Bioorganic Chemistry 88 (2019) 102912

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Substituted 1,3-dioxoisoindoline-4-aminoquinolines coupled *via* amide linkers: Synthesis, antiplasmodial and cytotoxic evaluation

Anu Rani[a], Jenny Legac[b], Philip J. Rosenthal[b], Vipan Kumar[a,*]

[a] Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, Punjab, India
[b] Department of Medicine, University of California, San Francisco, CA, USA

ARTICLE INFO

Keywords:
1,3-Dioxoisoindoline-4-aminoquinolines
Microwave
Antiplasmodial
Cytotoxicity
Selectivity index

ABSTRACT

Synthesis of C-5-substituted 1,3-dioxoisoindoline-4-aminoquinolines having amide group as a spacer was developed with an intent to evaluate their antiplasmodial activities. The synthesized dioxoisoindoline-aminoquinolines tethered with β-alanine as a spacer and secondary amine as substituent displayed good anti-plasmodial activities. Compound **7j**, with an optimum combination of β-alanine and an ethyl chain length as linker along with diethylamine as the secondary amine counterpart at dioxoisoindoline proved to be most potent and non-cytotoxic with IC_{50} of 0.097 μM against W2 strain of *P. falciparum* and a selective index of > 2000.

1. Introduction

P. falciparum, the causative organism of malaria, is the most virulent form of the parasite responsible for a maximum number of malaria-related deaths, worldwide [1]. According to WHO report 2018, there was a substantial reduction in malaria burden from 2010 to 2015 with number of cases falling from 239 million to 214 million, globally. However, the reversed progress in countries with the highest malaria burden has obstructed the global progress in malaria-controlling programs. The year 2017 witnessed 435,000 malaria deaths, affecting mostly children below the age of 5 years [2,3].

Several heterocyclic compounds *viz.* 4-aminoquinoline, 8-aminoquinoline, acridine-dione, pyridine, quinolone-tetroxane, indole, imidazolopiperazine and methoxy-thiazinoquinone derivatives have recently emerged as potential antimalarials [4,5]. Among these, quinoline is considered as one of the core heterocycles for the treatment of malaria, being present in a number of antimalarial drugs as well as clinical candidates *viz.* Chloroquine (CQ), Mefloquine, Amopyroquine, Amodiaquine, Primaquine, Pyronaridine, Isoquine, *tert*-butylisoquine, Ferroquine, Piperaquine and Tafenoquine as shown in Fig. 1 [4]. Chloroquine was the main-stay in the treatment of malaria for decades, however, the extensive use of CQ has resulted in the development of resistance in Southeast Asia, Oceania, and South America in the late 1950s and early 1960s [6]. Since then, CQ resistance has spread to nearly all parts of the world and paved the way for the development of Artemisinin Combination Therapy (ACT) [7]. The primary advantage of using ACT is the expeditious reduction in the majority of malaria parasites by Artemisinin while the partner drug clears the remaining parasites [8] However, the emergence of resistance to Artemisinin in the South-East Asian region has not only placed greater demand on the partner drugs but also jeopardized their future efficacy [9].

Despite the emergence of resistance, CQ still remains the first line treatment in countries endemic for uncomplicated *P. vivax* malaria [10] and is an excellent scaffold with restricted host toxicity, affordability and synthetic vulnerability [11]. The conjugation of 4-aminoquinoline with biologically active pharmacophores is considered a significant strategy which has propelled the scientific community for developing new aminoquinoline scaffolds with better activity and low incidence of resistance [12–15].

1,3-dioxoisoindolines are nitrogen-containing heterocycles with extensive pharmacological properties including; anti-convulsant, analgesic, anti-inflammatory, hypolipidemic and immunomodulatory, antiplasmodial, antitubercular and anticancer activities [16]. A series of 1,3-dioxoisoindolines functionalized with cyclic amines have shown to possess antiplasmodial activities with the compound possessing a piperidinopiperidine moiety exhibiting an IC_{50} of 1.16 μM [17]. Recently, we introduced a functionalized dioxoisoindoline ring in the side chain of 4-aminoquinoline in order to acess their anti-plasmodial activities. The compound with a tetrabromo substituted dioxoisoindoline was a promising candidate with an IC_{50} of 0.10 μM against CQ-resistance strain (W2) of *P. falciparum* [18].

In view of the above and in continuation of our effort to develop new antimalarials [19], the present manuscript encompasses the synthesis of substituted 1,3-dioxoindoline-4-aminoquinolines having an

* Corresponding author.
E-mail address: vipan_org@yahoo.com (V. Kumar).

https://doi.org/10.1016/j.bioorg.2019.04.006
Received 6 February 2019; Received in revised form 4 April 2019; Accepted 5 April 2019
Available online 11 April 2019

