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Regio- and Stereoselective Pd-Catalyzed Direct Arylation of Unactivated sp^3 C(3)−H Bonds of Tetrahydrofuran and 1,4-Benzodioxane Systems

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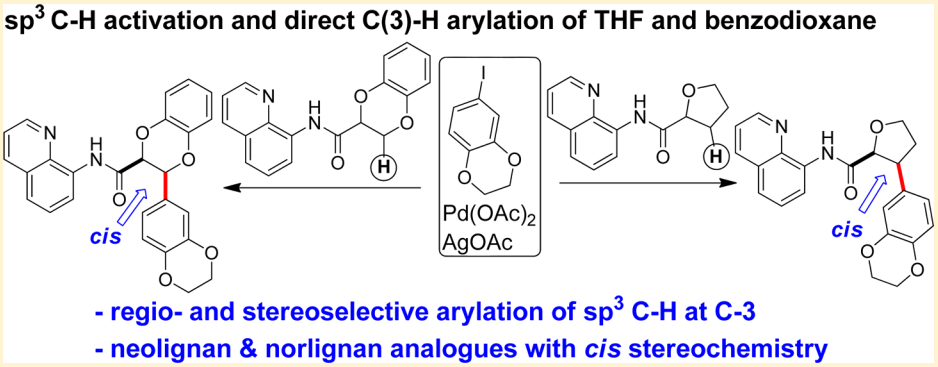
Supporting Information



ABSTRACT: An auxiliary-enabled Pd-catalyzed highly regio- and stereoselective sp^3 C−H activation and the direct arylation of the C3-position of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems, are reported. An efficient stereoselective construction of cis 2,3-disubstituted tetrahydrofuran derivatives (analogues of norlignans) and cis 2,3-disubstituted 1,4-benzodioxane derivatives (analogues of neolignans) is described. The direct C(sp^3)−H arylation of the C3-position of (*R*)- or (*S*)- tetrahydrofuran-2-carboxamides furnished the corresponding (2*R*,3*R*) and (2*S*,3*S*) C3-arylated THF scaffolds as major compounds with very high regio- and diastereoselectivities. The stereochemistry of the products obtained in this work were unambiguously assigned on the basis of the X-ray structure analyses of representative compounds **3b**, **3e**, **4p**, and **7**.

INTRODUCTION

Saturated oxygen hetereocycles, especially, tetrahydrofuran (THF)- and benzodioxane-based motifs are recurrently encountered in nature (e.g., lignans, annonaceous acetogenins, polyether ionophores/antibiotics, and macrodiolides), pharmaceuticals, and bioactive synthetic compounds.[1,2] Several substituted THF- and benzodioxane-based synthetic molecules and naturally occurring lignan, neolignan, and norlignan oxygen hetereocycles were found to exhibit a wide range of biological activities (e.g., anticancer, antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive activities).[1−4] There exist several naturally occurring THF−norlignan and benzodioxane−neolignan motifs possessing an aryl group at the C3-position (Figure 1), and many of them were found to exhibit various biological activities.[1,2] For example, recently, a family of THF−norlignans, such as metasequirins A, B, E, F, G, and H, were isolated[2a−c] and metasequirins E and F were evaluated for cytotoxicity against five human tumor cell lines.[2a] Further, benzodioxane−neolignan molecules, such as isoamericanol A, americanol A, isoamericanin A, and americanin A, were found to show neurotropic and acetylcholine-enhancing activities.[2d,e] The present investigation deals on the synthesis of analogues of norlignans and neolignans.

Due to their prevalence in natural products, biological activities, and ability to serve as building blocks in organic chemistry, numerous classical and modern stereoselective synthetic methods[1−4] including α-C−H functionalization[5] have been developed for producing bioactive and synthetic tetrahydrofuran and benzodioxane derivatives. In general, the majority of the tetrahydrofuran and benzodioxane derivatives were assembled mainly via the cyclization reaction[3,4] of predesigned starting materials having the required functional groups.

The direct functionalization of the unactivated C(sp^3)−H bonds of organic molecules is known to be a challenging task in the past decades. However, from the recent past decade, several exceptional reports appeared on the transition metal-catalyzed direct functionalization of C−H bonds present in organic molecules, and indeed, functionalization of organic molecules via C−H activation is emerging as one of the important

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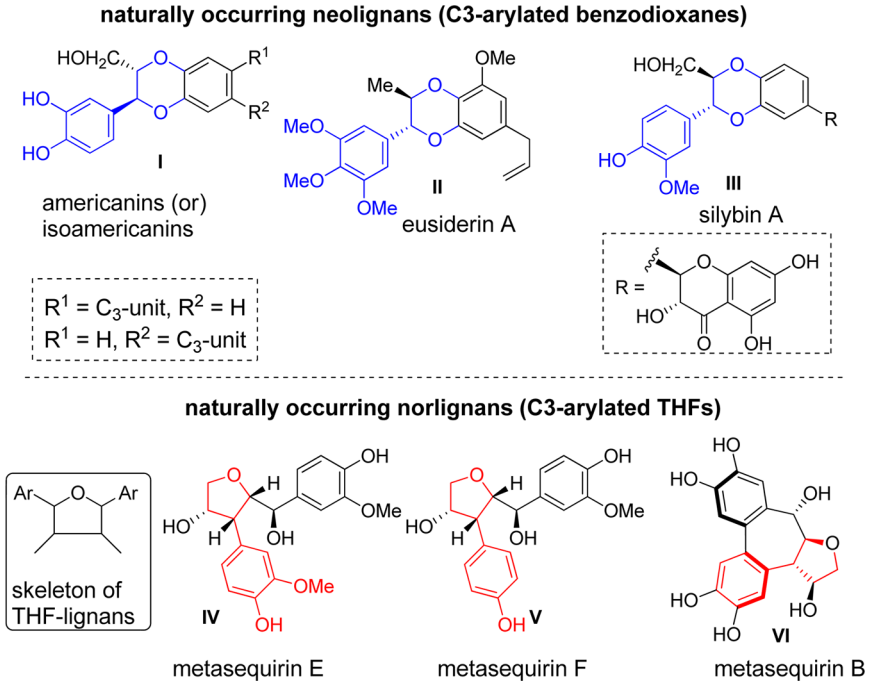
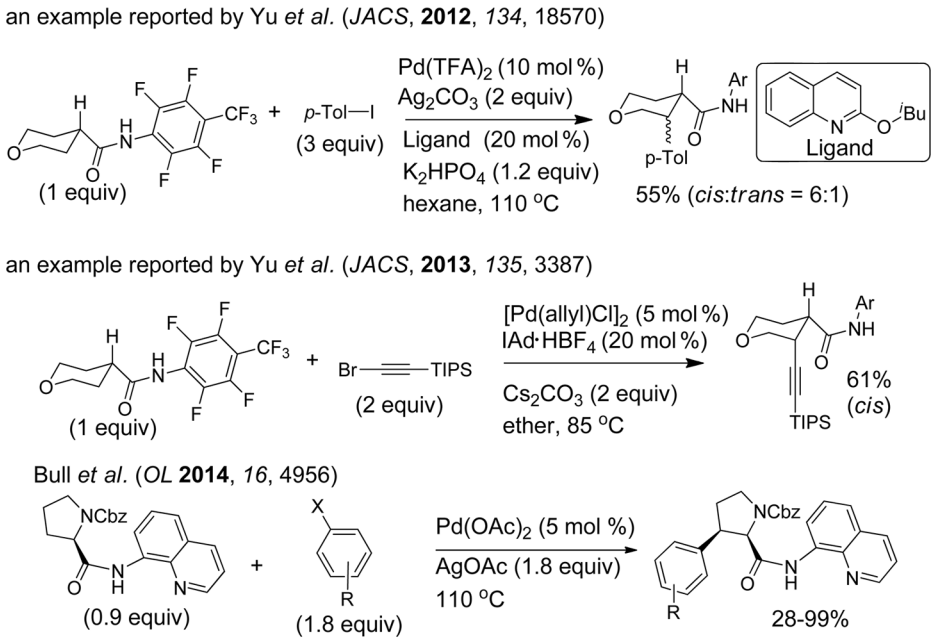


Figure 1. Representative examples of lignan natural products.

Scheme 1. Theme of This Work



- highly regio- and stereoselective arylation of sp^3 C(3)-H bond
- construction of neolignan & norlignan scaffolds

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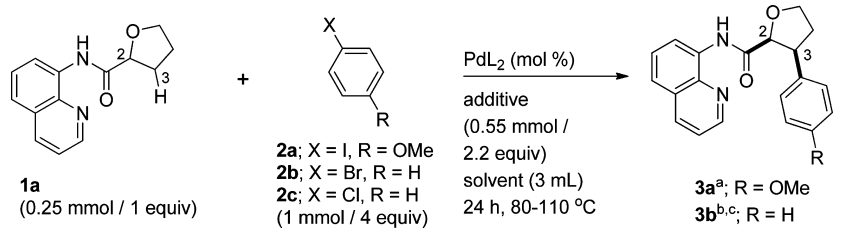
Table 1. Optimization of Reaction Conditions



entry	PdL_2 (mol %)	additive (mmol)	solvent (3 mL)	T (°C)	**3a**; yield (%)[a]
1	nil	AgOAc (0.55)	toluene	110	0
2	$Pd(OAc)_2$ (10)	nil	toluene	110	<15
3	$Pd(OAc)_2$ (5)	AgOAc (0.55)	toluene	110	70
4	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	81
5	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.55)	toluene	110	69
6	$Pd(OAc)_2$ (10)	K_2CO_3 (0.55)	toluene	110	0
7	$Pd(OAc)_2$ (10)	KOAc (0.55)	toluene	110	traces
8	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (0.55)	toluene	110	0
9	$PdCl_2$ (10)	AgOAc (0.55)	toluene	110	<10
10	$Pd(TFA)_2$ (10)	AgOAc (0.55)	toluene	110	0
11	$Pd(CH_3CN)_2Cl_2$ (10)	AgOAc (0.55)	toluene	110	69
12	$Pd(PPh_3)_4$ (10)	AgOAc (0.55)	toluene	110	30
13	$Pd(OAc)_2$ (10)	AgOAc (0.55)	CH_3CN	80	0
14	$Pd(OAc)_2$ (10)	AgOAc (0.55)	1,2-DCE	80	0
15	$Pd(OAc)_2$ (10)	AgOAc (0.55)	^{t}BuOH	85	0
16	$Pd(OAc)_2$ (10)	AgOAc (0.55)	1,4-dioxane	100	46
17	$Pd(OAc)_2$ (10)	AgOAc (0.55)	^{t}amylOH	110	57
18	$Pd(OAc)_2$ (10)	AgOAc (0.55)	toluene	110	0[b,c]

[a]The yield corresponds to the reaction of **1a** with **2a**. [b]The yield corresponds to the reaction of **1a** with **2b**. [c]The yield corresponds to the reaction of **1a** with **2c**.

strategies.[6−15] There exist several outstanding reports that dealing with the direct functionalization of C(sp^2)−H bonds present in organic molecules. On the other hand, the direct functionalization of the unactivated C(sp^3)−H bonds present in organic molecules is one of the emerging research areas.[6−15] Notably, an auxiliary-enabled, Pd-catalyzed arylation reaction of alkyl C(sp^3)−H bonds instigated by Daugulis, Yu, Chen, and others is emerging as one of the seminal methods for constructing C−C bonds. Along this line, the direct arylations of C(sp^3)−H bonds present in carbocyclic systems, such as cyclopropane, cyclobutane, medium-sized rings, the norbornane framework, and acyclic amino acid derivatives, have been successfully demonstrated by various research groups.[14,15]

Along this line, we envisioned the selective C−H functionalization and the direct arylation of the unactivated C(sp^3)−H bonds present in the THF and 1,4-benzodioxane systems for assembling new neolignan/norlignan scaffolds. To the best of our knowledge, there exist only rare papers dealing with the directing group-enabled, Pd-catalyzed C−H functionalization of the unactivated C(sp^3)−H bonds of saturated heterocycles, and a literature survey revealed that there is no report dealing with the Pd-catalyzed direct arylation of the C3-position of tetrahydrofuran and benzodioxane systems.[6−15] With regard to the functionalization of C(sp^3)−H bonds of saturated oxygen hetereocycles, there exist only two examples reported by Yu et al., which include the arylation[15a] and alkynylation[15b] of the C3-position of a tetrahydropyran derivative (Scheme 1). On the other hand, with regard to the functionalization of the unactivated C(sp^3)−H bonds of saturated nitrogen hetereocycles, recently, Bull et al. reported the direct arylation of the C(3)−H bond of a proline derivative.[15c] Wu et al. revealed the amination reaction involving the C(3)−H bond of a proline derivative.[15d] Earlier, Chen's group reported an example of the direct alkylation of the C(3)−H bond of a piperidine derivative.[15e]

In continuation of our lab's interest in C−H activation reactions, herein we report an auxiliary-enabled, Pd-catalyzed, highly regio- and stereoselective C(sp^3)−H activation/functionalization of the tetrahydrofuran and 1,4-benzodioxane systems. This work demonstrates a new route for the direct arylation of the C(3) position of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems and highly stereoselective construction of novel norlignan-type cis 2,3-disubstituted tetrahydrofurans and neolignan-type cis 2,3-disubstituted 1,4-benzodioxanes.

