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Dibrominative Spirocyclization of 2-Butynolyl Anilides: Synthesis of *gem*-Dibromospirocyclic Benzo[*d*][1,3]oxazines and Their Application in the Synthesis of 4*H*-Furo[3,2-*b*]indoles

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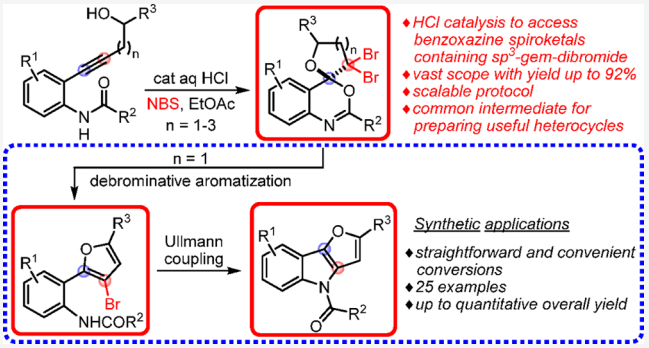
ABSTRACT: The combination of catalytic aqueous hydrochloric acid (HCl) and *N*-bromosuccinimide (NBS) generated electrophilic bromine monochloride (BrCl), which readily induced spiroannulation of 2-alkynolyl anilides (n = 1−3) to form *gem*-dibromospirocyclic benzo[*d*][1,3]oxazines in up to 92% yield. The reaction occurred under mild and metal-free conditions using EtOAc as a green solvent. The resulted spirocyclic products contained benzo[*d*][1,3]oxazine, which was useful both as a pharmacophore and synthetic precursor. In addition, the current protocol allowed to effortlessly introduce the sp^3-*gem*-dibromide carbon adjacent to the sterically demanding spiroketal center. These spiroheterocycles (n = 1) were shown to be synthetically versatile and conveniently maneuvered. Base-promoted debrominative aromatization of these spirocycles unmasked rare and synthetically useful 2-aryl-3-bromofurans in mostly excellent yields. These 3-bromofurans were well-suited substrates for intramolecular Ullmann C−N bond coupling to construct difficult-to-prepare 4*H*-furo[3,2-*b*]indoles. Additionally, the current protocol was flexible and adaptable to preparing the *gem*-dichloride variants.



INTRODUCTION

Alkyne serves as an excellent functional group for various notable transformations.[1] Its excellent ability to be activated by Brønsted and Lewis acids led to various useful annulation reactions for constructing functionalized cyclic structures.[2] Our own work demonstrated that halogen and interhalogen species generated *in situ*[3a] could be utilized in a number of electrophilic halogen-induced annulation processes leading to a variety of carbocyclic and heterocyclic scaffolds.[3b−d] In these works, TMSCl was employed, which, upon hydrolysis, led to the generation of HCl in the reaction that served as a crucial source of the chloride ion to react with *N*-halosuccinimide (NXS) under acidic conditions to form interhalogen species (X−Cl). It was shown that Cl_2, BrCl, and ICl could be prepared as a solution from the reaction of TMSCl and the corresponding NXS. Among numerous cyclic skeletons, both of natural and synthetic origins, spirocyclic structures represent a class of fascinating molecules with intricate architectures. The spiro centers in these molecules add three-dimensionality, spatial complexity, and spatial diversity that frequently exerted increased medicinal values.[4] These special properties of spirocyclic systems garnered much interest in the development of preparative methods.[5] Additionally, halogenated compounds are well-documented for their bioactivities, as observed in many natural products.[6] In medicinal chemistry, the presence of halogen can often improve bioactivities and other desired drug-like properties of these compounds.[7] The sp^3-carbon-centered geminal dihalides, or *gem*-dihalides, comprise a subclass of halogenated functional groups holding special status as useful synthons, especially of carbenes,[8a−c] and as precursors for cross-coupling reactions,[8d] thus making the development of methods for their preparation remain a topic of interest among synthetic chemists. However, most published methods for preparing sp^3-*gem*-dihalides involved carbonyl compounds as precursors undergoing complicated and lengthy reactions,[9] whereas alkynes were much less utilized due to several challenging issues, including the regioselectivity of hydrohalogenation and the competing elimination of HX to form vinyl halides as side products.

Building on our previous work, the *in situ* generation of the electrophilic halogen and its synthetic utilities in other reactions continued to be a main theme of our research.

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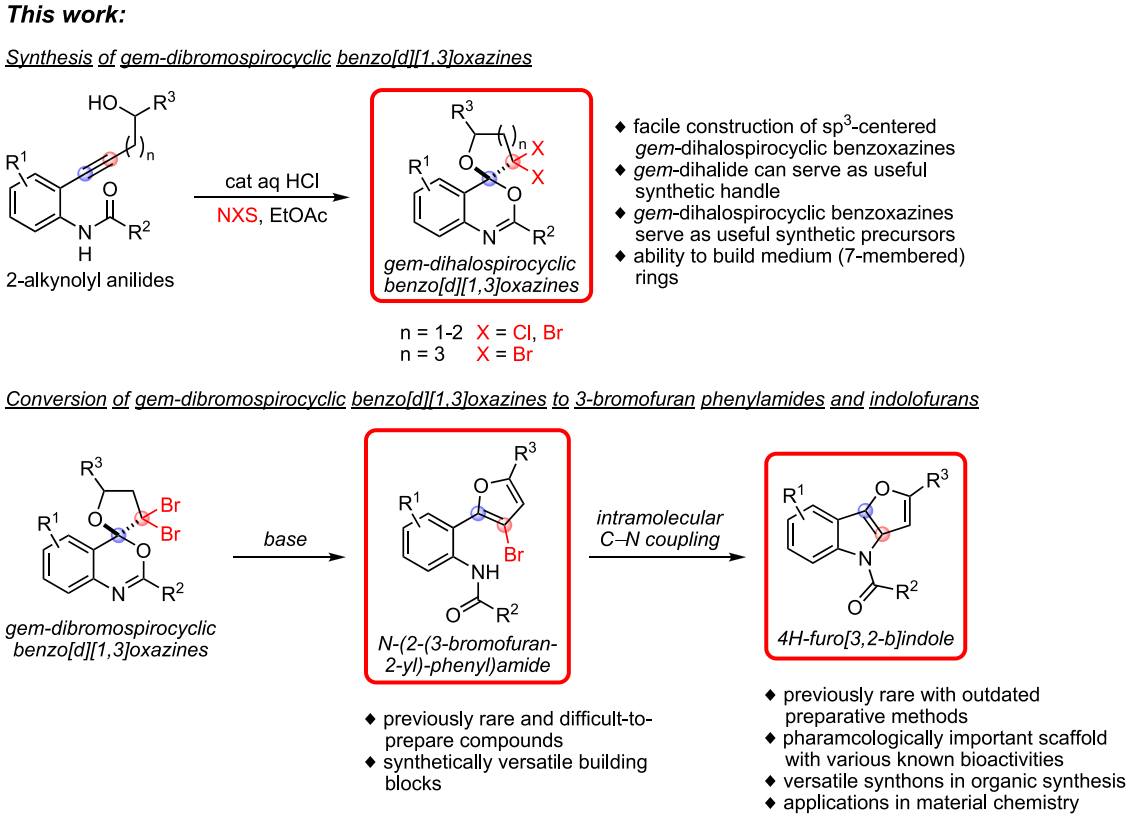
Scheme 1. Features of the Current Work



Relating to the important facets of spirocycles and *gem*-dihalides discussed thus far, novel uses of these electrophilic halogens were intended for *gem*-dihalogenative spiroannulation (Scheme 1). The electrophilic XCl could induce the spiroannulation of the 2-alkynolyl anilide to form *gem*-dihalospirocyclic benzo[*d*][1,3]oxazines (n = 1−3). In addition to the assembly of the pharmacologically useful benzoxazine nucleus,[10] the embedded sp^3-centered *gem*-dihalide moiety in these compounds was anticipated to serve as a useful synthetic handle for the synthesis of other heterocyclic systems (Scheme 1). A transformation of, especially, *gem*-dibromospirocyclic benzo[*d*][1,3]oxazines (n = 1) could unveil *N*-(2-(3-bromofuran-2-yl)-phenyl)amides which in turn was a suitable substrate for conversion to 4*H*-furo[3,2-*b*]indoles. In fact, this type of indolofuran nucleus is present in several bioactive compounds with bioactivities including analgesic, anti-inflammatory, and anticancer properties.[11] There are few existing preparative methods of this indolofuran and related core structures, and they involved lengthy procedures, needs for harsh conditions, expensive or difficult-to-access chemicals, and special equipment.[11a,b,12] At the same time, these indolofuran core structures have been shown to be synthetically useful for several notable transformations, particularly for preparing various indole-containing heterocycles.[13]

As shown in Scheme 2, we hypothesized that, when 2-butynolyl anilide **1** was treated with NBS and HCl, which generated BrCl,[3a] both Pathways **I** and **II** were possible. In Pathway **I**, a favorable 5-*endo*-trig cyclization of the hydroxyl group onto bromonium ion **A** led to bromodihydrofuran intermediate **B**. This intermediate could undergo another electrophilic bromination with another molecule of BrCl to form oxocarbenium ion intermediate **C**, which could then be intercepted intramolecularly by the nucleophilic oxygen of the anilide to form *gem*-dibromospirocyclic benzo[*d*][1,3]oxazine **2Br**. Pathway **II**, however, could not be discounted. The nucleophilic oxygen of the anilide could potentially add to bromonium ion **D** in a favorable 6-*exo*-trig fashion to generate benzoxazine intermediate **E**. Electron delocalization from the benzoxazine oxygen to abstract another bromine atom resulted in oxonium intermediate **F**, which could be intercepted by the remaining hydroxyl group in a favorable 5-*exo*-trig cyclization to give the spirocyclic benzoxazines (**2Br**) as the product.

Spirocycles **2Br** could serve as a novel and versatile precursor for sequential transformations to compounds **3Br** and **4**. The placement of *gem*-dibromide in spirocycle **2Br** was crucial for its conversion to 3-bromofuran **3Br**. This could be conceivably affected through a bromine atom abstraction by a bulky nucleophile to affect fragmentation which would lead to intermediate **G**. This intermediate then would readily undergo aerobic aromatization to result in the formation of 3-bromofuran **3Br**. Due to scarce records in literature for the synthesis of compounds **3Br**, a successful conversion from **2Br** would add value to the current work to ensure effective and reliable access to these compounds and to enable the exploration of their relatively unknown synthetic potentials. One foreseeable synthetic utility of compounds **3Br** was the conversion to indolofurans **4** via intramolecular C−N bond formation between the anilide nitrogen and the Br-bearing carbon at the 3-position of the furan ring.

Herein, we reported a successful development of a practical and efficient method for the simultaneous construction of sp^3-

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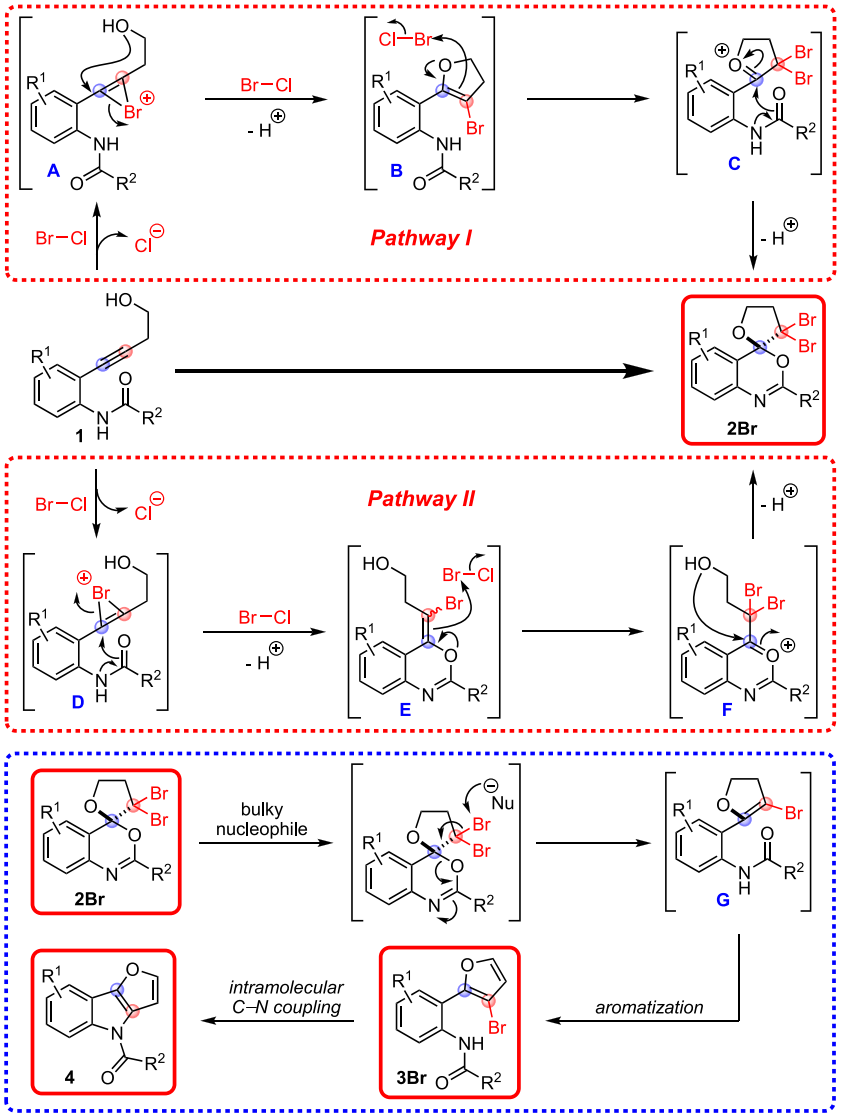
Scheme 2. Proposed Mechanisms for the Synthesis of *gem*-Dibromospirocycle 2Br and Its Sequential Transformations to 3Br and 4



gem-dibromide embedded within benzoxazine spirocycles (**2Br**). We also demonstrated that compounds **2Br** could be sequentially converted to 3-bromofurans **3Br** and indolofurans **4**. Furthermore, the developed method was shown to be applicable to preparing 6- and 7-membered spirocyclic ether systems as well as *gem*-dichloride variants.

RESULTS AND DISCUSSION

In order to realize the proposed transformations, starting material **1a** was prepared in two steps in an excellent overall yield and employed as the screening substrate in search of optimal conditions. According to the proposed mechanism in Scheme 2, 2.0 equiv of NBS was required; therefore, all reactions were optimized with this amount of NBS. As discussed above, a source of chloride and acidic proton was crucial for the generation of BrCl with NBS. With this requirement, hydrochloric acid (HCl) solution was appropriate for the reaction and was used as the Brønsted acid catalyst for the optimization. Unless noted otherwise, the stock HCl solution employed in the optimization was a 1.0 M aqueous solution prepared by diluting concentrated (~12 M) HCl with deionized water. In addition, solvents used in these studies were of AR grade unless specified. The results of these studies were summarized in Table 1.

The optimization started with using 1.0 M of HCl solution prepared in dry 1,4-dioxane. The initial reaction also employed dry dioxane as the solvent with the concentration of substrate **1a** maintained at 0.2 M, and the reaction was conducted at 0 °C. As shown in entries 1 and 2, the reactions gratifyingly provided the desired product (**2aBr**) as expected from the mechanism (Scheme 2). The reaction employing 2.0 equiv of HCl was found to afford product **2aBr** in lower yield (77%) than 0.5 equiv (86%) while requiring the same amount of time. A commercial solution of 4.0 M HCl in 1,4-dioxane was next investigated (entry 3) using dry dioxane as the solvent. The reaction went to completion within 30 min at 0 °C giving product **2aBr** in a slightly lower yield (82%). It was expected that adventitious water present in 1,4-dioxane did not negatively affect the reaction. Therefore, a more practical 1.0 M aqueous HCl solution was prepared and evaluated in the optimization. The reaction optimization was further conducted in AR-grade 1,4-dioxane using aqueous HCl solution.

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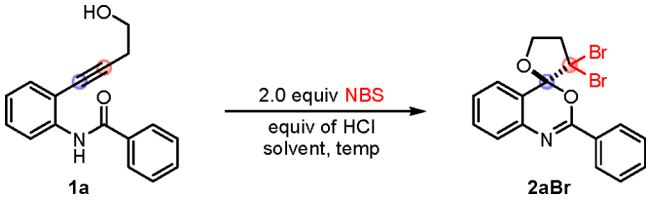
Table 1. Reaction Optimization for Conversion of 1a to 2aBr



entry	equiv of HCl	solvent	conc of 1a (M)	temp (°C)	time (min)	yield (%)[a]
1	2.0[b]	1,4-dioxane[d]	0.2	0	20	77
2	0.5[b]	1,4-dioxane[d]	0.2	0	20	86
3	0.5[c]	1,4-dioxane[d]	0.2	0	30	82
4	0.5	1,4-dioxane	0.2	rt	10	63[g]
5	0.5	acetone	0.2	rt	80	47
6	0.5	acetone	0.1	rt	80	47
7	0.5	EtOH	0.2	0	35	52
8	0.5	EtOH	0.2	rt	15	57
9	0.5	EtOH	0.1	rt	10	64
10	0.5	MTBE	0.1	rt	80	86
11	0.5	DCM	0.2	rt	10	80
12	0.5	DCE	0.2	rt	15	82
13	0.5	EtOAc	0.2	rt	15	87
14	0.5	EtOAc	0.05	rt	15	86
15	0.25	EtOAc	0.2	rt	22 h	17[e]
16	n/a[f]	EtOAc	0.2	rt	o/n	8[e]

[a]Isolated yields. [b]1.0 M stock solution prepared from conc HCl in dry 1,4-dioxane was used. [c]Commercial 4.0 M solution in 1,4-dioxane was used. [d]Dry 1,4-dioxane was used. [e]Complex mixture. [f]0.5 equiv of TMSCl was used instead of the aqueous HCl solution. MTBE = methyl *t*-butyl ether. DCM = dichloromethane. DCE = 1,2-dichloroethane. n/a = not applicable. o/n = overnight.

However, the reaction was attempted at room temperature (entry 4) to find that the reaction went to completion within 10 min while the yield dropped to 63% with a more complex mixture observed. Although a lower yield was obtained, this result showed that the reaction was largely feasible at room temperature, which was more practical. We continued to explore the reaction optimization at room temperature with other solvents. When the solvent was switched to acetone (entry 5), the reaction required 80 min to complete and could furnish only a 47% yield of **2aBr**. Keeping everything else identical to entry 5 while reducing the concentration of the substrate to 0.1 M gave an identical yield of the product (entry 6). Ethanol was next studied in entries 7−9 with different concentrations of **1a** and temperatures. By using 0.5 equiv of aq HCl at 0 °C, the reaction afforded a 52% yield of **2aBr** after 35 min (entry 7). When the reaction was conducted at room temperature, it went to completion within 15 min and 57% of **2aBr** was obtained (entry 8). When the substrate concentration was reduced to 0.1 M, yield of the product improved slightly to 64% (entry 9). The reaction was next investigated in methyl *t*-butyl ether (MTBE) as the solvent (entry 10). At 0.1 M of **1a** and 0.5 equiv of aq HCl at room temperature, the reaction became more sluggish (80 min) and furnished the desired product in 86% yield. The reactions were next attempted in DCM and DCE (entries 11 and 12). Both reactions in DCM and DCE at 0.2 M of **1a** at room temperature displayed fast conversion (10−15 min) to afford **2aBr** in comparable yields (80% and 82% yield, respectively). The reaction was next assessed in EtOAc (entries 13−16). By employing 0.5 equiv of aq HCl and 0.2 M concentration of **1a**, the reaction smoothly went to completion at room temperature within 15 min to give the desired product in an 87% yield (entry 13). Under the same conditions, except for reducing the concentration of **1a** to 0.05 M, the reaction still went to completion within 15 min at room temperature to afford the product in practically identical yield (86% yield, entry 14). However, when the reaction was conducted with a lower equiv of HCl (0.25 equiv, entry 15), the reaction was very sluggish, and only 17% of the desired product was afforded along with an inseparable and unidentifiable mixture after 22 h. As our previous work[3a] employed TMSCl and NBS to generate BrCl, we attempted the reaction using TMSCl (0.5 equiv), instead of HCl (entry 16). In this case, the reaction conducted at room temperature was very slow, and the reaction was allowed to stir overnight. Upon complete consumption of the substrate, the reaction was observed by TLC to be a complex mixture of products, and the desired product (**2aBr**) was isolated in only 8% yield. These results suggested that HCl was most appropriate for the current spiroannulation reaction. The conditions in entry 13, employing EtOAc, which is considered a green solvent,[14] were deemed practical and efficient and were, therefore, adopted as the optimal conditions to study the scope of the reaction.

The reaction of anilides **1** was studied with the results presented in Table 2. Although EtOAc was the main solvent used for these substrates, it was also found that 1,4-dioxane could perform better in some cases, and the results were noted accordingly in the table.

The reactions generally proceeded smoothly and rapidly (complete within 5−15 min in most cases) with NBS to generate compounds **2Br**. For compound **1a**, the reaction proceeded slightly more efficiently in EtOAc than in 1,4-dioxane, giving the desired **2aBr** in 87% yield (86% in dioxane). The structure of **2aBr** was confirmed by X-ray crystallographic analysis. Next, with R^2 = Ph, substituents R^1 were varied. The reaction of **1b** (R^1 = 6-Me) provided **2bBr** in 82% yield, while the same reaction in 1,4-dioxane provided **2bBr** in a better yield (88%), although this difference was negligible. When R^1 = 7-F (**1c**), product **2cBr** was obtained in a satisfactory yield (70%) while the reaction of **1d** (R^1 = 6-F) furnished product **2dBr** in 87%. These results seemed to suggest that the electron-withdrawing property of fluorine exerted no effect on the reaction. However, its different positions on the anilide ring imposed a significant difference in results with a more detrimental effect at C-7 (*para*- to the alkyne) than at C-6 (*para*- to the amide). The same trend was echoed as observed in substrates **1e** (R^1 = 7-Cl) and **1f** (R^1 = 6-Cl). For **1e**, the reaction afforded **2eBr** in 74% yield while **2fBr** was obtained in 87% yield from **1f**. These results of **1c−f** were decisive in concluding that an electron-withdrawing group was more damaging to the reaction outcome when located *para*- to the alkyne (**2cBr** and **2eBr**) than *para*- to the amide (**2dBr** and **2fBr**). Nevertheless, the reactions were still adequately efficient, providing the corresponding products in good to excellent yields in all cases. Reactions were well-tolerated to other electron-withdrawing substituents at C-6 as seen in compounds **1g** (R^1 = 6-CF_3) and **1h** (R^1 = 6-CN) as they provided the desired products in good to excellent yields (81% for **2gBr** and 79% for **2hBr**). However, for the strongly electron-withdrawing NO_2 group in substrate **1i** (R^1 = 6-NO_2), the reaction furnished the corresponding product (**2iBr**) in a

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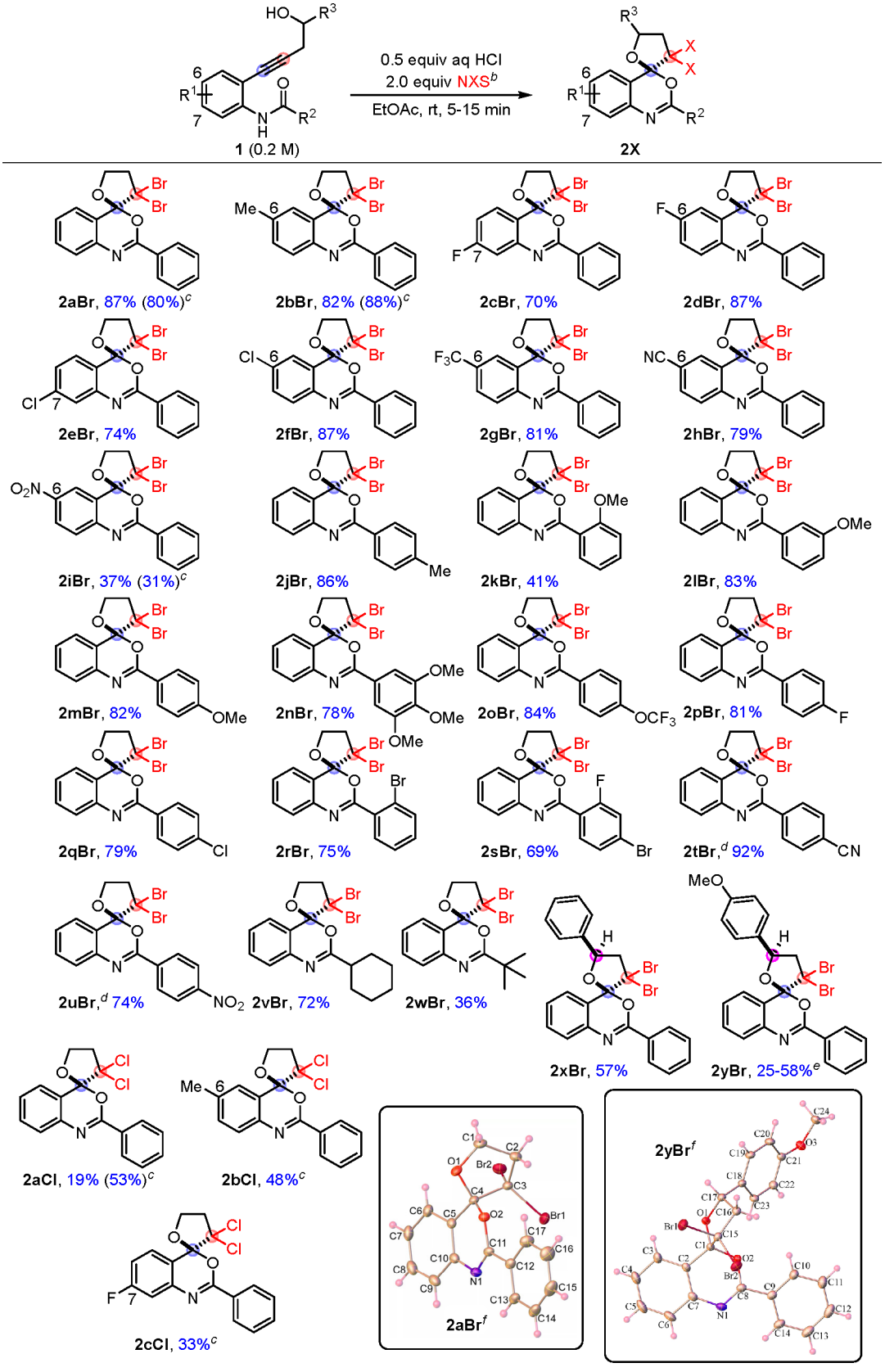
Table 2. Scope of Dibrominative Spirocyclization of 1 to Form 2Br[a]



[a]Isolated yields. [b]NCS (X = Cl) or NBS (X = Br) was used. [c]Reaction was performed in 1,4-dioxane. [d]Reaction required 30 min to complete. [e]Reactions were attempted in several solvents; see text for discussion. [f]Crystals of **2aBr** and **2yBr** were grown from a solution in MeOH with the nucleation induced by a small addition of hexane into the solution. Once crystal was formed, the solvent mixture was allowed to slowly evaporate at room temperature to allow the crystal to grow slowly.

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low yield (37%) in EtOAc and a lower but comparable yield (31%) in 1,4-dioxane.

Substrates **1** with a variation of R^2 (R^1 = H) were next examined. The reaction of **1j** (R^2 = 4-Me-Ph) proceeded excellently to give desired product **2jBr** in 86% yield. The reaction of substrate **1k** with the strongly electron-donating group R^2 = 2-OMe-Ph was less satisfactory (**2kBr**, 41%), which may be largely attributed to the steric bulkiness of the methoxy group at the *ortho*-position. This rationale was supported when the methoxy substituent was placed further away from the amide functional group as demonstrated with substrates **1l**–**m**, whose reactions provided corresponding products **2lBr** and **2mBr** in 83% and 82% yields, respectively. The reaction of substrate **1n** (R^2 = 3,4,5-$(OMe)_3$-Ph) furnished the corresponding product **2nBr** in a slightly lower but comparable yield (78%). Conversion of **1o** (R^2 = 4-OCF_3–Ph) proceeded smoothly to afford product **2oBr** in 84% yield. Substrates with R^2 as halogenated aryl groups were next examined. These substrates were well-tolerated under the reaction conditions. Both compounds **1p** (R^2 = 4-F-Ph) and **1q** (R^2 = 4-Cl-Ph) were converted efficiently to furnish corresponding products **2pBr** and **2qBr** in 81% and 79% yields, respectively. However, the reaction was slightly less efficient for **1r** (R^2 = 2-Br-Ph), which gave desired product **2rBr** in 75% yield. The efficiency of the reaction was reduced further for substrate **1s** (R^2 = 2-F-4-Br-Ph) which afforded product **2sBr** in moderate yield (69%). For these two latter cases, the steric hindrance of halogen atoms at the 2-position of the aryl rings was suspected as a probable cause of lower yields. The more strongly electron-withdrawing substituents were next evaluated with substrates **1t** (R^2 = 4-CN-Ph) and **1u** (R^2 = 4-NO_2-Ph). The reaction became more efficient with **1t** that desired product **2tBr** was obtained in 92% yield while the reaction of **1u** was less efficient; nevertheless, product **2uBr** could still be obtained in 74% yield. In these cases of **1t**–**u**, however, the reactions were slightly more sluggish, requiring up to 30 min to complete. R^2 alkyl groups were next studied with compounds **1v** (R^2 = Cy) and **1w** (R^2 = *t*-Bu). The reaction proceeded moderately well with **1v** to give the desired product (**2vBr**) in 72% yield while the reaction of **1w** was far less efficient and product **2wBr** was obtained in a low yield of 36%. These two latter cases repetitively suggested the sensitivity of the reaction toward the steric hindrance of the group attached to the amide. These cases showed that the bulkier *tert*-butyl group exerted a more negative effect on the reaction yield than the less bulky cyclohexyl group.

