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Palladium-Catalyzed Synthesis of 2-Aminobenzoxazinones by Aerobic Oxidative Coupling of Anthranilic Acids and Isocyanides

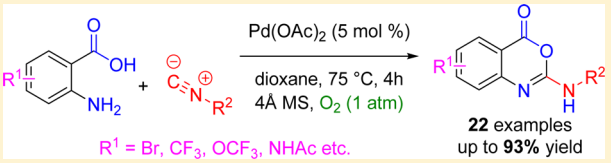
Tjøstil Vlaar,[†] Romano V. A. Orru,*[,†] Bert U. W. Maes,*[,‡] and Eelco Ruijter*[,†]

[†]Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute for Molecules Medicines and Systems (AIMMS), VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

[‡]Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium

Supporting Information

ABSTRACT: Isocyanides have emerged as valuable C_1 building blocks in palladium catalysis. Their potential has, however, mainly been exploited for the synthesis of amidines and amidine-containing heterocycles. To illustrate the broader applicability of isocyanides, we have recently developed a novel oxidative coupling of diamines and isocyanides furnishing valuable guanidine-containing heterocycles. We here report the extension of this protocol to the coupling of anthranilic acids and isocyanides leading to medicinally relevant 2-aminobenzoxazinones. This is a particularly challenging substrate class for this reaction due to the possibility of undesired decarboxylative pathways and the susceptibility of the products to nucleophilic attack. Therefore, this work underlines the generality and broad potential of the oxidative coupling of bisnucleophiles and isocyanides, facilitating the further implementation of this chemistry in library design.

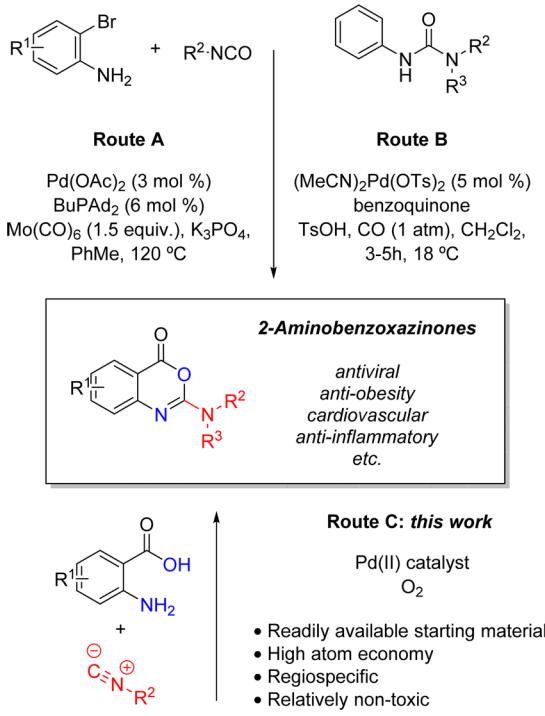


INTRODUCTION

Benzoxazinones are valuable nitrogen-containing heterocycles that exhibit a wide variety of biological activities.[1] Especially 2-amino-substituted benzoxazinones (Scheme 1) have frequently been studied during the past decades because of their pharmacological potential covering a range of possible applications, including antiviral, antiobesity, cardiovascular, and anti-inflammatory activities.[2] In the past decade, several Pd-catalyzed carbonylative approaches toward benzoxazinones have been developed,[3] but only a limited arsenal of synthetic methodologies is available for the synthesis of 2-amino-benzoxazinones.[4] Wu et al. developed a Pd^0-catalyzed carbonylative synthesis of 2-aminobenzoxazoles from 2-bromoanilines and isocyanates (Scheme 1, route A),[5] while Houlden et al. developed a carbonylative Pd^{II}-catalyzed procedure involving directed C−H activation of *N*-arylureas (Scheme 1, route B).[6] Although both methods deliver an original synthetic approach toward these scaffolds, they suffer from limitations, such as relatively poor atom economy, lack of regiocontrol in the product, limited substrate scope, and/or handling of toxic CO gas.

In the past several years, isocyanides have emerged as valuable C_1 building blocks in palladium catalysis, where they find application in the synthesis of valuable heterocycles and functional groups.[7,8] The potential of this reactivity has so far predominantly been used in the synthesis of amidines and imidates (Scheme 2A). We have recently addressed this limitation and introduced the Pd^{II}-catalyzed synthesis of cyclic guanidines by oxidative coupling of diamines and isocyanides using molecular oxygen as the stoichiometric oxidant (Scheme 2B).[9,10] Indeed, this novel reaction provides a sustainable approach toward various medicinally important heterocyclic

Scheme 1. Recent Approaches toward 2-Aminobenzoxazinones



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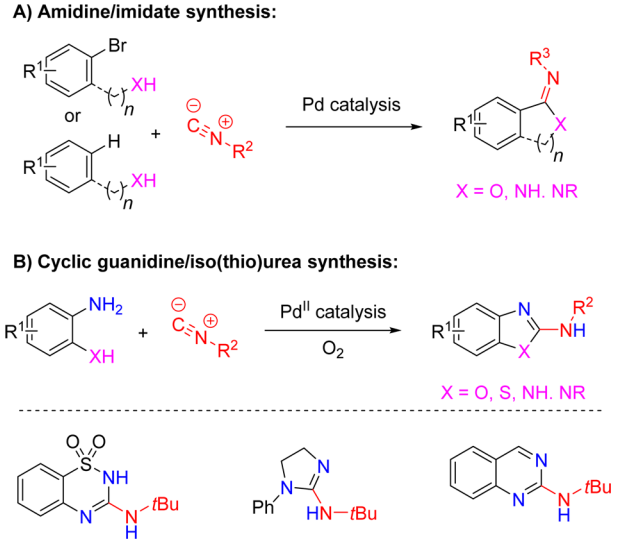
Scheme 2. Typical Pd-Catalyzed Imidoylative Amidine and Imidate Synthesis Using Isocyanides (A) and Oxidative Coupling of Bisnucleophiles and Isocyanides (B)

