, 30.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BF_3NO_3$ calcd 426.1488, found 426.1483; mp: 197−200 °C; HPLC: purity 98.6%, retention time 16.1 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-cyano-1,1′-biphenyl-3-yl)propanamide (112). Compound **112** (29.2 mg, 26.2%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.02 (s, 1H), 8.05 (s, 1H), 7.95−7.93 (m, 2H), 7.84 (d, J = 7.8 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.44−7.35 (m, 3H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.4, 141.3, 139.9, 138.5, 131.4, 131.1, 130.8, 130.2, 130.1, 129.5, 126.6, 121.5, 119.0, 118.9, 118.7, 117.4, 112.0, 69.7, 38.2, 29.4 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BN_2O_3$ calcd 383.1567, found 383.1563; mp: 113−116 °C; HPLC: purity 98.1%, retention time 13.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-cyano-1,1′-biphenyl-3-yl)propanamide (113). Compound **113** (51.0 mg, 60.7%) was prepared following a similar procedure to compound **68** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 9.02 (s, 1H), 8.00 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.7, 154.1, 145.3, 144.6, 139.9, 138.6, 132.7, 130.7, 129.4, 127.3, 126.5, 121.5, 119.2, 118.9, 118.6, 117.4, 110.0, 69.6, 38.1, 29.3 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BN_2O_3$ calcd 383.1567, found 383.1571; mp: 181−184 °C; HPLC: purity 97.9%, retention time 13.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-acetyl-1,1′-biphenyl-3-yl)propanamide (114). Compound **114** (71.2 mg, 30.6%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.02 (s, 1H), 8.13 (s, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.93 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.65−7.61 (m, 2H), 7.43−7.35 (m, 3H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.9, 170.7, 154.1, 145.4, 140.5, 139.9, 139.7, 137.4, 131.2, 130.8, 129.4, 127.4, 126.6, 125.9, 121.4, 119.0, 118.5, 117.3, 69.7, 38.2, 29.4, 26.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{24}H_{23}BNO_4$ calcd 422.1540, found 422.1541; mp: 122−126 °C; HPLC: purity 95.4%, retention time 13.3 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (115). Compound **115** (37.0 mg, 31.8%) was prepared following a similar procedure to compound **68** as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.01 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.98 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.0 Hz, 1H), 7.44−7.35 (m, 3H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 4.97 (s, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.61 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.4, 170.7, 154.1, 145.3, 144.4, 139.9, 139.3, 135.6, 130.7, 129.4, 128.9, 126.7, 126.6, 121.5, 118.9, 118.8, 117.4, 69.7, 38.2, 29.4, 26.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{24}H_{23}BNO_4$ calcd 400.1720, found 400.1722; mp: 167−171 °C; HPLC: purity 98.1%, retention time 13.4 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (116). Compound **116** was prepared following a similar procedure to compound **103** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.09 (s, 1H), 7.86 (s, 1H), 7.66−7.53 (m, 2H), 7.39−7.30 (m, 5H), 7.15 (d, J = 7.2 Hz, 1H), 7.10 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H), 3.81 (s, 3H), 2.96 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0, 160.2, 152.2, 142.1, 141.0, 140.1,140.0, 131.4, 131.0, 130.6, 130.5, 129.7, 122.1, 121.7, 119.4, 118.8, 117.9, 113.5, 112.6, 70.2, 55.6, 38.8, 31.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{23}BNO_4$ calcd 388.1720, found 388.1712; mp: 153−155 °C; HPLC: purity 97.1%, retention time 17.7 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-*N*-(3′,5′-dimethoxy-1,1′-biphenyl-3-yl)propanamide (117). Compound **117** was prepared following a similar procedure to compound **105** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 9.09 (s, 1H), 7.81 (s, 1H), 7.60 (s, 2H), 7.43−7.22 (m, 4H), 6.69 (s, 2H),