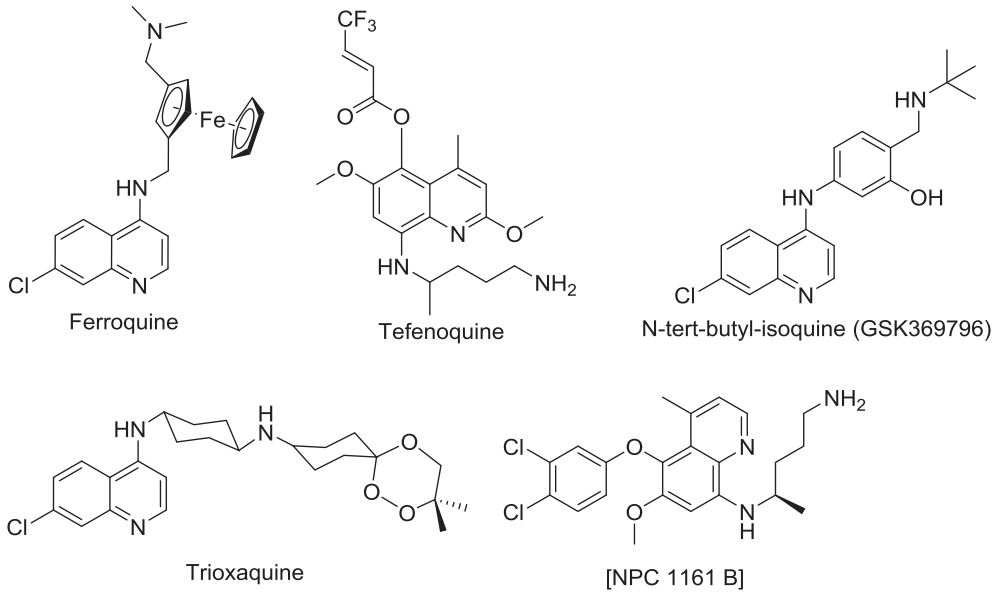


Fig. 1. Structures of 4-aminoquinoline and 8-aminoquinoline based molecules under clinical trials.

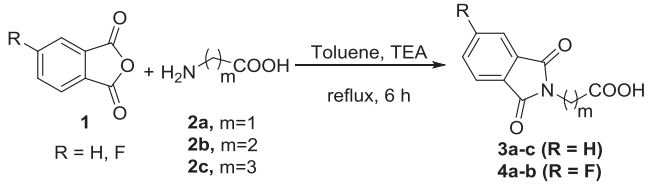
amide core between the two pharmacophores along with varied secondary amines at the C-5 position of dioxoindoline ring. The inclusion of amide-core has reported to enhance the anti-plasmodial activities against both CQ sensitive and the resistant strains of *P. falciparum* [20].

2. Results and discussion

2.1. Synthetic chemistry

For the synthesis of the desired 1,3-dioxoisoindoline-4-aminoquinolines, amide coupling was attempted to connect two pharmacophores followed by microwave heating to substitute fluoro at C-5 position with different secondary amines.

The one-set of precursor *viz.* 1,3-dioxoisoindolin-2-yl based carboxylic acids **3a-c** and **4a-b** were synthesized *via* heating substituted phthalic anhydrides with various amino acids in dry toluene using triethylamine as a base for 6 h. The synthesized acids *viz.* **3a-c** and **4a-b** were used in subsequent steps without further purification **(**Scheme 1**).** For the synthesis of conjugates **6a-l**, amide coupling of the precursors' **3a-c** with 7-chloroquinoline based diamines **5** [21] was attempted using EDC and HOBt in the presence of *N,N*-diisopropylethylamine (DIEA) in dry DMF at room temperature. Similar protocol was employed for the synthesis of **6m-r** having a fluoro-substtuent at C-5 position of dioxoisoindolines (Scheme 2). The structure to the synthesized dioxoisoindoline-4-aminoquinoline based amides were assigned on the basis of spectral data and analytical evidenced. For example, compound **6a** exhibited a molecular ion peak at 409.1041 in its high resolution mass spectrum (HRMS). The noteworthy features of its ^{1}H NMR spectrum included the presence of singlet at δ 3.31 because of ethylene (NH-CH_2-CH_2-NH); singlet at 4.18 because of glycine (CH_2) protons, two triplets at 7.33 (J = 5.0 Hz) and 8.45 (J = 5.6 Hz) because of −NH, a doublet of quinoline ring proton at 6.50 (J = 5.4 Hz) and a multiplet of four protons of dioxoisoindoline ring at 7.82–7.88. The presence of signals at δ 167.2 corresponding to carbonyl carbons and 168.0 because of amide carbonyl in the ^{13}C NMR spectrum along with methylenes at δ 37.9, 40.7 and glycine carbon at δ 42.3, as confirmed by the ^{13}C NMR (DEPT) spectrum, further validated the assigned structure.



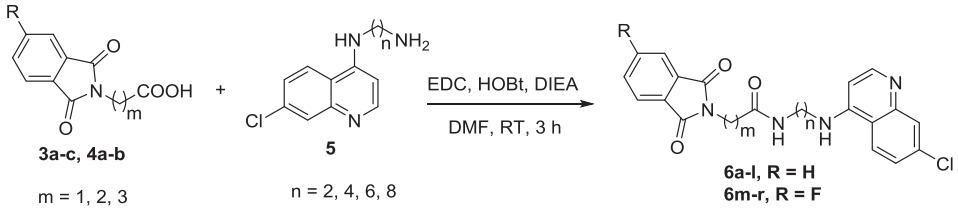
Scheme 1. Synthesis of unsubstituted **(3a-c)** and C-5 fluoro-substituted **(4a-b)** 2-(1,3-dioxoisoindolin-2-yl)acetic acid/3-(1,3-dioxoisoindolin-2-yl)propanoic acid/4-(1,3-dioxoisoindolin-2-yl)butanoic acid.

The synthesized conjugates **6m-r** were employed as precursors for affording the conjugates **7a-r** having a secondary amino functionality at C-5 position of dioxoisoindoline ring. Thus, the microwave heating of **6m-r** with various secondary amine in dry NMP at 160 °C for 5 min led to the synthesis of **7a-r** in moderate to good yields (Scheme 3). The synthesized conjugates **7a-r** were characterized using spectral and analytical techniques. For example, the compound **7j** showed a molecular ion peak at 494.1902 $[M+H]^+$ in its High-Resolution Mass Spectrum (HRMS). The salient features of its ^{1}H NMR spectrum included the appearance of triplet because of two methyl at δ 1.05 (J = 7.0 Hz) and multiplet at 3.22–3.26 corresponding to methylene protons of diethylamine, doublet at 2.37 (J = 7.3 Hz) and 3.69 (J = 7.3 Hz) because of methylene protons of dioxoisoindoline linked β-alanine, two doublet at 6.45 (J = 5.4 Hz) and 8.35 (J = 5.0 Hz) corresponding to quinoline ring protons along with two triplets at 7.29 (J = 5.4 Hz) and 8.23 (J = 5.3 Hz) because of the −NH protons. Its ^{13}C NMR spectrum revealed the appearance of signals at δ 168.0 and 168.6, corresponding to dioxoisoindoline carbonyls, a signal at 170.0 of amide carbonyl along with methylene carbons at δ 25.4, 27.5, 34.6, 37.7, 39.7, 42.7, 44.7 40.6 and 47.4 and diethylamine carbons at δ 12.6 and 53.2, as confirmed by ^{13}C NMR (DEPT) spectrum.

