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Synthesis, anti-mycobacterial and cytotoxic evaluation of substituted isoindoline-1,3-dione-4-aminoquinolines coupled *via* alkyl/amide linkers†

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A series of secondary amine-substituted isoindoline-1,3-dione-4-aminoquinolines were prepared *via* microwave heating and assayed for their anti-mycobacterial activities. The compound with a butyl chain as a spacer between the two pharmacophores and piperidine as the secondary amine component on the isoindoline ring was the most potent and non-cytotoxic among the synthesized compounds, exhibiting a minimum inhibitory concentration (MIC_{99}) of 6.25 μg mL^{-1} against *Mycobacterium tuberculosis*.

Introduction

Tuberculosis (TB) is a global pandemic caused by the single infectious agent *Mycobacterium tuberculosis*. TB has been a scourge to mankind for thousands of years and roughly more than one third of the world's population is latently infected.[1] In 2016, there were 10.4 million new cases of TB diagnosed with approximate mortality of 1.3 million among HIV-negative and an additional 374 000 deaths among HIV-positive people, mostly in developing countries.[2] According to the Revised National Tuberculosis Control Program (RNTCP), India accounts for one fourth of the global TB burden with 1.75 million TB patients, including data from both the public and private health sectors, while 33 820 drug-resistant TB patients are noted additionally.[3] Increasing cases of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB all over the world is hindering current TB treatment,[4] which includes the first-line drugs isoniazid (INH), rifampicin (RIF), pyrazinamide, ethambutol, and streptomycin, and the second line drugs, aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and terizidone.[5,6] The emergence of resistant strains warrants the urgent search for faster-acting, less harmful, more efficient drug candidates.

The quinoline core has received recent attention as it is one of the active key building blocks of many drugs. Bedaquiline – a diarylquinoline – was recently approved by Food and Drug Administration (FDA) and European Medicine Agency (EMA) for treating MDR-TB patients.[7–9] However, the drug comes with a black-box warning, which includes the risk of cardiac (QT prolongation) and hepatic dysfunction and heightened risk of mortality.[10] Mefloquine, an orally administered drug, is another quinoline derivative known for potent anti-tubercular activity.[11–15] Remarkably, numerous derivatives of mefloquine were reported to have good antibacterial and anti-mycobacterial activities.[16,17]

Isoindoline-1,3-dione and its derivatives were shown to possess interesting biological properties[18] against a wide panel of diseases and conditions, such as angiogenic disease,[19] inflammation,[20] cancer,[21,22] Parkinson's,[23] leprosy, AIDS and multiple myeloma (MM); as COX inhibitors; antidepressants and histone deacetylase inhibitors.[24] Synthesis of conjugates of the isoindoline-1,3-dione subunit with different active moieties afforded active antimicrobials against *Mycobacterium leprae* and *M. tuberculosis*.[25]

A recent report from our lab highlighted the anti-mycobacterial potential of isoindoline-1,3-dione-4-aminoquinolines, exhibiting comparable activity with ethionamide and cephalexin (Fig. 1).[26] In continuation of our efforts,[27] we present herein the synthesis and anti-mycobacterial

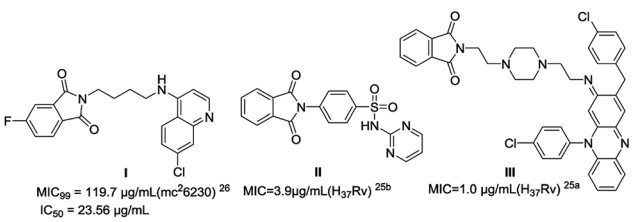

Fig. 1 Isoindoline-1,3-dione based active anti-TB compounds.

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† Electronic supplementary information (ESI) available: Scanned ^{1}H and ^{13}C NMR spectra of few representative compounds *viz.* **4c**, **4d**, **4f**, **4k**, **4m**, **4o**, **4s**, **7a**, **7c**, **7e**, **7i**, **7n**, **7q**, **8a**, **8c**, **8d**, **8j**, **8n** and **8p** are provided in the electronic supplementary information. See DOI: 10.1039/c8ra10532d

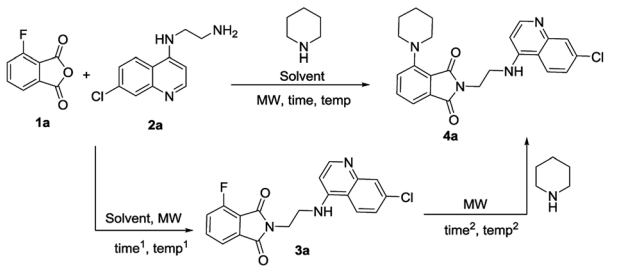
activities of secondary amino-substituted isoindoline-1,3-dione-4-aminoquinolines. The spacer length between two pharmacophores as well as the secondary amine functionality at the C4/C5 position of isoindoline-1,3-dione was meticulously altered for analysing the structure–activity relationship (SAR).

Results and discussion

Synthetic chemistry

For the synthesis of the desired isoindoline-1,3-dione-4-aminoquinolines with the secondary amine functionality at the C-4/C-5 position, microwave heating was attempted, as the reactions were sluggish when carried out under conventional heating. The microwave assisted reaction between 3-fluorophthalic anhydride **1a**, *N*-(7-chloroquinolin-4-yl)diamine **2a**[28] and piperidine was chosen as model reaction. Different solvents *viz*. DMF, DMSO and NMP were screened, both for the single-pot as well as for the step-wise synthesis and the results are provided in Scheme 1. As evident, the single pot synthesis gave the desired scaffold **4a**, albeit in moderate yields, when compared to the step-wise process. The solvent choice seems to be crucial and better yields were observed by heating in NMP because of its polar aprotic nature and ease of removal during purification procedure. Best results obtained *via* either heating in single pot synthesis at 160 °C for 5 min (70% yield) or in step-wise synthesis by heating at 140 °C for 2 min for step 1 and then at 160 °C for 2 min for step 2 (89% yield).

Having optimized the reaction conditions, the scope of the developed strategy was then explored for the synthesis of a series of C-4/C-5 secondary amine linked isoindoline-1,3-dione-4-aminoquinolines **4b–4t** following the stepwise microwave synthesis (Scheme 2). The structure assignment was done on the basis of spectral data and analytical evidences. For example, the compound **4s** exhibited a molecular ion peak at *m*/*z* 508.2084 $[M + H]^+$ in the High Resolution Mass Spectrum (HRMS). The noteworthy features of its ^{1}H NMR spectrum encompassed the appearance of multiplet at δ 1.76–1.86, two triplets at 3.34 (J = 6.6 Hz) and 3.73 (J = 6.4 Hz) because of methylenes, two triplets at 2.66 (J = 4.7 Hz) and 3.40 (J = 4.6 Hz)



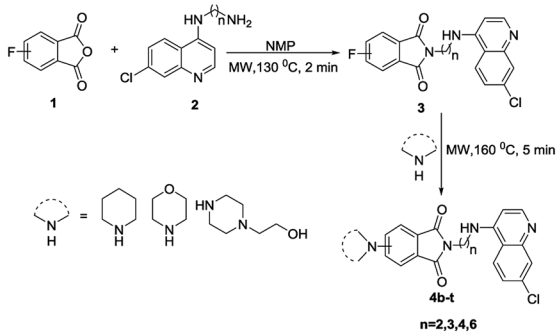
Solvent	time	temp	%yield
DMF	5min	170	49%
DMSO	5min	180	58%
NMP	5min	160	70%

single pot Microwave synthesis

Solvent	time^1	time^2	temp^1	temp^2	overall yields %
DMF	4min	5min	130	170	60%
DMSO	2min	5min	130	180	74%
NMP	2min	2min	140	160	89%

Stepwise Microwave synthesis

Scheme 1 Optimizing microwave-assisted synthesis of the C-4-piperidine ring substituted isoindoline-1,3-dione-4-aminoquinolines **4a**.

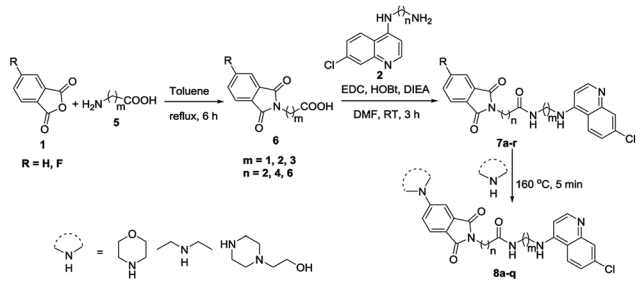


Scheme 2 Microwave-promoted synthesis of C-4/C-5 secondary amine substituted isoindoline-1,3-dione-4-aminoquinolines (**4b–t**).

because of piperazine ring protons and a doublet at δ 7.00 (J = 8.4 Hz) because of aromatic ring protons. The presence of absorption peaks at δ 169.1 and 168.7, corresponding to carbonyl carbons in the ^{13}C NMR spectrum along with methylenes at δ 25.5, 26.5, 37.2 and 42.8 and piperazine carbons at δ 47.6 and 52.4, as corroborated by the ^{13}C NMR (DEPT) spectrum, validated the assigned structure. For the synthesis of conjugates **7a–r**, amide coupling of **6** with *N*-(7-chloroquinolin-4-yl)diamine **2** was done using amide coupling reagents EDC–HOBt at room temperature. Further, C-5 flouro substituted conjugates **7m–r** were reacted with different secondary amines under microwave heating resulted in the formation of desired conjugates **8a–r** in good to excellent yields (Scheme 3). Spectral data and analytical evidences were used to assign the structure to the synthesized conjugates.

In vitro anti-mycobacterial evaluation

The synthesized scaffolds were assayed for their anti-mycobacterial activities against *M. tuberculosis* mc^{2}6230 and the result are enlisted in Table 1. As evident, all the synthesized compounds were not as active as isoniazid, but some of them showed promising activities. A closer analysis of Table 1 showed the dependence of activity on the nature of linker between two pharmacophores, the nature of substituent at C-4/C-5 position of isoindoline-1,3-dione as well as the linker used as spacer. Cytotoxic studies of all the synthesized compounds were also carried out against Vero cells so as to confirm whether the observed activities were due to their inherent anti-mycobacterial efficacy or cytotoxicity (Table 1, Fig. 2).



Scheme 3 Synthesis of C-5 substituted isoindoline-1,3-dione linked with 4-aminoquinolines *via* amide spacer **7a–r**, **8a–r**.

Table 1 *In vitro* anti-mycobacterial activity of synthesized compounds against *M. tuberculosis* mc^{2}6230 and cytotoxicity against Vero cells

Code	R	*m*	*n*	MIC_{99}[a] (μg mL^{-1})	IC_{50} (μg mL^{-1}) (cytotoxicity)	SI
4a	4-Piperidyl	—	2	100	25.55	0.26
4b	4-Piperidyl	—	3	12.5	96.87	7.75
4c	4-Piperidyl	—	4	6.25	26.59	4.25
4d	4-Piperidyl	—	6	6.25	56.87	9.10
4e	5-Piperidyl	—	2	12.5	13.95	1.12
4f	5-Piperidyl	—	3	12.5	>100.4	>8
4g	5-Piperidyl	—	4	6.25	>100	>16
4h	5-Piperidyl	—	6	12.5	99.3	7.94
4i	4-Morpholinyl	—	2	100	28.43	0.28
4j	4-Morpholinyl	—	3	50	>100	>2
4k	4-Morpholinyl	—	4	12.5	36.05	2.88
4l	4-Morpholinyl	—	6	6.25	22.26	3.56
4m	5-Morpholinyl	—	2	50	12.15	0.24
4n	5-Morpholinyl	—	3	50	14.73	0.29
4o	5-Morpholinyl	—	4	12.5	11.30	0.904
4p	5-Morpholinyl	—	6	6.25	3.537	0.57
4q	5-(2-(Piperazin-1-yl)ethan-1-ol)	—	2	100	4.91	0.05
4r	5-(2-(Piperazin-1-yl)ethan-1-ol)	—	3	12.5	9.017	0.72
4s	5-(2-(Piperazin-1-yl)ethan-1-ol)	—	4	12.5	15.00	1.2
4t	5-(2-(Piperazin-1-yl)ethan-1-ol)	—	6	12.5	29.84	2.38
7a	H	1	2	200	>100	>0.5
7b	H	1	4	25	>100	>4
7c	H	1	6	25	>100	>4
7d	H	1	8	12.5	>100	>8
7e	H	2	2	12.5	>100	>8
7f	H	2	4	50	>100	>2
7g	H	2	6	25	41.88	1.67
7h	H	2	8	25	>100	>4
7i	H	3	2	12.5	>100	>8
7j	H	3	4	25	>100	>4
7k	H	3	6	50	>100	>2
7l	H	3	8	12.5	52.93	4.23
7m	5-F	1	2	6.25	>100	>16
7n	5-F	1	4	25	>100	>4
7o	5-F	1	6	200	>100	>0.5
7p	5-F	2	2	200	41.0	0.20
7q	5-F	2	4	200	51.44	0.25
7r	5-F	2	6	200	28.42	0.14
8a	5-Morpholinyl	1	2	50	>100	>2
8b	5-Morpholinyl	1	4	12.5	>100	>8
8c	5-Morpholinyl	1	6	200	11.07	0.05
8d	5-Morpholinyl	2	2	100	13.42	0.13
8e	5-Morpholinyl	2	4	200	72.52	0.36
8f	5-Morpholinyl	2	6	200	>100	>0.5
8g	5-(Diethylamino)	1	2	50	21.28	0.42
8h	5-(Diethylamino)	1	4	12.5	23.78	1.90
8i	5-(Diethylamino)	1	6	100	>100	>1
8j	5-(Diethylamino)	2	2	50	100	9.5
8k	5-(Diethylamino)	2	4	200	44	0.22
8l	5-(Diethylamino)	2	6	100	>100	>1
8m	5-(2-(Piperazin-1-yl)ethan-1-ol)	1	2	50	>100	>2
8n	5-(2-(Piperazin-1-yl)ethan-1-ol)	1	4	100	>100	>1
8o	5-(2-(Piperazin-1-yl)ethan-1-ol)	1	6	200	>100	>0.5
8p	5-(2-(Piperazin-1-yl)ethan-1-ol)	2	2	ND	ND	—
8q	5-(2-(Piperazin-1-yl)ethan-1-ol)	2	4	100	97.65	0.97
8r	5-(2-(Piperazin-1-yl)ethan-1-ol)	2	6	25	>100	>4
INH	Isoniazid			0.019	>100	

[a] The MIC expressed in μg mL^{-1} were determined using the microdilution method in broth medium; *m*, *n* are alkyl chain length (Schemes 1–3).

