Journal Pre-proofs

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PII: S0968-0896(20)30452-1
DOI: https://doi.org/10.1016/j.bmc.2020.115622
Reference: BMC 115622

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 9 June 2020
Accepted Date: 26 June 2020

Please cite this article as: Imaizumi, T., Otsubo, S., Komai, M., Takada, H., Maemoto, M., Kobayashi, A., Otsubo, N., The design, synthesis and evaluation of 2-aminobenzoxazole analogues as potent and orally efficacious ChemR23 inhibitors, *Bioorganic & Medicinal Chemistry* (2020), doi: https://doi.org/10.1016/j.bmc.2020.115622

Title:

The design, synthesis and evaluation of 2-aminobenzoxazole analogues as potent and orally efficacious ChemR23 inhibitors

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Keywords:

SLE, pDC, Interferon, ChemR23, Internalization

Abstract

We previously reported 2-aminobenzoxazole analogue **1** as a potent ChemR23 inhibitor. The compound showed inhibitory activity against chemerin-induced calcium signaling through ChemR23 internalization in CAL-1 cells, which are cell lines of plasmacytoid dendric cells (pDCs). Furthermore, compound **2** inhibited chemotaxis of CAL-1 triggered by chemerin *in vitro*. However, we noted a difference in the ChemR23 response to our inhibitor between rodents and non-rodents in a previous study. To address this issue, we performed optimization of ChemR23 inhibitors using CAL-1 cells endogenously expressing human ChemR23 and conducted a pharmacokinetics study in cynomolgus monkeys. Various substituents at the 4-position of the benzoxazole ring exhibited potent *in vitro* bioactivity, while those at the 6-position were not tolerated. Among substituents, a carboxyl group was identified as key for improving the oral bioavailability in cynomolgus monkeys. Compound **38a** with the acidic part changed from a tetrazole group to a 1,2,4-oxadiazol-5-one group to improve bioactivity and pharmacokinetic parameters exhibited inhibitory activity against chemerin-induced chemotaxis *in vitro*. In addition, we confirmed the ChemR23 internalization of pDCs by compound **38a** orally administered to cynomolgus monkeys. These 2-aminobenzoxazole-based ChemR23 inhibitors may be useful as novel immunotherapeutic agents capable of suppressing the migration of pDCs, which are known to be major producers of type I interferons in the lesion area of certain autoimmune diseases, such as systemic lupus erythematosus and psoriasis.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by systemic inflammation and production of autoantibodies.[1,2] Although belimumab, a human monoclonal antibody that inhibits B-cell activating factor (BAFF), was approved as a new drug for SLE in 2011[3,4], the treatment of SLE still largely depends on steroids and immunosuppressive agents.[5] There have been many reports describing a relationship between SLE development and type-I interferon (IFN). Indeed, the anti-IFN-α monoclonal antibody sifalimumab was developed and met the primary endpoint at the phase II stage, although the development was discontinued due to issues from a business strategic perspective.[6] In addition, anifrolumab, a monoclonal antibody against the IFN receptor, achieved the primary endpoint in a phase III study for SLE patients recently.[7] The positive results with these biologics have driven the development of new drugs targeting IFN.

Plasmacytoid dendritic cells (pDCs) are specialized DCs that can produce large amounts of type I IFN through the activation of Toll-like receptors.[8-12] The molecular mechanism underlying the function and production of pDCs has been discussed in recent reviews, with the inactivation of pDCs considered an attractive approach to treating SLE.[13-15] While the IFN-targeted antibodies mentioned above would be useful for treating SLE the application of biologics remains limited to certain patient populations due to the administration route or for financial reasons. Therefore, a small-molecular drug with equivalent efficacy to the abovementioned biologics is expected to enjoy widespread usage.

From this perspective, an orally available small-molecular agent that can

control IFN production or pDC activation would meet a number of unmet medical needs. ChemR23 is a G-protein coupled receptor (GPCR) and is also known as chemoattractant-like receptor 1 (CMKLR1). This receptor is expressed on macrophages[16], natural killer cells and pDCs. [17] Chemerin, which is an inflammation-related protein, was discovered by Wittarmer at al. as a natural ligand for ChemR23.[18,19] Anti-ChemR23 antibody has been reported to suppress pDC migration induced by chemerin from psoriatic skin fibroblasts. [20-22]

In our previous paper[23], compound **1** inhibited chemerin-induced intracellular calcium fluctuation through the internalization of ChemR23 in the pDC line CAL-1.[24] In addition, compound **2**, in which a methyl amide group was introduced at the 5-position of the benzoxazole ring, showed an inhibitory effect against CAL-1 migration induced by chemerin in a concentration-dependent manner.[24] However, differences in the inhibitory concentration between CAL-1 cells and Ba/F3 cells expressing murine ChemR23 were confirmed for several compounds, and we faced difficulties optimizing our ChemR23 inhibitors for both rodent and non-rodent models (**Figure 1**).[23] The chemotaxis inhibition of CAL-1 by our ChemR23 inhibitors is presumably based on ChemR23 internalization,[23] and we confirmed ChemR23 internalization in pDCs from cynomolgus monkey by our compounds as well as chemerin. Therefore, we decided to carry out a further structure activity relationship (SAR) study and pharmacokinetic screening focusing on non-rodent species.

We herein report the synthesis and *in vitro* and *in vivo* activity of 2-aminobenzoxazole analogues that are orally bioavailable ChemR23 inhibitors in cynomolgus monkeys. Given our previously obtained SAR information showing

that modifications at the 5-position of benzoxazole did not markedly improve the inhibitory activity against ChemR23 signaling[24], we first performed further optimization at the 4- and 6-positions of benzoxazole. We then focused on the biphenyl tetrazole moiety to obtain good oral availability in cynomolgus monkeys.

2. Chemistry

Commercially available (*R*)-1-(4-bromophenyl)ethanamine (**6**) purchased from Alfa Aesar was selected as the starting material for all compounds. For the modifications of the 4- and 6-position on benzoxazole, the methyl esters **5a** and **5b** were prepared by a cyclization reaction of aminophenols **4a** and **4b** using potassium ethylxthanthate. After reductive amination of **6** with 1-butanal, the obtained secondary amine **7** was used for a coupling reaction with 2-chlorobenzoxazoles prepared from the 2-mercaptobenzoxazoles **5a** and **5b** by thionyl chloride to obtain compounds **8a** and **8b**, respectively. Basic hydrolysis of the ester group in compounds **8a** and **8b** produced carboxylic acids **9a** and **9b**, respectively. Amidation was then performed using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) as a condensation reagent. Finally, Suzuki coupling reaction of the intermediate **10a** with 2-cyanophenyl borate followed by tetrazole formation reaction in the presence of $TMSN_3$ and dibutyltin oxide provided the methylamide **11a**. Commercially available 2-(tetrazol-5-yl)phenylboronic acid was used to obtain amides **11a'** and **11b** more easily than **11a** and with good chemical yields (**Scheme 1**).

Further modifications of the 4-position of benzoxazole are outlined in **Scheme 2**. The carboxylic acid **13** was synthesized from the intermediate **8a** in three steps (Suzuki coupling, hydrolysis and tetrazole formation), and subsequent amidation with the appropriate amines afforded amides **14a** and **14b**. The primary alcohol **16** was formed by the hydride reduction of the ester **8a** and following introduction of a phenyltetrazole moiety. The methylether **17** was obtained via methylation of the alcohol **15** with iodomethane. Esterification of the

carboxylic acid **13** followed by nucleophilic addition using methylmagnesium bromide gave the *gem*-dimethyl alcohol **18**.

The syntheses of target compounds possessing amine, amide, urea, sulfonamide or acylsulfonamide groups are summarized in **Scheme 3**. Curtius rearrangement and subsequent hydrolysis reaction afforded amine **19**. Amino compound **20** was prepared by palladium coupling reaction with the corresponding boronic acid. The *N*-acetyl compound **21**, *N*-sulfonyl compound **22** and *N*,*N*-dimethyl urea **23** were prepared using the corresponding chloride or anhydride. The acylsulfonamide **24** was prepared by the activation of the carboxyl group as a carbonyl chloride followed by substitution with methanesulfonamide.

A series of aromatic ring-substituted analogues is described in **Scheme 4**. In order to avoid conflicts between two bromo groups, the bromide **7** was converted to the biphenyl analogue **27** by a coupling reaction prior to nucleophilic substitution reaction with the bromo-containing benzoxazole **26**. Replacement from the bromo moiety to the various heteroaryl ring was performed as follows: In brief, the 4-pyridine **29a** and 3-pyridine **29b** were synthesized via Suzuki-Miyaura coupling with boronic acid. The 2-pyridine **29c**, *N*-methylpyrrole **29d** and *N*-methylimidazole **29e** were prepared through a Stille reaction. 1-pyrrazole was introduced by an Ullmann type reaction, and these cyano analogues were converted into the desired tetrazole analogues **30a–f**.

Modification of the external benzene ring of the biphenyl moiety is shown in **Scheme 5**. After the conversion of bromide **31**[23] into pinacolborate **32**, various arylbromides were treated in the presence of palladium catalyst. The desired analogues **33a–o** were prepared by tin-mediated tetrazole formation reaction.

The synthetic approach for the 1,2,4-oxadiazol-5-one analogues possessing a carboxylic acid at the 4-position on benzoxazole is outlined in **Scheme 6**. Along with *n*-butyl-branched compound **8a**, cyclopropanemethyl-branched benzoxazole **35** was prepared, since the cyclopropanemethyl moiety was found to be a substituent showing equivalent *in vitro* activity with reduced lipophilicity. The consecutive coupling reactions were easily accomplished and afforded biphenyl compounds **36a–d** in good yields. The introduction of a hydroxyl amine unit to the cyano moiety was more difficult than expected because the 50% hydroxylamine solution reacted with the ester moiety on benzoxazole.[25] Eventually, hydroxylamine hydrochloride pretreated with sodium bicarbonate was used for *N*-hydroxyamidine formation at the cyano group.[26] The subsequent cyclization reaction with 1,1'-carbonyldiimidazole (CDI) afforded 1,2,4-oxadiazol-5-ones **37a–d**. Finally, the desired carboxylic acids **38a–d** were easily obtained by the hydrolysis of the methyl ester moiety. Analogues with *n*-butyl side chains **41a** and **41b** were also prepared in the same way as above.

3. Result and discussion

In the calcium assay using cell lines expressing human or mouse ChemR23, it was recognized that the half maximal inhibitory concentration (IC_{50}) values of some benzoxazole analogues were not correlated between human and mouse receptors.[23] For this reason, the *in vitro* activity was optimized using CAL-1 cells, a ChemR23-expressing pDC-like line established from a patient with blastic natural killer cell lymphoma.[24] For the *in vivo* study, we planned to use cynomolgus monkeys because of the confirmed high homology and no species difference between their ChemR23 and human ChemR23.

First, we compared the inhibitory activities of a series of *N*-methylamide analogues (**2**, **11a** and **11b**) to figure out the best position for the benzoxazole modification. The data indicated that modification of the 4- or 5-position showed better tolerability than that of the 6-position of the benzoxazole ring (**2**: 4-position, IC_{50} = 110 nM; **11a**: 5-position, IC_{50} = 38 nM; and **11b**: 6-position, IC_{50} > 3000 nM). Since we had previously confirmed the low tolerability for conversion of the 5-position, we decided to start exploration at the 4-position.[23]

The results of a SAR study at the 4-position on the benzoxazole ring are summarized in **Table 1**. The dimethylamide **11a'** (IC_{50} = 13 nM) showed an improved potency (by approximately 8-fold) compared with the methylamide **11a** or unsubstituted compound **1**. In addition, a terminal hydroxyl group in the amide chain was well tolerated with regard to the *in vitro* activity (**14b**: IC_{50} = 26 nM) compared to the des-hydroxy analogue (**14a**: IC_{50} = 62 nM). The primary hydroxyl analogue **16** (IC_{50} = 24 nM) showed an improved *in vitro* potency, whereas the *gem*-dimethylated tertiary alcohol **18** (IC_{50} = 340 nM) showed a decreased

activity. Since the methoxymethyl group retained strong activity (**17**: IC_{50} = 29 nM), the loss of potency of compound **18** was attributed to the bulkiness of the *gem*-dimethyl moiety. Acidic functional groups, such as carboxylic acid and its bioisostere acylsulfonamide, were found to be substituents that increased the potency by 6- to 8-fold compared with the unsubstituted compound **1** (**13**: IC_{50} = 17 nM, **24**: IC_{50} = 14 nM). Considering the strong activity of amino analogue **20** (IC_{50} = 27 nM), *N*-acetyl **21** (IC_{50} = 22 nM), *N,N*-dimethylurea **22** (IC_{50} = 32 nM) and *N*-methanesulfonyl **23** (IC_{50} = 14 nM), the 4-position of benzoxazole was expected to have broad tolerability. Among the 6-membered heteroaryl groups, the 2-pyridyl **30c** (IC_{50} = 110 nM) showed favorable potency over 4-pyridyl **30a** (IC_{50} = 300 nM) and 3-pyridyl **30b** (IC_{50} > 1000 nM). Among the 5-membered heteroaryl groups, *N*-methylpyrrole **30d** (IC_{50} = 130 nM) and pyrazole **30f** (IC_{50} = 330 nM) showed no improvement in the activity, but the *N*-methylimidazole **30e** (IC_{50} = 10 nM) exhibited the highest *in vitro* inhibitory activity among the modifications of the 4-position on the benzoxazole ring.

The results of the modifications at the external benzene ring are shown in **Table 2**. Regarding the conversion of the 3-position, fluorine **33a** retained potency, whereas the potency of chloro **33b** was attenuated 3-fold. It was revealed that the activity was significantly impaired by modification at the 4-position by trifluoromethyl **33c**, chloro **33d**, methyl **33d** or methoxy **33e**, although fluoro **33c** (IC_{50} = 57 nM) increased the potency slightly. No substituent was identified at the 6-position that could increase the activity. At the 5-position, although trifluoromethyl **33i** and methoxy **33l** were not tolerated, the potencies of fluoro **33h** (IC_{50} = 75 nM), chloro **33j** (IC_{50} = 75 nM) and methyl **33k** (IC_{50} = 53

nM) were increased (**Table 2**). These results were combined with those of other SAR studies as described below.

Pharmacokinetic studies after the oral administration of our ChemR23 inhibitors were conducted by cassette administration to cynomolgus monkeys, and the results are summarized in **Table 3**. Although most compounds, including the initial lead compound **1**, showed a poor oral absorption in cynomolgus monkeys, the carboxylic acid **13** and *N*-methylimidazolyl compound **30e** gave better results than any other compounds regarding the C_{max} value and bioavailability (F), which motivated us to embark on further modifications. We also paid special attention to carboxylic acid **13** because the structural features closely resembled those of Candesartan, a well-known drug for hypertension. Candesartan possesses the same two acidic moieties (carboxylic acid moiety and tetrazole moiety) and shows low bioavailability. Researchers in Takeda's group modified its carboxylic acid part to an ester part by utilizing a prodrug strategy and then developed Candesartan cilexetil which is capable of improving the oral absorption of Candesartan. [27-29] In addition, Azilsartan, which has a similar chemical structure to Candesartan, has been launched for the same therapeutic indication without a prodrug formation.[30] The oral absorption of Azilsartan was improved over that of Candesartan by the conversion of the tetrazole ring into a 1,2,4-oxadiazol-5-one ring (**Figure 2**). Although each of these strategies was attractive for application to our molecules to improve the bioavailability, we selected the methodology used for Azilsaltan for our optimization study because the *in vivo* pharmcokinetic (PK)-pharamcodynamics (PD) results were expected to be easier to understand than with the prodrug strategy.