RESULTS AND DISCUSSION

To examine the arylation of the methylene C(sp^3)−H bond of oxygen heterocycles, such as tetrahydrofuran and 1,4-benzodioxane systems, initially, we prepared the substrate **1a** by linking tetrahydrofuran-2-carboxylic acid chloride with Daugulis's bidentate directing group (8-aminoquinoline).[14a,b] Then to find out the best reaction conditions for achieving the C(3)−H arylation of substrate **1a**, we performed several reactions as shown in Table 1. We found the best reaction conditions comprising the reaction of substrate **1a**, aryl iodide **2a**, and AgOAc (additive) in the presence 5 or 10 mol % of the $Pd(OAc)_2$ catalyst, which afforded the C3-arylated product, cis 2,3-disubstituted tetrahydrofuran **3a** (norlignan analogue), in 70 and 81% yields, respectively (entries 3 and 4, Table 1). The C−H arylation of the substrate **1a** with **2a** in the presence of

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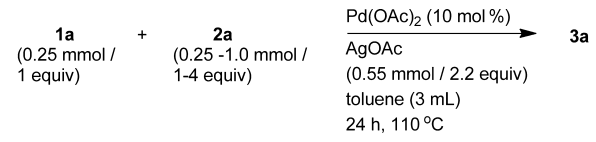
Ag_2CO_3 as an additive instead of AgOAc also gave the product **3a** in 69% yield (entry 5, Table 1).

The Pd-catalyzed C(3)−H arylation of substrate **1a** with **2a** in the presence of various other additives, such as K_2CO_3 or KOAc or $PhI(OAc)_2$ did not give the product **3a** (entries 6−8, Table 1). The C−H arylation of substrate **1a** in the presence of other palladium catalysts, such as $PdCl_2$ or $Pd(TFA)_2$ instead of $Pd(OAc)_2$, did not give satisfactory yields (entries 9 and 10, Table 1). However, the C−H arylation of **1a** in the presence of $Pd(CH_3CN)_2Cl_2$ and $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ furnished the product **3a** in 69 and 30% yields, respectively (entries 11 and 12, Table 1). The Pd-catalyzed C−H arylation of **1a** with **2a** in other solvents, such as MeCN or 1,2-DCE or *tert*-butyl alcohol, failed to afford the product **3a** (entries 13−15, Table 1). However, the Pd-catalyzed reaction of **1a** with **2a** in 1,4-dioxane or *tert*-amyl alcohol gave the product **3a** in 46 and 57% yields, respectively (entries 16 and 17, Table 1). Employing coupling partners **2b** or **2c** instead of **2a** was ineffective (entry 18, Table 1).

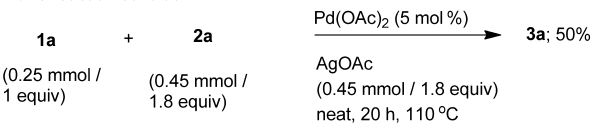
To find out how many equivalents of aryl iodide **2a** are required for producing the C3-arylated product **3a** with better yield, we investigated the C−H arylation of substrate **1a** by varying the quantity of **2a** (Table 2). The Pd-catalyzed C−H arylation of substrate **1a** with 1 equiv of **2a** gave the C3-arylated product **3a** in low yield (35%, entry 1, Table 2). Next, the Pd-catalyzed C−H arylation of substrate **1a** with 2 or 3 equiv of **2a** gave the C3-arylated product **3a** in 59% and 68% yields, respectively (entries 2 and 3, Table 2). The usage of 4 equiv of **2a** gave the C3-arylated product **3a** in very good yield (81%, entry 4, Tables 1 and 2). Along this line, we have also performed the Pd-catalyzed C−H arylation of substrate **1a** with 1.8 equiv of **2a** by using Bull's reaction conditions,[15c] which gave the C3-arylated product **3a** in 50% yield (Table 2).

Table 2. Optimization of Reaction Conditions



entry	**2a** (mmol)	**2a** (equiv)	ratio of **1a** : **2a**	**3a**: yield (%)
1	0.25	1	1 : 1	35
2	0.5	2	1 : 2	59
3	0.75	3	1 : 3	68
4	1.0	4	1 : 4	81

Bull's reaction condition



Subsequently, the generality of this bidentate directing-group-enabled, Pd-catalyzed direct arylation of the C(3)−H bond of the THF derivative **1a** was elaborated using a variety of aryl iodides (Scheme 2). The direct arylation of the methylene sp^3 C(3)−H bond of the substrate **1a** with various aryl iodides containing a substituent at the para or meta position (e.g., Ac, Cl, and NO_2) afforded the corresponding cis 2,3-disubstituted tetrahydrofurans **3b−g** in 56−76% yields. Similarly, the C3-arylated THF scaffolds **3h** and **3i** were obtained from the Pd-catalyzed C−H arylation of the substrate **1a** by using the corresponding benzodioxane- or benzodioxole-based aryl iodides as coupling partners. Further, the arylation of the substrate **1a** with multisubstituted aryl iodides gave the corresponding products **3j−l** in 40−58% yields. We have also carried out the Pd-catalyzed direct arylation of the C(3)-position of the THF derivative **1a** with a variety of hetero aryl iodides, which furnished the corresponding THF scaffolds **3m−r** possessing heteroaryl groups at the C3-position in 20−87% yields.

Representatively, recrystallization of C−H arylated products **3b** and **3e** formed single crystals, which were subjected to single-crystal X-ray structure analyses. The X-ray structures of the representative compounds **3b** and **3e** (see SI for the X-ray structures of **3b** and **3e**)[16] unambiguously confirmed that all these reactions were highly regio- and stereoselective and the direct C−H arylation occurred only at the C3-position of the substrate **1a** and selectively gave the 2,3-disubstituted tetrahydrofurans **3a−r** having cis stereochemistry (C2 and C3 stereocenters). In addition, characteristically, the C2 proton of all the compounds (**3a−r**) appeared as a doublet (chemical shift value range, δ = 4.71−4.91 ppm) due to its coupling with the C3 proton. The coupling constants (J) of the doublet peaks of the C2 proton of all the compounds (**3a−r**) were calculated from their respective ^{1}H NMR spectra and found to be in the range of 6.6−8.2 Hz (except the compound **3q** having a thiophene moiety at the C3-position, C2H, doublet, J = 6.3 Hz).[17a] Accordingly, the stereochemistry of the compounds **3a−r** were assigned as cis on the basis of the X-ray structure analyses of the compounds **3b** and **3e** coupled with the similarity in the NMR spectral pattern of the compounds **3a−r**.

Successively, we investigated the Pd-catalyzed C−H arylation of other substrates, such as **1bA**, **1bB**, and **1bC** (Figure 2). It is a limitation that the Pd-catalyzed C−H arylation reactions of substrates **1bA**, **1bB**, and **1bC** with **2a** were not successful (see the SI for additional information and individual reaction conditions). Furthermore, to find out the other working auxiliaries for selectively arylating the C(3)−H bond of THF derivatives, we performed the Pd-catalyzed reactions of substrates **1c−f**, **1dA**, **1eA**, and **1fA** with **2a** (Figure 2), and in these reactions we did not get any of the corresponding C−H arylated THF products. These reactions indicated that 8-aminoquinoline (Daugulis's auxiliary[14a,b]) is an effective auxiliary, as the substrate **1a** underwent the Pd-catalyzed C−H arylation more smoothly than the other substrates **1c−f**, **1dA**, **1eA**, and **1fA**.

Furthermore, we focused our attention to further extend the generality of this protocol, and we decided to investigate the Pd-catalyzed direct C−H arylation of the methylene C(sp^3)−H bond of the 1,4-benzodioxane system (Scheme 3). Along this line, initially, we assembled the substrate **1g** by linking the corresponding 1,4-benzodioxane carboxylic acid chloride with Daugulis's bidentate directing group (8-aminoquinoline). Then we performed the reaction of the substrate **1g** with phenyl iodide in the presence of AgOAc (2.2 equiv) and 10 mol % of the $Pd(OAc)_2$ catalyst, which successfully gave the C3-arylated product, cis 2,3-disubstituted 1,4-benzodioxane scaffold **4a** (neolignan analogue), in 65% yield (Scheme 3). Thenceforth, we capitalized on this success and synthesized a wide range neolignan-type cis 2,3-disubstituted 1,4-benzodioxane scaffolds **4b−q** (40−83%) from Pd-catalyzed direct arylation of the methylene sp^3 C(3)−H bond of the 1,4-benzodioxane system **1g** by using the corresponding aryl iodides, such as mono- and

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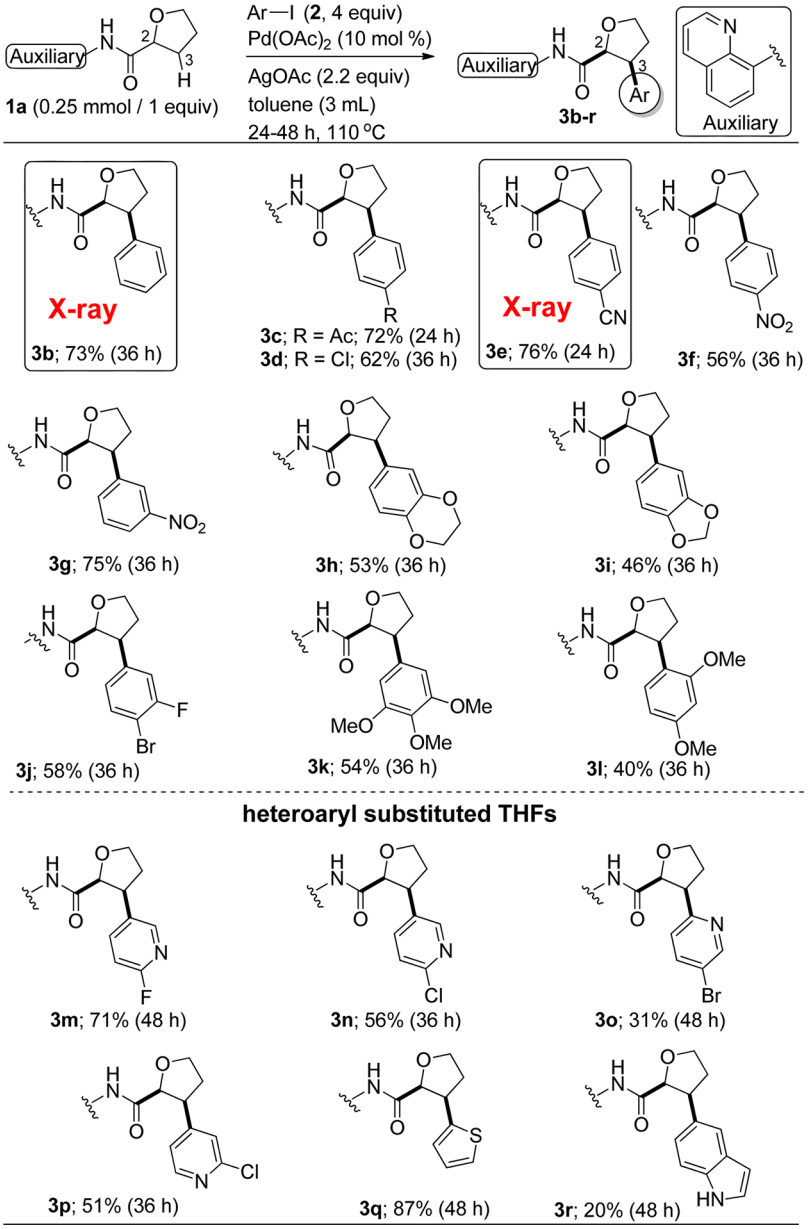
Scheme 2. Arylation of sp^3 C(3)−H Bond of 1a and Construction of Norlignan-THF Scaffolds



disubstituted aryl iodides, benzodioxane-based aryl iodide, and heteroaryl iodides.

