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DDQ-Mediated Three-Component Dioxygenation of Alkenes

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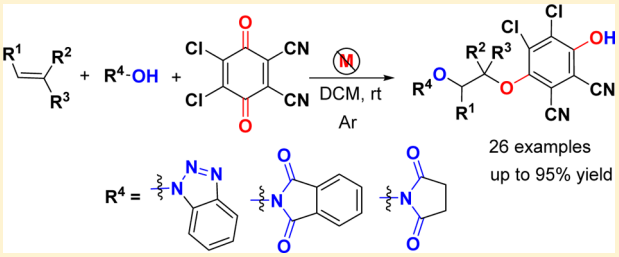
Supporting Information

ABSTRACT: A new DDQ-mediated three-component dioxygenation of alkenes has been established, providing a direct and metal-free access toward densely functionalized 4,5-dichloro-3-hydroxyphthalonitrile derivatives with generally good to excellent yields under mild conditions. During this process, DDQ plays dual roles as both a dehydrogenation reagent and a coupling partner, enabling oxidative coupling to form two C−O functionalities in a highly atom-economy fashion.

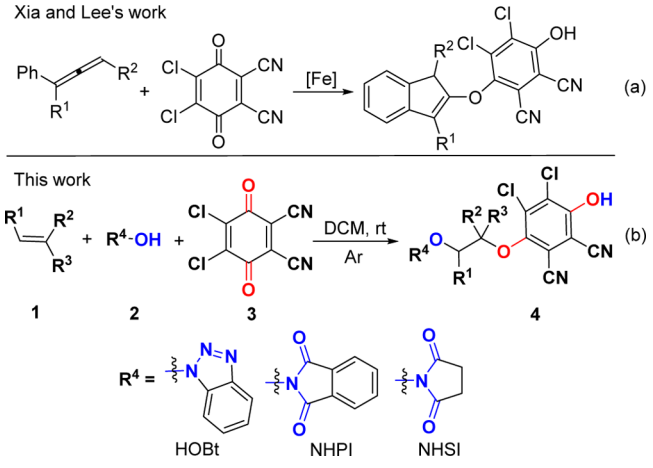


INTRODUCTION

Alkenes, which are a class of significant molecules in the academe and the industry, serve as versatile building blocks and are widely utilized for myriad challenging and intriguing transformations across C=C bond system.[1] Among which, direct 1,2-difunctionalization of alkenes has emerged as a valuable synthetic tool for the collection of highly functionalized backbones.[2] Specifically, dioxygenation of alkenes can readily result in two C−O functionalities via oxidative coupling processes, providing an efficient access toward functionalized oxo-containing compounds, which have high utility in organic synthesis.[3] Arguably, transition metal-catalyzed variants have taken a dominant position, and a variety of transition metal species have been utilized in dioxygenation of alkenes, such as Cu,[4] Pd,[5] Fe,[6] Ru,[7] and Mn.[8] Recently, the metal-free direct dioxygenation of alkenes has attracted considerable attention in organic community due to its environmentally friendly potential.[9] Despite these significant advances, the successful examples of metal-free dioxygenation are still limited, and thus the search for alternatives which allows to control the selectivity of the alkene dioxygenation, particularly involving atom-economy pathway, still remains challenging. To the best of our knowledge, the utilization of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) behaving as both a dehydrogenative reagent and a coupling partner to realize metal-free direct dioxygenation of alkenes is virtually unexplored.

On the other hand, DDQ is usually considered to serve as a dehydrogenation reagent while its potential as an oxygenated precursor is seldom investigated.[10] Very recently, Lee, Xia, and co-workers reported an interesting Fe-catalyzed carbocyclization of allenes with DDQ as an oxygenated reagent to yield aryloxylated indene derivatives (Scheme 1a).[11] Based on aforementioned studies and our interest in radical transformations,[12] we envisioned that DDQ might play dual roles as the radical initiator as well as an oxygenated precursor to achieve direct dioxygenation of alkenes using 1-hydroxybenzotriazole (HOBt)[13] as another one oxygenated reagent in one step. Herein, we reported the successful execution of this ideal and a new dioxygenation of alkenes was realized under one-pot oxidative conditions by using simple starting materials, such as styrenes **1**, HOBt (**2a**), and DDQ (**3**) without additional oxidant (Scheme 1b). With replacement of HOBt with *N*-hydroxyphthalimide (NHPI) **2b** and *N*-hydroxysuccinimide (NHSI) **2c**,[4,14] the reaction proceeded smoothly, affording the corresponding dioxygenated products (Scheme 1b). It is particularly interesting and rare that three-component dioxygenation of alkenes can be readily realized using DDQ as an oxygenated precursor in an atom-economy fashion via a radical process.