The *in vitro* potency and PK parameters of 1,2,4-oxadiazol-5-one analogues are summarized in **Table 4**. The PK parameters were obtained by oral cassette administration to cynomolgus monkeys at a dose of 1.0 mg/kg for each compound. To our delight, all of the prepared 1,2,4-oxadiazol-5-one analogues exhibited an improved oral availability. In addition, the effect of substituents on the external phenyl ring was also observed, as had been confirmed in the tetrazole analogs, and excellent potency was noted (IC_{50} = 1.2 nM and IC_{50} = 1.3 nM for chloro-substituted analogs **41b** and **38c**). Among these 1,2,4-oxadiazol-5-one analogues, compounds **38a** and **41b**, which possessed a good balance between *in vitro* potency and bioavailability, were selected for the additional PK study after oral administration alone with a higher dose (10 mg/kg). As a result, both compounds showed good oral absorption (**38a**: C_{max} = 6950 ng/mL, **41b**: C_{max} = 2110 ng/mL), although the half-life still had room for improvement (**38a**: $T_{1/2}$ = 1.0 hr, **41b**: $T_{1/2}$ = 2.0 hr). (**Table 5**). We also evaluated these two compounds using a chemotaxis assay with CAL-1 cells and confirmed that both compounds inhibited the migration of CAL-1 triggered by chemerin from a low concentration (**38a**: chemotaxis IC_{50} = 63 nM, **41b**: chemotaxis IC_{50} = 235 nM, **Figure 3**). The slight decrease in the potency against the chemotaxis assay from the calcium signaling assay was attributed to a difference in the free fraction ratio of the compounds, as this chemotaxis assay contains 0.1% (w/v) bovine serum albumin in the assay buffer. We determined that compound **38a** was preferable to **41b** for further *ex vivo* and *in vivo* studies in monkeys in terms of both the *in vitro* potency versus free plasma concentrations (**38a:** $(f_{u.p} \cdot C_{max})/IC_{50}$ = 1.0, **41b**: $(f_{u.p} \cdot C_{max})/IC_{50}$ = 0.5, **Table 5**) and chemotaxis inhibition potency.

The effective concentration range of the selected compound **38a** for *in vivo* ChemR23 internalization in cynomolgus monkeys was predicted beforehand using cynomolgus monkey whole blood. The internalization rate of ChemR23 on pDCs was calculated by a flow cytometry analysis using fluorescence-conjugated ChemR23 antibody after compound addition to the blood. The receptor internalization rate of 53% (*N* = 2, average) was observed at 30 μM of the compound, and a rate of 82% (*N* = 2, average) was observed at 100 μM (**Figure 4**). Based on these results, along with the monkey PK results of 10 mg/kg (oral administration [p.o.]), we estimated that the oral administration of 50 mg/kg could cause sufficient receptor internalization of ChemR23 by pDCs at the time of reaching C_{max}. The results of the *in vivo* test are shown in **Figure 5**, and the PK (plasma concentration)-PD (receptor internalization rate) correlation is summarized in **Table 6**. The internalization rate of ChemR23 on pDCs was measured at 2, 4 and 8 h after the oral administration of the test compound. The maximum pharmacological effect was confirmed at 4 h, and the internalization rate was 90% and 74% in each monkey (**Figure 5**). Plasma concentrations of compound **38a** were also measured at each time point, and it was confirmed that each animal had the maximum compound concentration at 4 h (**Table 6**). Based on *in vitro* experiments with CAL-1, we assumed that the internalization of ChemR23 would indicate the inhibition of pDC migration. Therefore, the reduction of pDCs in the tissue is expected to inhibit IFN-α production at the inflamed site, leading to the improvement of autoimmune diseases, particularly SLE or psoriasis. However, further structural optimization is desired to not only improve the short

half-life *in vivo*, but also to reduce the required dosage Optimization studies aimed at confirming pharmacological effects are ongoing.

4. Conclusion

In this study, we identified a benzoxazole analogue capable of reducing the ChemR23 expression on monkey pDCs *in vivo*. We initially modified the 4-position on the benzoxazole ring as a promising position to improve the potency and identified the carboxylic acid analogue **13**, which showed potent activity and slightly improved oral bioavailability in cynomolgus monkeys. To further improve the potency and pharmacokinetic parameters, we embarked on the conversion of the tetrazole group as well as the modification of the external benzene ring and ultimately discovered the promising 1,2,4-oxadiazole-5-one analogue **38a**, which was designed based on a previous study regarding Azilsaltan given its structural similarity to compound **13**. Compound **38a** showed high potency in both the calcium assay and chemotaxis assay and preferable pharmacokinetics and *ex vivo* effects in cynomolgus monkeys. Furthermore, compound **38a** showed an *in vivo* ChemR23 internalization effect on pDCs after its oral administration to cynomolgus monkeys. We expect that our ChemR23 inhibitors will suppress pDC migration into inflamed tissues and IFN production *in vivo*. A further study to elucidate the chemerin/ChemR23 axis in animal models using our compound will be reported in due course.

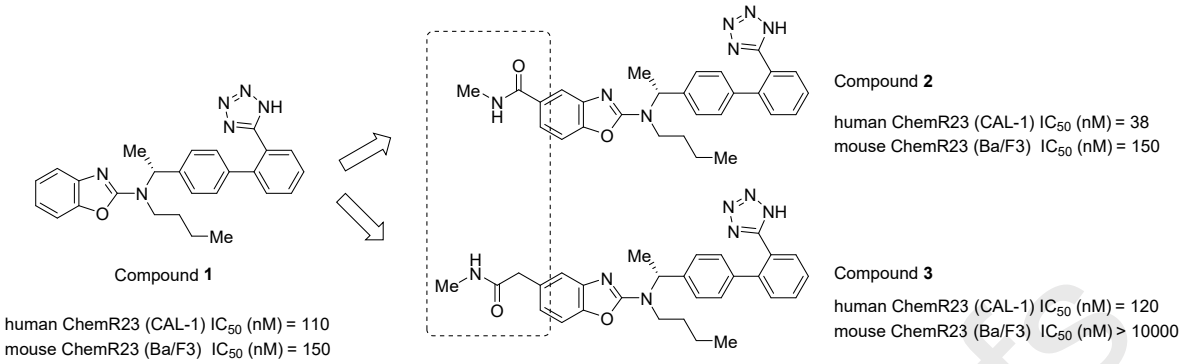
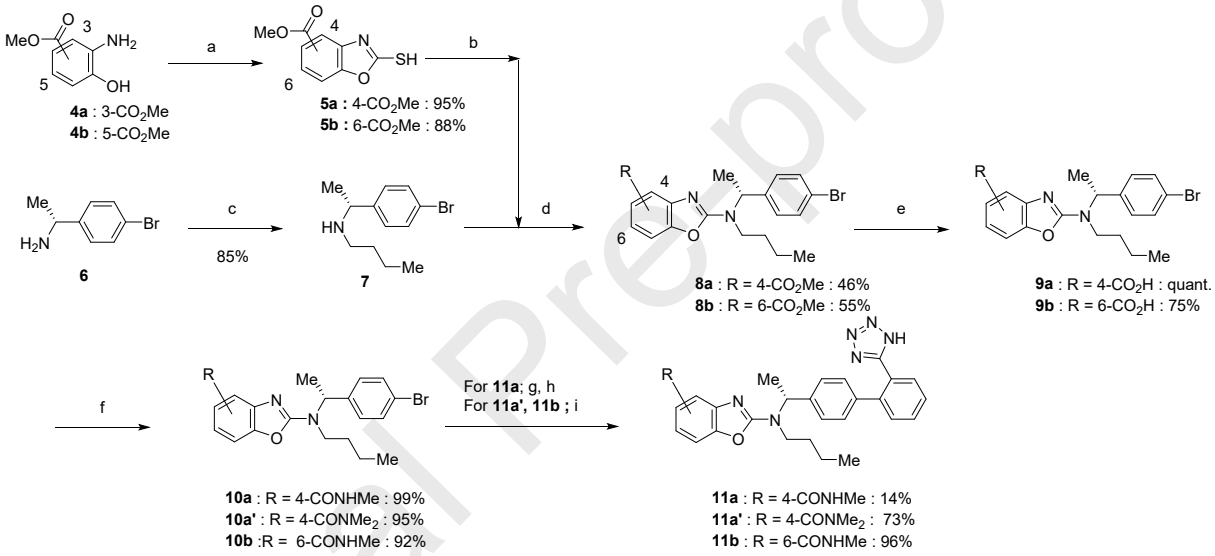
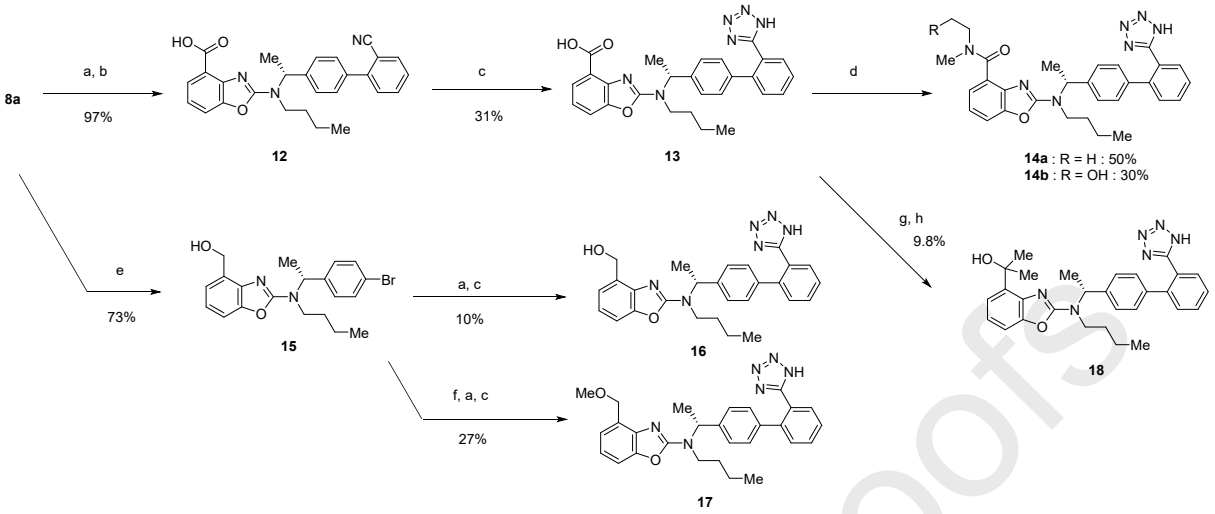


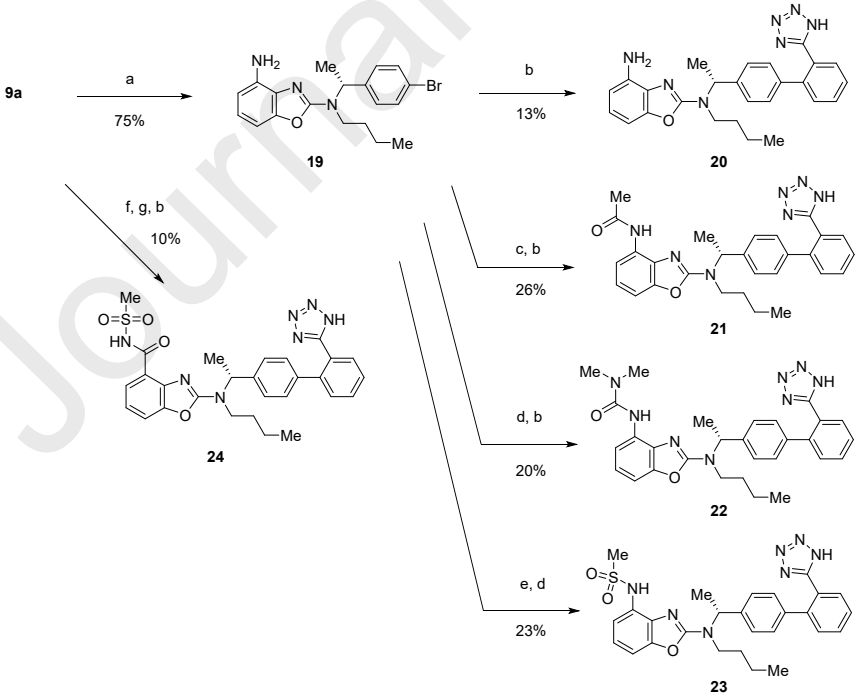
Figure 1. Summary of previous report.



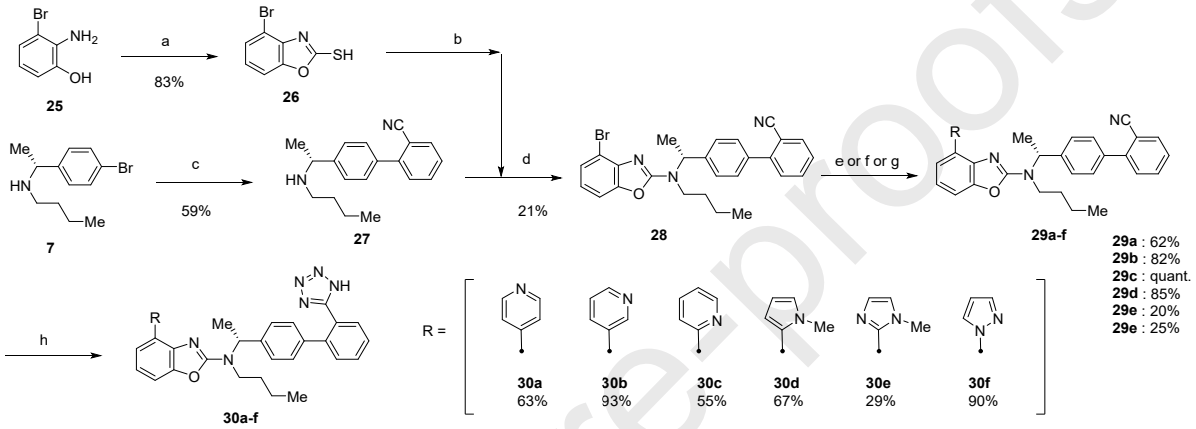
Scheme 1. Reagents and conditions: (a) potassium ethylxanthate, pyridine, 90 °C; (b) DMF, $SOCl_2$, reflux; (c) 1-butanal, $NaBH(OAc)_3$, MeOH, rt; (d) DIPEA, DMF, 50 °C; (e) $LiOH{\cdot}H_2O$, MeOH, 60 °C; (f) amines, THF, DIPEA, EDCI·HCl, $HOBt{\cdot}H_2O$, DMF, rt; (g) 2-cyanophenylboronic acid pinacol ester, $Pd(PPh_3)_4$, KOAc, DME, 85 °C; (h) $TMSN_3$, dibutyltin oxide, toluene, reflux; (i) 2-(tetrazol-5-yl)phenylboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 100 °C.



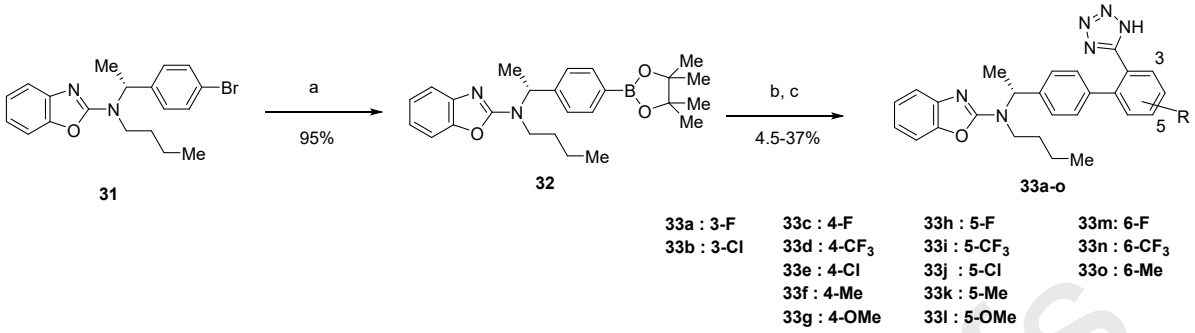
Scheme 2. Reagents and conditions: (a) 2-cyanophenylboronic acid pinacol ester, $Pd(PPh_3)_4$ (for **12**, **16**), $Pd(dppf)Cl_2$ (for **17**), $K_3PO_4 \cdot 7H_2O$ (for **12**, **17**), KOAc (for **16**), DME, 85 °C; (b) $LiOH \cdot H_2O$, MeOH, 60 °C; (c) $TMSN_3$, dibutyltin oxide, toluene, reflux; (d) amines, HATU, DIPEA, DMF, rt; (e) $LiAlH_4$, THF, 0 °C; (f) MeI, NaH, DMF, 0 °C; (g) H_2SO_4, MeOH, reflux; (h) MeMgBr, THF, rt.



