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DESIGN, SYNTHESIS AND EVALUATION OF NITRIC OXIDE-RELEASING DERIVATIVES OF *N*-(*n*-BUTYL)MATRINIC ACID AND *N*-(*n*-BUTYL)MATRINOL AS ANTI-HEPATOCELLULAR CARCINOMA AGENTS

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Abstract – A series of novel furoxan-based derivatives of *N*-*n*-butyl matrinic acid (**9a**-**m**) and *N*-*n*-butyl matrinol (**10a-m**) were synthesized and their anti-human hepatocellular carcinoma (HCC) activities were evaluated. All derivatives displayed potential inhibition of HepG2 cell proliferation. Among these derivatives, compounds **9a-f**, **9j** and **10b**, **10g-i** (IC_{50}: 0.69−4.66 μM) were superior to 5-FU (IC_{50}: 5.82 μM). The further study showed that compounds **9a**, **9c** and **9f** had higher antiproliferative activity on human hepatocellular carcinoma cells Bel-7402 (IC_{50}: 2.55-3.26 μM) and SMMC-7721 (IC_{50}: 5.26-5.79 μM).

INTRODUCTION

Human hepatocellular carcinoma (HCC) is one of the most deadly cancers and has become the second leading cause of death in China. Currently, there is no effective chemotherapy for HCC in humans in clinic. Therefore, development of new therapeutic agents will be of great significance.[1,2]

Matrine (**1**) is one of the major quinolizidine alkaloids which derived from several traditional Chinese medicinal herbs, including Sophora flavescens, Sophora and Sophora subprostrata.[3-5] It has attracted considerable attention because of its potential positive effects on human health and its broad biological activities, such as anticancer, anti-inflammatory, analgesic, and notable antiviral effects. In China, matrine has been used for the treatment of lipopolysaccharide-induced liver injury.[6-9] However, up to now, it has not been become an anticancer drug because of its moderate anti-tumor activities.[10] Therefore, it is significant to develop matrine derivatives with potential anticancer effects by structure modification.