Among isoindoline-1,3-dione-4-aminoquinolines linked *via* alkyl chain **4a–t**, the replacement of fluoro-substituent (compound **I**, Fig. 1) with secondary amine on isoindoline-1,3-dione ring, not only improved the anti-TB activity but also reduced their cytotoxicity, which were in the range of 5.03–20.92 μg mL^{-1}.[26] Introduction of a piperidine ring at the C-4/C-5

position among compounds, **4a–4h** revealed an increase in activity with the increase in alkyl chain length as evident by **4c** ($n = 4$), **4d** ($n = 6$) and **4g** ($n = 4$), exhibiting MIC values of 6.25. Similar improvement in anti-TB activities was observed with the induction of morpholine ring. The compounds **4k**, **4l**, **4o** and **4p** exhibited MIC of 12.5, 6.25, 12.5, 6.25 μg mL^{-1} respectively. Introduction of hydroxy-ethyl-piperazine as the secondary amine counterpart considerably enhanced the anti-

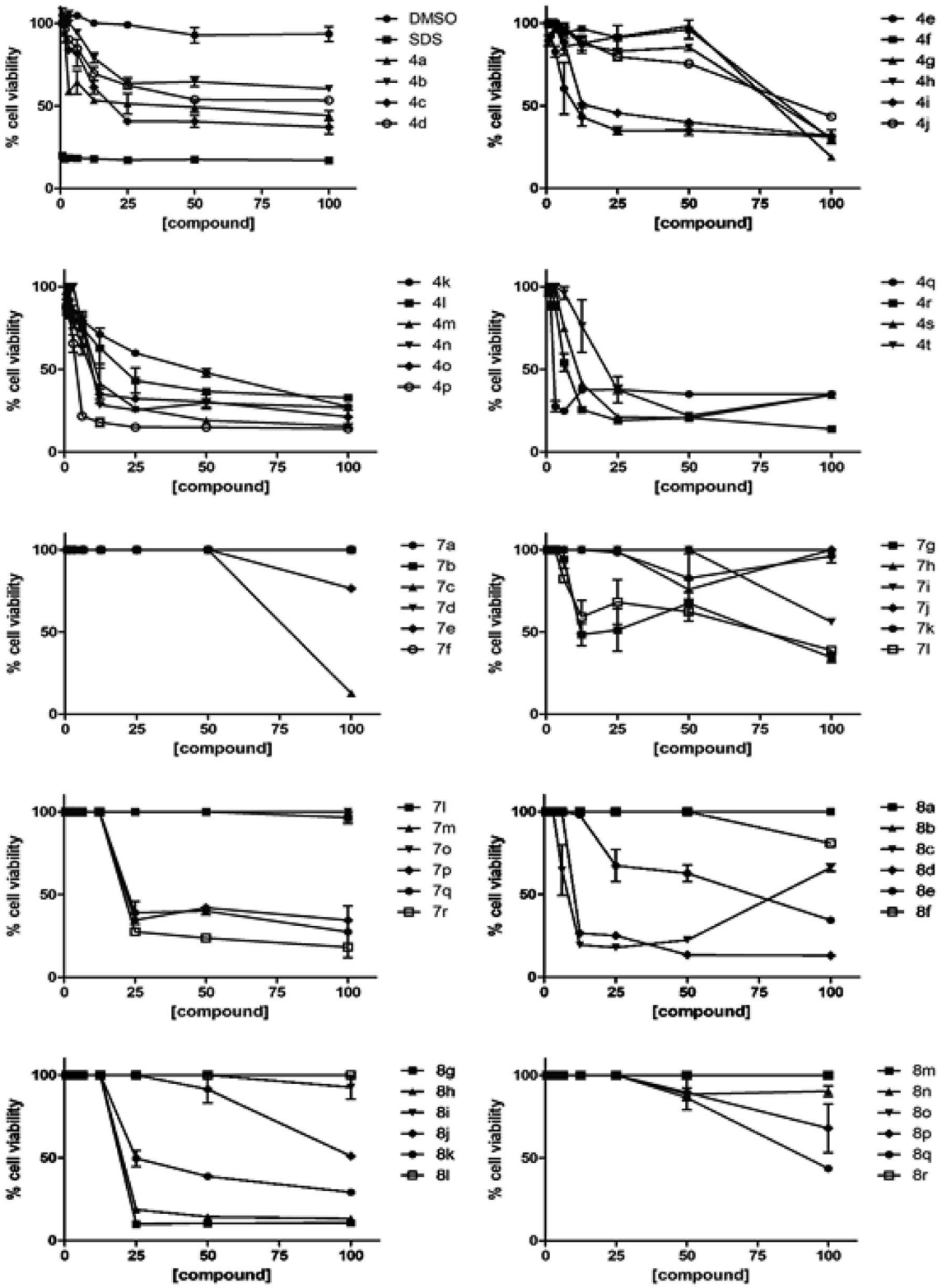


Fig. 2 Cytotoxicity of synthesized compounds (**4a–t**, **7a–r**, **8a–r**) on Vero cells. Shown are means and standard deviations calculated from two independent experiments. DMSO is included as a negative control, while SDS was included as a positive control.

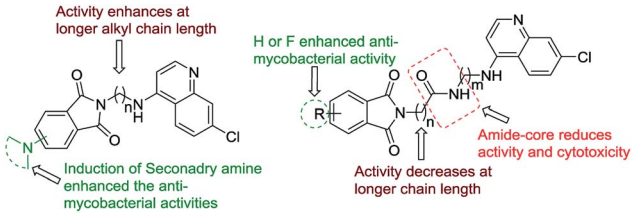


Fig. 3 Generalized SAR of synthesized isoindoline-1,3-dione-4-aminoquinolines

mycobacterial activity even at shorter chain lengths. **4r**, **4s** and **4t** having propyl, butyl and hexyl spacer length along with hydroxyl-ethyl-piperazine at C-5 position exhibited MIC values of 12.5 μg mL^{-1}, for all three compounds, but also increased their respective cytotoxicity.

Among the amide tethered isoindoline-1,3-dione-4-aminoquinoline **7a–r**, although a decrease in anti-mycobacterial activity has been observed in general, the compounds were non-cytotoxic in nature. Among the scaffold having $n = 1$ (Glycine), the compound **7d** (R = H, $n = 8$) and **7m** (R = F, $n = 2$) displayed better activity profiles compared to the other members of the series with MIC of 12.5 and 6.25 μg mL^{-1} respectively. The introduction of β-alanine and γ-aminobutyric acid showed more or less similar activity profiles with low cytotoxicity. The introduction of secondary amine functionality among the amide-linked series resulted in considerable loss of anti-mycobacterial activities except for the compound **8b** which was non-cytotoxic and exhibited a MIC of 12.5 μg mL^{-1}. The generalized SAR of the synthesized isoindoline-1,3-dione-4-aminoquinolines (both the alkyl chain as well as amide-core tethered) for their anti-mycobacterial activity against $mc^2$6230 strain of *M. tuberculosis* and cytotoxicity against Vero cells is depicted in Fig. 3.

Conclusion

In conclusion, the present describes the microwave-promoted synthesis of a series of C-4/C-5 secondary amine substituted isoindoline-1,3-dione-4-aminoquinolines coupled *via* alkyl/amide core as linker. The synthesized scaffolds were evaluated for their anti-mycobacterial profiles against the *M. tuberculosis* $mc^2$6230 strain while cytotoxicity was determined against Vero cells. The compound **4g** with an optimum combination of piperidine as the secondary amine at C-5 position and a butyl chain as spacer proved to be non-cytotoxic with a MIC_{99} of 6.25 μg mL^{-1}.

Experimental section

General

Veego Precision Digital Melting Point apparatus (MP-D) was used for the determination of melting points which are uncorrected. ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$)/DMSO-d_6 using Bruker 500 (500 MHz) and Jeol 400 (400 MHz) spectrometers while TMS is used as internal standard. Microwave reactions were performed in a Biotage® Initiator+ instrument using sealed 2–5 mL process vials. Reaction times refer to irradiation time at the target temperature, not the total irradiation time. The temperature was measured with an IR sensor. Chemical shift values are specified as parts per million (ppm) downfield from TMS, while coupling constant (J) values are in hertz. Patterns of splitting are designated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on Bruker 125 MHz and Jeol 100 MHz spectrometers in $CDCl_3$ and DMSO-d_6. High Resolution Mass Spectra (HRMS) were recorded on a Bruker-micrOTOF-Q II spectrometer using ESI as the ion source.

General procedure for the preparation of C-4/C-5 secondary amine substituted isoindoline-1,3-dione-4-aminoquinolines (4a–t)

To a microwave reaction vial was added a solution of C-3/C-4 fluoro-phthalic anhydride (1.0 mmol) in 0.5 mL of NMP (*N*-methylpyrrolidin-2-one) and 4-aminoquinoline-diamines (1.0 mmol). After sealing with a PTFE cap, the vessel was heated to 130 °C for 2 min in the microwave reactor. After accomplishment of the first step, as obvious from TLC, secondary amine (1.2 mmol) was added in the same reaction vial. The reaction mixture was again heated at 160 °C for 5 min in the microwave reactor and the completion was ascertained using TLC. After completion, the contents were poured in water (20 mL) resulting in the precipitation of the desired product. The obtained product was filtered and re-crystallized using absolute ethanol.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-4-(piperidin-1-yl) isoindoline-1,3-dione (4a). Yield 89%; dark yellow solid; mp 140–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63–1.68 (m, 2H, –$\mathbf{CH_2}$–); 1.79–1.85 (m, 4H, 2× –$\mathbf{CH_2}$–); 3.36 (t, $J = 5.2$ Hz, 4H, 2× –$\mathbf{CH_2}$–); 3.35–3.47 (m, 2H, –$\mathbf{CH_2}$–); 3.78 (t, $J = 6.4$ Hz, 2H, –$\mathbf{CH_2}$–); 5.39 (s, 1H, NH-exchangeable with D_2O); 6.41 (d, $J = 5.2$ Hz, 1H, Ar–H); 7.14 (d, $J = 8.2$ Hz, 1H, Ar–H); 7.32–7.37 (m, 2H, Ar–H); 7.54–7.58 (m, 1H, Ar–H); 7.82 (d, $J = 9.0$ Hz, 1H, Ar–H); 7.98 (s, 1H, Ar–H); 8.51 (d, $J = 5.2$ Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 25.7, 37.3, 43.2, 52.9, 99.1, 114.8, 117.3, 117.5, 121.3, 123.4, 125.3, 128.7, 134.6, 134.9, 135.2, 149.3, 149.9, 150.9, 152.1, 168.2, 168.8. HRMS calcd for $C_{24}H_{23}ClN_4O_2$ $[M + H]^+$ 435.1543 found 435.1547.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-4-(piperidin-1-yl) isoindoline-1,3-dione (4b). Yield 88%; dark yellow solid; mp 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62–1.67 (m, 2H, –$\mathbf{CH_2}$–); 1.82–1.88 (m, 4H, 2× –$\mathbf{CH_2}$–); 1.98 (m, 2H, –$\mathbf{CH_2}$–), 3.32 (t, $J = 5.1$ Hz, 4H, 2× –$\mathbf{CH_2}$–); 3.35–3.40 (m, 2H, –$\mathbf{CH_2}$–); 3.80 (t, $J = 6.4$ Hz, 2H, –$\mathbf{CH_2}$–); 5.36 (s, 1H, NH-exchangeable with D_2O); 6.40 (d, $J = 5.1$ Hz, 1H, Ar–H); 7.18 (d, $J = 8.2$ Hz, 1H, Ar–H); 7.32–7.36 (m, 2H, Ar–H); 7.51–7.55 (m, 1H, Ar–H); 7.81 (d, $J = 8.8$ Hz, 1H, Ar–H); 7.94 (s, 1H, Ar–H); 8.51 (d, $J = 5.2$ Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 25.5, 26.6, 37.2, 43.4, 52.7, 99.0, 114.6, 117.1, 117.4, 121.2, 123.4, 125.2, 128.8, 134.3, 134.8, 135.1, 149.4, 149.9, 150.8, 152.0, 168.1, 168.9. HRMS calcd for $C_{25}H_{25}ClN_4O_2$ $[M + H]^+$ 449.1700 found 449.1708.