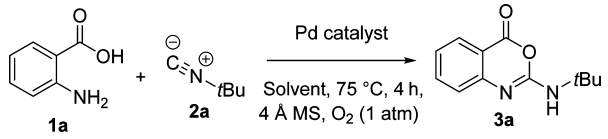


scaffolds and has already been implemented in flow chemistry.[11] We have previously shown that 2-amino(thio)-phenols also oxidatively couple with isocyanides under the same reaction conditions (Scheme 2B), and in line with this work we envisioned an attractive novel approach toward 2-aminobenzoxazinones by aerobic oxidative coupling of anthranilic acids and isocyanides (Scheme 1, route C).[9,12] This approach would entail important advantages such as complete control over regioselectivity, readily available substrates, and a high atom economy. It is, however, also a particularly challenging expansion of our cyclic guanidine synthesis due to the sensitivity of the benzoxazinone products to nucleophilic attack[4] and, most importantly, the tendency of benzoic acids to undergo decarboxylative processes in the presence of transition metals such as Pd^{II}.[13] In addition, benzoic acid derivatives may undergo palladium-catalyzed decarbonylative coupling with isocyanides at temperatures as low as 70 °C.[14] Moreover, isocyanides have also been reported to react with anthranilic acids to produce 4-quinazolinones.[15]

RESULTS AND DISCUSSION

We started our investigations by optimizing the reaction of anthranilic acid (**1a**) and *tert*-butyl isocyanide (**2a**; Table 1). We were not surprised that our previously established optimal conditions for the synthesis of cyclic guanidines[9] [1 mol % $Pd(OAc)_2$, 1.2 equiv *t*BuNC, 1 atm O_2, 4 Å molecular sieves (MS), toluene] gave rise to the formation of complex mixtures with only trace amounts of the desired product **3a** (entry 1, Table 1).[16] The reaction works better in 2-MeTHF (entry 2), and 4 Å MS and O_2 atmosphere (instead of air) proved beneficial (entries 3 and 4). A solvent screening indicated that the reaction only performs well in ethereal solvents, of which dioxane performed best, resulting in 82% conversion and 52% yield of **3a** after 4 h (entry 11). No purification or drying of the solvent is necessary, making the procedure operationally simple and convenient. Remarkably, the reaction does not proceed further if the reaction time is increased and only more side products are formed (entry 12). These results indicate that catalyst decomposition occurs, which is in stark contrast with our guanidine synthesis, where only low reaction rates

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	catalyst	% conversion of **1a** (GC)[b]	% yield of **3a** (GC)[b]
1	PhMe	$Pd(OAc)_2$ (1 mol %)	88	2
2	MeTHF	$Pd(OAc)_2$ (1 mol %)	68	24
3[c]	MeTHF	$Pd(OAc)_2$ (1 mol %)	58	10
4[d]	MeTHF	$Pd(OAc)_2$ (1 mol %)	55	4
5	*t*BuOH	$Pd(OAc)_2$ (1 mol %)	68	2
6	DMF	$Pd(OAc)_2$ (1 mol %)	50	2
7	DMSO	$Pd(OAc)_2$ (1 mol %)	32	1
8	MeCN	$Pd(OAc)_2$ (1 mol %)	67	0
9	DCE	$Pd(OAc)_2$ (1 mol %)	82	1
10	DME	$Pd(OAc)_2$ (1 mol %)	61	24
11	dioxane	$Pd(OAc)_2$ (1 mol %)	82	52
12[e]	dioxane	$Pd(OAc)_2$ (1 mol %)	97	48
13	dioxane	$Pd(OPiv)_2$ (1 mol %)	79	48
14	dioxane	$Pd(O_2CCF_3)_2$ (1 mol %)	61	22
15	dioxane	$PdCl_2(MeCN)_2$ (1 mol %)	79	54
16	dioxane	$Pd(PPh_3)_4$ (1 mol %)	81	53
17	dioxane	$Pd(OAc)_2$ (5 mol %)	99	92

[a]Standard conditions: Pd catalyst, anthranilic acid (**1a**, 0.5 mmol), *tert*-butyl isocyanide (**2a**, 0.6 mmol), 4 Å MS (150 mg) in the indicated solvent (2.5 mL) at 75 °C for 4 h under O_2 atmosphere (1 atm). [b]Yields and conversions were determined by GC analysis using dodecane as the internal standard. [c]No MS added. [d]Air atmosphere. [e]Reaction time 20 h. MS = molecular sieves, MeTHF = 2-methyltetrahydrofuran, DMF = *N*,*N*′-dimethylformamide, DMSO = dimethyl sulfoxide, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, Piv = *t*BuCO.

warranted higher catalyst loadings. Various palladium salts gave comparable yields and selectivities (entries 13−16), so we selected readily available and inexpensive palladium acetate to further our investigations. Increasing the catalyst loading to just 5 mol % resulted in an excellent 92% yield of **3a** (entry 17). We evaluated the substrate scope of this novel transformation with a catalyst loading of 5 mol % and a reaction time of 4 h (Table 2). We deliberately chose not to minimize the catalyst loading and reaction time for each specific example to underline the generality of this reaction. Electron-rich substrates perform very well (**3b**−**3j**), and even product **3h** containing three methoxy groups was readily obtained in 92% yield. Remarkably, substrates containing challenging substituents such as acetamido (**3i**, 68%) or trifluoromethoxy (**3j**, 62%) groups are also efficiently converted. Electron-withdrawing groups, such as the medicinally important fluoro (**3k** and **3o**) and trifluoromethyl

