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Original article

Design, synthesis and evaluation of 7-azaindazolyl-indolyl-maleimides as glycogen synthase kinase-3β (GSK-3β) inhibitors

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ABSTRACT

A series of 7-azaindazolyl-indolyl-maleimides were designed, synthesized and evaluated for their GSK-3β inhibitory activity. Most compounds exhibited potent activity against GSK-3β. Among them, compounds **17a**, **17b**, **17g**, **17i**, **29a** and **30** significantly reduced Aβ-induced Tau hyperphosphorylation, showin;g the inhibition of GSK-3β at the cell level. Preliminary structure–activity relationships were discussed based on the experimental data obtained.

1. Introduction

Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine protein kinase which was identified in the late 1970s. Mammalian GSK-3 exists in two isomers, GSK-3α and GSK-3β, which share high homology at the catalytic domain but significantly differ in their N-terminal domain (84% overall and 98% in catalytic domain). Both isomers ubiquitously exist in cells and tissues and have similar biochemical properties [1–4]. GSK-3 plays a critical role in glycogen metabolism, embryogenesis, mitotic regulation, inflammation and neuroplasticity [5–8]. Inhibition of GSK-3 may provide therapy for several diseases such as cancer, diabetes type-2, chronic inflammatory processes, stroke, bipolar disorders and Alzheimer's disease and so on [9–13]. Accordingly, searching for GSK-3 inhibitors is a very active area in both academic centers and pharmaceutical companies.

Various bisindolylmaleimides such as GF 109203X and Ro 31-8820 have been developed as potent GSK-3β inhibitors based on staurosporine, a microbial alkaloid that was identified as an early GSK-3β inhibitor (Fig. 1) [14–18]. Most of these bisindolylmaleimides have suffered from issues including toxicity, bad solubility and poor selectivity, which make them unsuitable for the treatment of diseases such as diabetes and Alzheimer's disease [19,20]. Recent efforts in replacing one indole with other heteroaryl substituents such as imidazo[1,2-*a*]pyridinyl and benzofuranyl led to the emergence of some monoindolylmaleimides (Fig. 1) exhibiting potent and selective GSK-3β inhibitory activity [21,22]. Among which, compound **603288-22-8**, an imidazo[1,2-*a*]pyridinyl-indolyl-maleimide derivative, has reached preclinical trials for the treatment of diabetes. In our previous studies, we have developed a series of 4-azaindolyl-indolyl-maleimides, and some of them showed potent inhibitory potency against GSK-3β [23]. The results revealed that the introduction of a nitrogen atom at 4-position of the indole ring could remarkably increase the selectivity for GSK-3β. Herein a series of 7-azaindazolyl-indolyl-maleimdes was designed and synthesized by introducing modified indole and 7-azaindazole pharmacophore into the maleimide scaffold. All synthesized compounds were evaluated for their GSK-3β inhibitory activities. Selected compounds **17g**, **17i** and **29a** were also tested for their inhibitory potency against other kinases (PKCE, IKK2 and Aurora A et al.) to assess kinase selectivity. Furthermore, the structure–activity relationships were discussed.

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2. Results and discussion

2.1. Chemistry

The synthetic route of target compounds **8**, **9** and **12a**–**f** is outlined in Scheme 1. 3-(Tributylstanny)-1*H*-pyrazolo[3,4-*b*]pyridine **6** was prepared following the reported method by using 2-chloronicotinonitrile **1** as a raw material [24–26]. Stille coupling of **6** with 3-chloro-4-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione **7** [27,28] in the presence of $Pd(PPh_3)_2Cl_2$ obtained 7-azaindazolyl-indolyl-maleimide **8** [29]. Compound **9** were prepared by treatment of **8** with neat NH_4OAc [28]. Reaction of **8** with methylamine in methanol afforded **10**, which was reacted with 5 mol/L KOH in ethanol to give **11** [30,31]. Compounds **12a**–**f** were obtained by reaction of **11** with corresponding **primary amines** in DMF [32].

The preparation of target compounds **15**, **17a**–**i** and **20** is illustrated in Scheme 2. Stille coupling of compound **6** with **13** in the presence of $Pd(PPh_3)_2Cl_2$ yielded compound **14**, which was reacted with alkyl halides to afford **16a**–**i**. Compound **18** was prepared by treating **14** with excessive 1,4-dibromobutane in the presence of Cs_2CO_3 [29]. Treatment of **18** with morpholine resulted in **19**. Compounds **15**, **17a**–**i** and **20** were prepared by treatment of **14**, **16a**–**i** and **19** with neat NH_4OAc at 140 °C respectively [30].

Compounds **27**, **29a**–**e** and **30** were prepared as shown in Scheme 3. Stille coupling of **6** with **21** afforded the intermediate **22**, which was subsequently reacted with 4-(3-chloropropyl)morpholine to yield **23** [29]. The deprotection of N-Boc group of **23** with concentrated hydrochloric acid afforded **24**. Alkylation of **24** with alkyl halides yielded **25** and **28a**–**e**. Reaction of **25** with potassium *t*-butoxide afforded compound **26**. Compounds **27**, **29a**–**e** and **30** were obtained by treatment of **26**, **28a**–**e** and **24** with $NH_3 \cdot H_2O$ in DMF respectively [33].

2.2. Biological activity and molecular modeling

2.2.1. Enzymatic activity

The GSK-3β inhibitory potency of all the 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 the reference compound [21]. The results are summarized in Tables 1 and 2.

As shown in Table 1, most compounds displayed moderate to potent inhibitory activity against GSK-3β. The potency of GSK-3β inhibition of tested compounds was mainly influenced by the substitutions on the maleimide nitrogen as well as the side chains on the nitrogen of the 7-azaindazole or indole ring. Replacement of the hydrogen on the nitrogen in maleimide ring with various substituents led to significant decrease in the potency, by comparing of **8**, **12a**–**f** with **9**, which indicated that the NH of the imide moiety is an essential element of the pharmacophore.

As expected, the hydrophilic side chain at N^1-position of the 7-azaindazole ring was a key feature for enhancing inhibitory potency (i.e. **17a**–**i**, **20**). Among them, compound **17a**, with a morpholine group at the end of the N^1-propyl chain, exhibited potent GSK-3β inhibitory activity with IC_{50} of 0.75 μM, which was about 16-fold more potent than N^1-position no substituted compound **15** (IC_{50} = 12.27 μM). Replacement of the N^1-terminal morpholine group in **17a** with a hydroxy group (**17b**) led to a slight drop in potency. Furthermore, replacement of the morpholine group with other substituents such as piperidine (**17c**), 4-methylpiperazine (**17d**), imidazole (**17e**) and dimethylamine (**17f**) resulted in 4–8-fold loss in potency.

A view on inhibitory data of compounds **17e**, **17g** and **17h** showed that changing the length of the N^1-alkyl linker could affect GSK-3β inhibitory potency. For example, compounds **17g** (IC_{50} = 0.81 μM) with a $(CH_2)_2$ linker and **17h** (IC_{50} = 0.96 μM) with