2-(4-((7-Chloroquinolin-4-yl)amino)butyl)-4-(piperidin-1-yl) isoindoline-1,3-dione (4c). Yield 89%; dark brown solid; mp 110–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64–1.67 (m, 2H, –$\mathbf{CH_2}$–);

1.80–1.89 (m, 8H, 4× –CH_2–); 3.30 (t, J = 5.3 Hz, 4H, 2× –CH_2–); 3.37–3.41 (m, 2H, –CH_2–); 3.77 (t, J = 6.5 Hz, 2H, –CH_2–); 5.37 (s, 1H, NH-exchangeable with D_2O); 6.41 (d, J = 5.4 Hz, 1H, Ar–H); 7.16 (d, J = 8.5 Hz, 1H, Ar–H); 7.33–7.37 (m, 2H, Ar–H); 7.53–7.56 (m, 1H, Ar–H); 7.80 (d, J = 8.9 Hz, 1H, Ar–H); 7.95 (s, 1H, Ar–H); 8.52 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 25.6, 25.9, 26.5, 37.2, 43.0, 52.7, 99.0, 114.7, 117.2, 117.4, 121.2, 123.2, 125.2, 128.7, 134.4, 134.7, 135.0, 149.1, 149.7, 150.9, 152.0, 168.1, 168.7. HRMS calcd for $C_{26}H_{27}ClN_4O_2$ $[M + H]^+$ 463.1856 found 463.1863.

2-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-4-(piperidin-1-yl) isoindoline-1,3-dione (4d). Yield 90%; dark brown solid; mp 85–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40–1.56 (m, 4H, 2× –CH_2–); 1.63–1.67 (m, 2H, –CH_2–); 1.70–1.78 (m, 4H, 2× –CH_2–); 1.80–1.83 (m, 4H, 2× –CH_2–); 3.28–3.33 (m, 6H, 3× –CH_2–); 3.68 (t, J = 5.5 Hz, 2H, –CH_2–); 5.21 (s, 1H, NH-exchangeable with D_2O); 6.41 (d, J = 5.4 Hz, 1H, Ar–H); 7.16 (d, J = 8.4 Hz, 1H, Ar–H); 7.33–7.37 (m, 2H, Ar–H); 7.52–7.55 (m, 1H, Ar–H); 7.76 (d, J = 8.9 Hz, 1H, Ar–H); 7.96 (s, 1H, Ar–H); 8.53 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.0, 25.9, 26.2, 26.3, 28.3, 28.5, 37.3, 42.8, 52.7, 99.0, 114.7, 117.2, 117.7, 121.0, 123.1, 125.2, 128.7, 134.5, 134.7, 134.9, 149.1, 149.7, 150.9, 152.0, 168.1, 168.7. HRMS calcd for $C_{28}H_{31}ClN_4O_2$ $[M + H]^+$ 491.2169 found 491.2162.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-5-(piperidin-1-yl) isoindoline-1,3-dione (4e). Yield 85%; yellow solid; mp 180–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64–1.76 (m, 6H, 3× –CH_2–); 3.37–3.44 (m, 6H, 3× –CH_2–); 3.79 (t, J = 6.1 Hz, 2H, –CH_2–); 6.11 (s, 1H, NH-exchangeable with D_2O); 6.42 (d, J = 5.3 Hz, 1H, Ar–H); 7.03 (d, J = 8.0 Hz, 1H, Ar–H); 7.27 (s, 1H, Ar–H); 7.41 (d, J = 9.0 Hz, 1H, Ar–H); 7.67 (d, J = 8.6 Hz, 1H, Ar–H); 7.92–7.97 (m, 2H, Ar–H); 8.51 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 25.3, 34.9, 39.7, 48.9, 98.8, 108.3, 117.2, 117.4, 118.4, 121.3, 125.1, 125.3, 128.7, 134.6, 134.8, 149.3, 149.6, 151.8, 155.4, 169.2, 169.7. HRMS calcd for $C_{24}H_{23}ClN_4O_2$ $[M + H]^+$ 435.1543 found 435.1549.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-5-(piperidin-1-yl) isoindoline-1,3-dione (4f). Yield 88%; yellow solid; mp 97–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65–1.78 (m, 6H, 3× –CH_2–); 2.00–2.05 (m, 2H, –CH_2–); 3.39–3.45 (m, 6H, 3× –CH_2–); 3.80 (t, J = 6.0 Hz, 2H, –CH_2–); 6.12 (s, 1H, NH-exchangeable with D_2O); 6.42 (d, J = 5.4 Hz, 1H, Ar–H); 7.01 (d, J = 8.0 Hz, 1H, Ar–H); 7.26 (s, 1H, Ar–H); 7.40 (d, J = 8.9 Hz, 1H, Ar–H); 7.65 (d, J = 8.5 Hz, 1H, Ar–H); 7.90–7.95 (m, 2H, Ar–H); 8.51 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 25.2, 26.7, 34.6, 39.2, 48.8, 98.6, 108.2, 117.2, 117.4, 118.3, 121.4, 125.0, 125.3, 128.6, 134.5, 134.8, 149.2, 149.5, 151.9, 155.4, 169.1, 169.6. HRMS calcd for $C_{25}H_{25}ClN_4O_2$ $[M + H]^+$ 449.1700 found 449.1712.

2-(4-((7-Chloroquinolin-4-yl)amino)butyl)-5-(piperidin-1-yl) isoindoline-1,3-dione (4g). Yield 87%; yellow solid; mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41–1.49 (m, 4H, 2× –CH_2–), 1.64–1.77 (m, 6H, 3× –CH_2–); 3.37–3.44 (m, 6H, 3× –CH_2–); 3.78 (t, J = 6.1 Hz, 2H, –CH_2–); 6.11 (s, 1H, NH-exchangeable with D_2O); 6.41 (d, J = 5.3 Hz, 1H, Ar–H); 7.00 (d, J = 8.1 Hz, 1H, Ar–H); 7.26 (s, 1H, Ar–H); 7.41 (d, J = 9.0 Hz, 1H, Ar–H); 7.64 (d, J = 8.6 Hz, 1H, Ar–H); 7.89–7.94 (m, 2H, Ar–H); 8.52 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1, 25.2, 26.7, 26.9, 34.5, 39.2, 48.7, 98.4, 108.1, 117.2, 117.3, 118.2, 121.4, 125.1, 125.2, 128.7, 134.4, 134.7, 149.1, 149.5, 151.7, 155.3, 169.0, 169.5. HRMS calcd for $C_{26}H_{27}ClN_4O_2$ $[M + H]^+$ 463.1856 found 463.1874.

2-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-5-(piperidin-1-yl) isoindoline-1,3-dione (4h). Yield 89%; yellow solid; mp 88–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31–1.35 (m, 4H, 2× –CH_2–), 1.52–1.56 (m, 2H, –CH_2–), 1.63–1.78 (m, 8H, 4× –CH_2–); 3.34–3.41 (m, 6H, 3× –CH_2–); 3.75 (t, J = 6.2 Hz, 2H, –CH_2–); 6.10 (s, 1H, NH-exchangeable with D_2O); 6.40 (d, J = 5.3 Hz, 1H, Ar–H); 7.01 (d, J = 8.0 Hz, 1H, Ar–H); 7.24 (s, 1H, Ar–H); 7.40 (d, J = 9.0 Hz, 1H, Ar–H); 7.64 (d, J = 8.5 Hz, 1H, Ar–H); 7.88–7.94 (m, 2H, Ar–H); 8.51 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 25.1, 26.7, 26.7, 28.3, 28.7, 34.3, 39.2, 48.4, 98.2, 108.0, 117.0, 117.2, 118.0, 121.2, 125.0, 125.2, 128.6, 134.5, 134.7, 149.1, 149.3, 151.6, 155.3, 169.1, 169.2. HRMS calcd for $C_{28}H_{31}ClN_4O_2$ $[M + H]^+$ 491.2169 found 491.2178.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-4-morpholinoisoindoline-1,3-dione (4i). Yield 92%; yellow solid; mp 163–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36–3.40 (m, 6H, 3× –CH_2–); 3.74 (t, J = 6.4 Hz, 2H, –CH_2–); 3.95 (t, J = 4.5 Hz, 4H, 2× –CH_2–); 5.30 (s, 1H, NH-exchangeable with D_2O); 6.36 (d, J = 5.2 Hz, 1H, Ar–H); 7.11 (d, J = 8.3 Hz, 1H, Ar–H); 7.31–7.38 (m, 2H, Ar–H); 7.57–7.61 (m, 1H, Ar–H); 7.75 (d, J = 9.0 Hz, 1H, Ar–H); 7.88 (d, J = 2.0 Hz, 1H, Ar–H); 8.46 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz) δ 37.5, 43.3, 51.7, 66.9, 99.0, 115.8, 117.1, 118.2, 121.4, 122.8, 125.4, 128.9, 134.4, 134.8, 135.6, 149.2, 149.8, 150.2, 152.1, 168.3, 168.6. HRMS calcd for $C_{23}H_{21}ClN_4O_3$ $[M + H]^+$ 437.1336 found 437.1344.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-4-morpholinoisoindoline-1,3-dione (4j). Yield 90%; yellow solid; mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.05 (m, 2H, –CH_2–); 3.34–3.39 (m, 6H, 3× –CH_2–); 3.71 (t, J = 6.5 Hz, 2H, –CH_2–); 3.94 (t, J = 4.3 Hz, 4H, 2× –CH_2–); 5.28 (s, 1H, NH-exchangeable with D_2O); 6.35 (d, J = 5.3 Hz, 1H, Ar–H); 7.12 (d, J = 8.4 Hz, 1H, Ar–H); 7.30–7.37 (m, 2H, Ar–H); 7.56–7.59 (m, 1H, Ar–H); 7.75 (d, J = 8.9 Hz, 1H, Ar–H); 7.89 (d, J = 2.0 Hz, 1H, Ar–H); 8.45 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz) δ 28.4, 37.3, 43.1, 51.6, 66.8, 99.0, 115.9, 117.1, 118.1, 121.3, 122.8, 125.4, 128.8, 134.5, 134.9, 135.6, 149.1, 149.8, 150.1, 152.1, 168.2, 168.7. HRMS calcd for $C_{24}H_{23}ClN_4O_3$ $[M + H]^+$ 451.1492 found 451.1477.

2-(4-((7-Chloroquinolin-4-yl)amino)butyl)-4-morpholinoisoindoline-1,3-dione (4k). Yield 89%; yellow solid; mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74–1.87 (m, 4H, 2× –CH_2–); 3.30–3.37 (m, 6H, 3× –CH_2–); 3.73 (t, J = 6.6 Hz, 2H, –CH_2–); 3.91 (t, J = 4.5 Hz, 4H, 2× –CH_2–); 5.29 (s, 1H, NH-exchangeable with D_2O); 6.37 (d, J = 5.4 Hz, 1H, Ar–H); 7.12 (d, J = 8.4 Hz, 1H, Ar–H); 7.31–7.39 (m, 2H, Ar–H); 7.54–7.58 (m, 1H, Ar–H); 7.73 (d, J = 9.0 Hz, 1H, Ar–H); 7.91 (d, J = 2.1 Hz, 1H, Ar–H); 8.47 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz) δ 25.7, 26.5, 37.4, 43.0, 51.5, 66.9, 99.1, 115.9, 117.2, 118.1, 121.2, 122.8, 125.3, 128.7, 134.5, 134.9, 135.5, 149.0, 149.8, 150.1, 152.0, 168.1, 168.6. HRMS calcd for $C_{25}H_{25}ClN_4O_3$ $[M + H]^+$ 465.1649 found 465.1665.

2-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-4-morpholinoisoindoline-1,3-dione (4l). Yield 88%; yellow solid; mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35–1.39 (m, 4H, 2× –CH_2–); 1.50–1.54 (m, 2H, –CH_2–); 1.64–1.77 (m, 4H, 2× –CH_2–); 3.29–3.36 (m, 6H, 3× –CH_2–); 3.72 (t, J = 6.5 Hz, 2H, –CH_2–); 3.90 (t, J = 4.6 Hz,

4H, 2× –CH_2–); 5.28 (s, 1H, NH-exchangeable with D_2O); 6.36 (d, J = 5.3 Hz, 1H, Ar–H); 7.11 (d, J = 8.5 Hz, 1H, Ar–H); 7.30–7.38 (m, 2H, Ar–H); 7.53–7.56 (m, 1H, Ar–H); 7.71 (d, J = 8.9 Hz, 1H, Ar–H); 7.90 (d, J = 2.0 Hz, 1H, Ar–H); 8.45 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz) δ 25.3, 26.6, 28.4, 28.8, 37.2, 43.2, 51.2, 66.7, 99.0, 115.8, 117.0, 118.0, 121.1, 122.6, 125.2, 128.7, 134.3, 134.7, 135.3, 149.1, 149.6, 150.2, 152.1, 168.0, 168.4. HRMS calcd for $C_{27}H_{29}ClN_4O_3$ $[M + H]^+$ 493.1962 found 493.1971.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-5-morpholinoisoindoline-1,3-dione (4m). Yield 89%; dark brown solid; mp 192–193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (t, J = 4.8 Hz, 4H, 2× –CH_2–); 3.52–3.55 (m, 2H, –CH_2–); 3.88 (t, J = 4.8 Hz, 4H, 2× –CH_2–); 4.15 (t, J = 5.2 Hz, 2H, –CH_2–); 6.13 (s, 1H, NH-exchangeable with D_2O); 6.36 (d, J = 5.3 Hz, 1H, Ar–H); 7.05 (d, J = 8.4 Hz, 1H, Ar–H); 7.30 (s, 1H, Ar–H); 7.43 (d, J = 8.9 Hz, 1H, Ar–H); 7.73 (d, J = 8.4 Hz, 1H, Ar–H); 7.80 (d, J = 8.9 Hz, 1H, Ar–H); 7.94 (s, 1H, Ar–H); 8.52 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 43.8, 47.5, 66.3, 98.6, 108.5, 117.1, 117.7, 120.1, 121.5, 125.2, 125.6, 128.5, 134.2, 134.9, 148.9, 149.7, 151.9, 155.6, 169.1, 169.5. HRMS calcd for $C_{23}H_{21}ClN_4O_3$ $[M + H]^+$ 437.1336 found 437.1349.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-5-morpholinoisoindoline-1,3-dione (4n). Yield 85%; dark brown solid; mp 185–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65–1.70 (m, 2H, –CH_2–); 3.36–3.45 (m, 6H, 3× –CH_2–); 3.80 (t, J = 6.4 Hz, 2H, –CH_2–); 3.90 (t, J = 4.7 Hz, 4H, 2× –CH_2–); 5.30 (s, 1H, NH-exchangeable with D_2O); 6.40 (d, J = 5.4 Hz, 1H, Ar–H); 7.04 (d, J = 8.4 Hz, 1H, Ar–H); 7.28 (s, 1H, Ar–H); 7.40 (d, J = 9.0 Hz, 1H, Ar–H); 7.70 (d, J = 8.3 Hz, 1H, Ar–H); 7.78 (d, J = 9.0 Hz, 1H, Ar–H); 7.94 (s, 1H, Ar–H); 8.52 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 37.5, 43.0, 47.8, 66.2, 99.0, 108.4, 117.0, 117.6, 120.5, 121.4, 124.9, 125.4, 128.6, 134.3, 134.8, 149.0, 149.6, 152.0, 155.5, 168.9, 169.3. HRMS calcd for $C_{24}H_{23}ClN_4O_3$ $[M + H]^+$ 451.1492 found 451.1486.

