A Concise Synthesis of Mono- and Polysubstituted and Diversely N-Functionalized Isoindolinones and Isoquinolones

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Abstract: A variety of differently substituted and diversely *N*-(sulfanyl)hydroxyalkyl functionalized isoindolinones and isoquinolones have been obtained by anionic cyclization of cyclic bromobenzyl or bromophenethylcarbamates and thiocarbamates.

Key words: lactams, carbanions, ring closure, ring opening, bicyclic compounds

Over the past few years, the isoindolinone ring system has emerged as a valuable pharmacophore due to the profound physiological and chemotherapeutic properties of many of its derivatives.[1] Many isoindolinone-centered compounds have indeed been shown to display very promising antiviral,[2] antileukemic,[3] anti-inflammatory,[4] antipsychotic,[5] and antiulcer[6] properties. For example compound **1**, a bioisostere of the corresponding lactone exhibits a significant antiviral activity against Hepatitis B virus,[7] and isoindolinone **2** is a selective cytokine inhibitory drug for managements of cancers[8] (Figure 1). The thioalkyl isoindolinone **3** has been studied as a reverse transcriptase inhibitor,[9] whereas the amino derivative **4** has been shown to display high selective binding affinities to $5HT_{1a}$ receptors.[10] Isoindolinones are also the key structural feature of structurally sophisticated naturally occurring molecules like phytotoxin porritoxin **5**.

Consequently, interest in the development of new synthetic methodologies for the preparation of functionalized isoindolinone derivatives continues unabated. An important aspect of the rationale leading to the discovery of this class of lactamic compounds endowed with biological activities hinges upon the preliminary construction of the isoindolinone template equipped with suitable substituents liable to secure the ultimate installation of appropriate functionalities. This strategy allows access to an array of diversely functionalized models,[1–7] but is also inevitably plagued with the exquisite arrangement of diverse and dense functionalities within the compact molecular framework.

Herein we delineate a tactically new synthetic approach to a range of differently substituted and diversely N-functionalized isoindolinones that is based upon the exploitation of the Parham cyclization process, that is, creation of

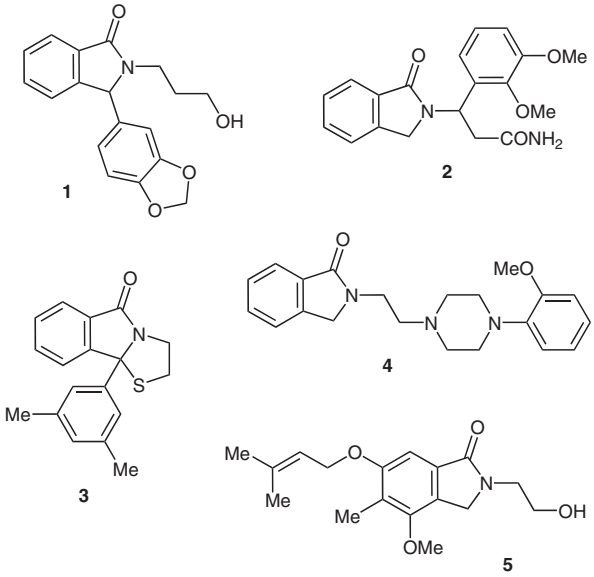
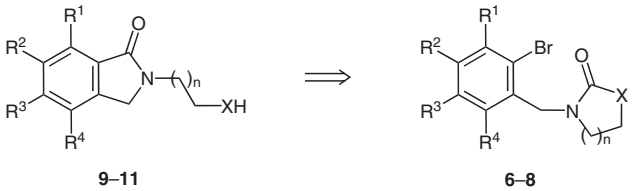


Figure 1 Some biologically active isoindolinone derivatives



Scheme 1

an aryl lithiated species and reaction with an internal electrophile.[11] The feasibility and versatility of this process has been further demonstrated by its extension to the isoquinolinones series. We initially anticipated that capture of the aryllithiated species derived from the parent compounds **6–8** (retrosynthetic Scheme 1) by an oxazolidinone (X = O, n = 1), a thiazolidinone (X = S, n = 1), or an oxazinanone (X = O, n = 2) acting as the internal electrophile would provide the potential for a direct access to diversely substituted isoindolinone ring systems with the concomitant connection of hydroxy and sulfanyl appendages, therefore providing the N-functionalized models **9–11**.

The first facet of the synthesis was then the assembling of the parent compounds **6–8** – candidates for the planned Parham cyclization process. In the first instance, the

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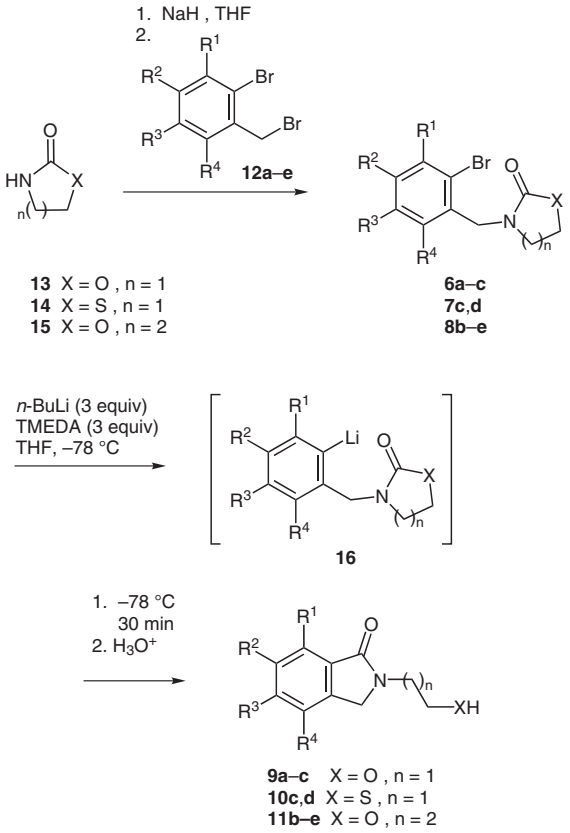

