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Synthesis of Spiro-β-lactam-pyrroloquinolines as Fused Heterocyclic Scaffolds through Post-transformation Reactions

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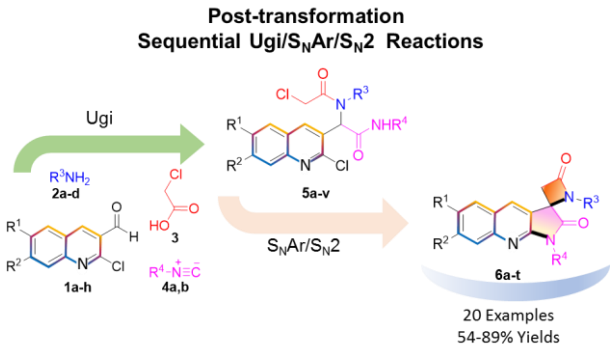


ABSTRACT

A sequential post-transformation of Ugi four-component reaction/nucleophilic substitution was developed for the synthesis of spiro-β-lactam-pyrroloquinolines. This method involves the Ugi-4CR of 2-chloro-3-formyl quinolines **1a-h**, amines **2a-d**, 2-chloroacetic acid **3**, and isocyanides **4a-b** for the synthesis of versatile precursors **5a-v**. The Ugi adducts were intramolecularly cyclized under basic conditions through the sequential S_NAr/S_N2 reaction to give spiro-β-lactam-pyrroloquinoline scaffolds **6a-t**. This approach is an efficient method for the synthesis of fused bioactive heterocyclic backbones containing quinoline, pyrrolidone and β-lactam with high bond forming efficiency.

KEYWORDS

Post-transformation reaction, Ugi-4CR/Nucleophilic substitution, Fused heterocyclic scaffolds, Spiro-β-lactam, Pyrroloquinoline.

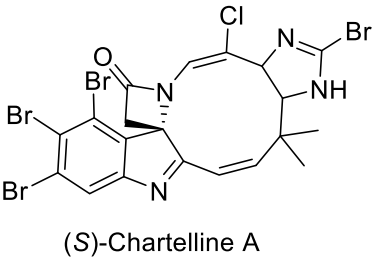
▪ INTRODUCTION

The developed organic chemistry is recently called as the art of synthesis that is due to the creation of complex organic molecules containing multi-fused heterocyclic moieties. Fused heterocyclic structures are found among different kinds of bioactive organic compounds, for example trapidil (triazolopyrimidine) as an antiplatelet drug, natural camptothecin (pyrano[3',4':6,7] indolizino[1,2-*b*]quinoline) as an antitumor agent, and zolpidem (imidazopyridine) as a hypnotic agent.[1] In this respect, the production of fused heterocyclic structures is considered a privileged task for scientists from the viewpoint of their synthesis and their medicinal activities.[2] In terms of their synthesis, designing a reaction to fuse heterocycles together is a burgeoning challenge in the world of organic synthesis. In recent years, many contributions have led to the synthesis of the fused heterocycles involving multistep sequences for assembling the starting materials, including microwave-assisted techniques,[3] intramolecular C–H activation,[4] catalyzed by transition metals,[5] or even metal-free methodologies.[6] Another environmentally benign approach known as the post-transformation reactions is also developed to fuse heterocycles.[7] The use of Ugi four-component reaction (4CR) post-transformations has received significant attention.[8] The most important parameter of a post-transformation synthesis is manipulated by targeted selection of the starting materials that could undergo further reactions, such as Heck, Suzuki, and substitution nucleophilic reactions, to give a complex cyclized structure.[9]

The chemistry of spiro-β-lactams has been explored for the preparation of a wide range of biologically important fused heterocycles.[10] Various reactive β-lactams (azetidin-2-one) are reported as antibacterial agents.[11] Spiro-β-lactam are also found in nature; (*S*)-chartelline A isolated from the marine bryozoan *Chartella papyracea* (Figure 1).[12] Besides, pyrrolo[2,3-*b*]quinolines, as aza-analogue of furoquinoline alkaloids, have greatly drawn the attention of synthetic chemists in recent years. Most of the known synthetic routes for the preparation of these compounds involve very complicated multistep reactions or require the presence of a metal complex catalyst.[13]

Figure 1. The Structure of Natural Chartelline A from the Marine Bryozoan *Chartella Papyracea*

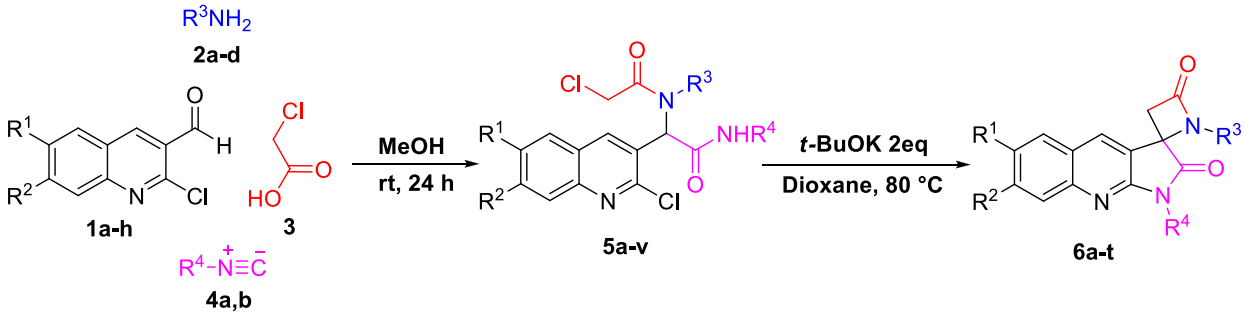
Chartella papyracea



(*S*)-Chartelline A

Prompted by the above mentioned topics and following of our interest in Ugi–post-transformational reactions, herein, we wish to report a concise post-transformation approach for the synthesis of spiro-β-lactam-pyrroloquinoline through a sequential Ugi-4CR/nucleophilic substitution reaction, employing 2-chloro-3-formylquinoline derivatives (as the aldehyde moiety) in the Ugi-4CR. It is noteworthy that the substitution reaction includes sequential S_NAr and S_N2 mechanisms to cyclize the Ugi adducts. As shown in Scheme 1, by treating 2-chloro-3-formyl quinolines **1a-h** with amines **2a-d**, chloroacetic acid **3**, and isocyanides **4a-b** through Ugi-4CR, a series of Ugi adducts **5a-v** were synthesized containing two nucleophile and two electrophile centers which can directly undergo intramolecular cyclization reaction in the presence of potassium *t*-butoxide as the base to give the desired spiro-β-lactam-pyrroloquinolines **6a-t**.

Scheme 1. Two Step Preparation of Spiro-β-lactam-pyrroloquinoline Scaffolds 6a-t via Ugi/ S_NAr/S_N2 Post-transformation Reactions

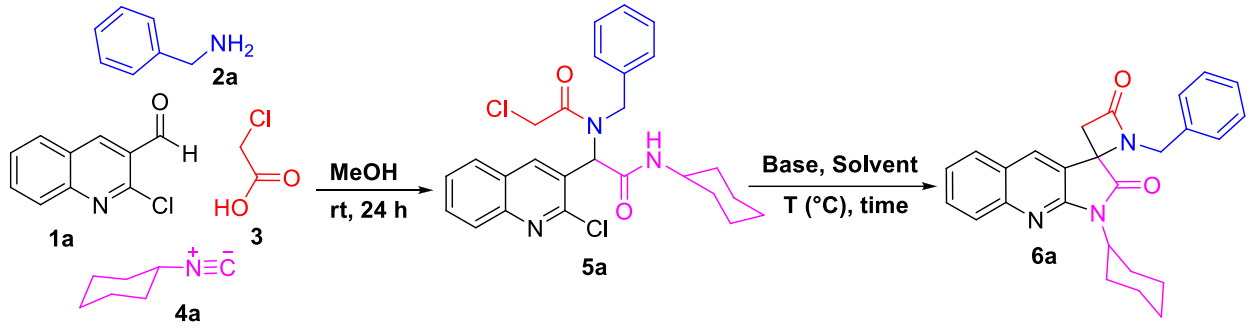


▪ RESULTS AND DISSCUSSIONS

The desired bifunctional precursors 2-chloro-3-formyl quinolines **1a-h** were synthesized utilizing a previously reported Vilsmeier-Haack cyclization from acetanilides in the presence of $POCl_3$.[14] Our primary investigations focused on the production of **5a** via Ugi-4CR of 2-chloro-3-

formylquinoline **1a**, benzylamine **2a**, 2-chloroacetic acid **3**, and cyclohexyl isocyanide **4a** in methanol at ambient temperature for 24 h as the model reaction. For the synthesis of target product **6a** from Ugi adduct **5a**, the reaction conditions were initially optimized as shown in Table 1. In this regard, the selected adduct **5a** was exposed to different inorganic and organic bases in various solvents at high temperatures. Carbonate salts (Cs_2CO_3 and K_2CO_3) in polar, nonpolar, and even protic solvents (CH_3CN, DMF, DMSO, toluene, MeOH, $CHCl_3$, dioxane) did not give the product higher than 30% yield. By the use of *t*-BuOK in different solvents (Table 1, entries 1-5), the highest reaction yield was found in dioxane. Hence, the effect of some other bases, including NaOMe, Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO), was examined in this reaction in dioxane (entries 6-9); however, none of them were effective. So, the effect of temperature over the reaction in *t*-BuOK/dioxane was investigated (entries 10 and 11). Entry 11 shows the optimum conditions for the model reaction.

Table 1. Optimization of the Reaction Conditions for the Synthesis of 6a as Model Reaction[a]

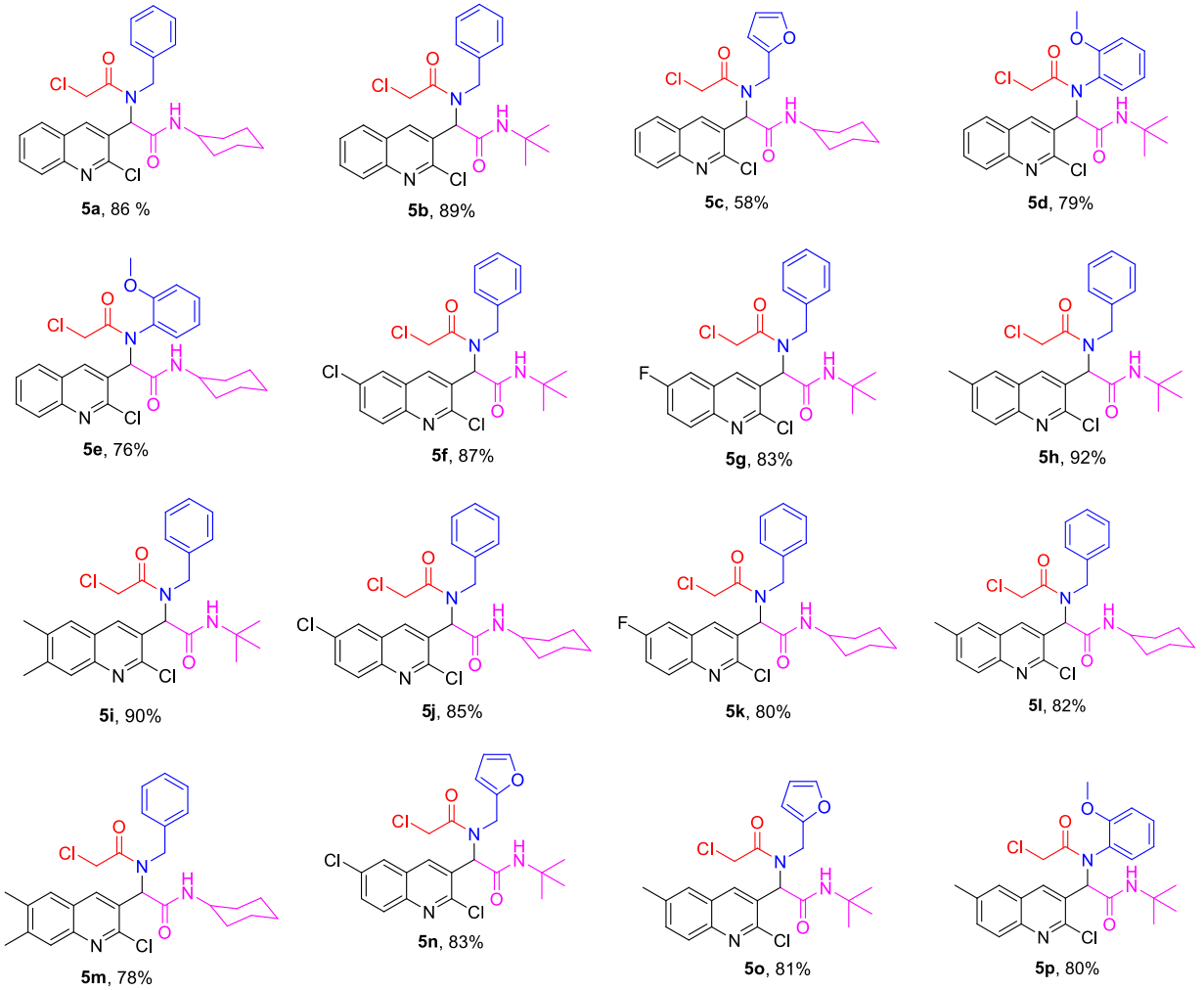


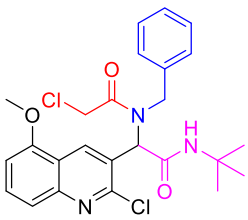
Entry	Base (2eq)	Solvent	Conditions	Time (h)	Yield[b] (%)
1	*t*-BuOK	DMF	100 °C	24	-
2	*t*-BuOK	DMSO	100 °C	24	-
3	*t*-BuOK	Toluene	100 °C	24	33
4	*t*-BuOK	CH_3CN	reflux	24	-
5	*t*-BuOK	Dioxane	100 °C	4	65
6	NaOMe	Dioxane	100 °C	4	-
7	Et_3N	Dioxane	100 °C	4	-
8	DBU	Dioxane	100 °C	4	-
9	DABCO	Dioxane	100 °C	4	-
10	*t*-BuOK	Dioxane	50 °C	6	75
11[c]	***t*-BuOK**	**Dioxane**	**80 °C**	**3**	**88**

[a]All reactions was performed using **5a** (1.0 mmol, 0.484 g), the base (2 eq) and 5 mL of solvent. [b]Isolated yields after flash chromatography. [c]Optimized reaction conditions.

