Bioorganic & Medicinal Chemistry 17 (2009) 4302–4312

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and biological evaluation of novel 4-azaindolyl-indolyl-maleimides as glycogen synthase kinase-3β (GSK-3β) inhibitors

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ARTICLE INFO

Article history:
Received 20 March 2009
Revised 8 May 2009
Accepted 12 May 2009
Available online 18 May 2009

Keywords:
4-Azaindolyl-indolyl-maleimides
Synthesis
Biological evaluation
GSK-3β inhibitors

ABSTRACT

A series of novel 4-azaindolyl-indolyl-maleimides were synthesized and evaluated for their GSK-3β inhibitory activity. Most compounds exhibited high potency to GSK-3β. Among them, compound **7c** was the most promising GSK-3β inhibitor. Preliminary structure–activity relationships were discussed based on the experimental data obtained and showed that different substituents on the indole ring and side chains at 1-position of indole had varying degrees of influence on the GSK-3β inhibitory potency. In a cell-based functional assay, compounds **7c** and **15a** significantly reduced Aβ-induced Tau hyperphosphorylation by inhibiting GSK-3β.

1. Introduction

Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine protein kinase. It was first identified in the late 1970s as a consequence of its phosphorylation activity toward glycogen synthase, the rate limiting enzyme of glycogen biosynthesis.[1,2] Today, it is known that GSK-3 plays a critical role in various cellular and physiological events.[3–6] From a drug discovery standpoint, inhibition of GSK-3 may provide therapy for several diseases such as cancer,[7] diabetes type-2,[8] chronic inflammatory processes,[9] stroke,[10] bipolar disorders and Alzheimer's disease.[11] Accordingly, searching for GSK-3 inhibitors is a very active area in both academic centers and pharmaceutical companies. Mammalian GSK-3 exists as two isoforms, GSK-3α and GSK-3β, which share high homology at their catalytic domain, but which have shown distinct pharmacology.[12,13] Staurosporine, a microbial alkaloid, was identified as a potent but nonselective GSK-3β inhibitor, based on which various bisindolylmaleimides have also been developed as potent GSK-3β inhibitors (Fig. 1).[14–17] These facts prompted us to design and synthesis a series of novel 4-azaindolyl-indolyl-maleimides to find more potent and selective GSK-3β inhibitors. In this paper, we described the synthesis of the 4-azaindolyl-indolyl-maleimides and the evaluation of these compounds as GSK-3β inhibitors. Their structure–activity relationship between 4-azaindol-1-yl **7a–m** and 4-azaindol-3-yl **15a–d** regio-isomers and in silico molecular modeling study in a homology GSK-3 protein are discussed as well.

2. Results and discussion

2.1. Chemistry

The synthetic routes of 3-(4-azaindol-1-yl)-4-(indol-3-yl)-maleimides **6a**, **7a–m** and **8** were diagrammed in Scheme 1. Indole adducts **2a–e** were readily synthesized from indoles **1a–e** by the method described in the literature with minor modifications.[18,19] Treatment of **2a–e** with benzenesulfonyl chloride ($PhSO_2Cl$) gave intermediates **3a–e**,[20] then condensation of **3a–e** with 4-azaindole in the presence of lithium diisopropylamide (LDA) in THF resulted in desired bisindolylmaleimide analogues **4a–e**,[20] followed by N-debenzenesulfonylation in the presence of tetrabutylammonium fluoride (TBAF) afforded **5a–e**,[20] which were reacted with different alkyl chlorides to yield **6a–m**.[21] The target compounds **7a–m** were obtained by reaction of **6a–m** with ammonium acetate (NH_4OAc).[22] Treatment of **5a** with the same procedure as preparation of **7a** yielded **8**.

On the other hand, reaction of 3-indoleacetamide **12** with **13a–c** yielded **14a–c**. Condensation of **14a–c** with **11**[23] in the presence of *t*-BuOK afforded 3-(4-azaindol-3-yl)-4-(indol-3-yl)-maleimides **15a–c**. Compound **14d** was synthesized following the method described in the literature with minor modifications.[24] Reaction of **14d** with **11** followed by removal of the silyl-protecting group with TBAF afforded compound **15d** (Scheme 2).

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doi:10.1016/j.bmc.2009.05.031

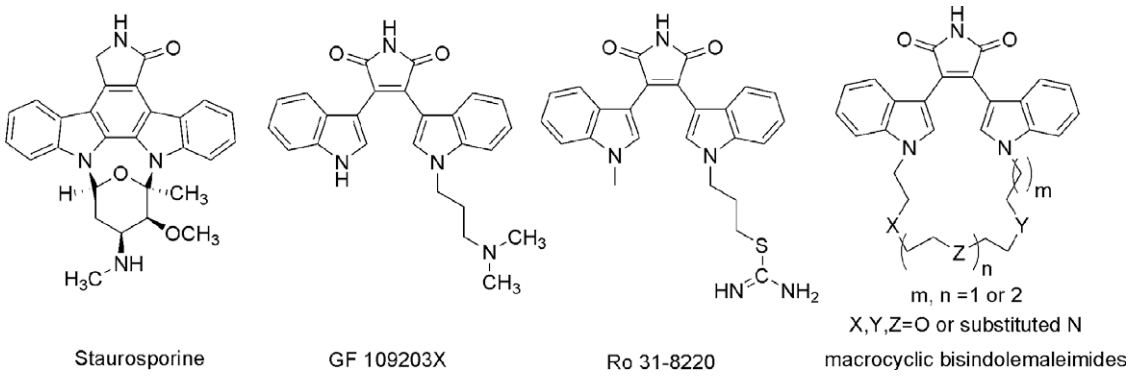
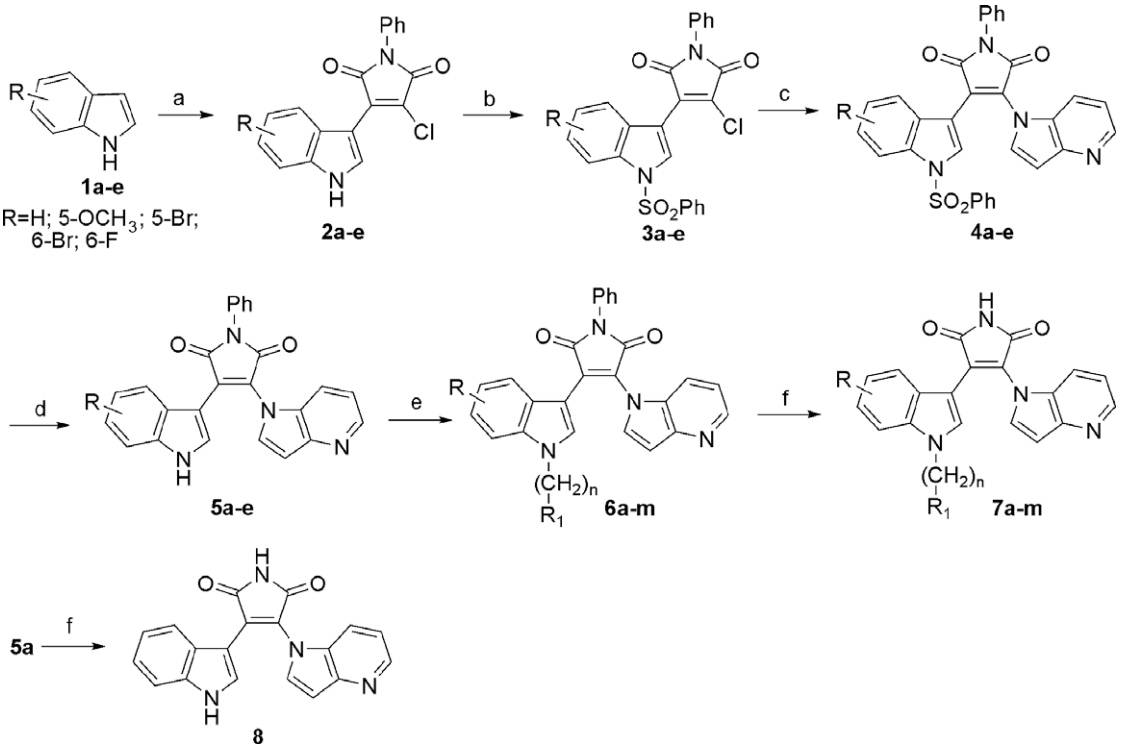


Figure 1. GSK-3β inhibitors.



Scheme 1. Synthetic route to compounds **6a**, **7a**–**m** and **8**. Reagents and conditions: (a) (i) ethyl magnesium bromide, Et_2O, benzene; (ii) *N*-phenyl-3,4-dichloromaleimide, THF, rt; (b) NaH, $PhSO_2Cl$, THF, −30 to −20 °C; (c) 4-azaindole, LDA, THF, −20 °C; (d) TBAF, THF, rt, 2 h; (e) R_1-$(CH_2)_3$-Cl, DMF, NaH, rt, then 75 °C, 6 h; (f) NH_4OAc, 140 °C, 4 h.