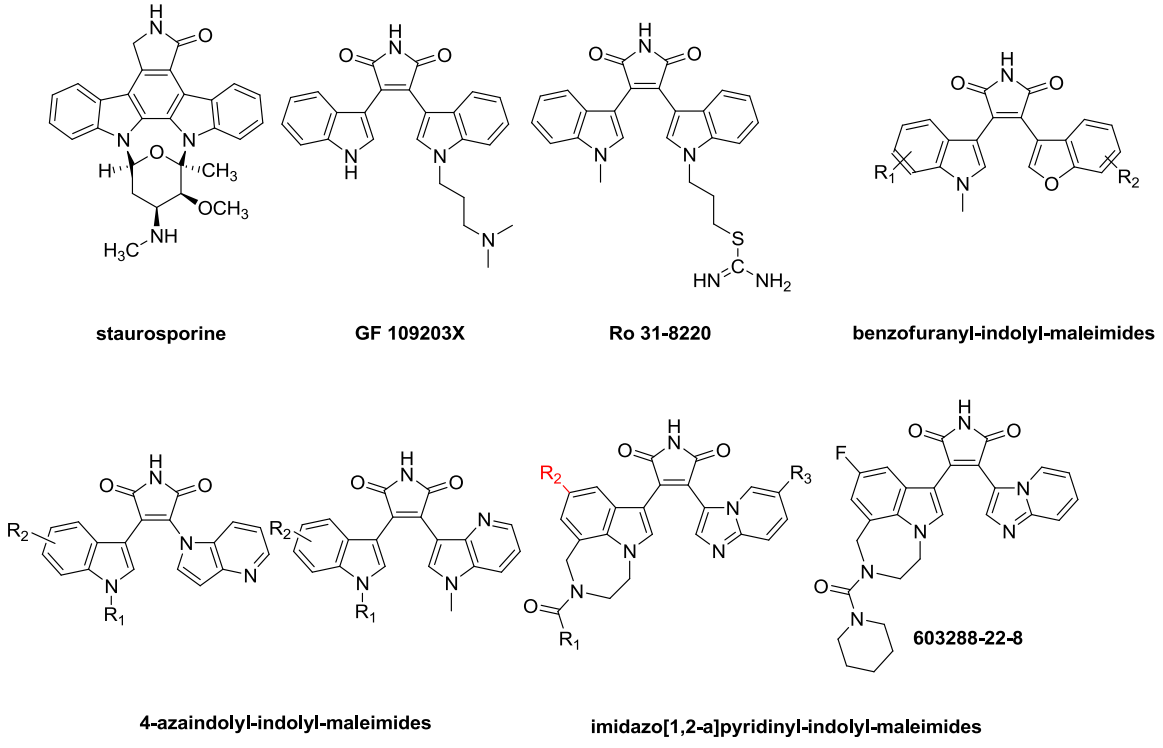
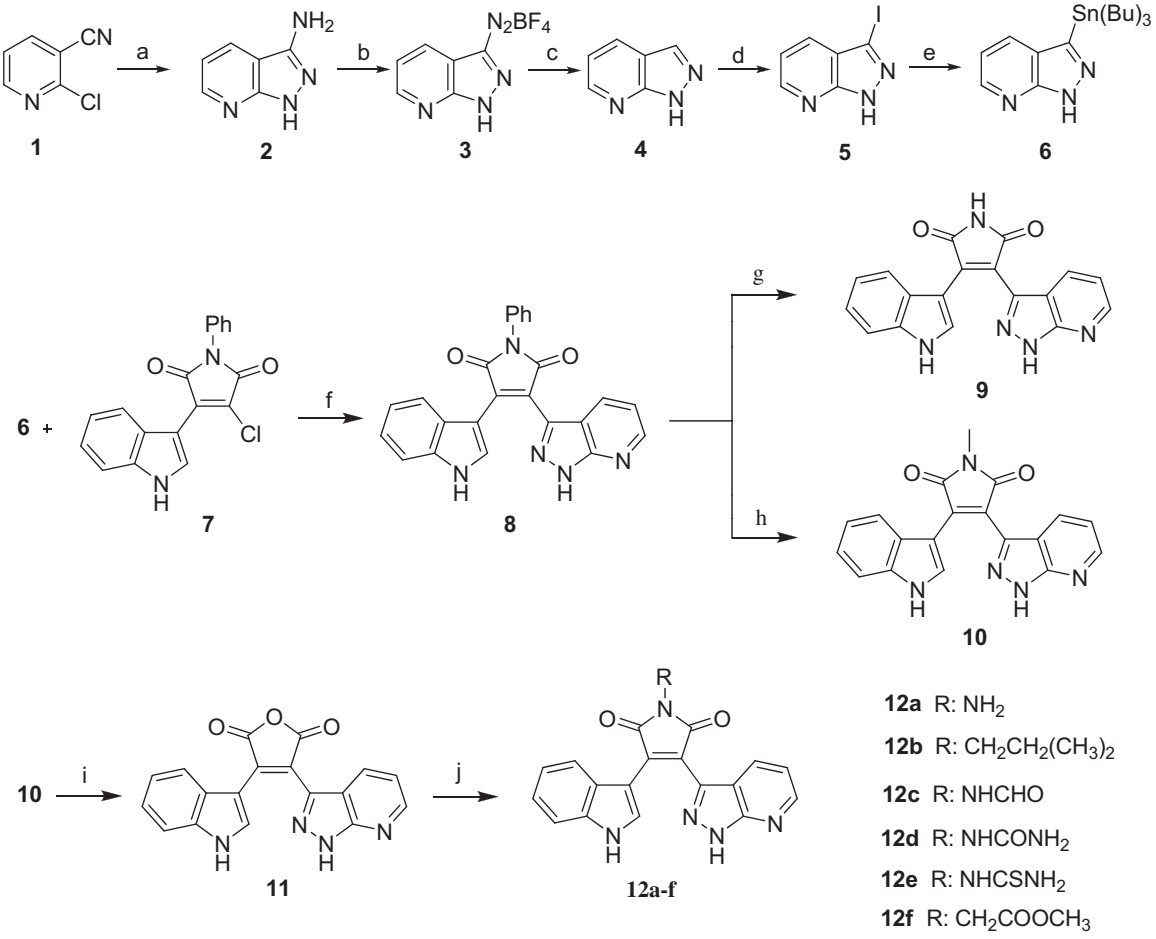


Fig. 1. GSK-3β inhibitors.



Scheme 1. The synthetic route for compounds **8**, **9** and **12a**–**f**. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 78%; (b) $CHMe_2CH_2CH_2NO_2$, HBF_4, CH_3OH, 0–5 °C, 70%; (c) HPO_2, H_2O, rt, 79%; (d) I_2, KOH, DMF, rt, 88%; (e) EtMgBr, $(Bu)_3SnCl$, THF, −5–0 °C, 61%; (f) $Pd(PPh_3)_2Cl_2$, LiCl, toluene, 100 °C, 55%; (g) NH_4OAc, 140 °C, 86%; (h) CH_3NH_2, CH_3OH, rt, 83%; (i) 5 mol/L KOH, EtOH, 30–35 °C, 70%; (j) R–NH_2, DMF or R–NH_2.HCl, DMF, base, 35–68%.

a $(CH_2)_4$ linker showed better inhibitory activities than compounds **17e** (IC_{50} = 4.89 μM) with a $(CH_2)_3$ linker. The same conclusion could also be draw from comparison the inhibitory potency of **17i** and **20** with **17a**.

Comparison of GSK-3β inhibitory data of compounds with various N-substituents on indole ring also revealed that compounds with *N*-methyl (**17a**, IC_{50} = 0.75 μM) or *N*-isopropyl (**29a**, IC_{50} = 0.38 μM) on indole ring were tolerated for GSK-3β inhibitory activity. However, the introduction of a large benzyl group (**29b**, IC_{50} = 1.90 μM) or a vinyl group (**27**, IC_{50} = 8.84 μM) on the indole nitrogen led to 2-fold and 10-fold loss in potency as compared to the case of compound **30** (IC_{50} = 0.83 μM) respectively.

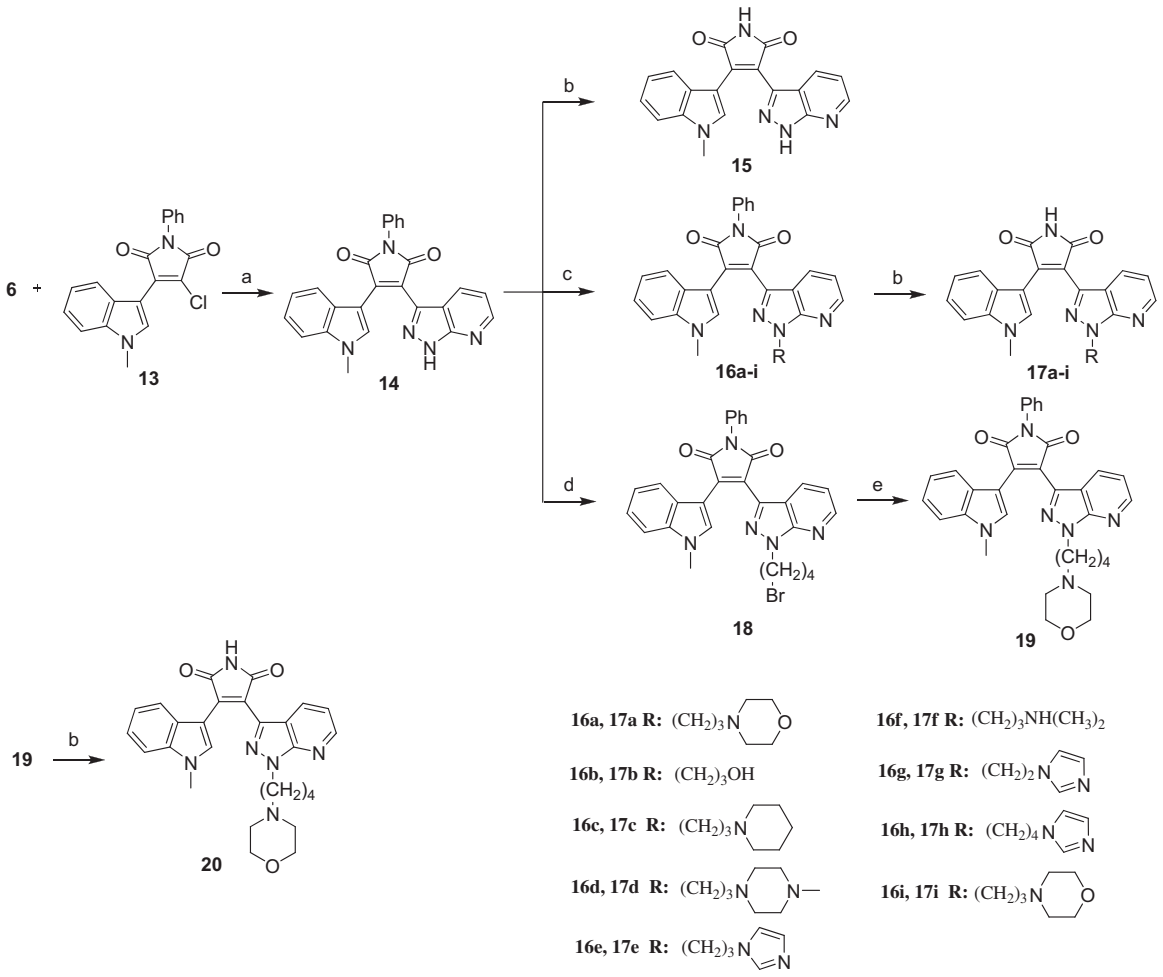
As reported in the literature [14], staurosporine was found to be a potent and nonselective kinase inhibitor. Staurosporine not only inhibits GSK-3β (IC_{50} = 0.2 μM), but also potently inhibits many other kinases (e.g. PKCE, IKK2, Aurora A, MEK1 and ERK1). In order to determine whether target compounds had selection to various kinases, compounds **17g**, **17i** and **29a** were evaluated for their inhibitory activities against PKCE, IKK2, Aurora A, MEK1 and ERK1 by using the Invitrogen Z′-LYTETM Kinase Assay kits. The results showed that **17g**, **17i** and **29a** displayed high selectivity for GSK-3β over other tested kinases (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 Serine 396 represents a direct functional assay to measure the cellular activity of GSK-3β inhibitors. Compounds **17a**, **17b**, **17g**, **17i**, **29a**, **29d**, **29e** and **30** were tested for the ability to reduce Tau phosphorylation at Ser 396 in human neuroblastoma SH-SY5Y cells. LiCl, a known inhibitor of GSK-3β [34], was used as control in this assay. As shown in Fig. 2, compounds **17a**, **17b**, **17g**, **17i**, **29a** and **30** significantly reduced Aβ-induced Tau hyperphosphorylation, showing the inhibition of GSK-3β at the cell level, while **29d** and **29e** have no significant cellular activity.