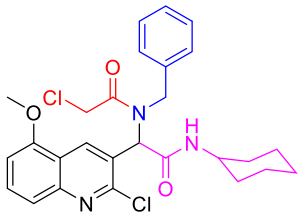
To study the generality of these conditions to produce the spiro-β-lactam-pyrroloquinoline derivatives, a series of Ugi adducts (Table 2) were primarily synthesized by using 2-chloro-3-formyl quinolines **1a-h**, amines **2a-c**, and isocyanides **4a-b**. Subsequently, these pseudo-peptide Ugi adducts **5a-v** were treated with *t*-BuOK under optimum conditions to obtain spiro-β-lactam-pyrroloquinolines **6a-t** (Table 3). The highest product yields were observed for **6a-b**. By comparing the results, it is obvious that the presence of electron-donating groups on quinoline moiety led to the decrease of product yields; the lowest yields were found for quinoline including dimethyl groups **6i** and **6m**, while methoxy including quinolines **5q-r** gave no cyclized products. The presence of electron-withdrawing substituents on the quinoline moiety did not affect the results significantly.

Table 2. Substrate Scope for the Synthesis of Ugi-Adducts 5a-v[a]

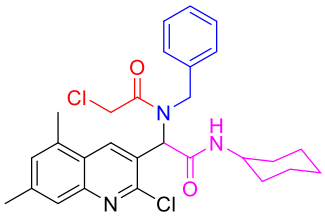




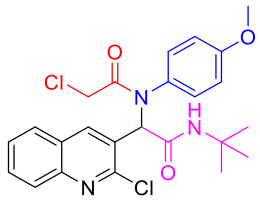
5q 89%



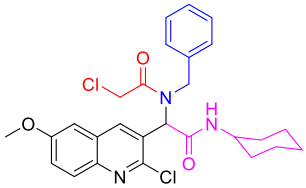
5r, 86%



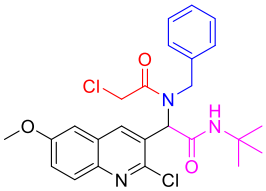
5s, 80%



5t 82%



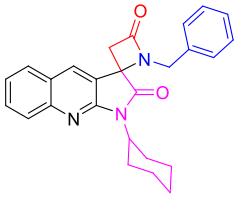
5u, 81%



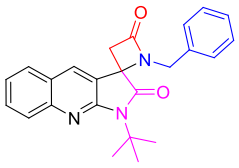
5v, 84%

[a]All reactions were performed using 2-chloro-3-formyl quinoline **1** (1.0 mmol), primary amine **2** (1.0 mmol), chloroacetic acid **3** (1.0 mmol), and isocyanide **4** (1.0 mmol) in 5 mL of methanol at room temperature for 24 h. The precipitate was filtered and used for the next step.

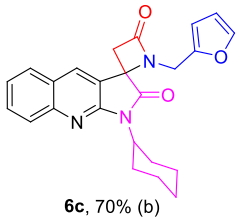
Table 3. Generality and Scope of the Spiro-β-lactam-pyrroloquinoline Skeletons 6a-t[a]



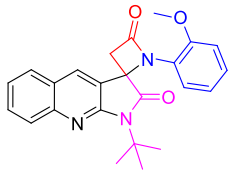
6a, 88% (b)



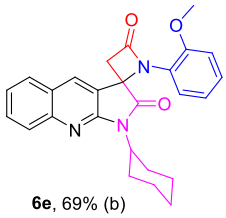
6b, 85 % (b)



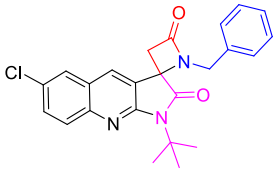
6c, 70% (b)



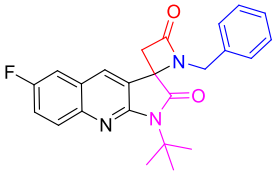
6d, 68% (b)



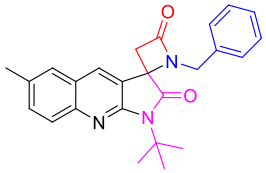
6e, 69% (b)



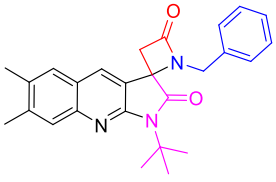
6f, 68% (b)



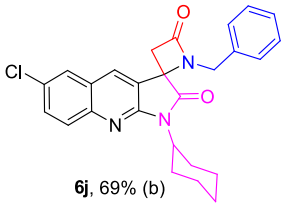
6g, 66% (b)



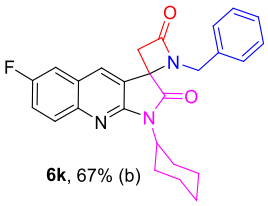
6h, 58% (c)



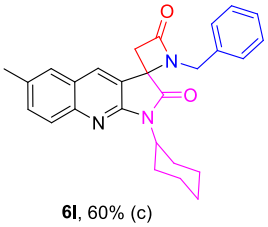
6i, 54% (c)



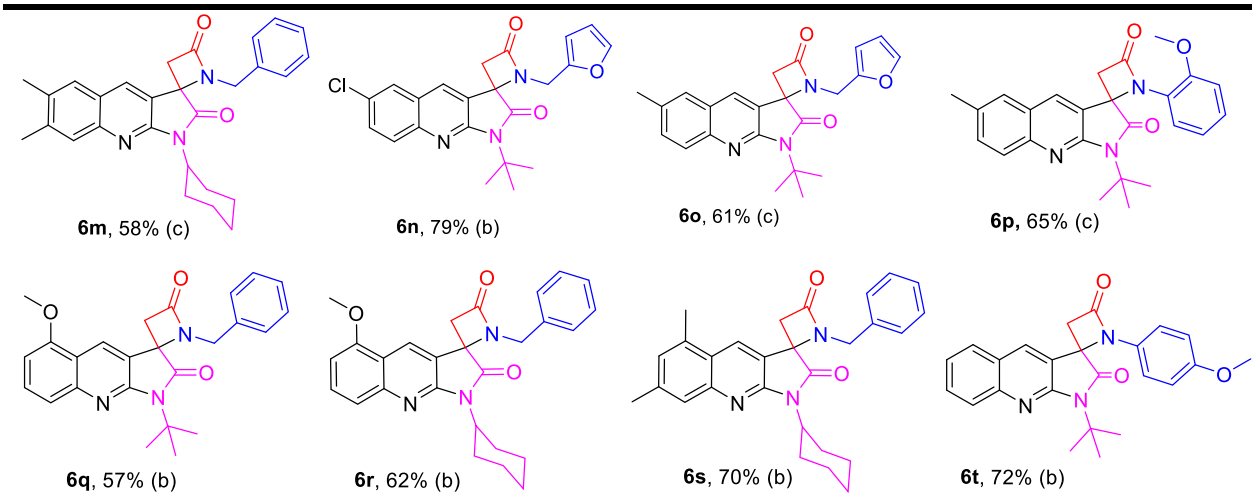
6j, 69% (b)



6k, 67% (b)



6l, 60% (c)

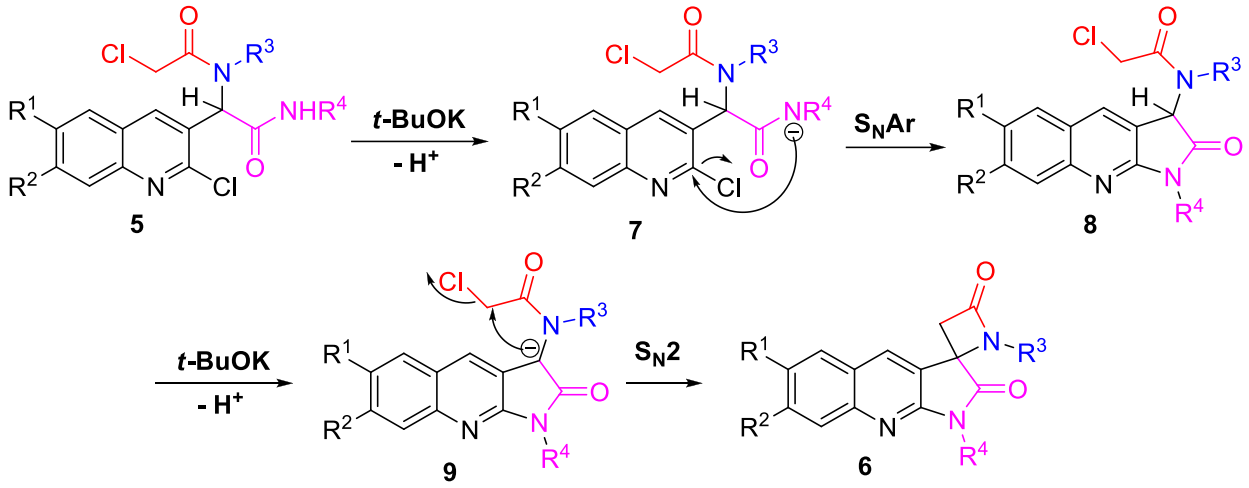


[a] All reactions were performed using Ugi-adducts **5a-v** (1.0 mmol), potassium tert-butoxide (2.0 eq) in dioxane (5 mL) at 80 °C. [b] Reaction was completed in 3 h. [c] Reaction was completed in 6h.

All Ugi adducts and spiro-β-lactam-pyrroloquinolines were characterized by FT-IR, ^{1}H and ^{13}C NMR, DEPT, and HRMS-ESI spectral analysis. In addition, X-ray diffraction analysis of the products **6b** confirmed the formation of pyrrolidinone and β-lactam moieties (see SI, S93-S95).

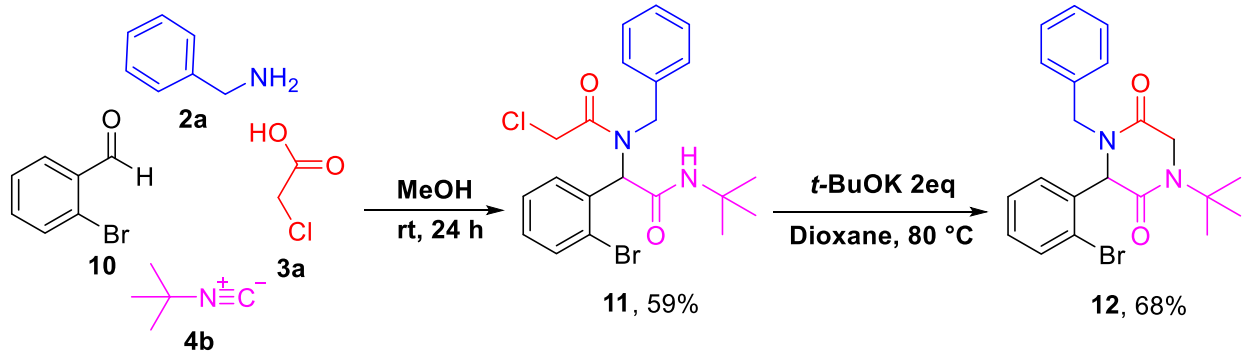
In order to propose a reaction mechanism for the formation of spiro-β-lactam-pyrroloquinolines, a sequential S_NAr/S_N2 mechanism seems to proceeded this reaction (Scheme 2). According to the previously reported mechanisms for the reaction of 2-chloro-3-formyl quinolines, a nucleophilic substitution reaction primarily occurred over quinoline moiety followed by a nucleophilic aromatic substitution which is due to high electrophilicity at C2-position of quinoline. Therefore, the conjugate base of quinoline **5** is produced by treating it with *t*-BuOK. In the structure of **7**, the anion form of amide attacks to the C-Cl through a S_NAr mechanism to constitute a pyrrolidinone ring. The second equivalent of the base reacts with the hydrogen atom of pyrrolidinone moiety in intermediate **8** to give carbanion **9**. Intramolecular S_N2 reaction of the latter leads to the target product **6**. Based on this proposed S_NAr/S_N2 mechanism, it can be concluded that *t*-BuOK plays as the proper base for the deprotection of amide and nucleophilic substitution on quinoline ring because of the existence of chlorine at C2-position. Then, after proton abstraction from –CH, a strong carbanion is formed and acts as a nucleophile, Cl atom of $ClCH_2CO$ is a suitable leaving group, and finally, heating provides the required activation energy for the S_N2 reaction.

Scheme 2. The Proposed Mechanism for the Synthesis of Spiro-β-lactam-pyrroloquinolines



Considering the success of this reaction, to confirm the effect of 2-chloro-3-formyl quinoline in the construction of the products, it was replaced with another β-halogenated carbaldehyde. Thus, 2-bromobenzaldehyde **7** was treated with benzyl amine **2a**, 2-chloroacetic acid **3**, and isocyanide **4b** (Scheme 3). The obtained Ugi adduct **11** was exposed to basic condition at 80 °C producing piperazine-2,5-dione **12** in good yield. Therefore, such replacement gave piperazine-2,5-dione instead of spiro-β-lactam-pyrroloquinolines that shows the tendency of 2-chloro-3-formyl quinoline to proceed the nucleophilic substitution reaction. Consequently, the formation of spiro-β-lactam-pyrroloquinolines owes to the high electrophilicity of 2-position at quinoline moiety because of the presence of nitrogen atom in its structure increasing its electrophilic properties compared to the simple phenyl ring in 2-bromobenzaldehyde **10**.

