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FULL PAPER

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# 3-(7-Azaindolyl)-4-indolylmaleimides as a novel class of mutant isocitrate dehydrogenase-1 inhibitors: Design, synthesis, and biological evaluation

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## Abstract

A series of 3-(7-azainodyl)-4-indolylmaleimides was designed, synthesized, and evaluated for their isocitrate dehydrogenase 1 (IDH1)/R132H inhibitory activities. Many compounds such as **11a**, **11c**, **11e**, **11g**, and **11s** exhibited favorable inhibitory effects on IDH1/R132H and were highly selective against the wild-type IDH1. Evaluation of the biological activities at the cellular level showed that compounds **11a**, **11c**, **11e**, **11g**, and **11s** could effectively suppress the production of 2-hydroxyglutaric acid in U87MG cells expressing IDH1/R132H. Preliminary structure–activity relationship (SAR) and molecular modeling studies were discussed based on the experimental data obtained. These findings may provide new insights into the development of novel IDH1/R132H inhibitors.

**KEYWORDS**
2-hydroxyglutaric acid, 3-(7-azaindoyl)-4-indolylmaleimides, isocitrate dehydrogenase 1 inhibitors, tumor

## 1 | INTRODUCTION

Isocitrate dehydrogenase 1 (IDH1) is a key rate-limiting enzyme in the tricarboxylic acid cycle, which mainly exists in the cytoplasm and

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peroxisomes.[1] IDH1 can catalyze the oxidative decarboxylation of isocitric acid to produce α-ketoglutaric acid (α-KG) and reduce $NADP^+$ to NADPH, using nicotinamide adenine dinucleotide phosphate ($NADP^+$) as the electron acceptor (Scheme 1).[2–4]

Recent studies have demonstrated a high mutation rate of IDH1 in many malignant tumors.[5] For example, the mutation rate of IDH1 reached 56, 70, and 5.5–10.4% in sarcoma,[6] glioma,[7,8] and acute myeloid leukemia (AML),[9–11] respectively. To date, all the IDH1 mutations were found at the R132 codon, including R132H, R132C, R132L, R132S, R132G, and R132Q, among which R132H was the predominant one, accounting for about 90%.[12–15] The IDH1 mutation causes a dramatic decrease in the production of α-KG following the oxidative decarboxylation of isocitric acid. Furthermore, IDH1 mutation exerts a new catalytic function that causes the reduction of α-KG to 2-hydroxyglutaric acid (2-HG), leading to massive accumulation of 2-HG in cells (Scheme 2).[13,16–18]

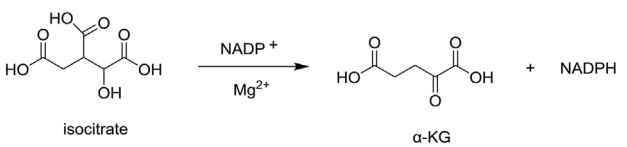
Because 2-HG and α-KG have a similar structure, they compete each other. For these two reasons, the activity of some α-KG-dependent dioxygenases including proline hydroxylase, Tet family DNA hydroxylase, and histone lysine methyltransferase decreases, leading to excessive DNA methylation and histone methylation, which can cause epigenetic disorders, cell differentiation inhibition, and eventually tumorigenesis.[19–23] Because of the key roles of IDH1 mutation in the development and progression of tumors, the mutated IDH1 (including IDH1/R132H) has become a potentially attractive target for anti-tumor therapies.[24] The search for their inhibitors has become a hot spot in the research and development of new anti-tumor drugs. During the past few years, many IDH1/R132H inhibitors with varied structures have been reported (Figure 1).[25–33] Among them, AGI-120 (developed by Agios Pharmaceuticals, Cambridge, MA, USA) and IDH305 (Novartis Pharmaceuticals, Basel, Switzerland) have entered clinical trials.

In our current study, a series of 3-(7-azaindolyl)-4-indolylmaleimide IDH1/R132H inhibitors was developed by carrying out high-throughput screening followed by structural modification of lead compounds. Their structure–activity relationship (SAR) and *in silico* molecular modeling study were discussed as well.

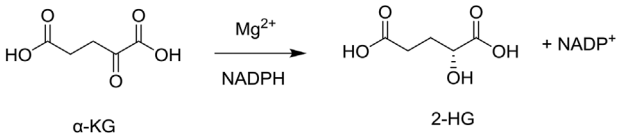
## 2 | RESULTS AND DISCUSSION

### 2.1 | Chemistry

The synthesis routes of target compounds **11a–t** are summarized in Scheme 3. Compounds **2a–i** were prepared from indole derivatives **1a–i** by acylation with oxalyl chloride in dry $Et_2O$, followed by




**SCHEME 1** Oxidative decarboxylation of isocitric acid to produce α-KG




**SCHEME 2** Reduction of α-KG to 2-HG

alcoholysis with sodium methoxide. *N*-Alkylation of **2a–i** with different alkyl halides using NaH as a base in dry N,N-Dimethylformamide (DMF) afforded key intermediates **3a–p**. The acylation of 7-azaindole **4** with $ClCOCO_2Et$ using anhydrous $AlCl_3$ as a catalyst gave compound **5**, which was reacted with $(Boc)_2O$ in the presence of a catalytic amount of DMAP affording the key intermediate **6a**. *N*-Alkylation of **5** with bromoethane and 2-bromopropane resulted in other key intermediates **6b** and **6c** respectively. *N*-Methylation of **4** with iodomethane afforded compound **7**, which can be easily converted to compound **8** following the same procedure as described for preparing compound **5**. Compound **8** was reduced with triethylsilane in trifluoroacetic acid (TFA) to provide acetic ether derivatives **9**, which was ammonolyzed by saturated solution of ammonia in methanol to give the key intermediate **10**. Maleimide condensation of **10** with **3a–p** or **2a** in the presence of *t*-BuOK afforded the target compounds **11a–q**, respectively.[34] Target compounds **11r–t** were prepared by the maleimide condensation of **6a–c** with **12** using the same procedure as described above.

### 2.2 | Biological activity

#### 2.2.1 | Enzymatic activity

All the prepared compounds **11a–t** were tested for their IDH1/R132H inhibitory activity. A well-known kinase inhibitor AG-120 developed by Agios Pharmaceuticals was used as the positive control. The results are presented in Table 1.