2-(4-((7-Chloroquinolin-4-yl)amino)butyl)-5-morpholinoisoindoline-1,3-dione (4o). Yield 85%; dark brown solid; mp 180–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85–1.90 (m, 4H, 2× –CH_2–); 3.36–3.41 (m, 6H, 3× –CH_2–); 3.77 (t, J = 6.5 Hz, 2H, –CH_2–); 3.89 (t, J = 4.8 Hz, 4H, 2× –CH_2–); 5.29 (s, 1H, NH-exchangeable with D_2O); 6.41 (d, J = 5.4 Hz, 1H, Ar–H); 7.04 (d, J = 8.4 Hz, 1H, Ar–H); 7.26 (s, 1H, Ar–H); 7.37 (d, J = 8.9 Hz, 1H, Ar–H); 7.68 (d, J = 8.4 Hz, 1H, Ar–H); 7.76 (d, J = 9.0 Hz, 1H, Ar–H); 7.95 (s, 1H, Ar–H); 8.52 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 26.5, 37.3, 42.9, 47.7, 66.3, 99.1, 108.3, 117.2, 117.6, 120.7, 121.1, 124.8, 125.3, 128.7, 134.4, 134.8, 149.1, 149.7, 152.0, 155.4, 168.6, 169.0. HRMS calcd for $C_{25}H_{25}ClN_4O_3$ $[M + H]^+$ 465.1649 found 465.1654.

2-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-5-morpholinoisoindoline-1,3-dione (4p). Yield 89%; yellow solid; mp 177–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39–1.48 (m, 4H, 2× –CH_2–); 1.60–1.69 (m, 4H, 2× –CH_2–); 3.35–3.42 (m, 6H, 3× –CH_2–); 3.76 (t, J = 6.2 Hz, 2H, –CH_2–); 3.86 (t, J = 4.5 Hz, 4H, 2× –CH_2–); 5.28 (s, 1H, NH-exchangeable with D_2O); 6.40 (d, J = 5.3 Hz, 1H, Ar–H); 7.02 (d, J = 8.3 Hz, 1H, Ar–H); 7.25 (s, 1H, Ar–H); 7.35 (d, J = 8.8 Hz, 1H, Ar–H); 7.66 (d, J = 8.3 Hz, 1H, Ar–H); 7.76 (d, J = 8.8 Hz, 1H, Ar–H); 7.93 (s, 1H, Ar–H); 8.53 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.4, 28.7, 28.9, 37.2, 42.9, 47.6, 66.1, 99.0, 108.2, 117.2, 117.5, 120.8, 121.1, 124.7, 125.2, 128.6, 134.4, 134.7, 149.0, 149.6, 152.1, 155.3, 168.5, 169.1. HRMS calcd for $C_{27}H_{29}ClN_4O_3$ $[M + H]^+$ 493.1962 found 493.1976.

2-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-5-(4-(2-hydroxyethyl)piperazin-1-yl)isoindoline-1,3-dione (4q). Yield 88%; dark brown solid; mp 211–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (t, J = 5.4 Hz, 2H, –CH_2); 2.69 (t, J = 5.0 Hz, 4H, 2× –CH_2–); 3.39 (t, J = 6.4 Hz, 2H, –CH_2–); 3.45 (t, J = 5.0 Hz, 4H, 2× –CH_2–); 3.70 (t, J = 5.3 Hz, 2H, –CH_2–); 3.77 (t, J = 6.5 Hz, 2H, –CH_2–); 6.41 (d, J = 5.5 Hz, 1H, Ar–H); 7.04 (d, J = 8.3 Hz, 1H, Ar–H); 7.23 (s, 1H, Ar–H); 7.35 (d, J = 9.0 Hz, 1H, Ar–H); 7.65 (d, J = 8.2 Hz, 1H, Ar–H); 7.75 (d, J = 8.9 Hz, 1H, Ar–H); 7.93 (s, 1H, Ar–H); 8.49 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 42.9, 47.8, 52.5, 57.9, 59.5, 99.1, 108.5, 117.0, 117.5, 120.1, 121.0, 124.9, 125.3, 128.9, 134.6, 134.8, 149.1, 149.8, 152.0, 155.3, 168.7, 169.1. HRMS calcd for $C_{25}H_{26}ClN_5O_3$ $[M + H]^+$ 480.1758 found 480.1771.

2-(3-((7-Chloroquinolin-4-yl)amino)propyl)-5-(4-(2-hydroxyethyl)piperazin-1-yl)isoindoline-1,3-dione (4r). Yield 89%; dark brown solid; mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99–2.05 (m, 2H, 2× –CH_2–), 2.63 (t, J = 5.3 Hz, 2H, –CH_2); 2.68 (t, J = 5.0 Hz, 4H, 2× –CH_2–); 3.36 (t, J = 6.6 Hz, 2H, –CH_2–); 3.43 (t, J = 5.1 Hz, 4H, 2× –CH_2–); 3.68 (t, J = 5.4 Hz, 2H, –CH_2–); 3.76 (t, J = 6.4 Hz, 2H, –CH_2–); 6.39 (d, J = 5.3 Hz, 1H, Ar–H); 7.03 (d, J = 8.3 Hz, 1H, Ar–H); 7.22 (s, 1H, Ar–H); 7.33 (d, J = 9.0 Hz, 1H, Ar–H); 7.63 (d, J = 8.3 Hz, 1H, Ar–H); 7.74 (d, J = 8.9 Hz, 1H, Ar–H); 7.93 (s, 1H, Ar–H); 8.48 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 37.8, 42.7, 47.7, 52.6, 57.6, 59.3, 99.1, 108.3, 117.2, 117.8, 120.2, 121.3, 124.9, 125.5, 128.6, 134.6, 134.9, 149.2, 149.8, 151.7, 155.4, 168.6, 169.2. HRMS calcd for $C_{26}H_{28}ClN_5O_3$ $[M + H]^+$ 494.1914, found 494.2160.

2-(4-((7-Chloroquinolin-4-yl)amino)butyl)-5-(4-(2-hydroxyethyl)piperazin-1-yl)isoindoline-1,3-dione (4s). Yield 87%; dark brown solid; mp 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.86 (m, 4H, 2× –CH_2–); 2.61 (t, J = 5.1 Hz, 2H, –CH_2); 2.66 (t, J = 4.7 Hz, 4H, 2× –CH_2–); 3.34 (t, J = 6.6 Hz, 2H, –CH_2–); 3.40 (t, J = 4.6 Hz, 4H, 2× –CH_2–); 3.66 (t, J = 5.1 Hz, 2H, –CH_2–); 3.73 (t, J = 6.4 Hz, 2H, –CH_2–); 6.37 (d, J = 5.3 Hz, 1H, Ar–H); 7.00 (d, J = 8.4 Hz, 1H, Ar–H); 7.22 (s, 1H, Ar–H); 7.34 (d, J = 8.9 Hz, 1H, Ar–H); 7.63 (d, J = 8.3 Hz, 1H, Ar–H); 7.73 (d, J = 8.9 Hz, 1H, Ar–H); 7.91 (s, 1H, Ar–H); 8.47 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 26.5, 37.2, 42.8, 47.6, 52.4, 57.7, 59.3, 99.0, 108.4, 117.1, 117.6, 120.1, 121.1, 124.8, 125.3, 128.6, 134.4, 134.8, 149.0, 149.6, 151.9, 155.2, 168.7, 169.1. HRMS calcd for $C_{27}H_{30}ClN_5O_3$ $[M + H]^+$ 508.2071 found 508.2084.

2-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-5-(4-(2-hydroxyethyl)piperazin-1-yl)isoindoline-1,3-dione (4t). Yield 85%; dark brown solid; mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.39 (m, 4H, 2× –CH_2–); 1.75–1.88 (m, 4H, 2× –CH_2–); 2.60 (t, J = 5.3 Hz, 2H, –CH_2–); 2.65 (t, J = 4.8 Hz, 4H, 2× –CH_2–); 3.33 (t, J = 6.5 Hz, 2H, –CH_2–); 3.40 (t, J = 4.9 Hz, 4H, 2× –CH_2–); 3.65 (t, J = 5.3 Hz, 2H, –CH_2–); 3.72 (t, J = 6.5 Hz, 2H, –CH_2–); 6.35 (d, J = 5.4 Hz, 1H, Ar–H); 7.01 (d, 8.4 Hz, 1H, Ar–H); 7.22 (s, 1H, Ar–H); 7.32 (d, J = 8.9 Hz, 1H, Ar–H); 7.61 (d, J = 8.4 Hz, 1H, Ar–H); 7.71 (d, J = 9.0 Hz, 1H, Ar–H); 7.90 (s, 1H, Ar–H); 8.45 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 25.5, 26.5, 26.7, 28.3, 28.5, 37.0, 42.7, 47.4, 52.3, 57.5, 59.4, 99.0, 108.3, 117.0, 117.4, 120.1, 121.4, 124.6, 125.2,

128.7, 134.4, 134.6, 149.0, 149.8, 152.0, 155.1, 168.4, 169.0. HRMS calcd for $C_{29}H_{34}ClN_5O_3$ $[M + H]^+$ 536.2384 found 536.2376.

General procedure for synthesis of amide linked substituted isoindoline-1,3-dione-4-aminoquinolines (7a–r, 8a–r)

Synthesis of C-5 substituted 2-(1,3-dioxoisoindolin-2-yl)acetic acid/3-(1,3-dioxoisoindolin-2-yl)propanoic acid/4-(1,3-dioxoisoindolin-2-yl)butanoic acid (**6**): C-4 substituted phthalic anhydride (1 mmol), amino acids (1.2 mmol) and triethylamine (Et_3N) (1.2 mmol) were mixed in toluene and the reaction mixture was refluxed for 6 h. The progress of the reaction was monitored by thin layer chromatography (TLC). Toluene was evaporated under reduced pressure and the solid residue was stirred with 1 N-HCl in ice-cold water. The resulted white powder was filtered, dried and used for subsequent step without any purification.

Synthesis of C-5 substituted *N*-(2-((7-chloroquinolin-4-yl)amino) alkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamides (7a–r)

1.0 mmol of C-5 substituted (1,3-dioxoisoindolin-2-yl)acetic acid, *N*-ethyl-*N*-dimethylaminopropyl carbodiimide (EDC) (1.1 mmol), hydroxybenzotriazole (HOBt) (1.2 mmol) and *N*,*N*-diisopropylethylamine (2.0 mmol) were mixed in minimum DMF and the obtained mixture was stirred for 5 min. Then, 4-aminoquinoline-diamines (1.0 mmol) was added to the reaction mixture and the stirring was continued for 5 h. The reaction end was proved by thin layer chromatography (TLC). Then, DMF was evaporated using rotary evaporator and cold water (20 mL) was added, and solid precipitates obtained were filtered and washed with cold water. The crude product was recrystallized in absolute ethanol.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7a).** Yield 82%; white solid; mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.31 (s, 4H, 2× –CH_2–); 4.18 (s, 2H, –CH_2–); 6.50 (d, J = 5.4 Hz, 1H, Ar–H); 7.33 (t, J = 5.0 Hz, 1H, NH-exchangeable with D_2O); 7.38 (dd, J = 1.8, 9.0 Hz, 1H, Ar–H); 7.74 (d, J = 2.0 Hz, 1H, Ar–H); 7.82–7.88 (m, 4H, Ar–H); 8.11 (d, J = 9.0 Hz, 1H, Ar–H); 8.36 (d, J = 5.0 Hz, 1H, Ar–H); 8.45 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (100 MHz, DMSO-d_6) δ 37.9, 40.7, 42.3, 99.1, 117.9, 123.7, 124.4, 124.6, 128.0, 132.2, 133.9, 135.1, 149.5, 150.5, 152.4, 167.2, 168.0. HRMS calcd for $C_{21}H_{17}ClN_4O_3$ $[M + H]^+$ 409.1023 found 409.1041.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7b).** Yield 81%; white solid; mp 129–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96–1.29 (m, 4H, 2× –CH_2–); 3.08–3.15 (m, 2H, –CH_2–); 3.25–3.29 (m, 2H, –CH_2–); 4.16 (s, 2H, –CH_2–); 6.46 (d, J = 5.5 Hz, 1H, Ar–H); 7.33 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 7.42 (dd, J = 2.4, 9.0 Hz, 1H, Ar–H); 7.76 (d, J = 2.3 Hz, 1H, Ar–H); 7.83–7.90 (m, 4H, Ar–H); 8.20–8.30 (m, 2H, Ar–H + NH-exchangeable with D_2O); 8.37 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.4, 27.2, 37.2, 40.2, 42.1, 99.2, 117.8, 123.7, 124.3, 124.7, 128.1, 132.2, 133.8, 135.2, 149.4, 150.4, 152.5, 167.0, 168.1. HRMS calcd for $C_{23}H_{21}ClN_4O_3$ $[M + H]^+$ 437.1336 found 437.1323.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7c).** Yield 85%; white solid; mp 110–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32–1.41 (m, 6H, 3× –CH_2–); 1.57–1.64 (m, 2H, –CH_2–); 3.00–3.05 (m, 2H, –CH_2–); 3.20–3.25 (m, 2H, –CH_2–); 4.13 (s, 2H, –CH_2–); 6.44 (d, J = 5.6 Hz, 1H, Ar–H); 7.38–7.42 (m, 2H, Ar–H + NH-exchangeable with D_2O); 7.74 (d, J = 2.2 Hz, 1H, Ar–H); 7.80–7.86 (m, 4H, Ar–H); 8.16 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); 8.25 (d, J = 9.0 Hz, 1H, Ar–H); 8.34 (d, J = 5.5 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5, 26.7, 28.2, 29.4, 39.1, 40.6, 42.9, 99.1, 117.8, 123.6, 124.7, 127.8, 132.3, 134.2, 135.0, 148.8, 150.9, 151.7, 166.3, 168.1. HRMS calcd for $C_{25}H_{25}ClN_4O_3$ $[M + H]^+$ 465.1649 found 465.1629.