Scheme 1. Profiling Applications of DDQ in Oxygenation



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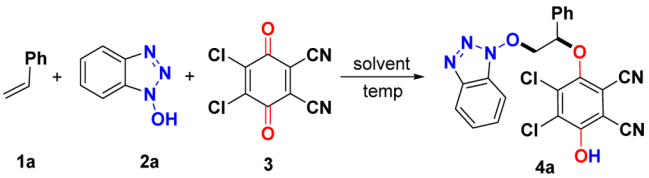
RESULTS AND DISCUSSION

We began our investigations by monitoring the reactivity of styrene (**1a**) with HOBt (**2a**) and DDQ (**3**). The reaction of **1a** with **2a** and **3** in a 2:1.5:1 mol ratio was carried out in dichloromethane (DCM) at 25 °C under argon conditions, affording the corresponding dioxygenated product **4a** in an excellent 95% yield (Table 1, entry 1). The solvent effect was

Table 1. Optimization of Reaction Conditions for Forming Product 4a



1a 2a 3 4a

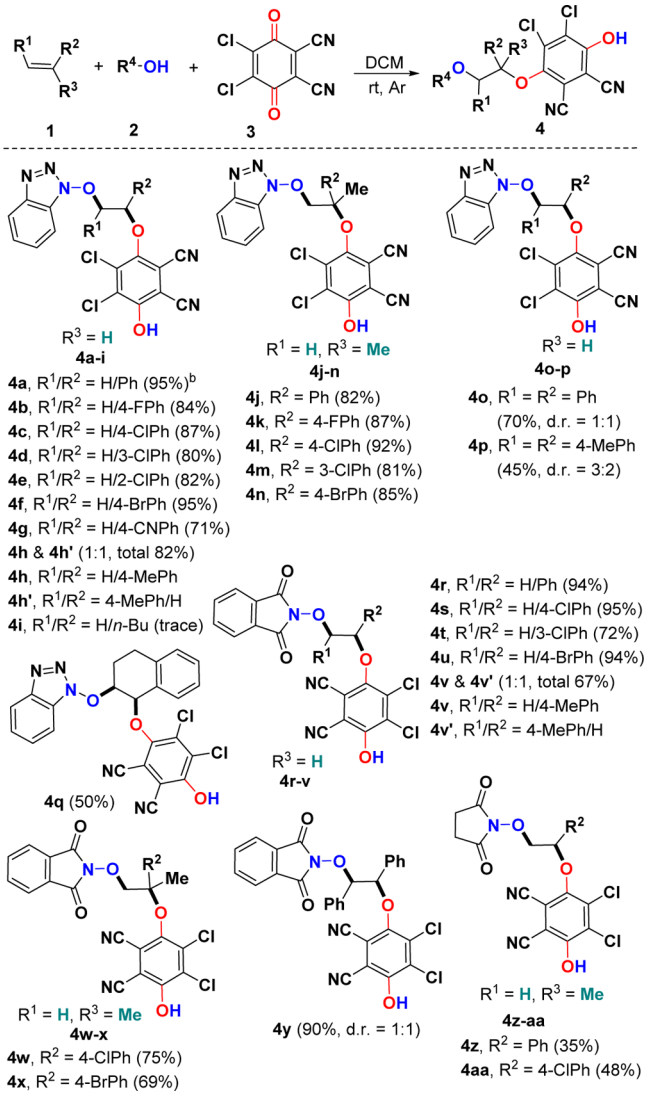
entry	solvent	t/°C	yield (%)[b]
1	DCM	25	95
2	toluene	25	messy
3	DMSO	25	N.D
4	MeOH	25	N.D
5	1,4-dioxane	25	90
6	CH_3CN	25	85
7	DMF	25	71
8	DCM	15	88
9	DCM	40	92
10	DCM	25	20[c]
11	DCM	25	70[d]

[a]Reaction conditions: **1a** (2 mmol), **2a** (1.5 mmol), and **3** (1.0 mmol), solvent (3.0 mL), under argon atmosphere, 5 h. [b]Isolated yield based on **3**. [c]Under air conditions. [d]The mole ratio of **1a**, **2a**, and **3** in 1:1:1.

then investigated (compare entries 2−7). Use of toluene as reaction media gave a messy system (entry 2) while both DMSO and MeOH completely suppressed the reaction process (entries 3−4). In another case of 1,4-dioxane, the reaction resulted in a high 90% yield (entry 5), but still lower than that in DCM. The other solvents, such as acetonitrile (CH_3CN) and *N*,*N*-dimethylformamide (DMF), lowered the yields to 85% and 71%, respectively (entries 6−7). Screening followed by the reaction temperatures revealed that a slightly lower conversion was observed with reaction temperature being at either 15 or 40 °C (entries 8−9). Afterward, the identical reaction was performed under air conditions, and the expected product **4a** was obtained in a very poor yield (20%, entry 10); this is caused by oxygen, which may have participated in this transformation to inhibit the generation of **4a**. It turned out that adjusting the ratio of **1a**, **2a**, and **3** to 1:1:1 was proven to be adverse for this transformation, as product **4a** was isolated in a lower yield of 70% (entry 11).

With the optimal reaction conditions for dioxygenation of alkenes in hand, we then commenced to evaluate the generalization and limitation of this transformation and found a broad range of styrenes are applicable to the present transformation. The results were shown in Scheme 2. Upon repeating the reaction with HOBt (**2a**) and DDQ (**3**), we were pleased to find that styrenes **1b−h** bearing electron-withdrawing, and -donating substituents at the *para*-, *meta*-, or *ortho*-positions of the arene ring did not hamper this reaction process, and the desired functionalized products **4b−h** were generated in good to excellent yields. Various substituents, including both electron-poor (fluoro: **1b**; chloro: **1c**, **1d**, and

Scheme 2. Scope of Three-Component Dioxygenation



[a]Reaction conditions: all reactions were performed with **1** (2 mmol), **2** (1.5 mmol), **3** (1.0 mmol), and DCM (3.0 mL) at room temperature under argon conditions for 5.0−24.0 h. [b]Isolated yield in brackets based on **3**.