2.2. Biological activity and molecular modeling

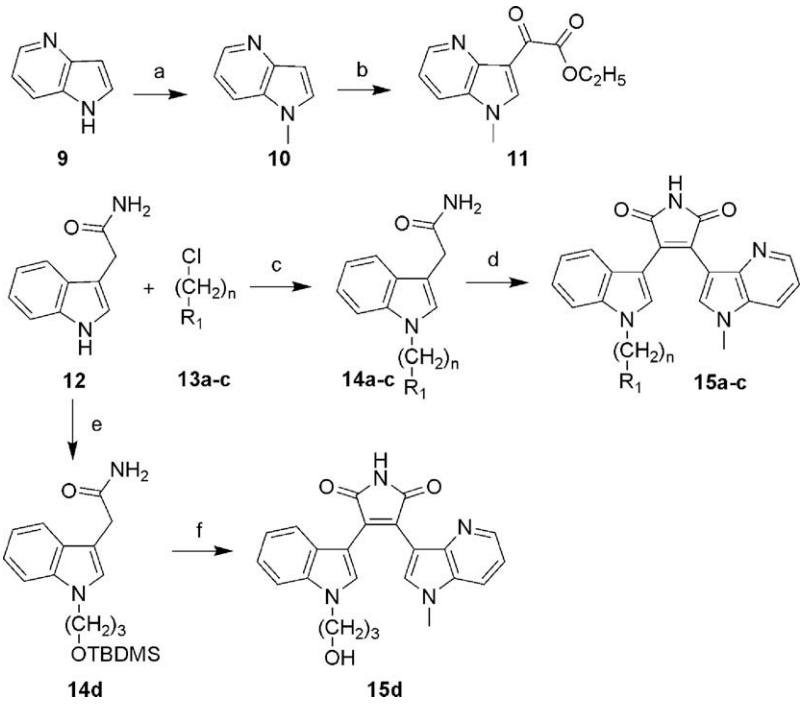
2.2.1. Enzymatic activity

The GSK-3β inhibitory potency of all target compounds was examined. In addition, the assays of inhibitory activity toward PKCE, IKK2, Aurora A, MEK1 and ERK1 were also conducted to determine the selectivity of tested compounds. Staurosporine, a well-known kinase inhibitor, was used as a reference compound in these assays. The results are summarized in Tables 1 and 2.

As shown in Table 1, most of the tested compounds displayed similar or more potent GSK-3β inhibitory activity in comparison with staurosporine. Among them, compound **6a**, with the hydrogen on the nitrogen in maleimide ring being replaced by phenyl, had less inhibitory activity toward GSK-3β. It suggested that a hydrogenbond donor in maleimide ring was essential for the GSK-3β inhibitory activity.

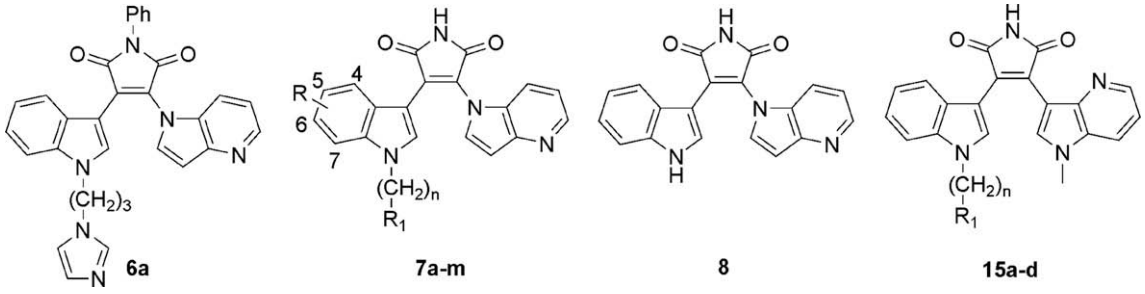
Comparing the inhibitory activity of compound **8** with all other target compounds except **6a**, it appeared that introduction of different hydrophilic side chains at N^1-position of the indole ring resulted in an obvious enhancement of GSK-3β inhibitory activity. Compound **7a**, with a alkyl-imidazole group at N^1-position of the indole ring, exhibited potent GSK-3β inhibitory activity with IC_{50} of 0.55 μM, which was about 56-fold more potent than **8** (IC_{50} = 30.6 μM). In series of 3-(4-azaindol-1-yl)-4-(indol-3-yl)-maleimides, the inhibitory activity of compounds was dependent on the sorts of side chain at N^1-position of the indole ring. Compounds **7a–e**, **7l** and **7m** containing a alkyl-imidazole group at N^1-position of the indole ring, showed more potent inhibitory activity toward GSK-3β than those with a alkyl-dimethylamino group at N^1-position (**7f–i**). Otherwise, the sorts of side chain at N^1-position of the indole ring had a slight influence on the inhibitory activity compared **15a** with **15b** and **15d** in series of 3-(4-azaindol-3-yl)-4-(indol-3-yl)-maleimides.

Comparing the inhibitory activity of **7a** with **7b–e**, it appeared that different substituents on the indole ring could affect the potency. Compound **7b** with bromine at 5-position of the indole ring



Scheme 2. Synthetic route to compounds **15a-d**. Reagents and conditions: (a) NaH, CH_3I, DMF, 0–5 °C; (b) anhydrous $AlCl_3$, ethyl oxalyl monochloride; (c) NaH, DMF, 0–5 °C, then 70 °C, 6 h; (d) **11**, *t*-BuOK, 0–5 °C, 1 h; (e) NaH, DMF, (3-bromopropoxy)(*tert*-butyl) dimethylsilane, rt; (f) (i) **11**, *t*-BuOK, 0–5 °C 1 h; (ii) TBAF, THF, rt, 2 h.

Table 1
GSK-3β inhibitory activity of the target compounds



Compds	R	R_1	*n*	IC_{50} (μM) ± SE[a]
Staurosporine				0.20 ± 0.0[b]
6a				>73.34
7a	H	Imidazol-1-yl	3	0.55 ± 0.01
7b	5-OCH_3	Imidazol-1-yl	3	0.48 ± 0.01
7c	5-Br	Imidazol-1-yl	3	0.14 ± 0.01
7d	6-Br	Imidazol-1-yl	3	0.95 ± 0.20
7e	6-F	Imidazol-1-yl	3	0.31 ± 0.11
7f	H	Dimethylamino	3	13.58 ± 0.23
7g	5-OCH_3	Dimethylamino	3	22.46 ± 2.30
7h	6-Br	Dimethylamino	3	2.26 ± 0.02
7i	6-F	Dimethylamino	3	12.44 ± 1.12
7j	H	Piperidin-1-yl	3	12.45 ± 1.08
7k	H	Morpholino	3	1.79 ± 0.07
7l	H	Imidazol-1-yl	2	0.26 ± 0.01
7m	H	Imidazol-1-yl	4	0.85 ± 0.01
8				30.6 ± 14.95
15a		Morpholino	3	0.76 ± 0.01
15b		Imidazol-1-yl	3	0.66 ± 0.16
15c		Morpholino	2	0.90 ± 0.02
15d		Hydroxy	3	1.14 ± 0.07

[a] SE: standard error mean.
[b] Lit.[25] IC_{50} = 0.056 ± 0.0069 μM.

Table 2
The selectivity to tested kinases of target compounds **7c**, **7l** and **15a**[a]

Kinase assay	$IC_{50} \pm SE$[b] (μM)			
	Staurosporine	**7c**	**7l**	**15a**
GSK-3β	0.20 ± 0.0	0.14 ± 0.01	0.26 ± 0.01	0.76 ± 0.01
PKCE	0.0015 ± 0.0001	>40	>40	>40
IKK2	1.41 ± 0.26	>40	>40	>40
Aurora A	0.018 ± 0.002	>40	>40	>40
MEK1	0.67 ± 0.035	>40	>40	>40
ERK1	1.31 ± 0.035	>40	>40	>40

[a] '>40' means <50% inhibition at 40 μM of compound.
[b] SE: standard error mean.

showed a fourfold activity increase toward GSK-3β as compared to **7a**. Methoxyl at the 5-position or fluorine at 6-position of the indole ring was tolerated, while bromine at 6-position led to some loss of activity.

The results in Table 1 also showed that when the 3-position of 4-azaindole was attached with maleimide ring, the resulting compounds **15a–d** also exhibited potent inhibitory activity toward GSK-3β. This fact indicated the attached position of 4-azaindole with maleimide has little effect on the activity.

As reported in the literature,[17] staurosporine was found to be a potent and nonselective kinase inhibitor. Although staurosporine potently inhibits GSK-3β (IC_{50} = 0.2 μM), it also potently inhibits many kinases (e.g., PKCE, IKK2, Aurora A, MEK1 and ERK1). The data of inhibitory activity toward PKCE, IKK2, Aurora A, MEK1 and ERK1 showed that compounds **7c**, **7l** and **15a** displayed high selectivity for GSK-3β over other tested kinases (see Table 2).

2.2.2. Cellular activity

Among the multiple cellular processes in which GSK-3β has been implicated, the ability to hyperphosphorylate Tau protein and induce neurofibrillary tangle was intensively studied. Therefore, the cell-based assay examining Tau phosphorylation at Ser 396 represents a direct functional assay to measure the cellular activity of GSK-3 inhibitors. Compounds **7b–d**, **7l**, 7**m** and **15a** were tested for the ability to reduce Tau phosphorylation at Ser 396 in human neuroblastoma SH-SY5Y cells. LiCl is a known inhibitor of GSK-3β and reduces Tau phosphorylation at Ser 396 in SH-SY5Y cells,[26] which was used as a reference compound in this assay. As shown in Figure 2, compounds **7c** and **15a** significantly reduced Aβ-induced Tau hyperphosphorylation, showing the inhibition of GSK-3β at the cell level, while compounds **7b**, **7d**, **7l** and **7m** exhibited no significant cellular activity.

