Organic LETTERS

Letter

pubs.acs.org/OrgLett

Syntheses of D-Glucose Derivatives Emitting Blue Fluorescence through Pd-Catalyzed C−N Coupling

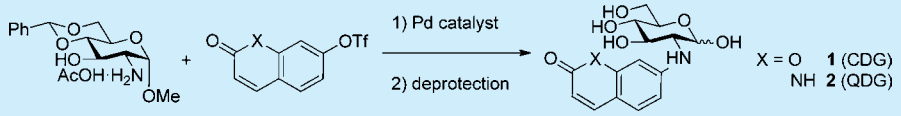
Yuji Otsuka,[†] Ayako Sasaki,[‡] Tadashi Teshima,[†] Katsuya Yamada,[*,‡] and Toshihiro Yamamoto[*,†,§]

[†]Peptide Institute, Inc., Saito Research Center, Ibaraki, Osaka 567-0085, Japan

[‡]Department of Physiology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori 036-8562, Japan

[§]Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

Supporting Information



ABSTRACT: Green fluorescence-emitting D-glucose derivatives such as 2-NBDG have been effectively used to monitor D-glucose uptake through glucose transporters GLUTs at the single cell level. By contrast, GLUT-permeable D-glucose derivatives emitting blue fluorescence have been long awaited. A glucose tracer, 2-deoxy-2-(2-oxo-2*H*-chromen-7-yl)amino-D-glucose (CDG) (**1**), together with related compounds have been synthesized by Pd-catalyzed C−N coupling. Of these, CDG (**1**) is a promising blue fluorescence-emitting candidate molecule that may enter into mammalian cells through GLUTs.

D-Glucose, the major energy source for most organisms, is taken up into mammalian cells through glucose transporters such as GLUTs.[1] To monitor the glucose uptake, not only radiolabeled tracers like [^{18}F]-fluoro-2-deoxy-D-glucose (FDG)[2] but also fluorescent tracers such as 2-[*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-D-glucose (2-NBDG)[3,4] (**3**) and 6-NBDG[5] have been effectively used. Indeed, we have shown that 2-NBDG (**3**) is taken up into mammalian cells through GLUTs in a time-, concentration-, and temperature-dependent manner with K_m values comparable to those reported for radiolabeled glucose tracers.[4] Such fluorescent tracers enabled imaging of D-glucose uptake at a spatiotemporal resolution higher than that of radiolabeled tracers.[6,7]

For more precisely evaluating the stereoselectivity of glucose uptake through GLUTs, we have synthesized 2-NBDLG, an antipode of 2-NBDG (**3**), as a control substrate.[8−10] We continued our pursuit of producing GLUT-transportable glucose derivatives having a fluorescent color distinct from 2-NBDG by evaluating stereoselectivity using these compounds together with 2-NBDLG. Such compounds include 2-[*N*-(2-oxa-1,3-diazol-4-yl)amino]-2-deoxy-D-glucose (2-BDG) (**4**) in which the nitro group of 2-NBDG (**3**) is replaced by hydrogen[9] and 2-deoxy-2-((6,8-difluoro-7-hydroxycoumarin-3-yl)carboxyamide)-D-glucose (2-PBDG) (**5**), which is obtained by the coupling of D-glucosamine and Pacific Blue succinimidyl ester.[11] However, 2-BDG (**4**) has no detectable fluorescence, and the fluorophore of 2-PBDG (**5**) seemed to show unexpected interaction with membrane-bound components in some tumor cells, although 2-PBDG (**5**) and its antipode 2-PBLG showed stereoselectivity in the uptake into healthy neurons.

Thus, our aim was to design blue fluorescence-emitting D-glucose derivatives that can be used more widely for monitoring the uptake of glucose through GLUTs. 2-Deoxy-2-(2-oxo-2*H*-chromen-7-yl)amino-D-glucose (CDG) (**1**) and 2-deoxy-2-(2-oxo-1,2-dihydroquinoline-7-yl)amino-D-glucose (QDG) (**2**) (Figure 1) have simple and compact structures bearing a coumarin and a quinolone structure, respectively, and their emission wavelength is shorter than that of 2-NBDG (**3**) (ca. 540 nm). The key structure of these molecules is the direct binding of the amino group of D-glucosamine to the 7 position of the coumarin dye.