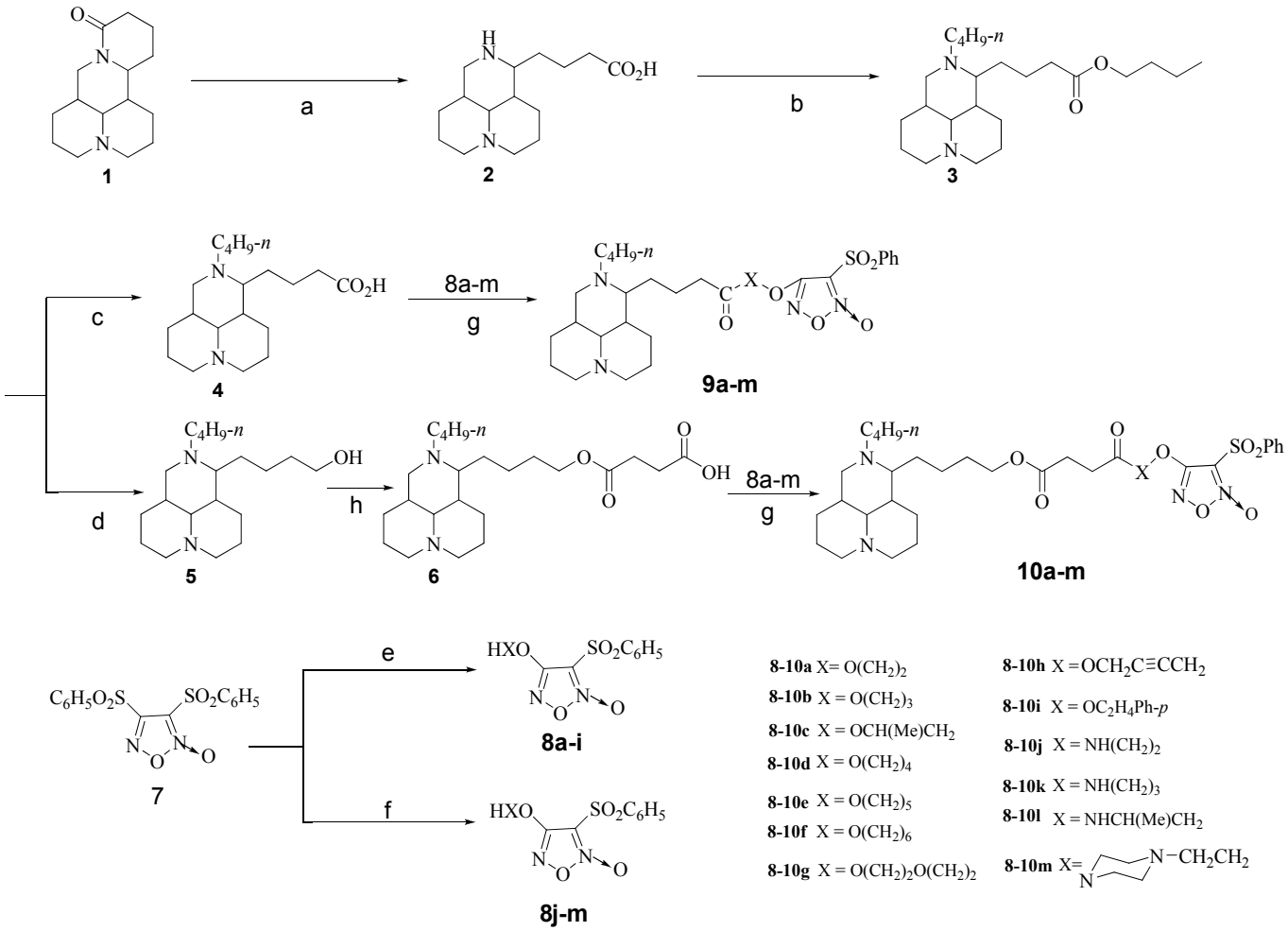
Nitric oxide (NO), as a short-lived, highly diffusible, multifunctional messenger molecule, plays key role in various physiological and pathological processes. Recently, it has been found that high concentration of NO exhibited cytotoxic activity and could induce the apoptosis of tumor cells, prevent tumors from metastasizing and assist macrophage to kill tumor cells.[11,12] Indeed, NO-donating anti-cancer agents have been investigated for their potential application for cancer therapy in clinic. For example, NO-aspirin has entered clinical studies for the treatment of colorectal cancer.[13] Furoxans is an important class of NO donors, which can produce high concentration of NO and exhibit strong anti-cancer activity.[14-17] Our previous study indicated that NO-donating *N*-benzyl matrinic acid derivatives exhibited higher anticancer activity than matrine and some are stronger than 5-FU.[18] In view of above research results, we design and synthesize two series of NO-donating *N*-*n*-butyl matrinic acid and *N*-*n*-butyl matrinol derivatives by using *N*-alkyl group replacement *N*-benzyl, and then test their activity against human hepatocellular carcinoma cells in vitro in order to find novel and more potential anti-cancer agents.

RESULTS AND DISCUSSION

The synthetic route of these target compounds is outlined in Scheme 1. The starting material matrine **1** was firstly reacted with sodium hydroxide, giving the hydrolytic ring-open derivative **2** as our previous protocol.[18] In the presence of potassium carbonate, **2** reacted with *n*-butyl bromide to gain compound **3**, which can produce **4** through hydrolysis with sodium hydroxide and offer **5** by reduction with lithium aluminum hydride. Compound **6** was obtained by treatment **5** with succinic anhydride under the condition of 4-*N,N*-dimethylaminopyridine (DMAP) in CH_2Cl_2. Finally, condensation of **4** and **6** with various mono(phenylsulfonyl)furoxans **8a-m**, were synthesized in a four-step sequence as previously described.[18] Thus we got target compounds **9a-m** and **10a-m**. The structures of all target compounds were further characterized by IR, MS and ^{1}H NMR.