2.2. In vitro anti-plasmodial evaluation

The synthesized scaffolds were assayed against CQ-resistance and mefloquine-sensitive W2 strain of *P. falciparum* and the observed activities are given in Table 1. Evidently, most of the synthesized scaffolds displayed good antiplasmodial activities with some of them have either comparable or better activities than standard drug, Chloroquine (CQ). Analyzing the activity data revealed an interesting Structure-Activity Relationships (SARs) among the synthesized compounds with activity showing dependence both on the nature of substituent at the dioxoindoline ring along with the length of alkyl chain (m, n) introduced as linker between two pharmacophores.

Among compounds **6a-l** (R = H); the activity increases with an increase in chain length as apparent from glycyl and β-alanyl linked



Scheme 2. Synthesis of unsubstituted **(6a-l)** and C-5 fluoro-substituted **(6m-r)** *N*-(2-((7-chloroquinolin-4-yl)amino)alkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamides.

compounds **6d** (n = 8, 0.24 μM) and **6h** (n = 8, 0.15 μM), respectively. The introduction of butyric acid, however reduced the antiplasmodial activity except for compound **6i** (n = 2); which exhibited IC_{50} values of 0.28 μM. Introducing a fluoro substituent at the C-5 position of dioxoisoindolines resulted in the reduction of antiplasmodial efficacy in case of glycine linked scaffolds (**6m-o**) while the activity improved considerably with the introduction of *β*-alanine at shorter chain lengths as evident by **6p** (0.36 μM) and **6q** (0.22 μM). Introducing different secondary amines (morpholine, diethylamine, 2-hydroxyethylpiperazine) at C-5 of dioxoisoindoline (**7a-r**) substantially improved the activity profiles presumably because of direct co-relation between the basicity and activity. The increase in basicity of the compound results in its better accumulation inside the acidic food vacuole of the parasite. Among the glycine tethered hybrids having a secondary amine at the C-5 position **(7a-c, 7g-l, 7m-o)**, the reduction in activity was observed even at longer alkyl chain lengths except for **7n** and **7o** having 2-hydroxyethylpiperazine, which exhibited IC_{50} values of 0.86 and 0.46 μM, respectively. The presence of alanine between the dioxoisoindoline core and amide linkage among hybrids, **7d-f, 7j-l** and **7p-r** improved the antiplasmodial activities in general with few of the conjugates exhibiting comparable or better activity profiles than the standard drug CQ. Cytotoxic studies of all the synthesized compounds were also carried out on mammalian Vero cells so as to confirm whether the observed activities were because of their inherent anti-plasmodial efficacy or cytotoxicity **(**Table 1**).** Analyzing the cytotoxicity of the synthesized conjugates revealed that most of the compounds were found to be non-cytotoxic (Table 1).

Comparing the activity and cytotoxicity profiles of the presently synthesized compounds with our previous report [18], the introduction of an amide linkage although did not improve the antiplasmodial activity but resulted in the reduction of the cytotoxicity as evident by compound **I** and **6h** (Fig. 2). Among fluoro substituted dioxoisoindoline-4-aminoquionolines, the introduction of amide core resulted in an improvement in antiplasmodial activity as apparent on comparing **II** and **6q.** The replacement of fluoro with secondary amine resulted in substantial improvement in both activity as well as cytotoxicity as shown by compound **7j**.

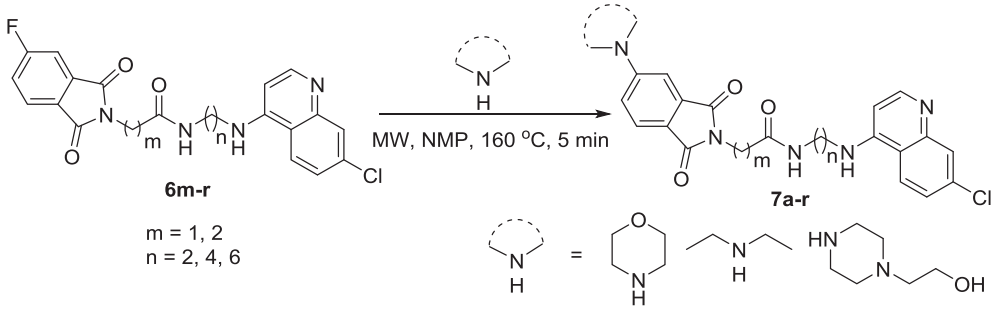
The ClogP value of chloroquine is reported to be 5.06 while the calculated ClogP values of the promising compounds were found to be 3.20, 4.10, and 3.15 respectively. Further, the protonation of secondary amino group of the synthesized compound is feasible under physiological condition. The ClogP values of protonated **7d**, **7j** and **7q** were calculated to be 0.04, 0.35 and −0.01 which are quite appropriate from the perspective of bioavailability [22]. The generalized antiplasmodial structure activity relationship/cytotoxicity and plausible antiplasmodial mechanism of the synthesized 5-secondary amino substituted 1,3-dioxoisoindoline-4-aminoquinolines tethered *via* amide bond is elucidated in Fig. 3.