2.2.3. Molecular modeling

To probe the possible binding conformation and protein–ligand interaction mode of a GSK-3β inhibitor, a molecular docking study of the optimum compound **7c** was performed using the Tripos FLEXIDOCK program,[27] based on the published GSK-3β crystal structure (1Q3D).[17] Figure 3 illustrates that there are two hydrogen-bond interactions between the maleimide portion of **7c** to Asp-133 and Val-135 backbone carbonyl and amide hydrogen, respectively. Another hydrogen-bond forms between the 3-position nitrogen atom of imidazole of the side chain and the residue of Asp-200. The 4-position nitrogen of azaindole is about 3.55 Å from the carboxyl group of Ile-62 and may not form an additional hydrogen bond interaction with Ile-62 but may keep hydrogen bonding with water around the catalytic site.

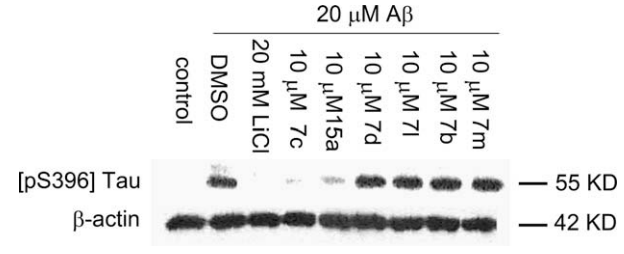


Figure 2. Effects of GSK-3β inhibitors on tau phosphorylation (ser396) in SH-SY5Y. cells.

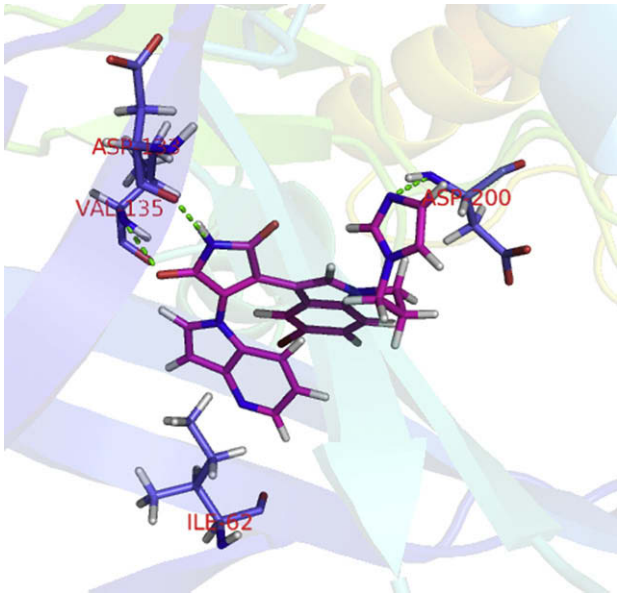


Figure 3. Docking of **7c** to GSK-3β crystal structure.

3. Conclusion

In summary, a series of novel 4-azaindolyl-indolyl-maleimide derivatives were prepared and tested for their biological activity. Most synthesized compounds showed potent GSK-3β inhibitory activities with compound **7c** being the most potent one. Among them, compounds **7c**, **7l** and **15a** exhibited high selectivity against PKCE, IKK2, Aurora A, MEK1 and ERK1. Further cell-based functional assay revealed that **7c** and **15a** could significantly reduce Aβ-induced Tau hyperphosphorylation by inhibiting GSK-3β. Preliminary structure–activity relationships and molecular modeling study provided further insight into interactions between the enzyme and its ligand. The results provided valuable information for the design of GSK-3β inhibitors.

4. Experimental

4.1. Chemistry

All reactions were monitored by thin-layer chromatography (TLC). All reagents were obtained from commercial sources and used without further purification unless stated. Et_2O, THF and benzene were distilled from sodium-benzophenone. DMF was distilled from calcium hydride. Melting points were determined with a BÜCHI Melting Point B-450 apparatus (Büchi Labortechnik, Flawil, Switzerland). The ^1H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on Bruker Avance DMX 400 using TMS as an internal standard (Bruker, Billerica, MA, USA). Chemical shifts are expressed in parts per million δ. ESI-MS were obtained on an Esquire-LC-00075 mass spectrometer (Bruker, USA). Elemental analyses were performed by ERBA-1110 analyzer (Carlo, Italy).

4.1.1. 3-Chloro-4-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (2a)

Ethyl magnesium bromide (4.98 g, 37.5 mmol) in Et_2O (15 mL) was added dropwise to a solution of **1a** (4.57 g, 39 mmol) in benzene (5 mL) at room temperature over 30 min. After stirring for 30 min, the mixture was added dropwise to a solution of *N*-phenyl-3,4-dichloromaleimide (6.05 g, 25 mmol) in THF (10 mL) over 2 h. The resulting mixture was stirred for 4 h at room temperature. After that, it was adjusted to weak acidity with 1 M aqueous hydrochloric acid and extracted with ethyl acetate (3 × 100 mL). The organic phase was combined and washed with brine (3 × 300 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from ethyl acetate to get 5.84 g (72.4%) of **2a** as a red solid, mp: 203–204 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.19–7.26 (m, 2H), 7.45–7.54 (m, 6H), 7.97 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 12.18 (br s, 1H).

4.1.2. 3-Chloro-4-(5-methoxy-1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (2b)

According to the procedure used to prepare **2a**, reaction of **1b** with *N*-phenyl-3,4-dichloromaleimide provided **2b** in 72.6% yield as an orange solid, mp: 185–187 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 3.78 (s, 3H), 6.90 (dd, J = 2.0, 8.4 Hz, 1H), 7.43–7.47 (m, 5H), 7.51–7.55 (m, 2H), 8.08 (d, J = 3.2 Hz, 1H), 12.10 (br s, 1H).

4.1.3. 3-(5-Bromo-1*H*-indol-3-yl)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (2c)

According to the procedure used to prepare **2a**, reaction of **1c** with *N*-phenyl-3,4-dichloromaleimide provided **2c** in 63.4% yield as a red solid, mp: 212–214 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.37 (dd, J = 2.4, 7.6 Hz, 1H), 7.44–7.47 (m, 3H), 7.51–7.53 (m, 3H), 8.15 (s, 1H), 8.20 (d, J = 3.2 Hz, 1H), 12.36 (br s, 1H).

4.1.4. 3-(6-Bromo-1*H*-indol-3-yl)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (2d)

According to the procedure used to prepare **2a**, reaction of **1d** with *N*-phenyl-3,4-dichloromaleimide provided **2d** in 70.1% yield as a red solid, mp: 205–207 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.33 (dd, J = 1.6, 8.0 Hz, 1H), 7.45–7.48 (m, 3H), 7.50–7.53 (m, 2H), 7.73 (d, J = 1.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 3.2 Hz, 1H), 12.27 (br s, 1H).

4.1.5. 3-Chloro-4-(6-fluoro-1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (2e)

According to the procedure used to prepare **2a**, reaction of **1e** with *N*-phenyl-3,4-dichloromaleimide provided **2e** in 66.4% yield as a red solid, mp: 205–208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.06 (t, J = 9.6 Hz, 1H), 7.33 (d, J = 9.6 Hz, 1H), 7.42–7.45 (m, 3H), 7.51–7.54 (m, 2H), 7.94–7.97 (m, 1H), 8.14 (d, J = 2.8 Hz, 1H), 12.22 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 341. Anal. Calcd for $C_{18}H_{10}ClFN_2O_2$: C, 63.45; H, 2.96; N, 8.22. Found: C, 63.68; H, 3.03; N, 8.03.

4.1.6. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (3a)

60% NaH (0.48 g, 12 mmol) was added portion-wise to a solution of **2a** (3.22 g, 10 mmol) in THF (15 mL) at −5 to 0 °C and stirred for additional 30 min. Then, benzenesulfonyl chloride (2.65 g, 15 mmol) in THF (5 mL) was added dropwise to the above mixture at −30 to −20 °C. The resulting mixture was stirred at −30 to −20 °C for 1 h. After that it was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 300 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (6:1, v/v) as eluent to afford 2.52 g (54.4%) of **3a** as a yellow crystalline powder, mp: 176–178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.34 (t, J = 8.0 Hz, 1H), 7.41–7.43 (m, 4H), 7.49–7.53 (m, 4H), 7.60 (t, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H). ESI-MS: m/z $[M+H]^+$ 463. Anal. Calcd for $C_{24}H_{15}ClN_2O_4S$: C, 62.27; H, 3.27; N, 6.05. Found: C, 62.41; H, 3.43; N, 6.15.

4.1.7. 3-Chloro-4-(5-methoxy-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (3b)

According to the procedure used to prepare **3a**, reaction of **2b** with benzenesulfonyl chloride provided **3b** in 49.7% yield as a yellow solid, mp: 166–168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.83 (s, 3H), 7.06 (dd, J = 1.6, 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.41–7.43 (m, 3H), 7.47–7.49 (m, 4H), 7.59 (t, J = 8.0 Hz, 1H), 7.93–7.95 (m, 3H), 8.26 (s, 1H). ESI-MS: m/z $[M+H]^+$ 493. Anal. Calcd for $C_{25}H_{17}ClN_2O_5S$: C, 60.91; H, 3.48; N, 5.68. Found: C, 60.80; H, 3.33; N, 5.79.