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6.51 (s, 1H), 4.93 (s, 2H), 3.79 (s, 6H), 2.96 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.7, 161.2, 142.7, 141.0, 139.9, 139.6, 131.6, 130.5, 129.9, 122.5, 121.8, 119.3, 118.1, 105.2, 99.6, 70.3, 55.7, 31.1 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{25}BNO_5$ calcd 418.1826, found 418.1823; mp: 58−60 °C; HPLC: purity 97.8%, retention time 17.8 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-6-yl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (118). Compound **118** was prepared following a similar procedure to compound **115** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 9.11 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.97 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.60 (s, 2H), 7.45−7.34 (m, 3H), 7.31 (d, J = 7.6 Hz, 1H), 4.93 (s, 2H), 2.97 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.60 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 198.1, 171.2, 152.2, 144.9, 140.2, 140.0, 139.9, 136.2, 131.4, 130.6, 130.0, 129.4, 127.3, 122.3, 121.7, 119.5, 118.0, 70.2, 38.8, 31.2, 27.2 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{23}BNO_4$ calcd 400.1720, found 400.1715; mp: 199−201 °C; HPLC: purity 97.0%, retention time 16.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-5-yl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (119). Compound **119** was prepared following a similar procedure to compound **103** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.05 (s, 1H), 7.85 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.41−7.27 (m, 4H), 7.23 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (t, J =2.4 Hz, 1H), 6.94 (dd, J = 8.0, 2.0 Hz, 1H), 4.94 (s, 2H), 3.81 (s, 3H), 2.97 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0, 160.2, 154.9, 144.5, 142.2, 141.1, 140.2, 130.9, 130.5, 129.8, 127.7, 122.1, 121.6, 119.4, 118.7, 117.9, 113.6, 112.6, 70.3, 55.6, 38.4, 31.5 ppm; HRMS (ESI): [M + H]$^+$ $C_{23}H_{23}BNO_4$ calcd 388.1720, found 388.1713; mp: 128−130 °C; HPLC: purity 98.9%, retention time 17.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-5-yl)-*N*-(3′,5′-dimethoxy-1,1′-biphenyl-3-yl)propanamide (120). Compound **120** was prepared following a similar procedure to compound **105** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 9.08 (s, 1H), 7.81 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.33−7.26 (m, 2H), 7.23 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 2.0 Hz, 2H), 6.50 (t, J = 2.0 Hz, 1H), 4.94 (s, 2H), 3.78 (s, 6H), 2.97 (t, J = 7.2 Hz, 2H), 2.66 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0, 161.3, 154.9, 144.5, 142.8, 141.1, 140.0, 130.9, 129.7,127.7, 122.2, 121.6, 118.9, 117.9, 105.2, 99.8, 70.3, 55.7, 38.4, 31.5 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{25}BNO_5$ calcd 418.1826, found 418.1818; mp: 59−61 °C; HPLC: purity 96.0%, retention time 17.6 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-5-yl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (121). Compound **121** was prepared following a similar procedure to compound **115** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ9.97 (s, 1H), 9.11 (s, 1H), 7.80 (s, 1H), 7.58 (t, J = 8.0 Hz, 2H), 7.38−7.28 (m, 4H), 6.69 (d, J = 2.4 Hz, 2H), 6.50 (t, J = 2.2 Hz, 1H), 5.07 (s, 2H), 3.79 (s, 6H), 2.87 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 198.0, 171.0, 154.9, 145.0, 144.5, 140.4, 139.9, 136.2, 130.9, 130.0, 129.5, 127.7, 127.3, 122.2, 121.6, 119.5, 118.0, 70.3, 38.4, 31.5, 27.3 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{23}BNO_4$ calcd 400.1720, found 400.1722; mp: 174−176 °C; HPLC: purity 97.5%, retention time 16.5 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-4-yl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (122). Compound **122** was prepared following a similar procedure to compound **103** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.11 (s, 1H), 7.84 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.42−7.25 (m, 5H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.6 Hz, 1H), 6.94 (dd, J = 8.4, 2.0 Hz, 1H), 5.07 (s, 2H), 3.81 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 170.9, 160.2, 152.8, 142.1, 141.1, 140.1, 134.8, 130.6, 130.5, 129.8, 128.8, 127.8, 122.1, 119.4, 118.4, 117.9, 113.6, 112.6, 69.6, 55.6, 36.8, 27.6 ppm; HRMS (ESI): [M + H]$^+$ $C_{23}H_{23}BNO_4$ calcd 388.1720, found 388.1714; mp: 60−62 °C; HPLC: purity 98.7%, retention time 17.7 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-4-yl)-*N*-(3′,5′-dimethoxy-1,1′-biphenyl-3-yl)propanamide (123). Compound **123** was prepared following a similar procedure to compound **105** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 9.11 (s, 1H), 7.80 (s, 1H), 7.58 (t, J = 8.0 Hz, 2H), 7.38−7.28 (m, 4H), 6.69 (d, J = 2.4 Hz, 2H), 6.50 (t, J = 2.0 Hz, 1H), 5.07 (s, 2H), 3.79 (s, 6H), 2.87 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0, 161.3, 152.8, 142.8, 141.1, 140.0, 134.8, 130.6, 129.7, 128.8, 127.8, 122.2, 118.9, 117.9, 105.2, 99.8, 69.6, 55.7, 36.8, 27.6 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{25}BNO_5$ calcd 418.1826, found 418.1819; mp: 58−60 °C; HPLC: purity 96.4%, retention time 17.8 min.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-4-yl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (124). Compound **124** was prepared following a similar procedure to compound **115** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.04 (s, 1H), 9.12 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.95 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.60−7.55 (m, 2H), 7.44−7.4 (m, 2H), 7.35−7.26 (m, 2H), 5.08 (s, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 198.8, 171.6, 152.7, 144.9, 139.9, 139.8, 136.1, 134.6, 130.8, 130.1 129.5, 128.8, 127.9, 127.3, 122.6, 119.7, 118.2, 69.6, 36.7, 27.5, 27.1 ppm; HRMS (ESI): [M + H]$^+$ $C_{24}H_{23}BNO_4$ calcd 400.1720, found 400.1714; mp: 175−177 °C; HPLC: purity 95.8%, retention time 16.7 min.

