C–N Bond-Linked Conjugates of Dibenz[*b*,*f*][1,4]oxazepines with 2-Oxindole

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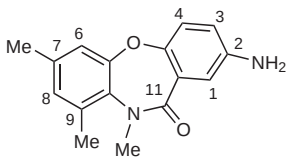
Abstract: An expeditious synthesis of highly functionalized dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones and dibenz[*b*,*f*][1,4]-oxazepine-11(10*H*)-carboxamides has been established via microwave-assisted one-pot U-4CR and intramolecular O-arylation. A Pd-catalyzed intramolecular amidation was successfully performed under microwave irradiation to furnish the novel conjugates of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones with a 2-oxindole linked through a C–N single bond.

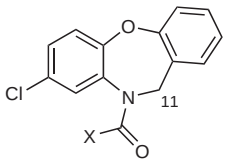
Key words: U-4CR, microwaves, heterocycles, palladium, lactams

Dibenz[*b*,*f*][1,4]oxazepines are found in many physiologically active compounds (Figure 1). Notably, compound **1** acts as a non-nucleoside inhibitor of HIV-1 reverse transcriptase with an IC_{50} value of 20 nM.[1] Other N-substituted dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones have been reported to exhibit antidepressant[2] and calcium antagonist activities.[3] Numerous derivatives **2** have been prepared and evaluated for PGE_2 antagonist and analgesic activities.[4] The majority of this class of active compounds features an N-substituted side chain with X = –NHNHC(O)R. In connection with our synthesis of bioactive heterocycles starting from 2-aminophenols,[5–7] we report here on a one-pot synthesis of highly functionalized dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **3** and dibenz-[*b*,*f*][1,4]oxazepine-11(10*H*)-carboxamides **4** via microwave-assisted one-pot U-4CR and O-arylation. Further post modification within **3** was successfully carried out, providing a novel class of conjugates **5** of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones with a 2-oxindole tethered through a C–N single bond.

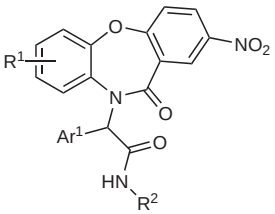
Nucleophilic aromatic substitution (S_NAr) is a common method used for synthesis of dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones starting from 2-aminophenols and 2-fluoro- or 2-chloro-5-nitrobenzoic acid.[8] For the 11-substituted analogues of **2** (X = O*t*-Bu), a benzylic lithiation–substitution strategy was applied by taking advantage of the *N*-Boc as the activator for α-lithiation.[9] For example, the 11-carboxylic acid of **2** (X = O*t*-Bu) was prepared in 97% yield. To the best of our knowledge, there is only one compound **3** (Ar^1 = $PhCH_2CH_2$, R^1 = H, R^2 = *i*-Pr) synthesized in 25% isolated yield via stepwise U-4CR[10,11]



1: HIV-1 RT inhibitor (IC_{50} = 20 nM)



2: PGE_2 antagonists



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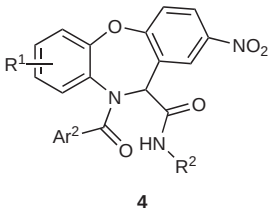

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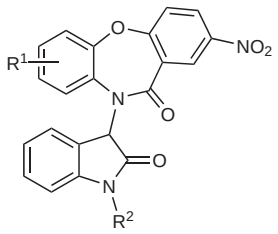

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Figure 1 Structures of dibenz[*b*,*f*][1,4]oxazepine-based HIV-1 RT inhibitor (**1**) and PGE_2 antagonists (**2**), and novel derivatives **3**–**5**

and S_NAr by using 2-fluoro-5-nitrobenzoic acid as the acid component.[12a] We envisaged that efficiency of the U-4CR–S_NAr[12] sequence to **3** could be improved by using controlled microwave heating in closed reaction vials.[7c,13] It might also allow replacing 2-fluoro-5-nitrobenzoic acid by 2-chloro-5-nitrobenzoic acid. Thus, a solution of 2-aminophenol **6**, aldehyde **7**, 2-chloro-5-nitrobenzoic acid (**8**), and isocyanide **9** in MeOH was heated at 80 °C in a closed reaction vial for 20 minutes on a technical microwave reactor, resulting in clean formation of **10** (Scheme 1). We initially tried the intramolecular S_NAr (O-arylation) by adding an aqueous solution of K_2CO_3 and heated the resultant mixture in refluxing MeOH. However, the expected dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one **3a** was not obtained from **10a** and instead the MeOH adduct was isolated (Table 1, entry 1). We reasoned that the intramolecular substitution might be difficult to occur in refluxing MeOH due to the ring strain. We then heated **10a** with the base in MeOH–H_2O (2:1) in a closed vial at 120 °C for 5–30 minutes, giving the desired

