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Novel formation of 1,3-oxazepine heterocycles via palladium-catalyzed intramolecular coupling reaction

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Abstract—The oxazepine ring systems containing pyridazinone moiety were constructed via palladium-catalyzed intramolecular coupling reaction. The best conditions for this reaction were $Pd(OAc)_2$ as a palladium source, 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) as the ligand, and K_2CO_3 as base at 80 °C in toluene. The products have potential applications as biological and medicinal relevant compounds.
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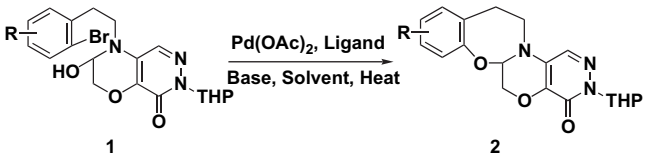
1. Introduction

The modification of the oxazepine nucleus is a versatile research area due to its presence in some natural products and biologically active substances.[1] There are many methods for the synthesis of oxazepine ring systems. However, new, simple, and efficient ways for constructing oxazepine rings are still in great demand.[2]

Palladium-catalyzed cross-coupling reactions Ar–X with carbon nucleophiles have found wide application in the synthesis of complex organic molecules due to their mild reaction conditions and high functional group compatibility.[3] Successful extension of these reactions to heteroatom nucleophiles including amines and thiols have been reported.[4] Recent advances in the Pd-catalyzed aryl aminations have extended the generality of this reaction to include a wide variety of amines. In contrast, the Pd-catalyzed coupling of Ar–X with alcohols still remains as an elusive goal in spite of its potential application in organic synthesis.[5] Aryl ethers, including oxygen heterocycles, are prominent in a large number of pharmacologically important molecules and are found in numerous secondary metabolites.[6] Available methods for the synthesis of aryl ethers via direct nucleophilic substitution of an aryl halide with an alcohol typically require harsh or restrictive conditions or a large excess of the alcohol and are limited in substrate scope.[7]

2. Results and discussion

To the best of our knowledge Buchwald and co-workers[8] have prepared a seven-membered ring via an intramolecular cycloamination, which is the first application of this cyclization to form these important tricyclic oxazepine ring systems. As a part of our continuing interest in the development of novel syntheses of heterocyclic systems,[9] we report herein our results in effecting an intramolecular Pd-catalyzed coupling reaction of an aryl halide with an alcohol (Scheme 1).



1 2

Scheme 1. The intramolecular Pd-catalyzed coupling reaction of an aryl halide with an alcohol.

Preparation of Substrate **1** is shown in Schemes 2 and 3. Substrate **1** was obtained from the corresponding pyridazino-1,4-oxazine **8** by bromination and reduction. Pyridazino-1,4-oxazine **8** was prepared by cyclization of chloroacetamide **7** with pyridazinone **6**. Chloroacetamide **7** was easily prepared by addition of various amines to 2-chloroacetyl chloride. Pyridazinone **6** was synthesized in four steps from commercially available mucochloric acid.

Treatment of mucochloric acid with hydrazine sulfate in refluxing ethanol/water (v/v = 1:1) in the presence of sodium acetate gave 4,5-dichloro-3(2*H*)-pyridazinone (**3**) in excellent yields.[10] The pyridazinone nitrogen of 4,5-dichloro-3(2*H*)-pyridazinone was protected by treatment of

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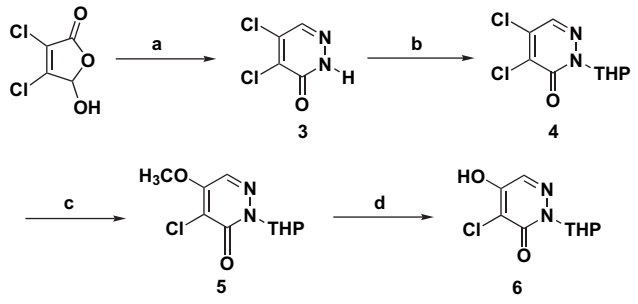
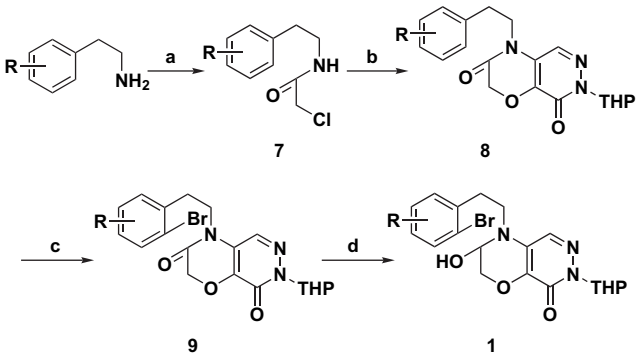
compound **3** with excess dihydropyran and *p*-toluenesulfonic acid in refluxing tetrahydrofuran to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**).[11] The compound **4** was followed by methoxide displacement to produce 4-chloro-5-methoxy pyridazinone **5**, which was then hydrolyzed with potassium hydroxide in refluxing water to give 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) in good yield (Scheme 2).



Scheme 2. (a) H_2NNH_2–H_2SO_4, AcONa, EtOH/H_2O, reflux; (b) DHP, PTSA, THF, reflux; (c) MeONa, MeOH, rt; and (d) KOH, H_2O, reflux.