The antiproliferative activity of all target compounds against human HCC HepG2 cells was evaluated by MTT assay,[19] using 5-fluorouracil (5-FU) as control. All target compounds exhibited better activity compared to matrine. Especially, 11 compounds (**9a-h, 9k-l, 10b, 10d, 10e-g**) displayed significant activity which was superior to 5-FU. Furthermore, compounds **9a**, **9c**, and **9f** exhibited optimal activity. The IC_{50} of **9a** (IC_{50} = 1.69 μmol/L), **9c** (IC_{50} = 0.69 μmol/L) and **9f** (IC_{50} = 0.94 μmol/L) against HCC HepG2 cells was 3-8 fold than those of 5-FU (IC_{50} = 5.82 μmol/L) (Table 1). Compared with above compounds (**9a, 9c, 9f**), the IC_{50} of *N*-benzyl derivatives was 2.16, 3.98 and 7.45 μmol/L against human HCC HepG2 cells in the previous experiment. That is to say, the replacement of benzyl group to alkyl group has better antiproliferative activity. Further test of these three compounds (**9a**, **9c**, and **9f**) for their in vitro activity against human HCC Bel-7402 and SMMC-7721 cells were done by the same method as described above, which revealed that these three compounds showed stronger toxicity activity than those

of matrine and 5-FU (Table 2). The results also indicated that the anti-proliferative effect of these three compounds (IC_{50} = 2.32-5.79 μmol/L) on HCC Bel-7402 and SMMC-7721 was powerful than that of 5-FU (IC_{50} = 7.57-10.05 μmol/L). Therefore, we are interested in further studies to determine whether those three compounds could become the candidates of anti-hepatocellular carcinoma agents.



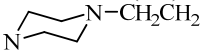
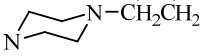
Scheme 1. Reactions and reagents: (a) 1, NaOH (aq.), 100 °C, 2 h; 2, 20% H_2SO_4. (b) *n*-BuBr, DMF, K_2CO_3, 60-70 °C, 5 h. (c) NaOH, EtOH, 0.5 h. (d) $LiAlH_4$, THF, 1 h. (e) diols, 25%NaOH, THF, rt, 2 h. (f) aminoalcohol, NaH, dry THF. (g) DMAP, EDCI, CH_2Cl_2. (h) succinic anhydride, DMAP, dry CH_2Cl_2, reflux, 3 h.

Different activities of the tested compounds may be attributed to the different connecting arms. For example, among the compounds **9a-9m**, the compounds **9b** and **9c** whose connecting arm were diols, but the compound **9c** with branched chain spacers, was more active than the corresponding compound **9b** with liner chain spacers; on the other hand, the compounds **9k** and **9l** with aminoalcohols as connecting arms showed the opposite effects: the compound **9k** with liner chain spacers exhibited higher activity than the compound **9l** with branched chain spacers. Besides, for the compounds **10a-10m**, the connecting arm may be the most influential factor, for example, the anti-proliferative activities of **10b**, **10d**, **10e-g** were much better than that of **10j-m**. The reason may be that, due to the introduction of the alkyl groups, the

hydrophobicity is increased and the molecular volume is expanded as well. Thus the anti-cancer activity of these compounds is strengthened.

In summary, two series of furoxan-based derivatives of *N*-*n*-butyl matrinic acid (**9a-m**) and *N*-*n*-butyl matrinol (**10a-m**) were synthesized, and their anti-proliferative activities in vitro were evaluated by MTT assay. Preliminary screening indicated that all target compounds showed inhibition of HCC cells proliferation. Moreover, 11 derivatives (**9a-f**, **9j** and **10b**, **10g-i**) manifested better activity than 5-FU against HCC cells. Particularly, compounds **9a**, **9c** and **9f** exhibited a great potency superior to 5-FU in cancer cells and deserved further investigation.