***(E)*-3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)acrylic Acid (126).** Compound **126** (338.5 mg, 74.0%) was prepared following a similar procedure to compound **65** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.38 (s, 1H), 9.30 (s, 1H), 8.05 (d, J = 16.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 16.2 Hz, 1H), 5.02 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 154.5, 142.6, 137.4, 131.2, 124.7, 122.8, 120.1, 69.7 ppm.

3-(1,3-Dihydro-1-hydroxy-2,1-benzoxaborol-7-yl)-*N*-phenylacrylamide (127). Compound **127** (26.5 mg, 32.3%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 9.26 (s, 1H), 8.09 (d, J = 15.8 Hz, 1H), 7.71−7.67 (m, 3H), 7.56 (t, J = 7.4 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 15.8 Hz, 1H), 5.03 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 154.7, 139.3, 139.1, 138.1, 131.4, 128.9, 123.6, 123.5, 123.1, 122.5, 119.4, 69.8 ppm; HRMS (ESI): [M + H]$^+$ $C_{16}H_{15}BNO_3$ calcd 280.1145, found 280.1150; mp: 200−203 °C; HPLC: purity 99.4%, retention time 11.2 min.

***N*-3-Diphenylpropanamide (129).** Compound **129** (77.0 mg, 51.3%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 7.56 (d, J = 7.76 Hz, 2H), 7.30−7.24 (m, 6H), 7.18 (t, J = 6.8 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 2.91 (t, J = 7.7 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 141.7, 139.7, 129.1, 128.8, 128.7, 126.4, 123.5, 119.5, 38.4, 31.3 ppm; HRMS (ESI): [M + H]$^+$ $C_{15}H_{16}NO$ calcd 226.1232, found 226.1230; mp: 91−94 °C; HPLC: purity 99.3%, retention time 10.9 min.

***N*-(3′-Methoxy-1,1′-biphenyl-3-yl)-3-phenylpropanamide (130).** Compound **130** (123.7 mg, 56.0%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s, 1H), 7.87 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.40−7.35 (m, 2H), 7.33−7.25 (m, 5H), 7.20−7.15 (m, 2H), 7.11 (d, J = 2.0 Hz, 1H), 6.95 (dd, J = 8.2, 2.2 Hz, 1H), 3.82 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 159.6, 141.6, 141.1, 140.5, 139.7, 130.0, 129.2, 128.3, 128.2, 125.9, 121.5, 118.9, 118.2, 117.3, 113.0, 112.1, 55.0, 37.9, 30.7 ppm; HRMS (ESI): [M + H]$^+$ $C_{22}H_{22}NO_2$ calcd 332.1651, found 332.1650; mp: 78−80 °C; HPLC: purity 99.4%, retention time 16.0 min.