As shown in Table 1, most of the tested compounds displayed moderate to potent inhibitory activity against IDH1/R132H. Among them, compound **11e** ($IC_{50}$ = 0.16 μM) and **11g** ($IC_{50}$ = 0.28 μM) exhibited more potent inhibition of IDH1/R132H than other analogues. SAR analysis showed that introduction of a suitable hydrophilic side chain, which may form hydrogen bond interactions with the enzyme, at the $N^1$-position of the indole ring is necessary for the activity. For example, compound **11a** ($IC_{50}$ = 0.40 μM) with a 3-(1*H*-imidazol-l-yl)propyl on the indole nitrogen was about 48-fold more potent than $N^1$-position no substituted compound **11q** ($IC_{50}$ = 19.39 μM). However, compounds **11m–p**, with a hydrophilic 3-(piperidin-1-yl)propyl, 3-morpholinopropyl, 3-(1*H*-1,2,4-triazol-1-yl)-propyl, and 3-(pyrrolidin-1-yl)propyl, respectively, exhibited weaker inhibitory activities than **11a**, which suggested that these hydrophilic side chains may not effectively form hydrogen bond interactions with the protein. In addition, comparing the inhibitory activity of **11a**, **11j**, and **11l** revealed that the length of the $N^1$-alkyl linker affected IDH1/R132H inhibitory potency. For example, compound **11a** ($IC_{50}$ = 0.40 μM) with a $(CH_2)_3$ linker showed better

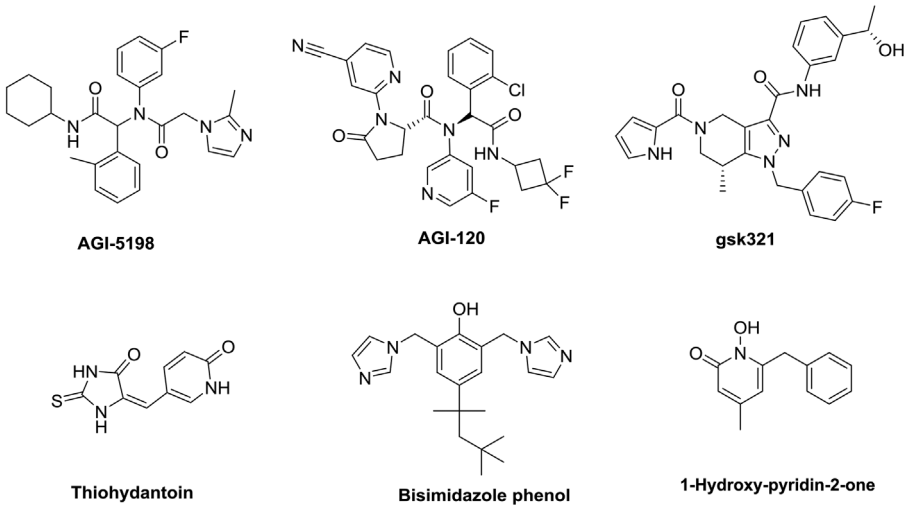



**FIGURE 1** IDH1/R132H inhibitors

inhibitory activity than compound **11j** ($IC_{50}$ = 0.86 μM) with a $(CH_2)_4$ linker and **11l** ($IC_{50}$ = 14.50 μM) with a $(CH_2)_2$ linker. The same conclusion could also be drawn from comparison of the inhibitory potency of **11e** and **11k**.

When comparing the inhibitory activity of **11b–i** with **11a**, it suggested that different substituents ($R_1$) on the indole ring affected the inhibitory potency for IDH1/R132H. Introduction of a chlorine (**11d**, $IC_{50}$ = 0.16 μM) or bromine (**11f**, $IC_{50}$ = 0.28 μM) atom at the 6-position of the indole ring led to about twofold enhancement of the activity as compared to **11a**. Fluorine at 6-position of the indole ring (**11d**, $IC_{50}$ = 0.36 μM) or benzyloxy group at 5-position of the indole ring (**11i**, $IC_{50}$ = 0.47 μM) was tolerated for the activity, while halogen atom at 5-position (i.e., **11b**, **11d**, and **11f**) or methyl at the 7-position (**11h**) showed less inhibitory potency.

Comparison of IDH1/R132H inhibitory data of compounds with various substituents at the $N^1$-position of the 7-azaindole ring revealed that compounds with a Me (**11a**, $IC_{50}$ = 0.40 μM) or Et (**11s**, $IC_{50}$ = 0.34 μM) on $N^1$-position of the 7-azaindole ring were tolerated for IDH1/R132H inhibitory activity. However, replacement of Me with H (**11r**, $IC_{50}$ = 0.83 μM) or i-Pr (**11t**, $IC_{50}$ = 1.42 μM) led to about 2- and 3.5-fold loss in potency as compared to the case of compound **11a**, respectively.

Because of the important physiological role of wild-type IDH1 (IDH1/WT), compounds which also strongly inhibit IDH1/WT catalytic activity are disadvantageous for their clinical application. The assay of inhibitory activity of selected compounds **11a**, **11c**, **11e**, **11g**, and **11s** toward IDH1/WT was also conducted to determine the enzyme selectivity. As shown in Table 2, all the tested compounds displayed high selectivity for IDH1/R132H over IDH1/WT.

### 2.2.2 | Cellular activity

IDH1 mutation gains a catalytic function that causes the reduction of α-KG to 2-HG, resulting in a high concentration of 2-HG that accumulates in cancer cells. Compounds **11a**, **11c**, **11e**, **11g**, and **11s** were tested for their ability to reduce the production of 2-HG using sensitive and specific LC/MS/MS methods. AGI-120, an IDH1/R132H inhibitor, was used as a reference compound in this assay. As shown in Figure 2, compounds **11a**, **11c**, **11e**, **11g**, and **11s** effectively inhibited 2-HG production in IDH1/R132H-expressing U87MG cells in a dose-independent manner, which correlates well with their inhibitory activity toward IDH1/R132H.

### 2.3 | Molecular modeling study

In order to explore the possible binding mode of the target compounds, a molecular modeling study of **11e** was performed using CDOCKER module in Discovery Studio 2.5, based on the published IDH1/R132H crystal structure (5DE1).[30] As seen in Figure 3, the amino and carbonyl in maleimide ring of **11e** can tightly interact with Arg109, Ala111, and Ile128 of IDH1/R132H via the hydrogen bonding network. The 7-position nitrogen of the 7-azaindazole ring acting as a hydrogen bond acceptor forms another H-bond with Arg119. The 7-azaindole and indole moiety of compound **11e** both have π–π interaction (T-shaped) with Trp124 residue. In addition, the chlorine atom (in green) of compound **11e** can fit in the hydrophobic pocket composed of Val255 and Met259, which is similar to that reported by Refs. [30,31]. The 3-position nitrogen of imidazole ring is about 3.7 and 3.4 Å from the NH of Arg119 and Leu120, respectively, and may keep water-mediated interaction with them.