Substrates containing a secondary hydroxyl group **1x** and **1y** were next studied. For substrate **1x** substituted with a phenyl group, the reaction proceeded moderately well to give the corresponding product (**2xBr**) in 57% as a single diastereomer as an amorphous solid. The yield was, however, inferior for the reaction of substrate **1y**, containing 4-OMe-Ph group, which was conducted in EtOAc at room temperature and resulted in only 36% of the product (**2yBr**). In this case, several unidentifiable side-products were observed. Although low yield, product **2yBr** was obtained as a single diastereomer in the crystalline form, the structure of which was confirmed by X-ray crystallographic analysis with the relative stereochemistry shown. This diastereomer was assumed to be lower in energy because the bulky 4-OMe-Ph group was projected to the less hindered side of the cyclic ether. With a similar pattern in ^{1}H NMR spectra of **2xBr** to **2yBr**, it was reasonable to suggest the same relative stereochemistry for the single diastereomer of compound **2xBr** (Table 2). The diastereoselectivity observed for this compound probably stemmed from the same reason as stated above. The formation of **2yBr** was also attempted in EtOAc at 0 °C which produced the desired product in a better yield (47%). However, yield became poorer when the reaction was conducted in DCM at room temperature, which afforded **2yBr** in only 25% yield. Finally, the reaction proceeded most optimally for **1y** in 1,4-dioxane at room temperature. In this solvent, the product (**2yBr**) was obtained in 58% yield.

N-Chlorosuccinimide (NCS) was also effective in the reactions of **1** to give *gem*-dichlorospirocyclic benzo[*d*][1,3]-oxazine derivatives **2Cl**, although the reactions were less efficient than those with NBS. As shown in Table 2, the reaction of **1a** in EtOAc only afforded the corresponding **2aCl** in 19% yield. However, when 1,4-dioxane was used as the solvent, the yield of **2aCl** was improved to 53%. Reactions of **1b** and **1c** with NCS, performed in dioxane, gave **2bCl** and **2cCl** in 48% and 33% yields, respectively. The trend of results observed for **2aCl**–**2cCl** similarly paralleled that of **2aBr**–**2cBr** and was probably due to the same reasons as described previously (*vide supra*). In contrast, attempts to synthesize the *gem*-diiodide variants employing *N*-iodosuccinimide (NIS) were proven fruitless as only decompositions were observed in these reactions.

We then investigated the conversion of **2Br** to **3Br** as proposed in Scheme 3. The optimal conditions were identified after a brief optimization[15] using **2aBr**; the reaction proceeded most optimally to furnish product **3aBr** in 98% yield using 2.0 equiv of *t*-BuOK in *N*-methyl-2-pyrrolidone (NMP) at room temperature. The scope of the reaction was studied with all compounds **2Br** prepared previously, as displayed in Table 3.

Conversion of **2Br** to **3Br** was generally well-behaved. For compounds **2aBr**–**2iBr** where R^2 = Ph and R^1 were varied, the reactions consistently produced compounds **3Br** in more than 80% yields, except for **2gBr** (R^1 = 6-CF_3) and **2iBr** (R^1 = 6-NO_2), which produced the corresponding **3gBr** and **3iBr** in satisfactory yields of 70% and 79%, respectively. With compounds **2jBr**-**2wBr** (R^1 = H, varying R^2), the reactions proceeded very well in most cases, giving the corresponding **3Br** products in good to excellent yields. For R^2 as substituted aryl groups, the conversions of these substrates provided products in excellent yields (86–99%), except for **2kBr** (R^2 = 2-OMe-Ph), **2tBr** (R^2 = 4-CN-Ph), and **2uBr** (R^2 = 4-NO_2–Ph). For **2kBr**, steric hindrance of the 2-OMe substituent may have negatively affected the yield of the product (**3kBr**, 75%), while, for **2tBr** and **2uBr**, the yields seemed to be negatively affected by the strong electron-withdrawing effect of the substituents (74% yields for both **3tBr** and **3uBr**). For substrates with nonaryl R^2 groups as in **2vBr** (R^2 = Cy) and **2wBr** (R^2 = *t*-Bu), the conversions proceeded reasonably well, although giving lower yields than those with aryl R^2 groups; **3vBr** and **3wBr** were obtained in 61% and 78% yields, respectively. As for substrates **2xBr** and **2yBr**, both reactions proceeded excellently to provide **3xBr** and **3yBr** in 93% and 99% yields, respectively. As expected from the mechanisms (Scheme 2), an aryl substituent on the spirocyclic ether ring did not cause any problem for the transformation of these compounds. The reaction was proven to be very robust for preparing compounds **3Br** with full control of substitution patterns on any portions of the molecules starting from properly prefunctionalized substrates.

Compound **3aBr** was used to study the conversion to indolofurans **4a**. The reaction was successfully optimized[15]

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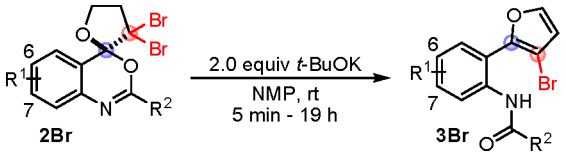
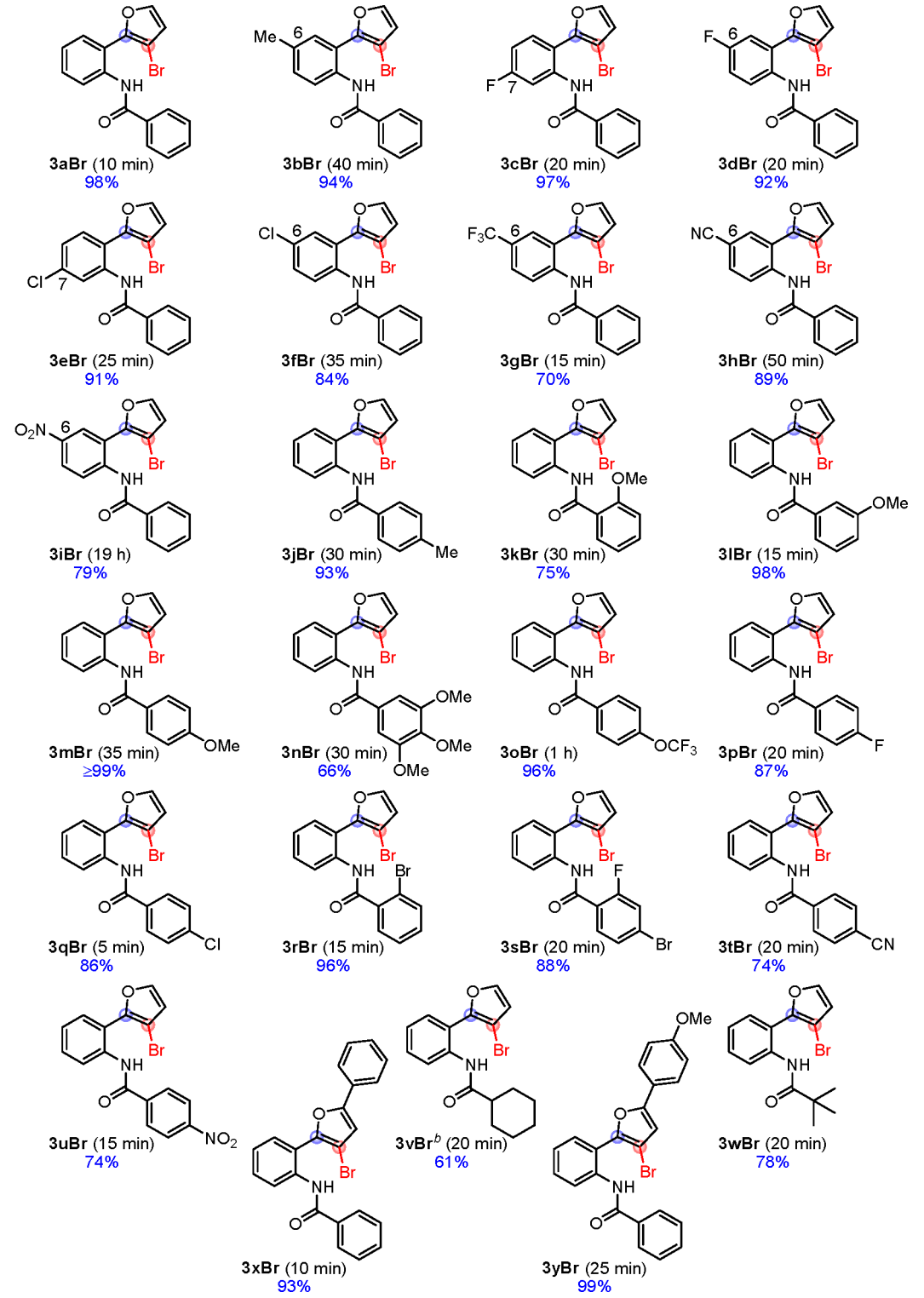
Table 3. Scope of the Transformations of Spirocycles 2Br to 3-Bromofurans 3Br[a]





[a]Isolated yield. [b]3.0 equiv of *t*-BuOK was required. NMP = *N*-methyl-2-pyrrolidone.

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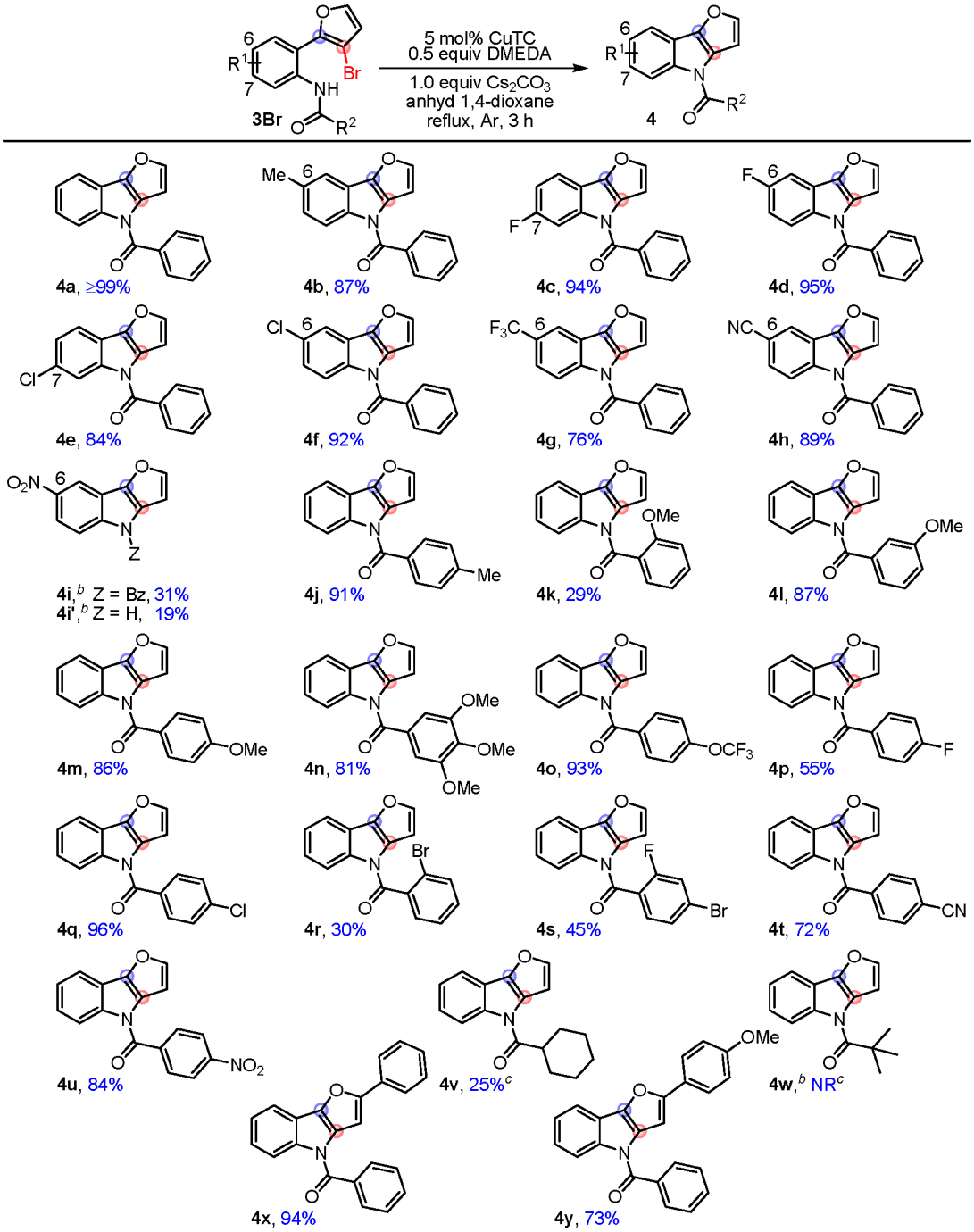
Table 4. Scope of Conversions of 3-Bromofurans 3Br to Indolofurans 4[a]



[a]Isolated yield. [b]Reaction time was 23 h. [c]Starting material was recovered. CuTC = copper(I) thiophene-2-carboxylate. DMEDA = *N*,*N*′-dimethylethylenediamine. NR = no reaction.

under modified Ullmann[16a−c] conditions based on a published procedure.[16d] The most optimal conditions utilized 5 mol % of copper(I) thiophene-2-carboxylate, or CuTC, 0.5 equiv of *N*,*N*′-dimethylethylenediamine (DMEDA) as the ligand and 1.0 equiv of Cs_2CO_3 in refluxing anhydrous 1,4-dioxane under an argon atmosphere. Under such conditions, **3aBr** was converted within 3 h to give the desired indolofuran (**4a**) in a quantitative yield. This sequence of reactions was also carried out with substrate **1a** in a 1.84 mmol scale, which could prepare product **4a** in 60% yield over three steps, showcasing the practicality of the current procedure. All compounds **3Br** prepared from the previous step were subjected to the optimal conditions with results summarized in Table 4.

Most reactions produced the corresponding products in good to excellent yields with the exception of a few cases. Compounds **3bBr**−**3iBr** (varying $R,^1$ R^2 = Ph) were converted to the corresponding products in good to excellent yields in almost all cases (76−95% yields), except for **3iBr** (R^1 = 6-NO_2). The reaction of **3iBr** required 23 h to complete to afford indolofuran **4i** in 31% yield along with *N*-debenzoylated indolofuran **4i′** in 19% yield, making the overall conversion moderately efficient (50% combined yields). The strong

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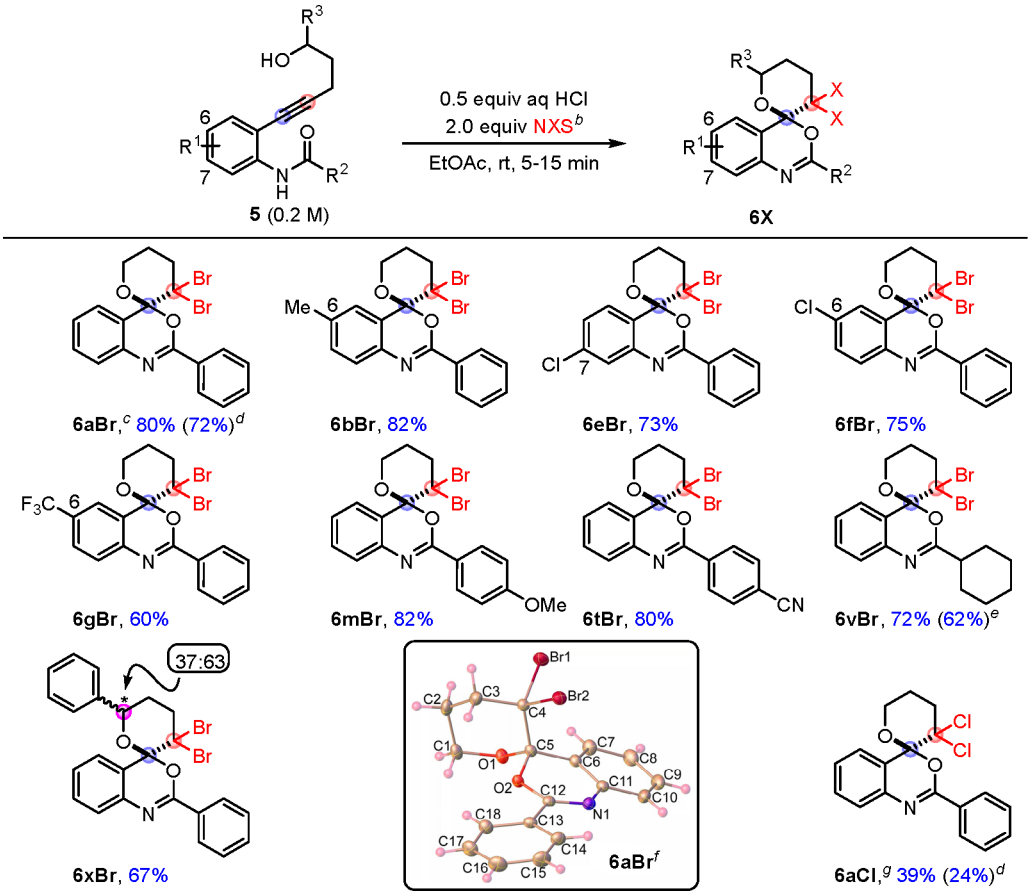
Table 5. Scope of Dibrominative Spirocyclization of 5 to Form 6Br[a]



[a]Isolated yields. [b]NCS (X = Cl) or NBS (X = Br) was used. [c]Reaction required 30 min to complete. [d]Reaction was performed in 1,4-dioxane. [e]Reaction was performed in DCM. [f]Crystal of **6aBr** was grown from a solution in MeOH with the nucleation induced by a small addition of hexane into the solution. Once crystal was formed, the solvent mixture was allowed to slowly evaporate at room temperature to allow the crystal to grow slowly. [g]Reaction required 3.5 h to complete.

electron-withdrawing effect of the NO_2 group present in **3iBr** noticeably reduced the efficiencies of the C−N bond formation. For the next series of substrates where R^1 = H and R^2 = aryl groups (**3jBr**−**3uBr**), the outcomes seemed to be more adversely affected by the steric effect of substituents on R^2 than their electronic properties. In most cases, products **4** were obtained in good to excellent yields (72−96%) regardless of the electronic properties of the substituents with only one exception in substrate **3pBr** (R^2 = 4-F-Ph). The presence of the 4-F substituent resulted in the production of product **4p** in 55% yield. The larger adversity imposed on these reactions by the steric effect was clearly illustrated in substrates **3kBr**, **3rBr**, and **3sBr** containing 2-substituents on the R^2 groups. Products were obtained in low to modest yields **4k** (R^2 = 2-OMe-Ph), 29%; **4r** (R^2 = 2-Br-Ph), 30%; and **4s** (R^2 = 2-F-4-Br-Ph), 45%. In contrast, reactions of **3vBr** (R^2 = Cy) and **3wBr** (R^2 = *t*-Bu) did not fare as well as those with R^2 as substituted aryl rings. In these latter cases, only 25% of **4v** was obtained along with the recovered starting material (**3vBr**), while the reaction of **3wBr** failed to yield **4w** completely, and the starting compound was fully recovered. Finally, compounds **3xBr** and **3yBr**, both containing 2,5-diaryl-3-bromofuran systems, were uneventfully converted under the standard conditions to give the corresponding products, **4x** and **4y**, in 94% and 73% yields, respectively. With these examples, the synthetic sequence was shown to be robust and effective for preparing indolofurans **4** with desired substituents and substitution patterns in the molecules starting with appropriately assembled substrates **1**.

The versatility of the reaction was further evaluated with substrates having longer pentynolyl pendant (**5**) with a focus on the formation of the *gem*-dibromospirocycles. The reaction of **5a** (0.2 M) with NBS proceeded rapidly (typically 5−15 min) to furnish the corresponding product **6aBr** in 80% yield in EtOAc and 72% yield in 1,4-dioxane. The structure of this crystalline product was unambiguously confirmed by X-ray crystallographic analysis. A brief scope of the reaction was next studied (Table 5).

The reaction of compound **5b** (R^1 = 6-Me) proceeded uneventfully to give the corresponding product (**6bBr**) in 82%. Substrates with R^1 as a halogen atom were next assessed. Both compounds **5e** (R^1 = 7-Cl) and **5f** (R^1 = 6-Cl) were successfully converted to corresponding products **6eBr** and **6fBr** in 73% and 75% yields, respectively. The difference in yields between **6eBr** and **6fBr** (73% vs 75%) was smaller than that between **2eBr** and **2fBr** (74% vs 87%), suggesting the less imposing electronic effects of substituent R^1 in the formation of the 6-membered spirocyclic ether ring. However, the electronic effect was more pronounced for compound **5g** (R^1 = 6-CF_3) as the reaction produced the corresponding product (**6gBr**) in a moderate yield (60%). For substrates with variations only on R^2 (R^1 = H), all reactions underwent

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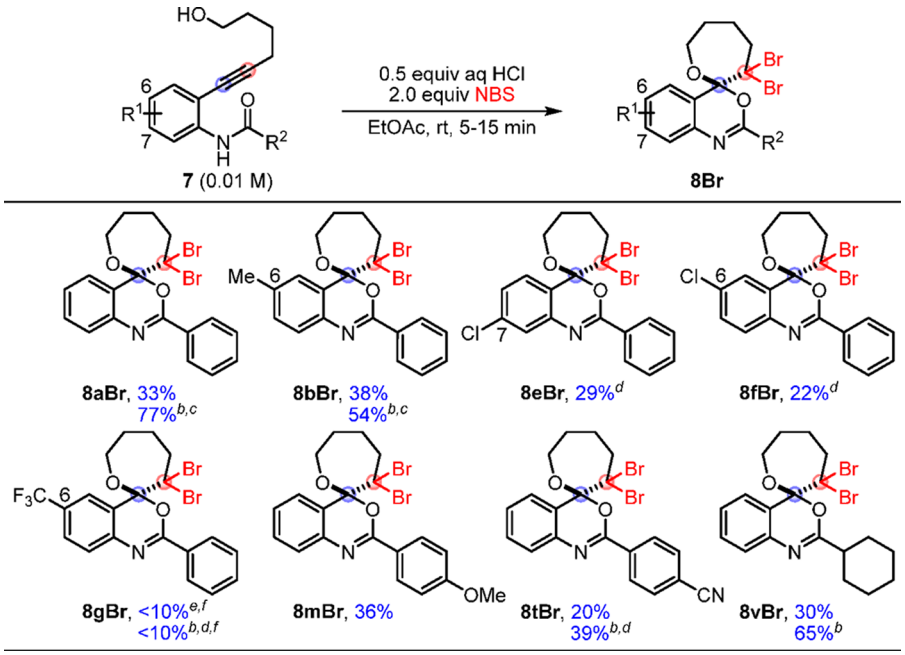
Table 6. Scope of Dibrominative Spirocyclization of 7 to Form 8Br[a]



[a]Isolated yields. [b]Reaction was conducted in DCM. [c]Reaction time was 3 h. [d]Reaction time was 2 h. [e]Reaction time was 40 min. [f]Contaminated by inseparable impurities.

smooth conversions to the desired products in good to excellent yields **6mBr** (R^2 = 4-OMe-Ph), 82%; **6tBr** (R^2 = 4-CN-Ph), 80%; and **6vBr** (R^2 = Cy), 72%. Among these, a larger steric hindrance of the cyclohexyl group (**5v**) seemed to somewhat deteriorate the reaction efficiency as observed with a slight drop in yield of **6vBr**. In addition, the reaction of **5v** was also attempted in DCM for comparison to find that the yield of **6vBr** was lower (62%) in this case, although the reaction was comparably rapid. The reaction was next attempted with substrate **5x** containing a phenyl substituent on the secondary hydroxyl group. The reaction led to the formation of the desired product (**6xBr**) in 67% combined yield as inseparable and unassignable diastereomers in a 37:63 ratio as determined by the ^{1}H NMR spectrum of the mixture.

The reaction was also applicable to using NCS to form **6Cl** as demonstrated with **5a**, whose reaction with NCS in EtOAc furnished **6aCl** in 39% yield, while the reaction in 1,4-dioxane provided the same product in 24% yield. Conversion of **5** to **6Cl** was less efficient than to **6Br**, reflecting the same general trend as those in Table 2 between the conversions of **1** to **2Br** and of **1** to **2Cl**.

Dibrominative spiroannulation was also studied with substrates **7** possessing hexynolyl pendant (Table 6). The reaction of **7a** (0.01 M in EtOAc) proceeded to give the corresponding 7-membered spirocyclic product (**8aBr**) in only 33% yield. However, the yield of **8aBr** could be improved to 77% when the reaction was conducted in DCM, although the reaction took longer (3 h). Regardless, reactions were less efficient when compared to the formation of 5-membered (**2Br**) and 6-membered (**6Br**) products even with a lower concentration of the substrate. This, however, was not totally unexpected as the formation of 7-membered rings is intrinsically less favorable compared to those of 5-membered and 6-membered rings.[17]

Nevertheless, this reaction remained useful for the formation of the 7-membered spirocycles. When compound **7b** (R^1 = 6-Me, R^2 = Ph) was subjected to the optimal conditions in EtOAc, product **8bBr** was obtained in 38% yield while the reaction carried out in DCM resulted in an improved yield (54%) although reaction also took longer to complete. The reactions of **7e** (R^1 = 7-Cl, R^2 = Ph) and **7f** (R^1 = 6-Cl, R^2 = Ph) gave products **8eBr** and **8fBr** in poor but comparable yields (29% and 22%, respectively). In addition, these reactions required longer reaction times to complete, even in EtOAc (2 h). The reaction of compound **7g** (R^1 = 6-CF_3, R^2 = Ph) resulted in a complex mixture, both in EtOAc and DCM, and provided less than 10% of impure **8gBr** in both cases. When R^1 = H and R^2 were varied to 4-OMe-Ph (**7m**) and 4-CN-Ph (**7t**), the reactions provided the desired products in low yields **8mBr**, 36% (in EtOAc); and **8tBr**, 20% (in EtOAc). However, when the reaction of **7t** was conducted in DCM, the yield of **8tBr** was improved to 39%, although the reaction took longer (2 h) to complete. Additionally, the reaction of **7v** (R^2 = Cy) afforded product **8vBr** in 30% yield in EtOAc while the reaction performed in DCM rapidly (15 min) furnished product **8vBr** in 65% yield. From these results, the formation of 7-membered spirocycles seemed to proceed better in DCM than in EtOAc. Furthermore, when compared to other arylamide substrates, the cyclohexanecarboxamide substrate (**7v**) was more readily converted to the corresponding spirocyclic product, with the exception of **7a**, resulting in both a faster conversion and a better yield.

CONCLUSIONS

In conclusion, a simple and convenient protocol to prepare various *gem*-dibromospirocyclic benzo[*d*][1,3]oxazine derivatives via dibrominative spirocyclization of 2-alkynolyl anilides was disclosed. The reaction was induced by electrophilic BrCl generated *in situ* from catalytic aqueous HCl and 2.0 equiv of NBS and could be performed over a wide range of substrates to form the desired spirocyclic products of 5- to 7-membered

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rings in good to excellent yields in most cases. Furthermore, the 5-membered *gem*-dibromospirocyclic products **2Br** were shown to be a useful building block in the conversion to 3-bromofuran **3Br**, mostly in good to excellent yields. In addition, most 3-bromofurans **3Br** were suitable substrates for conversion via intramolecular modified Ullmann coupling to yield indolofurans **4** in moderate to excellent efficiencies. These sequential reactions provided straightforward, scalable, and flexible access to indolofuran derivatives **4** in three steps from compounds **1**, making this procedure one of the only few methods available for preparing this fused indolofuran system. Many more synthetic potentials from this methodology could be realized and foreseen in the near future.

EXPERIMENTAL SECTION

General Procedure. Commercial grade chemicals were used without further purification, unless otherwise indicated. All solvents were used as received. Oven-dried glassware (110 °C at least for 2 h) was used in all reactions. Crude reaction mixtures were concentrated under reduced pressure on a rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06−0.2 mm; 70−230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets. Nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform ($CDCl_3$) with 300 and 400 MHz spectrometers, unless stated otherwise. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm, δ), relative to tetramethylsilane (TMS) as the internal reference. Chemical shifts for ^{19}F NMR spectra are reported in parts per million (ppm, δ) using hexafluorobenzene as the internal reference (δ = −164.9 ppm). Coupling constants (J) are reported in hertz (Hz). Infrared spectra were measured using an FT-IR spectrometer and are reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained using a time-of-flight (TOF) instrument.