2.2.3. Molecular modeling

To explore the possible binding mode of the target compounds, a molecular modeling study of the optimum compound **17i** was performed on SYBYL [35] using the Tripos FlexiDock program [36], based on the reported GSK-3β structure (PDB ID: 1Q3D). As it can be seen in Fig. 3, there are some important interactions between ligand and GSK-3β. The maleimide portion of **17i** makes key hydrogen bonding contacts with residues Asp-133 and Val-135 backbone carbonyl (distance: 2.20 Å) and amide hydrogen (distance: 2.02 Å), respectively. The oxygen atom of morpholine forms another hydrogen bond with Lys-183 (distance: 3.12 Å). The nitrogen of morpholine moiety of **17i** formed additional ionic interaction with the carboxyl group of Asp-200 (2.13 Å).



Scheme 2. The synthetic route for compounds **15**, **17a-i** and **20**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, LiCl, toluene, 100 °C, 55%; (b) NH_4OAc, 140 °C, 49–94%; (c) alkyl halides, K_2CO_3, DMF, 65–75 °C, 68–76%; (d) 1,4-dibromobutane, K_2CO_3, DMF, 60 °C, 77%; (e) morpholine, K_2CO_3, DMF, 60 °C, 66%.

3. Conclusion

In summary, a number of 7-azaindazolyl-indolyl-maleimides were designed, synthesized and tested for their GSK-3β inhibitory activity, most of them showed potent activity against GSK-3β. In a cell-based functional assay, selected compounds **17a**, **17b**, **17g**, **17i**, **29a** and **30** significantly reduced Aβ-induced Tau hyperphosphorylation by inhibiting GSK-3β. The preliminary structure–activity relationships and molecular modeling study provided further insight into interactions between the enzyme and its ligand. The results provide valuable information for the design of GSK-3β inhibitors.

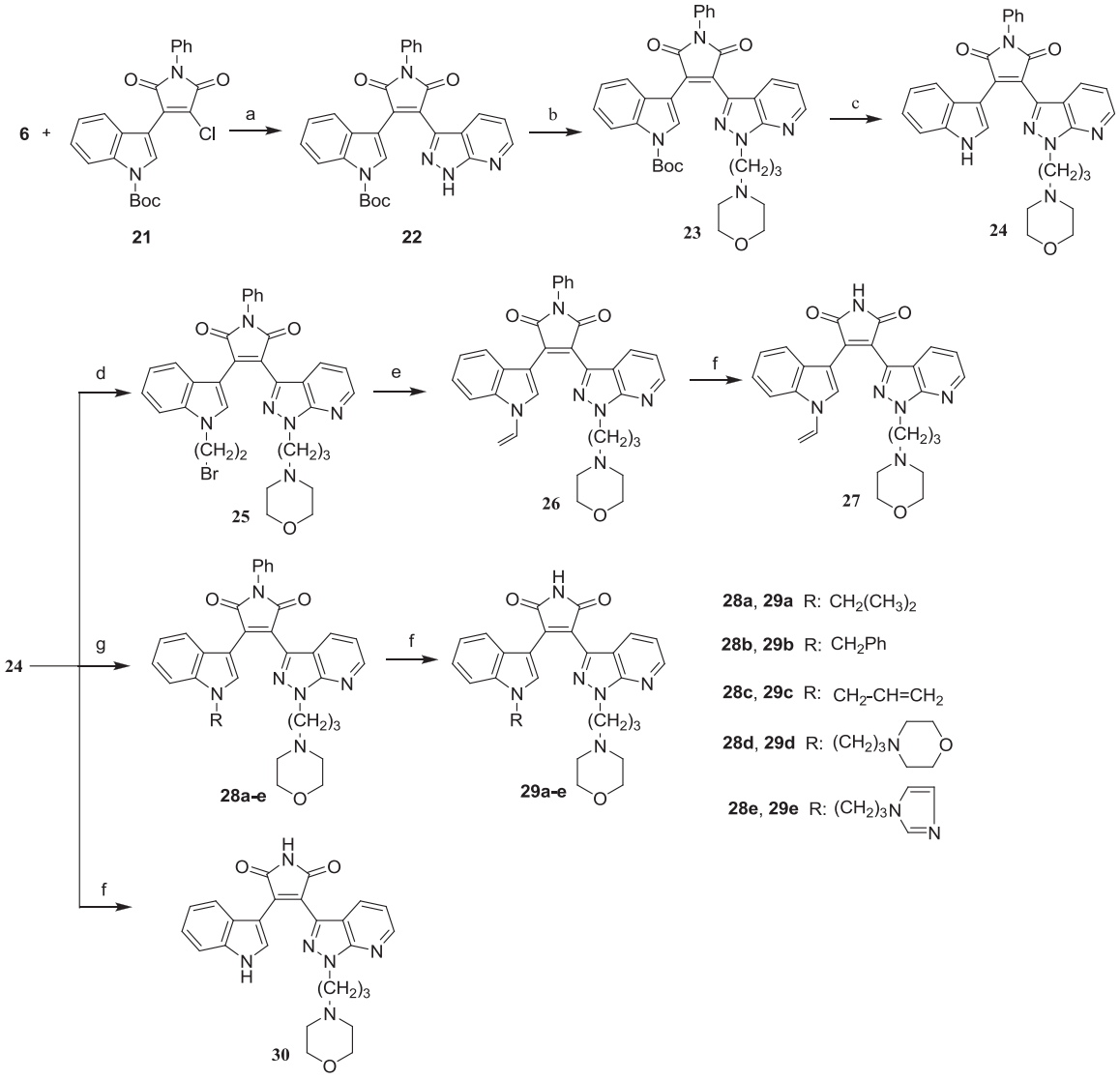
4. Experimental

4.1. Chemistry

Melting points were determined with a BÜCHI Melting Point B-450 apparatus (Büchi Labortechnik, Flawil, Switzerland). The ^1H NMR spectra were recorded on a Bruker Avance DMX 400 at 400 MHz (chemical shifts are expressed as δ values relative to TMS as internal standard). ESI (positive) was recorded on an Esquire-LC-00075 spectrometer. Element analyses were performed on an Eager 300 instrument. 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. Preparation methods and physicochemical properties for compounds **6**, **14**, **15**, **16a-h** and **17a-h** were reported in Ref. [26].

4.1.1. 3-(1H-Indol-3-yl)-1-phenyl-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**8**)

A mixture of 3-(tributylstanny)-*1H*-pyrazolo[3,4-b]pyridine **6** (2.0 g, 4.9 mmol), LiCl (0.48 g, 11.4 mmol), $Pd(PPh_3)_2Cl_2$ (0.48 g, 0.75 mmol), 3-chloro-4-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrrole-2,5-dione **7** (1.66 g, 5.14 mmol) and toluene (70 mL) was stirred at 100 °C for 10 h under N_2 atmosphere. After cooling, the reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (3 × 100 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford compound **8** (1.09 g, 55%) as a red solid, mp: >250 °C. ^1H NMR (DMSO-d_6, δ): 6.39 (1H, d, J = 8.0 Hz), 6.69 (1H, t, J = 8.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.15–7.18 (1H, m), 7.42–7.46 (2H, m), 7.51–7.55 (4H, m), 8.15 (1H, dd, J = 1.6, 8.4 Hz,), 8.25 (1H, d, J = 3.2 Hz), 8.54 (1H, dd, J = 1.6, 4.0 Hz), 12.04 (1H, s), 14.05 (1H, s). ESI-MS: m/z = 406 $[M + H]^+$. Anal. Calcd for $C_{24}H_{15}N_5O_2$: C, 71.10; H, 3.73; N, 17.27. Found: C, 71.38; H, 3.59; N, 17.13.