4.1.8. 3-(5-Bromo-1-benzenesulfonyl-1*H*-indol-3-yl)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (3c)

According to the procedure used to prepare **3a**, reaction of **2c** with benzenesulfonyl chloride provided **3c** in 43.5% yield as a yellow solid, mp: 136–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.42–7.46 (m, 3H), 7.51–7.55 (m, 5H), 7.62 (t, J = 7.6 Hz, 1H), 7.94–7.98 (m, 3H), 7.07 (d, J = 1.6 Hz, 1H), 8.32 (s, 1H). ESI-MS: m/z $[M+H]^+$ 541. Anal. Calcd for $C_{24}H_{14}BrClN_2O_4S$: C, 53.20; H, 2.60; N, 5.17. Found: C, 53.35; H, 2.43; N, 5.49.

4.1.9. 3-(6-Bromo-1-benzenesulfonyl-1*H*-indol-3-yl)-4-chloro-1-phenyl-1*H*-pyrrole-2,5-dione (3d)

According to the procedure used to prepare **3a**, reaction of **2d** with benzenesulfonyl chloride provided **3d** in 44.1% yield as a yellow solid, mp: 218–220 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.41–7.55 (m, 8H), 7.65 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 2H), 8.26 (d, J = 1.2 Hz, 1H), 8.29 (s, 1H). ESI-MS: m/z $[M+H]^+$ 541. Anal. Calcd for $C_{24}H_{14}BrClN_2O_4S$: C, 53.20; H, 2.60; N, 5.17. Found: C, 53.05; H, 2.71; N, 5.06.

4.1.10. 3-Chloro-4-(6-fluoro-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (3e)

According to the procedure used to prepare **3a**, reaction of **2e** with benzenesulfonyl chloride provided **3e** in 40.5% yield as a yellow solid, mp: 202–204 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.11 (td, J = 8.4 Hz, 1.2 Hz, 1H), 7.42–7.45 (m, 3H), 7.53–7.55 (m, 4H), 7.65 (t, J = 8.0 Hz, 1H), 7.79 (dd, J = 2.0, 7.6 Hz, 1H), 7.88–7.90 (m, 1H), 7.98–8.00 (m, 2H), 8.31 (s, 1H). ESI-MS: m/z $[M+H]^+$ 481. Anal. Calcd for $C_{24}H_{14}ClFN_2O_4S$: C, 59.94; H, 2.93; N, 5.83. Found: C, 59.75; H, 2.83; N, 5.99.

4.1.11. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4a)

A solution of 4-azaindole (0.71 g, 6 mmol) in THF (20 mL) was added to a solution of LDA (6 mmol) in THF (3 mL) at −10 °C under N_2 and stirred for 30 min at this temperature. The mixture was cooled to −20 °C and a solution of **3a** (2.31 g, 5 mmol) in THF (15 mL) was added dropwise. After addition, it was stirred at −20 °C for 1 h, and then poured into water (300 mL), extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (50:1, v/v) as eluent to afford 1.21 g (44.5%) of **4a** as an orange solid, mp: 130–132 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.15 (d, J = 8.0 Hz, 1H), 6.58–6.60 (m, 1H), 6.73 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.49–7.52 (m, 7H), 7.62 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 4.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H),

7.96 (d, J = 8.0 Hz, 2H), 8.32 (d, J = 4.4 Hz, 1H), 8.37 (s, 1H). ESI-MS: m/z $[M+H]^+$ 545. Anal. Calcd for $C_{31}H_{20}N_4O_4S$: C, 68.37; H, 3.70; N, 10.29. Found: C, 68.55; H, 3.81; N, 10.09.

4.1.12. 3-(5-Methoxy-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4b)

According to the procedure used to prepare **4a**, reaction of **3b** with 4-azaindole provided **4b** in 40.7% yield as a red solid, mp: 176–178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.12 (s, 3H), 5.56 (d, J = 2.4 Hz, 1H), 6.65–6.68 (m, 1H), 6.75 (dd, J = 1.6, 8.4 Hz, 1H), 6.97 (d, J = 3.2 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.46–7.53 (m, 7H), 7.61 (t, J = 7.6 Hz, 1H), 7.79–7.81 (m, 2H), 7.95 (d, J = 8.0 Hz, 2H), 8.37–8.39 (m, 2H). ESI-MS: m/z $[M+H]^+$ 575. Anal. Calcd for $C_{32}H_{22}N_4O_5S$: C, 66.89; H, 3.86; N, 9.75. Found: C, 66.65; H, 3.94; N, 10.01.

4.1.13. 3-(5-Bromo-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4c)

According to the procedure used to prepare **4a**, reaction of **3c** with 4-azaindole provided **4c** in 42.8% yield as a red solid, mp: 136–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.23 (d, J = 2.4 Hz, 1H), 6.58–6.60 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.24 (dd, J = 1.6, 8.0 Hz, 1H), 7.51–7.55 (m, 7H), 7.66 (t, J = 7.6 Hz, 1H), 7.80–7.83 (m, 2H), 7.92 (d, J = 7.6 Hz, 2H), 8.32 (s, 1H), 8.37 (dd, J = 1.2, 4.8 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 623. Anal. Calcd for $C_{31}H_{19}BrN_4O_4S$: C, 59.72; H, 3.07; N, 8.99. Found: C, 59.61; H, 3.16; N, 9.11.

4.1.14. 3-(6-Bromo-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4d)

According to the procedure used to prepare **4a**, reaction of **3d** with 4-azaindole provided **4d** in 34.8% yield as a red solid, mp: 160–163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.03 (d, J = 8.4 Hz, 1H), 6.64–6.66 (m, 1H), 6.89 (dd, J = 2.0, 8.4 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.44–7.50 (m, 3H), 7.54–7.58 (m, 4H), 7.67 (t, J = 8.0 Hz, 1H), 7.77 (d, J = 3.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 8.12 (d, J = 2.0 Hz, 1H), 8.32 (s, 1H); 8.38 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 623. Anal. Calcd for $C_{31}H_{19}BrN_4O_4S$: C, 59.72; H, 3.07; N, 8.99. Found: C, 59.94; H, 3.13; N, 9.21.

4.1.15. 3-(6-Fluoro-1-benzenesulfonyl-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (4e)

According to the procedure used to prepare **4a**, reaction of **3e** with 4-azaindole provided **4e** in 44.2% yield as a red solid, mp: 104–107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.10–6.12 (m, 1H), 6.52 (td, J = 2.0, 8.8 Hz, 1H), 6.61–6.63 (m, 1H), 7.01 (d, J = 3.2 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.54–7.58 (m, 7H), 7.66–7.68 (m, 2H), 7.79 (d, J = 3.2 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 8.34 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 563. Anal. Calcd for $C_{31}H_{19}FN_4O_4S$: C, 66.18; H, 3.40; N, 9.96. Found: C, 66.42; H, 3.33; N, 9.69.

4.1.16. 3-(1*H*-Indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (5a)

A mixture of TBAF (1.57 g, 6 mmol) and **4a** (1.09 g, 2 mmol) in THF (20 mL) was stirred at room temperature for 2 h. The reaction mixture was then poured into water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phase was washed with brine (3 × 300 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford 0.66 g (81.3%) of **5a** as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 6.06 (d, J = 8.0 Hz, 1H), 6.53 (t, J = 8.0 Hz, 1H), 6.90–6.92 (m, 2H), 6.97 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.46–7.49 (m, 2H), 7.54–7.57 (m, 4H), 7.89 (d, J = 3.6 Hz, 1H), 8.14 (d, J = 3.2 Hz, 1H), 8.29 (d, J = 4.4 Hz, 1H), 12.37 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 405. Anal. Calcd for $C_{25}H_{16}N_4O_2$: C, 74.25; H, 3.99; N, 13.85. Found: C, 74.45; H, 4.05; N, 13.99.

4.1.17. 3-(5-Methoxy-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (5b)

According to the procedure used to prepare **5a**, reaction of **4b** with TBAF provided **5b** in 79.5% yield as a red solid, mp: 226–229 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 3.09 (s, 3H), 5.42 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 2.0, 8.0 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.51–7.55 (m, 6H), 8.21 (d, J = 3.6 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 3.2 Hz, 1H), 8.68 (d, J = 4.8 Hz, 1H), 12.27 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 435. Anal. Calcd for $C_{26}H_{18}N_4O_3$: C, 71.88; H, 4.18; N, 12.90. Found: C, 71.98; H, 4.09; N, 12.79.

4.1.18. 3-(5-Bromo-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (5c)

According to the procedure used to prepare **5a**, reaction of **4c** with TBAF provided **5c** in 85.3% yield as a red solid, mp: 216–218 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 5.93 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 2.0, 8.0 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.54–7.59 (m, 6H), 8.20 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 3.2 Hz, 1H), 8.36 (d, J = 3.6 Hz, 1H), 8.70 (d, J = 4.8 Hz, 1H), 12.58 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 483. Anal. Calcd for $C_{25}H_{15}BrN_4O_2$: C, 62.13; H, 3.13; N, 11.59. Found: C, 62.35; H, 3.08; N, 11.67.

4.1.19. 3-(6-Bromo-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (5d)

According to the procedure used to prepare **5a**, reaction of **4d** with TBAF provided **5d** in 76.6% yield as a red solid, mp: 185–188 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 5.95 (d, J = 8.0 Hz, 1H), 6.77 (dd, J = 1.6, 8.0 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.54–7.58 (m, 6H), 7.63 (d, J = 1.6 Hz, 1H), 8.21–8.23 (m, 2H), 8.30 (d, J = 3.6 Hz, 1H), 8.68 (d, J = 4.8 Hz, 1H), 12.42 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 483. Anal. Calcd for $C_{25}H_{15}BrN_4O_2$: C, 62.13; H, 3.13; N, 11.59. Found: C, 62.27; H, 3.21; N, 11.85.