Scheme 3. Control Experiment for the Synthesis of Piperazine-2,5-dione 12



In conclusion, two-step sequential Ugi-4CR/S_NAr/S_N2 was employed in the synthesis of spiro-β-lactam-pyrroloquinoline scaffolds **6a-t**. The method is simple, safe, metal free and gives high yields of pure products. These products are valuable owing to the presence of β-lactam as antibacterial agent. The fused pyrroloquinoline moiety is also found in the structure of many natural products. This reaction plays a remarkably important role in providing innovative ways for the preparation of new β-lactam antibiotics.

▪ EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were commercially purchased and used as received without further purification. All reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 plates. Column chromatography purification was carried out on silica gel (63-200 mesh ASTM). Melting points (mp) were recorded using an Electrothermal 9100 apparatus and were uncorrected. Fourier transform infrared (FT-IR) spectra were recorded as KBr pellets using an AABFT-IR (FTLA 2000) spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker NMR spectrometer at 600 and 150 MHz or 300 and 75 MHz respectively. All chemical shifts were expressed in parts per million (δ) using TMS as internal standard and $CDCl_3$ or DMSO-*d6* as solvent, and coupling constants (*J*) were expressed in Hertz. High-resolution mass spectrometry (ESI-HRMS) measurements were obtained on an Agilent Q-TOF LC-MS, a Thermo Scientific Advantage and a Thermo Scientific Executive spectrometer. Crystal Growth for XRD porpose: CH_2Cl_2 was used as solvent at room temperature for crystal preparation.

General procedure of the synthesis of Ugi adducts (5a-v). To the stirring solution of aldehyde **1a-h** (1 mmol) in MeOH (5 mL) the primary amine **2a-d** (1 mmol) was added and, the reaction mixture was stirred for 1h at room temperature. Then, chloroacetic acid **3** (1 mmol, 94.5 mg) was added, and stirring was continued for 15 min, followed by the addition of isocyanide **4a-b** (1 mmol). The mixture was stirred at room temperature for 24h. The progress of the reaction was monitored by thin-layer chromatography (TLC) (*n*-hexane/ EtOAc 3:1). After the completion of the reaction, the formed precipitate **5a-v** was filtered, wash with MeOH, and dried in vacuo. Yields (58-92%)

General procedure of the synthesis of spiro-β-lactam-pyrroloquinolines (6a-t). Ugi-adduct **5** (1 mmol) was added to a solution of *t*-BuOK (2 eq) in dioxane (5.0 mL) in a round-bottom flask, and the reaction mixture was stirred at 80 °C in oil bath for 3-6 hr. The progress of the reaction was checked by using TLC. After completion, the reaction mixture was cooled to room temperature, water was addded and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was combined, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The obtained residue was purified by flash column chromatography on silica gel using (*n*-hexane/EtOAc 7:1) as the eluent to afford the spiro-β-lactam-pyrroloquinoline **6a-t**. Yields (54-88%)

General procedure of the synthesis of Ugi adduct 11.

A solution of 2-bromobenzaldehyde **7** (1 mmol) in MeOH (5 mL), was added by benzylamine **2a** (1 mmol), and the reaction mixture was stirred for 1h at room temperature. Then, chloroacetic acid **3** (1mmol, 94.5 mg) and *tert*-butyl isocyanide **4b** (1 mmol) were added and stirring was continued at room temperature for 24 h. The progress of the reaction was monitored by using thin-layer chromatography (TLC) (*n*-hexane/ EtOAc 3:1). After the completion of the reaction, the desired product **11** was precipitated, the colorless precipitate was filtered, washed with MeOH, and dried in vacuo. Yiled (59%)

General procedure of the synthesis of 2,5-diketopiperazine 12.

Ugi-adduct **8** (1 mmol) was added to a solution of *t*-BuOK (2 eq) in dioxane (5 mL), and the reaction mixture was stirred at 80 °C in oil bath for 4 h. The progress of the reaction was monitored by using TLC. After completion, the reaction mixture was cooled to room temperature, water was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was combined, washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. After the evaporation of the solvent, the resulting residue was purified by flash column chromatography on silica gel using (*n*-hexane/EtOAc 7:1) as the eluent to afford the desired product **12** as a colorless powder, 68%.

*N-Benzyl-2-chloro-N-(1-(2-chloroquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)acetamide (**5a**):* Yield 86% (415 mg); Colorless powder; mp: 181-183 °C, ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) 8.54 (s, 1H, H-4-quinoline), 7.92 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.77 (d, *J* = 8.1 Hz, 1H, H-Ar), 7.72 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.55 (t, *J* = 7.1 Hz, 1H, H-Ar), 7.08-7.05 (m, 3H, H-Ar), 7.00-6.99 (m, 2H, H-Ar), 6.32 (s, 1H, C(sp^3)–H), 6.10 (brs, 1H, -NH-amide), 4.79

(d, *J* = 17.4 Hz, 1H, -CH(A)-N), 4.70 (d, *J* = 17.4 Hz, 1H, -CH(B)-N), 4.09 (d, *J* = 12.7 Hz, 1H, -CH(A)-Cl), 4.05 (d, *J* = 12.7 Hz, 1H, -CH(B)-Cl), 3.84-3.73 (m, 1H, -NCH-Cyclohexyl), 1.93-1.83 (m, 2H, H-Cyclohexyl), 1.71–1.61 (m, 2H, H-Cyclohexyl), 1.59-1.53 (m, 1H, H-Cyclohexyl), 1.37-1.27 (m, 2H, H-Cyclohexyl), 1.20-1.03 (m, 3H, H-Cyclohexyl); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 166.9, 150.7, 146.8, 140.6, 135.8, 131.5, 128.7, 128.0, 127.7, 127.6, 126.7, 126.5, 126.0, 59.5, 50.1, 49.0, 41.9, 32.7, 29.7, 25.4, 24.8, 24.7; HRMS (ESI) m/z: Calcd for $C_{26}H_{28}Cl_2N_3O_2$ $[M + H]^+$ 484.1223, Found 484.1212.

N-Benzyl-N-(2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl)-2-chloroacetamide ***(5b)****:* Yield 89% (407 mg); Colorless powder, mp: 224-226 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.51 (s, 1H, H-4-quinoline), 7.90 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.77 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.71 (t, *J* = 7.3 Hz, 1H, H-Ar), 7.54 (t, *J* = 7.1 Hz, 1H, H-Ar), 7.10-7.03 (m, 3H, H-Ar), 6.97 (d, *J* = 6.0 Hz, 2H, H-Ar), 6.29 (s, 1H, $C(sp^3)$−H), 6.02 (s, 1H, -NH-amide), 4.80 (d, *J* = 17.5 Hz, 1H, -CH(A)-N), 4.71 (d, *J* = 17.5 Hz, 1H, -CH(B)-N), 4.10 (d, *J* = 12.8 Hz, 1H, -CH(A)-Cl), 4.05 (d, *J* = 12.8 Hz, 1H, -CH(B)-Cl), 1.33 (s, 9H, *t*-Bu); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 167.2, 150.8, 147.0, 140.3, 135.9, 131.4, 128.7, 128.0, 127.9, 127.6, 126.7, 126.6, 125.9, 59.6, 52.0, 49.9, 42.0, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{26}Cl_2N_3O_2$ $[M + H]^+$ 458.1369, Found 458.1360.

*2-Chloro-N-(1-(2-chloroquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)-N-(furan-2 ylmethyl) acetamide (****5c****):* Yield 58% (274 mg); Colorless powder, mp: 164-166 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.51 (s, 1H, H-4-quinoline), 7.96 (d, *J* = 8.4 Hz, 1H, H-Ar),), 7.82 (d, *J* = 8.1 Hz, 1H, H-Ar), 7.75 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.58 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.17 (s, 1H, H-Ar-furfuryl), 6.23 (s, 1H, $C(sp^3)$−H), 6.01 (s, 1H, H-Ar-furfuryl), 5.95 (d, *J* = 7.3 Hz, 1H, -NH-amide), 5.45 (s, 1H, H-Ar-furfuryl), 4.67 (AB quartet, *J* = 17.3 Hz, 2H, -CH_2-N), 4.45 (d, *J* = 12.8 Hz, 1H, -CH(A)-Cl), 4.34 (d, *J* = 12.8 Hz, 1H, -CH(B)-Cl),), 3.84-3.76 (m, 1H, -NCH-Cyclohexyl), 1.93-1.85 (m, 2H, H-Cyclohexyl), 1.72-1.64 (m, 2H, H-Cyclohexyl), 1.62-1.57 (m, 1H, H-Cyclohexyl), 1.39-1.29 (m, 2H, H-Cyclohexyl), 1.18-1.05 (m, 3H, H-Cyclohexyl); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 167.7, 166.9, 151.0, 149.1, 147.1, 142.7, 140.1, 131.3, 128.2, 128.0, 127.5, 126.7, 126.5, 110.4, 108.2, 59.1, 48.8, 43.0, 41.7, 32.7, 25.4, 24.7; HRMS (ESI) m/z: Calcd for $C_{24}H_{26}Cl_2N_3O_3$ $[M + H]^+$ 474.1341, Found 474.1334.

*N-(tert-Butyl)-2-(2-chloro-N-(2-methoxyphenyl)acetamido)-2-(2-chloroquinolin-3-yl) acetamide (****5d****):* Yield 79% (374 mg); Colorless solid, mp: 227-229 °C; ^{1}H NMR (300 MHz,

$CDCl_3$) (mixture of two rotamers (83:17)): δ(ppm) 8.33 (s, 1H, H-4-quinoline, minor rotamer), 8.05 (s, 1H, H-4-quinoline, major rotamer), 7.89 (d, *J* = 8.7 Hz, 1H, H-Ar, mixture of two rotamers), 7.72-7.59 (m, 2H, H-Ar, mixture of two rotamers), 7.53-7.37 (m, 2H, H-Ar, mixture of two rotamers), 7.15 (*t*, *J* = 7.9 Hz, 1H, H-Ar, mixture of two rotamers), 6.95 (*t*, *J* = 7.6 Hz, 1H, H-Ar, major rotamer), 6.87 (*t*, *J* = 7.6 Hz, 1H, H-Ar, minor rotamer), 6.79 (s, 1H, -NH-amide, mixture of two rotamers), 6.69 (*t*, *J* = 7.5 Hz, 1H, H-Ar, minor rotamer), 6.62 (s, 1H, C(sp3)−H, major rotamer), 6.44 (d, *J* = 8.6 Hz, 1H, , H-Ar, major rotamer), 6.30 (s, 1H, C(sp3)−H, minor rotamer), 3.90-3.77 (m, 2H, -C$\underline{H_2}$-Cl, mixture of two rotamers), 3.34 (s, 3H, -O-CH_3, mixture of two rotamers), 1.41 (s, 9H, *t*-Bu, mixture of two rotamers); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) for major rotamer : δ(ppm) 167.8, 167.3, 155.2, 151.9, 146.7, 141.5, 131.9, 131.0, 130.9, 128.0, 127.7, 126.9, 126.3, 126.0, 125.5,121.1, 111.1, 60.4, 55.0, 51.7, 42.7, 28.7; HRMS (ESI) m/z: Calcd for $C_{24}H_{26}Cl_2N_3O_3$ $[M + H]^+$ 474.1346, Found 474.1349, Calcd for $C_{24}H_{25}Cl_2N_3O_3Na$ $[M+Na]^+$ 496.1165, Found 496.1170.

*2-Chloro-N-(1-(2-chloroquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)-N-(2-methoxy phenyl) acetamide (**5e**):* Yield 76% (380 mg); Colorless solid, mp: 245-247 °C; ^1H NMR (300 MHz, $CDCl_3$) (mixture of two rotamers (83:17)): δ(ppm) 8.30 (s, 1H, H-4-quinoline, minor rotamer), 8.03 (s, 1H, H-4-quinoline, major rotamer), 7.97-7.84 (m, 1H, H-Ar, mixture of two rotamers), 7.74-7.61 (m, 2H, H-Ar, mixture of two rotamers), 7.55-7.33 (m, 2H, H-Ar, mixture of two rotamers), 7.22-7.10 (m, 1H, H-Ar, mixture of two rotamers), 7.04-6.91 (m, 1H, H-Ar, mixture of two rotamers), 6.88-6.64 (m, 2H, H-Ar, $C(sp^3)$−H, mixture of two rotamers), 6.43 (d, *J* = 8.5 Hz, 1H, -NH-amide, mixture of two rotamers), 3.93-3.78 (m, 3H, -C$\underline{H_2}$-Cl, -NC$\underline{H}$-Cyclohexyl, mixture of two rotamers), 3.33 (s, 3H, -O-CH_3, mixture of two rotamers), 2.12-1.99 (m, 1H, -CH-cyclohexyl, mixture of two rotamers), 1.89-1.55 (m, 4H, -CH-cyclohexyl, mixture of two rotamers), 1.44-1.09 (m, 5H, -CH-cyclohexyl, mixture of two rotamers); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) for major rotamer : δ(ppm) 167.8, 167.4, 155.2, 151.9, 146.7, 141.6, 132.0, 131.0, 130.9, 127.9, 127.7, 127.0, 126.2, 125.9, 125.4, 121.0, 111.1, 60.0, 55.0, 49.0, 42.7, 32.9, 32.8, 25.5, 24.8; MS (ESI) m/z: Found for $C_{26}H_{28}Cl_2N_3O_3$ [M+H] 601.4 and $C_{52}H_{54}Cl_4N_6NaO_6$ $[2M + Na]^+$ 1023.5; Anal. Calcd for $C_{26}H_{27}Cl_2N_3O_3$: C, 62.40; H, 5.44; N, 8.40. Found: C, 62.52; H, 5.49; N, 8.51.