Procedure for Preparing Compounds 1a−c, 1e−p, 1r−w, 5a,b, 5e−g, 5m, 5t, 5v, 7a,b, 7e−g, 7m, 7t, 7v (Acylation before Sonogashira Coupling) (Representative procedure: Preparation of Compound 1a). A 25 mL round-bottomed flask containing a magnetic stir bar was charged with 2-iodoaniline (1.034 g, 4.720 mmol, 1.00 equiv), followed by dry THF (10 mL), to give a clear solution. The reaction mixture was then added with benzoyl chloride (0.60 mL, 726.0 mg, 5.165 mmol, 1.09 equiv) and Et_3N (0.35 mL, 254.1 mg, 2.511 mmol, 0.53 equiv). The resulted mixture was allowed to stir at room temperature under argon overnight (17−18 h). Upon completion, the solvent was removed from the reaction mixture under reduced pressure, and the remaining crude material was purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to yield 1.283 g (84%) of the corresponding *N*-benzoyl-2-iodoaniline product as a white solid.

A 25 mL round-bottomed flask containing a magnetic stir bar was charged with *N*-benzoyl-2-iodoaniline (1.047 g, 3.240 mmol, 1.00 equiv), followed by $PdCl_2(PPh_3)_2$ (44.5 mg, 0.0634 mmol, 0.02 equiv), and CuI (16.7 mg, 0.0877 mmol, 0.03 equiv), 3 mL of MeCN, and 4 mL of Et_3N. The resulted yellow mixture was degassed by a steady stream of argon for 15 min. After degassing was complete, homopropargyl alcohol (0.26 mL, 240.8 mg, 3.436 mmol, 1.06 equiv) was added into the reaction via syringe, and the reaction mixture immediately turned dark brown. The mixture was allowed to stir at room temperature under argon overnight (17 h). Upon completion, the reaction was diluted with saturated aqueous NH_4Cl, and the separated aqueous layer was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator to give the crude product. The crude material was purified by SiO_2 column chromatography, eluting 30% EtOAc/hexane to furnish 805.3 mg (89%) of product **1a** as a brown solid.

Procedure for Preparing Compounds 1d and 1q (Sonogashira Coupling before Acylation) (Representative Case: Preparation of Compound 1d). A 25 mL round-bottomed flask containing a magnetic stir bar was charged sequentially with 4-fluoro-2-iodoaniline (318.4 mg, 1.343 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (19.6 mg, 0.0279 mmol, 0.02 equiv), CuI (11.0 mg, 0.0578 mmol, 0.04 equiv), and 4 mL of Et_3N. The resulted yellow heterogeneous mixture was degassed by a steady stream of argon for 15 min. After degassing was complete, the mixture was added with homopropargyl alcohol (0.10 mL, 92.6 mg, 1.321 mmol, 0.98 equiv) via syringe. The reaction mixture immediately turned dark brown and was allowed to stir at room temperature under argon overnight (16 h). Upon completion, the reaction mixture was diluted with saturated aqueous NH_4Cl, and the separated aqueous layer was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude material was purified by SiO_2 column chromatography eluting 50% EtOAc/hexane to furnish 218.2 mg (91%) of the desired product as a yellow solid.

A 25 mL round-bottomed flask containing a magnetic stir bar was charged with 2-butynolylaniline (343.5 mg, 1.960 mmol, 1.34 equiv) obtained from the previous step, followed by 5 mL of DCM. The resulted clear solution was added with benzoyl chloride (0.17 mL, 205.7 mg, 1.463 mmol, 1.00 equiv) via syringe, and the resulted reaction mixture was allowed to stir at room temperature overnight (18 h). Upon completion, the mixture was diluted with water, and the separated aqueous layer was extracted with DCM. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator to give the crude product. The crude material was purified by SiO_2 column chromatography, eluting 30% EtOAc/hexane to provide 461.9 mg (≥99%) of the desired product (**1d**) as a beige solid.

Procedure for Preparing Compounds 1x,y (Representative Case: Preparation of Compound 1x). A 25 mL round-bottomed flask was charged with benzaldehyde (572.6 mg, 5.396 mmol, 1.00 equiv) followed by 10 mL of dry THF to give a clear solution. The solution under an argon atmosphere was then added sequentially with zinc dust (1.895 g, 28.98 mmol, 5.37 equiv), diiodomethane (1.542 g, 5.470 mmol, 1.01 equiv), and propargyl bromide (0.53 mL, 887.4 mg, 7.040 mmol, 1.30 equiv). The reaction mixture was sonicated in a sonication bath for 2.5 h to complete the reaction. Upon completion, the reaction mixture was diluted with water, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane to furnish 548.4 mg (70%) of the desired benzylic alcohol as a clear yellow oil.

A 25 mL round-bottomed flask containing a magnetic stir bar and the benzylic alcohol obtained from the previous step (249.5 mg, 1.707 mmol, 1.00 equiv) was added with $PdCl_2(PPh_3)_2$ (24.7 mg, 0.035 mmol, 0.02 equiv), followed by *N*-benzoyl-2-iodoaniline (615.2 mg, 1.904 mmol, 1.12 equiv) and Et_3N (5 mL), to give a yellow reaction mixture. The reaction mixture was degassed by passing through a steady stream of argon for 15 min. A slurry of CuI (13.7 mg, 0.072 mmol, 0.04 equiv) in 1 mL of Et_3N was added into the reaction flask by syringe followed by a 1 mL Et_3N rinse. The reaction mixture immediately turned dark brown, and it was allowed to stir at room temperature under argon overnight (17 h). Upon completion, the reaction mixture was diluted with saturated aqueous NH_4Cl, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum to give the crude product as a brown oil. The crude material was purified by SiO_2 column chromatography, eluting 5−20% EtOAc/hexane to furnish 320.6 mg (55%) of the desired product (**1x**) as a brown solid.

Procedure for Preparing Compound 5x. A 25 mL round-bottomed flask containing a magnetic stir bar was charged with ethyl benzoylacetate (524.9 mg, 2.731 mmol, 1.00 equiv), followed by 13 mL of THF. The resulted clear solution was added sequentially with propargyl bromide (0.20 mL, 316.0 mg, 2.656 mmol, 0.97 equiv), K_2CO_3 (566.2 mg, 4.097 mmol, 1.50 equiv), and NaI (102.0 mg,

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0.681 mmol, 0.25 equiv). The reaction mixture immediately turned from a clear yellow solution to an orange heterogeneous mixture. This mixture was allowed to stir vigorously at room temperature overnight (23 h). Upon completion, the reaction mixture was diluted with water, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum to a crude material, which was purified by SiO_2 column chromatography, eluting 5−20% EtOAc/hexane to give 402.1 mg (64%) of pure 2-propargylated 1,3-ketoester.

The 1,3-ketoester (351.9 mg, 1.528 mmol, 1.00 equiv) obtained from the previous step was taken up in a 1:1 mixture of MeOH/H_2O (8 mL total) in a 25 mL round-bottomed flask with a magnetic stir bar. The resulted reaction mixture was added with KOH (229.9 mg, 4.097 mmol, 2.68 equiv) and was allowed to stir at room temperature for 3 h. Upon completion, the reaction mixture was diluted with water, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude decarboxylated product, which was further purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to afford 103.0 mg (43%) of the desired alkynone as a white solid.

The alkynone (93.9 mg, 0.594 mmol, 1.00 equiv) obtained from the previous step was dissolved in 1 mL of EtOH and was added with 5 drops of MeOH. The reaction mixture was added with $NaBH_4$ (23.2 mg, 0.613 mmol, 1.03 equiv) in one portion, and the resulted mixture was allowed to stir at room temperature for 1 h. Upon completion, the reaction mixture was diluted with water, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as a colorless oil. This crude material was purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to yield 84.3 mg (89%) of the desired alkynol as a colorless oil.

A 25 mL round-bottomed flask containing a magnetic stir bar was charged with the alkynol obtained from the previous step (74.2 mg, 0.463 mmol, 1.00 equiv), *N*-benzoyl-2-iodoaniline (180.4 mg, 0.558 mmol, 1.21 equiv), $PdCl_2(PPh_3)_2$ (6.8 mg, 0.010 mmol, 0.02 equiv), and 3 mL of MeCN. The resulted mixture was stirred and degassed by passing through a steady stream of argon for 25 min. Then a slurry of CuI (4.1 mg, 0.022 mmol, 0.05 equiv) in 1.0 mL of Et_3N was added into the reaction flask via syringe, followed by a 1 mL Et_3N rinse. The reaction mixture immediately turned from yellow to dark brown, and it was allowed to stir at room temperature overnight (16 h). Upon completion, the reaction was diluted with saturated aqueous NH_4Cl, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. The crude material was purified by SiO_2 column chromatography eluting 20% EtOAc/hexane to give 132.5 mg (67%) of desired product **5x** as a brown solid.

N-(2-Iodophenyl)benzamide: 1283 mg (84%, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 129.7−130.5 °C; IR (neat) ν_{max} 3265, 3058, 1650, 1527, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 8.1, 1.5 Hz, 1H), 8.29 (br s, 1H), 7.99−7.95 (m, 2H), 7.81 (dd, J = 8.0, 1.2 Hz, 1H), 7.61−7.49 (m, 3H), 7.42−7.36 (m, 1H), 6.87 (td, J = 7.7, 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 138.8, 138.3, 134.5, 132.2, 129.4, 129.0, 127.2, 126.1, 121.8, 90.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{11}ONI$ 323.9880, found 323.9875.

N-(2-Iodo-4-methylphenyl)benzamide: 474.1 mg (≥99%, yellow solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 161.5−162.3 °C; IR (neat) ν_{max} 3247, 1647, 1513, 1486, 1301, 818, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 8.1 Hz, 1H), 8.20 (br s, 1H), 7.96 (dd, J = 8.0, 1.2 Hz, 2H), 7.651−7.647 (m, 1H), 7.61−7.49 (m, 3H), 7.21 (dd, J = 8.4, 1.2 Hz, 1H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 139.0, 136.1, 135.8, 134.6, 132.1, 130.0, 128.9, 127.1, 121.6, 90.3, 20.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{12}INNaO$ 359.9856, found 359.9850.

N-(5-Fluoro-2-iodophenyl)benzamide: 673.1 mg (63%, white solid, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); mp 107.9−108.4 °C; IR (neat) ν_{max} 3264, 1686, 1651, 759, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 11.2, 3.2 Hz, 1H), 8.36 (br s, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.75 (dd, J = 8.4, 6.4 Hz, 1H), 7.63−7.59 (m, 1H), 7.56−7.52 (m, 2H), 6.68 (td, J = 8.4, 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 163.3 (d, C−F, $^1J_{C-F}$ = 245 Hz), 139.5 (d, C−F, $^3J_{C-F}$ = 12 Hz), 139.1 (d, C−F, $^3J_{C-F}$ = 9 Hz), 134.1, 132.4, 129.0, 127.1 113.1 (d, C−F, $^2J_{C-F}$ = 22 Hz), 109.1 (d, C−F, $^2J_{C-F}$ = 29 Hz), 82.3 (d, C−F, $^3J_{C-F}$ = 3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ − 113.37 to −113.44 (m); HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{13}H_8FINO$ 339.9629, found 339.9639.

N-(5-Chloro-2-iodophenyl)benzamide: 449.1 mg (≥99%, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 144.0−145.3 °C; IR (neat) ν_{max} 3264, 2924, 1651, 1517, 1400, 1019, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 2.4 Hz, 1H), 8.29 (br s, 1H), 7.96 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.63−7.51 (m, 3H), 6.89 (dd, J = 8.4, 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 139.2, 139.1, 135.5, 134.1, 132.4, 129.0, 127.1, 125.9, 121.5, 86.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_9{}^{35}ClINNaO$ 379.9310, found 379.9307.

N-(4-Chloro-2-iodophenyl)benzamide: 468.6 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 128.4−129.4 °C; IR (neat) ν_{max} 3264, 1686, 1651, 759, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 9.0 Hz, 1H), 8.25 (br s, 1H), 7.96−7.93 (m, 2H), 7.78 (d, J = 2.4 Hz, 1H), 7.61−7.49 (m, 3H), 7.37 (dd, J = 8.9, 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 137.8, 137.1, 134.1, 132.3, 129.9, 129.4, 129.0, 127.1, 122.1, 89.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_9{}^{35}ClINNaO$ 379.9310, found 379.9314.

N-(2-Iodo-4-(trifluoromethyl)phenyl)benzamide: 322.7 mg (67% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 137.0−137.5 °C; IR (neat) ν_{max} 3285, 1651, 1524, 1319, 1117, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 8.4 Hz, 1H), 8.46 (br s, 1H), 8.059−8.055 (m, 1H), 7.99−7.96 (m, 2H), 7.68−7.52 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4, 141.4, 135.7 (q, C−F, $^3J_{C-F}$ = 4 Hz), 134.0, 132.6, 129.1, 127.4 (q, C−F, $^2J_{C-F}$ = 33 Hz), 127.2, 126.6 (q, C−F, $^3J_{C-F}$ = 4 Hz), 122.9 (q, C−F, $^1J_{C-F}$ = 270 Hz), 120.7, 88.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.4 (s); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}F_3INO$ 391.9754, found 391.9745.

N-(4-Cyano-2-iodophenyl)benzamide: 355.1 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 147.2−148.0 °C; IR (neat) ν_{max} 3264, 2925, 2233, 1718, 1655, 1508, 1305, 1114, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 8.7 Hz, 1H), 8.52 (br s, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.98−7.95 (m, 2H), 7.69 (dd, J = 8.7, 1.8 Hz, 1H), 7.67−7.61 (m, 1H), 7.58−7.53 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 142.3, 142.0, 133.7, 133.4, 132.8, 129.2 127.2, 120.5, 117.1, 108.8, 88.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}ON_2I$ 348.9832, found 348.9825.

N-(2-Iodo-4-nitrophenyl)benzamide: 200.0 mg (45% yield, yellow solid, purified by recrystallization from DCM/hexane mixture); mp 172.2−172.5 °C; IR (neat) ν_{max} 3271, 3080, 1655, 1501, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 9.2 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.62 (br s, 1H), 8.29 (dd, J = 9.0, 2.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.66−7.63 (m, 1H), 7.59−7.55 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 143.9, 143.5, 134.2, 133.6, 132.9, 129.2, 127.3, 125.1, 119.6, 87.8; HRMS (ESI-TOF) m/z [M - H]$^-$ calcd for $C_{13}H_8O_3N_2I$ 366.9574, found 366.9582.

N-(2-Iodophenyl)-4-methylbenzamide: 384.0 mg (99% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 122.1−122.9 °C; IR (neat) ν_{max} 3230, 2921, 1650, 1522, 1304, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, J = 8.4, 1.5 Hz, 1H), 8.27 (br s, 1H), 7.87 (d, J = 8.1 Hz, 2H), 7.81 (dd, J = 8.0, 1.5 Hz, 1H), 7.43−7.37 (m, 1H), 7.32 (d, J = 8.1 Hz, 2H), 6.87 (td, J = 7.5, 1.5 Hz, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$

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NMR (75 MHz, $CDCl_3$) δ 165.3, 142.8, 138.8, 138.4, 131.7, 129.6, 129.4, 127.2, 125.9, 121.7, 90.1, 21.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{12}INNaO$ 359.9856, found 359.9855.

N-(2-Iodophenyl)-2-methoxybenzamide: 521.3 mg (95% yield, white solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 136.7−137.4 °C; IR (neat) ν_{max} 3291, 2964, 1657, 1599, 1302, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 8.50 (dd, J = 8.1, 1.5 Hz, 1H), 8.30 (dd, J = 7.8, 1.8 Hz, 1H), 7.81 (dd, J = 8.1, 1.5 Hz, 1H), 7.52−7.46 (m, 1H), 7.39−7.34 (m, 1H), 7.11 (td, J = 7.5, 0.9 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.83 (td, J = 7.5, 1.5 Hz, 1H), 4.08 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.4, 157.2, 139.8, 139.0, 133.4, 132.6, 128.9, 125.5, 122.8, 121.3, 111.4, 89.5, 56.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{13}O_2NI$ 353.9986, found 353.9971.

N-(2-Iodophenyl)-3-methoxybenzamide: 708.8 mg (66% yield, white solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 89.7−90.0 °C; IR (neat) ν_{max} 3267, 2832, 1650, 1037, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 8.1, 1.5 Hz, 1H), 8.28 (br s, 1H), 7.82 (dd, J = 8.0, 1.2 Hz, 1H), 7.53−7.50 (m, 2H), 7.43−7.37 (m, 2H), 7.14−7.10 (m, 1H), 6.88 (td, J = 7.7, 1.5 Hz, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.1, 160.1, 138.8, 138.3, 136.0, 129.9, 129.4, 126.0, 121.7, 118.8, 118.4, 112.5, 90.2, 55.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{13}O_2NI$ 353.9986, found 353.9982.

N-(2-Iodophenyl)-4-methoxybenzamide: 569.3 mg (97% yield, white solid, purified by SiO_2 column chromatography eluting 30−50% EtOAc/hexane); mp 151.8−152.4 °C; IR (neat) ν_{max} 3263, 2840, 1644, 1505, 1254, 1016, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, J = 8.3, 1.5 Hz, 1H), 8.22 (br s, 1H), 7.96−6.98 (m, 2H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.41−7.36 (m, 1H), 7.00 (dt, J = 9.0, 2.7 Hz, 2H), 6.89−6.83 (m, 1H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 164.8, 162.7, 138.7, 138.4, 129.3, 129.0, 126.7, 125.7, 121.6, 114.1, 90.1, 55.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{12}INNaO_2$ 375.9805, found 375.9810.

N-(2-Iodophenyl)-3,4,5-trimethoxybenzamide: 411.8 mg (74% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/DCM); mp 164.4−165.2 °C; IR (neat) ν_{max} 3270, 2943, 1651, 1126, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 8.3, 1.2 Hz, 1H), 8.24 (br s, 1H), 7.82 (dd, J = 8.0, 1.5 Hz, 1H), 7.44−7.39 (m, 1H), 7.21 (s, 2H), 6.89 (td, J = 7.5, 1.5 Hz, 1H), 3.96 (s, 6H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.0, 153.4, 141.5, 138.8, 138.2, 129.9, 129.5, 126.0, 121.5, 104.6, 90.1, 61.0, 56.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{16}INNaO_4$ 436.0016, found 436.0021.

N-(2-Iodophenyl)-4-(trifluoromethoxy)benzamide: 638.5 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 10% DCM/hexane); mp 119.2−119.5 °C; IR (neat) ν_{max} 3269, 1648, 1528, 1266, 1166, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J = 8.3, 0.9 Hz, 1H), 8.25 (br s, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.81 (dd, J = 8.0, 0.9 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.89 (td, J = 7.7, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.9, 152.0, 138.8, 138.0, 132.9, 129.4, 129.1, 126.3, 121.9, 120.9, 120.3 (q, C−F, $^1J_{C-F}$ = 257 Hz), 90.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 60.9 (s); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}F_3INO_2$ 407.9703, found 407.9697.

4-Fluoro-N-(2-iodophenyl)benzamide: 564.9 mg (>99% yield, white solid, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); mp 135.9−136.6 °C; IR (neat) ν_{max} 3268, 1913, 1649, 1501, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, J = 8.3, 1.2 Hz, 1H), 8.21 (br s, 1H), 8.01−7.95 (m, 2H), 7.81 (dd, J = 8.0, 1.5 Hz, 1H), 7.42−7.36 (m, 1H), 7.23−7.16 (m, 2H), 6.91−6.86 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.1 (d, C−F, $^1J_{C-F}$ = 252 Hz), 164.2, 138.8, 138.1, 130.7 (d, C−F, $^3J_{C-F}$ = 3 Hz), 129.5 (d, C−F, $^3J_{C-F}$ = 9 Hz), 129.4, 126.1, 121.8, 116.0 (d, C−F, $^2J_{C-F}$ = 23 Hz), 90.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 110.0 to −110.1 (m); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{10}FINO$ 341.9786, found 341.9782.

2-Bromo-N-(2-iodophenyl)benzamide: 560.9 mg (96% yield, white solid, purified by SiO_2 column chromatography eluting 2−10% EtOAc/hexane); mp 158.4−159.4 °C; IR (neat) ν_{max} 3249, 3023, 1655, 1518, 1306, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 7.8 Hz, 1H), 7.94 (br s, 1H), 7.81 (dd, J = 8.0, 1.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.45−7.31 (m, 3H), 6.90 (td, J = 8.1, 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.6, 139.0, 138.0, 137.5, 133.7, 131.8, 129.4, 129.3, 127.7, 126.5, 122.3, 119.4, 90.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_9{}^{79}BrINNaO$ 423.8804, found 423.8797.

4-Bromo-2-fluoro-N-(2-iodophenyl)benzamide: 704.6 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); mp 119.5−119.9 °C; IR (neat) ν_{max} 3392, 3072, 1677, 1526, 1431, 1301, 901, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ, 8.75 (d, J = 14.1 Hz, 1H), 8.38 (dd, J = 8.4, 1.2 Hz, 1H), 8.08 (t, J = 8.4 Hz, 1H), 7.84 (dd, J = 8.0, 1.5 Hz, 1H), 7.50−7.37 (m, 3H), 6.90 (td, J = 7.8, 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.5 (d, C−F, $^3J_{C-F}$ = 4 Hz), 159.9 (d, C−F, $^1J_{C-F}$ = 251 Hz), 139.1, 138.5, 133.5 (d, C−F, $^3J_{C-F}$ = 3 Hz), 129.2, 128.7 (d, C−F, $^3J_{C-F}$ = 3 Hz), 127.3 (d, C−F, $^3J_{C-F}$ = 10 Hz), 126.5, 122.8, 120.2, 119.9 (d, C−F, $^2J_{C-F}$ = 28 Hz), 90.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_9{}^{79}BrFINO$ 419.8891, found 419.8881.

4-Cyano-N-(2-iodophenyl)benzamide: 519.1 mg (98% yield, white solid, purified by SiO_2 column chromatography eluting 50% DCM/hexane); mp 154.1−154.4 °C; IR (neat) ν_{max} 3248, 3058, 2230, 1661, 1524, 1308, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32−8.29 (m, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.82−7.77 (m, 3H), 7.39 (t, J = 8.1 Hz, 1H), 6.92 (td, J = 7.7, 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.4, 138.8, 138.1, 137.5, 132.6, 129.3, 127.7 126.7, 122.2, 117.7, 115.5, 90.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 112.0 to −112.1 (m); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}$ IN_2O 348.9832, found 348.9836.

N-(2-Iodophenyl)-4-nitrobenzamide: 373.9 mg (40% yield, white solid, purified by SiO_2 column chromatography eluting 30−50% DCM/hexane); mp 148.3−148.6 °C; IR (neat) ν_{max} 3284, 2931, 1655, 1344, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42−8.37 (m, 3H), 8.29 (br s, 1H), 8.15−8.12 (m, 2H), 7.85 (dd, J = 8.1, 1.2 Hz, 1H), 7.46−7.41 (m, 1H), 6.97−6.92 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.2, 150.0, 140.0, 138.9, 137.6, 129.6, 128.4, 126.8, 124.2, 122.0, 90.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{10}O_3N_2I$ 368.9731, found 368.9731.

N-(2-Iodophenyl)cyclohexanecarboxamide: 599.9 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 135.7−136.2 °C; IR (neat) ν_{max} 3266, 2925, 2852, 1709, 1655, 1524, 1017, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 7.76 (dd, J = 8.0, 1.5 Hz, 1H), 7.52 (br s, 1H), 7.35−7.30 (m, 1H), 6.82 (td, J = 7.7, 1.5 Hz, 1H), 2.32 (tt, J = 11.4, 3.6 Hz, 1H), 2.07−2.02 (m, 2H), 1.89−1.84 (m, 2H), 1.74−1.71 (m, 1H), 1.56 (qd, J = 12.0, 3.0 Hz, 2H), 1.43−1.19 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 174.2, 138.6, 138.2, 129.2, 125.7, 122.0, 90.0, 46.5, 29.7, 25.7, 25.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}INNaO$ 352.0169, found 352.0168.

N-(2-Iodophenyl)pivalamide: 598.2 mg (76% yield, white solid, purified by SiO_2 column chromatography eluting 0−2% EtOAc/hexane); mp 65.6−66.9 °C; IR (neat) ν_{max} 3264, 2964, 1637, 1468, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.1, 1.5 Hz, 1H), 7.80 (br s, 1H), 7.75 (dd, J = 8.0, 1.5 Hz, 1H), 7.35−7.29 (m, 1H), 6.81 (td, J = 7.5, 1.5 Hz, 1H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 176.6, 138.5, 138.2, 129.1, 125.6, 121.6, 90.1, 40.0, 27.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{15}INO$ 304.0193, found 304.0182.

1-Phenylbut-3-yn-1-ol: 548.4 mg (70% yield, pale yellow oil, purified by SiO_2 column chromatography eluting 5−20% EtOAc/hexane); IR (neat) ν_{max} 3386, 3293, 3032, 1953, 1455, 1047, 756, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 4.83 (t, J = 6.3 Hz, 1H), 2.62 (dd, J = 3.2, 0.4 Hz, 1H), 2.60 (dd, J = 3.2, 0.4 Hz, 1H), 2.05 (td, J = 2.7, 0.3 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 142.4, 128.4, 127.9, 125.7, 80.7, 72.2, 70.9, 29.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_{10}NaO$ 169.0624, found 169.0625.

1-(4-Methoxyphenyl)but-3-yn-1-ol: 736.5 mg (84% yield, white solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 38.8−39.1 °C; IR (neat) ν_{max} 3407, 3289, 2838, 2120, 1513, 1244, 1031, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

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7.34−7.31 (m, 2H), 6.92−6.88 (m, 2H), 4.86−4.82 (m, 1H), 3.81 (s, 3H), 2.65−2.62 (m, 2H), 2.34 (d, J = 3.2 Hz, 1H), 2.07 (t, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 134.6, 127.0, 113.8, 80.8, 72.0, 70.8, 55.3, 29.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{12}NaO_2$ 199.0730, found 199.0731.

Ethyl 2-Benzoylpent-4-ynoate: 402.1 mg (64% yield, colorless oil, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); IR (neat) ν_{max} 3293, 2983, 1735, 1685, 1234, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05−8.03 (m, 2H), 7.62−7.59 (m, 1H), 7.51−7.47 (m, 2H), 4.58 (t, J = 7.6 Hz, 1H), 4.16 (qd, J = 7.2, 1.2 Hz, 2H), 2.94 (ddd, J = 17.2, 9.4, 2.8 Hz, 1H), 2.85 (ddd, J = 17.0, 7.0, 2.4 Hz, 1H), 2.00 (t, J = 2.4 Hz, 1H), 1.17 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.2, 168.1, 135.7, 133.7, 128.7, 128.6, 80.4, 70.3, 61.7, 53.0, 18.2, 13.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{14}NaO_3$ 253.0835, found 253.0841.

1-Phenylpent-4-yn-1-one: 103.0 mg (43% yield, white crystal, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 66.0−66.5 °C; IR (neat) ν_{max} 3268, 1678, 1205, 741, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.96 (m, 2H), 7.60−7.56 (m, 1H), 7.49−7.46 (m, 2H), 3.25 (t, J = 7.2 Hz, 2H), 2.64 (td, J = 7.6, 2.8 Hz, 2H), 1.99 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.6, 136.4, 133.3, 128.6, 128.0, 83.3, 68.7, 37.5, 13.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{10}NaO$ 181.0624, found 181.0630.

1-Phenylpent-4-yn-1-ol: 84.3 mg (89% yield, colorless oil, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); IR (neat) ν_{max} 3381, 3295, 2924, 2115, 1454, 1060, 763, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 4H), 7.29−7.23 (m, 1H), 4.78 (dd, J = 8.0, 5.2 Hz, 1H), 2.47 (br s, 1H), 2.34−2.15 (m, 2H), 1.99−1.97 (m, 1H), 1.96−1.92 (m, 1H), 1.90−1.81 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 128.4, 127.6, 125.7, 83.9, 72.9, 68.9, 37.3, 15.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{12}NaO$ 183.0780, found 183.0781.

4-(2-Aminophenyl)but-3-yn-1-ol: 694.1 mg (82% yield, brown oil, purified by SiO_2 column chromatography eluting 10−40% EtOAc/hexane); IR (neat) ν_{max} 3346, 2884, 1612, 1491, 1041, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.66−6.62 (m, 2H), 4.22 (br s, 2H), 3.73 (t, J = 6.0 Hz, 2H), 2.64 (t, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 147.6, 131.8, 129.0, 117.8, 114.3, 108.3, 92.3, 78.4, 60.8, 23.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{12}ON$ 162.0913, found 162.0911.