4.1.20. 3-(6-Fluoro-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (5e)

According to the procedure used to prepare **5a**, reaction of **4e** with TBAF provided **5e** in 81.8% yield as a red solid, mp: 215–218 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 5.95–5.98 (m, 1H), 6.52 (dd, J = 1.6, 8.8 Hz, 1H), 7.22–7.24 (m, 2H), 7.53–7.57 (m, 6H), 8.21–8.23 (m, 2H), 8.33 (d, J = 3.6 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 12.47 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 423. Anal. Calcd for $C_{25}H_{15}FN_4O_2$: C, 71.08; H, 3.58; N, 13.26. Found: C, 71.36; H, 3.41; N, 13.55.

4.1.21. 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6a)

60% NaH (12.8 mg, 0.32 mmol) was added portion-wise to a solution of **5a** (121 mg, 0.3 mmol) in DMF (25 mL) at room temperature. After stirring for 30 min, 1-(3-chloropropyl)-1*H*-imidazole (65 mg, 0.45 mmol) was added and the mixture was then headed to 75 °C for 6 h. After that, the mixture was poured into water (500 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phase was combined, washed with brine (3 × 300 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using dichlorometh-

ane/methanol/triethylamine (90:30:1, v/v/v) as eluent to afford 64 mg (41.7%) of **6a** as a red solid, mp: 126–128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.39–2.41 (m, 2H), 3.94 (t, J = 6.8 Hz, 2H), 4.17 (t, J = 6.8 Hz, 2H), 6.17 (d, J = 8.0 Hz, 1H), 6.69 (t, J = 8.0 Hz, 1H), 6.82–6.84 (m, 1H), 6.95 (br s, 1H), 6.98 (d, J = 3.6 Hz, 1H), 7.14–7.17 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.41–7.42 (m, 1H), 7.51–7.55 (m, 5H), 7.74 (d, J = 3.6 Hz, 1H), 7.98 (s, 1H), 8.39 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 513. Anal. Calcd for $C_{31}H_{24}N_6O_2$: C, 72.64; H, 4.72; N, 16.40. Found: C, 72.36; H,4.49; N, 16.25.

4.1.22. 3-(5-Methoxy-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6b)

According to the procedure used to prepare **6a**, reaction of **5b** with 1-(3-chloropropyl)-1*H*-imidazole provided **6b** in 33.2% yield as a red solid, mp: 56–58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.41–2.42 (m, 2H), 3.06 (s, 3H), 4.01 (t, J = 6.4 Hz, 2H), 4.18 (t, J = 6.4 Hz, 2H), 5.56 (d, J = 1.6 Hz, 1H), 6.69 (dd, J = 1.6, 8.4 Hz, 1H), 6.87–6.90 (m, 1H), 6.95 (d, J = 3.6 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.13 (br s, 1H), 7.41 (m, 2H), 7.50–7.54 (m, 4H), 7.73 (d, J = 3.6 Hz, 1H), 7.88 (br s, 1H), 8.01 (s, 1H), 8.40 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 543. Anal. Calcd for $C_{32}H_{26}N_6O_3$: C, 70.84; H, 4.83; N, 15.49. Found: C, 70.59; H, 4.68; N, 15.58.

4.1.23. 3-(5-Bromo-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6c)

According to the procedure used to prepare **6a**, reaction of **5c** with 1-(3-chloropropyl)-1*H*-imidazole provided **6c** in 31.3% yield as a red solid, mp: 135–137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.35–2.37 (m, 2H), 3.92 (t, J = 6.8 Hz, 2H), 4.12 (t, J = 6.8 Hz, 2H), 6.24 (d, J = 2.0 Hz, 1H), 6.79–6.82 (m, 1H), 6.92 (br s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.14 (br s, 1H), 7.17–7.21 (m, 2H), 7.42–7.45 (m, 1H), 7.52–7.56 (m, 5H), 7.74 (d, J = 3.6 Hz, 1H), 7.88 (s, 1H), 8.41 (d, J = 3.6 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 591. Anal. Calcd for $C_{31}H_{23}BrN_6O_2$: C, 62.95; H, 3.92; N, 14.21. Found: C, 62.76; H, 3.69; N, 14.25.

4.1.24. 3-(6-Bromo-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6d)

According to the procedure used to prepare **6a**, reaction of **5d** with 1-(3-chloropropyl)-1*H*-imidazole provided **6d** in 35.2% yield as a red solid, mp: 120–122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.38–2.40 (m, 2H), 3.95 (t, J = 6.4 Hz, 2H), 4.12 (t, J = 6.8 Hz, 2H), 6.02 (d, J = 8.4 Hz, 1H), 6.79–6.84 (m, 2H), 6.97–7.01 (m, 2H), 7.16 (br s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.32 (br s, 1H), 7.42–7.45 (m, 1H), 7.51–7.54 (m, 5H), 7.73 (d, J = 3.2 Hz, 1H), 7.90 (s, 1H), 8.41 (d, J = 3.6 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 591. Anal. Calcd for $C_{31}H_{23}BrN_6O_2$: C, 62.95; H, 3.92; N, 14.21. Found: C, 62.99; H,3.88; N, 14.45.

4.1.25. 3-(6-Fluoro-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6e)

According to the procedure used to prepare **6a**, reaction of **5e** with 1-(3-chloropropyl)-1*H*-imidazole provided **6e** in 37.5% yield as a red solid, mp: 90–92 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.38–2.40 (m, 2H), 3.97 (t, J = 6.4 Hz, 2H), 4.12 (t, J = 6.8 Hz, 2H), 6.06–6.09 (m, 1H), 6.46 (td, J = 9.2, 1.6 Hz 1H), 6.81–6.86 (m, 2H), 6.95 (br s, 1H), 6.99 (d, J = 3.2 Hz, 1H), 7.14 (br s, 1H), 7.28 (d, J = 8.0 Hz 1H), 7.40–7.44 (m, 1H), 7.51–7.54 (m, 4H), 7.65 (br s, 1H), 7.74 (d, J = 3.6 Hz, 1H); 7.93 (s, 1H); 8.40 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 531. Anal. Calcd for $C_{31}H_{23}FN_6O_2$: C, 70.18; H, 4.37; N, 15.84. Found: C, 70.26; H,4.56; N, 15.57.

4.1.26. 3-(1-(3-(Dimethylamino)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6f)

According to the procedure used to prepare **6a**, reaction of **5a** with 3-chloro-*N*,*N*-dimethylpropan-1-amine provided **6f** in 49.0% yield as a red solid, mp: 150–152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.04–2.06 (m, 2H), 2.26–2.32 (m, 8H), 4.30 (t, J = 6.8 Hz, 2H), 6.14 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 6.82–6.84 (m, 1H), 6.98 (d, J = 3.6 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.31–7.33 (m, 2H), 7.42–7.43 (m, 1H), 7.53–7.56 (m, 4H), 7.74 (d, J = 3.6 Hz, 1H), 8.09 (s, 1H), 8.39 (dd, J = 1.2, 4.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 490. Anal. Calcd for $C_{30}H_{27}N_5O_2$: C, 73.60; H, 5.56; N, 14.31. Found: C, 73.54; H,5.63; N, 14.48.

4.1.27. 3-(5-Methoxy-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6g)

According to the procedure used to prepare **6a**, reaction of **5b** with 3-chloro-*N*,*N*-dimethylpropan-1-amine provided **6g** in 41.7% yield as a red solid, mp: 178–180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.01–2.03 (m, 2H), 2.23–2.27 (m, 8H), 3.06 (s, 3H), 4.25 (t, J = 6.8 Hz, 2H), 5.55 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 2.0, 8.0 Hz, 1H), 6.88–6.89 (m, 1H), 6.94 (d, J = 3.6 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.40–7.42 (m, 2H), 7.50–7.53 (m, 4H), 7.73 (d, J = 3.6 Hz, 1H), 8.11 (s, 1H), 8.42 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 520. Anal. Calcd for $C_{31}H_{29}N_5O_3$: C, 71.66; H, 5.63; N, 13.48. Found: C, 71.47; H,5.44; N, 13.62.

4.1.28. 3-(6-Bromo-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6h)

According to the procedure used to prepare **6a**, reaction of **5d** with 3-chloro-*N*,*N*-dimethylpropan-1-amine provided **6h** in 44.0% yield as a red solid, mp: 82–84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.97–1.99 (m, 2H), 2.21–2.26 (m, 8H), 4.23 (t, J = 6.8 Hz, 2H), 5.98 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.81–6.82 (m, 1H), 6.97 (d, J = 3.6 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.41–7.43 (m, 1H), 7.52–7.56 (m, 5H), 7.71 (d, J = 3.6 Hz, 1H), 8.00 (s, 1H), 8.41 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 568. Anal. Calcd for $C_{30}H_{26}BrN_5O_2$: C, 63.39; H, 4.61; N, 12.32. Found: C, 63.51; H, 4.46; N, 12.51.

4.1.29. 3-(6-Fluoro-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6i)

According to the procedure used to prepare **6a**, reaction of **5e** with 3-chloro-*N*,*N*-dimethylpropan-1-amine provided **6i** in 35.0% yield as a red solid, mp: 128–130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.14–2.26 (m, 2H), 2.44 (s, 6H), 2.52 (t, J = 6.8 Hz, 2H), 4.29 (t, J = 6.8 Hz, 2H), 6.04–6.05 (m, 1H), 6.41 (t, J = 9.2 Hz, 1H), 6.81–6.83 (m, 1H), 6.99–7.01 (m, 2H), 7.24 (d, J = 6.4 Hz, 1H), 7.41–7.42 (m, 1H), 7.49–7.52 (m, 4H), 7.72 (d, J = 3.6 Hz, 1H), 8.04 (s, 1H); 8.38 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 508. Anal. Calcd for $C_{30}H_{26}FN_5O_2$: C, 70.99; H, 5.16; N, 13.80. Found: C, 70.71; H, 5.32; N, 13.53.