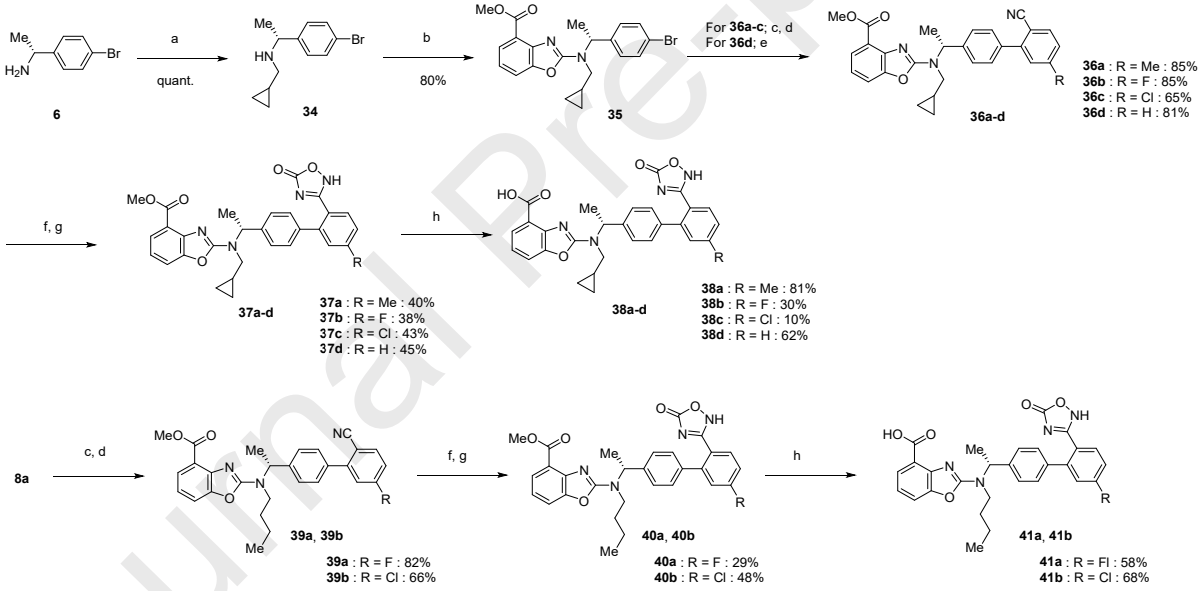
Scheme 3. Reagents and conditions: (a) DPPA, Et_3N, DMF, H_2O, 100 °C; (b) 2-(tetrazol-5-yl)phenylboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 100 °C; (c) Ac_2O, Et_3N, CH_2Cl_2, 0 °C; (d) $Me_2NC(O)Cl$, Et_3N, CH_2Cl_2, reflux; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C; (f) $(COCl)_2$, DMF, CH_2Cl_2, rt; (g) $MeSO_2NH_2$, DIPEA, DMF, 100 °C.



Scheme 4. Reagents and conditions: (a) potassium ethylxanthate, MeOH, reflux; (b) DMF, $SOCl_2$, reflux; (c) 2-cyanophenylboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 85 °C; (d) DIPEA, 1,4-dioxane, reflux; (e) 3-pyridylboronic acid or 4-pyridylboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 100 °C (for **29a** and **29b**), (f) 2-(tributylstannyl)pyridine or 1-methyl-2-(tributylstannyl)pyrrole or 1-methyl-2-(tributylstannyl)imidazole, $Pd(PPh_3)_4$, toluene, 100 °C (for 29**c**–**e**), (g) pyrazole CuI, Cs_2CO_3, DMF, 130 °C (for **29f**); (h) $TMSN_3$, dibutyltin oxide, toluene, reflux.

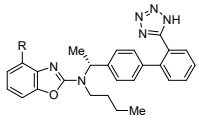


Scheme 5. Reagents and conditions: (a) bis(pinacolato)diboron, KOAc, $Pd(PPh_3)_4$, DME, reflux; (b) ArBr, $Pd(PPh_3)_4$, $K_3PO_4 \cdot 7H_2O$, DME, reflux; (c) $TMSN_3$, dibutyltin oxide, toluene, reflux.



Scheme 6. Reagents and conditions: (a) *c*-PrCHO, $NaBH_4$, MeOH rt; (b) 4-methoxycabonyl-2-chlorobenzoxazole prepared from **5a**, DIPEA, DMF, 60 °C; (c) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 100 °C; (d) ArBr, $Pd(PPh_3)_4$, Cs_2CO_3, 1,4-dioxane, H_2O, 100 °C; (e) 2-cyanophenylboronic acid pinacol ester, $Pd(PPh_3)_4$, $K_3PO_4 \cdot 7H_2O$, DME, 85 °C; (f) $NH_2OH \cdot HCl$, $NaHCO_3$, DMSO, 80 °C; (g) CDI, THF, 75 °C; (h) 3 M NaOH, EtOH, 60 °C.

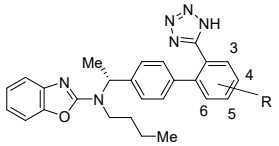
Table 1. The structure–activity relationship at the 4-position of the benzoxazole ring



Compd.	R	hChemR23 IC_{50}[a] (nM)	Compd.	R	hChemR23 IC_{50}[a] (nM)	Compd.	R	hChemR23 IC_{50}[a] (nM)
1		110	**16**		24	**30a**		300
11a		110	**18**		340	**30b**		>1000
11a'		13	**17**		29	**30c**		110
14a		62	**20**		27	**30d**		130
14b		26	**21**		22	**30e**		10
13		17	**22**		32	**30f**		330
24		14	**23**		14			

[a]human ChemR23 IC_{50}: 50% inhibitory concentration against chemerin-induced calcium signaling (all values are the mean of four measurements).

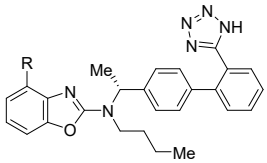
Table 2. The structure–activity relationship at the external phenyl ring



Compd.	R	hChemR23 IC_{50}[a] (nM)	Compd.	R	hChemR23 IC_{50}[a] (nM)
1	H	110	**33h**	5-F	75
33a	3-F	100	**33i**	5-CF_3	1320
33b	3-Cl	350	**33j**	5-Cl	65
33c	4-F	57	**33k**	5-Me	53
33d	4-CF_3	>3000	**33l**	5-OMe	860
33e	4-Cl	>3000	**33m**	6-F	160
33f	4-Me	2100	**33n**	6-CF_3	1300
33g	4-OMe	3000	**33o**	6-Me	210

[a]human ChemR23 IC_{50}: 50% inhibitory concentration against chemerin-induced calcium signaling (all values are the mean of four measurements).

Table 3. Pharmacokinetic properties of tetrazole analogues in cynomolgus monkeys



Compd.	R	C_{max}[a] (ng/mL)	$T_{1/2}$[a] (h)	$AUC_{0-\infty}$[a] (ng/mL·h)	$f_{u.p}$[b] (%)	F[a,c] (%)
1	-H	12.8	3.2	44.3	0.0713	1.8
11a	-CONHMe	9.74	1.3	25.7	0.0975	NT[d]
11a'	$-CONMe_2$	27.5	3.2	104	0.411	6.7
16	$-CH_2OH$	9.68	1.6	20	0.112	0.8
13	$-CO_2H$	115	3.7	429	0.0285	8.2
24	$-CONHSO_2Me$	22.6	2.7	22.2	0.103	NT[d]
30c	-2-pyridyl	64	5.9	248	0.129	NT[d]
30e	-2-Me-imidazole	79.9	3.9	152	0.299	7.5
21	-NHCOMe	13.2	2.2	41.6	0.102	NT[d]
23	$-NHSO_2Me$	26.5	4.7	73.8	0.0203	NT[d]

[a]The values shown as the means of three determinations by cassette dosing (1.0 mg/kg, p.o.).

[b]Plasma unbound fraction obtained from an equilibrium dialysis method.

[c]Compounds were administered at doses of 1.0 mg/kg (p.o.) and 0.1 mg/kg (iv) using a cassette dosing method.

[d]Not tested.

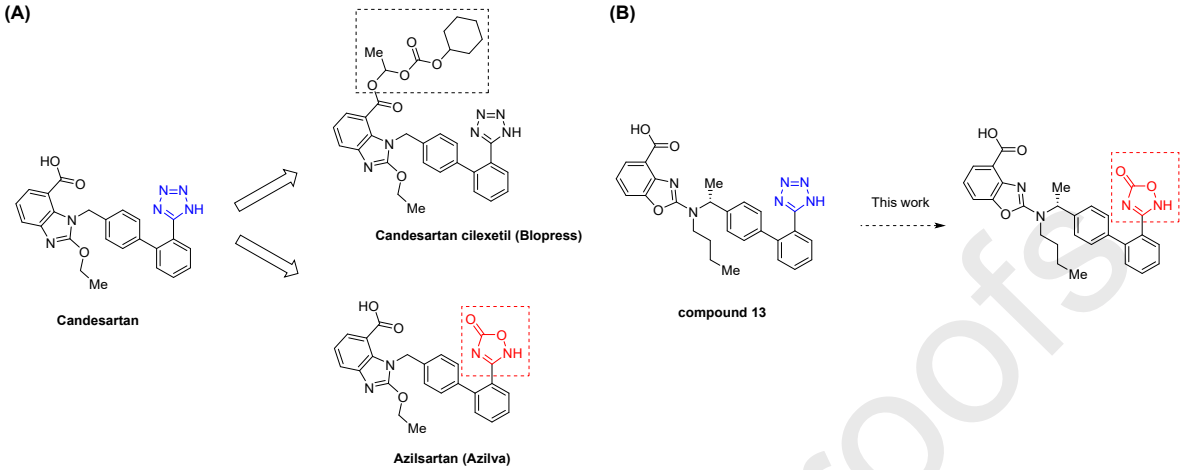
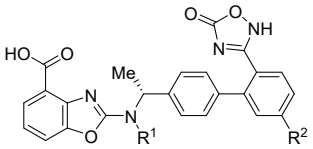


Figure 2. (A) The chemical structures of Candesartan, Candesartan cilexetil and Azilsartan. (**B**) Optimization strategy of compound **13** to improve the oral bioavailability in this study.

Table 4. Pharmacokinetic properties in cynomolgus monkeys and ChemR23 *in vitro* inhibitory activity of 1,2,4-oxadiazol-5-one analogues



Compd.	R^1	R^2	C_{max} [a] (ng/mL)	$T_{1/2}$ [a] (h)	$AUC_{0-\infty}$ [a] (ng/mL·h)	$f_{u.p}$ [b] %	F [a,c] (%)	IC_{50} [d] (nM)
41a	*n*-Bu-	F	610	2.2	1630	0.00736	NT[e]	2.7
41b	*n*-Bu-	Cl	361	2.0	1040	0.0135	42	1.2
38a	*c*-PrCH_2-	Me	1490	2.8	4830	0.0230	58	3.2
38b	*c*-PrCH_2-	F	1490	4.1	4410	0.00977	82	2.3
38c	*c*-PrCH_2-	Cl	518	0.8	1300	0.0108	NT[e]	1.3
38d	*c*-PrCH_2-	H	3830	2.6	11600	0.00851	60	11

[a]The values shown as the means of three determinations by cassette dosing (1.0 mg/kg, po).

[b]Plasma unbound fraction obtained from an equilibrium dialysis method.

[c]Compounds were administered at doses of 1.0 mg/kg (po) and 0.1 mg/kg (iv) using a cassette dosing method.

[d]human ChemR23 IC_{50}: 50% inhibitory concentration against chemerin-induced calcium signaling (all values are the mean of four measurements).

[e]Not tested.

Table 5. Pharmacokinetic parameters of compounds **38a** and **41b** in cynomolgus monkey plasma following 10 mg/kg oral administration

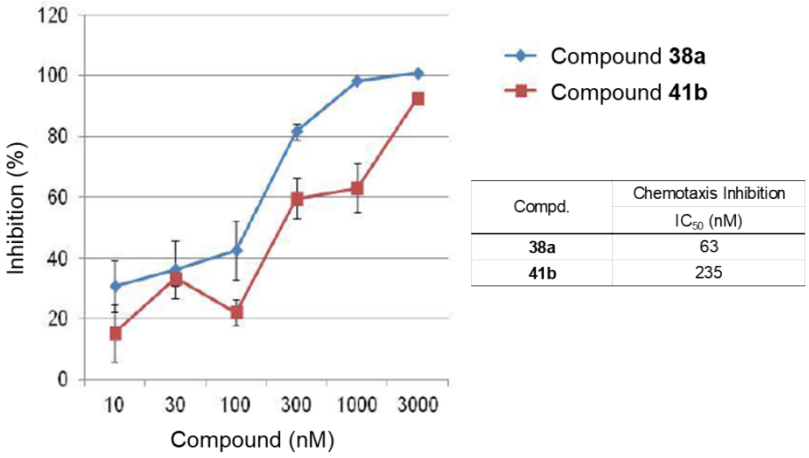
Compd.	Dose (mg/kg)	C_{max} [a] (ng/mL)	C_{8h} [a] (ng/mL)	$T_{1/2}$ [a] (h)	$AUC_{0-\infty}$ [a] (ng/mL*h)	MRT [a] (h)	$(f_{u.p} \cdot C_{max})$ [a–c] /IC_{50}
38a	10	6950	206	1.0	22200	2.9	1.0
41b	10	2110	ND[d]	2.0	7090	4.1	0.5

[a]The values shown as the means of three determinations.

[b]Plasma unbound fraction obtained from an equilibrium dialysis method.

[c]human ChemR23 IC_{50}: 50% inhibitory concentration against chemerin-induced calcium signaling (All values are the mean of four measurements).

[d]Not detected.



Compd.	Chemotaxis Inhibition IC_{50} (nM)
38a	63
41b	235

Figure 3. Effects of compound **38a** and compound **41b** against chemerin-induced chemotaxis using CAL-1 cells. Each point represents the mean ± SD of triplicate experiments.

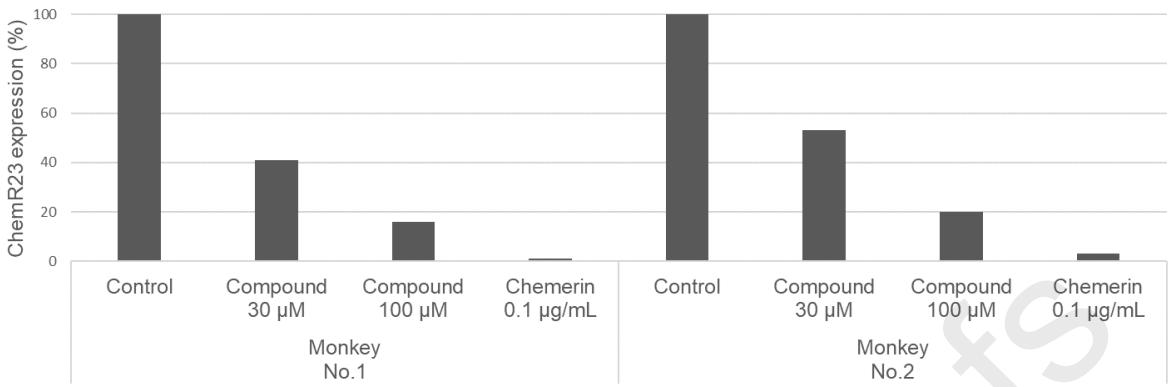


Figure 4. Effects of compound **38a** and chemerin on ChemR23 expression in whole blood of cynomolgus monkeys (*N=1* experiment, each individual).