***N*-(8-((7-Chloroquinolin-4-yl)amino)octyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7d).** Yield 76%; white solid; mp 101–102 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22–1.41 (m, 12H, 6× –CH_2–); 3.03–3.07 (m, 2H, –CH_2–); 3.22–3.26 (m, 2H, –CH_2–); 4.17 (s, 2H, –CH_2–); 6.45 (d, J = 5.3 Hz, 1H, Ar–H); 7.29 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 7.43 (dd, J = 2.3, 8.9 Hz, 1H, Ar–H); 7.77 (d, J = 2.3 Hz, 1H, Ar–H); 7.84–7.90 (m, 4H, Ar–H); 8.18 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); 8.27 (d, J = 9.0 Hz, 1H, Ar–H); 8.38 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.4, 26.6, 28.2, 28.4, 29.3, 29.6, 37.8, 40.6, 42.8, 99.2, 117.9, 123.4, 124.3, 127.9, 132.1, 134.2, 135.2, 148.7, 150.6, 151.4, 166.1, 168.0. HRMS calcd for $C_{27}H_{29}ClN_4O_3$ $[M + H]^+$ 493.1962 found 493.1956.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (7e).** Yield 81%; white solid; mp 182–183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (t, J = 7.2 Hz, 2H, –CH_2–); 2.25–2.30 (m, 4H, 2× –CH_2–); 3.75 (t, J = 7.4 Hz, 2H, –CH_2–); 6.56 (d, J = 5.8 Hz, 1H, Ar–H); 7.45 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 7.70–7.74 (m, 4H, Ar–H); 7.79 (d, J = 2.3 Hz, 1H, Ar–H); 7.93 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); 8.17 (d, J = 9.1 Hz, 1H, Ar–H); 8.29 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 8.40 (t, J = 5.8 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.6, 34.9, 37.6, 42.9, 99.0, 117.2, 123.4, 124.8, 125.4, 126.7, 132.0, 134.7, 135.3, 146.2, 149.6, 152.2, 168.1, 170.9. HRMS calcd for $C_{22}H_{19}ClN_4O_3$ $[M + H]^+$ 423.1179 found 423.1161.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (7f).** Yield 77%; white solid; mp 172–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23–1.33 (m, 4H, 2× –CH_2–); 2.41 (t, J = 7.1 Hz, 2H, –CH_2–); 3.05–3.14 (m, 2H, –CH_2–); 3.22–3.27 (m, 2H, –CH_2–); 3.73 (t, J = 7.2 Hz, 2H, –CH_2–); 6.45 (d, J = 5.4 Hz, 1H, Ar–H); 7.32 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 7.43 (dd, J = 2.2, 8.9 Hz, 1H, Ar–H); 7.74 (d, J = 2.2 Hz, 1H, Ar–H); 7.83–7.91 (m, 4H, Ar–H); 8.19–8.28 (m, 2H, Ar–H + NH-exchangeable with D_2O); 8.38 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.4, 27.1, 34.6, 38.2, 40.8, 42.2, 99.2, 117.5, 123.6, 124.3, 124.8, 128.3, 132.5, 133.7, 135.2, 149.6, 150.2, 152.6, 168.1, 170.8. HRMS calcd for $C_{24}H_{23}ClN_4O_3$ $[M + H]^+$ 451.1492 found 451.1466.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (7g).** Yield 79%; white solid; mp 122–123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.29–1.40 (m, 6H, 3× –CH_2–); 1.55–1.63 (m, 2H, –CH_2–); 2.40 (t, J = 7.2 Hz, 2H, –CH_2–); 3.01–3.07 (m, 2H, –CH_2–); 3.21–3.27 (m, 2H, –CH_2–); 3.72 (t, J = 7.2 Hz, 2H, –CH_2–); 6.44 (d, J = 5.3 Hz, 1H, Ar–H); 7.30 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 7.42 (dd, J = 2.2, 9.0 Hz, 1H, Ar–H); 7.73 (d, J = 2.1 Hz, 1H, Ar–H); 7.83–7.92 (m, 4H, Ar–H); 8.20–8.29 (m, 2H, Ar–H + NH-exchangeable with D_2O); 8.35 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.4, 26.7, 28.3, 29.1, 34.6, 39.4, 40.8, 42.2, 99.1, 117.7, 123.6, 124.2, 124.8, 128.4, 132.4, 133.7, 135.1,

149.5, 150.1, 152.3, 168.1, 170.7. HRMS calcd for $C_{26}H_{27}ClN_4O_3$ $[M + H]^+$ 479.1805 found 479.1814.

***N*-(8-((7-Chloroquinolin-4-yl)amino)octyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide (7h).** Yield 70%; white solid; mp 85–86 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.20–1.40 (m, 12H, 6× –CH_2–); 2.41 (t, J = 7.1 Hz, 2H, –CH_2–); 3.02–3.07 (m, 2H, –CH_2–); 3.21–3.26 (m, 2H, –CH_2–); 3.71 (t, J = 7.2 Hz, 2H, –CH_2–); 6.43 (d, J = 5.3 Hz, 1H, Ar–H); 7.31 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 7.41 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.75 (d, J = 2.0 Hz, 1H, Ar–H); 7.85–7.94 (m, 4H, Ar–H); 8.20–8.30 (m, 2H, Ar–H + NH-exchangeable with D_2O); 8.34 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.2, 26.6, 28.2, 28.5, 29.1, 29.5, 34.6, 37.8, 40.5, 42.2, 99.2, 117.5, 123.8, 124.2, 124.9, 128.5, 132.4, 133.9, 135.0, 149.5, 150.0, 152.5, 168.3, 170.9. HRMS calcd for $C_{28}H_{31}ClN_4O_3$ $[M + H]^+$ 507.2118 found 507.2129.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (7i).** Yield 83%; white solid; mp 177–178 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.77–1.83 (m, 2H, –CH_2–); 2.12 (t, J = 7.5 Hz, 2H, –CH_2–); 3.32 (t, J = 6.0 Hz, 2H, –CH_2–); 3.52–3.57 (m, 4H, 2× –CH_2–); 6.89 (d, J = 7.1 Hz, 1H, Ar–H); 7.77 (dd, J = 2.2, 9.1 Hz, 1H, Ar–H); 7.81–7.86 (m, 4H, Ar–H); 8.00 (d, J = 2.1 Hz, 1H, Ar–H); 8.16 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 8.53–8.57 (m, 2H, Ar–H); 9.54 (t, J = 5.9 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.3, 33.1, 37.5, 37.6, 43.2, 98.9, 115.9, 119.4, 123.4, 126.1, 127.3, 132.0, 134.8, 138.4, 138.9, 143.3, 156.1, 168.3, 172.6. HRMS calcd for $C_{23}H_{21}ClN_4O_3$ $[M + H]^+$ 437.1336 found 437.1321.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (7j).** Yield 74%; white solid; mp 145–146 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22–1.34 (m, 4H, 2× –CH_2–); 1.76–1.83 (m, 2H, –CH_2–); 2.11 (t, J = 7.1 Hz, 2H, –CH_2–); 3.08–3.15 (m, 2H, –CH_2–); 3.25–3.29 (m, 2H, –CH_2–); 3.56 (t, J = 7.2 Hz, 2H, –CH_2–); 6.85 (d, J = 7.1 Hz, 1H, Ar–H); 7.76 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 7.80–7.86 (m, 4H, Ar–H); 8.01 (d, J = 2.1 Hz, 1H, Ar–H); 8.14 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 8.54–8.59 (m, 2H, Ar–H); 8.85 (t, J = 5.5 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.4, 25.3, 27.5, 33.4, 37.6, 40.9, 43.2, 99.1, 115.7, 119.3, 123.4, 126.4, 127.3, 132.1, 134.8, 138.5, 138.8, 143.4, 156.1, 168.2, 172.4. HRMS calcd for $C_{25}H_{25}ClN_4O_3$ $[M + H]^+$ 465.1649 found 465.1633.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (7k).** Yield 75%; white solid; mp 158–159 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.18–1.25 (m, 2H, –CH_2–); 1.27–1.40 (m, 4H, 2× –CH_2–); 1.61–1.67 (m, 2H, –CH_2–); 1.78–1.85 (m, 2H, –CH_2–); 2.06–2.10 (m, 2H, –CH_2–); 2.91–2.99 (m, 2H, –CH_2–); 3.23–3.27 (m, 2H, –CH_2–); 3.57 (t, J = 7.1 Hz, 2H, –CH_2–); 6.46 (d, J = 5.4 Hz, 1H, Ar–H); 7.32 (t, J = 5.55 Hz, 1H, NH-exchangeable with D_2O); 7.44 (dd, J = 2.1, 8.9 Hz, 1H, Ar–H); 7.71 (d, J = 5.5 Hz, 1H, Ar–H); 7.76 (d, J = 2.3 Hz, 1H, Ar–H); 7.81–7.86 (m, 4H, Ar–H); 8.28 (d, J = 9.0 Hz, 1H, Ar–H); 8.38 (t, J = 5.5 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.5, 26.4, 26.9, 28.2, 29.7, 33.5, 38.4, 40.4, 43.5, 99.2, 115.6, 119.3, 123.5, 126.4, 127.2, 132.0, 134.9, 138.5, 138.9, 143.3, 156.2, 168.1, 172.2. HRMS calcd for $C_{27}H_{29}ClN_4O_3$ $[M + H]^+$ 493.1962 found 4931951.