1e; bromo: **1f**; and cyano: **1g**) and electron-rich (methyl, **1h**) groups at the different positions of the arene ring (R^2) would be compatible with the present oxidative system. Generally, substituents at the para position seemed to improve the reaction efficiency, as product **4c** could be obtained in slightly higher yields compared with those at *meta*- or *ortho*-position (**4d** and **4e**). Among them, a significant drop in the yield was observed for substrate with a cyano group linked to the phenyl ring as has been demonstrated with styrene **1g**, giving the expected product **4g** in a 71% yield because of the strong inductive effect of cyano group. Additionally, 4-methylstyrene **1h** was proven to be effective, but afforded an inseparable mixture of regioisomers **4h** and **4h′** with a total 82% yield in a closing 1:1 ratio by ^1H NMR analysis (Scheme 2). Unluckily, replacing the aryl group with an *n*-butyl group, 1-hexene **1i**, was not an effective component for this reaction (Scheme 2, **4i**), which may be ascribed to the instability of the C-radical intermediate. In addition, α-methylated styrenes **1j−n** could be accommodated, confirming the reaction efficiency, as products

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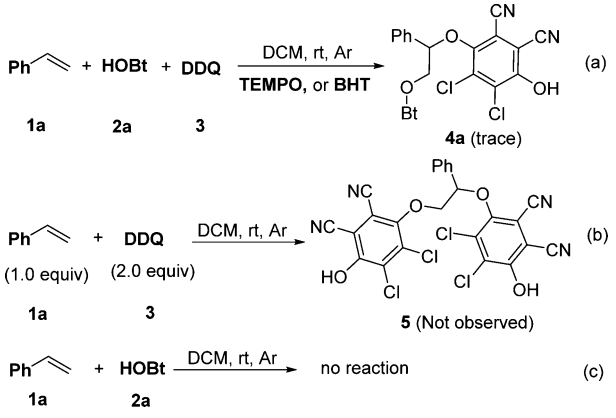
4j−n with one quaternary carbon−oxygen functionality were afforded in 81−92% yields. Alternatively, the internal alkenes, such as 1,2-diarylethenes **1o** and **1p**, were adaptable substrates for this dioxygenation, transforming into inseparable diastereoisomers **4o** (d.r. = 1:1) and **4p** (d.r. = 3:2) in 70% and 45% total yields, respectively. Eventually, 1,2-dihydronaphthalene could tolerate these oxidative conditions, and dioxygenated 1,2,3,4-tetrahydronaphthalene **4q** was isolated in a 50% yield.

To expand the synthetic utility of this methodology, *N*-hydroxyphthalimide (NHPI, **2b**) and *N*-hydroxysuccinimide (NHSI, **2c**) were selected as replacements of HOBt to explore the scope of this dioxygenation due to the fact that both NHPI and NHSI are easily converted into the corresponding phthalimide *N*-oxyl (PINO) and succinimide *N*-oxyl (SINO) radicals under the oxidizing conditions, intercepted by radical acceptors to form C−O bonds.[14] As expected, both these substrates were successfully engaged in the current metal-free oxidative coupling, delivering a series of new dioxygenated products **4r-aa** with yields ranging from 35 to 95%. Similar to the above-mentioned case of isomers **4h** and **4h′**, treatment of 4-methylstyrene **1h** with **2b** and **3** also resulted in an inseparable regioisomers **4v** and **4v′**, whereas 1,2-diphenylethenes **1o** led to a 90% yield of the diastereoisomer **4y** with a closing 1:1 ratio. Additionally, the low conversions were observed when NHSI served as an oxygenated partner, which may be ascribed to the relative instability of SINO radicals, generated in situ by DDQ-mediated oxidation of NHSI. Obviously, the present three-component dioxygenation can tolerate structurally diverse substrates with steric bulk and a different electronic nature, which offers a direct and reliable access toward functionalized oxo-containing molecules. Most functionalities of the resulting dioxygenated products could provide a flexible entry to their further structural modifications. The structures of these products **4** were determined by their NMR spectroscopy and HRMS. Furthermore, in the case of product **4a**, its structure was further confirmed by X-ray diffraction (see the Supporting Information).

To understand the mechanism, the following control experiments were conducted. Styrene **1a** was subjected to the reaction with 1.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylhydroxytoluene (BHT) (Scheme 3a), but only a trace amount of the expected product **4a** was detected, suggesting that a radical addition mechanism was involved in this transformation. Next, without HOBt, treatment of **1a** and 2.0 equiv of DDQ under standard conditions failed to yield the expected product **5** (Scheme 3b) whereas in the absence of DDQ, the reaction did not proceed and the starting materials were recovered (Scheme 3c), confirming that benzotriazole-*N*-oxyl (BTNO) radicals, generated in situ from HOBt mediated by DDQ, triggered addition to form a C-center radical intermediates, which were trapped by DDQ radicals.[4b,d]

Scheme 3. Control Experiments



On the basis of our own observations and information found in the literature,[10,13] we propose a plausible mechanism for forming products **4** as depicted in Scheme 4. In the first stage, a single electron transfer (SET) from the HOBt to DDQ generates a HOBt radical cation and a DDQ radical anion **A**. The anion oxygen of the DDQ radical anion **A** captures a proton from the HOBt radical cation and gives BTNO and a DDQ radical **B**.[10b] Next, the addition of BTNO into styrene **1a** gives a C-center radical **C**, which undergoes SET with **A** to access a C-center cation **D** and a DDQ anion **E**. Then, the attack of **E** on the C-center cation **D** generates the adduct **4a**.