***N*-(3′,5′-Dimethoxy-1,1′-biphenyl-3-yl)-3-phenylpropanamide (131).** Compound **131** (92 mg, 52.0%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s, 1H), 7.83 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.38−7.25 (m, 6H), 7.18 (t, J = 6.4 Hz, 1H), 6.71 (s, 2H), 6.52 (s, 1H), 3.80 (s, 6H), 2.93 (t, J = 7.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H)

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ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 160.8, 142.3, 141.1, 140.6, 139.6, 129.1, 128.2, 128.1, 125.9, 121.5, 118.3, 117.3, 104.7, 99.3, 55.2, 37.9, 30.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{24}NO_3$ calcd 362.1756, found 362.1743; mp: 94−96 °C; HPLC: purity 96.4%, retention time 18.0 min.

***N*-(4′-Acetyl-1,1′-biphenyl-3-yl)-3-phenylpropanamide (132).** Compound **132** (128.6 mg, 56.2%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.07 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.99 (s, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 6.8 Hz, 1H), 7.45−7.39 (m, 2H), 7.31−7.25 (m, 4H), 7.18 (t, J = 6.8 Hz, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.61 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.4, 170.6, 144.4, 141.1, 139.9, 139.4, 135.7, 129.5, 128.9, 128.3, 128.2, 126.7, 125.9, 121.7, 118.9, 117.4, 37.9, 30.7, 26.7 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{22}NO_2$ calcd 344.1651, found 344.1648; mp: 131−132 °C; HPLC: purity 99.6%, retention time 14.7 min.

(2-Bromo-3-((methoxymethoxy)methyl)phenyl)methanol (133). To a solution of compound **59** (15.0 g, 69 mmol) and DIPEA (10.5 g, 81 mmol) in dry THF (150 mL) was added MOMCl (6.2 g, 77 mmol) dropwise. After stirred at room temperature for 12 h, the reaction mixture was evaporated in vacuo. The residue was partitioned between DCM (100 mL) and H_2O (100 mL). The separated aqueous phase was then extracted with DCM (100 mL × 3). Organic phase was combined, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (DCM) to give compound **133** (5.6 g, 31.0%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49−7.48 (m, 1H), 7.43−7.39 (m, 2H), 5.47 (t, J = 5.6 Hz, 1H), 4.71 (s, 2H), 4.59 (s, 2H), 4.53 (d, J = 5.6 Hz, 2H), 3.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 141.4, 137.0, 127.6, 127.2, 127.0, 121.5, 95.6, 68.3, 62.8, 54.9 ppm.

2-Bromo-3-((methoxymethoxy)methyl)benzaldehyde (134). To a solution of compound **133** (5.5 g, 21 mmol) in DCM (100 mL) was added pyridinium chlorochromate (9.1 g, 42 mmol) and Celite (9.1 g). After stirred at room temperature for 12 h, the reaction mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 100/1) to give compound **134** (4.5 g, 82.5%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (s, 1H), 7.83 (dd, J = 7.6, 1.6 Hz, 1H), 7.54 (dd, J = 7.6, 1.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 4.79 (s, 2H), 4.73 (s, 2H), 3.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 139.0, 134.4, 133.7, 128.9, 127.6, 127.2, 96.2, 68.3, 55.6 ppm.

Ethyl (*E*)-3-(2-Bromo-3-((methoxymethoxy)methyl)phenyl)-acrylate (135). Compound **135** (4.7 g, 82.2%) was prepared following a similar procedure to compound **63** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 4.78 (s, 2H), 4.69 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.43 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 143.3, 138.7, 135.1, 130.1, 127.4, 126.8, 125.3, 121.4, 96.2, 69.1, 60.7, 55.6, 14.3 ppm.