***N*-(8-((7-Chloroquinolin-4-yl)amino)octyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide (7l).** Yield 78%; white solid; mp 152–153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20–1.39 (m, 12H, 6× –CH_2–); 1.75–1.84 (m, 2H, –CH_2–); 2.07–2.11 (m, 2H, –CH_2–); 3.02–3.06 (m, 2H, –CH_2–); 3.20–3.25 (m, 2H, –CH_2–); 3.54 (t, J = 7.2 Hz, 2H, –CH_2–); 6.44 (d, J = 5.2 Hz, 1H, Ar–H); 7.28 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 7.44 (dd, J = 2.2, 8.9 Hz, 1H, Ar–H); 7.75 (d, J = 2.3 Hz, 1H, Ar–H); 7.83–7.90 (m, 4H, Ar–H); 8.19 (d, J = 5.4 Hz, 1H, Ar–H); 8.27 (d, J = 8.9 Hz, 1H, Ar–H); 8.40 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.5, 26.4, 26.7, 28.1, 28.5, 29.4, 29.8, 33.3, 37.8, 40.5, 43.4, 99.1, 115.9, 119.34, 123.4, 126.6, 127.2, 132.1, 134.6, 138.7, 138.8, 143.3, 156.3, 168.2, 172.6. HRMS calcd for $C_{29}H_{33}ClN_4O_3$ $[M + H]^+$ 521.2275 found 521.2258.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide (7m).** Yield 81%; white solid; mp 192–193 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): 3.31 (s, 4H, 2× –CH_2–); 4.17 (s, 2H, –CH_2–); 6.51 (d, J = 5.5 Hz, 1H, Ar–H); 7.37–7.42 (m, 2H, Ar–H + NH-exchangeable with D_2O); 7.64–7.69 (m, 1H, Ar–H); 7.75 (d, J = 2.2 Hz, 1H, Ar–H); 7.77–7.80 (m, 1H, Ar–H); 7.93–7.96 (m, 1H, Ar–H); 8.13 (d, J = 9.0 Hz, Ar–H); 8.37 (d, J = 5.5 Hz, Ar–H); 8.45 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.7, 41.3, 42.5, 99.1, 111.3 (d, J = 22.9 Hz), 117.8, 121.5 (d, J = 23.7 Hz), 124.8, 125.1, 126.7 (d, J = 9.6 Hz), 127.9, 128.5 (d, J = 1.9 Hz), 133.4, 135.1 (d, J = 9.4 Hz), 149.7, 150.6, 152.5, 166.2 (d, J = 252.3 Hz), 166.7 (d, J = 2.3 Hz), 167.3, 169.7. HRMS calcd for $C_21H_{16}ClFN_4O_3$ $[M + H]^+$ 427.0929 found 427.0935.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide (7n).** Yield 85%; white solid; mp 140–141 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): 1.50–1.56 (m, 2H, –CH_2–); 1.62–1.68 (m, 2H, –CH_2–); 3.11–3.15 (m, 2H, –CH_2–); 3.27–3.31 (m, 2H, –CH_2–); 4.18 (s, 2H, –CH_2–); 6.50 (d, J = 5.6 Hz, 1H, Ar–H); 7.45–7.47 (m, 2H, Ar–H + NH-exchangeable with D_2O); 7.68–7.72 (m, 1H, Ar–H); 7.78 (d, J = 2.3 Hz, 1H, Ar–H); 7.81–7.83 (m, 1H, Ar–H); 7.97–7.99 (m, 1H, Ar–H); 8.25 (t, J = 5.7 Hz, NH-exchangeable with D_2O); 8.29 (d, J = 9.0 Hz, Ar–H); 8.39 (d, J = 5.5 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.7, 26.8, 35.2, 39.3, 42.9, 99.0, 111.7 (d, J = 23.3 Hz), 117.7, 121.5 (d, J = 23.4 Hz), 124.4, 124.8, 126.6 (d, J = 9.6 Hz), 127.9, 128.3 (d, J = 1.8 Hz), 133.9, 135.2 (d, J = 9.4 Hz), 149.1, 150.4, 152.2, 166.1 (d, J = 251.6 Hz), 166.9 (d, J = 2.3 Hz), 167.4, 169.8. HRMS calcd for $C_{23}H_{20}ClFN_4O_3$ $[M + H]^+$ 455.1242 found 455.1265.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide (7o).** Yield 84%; white solid; mp 131–132 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 1.36–1.44 (m, 4H, 2× –CH_2–); 1.54–1.62 (m, 4H, 2× –CH_2–); 3.01–3.07 (m, 2H, –CH_2–); 3.22–3.25 (m, 2H, –CH_2–); 4.17 (s, 2H, –CH_2–); 6.39 (d, J = 5.3 Hz, 1H, Ar–H); 7.30 (t, J = 5.4 Hz, NH-exchangeable with D_2O); 7.35 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.54–7.59 (m, 1H, Ar–H); 7.69–7.74 (m, 2H, Ar–H); 7.88–7.90 (m, 1H, Ar–H); 7.96 (t, J = 5.5 Hz, NH-exchangeable with D_2O); 8.22 (d, J = 9.0 Hz, Ar–H); 8.31 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5, 26.9, 28.5, 29.6, 39.5, 40.9, 42.5, 99.1, 111.4 (d, J = 23.7 Hz), 117.7, 121.9 (d, J = 23.7 Hz), 124.9, 125.4, 126.5 (d, J = 9.7 Hz), 127.8, 128.2 (d, J = 1.9 Hz), 133.7, 135.1 (d, J = 9.7 Hz), 149.6, 150.7, 152.3, 166.0 (d, J = 252.3 Hz), 166.8 (d, J = 2.4 Hz), 167.2, 169.6. HRMS calcd for $C_{25}H_{24}ClFN_4O_3$ $[M + H]^+$ 483.1555 found 483.1561.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (7p).** Yield 81%; white solid; mp 183–184 °C; ^{1}H NMR (DMSO-d$_6$, 400 MHz): 2.40 (t, J = 7.2 Hz, 2H, –**CH$_2$**–); 3.00–3.09 (m, 4H, 2× –**CH$_2$**–); 3.73 (t, J = 7.1 Hz, 2H, –**CH$_2$**–); 6.41 (d, J = 5.3 Hz, 1H, Ar–H); 7.29 (t, J = 5.5 Hz, NH-exchangeable with D$_2$O); 7.41 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.56–7.62 (m, 1H, Ar–H); 7.70–7.74 (m, 2H, Ar–H); 7.84–7.88 (m, 1H, Ar–H); 7.99 (t, J = 5.4 Hz, NH-exchangeable with D$_2$O); 8.22 (d, J = 9.1 Hz, Ar–H); 8.35 (d, J = 5.5 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 34.5, 37.9, 40.8, 42.4, 99.2, 111.3 (d, J = 23.2 Hz), 117.5, 121.2 (d, J = 23.4 Hz), 124.4, 124.8, 126.5 (d, J = 9.5 Hz), 127.8, 128.2 (d, J = 1.8 Hz), 133.7, 135.0 (d, J = 9.5 Hz), 149.6, 150.3, 152.2, 166.1 (d, J = 251.9 Hz), 166.5 (d, J = 2.3 Hz), 167.1, 169.9. HRMS calcd for $C_{27}H_{29}ClN_4O_3$ $[M]^+$ 492.1928 found 4921941. HRMS calcd for $C_{22}H_{18}ClFN_4O_3$ $[M + H]^+$ 441.1085 found 441.1097.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (7q).** Yield 76%; white solid; mp 177–178 °C; ^{1}H NMR (DMSO-d$_6$, 400 MHz): 1.38–1.45 (m, 2H, –**CH$_2$**–); 1.51–1.58 (m, 2H, –**CH$_2$**–); 2.38 (t, J = 7.2 Hz, 2H, –**CH$_2$**–); 2.98–3.03 (m, 2H, –**CH$_2$**–); 3.15–3.20 (m, 2H, –**CH$_2$**–); 3.72 (t, J = 7.3 Hz, 2H, –**CH$_2$**–); 6.39 (d, J = 5.4 Hz, 1H, Ar–H); 7.28 (t, J = 5.4 Hz, NH-exchangeable with D$_2$O); 7.39 (dd, J = 2.3, 9.1 Hz, 1H, Ar–H); 7.54–7.59 (m, 1H, Ar–H); 7.69–7.72 (m, 2H, Ar–H); 7.85–7.88 (m, 1H, Ar–H); 7.98 (t, J = 5.5 Hz, NH-exchangeable with D$_2$O); 8.21 (d, J = 9.0 Hz, Ar–H); 8.33 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 25.6, 27.1, 34.4, 35.1, 38.6, 42.5, 99.1, 111.4 (d, J = 23.5 Hz), 117.9, 121.5 (d, J = 23.5 Hz), 124.5, 124.6, 126.2 (d, J = 9.6 Hz), 127.8, 128.3 (d, J = 1.7 Hz), 133.9, 135.1 (d, J = 9.5 Hz), 149.4, 150.6, 152.3, 166.2 (d, J = 251.7 Hz), 166.8 (d, J = 2.4 Hz), 167.2, 169.8. HRMS calcd for $C_{24}H_{22}ClFN_4O_3$ $[M + H]^+$ 469.1398 found 469.1387.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (7r).** Yield 77%; white solid; mp 138–139 °C; ^{1}H NMR (DMSO-d$_6$, 400 MHz): 1.32–1.39 (m, 6H, 3× –**CH$_2$**–); 1.54–1.63 (m, 2H, –**CH$_2$**–); 2.39 (t, J = 7.1 Hz, 2H, –**CH$_2$**–); 3.00–3.05 (m, 2H, –**CH$_2$**–); 3.19–3.24 (m, 2H, –**CH$_2$**–); 3.71 (t, J = 7.2 Hz, 2H, –**CH$_2$**–); 6.38 (d, J = 5.3 Hz, 1H, Ar–H); 7.29 (t, J = 5.4 Hz, NH-exchangeable with D$_2$O); 7.37 (dd, J = 2.2, 9.0 Hz, 1H, Ar–H); 7.53–7.59 (m, 1H, Ar–H); 7.68–7.73 (m, 2H, Ar–H); 7.86–7.89 (m, 1H, Ar–H); 7.95 (t, J = 5.4 Hz, NH-exchangeable with D$_2$O); 8.20 (d, J = 9.1 Hz, Ar–H); 8.32 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 26.7, 26.9, 28.3, 29.5, 34.1, 39.3, 40.7, 42.4, 99.0, 111.5 (d, J = 23.4 Hz), 117.5, 121.8 (d, J = 23.7 Hz), 124.8, 125.3, 126.1 (d, J = 9.7 Hz), 127.9, 128.2 (d, J = 1.9 Hz), 133.8, 135.0 (d, J = 9.7 Hz), 149.5, 150.5, 152.2, 166.1 (d, J = 251.6 Hz), 166.9 (d, J = 2.5 Hz), 167.3, 169.7. HRMS calcd for $C_{26}H_{26}ClFN_4O_3$ $[M + H]^+$ 497.1711 found 497.1723.

General procedure for synthesis of C-5 secondary amine substituted *N*-((7-chloroquinolin-4-yl)aminoalkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamides 8a–r

In a microwave reaction vial was added a solution of C-5 fluoro substituted *N*-((7-chloroquinolin-4-yl)aminoalkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamides (1.0 mmol) in 0.5 mL of NMP (*N*-methylpyrrolidin-2-one) and secondary amines (1.2 mmol). After sealing with a PTFE cap, the vessel was heated to 160 °C for 5 min in the microwave reactor and the completion was ascertained using TLC. After completion, the contents were poured in water (20 mL) resulting in the precipitation of the desired product. The yellow product obtained was filtered and recrystallized using absolute ethanol.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (8a).** Yield 76%; yellow solid; mp 216–217 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 3.30–3.32 (m, 6H, 3× –**CH$_2$**–); 3.59–3.63 (m, 2H, –**CH$_2$**–); 3.74–3.76 (m, 4H, 2× –**CH$_2$**–); 4.12 (s, 2H, –**CH$_2$**–); 6.90 (d, J = 7.1 Hz, 1H, Ar–H); 7.25 (dd, J = 2.3, 8.5 Hz, 1H, Ar–H); 7.32 (d, J = 2.2 Hz, 1H, Ar–H); 7.66 (d, J = 8.4 Hz, 1H, Ar–H); 7.77 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 8.05 (d, J = 2.1 Hz, 1H, Ar–H); 8.55–8.57 (m, 3H, Ar–H); 9.55 (t, J = 5.9 Hz, 1H, NH-exchangeable with D$_2$O); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 39.1, 42.7, 47.6, 48.8, 66.5, 99.1, 108.3, 117.8, 118.1, 120.2, 124.5, 124.6, 125.1, 127.9, 133.5, 134.6, 149.4, 150.5, 152.3, 155.7, 166.4, 167.7, 168.4, 174.1. HRMS calcd for $C_{25}H_{24}ClN_5O_4$ $[M + H]^+$ 494.1550 found 494.1564.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (8b).** Yield 79%; yellow solid; mp 174–175 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 1.51–1.56 (m, 2H, –**CH$_2$**–); 1.63–1.69 (m, 2H, –**CH$_2$**–); 3.07–3.011 (m, 2H, –**CH$_2$**–); 3.25–3.28 (m, 2H, –**CH$_2$**–); 3.39–3.42 (m, 4H, 2× –**CH$_2$**–); 3.70–3.74 (m, 4H, 2× –**CH$_2$**–); 4.15 (s, 2H, –**CH$_2$**–); 6.46 (d, J = 5.3 Hz, 1H, Ar–H); 7.25 (dd, J = 2.2, 8.7 Hz, 1H, Ar–H); 7.28 (t, J = 5.4 Hz, 1H, NH-exchangeable with D$_2$O); 7.31 (d, J = 2.2 Hz, 1H, Ar–H); 7.45 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 7.68 (d, J = 8.8 Hz, 1H, Ar–H); 7.79 (d, J = 2.1 Hz, 1H, Ar–H); 8.16 (t, J = 5.5 Hz, 1H, NH-exchangeable with D$_2$O); 8.27 (d, J = 9.0 Hz, 1H, Ar–H); 8.39 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 25.4, 27.6, 37.9, 40.6, 42.7, 47.4, 66.3, 99.1, 108.5, 117.7, 118.2, 120.3, 124.5, 124.7, 125.2, 127.7, 133.9, 134.5, 149.6, 150.5, 152.7, 155.6, 166.4, 167.9, 168.2, 174.1. HRMS calcd for $C_{27}H_{28}ClN_5O_4$ $[M + H]^+$ 522.1863 found 522.1878.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (8c).** Yield 81%; yellow solid; mp 160–161 °C; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 1.30–1.45 (m, 6H, 3× –**CH$_2$**–); 1.64–1.67 (m, 2H, –**CH$_2$**–); 3.04–3.09 (m, 2H, –**CH$_2$**–); 3.23–3.27 (m, 2H, –**CH$_2$**–); 3.36–3.39 (m, 4H, 2× –**CH$_2$**–); 3.72–3.75 (m, 4H, 2× –**CH$_2$**–); 4.12 (s, 2H, –**CH$_2$**–); 6.45 (d, J = 5.4 Hz, 1H, Ar–H); 7.22 (dd, J = 2.4, 8.6 Hz, 1H, Ar–H); 7.27 (t, J = 5.5 Hz, 1H, NH-exchangeable with D$_2$O); 7.32 (d, J = 2.3 Hz, 1H, Ar–H); 7.42 (dd, J = 2.3, 8.9 Hz, 1H, Ar–H); 7.66 (d, J = 8.6 Hz, 1H, Ar–H); 7.77 (d, J = 2.2 Hz, 1H, Ar–H); 8.15 (t, J = 5.6 Hz, 1H, NH-exchangeable with D$_2$O); 8.26 (d, J = 9.0 Hz, 1H, Ar–H); 8.38 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 26.4, 26.7, 28.1, 29.4, 39.0, 42.7, 47.5, 48.9, 66.2, 99.0, 108.2, 117.9, 118.0, 120.1, 124.4, 124.5, 125.0, 127.9, 133.7, 134.7, 149.5, 150.5, 152.4, 155.7, 166.5, 167.8, 168.3, 174.2. HRMS calcd for $C_{29}H_{32}ClN_5O_4$ $[M + H]^+$ 550.2176 found 550.2188.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (8d).** Yield 76%; yellow solid; mp 208–209 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 2.38 (t, J = 7.3 Hz, 2H, –**CH$_2$**–); 3.20–3.28 (m, 8H, 4× –**CH$_2$**–); 3.67–3.73 (m, 6H, 3× –**CH$_2$**–); 6.44 (d, J = 5.6 Hz, 1H, Ar–H); 7.06 (dd, J =