Table 1. The structures and anti-proliferative effects of HepG2 cells of the target compounds

Compound	X	IC_{50}(μmol/L)[a]	Compound	X	IC_{50}(μmol/L)[a]
9a	$O(CH_2)_2$	1.69	**10a**	$O(CH_2)_2$	>20
9b	$O(CH_2)_3$	2.87	**10b**	$O(CH_2)_3$	4.66
9c	$OCH(Me)CH_2$	0.69	**10c**	$OCH(Me)CH_2$	>20
9d	$O(CH_2)_4$	3.19	**10d**	$O(CH_2)_4$	7.86
9e	$O(CH_2)_5$	3.06	**10e**	$O(CH_2)_5$	>20
9f	$O(CH_2)_6$	0.94	**10f**	$O(CH_2)_6$	>20
9g	$O(CH_2)_2O(CH_2)_2$	7.26	**10g**	$O(CH_2)_2O(CH_2)_2$	1.83
9h	OH_2CCCCH_2	>20	**10h**	OH_2CCCCH_2	4.25
9i	OC_2H_4Ph-*p*	>20	**10i**	OC_2H_4Ph-*p*	4.56
9j	$HN(CH_2)_2$	4.43	**10j**	$HN(CH_2)_2$	>20
9k	$HN(CH_2)_3$	5.85	**10k**	$HN(CH_2)_3$	>20
9l	$HNCH_2Me(CH)$	>20	**10l**	$HNCH_2Me(CH)$	>20
9m		>20	**10m**		>20
Matrine		8069	5-FU		5.82

[a] IC_{50}: a concentration required to inhibit tumor cell proliferation by 50 %. Data are expressed as the mean IC_{50} from the dose-response curves of at least three independent experiments.

Table 2. The cytotoxicity (IC_{50}, μmol/L) of **9a, 9c** and **9f** against HCC Bel-7402 and SMMC-7721 cell liners.

Compound	In vitro cytotoxicity(IC_{50}, μmol/L)	
	Bel-7402	SMMC-7721
9a	2.55	5.79
9c	2.32	5.26
9f	3.26	5.76
Matrine	1100	10081
5-FU	7.57	10.05

EXPERIMENTAL

Melting points were measured using a WRS-1B apparatus and were without any correction. ^1H NMR spectra were recorded on 400 MHz Bruker Avance DPX spectrometers and referenced with TMS as an internal standard. All NMR spectra were recorded in $CDCl_3$ at room temperature. IR spectra were

collected on Nicolet Avatar 6700 spectrometer using KBr film. ESI mass spectra were acquired using a Thermo Fisher LTQ Orbitrap XL Liquid chromatography-mass spectrometry instrument. The chromatograms were conducted on silica gel (100−200 mesh) and visualized under UV light at 254 and 365 nm. Compounds **8a-m** were synthesized as previously described.[18]

4-(Decahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid (2). Matrine (**1**, 2.48 g, 0.01 mol) was added to 10% NaOH aqueous solution (20 mL, 0.1 mol) and the mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and neutralized with 20% H_2SO_4, then concentrated under reduced pressure to dryness. The residue was dissolved in MeOH and filtered. The filtrate was concentrated under reduced pressure to dryness and yield **2** as white solid (2.23 g, 83.8%), mp 197.7-198.5 °C. ESI-MS *m/z*: 267.2306 $[M+H]^+$ (Calcd for $C_{15}H_{27}N_2O_2$ 267.2028); IR 3426, 2932, 2818, 1732 cm^{-1}.

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid butyl ester (3). *N*-Butyl bromide (4.3 ml, 0.04 mol), matrinic acid 2 (2.66 g, 0.01 mol) and K_2CO_3 (5.52 g, 0.04 mol) were added to DMF (20 mL), and the resulting mixture was heated to 60-70 °C and stirred for 5 h. The reaction solution was filtered to remove solids, the filtrate was dissolved in water (100 mL) and extracted with EtOAc (20 mL) three times. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography to give **3** as light yellow oil (2.81 g, 74.3%). ESI-MS *m/z*: 379.3564 $[M+H]^+$ (Calcd for $C_{23}H_{43}N_2O_2$ 379.3280); IR 2933, 2861, 2804, 2762, 1737 cm^{-1}.

