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ARTICLE

Structural analogues of quinoline alkaloids: Straightforward route to [1,3]dioxolo[4,5-*c*]quinolines with antibacterial properties

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Abstract

Compounds bearing [1,3]dioxolo-quinoline scaffolds have been found in quinoline-based natural products; the only exception is the [1,3]dioxolo[4,5-*c*]quinoline moiety with a rare occurrence in both natural and synthetic derivatives. In this article, we report the preparation of diversely substituted and functionalized [1,3]dioxolo[4,5-*c*]quinolines using [1,3]dioxolo[4,5-c]quinoline-4-carbaldehyde (DQC) as the common intermediate. DQC was synthesized on a large scale from anthranilic acid and chloroacetone as the starting materials, with the rearrangement of acetonyl-anthranilate as the key step. The developed method allows for the simple preparation of [1,3]dioxolo[4,5-*c*]quinolines with various C2 substituents on the quinoline scaffold. Additionally, the synthetic route was successfully applied to the preparation of 3-hydroxyquinoline-4(1*H*)-ones. The target compounds were tested against representative Gram-positive/negative bacteria, and two derivatives exhibited submicromolar minimum inhibitory concentrations against *Micrococcus luteus*.

1 | INTRODUCTION

Synthetic derivatives with the molecular framework resembling the structure of natural compounds are important derivatives in the field of drug discovery.[1] The main scaffolds of natural products have been frequently used as templates for the design of ligands to either improve their affinity for biological targets or to modify their pharmacological properties. In the field of natural products, an important and large group of compounds with diverse biological effects are the quinoline alkaloids.[2,3] These compounds are typically simple quinoline derivatives that possess alkoxy groups in different positions on the main scaffold. [4] Apart from the most commonly occurring methoxy groups, specific types of quinoline alkaloids contain the cyclic methylenedioxy moiety, which results in [1,3]dioxolo-quinolines. Depending on the mutual annellation of dioxole and quinoline rings, these heterocycles can be classified as [1,3]dioxolo[4,5-*b*]quinolines **I**, [1,3]dioxolo[4,5-*c*]quinolines **II**, [1,3]dioxolo[4,5-*f*]quinolines **III**, [1,3]dioxolo[4,5-*g*]quinolines **IV**, and [1,3]dioxolo[4,5-*h*]quinolines **V** (Figure 1). Within the group of quinoline alkaloids, derivatives based on [1,3]dioxolo-quinolines **I**, **III**, **IV**, and **V** have already been reported. The most frequently studied types of these compounds are [1,3]dioxolo[4,5-*g*]quinolines **IV** and [1,3]dioxolo[4,5-*h*]quinolines **V**, with the group of Orixa japonica alkaloids and furoquinolones being the best-known representatives. Similarly, synthetic compounds derived from **IV** have been widely

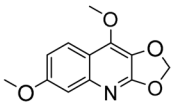
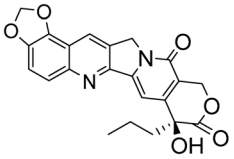
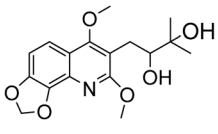
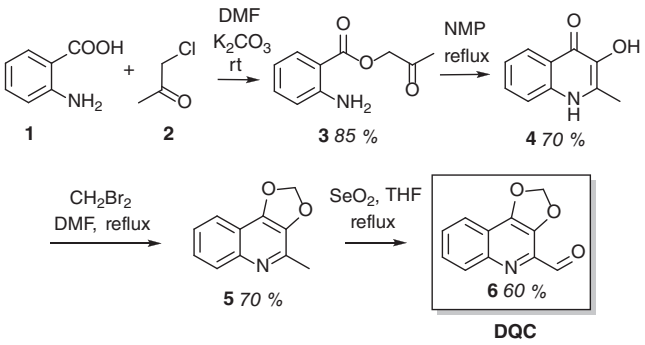
Dioxolo-quinoline template	Example of alkaloid	Natural source	Properties
I [1,3]dioxolo[4,5-*b*]quinoline		*Acronychia laurifolia* (ref.6) *Acanthosyris paulo-alvinii* (ref.7) *Sebastiania corniculata* (ref.8)	Nematicidal (ref.9)
II [1,3]dioxolo[4,5-*c*]quinoline	not reported	not reported	not reported
III [1,3]dioxolo[4,5-*f*]quinoline		*Ophiorrhiza trichocarpon* (ref.10)	Anticancer (ref.10)
IV [1,3]dioxolo[4,5*g*]quinoline	 Maculine	*Esenbeckia grandiflora* (ref.11)	Antiplasmodial (ref.12) Cytotoxic (ref.13)
V [1,3]dioxolo[4,5*h*]quinoline	 Orixine	*Orixa Japonica* (ref.14)	Antibacterial (ref.15)

FIGURE 1 Isomeric [1,3]dioxolo-quinolines, examples of related alkaloids and their reported biological properties[5–14] [Color figure can be viewed at wileyonlinelibrary.com]

reported in the literature.[15–25] In contrast, the [1,3]dioxolo[4,5-*c*]quinolines **II** have not been isolated from natural sources, and the synthetic derivatives of such heterocycles are an unexplored group of compounds, undoubtedly due to the problematic synthetic availability of the [1,3]dioxolo[4,5-*c*]quinoline scaffold. Inspired by this fact, we decided to develop a simple approach to [1,3]dioxolo[4,5-*c*]quinolines with variable substitution on the quinoline scaffold. With respect to the large number of antibacterial and antitumor quinoline derivatives reported to date, the activity of the synthesized compounds against representative bacterial strains was elucidated, and the most promising results are reported in this article.

2 | RESULTS AND DISCUSSION

Synthesis of the key intermediate began from anthranilic acid **1** (Scheme 1). After alkylation with chloroacetone **2**, the resulting 2-oxopropyl 2-aminobenzoate **3** was subjected to rearrangement in boiling *N*-methylpyrrolidin-2-one,[26] and 3-hydroxy-2-methylquinolin-4(1*H*)-one