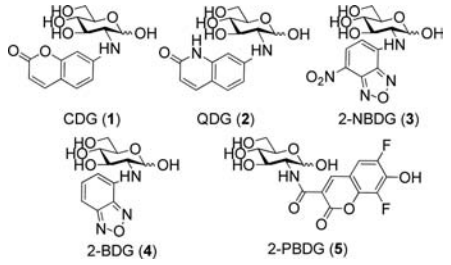


Figure 1. Structures of CDG (**1**), QDG (**2**), 2-NBDG (**3**), 2-BDG (**4**), and 2-PBDG (**5**).

In the case of an aromatic ring with a strong electron-withdrawing group such as a nitro group, for example, 2-NBDG (**3**), the aryl amino bond can be formed by a nucleophilic aromatic substitution reaction between a D-glucosamine and an aryl halide. Since CDG (**1**) and QDG (**2**) bear different types of fluorophores, a distinct synthetic approach was required for each case. We previously synthesized 2-BDG using Buchwald−Hartwig amination and expanded this method into the syntheses of CDG (**1**) and QDG (**2**). This amination is a powerful method that is widely used for the synthesis of aromatic C−N bonds from

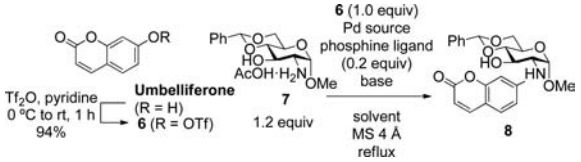
Received: January 27, 2016
Published: March 1, 2016

DOI: 10.1021/acs.orglett.6b00280
Org. Lett. 2016, 18, 1338−1341

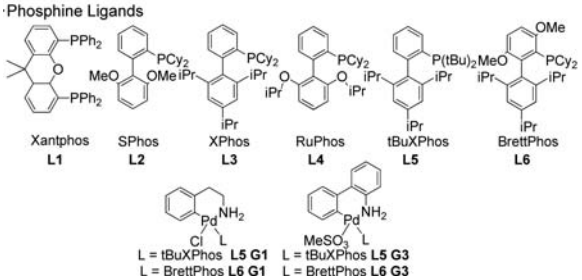
amine and aryl halides or aryl triflates.[12] Copper-catalyzed N-arylation is also able to provide *N*-arylglucosamine;[13] however, this reaction is usually applicable to aryl halides. Therefore, we chose the Pd-catalyzed reaction as aryl triflates are easily prepared from the corresponding phenols.

Coumarin-7-triflate (**6**) is readily prepared by triflation of the hydroxy group of umbelliferone in pyridine. With reference to a patent of a similar cross-coupling reaction with triflate **6**,[14] protected glucosamine **7** was used to optimize the reaction conditions (Table 1). Compound **7** was used because D-glucosamine hydrochloride is hardly soluble in the organic solvent and the free 3-hydroxy group does not have an influence on the cross-coupling reaction.

Table 1. Cross-Coupling of Coumarin Triflate with Glucosamine



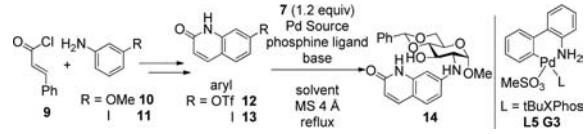
entry	Pd source (equiv)	phosphine ligands	base (equiv)	solvent	isolated yield (%)
1	$Pd_2(dba)_3$ (0.1)	**L1**	Cs_2CO_3 (2.5)	toluene	14
2	$Pd_2(dba)_3$ (0.1)	**L2**	Cs_2CO_3 (2.5)	toluene	20
3	$Pd_2(dba)_3$ (0.1)	**L3**	Cs_2CO_3 (2.5)	toluene	24
4	$Pd_2(dba)_3$ (0.1)	**L4**	Cs_2CO_3 (2.5)	toluene	32
5	$Pd_2(dba)_3$ (0.1)	**L5**	Cs_2CO_3 (2.5)	toluene	46
6	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (2.5)	toluene	48
7	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (0.5)	toluene	15
8	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (1.0)	toluene	89
9	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (1.0)	DMF	10
10	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (1.0)	dioxane	72
11	**L6 G1** (0.2)	**L6**	Cs_2CO_3 (1.0)	toluene	61
12	**L6 G3** (0.2)	**L6**	Cs_2CO_3 (1.0)	toluene	67
13	$Pd_2(dba)_3$ (0.1)	**L6**	*t*-BuONa (1.0)	toluene	0
14	$Pd_2(dba)_3$ (0.1)	**L6**	LHMDS (1.0)	toluene	trace