4.1.30. 3-(1-(3-(Piperidin-1-yl)propyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H* -pyrrole-2,5-dione (6j)

According to the procedure used to prepare **6a**, reaction of **5a** with 1-(3-chloropropyl)piperidine provided **6j** in 47.2% yield as a red solid, mp: 78–80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.43–1.46 (m, 2H), 1.60–1.63 (m, 4H), 2.03–2.06 (m, 2H), 2.28 (t, J = 6.4 Hz, 2H), 2.33–2.37 (m, 4H), 4.28 (t, J = 7.2 Hz, 2H), 6.13 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 6.79–6.82 (m, 1H), 6.98 (d, J = 3.2 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.27–7.30 (m, 2H), 7.40–7.44 (m, 1H),

7.51–7.54 (m, 4H), 7.73 (d, J = 3.2 Hz, 1H), 8.08 (s, 1H), 8.38 (dd, J = 1.6, 4.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 530. Anal. Calcd for $C_{33}H_{31}N_5O_2$: C, 74.84; H, 5.90; N, 13.22. Found: C, 74.65; H, 5.71; N, 13.47.

4.1.31. 3-(1-(3-Morpholinopropyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6k)

According to the procedure used to prepare **6a**, reaction of **5a** with 4-(3-chloropropyl)morpholine provided **6k** in 53.0% yield as a red solid, mp: 109–111 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.03–2.07 (m, 2H), 2.29 (t, J = 6.4 Hz, 2H), 2.40–2.44 (m, 4H), 3.73–3.77 (m, 4H), 4.32 (t, J = 6.8 Hz, 2H), 6.13 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 8.0 Hz, 1H), 6.80–6.83 (m, 1H), 6.98 (d, J = 3.6 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 7.28–7.32 (m, 2H), 7.40–7.43 (m, 1H), 7.49–7.53 (m, 4H), 7.73 (d, J = 3.6 Hz, 1H,), 8.09 (s, 1H), 8.39 (dd, J = 1.6, 4.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 532. Anal. Calcd for $C_{32}H_{29}N_5O_3$: C, 72.30; H, 5.50; N, 13.17. Found: C, 72.53; H, 5.64; N, 13.41.

4.1.32. 3-(1-(2-(1*H*-Imidazol-1-yl)ethyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6l)

According to the procedure used to prepare **6a**, reaction of **5a** with 1-(2-chloroethyl)-1*H*-imidazole provided **6l** in 36.0% yield as a red solid, mp: 115–117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 4.41 (t, J = 6.4 Hz, 2H), 4.52 (t, J = 6.4 Hz, 2H), 6.08 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.76 (br s, 1H), 6.91–6.94 (m, 1H), 7.02–7.06 (m, 4H), 7.17 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.38–7.42 (m, 1H), 7.47–7.53 (m, 4H), 7.58 (s, 1H), 7.78 (d, J = 4.0 Hz, 1H), 8.39 (d, J = 4.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 499. Anal. Calcd for $C_{30}H_{22}N_6O_2$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.41; H, 4.55; N, 16.59.

4.1.33. 3-(1-(4-(1*H*-Imidazol-1-yl)butyl)-1*H*-indol-3-yl)-1-phenyl-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (6m)

According to the procedure used to prepare **6a**, reaction of **5a** with 1-(4-chlorobutyl)-1*H*-imidazole provided **6m** in 36.9% yield as a red solid, mp: 81–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.80–1.83 (m, 2H), 1.87–1.89 (m, 2H), 3.91 (t, J = 6.4 Hz, 2H), 4.19 (t, J = 6.8 Hz, 2H), 6.18 (d, J = 8.0 Hz, 1H), 6.69 (t, J = 7.6 Hz, 1H), 6.80–6.86 (m, 2H), 6.99 (br s, 1H), 7.09 (t, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.40–7.44 (m, 1H), 7.49–7.53 (m, 5H), 7.72 (d, J = 3.6 Hz, 1H), 7.98 (s, 1H), 8.40 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 527. Anal. Calcd for $C_{32}H_{26}N_6O_2$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.76; H, 4.86; N, 16.13.

4.1.34. 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-*pyrrolo[3,2-b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7a)

Compound **6a** (28 mg, 0.055 mmol) was heated with ammonium acetate (1.16 g, 15 mmol) for 4 h at 140 °C. The mixture was cooled, poured into water (100 mL), adjusted to weak alkalinity with Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative thin layer chromatography using dichloromethane/methanol/triethylamine (90:30:1, v/v/v) as eluent to afford 20 mg (83.3%) of **7a** as a red solid, mp: 152–154 °C. 1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 2.48–2.50 (m, 2H), 4.27 (t, J = 6.4 Hz, 2H), 4.32 (t, J = 6.4 Hz, 2H), 6.01 (d, J = 8.0 Hz, 1H), 6.59 (t, J = 8.0 Hz, 1H), 6.89–6.90 (m, 2H), 7.03 (t, J = 8.0 Hz, 1H), 7.35–7.37 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 3.6 Hz, 1H), 7.99 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.97 (br s, 1H), 11.12 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 437. Anal. Calcd for $C_{25}H_{20}N_6O_2$: C, 68.80; H, 4.62; N, 19.25. Found: C, 68.72; H, 4.58; N, 19.17.

4.1.35. 3-(5-Methoxy-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7b)

According to the procedure used to prepare **7a**, reaction of **6b** with ammonium acetate provided **7b** in 82.3% yield as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.23–2.24 (m, 2H), 2.95 (s, 3H), 3.98 (t, J = 7.2 Hz, 2H), 4.20 (t, J = 6.8 Hz, 2H), 5.43 (d, J = 1.6 Hz, 1H), 6.55 (dd, J = 1.6, 8.4 Hz, 1H), 6.79 (d, J = 3.2 Hz, 1H), 6.86–6.88 (m, 1H,), 6.93 (br s, 1H), 7.12 (br s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.60 (br s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 8.28 (d, J = 4.0 Hz, 1H), 11.21 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 467. Anal. Calcd for $C_{26}H_{22}N_6O_3$: C, 66.94; H, 4.75; N, 18.02. Found: C, 66.71; H, 4.63; N, 18.15.

4.1.36. 3-(5-Bromo-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7c)

According to the procedure used to prepare **7a**, reaction of **6c** with ammonium acetate provided **7c** in 80.5% yield as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.22–2.24 (m, 2H), 3.93 (t, J = 6.8 Hz, 2H), 4.25 (t, J = 7.2 Hz, 2H), 6.08 (d, J = 2.4 Hz 1H), 6.81–6.84 (m, 1H), 6.90–6.91 (m, 2H), 7.12 (dd, J = 2.4, 8.4 Hz, 1H), 7.19 (br s, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.61 (br s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 8.06 (s, 1H), 8.26 (d, J=4.4 Hz, 1H), 11.34 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 515. Anal. Calcd for $C_{25}H_{19}BrN_6O_2$: C, 58.26; H, 3.72; N, 16.31. Found: C, 58.14; H, 3.82; N, 16.47.

4.1.37. 3-(6-Bromo-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7d)

According to the procedure used to prepare **7a**, reaction of **6d** with ammonium acetate provided **7d** in 83.7% yield as a red solid, mp: 104–106 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.23–2.25 (m, 2H), 3.95 (t, J = 7.2 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 5.98 (d, J = 8.4 Hz, 1H), 6.69 (dd, J = 2.0, 8.0 Hz, 1H), 6.82–6.84 (m, 1H), 6.87 (d, J = 3.6 Hz, 1H), 6.92 (br s, 1H), 7.21 (br s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.64 (br s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 3.6 Hz, 1H), 8.01 (s, 1H), 8.25 (d, J = 3.6 Hz, 1H), 11.36 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 515. Anal. Calcd for $C_{25}H_{19}BrN_6O_2$: C, 58.26; H, 3.72; N, 16.31. Found: C, 58.39; H, 3.70; N, 16.24.

4.1.38. 3-(6-Fluoro-1-(3-(1*H*-imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5- dione (7e)

According to the procedure used to prepare **7a**, reaction of **6e** with ammonium acetate provided **7e** in 84.1% yield as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.22–2.24 (m, 2H), 3.95 (t, J = 6.8 Hz, 2H), 4.22 (t, J = 6.8 Hz, 2H), 5.99–6.03 (m, 1H), 6.42 (td, J = 9.2, 2.4 Hz, 1H), 6.80–6.83 (m, 1H), 6.85 (d, J = 3.2 Hz, 1H), 6.92 (br s, 1H), 7.21 (br s, 1H), 7.28–7.32 (m, 2H), 7.63 (br s, 1H), 7.84 (d, J = 3.6 Hz, 1H), 8.01 (s, 1H), 8.24 (dd, J = 2.4, 4.4 Hz, 1H), 11.34 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 455. Anal. Calcd for $C_{25}H_{19}FN_6O_2$: C, 66.07; H, 4.21; N, 18.49. Found: C, 66.00; H, 4.09; N, 18.23.