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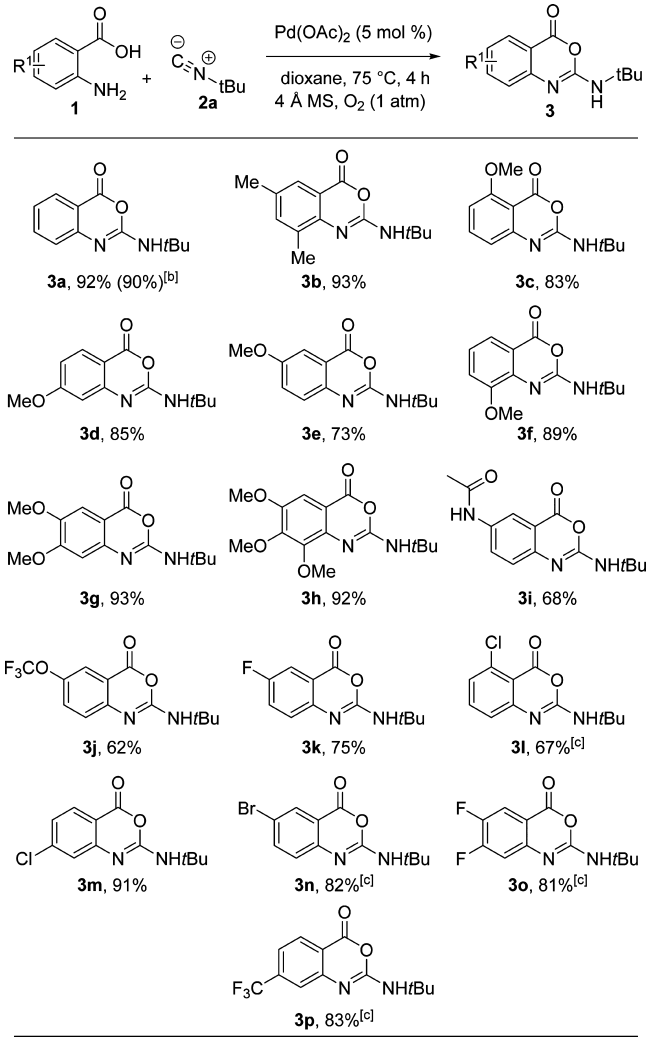
Table 2. Aerobic Oxidative Coupling of Diverse Anthranilic Acids with *tert*-Butyl Isocyanide[a]

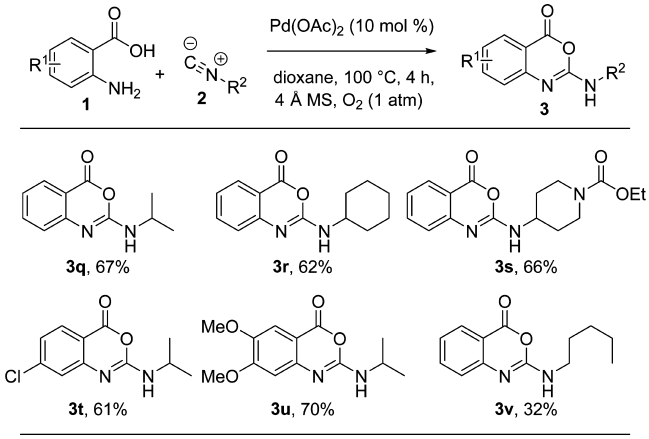


[a]Standard conditions: $Pd(OAc)_2$ (5 mol %), anthranilic acid derivative (1.0 mmol), *tert*-butyl isocyanide (1.2 mmol), 4 Å MS (300 mg) in dioxane (5 mL) at 75 °C for 4 h in O_2 atmosphere (1 atm). Yields refer to isolated material. [b]Yields in parentheses were of reactions performed on 10 mmol scale. [c]10 mol % $Pd(OAc)_2$ used.

(**3p**) groups,[17] were easily incorporated under the same reaction conditions (**3k**–**3p**), although in some isolated cases a higher catalyst loading was required to achieve high yields. Furthermore, 5-bromoanthranilic acid is converted to **3n** in 82% yield, which provides a plethora of opportunities for follow-up Pd^0-catalyzed functionalization of the product. The reaction is amenable to scale-up (10 mmol of **1a**) with negligible loss of yield, furnishing 1.97 g (90%) of product **3a**. Anthranilic acids bearing NO_2, I, OH, or COOH substituents only afforded trace amounts of products and were not isolated.

Isocyanides bearing groups other than *tert*-butyl unfortunately gave low yields of desired product under the standard conditions. Indeed, this is a well-known issue with Pd-catalyzed insertion reactions of isocyanides that typically limits the scope and applicability significantly, and in fact, many reactions have been reported where *only* *tert*-butyl isocyanide can be used.[7,8] We were therefore delighted to find that after modest adjustments to the reaction conditions [10 mol % $Pd(OAc)_2$, 100 °C, 2 equiv of isocyanide] good yields were obtained with various isocyanides (Table 3). Secondary aliphatic isocyanides are readily inserted independent of the electronic nature of the

Table 3. Aerobic Oxidative Coupling of Anthranilic Acids with Various Isocyanides[a]