In addition, reaction of substituted phenylethyl amines with chloroacetyl chloride in the presence of potassium carbonate in refluxing dichloromethane afforded compound **7** in excellent yields (Scheme 3). The reaction occurred at room temperature for 12 h or at refluxing temperature for 2 h. The compound **8** was synthesized by the reaction of various substituted phenylethyl-2-chloroacetamides **7** with pyridazinone **6**. The cyclization occurred smoothly in the presence of cesium carbonate at refluxing acetonitrile in 63–79% isolated yields via Smiles rearrangement.[9]



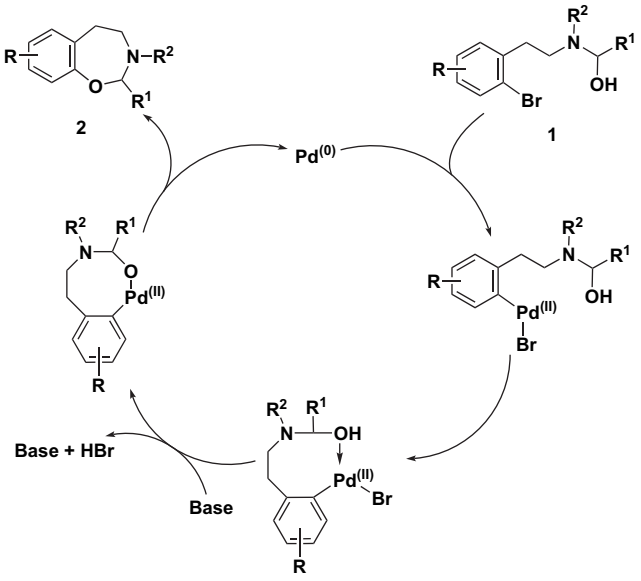
Scheme 3. (a) $ClCH_2COCl$, K_2CO_3, CH_2Cl_2, reflux; (b) **6**, Cs_2CO_3, CH_3CN, reflux; (c) NBS, DMF, rt, 100 °C; and (d) $NaBH_4$, CH_3OH, rt.

According to literature procedure,[12] bromination of **8** with NBS in *N*,*N*-dimethyl formamide gave rise to compound **9** in good yield. Toward the end of subjection, reduction of compound **9** in the present of sodium borohydride in methanol at room temperature afforded the corresponding reduced product **1**.

The different conditions reported for the intramolecular cycloamination to form seven-membered rings ($Pd(PPh_3)_4$, NaO*t*-Bu, and toluene)[8] resulted in poor yields of desired product **2**. Subjecting substrates **1** to the other reaction conditions ($Pd_2(dba)_3$, P(*o*-tolyl)$_3$, NaO*t*-Bu, and toluene) afforded no desired cyclic product. However, the use of (*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-bi-naphthyl (Tol-BINAP) and 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) ligands in place of P(*o*-tolyl)$_3$, either NaO*t*-Bu or K_2CO_3 as base and $Pd(OAc)_2$ as the Pd source gave the desired cyclic product **2** (Table 1).

The ligand DPPF proved to be more effective than DPPE, DPPBz, BINAP, and Tol-BINAP. Optimization of NaO*t*-Bu and K_2CO_3 as base showed that the use of a large excess of K_2CO_3 instead of NaO*t*-Bu afforded products in higher yields. Although it has been reported that the latter gives faster reactions, its high basicity often causes problems. Observed side products included dehalogenation of the aryl bromides and oxidation of the alcohol to the ketone. A steric effect was observed for Entry **g**, the increase of the steric congestion on phenyl ring with trimethoxy groups obviously reduced reaction yield. Under the conditions employed, oxazepine formation was not observed in toluene in the absence of Pd-catalyst for any of the substrates examined in Table 1.

The proposed mechanism for the intramolecular Pd-catalyzed coupling reaction of an aryl bromide with an alcohol is shown in Scheme 4. The reaction occurs by oxidative addition of the aryl bromide, subsequent generation of the palladium oxametallacycle, and C–O bond-forming reductive elimination. Although aryl bromide intermediates were generated independently and were shown to be kinetically competent to be intermediates, the oxametallacycles could not be observed or isolated.

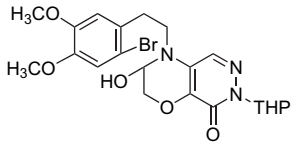
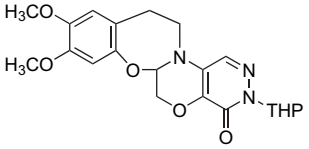
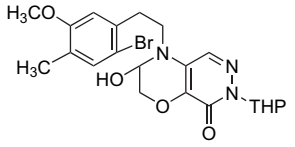
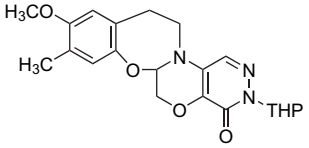
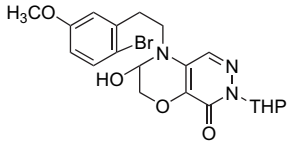
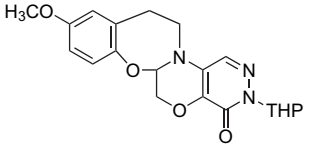
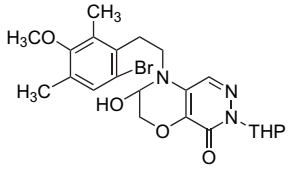
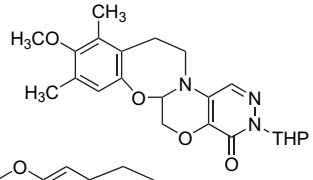
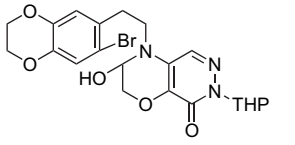
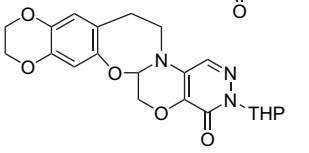
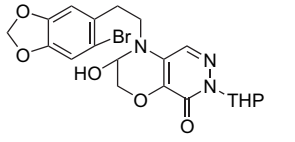
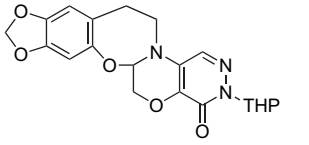
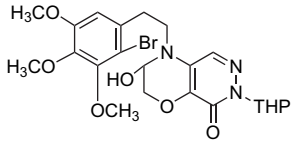
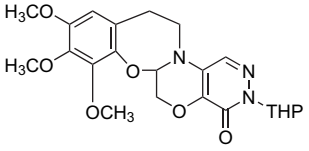
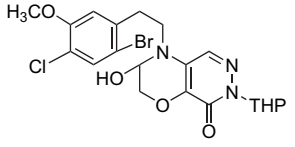
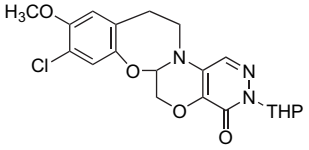
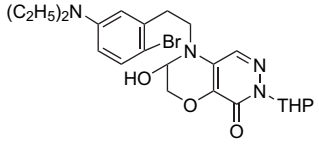
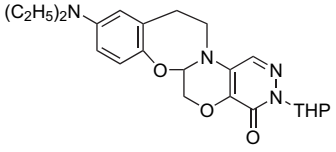
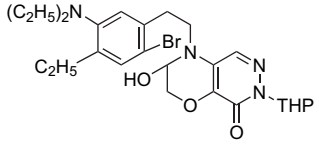
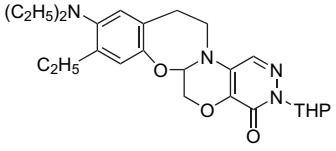


Scheme 4. The proposed mechanism for the intramolecular Pd-catalyzed coupling reaction of an aryl bromide with an alcohol.