Ethyl 3-(2-Bromo-3-((methoxymethoxy)methyl)phenyl)-propanoate (136). To a solution of compound **135** (1.5 g, 4.6 mmol) in a mixture of MeOH (15 mL) and THF (15 mL) was added $NaBH_4$ (870 mg, 23 mmol) and $NiCl_2{\cdot}6H_2O$ (1.1 g, 4.6 mmol) at 0 °C. After stirred at 0 °C for 1 h, the reaction was quenched with H_2O (100 mL) and then extracted with EtOAc (100 mL ×3). Organic phase was combined, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 20:1) to give compound **136** (0.5 g, 33%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, J = 7.6, 2.0 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.20 (dd, J = 7.6, 2.0 Hz, 1H), 4.77 (s, 2H), 4.67 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.43 (s, 3H), 3.10 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz,$CDCl_3$): δ 172.6, 140.3, 138.0, 129.5, 127.3, 127.2, 124.8, 96.1, 69.4, 60.5, 55.5, 34.1, 31.7, 14.2 ppm.

Ethyl 3-(3-((Methoxymethoxy)methyl)-2-vinylphenyl)-propanoate (137). To a solution of compound **136** (950 mg, 2.9 mmol) in DMF (20 mL) was added tributyl(vinyl)tin (1.1 g, 3.5 mmol) and $Pd(PPh_3)_4$ (170 mg, 0.15 mmol) under N_2 atomosphere. After heated to 120 °C for 12 h, the reaction mixture was cooled to room temperature and diluted with H_2O (100 mL). Then, the mixture was extracted with EtOAc (100 mL × 3). Organic phase was combined, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 20:1) to give compound **137** (0.7 g, 87.7%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.16 (dd, J = 7.6, 1.2 Hz, 1H), 6.80 (dd, J = 18.0, 11.6 Hz, 1H), 5.58 (dd, J = 11.6, 2.0 Hz, 1H), 5.34 (dd, J = 18.0, 2.0 Hz, 1H), 4.71 (s, 2H), 4.59 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.41 (s, 3H), 2.98 (t, J = 8.0 Hz, 2H), 2.54 (t, J = 8.0 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 138.5, 137.8, 135.5, 133.4, 128.4, 127.2, 127.1, 120.7, 95.9, 67.6, 60.4, 55.4, 35.1, 28.7, 14.2 ppm.

3-(3-((Methoxymethoxy)methyl)-2-vinylphenyl)propanoic Acid (138). Compound **138** (0.3 g, 71.0%) was prepared following a similar procedure to compound **65** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s, 1H), 7.29 (dd, J = 7.2, 2.0 Hz, 1H), 7.23−7.17 (m, 2H), 6.82 (dd, J = 18.0, 11.6 Hz, 1H), 5.57 (dd, J = 11.6, 2.0 Hz, 1H), 5.31 (dd, J = 18.0, 2.0 Hz, 1H), 4.64 (s, 2H), 4.50 (s, 2H), 3.29 (s, 3H), 2.84 (t, J = 8.0 Hz, 2H), 2.45 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 138.0, 137.7, 135.5, 133.4, 128.4, 127.4, 127.3, 121.0, 95.9, 67.7, 55.4, 34.8, 28.4 ppm.

3-(3-((Methoxymethoxy)methyl)-2-vinylphenyl)-*N*-phenyl-propanamide (139). Compound **139** (135 mg, 86.5%) was prepared following a similar procedure to compound **68** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.6 Hz, 1H), 7.35 (dd, J = 7.2, 2.0 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.24−7.19 (m, 2H), 7.11−7.07 (m, 2H), 6.82 (dd, J = 18.0, 11.6 Hz, 1H), 5.59 (dd, J = 11.6, 2.0 Hz, 1H), 5.36 (dd, J = 18.0, 2.0 Hz, 1H), 4.71 (s, 2H), 4.59 (s, 2H), 3.41 (s, 3H), 3.09 (t, J = 8.0 Hz, 2H), 2.58 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 138.5, 137.8, 137.7, 135.6, 133.5, 128.9, 128.6, 127.4, 127.3, 124.2, 120.9, 119.8, 95.9, 67.7, 55.4, 38.5, 29.2 ppm.