Scheme 2

oxazolidinone derivatives **6a–c** were readily obtained by coupling the corresponding *o*-bromobenzyl bromides **12a–c** with the sodium salt of oxazolidinone **13** (Scheme 2).

This simple operation allowed installation of the oxazolidinone unit and delivered the cyclic carbamate precursors **6a–c** (Table 1). To ensure the optimal formation of the mandatory lithiated species **16**, variation of the ethereal solvent (THF or Et_2O), base (*n*-BuLi or *t*-BuLi), temperature profile (–78 °, 0 °C, r.t.), course of the addition process (normal or reverse), and inclusion of anion modifiers (TMEDA, crown ether) were all screened in order to facilitate halogen/metal interconversion while sparing the oxazolidinone moiety. After considerable experimentation, we found that adding the parent compounds **6a–c** (1 equiv) in THF to *n*-BuLi (3 equiv) and TMEDA (3 equiv) in degassed THF at –78 °C for 30 minutes (reverse addition) led to complete consumption of the starting material and isolation solely of the targeted hydroxyethyl chain tethered isoindolinones **9a–c** in fairly good yields (Scheme 2, Table 1).

At this stage we set out to investigate the scope and limitations of this synthetic approach. We were then pleased to observe that the annulation/functionalization sequence could be successfully extended to the thiazolidinone series. Thus exposure of the sulfur analogue derivatives **7c**,**d**, similarly assembled by connecting **12c**,**d** to thiazolidinone **14**, to the same basic conditions led to the corresponding sulfanylethyl derivatives **10c**,**d** in quite satisfactory yields (Table 1). It was also demonstrated that ring enlargement of the heterocyclic unit embedded in the parent compound was not detrimental to the anionic cyclization process. Indeed, treatment of the oxazinanone derivatives **8b–e** under the same conditions triggered off the creation of the hydroxypropyl appendage, hence giving rise to the homologated isoindolinones **11b–e** in good yields (Table 1). The analytical and spectroscopic data of compounds **6**, **9–11** prepared are given in Table 2.

Table 1 Starting Materials and Isoindolinones **9–11**

Starting Materials								Carbamates **6–8**		Isoindolinones **9–11**	
o-Bromobenzyl bromides					Cyclic carbamates						
	R^1	R^2	R^3	R^4		X	n		Yield (%)[a]		Yield (%)[a]
12a	OMe	OMe	OMe	H	**13**	O	1	**6a**	59	**9a**	80
12b	OMe	OMe	H	H	**13**	O	1	**6b**	52	**9b**	74
12c	H	H	OMe	OMe	**13**	O	1	**6c**	59	**9c**	74
12c	H	H	OMe	OMe	**14**	S	1	**7c**	61	**10c**	71
12d	H	OMe	OMe	H	**14**	S	1	**7d**	63	**10d**	76
12b	OMe	OMe	H	H	**15**	O	2	**8b**	58	**11b**	74
12c	H	H	OMe	OMe	**15**	O	2	**8c**	68	**11c**	77
12d	H	OMe	OMe	H	**15**	O	2	**8d**	65	**11d**	79
12e	H	H	OMe	H	**15**	O	2	**8e**	49	**11e**	70

[a] Purified products.

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Table 2 Spectroscopic and Physical Data of Carbamates **6–8** and Isoindolinones **9–11** Prepared