In conclusion, a series of C-5 substituted 1,3-dioxoisoindoline-4-aminoquinolines has been urbanized with the aim of studying their structure–activity relationship against *P. falciparum*. Almost all of the synthesized scaffolds exhibited promising antiplasmodial activity and good selectivity index. The antiplasmodial activities were substantially enhanced with introduction of secondary amine at C-5 position of dioxoisoindoline ring while the inclusion of amide as spacer improved their cytotoxic profiles.

3. Experimental section

3.1. General

All starting materials and reagents were purchased from Sigma-Aldrich and Merck. Thin-layer chromatography was performed on a film of silica gel that contained a fluorescent indicator F_{254} supported on an aluminum sheet (Merck). 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 ($CDCl_3$) 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, dd: double doublet, m: multiplet, 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 DMSO-d_6. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. High-Resolution Mass Spectra (HRMS) were recorded on a Bruker-micrOTOF-Q II spectrometer using ESI as the ion source.



Scheme 3. Synthesis of C-5 amine substituted 1,3-dioxoisoindolines linked with 4-aminoquinolines *via* amide spacer **7a-r.**

Table 1
In vitro antiplasmodial activity of synthesized compounds (**6a-r, 7a-r)** against CQ resistant W2 strains of *P. falciparum* with cytotoxicity evaluation on mammalian Vero cells and their Selectivity index.

Code	R	m	n	% Yield	IC_{50} (μM) ± SD	IC_{50} (μM) (cytotoxicity)	SI	ClogP[a]
6a	H	1	2	82	5.65 ± 0.6	> 245	–	3.00
6b	H	1	4	81	3.66 ± 0.03	> 229.2	–	3.54
6c	H	1	6	85	3.35 ± 0.1	247.7	73.94	4.55
6d	H	1	8	76	0.24 ± 0.04	> 203.1	–	5.57
6e	H	2	2	81	0.30 ± 0.01	> 236.9	–	3.27
6f	H	2	4	77	0.41 ± 0.01	> 222.1	–	3.81
6g	H	2	6	79	0.29 ± 0.02	87.5	301.7	4.83
6h	H	2	8	70	0.15 ± 0.03	> 197.5	–	5.84
6i	H	3	2	83	0.28 ± 0.02	> 229.2	–	3.54
6j	H	3	4	74	0.84 ± 0.03	> 215.4	–	4.09
6k	H	3	6	76	1.57 ± 0.6	> 203.1	–	5.10
6l	H	3	8	78	0.58 ± 0.07	101.7	175.3	6.11
6m	5-F	1	2	82	1.99 ± 0.8	> 234.7	–	2.17
6n	5-F	1	4	85	1.05 ± 0.01	> 220.2	–	2.71
6o	5-F	1	6	84	1.49 ± 0.1	> 207.4	–	3.72
6p	5-F	2	2	81	0.36 ± 0.02	93.16	258.7	2.44
6q	5-F	2	4	76	0.22 ± 0.004	109.8	499.0	2.98
6r	5-F	2	6	77	0.66 ± 0.2	57.2	86.66	3.99
7a	5-Morpholinyl	1	2	76	3.21 ± 0.9	> 202.7	–	2.93
7b	5-Morpholinyl	1	4	79	1.28 ± 0.1	> 191.8	–	3.47
7c	5-Morpholinyl	1	6	81	1.78 ± 0.8	20.16	11.3	4.48
7d	5-Morpholinyl	2	2	76	0.13 ± 0.003	26.46	203.5	3.20
7e	5-Morpholinyl	2	4	82	0.22 ± 0.004	135.5	615.9	3.74
7f	5-Morpholinyl	2	6	78	0.64 ± 0.02	> 177.5	–	4.75
7g	5-(diethylamino)	1	2	79	1.14 ± 0.3	44.41	38.9	3.83
7h	5-(diethylamino)	1	4	78	1.17 ± 0.05	46.88	40.0	4.38
7i	5-(diethylamino)	1	6	79	1.22 ± 0.03	> 186.8	–	5.38
7j	5-(diethylamino)	2	2	70	**0.097 ± 0.006**	**202.7**	**2089**	**4.10**
7k	5-(diethylamino)	2	4	72	0.26 ± 0.01	84.41	324.6	4.65
7l	5-(diethylamino)	2	6	68	0.53 ± 0.004	> 182	–	5.66
7m	5-(2-(piperazin-1-yl)ethan-1-ol)	1	2	75	1.04 ± 0.004	> 186.5	–	2.34
7n	5-(2-(piperazin-1-yl)ethan-1-ol)	1	4	83	0.86 ± 0.2	> 177.2	–	2.88
7o	5-(2-(piperazin-1-yl)ethan-1-ol)	1	6	75	0.46 ± 0.07	> 168.8	–	3.89
7p	5-(2-(piperazin-1-yl)ethan-1-ol)	2	2	71	0.28 ± 0.05	ND	–	2.61
7q	5-(2-(piperazin-1-yl)ethan-1-ol)	2	4	68	0.14 ± 0.01	168.8	1205.7	3.15
7r	5-(2-(piperazin-1-yl)ethan-1-ol)	2	6	65	0.18 ± 0.006	> 164.9	–	4.16
CQ					0.23 ± 0.07			5.00

[a] ClogP calculated from molinspiration.