3. Conclusion

In summary, we have developed a useful synthetic method for oxazepine ring systems. The best conditions for this reaction were $Pd(OAc)_2$ as a palladium source, 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) as the ligand, and K_2CO_3 as base at 80 °C in toluene. This approach may give access to useful intermediates for the synthesis of natural products and hitherto unknown pharmaceuticals.

Table 1. Pd-catalyzed synthesis of oxazepines containing pyridazinone moiety

Entry	Substrate **1**	Ligand	Base	Product **2**	Yield (%)[a]
a		DPPF	K_2CO_3		62
b		DPPF	K_2CO_3		70
c		DPPF	K_2CO_3		65
d		DPPF	K_2CO_3		55
e		DPPF	K_2CO_3		63
f		DPPF	K_2CO_3		58
g		DPPF	K_2CO_3		26
h		DPPF	K_2CO_3		71
i		DPPF	K_2CO_3		53
j		DPPF	K_2CO_3		46

[a] Yields refer to the average of isolated yields for two or more runs.

4. Experimental

4.1. General

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra (300 MHz for ^1H and 75 MHz for ^{13}C) were recorded in $CDCl_3$ with $CHCl_3$ as an internal reference on a Varian spectrometer. IR spectra were recorded on FTIR Nicolet Impect 410 spectrophotometer. Elemental analyses were performed on a Perkin–Elmer 2400 elemental analyzer. Thin layer chromatography (TLC) was performed

on Merck silica gel plates, with the compounds being identified in one or more of the following manners: UV (UL listed 977c inspection equipment), 25% PMA solution (phosphomolybdic acid and ethanol). Column chromatography was performed on Merck D-6100 silica gel 60 (70–230 mesh, ASTM). All solvents were distilled before use. Glassware was dried in an oven at 110 °C overnight.

4.2. 4,5-Dichloro-3(2*H*)-pyridazinone (3)[9b]

To a 250-mL flask equipped with a magnetic stirrer was added sodium acetate (27.2 g, 213 mmol) and hydrazine sulfate (17.7 g, 213 mmol) in ethanol/H_2O (v/v:1/1) (120 mL). The mixture was heated to 60 °C for 1 h, then, mucochloric acid (30 g, 178 mmol) was added to the warm solution. The solution was stirred under reflux for 4 h, followed by cooling to room temperature, then, filtered. The residue was washed with water, dried at room temperature to obtain slight yellow product **3** in 92% yield. Mp 198–200 °C; IR (KBr) 3250, 3200, 3031, 2864, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.5, 137.2, 139.4, 167.5; Anal. Calcd for $C_4H_2Cl_2N_2O$: C, 29.12; H, 1.22; N, 16.98. Found: C, 29.16; H, 1.32; N, 17.06%.

4.3. 4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (4)

4,5-Dichloro-3(2*H*)-pyridazinone (30 g, 181.8 mmol), dihydropyran (19.4 g, 230.8 mmol), *p*-toluenesulfonic acid monohydrate (2.83 g, 14.9 mmol), and 160 mL of tetrahydrofuran were added to a 500-mL round bottomed flask equipped with a beating mantle, reflux condenser, and a mechanical stirrer. The mixture was stirred at reflux for 29 h. Additional dihydropyran was added at 6 h (13.3 g, 157.9 mmol) and at 21 h (7.8 g, 92.5 mmol). The reaction mixture was allowed to cool to room temperature overnight. The mixture was concentrated in vacuo to an oily residue. The residue was taken up in 160 mL of ethyl acetate and washed with 2 N sodium hydroxide. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to give 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**), which was a black oily solid, which was used without further purification in the next step. The product was purified by filtration through silica gel with ethyl acetate followed by evaporation and recrystallization from ethyl acetate/cyclohexane to give a white solid. Mp 75–77 °C; IR (KBr) 3078, 2923, 2853, 1670, 1573, 1460, 1382, 1320, 1235, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.01 (d, J=10.8 Hz, 1H), 4.13 (d, J=13.5 Hz, 1H), 3.70–3.81 (m, 1H), 2.03–2.17 (m, 2H), 1.58–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.9, 28.0, 66.7, 73.3, 112.0, 129.7, 132.8, 155.4; Anal. Calcd for $C_9H_{10}N_2O_2Cl_2$: C, 43.40; H, 4.05; N, 11.25. Found: C, 43.28; H, 4.16; N, 11.07%.

4.4. 4-Chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (5)

4,5-Dichloro-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**4**) from the previous step and 170 mL of methanol were added to a 500-mL round bottomed flask equipped with a glycol cooling jacket and a mechanical stirrer. The resulting solution was cooled to 0 °C and 87% potassium hydroxide (11.7 g, 181.7 mmol) was added in portions over approximately 1 h. The mixture was heated to 40 °C. Following the addition, the mixture was allowed to stir for an additional 3 h at ambient temperature. The reaction mixture was partitioned with 120 mL of ethyl acetate and 120 mL of water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). The organic solution was clarified by filtration and concentrated to give a dark semi-solid. The crude material was equally divided and added to two 220-mL flasks. The material was suspended and stirred in 120 mL hexane/ethyl ether (2:1). The washed material was vacuum filtered on a Buchner funnel and air dried overnight to give 34.1 g (77% over two steps) of 4-chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**5**) as a dark solid suitable for further transformations. The product was purified by recrystallization from ethyl acetate/cyclohexane to give a white solid. Mp 116–118 °C; IR (KBr) 3062, 2933, 2860, 1678, 1556, 1400, 1365, 1230, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.10–4.19 (m, 1H), 4.08 (s, 3H), 3.71–3.82 (m, 1H), 2.03–2.17 (m, 2H), 1.60–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 25.1, 28.2, 66.8, 68.3, 73.5, 111.4, 129.2, 134.0, 155.2; Anal. Calcd for $C_{10}H_{13}N_2O_3Cl$: C, 49.09; H, 5.36; N, 11.45. Found: C, 49.23; H, 5.33; N, 11.51%.