As shown in entry 1, compound **6** reacted with amine **7**, $Pd_2(dba)_3$ (0.1 equiv), **L1** (0.2 equiv), and Cs_2CO_3 (2.5 equiv) in toluene to afford the corresponding coupling product **8** in low yield. Cs_2CO_3, a weaker base than *t*-BuONa was used to avoid hydrolysis of the lactone of the coumarin. Next, we tried several biphenyl types of phosphine ligands reported by Buchwald et al.,[15] such as **L2**, **L3**, **L4**, **L5**, and **L6**. The coupling yields of product **8** using bulky ligands **L5** and **L6** were 46% and 48%, respectively, which were better than those using **L2**, **L3**, and **L4** (entries 2−6). We then changed the amount of base from 2.5 equiv to 1.0 equiv to obtain an 89% yield (entry 8), while 0.5 equiv base resulted in a low yield (entry 7). Although the results were fairly good (entry 8), different kinds of solvents, Pd sources, and bases were tried. The reaction with DMF as the solvent gave decomposed compounds (entry 9). However, 1,4-dioxane could be used as well as toluene (entry 10). The precatalysts that improve reactivity in Pd-catalyzed cross-coupling reactions were also evaluated.[16] Although these first- and third-generation precatalysts of **L6** were applied in the coupling reaction, neither of them increased the yield (entries 11 and 12). The reaction using other bases such as *t*-BuONa or LHMDS resulted in low yields (entries 13 and 14).

Supuran and colleagues reported that coumarin derivatives may interact with certain carbonic anhydrases (CAs) specifically expressed on the plasma membrane of some tumor cells and form 2-hydroxycinnamic acids by CA-mediated hydrolysis.[17] As an attempt to minimize possible hydrolysis of a coumarin structure, we further designed a quinoline-2-one derivative, QDG (**2**), in which the lactone of CDG (**1**) was exchanged by the lactam. The reagents to introduce a quinoline-2-one to an amino group, triflate **12** and iodide **13**, were synthesized from 3-methoxyaniline **10** and 3-iodoaniline **11**[18] by the reaction with cinnamoyl chloride **9**, respectively. The results of the cross-coupling of triflate **12** or iodide **13** with amine **7** are shown in Table 2. No products were obtained with $Pd_2(dba)_3$ as catalyst,

Table 2. Cross-Coupling of Quinoline-2-one Derivatives with Glucosamine



entry	aryl	Pd source (equiv)	phosphine ligands (0.2 equiv)	base (equiv)	solvent	isolated yield (%)
1	**13**	$Pd_2(dba)_3$ (0.1)	**L6**	Cs_2CO_3 (1)	toluene	0
2	**13**	$Pd_2(dba)_3$ (0.1)	**L6**	*t*-BuONa (10)	toluene	trace
3	**13**	$Pd_2(dba)_3$ (0.1)	**L5**	*t*-BuONa (10)	toluene	trace
4	**13**	**L6 G3** (0.2)	**L6**	*t*-BuONa (10)	toluene	45
5	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (10)	toluene	47
6	**13**	**L5 G1** (0.2)	**L5**	*t*-BuONa (10)	toluene	49
7	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (5)	toluene	47
8	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (10)	dioxane	55
9	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (5)	dioxane	53
10	**12**	**L5 G3** (0.2)	**L5**	*t*-BuONa (5)	dioxane	21
[a]11	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (5)	dioxane	68
[b]12	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (5)	dioxane	60
[b]13	**13**	**L5 G3** (0.2)	**L5**	*t*-BuONa (10)	dioxane	74

[a]**7** (2.0 equiv) was used. [b]**7** (3.0 equiv) was used.