## 3 | CONCLUSION

In summary, a series of 3-(7-azaindolyl)-4-indolylmaleimides was synthesized and biologically evaluated as IDH1/R132H inhibitors. Among them, compounds **11a**, **11c**, **11e**, **11g**, and **11s** exhibited high inhibitory potencies against IDH1/R132H and were highly selective

against the wild-type IDH1, which inhibited the cellular 2-HG production in a dose-dependent manner. Preliminary SAR study based on the experimental data and molecular modeling study provided information that could be useful for the design of novel IDH1/R132H inhibitors as antitumor agents.

## 4 | EXPERIMENTAL

### 4.1 | Chemistry

#### 4.1.1 | General

All reagents used in the synthesis were obtained commercially and used without further purification, unless otherwise specified. Melting points were determined with a BÜCHI Melting Point B-450 apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. $^1$H NMR spectra were recorded using TMS as the internal standard at 500 MHz and the coupling constants are reported in hertz. The reactions were followed by thin-layer chromatography (TLC) on glass-packed precoated silica gel plates and visualized in an iodine chamber or with a UV lamp. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. DMF was distilled from calcium hydride. Compounds **2a–i**, **3a**, **3d**, **3f**, **3l–p**, and **12** were synthesized according to literature procedures.[35–38]

The InChI codes together with some biological activity data are provided as Supporting Information.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-5-fluoro-1*H*-indol-3-yl)-2-oxoacetate (3b)**

To a solution of **2b** (2.4 g, 7.0 mmol) in anhydrous DMF (15 mL), 70% NaH (0.32 g, 8.0 mmol) was added portionwise at 0–5°C. After stirring for 30 min at room temperature, 1-(3-chloropropyl)-1*H*-imidazole (1.59 g, 11.0 mmol) was added. Then the mixture was stirred for 6 h at 60°C. After cooling, the mixture was then poured into water (100 mL) and extracted with ethyl acetate (50 mL × 3). The organic phase was combined and washed with brine (150 mL × 3), 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 **3b** (33.2% yield) as a light yellow solid, mp: 108–110°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.37 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 7.56 (s, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 4.38 (t, *J* = 7.0 Hz, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 3.97 (s, 3H), 2.42–2.36 (m, 2H). ESI-MS: *m/z* = 330 $[M+H]^+$.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-6-fluoro-1*H*-indol-3-yl)-2-oxoacetate (3c)**

According to the procedure used to prepare **3b**, reaction of **2c** with 1-(3-chloropropyl)-1*H*-imidazole provided **3c** in 39.5% yield as a light yellow solid, mp: 113–115°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.41 (dd, *J* = 8.8, 5.4 Hz, 1H), 8.34 (s, 1H), 7.53 (s, 1H), 7.17 (s, 1H), 7.13 (td, *J* = 9.0, 2.2 Hz, 1H), 6.98–6.95 (m, 2H), 4.14 (t, *J* = 7.0 Hz, 2H), 4.01 (t, *J* = 6.8 Hz, 2H), 3.98 (s, 3H), 2.48–2.38 (m, 2H). ESI-MS: *m/z* = 330 $[M+H]^+$.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-6-chloro-1*H*-indol-3-yl)-2-oxoacetate (3e)**

According to the procedure used to prepare **3b**, reaction of **2e** with 1-(3-chloropropyl)-1*H*-imidazole provided **3e** in 46.5% yield as a light yellow solid, mp: 135–136°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 8.5 Hz, 1H), 8.35 (s, 1H), 7.55 (s, 1H), 7.35 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.17 (s, 1H), 6.97 (s, 1H), 4.15 (t, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 7.0 Hz, 2H), 3.98 (s, 3H), 2.47–2.41 (m, 2H). ESI-MS: *m/z* = 346 $[M+H]^+$.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-6-bromo-1*H*-indol-3-yl)-2-oxoacetate (3g)**

According to the procedure used to prepare **3b**, reaction of **2g** with 1-(3-chloropropyl)-1*H*-imidazole provided **3g** in 29.6% yield as a light yellow solid, mp: 139–141°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.33–8.32 (m, 2H), 7.56 (s, 1H), 7.48 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.45 (d, *J* = 1.5 Hz, 1H), 7.17 (s, 1H), 6.96 (s, 1H), 4.15 (t, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 7.0 Hz, 2H), 3.97 (s, 3H), 2.50–2.38 (m, 2H). ESI-MS: *m/z* = 390 and 392 $[M+H]^+$.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-7-methyl-1*H*-indol-3-yl)-2-oxoacetate (3h)**

According to the procedure used to prepare **3b**, reaction of **2h** with 1-(3-chloropropyl)-1*H*-imidazole provided **3h** in 47.3% yield as a light yellow solid, mp: 106–107°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.37 (d, *J* = 7.9 Hz, 1H), 8.29 (s, 1H), 7.56 (s, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 7.3, 1.1 Hz, 1H), 6.98 (s, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 3.98 (s, 3H), 2.61 (s, 3H), 2.50–2.39 (m, 2H). ESI-MS: *m/z* = 326 $[M+H]^+$.