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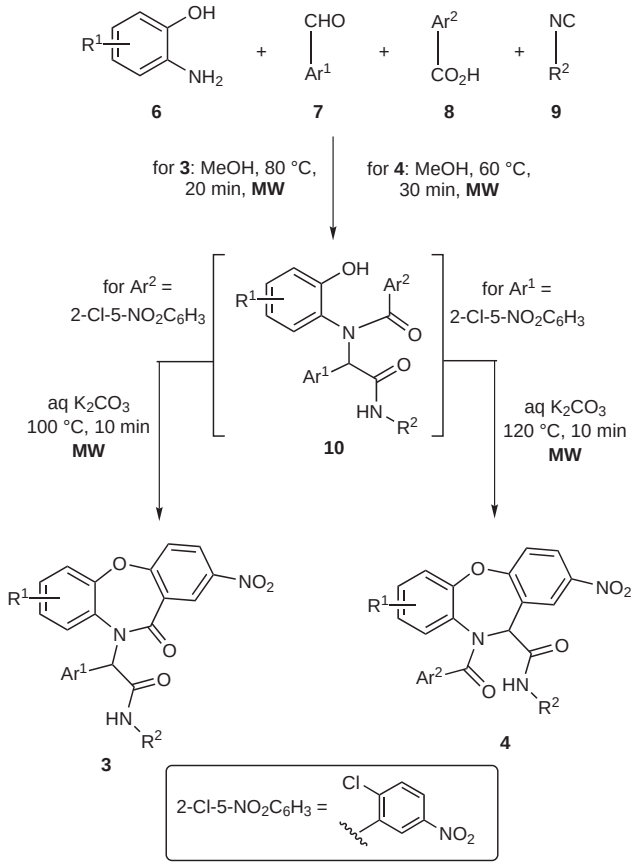

Scheme 1 Microwave-assisted one-pot synthesis of dibenz[*b*,*f*][1,4]-oxazepines **3** and **4** via U-4CR and intramolecular O-arylation

cyclization product **3a** in 43–75% yields (Table 1, entries 2–5). By lowering the temperature to 80–100 °C, we obtained **3a** in almost quantitative yields (Table 1, entries 6 and 7).

With the optimized reaction conditions, we developed a general one-pot protocol for synthesis of dibenz[*b*,*f*]-[1,4]oxazepin-11(10*H*)-ones **3a**–**h** by selecting six substituted 2-aminophenols and two isocyanides in combination with 2-bromobenzaldehyde and 2-chloro-5-nitrobenzoic acid. As shown in Scheme 1, a solution of **6**–**9** in MeOH was first heated at 80 °C for 20 min. After adding an aqueous solution of K_2CO_3 into the reaction vial through a syringe, the vial was heated again at 100 °C for 10 minutes. Dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones **3a**–**h** were prepared in 81–97% overall yields and the results are summarized in Table 2. The structure of **3c** was confirmed by X-ray crystallographic analysis (Figure 2),[14] featuring an 'antenna-like' curved 6/7/6-ring skeleton. Interestingly, compound **3c** forms a linear hydrogen-bond network in the crystals through the 2° amide moiety (Figure 3). The cyclohexyl ring is embedded into the pocket of the neighboring 6/7/6-ring skeleton.

We applied the microwave-assisted one-pot U-4CR and O-arylation protocol for the synthesis of **4** (Scheme 1). However, the U-4CR did not take place efficiently. We

Table 1 Optimization of Microwave-Assisted O-Arylation[a]

Entry	MW conditions	Yield (%)
1[b]	Refluxing MeOH	ND[c]
2[d]	120 °C, 20 min	43
3	120 °C, 15 min	43
4	120 °C, 30 min	46
5	120 °C, 5 min	75
6	100 °C, 10 min	94
7	80 °C, 30 min	93

[a] The U-4CR product **10a** was used as the substrate to form **3a** in MeOH–H_2O (2:1). All reactions were carried out on a technical microwave reactor in a closed pressurized vial with the temperature measured by an IR sensor. The reaction time is the hold time at the final temperature. K_2CO_3 (1.2 equiv) was used except for otherwise noted.
[b] Carried out in a open flask in an oil bath.
[c] The MeOH adduct of **10a** was formed.
[d] K_2CO_3 (1.5 equiv) was used.