In a representative case, the C−H arylated product **4p** was recrystallized and subjected to single-crystal X-ray structure analysis. The X-ray structure of the representative compound **4p** (see SI for the X-ray structure of **4p**[16]) clearly confirmed that the C−H arylation of the substrate **1g** was highly regio- and stereoselective and the direct C−H arylation occurred only at the C3-position of the substrate **1g** and selectively gave the 2,3-disubstituted 1,4-benzodioxanes **4a−q** with cis stereochemistry (C2 and C3 stereocenters). Characteristically, the C2 and C3 protons in compounds **4a−q** appeared as doublets, and the coupling constants (J) of the doublet peaks of C2 and C3 protons of compounds **4a−q** were calculated from their respective ^{1}H NMR spectra and found to be in the range of 2.8−3.1 Hz.[18] Accordingly, the stereochemistry of 2,3-disubstituted 1,4-benzodioxanes **4a−q** were assigned as cis on the basis of the X-ray structure analysis of the compound **4p** coupled with the similarity in their NMR spectral patterns and the characteristic coupling constant values of the doublet peaks of the C2 protons and C3 protons of compounds **4a−q**.

Subsequently, we decided to explore the direct C−H arylation of the unactivated sp^3 C(3)−H bond of chiral tetrahydrofuran-2-carboxamides and synthesize chiral C3-arylated tetrahydrofuran-2-carboxamides. In this regard, we assembled the chiral tetrahydrofuran-2-carboxamide substrates **1h** (*R*-isomer) and **1i** (*S*-isomer, Scheme 4). Then we performed the Pd-catalyzed direct C(sp^3)−H arylation of the substrates **1h** and **1i** with various aryl iodides. These reactions successfully furnished the corresponding chiral 2,3-disubstituted tetrahydrofurans **5a−g** (2*R*,3*R*, major isomer) and **6a−g** (2*S*,3*S*, major isomer) in 70−86% yields. Similarly, the C−H arylation of substrates **1h** and **1i** with 2-iodothiophene gave the products **5h** (2*R*,3*S*, major isomer) and **6h** (2*S*,3*R*, major isomer) in 81 and 90% yields, respectively (Scheme 4). The HPLC analyses of the compounds **5a−h** and **6a−h** revealed

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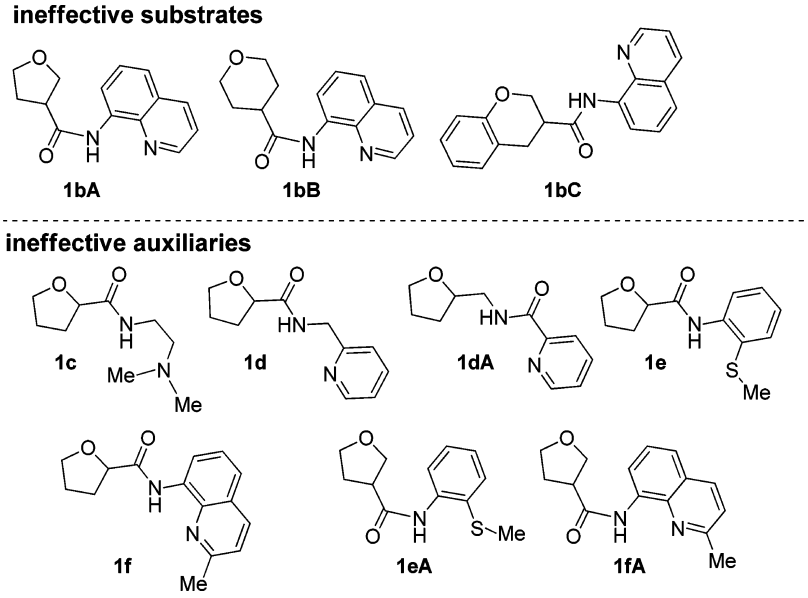
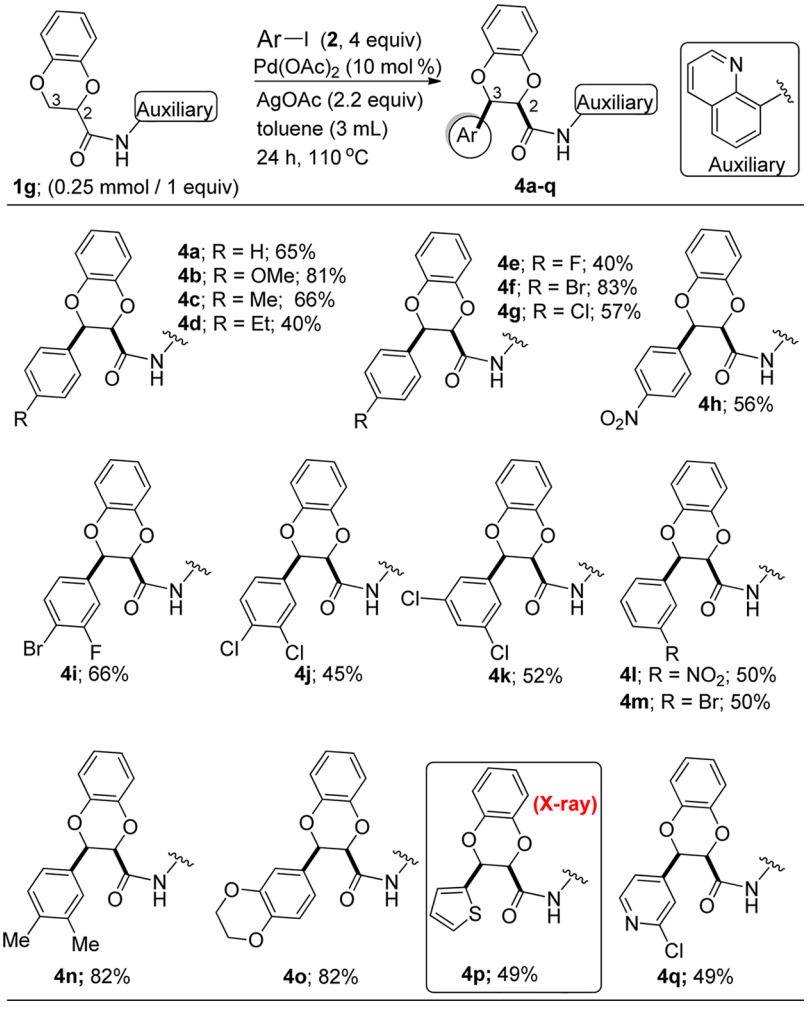


Figure 2. Investigation of C(sp^3)−H arylation reactions using other substrates and auxiliaries. Conditions: Substrate (0.25 mmol), **2a** or 1-iodo-4-methylbenzene (1 mmol, 4 equiv), $(Pd(OAc)_2$ (5−10 mol %), AgOAc (0.55 mmol, 2.2 equiv), toluene (3 mL), 24 h, and 110 °C. See Tables 3−5 in SI for additional information and individual reaction conditions.

Scheme 3. Arylation of sp^3 C(3)−H Bond of 1g and Construction of Benzodioxane−Neolignan Motifs



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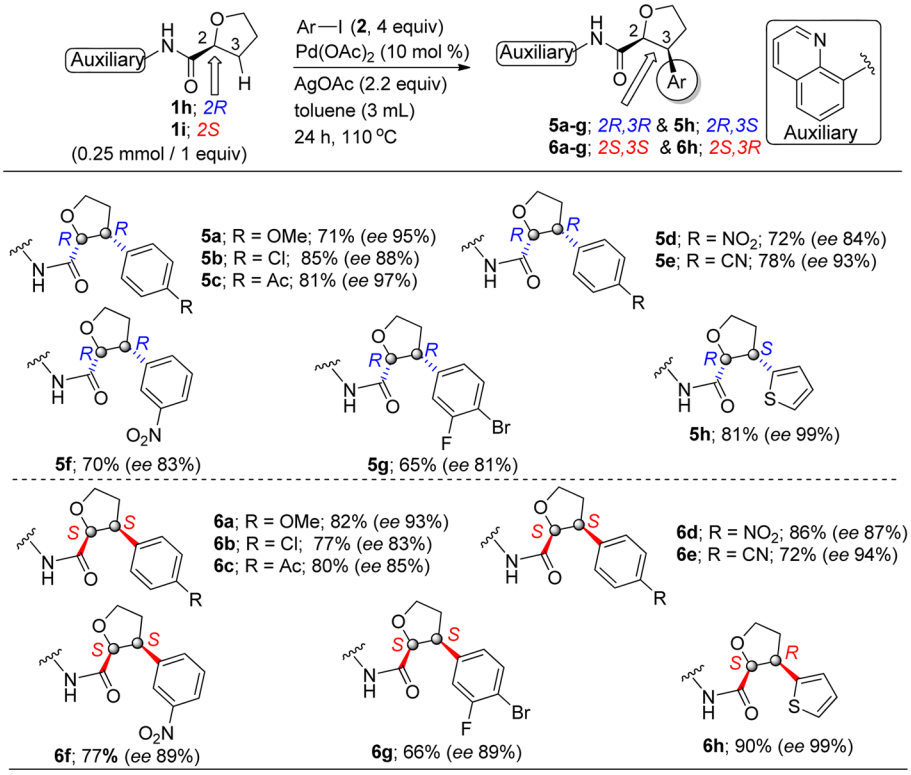
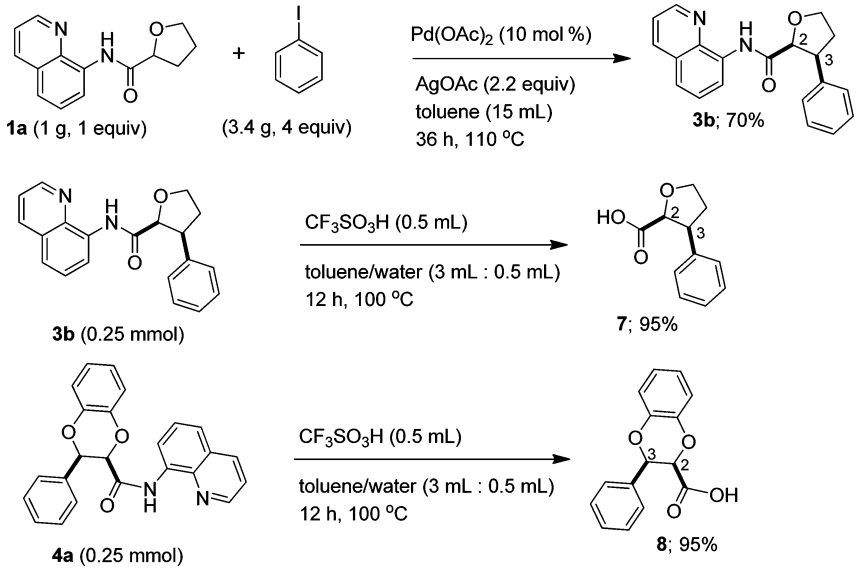
Scheme 4. Arylation of sp^3 C(3)−H Bond of 1h,i and Construction of Norlignan−THF Scaffolds



Scheme 5. Gram Scale Reaction and Removal of the Directing Group



that the C−H arylation of the chiral substrates **1h** and **1i** resulted the chiral products **5a−h** with ee 81 to >99% and **6a−h** with ee 83 to >99%, and perceptibly, partial racemizations were observed in most of the reactions under the experimental conditions. The direct C−H arylation of chiral substrates **1h** and **1i** occurred only at the C3-position and selectively gave the chiral 2,3-disubstituted tetrahydrofurans **5a−h** and **6a−h** with cis stereochemistry (C2 and C3 stereocenters). The compounds **5a−h** and **6a−h** were isolated in pure form as single diastereomers and characterized by NMR spectral data, mass, and HPLC analyses. The stereochemistry of compounds **5a−h** and **6a−h** (cis isomers) were assigned on the basis of the X-ray structure analyses of the compounds **3b** and **3e** and deliberations given for establishing the stereochemistry of the compounds **3a−r**.[17a]