Product[a,b]	Mp (°C) (appearance)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
6a	79–80 (white crystals)	3.53 (t, *J* = 7.9, 2 H, CH_2N), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.31 (t, *J* = 8.1, 2 H, OCH_2), 4.56 (s, 2 H, ArCH_2), 6.80 (s, 1 H_{arom})	44.5, 48.1, 56.3, 61.0, 61.1, 62.0, 109.1, 110.5, 130.7, 143.0, 150.9, 153.2, 158.6 (C=O)
6b	100–101 (white crystals)	3.48 (t, *J* = 8.1, 2 H, CH_2N), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.30 (t, *J* = 7.9, 2 H, OCH_2), 4.54 (s, 2 H, ArCH_2), 6.86 (d, *J* = 8.5, 1 H_{arom}), 7.11 (d, *J* = 8.3, 1 H_{arom})	44.3, 47.9, 56.1, 60.5, 61.9, 111.5, 119.7, 125.3, 127.9, 146.3, 153.3, 158.4 (C=O)
6c	56–57 (light yellow crystals)	3.30 (t, *J* = 8.0, 2 H, CH_2N), 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.17 (t, *J* = 8.0, 2 H, OCH_2), 4.58 (s, 2 H, ArCH_2), 6.74 (d, *J* = 8.9, 1 H_{arom}), 7.21 (d, *J* = 8.8, 1 H_{arom})	44.1, 47.6, 56.0, 56.1, 62.0, 112.9, 114.1, 115.2, 127.1, 148.9, 149.4, 158.5 (C=O)
7c	72–73 (white crystals)	3.04 (t, *J* = 7.2, 2 H, SCH_2), 3.31 (t, *J* = 7.2, 2 H, CH_2N), 3.73 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.55 (s, 2 H, ArCH_2), 6.73 (d, *J* = 8.9, 1 H_{arom}), 7.17 (d, *J* = 8.9, 1 H_{arom})	25.6, 43.2, 47.4, 56.0, 61.1, 113.6, 115.5, 128.0, 128.7, 149.2, 152.3, 171.4 (C=O)
7d	118–119 (white crystals)	3.25 (t, *J* = 7.3, 2 H, SCH_2), 3.56 (t, *J* = 7.3, 2 H, CH_2N), 3.82 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.53 (s, 2 H, ArCH_2), 6.85 (s, 1 H_{arom}), 6.96 (s, 1 H_{arom})	25.7, 47.9, 48.1, 56.1, 56.2, 112.8, 114.0, 115.1, 127.2, 148.8, 149.2, 172.4 (C=O)
8b	153–154 (white crystals)	2.03 (quint, *J* = 5.8, 2 H, CH_2), 3.25 (t, *J* = 6.2, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.28 (t, *J* = 5.3, 2 H, CH_2O), 4.64 (s, 2 H, ArCH_2), 6.86 (d, *J* = 8.6, 1 H_{arom}), 7.06 (d, *J* = 8.6, 1 H_{arom})	22.3, 44.9, 52.1, 56.1, 60.5, 66.6, 111.5, 119.5, 124.3, 128.4, 146.5, 153.0, 153.9 (C=O)
8c	(colorless oil)	1.95 (quint, *J* = 5.9, 2 H, CH_2), 3.02 (t, *J* = 6.1, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.19 (t, *J* = 5.3, 2 H, CH_2O), 4.84 (s, 2 H, ArCH_2), 6.80 (d, *J* = 8.9, 1 H_{arom}), 7.29 (d, *J* = 8.6, 1 H_{arom})	22.0, 43.0, 46.4, 55.9, 61.0, 66.2, 113.3, 115.6, 128.0, 128.8, 149.4, 152.3, 153.5 (C=O)
8d	90–91 (white crystals)	1.95 (quint, *J* = 5.8, 2 H, CH_2), 3.21 (t, *J* = 6.2, 2 H, NCH_2), 3.79, (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.21 (t, *J* = 5.3, 2 H, CH_2O), 4.60 (s, 2 H, ArCH_2), 6.92 (s, 1 H_{arom}), 6.94 (s, 1 H_{arom})	22.2, 44.5, 51.5, 56.0, 56.1, 66.5, 112.5, 114.0, 115.1, 128.0, 148.9, 149.1, 154.0 (C=O)
8e	65–66 (white crystals)	1.93 (quint, *J* = 5.8, 2 H, CH_2), 3.15 (t, *J* = 6.2, 2 H, NCH_2), 3.64, (s, 3 H, OCH_3), 4.17 (t, *J* = 5.3, 2 H, CH_2O), 4.49 (s, 2 H, ArCH_2), 6.59 (dd, *J* = 3.0, 8.7, 1 H_{arom}), 6.73 (d, *J* = 3.0, 1 H_{arom}), 7.30 (d, *J* = 8.7, 1 H_{arom})	22.2, 45.0, 52.3, 55.4, 66.7, 113.6, 114.4, 114.5, 133.4, 136.5, 153.8, 159.3 (C=O)
9a	147–148 (light grey crystals)	3.31 (br s, 1 H, OH), 3.61 (t, *J* = 4.6, 2 H, NCH_2), 3.79 (s, 3 H, OCH_3), 3.80–3.81 (m, 2 H, CH_2O), 3.83 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.31 (s, ArCH_2), 6.58 (s, 1 H_{arom})	46.1, 51.3, 56.3, 61.5, 61.7, 62.6, 101.1, 117.2, 139.1, 141.5, 151.2, 157.1, 168.2 (C=O)
9b	75–76 (orange crystals)	3.60 (t, *J* = 4.7, 2 H, NCH_2), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.92 (t, *J* = 5.3, 2 H, CH_2O), 4.30 (s, 2 H, ArCH_2), 6.91–6.95 (m, 2 H_{arom})	46.1, 50.7, 56.7, 61.4, 62.4, 116.4, 117.8, 124.8, 134.8, 146.9, 152.1, 167.9 (C=O)
9c	150–151 (light yellow crystals)	1.67 (br s, 1 H, OH), 3.68 (t, *J* = 4.9, 2 H, NCH_2), 3.83–3.84 (m, 2 H, CH_2O), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.36 (s, 2 H, ArCH_2), 6.96 (d, *J* = 8.4, 1 H_{arom}), 7.47 (d, *J* = 7.9, 1 H_{arom})	46.0, 49.4, 60.3, 61.3, 63.8, 112.7, 119.6, 125.9, 133.4, 143.6, 154.9, 169.5 (C=O)
10c	98–99 (light yellow crystals)	1.39 (t, *J* = 8.3, 1 H, SH), 2.72–2.81 (m, 2 H, CH_2S), 3.70 (t, *J* = 6.9, 2 H, NCH_2), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.42 (s, 2 H, ArCH_2), 6.95 (d, *J* = 8.3, 1 H_{arom}), 7.48 (d, *J* = 8.2, 1 H_{arom})	23.2, 45.7, 48.4, 56.2, 60.3, 112.7, 119.4, 125.9, 133.1, 143.4, 154.7, 168.3 (C=O)
10d	118–119 (light yellow crystals)	1.45 (t, *J* = 8.3, 1 H, SH), 2.83 (q, *J* = 7.4, 2 H, CH_2S), 3.78 (t, *J* = 6.9, 2 H, NCH_2), 3.94 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.41 (s, 2 H, ArCH_2), 6.92 (s, 1 H_{arom}), 7.31 (s, 1 H_{arom})	23.5, 45.8, 50.4, 56.2 (2 × CH_3), 105.0, 105.3, 124.8, 133.7, 149.7, 152.6, 169.0 (C=O)
11b	light brown oil	1.75 (quint, *J* = 6.1, 2 H, CH_2), 3.51 (t, *J* = 5.7, 2 H, NCH_2), 3.64 (t, *J* = 6.3, 2 H, CH_2O), 3.82 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.25 (s, 2 H, ArCH_2), 7.03–7.04 (m, 2 H_{arom})	30.7, 38.8, 49.4, 56.7, 58.3, 62.4, 116.5, 117.9, 124.5, 134.4, 146.9, 152.3, 167.9 (C=O)