Table 2 Synthesis of Dihydrodibenz[*b*,*f*][1,4]oxazepinones **3**[a]

Entry	**3**	R^1	R^2	Ar^1	Yield (%)	mp (°C)[b]
1	**3a**	H	Cy	*o*-BrC_6H_4	94	247–248
2	**3b**	8-Me	Cy	*o*-BrC_6H_4	96	201–203
3	**3c**	7-Me	Cy	*o*-BrC_6H_4	91	234–235
4	**3d**	8-Cl	Cy	*o*-BrC_6H_4	94	198–200
5	**3e**	8-*t*-Bu	Cy	*o*-BrC_6H_4	89	167–170
6	**3f**	H	Bn	*o*-BrC_6H_4	97	174–176
7	**3g**	8-Ph	Bn	*o*-BrC_6H_4	84	215–216
8	**3h**	8-Cl	Bn	*o*-BrC_6H_4	81	150–152

[a] The conditions for one-pot synthesis are (a) MeOH, 80 °C, 20 min for U-4CR; (b) MeOH–H_2O (2:1), 1.2 equiv of K_2CO_3, 100 °C, 10 min for O-arylation. See footnote 'a' in Table 1 for microwave reaction technique.
[b] Recrystallized from EtOAc–hexane.

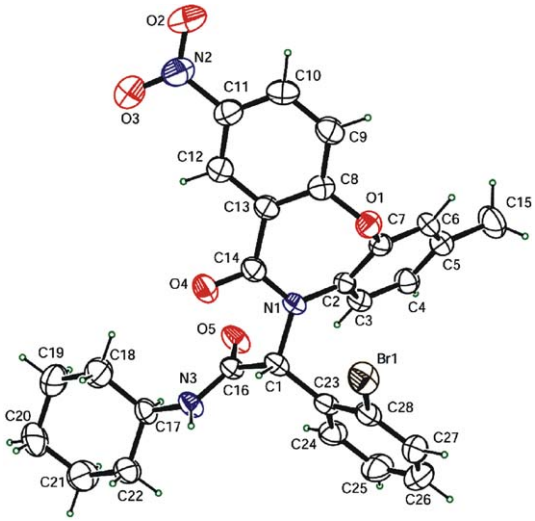

Figure 2 X-ray crystal structure of **3c**

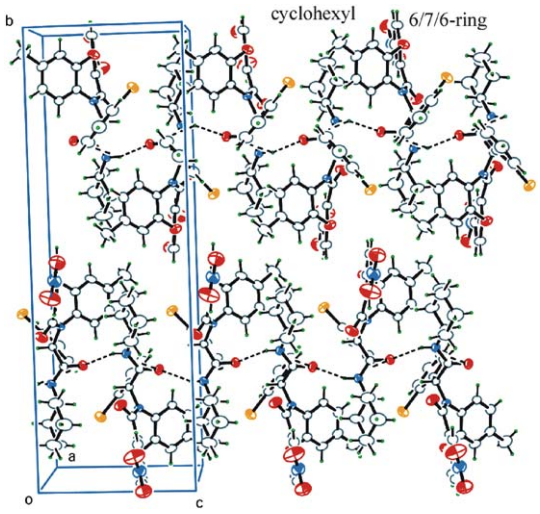

Figure 3 Four cell units in the crystal packing of **3c**, illustrating a linear hydrogen-bond network through the 2° amide moiety

assumed that 2-chloro-5-nitrobenzaldehyde condensed with the 2-aminophenol to form an electron-deficient imine, which might be difficult for protonation by the acid. Since formation of an immonium ion is suggested for the addition of an isocyanide in U-4CR,[11a] we expected that pK_a of the acid component might influence the end product yield. Indeed, we observed the pK_a effect on U-4CR by using four benzoic acids (Table 3). The overall yields of **4** were greatly improved with increasing acidity. In the case of *o*-bromobenzoic acid, **4d** was obtained in 49% yield (Table 3, entry 4).