4.5. 4-Chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (6)

To a 500-mL flask was added 4-chloro-5-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**5**) (45 g, 184 mmol) and potassium hydroxide (12.4 g, 220.8 mmol) in water (150 mL). The mixture solution was heated to reflux for 3 h, then, cooled to room temperature and 1 N HCl aqueous solution was added dropwise to cooled solution (pH= 5–6). The mixture solution was filtered and residue was washed with water. The crude product was purified by recrystallization from methanol/hexane to give 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) as a white solid in 86.5% yield. Mp 135–137 °C; IR (KBr) 3397, 2967, 2865, 2569, 1638, 1588, 1410, 1301, 1205, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.45–7.56 (m, 1H), 6.03 (d, J=10.5 Hz, 1H), 4.12 (d, J=13.2 Hz, 1H), 3.72–3.80 (m, 1H), 2.03–2.17 (m, 2H), 1.63–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 24.9, 28.2, 66.7, 73.5, 111.5, 129.1, 133.8, 155.3; Anal. Calcd for $C_9H_{11}N_2O_3Cl$: C, 46.87; H, 4.81; N, 12.15. Found: C, 46.95; H, 4.78; N, 12.10%.

4.6. *N*-(3,4-Dimethoxyphenethyl)-2-chloroacetamide (7a)

A solution of chloroacetyl chloride (3.6 g, 32.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of (3,4-dimethoxyphenyl)ethyl amine (5.3 g, 29.6 mmol) and K_2CO_3 (4.5 g, 32.6 mmol) in CH_2Cl_2 (150 mL) at room temperature. The mixture solution was refluxed for 2 h, cooled to room temperature and H_2O was added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash column chromatography using CH_2Cl_2 as eluent to afford

product **7** as a white solid with 92.1% yield. Mp 101–103 °C; IR (KBr) 3326, 3053, 2945, 1632, 1528, 1271, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67–6.82 (m, 3H), 6.53 (s, 1H), 4.23 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.26 (q, J=6.6 Hz, 2H), 2.55 (t, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 40.4, 45.8, 57.2, 58.0, 112.7, 115.4, 120.1, 133.6, 146.3, 147.8, 166.3; Anal. Calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.43. Found: C, 56.02; H, 6.19; N, 5.42%.

4.7. 4-(3,4-Dimethoxyphenethyl)-7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-dione (8a)

To a 250-mL flask equipped with a magnetic stirrer was added 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-3(2*H*)-pyridazinone (**6**) (4.24 g, 18.4 mmol), *N*-(3,4-dimethoxyphenethyl)-2-chloroacetamide (**7a**) (3.6 g, 18.4 mmol), and Cs_2CO_3 (7.2 g, 22.1 mmol) in CH_3CN (100 mL). The mixture was heated to reflux for 60 h, monitored by TLC. Then CH_3CN was removed under reduced pressure and CH_2Cl_2/H_2O was added. The phases were separated and aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using EtOAc/CH_2Cl_2 (30%) as eluent to afford the product **8a** as a thin yellow solid with 83.7% yield. Mp 181–183 °C; IR (KBr) 3020, 2940, 2861, 1702, 1659, 1625, 1532, 1430, 1376, 1315, 1276, 1245, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.69–6.80 (m, 3H), 6.10 (d, J=10.8 Hz, 1H), 4.74–4.87 (m, 1H), 3.96–4.15 (m, 3H), 3.73–3.86 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 (t, J=7.2 Hz, 2H), 2.02–2.12 (m, 2H), 1.61–1.74 (m, 4H), 1.57 (d, J=4.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 24.8, 28.9, 33.7, 43.0, 55.8, 68.8, 74.3, 76.6, 82.7, 108.1, 111.3, 111.7, 120.7, 124.9, 127.2, 129.2, 147.7, 149.0, 160.2, 164.4; Anal. Calcd for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.62; H, 6.16; N, 10.03%.

4.8. 4-(2-Bromo-4,5-dimethoxyphenethyl)-7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8(4*H*,7*H*)-dione (9a)

A solution of NBS (1.78 g, 10 mmol) in dry DMF (20 mL) was added to a solution of substrate **8a** (4.15 g, 10 mmol) in dry DMF (20 mL) and stirred at room temperature for 48 h. The mixture was poured into water (100 mL) and extracted with dichloromethane (200 mL). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to yield crude monobromide. The crude product was separated by flash column chromatography using EtOAc/CH_2Cl_2 (20%) as eluent to afford the product **9a** as a thin yellow solid with 82.2% yield. Mp 175–177 °C; IR (KBr) 3034, 2952, 2863, 1705, 1650, 1542, 1421, 1376, 1257, 1215, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.72–6.78 (m, 2H), 6.12 (d, J=10.8 Hz, 1H), 4.75–4.86 (m, 1H), 3.99–4.16 (m, 3H), 3.74–3.86 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.84 (t, J=7.5 Hz, 2H), 2.00–2.11 (m, 2H), 1.62–1.74 (m, 4H), 1.55 (d, J=5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.2, 28.8, 34.0, 43.2, 55.8, 68.6, 73.8, 75.5, 83.5, 106.3, 112.5, 119.8, 126.0, 128.2, 129.4, 135.6, 147.7, 148.6, 159.3, 164.8; Anal. Calcd for $C_{21}H_{24}BrN_3O_6$: C, 51.02; H, 4.89; N, 8.50. Found: C, 50.95; H, 4.97; N, 8.58%.