4-(2-Amino-5-fluorophenyl)but-3-yn-1-ol: 218.2 mg (91% yield, yellow solid, purified by SiO_2 column chromatography eluting 50% EtOAc/hexane); mp 81.5−82.0 °C; IR (neat) ν_{max} 3379, 3172, 2867, 2224, 1495, 863 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dd, J = 9.0, 2.7 Hz, 1H), 6.82 (td, J = 8.6, 3.0 Hz, 1H), 6.61 (dd, J = 9.0, 4.8 Hz, 1H), 4.06 (br s, 2H), 3.82 (t, J = 6.3 Hz, 2H), 2.36 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.2 (d, C−F, $^1J_{C-F}$ = 234 Hz), 144.2, 117.8, (d, C−F, $^2J_{C-F}$ = 23 Hz), 116.3 (d, C−F, $^2J_{C-F}$ = 23 Hz), 115.3 (d, C−F, $^3J_{C-F}$ = 8 Hz), 109.1 (d, C−F, $^3J_{C-F}$ = 9 Hz), 92.9, 78.1 (d, C−F, $^3J_{C-F}$ = 3 Hz), 61.0, 23.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{11}ONF$ 180.0819, found 180.0821.

N-(2-(3-Hydroxyprop-1-yn-1-yl)phenyl)benzamide: 90.2 mg (57% yield, yellow solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 92.1−92.7 °C; IR (neat) ν_{max} 3392, 2924, 1663, 1524, 1450, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 7.90−7.88 (m, 2H), 7.52−7.40 (m, 3H), 7.37−7.32 (m, 2H), 7.06−7.01 (m, 1H), 4.55 (s, 2H), 2.78 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 139.1, 134.4, 132.0, 131.6, 129.9, 128.8, 127.0, 123.5, 119.3, 111.8, 95.4, 80.8, 51.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{13}NNaO_2$ 274.0839, found 274.0833.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)benzamide (**1a**):* 805.3 mg (89% yield, brown solid, purified by SiO_2 column chromatography eluting 5−30% EtOAc/hexane); mp 77.1−78.1 °C; IR (neat) ν_{max} 3388, 2882, 1662, 1521, 755, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 7.94−7.91 (m, 2H), 7.56−7.44 (m, 3H), 7.40 (dd, J = 7.7, 1.5 Hz, 1H), 7.34 (td, J = 7.7, 1.5 Hz, 1H), 7.04 (td, J = 7.5, 1.2 Hz, 1H), 3.85 (t, J = 6.3 Hz, 1H), 2.77 (t, J = 6.0 Hz, 2H), 2.27 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 139.1, 134.7, 131.9, 131.6, 129.3, 128.8, 127.1, 123.4, 119.2, 112.6, 94.7, 77.5, 60.9, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1173.

*N-(2-(4-Hydroxybut-1-yn-1-yl)-4-methylphenyl)benzamide (**1b**):* 297.2 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 119.7−120.2 °C; IR (neat) ν_{max} 3390, 2920, 1659, 1519, 705, 577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 8.0, 1.2 Hz, 2H), 7.49−7.38 (m, 3H), 7.17 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 3.80 (t, J = 6.0 Hz, 2H), 3.02 (br s, 1H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 136.5 134.5, 133.0, 131.8, 131.7, 129.8, 128.6, 126.9, 119.1, 112.7, 94.4, 77.4, 60.8, 23.7, 20.5; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{18}H_{16}NO_2$ 278.1176, found 278.1186.

*N-(5-Fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1c**):* 78.2 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 50% EtOAc/hexane); mp 103.9−104.2 °C; IR (neat) ν_{max} 3394, 2947, 1671, 1527, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 8.37 (dd, J = 11.2, 2.4 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.55−7.52 (m, 1H), 7.49−7.45 (m, 2H), 7.37−7.33 (m, 1H), 6.74 (td, J = 18.4, 2.4 Hz, 1H), 3.86 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.0 Hz, 2H), 2.29 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 162.6 (d, C−F, $^1J_{C-F}$ = 246 Hz), 140.6 (d, C−F, $^3J_{C-F}$ = 12 Hz), 134.3, 132.7 (d, C−F, $^3J_{C-F}$ = 10 Hz), 132.2, 128.8, 127.1, 110.5 (d, C−F, $^2J_{C-F}$ = 23 Hz), 108.3 (d, C−F, $^3J_{C-F}$ = 3 Hz), 106.8 (d, C−F, $^2J_{C-F}$ = 29 Hz), 94.6, 76.6, 60.9, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 110.58 to −110.65 (m); HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{17}H_{13}O_2NF$ 282.0925, found 282.0935.

*N-(4-Fluoro-2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1d**):* 461.9 mg (≥99% yield, beige solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 94.9−95.3 °C; IR (neat) ν_{max} 3399, 1719, 1523, 1270, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.51 (dd, J = 9.0, 5.1 Hz, 1H), 7.93 (d, J = 6.9 Hz, 2H), 7.58−7.46 (m, 3H), 7.13−7.03 (m, 2H), 3.86 (t, J = 6.0 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 1.86 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 158.2 (d, C−F, $^1J_{C-F}$ = 242 Hz), 135.6 (d, C−F, $^3J_{C-F}$ = 2 Hz), 134.7, 132.0, 128.8 127.1, 120.9 (d, C−F, $^3J_{C-F}$ = 8 Hz), 118.0 (d, C−F, $^2J_{C-F}$ = 24 Hz), 116.3 (d, C−F, $^2J_{C-F}$ = 22 Hz), 114.2 (d, C−F, $^3J_{C-F}$ = 9 Hz), 95.7, 76.8 (d, C−F, $^3J_{C-F}$ = 2 Hz), 60.8, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 121.69 to −121.73 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}O_2NF$ 284.1081, found 284.1072.

*N-(5-Chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1e**):* 260.6 mg (≥99% yield, pale orange solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 116.8−117.3 °C; IR (neat) ν_{max} 3433, 3388, 2880, 2220, 1671, 1570, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 8.64 (d, J = 2.1 Hz, 1H), 7.92−7.89 (m, 2H), 7.57−7.44 (m, 3H), 7.30 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.4, 2.1 Hz, 1H), 3.89−3.84 (m, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.18−2.14 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 140.0, 135.1, 134.3, 132.22, 132.21, 128.8, 127.1, 123.6, 119.2, 110.9 95.8, 76.6, 60.8 23.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{14}{}^{35}ClNNaO_2$ 322.0605, found 322.0597.

*N-(4-Chloro-2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1f**):* 221.4 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 116.8−117.3 °C; IR (neat) ν_{max} 3392, 2943, 1663, 1516, 1403, 1310, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 7.2 Hz, 2H), 7.54−7.42 (m, 3H), 7.34 (d, J = 2.4 Hz, 1H), 7.28−7.24 (m, 1H), 3.85−3.83 (m, 2H), 2.76 (t, J = 6.0 Hz, 2H), 2.49 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 137.7, 134.3, 132.1, 131.1, 129.2, 128.8, 128.3, 127.1, 120.3, 114.2, 96.2, 76.3, 60.7, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}{}^{35}ClNO_2$ 300.0786, found 300.0790.

*N-(2-(4-Hydroxybut-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-benzamide (**1g**):* 237.9 mg (98% yield, yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 87.7−88.4 °C; IR (neat) ν_{max} 3387, 2941, 2227, 1675, 1527, 1333, 1121, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.97 (br s, 1H), 8.68 (d, J = 8.7

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Hz, 1H), 7.94−7.91 (m, 2H), 7.65 (s, 1H), 7.57−7.45 (m, 4H), 3.88 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 6.0 Hz, 2H), 2.28 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5, 141.8, 134.1, 132.4, 128.9, 128.6 (q, C−F, $^3J_{C-F}$ = 4 Hz), 127.2, 126.1 (q, C−F, $^3J_{C-F}$ = 4 Hz), 125.4 (q, C−F, $^2J_{C-F}$ = 33 Hz), 123.7 (q, C−F, $^1J_{C-F}$ = 270 Hz), 118.9, 112.9, 96.5, 76.2, 60.7, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.5 (s); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}F_3NNaO_2$ 356.0869, found 356.0867.

*N-(4-Cyano-2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1h**):* 263.8 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 50−70% DCM/hexane); mp 159.2−159.9 °C; IR (neat) ν_{max} 3488, 3382, 2946, 2229, 1673, 1518, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 8.74 (d, J = 8.7 Hz, 1H), 7.98−7.94 (m, 2H), 7.68 (d, J = 1.7 Hz, 1H), 7.63−7.57 (m, 2H), 7.54−7.49 (m, 2H), 3.89 (q, J = 6.0 Hz, 2H), 2.82 (t, J = 6.1 Hz, 2H), 1.88 (t, J = 5.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5, 142.8, 135.2, 134.0, 133.0, 132.6, 129.0, 127.3, 119.2, 118.2, 113.4, 106.6, 97.4, 75.5, 60.7, 23.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}N_2NaO_2$ 313.0948, found 313.0948.

*N-(2-(4-Hydroxybut-1-yn-1-yl)-4-nitrophenyl)benzamide (**1i**):* 117.2 mg (70% yield, white solid, purified by SiO_2 column chromatography eluting 20−50% EtOAc/hexane); mp 140.9−141.4 °C; IR (neat) ν_{max} 3397, 2908, 2227, 1691, 1246, 701 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.83 (br s, 1H), 8.41−8.37 (m, 1H), 8.37−8.26 (m, 2H), 8.02 (d, J = 7.5 Hz, 2H), 7.67−7.64 (m, 1H), 7.60−7.55 (m, 2H), 5.06 (t, J = 5.4 Hz, 1H), 3.64 (q, J = 6.3 Hz, 2H), 2.69 (t, J = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 165.2, 144.5, 143.0, 133.4, 132.6, 128.9, 127.7, 126.8, 124.2, 121.6, 115.9, 98.4, 75.3 59.3, 23.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}O_4N_2$ 311.1026, found 311.1025.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-4-methylbenzamide (**1j**):* 311.0 mg (≥99% yield, beige solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 100.8−101.6 °C; IR (neat) ν_{max} 3391, 2879, 1661, 1525, 1448, 1308, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.40 (dd, J = 7.8, 1.2 Hz, 1H), 7.37−7.32 (m, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.04 (td, J = 7.7, 1.2 Hz, 1H), 3.86 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.40 (s, 3H), 2.11 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 142.5, 139.3, 132.0, 131.6, 129.5, 129.3, 127.1, 123.3, 119.1, 112.5, 94.6, 77.7, 61.0, 23.9, 21.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{17}NNaO_2$ 302.1152, found 302.1149.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-2-methoxybenzamide (**1k**):* 412.9 mg (≥99% yield, pale yellow oil, purified by SiO_2 column chromatography eluting 30−50% EtOAc/hexane); IR (neat) ν_{max} 3315, 2932, 1650, 1527, 1040, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.32 (br s, 1H), 8.55 (d, J = 8.1 Hz, 1H), 8.23 (dd, J = 7.8, 1.8 Hz, 1H), 7.50−7.39 (m, 2H), 7.35−7.29 (m, 1H), 7.13−7.08 (m, 1H), 7.04−6.99 (m, 2H), 4.00 (s, 3H), 3.81 (t, J = 6.4 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 2.60 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.5, 157.3, 139.6, 133.3, 132.4, 132.3, 129.0, 123.3, 122.0, 121.6, 120.5, 113.1, 111.9, 92.7, 61.0, 56.3, 24.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}O_3N$ 296.1281, found 296.1279.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3-methoxybenzamide (**1l**):* 368.4 mg (58% yield, orange solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 109.0−109.4 °C; IR (neat) ν_{max} 3441, 2943, 2233, 1656, 1577, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 8.51−8.46 (m, 1H), 7.47−7.44 (m, 2H), 7.38−7.26 (m, 3H), 7.05−6.99 (m, 2H), 3.83−3.81 (m, 5H), 2.91 (br s, 1H), 2.77−2.72 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0, 159.7, 138.9, 135.95, 135.89, 131.4, 129.7, 129.0, 123.4, 119.0, 118.8, 117.6, 112.7, 95.0, 77.2, 60.7, 55.3, 23.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}O_3N$ 296.1281, found 296.1280.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-4-methoxybenzamide (**1m**):* 411.8 mg (96% yield, white solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 178.5−179.0 °C; IR (neat) ν_{max} 3428, 2958, 2231, 1611, 1024, 757, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 8.53 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.41−7.32 (m, 2H), 7.03 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.89−3.86 (m, 5H), 2.80 (t, J = 6.1 Hz, 2H), 2.07 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.8, 162.6, 139.4, 131.6, 129.3, 129.0, 127.0, 123.2, 119.1, 114.0, 112.4, 94.6, 77.7, 61.0, 55.4, 23.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}O_3N$ 296.1281, found 296.1282.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-3,4,5-trimethoxybenzamide (**1n**):* 206.1 mg (73% yield, white solid, purified by SiO_2 column chromatography eluting 50% EtOAc/hexane); mp 126.9−127.7 °C; IR (neat) ν_{max} 3467, 2939, 1642, 1502, 1333, 1230, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.53 (d, J = 8.3 Hz, 1H), 7.43 (dd, J = 7.6, 1.2 Hz, 1H), 7.40−7.35 (m, 1H), 7.18 (s, 2H), 7.07 (td, J = 7.5, 0.9 Hz, 1H), 3.95 (s, 6H), 3.92 (s, 3H), 3.85 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.0 Hz, 2H), 1.85 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0, 153.4, 141.7, 139.2, 131.7, 130.3, 129.5, 123.5, 119.2, 112.4, 105.0, 94.5, 77.8, 61.0, 60.9, 56.6, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.1493, found 356.1503.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-4-(trifluoromethoxy)-benzamide (**1o**):* 378.5 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 93.6−94.1 °C; IR (neat) ν_{max} 3389, 2928, 1665, 1505, 1252, 1054, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.04−8.00 (m, 2H), 7.41 (td, J = 7.7, 1.5 Hz, 1H), 7.36−7.30 (m, 3H), 7.07 (td, J = 7.7, 1.2 Hz, 1H), 3.87 (q, J = 6.0 Hz, 2H), 2.79 (t, J = 6.0 Hz, 2H), 1.95 (t, J = 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.9, 151.8, 138.9, 133.1, 131.6, 129.4, 129.1, 123.7, 120.7, 120.3 (q, C−F, $^1J_{C-F}$ = 257 Hz), 119.2, 112.7, 94.9, 77.5, 60.9, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 60.8 (s); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}F_3NNaO_3$ 372.0818, found 372.0821.

*4-Fluoro-N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1p**):* 389.9 mg (87% yield, orange solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 100.3−100.6 °C; IR (neat) ν_{max} 3437, 3390, 2916, 1655, 1501, 751, 583 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.45 (d, J = 8.4 Hz,1H), 7.96−7.90 (m, 2H), 7.38 (dd, J = 7.7, 1.2 Hz, 1H), 7.34−7.28 (m, 1H), 7.14−7.07 (m, 2H), 7.02 (td, J = 7.7, 1.2 Hz, 1H), 3.83 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.3 Hz, 2H), 2.62 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.9 (d, C−F, $^1J_{C-F}$ = 251 Hz), 164.2, 138.9, 131.5, 130.7 (d, C−F, $^3J_{C-F}$ = 3 Hz), 129.5 (d, C−F, $^3J_{C-F}$ = 9 Hz), 129.2, 123.6, 119.2, 115.8 (d, C−F, $^2J_{C-F}$ = 22 Hz), 112.8, 95.0, 77.3, 60.8, 23.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 110.4 to −110.5 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}O_2NF$ 284.1081, found 284.1082.

*4-Chloro-N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1q**);* 222.6 mg (68% yield, white solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 109.0−109.4 °C; IR (neat) ν_{max} 3379, 2891, 1653, 1527, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.40 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.37−7.33 (m, 3H), 7.31−7.25 (m, 1H), 7.01 (td, J = 7.6, 0.8 Hz, 1H), 3.82 (t, J = 5.9 Hz, 2H), 2.96 (br s, 1H), 2.73 (t, J = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.2, 138.6, 138.2, 132.7, 131.5, 129.1, 128.9, 128.5, 123.6, 119.1, 112.9, 95.2, 77.1, 60.7, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}O_2N^{35}Cl$ 300.0786, found 300.0788.

*2-Bromo-N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1r**):* 312.7 mg (98% yield, yellow oil, purified by SiO_2 column chromatography eluting 20−40% EtOAc/hexane); IR (neat) ν_{max} 3369, 2936, 2234, 1667, 1518, 1310, 1041, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 8.44 (d, J = 8.4 Hz,1H), 7.61−7.56 (m, 2H), 7.39−7.21 (m, 4H), 7.03 (td, J = 7.5, 0.9 Hz, 1H), 3.64 (t, J = 6.3 Hz, 2H), 2.93 (br s, 1H), 2.59 (t, J = 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5, 138.4, 137.4, 133.3, 131.5, 129.5, 128.8, 127.5, 123.8, 119.5, 119.0, 113.1, 94.7, 77.1, 60.4, 23.5; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{14}{}^{79}BrNNaO_2$ 366.0100, found 366.0094.

*4-Bromo-2-fluoro-N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)-benzamide (**1s**):* 372.1 mg (≥99% yield, yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 117.1−118.2 °C; IR (neat) ν_{max} 3454, 3389, 2888, 2224, 1678, 1579, 1537, 1314, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J = 15.0 Hz,

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1H), 8.53 (d, J = 8.4 Hz, 1H), 8.06 (t, J = 8.7 Hz, 1H), 7.45−7.30 (m, 4H), 7.04 (td, J = 7.8, 0.9 Hz, 1H), 3.87 (t, J = 6.3 Hz, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.31 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.1 (d, C−F, $^3J_{C-F}$ = 4 Hz), 159.7 (d, C−F, $^1J_{C-F}$ = 250 Hz), 139.1, 133.4 (d, C−F, $^3J_{C-F}$ = 3 Hz), 131.7, 129.2, 128.6 (d, C−F, $^3J_{C-F}$ = 3 Hz), 127.0 (d, C−F, $^3J_{C-F}$ = 10 Hz), 123.8, 120.2 (d, C−F, $^3J_{C-F}$ = 12 Hz), 119.74, 119.66 (d, C−F, $^2J_{C-F}$ = 28 Hz), 112.9, 94.6, 77.2, 60.9, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 114.05 to −114.15 (m); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{13}{}^{79}BrFNNaO_2$ 384.0006, found 383.9997.

*4-Cyano-N-(2-(4-hydroxybut-1-yn-1-yl)phenyl)benzamide (**1t**):* 349.4 mg (≥99% yield, pale yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 134.6−135.3 °C; IR (neat) ν_{max} 3385, 2891, 2231, 1663, 1526, 1447, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.41 (dd, J = 7.8, 1.2 Hz, 1H), 7.38−7.32 (m, 1H), 7.08 (td, J = 7.7, 0.9 Hz, 1H), 3.86 (q, J = 5.7 Hz, 2H), 2.78 (t, J = 6.0 Hz, 2H), 2.35 (t, J = 5.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 16.3.4, 138.5, 138.4, 132.5, 131.6, 129.3, 127.9, 124.1, 119.2, 117.9, 115.3, 112.9, 95.5, 77.1, 60.7, 23.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}N_2NaO_2$ 313.0948, found 313.0950.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)-4-nitrobenzamide (**1u**):* 351.3 mg (≥99% yield, brown solid, analytically pure after aqueous workup); mp 171.2−171.3 °C; IR (neat) ν_{max} 3381, 2949, 1524, 1044, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.34−8.31 (m, 2H), 8.16−8.13 (m, 1H), 7.44 (dd, J = 7.7, 1.5 Hz, 1H), 7.41−7.35 (m, 1H), 7.10 (td, J = 7.7, 0.9 Hz, 1H), 3.89 (t, J = 5.7 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 1.93 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.1, 149.8, 140.2, 138.6, 131.6, 129.4, 128.5, 124.2, 124.0, 119.3, 112.9, 95.4, 77.3, 60.9, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}O_4N_2$ 311.1026, found 311.1017.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)cyclohexanecarboxamide (**1v**):* 323.7 mg (95% yield, pale yellow solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 92.6−93.2 °C; IR (neat) ν_{max} 3387, 2929, 2855, 1671, 1519, 1447, 1056, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.4 Hz, 1H), 8.17 (br s, 1H), 7.35 (dd, J = 7.7, 1.5 Hz, 1H), 7.30−7.24 (m, 1H), 6.98 (td, J = 7.8, 0.6 Hz, 1H), 3.85 (br s, 2H), 2.76 (t, J = 6.0 Hz, 2H), 2.59 (br s, 1H), 2.31 (tt, J = 11.7, 3.3 Hz, 1H), 2.02−1.97 (m, 2H), 1.85−1.80 (m, 2H), 1.71−1.68 (m, 1H), 1.52 (qd, J = 12.0, 2.7 Hz, 2H), 1.39−1.16 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.6, 139.2, 131.3, 129.1, 123.0, 119.2, 112.3, 94.3, 77.5, 60.9, 46.4, 29.6, 25.7, 25.6, 23.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{22}NO_2$ 272.1645, found 272.1641.

*N-(2-(4-Hydroxybut-1-yn-1-yl)phenyl)pivalamide (**1w**):* 427.9 mg (94% yield, brown oil, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); IR (neat) ν_{max} 3400, 2961, 1669, 1519, 1447, 761, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 8.4 Hz, 1H), 8.36 (br s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 3.85 (t, J = 6.3 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 176.7, 139.2, 131.5, 129.3, 123.1, 119.0, 112.2, 94.0, 77.6, 61.0, 40.1, 27.6, 23.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{19}NNaO_2$ 268.1308, found 268.1305.

*N-(2-(4-Hydroxy-4-phenylbut-1-yn-1-yl)phenyl)benzamide (**1x**):* 320.6 mg (55% yield, brown solid, purified by SiO_2 column chromatography eluting 5−20% EtOAc/hexane); mp 98.9−99.0 °C; IR (neat) ν_{max} 3386, 2925, 1676, 1521, 1449, 1308, 1057, 754, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.89−7.85 (m, 2H), 7.56−7.22 (m, 10H), 7.04 (td, J = 7.7, 0.9 Hz, 1H), 4.97 (td, J = 6.0, 3.3 Hz, 1H), 2.95 (d, J = 6.3 Hz, 2H), 2.39 (d, J = 3.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4, 142.7, 139.3, 134.8, 131.9, 131.6, 129.4, 128.7, 128.6, 128.2, 127.2, 125.6, 123.4, 119.2, 112.5, 94.1, 78.2, 72.6, 30.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{19}NNaO_2$ 364.1308, found 364.1313.

*N-(2-(4-Hydroxy-4-(4-methoxyphenyl)but-1-yn-1-yl)phenyl)-benzamide (**1y**):* 377.4 mg (≥99% yield, brown solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 93.5−94.0 °C; IR (neat) ν_{max} 3386, 2906, 1662, 1513, 1246, 1033, 756, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.88−7.86 (m, 2H), 7.55−7.52 (m, 1H), 7.47−7.44 (m, 2H), 7.41−7.38 (m, 1H), 7.37−7.33 (m, 1H), 7.32−7.30 (m, 2H), 7.04 (td, J = 7.4, 0.8 Hz, 1H), 6.85−6.83 (m, 2H), 4.93−4.90 (m, 1H), 3.74 (s, 3H), 2.96 (dd, J = 16.8, 6.9 Hz, 1H), 2.91 (dd, J = 16.8, 5.6 Hz, 1H), 2.34 (br d, J = 2.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 159.4, 139.3, 134.84, 134.78, 131.9, 131.6 129.3, 128.7, 127.2, 126.9, 123.4, 119.1, 113.9, 112.5, 94.3, 78.1, 72.3, 55.2, 30.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{21}NNaO_3$ 394.1414, found 394.1414.

*N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)benzamide (**5a**):* 267.4 mg (98% yield, orange solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 81.5−82.0 °C; IR (neat) ν_{max} 3391, 2945, 2222, 1665, 1520, 754, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.2 Hz, 2H), 7.52−7.43 (m, 3H), 7.36 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 3.74 (t, J = 6.0 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.56 (br s, 1H), 1.88−1.82 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.2, 138.8, 134.7, 131.9, 131.4, 128.9, 128.7, 126.8, 123.4, 118.9, 112.9, 97.5, 76.2, 61.0, 31.3, 16.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{17}NNaO_2$ 302.1152, found 302.1151.

*N-(2-(5-Hydroxypent-1-yn-1-yl)-4-methylphenyl)benzamide (**5b**):* 233.0 mg (95% yield, yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 79.9−80.5 °C; IR (neat) ν_{max} 3393, 2934, 2224, 1661, 1517, 1308, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 7.89−7.87 (m, 2H), 7.54−7.43 (m, 3H), 7.19 (br s, 1H), 7.13 (dd, J = 8.4, 1.5 Hz, 1H), 3.76 (t, J = 5.7 Hz, 2H), 2.63 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.12−2.06 (m, 1H), 1.91−1.82 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 136.6, 135.0, 133.1, 131.9, 129.8, 128.8, 127.0, 119.1, 112.9, 97.1, 76.5, 61.3, 31.5, 20.7, 16.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_2$ 316.1308, found 316.1304.

*N-(5-Chloro-2-(5-hydroxypent-1-yn-1-yl)phenyl)benzamide (**5e**):* 190.1 mg (98% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 103.8−105.1 °C; IR (neat) ν_{max} 3389, 2937, 2215, 1569, 1516, 1415, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 8.65 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 6.9 Hz, 2H), 7.60−7.48 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.3, 2.1 Hz, 1H), 3.81−3.77 (m, 2H), 2.67 (t, J = 6.9 Hz, 2H), 1.94−1.85 (m, 2H), 1.57 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 140.0, 134.9, 134.5, 132.2, 128.9, 127.0, 123.6, 119.2, 111.1, 98.3, 75.6, 61.4, 31.3, 16.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{17}{}^{35}ClNO_2$ 314.0942, found 314.0948.

*N-(4-Chloro-2-(5-hydroxypent-1-yn-1-yl)phenyl)benzamide (**5f**):* 352.5 mg (96% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 88.7−88.3 °C; IR (neat) ν_{max} 3392, 2947, 2223, 1667, 1510, 1308, 822, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 8.48 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 6.9 Hz, 2H), 7.57−7.45 (m, 3H), 7.34−7.33 (m, 1H), 7.27 (dd, J = 9.0, 2.4 Hz, 1H), 3.76 (t, J = 5.7 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.10 (br s, 1H), 1.91−1.82 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 137.5, 134.5, 132.1, 131.0, 129.0, 128.8, 128.2, 126.9, 120.1, 114.4, 98.7, 75.2, 61.1, 31.2, 16.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{16}{}^{35}ClNNaO_2$ 336.0762, found 336.0761.

*N-(2-(5-Hydroxypent-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-benzamide (**5g**):* 161.9 mg (84% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 108.5−109.0 °C; IR (neat) ν_{max} 3316, 2951, 2229, 1660, 1533, 1334, 1116, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.94 (br s, 1H), 8.71 (d, J = 8.7 Hz, 1H), 7.94−7.91 (m, 2H), 7.66 (br s, 1H), 7.62−7.50 (m, 4H), 3.81 (t, J = 5.4 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.96−1.87 (m, 2H), 1.48 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4, 141.7, 134.5, 132.4, 129.0, 128.6 (q, C−F, $^3J_{C-F}$ = 4 Hz), 127.1, 126.0 (q, C−F, $^3J_{C-F}$ = 4 Hz), 125.6 (q, C−F, $^1J_{C-F}$ = 278 Hz), 125.4 (q, C−F, $^2J_{C-F}$ = 33 Hz), 118.8, 113.1, 99.0, 75.3, 61.3, 31.2, 16.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.5 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_2$ 348.1206, found 348.1206.

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N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)-4-methoxybenzamide (**5m**): 342.3 mg (93% yield, yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 65.2−65.3 °C; IR (neat) ν_{max} 3394, 2935, 2220, 1660, 1505, 1247, 1028, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.85−7.82 (m, 2H), 7.37−7.28 (m, 2H), 7.00 (t, J = 7.8 Hz, 1H), 6.95−6.92 (m, 2H), 3.79 (s, 3H), 3.77−3.75 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.52 (br s, 1H), 1.92−1.83 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.8, 162.5, 139.0, 131.4, 128.9, 128.8, 126.8, 123.1, 118.9, 113.9, 112.7, 97.3, 76.3, 61.1, 55.3, 31.3, 16.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_3$ 332.1257, found 332.1257.

4-Cyano-N-(2-(5-hydroxypent-1-yn-1-yl)phenyl)benzamide (**5t**): 245.0 mg (93% yield, beige solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 109.1−109.6 °C; IR (neat) ν_{max} 3401, 2934, 2229, 1653, 1532, 1449, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 3.81 (q, J = 5.6 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 1.92−1.86 (m, 2H), 1.61 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.3, 138.7, 138.4, 132.7 131.7, 129.2, 127.7, 124.1, 119.2, 117.9, 115.5, 113.1, 97.8, 76.3, 61.4, 31.3, 16.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_2$ 305.1285, found 305.1282.