We attempted an intramolecular amidation (N-arylation) within **3** under microwave heating to assemble a novel class of conjugates **5** (Figure 1). We have used a microwave-assisted CuI-catalyzed intramolecular amidation to construct the conjugates of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines with a 2-oxindole.[7c] However, the amidation conditions under Cu catalysis did not work for compounds **3**. In a very recent report, the Pd-catalyzed intramolecular amidation was used to form 2-oxindoles from the U-4CR products. However, only primary and benzylic isocyanide-derived substrates gave the amidation products in 25–45% yields.[15] We examined the Pd-catalyzed intramolecular amidation within **3** under controlled microwave heating.[16] Some results are listed in Table 4. With 5 mol% each of $Pd(OAc)_2$ and BINAP, **5a** was isolated in 77% and 85% yields, respectively, after heated in toluene at 150 °C for 40 and 60 minutes (Table 4, entries 1 and 2). The reaction carried out in DMSO at 180 °C did not yield **5a** (Table 4, entry 3). By increasing the catalyst loading to 10 mol%, a clean conversion of **3a** was realized to furnish **5a** in 94% yield (Table 4, entry 4).

With the optimized amidation conditions, we synthesized a number of the conjugates **5a**–**h** from **3a**–**h** in 70–94% yields (Table 5). Notably, our microwave-assisted Pd-catalyzed intramolecular amidation of the cyclohexyl-isocyanide-derived substrates **3a**–**e** afforded the 2-oxindole conjugates in good to excellent yields (Table 5,

Table 4 Optimization of Microwave-Assisted Amidation[a]

Entry	MW conditions	Yield (%)
1	Toluene, 150 °C, 40 min	77
2	Toluene, 150 °C, 60 min	85
3	DMSO, 180 °C, 40 min	Trace
4[b]	Toluene, 150 °C, 40 min	94

[a] Compound **3a** was used as the substrate to form **5a**. All reactions were carried out on a technical microwave reactor in the presence of 5 mol% $Pd(OAc)_2$, 5 mol% BINAP, and 2 equiv of K_2CO_3 except for otherwise noted. See footnote 'a' in Table 1 for microwave reaction technique.
[b] 10 mol% $Pd(OAc)_2$ and 10 mol% BINAP were used.

Table 3 Effect of pK_a on Microwave-Assisted Synthesis of **4**[a]

Entry	pK_a of **8**	**4**	R^1	R^2	Ar^2	Yield (%)
1	4.20	**4a**	8-Me	Cy	Ph	17
2	3.27	**4b**	8-Me	Cy	*o*-FC_6H_4	28
3	2.91	**4c**	8-Me	Cy	*o*-ClC_6H_4	38
4	2.85	**4d**	8-Me	Cy	*o*-BrC_6H_4	49

[a] Conditions for the one-pot synthesis: (a) MeOH, 60 °C, 30 min for U-4CR; (b) MeOH–H_2O (2:1), 1.2 equiv of K_2CO_3, 120 °C, 10 min for O-arylation. See footnote 'a' in Table 1 for microwave reaction technique.

Table 5 Microwave-Assisted Synthesis of Conjugates **5**[a]

Entry	5	R^1	R^2	Yield (%)	Mp (°C)[b]
1	**5a**	H	Cy	94	228–230
2	**5b**	8-Me	Cy	92	248–249
3	**5c**	7-Me	Cy	89	222–224
4	**5d**	8-Cl	Cy	76	249–250
5	**5e**	8-*t*-Bu	Cy	86	268–270
6	**5f**	H	Bn	88	210–212
7	**5g**	8-Ph	Bn	70	246–247
8	**5h**	8-Cl	Bn	90	NA[c]

[a] All reactions were carried out in toluene in the presence of 10 mol% $Pd(OAc)_2$, 10 mol% BINAP, and 2 equiv of K_2CO_3. The reactions were heated at 150 °C for 40 min. See footnote 'a' in Table 1 for microwave reaction technique.
[b] Recrystallized from EtOAc–hexane.
[c] Not crystalline.

entries 1–5). All compounds **5a**–**h** display atropisomerism in solution as evident from both ^{1}H NMR and ^{13}C NMR spectra taken at ambient temperature and at 80 °C.