Scheme 3. The synthetic route for compounds **27**, **29a**–**e** and **30**. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, LiCl, toluene, 100 °C, 40%; (b) 4-(3-chloropropyl)morpholine, K_2CO_3, DMF, 60 °C, 52%; (c) concentrated HCl, EtOH, 30–35 °C, 68%; (d) 1,2-dibromoethane, Cs_2CO_3, DMF, 60 °C, 55%; (e) potassium *tert*-butoxide, THF, 0–5 °C, 54%; (f) 28% $NH_3.H_2O$, DMF, 90 °C, 79–89%; (g) alkyl halides, NaH, DMF, 56–71%.

*4.1.2. 3-(1H-Indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**9**)*

A mixture of **8** (0.05 g, 0.12 mmol) and ammonium acetate (0.92 g, 12.0 mmol) was reacted at 140 °C for 6 h. After cooling, the mixture was poured into water (50 mL), adjusted to weak alkalinity with Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). The organic layer was combined, washed with brine (3 × 150 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford compound **9** (34.8 mg, 86%) as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 6.35 (1H, d, J = 8.0 Hz), 6.66 (1H, t, J = 8.0 Hz), 7.02 (1H, t, J = 7.6 Hz), 7.12–7.15 (1H, m), 7.39 (1H, d, J = 8.0 Hz), 8.05 (1H, d, J = 7.6 Hz), 8.16 (1H, s), 8.52 (1H, d, J = 4.0 Hz), 11.18 (1H, brs), 11.94 (1H, brs), 13.97 (1H, brs). ESI-MS: m/z = 330 $[M + H]^+$. Anal. Calcd for $C_{18}H_{11}N_5O_2$: C, 65.65; H, 3.37; N, 21.27. Found: C, 65.38; H, 3.47; N, 21.33.

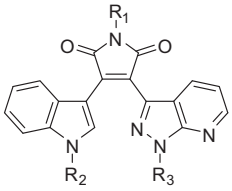
*4.1.3. 3-(1H-Indol-3-yl)-1-methyl-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**10**)*

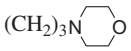
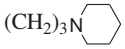
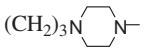
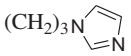
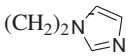
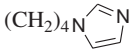
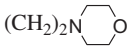
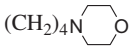
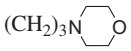
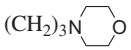
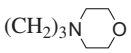
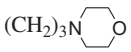
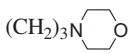
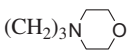
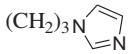
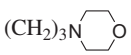
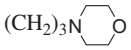
A mixture of **8** (0.57 g, 1.4 mmol) and a solution of methylamine in methanol (32.0%, 30 mL) was stirred at room temperature for 2 h. After that, the solvent was removed in vacuum and the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford **10** (0.4 g, 83%) as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 3.08 (3H, s), 6.34 (1H, d, J = 8.0 Hz), 6.66 (1H, t, J = 7.6 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.13–7.15 (1H, m), 7.40 (1H, d, J = 8.4 Hz), 8.03 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 3.2 Hz), 8.51(1H, d, J = 4.4 Hz), 11.97 (1H, s), 14.00 (1H, s). ESI-MS: m/z = 344 $[M + H]^+$ Anal. Calcd for $C_{19}H_{13}N_5O_2$: C, 66.47; H, 3.82; N, 20.40. Found: C, 66.31; H, 3.89; N, 20.62.

4.1.4. 3-(1H-Indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)furan-2,5-dione (11)

A mixture of **10** (0.4 g, 1.2 mmol), 5 M aqueous potassium hydroxide (17 mL) and ethanol (50 mL) was stirred at 25–30 °C for 5 h. After that, water (250 mL) was added to the mixture. The mixture was acidified with 2 M HCl and extracted with ethyl acetate (3 × 60 mL). The organic phase was combined, washed with brine (3 × 120 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (8:1, v/v) as eluent to afford **11** (0.27 g, 70%) as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ):

Table 1
GSK-3β[a] inhibitory activity of 7-azaindazolyl-indolyl-maleimides.



Copmd.	R_1	R_2	R_3	GSK-3β	
				$IC_{50}(\mu M) \pm SE$[b]	%Inhibition@20 μg/mL
ST				0.20 ± 0.01	
8		H	H		4.14 ± 7.49
9	H	H	H	7.31 ± 3.16	
12a	$CH_2CH_2(CH_3)_2$	H	H		28.56 ± 2.84
12b	NH_2	H	H		45.73 ± 10.04
12c	NHCHO	H	H		−7.42 ± 24.79
12d	$NHCONH_2$	H	H		−6.81 ± 9.95
12e	$NHCSNH_2$	H	H		33.70 ± 8.96
12f	CH_2COOCH_3	H	H		51.54 ± 13.76
15	H	CH_3	H	12.27 ± 2.24	
17a	H	CH_3		0.75 ± 0.20	
17b	H	CH_3	$(CH_2)_3OH$	1.09 ± 0.07	
17c	H	CH_3		2.66 ± 0.23	
17d	H	CH_3		3.34 ± 0.07	
17e	H	CH_3		4.89 ± 0.24	
17f	H	CH_3	$(CH_2)_3N(CH_3)_2$	5.69 ± 0.41	
17g	H	CH_3		0.81 ± 0.01	
17h	H	CH_3		0.96 ± 0.04	
17i	H	CH_3		0.36 ± 0.01	
20	H	CH_3		0.46 ± 0.01	
27	H	$CH=CH_2$		8.84 ± 0.11	
29a	H	$CH(CH_3)_2$		0.38 ± 0.01	
29b	H	CH_2Ph		1.90 ± 0.06	
29c	H	$CH_2{-}CH=CH_2$		0.96 ± 0.01	
29d	H			1.29 ± 0.11	
29e	H			0.68 ± 0.01	
30	H	H		0.83 ± 0.08	

[a] Assay details were described in the Experimental section.
[b] SE: standard error mean.

Table 2
The selectivity to tested kinases of target compounds **17g**, **17i** and **29a**.[a]

Kinase assay	$IC_{50} \pm SE$[b] (μM)			
	Staurosporine	**17g**	**17i**	**29a**
GSK-3β	0.20 ± 0.0	0.81 ± 0.01	0.36 ± 0.01	0.38 ± 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 lM of compound.
[b] SE: standard error mean.

6.45 (1H, d, J = 8.0 Hz), 6.75 (1H, t, J = 7.6 Hz), 7.07–7.13 (2H, m), 7.42 (1H, d, J = 8.0 Hz), 8.08 (1H, d, J = 8.0 Hz), 8.34 (1H, d, J = 3.2 Hz), 8.54 (1H, dd, J = 1.6, 4.8 Hz), 11.91 (1H, s), 13.95 (1H, s). ESI-MS: m/z = 331 $[M + H]^+$. Anal. Calcd for $C_{18}H_{10}N_4O_3$: C, 65.45; H, 3.05; N, 16.96. Found: C, 65.39; H, 3.09; N, 16.77.

*4.1.5. 1-Amino-3-(1H-indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**12a**)*

A mixture of **11** (30 mg, 0.09 mmol), hydrazine dihydrochloride (66 mg, 0.63 mmol), potassium carbonate (174 mg, 1.26 mmol) and DMF (2 mL) was stirred at room temperature for 4 h. After that, the mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was combined, washed with brine (3 × 60 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford **12a** (21.1 mg, 68%) as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 4.91(2H, s), 6.33 (1H, d, J = 8.0 Hz), 6.66 (1H, t, J = 7.6 Hz), 7.02 (1H, t, J = 7.6 Hz), 7.13–7.16 (1H, m), 7.40 (1H, d, J = 8.4 Hz), 7.99 (1H, d, J = 8.4 Hz), 8.19 (1H, d, J = 3.2 Hz), 8.51 (1H, dd, J = 1.6, 4.8 Hz), 11.97 (1H, s), 14.00 (1H, s). ESI-MS: m/z = 345 $[M + H]^+$. Anal. Calcd for $C_{18}H_{12}N_6O_2$: C, 62.79; H, 3.51; N, 24.41. Found: C, 62.93; H, 3.58; N, 24.52.

*4.1.6. General procedure for the synthesis of **12b-e***

A mixture of **11** (0.09 mmol), R–NH_2 (0.63 mmol) and DMF (2 mL) was stirred at 70 °C for 10 h. After cooling, the mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was combined, washed with brine (3 × 60 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford **12b-e**.

*4.1.6.1. 3-(1H-Indol-3-yl)-1-isobutyl-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**12b**).* According to the general method, reaction of **11** with 2-methylpropan-1-amine afforded **12b** in 65% yield as a red solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 0.92 (3H, s), 0.94 (3H, s), 2.05–2.08 (1H, m), 3.41 (2H, d, J = 7.6 Hz), 6.35 (1H, d, J = 8.0 Hz), 6.67 (1H, t, J = 7.6 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.13–7.14 (1H, m), 7.40 (1H, d, J = 8.0 Hz), 8.02 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 3.2 Hz), 8.52 (1H, d, J = 4.4 Hz), 11.98 (1H, s), 14.01(1H, s). ESI-MS: m/z = 386 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.69; H, 4.91; N, 18.02.