We also performed the Pd-catalyzed direct arylation of C(3)−H bond of the substrate **1a** with iodobenzene on a gram scale. This reaction gave the C3-arylated product **3b** in 70% yield (Scheme 5). Finally, we have attempted the removal of the bidentate directing group (8-aminoquinoline) from the C3-arylated cis 2,3-disubstituted THF and benzodioxane systems. Representatively, we carried out the hydrolysis of the carboxamides **3b** and **4a**. The hydrolysis of the carboxamides **3b** and **4a** under the standard hydrolysis reaction conditions

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(e.g., concd HCl- or NaOH-mediated hydrolysis) failed to afford the corresponding carboxylic acids **7** and **8**. Later we found that the hydrolysis of carboxamides **3b** and **4a** in the presence of triflic acid (TfOH) successfully gave the corresponding carboxylic acids **7** and **8** (Scheme 5). The stereochemistry of the compound **7** (C2 and C3 stereocenters) was unambiguously found to be cis (see SI for the X-ray structure of **7**),[16] and no significant epimerization was observed under the experimental condition employed for hydrolyzing the carboxamide **3b**. Additionally, the C2 proton in the compound **7** appeared as a doublet (δ = 4.65 ppm) due to its coupling with the C3 proton similar to that of its parent compound **3b** (C2H, doublet, δ = 4.78, J = 7.0 Hz). The coupling constant (J) of the doublet peak of the C2 proton of the compound **7** (cis isomer) was found to be 7.7 Hz similar to that of its parent compound **3b** (cis isomer).[17a] Likewise, the stereochemistry of the C2 and C3 stereocenters of the compound **8** was assigned as cis based on the coupling constant (J = 3.2 Hz) of the doublet peaks of the C2/C3 protons, which was found to be in agreement with the literature and that of its parent compound **4a** (cis isomer), in which the coupling constant (J) of the doublet peaks of the C2/C3 protons was 3.1 Hz.[18]

In summary, we have shown the bidentate directing group-aided, Pd-catalyzed, highly regio- and stereoselective sp^3 C−H activation and direct arylation of the C(3)−H position of tetrahydrofuran and 1,4-benzodioxane systems. The direct C−H arylation occurred only at the C3 position of racemic tetrahydrofuran-2-carboxamides and gave the corresponding racemic C3-arylated THF derivatives with excellent regio- and diastereoselectivities. Similarly, the C−H arylation of chiral (*R*)- or (*S*)-tetrahydrofuran-2-carboxamides resulted in the corresponding chiral (2*R*,3*R*) and (2*S*,3*S*) C3-arylated-THF scaffolds having cis stereochemistry with excellent regio- and diastereoselectivities and very good ee. Overall, this protocol has led to the production of a wide range of cis 2,3-disubstituted THF−norlignan and benzodioxane−neolignan scaffolds with very high regio- and stereoselectivities.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. FT-IR spectra of compounds were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of all compounds were recorded on 400 and 100 MHz spectrometers, respectively (using TMS as an internal standard). HRMS measurements reported in this work were obtained from a TOF mass analyzer using electrospray ionization (ESI). Column chromatography was carried out using silica gel 100−200 mesh. HPLC analyses were performed using OD-H (0.46 cm IDR, 25 cm length) as a chiral column (eluents, flow rate, detection method are listed in the HPLC charts). Reactions were performed in anhydrous solvent under a nitrogen atmosphere. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography analyses were performed on silica gel plates, and components were visualized by observation under iodine. Isolated yields of all the compounds are reported and yields were not optimized. In all the reactions, purification of the crude reaction mixture by the column chromatography gave only the major diastereomer (as single compound) in pure form, and we did not isolate any other compound in considerable quantity suitable for characterization.

Procedure for the Synthesis of the Carboxamides 1a−i, 1bA−bC, 1dA, 1eA, and 1fA. The corresponding carboxylic acid (1.5 mmol) was dissolved in $SOCl_2$ (4 mmol) and stirred for 24 h at rt under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuum and diluted with anhydrous DCM (3 mL) under a nitrogen atmosphere. Then the corresponding acid chloride in DCM was added to a separate RB flask containing amine (1 mmol) and Et_3N (1.1 mmol) in anhydrous DCM (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at rt for 10 min, and then the reaction mixture was refluxed for 12 h under a nitrogen atmosphere. After this period, the reaction mixture was diluted with DCM (5 mL) and washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum, and purification of the resulting reaction mixture by column chromatography (EtOAc/hexanes = 30:70) furnished the corresponding cyclic ether carboxamides **1a−i**, **1bA−bC**, **1dA**, **1eA**, and **1fA**.

General Procedure for the Pd-Catalyzed C−H Arylation of the Carboxamides 1a−i, 1bA−bC, 1dA, 1eA, and 1fA and Preparation of 3a−r, 4a−q, 5a−h, and 6a−h. A mixture of the corresponding cyclic ether carboxamide **1** (0.25 mmol, 1 equiv), $Pd(OAc)_2$ (5.6 mg, 10 mol %), ArI (1.0 mmol, 4 equiv), and AgOAc (91.8 mg, 0.55 mmol, 2.2 equiv) in anhydrous toluene (3 mL) was heated at 110 °C for 24−48 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum, and purification of the resulting reaction mixture by silica gel column chromatography furnished the corresponding C−H arylated cyclic ether carboxamides **3a−r**, **4a−q**, **5a−h**, and **6a−h** (see tables/schemes for specific examples).

Procedure for the Hydrolysis of the Amides 3b and 4a. To a RB flask (capacity 25 mL) fitted with a Liebig condenser (length = 15 cm) sealed at the top and having a J Young air inlet valve at the side of the RB flask was sequentially added the corresponding carboxamide **3b** or **4a** (0.25 mmol) dissolved in a mixture of toluene (3 mL) and water (0.5 mL) and CF_3SO_3H (0.5 mL) using syringes. The air inlet was closed, the reaction mixture was heated at 100 °C, and chilled water was circulated in the outer glass tube of the condenser. After 12 h, the reaction mixture was transferred from the RB flask into a separating funnel using a syringe, diluted with EtOAc, and extracted with saturated aqueous Na_2CO_3 solution (20 mL × 2). Then the combined aqueous layers were acidified with 1 N HCl (15 mL × 2) to get pH ∼ 2. Then the aqueous layers were extracted using EtOAc (10 mL × 2), the combined organic layers were dried over anhydrous Na_2SO_4, and evaporation in vacuum gave the corresponding carboxylic acid **7** or **8**.

***N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1a).** Following the general procedure, **1a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color solid; yield: 95% (230 mg); mp 85−87 °C; IR (KBr): 3441, 1653, 1554, 1260, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.82 (dd, 1H, J_1 = 6.2 Hz, J_2 = 2.8 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58−7.53 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.28−4.23 (m, 1H), 4.08 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.48−2.39 (m, 1H), 2.32−2.25 (m, 1H), 2.04−1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1154.

***N*-(Quinolin-8-yl)tetrahydrofuran-3-carboxamide (1bA).** Following the general procedure, **1bA** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as red color solid; yield: 90% (218 mg); mp 80−82 °C; IR (KBr): 3440, 1676, 1527, 1385, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br s, 1H), 8.72 (d, 1H, J_1 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 3.1 Hz, J_2 = 1.7 Hz), 8.03 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.45−7.38 (m, 2H), 7.34 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.06 (d, 2H, J = 6.9 Hz), 4.02−3.97 (m, 1H), 3.87−3.81 (m, 1H), 3.27−3.19 (m, 1H), 2.34−2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.2, 138.2, 136.3, 134.3, 127.8, 127.2, 121.7, 121.6, 116.5, 71.0, 68.4, 46.9, 30.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1158.

***N*-(Quinolin-8-yl)tetrahydro-2*H*-pyran-4-carboxamide (1bB).** Following the general procedure, **1bB** was obtained after purification by column chromatography on neutral alumina (EtOAc:hexanes = 40:60) as brown color solid. Yield: 88% (225 mg); mp 141−143 °C; IR (KBr): 3352, 1682, 1528, 1280, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.80 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.8 Hz), 8.19 (d, 1H, J = 8.3 Hz), 7.58−7.51

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(m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.14 (t, 1H, J = 3.0 Hz), 4.11 (t, 1H, J = 3.0 Hz), 3.55 (dt, 2H, J_1 = 11.0 Hz, J_2 = 3.5 Hz), 2.80−2.72 (m, 1H), 2.09−1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 148.2, 138.4, 136.5, 134.3. 128.0, 127.4, 121.7, 121.6, 116.5, 67.3, 43.6, 29.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1290.

***N*-(Quinolin-8-yl)chroman-3-carboxamide (1bC).** Following the general procedure, **1bC** was obtained after purification by column chromatography on neutral alumina (EtOAc:hexanes = 30:70) as yellow color liquid. Yield: 85% (258 mg); IR (DCM): 3343, 1682, 1528, 1228, 1068, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.17 (br s, 1H), 8.82−8.79 (m, 2H), 8.19 (d, 1H, J = 8.2 Hz), 7.59−7.54 (m, 2H), 7.48 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.17 (t, 2H, J = 8.0 Hz), 6.93 (dd, 2H, J_1 = 12.2 Hz, J_2 = 8.0 Hz), 4.66−4.62 (m, 1H), 4.30 (t, 1H, J = 10.4 Hz), 3.37 (dd, 1H, J_1 = 15.3 Hz, J_2 = 10.0 Hz), 3.27−3.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 154.0, 148.3, 138.4, 136.4, 134.1, 129.9, 127.9, 127.6, 127.4, 121.9, 121.7, 120.8, 120.5, 116.8, 116.7, 67.4, 41.3, 28.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_2$: 305.1290; found 305.1286.

***N*-(2-(Dimethylamino)ethyl)tetrahydrofuran-2-carboxamide (1c).** Following the general procedure, **1c** was obtained after purification by column chromatography on silica gel (MeOH:EtOAc = 10:90) as dark brown color liquid; yield: 40% (75 mg); IR (DCM): 3433, 1637, 1528, 1260, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (br s, 1H), 4.36 (dd, 1H, J_1 = 8.3 Hz, J_2 = 5.8 Hz), 3.99−3.86 (m, 2H), 3.41−3.29 (m, 2H), 2.41 (dt, 2H, J_1 = 6.3 Hz, J_2 = 1.5 Hz), 2.33−2.26 (m, 1H), 2.24 (s, 6H), 2.10−2.02 (m, 1H), 1.95−1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 78.5, 69.4, 58.1, 45.3, 36.4, 30.2, 25.5; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{19}N_2O_2$: 187.1447; found 187.1459.

***N*-(Pyridin-2-ylmethyl)tetrahydrofuran-2-carboxamide (1d).** Following the general procedure, **1d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 60:40) as dark brown color liquid; yield: 71% (146 mg); IR (DCM): 3396, 1650, 1530, 1075, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, 1H, J = 4.5 Hz), 7.68 (br s, 1H), 7.58 (t, 1H, J = 7.6 Hz), 7.18 (d, 1H, J = 7.6 Hz), 7.12 (t, 1H, J = 5.9 Hz), 4.56−4.40 (m, 2H), 4.35 (dd, 1H, J_1 = 8.3 Hz, J_2 = 6.1 Hz), 3.95−3.90 (m, 1H), 3.85−3.79 (m, 1H), 2.27−2.18 (m, 1H), 2.06−1.96 (m, 1H), 1.88−1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 156.7, 149.1, 136.7, 122.3, 121.8, 78.5, 69.4, 43.9, 30.2, 25.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.1134; found 207.1132.

***N*-((Tetrahydrofuran-2-yl)methyl)picolinamide (1dA).** Following the general procedure, **1dA** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as dark brown color liquid; yield: 80% (165 mg); IR (DCM): 3480, 1668, 1590, 1077, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57−8.55 (m, 1H), 8.36 (br s, 1H), 8.19 (d, 1H, J = 7.8 Hz), 7.84 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44−7.40 (m, 1H), 4.13−4.07 (m, 1H), 3.95−3.90 (m, 1H), 3.82−3.71 (m, 2H), 3.47−3.41 (m, 1H), 2.07−1.99 (m, 1H), 1.95−1.87 (m, 2H), 1.68−1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 149.8, 148.1, 137.3, 126.1, 122.2, 77.8, 68.3, 43.2, 28.8, 25.9; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.1134; found 207.1157.