***N*-(3′-Methoxy-1,1′-biphenyl-3-yl)-3-(3-((methoxymethoxy)methyl)-2-vinylphenyl)propanamide (140).** Compound **140** (150 mg, 79.0%) was prepared following a similar procedure to compound **68** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.37−7.31 (m, 5H), 7.27 (s, 1H), 7.21 (d, J = 6.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.10 (s, 1H), 6.89 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (dd, J = 18.0, 11.6 Hz, 1H), 5.59 (dd, J = 11.6, 2.0 Hz, 1H), 5.35 (dd, J = 18.0, 2.0 Hz, 1H), 4.70 (s, 2H), 4.59 (s, 2H), 3.85 (s, 3H), 3.41 (s, 3H), 3.11 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 159.8, 142.1, 141.9, 138.5, 138.1, 137.7, 135.6, 133.5, 129.7, 129.3, 128.6, 127.4, 127.3, 123.1, 120.9, 119.6, 118.8, 118.6, 112.9, 112.8, 95.9, 67.7, 55.4, 55.3, 38.5, 29.2 ppm.

***N*-(4′-Acetyl-1,1′-biphenyl-3-yl)-3-(3-((methoxymethoxy)-methyl)-2-vinylphenyl)propanamide (141).** Compound **141** (160 mg, 70.0%) was prepared following a similar procedure to compound **68** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.37−7.33 (m, 3H), 7.20−7.15 (m, 2H), 6.80 (dd, J = 18.0, 11.6 Hz, 1H), 5.55 (d, J = 11.6 Hz, 1H), 5.32 (d, J = 18.0 Hz, 1H), 4.69 (s, 2H), 4.57 (s, 2H), 3.39 (s, 3H), 3.10 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H), 2.59 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 170.9, 145.2, 140.4, 138.6, 138.4, 137.6, 135.7, 135.5, 133.3, 129.4, 128.8, 128.4, 127.2, 127.1, 127.0, 122.8, 120.7, 119.6, 118.6, 95.8, 67.6, 55.3, 38.2, 29.1, 26.6 ppm.

3-(2-Formyl-3-((methoxymethoxy)methyl)phenyl)-*N*-phenylpropanamide (142). To a solution of compound **139** (130 mg, 0.4 mmol) in a mixture of THF (4 mL) and H_2O (1.8 mL) were added $NaIO_4$ (200 mg, 0.94 mmol) and K_2OsO_4 (5 mg, 0.015 mmol). After stirred at room temperature for 12 h, the reaction mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 3:1) to give compound **142** (90 mg, 69.0%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56 (s, 1H), 8.17 (s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6

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Hz, 1H), 7.39 (d, J = 6.8 Hz, 1H), 7.30−7.26 (m, 3H), 7.07 (t, J = 7.6 Hz, 1H), 4.90 (s, 2H), 4.70 (s, 2H), 3.39 (s, 3H), 3.30 (t, J = 8.0 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 170.5, 143.5, 141.4, 138.0, 133.4, 131.6, 131.3, 128.8, 128.1, 124.0, 119.8, 95.9, 67.0, 55.6, 39.8, 30.2 ppm.

3-(2-Formyl-3-((methoxymethoxy)methyl)phenyl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (143). Compound **143** (70 mg, 58.3%) was prepared following a similar procedure to compound **142** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56 (s, 1H), 8.37 (s, 1H), 7.75 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.44−7.37 (m, 2H), 7.31−7.25 (m, 4H), 7.13 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 2.0 Hz, 1H), 6.87 (dd, J = 7.6, 2.0 Hz, 1H), 4.88 (s, 2H), 4.69 (s, 2H), 3.82 (s, 3H), 3.37 (s, 3H), 3.31 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 170.7, 159.7, 143.5, 142.1, 141.7, 141.3, 138.4, 133.4, 131.5, 131.3, 129.6, 129.1, 128.1, 122.8, 119.5, 118.8, 118.5, 112.7, 112.6, 95.9, 67.0, 55.6, 55.1, 39.7, 30.2 ppm.

3-(2-Formyl-3-((methoxymethoxy)methyl)phenyl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (144). Compound **144** (95 mg, 67.6%) was prepared following a similar procedure to compound **142** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.16 (s, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.90 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.43−7.39 (m, 2H), 7.36−7.32 (m, 2H), 4.92 (s, 2H), 4.71 (s, 2H), 3.40 (s, 3H), 3.33 (t, J = 8.0 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 170.7, 145.3, 143.4, 141.7, 140.6, 138.7, 135.9, 133.6, 131.7, 131.6, 129.5, 128.8, 128.5, 127.3, 122.9, 119.4, 118.5, 96.0, 67.1, 55.7, 40.2, 30.7, 26.7 ppm.