4.9. 4-(2-Bromo-4,5-dimethoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1a)

To a 100-mL flask equipped with a magnetic stirrer was added compound **9a** (2.47 g, 5 mmol) in CH_3OH (50 mL). The mixture was cooled to 0 °C in an ice bath and $NaBH_4$ (0.22 g, 6 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then CH_3OH was removed under reduced pressure. CH_2Cl_2 was added to the residue and stirred for 10 min, then filtered and washed with CH_2Cl_2. The solvent was evaporated in vacuo. The crude product was purified by flash column chromatography using EtOAc/CH_2Cl_2 as eluent to afford the product **1a** as a thin yellow solid with 89.6% yield. Mp 223–225 °C; IR (KBr) 3310, 3012, 2973, 2860, 1645, 1612, 1530, 1273, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.67–6.82 (m, 2H), 6.10 (d, J=10.8 Hz, 1H), 4.42–4.49 (m, 2H), 4.06–4.17 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.58–3.82 (m, 4H), 2.88–2.92 (m, 2H), 2.01–2.17 (m, 2H), 1.60–1.71 (m, 4H), 1.42–1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 25.1, 29.1, 34.1, 43.6, 47.0, 55.8, 67.4, 69.7, 74.2, 83.6, 109.5, 112.4, 121.6, 126.3, 127.9, 129.2, 136.2, 147.5, 149.3, 163.9; Anal. Calcd for $C_{21}H_{26}BrN_3O_6$: C, 50.82; H, 5.28; N, 8.47. Found: C, 50.77; H, 5.35; N, 8.42%.

4.10. 4-(2-Bromo-5-methoxy-4-methylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1b)

Mp 215–218 °C; IR (KBr) 3321, 3018, 2957, 2845, 1643, 1550, 1272, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.73–6.84 (m, 2H), 6.12 (d, J=10.8 Hz, 1H), 4.38–4.47 (m, 2H), 4.05–4.16 (m, 1H), 3.85 (s, 3H), 3.63–3.79 (m, 4H), 2.82–2.90 (m, 2H), 2.31 (s, 3H), 2.05–2.18 (m, 2H), 1.63–1.75 (m, 4H), 1.40–1.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.8, 28.4, 32.5, 36.5, 44.3, 47.6, 57.2, 67.9, 71.3, 84.1, 107.9, 115.3, 119.5, 124.8, 126.9, 129.4, 137.5, 148.1, 149.7, 162.5; Anal. Calcd for $C_{21}H_{26}BrN_3O_5$: C, 52.51; H, 5.46; N, 8.75. Found: C, 52.54; H, 5.51; N, 8.67%.

4.11. 4-(2-Bromo-5-methoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1c)

Mp 219–221 °C; IR (KBr) 3332, 3026, 2961, 2845, 1631, 1547, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.64–6.81 (m, 3H), 6.04 (d, J=10.5 Hz, 1H), 4.35–4.46 (m, 2H), 4.11–4.18 (m, 1H), 3.87 (s, 3H), 3.60–3.78 (m, 4H), 2.85–2.94 (m, 2H), 1.97–2.13 (m, 2H), 1.65–1.72 (m, 4H), 1.44–1.52 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.1, 30.6, 34.3, 44.2, 47.7, 56.4, 65.1, 74.8, 85.0, 110.6, 113.9, 121.3, 127.0, 129.1, 131.2, 135.5, 146.3, 148.7, 164.2; Anal. Calcd for $C_{20}H_{24}BrN_3O_5$: C, 51.51; H, 5.19; N, 9.01. Found: C, 51.61; H, 5.22; N, 8.93%.

4.12. 4-(6-Bromo-3-methoxy-2,4-dimethylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1d)

Mp 210–212 °C; IR (KBr) 3301, 3014, 2961, 2849, 1637, 1540, 1273, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.80 (s, 1H), 6.12 (d, J=10.2 Hz, 1H), 4.43–4.52 (m, 2H), 4.12–4.19 (m, 1H), 3.85 (s, 3H), 3.61–3.75 (m, 4H), 2.80–2.91 (m, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.07–2.15 (m, 2H), 1.63–1.74 (m, 4H), 1.42–1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 26.4, 29.1, 32.3, 33.6, 38.2, 43.8, 47.5, 59.7, 68.3, 71.8, 82.9, 109.1, 116.6, 118.9, 125.0, 127.2, 133.4, 137.2, 147.2, 148.6, 163.7; Anal. Calcd for $C_{22}H_{28}BrN_3O_5$: C, 53.45; H, 5.71; N, 8.50. Found: C, 53.39; H, 5.72; N, 8.44%.

4.13. 4-(2-(6-Bromo-2,3-dihydrobenzo[*b*][1,4]dioxin-7-yl)ethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1e)

Mp 220–222 °C; IR (KBr) 3296, 3021, 2963, 2842, 1633, 1614, 1537, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.72–6.82 (m, 2H), 6.14 (d, J=10.8 Hz, 1H), 4.40–4.48 (m, 2H), 4.06–4.28 (m, 5H), 3.62–3.80 (m, 4H), 2.87–2.96 (m, 2H), 2.05–2.16 (m, 2H), 1.63–1.73 (m, 4H), 1.42–1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.4, 28.6, 34.7, 44.7, 47.2, 57.9, 68.3, 69.9, 76.1, 84.6, 107.8, 111.6, 120.5, 127.2, 127.8, 131.5, 136.1, 145.4, 148.0, 163.5; Anal. Calcd for $C_{21}H_{24}BrN_3O_6$: C, 51.02; H, 4.89; N, 8.50. Found: C, 50.95; H, 4.96; N, 8.45%.