In conclusion, we have established a new and practical metal-free three-component dioxygenation of alkenes with HOBt (NHPI or NHSI) and DDQ in a highly atom-economy fashion, by which DDQ plays dual roles as both a dehydrogenation reagent and a coupling partner. The reaction shows attractive features in terms of the commercial accessibility, inexpensiveness, and stability of the starting materials, broad reaction scope, and mild reaction conditions, providing an efficient and reliable access to a range of densely functionalized 4,5-dichloro-3-hydroxyphthalonitrile derivatives with generally good yields. A detailed application of these resulting dioxygenated products with chemical potential is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Products 4. *Example for the Synthesis of* ***4a****.* Under argon conditions, 1-hydroxybenzotriazole (HOBt, **2a**, 1.5 mmol, 203 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.0 mmol, 226 mg) were introduced in a sealed 10 mL Schlenk tube, styrene (**1a**, 2.0 mmol, 208 mg) and CH_2Cl_2 (3.0 mL) were then successively added. Then, the mixture was stirred at room temperature for 5.0 h. After completion of the reaction (monitored by TLC, MeOH: DCM = 1:8), the reaction mixture was cooled to room temperature. Then, organic solvent was concentrated by a rotary evaporator, and the residue was purified by flash column chromatography (eluents, methanol/dichloromethane) to afford the pure product **4a**. (The synthesis of other compounds was similar to the above operation. Among them, reaction times for the synthesis of **4r**, **4w**, and **4aa** needed to be prolonged to 24.0 h).

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-phenylethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (****4a****).* White solid, 442 mg, 95% yield; mp 196−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.70−7.51 (m, 4H), 7.50−7.36 (m, 4H), 6.06−5.98 (m, 1H), 5.29−5.20 (m, 1H), 5.10−5.02 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.1, 149.4, 143.2, 134.6, 134.3, 130.0, 129.7, 129.1, 128.9, 128.6, 127.2, 125.5, 120.2, 113.9, 113.7, 109.7, 109.3, 102.4, 83.4, 81.9; IR (KBr, υ, cm^{-1}) 2993, 2233, 1550, 1445, 1414, 1316, 1260, 1200, 1104, 983, 911, 746; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{12}Cl_2N_5O_3^-$, 464.0317, [M−H]$^-$, found 464.0323.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(4-fluorophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (****4b****).* White solid, 407 mg, 84% yield; mp 198−200 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 8.4 Hz, 1H), 7.73−7.56 (m, 4H), 7.51−7.41 (m, 1H), 7.32−7.20 (m, 2H), 6.02−5.93 (m, 1H), 5.31−5.20 (m, 1H), 5.13−5.03 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.1 ($^1J_{CF}$ = 244.6 Hz), 155.3, 149.0, 143.1, 134.3, 131.1 ($^3J_{CF}$ = 8.6 Hz), 129.7, 128.9, 127.1, 125.5, 120.1, 116.0 ($^2J_{CF}$ = 21.5 Hz), 114.0, 113.6, 109.7, 109.3, 102.3, 82.8, 81.6. IR (KBr, υ, cm^{-1}) 2975, 2233, 1607, 1514, 1447, 1230, 1154, 1106, 918, 837, 753. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{11}Cl_2FN_5O_3^-$, 482.0223, [M−H]$^-$, found 482.0219.

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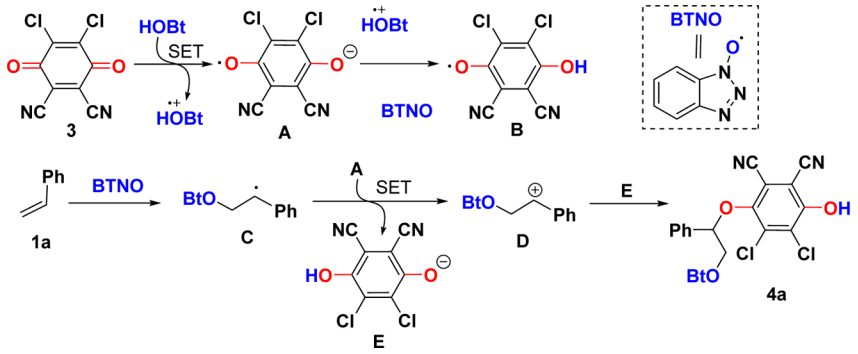
Scheme 4. Proposed Mechanism