3-(3-Hydroxy-1,3-dihydroisobenzofuran-4-yl)-*N*-phenylpropanamide (145). To a solution of compound **142** (90 mg, 0.28 mmol) in THF (2 mL) was added 4 M aqueous HCl (1 mL). After stirred at room temperature for 1 h, the reaction mixture was diluted in H_2O (20 mL) and extracted with EtOAc (20 mL × 3). Organic phase was combined, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 1:1) to give compound **145** (45 mg, 97.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.87 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.31−7.27 (m, 3H), 7.15 (d, J = 7.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 1.2 Hz, 1H), 5.20 (d, J = 12.8 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 3.01−2.88 (m, 2H), 2.64−2.59 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.2, 139.9, 139.1, 136.5, 135.9, 129.3, 128.6, 127.1, 122.9, 119.0, 118.8, 102.0, 71.6, 36.7, 26.8 ppm; HRMS (ESI): $[M + Na]^+$ $C_{17}H_{17}NO_3Na$ calcd 306.1106, found 306.1096; mp: 154−156 °C; HPLC: purity 97.8%, retention time 15.5 min.

3-(3-Hydroxy-1,3-dihydroisobenzofuran-4-yl)-*N*-(3′-methoxy-1,1′-biphenyl-3-yl)propanamide (146). Compound **146** (30 mg, 96.1%) was prepared following a similar procedure to compound **145** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 7.87 (t, J = 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.40−7.35 (m, 2H), 7.33−7.28 (m, 2H), 7.19−7.14 (m, 3H), 7.11 (t, J = 2.0 Hz, 1H), 6.93 (dd, J = 8.0, 2.0 Hz, 1H), 6.70 (d, J = 7.2 Hz, 1H), 6.47 (dd, J = 7.6, 2.0 Hz, 1H), 5.08 (d, J = 13.2 Hz, 1H), 4.86 (d, J = 13.2 Hz, 1H), 3.82 (s, 3H), 3.09−2.91 (m, 2H), 2.76−2.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.5, 159.6, 141.6, 140.5, 139.6, 139.5, 138.3, 136.5, 129.9, 129.2, 128.8, 127.1, 121.5, 118.8, 118.7, 118.2, 117.3, 113.0, 112.0, 99.8, 70.6, 55.0, 36.9, 26.9 ppm; HRMS (ESI): $[M + Na]^+$ $C_{24}H_{23}NO_4Na$ calcd 412.1525, found 412.1512; mp: 134−136 °C; HPLC: purity 96.2%, retention time 17.5 min.

3-(3-Hydroxy-1,3-dihydroisobenzofuran-4-yl)-*N*-(4′-acetyl-1,1′-biphenyl-3-yl)propanamide (147). Compound **147** (50 mg, 65.3%) was prepared following a similar procedure to compound **145** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 8.01 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 6.8 Hz, 1H), 7.44−7.39 (m, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.19−7.14 (m, 2H), 6.72 (d, J = 7.2 Hz, 1H), 6.48 (dd, J = 7.2, 2.0 Hz, 1H), 5.08 (d, J = 12.8 Hz, 1H), 4.86 (d, J = 12.8 Hz, 1H), 3.09−2.91 (m, 2H), 2.77−2.66 (m, 2H), 2.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.4, 170.6, 144.4, 139.9, 139.6, 139.3, 138.3, 136.5, 135.6, 129.4, 128.9, 128.8, 127.2, 126.7, 121.6, 118.9, 118.7, 117.4, 99.8, 70.6, 37.0, 26.9, 26.7 ppm; HRMS (ESI): $[M + Na]^+$ $C_{25}H_{23}NO_4Na$ calcd 424.1525, found 424.1512; mp: 136−138 °C; HPLC: purity 96.5%, retention time 16.6 min.