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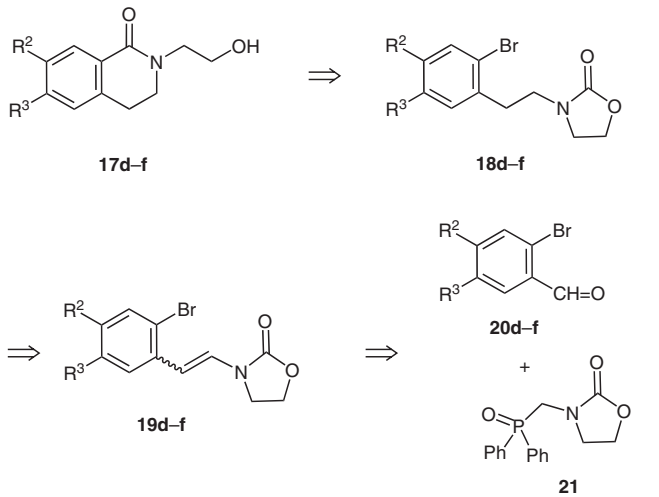
Table 2 Spectroscopic and Physical Data of Carbamates **6–8** and Isoindolinones **9–11** Prepared (continued)

Product[a,b]	Mp (°C) (appearance)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
11c	87–88 (fawn crystals)	1.79 (quint, *J* = 6.0, 2 H, CH_2), 3.53 (t, *J* = 5.8, 2 H, NCH_2), 3.68 (t, *J* = 6.3, 2 H, CH_2O), 3.89 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.37 (s, 2 H, ArCH_2), 6.98 (d, *J* = 8.2, 1 H_{arom}), 7.46 (d, *J* = 8.3, 1 H_{arom})	30.7, 38.9, 48.2, 56.2, 58.4, 60.3, 112.7, 119.4, 125.6, 133.0, 143.4, 154.7, 169.4 (C=O)
11d	121–122 (fawn crystals)	1.66 (br s, 1 H, OH), 1.74 (quint, *J* = 5.8, 2 H, CH_2), 3.48–3.50 (m, 2 H, NCH_2), 3.69 (t, *J* = 6.1, 2 H, CH_2O), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.26 (s, 2 H, ArCH_2), 6.86 (s, 1 H_{arom}), 7.24 (s, 1 H_{arom})	31.0, 38.9, 49.9, 56.0, 56.1, 58.5, 104.9, 105.0, 124.3, 134.8, 149.4, 152.4, 169.5 (C=O)
11e	70–71 (fawn crystals)	1.74 (quint, *J* = 6.0, 2 H, CH_2), 3.49 (t, *J* = 5.7, 2 H, NCH_2), 3.64 (t, *J* = 6.2, 2 H, CH_2O), 3.78 (s, 3 H, OCH_3), 3.99 (br s, 1 H, OH), 4.27 (s, 2 H, ArCH_2), 6.86–6.91 (m, 2 H_{arom}), 7.63 (d, *J* = 8.3, 1 H_{arom})	30.8, 38.8, 50.2, 55.7, 58.4, 107.7, 114.7, 124.8, 124.9, 143.5, 162.7, 169.6 (C=O)

[a] Satisfactory microanalyses obtained: C ± 0.31, H ± 0.25, N ± 0.26.
[b] IR (KBr or neat): **6a–c**, 1747–1760 cm^{-1} (C=O); **7c,d**, 1661–1668 cm^{-1} (C=O); **8b–e**, 1679–1687 cm^{-1} (C=O); **9–11**, 1648–1673 cm^{-1} (C=O); **10c,d**, 2506–2510 cm^{-1} (SH).

Encouraged by these results, we then set out to achieve a synthetic strategy prone to give access to the upper term of the series, that is, isoquinolones **17d–f**. On reliance with the conceptually related synthetic strategy portrayed in retrosynthetic Scheme 3, the development of a synthetic route to the parent compounds **18d–f** was required.