*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(4-chlorophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4c**).* Pale yellow solid, 434 mg, 87% yield; mp 212−214 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.71−7.53 (m, 4H), 7.51−7.35 (m, 3H), 5.76−5.66 (m, 1H), 5.22−5.11 (m, 1H), 5.07−4.96 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.6, 143.2, 138.9, 134.7, 134.3, 132.9, 132.0, 130.7, 128.9, 128.9, 127.2, 125.5, 120.1, 118.8, 115.4, 109.7, 107.3, 95.5, 82.0, 81.7. IR (KBr, υ, cm^{-1}) 2231, 1564, 1506, 1469, 1363, 1317, 1265, 1212, 1098, 1078, 802, 735. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{11}Cl_3N_5O_3^-$, 497.9927, [M−H]$^-$, found 497.9921.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(3-chlorophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4d**).* Pale yellow solid, 400 mg, 80% yield; mp 213-215 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.67−7.55 (m, 3H), 7.53−7.41 (m, 3H), 5.98−5.92 (m, 1H), 5.27−5.21 (m, 1H), 5.12−5.05 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.4, 149.1, 143.1, 137.3, 134.3, 133.7, 130.9, 129.8, 128.9, 128.4, 127.2, 125.5, 120.2, 114.0, 113.6, 109.7, 109.3, 102.4, 82.9, 81.5. IR (KBr, υ, cm^{-1}) 2940, 2242, 1558, 1507, 1418, 875, 724, 668. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{11}Cl_3N_5O_3^-$, 497.9927, [M−H]$^-$, found 497.9926.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(2-chlorophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4e**).* Pale yellow solid, 410 mg, 82% yield; mp 197−199 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 6.4 Hz, 1H), 7.64−7.53 (m, 2H), 7.52−7.39 (m, 4H), 6.10−5.99 (m, 1H), 5.24−5.11 (m, 1H), 5.04−4.92 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.4, 143.1, 139.7, 133.3, 132.8, 132.7, 131.99, 131.2, 130.2, 129.8, 129.0, 128.2, 127.1, 125.5, 120.2, 118.6, 115.1, 109.4, 107.3, 95.9, 81.7, 79.3. IR (KBr, υ, cm^{-1}) 2904, 2235, 2021, 1514, 1446, 1342, 1080, 744. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{11}Cl_3N_5O_3^-$, 497.9927, [M−H]$^-$, found 497.9930.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(4-bromophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4f**).* Pale yellow solid, 518 mg, 95% yield; mp 182−184 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.68−7.56 (m, 4H), 7.55−7.42 (m, 3H), 5.73−5.66 (m, 1H), 5.19−5.11 (m, 1H), 5.05−4.98 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.7, 143.1, 138.9, 135.1, 132.9, 132.0, 131.8, 131.0, 128.9, 127.2, 125.5, 122.9, 118.9, 118.8, 115.4, 109.7, 107.3, 95.5, 82.1, 81.7. IR (KBr, υ, cm^{-1}) 3098, 2231, 1564, 1506, 1491, 1362, 1264, 1211, 1099, 1078, 911, 799. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{11}BrCl_2N_5O_3^-$, 541.9422, [M−H]$^-$, found 541.9411.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(4-cyanophenyl)-ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4g**).* White solid, 349 mg, 71% yield; mp 190−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.89 (d, J = 8.4 Hz, 2H), 7.84 (s, 4H), 7.77 (d, J = 8.4 Hz, 2H), 5.63−5.56 (m, 1H), 4.81−4.73 (m, 1H), 4.66−4.57 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.7, 163.3, 142.3, 139.1, 135.2, 132.8, 132.7, 131.9, 129.5, 129.1, 123.7, 119.1, 118.8, 115.4, 112.0, 107.2, 95.5, 82.6, 79.3. IR (KBr, υ, cm^{-1}) 2232, 1573, 1514, 1482, 1350, 1261, 1176, 1090, 1038, 821, 769. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{11}Cl_2N_6O_3^-$, 489.0270 [M−H]$^-$, found 489.0272.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1-(p-tolyl)ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (Isomer, **4h**).* White solid, 393 mg, total 82% yield; mp 174−176 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.4 Hz, 1H), 7.71−7.54 (m, 7.5 Hz, 2H), 7.51−7.43 (m, 1H), 7.42−7.33 (m, 2H), 7.32−7.24 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 5.79−5.68 (m, 1H), 5.22−5.10 (m, 1H), 5.01−4.90 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.5, 165.4, 143.2, 139.2, 139.2, 138.1, 135.3, 132.8, 132.8, 132.2, 132.1, 132.1, 130.3, 129.5, 129.2, 128.8, 128.8, 128.8, 127.2, 127.2, 125.9, 125.5, 120.1, 118.7, 115.5, 109.7, 109.7, 107.4, 107.3, 95.6, 95.6, 82.5, 82.3, 82.2, 82.2, 21.4, 21.3. IR (KBr, υ, cm^{-1}) 2232, 1550, 1449, 1295, 1190, 1131, 1077, 764, 655. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{14}Cl_2N_5O_3^-$, 478.0474, [M−H]$^-$, found 478.0480.

*3-((1-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-2-phenylpropan-2-yl)-oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4j**).* White solid, 394 mg, 82% yield; mp 183−185 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 6.8 Hz, 2H), 7.59−7.51 (m, 1H), 7.49−7.38 (m, 4H), 7.33 (d, J = 8.4 Hz, 1H), 5.23−5.12 (m, 2H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.4, 151.3, 147.5, 143.1, 139.9, 136.4, 129.4, 129.1, 128.8, 128.6, 127.2, 125.4, 120.1, 114.4, 114.0, 111.7, 109.5, 102.9, 88.7, 86.0, 21.7. IR (KBr, υ, cm^{-1}) 2229, 1549, 1495, 1443, 1412, 1385, 1253, 1213, 1170, 1153, 1099, 1068, 900, 736, 697. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{14}Cl_2N_5O_3^-$, 478.0474, [M−H]$^-$, found 478.0487.