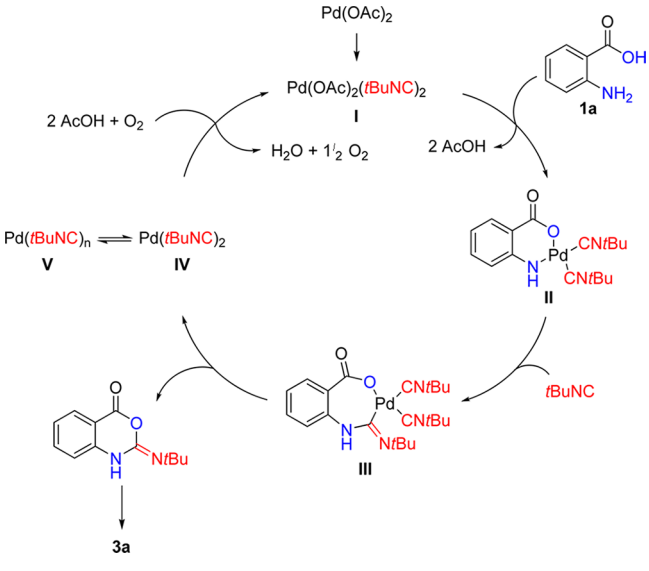


[a]Standard conditions: $Pd(OAc)_2$ (10 mol %), anthranilic acid derivative (1.0 mmol), isocyanide (2.0 mmol), 4 Å MS (300 mg) in dioxane (5 mL) at 100 °C for 4 h in O_2 atmosphere (1 atm). Yields refer to isolated material.

anthranilic acid used and give very useful products in 60–70% yield (**3q**–**3u**). Product **3s** derived from an isocyanide containing additional functionality is especially noteworthy and uncommon in this type of chemistry. Removal of the carbamate group would lead to a known pancreatic lipase inhibitor.[2f] A primary aliphatic isocyanide is also viable, although **3v** was only obtained in moderate yield. The use of an aromatic isocyanide (2,6-dimethylphenylisocyanide) did, unfortunately, not afford an appreciable amount of product.

A plausible mechanism for the oxidative coupling of anthranilic acids and isocyanides is depicted in Scheme 3. Intermediate **II** is formed by substitution of the acetate ligands by the benzoate and aniline moieties and subsequently undergoes migratory insertion of coordinated isocyanide. The resulting complex **III** then undergoes reductive elimination to

Scheme 3. Proposed Mechanism



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afford the product and Pd^0, which is reoxidized by molecular oxygen.[18] We have previously ruled out the involvement of oxidation of the isocyanide to the corresponding isocyanate and subsequent condensation as the mechanism.[9]

CONCLUSION

We have developed a Pd^{II}-catalyzed aerobic oxidative synthesis of 2-aminobenzoxazinones from readily available and relatively nontoxic starting materials. The reaction provides these medicinally valuable products with high atom economy, generating only water as a byproduct, and thereby prevents waste production. The procedure is operationally simple and does not require the handling of toxic gases such as CO. Furthermore, this challenging transformation further establishes the generality of the oxidative coupling of bisnucleophiles and isocyanides toward the synthesis of various heterocycles, which will be imperative for the further implementation of this chemistry in library synthesis.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Ethyl 4-isocyanopiperidine-1-carboxylate was prepared according to literature procedure.[9] Palladium acetate was stored in a desiccator from which small portions (±200 mg) were taken periodically. Cyclohexane was distilled prior to use. Other solvents were used as purchased. Powder 4 Å molecular sieves were activated before use. GC yield and conversion analysis was performed using a Zebron ZB-1 capillary column (30 m × 0.25 mm) with dodecane as internal standard. Infrared (IR) spectra were recorded neat, and wavelengths are reported in cm^{-1}. Signals are described as weak (w), medium (m), or strong (s). Nuclear magnetic resonance (NMR) spectra were recorded using the residual solvent as internal standard (^1H, δ 7.26 ppm; ^{13}C, δ 77.16 ppm for $CDCl_3$; ^1H, δ 2.50 ppm; ^{13}C, δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet), and m (multiplet) or combinations thereof. Electrospray ionization (ESI) high-resolution mass spectrometry (Q-TOF analysis) was carried out in positive ion mode (capillary potential of 4500 V). Compounds were visualized on TLC plates by UV detection (254 nm) unless mentioned otherwise.

General Procedure for Synthesis of 2-Aminobenzoxazinones (3) with *tert*-Butyl Isocyanide. A 25 mL round-bottom flask was charged with $Pd(OAc)_2$ (11.2 mg, 5 mol % or 22.5 mg, 10 mol %), anthranilic acid derivative (**1**, 1.0 mmol), and powdered 4 Å molecular sieves (300 mg). The flask was connected to a reflux condenser and the system was then put under vacuum and backfilled with O_2 (3×). Dioxane (5 mL) and *tert*-butyl isocyanide (**2a**, 136 μL, 1.2 mmol) were added, and the mixture was stirred at 75 °C for 4 h in O_2 atmosphere (1 atm, balloon). Subsequently, the reaction mixture was cooled to room temperature, filtered over Celite, and purified by flash chromatography with cyclohexane/ethyl acetate as eluent. *Note: the products are prone to ring-opening, so caution is required.*

2-(*tert*-Butylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3a). The title compound was isolated as a white solid. Yield: 201 mg, 92% (1 mmol scale) or 1.97 g, 90% (10 mmol scale). TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.29. Mp: 128.5−129.7 °C (lit.[6] mp 127−128 °C). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01 (dd, J = 7.9, 1.3 Hz, 1H), 7.60 (dt, J = 7.7, 1.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.15 (dt, J = 7.6, 0.8 Hz, 1H), 4.85 (s, 1H), 1.48 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.3, 152.2, 150.5, 136.6, 128.7, 124.7, 123.6, 113.5, 52.1, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3296 (m), 2972 (w), 1736 (s), 1626 (s), 1603 (s), 1568 (s), 1474 (s), 1361 (m), 1277 (s), 1198 (s), 1150 (s), 1070 (s), 758 (s). HRMS (ESI): m/z calcd for $C_{12}H_{15}N_2O_2$ ($[M + H]^+$) 219.1128, found 219.1130.