N-(2-(5-Hydroxypent-1-yn-1-yl)phenyl)cyclohexanecarboxamide (**5v**): 263.8 mg (97% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 99.9−100.2 °C; IR (neat) ν_{max} 3293, 2928, 1655, 1521, 1446, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.4 Hz, 1H), 8.09 (br s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.30−7.27 (m, 1H), 6.99 (t, J = 7.6 Hz, 1H), 3.86−3.85 (m, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.31 (tt, J = 11.6, 3.2 Hz, 1H), 2.02 (d, J = 12.4 Hz, 2H), 1.94−1.83 (m, 4H), 1.73−1.64 (m, 2H), 1.54 (qd, J = 12.0, 3.0 Hz, 2H), 1.39−1.21 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2, 139.1, 131.5, 129.0, 123.0, 119.1, 112.4, 96.4, 76.5, 61.6, 46.6, 31.4, 29.7, 25.73, 25.63, 16.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{24}NO_2$ 286.1802, found 286.1800.

N-(2-(5-Hydroxy-5-phenylpent-1-yn-1-yl)phenyl)benzamide (**5x**): 132.5 mg (67% yield, brown solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 92.4−93.2 °C; IR (neat) ν_{max} 3390, 3062, 1665, 1521, 1310, 755, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.88−7.86 (m, 2H), 7.51−7.47 (m, 1H), 7.41−7.39 (m, 2H), 7.37−7.36 (m, 1H), 7.34−7.25 (m, 6H), 7.05 (t, J = 7.6 Hz, 1H), 4.83 (dd, J = 8.0, 4.8 Hz, 1H), 2.72−2.56 (m, 2H), 2.27 (br s, 1H), 2.15−2.06 (m, 1H), 2.04−1.95 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 143.9, 139.0, 135.0, 131.9, 131.5, 129.1, 128.8, 128.6, 127.8, 127.0, 125.7, 123.4, 119.0, 112.9, 97.6, 76.6, 73.2, 37.8, 16.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{22}NO_2$ 356.1645, found 356.1642.

N-(2-(6-Hydroxyhex-1-yn-1-yl)phenyl)benzamide (**7a**): 263.8 mg (99% yield, yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 63.0−63.3 °C; IR (neat) ν_{max} 3390, 2937, 1676, 1521, 1310, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.93−7.90 (m, 2H), 7.59−7.48 (m, 3H), 7.42−7.33 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 3.66 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.3 Hz, 2H), 1.81−1.66 (m, 5H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 139.0, 135.1, 131.9, 131.5, 129.1, 128.8, 127.0, 123.4, 119.0, 112.9, 97.8, 76.4, 62.2, 31.9, 25.2, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_2$ 316.1308, found 316.1310.

N-(2-(6-Hydroxyhex-1-yn-1-yl)-4-methylphenyl)benzamide (**7b**): 306.5 mg (96% yield, pale orange solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 87.7−88.3 °C; IR (neat) ν_{max} 3338, 2922, 1653, 1310, 1057, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 7.92−7.89 (m, 2H), 7.58−7.47 (m, 3H), 7.22 (s, 1H), 7.15 (dd, J = 8.4, 1.8 Hz, 1H), 3.65 (t, J = 5.4 Hz, 2H), 2.56 (t, J = 6.6 Hz, 2H), 2.29 (s, 3H), 1.79−1.66 (m, 4H), 1.47 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 136.6, 135.2, 133.1, 131.88, 131.86, 129.8, 128.8, 127.0, 119.0, 112.9, 97.3, 76.6, 62.2, 31.9, 25.2, 20.7, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{21}NNaO_2$ 330.1465, found 330.1465.

N-(5-Chloro-2-(6-hydroxyhex-1-yn-1-yl)phenyl)benzamide (**7e**): 157.9 mg (92% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 102.5−102.9 °C; IR (neat) ν_{max} 3485, 3378, 2939, 2215, 1664, 1569, 1516, 1416, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.66 (d, J = 1.8 Hz, 1H), 7.91−7.88 (m, 2H), 7.60−7.48 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4, 2.1 Hz, 1H), 3.67 (br s, 2H), 2.58 (t, J = 6.6 Hz, 2H), 1.78−1.67 (m, 4H), 1.44 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 139.8, 134.9, 134.6, 132.2, 128.9, 127.0, 123.6, 119.1, 111.2, 98.7, 75.6, 62.1, 31.9, 25.1, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{18}{}^{35}ClNNaO_2$ 350.0918, found 350.0912.

N-(4-Chloro-2-(6-hydroxyhex-1-yn-1-yl)phenyl)benzamide (**7f**): 382.1 mg (97% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 90.6−90.9 °C; IR (neat) ν_{max} 3261, 2931, 2222, 1684, 1512 1304, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.51 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 6.9 Hz, 2H), 7.59−7.48 (m, 3H), 7.37−7.36 (m, 1H), 7.29 (dd, J = 9.0, 2.4 Hz, 1H), 3.66 (br s, 2H), 2.57 (t, J = 6.3 Hz, 2H), 1.80−1.65 (m, 4H), 1.58 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 137.5, 134.6, 132.1, 131.1, 129.0, 128.9, 128.2, 127.0, 120.1, 114.5, 99.1, 75.3, 62.1, 31.8, 25.1, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{18}{}^{35}ClNNaO_2$ 350.0918, found 350.0918.

N-(2-(6-Hydroxyhex-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-benzamide (**7g**): 159.6 mg (84% yield, white solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 100.7−101.3 °C; IR (neat) ν_{max} 3394, 3303, 2937, 2227, 1684, 1528, 1331, 1116, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.70 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H), 7.66 (s, 1H), 7.61−7.50 (m, 4H), 3.68 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.6 Hz, 2H), 1.82−1.71 (m, 4H), 1.61 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 141.6, 134.4, 132.4, 129.0, 128.6 (q, J_{C-F} = 4 Hz), 127.0, 125.9 (q, J_{C-F} = 4 Hz), 125.4 (q, J_{C-F} = 33 Hz), 123.7 (q, J_{C-F} = 270 Hz), 118.8, 113.2, 99.4, 75.2, 62.1, 31.8, 25.1, 19.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.5 (s); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{18}F_3NNaO_2$ 348.1182, found 348.1173.

N-(2-(6-Hydroxyhex-1-yn-1-yl)phenyl)-4-methoxybenzamide (**7m**): 347.5 mg (90% yield, pale orange solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 77.1−77.5 °C; IR (neat) ν_{max} 3433, 3387, 2939, 1652, 1508, 1255, 1064, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.52 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.05−6.96 (m, 3H), 3.85 (m, 3H), 3.67 (br s, 2H), 2.59−2.54 (m, 2H), 1.80−1.72 (m, 5H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.7, 162.5, 139.1, 131.5, 129.0, 128.8, 127.1, 123.1, 118.9, 114.0, 112.8, 97.7, 76.4, 62.1, 55.4, 31.9, 25.2, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{21}NNaO_3$ 346.1414, found 346.1411.

4-Cyano-N-(2-(6-hydroxyhex-1-yn-1-yl)phenyl)benzamide (**7t**): 313.1 mg (96% yield, pale yellow solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 118.6−119.4 °C; IR (neat) ν_{max} 3368, 2944, 2233, 1686, 1523, 1447, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.49 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.42 (dd, J = 7.8, 1.2 Hz, 1H), 7.39−7.33 (m, 1H), 7.09 (td, J = 7.5, 0.9 Hz, 1H), 3.70−3.69 (m, 2H), 2.57 (t, J = 6.6 Hz, 2H), 1.78−1.70 (m, 4H), 1.68 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.3, 138.8, 138.2, 132.7, 131.7, 129.1, 127.6, 124.1, 119.1, 117.8, 115.4, 113.2, 98.2, 76.1, 62.0, 31.7, 25.2, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{18}N_2NaO_2$ 341.1260, found 341.1258.

N-(2-(6-Hydroxyhex-1-yn-1-yl)phenyl)cyclohexanecarboxamide (**7v**): 336.5 mg (89% yield, orange solid, purified by SiO_2 column chromatography eluting 30% EtOAc/hexane); mp 78.1−78.8 °C; IR (neat) ν_{max} 3389, 2929, 1673, 1517, 1447, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.4 Hz, 1H), 8.08 (br s, 1H), 7.35 (dd, J = 7.6, 1.6 Hz, 1H), 7.29−7.25 (m, 1H), 6.99 (td, J = 7.6, 0.8 Hz, 1H), 3.73−3.70 (m, 2H), 2.57−2.54 (m, 2H), 2.29 (tt, J = 11.6, 3.6 Hz, 1H), 2.03−2.00 (m, 3H), 1.86−1.82 (m, 2H), 1.79−1.70 (m, 5H), 1.53 (qd, J = 12.0, 2.8 Hz, 2H), 1.39−1.19 (m, 3H); $^{13}C\{^1H\}$ NMR

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(100 MHz, $CDCl_3$) δ 174.2, 138.8, 131.4, 128.9 123.0, 119.0, 112.5, 97.3, 76.3, 62.0, 46.6, 31.8, 29.7, 25.7, 25.6, 25.1, 19.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{26}NO_2$ 300.1958, found 300.1963.

Procedure for Spiroannulation of Substrates 1 to Spirocycles 2X (Representative Case: Synthesis of Spirocycle 2aBr). A 5 mL round-bottomed flask containing a magnetic stir bar was charged with substrate **1a** (49.7 mg, 0.178 mmol, 1.00 equiv) and EtOAc (1.0 mL). The reaction mixture was added to a solution of 1 M aqueous HCl (0.09 mL, 0.09 mmol, 0.51 equiv) (effective concentration of **1a** ≈ 0.2 M), followed by NBS (64.2 mg, 0.361 mmol, 2.02 equiv). The reaction mixture was allowed to stir at room temperature until judged complete by TLC (typically 5−15 min). Upon completion, the mixture was diluted with water, and the separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude spirocyclic product, which was purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to give 65.6 mg (87%) of the pure desired product (**2aBr**) as a white crystalline solid.

The reaction of **1a** at a larger scale (514.3 mg, 1.841 mmol) was conducted employing the same procedure to afford 654.9 mg (84%) of **2aBr** as a white crystalline solid.

*3′,3′-Dibromo-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]-oxazine-4,2′-furan] (**2aBr**):* 65.6 mg (87% yield, white crystalline solid, purified by SiO_2 column chromatography eluting 15% EtOAc/hexane); mp 128.9−129.3 °C; IR (neat) ν_{max} 2922, 1629, 816, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13−8.10 (m, 2H), 7.76 (dd, J = 7.8, 0.9 Hz, 1H), 7.54−7.42 (m, 5H), 7.34−7.42 (m, 1H), 4.52−4.40 (m, 2H), 3.67 (dt, J = 13.5, 9.6 Hz, 1H), 3.11 (ddd, J = 13.8, 6.0, 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.3, 141.7, 131.7, 131.5, 131.3, 128.7, 128.3, 128.0, 125.9, 125.1, 117.3, 109.2, 66.6, 66.4, 45.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}O_2N^{79}Br_2$ 421.9386, found 421.9376.

*3′,3′-Dibromo-6-methyl-2-phenyl-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2bBr**):* 179.5 mg (82% yield, white solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 73.4−73.7 °C; IR (neat) ν_{max} 2904, 1631, 1287, 1084, 936, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 6.8 Hz, 2H), 7.57 (s, 1H), 7.54−7.43 (m, 3H), 7.34−7.30 (m, 2H), 4.49−4.40 (m, 2H), 3.71−3.63 (m, 1H), 3.14 (ddd, J = 13.8, 6.2, 1.4 Hz, 1H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.7, 139.4, 135.9,132.1, 131.9, 131.4, 129.0, 128.3, 128.0, 125.0, 117.0, 109.2, 66.6, 66.2, 45.1, 21.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}O_2N^{79}Br_2$ 435.9542, found 435.9540.

*3′,3′-Dibromo-7-fluoro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2cBr**):* 133.1 mg (70% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 162.3−162.6 °C; IR (neat) ν_{max} 2907, 1600, 1493, 1057, 929, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.75−7.70 (m, 1H), 7.54−7.43 (m, 3H), 7.12 (dd, J = 9.8, 2.1 Hz, 1H), 7.00 (td, J = 8.4, 2.1 Hz, 1H), 4.49−4.37 (m, 2H), 3.69−3.59 (m, 1H), 3.14 (dd, J = 13.5, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.5 (d, C−F, $^1J_{C-F}$ = 248 Hz), 156.4, 143.9 (d, C−F, $^3J_{C-F}$ = 12 Hz), 131.9, 131.4, 130.6 (d, C−F, $^2J_{C-F}$ = 20 Hz), 128.4, 128.2, 113.3 (d, C−F, $^3J_{C-F}$ = 3 Hz), 113.0 (d, C−F, $^2J_{C-F}$ = 22 Hz), 111.7 (d, C−F, $^2J_{C-F}$ = 23 Hz), 109.3, 66.7, 66.4, 44.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 112.9 to −113.0 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}{}^{79}Br_2FNO_2$ 439.9292, found 439.9300.

*3′,3′-Dibromo-6-fluoro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2dBr**):* 148.9 mg (87% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 147.7−148.9 °C; IR (neat) ν_{max} 2923, 1632, 1494, 1054, 795, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 6.0 Hz, 2H), 7.49−7.38 (m, 5H), 7.24−7.17 (m, 1H), 4.47−4.37 (m, 2H), 3.67−3.59 (m, 1H), 3.12 (dd, J = 10.5, 4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4 (d, C−F, $^1J_{C-F}$ = 244 Hz), 154.8, 138.1 (d, C−F, $^3J_{C-F}$ = 3 Hz), 131.6, 131.5, 128.3, 128.0, 126.7 (d, C−F, $^3J_{C-F}$ = 8 Hz), 118.9 (d, C−F, $^3J_{C-F}$ = 9 Hz), 118.4 (d, C−F, $^2J_{C-F}$ = 22 Hz), 115.6 (d, C−F, $^2J_{C-F}$ = 25 Hz) 108.7, 66.8, 65.6, 44.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 117.6 to −117.7 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}O_2N^{79}Br_2F$ 439.9292, found 439.9279.

*3′,3′-Dibromo-7-chloro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2eBr**):* 162.5 mg (74% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 164.3−165.0 °C; IR (neat) ν_{max} 2930, 2853, 2155, 1642, 931, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.58−7.46 (m, 4H), 7.32−7.28 (m, 1H), 4.53−4.42 (m, 2H), 3.73−3.62 (m, 1H), 3.18 (dd, J = 13.7, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.4, 143.1, 137.0, 131.9, 131.3, 130.0, 128.4, 128.2, 125.9, 125.0, 115.8, 109.2, 66.8, 66.1, 44.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}{}^{79}Br_2{}^{35}ClNO_2$ 455.8996, found 455.8999.

*3′,3′-Dibromo-6-chloro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2fBr**):* 141.4 mg (87% yield, pale yellow solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 144.4−145.6 °C; IR (neat) ν_{max} 2907, 1626, 1252, 1056, 935, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.74 (d, J = 2.4 Hz, 1H), 7.53−7.42 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 4.49−4.37 (m, 2H), 3.63 (dt, J = 13.5, 9.6 Hz, 1H), 3.13 (ddd, J = 10.5, 5.9, 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.7, 140.4, 131.8, 131.4, 131.1, 128.7, 128.4, 128.1, 126.5, 118.8, 108.8, 66.9 65.6, 45.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}{}^{79}Br_2{}^{35}ClNO_2$ 455.8996, found 455.8988.

*3′,3′-Dibromo-2-phenyl-6-(trifluoromethyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2gBr**):* 152.4 mg (81% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 96.3−96.9 °C; IR (neat) ν_{max} 2977, 1606, 1264, 1079, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15−8.12 (m, 2H), 8.02 (br s, 1H), 7.76−7.73 (m, 1H), 7.56−7.44 (m, 4H), 4.54−4.41 (m, 2H), 3.66 (dt, J = 18.3, 9.3 Hz, 1H), 3.16 (ddd, J = 14.4, 6.0, 1.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 157.1, 144.7, 132.2, 131.2, 128.44, 128.36, 128.2 (q, C−F, $^3J_{C-F}$ = 4 Hz), 127.6 (q, C−F, $^2J_{C-F}$ = 33 Hz), 126.4 (q, C−F, $^3J_{C-F}$ = 4 Hz), 125.5, 124.0 (q, C−F, $^1J_{C-F}$ = 270 Hz), 117.9, 109.0, 67.0, 65.8, 44.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.5 (s); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{13}{}^{79}Br_2F_3NO_2$ 489.9260, found 489.9268.

*3′,3′-Dibromo-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]-oxazine-4,2′-furan]-6-carbonitrile (**2hBr**):* 136.4 mg (79% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 163.0−163.9 °C; IR (neat) ν_{max} 2909, 2226, 1596, 1259, 1058, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 8.033−8.027 (m, 1H), 7.73 (dd, J = 8.1, 1.8 Hz, 1H), 7.58−7.53 (m, 1H), 7.47 (t, J = 7.5 Hz, 3H), 4.52−4.41 (m, 2H), 3.64 (dt, J = 13.8, 9.3 Hz, 1H), 3.17 (ddd, J = 13.7, 5.7, 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 157.8, 145.5, 134.7, 133.2, 132.5, 130.8, 128.5, 128.4, 125.8, 118.5, 108.9, 108.6, 67.2, 65.5, 44.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{13}{}^{79}Br_2N_2O_2$ 446.9338, found 446.9337.

*3′,3′-Dibromo-6-nitro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2iBr**):* 176.8 mg (37% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 153.4−154.2 °C; IR (neat) ν_{max} 2922, 1607, 1569, 1339, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.33−8.30 (m, 1H), 8.14 (d, J = 8.1 Hz, 2H), 7.59−7.46 (m, 4H), 4.51−4.41 (m, 2H), 3.70−3.59 (m, 1H), 3.19 (dd, J = 13.8, 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.3, 147.2, 144.9, 132.6, 130.7, 128.52, 128.47, 126.4, 125.8, 125.1, 118.2, 108.8, 67.3, 65.5, 44.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}O_4N_2{}^{79}Br_2$ 466.9237, found 466.9236.

*3′,3′-Dibromo-2-(p-tolyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]-oxazine-4,2′-furan] (**2jBr**):* 305.0 mg (86% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 130.0−130.7 °C; IR (neat) ν_{max} 2922, 1596, 1251, 1057, 935, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 2H), 7.75 (dd, J = 7.8, 1.2 Hz, 1H), 7.51−7.40 (m, 2H), 7.30−7.23 (m, 3H), 4.48−4.36 (m, 2H), 3.64 (dt, J = 13.8, 9.3 Hz, 1H), 3.11 (ddd, J = 13.7, 6.0, 1.8 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.5, 142.0, 141.8, 131.2, 129.1, 129.0, 128.7, 128.3, 125.6,

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125.0, 117.3, 109.1, 66.6, 66.4, 45.0, 21.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{16}{}^{79}Br_2NO_2$ 435.9542, found 435.9545.

*3′,3′-Dibromo-2-(2-methoxyphenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2kBr**):* 210.0 mg (41% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 104.6−104.9 °C; IR (neat) ν_{max} 2906, 1598, 1247, 925, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.52−7.40 (m, 3H), 7.30 (t, J = 7.5 Hz, 1H), 7.03−6.96 (m, 2H), 4.46−4.38 (m, 1H), 4.35−4.29 (m, 1H), 3.88 (s, 3H), 3.70 (dt, J = 13.5, 9.3 Hz, 1H), 3.05 (dd, J = 13.2, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.7, 155.8, 141.9, 132.4, 131.9, 131.2, 128.5, 125.8, 125.1, 121.4, 120.4, 116.8, 112.2, 109.1, 66.7, 55.9, 44.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{16}{}^{79}Br_2NO_3$ 451.9492, found 451.9494.

*3′,3′-Dibromo-2-(3-methoxyphenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2lBr**):* 136.5 mg (83% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 104.1−105.1 °C; IR (neat) ν_{max} 2906, 1629, 1577, 1285, 1035, 927, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 1H), 7.70−7.67 (m, 2H), 7.53−7.48 (m, 1H), 7.44−7.42 (m, 1H), 7.38−7.28 (m, 2H), 7.07−7.03 (m, 1H), 4.49−4.38 (m, 2H), 3.87 (s, 3H), 3.70−3.59 (m, 1H), 3.16−3.10 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.5, 155.2, 141.6, 133.1, 129.3, 128.7, 125.9, 125.2, 120.5, 117.6, 117.4, 113.1, 109.2, 66.7, 66.3, 55.4, 45.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{16}O_3N^{79}Br_2$ 451.9492, found 451.9479.

*3′,3′-Dibromo-2-(4-methoxyphenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2mBr**):* 336.6 mg (82% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 164.5−164.8 °C; IR (neat) ν_{max} 2928, 1596, 1170, 793, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.40 d, J = 7.2 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 4.48−4.36 (m, 2H), 3.83 (s, 3H), 3.69−3.58 (m, 1H), 3.12 (dd, J = 13.8, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 162.4, 155.2, 142.0, 131.2, 129.8, 128.6, 125.4, 124.8, 124.1, 117.2, 113.7, 109.0, 66.6, 66.4, 55.3, 45.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{16}ON^{79}Br_2$ 451.9492, found 451.9488.

*3′,3′-Dibromo-2-(3,4,5-trimethoxyphenyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2nBr**):* 163.0 mg (78% yield, white solid, purified by SiO_2 column chromatography eluting 5−20% EtOAc/hexane); mp 134.2−134.9 °C; IR (neat) ν_{max} 2939, 1583, 1348, 1125, 930, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.44−7.41 (m, 1H), 7.38 (s, 2H), 7.33−7.26 (m, 1H), 4.52−4.40 (m, 2H), 3.95 (s, 6H), 3.91 (s, 3H), 3.65−3.54 (m, 1H), 3.17 (dd, J = 13.5, 5.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.0, 152.9, 141.6, 141.3, 131.3, 128.7, 127.0, 125.8, 125.0, 117.2, 109.3, 105.5, 66.7, 66.2, 60.9, 56.3, 45.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{20}Br_2NO_5$ 511.9703, found 511.9690.

*3′,3′-Dibromo-2-(4-(trifluoromethoxy)phenyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2oBr**):* 143.5 mg (84% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 122.3−122.6 °C; IR (neat) ν_{max} 2920, 1629, 1603, 1248, 1152, 927, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18−8.13 (m, 2H), 7.77−7.74 (m, 1H), 7.54−7.49 (m, 1H), 7.43−7.40 (m, 1H), 7.35−7.27 (m, 3H), 4.52−4.39 (m, 2H), 3.63 (dt, J = 14.1, 9.6 Hz, 1H), 3.16 (ddd, J = 13.8, 6.3, 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.2, 151.6, 141.5, 131.4, 130.3, 129.8, 128.8, 126.2, 125.2, 120.39, 120.36 (q, C−F, $^1J_{C-F}$ = 257 Hz), 117.3, 109.5, 66.8, 66.2, 45.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}{}^{79}Br_2F_3NO_3$ 505.9209, found 505.9204.

*3′,3′-Dibromo-2-(4-fluorophenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2pBr**):* 450.6 mg (81% yield, white solid, purified by SiO_2 column chromatography eluting 5−20% EtOAc/hexane); mp 126.7−127.1 °C; IR (neat) ν_{max} 2905, 1632, 1506, 1082, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 8.4 Hz, 2H), 4.51−4.39 (m, 2H), 3.63 (dt, J = 13.8, 9.3 Hz, 1H), 3.19−3.12 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 164.9 (d, C−F, $^1J_{C-F}$ = 251 Hz), 154.5, 141.6, 131.4, 130.3 (d, C−F, $^3J_{C-F}$ = 9 Hz), 128.8, 128.0 (d, C−F, $^3J_{C-F}$ = 3 Hz), 125.9, 125.1, 117.3, 115.5 (d, C−F, $^2J_{C-F}$ = 22 Hz), 109.3, 66.7, 66.3, 45.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 111.1 to −111.2 (m); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}O_2N^{79}Br_2F$ 439.9292, found 439.9290.

*3′,3′-Dibromo-2-(4-chlorophenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2qBr**):* 68.9 mg (79% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 149.2−149.5 °C; IR (neat) ν_{max} 2920, 1631, 1107, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.6 Hz, 2H), 7.74 (dd, J = 7.7, 1.1 Hz, 1H), 7.49 (td, J = 7.8, 1.5 Hz, 1H), 7.42−7.39 (m, 3H), 7.30 (td, J = 15.0, 1.3 Hz, 1H), 4.47−4.35 (m, 2H), 3.59 (dt, J = 13.8, 9.3 Hz, 1H), 3.11 (ddd, J = 13.7, 6.1, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.4, 141.4, 137.7, 131.3, 130.3, 129.3, 128.7, 128.6, 126.1, 125.1, 117.3, 109.3, 66.7, 66.2, 45.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}O_2N^{79}Br_2{}^{35}Cl$ 455.8996, found 455.8996.

*3′,3′-Dibromo-2-(2-bromophenyl)-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2rBr**):* 207.0 mg (75% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 104.8−106.1 °C; IR (neat) ν_{max} 2972, 2905, 1640, 1064, 921, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.54−7.25 (m, 5H), 4.46−4.31 (m, 2H), 3.61−3.50 (m, 1H), 3.10−3.04 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.1, 141.1, 134.2, 133.5, 131.5 131.4, 128.8, 127.1, 126.4, 125.3, 121.4, 116.6, 109.5, 66.8, 66.5, 44.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}{}^{79}Br_3NO_2$ 499.8491, found 499.8500.

*3′,3′-Dibromo-2-(4-bromo-2-fluorophenyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2sBr**):* 138.8 mg (69% yield, white solid, purified by SiO_2 column chromatography eluting 2% EtOAc/hexane); 106.6−107.0 °C; IR (neat) ν_{max} 2973, 2906, 1626, 1599, 1483, 923, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 7.41−7.32 (m, 4H), 4.48−4.34 (m, 2H), 3.73−3.62 (m, 1H), 3.12−3.05 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.1 (d, C−F, $^1J_{C-F}$ = 261 Hz), 153.3 (d, C−F, $^3J_{C-F}$ = 4 Hz), 141.2, 132.6 (d, C−F, $^3J_{C-F}$ = 2 Hz), 131.4, 128.8, 127.6 (d, C−F, $^3J_{C-F}$ = 4 Hz), 126.4, 126.2 (d, C−F, $^3J_{C-F}$ = 10 Hz), 125.2, 120.6 (d, C−F, $^2J_{C-F}$ = 26 Hz), 119.1 (d, C−F, $^3J_{C-F}$ = 9 Hz), 117.2, 109.5, 66.9, 66.3, 44.6 (d, C−F, $^3J_{C-F}$ = 2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ − 111.1 (dd, J = 10.5, 8.3 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}{}^{79}Br_3FNO_2$ 517.8397, found 517.8389.

*4-(3′,3′-Dibromo-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan]-2-yl)benzonitrile (**2tBr**):* 156.6 mg (92% yield, yellow solid, purified by SiO_2 column chromatography eluting 5−15% EtOAc/hexane); mp 223.4−224.4 °C; IR (neat) ν_{max} 2923, 2226, 1630, 1311, 1059, 915, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.1 Hz, 2H), 7.77−7.72 (m, 3H), 7.53 (td, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 4.52−4.40 (m 2H), 3.61 (dt, J = 13.8, 9.6 Hz, 1H), 3.16 (dd, J = 13.8, 5.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.5, 141.0, 135.9, 132.1, 131.5, 128.8 128.4, 126.7, 125.5, 118.3, 117.4, 114.7, 109.6, 66.9, 66.1, 45.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}$ $Br_2N_2O_2$ 446.9338, found 466.9338.

*3′,3′-Dibromo-2-(4-nitrophenyl)-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2uBr**):* 117.8 mg (74% yield, yellow solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 156.9−157.4 °C; IR (neat) ν_{max} 3073, 2982, 1595, 1518, 1345, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 4H), 7.77 (d, J = 7.8 Hz, 1H), 7.54 (td, J = 7.8, 1.2 Hz, 1H), 7.45−7.43 (m, 1H), 7.36 (td, J = 7.5, 0.9 Hz, 1H), 4.54−4.42 (m, 2H), 3.62 (dt, J = 13.8, 9.3 Hz, 1H), 3.17 (ddd, J = 13.7, 6.3, 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.3, 149.5, 141.0, 137.6, 131.5, 128.9, 128.8, 126.9, 125.6, 123.5, 117.4, 109.7, 67.0, 66.1, 45.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}O_4N_2Br_2$ 466.9237, found 466.9229.

*3′,3′-Dibromo-2-cyclohexyl-4′,5′-dihydro-3′H-spiro[benzo[d]-[1,3]oxazine-4,2′-furan] (**2vBr**):* 210.5 mg (72% yield, yellow oil,

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purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); IR (neat) ν_{max} 2922, 1627, 1594, 1057, 931, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.8, 1.2 Hz, 1H), 7.46−7.41 (m, 1H), 7.28−7.21 (m, 2H), 4.41−4.24 (m, 2H), 3.53−3.42 (m, 1H), 3.03 (dd, J = 13.5, 6.3 Hz, 1H), 2.41 (tt, J = 11.7, 3.4 Hz, 1H), 2.11−2.07 (m, 1H), 2.03−1.98 (m, 1H), 1.84−1.80 (m, 2H), 1.71−1.68 (m, 1H), 1.60−1.42 (m, 2H), 1.39−1.15 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.4, 141.4, 131.1, 128.5, 125.3, 124.5, 116.6, 108.3, 66.7, 66.4, 44.6, 43.5, 30.0, 29.9, 25.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{20}{}^{79}Br_2NO_2$ 427.9855, found 427.9861.