*3-((1-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-2-(4-fluorophenyl)-propan-2-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4k**).* White solid, 433 mg, 87% yield; mp 168−170 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (d, J = 8.4 Hz, 0H), 7.82−7.74 (m, 1H), 7.61−7.54 (m, 1H), 7.47−7.38 (m, 1H), 7.30−7.20 (m, 1H), 5.23−5.11 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.4, 162.3 ($^1J_{CF}$ = 243.4.6 Hz), 143.1, 137.4, 137.2 ($^4J_{CF}$ = 2.8 Hz), 134.0, 132.6, 129.5 ($^3J_{CF}$ = 8.2 Hz), 128.8, 127.0, 125.4, 120.1, 118.59, 116.02, 115.1 ($^2J_{CF}$ = 21.1 Hz), 109.5, 109.4, 96.5, 86.3, 85.7, 21.3. IR (KBr, υ, cm^{-1}) 2216, 1604, 1559, 1509, 1457, 1355, 1236, 1164, 1077, 1000, 903, 743. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{13}Cl_2FN_5O_3^-$, 496.0379, [M−H]$^-$, found 496.0368.

*3-((1-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-2-(4-chlorophenyl)-propan-2-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4l**).* White solid, 472 mg, 92% yield; mp 174−175 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.60−7.54 (m, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.47−7.39 (m, 2H), 5.19 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.5, 147.2, 143.1, 139.5, 136.3, 133.7, 129.5, 129.1, 128.8, 128.5, 127.0, 125.5, 120.1, 114.3, 114.0, 111.7, 109.0, 103.0, 88.1, 85.8, 21.3. IR (KBr, υ, cm^{-1}) 2230, 1558, 1506, 1489, 1496, 1416, 1386, 1337, 1262, 1211, 1169, 1097, 902, 736. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{13}Cl_3N_5O_3^-$, 512.0084, [M−H]$^-$, found 512.0088.

*3-((1-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-2-(3-chlorophenyl)-propan-2-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4m**).* Yellow solid, 416 mg, 81% yield; mp 178−179 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.01 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.69 (d, J = 6.4 Hz, 1H), 7.60−7.50 (m, 1H), 7.49−7.39 (m, 3H), 7.34 (d, J = 8.4 Hz, 1H), 5.15 (d, J = 9.6 Hz, 1H), 5.05 (d, J = 9.6 Hz, 1H), 1.81 (s,

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3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.8, 146.8, 143.2, 143.1, 136.2, 133.5, 130.4, 129.6, 128.8, 128.8, 127.1, 127.0, 125.8, 125.5, 120.1, 114.4, 114.2, 111.7, 109.5, 102.9, 88.0, 85.7, 21.2. IR (KBr, υ, cm^{-1}) 2229, 1559, 1507, 1458, 1355, 1073, 741, 668. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{13}Cl_3N_5O_3^-$, 512.0084, [M−H]$^-$, found 512.0081.

*3-((1-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-2-(4-bromophenyl)-propan-2-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4n**).* Yellow solid, 475 mg, 85% yield; mp 160−161 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.60−7.54 (m, 2H), 7.49−7.38 (m, 2H), 5.23−5.07 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.2, 143.1, 140.8, 137.4, 134.0, 132.6, 131.3, 129.5, 128.8, 127.0, 125.4, 122.0, 120.1, 118.5, 116.0, 109.5, 109.5, 96.6, 86.3, 85.7, 20.9. IR (KBr, υ, cm^{-1}) 2709, 2216, 1558, 1497, 1458, 1397, 1355, 1262, 1209, 1080, 1008, 904, 743. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{13}BrCl_2N_5O_3^-$, 555.9579, [M−H]$^-$, found 555.9588.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1,2-diphenylethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (One Isomer, **4o**).* Pale yellow solid, 379 mg, 70% yield; mp 168−169 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.00−7.88 (m, 1H), 7.65 (d, J = 3.6 Hz, 1H), 7.56−7.27 (m, 9H), 7.21−7.08 (m, 3H), 6.43−6.25 (m, 1H), 6.23−6.01 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.7, 142.9, 139.5, 134.7, 134.6, 132.6, 132.3, 130.3, 130.0, 129.7, 129.4, 128.7, 128.6, 128.5, 127.9, 125.2, 119.9, 118.4, 115.6, 110.0, 107.5, 96.1, 94.2, 85.7. IR (KBr, υ, cm^{-1}) 2712, 2218, 1558, 1505, 1456, 1347, 1262, 1207, 1079, 744, 609. HRMS (ESI-TOF) m/z calcd for $C_{28}H_{16}Cl_2N_5O_3^-$, 540.0630, [M−H]$^-$, found 540.0635.

*3-(2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)-1,2-di-p-tolylethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (One Isomer, **4p**).* Yellow solid, 212 mg, 45% yield; mp 170−171 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.92 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.32−7.31 (m, 2H), 7.23−7.21 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.18 (d, J = 6.4 Hz, 1H), 6.00 (d, J = 7.2 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 163.5, 142.7, 139.5, 139.1, 132.6, 132.3, 131.6, 131.1, 129.9, 129.4, 129.3, 129.2, 128.5, 127.8, 126.7, 125.2, 119.9, 117.9, 115.4, 109.7, 107.5, 96.6, 92.6, 84.4, 21.2, 21.1. IR (KBr, υ, cm^{-1}) 2931, 2218, 2040, 1558, 1505, 1455, 1360, 1262, 1207, 1078, 1002, 814, 743. HRMS (ESI-TOF) m/z calcd for $C_{30}H_{20}Cl_2N_5O_3^-$, 568.0943, [M−H]$^-$, found 568.0937.