We conjectured that these compounds could be conceivably obtained by hydrogenation of the bromoarylenecarbamates **19d–f** and we envisaged building up these arylmethyleneoxazolidinones under the agency of the Horner process between the suitably substituted bromobenzaldehydes **20d–f** and the *N*-diphenylphosphinoylmethyloxazolidin-2-one (**21**). This phosphorylated cyclic carbamate was initially obtained by the two-step sequence depicted in Scheme 4. Chloromethylation of oxazolidinone **13** by treatment with paraformaldehyde and Me_3SiCl delivered the transient highly reactive chloromethylated compound **22**, which was subsequently intercepted with ethyl diphenylphosphinite to afford the desired phosphinoylmethylcarbamate **21** in an excellent yield. Horner reaction between metalated **21** and *o*-bromobenzaldehydes **20d–f** proceeded uneventfully to afford almost quantitatively the arylmethyleneoxazolidinones **19d–f** (Table 3). Stereochemical considerations about the central double bond were not crucial for the subsequent reduction reaction. This operation was readily and efficiently achieved by treatment of **19d–f** with Et_3SiH/TFA to provide excellent yields of the bromophenethyloxazolidinones **18d–f**. To our delight exposure of compounds **18d–f** to lithiated bases led to the isolation of the targeted hydroxyethylisoquinolones **17d–f** (Table 3). However, it is worth noting that the yield for this anionic cyclization/N-functionalization sequence was significantly improved by making use of *t*-BuLi (1.1 equiv) at –100 °C upon normal addition, that is, addition of the metalating agent onto the solution of the parent compound and TMEDA in THF (e.g., for **17f**: yield 53% versus 32% under conditions defined in Scheme 2). The analytical and spectroscopical data of compounds **17–19** prepared are listed in Table 4.



Scheme 3

Table 3 Starting Materials and Isoquinolones **17**

R^2	R^3	**19**	*E*/*Z*	Yield (%)	**18**	Yield (%)[a]	**17**	Yield (%)[a]
OMe	OMe	**19d**	65:35	74	**18d**	86	**17d**	53
H	OMe	**19e**	60:40	69	**18e**	81	**17e**	51
H	H	**19f**	65:35	73	**18f**	89	**17f**	49

[a] Purified products.

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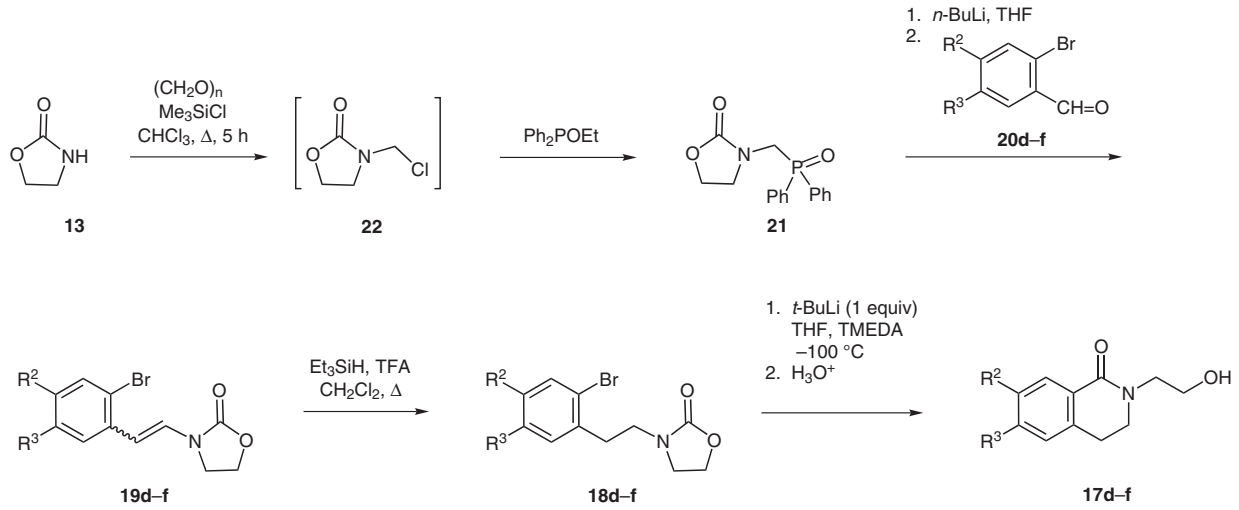

13 22 21 19d–f 18d–f 17d–f

Scheme 4

Table 4 Spectroscopic and Physical Data of Carbamates **19** and **18** and Isoquinolones **17** Prepared