4.1.39. 3-(1-(3-(Dimethylamino)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7f)

According to the procedure used to prepare **7a**, reaction of **6f** with ammonium acetate provided **7f** in 90.6% yield as a red solid, mp: 124–126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.16–2.20 (m, 2H), 2.33 (s, 6H), 2.41 (t, J = 6.8 Hz, 2H), 4.30 (t, J = 7.2 Hz, 2H), 6.04 (d, J = 8.0 Hz, 1H), 6.62 (t, J = 8.0 Hz, 1H), 6.82–6.83 (m, 1H), 6.97 (d, J = 3.6 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 3.6 Hz, 1H), 8.28 (s, 1H), 8.37 (dd, J = 1.6, 4.8 Hz, 1H), 10.84 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 414. Anal. Calcd for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.83; H, 5.58; N, 16.67.

4.1.40. 3-(5-Methoxy-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7g)

According to the procedure used to prepare **7a**, reaction of **6g** with ammonium acetate provided **7g** in 77.6% yield as a red solid, mp: 194–196 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 2.06–2.08 (m, 2H), 2.33–2.37 (m, 8H), 3.01 (s, 3H), 4.28 (t, J = 6.8 Hz, 2H), 5.46 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 2.0, 8.0 Hz, 1H), 6.87–6.88 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 3.6 Hz, 1H), 8.06 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 10.95 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 444. Anal. Calcd for $C_{25}H_{25}N_5O_3$: C, 67.70; H, 5.68; N, 15.79. Found: C, 67.63; H, 5.54; N, 15.88.

4.1.41. 3-(6-Bromo-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7h)

According to the procedure used to prepare **7a**, reaction of **6h** with ammonium acetate provided **7h** in 83.6% yield as a red solid, mp: 212–214 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 2.38–2.40 (m, 2H), 2.84 (s, 6H), 3.14 (t, J = 6.8 Hz, 2H), 4.43 (t, J = 6.4 Hz, 2H), 5.84 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 7.12–7.13 (m, 1H), 7.58–7.60 (m, 2H), 7.86 (d, J = 3.6 Hz, 1H), 8.15 (s, 1H), 8.41 (d, J = 4.4 Hz, 1H), 11.90 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 492. Anal. Calcd for $C_{24}H_{22}BrN_5O_2$: C, 58.55; H, 4.50; N, 14.22. Found: C, 58.48; H, 4.46; N, 14.08.

4.1.42. 3-(6-Fluoro-1-(3-(dimethylamino)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7i)

According to the procedure used to prepare **7a**, reaction of **6i** with ammonium acetate provided **7i** in 87.5% yield as a red solid, mp: 215–217 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 1.90–1.92 (m, 2H), 2.30–2.35 (m, 8H), 4.28 (t, J = 6.4 Hz, 2H), 5.99–6.00 (m, 1H), 6.42 (dd, J = 1.6, 8.4 Hz, 1H), 6.82–6.83 (m, 1H), 6.88 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 1.6, 8.4 Hz, 1H), 7.85 (d, J = 3.6 Hz, 1H), 8.05 (s, 1H), 8.27 (d, J = 4.4 Hz, 1H), 11.32 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 432. Anal. Calcd for $C_{24}H_{22}FN_5O_2$: C, 66.81; H, 5.14; N, 16.23. Found: C, 66.97; H, 5.01; N, 16.05.

4.1.43. 3-(1-(3-(Piperidin-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7j)

According to the procedure used to prepare **7a**, reaction of **6j** with ammonium acetate provided **7j** in 83.7% yield as a red solid, mp: 132–135 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.47–1.50 (m, 2H), 1.67–1.69 (m, 4H), 2.10–2.14 (m, 2H), 2.35 (t, J = 6.8 Hz, 2H), 2.45–2.48 (m, 4H), 4.29 (t, J = 6.8 Hz, 2H), 6.06 (d, J = 8.0 Hz, 1H), 8.02 (t, J = 8.0 Hz, 1H), 6.80–6.83 (m, 1H), 6.95 (d, J = 3.6 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 3.6 Hz, 1H), 8.08 (s, 1H), 8.38 (dd, J = 1.2, 4.0 Hz, 1H), 11.23 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 454. Anal. Calcd for $C_{27}H_{27}N_5O_2$: C, 71.50; H, 6.00; N, 15.44. Found: C, 71.39; H, 6.03; N, 15.31.

4.1.44. 3-(1-(3-Morpholinopropyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7k)

According to the procedure used to prepare **7a**, reaction of **6k** with ammonium acetate provided **7k** in 78.0% yield as a red solid, mp: 125–127 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 1.91–1.96 (m, 2H), 2.21–2.25 (m, 6H), 3.60–3.64 (m, 4H), 4.34 (t, J = 6.8 Hz, 2H), 6.10 (d, J = 8.0 Hz, 1H), 6.52 (t, J = 8.0 Hz, 1H), 6.81–6.83 (m, 1H), 6.87 (d, J = 3.6 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 3.6 Hz, 1H), 8.12 (s, 1H), 8.25 (dd, J = 1.2, 4.0 Hz, 1H), 11.31 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 456. Anal. Calcd for $C_{26}H_{25}N_5O_3$: C, 68.56; H, 5.53; N, 15.37. Found: C, 68.48; H, 5.56; N, 15.22.

4.1.45. 3-(1-(2-(1*H*-Imidazol-1-yl)ethyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7l)

According to the procedure used to prepare **7a**, reaction of **6l** with ammonium acetate provided **7l** in 82.0% yield as a red solid, mp: 108–110 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 4.42 (t, J = 6.4 Hz, 2H), 4.67 (t, J = 6.4 Hz, 2H), 5.92 (d, J = 8.0 Hz, 1H), 6.48 (t, J = 7.6 Hz, 1H), 6.86 (br s, 1H), 6.88–6.91 (m, 2H), 6.95 (t, J = 7.6 Hz, 1H), 7.07 (br s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.24 (br s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.82 (s, 1H), 7.89 (d, J = 3.2 Hz, 1H), 8.25 (d, J = 3.6 Hz, 1H), 11.30 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 423. Anal. Calcd for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.13; H, 4.34; N, 19.72.

4.1.46. 3-(1-(4-(1*H*-Imidazol-1-yl)butyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (7m)

According to the procedure used to prepare **7a**, reaction of **6m** with ammonium acetate provided **7m** in 81.0% yield as a red solid, mp: 94–96 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 1.66–1.70 (m, 4H), 3.96 (t, J = 6.8 Hz, 2H), 4.30 (t, J = 6.8 Hz, 2H), 6.01 (d, J = 8.0 Hz, 1H), 6.52 (t, J = 7.6 Hz, 1H), 6.73–6.76 (m, 1H), 6.84–6.87 (m, 2H), 6.97 (t, J = 8.0 Hz, 1H), 7.11 (br s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.59 (br s, 1H), 7.83 (d, J = 3.6 Hz, 1H), 8.09 (s, 1H), 8.23 (d, J = 3.6 Hz, 1H), 11.25 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 451. Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.32; H, 4.92; N, 18.66. Found. C, 69.19; H, 4.94; N, 18.51.

4.1.47. 3-(1*H*-Indol-3-yl)-4-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-1*H*-pyrrole-2,5-dione (8)

According to the procedure used to prepare **7a**, reaction of **5a** with ammonium acetate provided **8** in 85.1% yield as a red solid, mp: 188–190 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 5.95 (d, J = 7.6 Hz, 1H), 6.47 (t, J = 7.6 Hz, 1H), 6.86–6.94 (m, 3H), 7.30–7.33 (m, 2H), 7.84 (br s, 1H), 8.06 (br s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 11.29 (br s, 1H), 12.00 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 329. Anal. Calcd for $C_{19}H_{12}N_4O_2$: C, 69.51; H, 3.68; N, 17.06. Found: C, 69.44; H, 3.54; N, 17.22.

4.1.48. 1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine (1-methyl-4-azaindole, 10)

60% NaH (0.88 g, 22 mmol) was added fractionally to a solution of 4-azaindole (2.36 g, 20 mmol) in DMF (20 mL) at 0∼5 °C. After stirring for 30 min, iodomethane (3.4 g, 24 mmol) was added dropwise. After addition, the reaction mixture was stirred at 0–5 °C for 30 min and then 1 h at room temperature. After that, it was poured into water (300 mL) and extracted with dichloromethane (3 × 50 mL). The organic phase was combined and washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (4:1, v/v) as eluent to afford 2.23 g (84.5%) of **10** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 3.78 (s, 3H), 6.68 (br s, 1H), 7.09–7.12 (m, 1H), 7.23 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 4.4 Hz, 1H).

4.1.49. Ethyl 2-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-2-oxoacetate (11)

Anhydrous aluminum trichloride (12.16 g, 91.2 mmol) was added to a solution of 1-methyl-4-azaindole (2.23 g, 16.9 mmol) in dichloromethane (150 mL) and stirred for 1 h at room temperature. Ethyl oxalyl monochloride (5.50 g, 45.6 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 6 h. After that, the supernate was abandoned and 20% ammonium acetate aqueous (0–5 °C) was added to the reaction mixture. The mixture was stirred sufficiently and extracted with dichloromethane (3 × 100 mL). The organic phase was combined and washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized with ethyl acetate to afford 1.68 g (42.9%) of **11** as a white crystal, mp: 144–147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.41 (t, J = 7.2 Hz, 3H), 3.00 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.22–7.26 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.69 (d, J = 4.4 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 233. Anal.

Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.31; H, 5.41; N, 12.23.