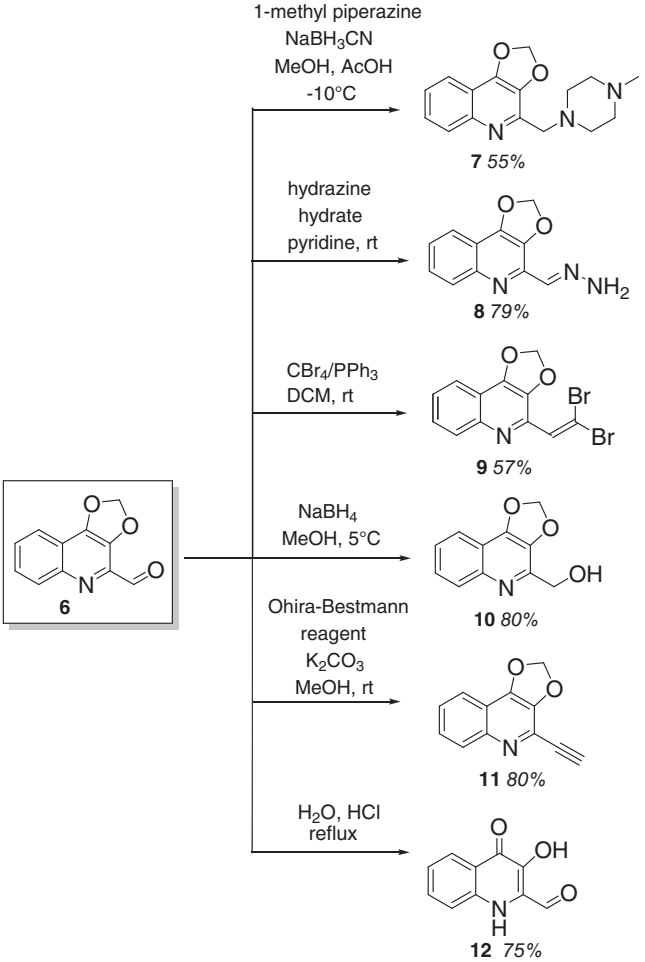
SCHEME 1 Preparation of the key intermediates 5 and 6

4 was obtained. Alkylation with dibromomethane yielded 4-methyl-[1,3]dioxolo[4,5-*c*]quinoline **5**, which was further oxidized using selenium dioxide to [1,3]dioxolo[4,5-*c*]quinoline-4-carbaldehyde **6** (DQC). The developed conditions were successfully used to synthesize the key intermediates in good yields that were scaled up to 50 g (compound **5**) and 10 g (compound **6**).

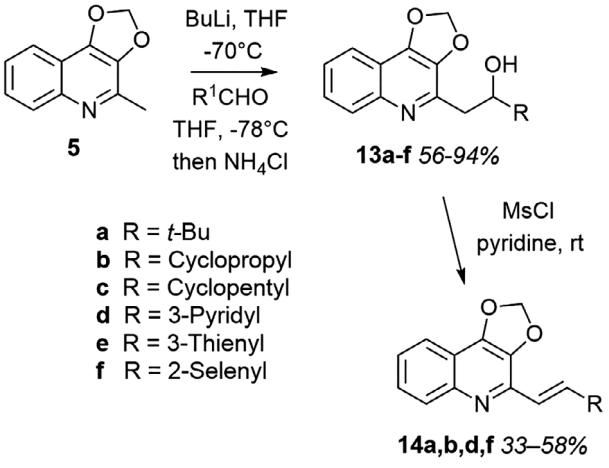
To demonstrate the applicability of DQC for structural diversification using nucleophiles, compound **6** was

subjected to reductive alkylation with 1-methylpiperazine, to condensation with hydrazine hydrate or to Corey-Fuchs reaction with dibromomethane/triphenylphosphine,[27] which yielded the corresponding products **7**-**9** (Scheme 2). Furthermore, the reduction of DQC with sodium borohydride afforded primary alcohol **10**, and the reaction of DQC with the Ohira-Bestmann reagent gave alkyne derivative **11** which can be further applied in the conjugation with azides.[28] It is worth mentioning that except for DQC **6**, compounds **9**-**11** with reactive functionalities represent useful intermediates to prepare other derivatives of [1,3]dioxolo[4,5-*c*]quinoline based on, for example, acylation or cycloaddition reactions. Finally, intermediate **6** was successfully hydrolyzed with hydrochloric acid to 3-hydroxyquinolin-4(1*H*)-one derivative **12** (see the wider application of this reaction later in the text). Not only DQC **6**, but also 4-methyl-[1,3]dioxolo[4,5-*c*]quinoline **5** can be considered as the reactive compound suitable for further modification of the [1,3]dioxolo[4,5-*c*]quinoline scaffold in the C2 position. To demonstrate the reactivity of picoline-like methyl group toward electrophiles, compound **5** was subjected to reaction with butyllithium followed by addition of representative aldehydes (Scheme 3). In each case, the corresponding secondary alcohols **13a-f** were obtained. Compounds **13** were further reacted with methanesulfonyl chloride in pyridine which yielded 2-styryl-[1,3]dioxolo[4,5-*c*]quinolines **14a-d**. Derivatives bearing cyclopentyl (**13c**) or 3-thienyl (**13e**) moiety gave after reaction with MsCl/pyridine a mixture of unknown compounds with traces of product. In the case of *t*-butylaldehyde and pyridine-3-carbaldehyde, alcohols **13a** and **13d** were not isolated but directly converted to styryl derivatives **14a**, **14c** respectively. The smooth hydrolysis of the [1,3]dioxolo[4,5-*c*]quinoline scaffold (see compound **12** in Scheme 2) indicated further applicability of the developed procedures in the field of 3-hydroxyquinolin-4(1*H*)-ones (3HQs). 2-Aryl-3HQs have been recently intensively studied as flavonol analogues, and their significant fluorescent and cytotoxic properties have been reported.[29–32]

It was proven that 2-aryl-3HQs interact with the elongation factor in the gamendazole binding site and that the 3-hydroxy-4-oxo moiety is directly involved in the structure of the pharmacophore.[33] On the other hand, 3HQs generally suffer from very low solubility resulting from an intermolecular hydrogen bond mediated by the 3-hydroxy group.[32] The limited solubility of 3HQs results in problematic bioavailability, and two different approaches (micellar dispersion and liposomal solubilization) have previously been suggested to overcome this problem.[34,35] In this regard, 2-aryl-[1,3]dioxolo[4,5-*c*]quinolines may serve as suitable prodrugs with better solubility and better ability to release the parent 3HQ after administration in vivo. Obviously, 2-aryl-[1,3]dioxolo[4,5-*c*]quinolines are not accessible from intermediates **5** or **6**, but the set of dioxolo-quinolines was prepared from the corresponding 3HQs (**15a-e**), which were pre-synthesized using previously published



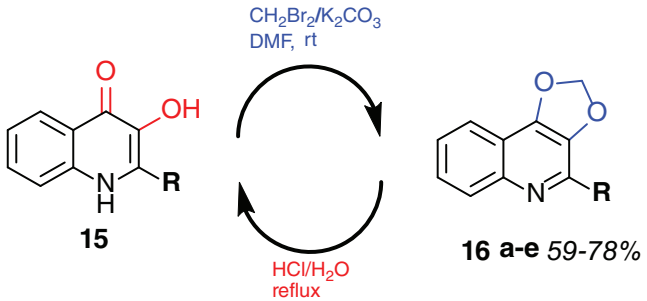
SCHEME 2 Reaction of DQC **6** with nucleophiles



SCHEME 3 Reaction of intermediate **5** with aldehydes

procedures.[26,36] The formation of 2-aryl-[1,3]dioxolo[4,5-*c*]quinolines from 2-aryl-3HQs (Scheme 4) was applicable to a broad range of starting 2-aryl-3HQs; dichloroacetic acid and dichloroacetamide were also used to cyclize the dioxole scaffold to provide **16f** and **16g** (see structures in experimental section). To our delight, the solubility of compounds **16** compared to 3HQs **15** was significantly higher, and their hydrolysis with hydrochloric acid smoothly afforded the corresponding 2-aryl-3HQs. Similarly, hydrolysis of representative 2-styryl-[1,3]dioxolo[4,5-*c*]quinolone **14a** yielded the corresponding 2-styryl-3HQ **17**.