*N-Benzyl-N-(2-(tert-butylamino)-1-(2,6-dichloroquinolin-3-yl)-2-oxoethyl)-2-chloro-acetamide (**5f**):* Yield 87% (427 mg); Colorless powder, mp: 206-209 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.44 (s, 1H, H-4-quinoline), 7.81 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.74 (s, 1H, H-Ar),

7.63 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.11-7.04 (m, 3H, H-Ar),), 6.97 (d, *J* = 5.9 Hz, 2H, H-Ar), 6.27 (s, 1H, C(sp^3)−H), 5.99 (s, 1H, -NH-amide), 4.81 (d, *J* = 17.4 Hz, 1H, -CH(A)-N), 4.73 (d, *J* = 17.4 Hz, 1H, -CH(B)-N), 4.09 (AB quartet, *J* = 12.6 Hz, 2H, -CH_2-Cl), 1.32 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 166.9, 151.1, 145.4, 139.1, 135.7, 133.4, 132.2, 129.6, 128.7, 127.8, 127.6, 127.2, 126.6, 125.9, 59.4, 52.2, 49.9, 41.9, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{25}Cl_3N_3O_2$ $[M + H]^+$ 492.0786, Found 492.0777.

*N-Benzyl-N-(2-(tert-butylamino)-1-(2-chloro-6-fluoroquinolin-3-yl)-2-oxoethyl)-2-chloroacetamide (**5g**):* Yield 83% (394 mg); Colorless powder, mp: 215-217 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.48 (s, 1H, H-4-quinoline), 7.91-7.86 (m, 1H, H-Ar), 7.49-7.43 (m, 1H, H-Ar), 7.38 (d, *J* = 7.6 Hz, 1H,H-Ar), 7.12-7.04 (m, 3H, H-Ar), 7.00-6.94 (m, 2H, H-Ar), 6.27 (s, 1H, C(sp^3)−H), 5.99 (s, 1H, -NH-amide), 4.81 (d, 1H, *J* = 17.3 Hz, -CH(A)-N), 4.73 (d, 1H, *J* = 17.3 Hz, -CH(B)-N), 4.09 (AB quartet, 2H, *J* = 12.3 Hz, -CH_2-Cl), 1.32 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 166.9, 161.6 (C-F, $^1J_{C\text{-}F}$ = 249.0 Hz), 160.0 (C-F, $^1J_{C\text{-}F}$ = 249.0 Hz), 150.2, 144.1, 139.4, 135.8, 130.6 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 130.5 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 128.7, 127.6, 127.4, 127.3, 125.9, 121.6, 121.4, 111.2 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 111.1 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 59.4, 52.2, 49.9, 41.9, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{25}Cl_2FN_3O_2$ $[M + H]^+$ 476.1318, Found 476.1327.

*N-Benzyl-N-(2-(tert-butylamino)-1-(2-chloro-6-methylquinolin-3-yl)-2-oxoethyl)-2-chloro-acetamide (**5h**):* Yield 92% (433 mg); Colorless powder, mp: 210-212 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.38 (s, 1H, H-4-quinoline), 7.78 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.56-7.49 (m, 2H, H-Ar), 7.10-7.01 (m, 3H, H-Ar), 6.99-6.93 (m, 2H, H-Ar), 6.26 (s, 1H, C(sp^3)−H), 6.10 (s, 1H, -NH-amide), 4.78 (d, *J* = 17.4 Hz, 1H, -CH(A)-N), 4.69 (d, *J* = 17.4 Hz, 1H, -CH(B)-N), 4.09 (d, *J* = 12.6 Hz, 1H, -CH(A)-Cl), 4.02 (d, *J* = 12.6 Hz, 1H, -CH(B)-Cl), 2.49 (s, 3H, -CH_3), 1.33 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.2, 167.3, 149.9, 145.7, 139.6, 137.7, 136.0, 133.7, 128.7, 127.5, 126.7, 126.5, 125.9, 59.7, 52.1, 49.8, 42.1, 28.5, 21.6; HRMS (ESI) m/z: Calcd for $C_{25}H_{28}Cl_2N_3O_2$ $[M + H]^+$ 472.1303, Found 472.1312.

*N-Benzyl-N-(2-(tert-butylamino)-1-(2-chloro-6,7-dimethylquinolin-3-yl)-2-oxoethyl)-2-chloroacetamide (**5i**):* Yield 90% (436 mg); Colorless powder, 224-226 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.36 (s, 1H, H-4-quinoline), 7.65 (s, 1H, H-Ar), 7.49 (s, 1H, H-Ar), 7.12-7.03 (m, 3H, H-Ar), 7.00-6.95 (m, 2H, H-Ar), 6.25 (s, 1H, C(sp^3)−H), 5.97 (s, 1H, -NH-amide), 4.76 (d, *J* = 17.5 Hz, 1H, -CH(A)-N), 4.68 (d, *J* = 17.5 Hz, 1H, -CH(B)-N), 4.09 (d, *J* = 12.8 Hz, 1H, -

CH(A)-Cl), 4.01 (d, *J* = 12.8 Hz, 1H, -CH(B)-Cl), 2.41 (s, 3H, -CH_3), 2.39 (s, 3H, -CH_3), 1.33 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 168.2, 167.4, 149.8, 146.2, 142.2, 139.2, 137.8, 136.0, 128.7, 127.5, 127.2, 127.1, 125.9, 125.4, 125.3, 59.8, 52.1, 49.8, 42.1, 28.5, 20.6, 20.1; HRMS (ESI) m/z: Calcd for $C_{26}H_{30}Cl_2N_3O_2$ $[M + H]^+$ 486.1763, Found 486.1755.

*N-Benzyl-2-chloro-N-(2-(cyclohexylamino)-1-(2,6-dichloroquinolin-3-yl)-2-oxoethyl) acetamide (**5j**):* Yield 85% (440 mg); Colorless powder, mp: 218-220 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.44 (s, 1H, H-4-quinoline), 7.80 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.74 (s, 1H, H-Ar), 7.62 (d, *J* = 8.6 Hz, 1H, H-Ar), 7.12-7.03 (m, 3H, H-Ar), 7.01-6.95 (m, 2H, H-Ar), 6.31 (s, 1H, $C(sp^3)$−H), 6.12 (d, *J* = 4.6 Hz, 1H, -NH-amide), 4.79 (d, *J* = 17.5 Hz, 1H, -CH(A)-N), 4.71 (d, *J* = 17.5 Hz, 1H, -CH(B)-N), 4.08 (AB quartet, *J* = 12.6 Hz, 2H, -CH_2-Cl), 3.82-3.70 (m, 1H, -NCH-Cyclohexyl), 1.91-1.82 (m, 2H, H-Cyclohexyl), 1.72-1.62 (m, 2H, H-Cyclohexyl), 1.60-1.53 (m, 1H, H-Cyclohexyl), 1.37-1.26 (m, 2H, H-Cyclohexyl), 1.18-1.04 (m, 3H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 166.7, 151.0, 145.4, 139.2, 135.7, 133.4, 132.2, 129.6, 128.7, 127.6, 127.2, 126.6, 126.0, 59.2, 50.1, 49.0, 41.8, 32.7, 32.6, 25.4, 24.7, 24.6; HRMS (ESI) m/z: Calcd for $C_{26}H_{27}Cl_3N_3O_2$ $[M + H]^+$ 518.1169, Found 518.1177.

*N-Benzyl-2-chloro-N-(1-(2-chloro-6-fluoroquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl) acetamide (**5k**):* Yield 80% (400 mg); Colorless powder, mp: 203-205 °C; ^1H-NMR (600 MHz, $CDCl_3$): δ(ppm) 8.49 (s, 1H, H-4-quinoline), 7.93-7.86 (m, 1H, H-Ar), 7.47 (t, *J* = 8.4 Hz, 1H, H-Ar), 7.38 (d, *J* = 8.1 Hz, 1H, H-Ar), 7.14-7.05 (m, 3H, H-Ar),), 7.02-6.95 (m, 2H, H-Ar), 6.31 (s, 1H, $C(sp^3)$−H), 6.02 (brs, 1H, -NH-amide), 4.79 (d, *J* = 16.8 Hz, 1H, -CH(A)-N), 4.72 (d, *J* = 16.8 Hz, 1H, -CH(B)-N), 4.09 (AB quartet, *J* = 14.3 Hz, 2H, -CH_2-Cl), 3.84-3.73 (m, 1H, -NCH-Cyclohexyl), 1.94-1.82 (m, 2H, H-Cyclohexyl), 1.78-1.62 (m, 3H, H-Cyclohexyl), 1.60-1.53 (m 1H, H-Cyclohexyl), 1.40-1.27 (m, 2H, H-Cyclohexyl), 1.20-1.05 (m, 2H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 166.7, 161.7 (C-F, $^1J_{C\text{-}F}$ = 249.0 Hz), 160.0 (C-F, $^1J_{C\text{-}F}$ = 249.0 Hz), 150.2, 144.1, 139.6, 135.7, 130.6 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 130.5 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 128.7, 127.6, 127.4, 127.3, 126.0, 121.6, 121.4, 111.3 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 111.1 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 59.3, 50.2, 48.9, 41.9, 32.7, 29.7, 25.4, 24.7, 24.6; HRMS (ESI) m/z: Calcd for $C_{26}H_{27}Cl_2FN_3O_2$ $[M + H]^+$ 502.1448, Found 502.1441.

*N-Benzyl-2-chloro-N-(1-(2-chloro-6-methylquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl) acetamide (**5l**):* Yield 82% (407 mg); Colorless powder, mp: 189-191 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.38 (s, 1H, H-4-quinoline), 7.77 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.55-7.49 (m, 2H, H-

Ar), 7.11-7.03 (m, 3H, H-Ar), 7.01-6.96 (m, 2H, H-Ar), 6.30 (s, 1H, C(sp^3)−H), 6.22 (d, *J* = 7.7 Hz, 1H, -NH-amide), 4.77 (d, *J* = 17.6 Hz, 1H, -CH(A)-N), 4.68 (d, *J* = 17.6 Hz, 1H, -CH(B)-N), 4.08 (d, *J* = 12.8 Hz, 1H, -CH(A)-Cl), 4.02 (d, *J* = 12.8 Hz, 1H, -CH(B)-Cl), 3.82-3.74 (m, 1H, -NCH-Cyclohexyl), 2.49 (s, 3H, $-CH_3$), 1.93-1.84 (m, 2H, H-Cyclohexyl), 1.72-1.60 (m, 2H, H-Cyclohexyl), 1.59-1.52 (m, 1H, H-Cyclohexyl), 1.36-1.26 (m, 2H, H-Cyclohexyl), 1.18-1.03 (m, 3H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 167.1, 149.8, 145.7, 139.7, 137.7, 135.9, 133.7, 128.7, 127.5, 126.8, 126.4, 126.0, 59.7, 50.1, 48.9, 41.9, 32.6, 25.4, 24.8, 24.7, 21.6; HRMS (ESI) m/z: Calcd for $C_{27}H_{30}Cl_2N_3O_2$ $[M + H]^+$ 498.1535, Found 498.1527.

*N-Benzyl-2-chloro-N-(1-(2-chloro-6,7-dimethylquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl) acetamide (**5m**):* Yield 78% (398 mg); Colorless powder, mp: 209-211 °C; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.35 (s, 1H, H-4-quinoline), 7.64 (s, 1H, H-Ar), 7.48 (s, 1H, H-Ar), 7.13-7.05 (m, 3H, H-Ar), 7.03-6.97 (m, 2H, H-Ar), 6.27 (s, 1H, C(sp^3)−H), 6.01 (d, *J*= 6.3 Hz, 1H, -NH-amide), 4.75 (d, *J* = 17.3 Hz, 1H, -CH(A)-N), 4.67 (d, 1H, *J* = 17.3 Hz, -CH(B)-N), 4.07 (d, *J* = 12.8 Hz, 1H, -CH(A)-Cl), 4.01 (d, *J* = 12.8 Hz, 1H, -CH(B)-Cl), 3.83-3.74 (m, 1H, -NCH-Cyclohexyl), 2.41 (s, 3H, $-CH_3$), 2.39 (s, 3H, $-CH_3$), 1.94-1.83 (m, 2H, H-Cyclohexyl), 1.72-1.61 (m, 2H, H-Cyclohexyl), 1.59-1.52 (m, 1H, H- Cyclohexyl), 1.37-1.26 (m, 2H, H-Cyclohexyl), 1.18-1.01 (m, 3H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.3, 167.2, 149.8, 146.4, 142.1, 139.2, 137.7, 136.0, 128.7, 127.5, 127.4, 127.1, 126.0, 125.3, 125.2, 59.8, 50.0, 48.9, 42.0, 32.7, 25.4, 24.8, 24.7, 20.6, 20.0; HRMS (ESI) m/z: Calcd for $C_{28}H_{32}Cl_2N_3O_2$ $[M + H]^+$ 512.1870, Found 512.1873, Calcd for $C_{28}H_{31}Cl_2KN_3O_2$ $[M + K]^+$ 550.1430, Found 550.1439.

*N-(tert-Butyl)-2-(2-chloro-N-(furan-2-ylmethyl)acetamido)-2-(2,6-dichloroquinolin-3-yl) acetamide (**5n**):* Yield 83% (400 mg); Colorless powder, mp: 217-219 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.43 (s, 1H, H-4-quinoline), 7.88 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.81 (d, *J* = 1.4 Hz, 1H, H-Ar), 7.67 (d, *J* = 8.7 Hz, 1H, H-Ar), 7.17 (s, 1H, H-Ar- furfuryl), 6.14 (s, 1H, C(sp^3)−H), 6.01 (s, 1H, -NH-amide), 5.92 (s, 1H, H-Ar- furfuryl), 5.46 (s, 1H, H-Ar- furfuryl), 4.67 (s, 2H, CH_2-N), 4.44 (d, *J* = 12.9 Hz, 1H, -CH(A)-Cl), 4.33 (d, *J* = 12.9 Hz, 1H, -CH(B)-Cl), 1.35 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 167.6, 166.9, 151.4, 149.0, 145.4, 142.7, 139.0, 133.3, 132.2, 129.7, 127.9, 127.3, 126.7, 110.5, 108.2, 59.2, 52.1, 43.1, 41.7, 28.5; HRMS (ESI) m/z: Calcd for $C_{22}H_{23}{}^{35}Cl_2{}^{37}ClN_3O_3$ $[M + H]^+$ 484.0746, Found 484.0737.