4.14. 4-(2-(5-Bromobenzo[*d*][1,3]dioxol-6-yl)ethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1f)

Mp 223–225 °C; IR (KBr) 3282, 3027, 2953, 2849, 1621, 1604, 1538, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 6.73–6.82 (m, 2H), 6.10 (d, J=10.5 Hz, 1H), 4.37–4.46 (m, 2H), 4.14–4.27 (m, 3H), 3.55–3.72 (m, 4H), 2.83–2.95 (m, 2H), 2.02–2.15 (m, 2H), 1.63–1.71 (m, 4H), 1.38–1.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 25.2, 28.7, 35.3, 46.0, 47.7, 56.1, 72.4, 76.5, 83.6, 108.5, 113.0, 121.3, 126.1, 127.9, 132.8, 135.9, 146.2, 148.6, 164.4; Anal. Calcd for $C_{20}H_{22}BrN_3O_6$: C, 50.01; H, 4.62; N, 8.75. Found: C, 50.10; H, 4.61; N, 8.63%.

4.15. 4-(2-Bromo-3,4,5-trimethoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1g)

Mp 225–226 °C; IR (KBr) 3332, 3017, 2946, 2862, 1640, 1617, 1535, 1275, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.86 (s, 1H), 6.13 (d, J=10.5 Hz, 1H), 4.43–4.52 (m, 2H), 4.07–4.16 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.62–3.80 (m, 4H), 2.87–2.95 (m, 2H), 2.00–2.14 (m, 2H), 1.62–1.71 (m, 4H), 1.41–1.51 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 25.6, 30.2, 34.5, 42.2, 47.9, 54.4, 67.5, 69.9, 71.6, 73.8, 84.0, 108.6, 112.2, 122.7, 127.3, 128.5, 129.8, 135.5, 146.1, 148.8, 163.3; Anal. Calcd for $C_{22}H_{28}BrN_3O_7$: C, 50.20; H, 5.36; N, 7.98. Found: C, 50.33; H, 5.47; N, 7.91%.

4.16. 4-(2-Bromo-4-chloro-5-methoxyphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1h)

Mp 211–213 °C; IR (KBr) 3322, 3016, 2965, 2855, 1638, 1546, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.64–6.78 (m, 2H), 6.06 (d, J=10.5 Hz, 1H), 4.30–4.41 (m, 2H), 4.13–4.20 (m, 1H), 3.89 (s, 3H), 3.60–3.73 (m, 4H), 2.88–2.97 (m, 2H), 1.99–2.13 (m, 2H), 1.62–1.71 (m, 4H), 1.45–1.54 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 24.3, 30.1, 35.2, 45.6, 46.7, 57.7, 65.2, 75.1, 84.6, 110.8, 114.9, 121.4, 126.8, 129.3, 134.5, 135.8, 145.3, 147.9, 164.6; Anal. Calcd for $C_{20}H_{23}BrClN_3O_5$: C, 47.97; H, 4.63; N, 8.39. Found: C, 48.05; H, 4.65; N, 8.48%.

4.17. 4-(2-Bromo-5-(diethylamino)phenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1i)

Mp 202–204 °C; IR (KBr) 3309, 3036, 2951, 2855, 1636, 1542, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.67–6.84 (m, 3H), 6.04 (d, J=10.5 Hz, 1H), 4.30–4.41 (m, 2H), 4.10–4.19 (m, 1H), 3.62–3.77 (m, 4H), 2.74–2.99 (m, 6H), 1.98–2.14 (m, 2H), 1.65–1.75 (m, 4H), 1.43–1.55 (m, 3H), 1.19 (t, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.7, 25.0, 31.8, 34.6, 43.1, 48.4, 56.7, 65.2, 73.3, 85.5, 112.6, 113.2, 123.0, 127.8, 131.1, 132.5, 135.2, 146.2, 148.6, 164.6; Anal. Calcd for $C_{23}H_{31}BrN_4O_4$: C, 54.44; H, 6.16; N, 11.04. Found: C, 54.28; H, 6.19; N, 10.87%.

4.18. 4-(2-Bromo-5-(diethylamino)-4-ethylphenethyl)-3,4-dihydro-7-(tetrahydro-2*H*-pyran-2-yl)-3-hydroxy-2*H*-pyridazino[4,5-*b*][1,4]oxazin-8(7*H*)-one (1j)

Mp 196–199 °C; IR (KBr) 3317, 3024, 2956, 2847, 1628, 1544, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.72–6.86 (m, 2H), 6.08 (d, J=10.5 Hz, 1H), 4.31–4.44 (m, 2H), 4.05–4.13 (m, 1H), 3.64–3.77 (m, 4H), 2.72–2.95 (m, 6H), 1.99–2.23 (m, 4H), 1.63–1.75 (m, 4H), 1.46–1.56 (m, 3H), 1.16–1.23 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 14.4, 23.9, 25.6, 29.4, 32.3, 34.2, 41.7, 48.1, 57.5, 67.3, 72.8, 85.4, 111.5, 113.0, 122.6, 127.9, 131.5, 133.4, 136.1, 145.2, 147.9, 164.3; Anal. Calcd for $C_{25}H_{35}BrN_4O_4$: C, 56.08; H, 6.59; N, 10.46. Found: C, 56.13; H, 6.45; N, 10.40%.

4.19. 9,10-Dimethoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2a)

A round bottom flask was flushed with nitrogen and charged with 5 mol % $Pd(OAc)_2$, 10 mol % DPPF, and toluene. The mixture was stirred under nitrogen for 10 min. In another round bottom flask substrate **1** and K_2CO_3 were weighed. Then, $Pd(OAc)_2$/DPPF solution was added, and the flask was rinsed with an additional toluene. The resulting mixture was heated to 80 °C under N_2 with vigorous stirring until the starting substrate **1** had disappeared as judged by TLC. After cooling down, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated and the crude product was purified by flash column chromatography using EtOAc/CH_2Cl_2 (30%) as eluent to afford the

product as a white solid in 62% yield. Mp 195–197 °C; IR (KBr) 3069, 2980, 2938, 2860, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 6.17–6.25 (m, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.40–4.46 (m, 2H), 4.10–4.15 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.73–3.78 (m, 1H), 3.58–3.67 (m, 2H), 2.87 (t, J=7.2 Hz, 2H), 2.08–2.17 (m, 2H), 1.61–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 24.8, 28.9, 33.7, 43.0, 55.8, 68.8, 74.3, 76.6, 82.7, 85.3, 111.3, 111.7, 120.7, 124.9, 127.2, 129.2, 148.0, 148.7, 155.2, 167.4; Anal. Calcd for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.76; H, 6.11; N, 10.02%.