The prepared [1,3]dioxolo[4,5-*c*]quinolines were tested for their antibiotic activity against representative Gram-positive (*Bacillus subtilis*, ATCC 6633; *Micrococcus luteus*, ATCC 10240; *Mycobacterium vaccae*, DSM 43514; *Staphylococcus aureus*, CCM 2524), and Gram-negative (*Pseudomonas aeruginosa*, CCM 3955; *Escherichia coli*, CCM 3954) bacteria using the agar diffusion assay.[37] (*E*)-4-styryl-[1,3]dioxolo[4,5-*c*]quinoline **16b** and (*E*)-4-(3,3-dimethylbut-1-en-1-yl)-[1,3]dioxolo[4,5-*c*]quinoline **14a** displayed noticeable antibacterial activities against *M. luteus* when tested at 2 mM, as indicated by the large inhibition zones (diameter ≥ 20 mm). These derivatives were subjected to a further assay[38] to determine their minimum inhibitory concentration (MIC). The MIC value against *M. luteus* was 0.2 μmol/L for both compounds, reaching the MIC of the control compound (ciprofloxacin, 0.26 μmol/L). In contrast, (*E*)-3-hydroxy-2-styrylquinolin-4(1*H*)-one **15b** (as the hydrolytic 3HQ analogue of **16b**) exhibited an order of magnitude higher MIC (3.13 μmol/L) against the same bacteria, which indicates the positive influence of the [1,3]dioxolo[4,5-*c*]quinoline scaffold on the resulting antibacterial activity. The other tested compounds were inactive.



SCHEME 4 Conversion of [1,3]dioxolo[4,5-*c*]quinolines to 3HQs and vice versa [Color figure can be viewed at wileyonlinelibrary.com]

3 | CONCLUSION

4-Methyl-[1,3]dioxolo[4,5-*c*]quinoline and [1,3]dioxolo[4,5-*c*]quinoline-4-carbaldehyde can be simply synthesized on a multigram scale from anthranilic acid and used as the key intermediates to access diverse [1,3]dioxolo[4,5-*c*]quinolines. These heterocycles resemble the structure of well-known quinoline alkaloids but have not been studied to date. The developed approach allows for the simple preparation of target compounds with variable C2 substitutions, and further modification of the quinoline moiety at the C5-8 positions is available in the case of variously substituted anthranilic acids. The biological potential of [1,3]dioxolo[4,5-*c*]quinolines was demonstrated by an antibacterial assay in which two compounds inhibited *M. luteus* with MIC values equal to ciprofloxacin. The [1,3]dioxolo[4,5-*c*]quinoline scaffold was readily hydrolyzed to the 3-hydroxyquinolin-4(1*H*)-one moiety, and for this reason, compounds **5** and **6** can be used as starting materials to prepare 3HQs that are not accessible by traditional methods based on anthranilate rearrangement.[34] Additionally, 2-aryl-[1,3]dioxolo[4,5-*c*]quinolines might be used as prodrugs of the cytotoxic 3-hydroxyquinolin-4(1*H*)-ones to overcome their solubility problems.

4 | EXPERIMENTAL SECTION

4.1 | General information

Reactions were monitored by thin layer chromatography (TLC) Merck Kieselgel 60F254. Compounds were visualized under UV light (254 nm). Column chromatography was performed on silica gel (VWR, 40-63 mesh). The purity of all compounds was determined by LC/MS (Waters 2695) with PDA detector (Waters, Milford, Massachusetts) and quadrupole mass spectrometer (hybrid Q-TOF micro mass spectrometer) using electrospray ionization ESI (Waters MS Technologies, Manchester, United Kingdom). Liquid chromatography was carried out using C18 reversed-phase column. Elution was by 0.01 M ammonium acetate (A) and acetonitrile/water (90/10) (B) with a linear gradient (0.6 mL/min). 1H and 13C NMR spectra were measured on Jeol ECA400II (400 MHz) at 23°C and reported in ppm. NMR spectra were recorded in $CDCl^3$ or DMSO-d_6 as a solvent. The 1H and 13C chemical shifts were referenced to the central signal of the solvent: $CDCl_3$ (d = 7.26 (1H), d = 77.0 (13C)); and DMSO-d_6 (d = 2.50 (1H) and d = 39.43 (13C)). Assignments were made with the aid of APT, HMQC, HMBC experiments. HPLC-HRMS analyses were performed on reverse phase gradient using

DionexUltimate 3000; column Phenomenex Gemini, 50 × 2,00 mm, 3 μm particles C_{18}; 80% acetonitrile and 20% buffer (0.01 M ammonium acetate) as mobile phase; wavelength λ 254 nm. High resolution mass determination was performed by ESI MS on a Fischer Sciencetific Exactive Plus Orbitrap mass spectrometer operating in positive and negative mode.

4.2 | Experimental procedures

Ohira-Bestmann reagent (dimethyl 1-[1-diazo-2-oxopropyl]phosphonate): Into a suspension of NaH (263 mg, 6.6 mmol, 60% disp. in mineral oil) in dry THF (16 mL), dimethyl-2-oxopropylphosphonate (1.00 mL, 6 mmol) was added dropwise at 0°C to 4°C. Reaction was kept at 0°C for 1 hour, then p-TsN_3 (2.6 g 50% solution in toluene, 6.6 mmol) was added and the reaction mixture was stirred at the same temperature for 30 minutes. Solvents were evaporated in vacuo and the crude product was purified by column chromatography (petrolether/EtOAc 1/1 → EtOAc).

4.2.1 | 2-Oxopropyl 2-aminobenzoate (3)

Compound **3** was prepared according to the literature[25] in 78% yield. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 9.9 Hz, 1H), 7.27 (t, J = 8.6 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.62 (s, 2H), 6.55 (t, J = 8.0 Hz, 1H), 4.93 (s, 2H), 2.14 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-D6) δ 202.3, 166.6, 151.5, 134.4, 130.8, 116.6, 114.8, 108.1, 68.2, 25.9.

4.2.2 | 3-Hydroxy-2-methylquinolin-4(1*H*)-one (4)

Compound **4** was prepared according to the literature[25] in 70% yield. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.49-7.55 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 2.38 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-D6) δ 168.6, 138.1, 137.2, 131.7, 129.9, 124.5, 122.3, 121.5, 117.6, 14.1.