2-(*tert*-Butylamino)-6,8-dimethyl-4*H*-benzo[*d*][1,3]oxazin-4-one (3b). The title compound was isolated as a white solid. Yield: 230 mg, 93%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.33. Mp: 172.2−173.1 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.66 (s, 1H), 7.31 (s, 1H), 4.73 (s, 1H), 2.39 (s, 3H), 2.32 (s, 3H), 1.49 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.0, 150.7, 146.8, 138.5, 132.9, 132.7, 125.6, 112.9, 51.9, 28.7, 20.9, 17.3 ppm. IR (neat): ν_{max} (cm^{-1}) 3296 (w), 3246 (m), 2970 (w), 1740 (m), 1720 (s), 1632 (s), 1614 (s), 1541 (m), 1483 (s), 1283 (m), 1211 (m), 1041 (m), 785 (s). HRMS (ESI): m/z calcd for $C_{14}H_{19}N_2O_2$ ($[M + H]^+$) 247.1441, found 247.1437.

2-(*tert*-Butylamino)-5-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3c). The title compound was isolated as a white solid. Yield: 205 mg, 83%. TLC (cyclohexane:EtOAc, 4:1 v/v): R_f = 0.19. Mp: 154.1−154.9 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.48 (t, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.80 (br, 1H), 3.93 (s, 3H), 1.44 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.4, 156.9, 153.0, 152.7, 137.0, 116.9, 105.0, 103.0, 56.3, 51.9, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3285 (m), 2962 (w), 1730 (s), 1632 (s), 1599 (s), 1566 (s), 1481 (s), 1454 (m), 1356 (m), 1304 (m), 1256 (m), 1119 (s), 1043 (m), 1009 (s), 800 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_3$ ($[M + H]^+$) 249.1234, found 249.1228.

2-(*tert*-Butylamino)-7-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3d). The title compound was isolated as a white solid. Yield: 210 mg, 85%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.19. Mp: 177.0−177.7 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, J = 8.8 Hz, 1H), 6.71 (dd, J = 8.8, 2.4 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 4.86 (br, 1H), 3.87 (s, 3H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 159.9, 153.1, 152.9, 130.4, 113.2, 106.4, 106.1, 55.7, 52.0, 29.0 ppm. IR (neat): ν_{max} (cm^{-1}) 3285 (m), 1713 (m), 1601 (s), 1568 (s), 1447 (s), 1360 (m), 1288 (s), 1213 (s), 1171 (s), 1063 (m), 962 (m), 839 (s), 770 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_3$ ($[M + H]^+$) 249.1234, found 249.1226.

2-(*tert*-Butylamino)-6-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3e). The title compound was isolated as a yellow solid. Yield: 182 mg, 73%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.24. Mp: 134.0−135.2 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, J = 2.7 Hz, 1H), 7.23 (dd, J = 8.9, 2.7 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.71 (s, 1H), 3.83 (s, 3H), 1.46 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.5, 155.9, 151.2, 144.9, 126.6, 126.1, 113.5, 108.4, 55.9, 51.9, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3292 (m), 1736 (s), 1630 (s), 1491 (s), 1437 (m), 1360 (w), 1319 (w), 1259 (m), 1205 (m), 1074 (m), 1038 (m), 1011 (m), 883 (m), 829 (s), 779 (m). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_3$ ($[M + H]^+$) 249.1234, found 249.1232.

2-(*tert*-Butylamino)-8-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3f). The title compound was isolated as an off-white solid. Yield: 220 mg, 89%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.12. Mp: 165.4−167.9 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, J = 7.6, 1.6 Hz, 1H), 7.11−7.05 (m, 2H), 5.17 (s, 1H), 3.92 (s, 3H), 1.46 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.8, 153.9, 152.4, 141.5, 123.2, 120.2, 116.9, 113.7, 56.5, 52.4, 29.4 ppm. IR (neat): ν_{max} (cm^{-1}) 3281 (m), 1732 (s), 1626 (s), 1601 (s), 1574 (s), 1541 (m), 1493 (s), 1447 (m), 1391 (w), 1348 (m), 1261 (s), 1217 (s), 1200 (s), 1107 (m), 1053 (s), 1013 (s), 744 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_3$ ($[M + H]^+$) 249.1234, found 249.1238.

2-(*tert*-Butylamino)-6,7-dimethoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3g). The title compound was isolated as an off-white solid. Yield: 258 mg, 93%. TLC (cyclohexane:EtOAc, 3:1 v/v): R_f = 0.34. Mp: 131.6−138.5 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (s, 1H), 6.69 (s, 1H), 4.73 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 1.46 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 157.0, 152.2, 147.3, 146.5, 107.8, 105.9, 105.2, 56.4, 56.3, 51.9 29.0 ppm. IR (neat): ν_{max} (cm^{-1}) 3281 (m), 1720 (s), 1609 (s), 1578 (m), 1489 (s), 1452 (m), 1389 (m), 1294 (s), 1240 (s), 1205 (s), 1136 (m), 1065 (m), 1009 (w), 932 (w), 858 (m), 839 (m), 809 (w), 768 (m). HRMS (ESI): m/z calcd for $C_{14}H_{19}N_2O_4$ ($[M + H]^+$) 279.1339, found 279.1333.