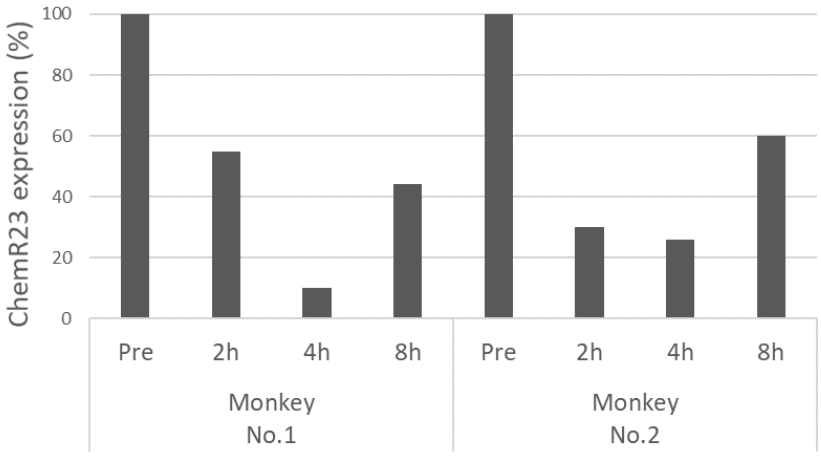


Figure 5. Expression of ChemR23 on the surface of pDCs after oral dosing of compound **38a** (50 mg/kg) to cynomolgus monkeys.

Table 6. *In vivo* PK (plasma concentration)-PD (receptor internalization rate) correlation after oral dosing of compound **38a** (50 mg/kg) to cynomolgus monkeys

	Time (hr)	Plasma Concentration (μmol/L)	ChemR23 Expression (%)
Monkey No.1	2	178	55
	4	204	10
	8	179	44
Monkey No.2	2	231	30
	4	259	26
	8	30.4	60

5. Experimental section

5.1. General statement

Unless otherwise indicated, all reagents and solvents were purchased from commercial sources and used without further purification. Moisture- or oxygen-sensitive reactions were conducted under an atmosphere of argon or nitrogen gas. Unless otherwise stated, ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz using JNM-AL400 instruments (JEOL Ltd., Japan) operating at the indicated frequencies. Chemical shifts are expressed in ppm (δ) relative to an internal standard: tetramethylsilane.

The following abbreviations are used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

Purification by silica gel column chromatography was carried out using Moritex systems (MORITEX Corporation, Japan) with prepacked cartridges. Liquid chromatography with tandem mass spectrometry (LC-MS) analyses were generally recorded using a Waters Micromass ZQ (ESI) (Nihon Waters K.K., Japan). High-resolution (HR)-LC-MS was conducted using a SYNAPT G2 (ESI) (Nihon Waters K.K., Japan). Chemical purities were assessed by high-performance liquid chromatography at UV 254 nm. Chemical yields were not optimized. (*R*)-1-(4-bromophenyl)ethanamine (99%, 98% ee) were purchased from Alfa Aesar (MA, USA). The syntheses of compounds **2** and **31** have already reported in a previous paper[23].

5.1.1. methyl 2-mercaptobenzo[*d*]oxazole-4-carboxylate (5a)

Methyl 2-amino-3-hydroxybenzoate (**4a**) (1.67 g, 10.0 mmol) was dissolved in

pyridine (200 mL). To this solution was added potassium ethylxanthate (4.77 g, 30.0 mmol). The mixture was stirred at 90 °C for 3 h. After cooling to room temperature, the resulting mixture was concentrated under reduced pressure, and then the residue was poured into ice-water (200 mL). Concentrated HCl was added until the pH was 4–6, and the formed precipitate was filtered and dried under vacuum to afford the titled compound (1.98 g, 95%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.80 (br s, 1H), 7.81–7.80 (m, 2H), 7.38 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 3.92 (s, 3H). LC-MS (ESI) *m/z* = 210 $[M + H]^+$.

5.1.2. (*R*)-*N*-[1-(4-bromophenyl)ethyl]butan-1-amine (7)

(*R*)-1-(4-bromophenyl)ethanamine (**6**) (2.00 g, 10.0 mmol) was dissolved in MeOH (50.0 mL). To this solution was added 1-butanal (1.78 mL, 20.0 mmol) and $NaBH(OAc)_3$ (4.24 g, 20.0 mmol). After stirring for 18 h at room temperature, 5% NaOH was added. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluted with 5%–10% MeOH in $CHCl_3$ to afford the titled compound (2.17 g, 85%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.72 (q, *J* = 6.8 Hz, 1H), 2.50–2.44 (m, 1H), 2.41–2.34 (m, 1H), 1.47–1.38 (m, 2H), 1.35–1.24 (m, 5H), 0.87 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 256 $[M + H]^+$.

5.1.3. methyl (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}benzo[*d*]oxazole-4-carboxylate (8a)

To a solution of compound **5a** (1.98 g, 9.45 mmol) in $SOCl_2$ (10 mL) was added DMF (205 mg, 2.40 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h and then cooled to room temperature. The resulting mixture was concentrated under reduced pressure to afford crude compound (1.92 g), which was used in the next step directly. To a stirring solution of this compound (1.20 g) and DIPEA (2.00 g, 15.0 mmol) in DMF (200 mL) was added compound **7** (1.25 g, 5.00 mmol) at 0 °C. The reaction mixture was heated at 50 °C overnight and then cooled to room temperature. The resulting mixture was poured into ice-water (400 mL) and extracted with AcOEt. The combined organic layer was washed with saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative thin-layer chromatography (TLC) to afford the titled compound (980 mg, 46% from compound **7**) as a yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.68–7.64 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.06 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 5.58 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.41–3.29 (m, 2H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.55–1.45 (m, 2H), 1.27–1.18 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 431 $[M + H]^+$.

5.1.4. (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}benzo[*d*]oxazole-4-carboxylic acid (9a)

To a mixture of compound **8a** (860 mg, 2.00 mmol) in MeOH (40 mL) was added $LiOH \cdot H_2O$ (560 mg, 20.0 mmol), and then the reaction mixture was stirred for 0.5 h at 60 °C. The mixture was concentrated under reduced pressure and then ice-water (50.0 mL) was added. 6 M HCl was added to the mixture until the pH was 4–6 and then extracted with AcOEt. The combined organic layer was washed

with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the titled compound (832 mg, quant.) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.13 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H), 5.64 (q, *J* = 6.8 Hz, 1H), 3.43-3.35 (m, 1H), 3.31–3.22 (m, 1H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.64–1.47 (m, 2H), 1.34–1.24 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 417 $[M + H]^+$.

5.1.5. (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}-*N*-methylbenzo[*d*]oxazole-4-carboxamide (10a)

To a mixture of compound **9a** (832 mg, 2.00 mmol) in DMF (100 mL) was added $HOBt·H_2O$ (520 mg, 4.00 mmol), $MeNH_2·HCl$ (260 mg, 4.00 mmol), DIPEA (1.04 g, 8.00 mmol) and EDCI·HCl (760 mg, 4.00 mmol) at 0 °C and then the reaction mixture was stirred overnight at room temperature. The mixture was poured into ice-water (200 mL) and extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to provide the titled compound (849 mg, 99%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.93 (q, *J* = 4.5 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.61 (q, *J* = 6.8 Hz, 1H), 3.42–3.34 (m, 1H), 3.26–3.18 (m, 1H), 3.06 (d, *J* = 4.5 Hz, 3H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.63–1.51 (m, 2H), 1.35–1.25 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 430 $[M + H]^+$.

5.1.6. (*R*)-2-({1-(2'-[1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*-methylbenzo[*d*]oxazole-4-carboxamide (11a)

To a solution of compound **10a** (430 mg, 1.00 mmol), KOAc (400 mg, 4.00 mmol), 2-cyanophenylboronic acid pinacol ester (448 mg, 2.00 mmol) and H_2O (0.50 mL) in DME (80.0 mL) was added $Pd(PPh_3)_4$ (114 mg, 0.099 mmol) under N_2 atmosphere. The reaction mixture was heated at 85 °C overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O (50.0 mL) was added. The mixture was extracted with AcOEt. The combined organic phase was washed with saturated $NaHCO_3$ aq. (50.0 mL) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford the desired compound. A solution of this compound, $TMSN_3$ (345 mg, 3.00 mmol) and dibutyltin oxide (370 mg, 1.50 mmol) in toluene (20.0 mL) was heated at 120 °C overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O (100 mL) was added. The mixture was extracted with AcOEt. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the titled compound (45.0 mg, 14%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.74 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 7.65–7.48 (m, 6H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.13–7.06 (m, 3H), 5.64 (q, *J* = 6.8 Hz, 1H), 3.53–3.36 (m, 2H), 2.90 (d, *J* = 4.8 Hz, 3H), 1.70 (d, *J* = 6.8 Hz, 3H), 1.56–1.43 (m, 2H), 1.29–1.24 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 496 $[M + H]^+$. Purity: 97.9%

5.1.7. (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}-*N*,*N*-

dimethylbenzo[*d*]oxazole-4-carboxamide (10a')

The titled compound (312 mg, 95%, colorless oil) was synthesized from compound **9a** (310 mg, 0.743 mmol) and dimethylamine (2.0 M in THF, 1.86 mL, 3.71 mmol) by a process analogous to the preparation of **10a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.48–7.44 (m, 2H), 7.28–7.24 (m, 4H), 7.02 (dd, *J* = 7.7, 7.7 Hz, 1H), 5.66 (q, *J* = 7.1 Hz, 1H), 3.35–3.27 (m, 1H), 3.20–3.12 (m, 1H), 3.17 (s, 3H), 2.97 (s, 3H), 1.66 (d, *J* = 7.1 Hz, 3H), 1.59–1.46 (m, 2H), 1.31–1.21 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H). LC-MS (ESI) *m/z* = 444 $[M + H]^+$.

5.1.8. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*,*N*-dimethylbenzo[*d*]oxazole-4-carboxamide (11a')

To a solution of compound **10a'** (300 mg, 0.675 mmol), Cs_2CO_3 (660 mg, 2.03 mmol), 2-(tetrazol-5-yl)phenylboronic acid (257 mg, 1.35 mmol) in DMF (9 mL) and H_2O (1 mL) was added $Pd(PPh_3)_4$ (78 mg, 0.068 mmol) under argon atmosphere. The reaction mixture was heated to 100 °C and stirred for 4 h. H_2O was added to the resulting mixture, which was then extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the titled compound (252 mg, 73%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.49–7.45 (m, 1H), 7.39–7.34 (m, 1H), 7.29–7.25 (m, 2H), 7.13–7.08 (m, 3H), 6.97–6.93 (m, 3H), 5.42 (q, *J* = 7.0 Hz, 1H), 3.44–3.34 (m, 1H), 3.26–3.13 (m, 1H), 3.09 (s, 3H), 2.98 (s, 3H), 1.69–1.54 (m, 2H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.36–1.25 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 510 $[M + H]^+$. Purity: 98.1%.

5.1.9. methyl 2-mercaptobenzo[*d*]oxazole-6-carboxylate (5b)

The titled compound (2.61 g, 88%, white solid) was synthesized from methyl 4-amino-3-hydroxybenzoate (**4b**) (2.37 g, 14.2 mmol) by a process analogous to the preparation of **5a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.25 (br s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H). LC-MS (ESI) *m/z* = 208 $[M - H]^-$.

5.1.10. methyl (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}benzo[*d*]oxazole-6-carboxylate (8b)

The titled compound (1.71 g, 55% from compound **7**, brown oil) was synthesized from compound **5b** (1.01 g, 4.85 mmol) and compound **7** (1.86 g, 7.28 mmol) by a process analogous to the preparation of **8a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.96–7.94 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.69 (q, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.36–3.13 (m, 2H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.60–1.45 (m, 2H), 1.31–1.22 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 431 $[M + H]^+$.

5.1.11. (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}benzo[*d*]oxazole-6-carboxylic acid (9b)

The titled compound (939 mg, 75%, brown amorphous) was synthesized from compound **8b** (1.30 g, 3.01 mmol) by a process analogous to the preparation of **9a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.05–8.01 (m, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 5.72 (q, *J* = 7.3 Hz, 1H), 3.42–

3.13 (m, 2H), 1.71 (d, *J* = 7.3 Hz, 3H), 1.63–1.42 (m, 2H), 1.34–1.20 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 417 $[M + H]^+$.

5.1.12. (*R*)-2-{[1-(4-bromophenyl)ethyl](butyl)amino}-*N*-methylbenzo[*d*]oxazole-6-carboxamide (10b)

The titled compound (190 mg, 92%, colorless oil) was synthesized from compound **9b** (200mg, 0.479 mmol) by a process analogous to the preparation of **10a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.81 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.33–7.24 (m, 3H), 6.48 (br s, 1H), 5.66 (q, *J* = 6.8 Hz, 1H), 3.35–3.12 (m, 2H), 3.01 (d, *J* = 4.9 Hz, 3H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.60–1.45 (m, 2H), 1.30–1.21 (m, 2H), 0.86 (t, *J* = 6.8 Hz, 3H). LC-MS (ESI) *m/z* = 430 $[M + H]^+$.

5.1.13. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*-methylbenzo[*d*]oxazole-6-carboxamide (11b)

The titled compound (105 mg, 96%, white solid) was synthesized from compound **10b** (95.0 mg, 0.221 mmol) by a process analogous to the preparation of **11a'**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 7.3 Hz, 1H), 7.62 (s, 1H), 7.57–7.50 (m, 1H), 7.48–7.36 (m, 3H), 7.15–7.12 (m, 3H), 7.01 (d, *J* = 7.7 Hz, 2H), 6.91 (br s, 1H), 5.26 (q, *J* = 6.6 Hz, 1H), 3.44–3.11 (m, 2H), 2.90 (d, *J* = 4.0 Hz, 3H), 1.63–1.50 (m, 2H), 1.59 (d, *J* = 6.6 Hz, 3H), 1.29–1.20 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 496 $[M + H]^+$. Purity: 99.9%.

5.1.14. (*R*)-2-{butyl[1-(2'-cyano-[1,1'-biphenyl]-4-yl)ethyl]amino}benzo[*d*]oxazole-4-carboxylic acid (12)

To a solution of compound **8a** (2.00 g, 4.62 mmol), $K_3PO_4{\cdot}7H_2O$ (8.01 g, 23.7 mmol), 2-cyanophenylboronic acid pinacol ester (2.18 g, 5.58 mmol) in DME (20.0 mL) was added $Pd(PPh_3)_4$ (200 mg, 0.173 mmol) under N_2 atmosphere. The reaction mixture was heated to 85 °C and stirred overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O (40 mL) was added. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography eluted with 66% AcOEt in petroleum ether. The obtained material was dissolved in MeOH (30 mL) and then was added $LiOH{\cdot}H_2O$ (810 mg, 17.7 mmol). The resulting mixture was stirred for 1 h at 70 °C. The solvent was removed under reduced pressure, and then 1 M HCl was added until the pH was 2–3. The mixture was extracted with AcOEt, and the combined organic phase was concentrated to afford the titled compound (1.50 g, 97%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.69–7.64 (m, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.53–7.44 (m, 5H), 7.13 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.71 (q, *J* = 7.0 Hz, 1H), 3.51–3.42 (m, 1H), 3.38–3.30 (m, 1H), 1.80 (d, *J* = 7.0 Hz, 3H), 1.66–1.53 (m, 2H), 1.36–1.26 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 440 $[M + H]^+$.