4.2.3 | 4-Methyl[1,3]dioxolo[4,5-*c*]quinoline (5)

To a 2000 mL round bottom flask with a thermometer, magnetic stirrer and reflux condenser, compound **4** (74.1 g, 0.42 mol), DMF (740 mL), K_2CO_3 (205.4 g, 1.49 mol) and CH_2Br_2 (71.5 mL, 1.03 mol) were successively added. Reaction mixture was heated at 120°C for 75 minutes under the nitrogen atmosphere. After cooling to room temperature, the volume was reduced to 500 mL, the precipitated material was collected by filtration and washed with DMF. The filtrate was poured into 3000 mL of ice-cold water and after 30 minutes of stirring, the crude product was filtered, washed with water, and dried under vacuum. Crude product was purified by crystallization from cyclohexane to give crystalline solid in 66% yield (52 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7,88(1H, td; 8,5; 0,9)(7); 7,77(1H, ddd, J = 8,2; 1,5; 0,7 Hz)(4); 7,58(1H,ddd, J = 8,5; 6,8; 1,6 Hz)(6); 7,49 (1H, ddd; J = 8,1; 6,9; 1,2)(5); 6,35 (2H,s)(11); 2,54(3H,s)(10). ^{13}C-NMR (101 MHz DMSO-D6) δ 147,6(3); 144,5(8); 142,9(1); 139,3(2); 128,5(7); 127,6(6); 125,7(5); 119,6(4); 114,7(9); 103,0(11); 19,0(10). HRMS: calcd for $C_{11}H_9NO_2$ (M + H): m/z 188.0667; found: m/z 188.0668.

4.2.4 | [1,3]Dioxolo[4,5-*c*]quinoline-4-carbaldehyde (6)

Into a solution of **5** (15.0 g, 80 mmol) in THF (150 mL), SeO_2 (13.3 g, 120 mmol) was added and the resulting suspension was heated to reflux for 3 hours. After cooling, the reaction mixture was evaporated to dryness and the residual material was dissolved in warm DCM (150 mL). DCM solution was extracted with 3 × 100 mL of diluted HCl (water/HCl 4/1). The combined aqueous layers were filtrated with charcoal (750 mg) and neutralized at 10°C with 40% NaOH solution to pH 8-8.5. Obtained yellow precipitate was filtered, washed with water and dried under vacuum. Aldehyde **6** was prepared in 60% yield (9.7 g) and used in further reactions without purification.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 10,09(1H, s)(10); 8,08 (1H,ddd, J = 8,6; 1,6; 0,8 Hz)(7); 7,88(1H, ddd, J = 8,0; 1,6; 0,8 Hz)(4); 7,73(1H,dt, J = 7,6; 1,7 Hz)(6); 7,68 (1H, dt; 7,5; 1,3)(5); 6,51 (2H,s)(11). 13C-NMR (101 MHz DMSO-d_6) δ 191,6(10); 151,5(3); 144,5(8); 140,1(2); 136,8(1); 129,9(7); 129,2(6); 129,0(5); 120,0(4); 116,2(9); 104,9(11). HRMS: calcd for $C_{11}H_7NO_3$ (M + H): m/z 202.0449; found: m/z 202.0449.

4.2.5 | 4-[(4-Methylpiperazin-1-yl)methyl][1,3]dioxolo[4,5-*c*]quinoline (7)

Into a solution of *N*-methylpiperazine (0.6 g, 6 mmol) and aldehyde **6** (1 g, 5 mmol) in methanol (50 mL), glacial acetic acid (0.42 mL, 6 mmol) was added. After stirring at rt for 1 hour, the reaction mixture was cooled at 10°C and $NaBH_3CN$ (1.6 g, 25 mmol) was added in

10 portions over 1 hour period. Temperature spontaneously raised to rt. Methanol was evaporated, the residual material was diluted with water (15 mL) and extracted with EtOAc (2 × 25 mL). Combined organic layers were extracted with 5% HCl (2 × 15 mL) and 1 × 15 mL of water, alkalized to pH ~12 with 40% NaOH and extracted with EtOAc (2 × 25 mL). Organic layers were washed with brine (1 × 15 mL) dried over Na_2SO_4 and evaporated. Oily residue was crystallized from cyclohexane to yield crystalline compound **7** in 56% yield (0.8 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.94 (1H, d, J = 8.3 Hz)(7), 7.80 (1H, dd, J = 8.3, 1.6 Hz)(4), 7.61 (1H, dt, J = 8.0, 1.6 Hz)(6), 7.53 (1H, ddd, J = 7.8, 7.3, 1.0 Hz) (5), 6.37 (2H,s)(16), 3.71 (2H, s)(10), 2.50(4H, brs)(11 + 14), 2.28 (4H, brs)(12 + 13), 2.12 (3H, s)(15). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148.4(3), 144.3(8), 142.6(1), 140.0 (2), 129.0(7), 127.7(6), 126.3(5), 119.6(4), 115.0(9), 103.1 (16), 59.2(10), 54.5(12 + 13), 52.7(11 + 14), 45.6(15). HRMS: calcd for $C_{16}H_{19}N_3O_2$ (M + H): m/z 286.1550; found: m/z 286.1548.

4.2.6 | 4-[(*E*)-Hydrazinylidenemethyl] [1,3]dioxolo[4,5-*c*]quinoline (8)

Into a solution of **6** (2 g, 10 mmol) in pyridine (20 mL), NH_2NH_2·H2O (1 mL) was added. Reaction mixture was stirred at rt for 6 hours, then diluted with water to volume of 200 mL and stirred overnight. Obtained precipitate was filtered, washed with water and dried under vacuum to provide pink solid in 79% yield (1.7 g). Product was crystallized from ethanol.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.87-7.85 (2H, m)(7 + 10), 7.74 (1H, ddd, J = 8.3, 1.3, 0,5 Hz)(4), 7.59-7,55 (3H, m)(6, NH2), 7.46 (1H, t, J = 8.0 Hz)(5), 6.35 (2H, s) (11). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148.6(3), 144.4(8), 141.1(1), 137.6(2), 135.2(10), 128.4(7), 127.8(6), 125.7(5), 119.5(4), 114.5(9), 103.0(11). HRMS: calcd for $C_{11}H_9N_2O_3$ (M + H): m/z 216.0768; found: m/z 216.0769.

4.2.7 | 4-(2,2-Dibromovinyl)-[1,3]dioxolo [4,5-*c*]quinoline (9)

PPh_3 (1.02 g, 3.89 mmol, 4 equiv.) was added to a solution of CBr_4 (0.66 g, 1.99 mmol, 2 equiv.) in dry CH_2Cl_2 (3 mL) at 0°C. At the same temperature, aldehyde (0.2 g, 0.995 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (5.8 mL) and the resulting solution was added dropwise into the reaction mixture. The mixture was warmed to room temperature and stirred for 50 minutes (TLC petrolether/EtOAc 1/1). The reaction mixture was quenched by 25 mL of water followed by extraction of product with DCM (3 × 20 mL). Purification was performed by column chromatography ($CHCl_3$/petrolether 3/1). It provided yellow solid which was stirred in cyclohexane, filtered and dried in a yield of 302 mg (57%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H) (7); 7.77 (d, J = 7.3 Hz, 1H) (4); 7.72 (s, 1H) (10); 7.56 (t, J = 8.6 Hz, 1H) (6); 7.46 (t, J = 8.0 Hz, 1H) (5); 6.27 (s, 2H) (12). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.6 (3), 145.2 (8), 138.8 (1), 138.3 (2), 130.7 (10), 129.4 (7), 128.4 (6), 126.7 (5), 119.9 (4), 115.6 (9), 103.1 (12), 96.5 (11); ESI-HRMS: calcd. For $C_{12}H_7NO_2Br_2$ [M + H]+: 357.8892, found: 357.8896.