2.3, 8.4 Hz, 1H, Ar–H); 7.16 (d, J = 2.2 Hz, 1H, Ar–H); 7.25 (t, J = 5.1 Hz, 1H, N–H-exchangeable with D_2O); 7.36 (dd, J = 2.3, 9.0 Hz, 1H, Ar–H); 7.50 (d, J = 8.6 Hz, 1H, Ar–H); 7.73 (d, J = 2.3 Hz, 1H, Ar–H); 8.02 (d, J = 9.0 Hz, 1H, Ar–H); 8.24 (t, J = 5.5 Hz, 1H, N–H-exchangeable with D_2O); 8.35 (d, J = 5.1 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 34.7, 34.8, 37.7, 42.8, 47.4, 66.2, 99.0, 108.0, 117.7, 117.8, 119.9, 124.2, 124.5, 124.7, 127.9, 133.8, 134.4, 149.4, 150.4, 152.3, 155.5, 168.0, 168.3, 170.9. HRMS calcd for $C_{26}H_{26}ClN_5O_4$ $[M + H]^+$ 508.1707 found 508.1716.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (8e).** Yield 82%; Yellow solid; mp 158–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52–1.57 (m, 2H, –CH_2–); 1.61–1.67 (m, 2H, –CH_2–); 2.36 (t, J = 7.1 Hz, 2H, –CH_2–); 3.19–3.28 (m, 8H, 4× –CH_2–); 3.65–3.71 (m, 6H, 3× –CH_2–); 6.42 (d, J = 5.4 Hz, 1H, Ar–H); 7.04 (dd, J = 2.2, 8.7 Hz, 1H, Ar–H); 7.14 (d, J = 2.2 Hz, 1H, Ar–H); 7.23 (t, J = 5.3 Hz, 1H, N–H-exchangeable with D_2O); 7.32 (dd, J = 2.2, 8.9 Hz, 1H, Ar–H); 7.51 (d, J = 8.7 Hz, 1H, Ar–H); 7.71 (d, J = 2.2 Hz, 1H, Ar–H); 8.01 (d, J = 9.0 Hz, 1H, Ar–H); 8.25 (t, J = 5.4 Hz, 1H, N–H-exchangeable with D_2O); 8.33 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.5, 27.4, 34.6, 34.9, 37.9, 42.9, 47.7, 66.1, 99.1, 108.2, 117.5, 117.9, 119.4, 124.1, 124.6, 124.8, 127.7, 133.6, 134.2, 149.1, 150.2, 152.1, 155.6, 168.1, 168.2, 170.7. HRMS calcd for $C_{28}H_{30}ClN_5O_4$ $[M + H]^+$ 536.2020 found 536.2009.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (8f).** Yield 78%; yellow solid; mp 126–127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31–1.46 (m, 6H, 3× –CH_2–); 1.53–1.56 (m, 2H, –CH_2–); 2.35 (t, J = 7.1 Hz, 2H, –CH_2–); 3.05–3.09 (m, 2H, –CH_2–); 3.23–3.27 (m, 2H, –CH_2–); 3.35–3.39 (m, 4H, 2× –CH_2–); 3.66–3.73 (m, 6H, 3× –CH_2–); 6.41 (d, J = 5.3 Hz, 1H, Ar–H); 7.03 (dd, J = 2.1, 8.6 Hz, 1H, Ar–H); 7.15 (d, J = 2.1 Hz, 1H, Ar–H); 7.25 (t, J = 5.2 Hz, 1H, N–H-exchangeable with D_2O); 7.33 (dd, J = 2.0, 8.9 Hz, 1H, Ar–H); 7.53 (d, J = 8.8 Hz, 1H, Ar–H); 7.73 (d, J = 2.1 Hz, 1H, Ar–H); 8.03 (d, J = 9.0 Hz, 1H, Ar–H); 8.26 (t, J = 5.3 Hz, 1H, N–H-exchangeable with D_2O); 8.34 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5, 26.9, 28.1, 29.5, 34.6, 38.2, 40.1, 42.8, 47.6, 66.2, 99.2, 108.1, 117.6, 117.8, 119.3, 124.2, 124.7, 124.8, 127.6, 133.7, 134.1, 149.3, 150.1, 152.4, 155.5, 168.1, 168.3, 170.5 HRMS calcd for $C_{30}H_{34}ClN_5O_4$ $[M + H]^+$ 564.2333 found 564.2326.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (8g).** Yield 79%; yellow solid; mp 197–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 (t, 6H, 2× –CH_3); 3.22–3.27 (m, 4H, 2× –CH_2–); 3.36–3.41 (m, 4H, 2× –CH_2–); 4.11 (s, 2H, –CH_2–); 6.52 (d, J = 5.5 Hz, 1H, Ar–H); 6.91 (d, J = 8.8 Hz, 1H, Ar–H); 6.97 (s, 1H, Ar–H), 7.46–7.50 (m, 2H, Ar–H, NH-exchangeable with D_2O); 7.56 (d, J = 8.6 Hz, 1H, Ar–H); 7.77 (s, 1H, Ar–H), 8.16 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 8.28 (d, J = 8.9 Hz, 1H, Ar–H); 8.38 (d, J = 5.6 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4, 37.6, 40.8, 42.6, 44.7, 99.0, 105.3, 114.7, 116.2, 117.8, 124.4, 124.6, 125.5, 127.2, 127.7, 134.1, 135.5, 150.7, 151.7, 152.2, 166.6, 167.6, 168.9 HRMS calcd for $C_{25}H_{26}ClN_5O_3$ $[M + H]^+$ 480.1758 found 480.1743.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (8h).** Yield 78%; yellow solid; mp 173–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, 6H, 2× –CH_3); 1.50–1.57 (m, 2H, –CH_2–); 1.62–1.68 (m, 2H, –CH_2–); 3.10–3.14 (m, 2H, –CH_2–); 3.27–3.31 (m, 2H, 2× –CH_2–); 3.39–3.43 (m, 4H, 2× –CH_2–); 4.10 (s, 2H, –CH_2–); 6.51 (d, J = 5.6 Hz, 1H, Ar–H); 6.92 (d, J = 8.7 Hz, 1H, Ar–H); 6.99 (s, 1H, Ar–H), 7.44–7.50 (m, 2H, Ar–H + NH-exchangeable with D_2O); 7.59 (d, J = 8.5 Hz, 1H, Ar–H); 7.78 (s, 1H, Ar–H), 8.18 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 8.29 (d, J = 9.0 Hz, 1H, Ar–H); 8.39 (d, J = 5.7 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5, 25.5, 27.1, 38.8, 41.5, 42.5, 44.8, 99.1, 105.2, 114.8, 116.3, 117.7, 124.5, 124.6, 125.4, 127.1, 127.4, 134.2, 135.3, 150.9, 151.6, 152.3, 166.7, 167.9, 168.6 HRMS calcd for $C_{27}H_{30}ClN_5O_3$ $[M + H]^+$ 508.2071 found 508.2079.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (8i).** Yield 79%; yellow solid; mp 158–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, 6H, 2× –CH_3); 1.32–1.44 (m, 6H, 3× –CH_2–); 1.63–1.67 (m, 2H, –CH_2–); 3.07–3.10 (m, 2H, –CH_2–); 3.25–3.30 (m, 2H, 2× –CH_2–); 3.37–3.41 (m, 4H, 2× –CH_2–); 4.11 (s, 2H, –CH_2–); 6.50 (d, J = 5.4 Hz, 1H, Ar–H); 6.90 (dd, J = 2.2, 8.8 Hz, 1H, Ar–H); 6.98 (d, J = 2.3 Hz, 1H, Ar–H), 7.43–7.50 (m, 2H, Ar–H + NH-exchangeable with D_2O); 7.54 (d, J = 8.6 Hz, 1H, Ar–H); 7.75 (d, J = 2.2 Hz 1H, Ar–H), 8.20 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 8.27 (d, J = 9.0 Hz, 1H, Ar–H); 8.37 (d, J = 5.4 Hz, 1H, Ar–H);^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4, 26.3, 26.9, 28.2, 29.5, 39.2, 41.3, 42.9, 44.6, 99.2, 105.1, 114.8, 116.3, 117.6, 124.7, 124.9, 125.4, 127.3, 127.7, 134.3, 135.3, 150.8, 151.6, 152.4, 166.6, 167.8, 168.7 HRMS calcd for $C_{29}H_{34}ClN_5O_3$ $[M + H]^+$ 536.2384 found 536.2371.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (8j).** Yield 70%; yellow solid; mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (t, J = 7.0 Hz, 6H, 2× –CH_3); 2.37 (t, J = 7.3 Hz, 2H, –CH_2); 3.22–3.26 (m, 4H, 2× –CH_2–); 3.38–3.42 (m, 4H, 2× –CH_2–); 3.69 (t, J = 7.3 Hz, 2H, –CH_3); 6.45 (d, J = 5.4 Hz, 1H, Ar–H); 6.76 (dd, J = 2.6, 8.8 Hz, 1H, Ar–H); 6.85 (d, J = 2.6 Hz, 1H, Ar–H), 7.29 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 7.37 (dd, J = 2.2, 9.0 Hz, 1H, Ar–H); 7.44 (d, J = 8.6 Hz, 1H, Ar–H); 7.73 (d, J = 2.4 Hz 1H, Ar–H), 8.05 (d, J = 9.0 Hz, 1H, Ar–H); 8.23 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 8.35 (d, J = 5.0 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.6, 34.6, 37.7, 41.1, 42.7, 44.8, 99.0, 105.0, 114.6, 116.2, 117.8, 124.3, 124.5, 124.6, 125.2, 127.8, 133.9, 135.0, 149.3, 150.5, 152.2, 168.1, 168.6, 170.9 HRMS calcd for $C_{26}H_{28}ClN_5O_3$ $[M + H]^+$ 494.1914 found 494.1902.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (8k).** Yield 72%; yellow solid; mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (t, J = 7.1 Hz, 6H, 2× –CH_3); 1.52–1.57 (m, 2H, –CH_2–); 1.60–1.67 (m, 2H, –CH_2–); 2.35 (t, J = 7.2 Hz, 2H, –CH_3); 3.11–3.15 (m, 2H, –CH_2–); 3.25–3.30 (m, 2H, –CH_2–); 3.37–3.41 (m, 4H, 2× –CH_2–); 3.67 (t, J = 7.2 Hz, 2H, –CH_3); 6.43 (d, J = 5.3 Hz, 1H, Ar–H); 6.77 (dd, J = 2.4, 8.7 Hz, 1H, Ar–H); 6.84 (d, J = 2.4 Hz, 1H, Ar–H), 7.26 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 7.37 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.45 (d, J = 8.7 Hz, 1H, Ar–H); 7.75 (d, J = 2.2 Hz 1H, Ar–H), 8.07 (d, J = 9.0 Hz, 1H, Ar–H); 8.25 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 8.36 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ 12.6, 25.4, 27.5, 34.6, 37.7, 39.7, 42.7, 44.7, 99.1, 105.2, 114.3, 116.1, 117.8, 124.2, 124.5, 124.7, 125.4, 127.9, 133.7, 135.1, 149.3, 150.6, 152.4, 168.1, 168.5, 170.7 HRMS calcd for $C_{28}H_{32}ClN_5O_3$ $[M + H]^+$ 522.2227 found 522.2239.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (8l).** Yield 68%; yellow solid; mp 142–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (t, J = 7.3 Hz, 6H, 2× –**CH**$_3$); 1.35–1.45 (m, 6H, 3× –**CH**$_2$–); 1.61–1.66 (m, 2H, –**CH**$_2$–); 2.37 (t, J = 7.2 Hz, 2H, –**CH**$_3$); 3.10–3.14 (m, 2H, –**CH**$_2$–); 3.24–3.30 (m, 2H, –**CH**$_2$–); 3.36–3.41 (m, 4H, 2× –**CH**$_2$–); 3.68 (t, J = 7.2 Hz, 2H, –**CH**$_3$); 6.42 (d, J = 5.2 Hz, 1H, Ar–H); 6.75 (dd, J = 2.2, 8.6 Hz, 1H, Ar–H); 6.85 (d, J = 2.4 Hz, 1H, Ar–H), 7.26 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 7.37 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 7.47 (d, J = 8.7 Hz, 1H, Ar–H); 7.77 (d, J = 2.2 Hz 1H, Ar–H), 8.06 (d, J = 9.0 Hz, 1H, Ar–H); 8.26 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 8.38 (d, J = 5.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.6, 26.4, 26.9, 28.5, 29.8, 34.6, 39.5, 41.1, 42.7, 44.5, 99.1, 105.3, 114.4, 116.1, 117.9, 124.2, 124.6, 124.8, 125.4, 127.8, 133.8, 135.2, 149.4, 150.7, 152.5, 168.1, 168.7, 170.6 HRMS calcd for $C_{30}H_{36}ClN_5O_3$ $[M + H]^+$ 550.2540 found 550.2521.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (8m).** Yield 75%; yellow solid; mp 218–219 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.45 (t, J = 6.1 Hz, 2H, –**CH**$_2$–); 2.54 (t, J = 4.8 Hz, 4H, 2× –**CH**$_2$–); 3.11–3.15 (m, 2H, –**CH**$_2$–); 3.26–3.29 (m, 2H, –**CH**$_2$–); 3.42 (t, J = 4.5 Hz, 4H, 2× –**CH**$_2$–); 3.53 (t, J = 6.1 Hz, 2H, –**CH**$_2$–); 4.10 (s, 2H, –**CH**$_2$–); 4.48 (s, 1H, –OH); 6.47 (d, J = 5.4 Hz, 1H, Ar–H); 7.21 (dd, J = 1.5, 8.6 Hz, 1H, Ar–H); 7.30 (d, J = 1.4 Hz, 1H, Ar–H); 7.35 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); 7.45 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.66 (d, J = 8.6 Hz, 1H, Ar–H); 7.78 (d, J = 2.0 Hz, 1H, Ar–H); 8.18 (t, J = 5.7 Hz, 1H, NH-exchangeable with D_2O); 8.29 (d, J = 9.0 Hz, 1H, Ar–H); 8.39 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.7, 42.4, 47.5, 49.1, 53.3, 59.1, 60.6, 99.0, 108.1, 117.3, 117.8, 119.4, 124.3, 124.6, 125.1, 127.9, 133.7, 134.7, 149.5, 150.6, 152.2, 155.5, 166.7, 167.8, 168.2 HRMS calcd for $C_{27}H_{29}ClN_6O_4$ $[M + H]^+$ 537.1972 found 537.1961.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (8n).** Yield 83%; yellow solid; mp 151–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.50–1.55 (m, 2H, –**CH**$_2$–); 1.62–1.68 (m, 2H, –**CH**$_2$–); 2.44 (t, J = 6.1 Hz 2H, –**CH**$_2$–); 2.55 (t, J = 4.9 Hz, 4H, 2× –**CH**$_2$–); 3.10–3.14 (m, 2H, –**CH**$_2$–); 3.25–3.29 (m, 2H, –**CH**$_2$–); 3.41 (t, J = 4.5 Hz, 4H, 2× –**CH**$_2$–); 3.54 (t, J = 6.1 Hz, 2H, –**CH**$_2$–); 4.11 (s, 2H, –**CH**$_2$–); 4.49 (s, 1H, –OH); 6.48 (d, J = 5.5 Hz, 1H, Ar–H); 7.22 (dd, J = 1.5, 8.5 Hz, 1H, Ar–H); 7.31 (d, J = 1.4 Hz, 1H, Ar–H); 7.34 (t, J = 5.6 Hz, 1H, NH-exchangeable with D_2O); 7.43 (dd, J = 2.2, 9.0 Hz, 1H, Ar–H); 7.65 (d, J = 8.5 Hz, 1H, Ar–H); 7.77 (d, J = 2.0 Hz, 1H, Ar–H); 8.19 (t, J = 5.7 Hz, 1H, NH-exchangeable with D_2O); 8.27 (d, J = 9.0 Hz, 1H, Ar–H); 8.38 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.5, 27.1, 38.8, 42.5, 47.3, 49.0, 53.2, 59.0, 60.5, 99.1, 108.2, 117.8, 117.9, 119.4, 124.4, 124.5, 125.0, 127.8, 133.8, 134.7, 149.4, 150.5, 152.2, 155.5, 166.6, 167.8, 168.3 HRMS calcd for $C_{29}H_{33}ClN_6O_4$ $[M + H]^+$ 565.2285 found 565.2268.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-2-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (8o).** Yield 75%; yellow solid; mp 118–119 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31–1.45 (m, 6H, 3× –**CH**$_2$–); 1.62–1.67 (m, 2H, –**CH**$_2$–); 2.46 (t, J = 6.2 Hz, 2H, –**CH**$_2$–); 2.54 (t, J = 4.8 Hz, 4H, 2× –**CH**$_2$–); 3.07–3.11 (m, 2H, –**CH**$_2$–); 3.20–3.27 (m, 2H, –**CH**$_2$–); 3.40 (t, J = 4.7 Hz, 4H, 2× –**CH**$_2$–); 3.55 (t, J = 6.2 Hz, 2H, –**CH**$_2$–); 4.10 (s, 2H, –**CH**$_2$–); 4.48 (s, 1H, –OH); 6.47 (d, J = 5.4 Hz, 1H, Ar–H); 7.20 (dd, J = 1.6, 8.6 Hz, 1H, Ar–H); 7.30 (d, J = 1.5 Hz, 1H, Ar–H); 7.34 (t, J = 5.5 Hz, 1H, NH-exchangeable with D_2O); 7.44 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.64 (d, J = 8.4 Hz, 1H, Ar–H); 7.75 (d, J = 2.0 Hz, 1H, Ar–H); 8.16 (t, J = 5.5 Hz, 1H, NH-exchangeable with D_2O); 8.25 (d, J = 9.0 Hz, 1H, Ar–H); 8.36 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.1, 26.8, 28.1, 29.4, 39.5, 42.9, 47.5, 49.1, 53.5, 59.1, 60.4, 99.0, 108.1, 117.9, 118.1, 119.3, 124.5, 124.8, 125.1, 127.9, 133.7, 134.6, 149.3, 150.6, 152.1, 155.7, 166.6, 167.7, 168.2 HRMS calcd for $C_{31}H_{37}ClN_6O_4$ $[M + H]^+$ 593.2598 found 593.2604.