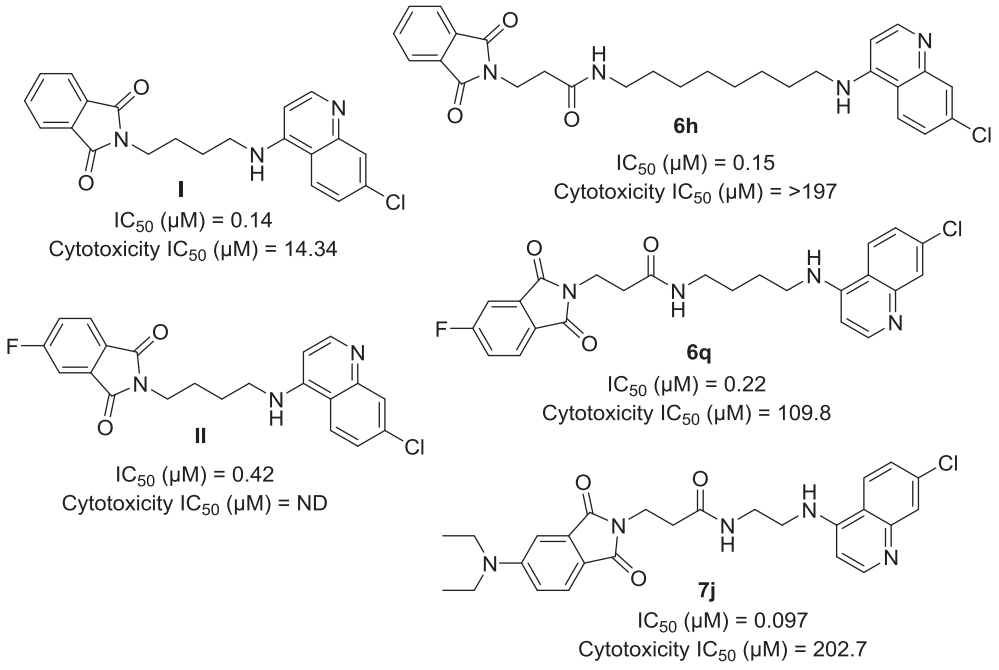


Fig. 2. Comparison of activity/cytotoxicity of **6h, 6q, 7j** with previously reported scaffolds **I** and **II**.

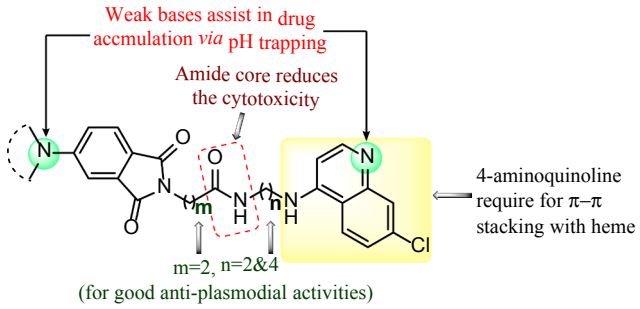


Fig. 3. Structure Activity Relationship (SAR) of 4-aminoquinoline based molecules.

3.2. General procedure for the synthesis of amide-linked substituted 1,3-dioxoisoindoline-4-aminoquinolines ***(6a-r, 7a-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 **(3a-c, 4a-b):**

Substituted Phthalic anhydrides (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 **(6a-r):**

1.0 mmol of (1,3-dioxoisoindolin-2-yl) 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.

3.2.1. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide ***(6a)***

White solid; mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.31 (s, 4H, 2x-**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. Anal Calcd (%): C, 61.69; H, 4.19; N, 13.70. found: C, 61.54; H, 4.27; N,13.62

3.2.2. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide ***(6b)***

White solid; mp 129–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96–1.29 (m, 4H, 2x-**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. Anal Calcd (%): C, 63.23; H, 4.85; N, 12.82. found: C, 63.35; H, 4.79; N,12.88.

3.2.3. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide ***(6c)***

White solid; mp 110–111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32–1.41 (m, 6H, 3x-**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. Anal Calcd (%): C, 64.58; H, 5.42; N, 12.05. found: C, 64.67; H, 5.49; N, 12.13.

3.2.4. N-(8-((7-chloroquinolin-4-yl)amino)octyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide ***(6d)***

White solid; mp 101–102 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22–1.41 (m, 12H, 6x-**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. Anal Calcd (%): C, 65.78; H, 5.93; N, 11.36; found: C, 65.65; H, 5.99; N, 11.41.

3.2.5. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide ***(6e)***

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, 2x-**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 $C_{22}H_{19}ClN_4O_3$ $[M]^+$ 423.1179 found 423.1161. Anal Calcd (%): C, 62.49; H, 4.53; N, 13.25; found: C, 62.51; H, 4.45; N, 13.17.

3.2.6. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide ***(6f)***

White solid; mp 172–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23–1.33 (m, 4H, 2x-**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. Anal Calcd (%): C, 63.93; H, 5.14; N, 12.43; found: C, 63.81; H, 5.08; N, 12.38.

3.2.7. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide ***(6g)***

White solid; mp 122–123 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.29–1.40 (m, 6H, 3x-**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. Anal Calcd (%): C, 65.20; H, 5.68; N, 11.70; found: C, 65.13; H, 5.51; N, 11.61.

3.2.8. N-(8-((7-chloroquinolin-4-yl)amino)octyl)-3-(1,3-dioxoisoindolin-2-yl)propanamide ***(6h)***

White solid; mp 85–86 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.20–1.40 (m, 12H, 6x-**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. Anal Calcd (%): C, 66.33; H, 6.16; N, 11.05; found: C, 66.44; H, 6.26; N, 11.17.

3.2.9. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide ***(6i)***

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, 2x-**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. Anal Calcd (%): C, 63.23; H, 4.85; N, 12.82; found: C, 63.44; H, 4.89; N, 12.77.

3.2.10. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide ***(6j)***

White solid; mp 145–146 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22–1.34 (m, 4H, 2x-**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. Anal Calcd (%): C, 64.58; H, 5.42; N, 12.05; found: C, 64.41; H, 5.31; N, 12.19.