4.2.8 | [1,3]Dioxolo[4,5-*c*]quinolin-4-ylmethanol (10)

Into a solution of **6** (1 g, 5 mmol) in methanol (10 mL), $NaBH_4$ (0.19 g, 5 mmol) was added in five parts over 30 minutes period at the temperature below 10°C. After 30 minutes, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 10 mL). Combined organic layers were dried with Na_2SO_4 and evaporated. Crude product was crystallized from toluene to obtain white crystals of **11** in a yield of 79% (0.8 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.95 (1H, d, J = 8.8 Hz)(7), 7.80 (1H, dd, J = 8.3, 1.0 Hz)(4), 7.62 (1H, dt, J = 7.5, 1.6 Hz)(6), 7.53 (1H, ddd, J = 7.8, 7.3, 1.0 Hz) (5), 6.38 (2H, s)(11), 5.40 (1H, t, J = 6.0 Hz)(OH), 4.69 (1H, d, J = 6.2 Hz)(10). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148.5(3), 145.6(1), 144.2(8), 138.9(2), 128.8(7), 127.8(6), 126.2(5), 119.6(4), 115.1(9), 103.3(11), 61.0(10). HRMS: calcd for $C_{11}H_9NO_3$ (M + H): m/z 204.0655; found: m/z 204.0656.

4.2.9 | 4-Ethynyl[1,3]dioxolo[4,5-*c*] quinoline (11)

Freshly prepared Ohira-Bestmann reagent (1.15 g, 6 mmol) was dissolved in methanol (30 mL) followed by addition of K_2CO_3 (2.1 g, 15 mmol) and aldehyde **6** (1.0 g, 5 mmol). Reaction mixture was stirred at rt for 1.5 hours (TLC hexane/EtOAc 4/1). After that, 2.5 g of NH_4Cl was added and after 5 minutes of stirring the suspension was diluted by water (150 mL). Precipitated orange solid was filtered, washed with water, dried under vacuum, and crystallized from 2-propanol to provide **12** in 80% yield (0.8 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 1H) (7), 7.76 (d, J = 8.3 Hz, 1H)(4), 7.57 (t, J = 7.8 Hz, 1H)(6), 7.46 (t, J = 7.5 Hz, 1H)(5), 6.31 (s, 2H)(12), 3.47 (s, 1H) (11). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 149.3(3), 145.9(8),

142.4(2), 129.4(7), 128.4(6), 127.0(5), 125.9(1), 119.7(4), 115.8(9), 103.4(12), 82.1(11), 78.0(10). HRMS: calcd for $C_{12}H_7NO_2$ (M + H): m/z 198.0550; found: m/z 198.0549.

4.2.10 | 3-Hydroxy-4-oxo-1,4-dihydroquinoline-2-carbaldehyde (12)

To suspension of aldehyde **6** (1 g, 5 mmol) in water (10 mL), conc. HCl was dropped to adjust pH ~1. The solution was heated at 75°C for 15 minutes. After precipitation, acetonitrile (2 mL) was added and reaction mixture was heated to reflux for 3 hours. Reaction mixture was cooled to rt, diluted with water (15 mL), cooled to 5°C. The precipitated material was filtered, washed with water and dried under vacuum. Pure product **13** was obtained by crystallization from DMF (20 mL) as a yellow powder in 69% yield (0.65 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.46 (1H, s)(NH), 10.40 (1H, s)(10), 10.40 (1H, brs)(OH), 8.11 (1H, dd, J = 8.3, 1.3 Hz)(4), 7.85 (1H, d, J = 8.6 Hz)(7), 7.63 (1H,dt, J = 7.8, 1,6 Hz)(6), 7.24 (1H, dt, J = 7.6, 1.0 Hz)(5). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 186.1(10), 173.1(3), 146.4(2), 138.1(8), 132.2(6), 124.7(1), 124.5(4), 122.5(9), 121.9(5), 119.1(7). HRMS: HRMS: calcd for $C_{10}H_7NO_3$ (M + H): m/z 190.0499; found: m/z 190.0499.

4.3 | General procedure for preparation of compounds 13 a-f

A solution of **5** (935 mg, 5 mmol) in dry THF (20 mL) was cooled to −70°C under nitrogen atmosphere. Over 30 minutes period, 2 M solution of n-BuLi in hexane (2.75 mL, 5.5 mmol) was added dropwise via syringe and after 75 minutes a solution of aldehyde (5.5 mmol) in dry THF (10 mL) was added. Reaction was kept at −70°C for 1 hour, then treated with NH_4Cl (0.5 g) and warmed up to rt. THF was evaporated and the residual material was extracted with EtOAc/water. Organic phase was dried over Na_2SO_4 and concentrated. Compounds **13a** and **13d** were used without further purification. Compounds **13b**,**c**,**e**,**f** were purified by crystallization or precipitation.

4.3.1 | 1-cyclopropyl-2-([1,3]dioxolo[4,5-*c*]quinolin-4-yl)ethanol (13b)

Crystallized from cyclohexane, yield 60% (770 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.6 Hz, 1H)(7), 7.78 (dd, J = 8.2, 0.9 Hz, 1H)(4), 7.58 (dt, J = 7.8, 1.6 Hz, 1H)(6), 7.50 (ddd, J = 7.7, 7.4, 1.3 Hz, 1H)(5), 6.33-6.35 (m, 2H)(15), 4.77 (d, J = 5.2 Hz, 1H)(OH), 3.55-3.49 (m, 1H)(11), 3.07-3.05 (m, 2H)(10), 0.96-0.88 (m, 1H)(12), 0.38-0.25 (m, 3H) + 0.04-(−0.01) (m, 1H)(13A,13B, 14A,14B). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 147.6(3), 145.0(1), 144.5(8), 139.7(2), 128.7(7), 127.6(6), 125.8(5), 119.6(4), 114.7(9), 102.9(15), 72.4(11), 41.1(10), 17.4(12), 2.2 + 2.0(13, 14). HRMS: calcd for $C_{15}H_{15}NO_3$ (M + H): m/z 258.1125; found: m/z 258.1126.