Biology: Cell Culture. All of the human cancer cell lines (MDA-MB231, SKOV3, HCT116, and H460) and human normal cell lines (WI-38) were obtained from the American Type Culture Collection. All of the three cancer cells were cultured in Dulbecco's modified Eagle's medium (DMEM) complete growth medium (high-glucose DMEM medium, supplemented with 10% fetal bovine serum, 100 units/mL penicillin, and 100 mg/mL streptomycin). WI-38 was cultured in minimum essential medium (MEM) complete growth medium (MEM, supplemented with 10% fetal bovine serum, and 1% nonessential amino acid). The cells were cultured in an incubator with 5% CO_2 at 37 °C under a humidified atmosphere.

In Vitro Cell Viability Assessment. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were performed to evaluate the cell viability. Cells were seeded into 96-well plates for 24 h, treated with compounds at various concentrations for 72 h. Subsequently, 20 μL of MTT (5 mg/mL) was added to each well. After incubation for 4 h, MTT solution was removed and DMSO (150 μL) was added to each well. Optical density was determined at 550 nm on a plate reader (Thermo Varioskan Flash). Each compound was tested in triplicate wells for each concentration. Data were analyzed by GraphPad Prism 5.

Annexin V−FITC/PI Apoptosis Assay. SKOV3 cells were seeded into six-well plates, cultured overnight, and treated with compound **103** at indicated concentrations. After 48 h of treatment, the cells were harvested, washed with phosphate-buffered saline (PBS), and co-stained with annexin V−FITC and PI according to the kit manual. Cell apoptosis was detected with an FACS Calibur cytometer. Samples were analyzed by flow cytometry, and 10 000 events were counted each time.

Western Blot Analysis. H460 cells were seeded into six-well plates, cultured overnight, and treated with compound **103** at indicated concentrations. After 48 h of incubation, the cells were harvested and lysed by radioimmunoprecipitation assay lysis buffer. Protein concentrations were quantified by the method of bicinchoninic acid with bovine serum albumin as the standard. Equal amounts of total cellular protein extract were separated by electrophoresis on sodium dodecyl sulfate−polyacrylamide gels and transferred to nitrocellulose membranes. After blocking with 5% nonfat milk, the membrane was incubated with the desired primary antibody overnight at the following dilutions: anticleaved caspase-9 (1:200), anticleaved caspase-3 (1:200), anticleaved PARP (1:200), and anti-β-actin (1:2000). Subsequently, the membrane was incubated with appropriate fluorescent secondary antibody and scanned by Odyssey CLx infrared laser imaging system.

Colony Formation Assay. SKOV3 cells were seeded in six-well tissue culture plates with a density of 100 cells per well and maintained in regular culture media. After 24 h, the cells were treated with compounds **103** at indicated concentrations. The culture media with the compounds were changed every 72 h. At the end of 2 weeks, the wells were washed twice with PBS and 2 mL of 0.05% crystal violet staining buffer was added to each well and incubated for 30 min. The wells were then washed with PBS for 5 min three times and allowed to dry. Photographs were then taken, visible colonies were counted, and surviving fractions were calculated. Experiments were performed in triplicate, and the surviving fractions were analyzed with one-way ANOVA using GraphPad Prism 5 software package. The error bars represent standard deviation.

In Vivo Tumor Growth Assessment. Female BALB/c nude mice of age 5 weeks were purchased from Shanghai Lingchang and maintained in pathogen-free conditions. SKOV3 cells were harvested during log phase growth and resuspended in DMEM at 5 × 10^7 cells/mL. Each mouse was inoculated subcutaneously with 5 × 10^6 cells. When the volume of tumors reached approximately 50 mm^3, the mice were divided into three groups (n = 6) randomly and treated intraperitoneally with compounds **103** and **115** at doses of 2 and 10

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mg/kg or vehicle control (5% ethanol, 20% poly(ethylene glycol)400, and 75% ddH_2O) once a day for 33 days. Tumor diameter and body weight were monitored once every 3 days by digital caliper and electronic balance, respectively. Tumor volume was calculated using the formula $(a \times b^2)/2$, where a is the larger diameter and b is the smaller diameter of tumor. Eventually, the mice were sacrificed and tumors were dissected. The experiment was approved by the Animal Ethics Committee of Shanghai Jiao Tong University.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.9b00736.

HPLC traces of synthesized compounds (PDF)
Molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PK, pharmacokinetics; AUC, area under the curve; po, per oral; iv, intravenous

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