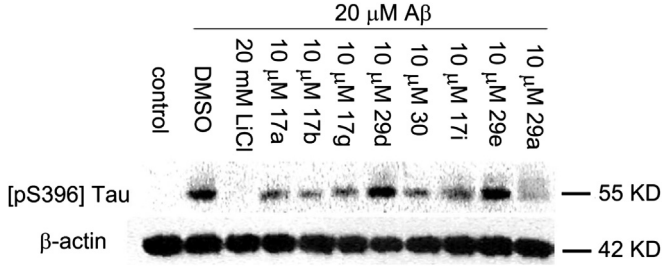


Fig. 2. Effects of GSK-3β inhibitors on tau phosphorylation (ser396) in SH-SY5Y cells.

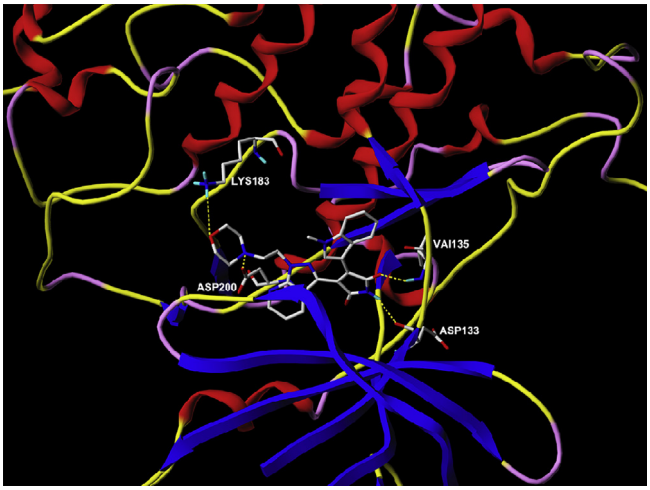


Fig. 3. Docking of **17i** to GSK-3β crystal structure.

*4.1.6.2. 1-Formamido-3-(1H-indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**12c**).* According to the general method, reaction of **11** with formohydrazide afforded **12c** in 36% yield, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 6.27 (1H, d, J = 8.0 Hz), 6.66 (1H, t, J = 7.6 Hz), 7.04 (1H, t, J = 7.6 Hz), 7.13–7.16 (1H, m), 7.42 (1H, d, J = 8.0 Hz), 7.93 (1H, dd, J = 1.6, 8.0 Hz), 8.23 (1H, d, J = 3.2 Hz), 8.38 (1H, s), 8.51 (1H, dd, J = 1.6, 4.8 Hz). ESI-MS: m/z = 373 $[M + H]^+$. Anal. Calcd for $C_{19}H_{12}N_6O_3$: C, 61.29; H, 3.25; N, 22.57. Found: C, 61.17; H, 3.29; N, 22.68.

*4.1.6.3. 3-(1H-Indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1-ureido-1H-pyrrole-2,5-dione (**12d**).* According to the general method, reaction of **11** with hydrazinecarboxamide afforded **12d** in 60% yield, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 6.33 (1H, d, J = 8.0 Hz), 6.43 (2H, brs), 6.67 (1H, t, J = 8.0 Hz), 7.03 (1H, t, J = 8.4 Hz), 7.12–7.16 (1H, m), 7.42 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 3.2 Hz), 8.50–8.53 (2H, m), 12.02 (1H, s), 14.06 (1H, s). ESI-MS: m/z = 388 $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}N_7O_3$: C, 58.91; H, 3.38; N, 25.31. Found: C, 59.05; H, 3.41; N, 25.17.

*4.1.6.4. 3-(1H-Indol-3-yl)-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1-thioureido-1H-pyrrole-2,5-dione (**12e**).* According to the general method, reaction of **11** with hydrazinecarbothioamide afforded **12e** in 52% yield, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 6.34 (1H, d, J = 8.0 Hz), 6.67 (1H, t, J = 7.6 Hz), 7.04 (1H, t, J = 7.6 Hz), 7.13–7.16 (1H, m), 7.42 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 7.6 Hz), 8.20 (1H, d, J = 3.2 Hz), 8.52 (1H, dd, J = 1.6, 4.4 Hz). ESI-MS: m/z = 404 $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}N_7O_2S$: C, 56.57; H, 3.25; N, 24.30; Found: C, 56.39; H, 3.29; N, 24.17.

*4.1.7. Methyl 2-(3-(1H-indol-3-yl)-2,5-dioxo-4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-2,5-dihydro-1H-pyrrol-1-yl)acetate (**12f**)*

A mixture of 11 (30 mg, 0.09 mmol), methyl glycinate hydrochloride (113 mg, 0.9 mmol), triethylamine (91 mg, 0.9 mmol) and DMF (4 mL) was stirred at 70 °C for 10 h. After cooling, the mixture was poured into water (80 mL) and extracted with ethyl acetate

(3 × 30 mL). The organic phase was combined, washed with brine (3 × 60 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (30:1, v/v) as eluent to afford 12f (15 mg, 41%) as an orange solid, mp: >250 °C. ^{1}H NMR (DMSO-d_6, δ): 3.73 (3H, s), 4.48 (2H, s), 6.34 (1H, d, J = 7.6 Hz), 6.68 (1H, t, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.14–7.16 (1H, m), 7.42 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 8.0 Hz), 8.23 (1H, d, J = 3.2 Hz), 8.52 (1H, d, J = 4.4 Hz), 12.04 (1H, s), 14.07 (1H, s). ESI-MS: m/z = 402 $[M + H]^+$ Anal. Calcd for $C_{21}H_{15}N_5O_4$: C, 62.84; H, 3.77; N, 17.45. Found: C, 63.05; H, 3.59; N, 17.33.

4.1.8. 3-(1-Methyl-1H-indol-3-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**16i**)

A mixture of **14** (0.24 mmol) [26], potassium carbonate (0.48 mmol), 4-(2-chloroethyl)morpholine (0.36 mmol) and DMF (10 mL) was stirred at 70 °C for 8 h. After cooling, the mixture was poured into water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **16i** in 67% yield as a red solid, mp: 140–142 °C. ^{1}H NMR ($CDCl_3$, δ): 2.52–2.58 (4H, m), 2.75 (2H, t, J = 6.8 Hz), 3.68–3.76 (4H, m), 3.92 (3H, s), 4.68 (2H, t, J = 6.8 Hz), 6.34 (1H, d, J = 8.0 Hz), 6.78 (1H, t, J = 7.6 Hz), 7.14–7.19 (2H, m), 7.34 (1H, d, J = 8.0 Hz), 7.38–7.42 (1H, m), 7.49–7.54 (4H, m), 8.16 (1H, s), 8.29 (1H, dd, J = 1.6, 8.0 Hz), 8.56 (1H, dd, J = 1.6, 4.0 Hz). ESI-MS: m/z = 533 $[M + H]^+$. Anal. Calcd for $C_{31}H_{28}N_6O_3$: C, 69.91; H, 5.30; N, 15.78; Found: C, 69.76; H, 5.11; N, 15.93.

4.1.9. 3-(1-Methyl-1H-indol-3-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**17i**)

Under N_2 atmosphere, a mixture of **16i** (0.057 mmol) and ammonium acetate (57.0 mmol) was reacted at 140 °C for 6 h. After cooling, the mixture was poured into water (20 mL), adjusted to weak alkalinity with Na_2CO_3 and extracted with ethyl acetate (3 × 20 mL). The organic layer was combined, washed with brine (3 × 50 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **17i** in 85% yield as a red solid, mp: 112–114 °C. ^{1}H NMR ($CDCl_3$, δ): 2.40–2.52 (4H, m), 2.63 (2H, t, J = 6.8 Hz), 3.60–3.72 (4H, m), 3.92 (3H, s), 4.59 (2H, t, J = 6.8 Hz), 6.28 (1H, d, J = 7.6 Hz), 6.75 (1H, t, J = 8.0 Hz), 7.13–7.17 (2H, m), 7.33 (1H, d, J = 8.4 Hz), 7.96 (1H, brs), 8.11 (1H, s), 8.19 (1H, dd, J = 1.6, 8.0 Hz), 8.56 (1H, dd, J = 1.6, 4.0 Hz). ^{13}C NMR ($CDCl_3$, δ):171.90, 171.58, 150.61, 148.92, 137.33, 135.54, 134.33, 134.26, 131.95, 125.21, 122.46, 122.11, 121.68, 120.74, 117.48, 115.38, 109.76, 104.89, 66.61 (2), 57.13, 53.31 (2), 44.27, 33.35. ESI-MS: m/z = 457 $[M + H]^+$. Anal. Calcd for $C_{25}H_{24}N_6O_3$: C, 65.78; H, 5.30; N, 18.41; Found: C, 65.59; H, 5.25; N, 18.53.

4.1.10. 3-(1-Methyl-1H-indol-3-yl)-4-(1-(4-bromobutyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**18**)

A mixture of **14** (200 mg, 0.48 mmol), potassium carbonate (199 mg, 1.44 mmol),1,4-dibromobutane (1.03 g, 4.8 mmol) and DMF (20 mL) was stirred at 60 °C for 1 h [37–45]. After cooling, the mixture was poured into water (200 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 vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (50:1, v/v) as eluent to afford compound **18** (205.0 mg, 77%) as a red solid, mp: 158–160 °C. ^{1}H NMR ($CDCl_3$, δ): 1.63–1.71 (2H, m), 1.74–1.80 (2H, m), 3.43 (2H, t, J = 6.8 Hz), 3.94 (3H, s), 4.45 (2H, t, J = 6.8 Hz), 6.34 (1H, d, J = 8.4 Hz), 6.74 (1H, t, J = 8.4 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.21–7.25 (1H, m), 7.43–7.46 (1H, m), 7.49–7.55 (5H, m), 8.21 (1H, d, J = 8.0 Hz), 8.29 (1H, s), 8.54 (1H, d, J = 4.4 Hz). ESI-MS: m/z = 554 and 556 $[M + H]^+$. Anal. Calcd for $C_{29}H_{24}BrN_5O_2$: C, 62.82; H, 4.36; N, 12.63; Found: C, 62.69; H, 4.24; N, 12.41.