*N-(tert-Butyl)-2-(2-chloro-6-methylquinolin-3-yl)-2-(2-chloro-N-(furan-2-ylmethyl) acetamido) acetamide (**5o**):* Yield 81% (371 mg); Colorless powder, mp: 223-225 °C; ^1H NMR

(600 MHz, $CDCl_3$): δ(ppm) 8.37 (s, 1H, H-4-quinoline), 7.83 (d, *J* = 8.2 Hz, 1H, H-Ar), 7.57 (d, *J* = 8.4 Hz, 2H, H-Ar), 7.14 (s, 1H, H-Ar-furfuryl), 6.17 (s, 1H, H-Ar-furfuryl), 6.00 (s, 1H, C(sp^3)−H), 5.97 (s, 1H, -NH-amide), 5.34 (s, 1H, H-Ar-furfuryl), 4.64 (s, 2H, C$\underline{H_2}$-N), 4.45 (d, *J* = 13.1 Hz, 1H, -C$\underline{H}$(A)-Cl), 4.33 (d, *J* = 13.1 Hz, 1H, -C$\underline{H}$(B)-Cl), 2.52 (s, 3H, -CH_3), 1.35 (s, 9H, *t*-Bu); $^{13}C^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 167.6, 167.4, 150.3, 149.3, 145.7, 142.5, 139.4, 137.7, 133.6, 127.7, 126.8, 126.7, 126.6, 110.4, 107.9, 59.3, 52.0, 42.8, 41.8, 28.6, 21.6; HRMS (ESI) m/z: Calcd for $C_{23}H_{26}Cl_2N_3O_3$ $[M + H]^+$ 462.1173, Found 462.1165.

*N-(tert-Butyl)-2-(2-chloro-6-methylquinolin-3-yl)-2-(2-chloro-N-(2-methoxyphenyl) acetamido) acetamide (**5p**):* Yield 80% (389 mg); Colorless solid, mp: 223-225 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) (mixture of two rotamers (84:16)): δ(ppm) 8.20 (s, 1H, H-4-quinoline, minor rotamer), 7.91 (s, 1H, H-4-quinoline, major rotamer), 7.83-7.72 (m, 1H, H-Ar, mixture of two rotamers), 7.68 (d, *J* = 7.3 Hz, 1H, H-Ar, mixture of two rotamers), 7.51-7.41 (m, 1H, H-Ar, mixture of two rotamers), 7.24 (s, 1H, H-Ar, mixture of two rotamers), 7.14 (*t*, *J* = 8.2 Hz, 1H, H-Ar, mixture of two rotamers), 6.97-6.85 (m, 1H, H-Ar, mixture of two rotamers), 6.82 (s, 1H, C(sp3)−H, minor rotamer), 6.78 (s, 1H, C(sp3)−H, major rotamer), 6.68 (*t*, *J* = 7.7 Hz, 1H, H-Ar, minor rotamer), 6.58 (s, 1H, -NH-amide, major rotamer), 6.43 (d, *J* = 8.2 Hz, 1H, H-Ar, major rotamer), 6.25 (s, 1H, -NH-amide, minor rotamer), 3.90-3.79 (m, 2H, C$\underline{H_2}$-Cl, mixture of two rotamers), 3.33 (s, 3H, -O-CH_3, mixture of two rotamers), 2.46 (s, 3H, -CH_3, minor rotamer), 2.41 (s, 3H, -CH_3, major rotamer), 1.39 (s, 9H, *t*-Bu, mixture of two rotamers); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) for major rotamer : δ(ppm) 167.9, 167.3, 155.2, 151.0, 145.3, 140.8, 136.9, 133.3, 132.0, 130.8, 127.3, 126.7, 126.3, 126.0, 125.4, 121.0,111.1, 60.5, 54.9, 51.7, 42.8, 28.6, 21.5; MS (ESI) m/z: Found for $C_{25}H_{28}{}^{35}Cl_2N_3O_3$ $[M + H]^+$ 488.3 and 999.5 for $C_{50}H_{54}{}^{35}Cl_4N_6O_6$ $[M + Na]^+$; Anal. Calcd for $C_{25}H_{27}Cl_2N_3O_3$: C, 61.48; H, 5.57; N, 8.60. Found: C, 61.59; H, 5.61; N, 8.69.

*N-Benzyl-N-(2-(tert-butylamino)-1-(2-chloro-5-methoxyquinolin-3-yl)-2-oxoethyl)-2-chloroacetamide (**5q**):* Yield 89% (433 mg); Colorless powder, mp: 199-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.33 (s, 1H, H-4-quinoline), 7.58 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.15-7.14 (m, 1H, H-Ar), 7.13-7.09 (m, 1H, H-Ar), 7.06-6.98 (m, 3H, H-Ar), 6.94-6.89 (m, 2H, H-Ar), 6.23 (s, 1H, C(sp^3)−H), 6.14 (brs, 1H, -NH-amide), 4.72 (d, *J* = 17.8 Hz, 1H, -C$\underline{H}$(A)-N), 4.63 (d, *J* = 17.8 Hz, 1H, -C$\underline{H}$(B)-N), 4.05 (d, *J* = 13.0 Hz, 1H, -C$\underline{H}$(A)-Cl), 3.97 (d, *J* = 13.0 Hz, 1H, -C$\underline{H}$(B)-Cl), 3.84 (s, 3H, -O-CH_3), 1.28 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 168.2, 167.6, 162.2, 151.3, 149.1, 139.7, 136.1, 128.9, 128.7, 127.5, 125.9, 123.8, 121.9, 120.7, 106.1, 59.6,

55.7, 52.1, 49.8, 42.1, 28.5; MS (ESI) m/z: Found for $C_{25}H_{27}Cl_2N_3NaO_3$ $[M + Na]^+$ 509.9862; Anal. Calcd for $C_{25}H_{27}Cl_2N_3O_3$: C, 61.48; H, 5.57; N, 8.60. Found: C, 61.54; H, 5.61; N, 8.70.

*N-Benzyl-2-chloro-N-(1-(2-chloro-5-methoxyquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)acetamide (**5r**):* Yield 86% (441 mg); Colorless powder, mp: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.34 (s, 1H, H-4-quinoline), 7.57 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.17-7.14 (m, 1H, H-Ar), 7.13-7.09 (m, 1H, H-Ar), 7.07-7.00 (m, 3H, H-Ar), 6.98-6.92 (m, 2H, H-Ar), 6.24 (s, 1H, C(sp^3)−H), 6.15 (brs, 1H, -NH-amide), 4.71 (d, *J* = 17.6 Hz, 1H, -C<u>H</u>(A)-N), 4.62 (d, *J* = 17.6 Hz, 1H, -C<u>H</u>(B)-N), 4.04 (d, *J* = 12.8 Hz, 1H, -C<u>H</u>(A)-Cl), 3.97 (d, *J* = 12.8 Hz, 1H, -C<u>H</u>(B)-Cl), 3.84 (s, 3H, -O-CH_3), 3.78-3.69 (m, 1H, -NC<u>H</u>-Cyclohexyl), 1.89-1.78 (m, 2H, H-Cyclohexyl), 1.63-1.56 (m, 2H, H-Cyclohexyl), 1.54-1.48 (m, 1H, H-Cyclohexyl), 1.32-1.20 (m, 2H, H-Cyclohexyl), 1.13-1.00 (m, 3H, H-Cyclohexyl); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ(ppm) 168.3, 167.3, 162.3, 151.3, 149.2, 139.9, 136.0, 129.0, 128.7, 127.5, 126.0, 123.6, 121.9, 120.8, 106.2, 59.6, 55.7, 50.0, 48.9, 42.0, 32.7, 25.4, 24.8, 24.7; MS (ESI) m/z: Found for $C_{27}H_{29}Cl_2N_3O_3$ $[M+H]^+$ 513.9998. Anal. Calcd for $C_{27}H_{29}Cl_2N_3O$: C, 63.04; H, 5.68; N, 8.17. Found: C, 63.10; H, 5.71; N, 8.19.

*N-Benzyl-2-chloro-N-(1-(2-chloro-5,7-dimethylquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)acetamide **(5s)**:* Yield 80% (409 mg); Colorless powder, mp: 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.47 (s, 1H, H-4-quinoline), 7.46 (s, 1H, H-Ar), 7.14 (s, 1H, H-Ar), 7.10-7.03 (m, 3H, H-Ar), 7.02-6.96 (m, 2H, H-Ar), 6.21 (s, 1H, C(sp^3)−H), 6.09 (d, *J* = 8.0 Hz, 1H, -NH-amide), 4.71 (d, *J* = 17.7 Hz, 1H, -C<u>H</u>(A)-N), 4.63(d, *J* = 17.7 Hz, 1H, -C<u>H</u>(B)-N), 4.03 (d, *J* = 12.7 Hz, 1H, -C<u>H</u>(A)-Cl), 3.96 (d, *J* = 12.7 Hz, 1H, -C<u>H</u>(B)-Cl), 3.79-3.69 (m, 1H, -NC<u>H</u>-Cyclohexyl), 2.50 (s, 3H, -CH_3), 2.41 (s, 3H, -CH_3), 1.89-1.79 (m, 2H, H-Cyclohexyl), 1.65-1.57 (m, 2H, H-Cyclohexyl), 1.54-1.47 (m, 1H, H-Cyclohexyl), 1.33-1.28 (m, 1H, H-Cyclohexyl), 1.27-1.22 (m, 1H, H-Cyclohexyl), 1.12-0.99 (m, 3H, H-Cyclohexyl); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ(ppm) 168.3, 167.2, 150.4, 148.0, 141.9, 136.6, 136.0, 134.8, 130.4, 128.7, 127.6, 126.1, 125.2, 124.8, 124.3, 60.2, 50.3, 48.9, 42.0, 32.6, 32.5, 25.4, 24.8, 24.7, 22.0, 18.6; MS (ESI) m/z: Found for $C_{28}H_{32}Cl_2N_3O_2$ $[M + H]^+$ 512.0133; Anal. Calcd for $C_{28}H_{31}Cl_2N_3O_2$: C, 65.62; H, 6.10; N, 8.20. Found: C, 65.66; H, 6.12; N, 8.23.

*N-(tert-butyl)-2-(2-chloro-N-(4-methoxyphenyl)acetamido)-2-(2-chloroquinolin-3-yl)acetamide (**5t**):* Yield 82% (388 mg); Colorless powder, mp: 248-251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.03 (s, 1H, H-4-quinoline), 7.87 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.72-7.57 (m, 2H, H-

Ar), 7.54 (d, *J* = 7.9 Hz, 1H, H-Ar), 7.43 (t, *J* = 7.5 Hz, 1H, H-Ar), 6.81-6.58 (m, 2H, H-Ar), 6.51-6.35 (m, 1H, H-Ar), 6.34 (s, 1H, C(sp^3)−H), 6.11 (brs, 1H, -NH-amide), 3.81 (AB quartet, *J* = 13.8 Hz, 2H, -C<u>H</u>$_2$-Cl), 3.56 (s, 3H, -O-CH_3), 1.34 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 167.8, 167.4, 159.6, 150.9, 147.1, 141.1, 131.3, 130.2, 128.1, 128.0, 127.4, 126.6, 126.2, 61.4, 55.3, 52.1, 42.6, 28.6; MS (ESI) m/z: Found for $C_{24}H_{26}Cl_2N_3O_3$ $[M + H]^+$ 474.2142; Anal. Calcd for $C_{24}H_{25}Cl_2N_3O_3$: C, 60.77; H, 5.31; N, 8.86. Found: C, 60.80; H, 5.34; N, 8.87.

*N-benzyl-2-chloro-N-(1-(2-chloro-6-methoxyquinolin-3-yl)-2-(cyclohexylamino)-2-oxoethyl)acetamide (**5u**):* Yield 81% (416 mg); Colorless solid, mp: 198-201 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.43 (s, 1H, H-4-quinoline), 7.81 (d, *J* = 9.1 Hz, 1H, H-Ar), 7.35 (d, *J* = 9.2 Hz, 1H, H-Ar), 7.13-7.06 (m, 3H, H-Ar), 7.03-6.98 (m, 3H, H-Ar), 6.25 (s, 1H, C(sp^3)−H), 6.08 (d, *J*= 8.0 Hz, 1H, -NH-amide), 4.77 (d, *J* = 17.6 Hz, 1H, -C<u>H</u>(A)-N), 4.69 (d, *J* = 17.6 Hz, 1H, -C<u>H</u>(B)-N), 4.09 (d, *J* = 13.2 Hz, 1H, -C<u>H</u>(A)-Cl), 4.04 (d, *J* = 13.2 Hz, 1H, -C<u>H</u>(B)-Cl), 3.89 (s, 3H, -O-CH_3), 3.82-3.75 (m, 1H, -NC<u>H</u>-Cyclohexyl), 1.93-1.83 (m, 2H, H-Cyclohexyl), 1.72-1.62 (m, 2H, H-Cyclohexyl), 1.60-1.54 (m, 1H, H- Cyclohexyl), 1.37-1.27 (m, 2H, H-Cyclohexyl), 1.18-1.04 (m, 3H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.2, 166.9, 158.5, 148.0, 143.0, 139.2, 135.8, 129.2, 128.7, 127.9, 127.6, 126.6, 126.1, 124.2, 105.4, 59.7, 55.7, 50.2, 48.9, 41.9, 32.7, 29.7, 25.4, 24.8, 24.7; HRMS (ESI) m/z: Calcd for $C_{27}H_{30}Cl_2N_3O_3$ $[M + H]^+$ 514.1492, Found 514.1483.