***N*-(2-(Methylthio)phenyl)tetrahydrofuran-2-carboxamide (1e).** Following the general procedure, **1e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as yellow color liquid; yield: 81% (192 mg); IR (DCM): 3441, 1685, 1523, 1275, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (br s, 1H), 8.36 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.47 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 7.32−7.28 (m, 1H), 7.09 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 4.54 (dd, 1H, J_1 = 8.5 Hz, J_2 = 5.4 Hz), 4.17−4.12 (m, 1H), 4.01 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.41 (s, 3H), 2.39−2.33 (m, 1H), 2.26−2.18 (m, 1H), 2.02−1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 137.5, 132.4, 128.6, 126.0, 124.5, 120.3, 79.0, 69.8, 30.4, 25.6, 18.5; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{12}H_{15}NNaO_2S$: 260.0721; found 260.0734.

***N*-(2-(Methylthio)phenyl)tetrahydrofuran-3-carboxamide (1eA).** Following the general procedure, **1eA** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as colorless solid. Yield: 70% (65 mg); mp 64−66 °C; IR (KBr): 3437, 1661, 1471, 1554, 1261, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.26 (d, 1H, J = 8.2 Hz), 7.46 (d, 1H, J = 7.2 Hz), 7.28 (t, 1H, J = 8.2 Hz), 7.08 (t, 1H, J = 7.2 Hz), 4.09−3.97 (m, 3H), 3.87 (dd, 1H, J_1 = 15.4 Hz, J_2 = 7.5 Hz), 3.17−3.11 (m, 1H), 2.39 (s, 3H), 2.29 (dd, 2H, J_1 = 14.0 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 137.9, 132.4, 128.6, 125.8, 124.6, 121.0, 70.9, 68.2, 46.8, 30.5, 18.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0902; found 238.0908.

***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-2-carboxamide (1f).** Following the general procedure, **1f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color solid; yield: 85% (217 mg); mp 83−85 °C; IR (KBr): 3440, 1603, 1573, 1260, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (br s, 1H), 8.76 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.4 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.48−7.47 (m, 2H), 7.32 (d, 1H, J = 8.4 Hz), 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.3 Hz), 4.29−4.24 (m, 1H), 4.12−4.07 (m, 1H), 2.77 (s, 3H), 2.44−2.37 (m, 1H), 2.33−2.25 (m, 1H), 2.04−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 157.4, 138.3, 136.2, 133.3, 126.2, 126.1, 122.4, 121.7, 116.4, 79.2, 69.7, 30.5, 25.5, 25.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1298.

***N*-(2-Methylquinolin-8-yl)tetrahydrofuran-3-carboxamide (1fA).** Following the general procedure, **1fA** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color liquid. Yield: 90% (230 mg); IR (DCM): 3342, 1683, 1530, 1384, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.05 (br s, 1H), 8.75−8.71 (m, 1H), 8.01 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J = 4.2 Hz), 7.31 (d, 1H, J = 8.4 Hz), 4.17−4.05 (m, 3H), 3.93 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.7 Hz), 3.41−3.27 (m, 1H), 2.75 (s, 3H), 2.43−2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 157.3, 137.7, 136.4, 133.7, 126.3, 126.0, 122.5, 121.5, 116.5, 71.1, 68.5, 47.0, 30.7, 25.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1290; found 257.1281.

***N*-(Quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (1g).** Following the general procedure, **1g** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color solid; yield: 84% (257 mg); mp 121−123 °C; IR (KBr): 3440, 1682, 1491, 1274, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.81 (t, 1H, J = 4.4 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.57 (d, 2H, J = 4.3 Hz), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27−7.24 (m, 1H), 7.01−6.92 (m, 3H), 4.97 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.7 Hz), 4.69 (dd, 1H, J_1 = 11.4 Hz, J_2 = 2.7 Hz), 4.44 (dd, 1H, J_1 = 11.4 Hz, J_2 = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 148.7, 143.4, 141.8, 138.7, 136.2, 133.5, 127.9, 127.1, 122.5, 122.5, 122.0, 121.8, 117.7, 117.7, 116.9, 73.8, 65.3 ; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{15}N_2O_3$: 307.1083; found 307.1094.

***(R)*-*N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1h).** Following the general procedure, **1h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as dark brown color liquid; yield: 90% (218 mg); ee 99%; $[\alpha]^{25}_D$ = −101.1 (*c* 0.05, DCM); IR (DCM): 3377, 2964, 1276, 1263, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.93 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.81 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.3 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56−7.50 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 4.63, (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.26−4.21 (m, 1H), 4.06 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.44−2.37 (m, 1H), 2.31−2.23 (m, 1H), 2.02−1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 121.9, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1138.

***(S)*-*N*-(Quinolin-8-yl)tetrahydrofuran-2-carboxamide (1i).** Following the general procedure, **1i** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as dark brown color liquid; yield: 88% (213 mg); ee 99%; $[\alpha]^{25}_D$ = +111.1 (*c* 0.05, DCM); IR (DCM): 3334, 1683, 1578, 1530, 1067, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.93 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.81 (dd, 1H, J_1 = 6.3 Hz, J_2 = 2.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58−7.53 (m, 2H), 7.46 (dd, 1H, J_1

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= 8.3 Hz, J_2 = 4.2 Hz), 4.64 (dd, 1H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 4.28−4.22 (m, 1H), 4.08 (dd, 1H, J_1 = 15.2 Hz, J_2 = 7.0 Hz), 2.48−2.38 (m, 1H), 2.32−2.24 (m, 1H), 2.04−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 148.6, 138.9, 136.2, 133.9, 128.0, 127.2, 122.0, 121.6, 116.5, 79.2, 69.8, 30.5, 25.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found 243.1130.

(2*R,3*R**)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3a).** Following the general procedure, **3a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color viscous liquid; yield: 81% (71 mg); IR (DCM): 3341, 1683, 1489, 1326, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.48 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47−7.40 (m, 3H), 7.21 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.8 Hz), 4.74 (d, 1H, J = 7.0 Hz), 4.63−4.57 (m, 1H), 4.21−4.15 (m, 1H), 3.90−3.85 (m, 1H), 3.62 (s, 3H), 2.58−2.53 (m, 1H), 2.31−2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1563.

(2*R,3*R**)-3-Phenyl-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3b).** Following the general procedure, **3b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 73% (58 mg); mp 102−104 °C; IR (DCM): 3441, 1642, 1527, 1275, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47−7.39 (m, 3H), 7.31−7.29 (m, 2H), 7.15 (t, 2H, J = 7.3 Hz), 7.05 (t, 1H, J = 7.3 Hz), 4.78 (d, 1H, J = 7.0 Hz), 4.65−4.59 (m, 1H), 4.24−4.18 (m, 1H), 3.94−3.89 (m, 1H), 2.64−2.55 (m, 1H), 2.37−2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.5, 140.5, 138.8, 136.1, 133.6, 128.2, 127.9, 127.9, 127.1, 126.7, 121.7, 121.5, 116.6, 83.9, 68.7, 48.0, 33.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{19}N_2O_2$: 319.1447; found 319.1460.

(2*R,3*R**)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3c).** Following the general procedure, **3c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as yellow color solid; yield: 72% (65 mg); mp 117−119 °C; IR (KBr): 3424, 1678, 1528, 1274, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.73 (d, 2H, J = 8.3 Hz), 7.47−7.39 (m, 3H), 7.38 (d, 2H, J = 8.3 Hz), 4.79 (d, 1H, J = 7.0 Hz), 4.65−4.59 (m, 1H), 4.24−4.18 (m, 1H), 3.99−3.94 (m, 1H), 2.65−2.57 (m, 1H), 2.42 (s, 3H), 2.34−2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1568.

(2*R,3*R**)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3d).** Following the general procedure, **3d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 62% (55 mg); mp 143−145 °C; IR (DCM): 3339, 1682, 1528, 1057, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.49−7.41 (m, 3H), 7.22 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.61−4.55 (m, 1H), 4.22−4.16 (m, 1H), 3.91−3.86 (m, 1H), 2.62−2.53 (m, 1H), 2.29−2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.2, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1070.

(2*R,3*R**)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3e).** Following the general procedure, **3e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as colorless solid; yield: 76% (65 mg); mp 200−202 °C; IR (KBr): 3431, 1636, 1531, 1275, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.52−7.49 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.44−7.38 (m, 5H), 4.78 (d, 1H, J = 7.0 Hz), 4.64−4.58 (m, 1H), 4.25−4.19 (m, 1H), 3.97−3.92 (m, 1H), 2.68−2.59 (m, 1H), 2.32−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.6, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1408.

(2*R,3*R**)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3f).** Following the general procedure, **3f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 56% (51 mg); mp 160−162 °C; IR (KBr): 3396, 1664, 1596, 1076, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, J = 8.8 Hz), 7.49−7.39 (m, 5H), 4.80 (d, 1H, J = 7.0 Hz), 4.65−4.60 (m, 1H), 4.25−4.19 (m, 1H), 4.03−3.98 (m, 1H), 2.69−2.60 (m, 1H), 2.32−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1309.

(2*R,3*R**)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3g).** Following the general procedure, **3g** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 75% (68 mg); mp 109−111 °C; IR (KBr): 3441, 1684, 1528, 1259, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.17 (t, 1H, J = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.87−7.84 (m, 1H), 7.60 (d, 1H, J = 7.7 Hz), 7.47−7.42 (m, 2H), 7.38 (t, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 4.78 (d, 1H, J = 6.8 Hz), 4.70−4.64 (m, 1H), 4.26−4.20 (m, 1H), 4.03−3.98 (m, 1H), 2.70−2.61 (m, 1H), 2.36−2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0, 127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1310.

(2*R,3*R**)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (3h).** Following the general procedure, **3h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as colorless liquid; yield: 53% (50 mg); IR (DCM): 3440, 1677, 1528, 1282, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.55 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.52 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.46−7.42 (m, 3H), 6.80 (d, 1H, J = 2.0 Hz), 6.75 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 6.60 (d, 1H, J = 8.3 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.60−4.55 (m, 1H), 4.20−4.14 (m, 1H), 4.09−3.94 (m, 4H), 3.82−3.78 (m, 1H), 2.58−2.49 (m, 1H), 2.30−2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 148.5, 143.0, 142.2, 138.8, 136.0, 133.7, 127.9, 127.1, 121.6, 121.4, 120.9, 116.9, 116.8, 116.6, 83.8, 68.6, 64.1, 47.3, 33.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_4$: 377.1501; found 377.1508.

(2*R,3*R**)-3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3i).** Following the general procedure, **3i** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color liquid; yield: 46% (42 mg); IR (DCM): 3432, 1637, 1528, 1269, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.51 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47−7.42 (m, 3H), 6.79 (d, 1H, J = 1.7 Hz), 6.75 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.7 Hz), 6.57 (d, 1H, J = 8.0 Hz), 5.76 (d, 1H, J = 1.5 Hz), 5.66 (d, 1H, J = 1.5 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.61−4.55 (m, 1H), 4.21−4.15 (m, 1H), 3.86−3.81 (m, 1H), 2.60−2.51 (m, 1H), 2.30−2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 148.5, 147.4, 146.1, 138.8, 136.1, 134.3, 133.6, 127.9, 127.1, 121.7, 121.5, 121.1, 116.6, 108.4, 108.0, 100.7, 83.8, 68.5, 47.7, 33.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_4$: 363.1345; found 363.1352.

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(2*R,3*R**)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3j).** Following the general procedure, **3j** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 58% (60 mg); mp 99−101 °C; IR (KBr): 3339, 1686, 1530, 1325, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50−7.42 (m, 3H), 7.30−7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.1 Hz), 6.95 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.1 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.60−4.54 (m, 1H), 4.22−4.15 (m, 1H), 3.88−3.84 (m, 1H), 2.63−2.54 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.6 Hz), 148.6, 142.6 (d, J_{C-F} = 6.4 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, J_{C-F} = 3.0 Hz), 122.1, 121.6, 116.7, 116.0 (d, J_{C-F} = 22.2 Hz), 107.0 (d, J_{C-F} = 20.7 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0465.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-2-carboxamide (3k).** Following the general procedure, **3k** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 60:40) as brown color solid; yield: 54% (55 mg); mp 89−91 °C; IR (DCM): 3441, 1681, 1590, 1127, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.53 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.5 Hz), 8.55 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.2 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.47−7.40 (m, 3H), 6.49 (s, 2H), 4.73 (d, 1H, J = 6.6 Hz), 4.61−4.55 (m, 1H), 4.22−4.16 (m, 1H), 3.85−3.81 (m, 1H), 3.63 (s, 6H), 3.44 (s, 3H), 2.62−2.53 (m, 1H), 2.32−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 152.8, 148.3, 138.6, 136.5, 136.4, 136.2, 133.6, 127.9, 127.2, 121.7, 121.5, 116.4, 104.8, 84.0, 68.6, 60.4, 55.7, 48.2, 33.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_5$: 409.1763; found 409.1768.