**Methyl 2-(1-(3-(1*H*-imidazol-1-yl)propyl)-5-(benzyloxy)-1*H*-indol-3-yl)-2-oxoacetate (3i)**

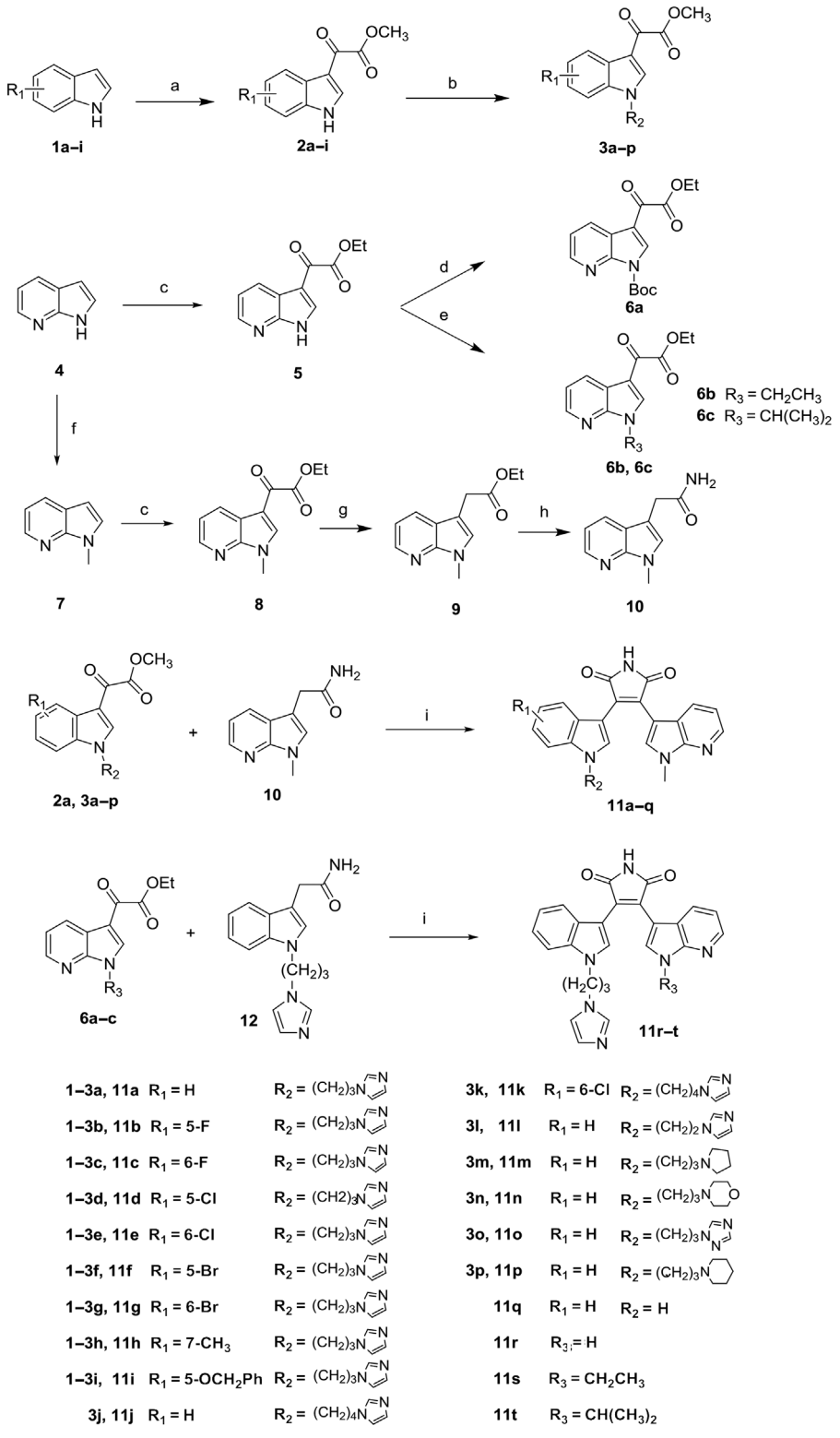
According to the procedure used to prepare **3b**, reaction of **2i** with 1-(3-chloropropyl)-1*H*-imidazole provided **3i** in 43.8% yield as a light yellow solid, mp: 147–148°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 7.55–7.49 (m, 3H), 7.44–7.38 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 7.16 (s, 1H), 7.07 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.95 (s, 1H), 5.18 (s, 2H), 4.14 (t, *J* = 7.0 Hz, 2H), 4.00–3.95 (m, 5H), 2.46–2.39 (m, 2H). ESI-MS: *m/z* = 418 $[M+H]^+$.

**Methyl 2-(1-(4-(1*H*-imidazol-1-yl)butyl)-1*H*-indol-3-yl)-2-oxoacetate (3j)**

According to the procedure used to prepare **3b**, reaction of **2a** with 1-(4-chlorobutyl)-1*H*-imidazole provided **3j** in 43.9% yield as a light yellow solid, mp: 97–98°C. $^1$H NMR (500 MHz,$CDCl_3$) δ: 8.51–8.44 (m, 1H), 8.38 (s, 1H), 7.45 (s, 1H), 7.42–7.31 (m, 3H), 7.08 (t, *J* = 1.1 Hz, 1H), 6.86 (t, *J* = 1.3 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 3.97 (s, 3H), 3.95 (t, *J* = 6.7 Hz, 2H), 1.96–1.79 (m, 4H). ESI-MS: *m/z* = 326 $[M+H]^+$.

**Methyl 2-(1-(4-(1*H*-imidazol-1-yl)butyl)-6-chloro-1*H*-indol-3-yl)-2-oxoacetate (3k)**

According to the procedure used to prepare **3b**, reaction of **2e** with 1-(4-chlorobutyl)-1*H*-imidazole provided **3k** in 39.7% yield as a light



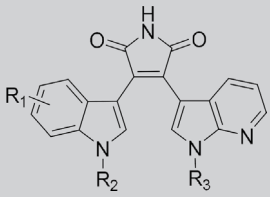

**SCHEME 3** Synthetic route to compounds **11a–t**. Reagents and conditions: (a) (i) oxalyl chloride, diethyl ether; (ii) $CH_3ONa$, $CH_3OH$; (b) NaH, DMF, $R_2X$; (c) $AlCl_3$, $ClCOCO_2Et$; (d) $(Boc)_2O$, DMAP, THF; (e) cesium carbonate, DMF, $R_3Br$; (f) NaH, DMF, $CH_3I$; (g) triethylsilane, trifluoroacetic acid; (h) $NH_3$, methanol; (i) *t*-BuOK, THF; (ii) concentrated HCl

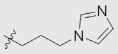
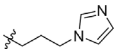
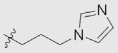
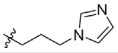
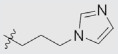
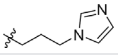
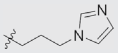
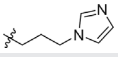
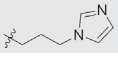
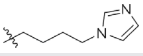
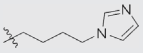
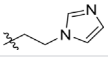
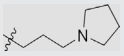
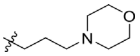
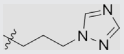
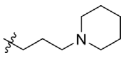
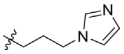
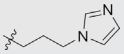
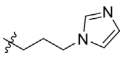
yellow solid, mp: 68–69°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.38–8.33 (m, 2H), 7.46 (s, 1H), 7.36–7.29 (m, 2H), 7.08 (s, 1H), 6.89–6.87 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 4.02–3.93 (m, 5H), 1.94–1.75 (m, 4H). ESI-MS: *m/z* = 360 $[M+H]^+$.