Product[a,b]	Mp (°C) (Appearance)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
(*E*)-**19d**	167–168 (yellow crystals)	3.88 (s, 3 H, OCH_3), 3.89–3.95 (m, 5 H, NCH_2 + OCH_3), 4.55 (t, *J* = 8.1, 2 H, OCH_2), 6.03 (d, *J* = 14.6, 1 H, ArC*H*=), 6.96 (s, 1 H_{arom}), 7.01 (s, 1 H_{arom}), 7.25 (d, *J* = 14.6, 1 H, =CHN)	42.6, 56.2 (2 × CH_3), 62.4, 107.8, 110.1, 113.4, 115.4, 124.4, 127.7, 148.6, 148.8, 155.5 (C=O)
(*Z*)-**19d**	(yellow oil)	3.35 (t, *J* = 8.0, 2 H, NCH_2), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.27 (t, *J* = 8.0, 2 H, OCH_2), 5.79 (d, *J* = 9.7, 1 H, ArC*H*=), 6.71–6.74 (m, 2 H_{arom}), 7.03 (d, *J* = 9.6, 1 H, =CHN)	44.4, 56.1 (2 × CH_3), 62.7, 110.7, 113.7, 114.6, 114.7, 124.8, 127.9, 147.6, 148.4, 158.6 (C=O)
(*E*)-**19e**	130–131 (yellow crystals)	3.70 (s, 3 H, OCH_3), 3.78 (t, *J* = 8.1, 2 H, NCH_2), 4.41 (t, *J* = 8.0, 2 H, OCH_2), 5.93 (d, *J* = 14.6, 1 H, ArC*H*=), 6.55 (dd, *J* = 2.9, 8.9, 1 H_{arom}), 6.90 (d, *J* = 2.8, 1 H_{arom}), 7.24–7.32 (m, 2 H, 1 H_{arom} + =CHN)	42.5, 55.6, 62.5, 110.0, 110.4, 113.8, 114.7, 125.9, 133.5, 136.3, 155.4, 159.1 (C=O)
(*Z*)-**19e**	89–90 (white crystals)	3.26 (t, *J* = 8.0, 2 H, NCH_2), 3.72 (s, 3 H, OCH_3), 4.19 (t, *J* = 8.0, 2 H, OCH_2), 5.72 (d, *J* = 9.8, 1 H, ArC*H*=), 6.62–6.69 (m, 3 H_{arom}), 7.36 (d, *J* = 8.7, 1 H, =CHN)	44.5, 55.6, 62.7, 110.5, 114.6, 115.0, 117.1, 125.1, 132.8, 137.1, 156.8, 158.2 (C=O)
(*E*)-**19f**	(fawn oil)	3.91 (t, *J* = 8.1, 2 H, NCH_2), 4.53 (t, *J* = 8.1, 2 H, CH_2O), 6.09 (d, *J* = 14.6, 1 H, ArC*H*=), 7.06–7.13 (m, 1 H_{arom}), 7.22–7.36 (m, 2 H, 1 H_{arom} + =CHN), 7.49–7.59 (m, 2 H_{arom})	42.5, 62.5, 109.9, 125.9, 127.6, 128.0, 128.7, 133.0, 135.7, 140.0, 156.9 (C=O)
(*Z*)-**19f**	96–97 (white crystals)	3.29 (t, *J* = 8.0, 2 H, NCH_2), 4.26 (t, *J* = 8.0, 2 H, OCH_2), 5.85 (d, *J* = 9.8, 1 H, ArC*H*=), 6.78 (d, *J* = 9.8, 1 H, =CHN), 7.13–7.18 (m, 1 H_{arom}), 7.22–7.33 (m, 2 H_{arom}), 7.58 (dd, *J* = 1.1, 8.0, 1 H_{arom})	44.6, 62.6, 110.7, 124.5, 125.1, 126.7, 128.9, 131.5, 132.3, 136.3, 155.9 (C=O)
18d	80–81 (fawn crystals)	2.88 (t, *J* = 7.7, 2 H, ArCH_2), 3.41–3.46 (m, 4 H, 2 × NCH_2), 3.78 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.21 (t, *J* = 8.0, 2 H, OCH_2), 6.73 (s, 1 H_{arom}), 6.93 (s, 1 H_{arom})	33.6, 43.9, 45.0, 56.1 (2 × CH_3), 61.8, 113.1, 114.0, 115.4, 129.4, 148.3, 148.5, 158.4 (CO)
18e	(fawn oil)	2.79 (t, *J* = 7.4, 2 H, ArCH_2), 3.31–3.37 (m, 4 H, 2 × NCH_2), 3.59 (s, 3 H, OCH_3), 4.08 (t, *J* = 8.0, 2 H, OCH_2), 6.50 (dd, *J* = 3.0, 8.8, 1 H_{arom}), 6.68 (d, *J* = 3.0, 1 H_{arom}), 7.23 (d, *J* = 8.8, 1 H_{arom})	34.1, 43.8, 44.8, 55.3, 61.8, 114.1, 114.5, 116.1, 133.2, 138.6, 158.2, 159.0 (C=O)
18f	(fawn oil)	2.80 (t, *J* = 7.4, 2 H, ArCH_2), 3.25–3.32 (m, 4 H, 2 × NCH_2), 4.02 (t, *J* = 7.6, 2 H, OCH_2), 6.86–6.92 (m, 1 H_{arom}), 7.04–7.07 (m, 2 H_{arom}), 7.31–7.34 (m, 1 H_{arom})	33.9, 43.8, 44.8, 61.8, 124.3 (CH), 124.3 (CBr), 128.4, 130.8, 132.7, 137.7, 158.2 (C=O)
17d	90–91 (white crystals)	2.98 (t, *J* = 6.8, 2 H, ArCH_2), 3.67 (t, *J* = 6.8, 2 H, NCH_2), 3.76 (t, *J* = 4.6, 2 H, NCH_2), 3.91 (t, *J* = 4.0, 2 H, OCH_2), 3.95 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 6.67 (s, 1 H_{arom}), 7.59 (s, 1 H_{arom})	27.7, 48.0, 51.3, 56.1 (2 × CH_3), 61.7, 109.2, 110.3, 121.6, 131.9, 147.9, 151.9, 166.1 (C=O)