(2*R,3*R**)-3-(2,4-Dimethoxyphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3l).** Following the general procedure, **3l** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 40% (38 mg); mp 105−107 °C; IR (KBr): 3424, 1614, 1529, 1260, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 8.87 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.53 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.48−7.41 (m, 3H), 7.07 (d, 1H, J = 8.4 Hz), 6.39 (d, 1H, J = 2.4 Hz), 6.26 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.5 Hz), 4.91 (d, 1H, J = 8.2 Hz), 4.62−4.57 (m, 1H), 4.20−4.12 (m, 2H), 3.85 (s, 3H), 3.67 (s, 3H), 2.47−2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 159.5, 158.3, 148.3, 138.7, 136.1, 134.0, 127.9, 127.9, 127.2, 121.5, 121.4, 119.8, 116.4, 103.9, 98.4, 81.8, 68.7, 55.5, 55.1, 41.5, 30.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_4$: 379.1658; found 379.1672.

(2*R,3*R**)-3-(6-Fluoropyridin-3-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3m).** Following the general procedure, **3m** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 70:30) as yellow color solid; yield: 71% (60 mg); mp 117−119 °C; IR (KBr): 3441, 1679, 1528, 1259, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.44 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.6 Hz), 8.14−8.11 (m, 2H), 7.70 (dt, 1H, J_1 = 8.0 Hz, J_2 = 2.6 Hz), 7.49−7.40 (m, 3H), 6.68 (dd, 1H, J_1 = 8.5 Hz, J_2 = 3.0 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.61−4.55 (m, 1H), 4.23−4.17 (m, 1H), 3.94−3.89 (m, 1H), 2.65−2.56 (m, 1H), 2.27−2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 162.6 (d, J_{C-F} = 236.5 Hz), 148.6, 146.8 (d, J_{C-F} = 14.6 Hz), 140.6 (d, J_{C-F} = 7.8 Hz), 138.7, 136.2, 133.9 (d, J_{C-F} = 4.6 Hz), 133.2, 127.9, 127.1, 122.2, 121.6, 116.6, 108.9 (d, J_{C-F} = 37.4 Hz), 83.4, 68.5, 44.5, 33.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}FN_3O_2$: 338.1305; found 338.1315.

(2*R,3*R**)-3-(6-Chloropyridin-3-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3n).** Following the general procedure, **3n** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 80:20) as colorless solid; yield: 56% (50 mg); mp 127−129 °C; IR (DCM): 3435, 1579, 1459, 1325, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.7 Hz), 8.32 (d, 1H, J = 2.5 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.56 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.6 Hz), 7.50−7.41 (m, 3H), 7.08 (d, 1H, J = 8.3 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.60−4.54 (m, 1H), 4.23−4.17 (m, 1H), 3.92−3.87 (m, 1H), 2.66−2.57 (m, 1H), 2.25−2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 149.8, 149.1, 148.7, 138.7, 138.2, 136.2, 135.3, 133.2, 127.9, 127.1, 123.8, 122.2, 121.6, 116.7, 83.3, 68.5, 44.6, 33.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009; found 354.1023.

(2*R,3*R**)-3-(5-Bromopyridin-2-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3o).** Following the general procedure, **3o** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 80:20) as brown color liquid; yield: 31% (31 mg); IR (DCM): 3436, 1638, 1530, 1275, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.45 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.40−8.39 (m, 1H), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.60 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.51−7.43 (m, 3H), 7.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.4 Hz), 4.87 (d, 1H, J = 7.6 Hz), 4.70 (dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.21 (dd, 1H, J_1 = 14.9 Hz, J_2 = 6.9 Hz), 4.04 (dd, 1H, J_1 = 13.9 Hz, J_2 = 6.9 Hz), 2.49 (dd, 2H, J_1 = 13.9 Hz, J_2 = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 158.5, 150.1, 148.6, 138.8, 138.5, 136.1, 133.6, 127.9, 127.1, 124.7, 121.8, 121.5, 118.7, 116.5, 83.3, 69.5, 48.9, 32.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}BrN_3O_2$: 398.0504; found 398.0512.

(2*R,3*R**)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3p).** Following the general procedure, **3p** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 80:20) as brown color solid; yield: 51% (45 mg); mp 98−100 °C; IR (DCM): 3441, 1684, 1527, 1275, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.43 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.11 (d, 1H, J = 5.2 Hz), 7.51−7.41 (m, 3H), 7.26 (d, 1H, J = 1.4 Hz), 7.13 (dd, 1H, J_1 = 5.2 Hz, J_2 = 1.6 Hz), 4.77 (d, 1H, J = 6.7 Hz), 4.61−4.55 (m, 1H), 4.24−4.18 (m, 1H), 3.87−3.83 (m, 1H), 2.66−2.57 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 153.3, 151.5, 149.4, 148.7, 138.7, 136.2, 133.0, 127.9, 127.1, 123.7, 122.3, 122.0, 121.6, 116.8, 83.4, 68.5, 46.9, 33.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}ClN_3O_2$: 354.1009; found 354.1025.

(2*R,3*S**)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)-tetrahydrofuran-2-carboxamide (3q).** Following the general procedure, **3q** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color solid; yield: 87% (71 mg); mp 134−136 °C; IR (DCM): 3424, 1643, 1275, 1094, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.49−7.43 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, J = 6.3 Hz), 4.62 (dd, 1H, J_1 = 16.1 Hz, J_2 = 7.5 Hz), 4.28−4.22 (m, 2H), 2.66−2.57 (m, 1H), 2.37−2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.1029.

(2*R,3*R**)-3-(1*H*-Indol-5-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (3r).** Following the general procedure, **3r** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 80:20) as dark brown color liquid; yield: 20% (18 mg); IR (DCM): 3339, 1731, 1672, 1325, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.86 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.40 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.09 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.03 (br s, 1H), 7.55 (s, 1H), 7.45−7.39 (m, 2H), 7.33 (t, 1H, J = 8.0 Hz), 7.11−7.05 (m, 2H), 7.00 (t, 1H, J = 3.0 Hz), 6.32 (t, 1H, J = 2.2 Hz), 4.81 (d, 1H, J = 7.2 Hz), 4.69−4.64 (m, 1H), 4.24−4.18 (m, 1H), 4.04−3.99 (m, 1H), 2.64−2.55 (m, 1H), 2.42−2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 148.4, 138.8, 136.0, 134.8, 133.7, 131.5, 127.8, 127.1, 124.1, 122.3, 121.5, 121.4, 119.7, 116.6, 110.8, 102.4, 84.1, 68.8, 48.3, 34.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{20}N_3O_2$: 358.1556; found 358.1565.

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(2*R,3*R**)-3-Phenyl-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4a).** Following the general procedure, **4a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 65% (62 mg); mp 168−170 °C; IR (KBr): 3423, 1643, 1533, 1260, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (t, 1H, J = 4.2 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53−7.52 (m, 2H), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (d, 2H, J = 7.1 Hz), 7.28−7.26 (m, 1H), 7.22−7.00 (m, 6H), 5.95 (d, 1H, J = 3.1 Hz), 5.14 (d, 1H, J = 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.3, 142.1, 138.7, 136.1, 135.8, 133.4, 128.4, 127.9, 127.1, 123.3, 122.4, 121.7, 121.5, 117.8, 117.4, 116.9, 76.4, 76.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3$: 383.1396; found 383.1413.

(2*R,3*R**)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4b).** Following the general procedure, **4b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 81% (84 mg); mp 119−121 °C; IR (KBr): 3431, 1634, 1531, 1259, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.72 (dd, 1H, J_1 = 5.9 Hz, J_2 = 3.0 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.6 Hz), 7.53−7.52 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.28−7.26 (m,1H), 7.08−6.99 (m, 3H), 6.71 (d, 2H, J = 8.8 Hz), 5.88 (d, 1H, J = 3.1 Hz), 5.12 (d, 1H, J = 3.1 Hz), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 159.5, 148.6, 143.2, 142.0, 138.7, 136.1, 133.4, 128.5, 128.0, 127.9, 127.1, 123.3, 122.4, 121.7, 121.4, 117.7, 117.5, 116.9, 113.8, 76.4, 75.6, 55.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_4$: 413.1501; found 413.1515.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-3-(*p*-tolyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4c).** Following the general procedure, **4c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color liquid; yield: 66% (65 mg); IR (DCM): 3431, 1636, 1534, 1363, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.74 (t, 1H, J = 4.6 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53−7.52 (m, 2H), 7.43 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.28−7.26 (m, 3H), 7.10−6.98 (m, 5H), 5.91 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 3.0 Hz), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 148.5, 143.3, 142.1, 138.7, 138.1, 136.1, 133.4, 132.8, 129.1, 127.9, 127.1, 127.0, 123.2, 122.4, 121.7, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 21.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1552; found 397.1562.

(2*R,3*R**)-3-(4-Ethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4d).** Following the general procedure, **4d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 40% (41 mg); mp 95−97 °C; IR (DCM): 3333, 1687, 1533, 1255, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.80 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.5 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.54−7.53 (m, 2H), 7.44 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.28−7.25 (m, 3H), 7.09−7.02 (m, 3H), 7.00 (d, 2H, = 8.0 Hz), 5.91 (d, 1H, J = 3.1 Hz), 5.12 (d, 1H, J = 3.1 Hz), 2.45 (q, 2H, J = 7.6 Hz), 1.01 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 148.5, 144.3, 143.3, 142.1, 138.7, 136.1, 133.4, 133.0, 127.9, 127.8, 127.1, 127.0, 123.2, 122.3, 121.6, 121.4, 117.7, 117.4, 116.9, 76.5, 75.8, 28.4, 15.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3$: 411.1709; found 411.1697.

(2*R,3*R**)-3-(4-Fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4e).** Following the general procedure, **4e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as colorless solid; yield: 40% (40 mg); mp 96−98 °C; IR (DCM): 3433, 1637, 1275, 1260, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.8 Hz, J_2 = 2.1 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57−7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.35 (dd, 2H, J_1 = 8.7 Hz, J_2 = 5.3 Hz), 7.28−7.26 (m, 1H), 7.10−7.00 (m, 3H), 6.87 (t, 2H, J = 8.7 Hz), 5.91 (d, 1H, J = 3.1 Hz), 5.11 (d, 1H, J = 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 162.6 (d, J_{C-F} = 245.7 Hz), 148.6, 143.0, 141.9, 138.7, 136.2, 133.2, 131.7 (d, J_{C-F} = 3.1 Hz), 129.0 (d, J_{C-F} = 8.4 Hz), 127.9, 127.1, 123.4, 122.6, 121.7, 121.6, 117.8, 117.4, 116.9, 115.4 (d, J_{C-F} = 21.2 Hz), 76.2, 75.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}FN_2O_3$: 401.1301; found 401.1314.

(2*R,3*R**)-3-(4-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4f).** Following the general procedure, **4f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color solid; yield: 83% (96 mg); mp 146−148 °C; IR (KBr): 3424, 1684, 1490, 1257, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58−7.51 (m, 2H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33−7.22 (m, 5H), 7.10−7.00 (m, 3H), 5.90 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.1, 134.9, 133.2, 131.5, 128.8, 127.9, 127.1, 123.5, 122.6, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}BrN_2O_3$: 461.0501; found 461.0506.

(2*R,3*R**)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4g).** Following the general procedure, **4g** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 57% (59 mg); mp 148−149 °C; IR (KBr): 3431, 1785, 1635, 1533, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.5 Hz, J_2 = 2.4 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.57−7.51 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30 (d, 2H, J = 8.6 Hz), 7.28−7.26 (m, 1H), 7.15 (d, 2H, J = 8.6 Hz), 7.11−7.01 (m, 3H), 5.92 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 148.7, 143.0, 141.9, 138.7, 136.2, 134.4, 134.3, 133.2, 128.6, 128.5, 127.9, 127.1, 123.5, 122.6, 121.8, 121.7, 117.8, 117.4, 116.9, 76.2, 75.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}ClN_2O_3$: 417.1006; found 417.0993.