5.1.15. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazole-4-carboxylic acid (13)

To a solution of compound **12** (30.0 mg, 0.0683 mmol), dibutyltin oxide (34.2 mg, 0.137 mmol) in toluene (5.0 mL) was added $TMSN_3$ (39.4 mg, 0.342 mmol). The mixture was heated to 120 °C overnight. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC to afford the titled compound (10.1 mg, 31%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.66 (d, *J* = 8.0 Hz, 1H), 7.62–7.61 (m, 1H), 7.55 (d, *J* = 6.8 Hz, 1H), 7.32–7.41(m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 5.62 (q, *J* = 6.8 Hz, 1H), 3.47–3.21 (m, 2H), 1.68 (d, *J* = 6.8 Hz, 3H), 1.52–1.43 (m, 2H), 1.29–1.20 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 483 $[M + H]^+$. Purity: 99.9%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 483.2145; found, 483.2165.

5.1.16. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*-ethyl-*N*-methylbenzo[*d*]oxazole-4-carboxamide (14a)

To a solution of compound **13** (100 mg, 0.207 mmol) in DMF (5.0 mL) was added HATU (122 mg, 0.321 mmol), DIPEA (55.0 mg, 0.426 mmol) and *N*-ethylmethylamine (15.0 mg, 0.254 mmol). The mixture was stirred for 2 h, and then H_2O was added. The mixture was extracted with CH_2Cl_2, washed by brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the titled compound (55.4 mg, 50%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.56–7.54 (m, 1H), 7.46–7.33 (m, 4H), 7.27–7.23 (m, 2H), 7.12–7.00 (m, 4H), 5.56–5.41 (m, 1H), 3.52–3.47 (m, 2H), 3.28–3.16 (m, 2H), 2.97–2.80 (m, 3H), 1.67–1.64 (m, 3H), 1.54–1.35 (m, 2H),

1.22–1.20 (m, 2H), 1.15–1.00 (m, 3H), 0.87–0.81 (m, 3H). LC-MS (ESI) *m/z* = 524 $[M + H]^+$. Purity: 98.9%.

5.1.17. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*-(2-hydroxyethyl)-*N*-methylbenzo[*d*]oxazole-4-carboxamide (14b)

The titled compound (33.6 mg, 30% from compound **13**, white solid) was synthesized with a *N*-methylethanolamine by a process analogous to the preparation of **14a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.63–7.60 (m, 2H), 7.54–7.44 (m, 3H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.13–7.03 (m, 4H), 5.50–5.47 (m, 1H), 3.61–3.43 (m, 4H), 3.28–3.22 (m, 2H), 3.03–2.86 (m, 3H), 1.67–1.65 (m, 3H), 1.55–1.35 (m, 2H), 1.27–1.19 (m, 2H), 0.87–0.81 (m, 3H). LC-MS (ESI) *m/z* = 540 $[M + H]^+$. Purity: 99.9%.

5.1.18. (*R*)-(2-{[1-(4-bromophenyl)ethyl](butyl)amino}benzo[*d*]oxazol-4-yl)methanol (15)

To a solution of compound **8a** (430 mg, 1.00 mmol) in THF (50.0 mL) was added $LiAlH_4$ (94.6 mg, 2.50 mmol) in portions at 0 ºC. The mixture was stirred for 1 h at room temperature and then cooled to 0 ºC. To the mixture was added H_2O (0.52 mL), followed by the addition of 10% NaOH (0.16 mL). The mixture was filtered over Na_2SO_4, and the filtrate was concentrated to afford the titled compound (295 mg, 73%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.49–7.45 (m, 2H), 7.28–7.20 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.04–6.95 (m, 2H), 5.66–5.60 (q, *J* = 7.2 Hz, 1H), 4.96 (d, *J* = 4.8 Hz, 2H), 3.12–3.35 (m, 2H), 1.67

(d, *J* = 7.2 Hz, 3H), 1.47–1.57 (m, 2H), 1.21–1.31 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 403 $[M + H]^+$.

5.1.19. (*R*)-[2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazol-4-yl]methanol (16)

To a solution of compound **15** (402 mg, 1.00 mmol), KOAc (400 mg, 4.00 mmol), 2-cyanophenylboronic acid pinacol ester (448 mg, 2.00 mmol) and H_2O (0.50 mL) in DME (50.0 mL) was added $Pd(PPh_3)_4$ (100 mg, 0.87 mmol) under N_2 atmosphere. The reaction mixture was heated at 85 °C overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O was added. The mixture was extracted with AcOEt. The combined organic layer was washed with saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford the desired compound. A solution of this compound (260 mg), $TMSN_3$ (345 mg, 3.00 mmol) and dibutyltin oxide (370 mg, 1.50 mmol) in toluene (50.0 mL) was heated at 120 °C overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O was added. The mixture was extracted with AcOEt. The combined organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC to afford the titled compound (44.6 mg, 10%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.64–7.49 (m, 4H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.18–7.08 (m, 4H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.52 (q, *J* = 7.3 Hz, 1H), 4.65 (s, 2H), 3.39–3.26 (m, 2H), 1.65 (d, *J* = 7.3 Hz, 3H), 1.56–1.39 (m, 2H), 1.27–1.21 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). LC-MS

(ESI) *m/z* = 469 $[M + H]^+$. Purity: 97.0%.

5.1.20. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(methoxymethyl)benzo[*d*]oxazol-2-amine (17)

To a solution of compound **15** (100 mg, 0.249 mmol) in DMF (10 mL) was added NaH (60% in mineral oil, 12.0 mg, 0.299 mmol) at 0 °C. After stirring for 0.5 h, MeI (42.4 mg, 0.299 mmol) was added to the reaction mixture at 0 °C, and the mixture was then stirred for 1 h at the same temperature. To the reaction mixture was added H_2O, followed by extraction with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and dried under reduced pressure. The residue was purified by preparative TLC with 33% AcOEt in petroleum ether to afford the desired compound.

To a solution of this compound (90.0 mg), $K_3PO_4 \cdot 7H_2O$ (219 mg, 0.648 mmol) and 2-cyanophenylboronic acid pinacol ester (59.3 mg, 0.259 mmol) in DME (5.00 mL) was added $Pd(dppf)Cl_2$ (12.7 mg, 0.0173 mmol) under N_2 atmosphere. The reaction mixture was heated to 85 °C and stirred overnight. The resulting mixture was concentrated under reduced pressure, and then H_2O was added. The mixture was extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC with 50% AcOEt in petroleum ether to afford the desired compound. The mixture of this compound, $TMSN_3$ (65.6 mg, 0.570 mmol) and dibutyltin oxide (56.9 mg, 0.228 mmol) in toluene (5 mL) was then heated to 120 °C and stirred overnight before being cooled to room temperature. The resulting mixture was concentrated under pressure and purified by preparative

TLC with 10% MeOH in CH_2Cl_2 to afford the titled compound (14.8 mg, 27%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.63–7.60 (m, 2H), 7.54–7.48 (m, 2H), 7.34–7.32 (m, 3H), 7.15–7.09 (m, 3H), 6.98–6.96 (m, 1H), 5.57 (d, *J* = 6.8 Hz, 1H), 4.60 (s, 2H), 3.39–2.23 (m, 2H), 3.33 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.49–1.42 (m, 2H), 1.25–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 483 $[M + H]^+$. Purity: 99.9%.

5.1.21. (*R*)-2-[2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazol-4-yl]propan-2-ol (18)

To a solution of compound **13** (67.0 mg, 0.139 mmol) in MeOH (3 mL) was added concentrated H_2SO_4 (0.50 mL). The reaction mixture was refluxed and stirred overnight. The resulting mixture was concentrated under reduced pressure and then poured into water, extracted with CH_2Cl_2 and saturated $NaHCO_3$ aq. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by preparative TLC with 10% MeOH in CH_2Cl_2 to the desired compound. To a solution of this compound in THF (10 mL) was added CH3MgBr (1 M in diethyl ether, 0.888 mL, 0.888 mmol), drop-wise, at -30 °C. The solution was then warmed to room temperature. After 0.5 h, the reaction was quenched with saturated NH4Cl aq. at 0 °C. The solution was concentrated, diluted with CH_2Cl_2, washed with brine, dried and concentrated under reduced pressure. The residue was purified by preparative TLC with 10% MeOH in CH_2Cl_2 to afford the titled compound (5.4 mg, 9.8%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.95 (d, *J* = 6.8 Hz, 1H), 7.60–7.56 (m, 1H), 7.52–7.48 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.17–7.13 (m, 3H), 6.96–6.93 (m,

2H), 5.67–5.64 (m, 1H), 4.80 (br s, 1H), 3.92–3.82 (m, 1H), 3.59–3.52 (m, 1H), 1.86–1.77 (m, 5H), 1.57–1.49 (m, 8H), 1.05 (t, *J* = 7.2Hz, 3H). LC-MS (ESI) *m/z* = 497 $[M + H]^+$. Purity: 99.9%.

5.1.22. (*R*)-2*N*-[1-(4-bromophenyl)ethyl]-2*N*-butylbenzo[*d*]oxazole-2,4-diamine (19)

To a mixture of compound **9a** (2.30 g, 5.53 mmol) and Et_3N (838 mg, 8.30 mmol) in DMF (30 mL) was added DPPA (2.28 g, 8.30 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 4 h. To the mixture was added H_2O, followed by stirring for 1 h at 100 °C. The mixture was extracted with AcOEt and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 10% AcOEt in petroleum ether to afford the titled compound (1.60 g, 75%) as a yellow oil. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.55 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 8.0 Hz, *J* = 7.2 Hz,1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 1H), 5.47–5.53 (q, *J* = 7.2 Hz, 1H), 5.00 (br s, 2H), 3.17–3.31 (m, 2H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.52–1.41 (m, 2H), 1.25–1.19 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 388 $[M + H]^+$.

5.1.23. (*R*)-2*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-2*N*-butylbenzo[*d*]oxazole-2,4-diamine (20)

To a solution of compound **19** (200 mg, 0.520 mmol), Cs_2CO_3 (504 mg, 1.56 mmol), 2-(tetrazol-5-yl)phenylboronic acid (118 mg, 0.620 mmol) in DMF (5.0 mL)

and H_2O (0.5 mL) was added $Pd(PPh_3)_4$ (60.0 mg, 0.052 mmol) under N_2 atmosphere. The reaction mixture was heated to 100 °C and stirred for 5 h. To the resulting mixture was added H_2O, and then the mixture was extracted with 10% MeOH in CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (MeOH: CH_2Cl_2 = 1:8) to afford the titled compound (30.2 mg, 13%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.58 (d, *J* = 7.6 Hz, 1H), 7.39–7.52 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.71 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.54 (q, *J* = 7.2 Hz, 1H), 3.21–316 (m, 2H), 1.64 (d, *J* = 7.2 Hz, 3H), 1.48–1.45 (m, 2H), 1.25–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 454 $[M + H]^+$. Purity 97.8%.

5.1.24. (*R*)-*N*-[2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazol-4-yl]acetamide (21)

To a solution of compound **19** (200 mg, 0.520 mmol) in CH_2Cl_2 (5.0 mL) was added Et_3N (62.6 mg, 0.620 mmol) and Ac_2O (63.3 mg, 0.620 mmol). The solution was stirred for 5 h at 0 °C and then concentrated under reduced pressure. The residue was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (AcOEt: petroleum ether = 1:5). The obtained compound was used for the synthesis of the titled compound with a similar manner for compound **20** to afford the titled compound (36.5 mg, 26%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.53 (br s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.2 Hz,

1H), 7.47–7.35 (m, 3H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.16–7.10 (m, 3H), 6.92 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 1H), 5.71 (q, *J* = 7.2 Hz, 1H), 3.22–3.16 (m, 2H), 2.12 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.51–1.45 (m, 2H), 1.27–1.20 (m, 2H), 0.841 (t, *J* = 7.6 Hz, 3H). LC-MS (ESI) *m/z* = 496 $[M + H]^+$. Purity: 99.9%.

5.1.25. (*R*)-3-[2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazol-4-yl]-1,1-dimethylurea (22)

To a solution of compound **19** (300 mg, 0.790 mmol) in CH_2Cl_2 (5.0 mL) was added Et_3N (159 mg, 1.58 mmol) and *N*,*N*-dimethylcarbamoyl chloride (101 mg, 0.950 mmol). The reaction mixture was refluxed overnight, and then H_2O was added. The residue was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (AcOEt: petroleum ether = 1:5). The obtained compound was used for the synthesis of the titled compound in a similar manner to that of compound **20** to afford the titled compound (48.4 mg, 20%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.62 (br s, 1H), 7.57–7.51 (m, 2H), 7.38–7.31 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.12–7.06 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.90 (q, *J* = 7.2Hz, 1H), 3.39–3.38 (m, 2H), 2.96 (s, 6H), 1.66 (d, *J* = 7.2 Hz, 3H), 1.53–1.49 (m, 2H), 1.28–1.23 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). LC-MS (ESI) *m/z* = 525 $[M + H]^+$. Purity: 99.9%.

5.1.26. (*R*)-*N*-[2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)benzo[*d*]oxazol-4-yl]methanesulfonamide (23)

To a solution of compound **22** (200 mg, 0.520 mmol) in CH_2Cl_2 (5.0 mL) was

added Et_3N (104 mg, 1.04 mmol) and methanesulfonyl chloride (70.7 mg, 0.620 mmol). The solution was stirred for 5 h at 0 °C. The residue was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (AcOEt: petroleum ether = 1:5). The obtained compound was used for the synthesis of the titled compound in a similar manner to that of compound **20** to afford the titled compound (35.6 mg, 23%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.49 (br s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.50–7.26 (m, 6H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.93–7.02 (m, 2H), 5.53 (q, *J* = 6.8 Hz, 1H), 3.39–3.26 (m, 2H), 3.19 (s, 3H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.54–1.48 (m, 2H), 1.27–1.21 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 532 $[M + H]^+$. Purity: 94.8%.

5.1.27. (*R*)-2-({1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}(butyl)amino)-*N*-(methylsulfonyl)benzo[*d*]oxazole-4-carboxamide (24)

To a solution of compound **6a** (450 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (204 mg, 1.62 mmol) and a drop of DMF at 0 °C under N_2 atmosphere. The reaction mixture was stirred at same temperature for 5 h and then concentrated under reduced pressure. To a solution of the obtained compound in DMF (5 mL) was added DIPEA (250 mg, 1.94 mmol) and methanesulfonamide (110 mg, 1.16 mmol). The solution was stirred for 5 h at 0 °C and concentrated under reduced pressure. The residue was extracted with AcOEt and H_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC with

20% AcOEt in petroleum ether. The obtained compound was used for the synthesis of the titled compound in a similar manner to that of compound **20** to afford the titled compound (34.3 mg, 10%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.76 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.44–7.31 (m, 6H), 7.22–7.11 (m, 3H), 5.48 (q, *J* = 6.8 Hz, 1H), 3.47 (s, 3H), 3.25–3.22 (m, 2H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.62–1.53 (m, 2H), 1.31–1.26 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 560 $[M + H]^+$. Purity: 92.4%.

5.1.28. 4-bromobenzo[*d*]oxazole-2-thiol (26)

The titled compound (2.04 g, 83%, white solid) was synthesized from 2-amino-3-bromophenol (**25**) (2.00 g, 10.6 mmol) by a process analogous to the preparation of **5a** with MeOH as a solvent instead of pyridine. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.93 (br s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 8.8, 7.8 Hz, 1H). LC-MS (ESI) *m/z* = 228 $[M - H]^-$.