*3-((2-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)naphthalen-1-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4q**).* Pale yellow solid, 231 mg, 50% yield; mp 185−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.08 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.65−7.58 (m, 1H), 7.52−7.45 (m, 1H), 7.45−7.39 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.26−7.15 (m, 2H), 5.69 (d, J = 3.6 Hz, 1H), 5.48−5.42 (m, 1H), 3.23−2.98 (m, 2H), 2.50−2.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.4, 148.1, 143.1, 137.8, 134.4, 131.2, 130.1, 129.8, 129.6, 129.5, 129.2, 127.8, 126.6, 125.6, 120.3, 113.9, 113.1, 109.9, 109.5, 102.2, 86.1, 79.5, 24.2, 23.3. IR (KBr, υ, cm^{-1}) 2228, 1602, 1558, 1446, 1418, 1339, 1267, 1218, 1101, 1000, 933, 747, 668. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{14}Cl_2N_5O_3^-$, 490.0474, [M−H]$^-$, found 490.0466.

*4,5-Dichloro-3-(2-((1,3-dioxoisoindolin-2-yl)oxy)-1-phenylethoxy)-6-hydroxyphthalonitrile (**4r**).* Pale yellow solid, 464 mg, 94% yield; mp 177−179 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (s, 4H), 7.53−7.46 (m, 2H), 7.43−7.32 (m, 3H), 5.68−5.61 (m, 1H), 4.85−4.76 (m, 1H), 4.62−4.53 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.4, 163.3, 139.3, 136.2, 135.1, 132.7, 132.1, 129.5, 129.0, 128.8, 128.6, 123.6, 118.8, 115.5, 107.3, 95.6, 82.9, 79.8. IR (KBr, υ, cm^{-1}) 2997, 2216, 1791, 1733, 1559, 1457, 345, 1260, 1186, 1080, 993, 877, 699. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{12}Cl_2N_3O_5^-$, 492.0154, [M−H]$^-$, found 492.0173.

*4,5-Dichloro-3-(1-(4-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)-oxy)ethoxy)-6-hydroxyphthalonitrile (**4s**).* Pale yellow solid, 502 mg, 95% yield; mp 178−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (s, 4H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 5.59−5.53 (m, 1H), 4.80−4.72 (m, 1H), 4.62−4.54 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.6, 163.4, 139.1, 135.6, 135.1, 134.0, 132.8, 132.0, 130.6, 129.1, 128.8, 123.7, 118.9, 115.4, 107.3, 95.5, 82.3, 79.4. IR (KBr, υ, cm^{-1}) 2996, 2216, 1732, 1559, 1466, 1344, 1210, 1188, 1080, 877, 797, 696. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{11}Cl_3N_3O_5^-$, 525.9764, [M−H]$^-$, found 525.9775.

*4,5-Dichloro-3-(1-(3-chlorophenyl)-2-((1,3-dioxoisoindolin-2-yl)-oxy)ethoxy)-6-hydroxyphthalonitrile (**4t**).* Pale yellow solid, 380 mg, 72% yield; mp 177−179 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (s, 4H), 7.63 (s, 1H), 7.52−7.40 (m, 3H), 5.60−5.54 (m, 1H), 4.81−4.73 (m, 1H), 4.63−4.55 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.2, 163.3, 139.6, 140.0, 135.1, 133.5, 132.6, 132.1, 130.7, 129.3, 129.1, 128.4, 127.3, 123.7, 118.6, 115.4, 107.4, 95.8, 82.4, 79.5. IR (KBr, υ, cm^{-1}) 2218, 1791, 1733, 1653, 1558, 1507, 1457, 1339, 1187, 1080, 991, 876, 787. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{11}Cl_3N_3O_5^-$, 525.9764, [M−H]$^-$, found 525.9769.

*3-(1-(4-Bromophenyl)-2-((1,3-dioxoisoindolin-2-yl)oxy)ethoxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4u**).* Pale yellow solid, 539 mg, 94% yield; mp 180−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (brs, 4H), 7.60 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 5.59−5.52 (m, 1H), 4.80−4.72 (m, 1H), 4.61−4.54 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.6, 163.3, 139.1, 136.0, 135.2, 132.8, 132.0, 131.7, 130.8, 129.0, 123.7, 122.7, 118.8, 115.4, 107.2, 95.5, 82.4, 79.4. IR (KBr, υ, cm-1) 2901, 2218, 1734, 1719, 1590, 1487, 1219, 1179, 1080, 1045, 877, 759. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{11}BrCl_2N_3O_5^-$, 569.9259, [M−H]$^-$, found 569.9263.

*4,5-Dichloro-3-(2-((1,3-dioxoisoindolin-2-yl)oxy)-1-(p-tolyl)-ethoxy)-6-hydroxyphthalonitrile (One Isomer, **4v**).* Pale yellow solid, 340 mg, total 67% yield; mp 175−176 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (s, 4H), 7.38−7.26 (m, 2H), 7.26−7.13 (m, 2H), 5.65−5.57 (m, 1H), 4.81−4.73 (m, 1H), 4.57−4.50 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.6, 163.3, 139.0, 138.9, 137.9, 135.1, 133.1, 132.0, 129.4, 129.0, 128.6, 123.6, 118.9, 115.6, 107.3, 95.4, 82.6, 79.7, 21.3. IR (KBr, υ, cm^{-1}) 2218, 1790, 1732, 1660, 1543, 1509, 1444, 1232, 1186, 1085, 886, 769. HRMS (ESI-TOF) m/z calcd for $C_{25}H_{14}Cl_2N_3O_5^-$, 506.0311, [M−H]$^-$, found 506.0327.