4.20. 10-Methoxy-9-methyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2b)

Prepared as a thin yellow solid in 70% yield. Mp 189–191 °C; IR (KBr) 3067, 2983, 2945, 2862, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.85 (s, 1H), 6.68 (s, 1H), 6.14–6.23 (m, 1H), 6.04 (d, J=10.2 Hz, 1H), 4.37–4.45 (m, 2H), 4.11–4.15 (m, 1H), 3.87 (s, 3H), 3.70–3.76 (m, 1H), 3.60–3.68 (m, 2H), 2.86 (t, J=7.2 Hz, 2H), 2.31 (s, 3H), 2.05–2.16 (m, 2H), 1.64–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.7, 28.7, 33.7, 42.6, 56.3, 68.9, 75.1, 76.3, 82.6, 85.4, 111.8, 111.9, 122.3, 124.7, 126.7, 129.2, 148.0, 148.7, 154.9, 167.5; Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.26; H, 6.32; N, 10.45%.

4.21. 10-Methoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]-cyclohepta[1,2-*a*]naphthalen-4-one (2c)

Prepared as a white solid in 65% yield. Mp 202–205 °C; IR (KBr) 3072, 2985, 2947, 2870, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.71–6.85 (m, 3H), 6.18–6.27 (m, 1H), 6.10 (d, J=10.5 Hz, 1H), 4.40–4.47 (m, 2H), 4.08–4.14 (m, 1H), 3.86 (s, 3H), 3.71–3.77 (m, 1H), 3.59–3.69 (m, 2H), 2.83 (t, J=6.9 Hz, 2H), 2.10–2.18 (m, 2H), 1.60–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 24.7, 29.1, 34.0, 42.7, 56.3, 68.8, 75.8, 82.5, 84.2, 111.5, 112.4, 115.4, 121.6, 124.95, 127.3, 128.3, 147.9, 148.7, 156.4, 168.0; Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.38; H, 6.07; N, 10.79%.

4.22. 10-Methoxy-9,11-dimethyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2d)

Prepared as a white solid in 55% yield. Mp 192–194 °C; IR (KBr) 3062, 2955, 2857, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 6.82 (s, 1H), 6.22–6.31 (m, 1H), 6.11 (d, J=10.5 Hz, 1H), 4.36–4.43 (m, 2H), 4.10–4.15 (m, 1H), 3.88 (s, 3H), 3.68–3.75 (m, 1H), 3.60–3.67 (m, 2H), 2.84 (t, J=7.5 Hz, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.06–2.16 (m, 2H), 1.67–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 24.8, 25.7, 29.5, 34.6, 42.7, 55.9, 68.8, 75.3, 76.3, 83.2, 85.4, 111.7, 122.2, 124.9, 126.6, 128.0, 135.3, 148.3, 149.5, 155.1, 167.7; Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.82; H, 6.62; N, 10.11%.

4.23. 3-(Tetrahydro-pyran-2-yl)-6,6a,10,11,14,15-hexahydro-3*H*-5,7,9,12-tetraoxa-2,3,15a-triaza-cyclohepta[1,2-*a*;4,5-*b*']dinaphthalen-4-one (2e)

Prepared as a white solid in 63% yield. Mp 205–207 °C; IR (KBr) 3066, 2983, 2948, 2849, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.80 (s, 1H), 6.71 (s, 1H), 6.19–6.27 (m, 1H), 6.09 (d, J=10.2 Hz, 1H), 4.22–4.45 (m, 6H), 4.08–4.15 (m, 1H), 3.73–3.80 (m, 1H), 3.56–3.65 (m, 2H), 2.85 (t, J=6.9 Hz, 2H), 2.10–2.19 (m, 2H), 1.60–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 24.8, 28.9, 34.1, 43.3, 56.2, 68.3, 74.1, 76.0, 82.1, 84.7, 111.4, 111.7, 121.3, 125.6, 127.3, 129.9, 146.3, 149.6, 155.1, 167.5; Anal. Calcd for $C_{21}H_{23}N_3O_6$: C, 61.01; H, 5.61; N, 10.16. Found: C, 60.95; H, 5.71; N, 10.13%.

4.24. 9,10-Methylenedioxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2f)

Prepared as a white solid in 58% yield. Mp 209–211 °C; IR (KBr) 3058, 2976, 2943, 2862, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.8 (s, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 6.16–6.25 (m, 1H), 6.08 (d, J=10.8 Hz, 1H), 4.95 (s, 2H), 4.39–4.46 (m, 2H), 4.07–4.13 (m, 1H), 3.71–3.79 (m, 1H), 3.60–3.68 (m, 2H), 2.92 (t, J=7.5 Hz, 2H), 2.05–2.15 (m, 2H), 1.60–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 24.7, 28.4, 33.5, 42.2, 56.7, 68.4, 76.2, 83.1, 85.3, 111.7, 112.5, 122.0, 124.4, 127.6, 130.2, 147.7, 150.2, 154.8, 167.6; Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.15; H, 5.43; N, 10.37%.

4.25. 8,9,10-Trimethoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2g)

Prepared as a white solid in 26% yield. Mp 212–215 °C; IR (KBr) 3062, 2971, 2943, 2848, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.68 (s, 1H), 6.15–6.23 (m, 1H), 6.06 (d, J=10.2 Hz, 1H), 4.41–4.48 (m, 2H), 4.13–4.19 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.70–3.76 (m, 1H), 3.53–3.62 (m, 2H), 2.85 (t, J=7.5 Hz, 2H), 2.08–2.16 (m, 2H), 1.58–1.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.9, 29.1, 33.5, 43.7, 57.0, 69.4, 71.2, 74.6, 77.3, 82.7, 85.1, 111.4, 121.8, 125.4, 128.0, 131.6, 138.3, 148.0, 149.6, 154.4, 167.7; Anal. Calcd for $C_{22}H_{27}N_3O_7$: C, 59.32; H, 6.11; N, 9.43. Found: C, 59.46; H, 6.17; N, 9.38%.