4.3.2 | 1-Cyclopentyl-2-([1,3]dioxolo[4,5-*c*]quinolin-4-yl)ethanol (13c)

The crude product was dissolved in diethyl ether, filtered with charcoal and evaporated. Residual material was purified by precipitation (from petroleum ether to EtOAc) to give pale yellow solid in 56% yield (800 mg).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.3 Hz, 1H)(7), 7.78 (dd, J = 8.3, 0.8 Hz, 1H)(4), 7.58 (ddd, J = 8.3, 7.8, 1.4, 1H)(6), 7.50 (dt, J = 7.5, 1.0 Hz, 1H)(5), 6.34 (s, 2H)(17), 4.69 (d, J = 5.7 Hz, 1H)(OH), 3.98-3.91 (m, 1H)(11), 3.01-2.88 (m, 2H)(10A,B), 1.92-1.84 (m, 1H)(12), 1.72-1.27 (m, 8H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 147,7 (3) 145,5(1) 144,5(8) 139,7(2) 128,7(7) 127,6(6) 125,8 (5) 119,6(4) 114,7(9) 102,9(17) 72,2(11) 45,7(12) 39,9 (10) 18,7+ 27,5(13,16) 25,5 + 25,3(14,15). HRMS: calcd for $C_{17}H_{19}NO_3$ (M + H): m/z 286.1438; found: m/z 286.1439.

4.3.3 | 2-([1,3]Dioxolo[4,5-*c*]quinolin-4-yl)-1-(thiophen-3-yl)ethan-1-ol (13e)

Crude product was refluxed in diethyl ether (30 mL) which gave, after filtration and evaporation, gray powder in 94% yield (1.4 g). Crystallization from 2-propanol furnished white crystals. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.93 (td, J = 8.3, 0.8 Hz, 1H)(7), 7.79 (ddd, J = 8.0, 1.6, 0.5 Hz,1H)(4), 7.60 (ddd, J = 7.8, 7.5, 1.6 Hz, 1H)(6), 7.51 (dt, J = 7.5, 1.0 Hz, 1H)(5), 7.45 (dd, J = 4.9, 3.1 Hz, 1H)(14), 7.33-7.32 (m, 1H)(15), 7.12 (dd, J = 5.1, 1.2 Hz, 1H)(13), 6.35-6.29 (m, 2H)(16), 5.46 (d, J = 5.2 Hz, 1H)(OH), 5.32-5.28 (m, 1H)(11), 3.29-3.18 (m, 2H)(10). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 147.8(3), 146.9(12), 144.5(8), 144.3 (1), 139.8(2), 128.7(7), 127.7(6), 126.3(13), 125.9 + 125.8 (5,14), 120.4(15), 119.6(4), 114.8(9), 103.0(16), 67.6(11), 42.1(10). HRMS: calcd for HRMS: calcd for $C_{16}H_{13}NO_3S$ (M + H): m/z 300.0650; found: m/z 300.0652.

4.3.4 | 2-([1,3]Dioxolo[4,5-*c*]quinolin-4-yl)-1-(selenophen-2-yl)ethan-1-ol (13f)

The crude product was refluxed in diethyl ether (30 mL) which gave, after filtration and evaporation, gray powder

in 72% yield (1.25 g). Crystallization from acetone furnished white crystals. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.00 (dd, J = 5.4, 1.3 Hz, 1H)(15), 7.94 (d, J = 8.6 Hz, 1H)(7), 7.80 (ddd, J = 8.3, 1.6, 0.8 Hz, 1H)(4), 7.61 (ddd, J = 7.8, 7.7, 1.5, 1H)(6), 7.52 (ddd, J = 7.7, 7.4, 1.3 Hz, 1H)(5), 7.14 (dd, J = 5.4, 3.6 Hz, 1H)(14), 7.05 (td, J = 2.3, 1.2 Hz, 1H)(13), 6.36-6.30 (m, 2H)(16), 5.99 (d, J = 4.9 Hz, 1H)(OH), 5.49-5.47 (m, 1H)(11), 3.31-3.24 (m, 2H)(10). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 158.0(12), 147.9(3), 144.5(8), 143.7(1), 139.8(2), 129.6(15), 128.8(14), 128.7(7), 127.8(6), 126.0(5), 124.2(13), 119.7(4), 114.8(9), 103.1(16), 69.1(11), 43.5(10). HRMS: calcd for $C_{16}H_{13}NO_3Se$ (M + H): m/z 348.0133; found: m/z 348.0131.

4.4 | Synthesis of compounds 14 a-c

Into a solution of **13** (2.5 mmol) in pyridine (7.5 mL), MsCl (232 μL, 3.0 mmol) was added and the mixture was stirred for 16 hours. Mixture was poured into ice-cold water (50 mL) and stirred for 1 hour. The resulting suspension (compound **14b** and **14c**) was filtered, dried under vacuum and purified by crystallization. Compound **14a** was purified by extraction with EtOAc followed by column chromatography (hexane/EtOAc 4/1) which furnished green-yellow solid.

4.4.1 | 4-[(1*E*)-3,3-dimethylbut-1-en-1-yl][1,3]dioxolo[4,5-*c*]quinoline (14a)

Prepared from compound **13a** as a green-yellow solid in 45% yield (290 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7,89(1H, d; J = 8,8 Hz)(7); 7,76(1H, d, J = 8,3 Hz)(4); 7,59 (1H, dt, J = 7,8; 1,0 Hz)(6), 7,48(1H,dt, J = 7,8; 1,0 Hz)(5); 7,05(1H,d, J = 16,6 Hz)(11); 6,52 (1H, d; J = 16,6 Hz)(10); 6,40(2H,s)(16); 1,15(9H,s)(13 + 14 + 15). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149,4(11); 148,6(3); 144,7(8), 140,9(1); 138,3(2); 128,7(7); 128,0(6); 125,9(5); 121,2(10); 119,6(4); 114,6(9); 103,2(16); 33,6(12); 29,0(3C)(13 + 14 + 15). HRMS: calcd for $C_{16}H_{17}NO_2$ (M + H): m/z 256.1350; found: m/z 256.1333.

4.4.2 | 4-[(*E*)-2-cyclopropylethenyl][1,3]dioxolo[4,5-*c*]quinoline (14b)

Prepared from compound **13b**, crystallization from diethyl ether gave pale green solid in 50% yield (300 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8.3 Hz, 1H)(7), 7.74 (ddd, J = 8.2, 1.3, 0.8 Hz, 1H)(4), 7.57 (dt, J = 7.8, 1.6 Hz, 1H)(6), 7.46 (dt, J = 7.5, 1.0 Hz, 1H)(5), 6.72 (d, J = 15.8 Hz, 1H)(10), 6.49 (dd, J = 15.8, 9.6 Hz, 1H)(11), 6.37 (s, 2H)(15), 1.78-1.69 (m, 1H)(12), 0.94-0.90 (m, 2H), 0.66-0.62 (m, 2H)(13, 14). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148.4(3), 144.7(8), 144.3(11), 140.9(1), 138.0(2), 128.6(7), 128.0(6), 125.7(5), 123.2(10), 119.6(4), 114.5(9), 103.1(15), 15.1(12), 8.0(2C)(13 + 14). HRMS: calcd for $C_{15}H_{13}NO_2$ (M + H): m/z 240.1019; found: m/z 240.1018.