4.1.50. 2-(1-(3-Morpholinopropyl)-1*H*-indol-3-yl)acetamide (14a)

60% NaH (0.8 g, 20 mmol) was added fractionally to a solution of 2-(1*H*-indol-3-yl)acetamide (**12**) (3.48 g, 20 mmol) in DMF (20 mL) at 0–5 °C. After stirring for 30 min, 4-(3-chloropropyl)morpholine (**13a**) (4.90 g, 30 mmol) was added. Then the mixture was warmed to 70 °C and reacted for 6 h. After that, the reaction mixture was cooled, poured into water (300 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (180:3:1, v/v/v) as eluent to afford 2.51 g (41.7%) of **14a** as a white solid, mp: 115–117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.96–2.00 (m, 2H), 2.16 (t, J = 6.4 Hz, 2H), 2.36–2.40 (m, 4H), 3.69–3.73 (m, 6H), 4.19 (t, J = 6.8 Hz, 2H), 5.62–5.64 (m, 2H), 7.06 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 302. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.63; H, 7.48; N, 14.13.

4.1.51. 2-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl) acetamide (14b)

According to the procedure used to prepare **14a**, reaction of 2-(1*H*-indol-3-yl)acetamide (**12**) with 1-(3-chloropropyl)-1*H*-imidazole (**13b**) afforded **14b** in 39.2% yield as a white solid, mp:156–158 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.33–2.39 (m, 2H), 3.69 (s, 2H), 3.91 (t, J = 6.4 Hz, 2H), 4.09 (t, J = 7.2 Hz, 2H), 5.74–5.78 (m, 2H), 6.89 (br s, 1H), 6.98 (br s, 1H), 7.07 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.21–7.27 (m, 2H), 7.40 (br s, 1H), 7.59 (d, J = 7.6 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 283. Anal. Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.19; H, 6.51; N, 19.63.

4.1.52. 2-(1-(2-Morpholinoethyl)-1*H*-indol-3-yl)acetamide (14c)

According to the procedure used to prepare **14a**, reaction of 2-(1*H*-indol-3-yl)acetamide (**12**) with 4-(2-chloroethyl)morpholine (**13c**) afforded **14c** in 50.9% yield as a white solid, mp: 73–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.48–2.52 (m, 4H), 2.75 (t, J = 6.4 Hz, 2H), 3.68–3.73 (m, 6H), 4.24 (t, J = 6.4 Hz, 2H), 5.50 (br s, 1H), 5.65 (br s, 1H), 7.12–7.16 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H). ESI-MS: m/z $[M+H]^+$ 288. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.03; H, 7.48; N, 14.46.

4.1.53. 2-(1-(3-Propoxy) (*tert*-butyl)dimethylsilanyl)-1*H*-indol-3-yl)acetamide (14d)

60% NaH (0.8 g, 20 mmol) was added fractionally to a solution of 2-(1*H*-indol-3-yl)acetamide (3.48 g, 20 mmol) in DMF (20 mL) at 0–5 °C. After stirring for 30 min, (3-bromopropoxy) (*tert*-butyl)dimethylsilane (7.6 g, 30 mmol) was added and reacted for 2 h at room temperature. After that, the reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined and washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (4:1, v/v) as eluent to afford 4.76 g (68.7%) of **14d** as a white solid, mp: 62–64 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 0.06 (s, 6H), 0.92 (s, 9H), 1.98–2.03 (m, 2H), 3.57 (t, J = 6.4 Hz, 2H), 4.24 (t, J = 6.8 Hz, 2H), 5.64 (br s, 2H), 7.07 (s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H).

4.1.54. 3-(1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-4-(1-(3-morpholinopropyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (15a)

A solution of *t*-BuOK (100 mg, 0.9 mmol) in THF was added dropwise to a solution of **11** (91 mg, 0.39 mmol) and **14a** (90 mg, 0.3 mmol) in THF (20 mL) at 0–5 °C. After stirring for 1 h, the mixture was poured into 10% ammonium chloride aqueous (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined and washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using ethyl acetate/methanol/triethylanine (150:3:1, v/v/v) as eluent to afford 15.8 mg (11.2%) of **15a** as a red solid, mp: 134–136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.02–2.05 (m, 2H), 2.28 (t, J = 6.8 Hz, 2H), 2.43–2.47 (m, 4H), 3.72–3.76 (m, 4H), 3.90 (s, 3H), 4.29 (t, J = 6.8 Hz, 2H), 6.52–6.56 (m, 2H), 6.95–6.98 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 8.01–8.04 (m, 2H), 10.35 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 470. Anal. Calcd for $C_{27}H_{27}N_5O_3$: C, 69.07; H, 5.80; N, 14.92. Found: C, 69.14; H, 5.84; N, 14.82.

4.1.55. 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (15b)

According to the procedure used to prepare **15a**, reaction of **11** with **14b** provided **15b** in 13.2% yield as a red solid, mp: 94–96 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.42–2.46 (m, 2H), 3.90 (s, 3H), 3.97 (t, J = 6.8 Hz, 2H), 4.18 (t, J = 6.4 Hz, 2H), 6.56 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.92–6.99 (m, 2H), 7.07–7.16 (m, 3H), 7.46 (br s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.83 (br s, 1H), 7.91 (br s, 1H), 10.24 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 451. Anal. Calcd for $C_{26}H_{22}N_6O_2$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.21; H, 4.96; N, 18.81.

4.1.56. 3-(1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-4-(1-(2-morpholinoethyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (15c)

According to the procedure used to prepare **15a**, reaction of **11** with **14c** provided **15c** in 9.3% yield as a red solid, mp: 103–105 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 2.33–2.37 (m, 4H), 2.43 (t, J = 6.4 Hz, 2H), 3.52–3.56 (m, 4H), 3.75 (s, 3H), 4.12 (t, J = 6.8 Hz, 2H), 6.40 (t, J = 8.0 Hz, 1H), 6.49 (t, J = 8.0 Hz, 1H), 6.80–6.85 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.81–7.85 (m, 2H), 10.19 (br s, 1H). ESI-MS: m/z $[M+H]^+$ 456. Anal. Calcd for $C_{26}H_{25}N_5O_3$: C, 68.56; H, 5.53; N, 15.37. Found: C, 68.21; H, 5.81; N, 15.65.

4.1.57. 3-(1-(3-Hydroxypropyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (15d)

A solution of potassium *t*-BuOK (100 mg, 0.9 mmol) in THF was added dropwise to a solution of **11** (91 mg, 0.39 mmol) and **14d** (104 mg, 0.3 mmol) in THF (20 mL) at 0–5 °C. After stirring for 1 h, the mixture was poured into 10% ammonium chloride aqueous (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined and washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was solved with THF (10 mL), and then TBAF (0.3 mmol) was added. After stirring for 1 h at room temperature, the mixture was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined and washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford 14 mg (11.7%) of **15d** as a red solid, mp: 226–228 °C. ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz, δ): 2.02–2.06 (m, 2H), 3.55–3.58 (m, 2H), 3.89 (s, 3H), 4.11 (t, J = 6.4 Hz, 1H), 4.29 (t, J = 6.8 Hz, 2H), 6.56 (t, J = 8.0 Hz, 1H), 6.66 (t, J = 8.0 Hz, 1H), 6.95–6.70 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.90

(br s, 1H), 8.01 (d, J = 4.0 Hz, 1H), 10.45 (s, 1H). ESI-MS: m/z $[M+H]^+$ 401. Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.87; H, 5.08; N, 13.89.

4.2. Pharmacology

4.2.1. GSK-3β purification and activity assay

The GSK-3β cDNA was obtained from UniGene (3667B03) and inserted into pGEX-KG vector. The recombinant GST-GSK-3β protein was expressed in *Escherichia coli* strain BL21-CodonPlus (DE3), purified by GSTrap affinity chromatography, and cleaved by thrombin.

The GSK-3β kinase assay was carried out with the Invitrogen Z′-LYTE™ Kinase Assay kit, with a final enzyme concentration of 50 nM. All reactions were carried out in triplicate, blank values were subtracted, and the GSK-3β activity was expressed in picomoles of phosphate incorporated in CREB per minute or in percentage of maximal activity. The IC_{50} (concentration at which a 50% of enzyme inhibition is shown) values are gathered.

4.2.2. Cell culture and western-blot

SH-SY5Y human neuroblastoma cells were obtained from ATCC (The American Type Culture Collection). Cells were cultured in 1:1 DMEM:Ham's F12 containing 10% (v/v) fetal bovine serum (HyClone), 1% penicillin, and 1% streptomycin at a humidified atmosphere with 5% CO_2. The medium was changed every 2 days. For experiments, cells were and grown in 12-well plates until ~80% confluence, serum-deprived for 12 h, incubated with GSK-3β inhibitors for 1 h and $A\beta_{25-35}$ (Amyloid beta peptide 25–35, Sigma) for another 6 hours. Cells were rinsed twice with ice-cold PBS and lysed with 1 × SDS loading buffer. Samples were electrophoresed on 10% SDS-polyacrylamide gels, and transferred to PVDF membranes. The membranes were blocked for 1 h with 5% (w/v) milk, incubated with rabbit anti-Tau [pS396] phosophospecific antibody (Abcam) for 2 h and the anti-rabbit secondary antibody for 1 h. Antigen–antibody complexes were detected by the ECL Kit.

4.2.3. PKCE, IKK2, Aurora A, MEK1 and ERK1 assays

The recombinant PKCE and IKK2 were expressed in Bac-to-Bac baculovirus system, and recombinant Auroa a, MEK1 and ERK1 were expressed in *Escherichia coli* system. All these kinase assays were carried out by using the Invitrogen Z′-LYTETM Kinase Assay kits.

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