4.26. 9-Chloro-10-methoxy-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2h)

Prepared as a white solid in 71% yield. Mp 202–204 °C; IR (KBr) 3053, 2948, 2855, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.82 (s, 1H), 6.65 (s, 1H), 6.23–6.30 (m, 1H), 6.05 (d, J=10.8 Hz, 1H), 4.41–4.48 (m, 2H), 4.14–4.19 (m, 1H), 3.87 (s, 3H), 3.62–3.67 (m, 1H), 3.50–3.58 (m, 2H), 2.72 (t, J=7.5 Hz, 2H), 2.04–2.12 (m, 2H), 1.57–1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 27.9, 34.2, 42.3, 58.1, 65.8, 74.3, 76.5, 81.4, 84.2, 111.5, 113.7, 121.8, 124.5, 128.2, 130.8, 146.1, 148.8, 155.0,

166.4; Anal. Calcd for $C_{20}H_{22}ClN_3O_5$: C, 57.21; H, 5.28; N, 10.01. Found: C, 57.26; H, 5.32; N, 10.08%.

4.27. 10-Diethylamino-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2i)

Prepared as a thin yellow solid in 53% yield. Mp 182–184 °C; IR (KBr) 3058, 2961, 2945, 2850, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.72–6.83 (m, 3H), 6.14–6.21 (m, 1H), 6.06 (d, J=10.2 Hz, 1H), 4.36–4.41 (m, 2H), 4.06–4.12 (m, 1H), 3.70–3.77 (m, 1H), 3.56–3.65 (m, 2H), 3.32 (q, J=6.6 Hz, 4H), 2.83 (t, J=6.9 Hz, 2H), 2.10–2.18 (m, 2H), 1.60–1.70 (m, 4H), 1.22 (t, J=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.3, 24.8, 28.9, 33.8, 42.7, 45.7, 56.6, 75.4, 82.0, 83.9, 111.6, 112.1, 116.4, 122.7, 124.8, 127.4, 128.3, 146.7, 148.3, 158.2, 167.3; Anal. Calcd for $C_{23}H_{30}N_4O_4$: C, 64.77; H, 7.09; N, 13.14. Found: C, 64.67; H, 7.07; N, 13.02%.

4.28. 10-Diethylamino-9-ethyl-3-(tetrahydro-pyran-2-yl)-6,6a,12,13-tetrahydro-3*H*-5,7-dioxa-2,3,13a-triaza-benzo[4,5]cyclohepta[1,2-*a*]naphthalen-4-one (2j)

Prepared as a thin yellow solid in 46% yield. Mp 186–187 °C; IR (KBr) 3046, 2957, 2843, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 6.16–6.26 (m, 1H), 6.04 (d, J=9.9 Hz, 1H), 4.37–4.44 (m, 2H), 4.05–4.11 (m, 1H), 3.68–3.76 (m, 1H), 3.55–3.63 (m, 2H), 3.36 (q, J=6.6 Hz, 4H), 2.86 (t, J=6.9 Hz, 2H), 2.43 (q, J=5.4 Hz, 2H), 2.11–2.18 (m, 2H), 1.62–1.71 (m, 4H), 1.25 (t, J=6.3 Hz, 6H), 1.15 (t, J=5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 14.2, 17.6, 22.9, 24.7, 29.8, 35.2, 42.7, 46.3, 57.8, 74.3, 82.1, 84.2, 111.3, 117.1, 122.4, 125.7, 127.7, 129.7, 133.5, 145.3, 148.0, 157.8, 167.4; Anal. Calcd for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 65.95; H, 7.49; N, 12.36%.

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References and notes

1. (a) Serrano-Wu, M. H.; Laurent, D. R. S.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2757; (b) Matyus, P.; Varga, I.; Zara, E.; Mezei, A.; Behr, A.; Simay, A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2857; (c) Hallinan, E. A.; Hagen, T. J.; Tsymbalov, S.; Stapelfeld, A.; Savage, M. A. *Bioorg. Med. Chem.* **2001**, *9*, 1.
2. (a) Allaway, C. L.; Daly, M.; Nieuwenhuyzen, M.; Saunders, G. C. *J. Fluorine Chem.* **2002**, *115*, 91; (b) Chelucci, G.; Saba, A.; Valenti, R.; Bacchi, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3449; (c) Ouyang, X.; Tamayo, N.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 2827.
3. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (b) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (d) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875; (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
4. (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969; (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609; (c) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937; (d) Arnould, J. C.; Didelot, M.; Cadilhac, C.; Pasquet, M. J. *Tetrahedron Lett.* **1996**, *37*, 4523.
5. (a) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11695; (b) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236; (c) Ito, A.; Ono, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1072; (d) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027; (e) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.
6. (a) Ellis, G. P. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, NY, 1977; Vol. 31; (b) Mustafa, A. *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, NY, 1974; Vol. 29.
7. (a) Keeggstra, M. A.; Peters, T. H.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633; (b) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, *63*, 193; (c) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561; (d) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775.
8. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.
9. (a) Cho, S.-D.; Park, Y.-D.; Kim, J.-J.; Lee, S.-G.; Ma, C.; Song, S.-Y.; Joo, W.-H.; Falck, J. R.; Shiro, M.; Shin, D.-S.; Yoon, Y.-J. *J. Org. Chem.* **2003**, *68*, 7918; (b) Ma, C.; Cho, S.-D.; Falck, J. R.; Shin, D.-S. *Heterocycles* **2004**, *63*, 75; (c) Cho, S.-D.; Song, S.-Y.; Park, Y.-D.; Kim, J.-J.; Joo, W.-H.; Shiro, M.; Falck, J. R.; Shin, D.-S.; Yoon, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 8995.
10. (a) Mowry, D. T. *J. Am. Chem. Soc.* **1953**, *75*, 1909; (b) Niedballa, C.; Vorbruggen, H. *J. Org. Chem.* **1974**, *36*, 3672; (c) Dury, J.; Meier, K.; Eichenberger, K. *Helv. Chim. Acta* **1954**, *37*, 121; (d) Kuraishi, T. *Pharm. Bull.* **1956**, *5*, 376.
11. Bryant, R. D.; Kunng, F. A.; South, M. S. *J. Heterocycl. Chem.* **1995**, *32*, 1473.
12. Outten, R. A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 5064.