*N-benzyl-N-(2-(tert-butylamino)-1-(2-chloro-6-methoxyquinolin-3-yl)-2-oxoethyl)-2-chloroacetamide (**5v**):* Yield 84% (409 mg); Colorless solid, mp: 217-219 °C; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.43 (s, 1H, H-4-quinoline), 7.80 (d, *J* = 9.2 Hz, 1H, H-Ar), 7.34 (d, *J* = 9.2 Hz, 1H, H-Ar), 7.11-7.05 (m, 3H, H-Ar), 7.01-6.97 (m, 3H, H-Ar), 6.23 (s, 1H, C(sp^3)−H), 6.04 (s, 1H, -NH-amide), 4.78 (d, *J* = 17.7 Hz, 1H, -C<u>H</u>(A)-N), 4.70 (d, *J* = 17.7 Hz, 1H, -C<u>H</u>(B)-N), 4.10 (d, *J* = 13.0 Hz, 1H, -C<u>H</u>(A)-Cl), 4.04 (d, *J* = 13.0 Hz, 1H, -C<u>H</u>(B)-Cl), 3.89 (s, 3H, -O-CH_3), 1.33 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 168.2, 167.2, 158.5, 148.0, 142.9, 139.1, 135.9, 129.2, 128.7, 127.9, 127.6, 126.7, 126.0, 124.2, 105.3, 59.7, 55.7, 52.1, 49.9, 42.0, 29.7, 28.5; HRMS (ESI) m/z: Calcd for $C_{25}H_{28}Cl_2N_3O_3$ $[M + H]^+$ 488.1344, Found 488.1352.

*1-Benzyl-1'-cyclohexylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6a**):* Yield 88% (362 mg); Colorless powder, mp: 179-181 °C; IR (KBr, cm^{-1}) ν_{max} = 1769 (C=O), 1720 (C=O), 1640 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.91 (s, 1H, H-4-quinoline), 7.68-7.62 (m, 2H, H-Ar), 7.59 (d, *J* = 7.0 Hz, 1H, H-Ar), 7.42-7.36 (m, 1H, H-Ar), 7.00 (t, *J* = 7.1 Hz,

2H, H-Ar), 6.97-6.92 (m, 3H, H-Ar), 4.38 (d, *J* = 11.4 Hz, 1H, -CO-CH(A)), 4.33 (d, *J* = 14.6 Hz, 1H, -CH(A)-N), 4.25 (d, *J* = 14.6 Hz, 1H, -CH(B)-N), 3.47 (d, *J* = 11.4 Hz, 1H, -CO-CH(B)), 3.20-3.13 (m, 1H, -NCH-Cyclohexyl), 2.42-2.34 (m, 1H, H-Cyclohexyl), 2.32-2.24 (m, 1H, H-Cyclohexyl), 1.88-1.80 (m, 2H, H-Cyclohexyl), 1.73-1.67 (m, 1H, H-Cyclohexyl), 1.65-1.53 (m, 2H, H-Cyclohexyl), 1.45-1.35 (m, 2H, H-Cyclohexyl), 1.33-1.23 (m, 1H, H-Cyclohexyl); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.2, 165.5, 155.2, 147.1, 133.4, 131.5, 130.5, 129.0, 128.5, 128.1, 128.0, 127.8, 125.1, 120.0, 58.6, 52.7, 49.8, 45.6, 29.7, 28.7, 25.8, 25.1; HRMS (ESI) m/z: Calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.1977, Found 412.1986, Calcd for $C_{52}H_{51}N_6O_4$ $[2M+H]^+$ 823.3789, Found 823.3797.

*1-Benzyl-1'-(tert-butyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6b**):* Yield 85% (327 mg); Colourless crystal, mp: 195-197 °C; IR (KBr, cm^{-1}) ν_{max} = 1776 (C=O), 1720 (C=O), 1633 (C=N) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.85 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.66 (s, 1H, H-4-quinoline), 7.62 (t, *J* = 7.0 Hz, 1H, H-Ar), 7.60 (d, *J* = 7.5 Hz, 1H, H-Ar), 7.39 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.04 (t, *J* = 7.2 Hz, 1H, H-Ar), 7.03 (d, *J* = 7.3 Hz, 1H, H-Ar), 7.01 (d, *J* = 6.9 Hz, 1H, H-Ar), 6.98 (d, *J* = 7.2 Hz, 2H, H-Ar), 4.37 (d, *J* = 14.7 Hz, 1H, -CH(A)-N), 4.20 (d, *J* = 14.7 Hz, 1H, -CH(B)-N), 3.44 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.13 (d, *J* = 14.3 Hz, 1H, -CO-CH(B)), 1.70 (s, 9H, *t*-Bu); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 174.0, 165.7, 156.9, 147.3, 133.5, 130.5, 130.1, 129.1, 128.5, 128.4, 128.0, 127.8, 125.1, 124.8, 120.0, 59.6, 58.9, 49.8, 45.4, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{24}N_3O_2$ $[M + H]^+$ 386.1869, Found 386.1864, Calcd for $C_{48}H_{47}N_6O_4$ $[2M + H]^+$ 771.3650, Found 771.3641.

For X-ray measurements, single crystals of **6b** was mounted on a MiTeGen loop with grease and examined using a Bruker D8 Venture APEX diffractometer equipped with a Photon 100 CCD area detector at 296 (2) K using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were collected using APEX-II software,[15] integrated using SAINT[16] and corrected for absorption using a multi-scan approach (SADABS).[17] Final cell constants were determined from full leastsquares refinement of all observed reflections. The structure was solved using intrinsic phasing (SHELXT).[18] All non-hydrogen atoms were located in subsequent difference maps and refined anisotropically with SHELXL- 2016/6. Hydrogen atoms were added at calculated positions and refined with a riding model. The structure has been deposited with the CCDC (CSD deposition numbers 1989593).

*1'-Cyclohexyl-1-(furan-2-ylmethyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6c**):* Yield 70% (280 mg); Colorless powder, mp: 128-130 °C; IR (KBr, cm^{-1}) ν_{max} = 1789 (C=O), 1727 (C=O), 1642 (C=N) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.87 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.73 (s, 1H, H-4-quinoline), 7.64 (t, *J* = 8.3 Hz, 1H, H-Ar), 7.62 (d, *J* = 7.8 Hz, 1H, H-Ar), 7.39 (t, *J* = 7.4 Hz, 1H, H-Ar), 6.84 (s, 1H, H-Ar-furfuryl), 5.93 (d, *J* = 2.9 Hz, 1H, H-Ar-furfuryl), 5.84 (s, 1H, H-Ar-furfuryl), 4.47 (d, *J* = 15.4 Hz, 1H, -CH(A)-N), 4.44-4.39 (m, 1H, -NCH-Cyclohexyl), 4.19 (d, 15.4 Hz, 1H, -CH(B)-N), 3.45 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.14 (d, 1H, *J* = 14.3 Hz, -CO-CH(B)), 2.50-2.40 (m, 2H, H-Cyclohexyl), 1.92-1.86 (m, 2H, H-Cyclohexyl), 1.75-1.68 (m, 3H, H-Cyclohexyl), 1.47-1.39 (m, 2H, H-Cyclohexyl), 1.37-1.29 (m, 1H, H-Cyclohexyl); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ(ppm) 173.3, 165.2, 155.4, 147.5, 146.8, 142.6, 130.6, 130.2, 128.1, 128.0, 125.5, 125.0, 120.1, 110.2, 109.9, 58.5, 52.5, 49.5, 37.4, 28.9, 28.7, 25.9, 25.2; HRMS (ESI) m/z: Calcd for $C_{24}H_{24}N_3O_3$ $[M + H]^+$ 402.2220, Found 402.2209 and Calcd for $C_{24}H_{23}N_3NaO_3$ $[M + Na]^+$ 424.1985, Found 424.1977.

*1'-(tert-Butyl)-1-(2-methoxyphenyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6d**):* Yield 68%; Colorless powder; mp: 155-157 °C; IR (KBr, cm^{-1}) ν_{max} = 1773 (C=O), 1732 (C=O), 1651 (C=N) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$): δ(ppm) 8.15 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.90 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.84 (s, 1H, H-4-quinoline), 7.65 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.61 (t, *J* = 7.7 Hz, 1H, H-Ar), 7.38 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.00 (t, *J* = 7.8 Hz, 1H, H-Ar), 6.91 (t, *J* = 7.7 Hz, 1H, H-Ar), 6.66 (d, *J* = 8.2 Hz, 1H, H-Ar), 3.59 (d, *J* = 14.6 Hz, 1H, -CO-CH(A)), 3.27 (d, *J* = 14.6 Hz, 1H, -CO-CH(B)), 3.24 (s, 3H, -O-CH_3), 1.89 (s, 9H, *t*-Bu); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ(ppm) 175.2, 164.3, 157.0, 149.0, 147.0, 129.7, 128.6, 128.4, 127.9, 125.9, 125.5, 125.0, 124.9, 123.3, 122.3, 121.30, 112.1, 62.0, 59.5, 55.3, 51.2, 28.9; HRMS (ESI) m/z: Calcd for $C_{24}H_{24}N_3O_3$ $[M + H]^+$ 402.1748, Found 402.1757; Calcd for $C_{48}H_{46}N_6NaO_6$ $[2M+Na]^+$ 825.3275, Found 825.3266.

*1'-Cyclohexyl-1-(2-methoxyphenyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6e**):* Yield 69% (294 mg); Colorless powder, mp: 163-166 °C; IR (KBr, cm^{-1}) ν_{max} = 1774 (C=O), 1732 (C=O), 1646 (C=N) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.12 (d, *J* = 7.9 Hz, 1H, H-Ar), 7.99 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.89 (s, 1H, H-4-quinoline), 7.67 (d, *J* = 7.9 Hz, 1H, H-Ar), 7.64 (t, *J* = 7.7 Hz, 1H, H-Ar), 7.40 (t, *J* = 7.5 Hz, 1H, H-Ar), 7.00 (t, *J* = 7.7 Hz, 1H, H-Ar), 6.91 (t, *J* = 7.7 Hz, 1H, H-Ar), 6.66 (d, *J* = 8.1 Hz, 1H, H-Ar), 4.61-4.54 (m, 1H, -NCH-Cyclohexyl), 3.62 (d, *J* = 14.7 Hz, 1H, -CO-CH(A)), 3.30 (d, *J* = 14.7 Hz, 1H, -CO-CH(B)), 3.25

(s, 3H, -O-CH_3), 2.58-2.48 (m, 2H, H-Cyclohexyl), 1.94-1.87 (m, 2H, H-Cyclohexyl), 1.84-1.77 (m, 2H, H-Cyclohexyl), 1.75-1.70 (m, 1H, H-Cyclohexyl), 1.52-1.43 (m, 2H, H-Cyclohexyl), 1.40-1.30 (m, 1H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 174.1, 164.1, 155.4, 149.1, 146.7, 130.2, 129.7, 128.1, 127.7, 126.1, 125.4, 125.2, 125.1, 123.1, 122.5, 121.3, 112.0, 61.6, 55.3, 52.7, 51.0, 29.7, 29.0, 26.0, 25.9, 25.2; HRMS (ESI) m/z: Calcd for $C_{26}H_{26}N_3O_3$ $[M + H]^+$ 428.1920, Found 428.1909; Calcd for $C_{26}H_{25}N_3NaO_3$ $[M + Na]^+$ 450.1621, Found 450.1612.

*1-Benzyl-1'-(tert-butyl)-6'-chlorospiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6f**):* Yield 68% (285 mg); Colorless powder, mp: 162-165 °C; IR (KBr, cm^{-1}) ν_{max} = 1777 (C=O), 1728 (C=O), 1639 (C=N) cm^{-1}; ^1H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.77 (d, *J* = 8.6 Hz, 1H, H-Ar), 7.56-7.53 (m, 3H, H-Ar, H-4-quinoline), 7.05-6.98 (m, 3H, H-Ar), 6.97 (d, *J* = 7.3 Hz, 2H, H-Ar), 4.29 (AB quartet, *J* = 14.6 Hz, 2H, -C<u>H</u>$_2$-N), 3.43 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(A)), 3.12 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(B)), 1.69 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.8, 165.4, 157.1, 145.6, 133.3, 130.7, 130.5, 129.9, 129.5, 129.1, 128.5, 128.1, 126.5, 125.4, 121.3, 59.8, 58.7, 49.9, 45.5, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{23}ClN_3O_2$ $[M + H]^+$ 420.1326, Found 420.1335; Calcd for $C_{48}H_{45}Cl_2N_6O_4$ $[2M + H]^+$ 839.2595, Found 839.2603.

*1-Benzyl-1'-(tert-butyl)-6'-fluorospiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6g**):* Yield 66% (265 mg); Colorless powder, mp: 224-227 °C; IR (KBr, cm^{-1}) ν_{max} = 1776 (C=O), 1726 (C=O), 1637 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.82 (dd, *J* = 9.0, 5.4 Hz, 1H, H-Ar), 7.56 (s, 1H, H-4-quinoline), 7.38 (dt, *J* = 8.7, 2.8 Hz, 1H, H-Ar), 7.22 (dd, *J* = 8.6, 2.7 Hz, 1H, H-Ar), 7.03 (t, *J* = 7.1 Hz, 1H, H-Ar), 7.02 (d, *J* = 7.3 Hz, 1H, H-Ar), 7.00 (d, *J* = 6.8 Hz, 1H, H-Ar), 6.97 (d, *J* = 7.5 Hz, 2H, H-Ar), 4.29 (AB quartet, *J* = 14.7 Hz, 2H, -<u>CH</u>$_2$-N), 3.44 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(A)), 3.12 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(B)), 1.70 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.8, 165.5, 160.3 (C-F, $^1J_{C\text{-}F}$ = 244.5 Hz), 158.6 (C-F, $^1J_{C\text{-}F}$ = 244.5 Hz), 156.5, 144.1, 133.4, 130.5 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 130.4 (C-F, $^3J_{C\text{-}F}$ = 9.0 Hz), 129.9, 129.8, 129.1, 128.5, 128.0, 125.3, 125.2, 121.2, 119.6, 119.4, 111.4 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 111.2 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 59.7, 58.8, 49.9, 45.5, 28.5; HRMS (ESI) m/z: Calcd for $C_{24}H_{23}FN_3O_2$ $[M + H]^+$ 404.1640, Found 404.1647; Calcd for $C_{48}H_{45}F_2N_6O_4$ $[2M + H]^+$ 807.3220, Found 807.3229.