5.1.29. (*R*)-4'-[1-(butylamino)ethyl]-[1,1'-biphenyl]-2-carbonitrile (27)

The titled compound (2.11 g, 59%, yellow oil) was synthesized from compound **7** (3.30 g, 12.9 mmol) by a process analogous to the preparation of **11a** (reagent and condition (g) in Scheme 1). The crude material was purified by silica gel column chromatography eluted with 10% MeOH in $CHCl_3$ to afford the titled compound. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 7.8 Hz, 1H), 7.65–7.60 (m, 1H), 7.56–7.50 (m, 3H), 7.46–7.39 (m, 3H), 5.83 (q, *J* = 6.8 Hz, 1H), 2.58–2.43 (m, 2H), 1.51–1.43 (m, 2H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.38–1.30 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 279 $[M + H]^+$.

5.1.30. (*R*)-4'-{1-[(4-bromobenzo[*d*]oxazol-2-yl)(butyl)amino]ethyl}-[1,1'-biphenyl]-2-carbonitrile (28)

The titled compound was synthesized from amine **27** (2.11 g, 7.58 mmol) and compound **26** (2.02 g, 8.69 mmol) by a process analogous to the preparation of **8a**. The crude material was purified by silica gel column chromatography with 20%–50% AcOEt in heptane to afford the titled compound (744 mg, 21%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.8 Hz, 1H), 7.66–7.62 (m, 1H), 7.56–7.41 (m, 6H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.26–7.19 (m, 1H), 6.88 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.87 (q, *J* = 7.4 Hz, 1H), 3.45–3.36 (m, 1H), 3.27–3.19 (m, 1H), 1.75 (d, *J* = 7.4 Hz, 3H), 1.63–1.49 (m, 2H), 1.34–1.22 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 474 $[M + H]^+$.

5.1.31. (*R*)-4'-(1-{butyl[4-(pyridin-4-yl)benzo[*d*]oxazol-2-yl]amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29a)

To a solution of compound **28** (147 mg, 0.310 mmol) in DMF (4.5 mL) was added H_2O (0.5 mL), Cs_2CO_3 (303 mg, 0.930 mmol), pyridin-4-ylboronic acid (76.0 mg, 0.620 mmol) and $Pd(PPh_3)_4$ (36.0 mg, 0.031 mmol). The flask was evacuated and backfilled with argon. The mixture was stirred at 100 °C for 16 h. After cooling to room temperature, saturated NH_4Cl aq. was added. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$, filtered through a celite bed and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluted with 10%–33% AcOEt in heptane to afford the titled compound (90.0 mg, 62%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.68–

8.66 (m, 2H), 8.07–8.04 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.69–7.62 (m, 2H), 7.58–7.38 (m, 6H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.13–7.09 (m, 1H), 5.81 (q, *J* = 7.5 Hz, 1H), 3.50–3.40 (m, 1H), 3.34–3.25 (m, 1H), 1.78 (d, *J* = 7.5 Hz, 3H), 1.70–1.57 (m, 2H), 1.36–1.24 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 473 $[M + H]^+$.

5.1.32. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(pyridin-4-yl)benzo[*d*]oxazol-2-amine (30a)

A solution of compound **29a** (86.0 mg, 0.182 mmol), $TMSN_3$ (126 mg, 1.09 mmol) and dibutyltin oxide (45.0 mg, 0.182 mmol) in toluene (5.0 mL) was heated at 120 °C overnight. To the resulting mixture was added $TMSN_3$ (126 mg, 1.09 mmol) and dibutyltin oxide (45.0 mg, 0.182 mmol). After stirring for 24 h, MeOH was added to the mixture and concentrated under reduced pressure. The residue was purified by preparative HPLC to afford the titled compound (59.0 mg, 63%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.47 (d, *J* = 6.8 Hz, 2H), 8.28 (d, *J* = 6.8 Hz, 2H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.58–7.54 (m, 1H), 7.51–7.46 (m, 2H), 7.43 (d, *J* = 6.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.12–7.08 (m, 1H), 5.60 (q, *J* = 6.8 Hz, 1H), 3.50–3.40 (m, 1H), 3.33–3.24 (m, 1H), 1.70 (d, *J* = 6.8 Hz, 3H), 1.66–1.56 (m, 2H), 1.38–1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 516 $[M + H]^+$. Purity: 99.2%.

5.1.33. (*R*)-4'-(1-{butyl[4-(pyridin-3-yl)benzo[*d*]oxazol-2-yl]amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29b)

The titled compound (120 mg, 82%) was synthesized from compound **28** (147

mg, 0.310 mmol) by a process analogous to the preparation of **29a**. The crude material was purified by silica gel column chromatography eluted with 10%–33% AcOEt in heptane. While the obtained compound included impurities, it was used for the next step without further purification. LC-MS (ESI) *m/z* = 473 $[M + H]^+$.

5.1.34. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(pyridin-3-yl)benzo[*d*]oxazol-2-amine (30b)

The titled compound was synthesized from compound **29b** (118 mg, 0.250 mmol) by a process analogous to the preparation of **30a**. The crude material was purified by silica gel column chromatography eluted with 0%–10% MeOH in $CHCl_3$ to afford the titled compound (120 mg, 93%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.96 (s, 1H), 8.42 (d, *J* = 4.9 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.58–7.54 (m, 1H), 7.51–7.47 (m, 2H), 7.41 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.33–7.29 (m, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.13–7.08 (m, 3H), 5.22 (q, *J* = 6.9 Hz, 1H), 3.70–3.61 (m, 1H), 3.51–3.42 (m, 1H), 1.81–1.66 (m, 2H), 1.70 (d, *J* = 6.9 Hz, 3H), 1.47–1.38 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 3H). LC-MS (ESI) *m/z* = 516 $[M + H]^+$. Purity: 99.2%.

5.1.35. (*R*)-4'-(1-{butyl[4-(pyridin-2-yl)benzo[*d*]oxazol-2-yl]amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29c)

To a solution of compound **28** (126 mg, 0.266 mmol) in toluene (10 mL) was added 2-(tributylstannyl)pyridine (0.255 mL, 0.797 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.027 mmol). The flask was evacuated and backfilled with argon. The mixture was stirred at reflux for 24 h. After cooling to room temperature, saturated NaH_4Cl

was added. The mixture was extracted with AcOEt, dried over $MgSO_4$, filtered through and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluted with 20%–33% AcOEt in heptane to afford the titled compound (160 mg, quant.). While the obtained compound included impurities, it was used for the next step without further purification. LC-MS (ESI) *m/z* = 473 $[M + H]^+$.

5.1.36. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(pyridin-2-yl)benzo[*d*]oxazol-2-amine (30c)

The titled compound was synthesized from compound **29c** (160 mg, 0.339 mmol) by a process analogous to the preparation of **29a**. The crude material was purified by silica gel column chromatography eluted with 0%–10% MeOH-$CHCl_3$ to afford the titled compound (96.0 mg, 55%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, *J* = 8.2 Hz, 1H), 8.50 (m, 1H), 7.87–7.81 (m, 1H), 7.79–7.76 (m, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.36–7.32 (m, 2H), 7.23–7.19 (m, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.02–6.96 (m, 1H), 6.86–6.80 (m, 3H), 5.53 (q, *J* = 7.2 Hz, 1H), 3.46–3.37 (m, 1H), 3.25–3.17 (m, 1H), 1.67–1.54 (m, 2H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.36–1.23 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 516 $[M + H]^+$. Purity: 97.2%.

5.1.37. (*R*)-4'-(1-{butyl[4-(1-methyl-1*H*-pyrrol-2-yl)benzo[*d*]oxazol-2-yl]amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29d)

The titled compound was synthesized from compound **28** (200 mg, 0.422 mmol) and 1-methyl-2-(tributylstannyl)pyrrole (0.348 mL, 1.05 mmol) by a process

analogous to the preparation of **29c**. The crude material was purified by silica gel column chromatography eluted with 10%–15% AcOEt in heptane to afford the titled compound (170 mg, 85%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.8 Hz, 1H), 7.66–7.62 (m, 1H), 7.54–7.42 (m, 6H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.04–7.00 (m, 1H), 6.76–6.74 (m, 1H), 6.38–6.35 (m, 1H), 6.25–6.22 (m, 1H), 5.77 (q, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 3.44–3.35 (m, 1H), 3.27–3.18 (m, 1H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.63–1.51 (m, 2H), 1.33–1.23 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 475 $[M + H]^+$.

5.1.38. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(1-methyl-1*H*-pyrrol-2-yl)benzo[*d*]oxazol-2-amine (30d)

The titled compound was synthesized from compound **29d** (165 mg, 0.348 mmol) by a process analogous to the preparation of **30a**. The crude material was purified by silica gel column chromatography eluted with 10%–20% MeOH in $CHCl_3$ to afford the titled compound (121 mg, 67%) as a green solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.17 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.59–7.50 (m, 2H), 7.40 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.29–7.25 (m, 1H), 7.19–7.16 (m, 3H), 7.05 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.76–6.74 (m, 1H), 6.31 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.20 (dd, *J* = 3.5, 2.5 Hz, 1H), 5.50 (q, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.55–3.47 (m, 1H), 3.43–3.34 (m, 1H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.74–1.63 (m, 2H), 1.43–1.33 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). LC-MS (ESI) *m/z* = 518 $[M + H]^+$. Purity: 99.2%.

5.1.39. (*R*)-4'-(1-{butyl[4-(1-methyl-1*H*-imidazol-2-yl)benzo[*d*]oxazol-2-yl]amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29e)

The titled compound was synthesized from compound **28** (200 mg, 0.422 mmol) and 1-methyl-2-(tributylstannyl)imidazole (0.337 mL, 1.05 mmol) by a process analogous to the preparation of **29c**. The crude material was purified by silica gel column chromatography eluted with 5%-10% MeOH in $CHCl_3$ to afford the titled compound (41.0 mg, 20%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, *J* = 7.7 Hz, 1H), 7.67–7.61 (m, 1H), 7.56–7.41 (m, 7H), 7.34 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.17 (d, *J* = 1.1 Hz, 1H), 7.12–7.06 (m, 1H), 7.00 (d, *J* = 1.1 Hz, 1H), 5.71 (q, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 3.48–3.35 (m, 1H), 3.32–3.20 (m, 1H), 1.73 (d, *J* = 7.0 Hz, 3H), 1.64–1.51 (m, 2H), 1.35–1.22 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H). LC-MS (ESI) *m/z* = 476 $[M + H]^+$.

5.1.40. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(1-methyl-1*H*-imidazol-2-yl)benzo[*d*]oxazol-2-amine (30e)

The titled compound was synthesized from compound **29e** (41.1 mg, 0.0865 mmol) by a process analogous to the preparation of **30c**. The crude material was purified by preparative TLC with 10% MeOH in $CHCl_3$ to afford the titled compound (13.1 mg, 29%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 7.0 Hz, 1H), 7.54–7.34 (m, 6H), 7.25–7.22 (m, 1H), 7.15–7.04 (m, 5H), 5.43 (q, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.60–3.46 (m, 1H), 3.42–3.28 (m, 1H), 1.73–1.59 (m, 2H), 1.68 (d, *J* = 7.0 Hz, 3H), 1.43–1.28 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 519 $[M + H]^+$. Purity: 98.1%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 519.2621; found, 519.2625.

5.1.41. (*R*)-4'-(1-{[4-(1*H*-pyrazol-1-yl)benzo[*d*]oxazol-2-

yl](butyl)amino}ethyl)-[1,1'-biphenyl]-2-carbonitrile (29f)

Compound **28** (180 mg, 0.379 mmol) was dissolved in DMF (3 mL). To this solution was added Cs_2CO_3 (371 mg, 1.14 mmol), pyrazole (77.0 g, 1.14 mmol) and copper(I) iodide (36.0 mg, 0.190 mmol). The flask was evacuated and backfilled with argon. The mixture was stirred at 130 °C for 18 h. After cooling to room temperature, saturated NH_4Cl aq. was added. The mixture was extracted with AcOEt, dried over $MgSO_4$, filtered through celite bed, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluted with 10%–20% AcOEt in heptane to afford the titled compound (43.5 mg, 25%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.10 (d, *J* = 1.1 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.76 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.72 (d, *J* = 1.1 Hz, 1H), 7.67–7.61 (m, 1H), 7.58–7.48 (m, 5H), 7.46–7.41 (m, 1H), 7.18 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.09 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.48–6.46 (m, 1H), 5.80 (q, *J* = 7.0 Hz, 1H), 3.51–3.38 (m, 1H), 3.36–3.21 (m, 1H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.68–1.56 (m, 2H), 1.38–1.23 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 462 $[M + H]^+$.

5.1.42. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butyl-4-(1*H*-pyrazol-1-yl)benzo[*d*]oxazol-2-amine (30f)

The titled compound was synthesized from compound **29f** (43.0 mg, 0.093 mmol) by a process analogous to the preparation of **30a**. The crude material was purified by preparative TLC with 10% MeOH in $CHCl_3$ to afford the titled compound (42.1 mg, 90%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.89 (m, *J* = 2.9 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.56–7.47 (m,

2H), 7.34–7.31 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.11–7.00 (m, 3H), 6.47–6.46 (m, 1H), 5.62 (q, *J* = 7.0 Hz, 1H), 3.48–3.40 (m, 1H), 3.30–3.21 (m, 1H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.68–1.59 (m, 2H), 1.39–1.25 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). LC-MS (ESI) *m/z* = 505 $[M + H]^+$. Purity: 95.2%.

5.1.43. (*R*)-*N*-butyl-*N*-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}benzo[*d*]oxazol-2-amine (32)

To a solution of compound **31** (5.90 g, 15.9 mmol), KOAc (6.20 g, 63.6 mmol) and bis(pinacolato)diboron (8.10 g, 31.8 mmol) in DME (100 mL) was added $Pd(PPh_3)_4$ (200 mg, 0.173 mmol) under N_2 atmosphere. The reaction mixture was refluxed overnight. The resulting mixture was concentrated under reduced pressure, and then saturated $NaHCO_3$ aq. was added. The mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluted with 5% AcOEt in petroleum ether to afford the target compound (6.30 g, 95%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.28–7.24 (m, 1H), 7.15–7.11 (m, 1H), 5.69 (q, *J* = 7.2 Hz, 1H), 3.43–3.33 (m, 1H), 3.28–3.20 (m, 1H), 1.74 (d, *J* = 7.2 Hz, 3H), 1.59–1.38 (m, 2H), 1.36–1.18 (m, 14H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 421 $[M + H]^+$.

5.1.44. (*R*)-*N*-butyl-*N*-{1-[5'-chloro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33j)

To a solution of compound **32** (350 mg, 0.833 mmol), 2-bromo-4-

chlorobenzonitrile (269 mg, 1.25 mmol) and $K_3PO_4 \cdot 7H_2O$ (1.13 g, 3.33 mmol) in DME (30.0 mL) was added $Pd(PPh_3)_4$ (40.0 mg, 0.035 mmol) under N_2 atmosphere. The reaction mixture was refluxed for 5 h. The resulting mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC. The obtained compound was dissolved in toluene (30 mL). To this solution was added $TMSN_3$ (195 mg, 1.69 mmol) and dibutyltin oxide (211 mg, 0.846 mmol). The mixture was heated at 120 °C overnight under N_2. The resulting mixture was concentrated under reduced pressure and extracted with $CHCl_3$ and H_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified preparative TLC and preparative HPLC to afford the titled compound (39.2 mg, 10%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.65 (d, *J* = 8.4 Hz, 1H), 7.56–7.54 (m, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32–7.28 (m, 3H), 7.15–7.11 (m, 3H), 7.01–6.97 (m, 1H), 5.53 (q, *J* = 7.2 Hz, 1H), 3.45–3.23 (m, 2H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.50–1.45 (m, 2H), 1.26–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 473 $[M + H]^+$. Purity: 99.4%.