*4,5-Dichloro-3-((2-(4-chlorophenyl)-1-((1,3-dioxoisoindolin-2-yl)-oxy)propan-2-yl)oxy)-6-hydroxyphthalonitrile (**4w**).* Pale yellow solid, 407 mg, 75% yield; mp 156−157 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.89−7.74 (m, 4H), 7.64 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 4.83 (d, J = 9.6 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.5, 163.1, 140.0, 137.3, 135.2, 134.0, 132.6, 129.3, 128.9, 128.2, 123.6, 118.7, 116.0, 109.1, 96.3, 85.5, 83.0, 79.7, 21.5. IR (KBr, υ, cm^{-1}) 2216, 1790, 1732, 1557, 1494, 1465, 1353, 1258, 1187, 1133, 1080, 1003, 902, 700. HRMS (ESI-TOF) m/z calcd for $C_{25}H_{13}Cl_3N_3O_5^-$, 539.9921, [M−H]$^-$, found 539.9922.

*3-((2-(4-Bromophenyl)-1-((1,3-dioxoisoindolin-2-yl)oxy)propan-2-yl)oxy)-4,5-dichloro-6-hydroxyphthalonitrile (**4x**).* Yellow solid, 405 mg, 69% yield; mp 163−164 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.85−7.78 (m, 4H), 7.59−7.51 (m, 4H), 4.81 (d, J = 9.6 Hz, 1H), 4.63 (d, J = 9.6 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 165.4, 163.1, 140.5, 137.2, 135.2, 134.0, 132.5, 131.1, 129.6, 128.9, 123.6, 121.9, 118.6, 116.0, 109.3, 96.2, 85.6, 83.0, 21.4. IR (KBr, υ, cm^{-1}) 2216, 1790, 1732, 1556, 1493, 1455, 1352, 1258, 1187, 1079, 1007, 876, 696. HRMS (ESI-TOF) m/z calcd for $C_{25}H_{13}BrCl_2N_3O_5^-$, 583.9416, [M−H]$^-$, found 583.9415.

*4,5-Dichloro-3-(2-((1,3-dioxoisoindolin-2-yl)oxy)-1,2-diphenylethoxy)-6-hydroxyphthalonitrile (One Isomer, **4y**).* Pale yellow solid, 513 mg, 90% yield; mp 164−165 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.36 (s, 1H), 7.81−7.73 (m, 5H), 7.72−7.67 (m, 2H), 7.61−7.54 (m, 4H), 7.41−7.28 (m, 8H), 7.28−7.21 (m, 2H), 7.19−7.11 (m, 5H), 6.12 (s, 2H), 6.05 (d, J = 7.8 Hz, 1H), 5.93 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 164.6, 163.2, 138.5, 135.3, 134.7, 134.5, 132.4, 132.1, 129.8, 129.7, 129.5, 128.5, 128.4, 128.3, 123.6, 118.3, 115.6, 115.5, 107.4, 95.7, 88.1, 84.3, 79.7. IR (KBr, υ, cm^{-1}) 2217, 1789, 1724, 1559, 1500, 1456, 1361, 1259, 1204, 1076, 1000, 916, 757, 699. HRMS (ESI-TOF) m/z calcd for $C_{30}H_{16}Cl_2N_3O_5^-$, 568.0467, [M−H]$^-$, found 568.0463.

*4,5-Dichloro-3-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-1-phenylethoxy)-6-hydroxyphthalonitrile (**4z**).* Pale yellow solid, 156 mg, 35%

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yield; mp 157−158 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.49−7.43 (m, 2H), 7.42−7.34 (m, 3H), 5.61−5.53 (m, 1H), 4.67−4.59 (m, 1H), 4.41−4.34 (m, 1H), 2.53 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 172.2, 165.0, 139.7, 136.2, 132.6, 132.2, 129.5, 128.9, 128.5, 118.6, 115.4, 107.5, 95.8, 83.0, 78.6, 25.9. IR (KBr, υ, cm^{-1}) 2217, 1790, 1724, 1597, 1500, 1421, 1223, 1108, 1013, 854, 695. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{12}Cl_2N_3O_5^-$, 444.0154, [M−H]$^-$, found 444.0159.

*4,5-Dichloro-3-(1-(4-chlorophenyl)-2-((2,5-dioxopyrrolidin-1-yl)-oxy)ethoxy)-6-hydroxyphthalonitrile (**4aa**).* Pale yellow solid, 229 mg, 48% yield; mp 160−161 °C. ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.53−7.43 (m, 4H), 5.52−5.45 (m, 1H), 4.63−4.56 (m, 1H), 4.42−4.36 (m, 1H), 2.55 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 172.2, 165.5, 139.2, 135.4, 134.1, 132.7, 132.0, 130.5, 128.8, 118.8, 115.4, 107.3, 95.6, 82.3, 78.2, 25.9. IR (KBr, υ, cm^{-1}) 2216, 1787, 1732, 1659, 1508, 1443, 1208, 1142, 990, 721. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{11}Cl_3N_3O_5^-$, 477.9764, [M−H]$^-$, found 477.9752.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01988.

^{1}H and ^{13}C NMR spectra for all pure products (PDF)

X-ray crystallographic data for **4a** (CIF)

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Notes

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