L5 or **L6** as a ligand, and Cs_2CO_3 or *t*-BuONa as a base (entries 1−3). We next used the precatalyst **L6 G3** as a Pd source; it improved to the yield to 45% (entry 4). In the case of **L5 G3** (entry 5), the yield was similar to that with **L6 G3**. However, the reaction proceeded to give the desired product **14** in a shorter time. To reduce overreaction, we selected **L5 G3** as a Pd source for the following optimization. The reaction with 1,4-dioxane as the solvent led to a 55% yield of product because the hydrolysis of iodide **13** was avoided (entry 6). On the other hand, triflate **12** (entry 8) was hydrolyzed immediately under the same conditions to give a lower yield compared to that of entry 7. We assumed that the moderate yield was caused by decomposition of the glucosamine component **7**. By increasing the quantity of compound **7** from 1.2 equiv to 2−3 equiv, we finally obtained the desired product **14** in 74% yield based on iodide **13** (entry 11).

Final deprotection of compounds **8** and **14** by treatment with 80% AcOH in water followed by 6 M aqueous hydrochloric acid

DOI: 10.1021/acs.orglett.6b00280
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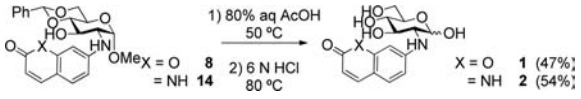
gave the desired products **1** and **2** in yields of 47% and 54%, respectively (Scheme 1).

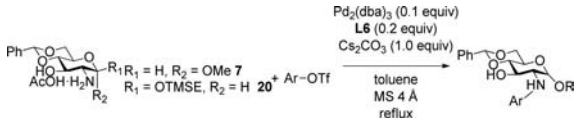
Scheme 1. Final Deprotection of Coupling Products



On the basis of these results, we extended our method to other fluorescent glucose derivatives. We synthesized several glucose derivatives whose fluorescent groups were 3-methylcoumarin, 3-trifluoromethylcoumarin, 4-methylcoumarin, 4-(trifluoromethyl)coumarin, and resorufin. Some of these derivatives have emission wavelengths longer than those of CDG (**1**) and QDG (**2**). For example, 4-(trifluoromethyl)coumarin derivatives exhibit green fluorescence and resorufin derivatives red fluorescence. Syntheses of the triflates of these fluorophores are shown in Scheme S1 (Supporting Information).

We performed the cross-coupling reactions of these fluorescent dyes (Table 3). The cross-coupling reactant derived

Table 3. Pd-Catalyzed Coupling Reaction of Glucosamines 7 and 20 with Different Fluorescent Dyes

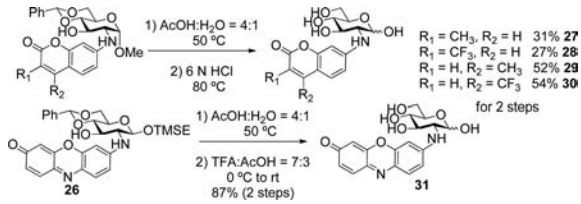


entry	sugar component (1.2 equiv)	aryl (1.0 equiv)	product	isolated yield (%)
1	7	15	21	83
2	7	16	22	52
3	7	17	23	88
[a]4	7	18	24	59
[b]5	7	19	25	62
6	20	19	26	24

[a]7 (3.0 equiv) was used. [b]**L2** and **L2** precatalysts were used instead of **L6** and $Pd_2(dba)_3$.