5.1.45. (*R*)-*N*-butyl-*N*-{1-[3'-fluoro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33a)

The titled compound (6.3 mg, 6.7%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.59–7.52 (m, 1H), 7.27–7.22 (m, 3H), 7.15–7.08 (m, 4H), 7.03–6.99 (m, 3H), 5.46 (q, *J* = 6.8 Hz, 1H), 3.27–3.05 (m, 2H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.49–1.44 (m, 2H), 1.22–1.17 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 457 $[M + H]^+$. Purity:

99.9%.

5.1.46. (*R*)-*N*-butyl-*N*-{1-[3'-chloro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33b)

The titled compound (52.7 mg, 37%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.65–7.59 (m, 2H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.30–7.25 (m, 3H), 7.15–7.06 (m, 3H), 7.01–6.97 (m, 1H), 5.48 (q, *J* = 6.8 Hz, 1H), 3.29–3.18 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.45–1.33 (m, 2H), 1.21–1.16 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 473 $[M + H]^+$. Purity: 99.9%.

5.1.47. (*R*)-*N*-butyl-*N*-{1-[4'-fluoro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33c)

The titled compound (8.8 mg, 6.8%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.62–7.58 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.30–7.22 (m, 5H), 7.15–7.11 (m, 3H), 7.01–6.99 (m, 1H), 5.53 (q, *J* = 7.1 Hz, 1H), 3.37–3.23 (m, 2H), 1.64 (d, *J* = 7.1 Hz, 3H), 1.49–1.48 (m, 2H), 1.26–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H).
LC-MS (ESI) *m/z* = 467 $[M + H]^+$. Purity: 99.9%.

5.1.48. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butylbenzo[*d*]oxazol-2-amine (33d)

The titled compound (8.8 mg, 8.3%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.84 (s, 1H),

7.79 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.30–7.25 (m, 4H), 7.16–7.12 (m, 3H), 7.03–6.99 (m, 1H), 5.57 (q, *J* = 7.2 Hz, 1H), 3.30–3.18 (m, 2H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.54–1.44 (m, 2H), 1.28–1.22 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 507 $[M + H]^+$. Purity: 97.9%.

5.1.49. (*R*)-*N*-butyl-*N*-{1-[4'-chloro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33e)

The titled compound (8.6 mg, 7.1%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 6.4 Hz, 1H), 7.68–7.65 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33–7.28 (m, 3H), 7.15–7.08 (m, 3H), 7.01–6.99 (m, 1H), 5.54 (q, *J* = 7.2 Hz, 1H), 3.29–3.11 (m, 2H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.50–1.39 (m, 2H), 1.26–1.19 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 473 $[M + H]^+$. Purity: 97.5%.

5.1.50. (*R*)-*N*-butyl-*N*-{1-[4'-methyl-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33f)

The titled compound (11.6 mg, 4.5%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.43–7.38 (m, 3H), 7.33–7.26 (m, 4H), 7.17–7.15 (m, 1H), 7.11–7.08 (m, 2H), 7.05–7.02 (m, 1H), 5.57 (q, *J* = 6.4 Hz, 1H), 3.30–3.22 (m, 2H), 2.43 (s, 3H), 1.69 (d, *J* = 6.4 Hz, 3H), 1.54–1.44 (m, 2H), 1.29–1.22 (m, 2H), 0.90–0.85 (m, 3H). LC-MS (ESI) *m/z* = 453 $[M + H]^+$, Purity: 99.4%.

5.1.51. (*R*)-*N*-butyl-*N*-[1-{4'-methoxy-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl}ethyl]benzo[*d*]oxazol-2-amine (33g)

The titled compound (74.0 mg, 28%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.41 (d, *J* = 8.0 Hz, 1H), 7.30–7.26 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.15–7.10 (m, 2H), 7.06–6.96 (m, 4H), 5.53–5.48 (q, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.34–3.21 (m, 2H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.58–1.47 (m, 2H), 1.25–1.20 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 469 $[M + H]^+$. Purity: 98.1%.

5.1.52. (*R*)-*N*-butyl-*N*-{1-[5'-fluoro-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33h)

The titled compound (7.5 mg, 6.6%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.62–7.60 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.33–7.25 (m, 5H), 7.15–7.11 (m, 3H), 7.01–6.97 (m, 1H), 5.52 (q, *J* = 7.2 Hz, 1H), 3.25–3.17 (m, 2H), 1.65 (d, *J* = 7.2 Hz, 3H), 1.50–1.45 (m, 2H), 1.26–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 457 $[M + H]^+$. Purity: 95.1%.

5.1.53. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butylbenzo[*d*]oxazol-2-amine (33i)

The titled compound (28.0 mg, 19%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.90–7.85 (m, 2H), 7.71 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.34–7.28 (m, 3H), 7.18–7.11 (m, 4H), 6.99–6.97 (m, 1H), 5.55 (q, *J* = 7.2 Hz, 1H), 3.37–3.21 (m, 2H), 1.65 (d, *J* =

7.2 Hz, 3H), 1.52–1.43 (m, 2H), 1.26–1.20 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 507[M + H]$^+$. Purity: 99.8%.

5.1.54. (*R*)-*N*-butyl-*N*-{1-[5'-methyl-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33k)

The titled compound (12.4 mg, 14%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, CD_3OD) δ: 7.48 (d, *J* = 8.4 Hz, 1H), 7.32–7.26 (m, 6H), 7.18–7.11 (m, 3H), 7.03–7.01 (m, 1H), 5.57 (q, *J* = 7.2 Hz, 1H), 3.33–3.23 (m, 2H), 2.44 (s, 3H), 1.67 (d, *J* = 7.2 Hz, 3H), 1.55–1.40 (m, 2H), 1.29–1.23 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 453 [M + H]$^+$. Purity: 99.0%.

5.1.55. (*R*)-*N*-butyl-*N*-{1-[5'-methoxy-2'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33l)

The titled compound (16.0 mg, 12%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.44–7.41 (m, 2H), 7.32–7.21 (m, 5H), 7.12 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.02–6.91 (m, 3H), 5.59 (q, *J* = 7.2 Hz, 1H), 3.35–3.23 (m, 2H), 1.98 (s, 3H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.46–1.44 (m, 2H), 1.20–1.12 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 469 [M + H]$^+$. Purity: 91.9%.

5.1.56. (*R*)-*N*-butyl-*N*-{1-[2'-fluoro-6'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33m)

The titled compound (13.8 mg, 15%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.53–7.46 (m, 2H), 7.42–7.29 (m, 5H), 7.15–7.10 (m, 3H), 6.99–6.97 (m, 1H), 5.56 (q, *J* = 6.8 Hz, 1H), 3.35–3.21 (m, 2H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.50–1.33 (m, 2H), 1.23–1.14 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 457 $[M + H]^+$. Purity: 99.7%.

5.1.57. (*R*)-*N*-{1-[2'-(1*H*-tetrazol-5-yl)-6'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]ethyl}-*N*-butylbenzo[*d*]oxazol-2-amine (33n)

The titled compound (33.4 mg, 22%, white solid) was synthesized by a process analogous to the preparation of **33j**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.97–7.93 (m, 2H), 7.75–7.71 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34–7.28 (m, 3H), 7.16–7.08 (m, 3H), 7.00–6.98 (m, 1H), 5.59 (q, *J* = 6.8 Hz, 1H), 3.22–3.17 (m, 2H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.53–1.42 (m, 2H), 1.17–1.11 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 507 $[M + H]^+$. Purity: 99.9%.

5.1.58 (*R*)-*N*-butyl-*N*-{1-[2'-methyl-6'-(1*H*-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]ethyl}benzo[*d*]oxazol-2-amine (33o)

The titled compound (27.0 mg, 23%, white solid) was synthesized by a process analogous to the preparation of **36o**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.63 (d, *J* = 2.4 Hz, 1H), 7.53–7.50 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.27–7.24 (m, 3H), 7.12–7.06 (m, 3H), 6.96–6.94 (m, 1H), 5.50 (q, *J* = 6.8 Hz, 1H), 3.39–3.28 (m, 2H), 2.50 (s, 3H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.46–1.43 (m, 2H), 1.22–1.17 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 453 $[M + H]^+$. Purity: 97.0%.

5.1.59. (*R*)-1-(4-bromophenyl)-*N*-(cyclopropylmethyl)ethan-1-amine (34)

(*R*)-1-(4-bromophenyl)ethan-1-amine (**6**) (10.0 g, 50.0 mmol) was dissolved in MeOH (250 mL). To this solution was added cyclopropanecarboxaldehyde (4.86 mL, 65.0 mmol). After stirring for 16 h at room temperature, $NaBH_4$ (2.46 g, 65.0 mmol) was slowly added at 0 °C. After stirring for 4 h at room temperature, 5% NaOH was added at the same temperature. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the titled compound (12.8 g, quant.) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.46–7.42 (m, 2H), 7.21–7.19 (m, 2H), 3.77 (q, *J* = 6.7 Hz, 1H), 2.35 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.23 (dd, *J* = 12.0, 7.0 Hz, 1H), 1.34 (d, *J* = 6.7 Hz, 3H), 0.96–0.88 (m, 1H), 0.48–0.42 (m, 2H), 0.09–-0.02 (m, 2H). LC-MS (ESI) *m/z* = 254 $[M + H]^+$.

5.1.60. methyl (*R*)-2-{[1-(4-bromophenyl)ethyl](cyclopropylmethyl)amino}benzo[*d*]oxazole-4-carboxylate (35)

To a solution of compound **5a** (9.50 g, 45.4 mmol) in $SOCl_2$ (49.7 mL, 681 mmol) was added DMF (0.176 mL, 2.27 mmol) at room temperature. The reaction mixture was heated at reflux for 4 h and then cooled to room temperature. After the reaction mixture had been concentrated under reduced pressure, the residue was dissolved in DMF (152 mL). To this solution was added compound **34** (7.75 g, 30.5 mmol) and DIPEA (32.0 mL, 183 mmol). The reaction mixture was heated at 60 °C for 60 h and then cooled to room temperature. To the resulting mixture

was added saturated NH_4Cl aq., and the mixture was then extracted with AcOEt. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography with 15%–20% AcOEt in heptane to afford the titled compound (10.4 g, 80% from compound **34**) as a brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.82 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.03 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 3.97 (s, 3H), 3.32 (dd, *J* = 15.0, 7.0 Hz, 1H), 3.17 (dd, *J* = 15.0, 6.8 Hz, 1H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.03–0.95 (m, 1H), 0.51–0.40 (m, 2H), 0.28–0.22 (m, 1H), 0.18–0.12 (m, 1H). LC-MS (ESI) *m/z* = 429 $[M + H]^+$.

5.1.61. methyl (*R*)-2-{[1-(2'-cyano-5'-methyl-[1,1'-biphenyl]-4-yl)ethyl](cyclopropylmethyl)amino}benzo[d]oxazole-4-carboxylate (36a)

A solution of compound **35** (5.54 g, 12.9 mmol) dissolved in 1,4-dioxane (129 mL) was added $Pd(dppf)Cl_2$ (1.89 g, 2.58 mmol), bis(pinacolato)diboron (8.19 g, 32.3 mmol) and KOAc (6.33 g, 64.5 mmol) under argon atmosphere. The reaction mixture was heated at 100 °C for 4 h. The resulting mixture was concentrated under reduced pressure, and then saturated NH_4Cl aq. was added. The mixture was filtered through a celite pad and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. A solution of this crude material was dissolved in 1,4-dioxane (129 mL) and H_2O (13 mL). To this solution was added 2-bromo-4-methylbenzonitrile (7.59 g, 38.7 mmol), $Pd(PPh_3)_4$ (1.49 g, 1.29 mmol) and Cs_2CO_3 (16.8 g, 51.6 mmol). The reaction mixture was heated at 100 °C for 5 h,

and the resulting mixture was filtered through a celite pad and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 33%–55% AcOEt in heptane to afford the titled compound (5.12 g, 85%) as a white amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.54–7.52 (m, 4H), 7.41 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.30 (d, *J* = 0.9 Hz, 1H), 7.24 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.03 (dd, *J* = 8.2, 7.9 Hz, 1H), 5.90 (q, *J* = 7.1 Hz, 1H), 3.98 (s, 3H), 3.36 (dd, *J* = 14.7, 7.0 Hz, 1H), 3.27 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.45 (s, 3H), 1.81 (d, *J* = 7.1 Hz, 3H), 1.09–1.01 (m, 1H), 0.53–0.41 (m, 2H), 0.32–0.23 (m, 1H), 0.21–0.13 (m, 1H). LC-MS (ESI) *m/z* = 466 $[M + H]^+$.

5.1.62. methyl (*R*)-2-((cyclopropylmethyl){1-[5'-methyl-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylate (37a)

To a stirred solution of $NH_2OH \cdot HCl$ (6.96 g, 100 mmol) in DMSO (37 mL) was added $NaHCO_3$ (11.2 g, 134 mmol). The reaction mixture was stirred for 1 h at 50 °C. To the reaction mixture was added compound **36a** (3.11 g, 6.68 mmol) dissolved in DMSO (30 mL), following by stirring for 42 h at 80 °C. The mixture was cooled to room temperature, and then H_2O was added. The precipitate was collected by filtration, dried and purified by silica gel column chromatography with 5%–7% MeOH in $CHCl_3$. The obtained compound (1.61 g) was dissolved in THF (32 mL).

To this solution, CDI (1.57 g, 9.69 mmol) was added slowly at 0 °C. After

stirring for 3.5 h at 75 °C, 1 M HCl was added. The resulting mixture was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 1%–3% MeOH in $CHCl_3$ to afford the titled compound (1.38 g, 40%) as a white amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.38 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.30–7.25 (m, 3H), 7.19 (s, 1H), 7.01 (dd, *J* = 8.1, 8.1 Hz, 1H), 5.80 (q, *J* = 7.0 Hz, 1H), 3.92 (s, 3H), 3.33 (dd, *J* = 14.8, 7.0 Hz, 1H), 3.21 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.43 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.10–0.94 (m, 1H), 0.54–0.41 (m, 2H), 0.33–0.10 (m, 2H). LC-MS (ESI) *m/z* = 525 $[M + H]^+$.

5.1.63. (*R*)-2-((cyclopropylmethyl){1-[5'-methyl-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylic acid (38a)

Compound **37a** (2.05 g, 3.91 mmol) was dissolved in EtOH (30 mL). To this solution was added 3 M NaOH (7.82 mL, 19.5 mmol). After stirring for 1 h at 60 °C, the mixture was cooled to 0 °C and then 1 M HCl (120 mL) was added. After stirring for 10 minutes, the precipitate was collected by filtration, washed by H_2O and dried to afford the titled compound (1.61 g, 81%) as as a white amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.36 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.64 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.57–7.49 (m, 3H), 7.40–7.30 (m, 4H), 7.09 (dd, *J* = 7.9, 7.9 Hz, 1H), 5.71 (q, *J* = 7.0 Hz, 1H), 3.37 (dd, *J* = 14.8, 6.8 Hz, 1H), 3.26 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.42 (s, 3H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.03–

0.91 (m, 1H), 0.47–0.35 (m, 2H), 0.35–0.24 (m, 1H), 0.14–0.04 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.7, 162.5, 159.3, 157.4, 148.0, 143.0, 142.8, 140.5, 139.8, 138.7, 131.8, 129.6, 129.2(2C), 129.1, 127.7(2C), 125.8, 120.7, 118.8, 116.2, 113.1, 56.7, 50.8, 21.5, 17.1, 10.7, 4.7, 4.5. LC-MS (ESI) *m/z* = 511 $[M + H]^+$, Purity: 99.9%. $[\alpha]^{25}_D$ = 132.7 (*c* 0.77, $CHCl_3$). HR-LC-MS (ESI) $[M + H]^+$ calcd, 511.1982; found, 511.1971.