### Ethyl 2-oxo-2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetate (5)

To a mixture of **4** (1.2 g, 10 mmol), anhydrous aluminum chloride (18.0 g, 135 mmol) and 200 mL of anhydrous dichloromethane, ethyl oxalyl chloride (8.2 g, 60 mmol) in 30 mL anhydrous dichloromethane

**TABLE 1** IDH1/R132H inhibitory activities of target compounds



| Compd. | $R_1$ | $R_2$ | $R_3$ | $IC_{50}$ (μM) ± SE or inhibition% at ~20 μg/mL |
|---|---|---|---|---|
| AG-120 | | | | 0.20 ± 0.08 |
| **11a** | H |  | $CH_3$ | 0.40 ± 0.13 |
| **11b** | 5-F |  | $CH_3$ | 0.74 ± 0.06 |
| **11c** | 6-F |  | $CH_3$ | 0.36 ± 0.04 |
| **11d** | 5-Cl |  | $CH_3$ | 1.54 ± 0.37 |
| **11e** | 6-Cl |  | $CH_3$ | 0.16 ± 0.04 |
| **11f** | 5-Br |  | $CH_3$ | 1.75 ± 0.43 |
| **11g** | 6-Br |  | $CH_3$ | 0.28 ± 0.018 |
| **11h** | 7-Me |  | $CH_3$ | 0.62 ± 0.04 |
| **11i** | 5-$OCH_2Ph$ |  | $CH_3$ | 0.47 ± 0.07 |
| **11j** | H |  | $CH_3$ | 0.86 ± 0.31 |
| **11k** | 6-Cl |  | $CH_3$ | 0.63 ± 0.05 |
| **11l** | H |  | $CH_3$ | 14.50 ± 2.43 |
| **11m** | H |  | $CH_3$ | 20.33% |
| **11n** | H |  | $CH_3$ | 27.51% |
| **11o** | H |  | $CH_3$ | 45.81% |
| **11p** | H |  | $CH_3$ | 14.80% |
| **11q** | H | H | $CH_3$ | 19.39 ± 2.86 |
| **11r** | H |  | H | 0.83 ± 0.24 |
| **11s** | H |  | Et | 0.34 ± 0.06 |
| **11t** | H |  | i-Pr | 1.42 ± 0.18 |

SE, standard error mean.

was added dropwise. After addition, the mixture was stirred at room temperature for 6 h. The supernatant was abandoned and 20% ammonium acetate aqueous was added to the reaction mixture at 0–5°C. The mixture was stirred sufficiently and extracted with dichloromethane (50 mL × 3). The organic phase was combined, 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 (3:1, v/v) as eluent to afford **5** in 49.1% yield as a light yellow

**TABLE 2** IDH1/WT inhibitory activity of selected compounds

| Compd. | $IC_{50}$ (μM) |
|---|---|
| **11a** | ≥10 |
| **11c** | ≥10 |
| **11e** | ≥10 |
| **11g** | ≥10 |
| **11s** | ≥10 |

solid, mp: 98–99°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 12.27 (s, 1H), 8.78 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.72 (s, 1H), 8.47 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). ESI-MS: *m/z* = 219 $[M+H]^+$.

### *tert*-Butyl 3-(2-ethoxy-2-oxoacetyl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (6a)

A solution of **5** (0.50 g, 2.3 mmol), DMAP (14 mg, 0.01 mmol), and $(Boc)_2O$ (0.63 g, 2.9 mmol) in 30 mL dry THF was stirred at room temperature for 1 h. The mixture was then 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 **6a** in 80.6% yield as a light yellow solid, mp: 79–81°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.89 (s, 1H), 8.69 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.61 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.73 (s, 9H), 1.48 (t, *J* = 7.2 Hz, 3H). ESI-MS: *m/z* = 319 $[M+H]^+$.

### Ethyl 2-(1-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoacetate (6b)

A mixture of **5** (0.50 g, 2.3 mmol), cesium carbonate (1.6 g, 5 mmol), and bromoethane (0.35 g, 3.0 mmol) in 25 mL of anhydrous DMF was stirred at 50°C for 2 h. After cooling, the mixture was then poured into water (100 mL) and extracted with ethyl acetate (60 mL × 3). The organic phase was combined and washed with brine (180 mL × 3), 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 (2:1, v/v) as eluent to afford **6b** in 55.3% yield as a light yellow solid, mp: 72–73°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.55 (s, 1H), 8.43 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.32–7.27 (m, 1H), 4.47–4.40 (m, 4H), 1.58 (t, *J* = 7.5 Hz, 3H), 1.46 (t, *J* = 7.0 Hz, 3H). ESI-MS: *m/z* = 247 $[M+H]^+$.

### Ethyl 2-(1-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoacetate (6c)

According to the procedure used to prepare **6b**, reaction of **5** with 2-bromopropane provided **6c** in 52.1% yield as a light yellow solid. $^1$H NMR (500 MHz,$CDCl_3$) δ: 8.68 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.60 (s, 1H), 8.43 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.27–5.21 (m, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 6H), 1.46 (t, *J* = 7.2 Hz, 3H). ESI-MS: *m/z* = 261 $[M+H]^+$.

### 1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (7)

To a solution of 1*H*-pyrrolo[2,3-*b*]pyridine **4** (1.6 g, 10 mmol) in 30 mL anhydrous DMF, 70% NaH (0.96 g, 28 mmol) was added portionwise at 0–5°C. After stirring for 30 min, a solution of iodomethane (4.3 g, 30 mmol) in 5 mL anhydrous DMF was added dropwise. After addition, the mixture was stirred for 1 h at 0–5°C and then 1 h at room temperature. The mixture was then poured into water (100 mL) and extracted with dichloromethane (40 mL × 3). The organic phase was combined and washed with brine (120 mL × 3), 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 (3:1, v/v) as eluent to afford **7** in 85.0% yield as a light yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.34 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.17 (d, *J* = 3.4 Hz, 1H), 7.05 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 3.89 (s, 3H). ESI-MS: *m/z* = 133 $[M+H]^+$.