3.2.11. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide ***(6k)***

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, 2x-**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. Anal Calcd (%): C, 65.78; H, 5.93; N, 11.36; found: C, 65.65; H, 5.82; N, 11.44.

3.2.12. N-(8-((7-chloroquinolin-4-yl)amino)octyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide ***(6l)***

White solid; mp 152–153 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.20–1.39 (m, 12H, 6x-**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. Anal Calcd (%): C, 66.85; H, 6.38; N, 10.75; found: C, 66.79; H, 6.49; N, 10.61.

3.2.13. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide ***(6m)***

White solid; mp 192–193 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): 3.31 (s, 4H, 2x-**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 $C_{21}H_{16}ClFN_4O_3$ $[M+H]^+$ 427.0929 found 427.0935. Anal Calcd (%): C, 59.09; H, 3.78; N, 13.13; found: C, 59.22; H, 3.68; N, 13.33.

3.2.14. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide ***(6n)***

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. Anal Calcd (%): C, 60.73; H, 4.43; N, 12.32; found: C, 60.59; H, 4.38; N, 12.21.

3.2.15. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-2-(5-fluoro-1,3-dioxoisoindolin-2-yl)acetamide ***(6o)***

White solid; mp 131–132 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 1.36–1.44 (m, 4H, 2x-**CH_2**-); 1.54–1.62 (m, 4H, 2x-**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. Anal Calcd (%): C, 62.18; H, 5.01; N, 11.60; found: C, 62.33; H, 5.12; N, 11.51.

3.2.16. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (6p)

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, 2x-**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_2O); 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_2O); 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. Anal Calcd (%): C, 59.94; H, 4.12; N, 12.71; found: C, 59.77; H, 4.41; N, 12.59.

3.2.17. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (6q)

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_2O); 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_2O); 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. Anal Calcd (%): C, 61.47; H, 4.73; N, 11.95; found: C, 61.55; H, 4.88; N, 11.87.

3.2.18. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-(5-fluoro-1,3-dioxoisoindolin-2-yl)propanamide (6r)

White solid; mp 138–139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): 1.32–1.39 (m, 6H, 3x-**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_2O); 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_2O); 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. Anal Calcd (%): C, 62.84; H, 5.27; N, 11.27; found: C, 62.77; H, 5.33; N, 11.16.

General procedure for synthesis of C-5 secondary amine substituted *N*-(2-((7-chloroquinolin-4-yl)amino)alkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamides (7a-r): In a microwave reaction vial was added a solution of C-5 fluoro substituted *N*-(7-chloroquinolin-4-yl) amino)alkyl)-2-(1,3-dioxoisoindolin-2-yl)alkylamide **6m-l** (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 ^{0}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 re-crystallized using absolute ethanol.

3.2.19. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (7a)

Yellow solid; mp 216–217 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.30–3.32 (m, 6H, 3x-**CH$_2$**-); 3.59–3.63 (m, 2H, −**CH$_2$**−); 3.74–3.76 (m, 4H, 2x-**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_2O); ^{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. Anal Calcd (%): C, 60.79; H, 4.90; N, 14.18; found: C, 60.83; H, 4.79; N, 14.31.

3.2.20. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (7b)

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, 2x-**CH$_2$**-); 3.70–3.74 (m, 4H, 2x-**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_2O); 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_2O); 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. Anal Calcd (%): C, 62.13; H, 5.41; N, 13.42; found: C, 62.31; H, 5.33; N, 13.53.

3.2.21. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-2-(5-morpholino-1,3-dioxoisoindolin-2-yl)acetamide (7c)

Yellow solid; mp 160–161 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.30–1.45 (m, 6H, 3x-**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, 2x-**CH$_2$**-); 3.72–3.75 (m, 4H, 2x-**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_2O); 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_2O); 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. Anal Calcd (%): C, 63.32; H, 5.86; N, 12.73; found: C, 63.51; H, 5.65; N, 12.68.

3.2.22. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (7d)

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, 4x-**CH$_2$**-); 3.67–3.73 (m, 6H, 3x-**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. Anal Calcd (%): C, 61.48; H, 5.16; N, 13.79; found: C, 61.55; H, 5.26; N, 13.88.

3.2.23. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (7e)

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, 4x-**CH$_2$-**); 3.65–3.71 (m, 6H, 3x-**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. Anal Calcd (%): C, 62.74; H, 5.64; N, 13.07; found: C, 62.87; H, 5.55; N, 13.20.

3.2.24. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-(5-morpholino-1,3-dioxoisoindolin-2-yl)propanamide (7f)

Yellow solid; mp 126–127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31–1.46 (m, 6H, 3x-**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, 2x-**CH$_2$-**); 3.66–3.73 (m, 6H, 3x-**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. Anal Calcd (%): C, 63.88; H, 6.08; N, 12.42; found: C, 63.97; H, 6.19; N, 12.33.

3.2.25. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (7g)

Yellow solid; mp 197–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 (t, 6H, 2x-**CH$_3$**); 3.22–3.27 (m, 4H, 2x-**CH$_2$-**); 3.36–3.41 (m, 4H, 2x-**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. Anal Calcd (%): C, 62.56; H, 5.46; N, 14.59; found: C, 62.65; H, 5.39; N, 14.67.

3.2.26. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (7h)

Yellow solid; mp 173–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, 6H, 2x-**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, 2x-**CH$_2$-**); 3.39–3.43 (m, 4H, 2x-**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. Anal Calcd (%): C, 63.84; H, 5.95; N, 13.79; found: C, 63.72; H, 5.80; N, 13.66.