(2*R,3*R**)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4h).** Following the general procedure, **4h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as red color solid; yield: 56% (60 mg); mp 153−155 °C; IR (KBr): 3424, 1637, 1528, 1290, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.76 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.69 (dd, 1H, J_1 = 7.0 Hz, J_2 = 1.6 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 8.04 (d, 2H, J = 8.6 Hz), 7.58−7.52 (m, 4H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29−7.27 (m, 1H), 7.14−7.04 (m, 3H), 6.03 (d, 1H, J = 3.0 Hz), 5.17 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 148.7, 147.7, 143.1, 142.8, 141.8, 138.6, 136.2, 133.0, 128.0, 127.9, 127.0, 123.8, 123.5, 122.9, 122.1, 121.8, 118.0, 117.4, 116.9, 76.1, 75.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_5$: 428.1246; found 428.1241.

(2*R,3*R**)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4i).** Following the general procedure, **4i** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 66% (79 mg); mp 117−119 °C; IR (KBr): 3329, 1685, 1490, 1256, 871 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59−7.52 (m, 2H), 7.47 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.34 (dd, 1H, J_1 = 8.3 Hz, J_2 = 7.1 Hz), 7.28−7.26 (m, 1H), 7.15 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.0 Hz), 7.11−7.03 (m, 4H), 5.90 (d, 1H, J = 3.0 Hz), 5.12 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 158.9 (d, J_{C-F} = 246.0 Hz), 148.7, 142.7, 141.8, 138.7, 137.6 (d, J_{C-F} = 6.5 Hz), 136.2, 133.4, 133.1, 127.9, 127.1, 124.0 (d, J_{C-F} = 3.5 Hz), 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 115.4 (d, J_{C-F} = 23.4 Hz), 109.1 (d, J_{C-F} = 20.6 Hz), 76.0, 74.9 (d, J_{C-F} = 1.2 Hz); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{17}BrFN_2O_3$: 479.0407; found 479.0403.

(2*R,3*R**)-3-(3,4-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4j).** Following the general procedure, **4j** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 25:75) as colorless

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solid; yield: 45% (51 mg); mp 170−172 °C; IR (KBr): 3328, 1597, 1491, 1254, 1031, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.9 Hz, J_2 = 1.7 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.58−7.52 (m, 2H), 7.49−7.45 (m, 2H), 7.28−7.18 (m, 3H), 7.10−7.01 (m, 3H), 5.87 (d, 1H, J = 3.0 Hz), 5.11 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 148.7, 142.7, 141.8, 138.7, 136.2, 136.1, 133.1, 132.6, 132.5, 130.4, 129.2, 127.9, 127.0, 126.4, 123.6, 122.7, 121.9, 121.8, 117.9, 117.4, 117.0, 76.1, 74.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O_3$: 451.0616; found 451.0599.

(2*R,3*R**)-3-(3,5-Dichlorophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4k).** Following the general procedure, **4k** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 25:75) as colorless solid; yield: 52% (59 mg); mp 213−215 °C; IR (KBr): 3393, 1597, 1393, 1194, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.70 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.3 Hz), 8.16 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 1H), 7.58−7.53 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.29−7.26 (m, 1H), 7.25 (dd, 2H, J_1 = 1.8 Hz, J_2 = 0.5 Hz), 7.13 (t, 1H, J = 1.9 Hz), 7.11- 7.08 (m, 1H), 7.07−7.04 (m, 2H), 5.84 (d, 1H, J = 3.0 Hz), 5.11 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 148.7, 142.7, 141.7, 139.2, 138.7, 136.2, 134.9, 133.0, 128.6, 127.9, 127.1, 125.6, 123.7, 122.7, 122.0, 121.8, 118.0, 117.4, 117.1, 76.0, 75.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_2O_3$: 451.0616; found 451.0600.

(2*R,3*R**)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4l).** Following the general procedure, **4l** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 50% (54 mg); mp 205−207 °C; IR (KBr): 3417, 1683, 1531, 1256, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.67 (br s, 1H), 8.78 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.69 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.27 (t, 1H, J = 2.1 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.02 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.3 Hz), 7.71 (d, 1H, J = 7.7 Hz), 7.58−7.51 (m, 2H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.38 (t, 1H, J = 8.0 Hz), 7.30−7.28 (m, 1H), 7.14−7.04 (m, 3H), 6.02 (d, 1H, J = 3.0 Hz), 5.19 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 148.7, 148.1, 142.7, 141.7, 138.6, 138.0, 136.2, 133.1, 133.0, 129.4, 127.9, 127.1, 123.8, 123.3, 122.8, 122.3, 122.1, 121.8, 118.0, 117.5, 117.0, 76.1, 75.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_5$: 428.1246; found 428.1257.

(2*R,3*R**)-3-(3-Bromophenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4m).** Following the general procedure, **4m** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as brown color liquid; yield: 50% (58 mg); IR (DCM): 3440, 1682, 1531, 1255, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.81 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.9 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.55−7.51 (m, 3H), 7.45 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.31−7.25 (m, 3H), 7.10−7.06 (m, 4H), 5.89 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.6, 143.0, 141.9, 138.7, 138.1, 136.1, 133.2, 131.5, 130.2, 129.9, 127.9, 127.1, 125.6, 123.5, 122.6, 122.5, 121.8, 121.7, 117.9, 117.4, 117.0, 76.2, 75.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{18}BrN_2O_3$: 461.0501; found 461.0503.

(2*R,3*R**)-3-(3,4-Dimethylphenyl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4n).** Following the general procedure, **4n** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless liquid; yield: 82% (84 mg); IR (DCM): 3440, 1641, 1533, 1275, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.79 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.73 (t, 1H, J = 4.2 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.53−7.52 (m, 2H), 7.44 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.27−7.25 (m, 1H), 7.13−6.98 (m, 5H), 6.93 (d, 1H, J = 7.8 Hz), 5.86 (d, 1H, J = 3.1 Hz), 5.13 (d, 1H, J = 3.1 Hz), 2.04 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 148.5, 143.3, 142.1, 138.7, 136.8, 136.5, 136.1, 133.5, 133.1, 129.7, 128.5, 127.8, 127.1, 124.3, 123.2, 122.3, 121.6, 121.4, 117.7, 117.5, 116.9, 76.6, 75.8, 19.7, 19.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_3$: 411.1709; found 411.1694.

(2*R,3*R**)-*N*-(Quinolin-8-yl)-2,2′,3,3′-tetrahydro-[2,6′-bibenzo[*b*][1,4]dioxine]-3-carboxamide (4o).** Following the general procedure, **4o** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as colorless liquid; yield: 82% (90 mg); IR (DCM): 3334, 1595, 1533, 1253, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 8.83 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.73 (dd, 1H, J_1 = 5.5 Hz, J_2 = 3.4 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.54−52 (m, 2H), 7.45 (dd, 1H, J_1 = 8.2 Hz, J_2 = 4.2 Hz), 7.27−7.24 (m, 1H), 7.07−6.97 (m, 3H), 6.90−6.86 (m, 2H), 6.67 (d, 1H, J = 8.2 Hz), 5.82 (d, 1H, J = 3.1 Hz), 5.09 (d, 1H, J = 3.1 Hz), 4.07 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 148.6, 143.6, 143.2, 143.1, 142.0, 138.7, 136.1, 133.4, 129.1, 127.9, 127.1, 123.3, 122.3, 121.7, 121.4, 120.5, 117.8, 117.4, 117.1, 116.9, 116.3, 76.4, 75.4, 64.2, 64.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2O_5$: 441.1450; found 441.1467.

(2*R,3*S**)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4p).** Following the general procedure, **4p** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 30:70) as colorless solid; yield: 49% (48 mg); mp 184−186 °C; IR (DCM): 3439, 1682, 1533, 1490, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.91 (br s, 1H), 8.90 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.74 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 8.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.59−7.54 (m, 2H), 7.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.33−7.29 (m, 1H), 7.16−7.15 (m, 1H), 7.12 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.2 Hz), 7.05−7.02 (m, 3H), 6.82 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.6 Hz), 6.24 (d, 1H, J = 2.8 Hz), 5.15 (d, 1H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.8, 141.7, 141.7, 138.8, 136.2, 136.2, 133.4, 127.9, 127.7, 127.1, 126.6, 126.4, 123.4, 122.5, 121.9, 121.8, 118.1, 117.7, 116.9, 75.7, 71.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_3$ S: 389.0960; found 389.0970.

(2*R,3*R**)-3-(2-Chloropyridin-4-yl)-*N*-(quinolin-8-yl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide (4q).** Following the general procedure, **4q** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as colorless liquid; yield: 49% (51 mg); IR (DCM): 3416, 1667, 1531, 1325, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.69 (br s, 1H), 8.82 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.71 (dd, 1H, J_1 = 7.1 Hz, J_2 = 1.7 Hz), 8.20−8.16 (m, 2H), 7.60−7.54 (m, 2H), 7.48 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.2 Hz), 7.30−7.26 (m, 2H), 7.19 (dd, 1H, J_1 = 5.3 Hz, J_2 = 1.1 Hz), 7.14−7.05 (m, 3H), 5.92 (d, 1H, J = 3.0 Hz), 5.15 (d, 1H, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 151.8, 149.7, 148.8, 148.0, 142.5, 141.7, 138.7, 136.2, 132.9, 127.9, 127.0, 123.8, 122.9, 122.5, 122.3, 121.9, 120.4, 118.1, 117.3, 117.1, 75.7, 74.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{17}ClN_3O_3$: 418.0958; found 418.0957.

(2*R*,3*R*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (5a). Following the general procedure, **5a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 71% (60 mg); ee 95%; $[\alpha]^{25}_D$ = −243.5 (c 0.10, DCM); mp 90−92 °C; IR (DCM): 3340, 1682, 1530, 1255, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.59 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.48 (dd, 1H, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.48−7.41 (m, 3H), 7.21 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.8 Hz), 4.74 (d, 1H, J = 7.0 Hz), 4.63−4.58 (m, 1H), 4.22−4.16 (m, 1H), 3.90−3.85 (m, 1H), 3.62 (s, 3H), 2.60−2.52 (m, 1H), 2.33−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1553.

(2*R*,3*R*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (5b). Following the general procedure, **5b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 60:40) as colorless solid; yield: 85% (75 mg); ee 88%; $[\alpha]^{25}_D$ = −216.8 (c 0.10, DCM); mp 130−132 °C; IR (KBr): 3336, 1682, 1528, 1325, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.49−7.41 (m, 3H), 7.22 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.6 Hz), 4.75 (d, 1H, J = 7.0 Hz), 4.61−4.56 (m, 1H), 4.22−4.16

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(m, 1H), 3.91−3.86 (m, 1H), 2.62−2.53 (m, 1H), 2.29−2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 139.2, 138.8, 136.2, 133.5, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.5, 116.6, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1051.

(2*R*,3*R*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (5c). Following the general procedure, **5c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 70:30) as yellow color solid; yield: 81% (73 mg); ee 97%; $[\alpha]^{25}_D$ = −239.6 (*c* 0.10, DCM); mp 148−150 °C; IR (KBr): 3441, 1607, 1528, 1267, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47−7.39 (m, 3H), 7.37 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 4.65−4.59 (m, 1H), 4.24−4.18 (m, 1H), 3.99−3.94 (m, 1H), 2.63−2.58 (m, 1H), 2.42 (s, 3H), 2.32−2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 168.0, 148.6, 146.4, 138.7, 136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1545.

(2*R*,3*R*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5d). Following the general procedure, **5d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as red color solid; yield: 72% (65 mg); ee 84%; $[\alpha]^{25}_D$ = −229.2 (*c* 0.10, DCM); mp 139−141 °C; IR (KBr): 3439, 1682, 1523, 1344, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, *J* = 8.8 Hz), 7.50−7.39 (m, 5H), 4.80 (d, 1H, *J* = 7.0 Hz), 4.66−4.61 (m, 1H), 4.26−4.20 (m, 1H), 4.03−3.99 (m, 1H), 2.70−2.61 (m, 1H), 2.33−2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1298.

(2*R*,3*R*)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (5e). Following the general procedure, **5e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as colorless solid; yield: 78% (67 mg); ee 93%; $[\alpha]^{25}_D$ = −223.4 (*c* 0.10, DCM); mp 182−184 °C; IR (KBr): 3424, 1677, 1528, 1260, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.40 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51−7.48 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.42−7.37 (m, 5H), 4.77 (d, 1H, *J* = 7.0 Hz), 4.63−4.57 (m, 1H), 4.23−4.17 (m, 1H), 3.96−3.92 (m, 1H), 2.67−2.58 (m, 1H), 2.30−2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 33.4; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1395.