5.1.64. methyl (*R*)-2-{[1-(2'-cyano-5'-fluoro-[1,1'-biphenyl]-4-yl)ethyl](cyclopropylmethyl)amino}benzo[d]oxazole-4-carboxylate (36b)

The titled compound (280 mg, 85% from compound **35**, yellow oil) was synthesized by a process analogous to the preparation of **36a**. LC-MS (ESI) *m/z* = 470 $[M + H]^+$.

5.1.65. methyl (*R*)-2-((cyclopropylmethyl){1-[5'-fluoro-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylate (37b)

The titled compound (100 mg, 38% from compound **36b**, yellow oil) was synthesized by a process analogous to the preparation of **37a**. LC-MS (ESI) *m/z* = 529 $[M + H]^+$.

5.1.66. (*R*)-2-((cyclopropylmethyl){1-[5'-fluoro-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylic acid (38b)

The titled compound (29.0 mg, 30% from compound **37b**, white amorphous solid) was synthesized from a process analogous to the preparation of **38a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.46 (br s, 1H), 7.68–7.60 (m, 3H), 7.44–7.46 (m, 2H), 7.24–7.35 (m, 4H), 7.06 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 5.67 (q, *J* = 6.8 Hz, 1H), 3.39–3.23 (m, 2H), 1.74 (d, *J* = 6.8 Hz, 3H), 1.02–0.99 (m, 1H), 0.44–0.38 (m, 2H), 0.30–0.28 (m, 1H), 0.14–0.12 (m, 1H). LC-MS (ESI) *m/z* = 515 $[M + H]^+$. Purity: 90.2%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 515.1731; found, 515.1740.

5.1.67. methyl (*R*)-2-{[1-(5'-chloro-2'-cyano-[1,1'-biphenyl]-4-yl)ethyl](cyclopropylmethyl)amino}benzo[d]oxazole-4-carboxylate (36c)

The titled compound (400 mg, 65% from compound **35**, yellow oil) was synthesized by a process analogous to the preparation of **36a**. LC-MS (ESI) *m/z* = 486 $[M + H]^+$.

5.1.68. methyl (*R*)-2-((cyclopropylmethyl){1-[5'-chloro -2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylate (37c)

The titled compound (275 mg, 43% from compound **36c**, yellow amorphous solid) was synthesized by a process analogous to the preparation of **37a**. LC-MS (ESI) *m/z* = 545 $[M + H]^+$.

5.1.69. (*R*)-2-({1-[5'-chloro-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}(cyclopropylmethyl)amino)benzo[*d*]oxazole-4-carboxylic acid (38c)

The titled compound (25.7 mg, 10% from compound **37c**, white amorphous solid) was synthesized by a process analogous to the preparation of **38a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.46 (br s, 1H), 7.68–7.56 (m, 5H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 5.69 (q, *J* = 7.2 Hz, 1H), 3.28–3.22 (m, 2H), 1.74 (d, *J* = 7.2 Hz, 3H), 0.97–0.95 (m, 1H), 0.43–0.36 (m, 2H), 0.32–0.27 (m, 1H), 0.11–0.07 (m, 1H). LC-MS (ESI) *m/z* = 531 $[M + H]^+$. Purity: 99.9%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 531.1435; found, 531.1437.

5.1.70. methyl (*R*)-2-{[1-(2'-cyano-[1,1'-biphenyl]-4-yl)ethyl](cyclopropylmethyl)amino}benzo[d]oxazole-4-carboxylate (36d)

The titled compound (1.00 g, 81% from compound **35**, yellow oil) was synthesized by a process analogous to the preparation of **12**. LC-MS (ESI) *m/z* = 452 $[M + H]^+$.

5.1.71. methyl (*R*)-2-((cyclopropylmethyl){1-[2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}amino)benzo[*d*]oxazole-4-carboxylate (37d)

The titled compound (100 mg, 45% from compound **36d**, white amorphous solid) was synthesized by a process analogous to the preparation of **37a**. LC-MS (ESI) *m/z* = 511 $[M + H]^+$.

5.1.72. (*R*)-2-((cyclopropylmethyl){1-[2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)ethyl)amino)benzo[*d*]oxazole-4-carboxylic acid (38d)

The titled compound (60.0 mg, 62% from compound **37d**, white amorphous solid) was synthesized by a process analogous to the preparation of **38a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.42 (br s, 1H) 7.69–7.63 (m, 4H), 7.57–7.50 (m, 4H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 5.70 (q, *J* = 6.8 Hz, 1H), 3.39–3.23 (m, 2H), 1.74 (d, *J* = 6.8 Hz, 3H), 0.98–0.95 (m, 1H), 0.43–0.36 (m, 2H), 0.31–0.27 (m, 1H), 0.11–0.07 (m, 1H). LC-MS (ESI) *m/z* = 497 $[M + H]^+$. Purity: 99.5%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 497.1825; found, 497.1831.

5.1.73. methyl (*R*)-2-{[1-(5'-fluoro-2'-cyano-[1,1'-biphenyl]-4-yl)ethyl] butylamino}benzo[d]oxazole-4-carboxylate (39a)

The titled compound (270 mg, 82% from compound **8a**, white solid) was synthesized by a process analogous to the preparation of **36a**. LC-MS (ESI) *m/z* = 472 $[M + H]^+$.

5.1.74. methyl (*R*)-2-butyl-{1-[5'-fluoro -2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}aminobenzo[*d*]oxazole-4-carboxylate (40a)

The titled compound (90 mg, 29% from compound **39a**, white amorphous solid) was synthesized by a process analogous to the preparation of **36a**. LC-MS (ESI) *m/z* = 531 $[M + H]^+$.

5.1.75. (*R*)-2-butyl-{1-[5'-fluoro-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}aminobenzo[*d*]oxazole-4-carboxylic acid (41a)

The titled compound (50.1 mg, 58% from compound **40a**, white amorphous solid)

was synthesized by a process analogous to the preparation of **38a**. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.42 (br s, 1H), 7.73–7.63 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.43–7.35 (m, 4H), 7.07 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 5.68 (q, *J* = 6.8 Hz, 1H), 3.45–3.39 (m, 2H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.57–1.42 (m, 2H), 1.29–1.20 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI) *m/z* = 517 $[M + H]^+$. Purity: 95.7%. HR-LC-MS (ESI) *m/z* $[M + H]^+$ calcd, 517.1887; found, 517.1887.

5.1.76. methyl (*R*)-2-{[1-(5'-chloro-2'-cyano-[1,1'-biphenyl]-4-yl)ethyl] butylamino}benzo[d]oxazole-4-carboxylate (39b)

The titled compound (2.80 g, 66% from compound **8a**, white solid) was synthesized by a process analogous to the preparation of **36a**. LC-MS (ESI) *m/z* = 488 $[M + H]^+$.

5.1.77. methyl (*R*)-2-butyl-{1-[5'-chloro -2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}aminobenzo[*d*]oxazole-4-carboxylate (40b)

The titled compound (1.50 g, 48% from compound **39b**, white amorphous solid) was synthesized by a process analogous to the preparation of **37a**. LC-MS (ESI) *m/z* = 547 $[M + H]^+$.

5.1.78. (*R*)-2-butyl-{1-[5'-chloro-2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl]ethyl}aminobenzo[*d*]oxazole-4-carboxylic acid (41b)

The titled compound (1.00 g, 68% from compound **40b**, white amorphous solid) was synthesized by a process analogous to the preparation of **38a**. ^{1}H-NMR (400

MHz, DMSO-d_6) δ: 12.50 (br s, 1H), 7.72–7.61 (m, 5H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz,1H), 5.70 (q, *J* = 6.8 Hz, 1H), 3.42–3.34 (m, 2H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.55–1.40 (m, 2H), 1.27–1.21 (m, 2H), 0.84 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 166.1, 163.1, 159.8, 157.8, 149.1, 143.6, 142.7, 140.4, 136.9, 136.5, 132.1, 130.3, 128.9(2C), 127.9, 127.3(2C), 125.5, 121.4, 119.5, 117.6, 112.6, 55.7, 44.5, 30.8, 19.5, 17.1, 13.5. LC-MS (ESI) *m/z* = 533 $[M + H]^+$. Purity: 98.1%. $[\alpha]^{25}_D$ = 160.4 (*c* 0.96, $CHCl_3$). HR-LC-MS (ESI) $[M + H]^+$ calcd, 533.1592; found, 533.1601.

5.2. Biological assay

5.2.1. Human ChemR23 assay

CAL-1 cells were suspended in RPMI 1640 containing 10 mM HEPES, Calcium-3 (as described in the manufacturer's protocol) and amaranth (final, 0.75 mg/mL). Cells were plated onto a 384-well plate (1×10^4 cells/40 μL), and 5 μL of compounds dissolved in assay buffer (final, 0–10 μM) was added. After incubation at 37 °C for 45 min, 5 μL of human chemerin dissolved in assay buffer containing 1% (w/v) bovine serum albumin (final, 50 ng/mL) was added, and the intracellular calcium ion concentrations were measured using an FDSS6000 (Hamamatsu Photonics K.K.).

5.2.2. Chemotaxis assay

CAL-1 cells were treated with various concentrations of compounds dissolved in assay buffer (as above) containing 0.1% (w/v) bovine serum albumin (final, 0–10 μM). Cells (2.0×10^5 cells, 200 μL) and 5 ng/mL of chemerin dissolved in assay

buffer containing 0.1 % (w/v) bovine serum albumin (600 μL) were applied to the top and bottom wells, respectively, of 8-μm-pore chambers. After incubation at 37 °C for 4 h, the numbers of cells in the bottom wells were counted using CellTiter-Glo reagent.

5.2.3. Pharmacokinetic analyses in monkeys

Test compounds were administered orally (1.0 mg/kg, suspension in 0.5% methylcellulose) or intravenously (0.1 mg/kg, DMF/0.1M NaOH/distilled water = 10/5/85 v/v/v) by cassette dosing to monkeys under fed conditions. For the PK test with dosing alone, compounds were administered orally (10 mg/kg, suspension in 0.5% methylcellulose) to monkeys under fed conditions. After administration, blood samples were collected and centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with ice-cold acetonitrile containing an internal standard. The pretreated samples were analyzed with a calibration curve sample using LC/MS/MS. The compound concentrations were determined from the peak area ratios of the test compounds to the internal standard (IS) using the calibration curve.

5.2.4. Determination of unbound fraction in plasma

The value of the unbound fraction ($f_{u,p}$) in monkey plasma was calculated from the observed unbound fraction ($f'_{u,p}$) in plasma diluted with phosphate-buffered saline (PBS) using the following equation:

$$f_{u,p} = \frac{f'_{u,p}}{f'_{u,p} + D \times (1 - f'_{u,p})}$$ D: dilution factor

The $f'_{u,p}$ value was determined using High Throughput Dialysis HTD 96b (HTDialysis LLC,) with a dialysis device following the manufacturer's instructions. One hundred microliters of PBS was added to one side of the dialysis well (PBS side) separated by the dialysis membrane (Dialysis Membrane Strips, MWCO 12000 to 14000; HTDialysis, LLC) on the dialysis device, and 100 µL of the diluted plasma containing the test compound at 1 µM (final concentration of DMSO: 0.05% [v/v]) was added to the other side of the dialysis well (plasma side). After incubation in a CO_2 incubator at 37 ºC for 16–24 h, each solution (from the PBS side and the plasma side) was collected and pretreated by deproteination with ice-cold acetonitrile containing IS. The pretreated sample was injected into an LC-MS/MS system. The $f'_{u,p}$ value was calculated as the ratio of the IS peak area ratio on the buffer side to the IS peak area ratio on the plasma side.

5.2.5. *Ex vivo* blood study

The FACS buffer was PBS (Thermo Fisher Scientific, Inc.) containing 2 mM ethylenediaminetetraacetic acid (Thermo Fisher Scientific, Inc.), 2% fetal bovine serum (Merck Millipore) and 0.09% sodium azide (Kanto Chemical Co., Inc.). Buffer A was mouse anti-human ChemR23 (R&D Systems) or Mouse IgG3 isotype control (R&D Systems) that had been biotinylated using a Biotin Labeling Kit - NH_2 (Dojindo Laboratories); 5 µL of each biotinylated antibody was dissolved in 495 µL of FACS buffer. Buffer B was 1 µL of Streptavidin-PE (BD Biosciences), 15 µL of APC mouse anti-human HLA-DR (BD Biosciences) and 75 µL of FITC mouse anti-human CD123 (BD Biosciences) dissolved in 409 µL FACS buffer.

Blood was collected from the saphenous or femoral vein of a monkey.

Compounds (2 μL) dissolved in DMA (final, 100 or 300 μM in 2 mL blood) or chemerin in PBS (final, 0.1 μg/mL in 2 mL blood) were incubated for 30 minutes at 37 °C. Samples were layered on Leucosep (Greiner Bio-One) filled with 3 mL of Ficoll-Paque PLUS (GE Healthcare). After density gradient centrifugation (2000 rpm, 20 minutes, room temperature, CF7D; himac), the middle layer containing leukocytes was separated and further centrifuged (10 mL of FACS buffer, 1500 rpm, 5 minutes, 4 °C and then 5 mL of FACS buffer, 1000 rpm, 5 minutes, 4 °C). Cells suspended in 1 mL of FACS buffer were also centrifuged (1500 rpm, 3 minutes, 4 °C).

The ChemR23 expression on pDC in cynomolgus monkeys was analyzed as follows: Human FcR blocking reagent (10 μL; Miltenyi Biotec) was added to each tube and reacted at 4 °C for 5 minutes. Buffer A (100 μL) was then added to each tube and reacted at 4 °C for 30 minutes. To this mixture, 1 mL of FACS buffer was added, and the mixture was centrifuged (1500 rpm and 4 °C, 5 minutes). Buffer B (100 μL) was added to each tube and reacted at 4 °C for 30 minutes. To this mixture, FACS buffer (1 mL) was added, and the mixture was centrifuged (1500 rpm and 4 °C, 5 minutes). FACS buffer (500 μL) was added to each tube, and the cell suspension was transferred to round-bottom tubes. Samples were measured by a FACSVerse (BD Biosciences) and FlowJo (Tomy Digital Biology Co., Ltd.). The white blood cells were gated from the Forward Scatter and Side Scatter. PDCs were defined as HLA-DR and CD123 positive fractions. The ChemR23 expression on pDCs was calculated by the geometric mean fluorescent intensity (GeoMFI). The ChemR23 internalization rate was calculated using the following formula:

ChemR23 Internalization (%) = (PC-S) / (PC-NC) x 100

NC: GeoMFI of the sample stained with isotype control antibody after adding the DMA, PC: GeoMFI of the sample stained with ChemR23 antibody after adding the DMA, S: GeoMFI of the sample stained with ChemR23 antibody after adding the test compound.

5.2.5. *In vivo* internalization test

Compound **38a** was orally administered at the dose of 50 mg/kg (suspension in 0.5% methylcellulose) to cynomolgus monkeys. Blood was collected before and 2, 4 and 8 h after the oral administration using the same method above. ChemR23 on pDCs was stained with the same procedure described above. The ChemR23 internalization was represented as the ratio of the ChemR23 expression at each time point in comparison to its expression at the pre-dose stage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful to Hideyuki Onodera, Kazuo Kubo and Katsuya Kobayashi for their helpful support and discussions. The authors thank Kyoko Tsutsumi for performing the LC-MS analysis and spectral measurements in this research. We sincerely thank Drs. T. Maeda and S. Kamihira (Nagasaki University, Japan) for providing the CAL-1 cells. This cell line invented at Nagasaki University was used as a research material under license.

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Graphical Abstract