3.2.27. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-2-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)acetamide (7i)

Yellow solid; mp 158–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, 6H, 2x-**CH$_3$**); 1.32–1.44 (m, 6H, 3x-**CH$_2$-**); 1.63–1.67 (m, 2H, −**CH$_2$**−); 3.07–3.10 (m, 2H, −**CH$_2$**−); 3.25–3.30 (m, 2H, 2x-**CH$_2$-**); 3.37–3.41 (m, 4H, 2x-**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. Anal Calcd (%): C, 64.98; H, 6.39; N, 13.06; found: C, 64.80; H, 6.49; N, 13.18.

3.2.28. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (7j)

Yellow solid; mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05 (t, J = 7.0 Hz, 6H, 2x-**CH$_3$**); 2.37 (t, J = 7.3 Hz, 2H, **–CH$_2$**); 3.22–3.26 (m, 4H, 2x-**CH$_2$-**); 3.38–3.42 (m, 4H, 2x-**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. Anal Calcd (%): C, 63.22; H, 5.71; N, 14.18; found: C, 63.32; H, 5.66; N, 14.27.

3.2.29. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (7k)

Yellow solid; mp 161–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (t, J = 7.1 Hz, 6H, 2x-**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, 2x-**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. Anal Calcd (%): C, 64.42; H, 6.18; N, 13.42; found: C, 64.36; H, 6.27; N, 13.39.

3.2.30. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-(5-(diethylamino)-1,3-dioxoisoindolin-2-yl)propanamide (7l)

Yellow solid; mp 142–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08

(t, J = 7.3 Hz, 6H, 2x-**CH_3**); 1.35–1.45 (m, 6H, 3x-**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, 2x-**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. Anal Calcd (%): C, 65.50; H, 6.60; N, 12.73; found: C, 65.55; H, 6.52; N, 12.65.

3.2.31. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-2-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (7m)

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, 2x-**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, 2x-**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. Anal Calcd (%): C, 60.39; H, 5.44; N, 15.65; found: C, 60.49; H, 5.38; N, 15.77.

3.2.32. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-2-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (7n)

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, 2x-**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, 2x-**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. Anal Calcd (%): C, 61.64; H, 5.89; N, 14.87; found: C, 61.58; H, 5.79; N, 14.79.

3.2.33. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-2-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)acetamide (7o)

Yellow solid; mp 118–119 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.31–1.45 (m, 6H, 3x-**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, 2x-**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, 2x-**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. Anal Calcd (%): C, 62.78; H, 6.29; N, 14.17; found: C, 62.70; H, 6.33; N, 14.24.

3.2.34. N-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (7p)

Yellow solid; mp 211–212 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.42–2.45 (m, 4H, 2x-**CH_2-**); 2.53 (t, J = 5.1 Hz, 4H, 2x-**CH_2-**); 3.26–3.31 (m, 4H, 2x-**CH_2-**); 3.33–3.35 (m, 4H, 2x-**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. Anal Calcd (%): C, 61.03; H, 5.67; N, 15.25; found: C, 61.17; H, 5.78; N, 15.16.

3.2.35. N-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (7q)

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, 2x-**CH_2-**); 2.55 (t, J = 5.0 Hz, 4H, 2x-**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, 2x-**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. Anal Calcd (%): C, 62.22; H, 6.09; N, 14.51; found: C, 62.32; H, 6.19; N, 14.43.

3.2.36. N-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-(5-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-dioxoisoindolin-2-yl)propanamide (7r)

Yellow solid; mp 102–103 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.32–1.44 (m, 6H, 3x-**CH_2-**); 1.63–1.68 (m, 2H, −**CH_2**−); 2.42–2.48 (m, 4H, 2x-**CH_2-**); 2.54 (t, J = 5.0 Hz, 4H, 2x-**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, 2x-**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. Anal Calcd (%): C, 63.30; H, 6.47; N, 13.84; found: C, 63.21; H, 6.33; N, 13.79.

3.3. Methods for assessment of the antiplasmodial activity of test compounds

The W2 strain of *P. falciparum* was cultured in RPMI-1640 medium

with 0.5% Albumax I (Gibco) following the standard procedures and using 5% D-sorbitol to synchronize parasites. To initiate at the ring stage, microwell cultures were incubated with different concentrations of the compounds for 48 h. The compounds were added from DMSO stocks keeping 0.1% as the maximum concentration of DMSO. Controls lacking inhibitors included 0.1% DMSO. The culture medium was removed after 48 h when control cultures had developed new rings which were further incubated at RT for 48 h at pH 7.4 with 1% formaldehyde in PBS. Fixed parasites were then shifted to 0.1% Triton X-100 in PBS containing 1 nM YOYO-1 dye (Molecular Probes). Using Cell Quest software (Beckton Dickinson), parasitemia was determined from dot plots (forward scatter vs. fluorescence) acquired on a FACSort flow cytometer. The determination of IC_{50} values for growth inhibition was done from plots of percent control parasitemia over inhibitor concentration with Prism 5.0 program, (GraphPad Software), with data from duplicate experiments fitted by non-linear regression [23].

3.4. Cytotoxicity assay

Cell viability was determined using Vero cells (ATCC, Sigma, Germany) cultured in RPMI medium (Gibco, USA), provided with 10% de-complemented fetal calf serum, under a 5% CO_2 atmosphere so as to determine cell viability. Cells were seeded in 96-well plates at a density of 2×10^4 cells/well in 160 μL medium and incubated overnight at 37 °C to allow cells to adhere. Compounds (Stock solution in DMSO) were freshly diluted to appropriate concentrations in DMEM, to allow the addition of 20 μL volumes of the diluted compounds to the cells that resulted in final compound concentrations of 100 μg/mL, 50 μg/mL, and 25 μg/mL. No cytotoxic effect of DMSO was observed at 1% (v/v) which was the maximum final concentration of DMSO. After 24 h incubation at 37 °C, 20 μL of 1 mg/mL resazurin (Sigma, Germany) was added to each well and the cells were incubated for an additional 3 h 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 (1%, 0.5%, 0.25%) and multiplying this value by 100. The IC_{50} is defined as the lowest concentration of compound tested at which at least 50% cell viability was observed.