4.1.11. 3-(1-Methyl-1H-indol-3-yl)-4-(1-(4-morpholinobutyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**19**)

A mixture of **18** (150 mg, 0.27 mmol), potassium carbonate (112 mg, 0.81 mmol), morpholine (238 mg, 2.7 mmol) and DMF (30 mL) was stirred at 60 °C for 1 h. After cooling, the mixture was poured into water (200 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 vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **19** (100.0 mg, 66%) as a red solid, mp: 166–168 °C. ^{1}H NMR ($CDCl_3$, δ): 1.41–1.48 (2H, m), 1.67–1.74 (2H, m), 2.28 (2H, t, J = 6.8 Hz), 2.35–2.43 (4H, m), 3.63–3.74 (4H, m), 3.90 (3H, s), 4.44 (2H, t, J = 6.8 Hz), 6.32 (1H, d, J = 8.0 Hz), 6.76 (1H, t, J = 7.6 Hz), 7.11–7.16 (2H, m), 7.32 (1H, d, J = 8.0 Hz), 7.36–7.42 (1H, m), 7.50–7.54 (4H, m), 8.18 (1H, s), 8.25 (1H, dd, J = 1.6, 8.0 Hz), 8.55 (1H, dd, J = 1.6, 4.0 Hz). ESI-MS: m/z = 561 $[M + H]^+$. Anal. Calcd for $C_{33}H_{32}N_6O_3$: C, 70.70; H, 5.75; N, 14.99; Found: C, 70.56; H, 5.63; N, 14.81.

4.1.12. 3-(1-Methyl-1H-indol-3-yl)-4-(1-(4-morpholinobutyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**20**)

According to the procedure used to prepare **17a**, the reaction of **19** with ammonium acetate afforded **20** in 87% yield as a red solid, mp: 126–128 °C. ^{1}H NMR ($CDCl_3$, δ): 1.44–1.51 (2H, m), 1.69–1.75 (2H, m), 2.32 (2H, t, J = 6.8 Hz), 2.38–2.49 (4H, m), 3.67–3.75 (4H, m), 3.90 (1H, s), 4.45 (2H, t, J = 6.8 Hz), 6.26 (1H, d, J = 8.0 Hz), 6.74 (1H, t, J = 7.6 Hz), 7.10–7.15 (2H, m), 7.30 (1H, d, J = 8.0 Hz), 8.06 (1H, brs), 8.11 (1H, s), 8.14 (1H, dd, J = 1.6, 8.0 Hz), 8.54 (1H, dd, J = 1.6, 4.0 Hz). ^{13}C NMR ($CDCl_3$, δ):171.94, 171.60, 150.49, 148.90, 137.35, 135.56, 134.39, 134.07, 131.87, 125.25, 122.50, 122.08, 121.77, 120.73, 117.44, 115.44, 109.76, 104.89, 66.61 (2), 58.15, 53.36 (2), 47.05, 33.40, 27.47, 23.22. ESI-MS: m/z = 485 $[M + H]^+$. Anal. Calcd for $C_{27}H_{28}N_6O_3$: C, 66.93; H, 5.82; N, 17.34; Found: C, 66.79; H, 5.88; N, 17.56.

4.1.13. 3-(1-(tert-Butyloxycarbonyl)-1H-indol-3-yl)-4-chloro-1-phenyl-1H-pyrrole-2,5-dione (**21**)

To a solution of **7** (6.4 g, 20.0 mmol) in THF (250 mL), di-*tert*-butyl dicarbonate (5.5 g, 25.0 mmol) and catalytic amount of DMAP (0.5%) were added and the mixture was stirred for 3 h at room temperature. After removal of the solvent in vacuum, the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (40:1, v/v) as eluent to afford **21** (7.8 g, 92%) as a yellow solid, mp: 150–152 °C. ^{1}H NMR (DMSO-d_6, δ): 1.70 (9H, s), 7.35–7.36 (1H, m), 7.40–7.43 (4H, m), 7.48–7.50 (2H, m), 7.90 (1H, d, J = 6.4 Hz), 8.25–8.27 (2H, m). ESI-MS: m/z = 423 $[M + H]^+$. Anal. Calcd for $C_{23}H_{19}ClN_2O_4$: C, 65.33; H, 4.53; N, 6.62; Found: C, 65.44; H, 4.68; N, 6.59.

4.1.14. 3-(1-(tert-Butyloxycarbonyl)-1H-indol-3-yl)-1-phenyl-4-(1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**22**)

According to the procedure used to prepare **8**, the reaction of **6** with **21** afforded **22** in 40% yield as a yellow solid, mp: 215–218 °C. ^{1}H NMR ($CDCl_3$, δ): 1.69 (9H, s), 6.50 (1H, d, J = 7.6 Hz), 6.83 (1H, t, J = 8.0 Hz), 7.17–7.21 (2H, m), 7.41–7.44 (1H, m), 7.50–7.55 (4H, m), 8.17 (1H, d, J = 8.4 Hz), 8.30 (1H, d, J = 8.0 Hz), 8.49 (1H, s), 8.58 (1H, dd, J = 1.6, 4.0 Hz), 12.48 (1H, brs). ESI-MS: m/z = 506 $[M + H]^+$. Anal. Calcd for $C_{29}H_{23}N_5O_4$: C, 68.90; H, 4.59; N, 13.85; Found: C, 68.83; H, 4.61; N, 13.99.

*4.1.15. 3-(1-(tert-Butyloxycarbonyl)-1H-indol-3-yl)-1-phenyl-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**23**)*

A mixture of **22** (443 mg, 1.0 mmol), potassium carbonate (276 mg, 2.0 mmol), 4-(3-chloropropyl)morpholine (245 mg, 1.5 mmol) and DMF (30 mL) was stirred at 60 °C for 10 h. After cooling, the mixture was poured into water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **23** (295.0 mg, 52%) as a yellow solid, mp: 122–124 °C. ^{1}H NMR ($CDCl_3$, δ): 1.70 (9H, s), 1.84–1.89 (2H, m), 2.30–2.37 (6H, m), 3.64–3.72 (4H, m), 4.47 (2H, t, J = 6.8 Hz), 6.47 (1H, d, J = 8.0 Hz), 6.87 (1H, t, J = 8.0 Hz), 7.19–7.24 (2H, m), 7.40–7.43 (1H, m), 7.50–7.54 (4H, m), 8.20 (1H, d, J = 8.0 Hz), 8.38 (1H, dd, J = 1.6, 8.0 Hz), 8.47 (1H, s), 8.57 (1H, dd, J = 1.6, 4.0 Hz). ESI-MS: m/z = 633 $[M + H]^+$. Anal. Calcd for $C_{36}H_{36}N_6O_5$: C, 68.34; H, 5.74; N, 13.28; Found: C, 68.62; H, 5.71; N, 13.39.

*4.1.16. 3-(1H-Indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine)-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**24**)*

To a solution of **23** (275 mg, 0.5 mmol) in ethanol (30 mL), concentrated hydrochloric acid (15 mL) was added. The mixture was stirred at 30–35 °C for 12 h. After that, it was poured into water (300 mL), adjusted to weak alkalinity with Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). The organic layer was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **24** (182 mg, 68%) as a red solid, mp: 123–125 °C. ^{1}H NMR ($CDCl_3$, δ): 1.85–1.89 (2H, m), 2.22–2.31 (6H, m), 3.57–3.66 (4H, m), 4.50 (2H, t, J = 6.8 Hz), 6.42 (1H, d, J = 8.0 Hz), 6.77 (1H, t, J = 7.6 Hz), 7.08–7.12 (2H, m), 7.34 (1H, d, J = 7.6 Hz), 7.38–7.42 (1H, m), 7.49–7.55 (4H, m), 8.20 (1H, d, J = 3.2 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.55 (1H, d, J = 4.4 Hz), 9.13 (1H, brs). ESI-MS: m/z = 533 $[M + H]^+$. Anal. Calcd for $C_{31}H_{28}N_6O_3$: C, 69.91; H, 5.30; N, 15.78; Found: C, 67.13; H, 5.41; N, 15.99.