4.4.3 | 4-[(*E*)-2-(Pyridin-3-yl)ethenyl][1,3]dioxolo[4,5-*c*]quinoline (14d)

Prepared from compound **13d**. Purification was performed by reflux in methanol followed by filtration and precipitation with diethyl ether which furnished yellow solid in 58% yield (800 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H)(13), 8.53-8.52 (m, 1H)(14), 8.18 (dd, J = 8.0, 1.3 Hz, 1H)(16), 7.94 (d, J = 8.3 Hz, 1H)(7), 7.82-7.76 (m, 2H)(11,4), 7.61 (ddd, J = 8.3, 7.3, 1.6 Hz, 1H)(6), 7.52-7.41 (m, 3H)(5,10,15), 6.46 (s, 2H)(17). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149.5(14), 148.9(13), 148.9(3), 144.8(8), 139.9(1), 139.0(2), 133.3(16), 131.9(11), 131.7(12), 128.8(7), 128.3(6), 126.3(5), 125.8(10), 123.8(15), 119.7(4), 114.8(9), 103.5(17). HRMS: calcd for $C_{17}H_{12}N_2O_2$ (M + H): m/z 277.0972; found: m/z 277.0976.

4.5 | Preparation of compound 14f

Into a solution of **13f** (867 mg, 2.5 mmol) in pyridine (7.5 mL), MsCl (232 μL, 3.0 mmol) was added. Reaction mixture was heated at 100°C for 5 hours, cooled to rt, diluted with water and stirred overnight. After evaporation of solvents, the residual material was dissolved in acetonitrile (25 mL) and DBU (1.49 mL, 10 mmol) was added. After stirring for 1 hour at rt, the temperature was increased to reflux and kept for 30 minutes. After cooling to rt the solvent was evaporated followed by addition of ice-cold water (25 mL). After 30 minutes of stirring, the suspension was filtrated and dried to obtain brown solid. Crude product was refluxed in toluene (55 mL) and charcoal, filtrated and evaporated. Pure product was obtained by crystallization from methanol to provide pale yellow solid in 33% yield (271 mg).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 5.4 Hz, 1H)(15), 7.99 (d, J = 15.8 Hz, 1H)(11), 7.91 (d, J = 8.6 Hz, 1H)(7), 7.78 (dd, J = 8.1, 1.0 Hz, 1H)(4), 7.63-7.58 (m, 2H)(6,13), 7.50 (dt, J = 7.5, 1.0, 1H)(5), 7.33 (dd, J = 5.6, 3.8 Hz, 1H)(14), 6.97 (d, J = 16.1 Hz, 1H)(10), 6.45 (s, 2H)(16). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148.7(3), 147.4(12), 144.9(8), 140.1(1), 138.7(2), 132.8(15), 132.2(13), 131.1(11), 130.6(14), 128.7(7), 128.3(6), 126.1(5), 123.7(10), 119.7(4), 114.8(9), 103.5(16). HRMS: calcd for

$C_{16}H_{11}NO_2Se$ (M + H): m/z 330.0028; found: m/z 330.0026.

4.6 | Preparation of compounds 16a, b, c, d, e

Into a solution of **15** (5 mmol) in DMF (12.5 mL), K_2CO_3 (2.42 g, 17.5 mmol) and CH_2Br_2 (0.83 mL, 12 mmol) were added. Suspension was refluxed until disappearance of starting material (TLC hexane/EtOAc 7/3). Reaction mixture was poured into ice-cold water (125 mL). A precipitated solid (for compounds **16c**, **16d**, and **16e**) was isolated by filtration and purified by crystallization. Compounds **16a** and **16b** furnished oily material to which diethyl ether (50 mL) was added together with charcoal (100 mg). After 30 minutes of stirring a mixture was filtered through glass filter, layers were separated and aqueous layer was extracted with diethyl ether (2 × 25 mL). Combined organic phases were dried over $MgSO_4$, evaporated and purified by crystallization.

4.6.1 | 4-Phenyl[1,3]dioxolo[4,5-*c*]quinoline (16a)

Crystallization from ethanol gave pale pink solid in 78% yield (970 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8,33-8,30 (2H, m)(11 + 15); 8,02 (1H,ddd, J = 8,6; 1,0; 0,7; Hz)(7); 7,84(1H,ddd, J = 8,3; 1,5; 0,7 Hz)(4); 7,65(1H,ddd, J = 8,6; 6,8; 1,5 Hz)(6); 7,59-7,48 (4H, m)(12 + 14, 5, 13); 6,47 (2H,s)(16). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149,6(3); 144,7(8); 140,8(1); 138,8(2); 135,4(10); 129,7(13), 129,2(7); 128,6(2C)(12 + 14); 128,4(6); 127,7(2C)(11 + 15); 126,4(5); 119,7(4); 114,9(9); 103,2(16). HRMS: calcd for $C_{16}H_{11}NO_2$ (M + H): m/z 250.0863; found: m/z 250.0863.

4.6.2 | 4-[(*E*)-2-Phenylethenyl][1,3]dioxolo[4,5-*c*]quinoline (16b)

Crystallization from cyclohexane furnished yellow solid in 69% yield (950 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7,95(1H, d; 8,6)(7); 7,83(1H, d, J = 16.5 Hz)(11); 7,79(1H, ddd, J = 8,3; 1,4; 0,6 Hz)(4), 7,72(2H,d, J = 7,3 Hz)(13 + 17); 7,62(1H,ddd, J = 8,5; 6,8; 1,5 Hz)(6); 7,51 (1H, ddd; J = 8,1; 6,9; 1,1)(5); 7,45-7,37 (4H,m)(14 + 16, 10, 15); 6,47(2H,s)(18). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 148,8(3); 144,9(8); 140,5(1); 138,8(2); 136,0(12); 135,5(11); 128,9(3C)(14 + 16, 15); 128,8(7); 128,3(6); 127,2 (2C)(13 + 17); 126,2(5); 123,9(10); 119,7(4); 114,8(9); 103,5(18). HRMS: calcd for $C_{18}H_{13}NO_2$ (M + H): m/z 276.1019; found: m/z 276.1022.

4.6.3 | 4-(Thiophen-2-yl)[1,3]dioxolo[4,5-*c*]quinoline (16c)

Crystallization from ethanol furnished yellow powder in 72% yield (920 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.7 Hz, 1H)(7), 7.88 (dd, J = 3.8, 1.2 Hz, 1H)(13), 7.81-7.78 (m, 2H)(4,11), 7.63 (dt, J = 7.8, 1.6 Hz, 1H)(6), 7.51 (dt, J = 7,5, 1,0 Hz, 1H)(5), 7.26 (dd, J = 5.1, 3.8 Hz, 1H)(12), 6.50 (s, 2H)(14). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149.3(3), 144.6(8), 140.3(10), 137.0(2), 136.8(1), 129.4 (11), 128.5(2C) + 128.5(7,6,12), 126.1(5), 119.7(4), 114.8 (9), 103.7(14). HRMS: calcd for $C_{14}H_9NO_2S$ (M + H): m/z 256.0427; found: m/z 256.0423.