### Ethyl 2-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoacetate (8)

According to the procedure used to prepare **5**, reaction of **7** with ethyl oxalyl chloride provided **8** in 31.1% yield as a light yellow solid, mp: 96–98°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 8.71 (s, 1H), 8.52–8.43

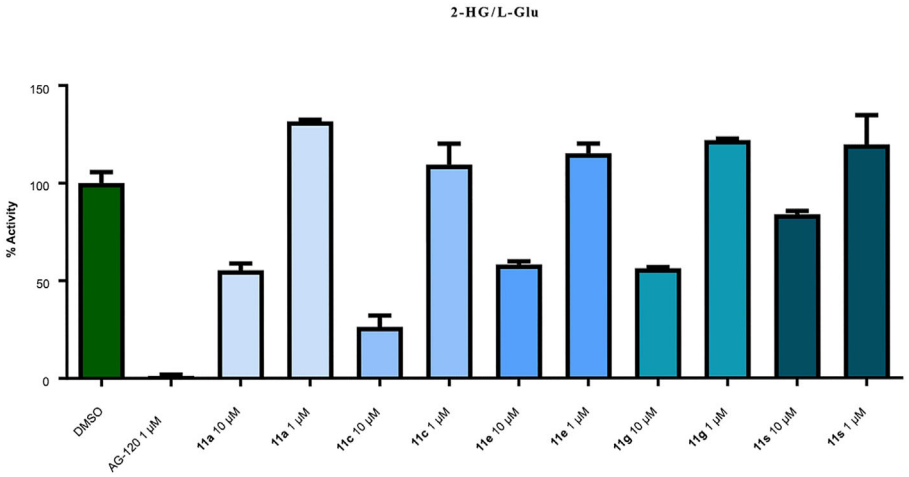



**FIGURE 2** Compounds **11a**, **11c**, **11e**, **11g**, and **11s** inhibited 2-HG production in IDH1/R132H expressing U87MG cells

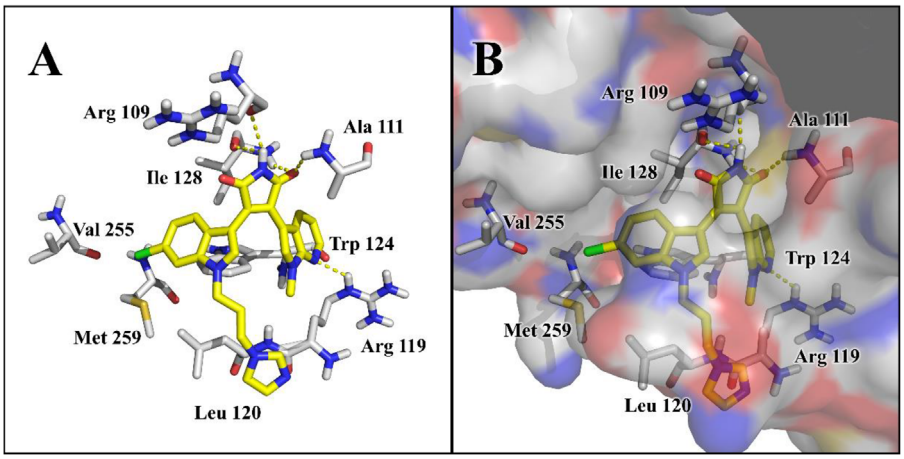



**FIGURE 3** Compound **11e** docked into IDH1/R132H crystal structure. (A) Binding mode of compound **11e** (in yellow); (B) compound **11e** bound to IDH1/R132H after surfacing receptor

(m, 2H), 7.39 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ESI-MS: *m/z* = 233 $[M+H]^+$.

### Ethyl 2-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetate (9)

A mixture of **8** (3.8 g, 16.5 mmol) and triethylsilane (10.4 g, 67.2 mmol) in 75 mL of trifluoroacetic acid was stirred at 55°C for 10 h. After cooling, the mixture was then poured into water (200 mL), alkalized with sodium bicarbonate, and extracted with ethyl acetate (100 mL × 3). The organic phase was combined, 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 **9** in 73.0% yield as a light yellow solid, mp: 107–108°C. $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.09 (s, 1H), 7.00 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). ESI-MS: *m/z* = 219 $[M+H]^+$.

### 2-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetamide (10)

A mixture of **9** (1.76 g, 8 mmol) and saturated solution of ammonia in methanol (10 mL) was stirred at 90°C in a sealed tube for 2 h. After cooling, the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using ethyl acetate/methanol (50:1, v/v) as eluent to afford **10** in 36.7% yield as a white solid, mp: 161–163°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 8.24 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.39 (brs, 1H), 7.35 (s, 1H), 7.07 (dd, *J* = 7.8, 4.6 Hz, 1H), 6.87 (brs, 1H), 3.79 (s, 3H), 3.48 (s, 2H). ESI-MS: *m/z* = 190 $[M+H]^+$.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11a)

To a solution of **3a** (0.37 mmol) and **10** (0.28 mmol) in anhydrous THF (20 mL), 1M *t*-BuOK in *t*-butanol (0.84 mL, 0.84 mmol) was added dropwise at −10 to 0°C. After stirring for 2 h at room temperature, concentrated hydrochloric acid (5 mL) was added and the resultant mixture was stirred for 30 min at room temperature, then poured into ice water (100 mL), alkalized with sodium bicarbonate, and extracted with ethyl acetate (100 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was then purified by flash column chromatography on silica gel using DCM/MeOH (60:1, v/v) as eluent to afford **11a** in 11.3% yield as a red solid, mp: 207–209°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.02 (s, 1H), 8.12 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.03 (s, 1H), 7.80 (s, 1H), 7.62 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.67 (dd, *J* = 8.2, 4.7 Hz, 1H), 4.23 (t, *J* = 7.0 Hz, 2H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.30–2.18 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{23}N_6O_2$ calcd. 451.1877. Found 451.1873.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-5-fluoro-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11b)

According to the procedure used to prepare **11a**, reaction of **3b** with **10** provided **11b** in 12.1% yield as a red solid, mp: 172–174°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.04 (s, 1H), 8.15 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.06 (s, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.46 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.19 (s, 1H), 7.00 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.99–6.89 (m, 2H), 6.71 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.56 (dd, *J* = 10.2, 2.6 Hz, 1H), 4.22 (t, *J* = 7.1 Hz, 2H), 3.95 (t, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 2.24–2.17 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}FN_6O_2$ calcd. 469.1783. Found 469.1781.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-6-fluoro-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11c)

According to the procedure used to prepare **11a**, reaction of **3c** with **10** provided **11c** in 14.6% yield as a red solid, mp: 225–226°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.05 (s, 1H), 8.14 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.06 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.35 (dd, *J* = 10.0, 2.0 Hz, 1H), 7.20 (s, 1H), 6.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93 (s, 1H), 6.84 (dd, *J* = 8.8, 5.4 Hz, 1H), 6.70 (dd, *J* = 8.2, 4.6 Hz, 1H), 6.61 (td, *J* = 9.5, 2.0 Hz, 1H), 4.20 (t, *J* = 7.0 Hz, 2H), 3.96 (t, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 2.25–2.18

(m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}FN_6O_2$ calcd. 469.1783. Found 469.1779.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-5-chloro-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11d)