2-(*tert*-Butylamino)-6,7,8-trimethoxy-4*H*-benzo[*d*][1,3]-oxazin-4-one (3h). The title compound was isolated as a white solid. Yield: 285 mg, 92%. TLC (cyclohexane:EtOAc, 3:1 v/v): R_f = 0.44. Mp: 144.6−146.0 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.22 (s, 1H), 4.85 (br, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 1.48 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 151.4, 150.1, 149.8, 145.7, 140.5, 108.2, 104.1, 62.0, 61.5, 56.3, 52.0, 29.0 ppm. IR (neat):

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ν_{max} (cm^{-1}) 3300 (m), 2935 (w), 1718 (m), 1628 (s), 1533 (w), 1470 (s), 1427 (s), 1393 (w), 1366 (s), 1306 (m), 1286 (m), 1207 (m), 1111 (s), 1078 (s), 1041 (s), 1013 (m), 984 (s), 937 (m), 849 (m), 760 (m). HRMS (ESI): *m*/*z* calcd for $C_{15}H_{21}N_2O_5$ ($[M + H]^+$) 309.1445, found 309.1440.

***N*-(2-(*tert*-Butylamino)-4-oxo-4*H*-benzo[*d*][1,3]oxazin-6-yl)-acetamide (3i).** The title compound was isolated as an off-white solid. Yield: 186 mg, 68%. TLC (cyclohexane:EtOAc, 1:1 v/v): R_f = 0.34. Mp: 240.6−242.5 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.07 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.61 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 2.05 (s, 3H), 1.38 (s, 9H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.2, 159.7, 151.7, 146.0, 134.6, 128.3, 124.5, 116.5, 112.5, 50.8, 28.3, 23.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3327 (m), 2978 (w), 1738 (s), 1676 (m), 1637 (s), 1616 (s), 1545 (s), 1495 (s), 1421 (w), 1360 (m), 1269 (s), 1256 (s), 1202 (s), 1065 (m), 903 (w), 839 (s), 777 (m). HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}N_3O_3$ ($[M + H]^+$) 276.1343, found 276.1331.

2-(*tert*-Butylamino)-6-(trifluoromethoxy)-4*H*-benzo[*d*][1,3]-oxazin-4-one (3j). The title compound was isolated as a white solid. Yield: 188 mg, 62%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.30. Mp: 129.6−130.7 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 4.95 (s, 1H), 1.48 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 152.3, 149.3, 144.5 (q, *J* = 1.7 Hz), 130.2, 126.5, 120.6 (q, *J* = 258 Hz), 120.4, 113.9, 52.3, 28.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3288 (m), 2978 (w), 1751 (s), 1634 (s), 1609 (s), 1541 (w), 1487 (s), 1394 (w), 1364 (w), 1254 (s), 1209 (s), 1198 (s), 1161 (s), 1063 (m), 1014 (m), 897 (m), 831 (m), 779 (m). HRMS (ESI): *m*/*z* calcd for $C_{13}H_{14}F_3N_2O_3$ ($[M + H]^+$) 303.0951, found 303.0943.

2-(*tert*-Butylamino)-6-fluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (3k). The title compound was isolated as a white solid. Yield: 178 mg, 75%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.33. Mp: 131.9−133.0 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (dd, *J* = 8.1, 2.9 Hz, 1H), 7.33 (dt, *J* = 8.5, 2.9 Hz, 1H), 7.25 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.87 (s, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6 (d, *J* = 3.5 Hz), 158.6 (d, *J* = 244 Hz), 151.7, 147.1 (d, *J* = 1.4 Hz), 126.6 (d, *J* = 7.5 Hz), 124.9 (d, *J* = 23.8 Hz), 114.0 (d, *J* = 8.7 Hz), 113.4 (d, *J* = 23.7 Hz), 52.1, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3312 (m), 2978 (w), 1744 (s), 1636 (s), 1610 (s), 1576 (m), 1529 (m), 1487 (s), 1475 (s), 1460 (s), 1393 (m), 1358 (m), 1339 (m), 1271 (s), 1246 (m), 1198 (s), 1115 (m), 1057 (m), 1013 (w), 916 (w), 879 (m), 849 (m), 829 (s), 777 (s). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}FN_2O_2$ ($[M + H]^+$) 237.1034, found 237.1031.

2-(*tert*-Butylamino)-5-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one (3l). Ten mole percent of $Pd(OAc)_2$ was used. The title compound was isolated as an off-white solid. Yield: 170 mg, 67%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.29. Mp: 159.8−161.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.17−7.13 (m, 2H), 4.94 (s, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.9, 153.1, 152.5, 135.9, 135.8, 126.0, 123.8, 111.2, 52.2, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3269 (m), 1747 (s), 1630 (s), 1591 (s), 1553 (s), 1423 (m), 1393 (w), 1366 (m), 1279 (m), 1207 (s), 1167 (m), 1049 (m), 947 (s), 800 (s), 771 (w). HRMS (ESI): m/z calcd for $C_{12}H_{14}ClN_2O_2$ ($[M + H]^+$) 253.0738, found 253.0755.

2-(*tert*-Butylamino)-7-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one (3m). The title compound was isolated as a white solid. Yield: 229 mg, 91%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.30. Mp: 174.5−175.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.09 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.00 (s, 1H), 1.48 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 152.8, 151.6, 142.9, 130.0, 124.4, 124.1, 111.9, 52.3, 28.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3298 (m), 1736 (s), 1630 (s), 1589 (s), 1560 (s), 1456 (s), 1441 (s), 1393 (w), 1362 (m), 1327 (m), 1306 (w), 1275 (m), 1209 (s), 1078 (m), 1059 (s), 943 (s), 912 (w), 820 (w), 795 (w), 768 (s). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}ClN_2O_2$ ($[M + H]^+$) 253.0738, found 253.0735.