(2*R*,3*R*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (5f). Following the general procedure, **5f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 70% (64 mg); ee 83%; $[\alpha]^{25}_D$ = −219.2 (*c* 0.10, DCM); mp 103−105 °C; IR (DCM): 3441, 1637, 1260, 1093, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.85 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.17 (t, 1H, *J* = 2.0 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.87−7.85 (m, 1H), 7.62−7.59 (m, 1H), 7.47−7.43 (m, 2H), 7.39 (t, 1H, *J* = 8.0 Hz), 7.27 (t, 1H, *J* = 8.0 Hz), 4.78 (d, 1H, *J* = 6.8 Hz), 4.71−4.65 (m, 1H), 4.27−4.21 (m, 1H), 4.04−3.99 (m, 1H), 2.71−2.62 (m, 1H), 2.37−2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.5, 133.1, 129.0, 127.8, 127.0, 122.7, 122.1, 121.9, 121.7, 116.5, 83.7, 68.6, 47.5, 33.3; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1290.

(2*R*,3*R*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (5g). Following the general procedure, **5g** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 65% (68 mg); ee 81%; $[\alpha]^{25}_D$ = −153.6 (*c* 0.10, DCM); mp 100−102 °C; IR (KBr): 3425, 1682, 1485, 1530, 1092, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51−7.43 (m, 3H), 7.30−7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.0 Hz), 6.95 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 4.74 (d, 1H, *J* = 6.8 Hz), 4.61−4.55 (m, 1H), 4.22−4.16 (m, 1H), 3.89−3.84 (m, 1H), 2.64−2.55 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.3 Hz), 148.6, 142.6 (d, J_{C-F} = 6.5 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, J_{C-F} = 3.2 Hz), 122.1, 121.6, 116.7, 116.0 (d, J_{C-F} = 22.3 Hz), 107.1 (d, J_{C-F} = 20.0 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0434.

(2*R*,3*S*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (5h). Following the general procedure, **5h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 81% (66 mg); ee 99%; $[\alpha]^{25}_D$ = −134.2 (*c* 0.10, DCM); mp 100−102 °C; IR (DCM): 3436, 1637, 1557, 1275, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.56 (dd, 1H, J_1 = 7.0 Hz, J_2 = 2.0 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50−7.43 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, *J* = 6.3 Hz), 4.61 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 4.28−4.22 (m, 2H), 2.66−2.57 (m, 1H), 2.37−2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.6, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.4, 43.3, 34.6; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.1003.

(2*S*,3*S*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (6a). Following the general procedure, **6a** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 82% (71 mg); ee 93%; $[\alpha]^{25}_D$ = +218.4 (*c* 0.10, DCM); mp 100−102 °C; IR (KBr): 3432, 1636, 1528, 1260, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.49 (dd, 1H, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 8.11 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.47−7.40 (m, 3H), 7.21 (d, 2H, *J* = 8.8 Hz), 6.68 (d, 2H, *J* = 8.8 Hz), 4.74 (d, 1H, *J* = 7.0 Hz), 4.63−4.57 (m, 1H), 4.21−4.15 (m, 1H), 3.90−3.85 (m, 1H), 3.61 (s, 3H), 2.58−2.51 (m, 1H), 2.32−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.2, 148.5, 138.8, 136.1, 133.6, 132.5, 128.9, 127.9, 127.1, 121.7, 121.5, 116.6, 113.6, 83.9, 68.7, 55.0, 47.2, 33.8; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3$: 349.1552; found 349.1566.

(2*S*,3*S*)-3-(4-Chlorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (6b). Following the general procedure, **6b** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as colorless solid; yield: 77% (68 mg); ee 83%; $[\alpha]^{25}_D$ = +147.6 (*c* 0.10, DCM); mp 138−140 °C; IR (DCM): 3437, 1637, 1486, 1252, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.50−7.42 (m, 3H), 7.22 (d, 2H, *J* = 8.6 Hz), 7.11 (d, 2H, *J* = 8.6 Hz), 4.75 (d, 1H, *J* = 7.0 Hz), 4.62−4.56 (m, 1H), 4.22−4.16 (m, 1H), 3.91−3.86 (m, 1H), 2.63−2.54 (m, 1H), 2.29−2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.6, 139.2, 138.8, 136.2, 133.4, 132.5, 129.3, 128.4, 127.9, 127.1, 121.9, 121.6, 116.6, 83.7, 68.6, 47.3, 33.7; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2O_2$: 353.1057; found 353.1039.

(2*S*,3*S*)-3-(4-Acetylphenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6c). Following the general procedure, **6c** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 70:30) as yellow color solid; yield: 80% (72 mg); ee 85%; $[\alpha]^{25}_D$ = +264.3 (*c* 0.10, DCM); mp 142−144 °C; IR (KBr): 3437, 1638, 1528, 1092, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.42 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.12 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.47−7.39 (m, 3H), 7.38 (d, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 4.65−4.59 (m, 1H), 4.24−4.18 (m, 1H), 3.99−3.94 (m, 1H), 2.66−2.57 (m, 1H), 2.42 (s, 3H), 2.34−2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 168.0, 148.6, 146.4, 138.7,

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136.2, 135.5, 133.4, 128.4, 128.2, 127.9, 127.1, 122.0, 121.6, 116.6, 83.8, 68.7, 47.8, 33.6, 26.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$: 361.1552; found 361.1544.

(2*S*,3*S*)-3-(4-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6d). Following the general procedure, **6d** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 86% (78 mg); ee 87%; $[\alpha]^{25}_D$ = +280.3 (c 0.10, DCM); mp 134−136 °C; IR (DCM): 3336, 1598, 1486, 1344, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.13 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 8.00 (d, 2H, J = 8.8 Hz), 7.49−7.38 (m, 5H), 4.80 (d, 1H, J = 7.0 Hz), 4.65−4.59 (m, 1H), 4.25−4.19 (m, 1H), 4.02−3.98 (m, 1H), 2.67−2.60 (m, 1H), 2.32−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.7, 138.7, 136.3, 133.2, 128.8, 127.9, 127.1, 123.5, 122.2, 121.7, 116.6, 83.7, 68.6, 47.6, 33.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1281.

(2*S*,3*S*)-3-(4-Cyanophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6e). Following the general procedure, **6e** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as colorless solid; yield: 72% (62 mg); ee 94%; $[\alpha]^{25}_D$ = +218.8 (c 0.10, DCM); mp 176−178 °C; IR (KBr): 3425, 1712, 1530, 1266, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.60 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 8.15 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.52−7.49 (m, 1H), 7.46 (dd, 1H, J_1 = 8.3 Hz, J_2 = 4.0 Hz), 7.44−7.38 (m, 5H), 4.78 (d, 1H, J = 6.9 Hz), 4.63−4.58 (m, 1H), 4.24−4.18 (m, 1H), 3.97−3.92 (m, 1H), 2.67−2.58 (m, 1H), 2.31−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.6, 146.4, 138.7, 136.3, 133.2, 132.0, 128.8, 127.9, 127.1, 122.2, 121.7, 118.8, 116.6, 110.5, 83.7, 68.6, 47.8, 34.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found 344.1412.

(2*S*,3*S*)-3-(3-Nitrophenyl)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (6f). Following the general procedure, **6f** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 50:50) as brown color solid; yield: 77% (70 mg); ee 89%; $[\alpha]^{25}_D$ = +235.9 (c 0.10, DCM); mp 114−116 °C; IR (DCM): 3335, 1683, 1528, 125, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.57 (br s, 1H), 8.84 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.6 Hz), 8.37 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 8.16 (t, 1H, J = 2.0 Hz), 8.10 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.86−7.83 (m, 1H), 7.61−7.59 (m, 1H), 7.46−7.42 (m, 2H), 7.38 (t, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 4.78 (d, 1H, J = 6.8 Hz), 4.70−4.64 (m, 1H), 4.26−4.19 (m, 1H), 4.03−3.98 (m, 1H), 2.70−2.61 (m, 1H), 2.37−2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.7, 148.0, 142.8, 138.6, 136.1, 134.4, 133.2, 129.0, 127.8, 126.9, 122.7, 122.1, 121.9, 121.7, 116.5, 83.6, 68.6, 47.5, 33.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$: 364.1297; found 364.1304.

(2*S*,3*S*)-3-(4-Bromo-3-fluorophenyl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carbhoxamide (6g). Following the general procedure, **6g** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 60:40) as brown color solid; yield: 66% (69 mg); ee 89%; $[\alpha]^{25}_D$ = +149.8 (c 0.10, DCM); mp 110−112 °C; IR (KBr): 3440, 1638, 1530, 1275, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.58 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.47 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.7 Hz), 8.14 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.51−7.43 (m, 3H), 7.30−7.26 (m, 1H), 7.08 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.0 Hz), 6.96 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 4.74 (d, 1H, J = 6.8 Hz), 4.61−4.55 (m, 1H), 4.22−4.16 (m, 1H), 3.89−3.84 (m, 1H), 2.64−2.55 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 158.7 (d, J_{C-F} = 245.4 Hz), 148.6, 142.6 (d, J_{C-F} = 6.5 Hz), 138.7, 136.2, 133.3, 133.1, 127.9, 127.1, 125.0 (d, J_{C-F} = 3.2 Hz), 122.1, 121.6, 116.7, 116.0 (d, J_{C-F} = 22.3 Hz), 107.1 (d, J_{C-F} = 20.0 Hz), 83.6, 68.4, 47.2, 33.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{17}BrFN_2O_2$: 415.0457; found 415.0443.

(2*S*,3*R*)-*N*-(Quinolin-8-yl)-3-(thiophen-2-yl)tetrahydrofuran-2-carboxamide (6h). Following the general procedure, **6h** was obtained after purification by column chromatography on silica gel (EtOAc:hexanes = 40:60) as brown color solid; yield: 90% (73 mg); ee 99%; $[\alpha]^{25}_D$ = +169.4 (c 0.10, DCM); mp 98−100 °C; IR (KBr): 3436, 1680, 1531, 1325, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (br s, 1H), 8.88 (dd, 1H, J_1 = 4.2 Hz, J_2 = 1.7 Hz), 8.58 (dd, 1H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 8.11 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 7.48−7.41 (m, 3H), 7.00 (dd, 1H, J_1 = 5.1 Hz, J_2 = 1.0 Hz), 6.96 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.0 Hz), 6.79 (dd, 1H, J_1 = 5.1 Hz, J_2 = 3.5 Hz), 4.74 (d, 1H, J = 6.3 Hz), 4.61 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 4.28−4.21 (m, 2H), 2.65−2.56 (m, 1H), 2.36−2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 148.5, 142.4, 138.8, 136.1, 133.7, 127.9, 127.1, 126.5, 125.5, 123.9, 121.8, 121.5, 116.6, 83.6, 68.3, 43.3, 34.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2S$: 325.1011; found 325.0998.

(2*R,3*R**)-3-Phenyltetrahydrofuran-2-carboxylic Acid (7).**[17b] Following the general procedure, the compound **7** was obtained as brown color solid (the crude material was almost pure); yield: 95% (46 mg); mp 216−218 °C; IR (KBr): 3432, 1637, 1275, 1260, 764, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.19 (m, 5H), 5.03 (br s, 1H), 4.65 (d, 1H, J = 7.7 Hz), 4.43−4.37 (m, 1H), 4.06 (dd, 1H, J_1 = 15.0 Hz, J_2 = 7.5 Hz), 3.76 (dd, 1H, J_1 = 15.0 Hz, J_2 = 7.5 Hz), 2.48−2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 138.6, 128.5, 127.8, 127.3, 81.4, 68.9, 48.0, 32.2; HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{11}H_{11}O_3$: 191.0708; found 191.0700. The stereochemistry of the compound **7** has been assigned based on the X-ray structure analysis (see the SI for the X-ray structure).

(2*R,3*R**)-3-Phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxylic Acid (8).**[18a] Following the general procedure, the compound **8** was obtained as brown color viscous liquid (the crude material was almost pure); yield: 95% (59 mg); IR (DCM): 3456, 1723, 1598, 1257, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.35 (m, 5H), 7.08−6.95 (m, 4H), 6.43 (br s, 1H), 5.51 (d, 1H, J = 3.2 Hz), 5.04 (d, 1H, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 143.0, 141.8, 134.8, 128.9, 128.6, 126.5, 122.5, 122.2, 117.4, 117.2, 75.1, 75.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_4$: 257.0814; found 257.0821. The stereochemistry of the compound **8** has been assigned based on the stereochemistry of its parent compound **4a**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray structures and CIF files, copies of ^1H, ^{13}C, and NOESY NMR charts, and HPLC analysis charts. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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