According to the procedure used to prepare **11a**, reaction of **3d** with **10** provided **11d** in 16.9% yield as a red solid, mp: 113–115°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.07 (s,1H), 8.15 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.30 (s, 1H), 7.11–7.07 (m, 2H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.88 (d, *J* = 2,0 Hz, 1H), 6.73 (dd, *J* = 8.0, 4.7 Hz, 1H), 4.23 (t, *J* = 7.0 Hz, 2H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 2.24–2.18 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}ClN_6O_2$ calcd. 485.1487. Found 485.1478.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-6-chloro-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11e)

According to the procedure used to prepare **11a**, reaction of **3e** with **10** provided **11e** in 17.5% yield as a red solid, mp: 144–146°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.07 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.08 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.20 (s, 1H), 6.96 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.93 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.76 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.71 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.96 (t, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 2.23–2.18 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}ClN_6O_2$ calcd. 485.1487. Found 485.1490.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-5-bromo-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11f)

According to the procedure used to prepare **11a**, reaction of **3f** with **10** provided **11f** in 14.3% yield as a red solid, mp: 135–137°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.07 (s, 1H), 8.16 (dd, *J* = 4.5, 1.5 Hz 1H), 8.10 (s, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.37 (s, 1H), 7.21–7.15 (m, 2H), 7.02–6.98 (m, 2H), 6.73 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.24 (t, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 2.25–2.20 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}BrN_6O_2$ calcd. 529.0982. Found 529.0971.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-6-bromo-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11g)

According to the procedure used to prepare **11a**, reaction of **3g** with **10** provided **11g** in 12.9% yield as a red solid, mp: 204–206°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.06 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.08 (s, 1H), 7.78 (s, 1H), 7.75 (d, *J* = 1.5 Hz, 1H), 7.67 (s, 1H), 7.22 (s, 1H), 6.99–6.93 (m, 2H), 6.88 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 8.0, 4.7 Hz, 1H), 4.23 (t, *J* = 7.0 Hz, 2H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.89 (s, 3H), 2.24–2.18 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{26}H_{22}BrN_6O_2$ calcd. 529.0982. Found 529.0994.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-7-methyl-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11h)

According to the procedure used to prepare **11a**, reaction of **3h** with **10** provided **11h** in 10.0% yield as an orange solid, mp: 140–142°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.01 (s, 1H), 8.13 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.02 (s, 1H), 7.70 (s, 1H), 7.67 (s, 1H), 7.23 (s, 1H), 7.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.93 (s, 1H), 6.77 (d, *J* = 6.8 Hz, 1H), 6.73–6.65 (m, 2H), 6.61–6.54 (m, 1H), 4.38 (t, *J* = 7.5 Hz, 2H), 4.03 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 2.26–2.16 (m, 2H), 1.24 (s, 3H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{25}N_6O_2$ calcd. 465.2034. Found 465.2042.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-5-(benzyloxy)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11i)

According to the procedure used to prepare **11a**, reaction of **3i** with **10** provided **11i** in 21.1% yield as an orange solid, mp: 121–123°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.02 (s, 1H), 8.18 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.64 (s, 1H), 7.37–7.28 (m, 4H), 7.23–7.19 (m, 2H), 7.16 (d, *J* = 7.0 Hz, 2H), 6.93 (s, 1H), 6.75 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.71 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 4.16 (s, 2H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 2.30–2.22 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{33}H_{29}N_6O_3$ calcd. 557.2296. Found 557.2292.

### 3-(1-(4-(1*H*-Imidazol-1-yl)butyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11j)

According to the procedure used to prepare **11a**, reaction of **3j** with **10** provided **11j** in 26.1% yield as an orange solid, mp: 133–135°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.01 (s, 1H), 8.14–8.10 (m, 2H), 8.04 (s, 1H), 7.82 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 7.09–7.01 (m, 1H), 6.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 7.6 Hz, 1H), 6.61 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.29 (t, *J* = 6.1 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 1.74–1.67 (m, 4H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{25}N_6O_2$ calcd. 465.2034. Found 465.2051.

### 3-(1-(4-(1*H*-Imidazol-1-yl)butyl)-6-chloro-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11k)

According to the procedure used to prepare **11a**, reaction of **3k** with **10** provided **11j** in 24.7% yield as a red solid, mp: 129–131°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.04 (s, 1H), 8.15 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.08 (s, 1H), 7.81 (s, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.61 (s, 1H), 7.14 (s, 1H), 6.90–6.87 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.74 (t, *J* = 8.5 Hz, 1H), 6.64 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.29 (t, *J* = 6.1 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.89 (s, 3H), 1.73–1.61 (m, 4H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{24}ClN_6O_2$ calcd. 499.1644. Found 499.1631.

### 3-(1-(2-(1*H*-Imidazol-1-yl)ethyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11l)

According to the procedure used to prepare **11a**, reaction of **3l** with **10** provided **11l** in 14.3% yield as a red solid, mp: 150–152°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 11.02 (s, 1H), 8.16–8.10 (m, 1H), 8.04 (s, 1H),

7.68 (s, 1H), 7.47–7.41 (m, 2H), 7.19 (s, 1H), 7.01–6.90 (m, 2H), 6.88 (s, 1H), 6.76 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.65–6.55 (m, 2H), 4.68 (t, *J* = 5.9 Hz, 2H), 4.47 (t, *J* = 5.9 Hz, 2H), 3.90 (s, 3H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{25}H_{21}N_6O_2$ calcd. 437.1721. Found 437.1736.

### 3-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-(1-(3-(pyrrolidin-1-yl)propyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (11m)

According to the procedure used to prepare **11a**, reaction of **3m** with **10** provided **11m** in 12.3% yield as a red solid, mp: >250°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.03 (s, 1H), 8.15 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74–6.69 (m, 2H), 4.35 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 3.10–3.01 (m, 6H), 2.13–2.03 (m, 2H), 1.90–1.80 (m, 4H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{28}N_5O_2$ calcd. 454.2238. Found 454.2245.

### 3-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-(1-(3-morpholinopropyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (11n)

According to the procedure used to prepare **11a**, reaction of **3n** with **10** provided **11n** in 16.1% yield as a red solid, mp: 86–88°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.00 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.71–6.63 (m, 2H), 4.30 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 3H), 3.63–3.54 (t, *J* = 4.5 Hz, 4H), 2.4–2.23 (m, 4H), 2.15 (t, *J* = 6.5 Hz, 2H), 1.92–1.85 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{28}N_5O_3$ calcd. 470.2187. Found 470.2196.