In summary, we have established a general and efficient one-pot synthesis of highly functionalized dibenz-[*b*,*f*][1,4]oxazepines via microwave-assisted one-pot U-4CR and intramolecular O-arylation. Further post modification has also successful by formation of a 2-oxindole unit via the Pd-catalyzed intramolecular N-arylation under controlled microwave heating, which afforded superior results than a recent report[15] in terms of both product yields and substrate scope. In addition to the relevance of biological activity, the unique structures of dibenz[*b*,*f*][1,4]oxazepines **3**, **4**, and the conjugates **5**[17] may have potentials for studies in other areas, such as molecular recognition.

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(17) **Selected Spectroscopic Data.**

Compound **3c**: a white crystalline solid; mp 234–235 °C (EtOAc–hexane). IR (KBr): 3422, 2929, 1647, 1344 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.4 Hz, 1 H), 8.22 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 6.89 (s, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 6.13 (s, 1 H), 6.01 (br s, 1 H), 3.94–3.86 (m, 1 H), 2.14 (s, 3 H), 2.02–1.93 (m, 2 H), 1.71–1.55 (m, 3 H), 1.40–1.30 (m, 2 H), 1.23–1.12 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 165.6, 165.4, 154.4, 145.1, 138.3, 133.7, 133.6, 132.2, 130.5, 129.2, 128.7, 127.5, 127.5, 126.8 (br), 126.1, 121.7, 121.6, 68.3 (br and very weak), 49.4, 33.1, 33.1, 31.2 (for minor atropisomer), 25.8, 25.1, 25.0, 20.9 (two carbons are missing due to atropisomerism). MS (+ESI): *m/z* (%) = 586 (100) [M + Na^+]. Anal. Calcd for $C_{28}H_{26}BrN_3O_5$: C, 59.58; H, 4.64; N, 7.44. Found: C, 59.32; H, 4.63; N, 7.56.

Compound **4a**: a white crystalline solid; mp 171–174 °C (EtOAc–hexane); R_f = 0.25 (17% EtOAc in hexane). IR (KBr): 3280, 2929, 1654, 1522, 1345, 1266 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 8.8, 2.4 Hz, 1 H), 8.11 (d, *J* = 2.8 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.27–7.23 (m, 2 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.76 (s, 1 H), 6.40 (s, 1 H), 6.28 (br d, *J* = 8.0 Hz, 1 H), 3.70–3.60 (m, 1 H), 1.94 (s, 3 H), 1.88–1.84 (m, 1 H), 1.80–1.50 (m, 4 H), 1.40–1.08 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 166.3, 158.8, 148.9, 142.7, 135.3, 133.4, 131.5, 131.4, 130.1 (x2), 129.9 (x2), 128.9, 128.2, 127.5, 124.6, 123.8, 122.1, 121.2, 61.3, 48.4, 33.2, 32.7, 25.3, 24.6, 20.4. MS (+ESI): *m/z* (%) = 508 (100) [M + Na^+], 486 (14) [M + H^+]. Anal. Calcd for $C_{28}H_{27}N_3O_5$: C, 69.26; H, 5.61; N, 8.65. Found: C, 69.28; H, 5.65; N, 8.65.

Compound **5c**: a white crystalline solid; mp 222–224 °C. IR (KBr): 3448, 2924, 1654, 1348 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 80 °C): δ = 8.42 (br s, 1 H), 8.37 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.59 (d, *J* = 9.0 Hz, 1 H), 7.30–7.26 (m, 4 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 7.08 (br s, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 5.90–5.60 (br s, 1 H), 4.14–4.08 (m, 1 H), 2.31 (s, 3 H), 2.29–2.09 (m, 2 H), 1.89–1.70 (m, 5 H), 1.46–1.24 (m, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6, 80 °C): δ = 172.0, 164.3, 162.8 (br and weak), 152.5, 144.8, 143.2, 137.8, 131.4 (br and weak), 128.9, 128.7, 127.5, 127.5, 126.2, 125.5, 123.5 (br), 123.1 (br), 122.0, 121.8, 121.7, 109.8, 62.8 (br and weak), 52.6, 28.7, 28.4, 25.6, 25.0, 20.1. MS (+ESI): *m/z* 506 (100) [M + Na^+]. Anal. Calcd for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.21; N, 8.69. Found: C, 69.55; H, 5.23; N, 8.69.