*3′,3′-Dibromo-2-(tert-butyl)-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2wBr**):* 67.2 mg (36% yield, yellow oil, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); IR (neat) ν_{max} 3362, 2969, 1619, 1233, 928, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ, 7.75 (dd, J = 7.7, 1.5 Hz, 1H), 7.47 (td, J = 7.7, 1.2 Hz, 1H), 7.34−7.32 (m, 1H), 7.30−7.25 (m, 1H), 4.45−4.37 (m, 1H), 4.31 (t, J = 9.3 Hz, 1H), 3.50 (dt, J = 13.5, 9.3 Hz, 1H), 3.11−3.05 (m, 1H), 1.34 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.6, 141.6, 131.1, 128.4, 125.4, 124.8, 116.2, 108.4, 66.6, 66.3, 44.6, 37.3, 28.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{18}{}^{79}Br_2NO_2$ 401.9699, found 401.9704.

*3′,3′-Dibromo-2,5′-diphenyl-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2xBr**):* 173.2 mg (57% yield, white amorphous solid, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); mp 115.1−115.9 °C; IR (neat) ν_{max} 3064, 1631, 1254, 1065, 935, 766, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.84 (dd, J = 7.8, 0.9 Hz, 1H), 7.61−7.58 (m, 2H), 7.56−7.30 (m, 9H), 5.71 (dd, J = 9.9, 6.0 Hz, 1H), 3.55 (dd, J = 13.8, 9.9 Hz, 1H), 3.44 (dd, J = 13.8, 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.4, 141.7, 139.3, 131.8, 131.6, 131.4, 129.0, 128.8, 128.43, 128.40, 128.1, 126.2, 125.9, 125.2, 117.6, 109.6, 81.6, 66.7, 53.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}{}^{79}Br_2NO_2$ 497.9699, found 497.9700.

*3′,3′-dibromo-5′-(4-methoxyphenyl)-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]oxazine-4,2′-furan] (**2yBr**):* 44.0 mg (36% yield, white crystalline solid, purified by SiO_2 column chromatography eluting 2−5% EtOAc/hexane); mp 127.9−128.2 °C; IR (neat) ν_{max} 2931, 1630, 1514, 1250, 1033, 930, 830, 767, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2H), 7.82 (dd, J = 7.6, 1.2 Hz, 1H), 7.54−7.50 (m, 4H), 7.49−7.45 (m, 3H), 7.32 (td, J = 7.2, 1.2 Hz, 1H), 6.95−6.91 (m, 2H), 5.66 (dd, J = 10.2, 5.6 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, J = 13.6, 10.0 Hz, 1H), 3.39 (dd, J = 14.0, 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 155.5, 141.7, 131.8, 131.6, 131.4, 131.0, 129.0, 128.5, 128.2, 127.8, 125.9, 125.2, 117.7, 114.2, 109.5, 81.5, 66.8, 55.3, 53.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{20}{}^{79}Br_2NO_3$ 527.9804, found 527.9804.

*3′,3′-Dichloro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo[d][1,3]-oxazine-4,2′-furan] (**2aCl**):* 26.0 mg (19% yield, white crystal, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 133.9−134.2 °C; IR (neat) ν_{max} 3060, 1628, 767, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.46−7.37 (m, 5H), 7.25 (t, J = 7.6 Hz, 1H), 4.46 (t, J = 8.8 Hz, 1H), 4.40−4.34 (m, 1H), 3.38−3.30 (m, 1H) 2.96−2.91 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.2, 141.6, 131.7, 131.6, 131.3, 128.4, 128.3, 128.0, 126.0, 125.1, 116.9, 109.1, 90.9, 66.2, 42.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{14}O_2N^{35}Cl_2$ 334.0396, found 334.0390.

*3′,3′-Dichloro-6-methyl-2-phenyl-4′,5′-dihydro-3′H-spiro-[benzo[d][1,3]oxazine-4,2′-furan] (**2bCl**):* 31.3 mg (48% yield, white solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 164.5−165.0 °C; IR (neat) ν_{max} 3271, 2908, 1629, 1061, 832, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.0, 1.5 Hz, 2H), 7.52−7.41 (m, 4H), 7.34−7.28 (m, 2H), 4.52 (td, J = 8.4, 1.5 Hz, 1H), 4.47−4.38 (m, 1H), 3.40 (dt, J = 13.5, 9.6 Hz, 1H), 2.99 (ddd, J = 13.2, 6.6, 1.5 Hz, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.6, 139.3, 136.0, 132.1, 131.9, 131.4, 128.7, 128.3, 127.9, 125.0, 116.6, 109.1, 90.8, 66.2, 42.6, 21.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}O_2N^{35}Cl_2$ 348.0553, found 348.0548.

*3′,3′-Dichloro-7-fluoro-2-phenyl-4′,5′-dihydro-3′H-spiro[benzo-[d][1,3]oxazine-4,2′-furan] (**2cCl**):* 19.9 mg (33% yield, white solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 156.2−156.7 °C; IR (neat) ν_{max} 2910, 1598, 1059, 954 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13−8.09 (m, 2H), 7.62 (dd, J = 8.7, 8.0 Hz, 1H), 7.56−7.43 (m, 3H), 7.12 (dd, J = 9.5, 2.7 Hz, 1H), 7.00 (td, J = 8.4, 2.7 Hz, 1H), 4.52 (td, J = 8.6, 1.5 Hz, 1H), 4.46−4.38 (m, 1H), 3.38 (dt, J = 13.5, 9.6 Hz, 1H), 3.00 (ddd, J = 13.4, 6.6, 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.6 (d, C−F, $^1J_{C-F}$ = 248 Hz), 156.3, 143.8 (d, C−F, $^3J_{C-F}$ = 12 Hz), 131.9, 131.4, 130.3 (d, C−F, $^3J_{C-F}$ = 10 Hz), 128.4, 128.1, 113.2 (d, C−F, $^2J_{C-F}$ = 22 Hz), 112.9, (d, C−F, $^3J_{C-F}$ = 3 Hz), 111.8 (d, C−F, $^2J_{C-F}$ = 23 Hz) 109.2, 90.9, 66.3, 42.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 112.96 to −113.02 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}O_2N^{35}Cl_2F$ 352.0302, found 352.0297.

Procedure for Spiroannulation of Substrates 5 to Spirocycles 6X (Representative Case: Synthesis of Spirocycle 6aBr). A 10 mL round-bottomed flask containing a magnetic stir bar was charged with substrate **5a** (161.8 mg, 0.579 mmol, 1.00 equiv), 2.9 mL of EtOAc (effective concentration of **5a** ≈ 0.2 M), and 0.29 mL of a solution of 1.0 M aqueous HCl (0.29 mmol, 0.5 equiv). The resulted solution was then added with NBS (208.9 mg, 1.174 mmol, 2.03 equiv) and was allowed to stir at room temperature. Upon completion as judged by TLC (typically 5−15 min), the reaction mixture was diluted with water. The separated aqueous phase was extracted with EtOAc, and the combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude spirocyclic product. The crude material was purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to give 203.3 mg (80%) of pure compound **6aBr** as a white solid.

*3′,3′-Dibromo-2-phenyl-3′,4′,5′,6′-tetrahydrospiro[benzo[d][1,3]oxazine-4,2′-pyran] (**6aBr**):* 203.3 mg (80% yield, white solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 125.8−126.0 °C; IR (neat) ν_{max} 2966, 1633, 956, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 7.90 (dd, J = 7.8, 1.2 Hz, 1H), 7.55−7.44 (m, 4H), 7.38 (dd, J = 7.8, 1.2 Hz, 1H), 7.30 (td, J = 7.5, 1.5 Hz, 1H), 4.53−4.44 (m, 1H), 4.01 (dd, J = 11.7, 5.7 Hz, 1H), 3.47−3.37 (m, 1H), 2.75 (d, J = 14.4 Hz, 1H), 2.69−2.54 (m, 1H), 1.70 (dd, J = 14.0, 3.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.3, 140.1, 132.0, 131.6, 130.8, 128.9, 128.5, 127.7, 126.0, 125.0, 120.4, 100.3, 71.8, 61.2, 41.4, 24.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}O_2N^{79}Br$ 435.9542, found 435.9540.

*3′,3′-Dibromo-6-methyl-2-phenyl-3′,4′,5′,6′-tetrahydrospiro-[benzo[d][1,3]oxazine-4,2′-pyran] (**6bBr**):* 134.0 mg (82% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 152.3−152.8 °C; IR (neat) ν_{max} 2961, 2103, 1634, 1251, 1066, 1021, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, 2H, J = 7.8, 1.2 Hz), 7.72 (br s, 1H), 7.55−7.45 (m, 3H), 7.28−7.26 (m, 2H), 4.56−4.46 (m, 1H), 4.04 (dd, J = 11.7, 5.7 Hz, 1H), 3.44 (td, J = 13.7, 3.9 Hz, 1H), 2.79−2.55 (m, 2H), 2.43 (s, 3H), 1.76−1.71 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.7, 137.8, 136.1, 132.1, 131.7, 131.4, 129.2, 128.5, 127.7, 124.9, 120.1, 100.3, 71.8, 61.3, 41.5, 24.4, 21.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{18}{}^{79}Br_2NO_2$ 449.9699, found 449.9705.

*3′,3′-Dibromo-7-chloro-2-phenyl-3′,4′,5′,6′-tetrahydrospiro-[benzo[d][1,3]oxazine-4,2′-pyran] (**6eBr**):* 203.3 mg (73% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 132.5−133.0 °C; IR (neat) ν_{max} 2963, 1632, 1594, 1091, 962, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.58−7.49 (m, 3H), 7.400−7.395 (m, 1H), 7.30−7.27 (m, 1H), 4.53−4.46 (m, 1H), 4.03 (dd, J = 11.6, 5.6 Hz, 1H), 3.42 (td, J = 13.6, 4.0 Hz, 1H), 2.78 (d, J = 14.4 Hz, 1H), 2.68−2.56 (m, 1H), 1.75 (dd, J = 14.0, 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.2, 142.5, 137.5, 132.9, 132.4, 131.1, 129.5, 128.8, 127.0 125.7, 119.8, 101.3, 72.5, 62.3, 42.2, 25.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}{}^{79}Br_2{}^{35}ClNO_2$ 469.9153, found 469.9157.

*3′,3′-Dibromo-6-chloro-2-phenyl-3′,4′,5′,6′-tetrahydrospiro-[benzo[d][1,3]oxazine-4,2′-pyran] (**6fBr**):* 178.5 mg (75% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 166.0−166.4 °C; IR (neat) ν_{max} 2964, 1632,

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1475, 1252, 1064, 759, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17−8.13 (m, 2H), 7.89 (d, J = 2.4 Hz, 1H), 7.57−7.46 (m, 3H), 7.43 (dd, J = 8.4, 2.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 4.53−4.44 (m, 1H), 4.07−4.01 (m, 1H), 3.46−3.36 (m, 1H), 2.79−2.74 (m, 1H), 2.71−2.54 (m, 1H), 1.77−1.71 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.6, 138.9, 131.8, 131.7, 131.3, 131.0, 129.0, 128.5, 127.8, 126.3, 121.7, 100.0, 71.0, 61.4, 41.3, 24.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}{}^{79}Br_2{}^{35}ClNO_2$ 469.9153, found 469.9157.

3′,3′-Dibromo-2-phenyl-6-(trifluoromethyl)-3′,4′,5′,6′-tetrahydrospiro[benzo[d][1,3]oxazine-4,2′-pyran] (**6gBr**): 91.1 mg (60% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 165.2−165.5 °C; IR (neat) ν_{max} 2931, 1606, 1258, 1090, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19−8.17 (m, 3H), 7.71 (dd, J = 8.4, 1.5 Hz, 1H), 7.59−7.45 (m, 4H), 4.53−4.44 (m, 1H), 4.05 (dd, J = 11.7, 5.7 Hz, 1H), 3.41 (td, J = 13.8, 4.2 Hz, 1H), 2.80−2.75 (m, 1H), 2.71−2.54 (m, 1H), 1.74 (dd, J = 14.1, 3.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.1, 143.1, 132.2, 131.4, 128.6, 128.1, 127.8 (q, C−F, $^2J_{C-F}$ = 33 Hz), 127.7 (q, C−F, $^3J_{C-F}$ = 4 Hz), 126.7 (q, C−F, $^3J_{C-F}$ = 4 Hz), 125.3, 124.0 (q, C−F, $^1J_{C-F}$ = 270 Hz), 120.7, 100.2, 71.0, 61.5, 41.2, 24.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}{}^{79}Br_2F_3NO_2$ 503.9416, found 503.9419.

3′,3′-Dibromo-2-(4-methoxyphenyl)-3′,4′,5′,6′-tetrahydrospiro-[benzo[d][1,3]oxazine-4,2′-pyran] (**6mBr**): 127.6 mg (82% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 184.2−184.7 °C; IR (neat) ν_{max} 2919, 1625, 1254, 1068, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 9.0 Hz, 2H), 4.53−4.44 (m, 1H), 4.04−3.99 (m, 1H), 3.87 (s, 3H), 3.42 (td, J = 13.5, 4.5 Hz, 1H), 2.78−2.73 (m, 1H), 2.70−2.53 (m, 1H), 1.74−1.70 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 162.4, 154.2, 140.4, 130.8, 130.0, 128.8, 125.6, 124.7, 124.3, 120.2, 113.9, 100.2, 71.9, 61.2, 55.4, 41.4, 24.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{18}{}^{79}Br_2F_3NO_3$ 465.9648, found 465.9655.

4-(3′,3′-Dibromo-3′,4′,5′,6′-tetrahydrospiro[benzo[d][1,3]-oxazine-4,2′-pyran]-2-yl)benzonitrile (**6tBr**): 126.7 mg (80% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 192.6−193.0 °C; IR (neat) ν_{max} 2952, 2229, 1633, 1255, 1066, 978, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.53−7.48 (m, 1H), 7.40−7.34 (m, 2H), 4.51−4.43 (m, 1H), 4.09−4.03 (m, 1H), 3.36 (td, J = 13.8, 3.6 Hz, 1H), 2.81−2.73 (m, 1H), 2.71−2.58 (m, 1H), 1.76 (d, J = 12.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 152.5, 139.5, 136.2 132.3, 131.1, 129.1, 128.2, 127.0, 125.3, 120.4, 118.3, 114.8, 100.8, 71.3, 61.4, 41.4 24.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}{}^{79}Br_2N_2O_2$ 460.9495, found 460.9491.

3′,3′-Dibromo-2-cyclohexyl-3′,4′,5′,6′-tetrahydrospiro[benzo[d]-[1,3]oxazine-4,2′-pyran] (**6vBr**): 126.5 mg (72% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 109.5−110.1 °C; IR (neat) ν_{max} 2930, 1650, 1078, 967, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J = 7.8, 1.2 Hz, 1H), 7.41 (td, J = 7.7, 1.5 Hz, 1H), 7.27−7.20 (m, 2H), 4.37−4.28 (m, 1H), 3.93 (dd, J = 11.4, 5.7 Hz, 1H), 3.28 (td, J = 13.4, 4.2 Hz, 1H), 2.71−2.66 (m, 1H), 2.62−2.44 (m, 2H), 2.16−2.03 (m, 2H), 1.87−1.83 (m, 2H), 1.74−1.72 (m, 1H), 1.65−1.51 (m, 3H), 1.41−1.19 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 162.2, 139.8, 130.7, 128.7, 125.6, 124.4, 120.0, 99.5, 72.3, 61.0, 43.9, 41.3, 30.1, 30.0, 25.8, 24.4; HRMS (ESI-TOF) m/z $[M + H]^+$ (Br−79) calcd for $C_{18}H_{22}{}^{79}Br_2NO_2$ 442.0012, found 442.0011.

3′,3′-Dibromo-2,6′-diphenyl-3′,4′,5′,6′-tetrahydrospiro[benzo-[d][1,3]oxazine-4,2′-pyran] (**6xBr**): 116.2 mg (67% yield, white solid, purified by SiO_2 column chromatography eluting 2% EtOAc/hexane); (63:37); mp 181.6−182.1 °C; IR (neat) ν_{max} 3063, 2929, 1635, 1252, 1063, 766, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23−8.20 (m, 1.07H, minor), 8.01 (dd, J = 7.8, 1.5 Hz, 0.53H, minor), 7.92 (dd, J = 8.1, 1.2 Hz, 1H, major), 7.76−7.73 (m, 2H, major), 7.57−7.15 (m, 17H, major+minor), 5.53 (dd, J = 12.6, 3.3 Hz, 0.56H, minor), 5.24 (t, J = 6.0 Hz, 1H), 3.54 (ddd, J = 17.1, 12.9, 3.9 Hz, 0.61H, minor), 3.45 (ddd, J = 15.0, 7.2, 5.4 Hz, 1H, major), 3.15 (ddd, J = 15.0, 7.5, 5.7 Hz, 1H, major), 2.83 (dt, J = 14.4, 3.9 Hz, 0.60H, minor), 2.90−2.47 (m, 2.72H, major+minor), 2.02 (dq, J = 14.1, 3.0 Hz, 0.57H, minor); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.7, 154.3, 140.8, 140.3, 140.1, 132.0, 131.64, 131.60, 131.3, 130.9, 130.7, 129.1, 128.53, 128.50, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 126.1, 126.0, 125.7, 125.6, 125.0, 120.9, 120.4, 101.1, 101.0, 73.6, 73.2, 71.5, 70.1, 41.6, 41.4, 32.6, 28.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{20}{}^{79}Br_2NO_2$ 511.9855, found 511.9851.

3′,3′-Dichloro-2-phenyl-3′,4′,5′,6′-tetrahydrospiro[benzo[d]-[1,3]oxazine-4,2′-pyran] (**6aCl**): 50.4 mg (39% yield, white solid, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 124.2−124.9 °C; IR (neat) ν_{max} 2973, 1632, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 7.80 (dd, J = 7.8, 0.9 Hz, 1H), 7.55−7.44 (m, 4H), 7.39 (dd, J = 7.8, 1.2 Hz, 1H), 7.30 (td, J = 7.5, 1.5 Hz, 1H), 4.51−4.41 (m, 1H), 3.99 (dd, J = 11.9, 5.4 Hz, 1H), 3.15 (td, J = 13.7, 3.9 Hz, 1H), 2.61−2.43 (m, 2H), 1.85−1.78 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.1, 140.2, 132.0, 131.6, 130.9, 128.6, 128.5, 127.7, 126.2, 125.0, 119.6, 100.9, 90.8, 61.3, 38.7, 23.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{16}O_2N^{35}Cl_2$ 348.0553, found 348.0545.

Procedure for Spiroannulation of Substrates 7 to Spirocycles 8X (Representative Case: Synthesis of Spirocycle 8aBr). A 250 mL round-bottomed flask containing a magnetic stir bar was charged with substrate **7a** (504.5 mg, 1.720 mmol, 1.00 equiv) and DCM (172 mL, effective concentration of **7a** ≈ 0.01 M). The resulted solution was then added with a solution of 1 M aqueous HCl (0.86 mL, 0.86 mmol, 0.50 equiv), followed by NBS (613.1 mg, 3.445 mmol, 2.00 equiv). The reaction mixture was allowed to stir at room temperature for 3 h. Upon completion, the reaction mixture was diluted with water, and the biphasic mixture was extracted with DCM. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude spirocyclic product. The crude material was purified by SiO_2 column chromatography, eluting 5% EtOAc/hexane to give 598.7 mg (77%) of pure product **8aBr** as a white solid.

3′,3′-Dibromo-2-phenylspiro[benzo[d][1,3]oxazine-4,2′-oxepane] (**8aBr**): 598.7 mg (77% yield, white solid, purified by SiO_2 column chromatography eluting 2% EtOAc/hexane); mp 177.0−178.0 °C; IR (neat) ν_{max} 2953, 1635, 1248, 764, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.1, 1.2 Hz, 2H), 8.04 (dd, J = 7.8, 0.9 Hz, 1H), 7.57−7.43 (m, 4H), 7.38−7.29 (m, 2H), 4.32−4.25 (m, 1H), 3.99−3.89 (m, 1H), 3.25−3.15 (m, 1H), 2.91−2.84 (m, 1H), 2.22−2.03 (m, 3H), 1.95−1.86 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.1, 139.0, 131.8, 131.6, 130.4, 128.5, 128.3, 127.8, 126.4, 125.0, 123.4, 103.3, 77.9, 64.3, 46.7, 29.0, 24.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{18}{}^{79}Br_2NO_2$ 449.9699, found 449.9692.

3′,3′-Dibromo-6-methyl-2-phenylspiro[benzo[d][1,3]oxazine-4,2′-oxepane] (**8bBr**): 83.9 mg (54% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 144.1−144.6 °C; IR (neat) ν_{max} 2923, 1638, 1250, 1068, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.85 (br s, 1H), 7.55−7.45 (m, 3H), 7.26−7.24 (m, 2H), 4.31−4.24 (m, 1H), 3.97−3.88 (m, 1H), 3.23−3.13 (m, 1H), 2.90−2.82 (m, 1H), 2.44 (s, 3H), 2.25−2.01 (m, 3H), 1.93−1.84 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.4, 136.7, 136.3, 131.9, 131.4, 131.2, 128.6, 128.5, 127.6, 124.8, 123.0, 103.2, 78.0, 64.3, 46.7, 29.0, 24.2, 21.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{19}{}^{79}Br_2NO_2$ 463.9855, found 463.9855.

3′,3′-Dibromo-7-chloro-2-phenylspiro[benzo[d][1,3]oxazine-4,2′-oxepane] (**8eBr**): 65.6 mg (29% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 115.8−116.5 °C; IR (neat) ν_{max} 2919, 1634, 1593, 1234, 1067, 734, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18−8.14 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.59−7.47 (m, 3H), 7.40 (d, J = 2.1 Hz, 1H), 7.28 (dd, J = 8.6, 2.1 Hz, 1H), 4.31−4.24 (m, 1H), 3.99−3.89 (m, 1H), 3.23−3.13 (m, 1H), 2.91−2.83 (m, 1H), 2.22−2.13 (m, 2H), 2.11−2.00 (m, 1H), 1.97−1.86 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.2, 140.5, 136.0, 131.9, 131.4, 129.6, 128.6, 127.9, 126.3,

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124.8, 121.9, 103.3, 77.6, 64.6, 46.5, 28.9, 24.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{17}{}^{79}Br_2{}^{35}ClNO_2$ 483.9309, found 483.9311.

*3′,3′-Dibromo-6-chloro-2-phenylspiro[benzo[d][1,3]oxazine-4,2′-oxepane] (**8fBr**):* 67.6 mg (22% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 161.3−161.6 °C; IR (neat) ν_{max} 2925, 1640, 1248, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 2H, J = 6.0 Hz), 8.030−8.025 (m, 1H), 7.57−7.49 (m, 3H), 7.43−7.40 (m, 1H), 7.32−7.26 (m, 1H), 4.31−4.26 (m, 1H), 3.99−3.93 (m, 1H), 3.21−3.14 (m, 1H), 2.89−2.85 (m, 1H), 2.19−2.13 (m, 2H), 2.10−1.91 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.4, 137.7, 131.8, 131.6, 131.5, 130.5, 128.6, 128.5, 127.8, 126.2, 124.6, 103.0, 77.2, 64.7, 46.5, 28.9, 24.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{17}{}^{79}Br_2{}^{35}ClNO_2$ 483.9309, found 483.9311.

*3′,3′-Dibromo-2-(4-methoxyphenyl)spiro[benzo[d][1,3]oxazine-4,2′-oxepane] (**8mBr**):* 62.8 mg (36% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 164.2−164.5 °C; IR (neat) ν_{max} 2921, 1635, 1935, 1598, 1246, 1030, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.35−7.26 (m, 2H), 7.00 (d, J = 9.0 Hz, 2H), 4.30−4.23 (m, 1H), 3.97−3.90 (m, 1H), 3.87 (s, 3H), 3.22−3.13 (m, 1H), 2.90−2.83 (m, 1H), 2.20−2.01 (m, 3H), 1.93−1.88 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 162.4, 154.0, 139.2, 130.3, 129.6, 128.2, 125.9, 124.7, 124.2, 123.2, 113.9, 103.1, 78.1, 64.2, 55.4, 46.7, 29.0, 24.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{20}{}^{79}Br_2NO_3$ 479.9804, found 479.9810.

*4-(3′,3′-Dibromospiro[benzo[d][1,3]oxazine-4,2′-oxepan]-2-yl)-benzonitrile (**8tBr**):* 58.9 mg (39% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 177.0−178.0 °C; IR (neat) ν_{max} 2924, 1637, 1250, 1073, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.50−7.45 (m, 1H), 7.39−7.34 (m, 2H), 4.32−4.25 (m, 1H), 4.01−3.92 (m, 1H), 3.18−3.09 (m, 1H), 2.91−2.86 (m, 1H), 2.18−2.05 (m, 3H), 1.94−1.89 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.3, 138.4, 136.0, 132.3, 130.6, 128.4, 128.2, 127.2, 125.3, 123.4, 118.3, 114.8, 103.8, 77.4, 64.6, 46.5, 29.0, 24.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{17}{}^{79}Br_2N_2O_2$ 474.9651, found 474.9654.

*2′,2′-Dibromo-2-cyclohexylspiro[benzo[d][1,3]oxazine-4,1′-cycloheptane] (**8vBr**):* 262.3 mg (65% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 127.4−127.8 °C; IR (neat) ν_{max} 2928, 1655, 1119, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.8, 1.2 Hz, 1H), 7.38 (td, J = 7.5, 1.2 Hz, 1H), 7.25 (td, J = 7.5, 1.5 Hz, 1H), 7.21−7.18 (m, 1H), 4.16−4.09 (m, 1H), 3.89−3.79 (m, 1H), 3.09−3.00 (m, 1H), 2.86−2.79 (m, 1H), 2.49 (td, J = 11.7, 3.3 Hz, 1H), 2.14−1.93 (m, 5H), 1.87−1.72 (m, 4H), 1.66−1.50 (m, 2H), 1.42−1.18 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.7, 138.6, 130.2, 128.1, 125.9, 124.3 123.0, 102.4, 78.3, 64.2, 47.1, 44.2, 30.1, 29.8, 29.1, 25.9, 25.8, 23.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{24}{}^{79}Br_2NO_2$ 456.0168, found 456.0167.

Procedure for Conversion of Spirocycles 2Br to 3-Bromofurans 3Br (Representative Case: Synthesis of 3-Bromofuran 3aBr). To 10 mL round-bottomed flask containing a magnetic stir bar was added compound **2aBr** (472.4 mg, 1.117 mmol, 1.00 equiv), followed by 5.0 mL of NMP. The resulted clear colorless solution was then added with *t*-BuOK (175.0 mg, 1.559 mmol, 1.40 equiv), which immediately turned the reaction mixture to dark purple. The mixture was allowed to stir at room temperature for 10 min. Upon completion (judged by TLC), the reaction mixture was diluted with 1 M aqueous HCl and water. The separated aqueous layer was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield a crude brown material. This material was purified by SiO_2 column chromatography eluting 10% EtOAc/hexane to furnish 375.3 mg (98%) of product **3aBr** as a brown solid.

*N-(2-(3-Bromofuran-2-yl)phenyl)benzamide (**3aBr**):* 375.3 mg (98% yield, brown solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 91.2−91.8 °C; IR (neat) ν_{max} 3325, 1675, 1520, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.51 (dd, J = 8.4, 0.8 Hz, 1H), 7.83−7.80 (m, 2H), 7.63 (dd, J = 8.1, 1.6 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.54−7.43 (m, 4H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.2, 148.2, 142.7, 135.9, 134.9, 131.8, 130.3, 130.1, 128.8, 126.9, 124.0, 122.1, 119.2, 115.9, 99.2; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}{}^{79}Br$ N O_2 342.0124, found 342.0125.

*N-(2-(3-Bromofuran-2-yl)-4-methylphenyl)benzamide (**3bBr**):* 137.5 mg (94% yield, white solid, purified by SiO_2 column chromatography eluting 5−20% EtOAc/hexane); mp 139.6−139.9 °C; IR (neat) ν_{max} 3246, 1642, 1530, 1318, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.82−7.79 (m, 2H), 7.55−7.43 (m, 5H), 7.29 (dd, J = 8.4, 1.5 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.1, 148.3, 142.7, 135.0, 133.8, 133.4, 131.7, 131.0, 130.4, 128.4, 126.9, 122.3, 119.3, 115.8, 99.0, 20.8; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{15}{}^{79}BrNO_2$ 356.0281, found 356.0272.