*4.1.17. 3-(1-(2-Bromoethyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b] pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**25**)*

A mixture of **24** (159 mg, 0.3 mmol), cesium carbonate (196 mg, 0.6 mmol), 1,2-dibromoethane (564 mg, 3.0 mmol) and DMF (20 mL) was stirred at 60 °C for 2 h. After cooling, the mixture was poured into water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **25** (105 mg, 55%) as a red solid, mp: 84–86 °C. ^{1}H NMR ($CDCl_3$, δ): 1.88–1.90 (2H, m), 2.24–2.33 (6H, m), 3.61–3.67(4H, m), 3.74 (2H, t, J = 6.8 Hz), 4.51 (2H, t, J = 6.8 Hz), 4.63 (2H, t, J = 6.8 Hz), 6.43 (1H, d, J = 8.0 Hz), 6.78 (1H, t, J = 8.0 Hz), 7.12–7.14 (2H, m), 7.33 (1H, d, J = 8.0 Hz), 7.41–7.42 (1H, m), 7.50–7.54 (4H, m), 8.17 (1H, dd, J = 1.6, 8.0 Hz), 8.24 (1H, s), 8.54 (1H, dd, J = 1.6, 4.4 Hz); ESI-MS: m/z = 639 and 641 $[M + H]^+$. Anal. Calcd for $C_{33}H_{31}BrN_6O_3$: C, 61.97; H, 4.89; N, 13.14; Found: C, 67.13; H, 5.41; N, 15.99.

*4.1.18. 3-(1-(3-Morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-3-(1-vinyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione (**26**)*

To a solution of **25** (90 mg, 0.14 mmol) in THF (2 mL), a solution of potassium *tert*-butoxide in THF (0.15 mL, 0.15 mmol) was added dropwise at 0–5 °C. After addition, the mixture was stirred at 0–5 °C for 2 h. After that, it was concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **26** (42.6 mg, 54%) as a red solid, mp: 123–125 °C. ^{1}H NMR ($CDCl_3$, δ): 2.04–2.06 (2H, m), 2.39–2.48 (6H, m), 3.68–3.77 (4H, m), 4.51 (2H, t, J = 6.8 Hz), 5.04 (1H, t, J = 8.0 Hz), 5.48 (1H, t, J = 16.0 Hz), 6.43 (1H, d, J = 8.0 Hz), 6.83 (1H, t, J = 8.0 Hz), 7.18–7.26 (3H, m), 7.39–7.43 (1H, m), 7.47 (1H, d, J = 8.0 Hz), 7.50–7.54 (4H, m), 8.32 (1H, d, J = 8.0 Hz), 8.46 (1H, s), 8.57 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 559 $[M + H]^+$. Anal. Calcd for $C_{33}H_{30}N_6O_3$: C, 70.95; H, 5.41; N, 15.04; Found: C, 71.11; H, 5.55; N, 15.18.

*4.1.19. General procedure for the synthesis of **28a** and **28b***

To a solution of **24** (53 mg, 0.1 mmol) in DMF (25 mL), 60% NaH (4.2 mg, 0.105 mmol) was added portionwise at room temperature. After stirring for 30 min, alkyl halide (0.15 mmol) was added and the mixture was then reacted at 60 °C for 10 h. After cooling, the mixture was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **28a** and **28b**.

*4.1.19.1. 3-(1-Isopropyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**28a**).* According to the general method, the reaction of **24** with 2-bromopropane afforded **28a** in 61% yield as a red solid, mp: 116–118 °C. ^{1}H NMR ($CDCl_3$, δ): 1.63 (6H, d, J = 6.5 Hz), 1.85–1.92 (2H, m), 2.21–2.29 (6H, m), 3.59–3.65 (4H, m), 4.51(2H, t, J = 6.8 Hz), 4.70–4.76 (1H, m), 6.37 (1H, d, J = 8.0 Hz), 6.77 (1H, t, J = 8.0 Hz), 7.11–7.15 (2H, m), 7.37–7.42 (2H, m), 7.49–7.54 (4H, m), 8.25 (1H, d, J = 8.0 Hz), 8.38 (1H, s), 8.55 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 575 $[M + H]^+$. Anal. Calcd for $C_{34}H_{34}N_6O_3$: C, 71.06; H, 5.96; N, 14.62; Found: C, 71.33; H, 6.05; N, 14.87.

*4.1.19.2. 3-(1-Benzyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**28b**).* According to the general method, the reaction of **24** with (chloromethyl) benzene afforded **28b** in 71% yield as a red solid, mp: 142–144 °C. ^{1}H NMR ($CDCl_3$, δ): 2.16–2.23 (2H, m), 2.42–2.58 (6H, m), 3.72–3.81 (4H, m), 4.53 (2H, t, J = 6.8 Hz), 5.41 (2H, s), 6.41 (1H, d, J = 8.0 Hz), 6.79 (1H, t, J = 8.4 Hz), 7.09–7.16 (2H, m), 7.23–7.27 (2H, m), 7.30–7.42 (5H, m), 7.48–7.53 (4H, m), 8.22 (1H, d, J = 8.0 Hz), 8.28 (1H, s), 8.57 (1H, d, J = 4.4 Hz). ESI-MS: m/z = 623 $[M + H]^+$. Anal. Calcd for $C_{38}H_{34}N_6O_3$: C, 73.29; H, 5.50; N, 13.50; Found: C, 73.45; H, 5.34; N, 13.64.

*4.1.20. 3-(1-Allyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**28c**)*

To a solution of **24** (53 mg, 0.1 mmol) in DMF (25 mL), 60% NaH (4.2 mg, 0.105 mmol) was added portionwise at room temperature. After stirring for 30 min, 3-bromoprop-1-ene (18 mg, 0.15 mmol) was added and the mixture was then stirred at room temperature for 2 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 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **28c** (33 mg, 58%) as a red solid, mp: 71–73 °C. ^{1}H NMR ($CDCl_3$, δ): 1.83–1.92 (2H, m), 2.18–2.32 (6H, m), 4.01–4.13 (4H, m), 4.49 (2H, t, J = 6.8 Hz), 4.82 (2H, d, J = 4.8 Hz), 5.25–5.29 (2H, m), 6.05–6.12 (1H, m), 6.37 (1H, d, J = 8.0 Hz), 6.77 (1H, t, J = 7.6 Hz), 7.10–7.15 (2H, m), 7.32 (1H, d,

J = 8.0 Hz), 7.36–7.41 (1H, m), 7.49–7.55 (4H, m), 8.22 (1H, s), 8.25 (1H, dd, J = 1.6, 8.0 Hz), 8.55 (1H, dd, J = 1.6, 4.4 Hz). ESI-MS: m/z = 573 $[M + H]^+$. Anal. Calcd for $C_{34}H_{32}N_6O_3$: C, 71.31; H, 5.63; N, 14.68; Found: C, 71.59; H, 5.54; N, 14.61.

*4.1.21. General procedure for the synthesis of **28d** and **28e***

To a solution of **24** (53 mg, 0.1 mmol) in DMF (25 mL), 60% NaH (4.2 mg, 0.105 mmol) was added portionwise at room temperature. After stirring for 30 min, alkyl halide (0.15 mmol) was added and the mixture was then reacted at 80 °C for 10 h. After cooling, the mixture was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 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 (120:4:1, v/v/v) as eluent to afford **28d** and **28e**.

*4.1.21.1. 3-(1-Morpholinopropyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**28d**).* According to the general method, the reaction of **24** with 4-(3-chloropropyl)morpholine afforded **28d** (40 mg, 58%) as a red solid, mp: 156–158 °C. ^{1}H NMR ($CDCl_3$, δ): 2.07–2.12 (2H, m), 2.18–2.22 (2H, m), 2.52–2.64 (12H, m), 3.80–3.89 (8H, m), 4.38 (2H, t, J = 6.8 Hz), 4.54 (2H, t, J = 6.8 Hz), 6.41 (1H, d, J = 8.0 Hz), 6.79 (1H, t, J = 7.6 Hz), 7.12–7.17 (2H, m), 7.38–7.41 (2H, m), 7.48–7.53 (4H, m), 8.12 (1H, dd, J = 1.6, 8.0 Hz), 8.28 (1H, s), 8.56 (1H, dd, J = 1.6, 4.4 Hz). ESI-MS: m/z = 660 $[M + H]^+$. Anal. Calcd for $C_{38}H_{41}N_7O_4$: C, 69.18; H, 6.26; N, 14.86; Found: C, 69.37; H,6.44; N, 14.69.

*4.1.21.2. 3-(1-(3-(1H-Imidazol-1-yl)propyl)-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1-phenyl-1H-pyrrole-2,5-dione (**28e**).* According to the general method, the reaction of **24** with 1-(3-chloropropyl)-1*H*-imidazole afforded **28e** in 56% yield as a scarlet solid, mp: 68–70 °C. ^{1}H NMR ($CDCl_3$, δ): 1.89–1.93 (2H, m), 2.27–2.35 (6H, m), 2.41–2.45 (2H, m), 3.61–3.67 (4H, m), 4.01 (2H, t, J = 6.8 Hz), 4.20 (2H, t, J = 6.8 Hz), 4.49 (2H, t, J = 6.8 Hz), 6.37 (1H, d, J = 8.0 Hz), 6.79 (1H, t, J = 8.0 Hz), 6.98 (1H, brs), 7.12–7.17 (3H, m), 7.22 (1H, d, J = 8.0 Hz), 7.39–7.42 (1H, m), 7.50–7.55 (4H, m), 7.56 (1H, brs), 8.17 (1H, s), 8.25 (1H, dd, J = 1.6, 8.0 Hz), 8.55 (1H, dd, J = 1.6, 4.4 Hz). ESI-MS: m/z = 641 $[M + H]^+$. Anal. Calcd for $C_{37}H_{36}N_8O_3$: C, 69.36; H, 5.66; N, 17.49; Found: C, 69.55; H,5.58; N, 17.61.