*1-Benzyl-1'-(tert-butyl)-6'-methylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6h**):* Yield 58% (231 mg); Colorless powder, mp: 179-182 °C; IR (KBr, cm^{-1}) ν_{max} = 1772 (C=O), 1728 (C=O), 1638 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.75 (d, *J* = 8.5 Hz,

1H, H-Ar), 7.60 (s, 1H, H-4-quinoline), 7.45 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.38 (s, 1H, H-Ar), 7.07-7.01 (m, 3H, H-Ar), 6.96 (d, *J* = 6.9 Hz, 2H, H-Ar), 4.40 (d, *J* = 14.7 Hz, 1H, -CH(A)-N), 4.15 (d, *J* = 14.7 Hz, 1H, -CH(B)-N), 3.43 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.11 (d, *J* = 14.3 Hz, 1H, -CO-CH(B)), 2.48 (s, 3H, $-CH_3$), 1.67 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.9, 165.8, 156.3, 145.7, 134.9, 133.5, 132.1, 130.0, 129.1, 128.5, 128.1, 127.9, 126.9, 124.8, 119.8, 59.5, 58.9, 49.7, 45.3, 28.5, 21.3; HRMS (ESI) m/z: Calcd for $C_{25}H_{26}N_3O_2$ $[M + H]^+$ 400.2035, Found 400.2044; Calcd for $C_{50}H_{51}N_6O_4$ $[2M + H]^+$ 799.4024, Found 799.4034.

*1-Benzyl-1'-(tert-butyl)-6',7'-dimethylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6i**):* Yield 54% (223 mg); Colorless powder, mp: 196-198 °C; IR (KBr, cm^{-1}) ν_{max} = 1774 (C=O), 1732 (C=O), 1634 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.65 (s, 1H, H-4-quinoline), 7.59 (s, 1H, H-Ar), 7.35 (s, 1H, H-Ar), 7.08-7.03 (m, 3H, H-Ar), 6.97 (d, *J* = 7.1 Hz, 2H, H-Ar), 4.41 (d, *J* = 14.7 Hz, 1H, -CH(A)-N), 4.12 (d, *J* = 14.7 Hz, 1H, -CH(B)-N), 3.42 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.11 (d, *J* = 14.3 Hz, 1H, -CO-CH(B)), 2.42 (s, 3H, $-CH_3$), 2.39 (s, 3H, $-CH_3$), 1.66 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 174.0, 165.9, 156.4, 146.1, 140.4, 134.7, 133.5, 129.7, 129.1, 128.5, 128.1, 127.9, 127.3, 123.2, 118.8, 59.4, 59.0, 49.7, 45.3, 28.5, 20.3, 19.8; HRMS (ESI) m/z: Calcd for $C_{26}H_{28}N_3O_2$ $[M + H]^+$ 414.2205, Found 414.2214; Calcd for $C_{52}H_{55}N_6O_4$ $[2M + H]^+$ 827.4236, Found 827.4245.

*1-Benzyl-6'-chloro-1'-cyclohexylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6j**):* Yield 69% (307 mg); Colorless powder, mp: 213-216 °C; IR (KBr, cm^{-1}) ν_{max} = 1779 (C=O), 1735 (C=O), 1642 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.77 (d, *J* = 8.6 Hz, 1H, H-Ar), 7.55 (d, *J* = 7.5 Hz, 1H, H-Ar), 7.54 (brs, 1H, H-Ar), 7.50 (s, 1H, H-4-quinoline), 7.01-6.97 (m, 2H, H-Ar), 6.96-6.93 (m, 3H, H-Ar), 4.38 (d, *J* = 14.6 Hz, 1H, -CH(A)-N), 4.34-4.27 (m, 1H, -NCH-Cyclohexyl), 4.21 (d, *J* = 14.6 Hz, 1H, -CH(B)-N), 3.46 (d, *J* = 14.4 Hz, 1H, -CO-CH(A)), 3.15 (d, *J* = 14.4 Hz, 1H, -CO-CH(B)), 2.39-2.25 (m, 2H, H-Cyclohexyl), 1.89-1.82 (m, 2H, H-Cyclohexyl), 1.73-1.66 (m, 1H, H-Cyclohexyl), 1.62-1.54 (m, 2H, H-Cyclohexyl), 1.42-1.33 (m, 2H, H-Cyclohexyl), 1.31-1.22 (m, 1H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.1, 165.2, 155.5, 145.8, 133.3, 130.8, 130.4, 130.1, 129.5, 129.0, 128.5, 128.1, 126.7, 125.8, 121.2, 58.5, 52.6, 49.7, 45.7, 28.7, 28.6, 25.8, 25.1; HRMS (ESI) m/z: Calcd for $C_{26}H_{25}ClN_3O_2$ $[M + H]^+$ 446.1521, Found 446.1530; Calcd for $C_{52}H_{48}Cl_2N_6NaO_4$ $[2M + Na]^+$ 913.2740, Found 913.2749.

*1-Benzyl-1'-cyclohexyl-6'-fluorospiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6k**):* Yield 67% (287 mg); Colorless powder; mp: 194-196 °C; IR (KBr, cm^{-1}) ν_{max} = 1765 (C=O), 1724 (C=O), 1643 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.83 (dd, *J* = 9.1, 5.2 Hz, 1H, H-Ar), 7.53 (s, 1H, H-4-quinoline), 7.37 (dt, *J* = 8.6, 2.7 Hz, 1H, H-Ar), 7.20 (dd, *J* = 8.6, 2.7 Hz, 1H, H-Ar), 6.99 (t, *J* = 7.4 Hz, 1H, H-Ar), 6.98 (d, *J* = 7.2 Hz, 1H, H-Ar),6.97-6.93 (m, 3H, H-Ar), 4.39 (d, *J* = 14.6 Hz, 1H, -CH(A)-N), 4.34-4.28 (m, 1H, -NCH-Cyclohexyl), 4.19 (d, *J* = 14.6 Hz, 1H, -CH(B)-N), 3.47 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.15 (d, *J* = 14.3 Hz, 1H, -CO-CH(B)), 2.40-2.27 (m, 2H, H-Cyclohexyl), 1.89-1.82 (m, 2H, H-Cyclohexyl), 1.72-1.68 (m, 1H, H-Cyclohexyl), 1.63-1.55 (m, 2H, H-Cyclohexyl), 1.43-1.33 (m, 2H, H-Cyclohexyl), 1.32-1.24 (m, 1H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.0, 165.3, 160.2 (C-F, $^1J_{C\text{-}F}$ = 244.5 Hz), 158.5 (C-F, $^1J_{C\text{-}F}$ = 244.5 Hz), 154.8, 144.2, 133.4, 130.4 (C-F, $^3J_{C\text{-}F}$ = 4.5 Hz), 130.3 (C-F, $^3J_{C\text{-}F}$ = 4.5 Hz), 130.1, 130.0, 129.0, 128.5, 128.0, 125.7, 125.6, 121.1, 119.7, 119.5, 111.7 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 111.5 (C-F, $^2J_{C\text{-}F}$ = 22.5 Hz), 58.6, 52.5, 49.6, 45.7, 28.7, 28.6, 25.9, 25.1; HRMS (ESI) m/z: Calcd for $C_{26}H_{25}FN_3O_2$ $[M+H]^+$ 430.1941, Found 430.1951; Calcd for $C_{52}H_{48}F_2N_6NaO_4$ $[2M + Na]^+$ 881.3635, Found 881.3644; Calcd for $C_{26}H_{26}FN_3O_2$ $[M + 2H]^{2+}$ 215.0613, Found 215.0621.

*1-Benzyl-1'-cyclohexyl-6'-methylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6l**):* Yield 60% (255 mg); Colorless powder; mp: 215-217 °C; IR (KBr, cm^{-1}) ν_{max} = 1778 (C=O), 1733 (C=O), 1638 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.91-7.87 (m, 1H, H-Ar), 7.60 (s, 1H, H-4-quinoline), 7.48 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.37 (s, 1H, H-Ar), 7.02 (t, *J* = 7.2 Hz, 2H, H-Ar), 6.99-6.94 (m, 3H, H-Ar), 4.46-4.37 (m, 1H, -NCH-Cyclohexyl), 4.29 (s, 2H, -CH_2-N), 3.46 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.16 (d, *J* = 14.3 Hz, 1H, -CO-CH(B)), 2.48 (s, 3H, -CH_3), 2.38-2.30 (m, 1H, H-Cyclohexyl), 2.28-2.20 (m, 1H, H-Cyclohexyl), 1.87-1.80 (m, 2H, H-Cyclohexyl), 1.71-1.65 (m, 1H, H-Ar), 1.63-1.52 (m, 2H, H-Cyclohexyl), 1.45-1.36 (m, 2H, H-Cyclohexyl), 1.32-1.24 (m, 1H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.1, 165.5, 154.5, 135.2, 133.3, 133.2, 132.7, 132.6, 131.3, 131.1, 129.0, 128.5, 128.0, 127.2, 127.1, 125.1, 119.9, 58.6, 52.9, 49.6, 45.6, 29.7, 28.7, 28.6, 25.8, 25.1, 21.3; HRMS (ESI) m/z: Calcd for $C_{27}H_{28}N_3O_2$ $[M + H]^+$ 426.2130, Found 426.2138; Calcd for $C_{54}H_{54}N_6NaO_4$ $[2M + Na]^+$ 873.3833, Found 873.3842.

*1-Benzyl-1'-cyclohexyl-6',7'-dimethylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6m**):* Yield 58% (255 mg); Colorless powder; mp: 203-205 °C; IR (KBr, cm^{-1})

ν_{max} = 1772 (C=O), 1717 (C=O), 1639 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.68 (s, 1H, H-4-quinoline), 7.60 (s, 1H, H-Ar), 7.37 (s, 1H, H-Ar), 7.08-7.01 (m, 3H, H-Ar), 6.99 (d, *J* = 7.1 Hz, 2H, H-Ar), 4.34 (d, *J* = 14.7 Hz, 1H, -CH(A)-N), 4.33-4.30 (m, 1H, -NCH-Cyclohexyl), 4.28 (d, *J* = 14.7 Hz, 1H, -CH(B)-N), 3.49 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.18 (d, 1H, *J* = 14.3 Hz, -CO-CH(B)), 2.46 (s, 3H, $-CH_3$), 2.42 (s, 3H, $-CH_3$), 2.39-2.34 (m, 1H, H-Cyclohexyl), 2.33-2.25 (m, 1H, H-Cyclohexyl), 1.90-1.83 (m, 2H, H-Cyclohexyl), 1.74-1.68 (m, 1H, H-Cyclohexyl), 1.63-1.53 (m, 2H, H-Cyclohexyl), 1.45-1.36 (m, 2H, H-Cyclohexyl), 1.34-1.27 (m, 1H, H-Cyclohexyl); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.3, 165.7, 154.8, 146.3, 140.5, 134.5, 133.4, 130.3, 129.0, 128.4, 127.9, 127.8, 127.6, 123.6, 118.7, 58.7, 52.3, 49.5, 45.5, 28.7, 28.6, 25.9, 25.2, 20.3, 19.8; HRMS (ESI) m/z: Calcd for $C_{28}H_{30}N_3O_2$ $[M + H]^+$ 440.2438, Found 440.2430; Calcd for $C_{56}H_{58}N_6NaO_4$ $[2M + Na]^+$ 901.4415, Found 901.4406.

*1'-(tert-Butyl)-6'-chloro-1-(furan-2-ylmethyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6n**):* Yield 79% (323 mg); Colorless powder; mp: 195-198 °C; IR (KBr, cm^{-1}) ν_{max} = 1776 (C=O), 1734 (C=O), 1644 (C=N) cm^{-1};^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.79 (d, *J* = 8.8 Hz, 1H, H-Ar), 7.61 (s, 2H, H-Ar), 7.55 (dd, *J* = 8.8, 1.9 Hz, 1H, H-Ar), 6.86 (s, 1H, H-Ar-furfuryl), 5.95 (d, *J* = 3.1 Hz, 1H, H-Ar-furfuryl), 5.87 (s, 1H, H-Ar-furfuryl), 4.45 (d, *J* = 15.4 Hz, 1H, -CH(A)-N), 4.21 (d, *J* = 15.4 Hz, 1H, -CH(B)-N), 3.41 (d, *J* = 14.3 Hz, 1H, -CO-CH(A)), 3.10 (d, 1H, *J* = 14.3 Hz, -CO-CH(B)), 1.81 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 173.9, 165.1, 157.2, 146.8, 145.6, 142.6, 130.6, 130.5, 129.8, 129.0, 126.5, 125.6, 121.5, 110.3, 109.9, 59.9, 58.7, 49.9, 37.3, 28.6; HRMS (ESI) m/z: Calcd for $C_{22}H_{21}ClN_3O_3$ $[M + H]^+$ 410.1440, Found 410.1432.