***N*-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-3-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (8p).** Yield 69%; yellow solid; mp 211–212 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.42–2.45 (m, 4H, 2× –**CH**$_2$–); 2.53 (t, J = 5.1 Hz, 4H, 2× –**CH**$_2$–); 3.26–3.31 (m, 4H, 2× –**CH**$_2$–); 3.33–3.35 (m, 4H, 2× –**CH**$_2$–); 3.52–3.55 (m, 2H, –**CH**$_2$–); 3.76 (t, J = 7.1 Hz, 2H, –**CH**$_2$–); 4.47 (s, 1H, OH); 6.49 (d, J = 5.4 Hz, 1H, Ar–H); 7.11 (dd, J = 2.3, 8.5 Hz, 1H, Ar–H); 7.19 (d, J = 2.3 Hz, 1H, Ar–H); 7.28 (t, J = 5.2 Hz, 1H, NH-exchangeable with D_2O); 7.40 (dd, J = 2.2, 9.0 Hz, 1H, Ar–H); 7.53 (d, J = 8.4 Hz, 1H, Ar–H); 7.77 (d, J = 2.3 Hz, 1H, Ar–H); 8.08 (d, J = 8.9 Hz, 1H, Ar–H); 8.25 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 8.39 (d, J = 5.4 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 34.7, 34.8, 37.7, 42.7, 47.2, 53.2, 59.0, 60.5, 99.0, 107.9, 117.7, 117.8, 119.2, 124.2, 124.5, 124.8, 127.9, 133.8, 134.5, 149.4, 150.4, 152.3, 153.3, 168.0, 168.4, 170.9. HRMS calcd for $C_{28}H_{31}ClN_6O_4$ $[M + H]^+$ 551.2129 found 551.2141.

***N*-(4-((7-Chloroquinolin-4-yl)amino)butyl)-3-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (8q).** Yield 68%; yellow solid; mp 162–163 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.50–1.55 (m, 2H, –**CH**$_2$–); 1.62–1.68 (m, 2H, –**CH**$_2$–); 2.41–2.47 (m, 4H, 2× –**CH**$_2$–); 2.55 (t, J = 5.0 Hz, 4H, 2× –**CH**$_2$–); 3.13–3.16 (m, 2H, –**CH**$_2$–); 3.27–3.31 (m, 2H, –**CH**$_2$–); 3.41 (t, J = 4.5 Hz, 4H, 2× –**CH**$_2$–); 3.54 (t, J = 6.1 Hz, 2H, –**CH**$_2$–); 3.75 (t, J = 7.1 Hz, 2H, –**CH**$_2$–); 4.48 (s, 1H, OH); 6.47 (d, J = 5.5 Hz, 1H, Ar–H); 7.10 (dd, J = 2.2, 8.6 Hz, 1H, Ar–H); 7.18 (d, J = 2.2 Hz, 1H, Ar–H); 7.27 (t, J = 5.3 Hz, 1H, NH-exchangeable with D_2O); 7.41 (dd, J = 2.1, 9.0 Hz, 1H, Ar–H); 7.52 (d, J = 8.5 Hz, 1H, Ar–H); 7.78 (d, J = 2.2 Hz, 1H, Ar–H); 8.05 (d, J = 9.0 Hz, 1H, Ar–H); 8.27 (t, J = 5.4 Hz, 1H, NH-exchangeable with D_2O); 8.40 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.4, 27.9, 34.6, 37.9, 39.1, 42.7, 47.8, 53.1, 59.1, 60.6, 99.1, 107.8, 117.4, 117.9, 119.1, 124.3, 124.5, 124.9, 127.8, 133.9, 134.6, 149.6, 150.3, 152.5, 153.5, 168.1, 168.7, 170.6. HRMS calcd for $C_{30}H_{35}ClN_6O_4$ $[M + H]^+$ 579.2442 found 579.2457.

***N*-(6-((7-Chloroquinolin-4-yl)amino)hexyl)-3-(5-(4-(2-hydroxyethyl) piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (8r).** Yield 64%; yellow solid; mp 102–103 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.32–1.44 (m, 6H, 3× –**CH**$_2$–); 1.63–1.68 (m, 2H, –**CH**$_2$–); 2.42–2.48 (m, 4H, 2× –**CH**$_2$–); 2.54 (t, J = 5.0 Hz, 4H, 2× –**CH**$_2$–); 3.11–3.15 (m, 2H, –**CH**$_2$–); 3.24–3.30 (m, 2H, –**CH**$_2$–); 3.43 (t, J = 4.8 Hz, 4H, 2× –**CH**$_2$–); 3.57 (t, J = 6.1 Hz, 2H, –**CH**$_2$–); 3.75 (t, J = 7.1 Hz, 2H, –**CH**$_2$–); 4.47 (s, 1H, OH); 6.45 (d, J = 5.4 Hz, 1H, Ar–H); 7.09 (dd, J = 2.1, 8.7 Hz, 1H, Ar–H); 7.16 (d, J = 2.1 Hz, 1H, Ar–H); 7.28 (t, J = 5.1 Hz, 1H, NH-exchangeable with D_2O); 7.40 (dd, J = 2.0, 9.0 Hz, 1H, Ar–H); 7.51 (d, J = 8.4 Hz, 1H, Ar–H); 7.79 (d, J = 2.1 Hz, 1H, Ar–H); 8.07 (d, J

= 9.0 Hz, 1H, Ar–H); 8.29 (t, J = 5.5 Hz, 1H, NH-exchangeable with D_2O); 8.41 (d, J = 5.3 Hz, 1H, Ar–H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.3, 26.9, 28.4, 29.6, 34.5, 39.7, 42.8, 47.4, 49.3, 53.7, 59.3, 60.6, 99.0, 107.7, 117.5, 117.9, 119.3, 124.4, 124.8, 124.8, 127.9, 133.8, 134.7, 149.5, 150.5, 152.8, 153.8, 168.2, 168.9, 170.5. HRMS calcd for $C_{32}H_{39}ClN_6O_4$ $[M + H]^+$ 607.2755 found 607.2769.

Materials and methods

Bacterial strains and growth conditions

M. tuberculosis mc^{2}6230 (ref. 29) was grown at 37 °C in Middlebrook 7H9 supplemented with oleic-albumin-dextrose-catalase enrichment (OADC) and 109 μM of pantothenic acid (complete 7H9).

Drug susceptibility testing

The vulnerability of *M. tuberculosis* mc^{2}6230 to the synthesized compounds was determined as reported previously.[30] Briefly, an exponentially growing culture was diluted in complete 7H9 to and OD_{600} = 0.01. The bacteria were then seeded in 100 μL volumes in all the wells of a 96-well plate except the first column of wells which contained 200 μL of bacterial suspension. Compounds (stock concentration 10 mg mL^{-1}) were directly added to the wells of the first column so as to achieve a concentration of 200 μg mL^{-1} (or 100 μg mL^{-1} in cases where precipitation at the higher concentration was observed). Two-fold serial dilutions were then carried out by transferring 100 μL of bacterial suspension from the first column of wells to the second column, mixing, and repeating this procedure for each consecutive column. The plates were then placed in sealed plastic bags and incubated at 37 °C. After 7 days of incubation, plates were visually inspected to determine the MIC, which was defined as the minimal concentration of compound at which no growth of bacteria was observed. Drug susceptibility testing was completed twice, with each compound tested in duplicate. Isoniazid was included as a positive control.

Cytotoxicity assay

Cell viability was determined using Vero cells (ATCC, Sigma, Germany) grown in RPMI medium (Gibco, USA), supplemented with 10% decomplemented fetal calf serum, under a 5% CO_2 atmosphere. Cells were seeded in 96-well plates at a density of 2 × 10^4 cells per well in 160 μL medium and incubated overnight at 37 °C to allow cells to adhere. Compounds (dissolved in DMSO) were freshly diluted to appropriate concentrations in RPMI, so as to allow addition of 20 μL volumes of the diluted compounds to the cells that resulted in final compound concentrations ranging from 100 μg mL^{-1} to 0.78 μg mL^{-1}. The maximum final concentration of DMSO was 1% (v/v) and no cytotoxic effect of DMSO was observed at this concentration. After 24 h incubation at 37 °C, 20 μL of 1 mg mL^{-1} resazurin (Sigma, Germany) was added to each well and the cells were incubated for an additional 3 hours at 37 °C. Fluorescence was measured in a Polarstar Omega fluorometer using appropriate filters (540 nm excitation and 590 nm emission wave length). Percentage survival was determined by dividing fluorescence values obtained in the compound containing wells by values obtained for control wells containing cells incubated with a dilution series of DMSO and multiplying this value by 100. SDS (20%) was included as a positive control. Cytotoxic evaluation was completed twice, with each compound tested in duplicate. The IC_{50} is defined as the lowest concentration of compound tested at which exactly 50% cell viability was observed and was calculated using a non-linear regression curve using Graphpad Prism 5. The SI values were determined as a function of IC_{50}/MIC_{99}.

Conflicts of interest

The authors declare no conflict of interest.

Abbreviations

MIC_{990}	99% minimum inhibitory concentration
MW	microwave
+SAR	Structure activity relationship
NMP	*N*-Methyl-2-pyrrolidone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
SI value	Selectivity index
IC_{50}	50% inhibitory concentration

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