*4.1.22. General procedure for the synthesis of **27**, **29a–e** and **30***

A mixture of **26**, **28a–e** and **24** (0.05mol), 28% aqueous ammonia (1 mL) and DMF (2 mL) was stirred at 90 °C for 4 h. After cooling, it was poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was combined, washed with brine (3 × 100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol/triethylamine (120:4:1, v/v/v) as eluent to afford **27**, **29a–e** and **30** respectively.

*4.1.22.1. 3-(1-(3-Morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-4-(1-vinyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione (**27**).* According to the general method, the reaction of **26** with aqueous ammonia afforded **27** in 87% yield as a red solid, mp: 165–167 °C. ^{1}H NMR ($CDCl_3$, δ): 1.81–1.87 (2H, m), 2.20–2.28 (6H, m), 3.59–3.65 (4H, m), 4.49 (2H, t, J = 6.8 Hz), 5.02 (1H, t, J = 8.8 Hz), 5.45 (1H, t, J = 16.0 Hz), 6.41 (1H, d, J = 8.0 Hz), 6.79 (1H, t, J = 8.0 Hz), 7.19–7.24 (3H, m), 7.44 (1H, d, J = 8.0 Hz), 7.85 (1H, brs), 8.23 (1H, d, J = 8.0 Hz), 8.39 (1H, s), 8.55 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 483 $[M + H]^+$. Anal. Calcd for $C_{27}H_{26}N_6O_3$: C, 67.21; H, 5.43; N, 17.42; Found: C, 67.38; H, 5.48; N, 17.65.

*4.1.22.2. 3-(1-Isopropyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole –2,5-dione (**29a**).* According to the general method, the reaction of **28a** with aqueous ammonia afforded **29a** in 84% yield as a red solid, mp: 99–101 °C. ^{1}H NMR ($CDCl_3$, δ): 1.65 (6H, d, J = 6.5 Hz), 1.89–1.97 (2H, m), 2.24–2.34 (6H, m), 3.63–3.68 (4H, m), 4.52 (2H, t, J = 6.8 Hz), 4.69–4.76 (1H, m), 6.36 (1H, d, J = 8.0 Hz), 6.76 (1H, t, J = 8.0 Hz), 7.10–7.15 (2H, m), 7.36 (1H, d, J = 8.0 Hz), 7.83 (1H, brs), 8.15 (1H, dd, J = 1.6, 8.0 Hz), 8.28 (1H, s), 8.56 (1H, dd, J = 1.6, 4.0 Hz). ^{13}C NMR ($CDCl_3$, δ): 171.41, 171.15, 150.66, 149.06, 136.44, 134.79, 134.18, 131.87, 131.41, 125.65, 122.43, 122.32, 121.55, 120.89, 117.58, 115.52, 110.12, 105.20, 66.65 (2), 55.71, 53.27 (2), 48.02, 45.52, 26.15, 22.66 (2). ESI-MS: m/z = 499 $[M + H]^+$. Anal. Calcd for $C_{28}H_{30}N_6O_3$: C, 67.45; H, 6.06; N, 16.86; Found: C, 67.38; H, 6.12; N, 16.98.

*4.1.22.3. 3-(1-Benzyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**29b**).* According to the general method, the reaction of **28b** with aqueous ammonia afforded **29b** in 86% yield as a red solid, mp: 174–176 °C. ^{1}H NMR ($CDCl_3$, δ): 1.88–1.96 (2H, m), 2.25–2.33 (6H, m), 3.58–3.66 (4H, m), 4.51 (2H, t, J = 6.8 Hz), 5.38 (2H, s), 6.43 (1H, d, J = 8.0 Hz), 6.77 (1H, t, J = 8.0 Hz), 7.07–7.13 (2H, m), 7.20–7.26 (3H, m), 7.32–7.35 (3H, m), 8.13 (1H, d, J = 8.0 Hz), 8.17–8.24 (2H, m), 8.55 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 547 $[M + H]^+$. Anal. Calcd for $C_{32}H_{30}N_6O_3$: C, 67.45; H, 6.06; N, 16.86; Found: C, 67.38; H, 6.12; N, 16.98.

*4.1.22.4. 3-(1-Allyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**29c**).* According to the general method, the reaction of **28c** with aqueous ammonia afforded **29c** in 79% as a red solid, mp: 148–150 °C. ^{1}H NMR ($CDCl_3$, δ): 1.88–1.99 (2H, m), 2.25–2.41 (6H, m), 3.60–3.73 (4H, m), 4.52 (2H, t, J = 7.2 Hz), 4.82 (2H, d, J = 5.6 Hz), 5.24 (1H, d, J = 17.2 Hz), 5.33 (1H, d, J = 10.0 Hz), 6.01–6.11 (1H, m), 6.34 (1H, d, J = 8.0 Hz), 6.75 (1H, t, J = 8.0 Hz), 7.10–7.15 (2H, m), 7.31 (1H, d, J = 8.0 Hz), 8.06 (1H, brs), 8.14–8.18 (2H, m), 8.55 (1H, dd, J = 1.6, 4.0 Hz). ^{13}C NMR ($CDCl_3$, δ):171.73, 171.46, 150.55, 148.96, 136.74, 134.65, 134.43, 134.04, 132.23, 131.85, 125.53, 122.57, 122.23, 122.13, 120.84, 118.49, 117.51, 115.47, 110.22, 105.26, 66.56 (2), 55.62, 53.16 (2), 49.44, 45.48, 26.02. ESI-MS: m/z = 497 $[M + H]^+$. Anal. Calcd for $C_{28}H_{28}N_6O_3$: C, 67.73; H, 5.68; N, 16.92; Found: C, 67.58; H, 5.72; N, 17.03.

*4.1.22.5. 3-(1-Morpholinopropyl-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**29d**).* According to the general method, the reaction of compound **28d** with aqueous ammonia afforded **29d** in 89% as a jacinth solid, mp: 115–117 °C. ^{1}H NMR ($CDCl_3$, δ): 1.97–2.03 (2H, m), 2.09–2.14 (2H, m), 2.36–2.51 (12H, m), 3.70–3.81 (8H, m), 4.34 (2H, t, J = 6.8 Hz), 4.52 (2H, t, J = 6.8 Hz), 6.26 (1H, d, J = 8.0 Hz), 6.73 (1H, t, J = 8.0 Hz), 7.10–7.15 (2H, m), 7.37 (1H, d, J = 8.0 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.17 (1H, brs), 8.21 (1H, s), 8.55 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 584 $[M + H]^+$. Anal. Calcd for $C_{32}H_{37}N_7O_4$: C, 65.85; H, 6.39; N, 16.80; Found: C, 65.88; H, 6.31; N, 17.08.

*4.1.22.6. 3-(1-(3-(1H-Imidazol-1-yl)propyl)-1H-indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo[3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**29e**).* According to the general method, the reaction of **28e** with aqueous ammonia afforded compound **29e** in 81% as a red solid, mp: 84–86 °C. ^{1}H NMR ($CDCl_3$, δ): 1.85–1.91 (2H, m), 2.23–2.31 (6H, m), 2.41–2.46 (2H, m), 3.58–3.65 (4H, m), 3.99 (2H, t, J = 6.4 Hz), 4.18 (2H, t, J = 6.4 Hz), 4.48 (2H, t, J = 6.8 Hz), 6.32 (1H, d, J = 8.0 Hz), 6.76 (1H, t, J = 8.4 Hz), 7.00 (1H, brs), 7.16–7.21 (4H, m), 7.62 (1H, brs), 8.09 (1H, s), 8.14–8.19 (2H, m), 8.55 (1H, d, J = 4.0 Hz). ESI-MS: m/z = 565 $[M + H]^+$. Anal. Calcd for $C_{31}H_{32}N_8O_3$: C, 65.94; H, 5.71; N, 19.85; Found: C, 65.88; H, 5.41; N, 19.98.

*4.1.22.7. 3-(1H-Indol-3-yl)-4-(1-(3-morpholinopropyl)-1H-pyrazolo [3,4-b]pyridine-3-yl)-1H-pyrrole-2,5-dione (**30**).* According to the general method, compound **24** reacted with aqueous ammonia to afford compound **30** in 81% as a jacinth solid, mp: 218–220 °C. ^{1}H NMR ($CDCl_3$, δ): 1.91–1.97 (2H, m), 2.28–2.37 (6H, m), 3.63–3.70 (4H, m), 4.53 (2H, t, J = 6.8 Hz), 6.45 (1H, d, J = 8.0 Hz), 6.78 (1H, t, J = 8.0 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.14–7.17 (1H, m), 7.33 (1H, d, J = 8.0 Hz), 8.15–8.19 (3H, m), 8.57 (1H, d, J = 4.4 Hz), 9.19 (1H, brs). Anal. Calcd for $C_{25}H_{24}N_6O_3$: C, 65.78; H, 5.30; N, 18.41; Found: C, 18.59; H, 5.35; N, 18.57.

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 h. 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 coil system. All these kinase assays were carried out by using the Invitrogen Z′-LYTETM Kinase Assay kits.

4.3. Molecular docking with Flexidock program

The binding pocket was defined all residues within 4 Å of the ligand within the CysLT2 complex proposed by LigandFit. All single bonds of residue side chains inside the binding pocket were regarded as rotatable or flexible. The docked ligand was allowed to rotate on all of single bonds and move flexibly within the tentative binding pocket.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.07.046.

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