*1'-(tert-Butyl)-1-(furan-2-ylmethyl)-6'-methylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6o**):* Yield 61% (237 mg); Colorless powder; mp: 159-161 °C; IR (KBr, cm^{-1}) ν_{max} = 1775 (C=O), 1731 (C=O), 1643 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 7.79 (d, *J* = 8.4 Hz, 1H, H-Ar), 7.65 (s, 1H, H-4-quinoline), 7.45 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.41 (s, 1H, H-Ar), 6.90 (s, 1H, H-Ar-furfuryl), 5.94 (d, *J* = 3.1 Hz, 1H, H-Ar-furfuryl), 5.89 (s, 1H, H-Ar-furfuryl), 4.38 (d, *J* = 15.4 Hz, 1H, -CH(A)-N), 4.26 (d, *J* = 15.4 Hz, 1H, -CH(B)-N), 3.41 (d, *J* = 14.2 Hz, 1H, -CO-CH(A)), 3.09 (d, *J* = 14.2 Hz, 1H, -CO-CH(B)), 2.48 (s, 3H, $-CH_3$), 1.81 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 174.0, 165.4, 156.4, 146.9, 145.4, 142.6, 134.9, 132.1, 129.6, 128.0, 126.9, 124.9, 120.0, 110.3, 109.8, 59.7, 58.8, 49.8, 37.2, 28.7, 21.3; HRMS

(ESI) m/z: Calcd for $C_{23}H_{24}N_3O_3$ $[M + H]^+$ 390.1823, Found 390.1832; Calcd for $C_{23}H_{23}N_3NaO_3$ $[M + Na]^+$ 412.1617, Found 412.1625.

*1'-(tert-Butyl)-1-(2-methoxyphenyl)-6'-methylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6p**):* Yield 65% (278 mg); Colorless powder; mp: 188-191 °C; IR (KBr, cm^{-1}) ν_{max} = 1765 (C=O), 1733 (C=O), 1655 (C=N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ(ppm) 8.14 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.79 (d, *J* = 8.5 Hz, 1H, H-Ar), 7.75 (s, 1H, H-4-quinoline), 7.44 (d, *J* = 8.6 Hz, 1H, H-Ar), 7.41 (s, 1H, H-Ar), 6.99 (t, *J* = 7.7 Hz, 1H, H-Ar),), 6.90 (t, *J* = 7.7 Hz, 1H, H-Ar), 6.65 (d, 1H, *J* = 8.2 Hz, H-Ar), 3.58 (d, *J* = 14.6 Hz, 1H, -CO-C<u>H</u>(A)), 3.25 (d, *J* = 14.4 Hz, 1H, -CO-C<u>H</u>(B)), 3.24 (s, 3H, -O-CH_3), 2.45 (s, 3H, -CH_3), 1.88 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 175.2, 164.4, 156.4, 149.0, 145.3, 134.8, 131.7, 128.2, 128.1, 127.0, 125.9, 125.5, 124.9, 123.2, 122.3, 121.3, 112.1, 62.1, 59.3, 55.3, 51.2, 28.9, 21.3; HRMS (ESI) m/z: Calcd for $C_{25}H_{26}N_3O_3$ $[M + H]^+$ 416.1874, Found 416.1867; Calcd for $C_{25}H_{25}N_3NaO_3$ $[M + Na]^+$ 438.1590, Found 438.1580.

*1-Benzyl-1'-(tert-butyl)-5'-methoxyspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6q**):* Yield 57% (236 mg); Colorless powder; mp: 181-183 °C; IR (KBr, cm^{-1}) ν_{max} = 1770 (C=O), 1727 (C=O), 1622 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.62 (s, 1H, H-4-quinoline), 7.52 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.25 (d, *J* = 2.5 Hz, 1H, H-Ar), 7.13-7.06 (m, 4H, H-Ar),7.02 (dd, *J* = 7.4, 2.1 Hz, 2H, H-Ar), 4.42 (d, *J* = 14.6 Hz, 1H, -C<u>H</u>(A)-N), 4.21 (d, *J* = 14.6 Hz, 1H, -C<u>H</u>(B)-N), 3.98 (s, 3H, -O-CH_3), 3.46 (d, *J* = 14.2 Hz, 1H, -CO-C<u>H</u>(A)), 3.15 (d, *J* = 14.2 Hz, 1H, -CO-C<u>H</u>(B)), 1.73 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 174.2, 165.9, 161.4, 157.5, 149.2, 133.6, 130.2, 129.1, 128.8, 128.5, 127.9, 119.6, 117.2, 117.1, 107.7, 59.5, 59.0, 55.5, 49.6, 45.3, 28.6; MS (ESI) m/z: Found for $C_{25}H_{26}N_3O_3$ $[M + H]^+$ 416.2991; Anal. Calcd for $C_{25}H_{25}N_3O_3$: C, 72.27; H, 6.07; N, 10.11. Found: C, 72.31; H, 6.10; N, 10.14.

*1-Benzyl-1'-cyclohexyl-5'-methoxyspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6r**):* Yield 62% (273 mg); Colorless powder, mp: 165-167 °C; IR (KBr, cm^{-1}) ν_{max} = 1770 (C=O), 1727 (C=O), 1625 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.59 (s, 1H, H-4-quinoline), 7.50 (d, *J* = 8.9 Hz, 1H, H-Ar), 7.27 (d, *J* = 2.4 Hz, 1H, H-Ar), 7.08-7.02 (m, 4H, H-Ar), 7.01-6.98 (m, 2H, H-Ar), 4.39-4.33 (m, 1H, -NC<u>H</u>-Cyclohexyl), 4.32 (AB quartet, *J* = 14.6 Hz, 2H, C<u>H</u>$_2$-N), 3.98 (s, 3H, -O-CH_3), 3.49 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(A)), 3.19 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(B)), 2.45-2.25 (m, 2H, H-Cyclohexyl), 1.92-1.85 (m, 2H, H-Cyclohexyl), 1.76-1.69 (m, 1H, H-Cyclohexyl), 1.66-1.55 (m, 2H, H-Cyclohexyl), 1.48-1.35 (m, 2H, H-Cyclohexyl),

1.34-1.26 (m, 1H, H-Cyclohexyl); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 173.5, 165.6, 161.5, 155.8, 149.4, 133.5, 130.9, 129.1, 129.0, 128.4, 127.9, 119.9, 117.1, 117.0, 107.5 58.8, 55.6, 52.3, 49.4, 45.5, 28.7, 28.6, 25.9, 25.2; MS (ESI) m/z: Found for $C_{27}H_{27}N_3NaO_3$ $[M + Na]^+$ 464.0472; Anal. Calcd for $C_{27}H_{27}N_3O_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.49; H, 6.20; N, 9.55.

*1-Benzyl-1'-cyclohexyl-5',7'-dimethylspiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione (**6s**):* Yield 70% (307 mg); Colorless powder, mp: 179-182 °C; IR (KBr, cm^{-1}) ν_{max} = 1764 (C=O), 1714 (C=O), 1634 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.71 (s, 1H, H-4-quinoline), 7.56 (s, 1H, H-Ar), 7.09 (s, 1H, H-Ar), 7.07-7.03 (m, 1H, H-Ar), 7.02-7.01 (m, 1H, H-Ar), 7.00-6.97 (m, 3H, H-Ar), 4.43 (d, *J* = 14.6 Hz, 1H, -C<u>H</u>(A)-N), 4.40-4.33 (m, 1H, -NC<u>H</u>-Cyclohexyl), 4.20 (d, *J* = 14.6 Hz, 1H, -C<u>H</u>(B)-N), 3.52 (d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(A)), 3.21(d, *J* = 14.3 Hz, 1H, -CO-C<u>H</u>(B)), 2.50 (s, 3H, $-CH_3$), 2.49 (s, 3H, $-CH_3$), 2.45-2.31 (m, 2H, H-Cyclohexyl), 1.92-1.86 (m, 2H, H-Cyclohexyl), 1.76-1.69 (m, 1H, H-Cyclohexyl), 1.68-1.59 (m, 2H, H-Cyclohexyl), 1.48-1.26 (m, 3H, H-Cyclohexyl); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 173.5, 165.6, 155.1, 148.0, 140.5, 134.5, 133.8, 128.9, 128.4, 128.0, 127.9, 127.6, 125.7, 122.4, 118.1, 59.0, 53.5, 52.4, 49.7, 45.6, 28.8, 28.7, 25.9, 25.2, 21.7, 18.8; MS (ESI) m/z: Found for $C_{56}H_{58}N_6NaO_4$ $[2M + Na]^+$ 901.1141; Anal. Calcd for $C_{28}H_{29}N_3O_2$: C, 76.51; H, 6.65; N, 9.56. Found: C, 76.54; H, 6.68; N, 9.59.

*1'-(tert-butyl)-1-(4-methoxyphenyl)spiro[azetidine-2,3'-pyrrolo[2,3-b]quinoline]-2',4(1'H)-dione **(6t):*** Yield 72% (289 mg); Colorless powder; mp: 202-204 °C; IR (KBr, cm^{-1}) ν_{max} = 1767 (C=O), 1721 (C=O), 1647 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.03 (s, 1H, H-4-quinoline), 8.00 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.75-7.69 (m, 2H, H-Ar), 7.46 (t, *J* = 7.1 Hz, 1H, H-Ar), 7.01 (d, *J* = 9.0 Hz, 2H, H-Ar), 6.73 (d, *J* = 9.0 Hz, 2H, H-Ar), 3.70 (s, 3H, -O-CH_3), 3.63 (d, *J* = 14.6 Hz, 1H, -CO-C<u>H</u>(A)), 3.34 (d, *J* = 14.6 Hz, 1H, -CO-C<u>H</u>(B)), 1.95 (s, 9H, *t*-Bu); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ(ppm) 174.0, 162.5, 156.9, 156.5, 147.7, 130.9, 130.5, 130.1, 128.6, 128.1, 125.4, 125.0, 120.2, 118.1, 114.5, 60.2, 59.1, 55.4, 49.7, 28.8; MS (ESI) m/z: Found for $C_{24}H_{24}N_3O_3$ $[M + H]^+$ 402.2573; Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.83; H, 5.80; N, 10.50.

N-benzyl-N-(1-(2-bromophenyl)-2-(tert-butylamino)-2-oxoethyl)-2-chloroacetamide (**11**): Yield 59% (266 mg); Colorless powder, mp: 163-164 °C; ^{1}H NMR (600 MHz, DMSO-d_6) (mixture of two rotamers (59:41)): δ(ppm) 8.07 (d, 1H, H-Ar, mixture of two rotamers), 7.46-7.35 (m, 2H, H-Ar, mixture of two rotamers), 7.32-7.27 (m, 1H, H-Ar, mixture of two rotamers), 7.20-7.07 (m,

4H, H-Ar, mixture of two rotamers), 7.05-7.00 (m, 2H, H-Ar, mixture of two rotamers, and -NH-amide, minor rotamer), 6.83 (brs, -NH-amide, major rotamer), 6.22 (s, 1H, C(sp^3)−H, major rotamer), 5.67 (s, 1H, C(sp^3)−H, minor rotamer), 4.88 (d, *J* = 15.8 Hz, 1H, -CH(A)-N, minor rotamer), 4.77 (d, *J* = 18.3 Hz, 1H, -CH(A)-N, major rotamer), 4.66 (d, *J* = 18.3 Hz, 1H, -CH(B)-N, major rotamer), 4.57 (d, *J* = 13.6 Hz, 1H, -CH(B)-N, minor rotamer), 4.38 (d, *J* = 14.5 Hz, 1H, -CH(A)-Cl, mixture of two rotamers), 4.33 (d, *J* = 14.2 Hz, 1H, -CH(B)-Cl, minor rotamer), 4.23 (d, *J* = 14.2 Hz, 1H, -CH(B)-Cl, major rotamer), 1.17 (s, 9H, *t*-Bu, minor rotamer), 1.13 (s, 9H, *t*-Bu, major rotamer); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) for major rotamer : δ(ppm) 167.6, 167.0, 137.4, 136.0, 132.7, 130.0, 129.8, 128.1, 127.3, 127.0, 125.9, 125.6, 62.2, 50.6, 48.6, 42.8, 28.1; HRMS (ESI) m/z: Calcd for $C_{21}H_{25}{}^{81}BrClN_2O_2$ $[M + H]^+$ 453.0762, Found 453.0761, Calcd for $C_{21}H_{25}BrClN_2O_2$ $[M + H]^+$ 451.0782, Found 451.0783, Calcd for $C_{21}H_{25}{}^{81}Br{}^{37}ClN_2O_2$ $[M + H]^+$ 455.0732, Found 455.0732, Calcd for $C_{21}H_{24}NaBrClN_2O_2$ $[M + H]^+$ 473.0602, Found 473.0598, Calcd for $C_{21}H_{24}NaBr{}^{37}ClN_2O_2$ $[M + H]^+$ 475.0572, Found 473.0576, Calcd for $C_{21}H_{24}Na{}^{81}Br{}^{37}ClN_2O_2$ $[M + H]^+$ 477.0552, Found 477.0548.

*(S)-4-benzyl-3-(2-bromophenyl)-1-(tert-butyl)piperazine-2,5-dione (**12**):* Yield 68% (282 mg); Colorless powder, mp: 119-121 °C; ^1H-NMR (600 MHz, $CDCl_3$): δ(ppm) 7.58 (d, *J* = 8.0 Hz, 1H, H-Ar), 7.30-7.25 (m, 4H, H-Ar), 7.20-7.15 (m, 3H, H-Ar), 7.10 (d, *J* = 7.6 Hz, 1H, H-Ar), 5.25 (s, 1H, C(sp^3)-H), 5.24 (d, *J* = 14.1 Hz, 1H, -CO-CH(A)-N), 4.27 (s, 2H, -CH_2-N), 3.41 (d, *J* = 14.7 Hz, 1H, -CO-CH(B)-N), 1.41 (s, 9H, *t*-Bu); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ(ppm) 163.9, 163.8, 136.4, 135.0, 134.1, 130.4, 130.3, 128.8, 128.7, 128.0, 123.6, 63.7, 58.4, 47.4, 46.8, 27.6; HRMS (ESI) m/z: Calcd for $C_{21}H_{24}BrN_2O_2$ $[M + H]^+$ 415.1016, Found 415.1018, Calcd for $C_{21}H_{24}{}^{81}BrN_2O_2$ $[M + H]^+$ 417.0995, Found 417.0998.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

All ^1H, ^{13}C NMR spectra and HRMS for compounds **5a-r, 6a-p, 11 and 12** and IR spectra of compounds **6a-p** as well as X-ray crystallography data for compounds **6b** are given in the supporting information.

The codes CCDC 1989593 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing at

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