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Table 4 Spectroscopic and Physical Data of Carbamates **19** and **18** and Isoquinolones **17** Prepared (continued)

Product[a,b]	Mp (°C) (Appearance)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
17e	108–109 (white crystals)	2.93 (t, *J* = 6.6, 2 H, ArCH_2), 3.61 (t, *J* = 6.6, 2 H, NCH_2), 3.67 (t, *J* = 5.3, 2 H, NCH_2), 3.81–3.84 (m, 5 H, OCH_3 + OCH_2), 3.96 (br s, 1 H, OH), 6.63 (s, 1 H_{arom}), 6.79 (dd, *J* = 2.4, 8.6, 1 H_{arom}), 7.94 (d, *J* = 8.6, 1 H_{arom})	28.4, 47.8, 51.1, 55.4, 61.5, 111.9, 112.5, 121.9, 130.2, 140.4, 162.3, 166.0 (C=O)
17f	43–44 (Lit.[19] 44.5–45) (white crystals)	2.93 (t, *J* = 6.7, 2 H, ArCH_2), 3.60 (t, *J* = 6.6, 2 H, NCH_2), 3.65 (t, *J* = 5.4, 2 H, NCH_2), 3.80 (t, *J* = 5.4, 2 H, OCH_2), 4.11 (br s, 1 H, OH), 7.11 (d, *J* = 7.4, 1 H_{arom}), 7.26 (td, *J* = 1.0, 7.5, 1 H_{arom}), 7.36 (td, *J* = 1.5, 7.4, 1 H_{arom}), 7.96 (dd, *J* = 1.5, 7.5, 1 H_{arom})	28.0, 47.7, 50.9, 61.1, 126.9, 128.0, 128.6, 129.1, 131.8, 138.3, 165.6 (C=O)

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.30, N ± 0.25.
[b] IR (KBr or neat): **18d–f**, 1719–1736 cm^{-1} (C=O); **17d–f**, 1624–1638 cm^{-1} (C=O).

In summary, a concise and flexible approach to N-functionalized isoindolinones and isoquinolinones was developed via the anionic cyclization of bromobenzyl and bromophenethylcarbamates derivatives. The method is versatile in scope because various hydroxy and sulfanylalkyl chains can be introduced easily on the compact heterocyclic framework. The tethered functionalities may serve as a handle for further synthetic planning and we believe that this methodology opens a way to a wide range of biologically important derivatives of these classes of compounds.

Melting point determinations were carried out on a Reichert-Thermopan apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, on a Bruker AM 300 spectrometer as solutions in $CDCl_3$ with TMS as internal standard; ^{31}P NMR spectra at 121 MHz with H_3PO_4 as external standard. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. For flash chromatography, silica gel 60 M (230–400 mesh ASTM) was used. All solvents were dried and distilled according to standard procedures. Dry glassware for moisture-sensitive reactions was obtained by oven drying and assembly under argon. An inert atmosphere was obtained with a stream of argon and glassware equipped with rubber septa; reagent transfer was performed by syringe.

The *o*-bromobenzyl bromides **12a**,[12] **12b**,[13] **12c**,[14] **12d**,[15] **12e**,[16] were prepared according to reported procedures. The thiazolidin-2-one (**14**)[17] and the [1,3]oxazinan-2-one (**15**)[18] were synthesized according to the literature procedures.

3-[(Diphenylphosphinoyl)methyl]oxazolidin-2-one (21)

A solution of oxazolidin-2-one **13** (3.24 g, 37.2 mmol), paraformaldehyde (1.12 g, 37.2 mmol) and chlorotrimethylsilane (14.2 mL, 112 mmol) in $CHCl_3$ (180 mL) was refluxed for 5 h. After cooling, the solvent and excess reagent were evaporated under vacuum (0.02 Torr) and the crude oily 3-(chloromethyl)oxazolidin-2-one (**22**) was used in the next step without further purification. Neat compound **22** (3.53 g, 26.0 mmol) was treated with ethyl diphenylphosphinite (6.09 g, 26.0 mmol). A vigorous agitation was maintained until formation of a solid residue, which was triturated with Et_2O, filtered, and recrystallized from hexane–toluene to afford **21** as white crystals (5.37 g, 68%); mp 173–174 °C.

IR (KBr): 1740 (C=O), 1185 cm^{-1} (P=O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 2 H, NCH_2P), 4.08–4.14 (m, 4 H, 2 × CH_2), 7.36–7.41 (m, 6 H_{arom}), 7.72–7.75 (4 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.6 (d, $J_{C,P}$ = 80.2 Hz, CH_2P), 45.8 (d, $J_{C,P}$ = 2.7 Hz, CH_2N), 62.2 (d, $J_{C,P}$ = 2.7 Hz, OCH_2), 128.7 (d, $J_{C,P}$ = 11.5 Hz, 2 × CH), 128.8 (d, $J_{C,P}$ = 12.0 Hz, 2 × CH), 130.8 (d, $J_{C,P}$ = 9.8 Hz, 2 × CH), 130.9 (d, $J_{C,P}$ = 9.8 Hz, 2 × CH), 131.1 (d, $J_{C,P}$ = 98.0 Hz, 2 × C), 132.4 (d, $J_{C,P}$ = 2.7 Hz, CH), 132.5 (d, $J_{C,P}$ = 2.9 Hz, CH), 158.3 (d, $J_{C,P}$ = 4.4 Hz, C=O).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 29.5.