*N-(2-(3-Bromofuran-2-yl)-5-fluorophenyl)benzamide (**3cBr**):* 93.8 mg (97% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 132.3−133.0 °C; IR (neat) ν_{max} 3454, 3110, 1684, 1545, 1256, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.42 (dd, J = 11.3, 2.4 Hz, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.61−7.44 (m, 5H), 6.91 (td, J = 7.8, 2.4 Hz, 1H), 6.64 (d, J = 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.1, 163.4 (d, C−F, $^1J_{C-F}$ = 247 Hz), 147.3, 142.8, 137.8 (d, C−F, $^3J_{C-F}$ = 13 Hz), 134.5, 132.1, 131.6 (d, C−F, $^3J_{C-F}$ = 10 Hz), 128.8, 126.9, 115.9, 114.6 (d, C−F, $^3J_{C-F}$ = 3 Hz), 110.9 (d, C−F, $^2J_{C-F}$ = 22 Hz), 109.0 (d, C−F, $^2J_{C-F}$ = 28 Hz), 99.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 111.1 to −111.2 (m); HRMS (ESI−TOF) m/z (M +Na)$^+$ calcd for $C_{17}H_{11}{}^{79}BrFNNaO_2$ 381.9849, found 381.9844.

*N-(2-(3-Bromofuran-2-yl)-4-fluorophenyl)benzamide (**3dBr**):* 217.1 mg (92% yield, white solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 103.8−104.1 °C; IR (neat) ν_{max} 3441, 3307, 1670, 1522, 867, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 8.42 (dd, J = 9.0, 3.0 Hz, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.56−7.52 (m, 2H), 7.49−7.44 (m, 2H), 7.38 (dd, J = 9.2, 2.7 Hz, 1H), 7.17 (td, J = 8.3, 3.0 Hz, 1H), 6.64 (d, J = 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.2, 158.7 (d, C−F, $^1J_{C-F}$ = 243 Hz), 146.9 (d, C−F, $^3J_{C-F}$ = 2 Hz), 143.0, 134.7, 131.9, 128.8, 126.9, 124.4 (d, C−F, $^3J_{C-F}$ = 8 Hz), 121.1 (d, C−F, $^3J_{C-F}$ = 8 Hz), 116.9 (d, C−F, $^2J_{C-F}$ = 22 Hz), 116.4 (d, C−F, $^2J_{C-F}$ = 24 Hz), 116.1, 99.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 120.6 to −120.7 (m); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}{}^{79}BrFNO_2$ 360.0030, found 360.0032.

*N-(2-(3-Bromofuran-2-yl)-5-chlorophenyl)benzamide (**3eBr**):* 81.0 mg (91% yield, white solid, purified by SiO_2 column chromatography eluting 1% EtOAc/DCM); mp 137.6−138.0 °C; IR (neat) ν_{max} 3430, 2923, 2361, 1676, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.66 (d, J = 2.1 Hz, 1H), 7.81−7.79 (m, 2H), 7.58−7.45 (m, 5H), 7.19 (dd, J = 8.4, 2.1 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.1, 147.3, 143.0, 137.0, 136.2, 134.5, 132.2, 131.0, 128.9, 126.9, 124.1, 121.9, 117.2, 116.1, 99.6; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}{}^{79}Br^{35}ClNO_2$ 375.9735, found 375.9733.

*N-(2-(3-Bromofuran-2-yl)-4-chlorophenyl)benzamide (**3fBr**):* 153.2 mg (84% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 137.1−137.5 °C; IR (neat) ν_{max} 3430, 2923, 2361, 1676, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 8.49 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 2.4 Hz, 1H), 7.58−7.53 (m, 2H), 7.50−7.42 (m, 3H), 6.65 (d, J = 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 146.7, 143.2, 134.6, 134.5, 132.1, 130.1, 129.6, 129.1, 128.9, 127.0, 123.4, 120.5, 116.1, 99.9; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}{}^{79}Br^{35}ClNO_2$ 375.9734, found 375.9731.

*N-(2-(3-Bromofuran-2-yl)-4-(trifluoromethyl)phenyl)benzamide (**3gBr**):* 211.0 mg (70% yield, white solid, purified by SiO_2 column chromatography eluting 2−10% EtOAc/hexane); mp 96.0−96.3 °C; IR (neat) ν_{max} 3439, 3067, 1687, 1522, 1329, 1122, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (br s, 1H), 8.73 (d, J = 8.7 Hz, 1H), 7.91 (s, 1H), 7.82 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 9.0 Hz, 1H), 7.60−

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7.59 (m, 1H), 7.56−7.54 (m, 1H), 7.50−7.45 (m, 2H), 6.67 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 146.7, 143.3, 138.9, 134.3, 132.3, 128.9, 127.2 (q, C−F, $^3J_{C-F}$ = 4 Hz), 127.1 (q, C−F, $^3J_{C-F}$ = 4 Hz), 126.9, 126.0, 123.8 (q, C−F, $^1J_{C-F}$ = 269 Hz), 121.8, 118.9, 116.2, 100.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 65.5 (s); HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{11}{}^{79}BrF_3NNaO_2$ 431.9817, found 431.9813.

*N-(2-(3-Bromofuran-2-yl)-4-cyanophenyl)benzamide (**3hBr**):* 207.7 mg (89% yield, yellow solid, purified by SiO_2 column chromatography eluting 1% EtOAc/DCM); mp 182.4−182.7 °C; IR (neat) ν_{max} 3428, 3128, 2224 1698, 1512, 1303 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.80 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.83−7.80 (m, 2H), 7.76 (dd, J = 8.7, 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.59−7.56 (m, 1H), 7.53−7.48 (m, 2H), 6.71 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, 145.9, 143.6, 139.9, 134.1, 133.92, 133.86, 132.5, 129.0, 127.0, 121.8, 119.1, 118.3, 116.4, 107.2, 100.8; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}{}^{79}BrN_2O_2$ 367.0077, found 367.0077.

*N-(2-(3-Bromofuran-2-yl)-4-nitrophenyl)benzamide (**3iBr**):* 58.7 mg (79% yield, yellow solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 186.3−186.6 °C; IR (neat) ν_{max} 3440, 2922, 1698, 1506, 1342, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (br s, 1H), 8.88 (d, J = 6.9 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H), 8.34 (dd, J = 6.9, 2.1 Hz, 1H), 7.84 (d, J = 5.7 Hz, 2H), 7.65 (d, J = 1.5 Hz, 1H), 7.60 (t, J = 5.4 Hz, 1H), 7.52 (t, J = 5.7 Hz, 2H), 6.73 (d, J = 1.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 145.8, 143.7, 143.0, 141.5, 134.1, 132.6, 129.1, 127.0, 125.7, 125.6, 121.2, 118.7, 116.5, 101.1; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}{}^{79}BrN_2O_4$ 386.9975, found 386.9976.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-methylbenzamide (**3jBr**):* 80.5 mg (93% yield, orange solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 94.2−94.6 °C; IR (neat) ν_{max} 3442, 2923, 1675, 1304, 945, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.65 (dd, J = 7.8, 1.2 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.52−7.47 (m, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 2.42 (s, 3H) ; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 148.1, 142.7, 142.3, 136.0, 132.0, 130.1, 130.0, 129.4, 126.8, 123.8, 122.1, 119.0, 115.8, 99.0, 21.4; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{14}{}^{79}BrNNaO$ 378.0100, found 378.0095.

*N-(2-(3-Bromofuran-2-yl)phenyl)-2-methoxybenzamide (**3kBr**):* 47.4 mg (75% yield, yellow oil, purified by SiO_2 column chromatography eluting 1% EtOAc/DCM); IR (neat) ν_{max} 3335, 1664, 1525, 1308, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.29 (dd, J = 7.8, 1.8 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.50−7.43 (m, 3H), 7.19 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 1.8 Hz, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.3, 157.3, 148.5, 143.0, 137.0, 133.2, 132.6, 130.6, 130.3, 123.6, 122.5, 121.8, 121.4, 119.5, 115.3, 111.3, 99.4, 55.9; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{14}{}^{79}BrNNaO_3$ 394.0049, found 394.0054.

*N-(2-(3-Bromofuran-2-yl)phenyl)-3-methoxybenzamide (**3lBr**):* 442.5 mg (98% yield, yellow oil, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); IR (neat) ν_{max} 3433, 3320 1676, 1582, 1521, 1307, 1046, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.49 (d, J = 8.1 Hz, 1H), 7.63 (dd, J = 7.7, 1.5 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.50−7.44 (m, 1H), 7.41−7.40 (m, 1H), 7.38−7.30 (m, 2H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 7.08−7.04 (m, 1H), 6.63 (d, J = 8.1 Hz, 1H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0, 159.9, 148.1, 142.8, 136.4, 135.9, 130.3, 130.1, 129.7, 124.0, 122.1, 119.2, 118.6, 118.2, 115.9, 112.3, 99.2, 55.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}{}^{79}BrNO_3$ 372.0230, found 372.0223.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-methoxybenzamide (**3mBr**):* 84.9 mg (≥99% yield, yellow solid, purified by SiO_2 column chromatography eluting 20% EtOAc/hexane); mp 90.2−90.4 °C; IR (neat) ν_{max} 3440, 2925, 1527, 1246, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 8.49 (dd, J = 8.3, 0.8 Hz, 1H), 7.80−7.75 (m, 2H), 7.62 (dd, J = 7.8, 1.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.49−7.44 (m, 1H), 7.20 (td, J = 7.6, 1.2 Hz, 1H), 6.97−6.92 (m, 2H), 6.63 (d, J = 2.0 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.7, 162.5, 148.2, 142.7, 136.1, 130.2, 130.1, 128.8, 127.1, 123.7, 122.1, 119.0, 115.9, 114.0, 99.1, 55.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}{}^{79}BrNO_3$ 372.0230, found 372.0226.

*N-(2-(3-Bromofuran-2-yl)phenyl)-3,4,5-trimethoxybenzamide (**3nBr**):* 291.6 mg (66% yield, beige solid, purified by SiO_2 column chromatography eluting 20−30% EtOAc/hexane); mp 104.5−105.3 °C; IR (neat) ν_{max} 3312, 2922, 2361, 1500, 1126, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 8.48 (d, J = 8.1 Hz, 1H), 7.60−7.45 (m, 3H), 7.21 (t, J = 7.2 Hz, 1H), 7.04 (br s, 2H), 6.62 (br s, 1H), 3.89 (br s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.7, 153.1, 148.1, 142.8, 141.0, 135.9, 130.3, 130.1, 130.0, 123.9, 121.7, 119.0, 115.6, 104.2, 99.1, 60.8, 56.1; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{19}{}^{79}BrNO_5$ 432.0441, found 432.0440.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-(trifluoromethoxy)-benzamide (**3oBr**):* 119.5 mg (96% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 137.7−138.3 °C; IR (neat) ν_{max} 3301, 2925, 1652, 1266, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (br s, 1H), 8.44 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.31−7.21 (m, 3H), 6.64 (d, J = 1.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.9, 151.7, 148.0, 142.8, 135.5, 133.3, 130.3, 130.2, 128.8, 124.3, 122.3, 120.7, 120.3 (q, C−F, $^1J_{C-F}$ = 258 Hz), 119.4, 116.0, 99.2; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}{}^{79}BrF_3NO_3$ 425.9947, found 425.9946.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-fluorobenzamide (**3pBr**):* 80.7 mg (87% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 126.1−126.3 °C; IR (neat) ν_{max} 3458, 3104, 1616, 1237, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 7.86−7.79 (m, 2H), 7.64 (dd, J = 7.8, 1.5 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.51−7.46 (m, 1H), 7.22 (dd, J = 7.5, 1.2 Hz, 1H), 7.18−7.11 (m, 2H), 6.64 (dd, J = 2.1, 0.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.8 (d, J_{C-F}= 251 Hz), 164.1, 148.1, 142.7, 135.7, 131.0 (d, J_{C-F}= 3 Hz), 130.2 (d, J_{C-F}= 8 Hz), 129.3 (d, J_{C-F}= 9 Hz), 124.2, 122.3, 119.3, 115.93, 115.90, 115.6, 99.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 110.5 to −110.6 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}{}^{79}BrFNO_2$ 360.0030, found 360.0026.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-chlorobenzamide (**3qBr**):* 56.2 mg (86% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 136.9−137.1 °C; IR (neat) ν_{max} 2922, 2852, 1681, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.76−7.73 (m, 2H), 7.63 (dd, J = 7.8, 1.5 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.50−7.42 (m, 3H), 7.26−7.20 (m, 1H), 6.63 (d, J = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.2, 148.1, 142.8, 138.1, 135.6, 133.3, 130.3, 130.2, 129.0, 128.3, 124.3, 122.2, 119.3, 116.0, 99.2; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}{}^{79}Br^{35}ClNO_2$ 375.9735, found 375.9726.

*2-Bromo-N-(2-(3-bromofuran-2-yl)phenyl)benzamide (**3rBr**):* 144.0 mg (96% yield, yellow oil, purified by SiO_2 column chromatography eluting 2−10% EtOAc/hexane); IR (neat) ν_{max} 3411, 3062, 1679, 1517, 1306, 946, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 8.4 Hz, 1H), 8.37 (br s, 1H), 7.63−7.57 (m, 3H), 7.50−7.44 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.30−7.21 (m, 2H), 6.55 (d, J = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4, 147.7, 142.8 137.6, 135.3, 133.5, 131.5, 130.2, 130.1, 129.6, 127.6, 124.4, 122.4, 119.5, 119.1, 115.6, 99.2; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}{}^{79}Br_2NO_2$ 419.9229, found 419.9228.

*4-Bromo-N-(2-(3-bromofuran-2-yl)phenyl)-2-fluorobenzamide (**3sBr**):* 160.7 mg (88% yield, white solid, purified by SiO_2 column chromatography eluting 1% EtOAc/hexane); IR (neat) ν_{max} 3430, 2923, 1680, 1538, 1448, 1306, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, J = 14.4 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.05 (t, J = 8.4 Hz, 1H), 7.61 (dd, J = 7.5 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.49−7.41 (m, 2H), 7.31 (dd, J = 11.7, 1.5 Hz, 1H), 7.25−7.20 (m, 1H), 6.61 (d, J = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.2 (d, C−F, $^3J_{C-F}$ = 4 Hz), 159.8 (d, C−F, $^1J_{C-F}$ = 250 Hz), 147.6, 142.8, 135.7, 133.5 (d, C−F, $^3J_{C-F}$ = 3 Hz), 130.2, 130.1, 128.5 (d,

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C−F, $^3J_{C-F}$ = 3 Hz), 126.9 (d, C−F, $^3J_{C-F}$ = 10 Hz), 124.4, 122.7, 120.4 (d, C−F, $^3J_{C-F}$ = 11 Hz), 119.64, 119.63 (d, C−F, $^2J_{C-F}$ = 28 Hz), 115.6, 99.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 114.5 to −114.6 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}{}^{79}Br_2FNO_2$ 437.9135, found 437.9135.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-cyanobenzamide (**3tBr**):* 550.5 mg (74% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/DCM); mp 170.7−171.7 °C; IR (neat) ν_{max} 3386, 2959, 1677, 1518, 1310, 1039, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 7.5, 0.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.53−7.47 (m, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.4, 147.9, 142.9, 138.8, 135.2, 132.6, 130.4, 130.3, 127.6, 124.8, 122.3, 119.5, 117.8, 116.1, 115.5, 99.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{12}{}^{79}BrN_2O_3$ 367.0077, found 367.0083.

*N-(2-(3-Bromofuran-2-yl)phenyl)-4-nitrobenzamide (**3uBr**):* 368.2 mg (74% yield, yellow solid, purified by SiO_2 column chromatography eluting 5% EtOAc/DCM); mp 182.5−183.4 °C; IR (neat) ν_{max} 3323, 2921, 1655, 1516, 1345, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 7.67 (dd, J = 7.8, 1.5 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.53−7.48 (m, 1H), 7.30−7.25 (m, 1H), 6.66 (d, J = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.2, 149.8, 147.9, 142.9, 140.5, 135.1, 130.4, 130.3, 128.1, 124.8, 124.0, 122.4, 119.6, 116.1, 99.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}{}^{79}BrN_2O_4$ 386.9975, found 386.9973.

*N-(2-(3-Bromofuran-2-yl)phenyl)cyclohexanecarboxamide (**3vBr**):* 104.6 mg (61% yield, brown solid, purified by SiO_2 column chromatography eluting 1% EtOAc/DCM); mp 102.7−103.1 °C; IR (neat) ν_{max} 3222, 2924, 2854, 1651, 1535, 1450, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 8.1 Hz, 1H), 7.83 (br s, 1H), 7.57−7.54 (m, 2H), 7.42 (t, J = 8.4 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 1.8 Hz, 1H), 2.19 (tt, J = 11.7, 3.3 Hz, 1H), 1.95−1.91 (m, 2H), 1.82−1.79 (m, 2H), 1.70−1.62 (m, 1H), 1.51−1.40 (m, 2H), 1.36−1.20 (m, 3H) ; $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.1, 148.2, 142.7, 136.0, 130.2, 130.1, 123.7, 122.1, 118.9, 115.7, 99.0, 46.6, 29.5, 25.7, 25.6; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{19}{}^{79}BrNO_2$ 348.0594, found 348.0593.

*N-(2-(3-Bromofuran-2-yl)phenyl)pivalamide (**3wBr**):* 193.3 mg (78% yield, yellow oil, purified by SiO_2 column chromatography eluting 1% EtOAc/DCM); IR (neat) ν_{max} 3451, 2964, 1686, 1510, 1300, 1158, 947, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.4 Hz, 1H), 8.17 (br s, 1H), 7.57 (dd, J = 7.7, 1.8 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.45−7.39 (m, 1H), 7.16 (td, J = 7.5, 0.6 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 1.24 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 176.5, 148.3, 142.5, 136.2, 130.2, 130.0, 123.6, 121.9, 118.8, 115.8, 99.0, 39.8, 27.4; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{17}{}^{79}BrNO_2$ 322.0437, found 322.0441.

*N-(2-(3-Bromo-5-phenylfuran-2-yl)phenyl)benzamide (**3xBr**):* 114.4 mg (93% yield, white solid, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 117.6−117.8 °C; IR (neat) ν_{max} 3438, 2924, 1650, 1581, 1525, 1450, 1340, 958, 759, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.56 (d, J = 8.4 Hz, 1H), 7.80−7.77 (m, 2H), 7.73 (dd, J = 8.4, 1.2 Hz, 1H), 7.62−7.59 (m, 2H), 7.51−7.48 (m, 1H), 7.46−7.43 (m, 1H), 7.41−7.33 (m, 3H), 7.30−7.21 (m, 3H), 6.85 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2, 153.9, 147.3, 135.9, 134.7, 131.8, 130.2, 130.0, 129.0, 128.9, 128.65, 128.59, 127.0, 124.0, 123.9, 122.1, 119.0, 110.7, 101.0; HRMS (ESI−TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{16}{}^{79}BrNNaO_2$ 440.0257, found 440.0264.

*N-(2-(3-Bromo-5-(4-methoxyphenyl)furan-2-yl)phenyl)-benzamide (**3yBr**):* 58.8 mg (99% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 139.1−139.4 °C; IR (neat) ν_{max} 3439, 1677, 1498, 1250, 1027, 958, 832, 758, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.56 (d, J = 8.4 Hz, 1H), 7.80−7.77 (m, 2H), 7.72 (dd, J = 7.8, 1.2 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.50−7.41 (m, 2H), 7.30−7.20 (m, 3H), 6.89 (d, J = 9.0 Hz, 2H), 6.70 (s, 1H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1, 159.9, 154.0, 146.5, 135.8, 134.8, 131.7, 130.0, 129.9, 128.6, 127.0, 125.4, 123.9, 122.0, 121.9, 119.1, 114.3, 109.2, 101.0, 55.3; HRMS (ESI−TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{18}{}^{79}BrNNaO_3$ 470.0362, found 470.0359.

Procedure for Intramolecular Ullmann Coupling of 3-Bromofurans 3Br to Indolofurans 4 (Representative Case: Synthesis of Indolofuran 4a). A 10 mL round-bottomed flask containing a magnetic stir bar was charged with substrate **3aBr** (101.7 mg, 0.297 mmol, 1.00 equiv), CuTC (2.9 mg, 0.015 mmol, 0.05 equiv), Cs_2CO_3 (97.8 mg, 0.300 mmol, 1.01 equiv), DMEDA (13 μL, 10.7 mg, 0.121 mmol, 0.41 equiv), and 2 mL of dry 1,4-dioxane. The resulted mixture was heated in an oil bath at reflux under argon for 3 h. Upon completion (judged by TLC), the reaction was cooled down to room temperature, and the mixture was diluted with saturated aqueous NH_4Cl. The separated aqueous phase was extracted with EtOAc. Combined organic phases were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum to give the crude material. The crude product was purified by SiO_2 column chromatography eluting 10% EtOAc/hexane to give 69.7 mg (≥99%) of the desired product (**4a**) as a white solid.

The reaction of **3aBr** at a larger scale (374.6 mg, 1.095 mmol) was conducted, employing the same procedure to afford 267.7 mg (94%) of **4a** as a white solid.

*(4H-Furo[3,2-b]indol-4-yl)(phenyl)methanone (**4a**):* 69.7 mg (≥99% yield, white solid, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 97.9−98.7 °C; IR (neat) ν_{max} 3125, 1676, 1354, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47−8.43 (m, 1H), 7.73−7.70 (m, 2H), 7.69−7.60 (m, 2H), 7.56−7.51 (m, 2H), 7.38−7.31 (m, 3H), 5.61 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2, 145.2, 144.3, 139.9, 135.2, 131.8, 130.1, 128.6, 128.4, 124.5, 124.3, 118.6, 117.8, 116.3, 103.0; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}NO_2$ 262.0863, found 262.0864.

*(7-Methyl-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4b**):* 53.1 mg (87% yield, yellow oil, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); IR (neat) ν_{max} 2923, 1683, 1354, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 1H), 7.72−7.69 (m, 2H), 7.65−7.60 (m, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.47 (s, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.15 (d J = 8.4 Hz, 1H), 5.59 (d, J = 1.8 Hz, 1H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.0, 145.0, 144.2, 138.1, 135.3, 134.0, 131.6, 130.2, 128.5, 128.3, 125.6, 118.7, 117.4, 116.4, 102.9, 21.4; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{13}NNaO_2$ 298.0839, found 298.0834.

*(6-Fluoro-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4c**):* 44.8 mg (94% yield, yellow oil, purified by SiO_2 column chromatography eluting 2% EtOAc/hexane); IR (neat) ν_{max} 3129, 1686, 1354, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, J = 10.5, 2.1 Hz, 1H), 7.73−7.70 (m, 2H), 7.67−7.61 (m, 1H), 7.60−7.52 (m, 3H), 7.29 (d, J = 2.1 Hz, 1H), 7.10 (td, J = 8.7, 2.4 Hz, 1H), 5.59 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2, 160.5 (d, C−F, $^1J_{C-F}$ = 240 Hz), 144.9 (d, C−F, $^3J_{C-F}$ = 1 Hz), 143.7, 140.0 (d, C−F, $^3J_{C-F}$ = 12 Hz), 134.7, 132.0, 130.3 (d, C−F, $^3J_{C-F}$ = 3 Hz), 128.6, 128.4, 116.7 (d, C−F, $^3J_{C-F}$ = 10 Hz), 115.2 (d, C−F, $^3J_{C-F}$ = 2 Hz), 112.1 (d, C−F, $^2J_{C-F}$ = 24 Hz), 105.7 (d, C−F, $^2J_{C-F}$ = 29 Hz), 103.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 119.25 to −119.32 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2$ 280.0768, found 280.0768.

*(7-Fluoro-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4d**):* 75.9 mg (95% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 125.1−125.5 °C; IR (neat) ν_{max} 2926, 1687, 1438, 1351, 1135, 860, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, J = 9.3, 4.8 Hz, 1H), 7.71−7.69 (m, 2H), 7.66−7.61 (m, 1H), 7.56−7.51 (m, 2H), 7.32−7.28 (m, 2H), 7.03 (td, J = 9.2, 2.4 Hz, 1H), 5.57 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.8 (d, C−F, $^1J_{C-F}$ = 240 Hz), 158.2, 145.8, 143.5 (d, C−F, $^3J_{C-F}$ = 4 Hz), 136.0 (d, C−F, $^3J_{C-F}$ = 1 Hz), 134.9, 131.9, 131.5 128.6, 128.3, 119.3 (d, C−F, $^3J_{C-F}$ = 11 Hz), 118.4 (d, C−F, $^3J_{C-F}$ = 9 Hz), 111.6 (d, C−F, $^2J_{C-F}$ = 25 Hz), 102.9, 102.6 (d, C−F, $^2J_{C-F}$ = 26 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ − 120.7 to −120.8 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2$ 280.0768, found 280.0775.

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*(6-Chloro-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4e**):* 50.9 mg (84% yield, beige solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 138.6−139.1 °C; IR (neat) ν_{max} 2924, 1687, 1349, 1295, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.70 (d, J = 7.2 Hz, 2H), 7.66−7.62 (m, 1H), 7.56−7.52 (m, 3H), 7.32−7.30 (m, 2H), 5.56 (d, J = 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 145.5, 143.5, 139.9, 134.6, 132.0, 130.6, 130.2, 128.6, 128.3, 124.6, 118.1, 116.9, 116.7, 102.9; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}{}^{35}ClNO_2$ 296.0473, found 296.0471.

*(7-Chloro-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4f**):* 61.3 mg (92% yield, white solid, purified by SiO_2 column chromatography eluting 2−10% EtOAc/hexane); mp 126.6−126.9 °C; IR (neat) ν_{max} 3130, 1684, 1349, 1304, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.9 Hz, 1H), 7.73−7.71 (m, 2H), 7.67−7.63 (m, 2H), 7.55 (t, J = 7.7 Hz, 2H), 7.34 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 8.9, 2.1 Hz, 1H), 5.60 (d, J = 1.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 145.9, 143.0, 138.1, 134.7, 132.0, 131.3, 129.9, 128.7, 128.4, 124.4, 119.5, 118.8, 116.1, 102.9; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}{}^{35}ClNO_2$ 296.0473, found 296.0469.

*Phenyl(7-(trifluoromethyl)-4H-furo[3,2-b]indol-4-yl)methanone (**4g**):* 126.8 mg (76% yield, beige solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 92.9−93.2 °C; IR (neat) ν_{max} 1689, 1354, 1303, 1116, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.7 Hz, 1H), 7.90 (s, 1H), 7.73−7.62 (m, 3H), 7.56−7.51 (m, 3H), 7.34 (d, J = 1.8 Hz, 1H), 5.63 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1, 146.2, 143.2, 141.1, 134.4, 132.2, 131.7, 128.7, 128.5, 126.3 (q, C−F, $^2J_{C-F}$ = 32 Hz), 124.4 (q, C−F, $^1J_{C-F}$ = 270 Hz), 121.0 (q, C−F, $^3J_{C-F}$ = 4 Hz), 118.0, 117.8, 113.5 (q, C−F, $^3J_{C-F}$ = 4 Hz), 102.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 64.6 (s); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{11}F_3NO_2$ 330.0736, found 330.0735.

*4-Benzoyl-4H-furo[3,2-b]indole-7-carbonitrile (**4h**):* 104.6 mg (89% yield, white solid, purified by SiO_2 column chromatography eluting 70% DCM/hexane); mp 184.7−185.0 °C; IR (neat) ν_{max} 2924, 2227, 1683, 1355, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.74−7.73 (m, 2H), 7.71−7.67 (m, 1H), 7.59−7.54 (m, 3H), 7.41 (d, J = 2.0 Hz, 1H), 5.66 (d, J = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.0, 146.7, 142.4, 141.1, 134.0, 132.5, 132.1, 128.7, 128.5, 127.4 120.4, 119.1, 118.23, 118.16, 107.4, 102.8; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{11}N_2O_2$ 287.0815, found 287.0822.

*(7-Nitro-4H-furo[3,2-b]indol-4-yl)(phenyl)methanone (**4i**):* 12.4 mg (31% yield, yellow solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 158.9−159.4 °C; IR (neat) ν_{max} 3136, 1692, 1516, 1344, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58−8.55 (m, 2H), 8.23 (dd, J = 9.2, 2.4 Hz, 1H), 7.76 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 6.8 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 7.44 (d, J = 2.0 Hz, 1H), 5.69 (d, J = 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 146.9, 144.3, 142.9, 142.4, 133.9, 132.9, 132.7, 128.8, 128.6, 119.5, 118.2, 117.7, 112.3, 103.0; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}{}^{79}BrN_2O_4$ 307.0713, found 307.0706.

*7-Nitro-4H-furo[3,2-b]indole (**4i′**):* 5.1 mg (19% yield, orange solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 210.0−210.3 °C; IR (neat) ν_{max} 3320, 1499, 1308, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 8.22 (br s, 1H), 8.13 (dd, J = 9.0, 1.2 Hz, 1H), 7.65 (s, 1H), 7.45 (d, J = 9.2 Hz, 1H), 6.67 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.4, 143.09, 143.07, 142.5, 133.5, 118.1, 114.4, 114.1, 112.7, 100.4; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{10}H_6N_2NaO_3$ 225.0271, found 225.0274.