2-(*tert*-Butylamino)-6-bromo-4*H*-benzo[*d*][1,3]oxazin-4-one (3n). Ten mole percent of $Pd(OAc)_2$ was used. The title compound was isolated as a white solid. Yield: 244 mg, 82%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.30. Mp: 180.5−181.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (d, *J* = 2.3 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 4.96 (s, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 152.3, 149.5, 139.6, 130.9, 126.5, 115.8, 114.9, 52.3, 28.9 ppm. IR (neat): ν_{max} (cm^{-1}) 3290 (m); 2978 (w), 1742 (s), 1624 (s), 1593 (s), 1556 (m), 1470 (s), 1391 (m), 1362 (m), 1321 (m), 1273 (s), 1230 (m), 1209 (s), 1132 (m), 1064 (s), 1013 (m), 906 (m), 833 (s), 779 (s). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}BrN_2O_2$ ($[M + H]^+$) 297.0233, found 297.0219.

2-(*tert*-Butylamino)-6,7-difluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (3o). Ten mole percent of $Pd(OAc)_2$ was used. The title compound was isolated as a white solid. Yield: 207 mg, 81%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.28. Mp: 163.8−164.6 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (t, *J* = 9.1 Hz, 1H), 7.04 (dd, *J* = 11.2, 6.9 Hz, 1H), 4.95 (br, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.7, 156.6 (dd, *J* = 259, 14.4 Hz), 152.5, 148.7 (d, *J* = 12.5 Hz), 147.3 (dd, *J* = 248, 14.3 Hz), 116.0 (dd, *J* = 19.2, 2.7 Hz), 112.6 (d, *J* = 18.5 Hz), 109.5 (d, *J* = 5.2 Hz), 52.4, 28.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3279 (m), 2970 (w), 1745 (s), 1639 (s), 1618 (s), 1580 (m), 1549 (m), 1489 (s), 1393 (w), 1362 (m), 1286 (s), 1242 (m), 1207 (s), 1171 (s), 1132 (w), 1057 (s), 1011 (w), 897 (s), 856 (s), 798 (m), 775 (s). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}F_2N_2O_2$ ($[M + H]^+$) 255.0940, found 255.0930.

2-(*tert*-Butylamino)-7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]-oxazin-4-one (3p). Ten mole percent of $Pd(OAc)_2$ was used. The title compound was isolated as a white solid. Yield: 238 mg, 83%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.28. Mp: 166.0−168.2 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 5.11 (br, 1H), 1.49 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 152.7, 150.8, 137.9 (q, *J* = 32.6 Hz), 129.7, 123.4 (q, *J* = 274 Hz), 122.1, 119.5 (q, *J* = 3.4 Hz), 115.9, 52.4, 28.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3298 (m), 1742 (s), 1639 (m), 1609 (s), 1572 (s), 1541 (m), 1455 (s), 1396 (w), 1348 (m), 1308 (s), 1267 (m), 1256 (m), 1211 (m), 1200 (m), 1167 (s), 1128 (s), 1057 (s), 1045 (m), 947 (s), 897 (s), 829 (m), 781 (s). HRMS (ESI): *m*/*z* calcd for $C_{13}H_{14}F_3N_2O_2$ ($[M + H]^+$) 287.1002, found 287.0994.

General Procedure for Synthesis of 2-Aminobenzoxazinones (3) with Other Isocyanides. A 25 mL round-bottom flask was charged with $Pd(OAc)_2$ (22.5 mg, 10 mol %), anthranilic acid derivative (**1**, 1.0 mmol), and powdered 4 Å molecular sieves (300 mg). The flask was connected to a reflux condenser and the system was then put under vacuum and backfilled with O_2 (3×). Dioxane (5 mL) and isocyanide (**2**, 2.0 mmol) were added, and the mixture was stirred at 100 °C for 4 h in O_2 atmosphere (1 atm, balloon). Subsequently, the reaction mixture was cooled to room temperature, filtered over Celite, and purified by flash chromatography with cyclohexane/ethyl acetate as eluent. In some cases, a second column using a different solvent system (DCM/cyclohexane) was required to obtain high purity material.

2-(Isopropylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3q). The title compound was isolated as a white solid. Yield: 137 mg, 67%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.18. Mp: 150.5−151.0 °C (lit.[6] mp 150−151 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63−7.59 (m, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 4.90 (br, 1H), 4.13 (octet, *J* = 6.7 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 153.2, 150.7, 136.8, 128.8, 124.4, 123.6, 113.3, 43.8, 22.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3294 (m), 2982 (w), 1736 (s), 1628 (s), 1599 (s), 1566 (s), 1535 (m), 1472 (s), 1385 (w), 1367 (w), 1348 (m), 1329 (w), 1313 (m), 1269 (s), 1238 (s), 1171 (m), 1148 (m), 1134 (m), 1107 (w), 1055 (s), 1030 (w), 1007 (m), 941 (m), 874 (w), 760 (s). HRMS (ESI): *m*/*z* calcd for $C_{11}H_{13}N_2O_2$ (M + H) 205.0972, found 205.096.