4.6.4 | 4-(Furan-2-yl)[1,3]dioxolo[4,5-*c*]quinoline (16d)

Crystallization from 2-propanol furnished white crystals in 59% yield (706 mg). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.97-7.95 (m, 2H)(13, 7), 7.79 (ddd, J = 8.3, 1.4, 0.6 Hz, 1H) (4), 7.63 (dt, J = 7.8, 1,6 Hz, 1H)(6), 7.51 (dt, J = 7.6, 1.2 Hz, 1H)(5), 7.21 (dd, J = 3.6, 0.8 Hz, 1H)(11), 6.74 (dd, J = 3.5, 1.7 Hz, 1H)(12), 6.48 (s, 2H)(14).^{13}C-NMR (101 MHz, DMSO-d_6) δ 149.2(3), 149.1(10), 144.8(13), 144.7(8), 136.9 (2), 133.2(1), 128.8(7), 128.4(6), 126.2(5), 119.7(4), 114.7(9), 112.8(11), 112.2(12), 103.7(14). HRMS: calcd for $C_{14}H_9NO_9$ (M + H): m/z 240.0655; found: m/z 240.0654.

4.6.5 | 4-(Selenophen-2-yl)-[1,3]dioxolo[4,5-*c*]quinoline (16e)

Crystallization from ethanol furnished white crystals in 73% yield (1.1 g). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 5.4 Hz, 1H)(11), 8.07 (d, J = 3.9 Hz, 1H)(13), 7.90 (d, J = 8.6 Hz, 1H)(7), 7.79 (d, J = 8.0 Hz, 1H)(4), 7.61 (dd, J = 8.3, 7.0 Hz, 1H)(6), 7.48-7.52 (m, 2H)(5,12), 6.50 (s, 2H)(14). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149.2(3), 146.7(10), 144.7(8), 138.3(1), 136.5(2), 135.0(11), 131.1 (12), 130.3(13), 128.5+ 128.5(6,7) 126.1(5) 119.7(4) 114.8 (9) 103.7(14). HRMS: calcd for $C_{14}H_9NO_2Se$ (M + H): m/z 303.9871; found: m/z 303.9869.

4.7 | Preparation of compound 16f

Into a solution of **15a** (2.0 g, 8.43 mmol) in DMF (25 mL), K_2CO_3 (4.1 g, 29.5 mmol) was added and the suspension was heated to reflux under nitrogen atmosphere. Meanwhile a solution of sodium salt of dichloroacetic acid was prepared pouring $NaHCO_3$ (3.4 g, 40.4 mmol) into dichloroacetic acid (3.32 mL, 40.4 mmol)

in DMF (10 mL). Approximately a half of the prepared solution was dropped into refluxed reaction mixture over 15 minutes period. Reaction was kept for 50 minutes under reflux and after that the other half of solution was added. Reaction was kept for additional 45 minutes under the same temperature. DMF was evaporated and the residue was quenched with water (50 mL) followed by filtration. Obtained solution was cooled at 5°C, acidified with diluted HCl (HCl/H_2O 1/10) to pH ~ 4 and precipitate was filtered and dried. Crude product was crystallized from methanol (25 mL) to provide pale pink solid in 72% yield (1.8 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8,32-8,30(2H, m)(11 + 15); 8,05 (1H,d, J = 8,6 Hz)(7); 7,88 (1H,dd, J = 8,3; 0,8 Hz)(4); 7,70 (1H,ddd, J = 8,5; 6,9; 1,5 Hz)(6); 7,61-7,57 (3H, m)(12 + 14, 5); 7,55-7,51 (1H, m)(13); 7,02 (1H,s)(16). ^{13}C-NMR (101 MHz, DMSO-D6) δ 166,1(17); 148,8 (3); 144,9(8); 140,8(1); 138,1(2); 135,1(10); 129,9(13); 129,2 (7); 128,7(6); 128,7(2C)(12 + 14); 127,8(2C)(11 + 15); 126,8(5); 119,7(4); 114,7(9); 104,7(16). HRMS: calcd for $C_{17}H_{11}NO_4$ (M + H): m/z 294.0722; found: m/z 294.0724.

4.8 | Preparation of compound 16g

Into a solution of **15a** (2.0 g, 8.43 mmol) in DMF (20 mL), K_2CO_3 (4.1 g, 29.5 mmol) was added and suspension was warmed up to reflux under nitrogen atmosphere. A solution of dichloroacetamide (2.6 g, 20.2 mmol) in DMF (10 mL) was added dropwise over 45 minutes period. Reaction mixture was poured into ice-cold water (125 mL) and precipitate was filtered, washed with water and dried. Crude product was crystallized from DMF/H_2O to obtain beige solid in 70% yield (1.7 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 8,34-8,31(2H, m)(11 + 15); 8,29(1H,brs) + 7,94(1H,brs)(NH2); 8,04 (1H,d, J = 8,6 Hz)(7); 7,86 (1H,dd, J = 8,0; 0,8 Hz)(4); 7,68 (1H, dt, J = 7,7; 1,3 Hz)(6); 7,60-7,56 (3H, m)(12 + 14, 5); 7,52 (1H, tt, J = 7.3; 1.3 Hz)(13); 6.80 (1H,s)(16). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 165,9(17); 149,1(3); 144,8(8); 140,7 (1); 138,5(2); 135,3(10); 129,8(13); 129,1(7); 128,6(2C)(12 + 14); 128,5 (6); 127,8(2C)(11 + 15); 126,5(5); 119,9(4); 114,7(9); 105,9(16). HRMS: calcd for $C_{17}H_{12}N_2O_3$ (M + H): m/z 293.0921; found: m/z 293.0921.

4.9 | Hydrolysis of compound 14a to compound 17

A suspension of **14a** (216 mg, 0.846 mmol) in 5 mL of diluted HCl (HCl/H_2O 1/1) was heated to reflux. After 5 minutes brown oil appeared which slowly transformed to yellow precipitate. Reaction was stirred for 3 hours (TLC hexane/EtOAC 7/3). The precipitate was filtered, washed with water and dried under vacuum. Crude product was purified by crystallization from 2-propanol/hexane to provide yellow crystals in 63% yield (130 mg).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 14.00 (s, 1H); 10.60 (s, 2H); 8.26 (d, J = 8.6 Hz, 2H) (4,7); 7.78 (t, J = 8.6 Hz, 1H) (6); 7.54 (t, J = 7.8 Hz, 1H) (5); 7.45 (d, J = 16.6 Hz, 1H) (11); 6.84 (d, J = 16.1 Hz, 1H) (10); 1.01-1.17 (m, 9H) (13,14,15). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 159.2 (3); 154.1 (11); 139.8 (1); 135.9 (8,2); 131.3 (6); 125.4 (5); 122.8 (4); 119.7 (9); 119.0 (7); 114.1 (10); 34.5 (12); 28.7 (13,14,15). HRMS: calcd for $C_{15}H_{16}NO_2$ (M + H): m/z 242.1191; found: m/z 242.1176.

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