*(4H-Furo[3,2-b]indol-4-yl)(p-tolyl)methanone (**4j**):* 38.6 mg (91% yield, white solid, purified by SiO_2 column chromatography eluting 5−15% EtOAc/hexane); mp 142.7−143.1 °C; IR (neat) ν_{max} 2925, 1595, 1305, 1030, 751, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 7.68−7.61 (m, 3H), 7.36−7.31 (m, 5H), 5.72 (d, J = 2.1 Hz, 1H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.3, 145.1, 144.2, 142.5, 139.9, 132.2, 130.3, 129.2, 128.7, 124.4, 124.1, 118.5, 117.7, 116.2, 103.1, 21.7; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{13}NNaO_2$ 298.0839, found 298.0839.

*(4H-Furo[3,2-b]indol-4-yl)(2-methoxyphenyl)methanone (**4k**):* 11.0 mg (29% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 125.0−125.4 °C; IR (neat) ν_{max} 2933, 1685, 1359, 1021, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.67−7.65 (m, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 6.4 Hz, 1H), 7.35−7.28 (m, 3H), 7.12 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 5.31 (br s, 1H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 156.5, 145.3, 144.4, 139.4, 132.1, 129.9 128.4, 125.6, 124.6, 124.3, 120.9, 118.7, 117.9, 116.2, 111.4, 102.1, 55.7; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{13}NNaO_3$ 314.0788, found 314.0790.

*(4H-Furo[3,2-b]indol-4-yl)(3-methoxyphenyl)methanone (**4l**):* 292.3 mg (87% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 65.8−66.2 °C; IR (neat) ν_{max} 2939, 1683, 1307, 1040, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46−8.44 (m, 1H), 7.68−7.65 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.37−7.32 (m, 3H), 7.29−7.26 (m, 1H), 7.24−7.23 (m, 1H), 7.15 (dd, J = 8.3, 2.4 Hz, 1H), 5.67 (d, J = 1.8 Hz, 1H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.0, 159.6, 145.2, 144.3, 139.8, 136.3, 130.1, 129.7, 124.5, 124.2, 120.5, 118.6, 118.0, 117.8, 116.3, 113.1, 103.0, 55.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{14}NO_3$ 292.0968, found 292.0963.

*(4H-Furo[3,2-b]indol-4-yl)(4-methoxyphenyl)methanone (**4m**):* 53.3 mg (86% yield, white solid, purified by SiO_2 column chromatography eluting 10−20% EtOAc/hexane); mp 100.6−101.0 °C; IR (neat) ν_{max} 2989, 1670, 1300, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42−8.36 (m, 1H), 7.76−7.71 (m, 2H), 7.69−7.64 (m, 1H), 7.35−7.29 (m, 3H), 7.04−6.99 (m, 2H), 5.86 (d, J = 2.1 Hz, 1H), 3.90 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 162.7, 145.1, 144.1, 139.9, 131.0, 130.4, 127.0, 124.3, 123.9, 118.4, 117.6, 116.2, 113.8, 103.1, 55.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{14}NO_3$ 292.096, found 292.0966.

*(4H-Furo[3,2-b]indol-4-yl)(3,4,5-trimethoxyphenyl)methanone (**4n**):* 65.4 mg (81% yield, white solid, purified by SiO_2 column chromatography eluting 10% EtOAc/hexane); mp 102.6−103.7 °C; IR (neat) ν_{max} 2940, 1682, 1584, 1353, 1124, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 7.71−7.68 (m, 1H), 7.38−7.32 (m, 3H), 6.99 (s, 2H), 5.86 (d, J = 2.1 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.6, 153.2, 145.2, 144.3, 141.1, 139.8, 130.1 129.9, 124.5, 124.2, 118.5, 117.7, 116.3, 106.0, 103.1, 61.1, 56.3; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{20}H_{17}NNaO_5$ 374.0999, found 374.0990.

*(4H-Furo[3,2-b]indol-4-yl)(4-(trifluoromethoxy)phenyl)-methanone (**4o**):* 58.5 mg (93% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 76.4−77.4 °C; IR (neat) ν_{max} 2928, 1685, 1388, 1258, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45−8.42 (m, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.70−7.67 (m, 1H), 7.40−7.32 (m, 5H), 5.66 (d, J = 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8, 151.7 (q, C−F, $^3J_{C-F}$ = 2 Hz), 145.4, 144.6, 139.9, 133.5, 130.5, 129.7, 124.7, 124.5, 120.7, 120.3 (q, C−F, $^1J_{C-F}$ = 257 Hz), 118.6, 117.8, 116.4, 102.7; HRMS (ESI−TOF) m/z $(M+Na)^+$ calcd for $C_{18}H_{10}F_3NNaO_3$ 368.0505, found 368.0495.

*(4-Fluorophenyl)(4H-furo[3,2-b]indol-4-yl)methanone (**4p**):* 51.5 mg (55% yield, colorless crystal, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 98.9−99.8 °C; IR (neat) ν_{max} 3071, 1687, 1307, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41−8.39 (m, 1H), 7.77−7.73 (m, 2H), 7.67−7.65 (m, 1H), 7.36−7.31 (m, 3H), 7.21 (t, J = 8.8 Hz, 2H), 5.70 (d, J = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 164.8 (d, C−F, $^1J_{C-F}$ = 252 Hz), 145.3, 144.4, 139.8, 131.2, 131.1, 131.0, 129.9, 124.4 (d, C−F, $^2J_{C-F}$ = 24 Hz), 118.5, 117.7, 116.3, 115.8 (d, C−F, $^2J_{C-F}$ = 22 Hz), 102.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 109.45 to −109.52 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}FNO_2$ 280.0768, found 280.0775.

*(4-Chlorophenyl)(4H-furo[3,2-b]indol-4-yl)methanone (**4q**):* 57.9 mg (96% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 130.6−130.8 °C; IR (neat) ν_{max} 3110, 1684, 1354, 1310, 1089, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42−8.39 (m, 1H), 7.68−7.64 (m, 3H), 7.52−7.49 (m,

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2H), 7.36−7.30 (m, 3H), 5.70 (d, J = 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.0, 145.3, 144.4, 139.8, 138.2, 133.4, 130.0, 129.7, 128.9, 124.6, 124.4, 118.5, 117.7, 116.3, 102.8; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}ClNO_2$ 296.0473, found 296.0475.

*(2-Bromophenyl)(4H-furo[3,2-b]indol-4-yl)methanone (**4r**):* 24.3 mg (30% yield, brown solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 159.9−160.2 °C; IR (neat) ν_{max} 3128, 1682, 1367, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.68−7.66 (m, 1H), 7.54−7.44 (m, 3H), 7.38−7.29 (m, 3H), 5.02 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 145.7, 144.8, 139.4, 137.8, 133.2, 131.8, 129.3, 128.4, 127.9, 124.9, 124.8, 119.6, 119.0, 118.3, 116.4, 101.8; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}{}^{79}BrNO_2$ 339.9968, found 339.9968.

*(4-Bromo-2-fluorophenyl)(4H-furo[3,2-b]indol-4-yl)methanone (**4s**):* 31.2 mg (45% yield, white solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 174.8−175.3 °C; IR (neat) ν_{max} 3085, 2853, 1675, 1604, 1371, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.71−7.68 (m, 1H), 7.55−7.48 (m, 3H), 7.43−7.36 (m, 3H), 5.61 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 162.6, 159.0 (d, C−F, $^1J_{C-F}$ = 255 Hz), 145.7, 144.9, 139.5, 130.5 (d, C−F, $^3J_{C-F}$ = 4 Hz), 129.1, 128.2 (d, C−F, $^3J_{C-F}$ = 4 Hz), 126.0 (d, C−F, $^3J_{C-F}$ = 9 Hz), 124.9 (d, C−F, $^3J_{C-F}$ = 6 Hz), 123.2 (d, C−F, $^2J_{C-F}$ = 17 Hz), 120.4, 120.1, 118.9, 117.8, 116.5, 101.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 114.26 to −114.30 (m); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{10}{}^{79}BrFNO_2$ 357.9873, found 357.9881.

*4-(4H-Furo[3,2-b]indole-4-carbonyl)benzonitrile (**4t**):* 56.5 mg (72% yield, white solid, purified by SiO_2 column chromatography eluting 50% DCM/hexane to 20% EtOAc/hexane); mp 171.3−171.7 °C; IR (neat) ν_{max} 3352, 2976, 1647, 1045, 879 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44−8.41 (m, 1H), 7.88−7.82 (m, 4H), 7.72−7.67 (m, 1H), 7.42−7.34 (m, 3H), 5.56 (d, J = 0.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.1, 145.6, 144.9, 139.8, 139.1, 132.5, 129.3, 129.0, 125.0, 124.9, 118.8, 117.8, 117.7, 116.6, 115.5, 102.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{11}N_2O_2$ 287.0815, found 287.0818.

*(4H-Furo[3,2-b]indol-4-yl)(4-nitrophenyl)methanone (**4u**):* 68.3 mg (84% yield, yellow solid, purified by SiO_2 column chromatography eluting 30−50% DCM/hexane); mp 147.9−148.4 °C; IR (neat) ν_{max} 3077, 1685, 1525, 1308, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40−8.37 (m, 3H), 7.90−7.87 (m, 2H), 7.68−7.66 (m, 1H), 7.37−7.34 (m, 3H), 5.56 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8, 149.6, 145.6, 144.9, 140.8, 139.7, 129.4, 129.2, 125.0, 124.9, 123.9, 118.8, 117.8, 116.6 102.5; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{11}N_2O_4$ 307.0713, found 307.0718.

*Cyclohexyl(4H-furo[3,2-b]indol-4-yl)methanone (**4v**):* 16.0 mg (25% yield, yellow oil, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); IR (neat) ν_{max} 2931, 1699, 1268, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65−8.63 (m, 1H), 7.67−7.64 (m, 1H), 7.57 (d, J = 2.1 Hz, 1H), 7.35−7.29 (m, 2H), 6.67 (d, J = 1.8 Hz, 1H), 3.04 (tt, J = 11.4, 3.3 Hz, 1H), 2.08−2.04 (m, 2H), 1.97−1.92 (m, 2H), 1.82−1.64 (m, 3H), 1.51−1.25 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.7, 145.8, 144.6, 139.6, 128.0, 124.8, 123.9, 118.3, 118.0, 116.1, 102.8, 44.4, 29.0, 25.75, 25.71; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{18}NO_2$ 268.1332, found 268.1339.

*Phenyl(2-phenyl-4H-furo[3,2-b]indol-4-yl)methanone (**4x**):* 49.7 mg (94% yield, white solid, purified by SiO_2 column chromatography eluting 5−10% EtOAc/hexane); mp 169.5−169.8 °C; IR (neat) ν_{max} 2923, 1679, 1442, 1367, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42−8.40 (m, 1H), 7.76−7.74 (m, 2H), 7.71−7.64 (m, 2H), 7.60−7.54 (m, 4H), 7.37−7.30 (m, 4H), 7.27−7.22 (m, 1H), 5.85 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1, 156.7, 143.8, 139.7, 135.1, 131.9, 131.7, 130.7, 128.7, 128.6, 128.5, 127.9, 124.5, 124.4 123.8, 118.5, 117.7, 116.2, 97.6; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{16}NO_2$ 338.1176, found 338.1175.

*(2-(4-Methoxyphenyl)-4H-furo[3,2-b]indol-4-yl)(phenyl)-methanone (**4y**):* 30.5 mg (73% yield, yellow solid, purified by SiO_2 column chromatography eluting 5% EtOAc/hexane); mp 176.0−176.5 °C; IR (neat) ν_{max} 2925, 1683, 1255, 1023, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42−8.39 (m, 1H), 7.77−7.74 (m, 2H), 7.69−7.64 (m, 2H), 7.58−7.50 (m, 4H), 7.38−7.27 (m, 2H), 6.91−6.86 (m, 2H), 5.72 (s, 1H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2, 159.5, 156.9, 143.2, 139.4, 135.2, 131.9, 131.8, 128.6, 128.5, 125.3, 124.3, 124.1, 123.7, 118.6, 117.6, 116.0, 114.2, 96.2, 55.3; HRMS (ESI−TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{17}NNaO_3$ 390.1101, found 390.1096.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00086.

Optimization studies for the conversions of compounds **2aBr** to **3aBr** and **3aBr** to **4a**, copies of ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra, copies of high-resolution mass spectra of all compounds, and X-ray diffraction parameters and thermal ellipsoid plots (PDF)

Accession Codes

CCDC 2057692−2057694 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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■ REFERENCES

(1) (a) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry. Chemistry, Biology and Material Science*; Wiley-VCH: Weinheim, Germany, 2005. (b) Trost, B. M.; Tracy, J. S. Organic Synthesis. Use of Alkynes as a Key to Innovation in Designing Structure for Function. *Isr. J. Chem.* **2018**, *58*, 18−27. (c) Voronin, V. V.; Ledovskaya, M. S.; Bogachenkov, A. S.; Rodygin, K. S.; Ananikov, V. P. Acetylene in Organic Synthesis: Recent Progress and New Uses. *Molecules* **2018**, *23*, 2442.

(2) (a) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028−9072. (b) Gupta, A.; Flynn, B. L. Electrophilic Activation of P-Alkynes in the Synthesis of P-Substituted and P-Centered Heterocycles. *J. Org. Chem.* **2016**, *81*, 4012−4019. (c) Takeda, Y.; Kajihara, R.; Kobayashi, N.; Noguchi, K.; Saito, A. Molecular-Iodine-Catalyzed Cyclization of 2-Alkynylanilines via Iodocyclization−Protodeiodination Sequence. *Org. Lett.* **2017**, *19*, 6744−6747. (d) Garkhedkar, A. M.; Gore, B. S.; Hu, W.-P.; Wang, J.-J. Lewis Acid Catalyzed Atom-Economic Synthesis of C2-Substituted Indoles from *o*-Amido Alkynols. *Org. Lett.* **2020**, *22*, 3531−3536.

(3) (a) Maibunkaew, T.; Thongsornkleeb, C.; Tummatorn, J.; Bunrit, A.; Ruchirawat, S. Practical and Metal-Free Electrophilic Aromatic Halogenation by Interhalogen Compounds Generated In Situ from *N*-Halosuccinimide and Catalytic TMSCl. *Synlett* **2014**, *25*, 1769−1775. (b) Kaewsri, W.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. Isomerizable (*E*/*Z*)-alkynyl-*O*-methyl oximes employing TMSCl−NCS in chlorinative cyclization for the direct synthesis of 4-chloroisoxazoles. *RSC Adv.* **2016**, *6*, 48666−48675. (c) Kaewsri, W.; Norseeda, K.; Ruengsangtongkul, S.; Chaisan, N.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. Synthesis of 2-Cyclohexenone-2-carboxylate and 4-Chloro2-cyclohexenone-2-carboxylate Derivatives by Cyclization of Alkyne-Tethered 1,3-Ketoesters. *Asian J. Org. Chem.* **2018**, *7*, 203−211. (d) Norseeda, K.; Chaisan, N.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. Metal-Free Synthesis of 4-Chloroisocoumarins by TMSCl-Catalyzed NCS-Induced Chlorinative Annulation of 2-Alkynylaryloate Esters. *J. Org. Chem.* **2019**, *84*, 16222−16236.

(4) (a) Zheng, Y.; Tice, C. M.; Singh, S. B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673−3682. (b) Zheng, Y.-J.; Tice, C. M. The utilization of spirocyclic scaffolds in novel drug discovery. *Expert Opin. Drug Discovery* **2016**, *11*, 831−834. (c) Muller, G.; Berkenbosch, T.; Benningshof, J. C. J.; Stumpfe, D.; Bajorath, J. Charting Biologically Relevant Spirocyclic Compound Space. *Chem. - Eur. J.* **2017**, *23*, 703−710. (d) Chupakhin, E.; Babich, O.; Prosekov, A.; Asyakina, L.; Krasavin, M. Spirocyclic Motifs in Natural Products. *Molecules* **2019**, *24*, 4165.

(5) (a) Thaler, F.; Varasi, M.; Abate, A.; Carenzi, G.; Colombo, A.; Bigogno, C.; Boggio, R.; Zuffo, R. D.; Rapetti, D.; Resconi, A.; Regalia, N.; Vultaggio, S.; Dondio, G.; Gagliardi, S.; Minucci, S.; Mercurio, C. Synthesis and biological characterization of spiro[2*H*-(1,3)-benzoxazine-2,4′-piperidine] based histone deacetylase inhibitors. *Eur. J. Med. Chem.* **2013**, *64*, 273−284. (b) Badarau, E.; Robert, F.; Massip, S.; Jakob, F.; Lucas, S.; Friebe, D.; Hennen, S.; Frormann, S.; Ghosez, L. Discovery of a subnanomolar and selective spirocyclic agonist of the glucocorticoid receptor. *Eur. J. Med. Chem.* **2019**, *161*, 354−363. (c) García, M.; Virgili, M.; Alonso, M.; Alegret, C.; Fernández, B.; Port, A.; Pascual, R.; Monroy, X.; Vidal-Torres, A.; Serafini, M.-T.; Vela, J. M.; Almansa, C. 4-Aryl-1-oxa-4,9-diazaspiro-[5.5]undecane Derivatives as Dual μ-Opioid Receptor Agonists and σ_1 Receptor Antagonists for the Treatment of Pain. *J. Med. Chem.* **2020**, *63*, 2434−2454. (d) Yuan, X.; Bu, H.; Zhou, J.; Yang, C.-Y.; Zhang, H. Recent Advances of SHP2 Inhibitors in Cancer Therapy: Current Development and Clinical Application. *J. Med. Chem.* **2020**, *63*, 11368−11396.

(6) (a) Laus, G. Biological Activities of Natural Halogen Compounds. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: Amsterdam, The Netherlands, 2001; Vol. *25*, pp 757−809. (b) La Barre, S.; Potin, P.; Leblanc, C.; Delage, L. The Halogenated Metabolism of Brown Algae (Phaeophyta), Its Biological Importance and Its Environmental Significance. *Mar. Drugs* **2010**, *8*, 988−1010. (c) Cabrita, M. T.; Vale, C.; Rauter, A. P. Halogenated Compounds from Marine Algae. *Mar. Drugs* **2010**, *8*, 2301−2317. (d) Gribble, G. W. Biological Activity of Recently Discovered Halogenated Marine Natural Products. *Mar. Drugs* **2015**, *13*, 4044−4136.

(7) (a) Hernandes, M.; Cavalcanti, S. M.; Moreira, D. R.; de Azevedo Junior, W.; Leite, A. C. Halogen Atoms in the Modern Medicinal Chemistry: Hints for the Drug Design. *Curr. Drug Targets* **2010**, *11*, 303−314. (b) Wilcken, R.; Zimmermann, M. O.; Lange, A.; Joerger, A. C.; Boeckler, F. M. Principles and Applications of Halogen Bonding in Medicinal Chemistry and Chemical Biology. *J. Med. Chem.* **2013**, *56*, 1363−1388. (c) Jiang, S.; Zhang, L.; Cui, D.; Yao, Z.; Gao, B.; Lin, J.; Wei, D. The Important Role of Halogen Bond in Substrate Selectivity of Enzymatic Catalysis. *Sci. Rep.* **2016**, *6*, 34750. (d) Ho, P. S. Halogen bonding in medicinal chemistry: from observation to prediction. *Future Med. Chem.* **2017**, *9*, 637−640.

(8) (a) Kropp, P. J.; Pienta, N. J. Photochemistry of Alkyl Halides. 9. Geminal Dihalides. *J. Org. Chem.* **1983**, *48*, 2084−2090. (b) Ashby, E. C.; Deshpande, A. K. Mechanism of Reaction of Geminal Dihalides with Lithium Aluminum Hydride. Evidence for Single Electron Transfer as the Major Reaction Pathway. *J. Org. Chem.* **1994**, *59*, 3798−3805. (c) Ashby, E. C.; Deshpande, A. K. Electron Transfer in the Reactions of Geminal Dihalides with Ph_2P^-. Evidence for the Formation of a Carbene Intermediate from a Radical Precursor. *J. Org. Chem.* **1995**, *60*, 7117−7124. (d) Liang, Y.; Fu, G. C. G. C. Catalytic Asymmetric Synthesis of Tertiary Alkyl Fluorides: Negishi Cross-Couplings of Racemic α,α-Dihaloketones. *J. Am. Chem. Soc.* **2014**, *136*, 5520−5524.

(9) (a) Buysch, H.-J.; Scholz, K.-H. Process for Preparing Geminal Dihalides. U.S. Patent 4,044,060, August 23, 1977. (b) Furrow, M. E.; Myers, A. G. Practical Procedures for the Preparation of *N*-*tert*-Butyldimethylsilylhydrazones and Their Use in Modified Wolff-Kishner Reductions and in the Synthesis of Vinyl Halides and *gem*-Dihalides. *J. Am. Chem. Soc.* **2004**, *126*, 5436−5445. (c) Cloarec, J.-M.; Charette, A. B. Highly Efficient Two-Step Synthesis of C-sp^3-Centered Geminal Diiodides. *Org. Lett.* **2004**, *6*, 4731−4734. (d) Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. A Mild Synthesis of Vinyl Halides and *gem*-Dihalides Using Triphenyl Phosphite−Halogen-Based Reagents. *J. Org. Chem.* **2007**, *72*, 2216−2219.

(10) Zinad, D. S.; Mahal, A.; Mohapatra, R. K.; Sarangi, A. K.; Pratama, M. R. F. Medicinal chemistry of oxazines as promising agents in drug discovery. *Chem. Biol. Drug Des.* **2020**, *95*, 16−47.

(11) (a) Nakashima, Y.; Kawashima, Y.; Amanuma, F.; Sota, K.; Tanaka, A.; Kameyama, T. Furo[3,2-*b*]indole Derivatives I. Synthesis and Analgesic and Anti-inflammatory Activities of 4,5-Disubstituted-furo[3,2-*b*]indole-2-carboxamide Derivatives. *Chem. Pharm. Bull.* **1984**, *32*, 4271−4280. (b) Nakashima, Y.; Kawashima, Y.; Sato, M.; Okuyama, S.; Amanuma, F.; Sota, K.; Kameyama, T. Furo[3,2-*b*]indole Derivatives II. Synthesis and Analgesic and Anti-inflammatory Activities of 4-Alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole Derivatives. *Chem. Pharm. Bull.* **1985**, *33*, 5250−5257.

https://dx.doi.org/10.1021/acs.joc.1c00086
J. Org. Chem. 2021, 86, 4671−4698

(c) Kawashima, Y.; Sato, M.; Hatada, Y.; Okuyama, S.; Amanuma, F.; Nakashima, Y.; Sota, K.; Moriguchi, I. Furo[3,2-*b*]indole Derivatives III. Structure-Activity Studies of 4,6-Disubstituted *N*-(3-Piperidinopropyl)furo[3,2-*b*]indole-2-carboxamide Derivatives for Analgesic and Antiinflammatory Activities. *Chem. Pharm. Bull.* **1986**, *34*, 3267−3272. (d) Kawashima, Y.; Amanuma, F.; Sato, M.; Okuyama, S.; Nakashima, Y.; Sota, K.; Moriguchi, I. Structure-Activity Studies of 4,6-Disubstituted 2-(Morpholinocarbonyl)furo-[3,2-*b*]indole Derivatives with Analgesic and Antiinflammatory Activities. *J. Med. Chem.* **1986**, *29*, 2284−2290. (e) Zhuang, S.-H.; Lin, Y.-C.; Chou, L.-C.; Hsu, M.-H.; Lin, H.-Y.; Huang, C.-H.; Lien, J.-C.; Kuo, S.-C.; Huang, L.-J. Synthesis and anticancer activity of 2,4-disubstituted furo[3,2-*b*]indole derivatives. *Eur. J. Med. Chem.* **2013**, *66*, 466−479.

(12) (a) Tanaka, A.; Yakushijin, K.; Yoshina, S. Synthesis of 4*H*-Furo[3,2-*b*]indole Derivatives. A New Heterocyclic Ring System. *J. Heterocycl. Chem.* **1977**, *14*, 975−979. (b) Tanaka, A.; Yakushijin, K.; Yoshina, S. Synthesis of 4*H*-Furo[3,2-*b*]indoles. (II). Bromination, Acylation and Nitration of 4*H*- and 4-Benzoylfuro[3,2-*b*]indoles. *J. Heterocycl. Chem.* **1978**, *15*, 123−125. (c) Tanaka, A.; Yakushijin, K.; Yoshina, S. Synthesis of 4*H*-Furo[3,2-*b*]indole Derivatives. III. Preparation of 4*H*-Furo[3,2-*b*]indole-2-carboxylic Acid Derivatives. *J. Heterocycl. Chem.* **1979**, *16*, 785−788. (d) Pudlo, M.; Csanyi, D.; Moreau, F.; Hajos, G.; Riedl, Z.; Sapi, J. First Suzuki-Miyaura type cross-coupling of *ortho*-azidobromobenzene with arylboronic acids and its application to the synthesis of fused aromatic indole-heterocycles. *Tetrahedron* **2007**, *63*, 10320−10329. (e) Zhang, Z.; Fang, S.; Liu, Q.; Zhang, G. Microwave-Assisted Facile Synthesis of Furo[3,2-*b*]indole Derivatives *via* Silver(I)-Mediated [3 + 2] Cycloaddition. *Adv. Synth. Catal.* **2012**, *354*, 927−932.

(13) (a) Pirovano, V.; Brambilla, E.; Rizzato, S.; Abbiati, G.; Bozzi, M.; Rossi, E. Gold-Catalyzed Cascade Reactions of 4*H*-Furo[3,2-*b*]indoles with Allenamides: Synthesis of Indolin-3-one Derivatives. *J. Org. Chem.* **2019**, *84*, 5150−5166. (b) Brambilla, E.; Pirovano, V.; Giannangeli, M.; Abbiati, G.; Caselli, A.; Rossi, E. Gold-catalyzed cascade reactions of 4*H*-furo[3,2-*b*]indoles with propargyl esters: synthesis of 2-alkenylidene-3-oxoindolines. *Org. Chem. Front.* **2019**, *6*, 3078−3084. (c) Pirovano, V.; Caselli, A.; Colombo, A.; Dragonetti, C.; Giannangeli, M.; Rossi, E.; Brambilla, E. Synthesis of 2-alkenylidene-3-oxoindolines: cascade reactions of 4*H*-furo[3,2-*b*]-indoles with diazoacetates catalyzed by a Cu(I) macrocyclic pyridine-containing ligand (PcL) complex. *ChemCatChem* **2020**, *12*, 5250−5255. (d) Pirovano, V.; Brambilla, E.; Moretti, A.; Rizzato, S.; Abbiati, G.; Nava, D.; Rossi, E. Synthesis of Cyclohepta[*b*]indoles by (4 + 3) Cycloaddition of 2-Vinylindoles or 4*H*-Furo[3,2-*b*]indoles with Oxyallyl Cations. *J. Org. Chem.* **2020**, *85*, 3265−3276.

(14) (a) Nelson, W. M. *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: New York, USA, 2003. (b) Capello, C.; Fischer, U.; Hungerbühler, K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents. *Green Chem.* **2007**, *9*, 927−934. (c) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546−4551. (d) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chem. Processes*. [Online] **2016**, *4*, DOI: 10.1186/s40508-016-0051-z (accessed September 19, 2020).

(15) See Supporting Information for details of these optimization studies.

(16) (a) Shaughnessy, K. H.; Ciganek, E.; DeVasher, R. B. *Copper-Catalyzed Amination of Aryl and Alkenyl Electrophiles*; Wiley: Hoboken, New Jersey, 2017. (b) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. Mechanistic Studies on the Copper-Catalyzed *N*-Arylation of Amides. *J. Am. Chem. Soc.* **2009**, *131*, 78−88. (c) Lin, H.; Sun, D. Recent Synthetic Developments and Applications of the Ullmann Reaction. A Review. *Org. Prep. Proced. Int.* **2013**, *45*, 341−394. (d) Hu, T.; Li, C. Synthesis of Lactams via Copper-Catalyzed Intramolecular Vinylation of Amides. *Org. Lett.* **2005**, *7*, 2035−2038.

(17) (a) Illuminati, G.; Mandolini, L.; Masci, B. Ring-closure reactions. V. Kinetics of five- to ten-membered ring formation from o-.omega.-bromoalkylphenoxides. Influence of the O-heteroatom. *J. Am. Chem. Soc.* **1975**, *97*, 4960−4966. (b) Illuminati, G.; Mandolini, L. Ring Closure Reactions of Bifunctional Chain Molecules. *Acc. Chem. Res.* **1981**, *14*, 95−102. (c) Casadei, M. A.; Galli, C.; Mandolini, L. Ring-Closure Reactions. 22. Kinetics of Cyclization of Diethyl (ω-Bromoalky1)malonates in the Range of 4- to 21-Membered Rings. Role of Ring Strain. *J. Am. Chem. Soc.* **1984**, *106*, 1051−1056. (d) Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. Ring-closure Reactions. Part 23. Kinetics of Formation of Three- to Seven-membered-ring *N*-Tosylazacycloalkanes. The Role of Ring Strain in Small- and Common-sized-ring Formation. *J. Chem. Soc., Perkin Trans. 2* **1985**, *2*, 1345−1349. (e) Galli, C.; Mandolini, L. The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules. *Eur. J. Org. Chem.* **2000**, *2000*, 3117−3125.

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