2-(Cyclohexylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3r). The title compound was isolated as a white solid. Yield: 151 mg, 62%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.22. Mp: 209.6−210.7 °C (lit.[19] mp 208−210 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63−7.59 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.82 (br, 1H), 3.86−3.77 (m, 1H), 2.11−2.01 (m, 2H), 1.82−1.70 (m, 2H), 1.68−1.60 (m, 1H), 1.49−1.38 (m, 2H), 1.32−1.19 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 153.2, 150.8, 136.8, 128.9, 124.3, 123.6, 113.3, 50.3, 33.1, 25.6, 24.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3286 (m), 2920 (m), 2853 (m), 1734 (s), 1630

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(s), 1601 (s), 1568 (s), 1541 (m), 1474 (s), 1344 (w), 1341 (w), 1313 (m), 1279 (m), 1250 (m), 1231 (m), 1153 (m), 1119 (w), 1047 (m), 1020 (s), 957 (m), 891 (m), 870 (w), 758 (s). HRMS (ESI): m/z calcd for $C_{14}H_{17}N_2O_2$ ($[M + H]^+$) 245.1285, found 245.1279.

Ethyl 4-((4-Oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)amino)-piperidine-1-carboxylate (3s). The title compound was isolated as a white solid. Yield: 210 mg, 66%. TLC (cyclohexane:EtOAc, 2:1 v/v): R_f = 0.21. Mp: 198.9−201.3 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, J = 7.9, 1.1 Hz, 1H), 7.64−7.60 (m, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.19−7.15 (m, 1H), 5.24 (d, J = 7.4 Hz, 1H), 4.23−4.04 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.04−3.94 (m, 1H), 3.06−2.97 (m, 2H), 2.12−2.05 (m, 2H), 1.53−1.43 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.1, 155.6, 153.0, 150.4, 136.9, 128.9, 124.4, 123.9, 113.4, 61.6, 48.7, 42.7, 31.9, 14.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3269 (m), 1742 (m), 1693 (s), 1628 (s), 1605 (s), 1570 (w), 1541 (w), 1475 (m), 1433 (m), 1373 (m), 1302 (m), 1271 (m), 1225 (s), 1142 (s), 1086 (m), 1049 (m), 1024 (m), 872 (w), 762 (s). HRMS (ESI): m/z calcd for $C_{16}H_{20}N_3O_4$ ($[M + H]^+$) 318.1454, found 318.1468.

2-(Isopropylamino)-7-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one (3t). The title compound was isolated as a white solid. Yield: 145 mg, 61%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.20. Mp: 153.3−153.9 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, J = 8.5 Hz, 1H), 7.25 (s, 1H), 7.09 (dd, J = 8.5, 1.9 Hz, 1H), 4.99 (br, 1H), 4.16−4.06 (m, 1H), 1.28 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 153.8, 151.9, 143.1, 130.1, 124.1,[20] 111.7, 44.0, 22.7 ppm. IR (neat): ν_{max} (cm^{-1}) 3298 (m), 1736 (s), 1632 (s), 1589 (s), 1556 (s), 1454 (s), 1439 (s), 1387 (w), 1369 (w), 1333 (m), 1271 (m), 1259 (m), 1227 (m), 1161 (m), 1132 (m), 1074 (m), 1047 (s), 945 (m), 924 (s), 868 (s), 820 (m), 766 (s). HRMS (ESI): m/z calcd for $C_{11}H_{12}ClN_2O_2$ ($[M + H]^+$) 239.0582, found 239.0576.

2-(Isopropylamino)-6,7-dimethoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3u). The title compound was isolated as an off-white solid. Yield: 184 mg, 70%. TLC (cyclohexane:EtOAc, 2:1 v/v): R_f = 0.28. Mp: 194.0−196.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (s, 1H), 6.69 (s, 1H), 4.80 (br, 1H), 4.12−4.04 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 1.27 (d, J = 6.5 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.8, 157.1, 153.2, 147.4, 146.5, 107.9, 105.5, 105.0, 56.4, 56.3, 43.7, 22.8 ppm. IR (neat): ν_{max} (cm^{-1}) 3281 (m), 1715 (s), 1610 (s), 1574 (m), 1493 (s), 1479 (m), 1454 (m), 1435 (s), 1383 (m), 1281 (m), 1231 (m), 1213 (s), 1167 (m), 1134 (s), 1055 (m), 1043 (m), 999 (m), 945 (w), 858 (s), 841 (s), 798 (s), 770 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_4$ ($[M + H]^+$) 265.1183, found 265.1179.

2-(*n*-Pentylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3v). The title compound was recrystallized from cyclohexane and isolated as an off-white solid. Yield: 74 mg, 32%. TLC (cyclohexane:EtOAc, 8:1 v/v): R_f = 0.18. Mp: 124.7−126.8 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, J = 7.8, 0.8 Hz, 1H), 7.64−7.60 (m, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 5.02 (br, 1H), 3.43 (t, J = 7.0 Hz, 2H), 1.67−1.60 (m, 2H), 1.40−1.34 (m, 4H), 0.94−0.90 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 154.0, 150.5, 136.9, 128.9, 124.3, 123.7, 113.3, 41.7, 29.1, 29.0, 22.4, 14.1 ppm. IR (neat): ν_{max} (cm^{-1}) 3302 (m), 2951 (w), 2928 (m), 2862 (w), 1742 (s), 1634 (s), 1601 (s), 1568 (m), 1474 (s), 1377 (w), 1271 (m), 1238 (m), 1153 (m), 1045 (m), 1013 (m), 957 (w), 878 (w), 760 (s). HRMS (ESI): m/z calcd for $C_{13}H_{17}N_2O_2$ ($[M + H]^+$) 233.1285, found 233.1288.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for compounds **3a**−**3v**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: r.v.a.orru@vu.nl.
*E-mail: bert.maes@ua.ac.be.
*E-mail: e.ruijter@vu.nl.

Notes

The authors declare no competing financial interests.

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