### 3-(1-(3-(1*H*-1,2,4-Triazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11o)

According to the procedure used to prepare **11a**, reaction of **3o** with **10** provided **11o** in 30.3% yield as a red solid, mp: 121–123°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.00 (s, 1H), 8.51 (s, 1H), 8.11 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74–6.66 (m, 2H), 4.30 (t, *J* = 7.0 Hz, 2H), 4.17 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 2.32–2.25 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{25}H_{22}N_7O_2$ calcd. 452.1829. Found 452.1844.

### 3-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-(1-(3-(piperidin-1-yl)propyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (11p)

According to the procedure used to prepare **11a**, reaction of **3p** with **10** provided **11p** in 15.4% yield as a red solid, mp: 206–207°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.00 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.03 (s, 1H), 7.79 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.71–6.63 (m, 2H), 4.27 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 3H), 2.29–2.18 (m, 4H), 2.11 (t, *J* = 7.0 Hz, 2H), 1.91–1.80 (m, 2H), 1.52–1.47 (m, 4H), 145–1.32 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{28}H_{30}N_5O_2$ calcd. 468.2394. Found 468.2382.

### 3-(1*H*-Indol-3-yl)-4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11q)

According to the procedure used to prepare **11a**, reaction of **2a** with **10** provided **11q** in 9.1% yield as a red solid, mp: >250°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.75 (s, 1H), 10.98 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 3.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.71 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.64 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{20}H_{15}N_4O_2$ calcd. 343.1190. Found 343.1189.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11r)

According to the procedure used to prepare **11a**, reaction of **6a** with **12** provided **11r** in 12.3% yield as a red solid, mp: 107–109°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 12.24 (s 1H), 11.02 (s, 1H), 8.62 (s, 1H), 8.08 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.86–7.81 (m, 2H), 7.59 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.74–6.66 (m, 2H), 4.31 (t, *J* = 7.2 Hz, 2H), 4.15 (t, *J* = 7.2 Hz, 2H), 2.38–2.28 (m, 2H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{25}H_{21}N_6O_2$ calcd. 437.1721. Found 437.1733.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1-ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11s)

According to the procedure used to prepare **11a**, reaction of **6b** with **12** provided **11s** in 13.8% yield as a red solid, mp: 199–201°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.03 (s, 1H), 8.14 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.94 (s, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 6.77–6.67 (m, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.25 (t, *J* = 7.0 Hz, 2H), 4.00 (t, *J* = 7.0 Hz, 2H), 2.29–2.24 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{27}H_{25}N_6O_2$ calcd. 465.2034. Found 465.2051.

### 3-(1-(3-(1*H*-Imidazol-1-yl)propyl)-1*H*-indol-3-yl)-4-(1-isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (11t)

According to the procedure used to prepare **11a**, reaction of **6c** with **12** provided **11t** in 11.8% yield as a red solid, mp: 165–167°C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 11.04 (s, 1H), 8.16 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.87 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (s, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), δ 6.84–6.78 (m, 1H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.11–5.04 (m, 1H), 4.26 (t, *J* = 7.0 Hz, 2H), 4.01 (t, *J* = 7.0 Hz, 2H), 2.31–2.23 (m, 2H), 1.39 (d, *J* = 6.5 Hz, 6H). HRMS (ESI) *m/z* $[M+H]^+$ for $C_{28}H_{27}N_6O_2$ calcd. 479.2190. Found 479.2173.

## 4.2 | Biological activity assays

### 4.2.1 | IDH1/R132H inhibition assay

Full-length human IDH1/R132H was expressed as N-terminal GST-fusion protein using Escherichia coli expression system. Enzyme inhibition assay for IDH1(R132H) was performed in a 384-well microplate in 25 mM Tris-HCl buffer (pH 7.0) containing the enzyme (27 nM), 8 mM $MnCl_2$, 12 μM NADPH, and increasing concentrations of an inhibitor. Upon incubation for 15 min, α-KG (1 mM) was added to initiate the reaction. The NADPH of probe was detected by monitoring the increase of fluorescence with Envision, at 355 nm excitation and

460 nm emission (PerkinElmer). The $IC_{50}$ data were calculated using the software GraphPad Prism and the equation "sigmoidal dose-response (variable slope)" was chosen for curve fitting.

### 4.2.2 | IDH1/WT inhibition assay

Full-length human IDH1/WT was expressed as N-terminal GST-fusion protein using Escherichia coli expression system. The inhibition assay of IDH1/WT was carried out in 25 mM Tris-HCl buffer (pH 7.0) containing the enzyme (30 nM), 1 mM $MgCl_2$, 75 μM NADP, an inhibitor, and 100 μM sodium (D)-isocitrate. And the NADPH of probe was detected by monitoring the increase of fluorescence with Envision (PerkinElmer), at 355 nm excitation and 460 nm emission. The $IC_{50}$ data were calculated using the software GraphPad Prism and the equation "sigmoidal dose-response (variable slope)" was chosen for curve fitting.

### 4.2.3 | U87MG IDH1 R132H-pruo cell-based assays and LC-MS/MS measurement of 2-HG

R132H mutations were introduced into human IDH1 by standard molecular biology techniques. Human glioma U87MG cell lines were transfected using standard techniques. U87MG IDH1 R132H-puro cells were maintained in DMEM containing 10% FBS, 1× penicillin/streptomycin, and 1 μg/mL puromycin. Cells were seeded at a density of 20000 cells/well into 96-well microtiter plates and incubated overnight at 37°C and 5% $CO_2$. The next day compounds were prepared in 100% DMSO and then diluted in medium for a final concentration of 0.2% DMSO. Medium was removed from the cell plates and 200 μL of the compound dilutions were added to each well. After 48 h of incubation with compound at 37°C, medium was removed from each well and pelleted cells were washed twice with ice-cold PBS before sequential quenching with −80°C 80% methanol/20% water. Intracellular 2-HG and L-glutamic acid were measured by LC-MS/MS.[39]

### 4.3 | Molecular modeling

The structure of IDH1/R132H (pdb:5DE1)[30] was chosen for the docking template. The IDH1/R132H was kept and selected, polar hydrogen were added, and CHARMm force field was employed. Binding sphere (radius: 10) was selected from the active site using the binding site tools. For tested compound **11e**, all hydrogens were added and CHARMm force fields were again employed, each compound was minimized by Dreiding Minimize tool. CDOCKER (Discovery Studio 2.5) was used for the docking simulation. The docking parameters were as follows: top hits, 10; random conformations, 30; random conformations dynamics steps, 1000; grid extension, 8.0; random dynamics time step, 0.002. Final docked conformations were scored by -CDOCKING ENERAGE.

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## CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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