from compounds **15** and **17** resulted in good yields (entries 1 and 3), whereas compounds **16** and **18** resulted in lower yields (entries 2 and 4). This result may be explained by destabilization of the coumarin intermediate on the Pd complex by an electron-withdrawing trifluoromethyl group. Final deprotection was also performed under acidic conditions as shown in Scheme 2. 2-Deoxy-2-(2-oxo-2*H*-4-methylchromen-7-yl)amino-D-glucose (4-MCDG) (**29**) and 2-deoxy-2-(2-oxo-2*H*-4-trifluoromethylchromen-7-yl)amino-D-glucose (4-TFMCDG) (**30**) were obtained in a similar manner as for CDG (**1**) and QDG (**2**). However, the yields were low for 2-deoxy-2-(2-oxo-2*H*-3-

Scheme 2. Final Deprotection of Coupling Products



methylchromen-7-yl)amino-D-glucose (3-MCDG) (**27**) and 2-deoxy-2-(2-oxo-2*H*-3-trifluoromethylchromen-7-yl)amino-D-glucose (3-TFMCDG) (**28**) due to decomposition of the aromatic component.

In the case of the resorufin derivative, the desired compound **25** was obtained in low yield because of degradation of **19** (entry 5). During subsequent final deprotection to obtain the final product 2-deoxy-2-(3-oxo-3*H*-phenoxazin-7-yl)amino-D-glucose (RDG) (**31**), the C–N bond was hydrolyzed to a glucosamine and the fluorescent dye under the conditions used to synthesize coumarin derivatives (data not shown). Therefore, we next applied the coupling reaction with trimethylsilylethyl (TMSE) glycoside **26**,[9] which can be cleaved under mild acidic conditions. Finally, TMSE glycoside **26** was readily deprotected under TFA condition to give RDG (**31**) in good yield. Thus, acid-labile dyes could be obtained using this protecting group, although the coupling reaction gave rise to a low yield due to steric hindrance by the TMSE group (entry 6).

The fluorescence spectra of CDG (**1**), QDG (**2**), and compounds **27**–**31** are shown in Figure 2. The emission maxima

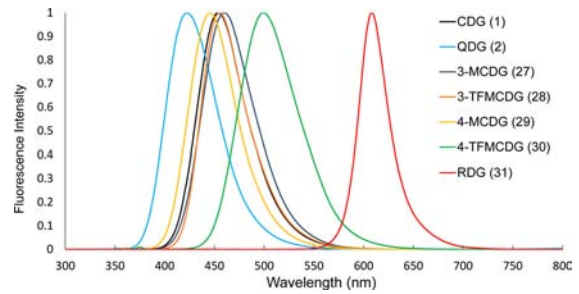


Figure 2. Fluorescent spectra of CDG (**1**) and its derivatives in H_2O containing 0.1% (v/v) DMSO.

of CDG (**1**) (455 nm), QDG (**2**) (423 nm), 3-MCDG (**27**) (460 nm), and 4-MCDG (**29**) (446 nm) were blue-shifted relative to that of 2-NBDG (**3**) (540 nm). 4-TFMCDG (**30**) exhibited a green fluorescence, excitation maxima 378 nm, emission maxima 500 nm. RDG (**31**) showed a red fluorescence with its emission maximum (608 nm) being far from that of 2-NBDG (**3**).

To test if CDG (**1**) is taken up into living mammalian cells through GLUTs, 100 μM of CDG (**1**) was administered for 5 min to insulin-secreting mouse insulinoma MIN6 cells.[19] The fluorescence intensity of the cells was compared before and after administration in the absence or presence of GLUT inhibitor cytochalasin B in a manner similar to that reported previously.[10] Cytochalasin B (10 μM) markedly decreased uptake of CDG (**1**) to 47.3 ± 13.0%, suggesting a contribution of GLUTs to the uptake (**1**) (Figure 3A). Consistently, 50 mM of D-glucose competitively inhibited the uptake of CDG (**1**) to 71.1 ± 11.4% ($p < 0.0001$, ANOVA and Bonferroni–Dunn test), but no such inhibition was detected by the same amount of L-glucose (103.2 ± 16.5%). Inhibition by cytochalasin B was less prominent for