Acknowledgment

The authors thank Council of Scientific and Industrial Research (CSIR), New Delhi, India by AR for financial support (Ref. No. 09/254(0269)/2017-EMR-I). Science and Engineering Research Board (SERB), New Delhi is gratefully acknowledged by VK for financial assistance (Grant no. EMR/2015/001687).

Conflict of interest

The authors have declared no conflict of interest.

Appendix A. Supplementary material

Scanned ^1H and ^{13}C NMR spectra of few representative compounds *viz.* **6a, 6c, 6e, 6i, 6n, 6q, 7a, 7c, 7d, 7j, 7n** and **7p** are provided in the electronic supplementary information. Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.04.006.

References

[1] (a) E.A. Ashley, A.P. Phyo, C.J. Woodrow, Malaria. Lancet 391 (2018) 1608;
(b) D. Pesic, K. Starcevic, A. Toplak, E. Herreros, J. Vidal, M.J. Almela, D. Jelic, S. Alihodzic, R. Spaventi, M. Peric, J. Med. Chem. 55 (2012) 3216.
[2] World Malaria Report, World Health Organization, 2018. Online, http://apps.who.int/iris/bitstream/handle/10665/275867/9789241565653-eng.pdf?ua=1.
[3] World malaria report 2017. Geneva, Switzerland: World Health Organization; 2017. World Health Organization http://apps.who.int/iris/bitstream/10665/ 259492/1/9789241565523-eng.pdf?ua=1.
[4] S. Kumar, R.K. Singh, B. Patial, S. Goyal, T.R. Bhardwaj, J. Enzyme Inhib. Med. Chem. 31 (2016) 173.
[5] C. Imperatorea, M. Persicoa, M. Senesea, A. Aielloa, M. Casertanoa, P. Lucianoa, N. Basilicob, S. Parapinib, A. Paladinoc, C. Fattorussoa, M. Mennaa, Bio. Chem. 85 (2019) 240.
[6] https://www.cdc.gov/malaria/malaria_worldwide/reduction/drug_resistance.html.
[7] R.M. Beteck, F.J. Smit, R.K. Haynes, D.D. N'Da, Malar. J. 13 (2014) 339.
[8] A.M. Dondorp, S. Yeung, L. White, C. Nguon, N.P.J. Day, D. Socheat, L. von Seidlein, Nat. Rev. Microbiol. 8 (2010) 272.
[9] B. Aneja, B. Kumar, M.A. Jairajpuri, M. Abid, RSC Adv. 6 (2016) 18364.
[10] R.R. Soares, J.M.F. deSilva, B.C. Carlos, C.C. deFonseca, L.S.A. deSouza, F.V. Lopes, de, P.R.M. Dias, P.O.L. Moreira, C. Abramo, G.H.R. Viana, P.F. de Varotti, A.D. deSilva, K.K.G. Scopel, Bioorg. Med. Chem. Lett. 25 (2015) 2308.
[11] M.C. Joshi, J. Okombo, S. Nsumiwa, J. Ndove, D. Taylor, L. Wiesner, R. Hunter, K. Chibale, T.J. Egan, J. Med. Chem. 60 (2017) 10245.
[12] F. Bellot, F. Cosledan, L. Vendier, J. Brocard, B. Meunier, A. Robert, J. Med. Chem. 53 (2010) 4103.
[13] A. Kumar, K. Srivastava, S.R. Kumar, M.I. Siddiqi, S.K. Puri, J.K. Saxena, P.M.S. Chauhan, Eur. J. Med. Chem. 46 (2011) 676.
[14] S. Manohar, U.C. Rajesh, S.I. Khan, B.L. Tekwani, D.S. Rawat, A.C.S. Med, Chem. Lett. 3 (2012) 555.
[15] E.M. Guantai, K. Ncokazi, T.J. Egan, J. Gut, P.J. Rosenthal, R. Bhampidipati, A. Kopinathan, P.J. Smith, K. Chibale, J. Med. Chem. 54 (2011) 3637.
[16] U. Sharma, P. Kumar, B. Kumar, Mini Rev. Med. Chem. 10 (2010) 678.
[17] A.K. Singh, V. Rajendran, A. Pant, P.C. Ghosh, N. Singh, N. Latha, S. Garg, K.C. Pandey, B.K. Singh, B. Rathi, Bioorg. Med. Chem. 23 (2015) 1817.
[18] A. Rani, A. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 143 (2018) 150.
[19] (a) A. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 125 (2017) 269;
(b) A. Singh, A. Rani, J. Gut, P.J. Rosenthal, V. Kumar, Chem. Biol. Drug Des. 90 (2017) 590;
(c) S. Kumar, A. Saini, J. Gut, P.J. Rosenthal, R. Raj, V. Kumar, Eur. J. Med. Chem. 138 (2017) 993;
(d) R. Raj, A. Saini, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 95 (2015) 230;
(e) P. Singh, R. Raj, P. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 71 (2014) 128.
[20] G. Kaur, K. Singh, E. Pavadai, M. Njoroge, M. Espinoza-Moraga, C. De Kock, P.J. Smith, S. Wittlind, K. Chibale, Med. Chem. Comm. 6 (2015) 2023.
[21] De. Dibyendu, F.M. Krogstad, L.D. Byers, D.J. Krogstad, J. Med. Chem. 41 (1998) 4918.
[22] http://www.molinspiration.com/cgi-bin/properties.
[23] P.J. Singh, Rosenthal, Antimicrob. Agent Chemother. 45 (2001) 949.