Anal. Calcd for $C_{16}H_{16}NO_3P$: C, 63.79; H, 5.35; N, 4.65. Found: C, 63.53; H, 5.46; N, 4.82.

N-Substituted Oxazolidin-2-ones 6a–c, Thiazolidin-2-ones 7c,d, and [1,3]Oxazinan-2-ones 8b–e; General Procedure

A solution of the heterocyclic compound **13**–**15** (4.0 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (prepared by washing 1.1 equiv of a 60% suspension in mineral oil with pentane, 0.176 g, 4.4 mmol) in THF (20 mL) under argon, and the mixture was further stirred at r.t. for 1 h. A solution of the *o*-bromobenzyl bromide **12a**–**e** (4.0 mmol) in THF (10 mL) was added dropwise and the mixture was refluxed overnight. After cooling, H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica gel [**6a–c**: EtOAc–hexanes–CH_2Cl_2 (30:30:40); **7d**: EtOAc–hexanes–CH_2Cl_2 (40:30:30); **7c**: acetone–hexanes–CH_2Cl_2 (10:10:80); **8b**: acetone–hexanes (50:50); **8d**: acetone–hexanes (60:40); **8e**: acetone–hexanes (70:30); **8c**: acetone–CH_2Cl_2 (40:60)] (Tables 1 and 2).

Isoindolinones 9a–c, 10c,d, and 11b–e; General Procedure

A solution of *n*-BuLi (2 M in hexane, 1.50 mL, 3.0 mmol) and TMEDA (350 mg, 3.0 mmol) in anhyd THF (4 mL) was carefully degassed by 3 freeze-thaw cycles and stirred at –78 °C under dry deoxygenated argon. A solution of compound **6**, **7**, or **8** (1.0 mmol) in degassed THF (16 mL) was then added dropwise through a cannula. The mixture was stirred at –78 °C for 30 min. After quenching with aq sat. NH_4Cl (5 mL) and dilution with H_2O (30 mL), THF was removed under vacuum in a rotary evaporator and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under vacuum to leave the isoindolinone as a solid residue, which was purified by flash column chromatography on silica gel [**9a–c**, **11d**: acetone–hexanes (80:20); **10c**,**d**, **11b**: acetone–hexanes (60:40); **11c**,**e**: acetone–hexanes (70:30)] (Tables 1 and 2).

o-Bromoarylmethyleneoxazolidinones 19d–f; General Procedure

A solution of *n*-BuLi (1.6 M in hexane, 3.45 mL, 5.5 mmol) was added dropwise to a solution of the phosphorylated derivative **21** (1.51 g, 5.0 mmol) in anhyd THF (100 mL). The mixture was stirred

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at –78 °C under argon for 1 h, then a solution of *o*-halogenobenzaldehyde **20d–f** (5.5 mmol) in anhyd THF (20 mL) was added dropwise. The mixture was allowed to warm to r.t. over 2 h and then refluxed overnight. After cooling, quenching with aq sat. NH_4Cl (5 mL) and dilution with H_2O (30 mL), THF was removed under vacuum in a rotary evaporator. The aqueous residue was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum to afford compound **19d–f** as a mixture of *E*- and *Z*-isomers. Flash column chromatography on silica gel allowed the separation of the isomers [**19d**: Et_2O–hexanes–CH_2Cl_2 (30:20:50); **19e**: Et_2O–hexanes–CH_2Cl_2 (20:40:40); **19f**: EtOAc–hexanes (50:50)], but the subsequent reduction reaction was performed on the mixture of stereoisomers (Tables 3 and 4).

***o*-Bromophenethyloxazolidinones 18d–f; General Procedure**

Triethylsilane (0.7 g, 0.96 mL, 6.0 mmol) and trifluoroacetic acid (0.15 mL, 2.0 mmol) were sequentially added dropwise to a stirred solution of **19d–f** (2.0 mmol, mixture of *E*- and *Z*-isomers) in CH_2Cl_2 (5 mL) and the mixture was refluxed overnight. After cooling, aq sat. $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under vacuum to leave a brown oily residue, which was purified by flash column chromatography on silica gel [**18d**: EtOAc–hexanes (70:30); **18e**,**f**: EtOAc–hexanes–MeOH (60:35:5)] (Tables 3 and 4).

Hydroxyethylisoquinolones 17d–f; General Procedure

A solution of *o*-bromophenethyloxazolidinone **18d–f** (1.0 mmol) and TMEDA (128 mg, 1.1 mmol) in anhyd THF (20 mL) was carefully degassed by three freeze-thaw cycles and stirred at –78 °C under dry deoxygenated argon. The mixture was cooled to –100 °C and *t*-BuLi (2 M in pentane, 0.55 mL, 1.1 mmol) was added dropwise. The mixture was stirred for 30 min at this temperature, and then quenched with aq sat. NH_4Cl (5 mL). Dilution with H_2O (30 mL) and evaporation of THF under vacuum in a rotary evaporator left an aqueous residue, which was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum to afford the isoquinolone **17d–f** as a solid residue which was purified by flash column chromatography on silica gel (acetone–CH_2Cl_2–MeOH, 25:70:5) (Tables 3 and 4).

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