DOI: 10.1021/acs.orglett.6b00280
Org. Lett. 2016, 18, 1338–1341

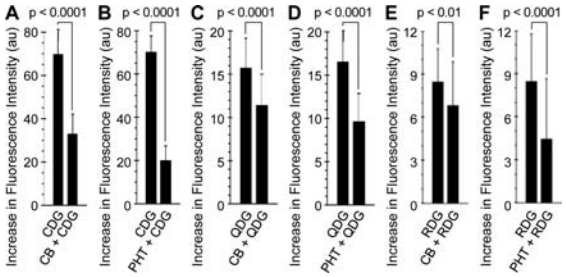


Figure 3. Increase in the fluorescence intensity of MIN6 cells with either CDG (**1**) (A, B), QDG (**2**) (C, D), or RDG (**31**) (E, F) in the absence or presence of cytochalasin B (CB) (A, C, E) or phloretin (PHT) (B, D, F). Values are expressed as mean ± SD. Unpaired *t*-test was used for statistical analysis. Similar values were obtained in duplicated (CDG (**1**), QDG (**2**)) or triplicated (RDG (**31**)) experiments (data not shown).

uptake of QDG (**2**) and RDG (**31**) (Figure 3C, E). The fluorescence increase in the presence to the absence of cytochalasin B was 72.7 ± 22.9% and 80.7 ± 35.9% for 100 μM of QDG (**2**) and RDG (**31**), respectively, indicating a tight selectivity of GLUTs for the attached fluorophore. In addition, the portion of cytochalasin B-inhibitable uptake to the total uptake of CDG (**1**) into MIN6 cells was larger than that of QDG (**2**) ($p < 0.0001$, unpaired *t*-test), implying that the proposed interaction of coumarin structure with CAs in the plasma membrane[11] might not operate in CDG (**1**).

We have recently proposed a cytochalasin B-insensitive, possibly non-GLUT-mediated, glucose transport,[10] which is sensitive to phloretin, a broad spectrum inhibitor against transporters/channels including GLUTs and aquaporins. Indeed, phloretin (150 μM) remarkably inhibited uptake of all three compounds tested; the increase in fluorescence intensity in the presence of compared to the absence of phloretin was 28.5 ± 9.7%, 58.3 ± 19.8%, and 52.6 ± 49.6% for CDG (**1**), QDG (**2**), and RDG (**31**), respectively (Figure 3B,D,F). These results might reflect the complex nature of glucose transport in mammalian cells.

In summary, we have developed a fluorescent glucose tracer CDG (**1**) and its derivatives by using a Pd-catalyzed C−N coupling reaction between the amino group of a glucosamine and a fluorescent dye.[20] Pharmacological profiles with or without inhibitors (cytochalasin B, phloretin, and a large amount of glucose) suggest that a blue fluorescence-emitting CDG (**1**) is taken up into MIN6 cells through GLUTs in a manner similar to that reported for a green fluorescence-emitting 2-NBDG (**3**).[4,10] Bioassays of other derivatives synthesized in this study are underway. The present synthetic approach may provide a powerful tool for exploring uptake of D-glucose into living mammalian cells with glucose derivatives bearing a small fluorophore.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00280.

Properties of all new compounds and detailed experimental procedures (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kyamada@hirosaki-u.ac.jp (biology).

*E-mail: yamamoto@peptide.co.jp (synthesis).

Notes

The authors declare the following competing financial interest(s): T.T., K.Y., and T.Y. received grants above noted from the Japanese government for developing potential cancer diagnostic agents, in which A.S. and Y.O. are collaborators. T.T., K.Y., and T.Y. (in one case, Y.O. and A.S. as well) are co-applicants for multiple patents including those cited in the references. A.S. and K.Y. assigned ownership of the patent to Hirosaki University.

■ ACKNOWLEDGMENTS

This research was supported by the Adaptable and Seamless Technology Transfer Program through Target-Driven R&D (A-STEP) from the Japan Science and Technology Agency. We are grateful to Prof. Junichi Miyazaki (Osaka University) for providing the MIN6 cells.

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DOI: 10.1021/acs.orglett.6b00280
Org. Lett. 2016, 18, 1338−1341