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid (4). Compound **3** (5.15 g, 13.6 mmol) was added to saturated NaOH-ethanol solution (40 mL). The mixture was stirred at 60 °C for 0.5 h. The reaction mixture was cooled to room temperature and neutralized with 20% H_2SO_4, then concentrated under reduced pressure to dryness. The residue was dissolved in water and extracted with EtOAc (20 mL). The water layer was concentrated under reduced pressure to dryness. The residue was dissolved in MeOH and filtered. The filtrate was concentrated under reduced pressure to give **4** as light white solid (4.08 g, 93.1%), mp 112.1-113.3 °C. ESI-MS *m/z*: 323.2684 $[M+H]^+$ (Calcd for $C_{19}H_{35}N_2O_2$ 323.2654); IR 3382, 2950, 2871, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (m, 1H, OH), 3.64-3.40 (m, 2H, CH_2), 2.57-2.40 (m, 10H, N-CH_2, N-CH), 1.91 (m, 2H, CH), 1.86-1.62 (m, 2H, CH), 1.58-1.11 (m, 16H, CH_2), 0.96-0.33 (t, 3H, CH_3).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butan-1-ol (5). Compound **3** (3.78 g, 0.01 mol) was added to dried THF (30 mL), then added $LiAlH_4$ (0.76 g, 0.02 mol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was added water dropwise at 0 °C until no bubbles gave. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with EtOAc (20 mL) three times. The organic layer was

washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to gain **5** as light yellow oil (2.33g, 75.6%). ESI-MS *m/z*: 309.2892 $[M+H]^+$ (Calcd for $C_{19}H_{37}N_2O$ 309.2861); IR 3396, 3324, 2927, 2855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 1H, OH), 3.57 (t, 2H, OCH_2), 3.02-2.32 (m, 10H, N-CH_2, N-CH), 1.96-1.21 (m, 18H, CH_2, CH), 1.86-1.62 (m, 2H, CH), 0.91 (t, 3H, CH_3).

Succinic acid mono-[4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl] ester (6). Compound **5** (3.08 g, 0.01 mol), succinic anhydride (2.0 g, 0.02 mol) and DMAP (1.22 g, 0.01 mol) were added to a CH_2Cl_2 (20 mL), the mixture was stirred and refluxed for 5 h. After 5 h, the reaction mixture was poured into water and neutralized with a saturated aqueous Na_2CO_3 solution. The aqueous mixture was then extracted with CH_2Cl_2 (20 mL) three times. The organic layer was collected, dried (over Na_2SO_4) and concentrated under reduced pressure to obtain **6** as light yellow oil (3.74 g, 91.7%). ESI-MS *m/z*: 409.3106 $[M+H]^+$ (Calcd for $C_{23}H_{41}N_2O_4$ 409.3022).

General Procedure for the synthesis of 9a-m.

Compound **4** (84 mg, 0.26 mmol), DMAP (32 mg, 0.26 mmol), and **8a-m** (0.17 mmol) were dissolved in dry CH_2Cl_2 (6 mL), then added dropwise the solution of EDCI (50 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at room temperature for 48 h. After 48 h, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was collected, dried (over Na_2SO_4) and concentrated under reduced pressure. The residue was purified by TLC with 10:1 (v/v) CH_2Cl_2-MeOH.

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 2-(4-benzenesulfonyl-furazan-3-yloxy)-ethyl ester (9a). The title compound was obtained starting from **8a** and **4** (light yellow oil, 54.3%). ESI-MS *m/z*: 591.2817 $[M+H]^+$ (Calcd for $C_{29}H_{43}N_4O_7S$ 591.2808); IR 2933, 2866, 2797, 2768, 2734, 1382, 1732, 1624, 1552, 1252, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85-0.90 (m, 3H, CH_3), 1.31~2.13 (m, 26H, CH, CH_2), 2.34 (t, 2H, O=CCH_2), 2.72 (t, 2H, N-CH_2), 4.41-4.45 (t, 2H, OCH_2), 4.53~4.58 (t, 2H, OCH_2), 7.56 (t, 2H, ArH), 7.70 (t, 1H, ArH), 7.99 (d, 2H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 3-(4-benzenesulfonyl-furazan-3-yloxy)-propyl ester (9b). The title compound was obtained starting from **8b** and **4** (light yellow oil, 59.6%). ESI-MS *m/z*: 605.2984 $[M+H]^+$ (Calcd for $C_{30}H_{45}N_4O_7S$ 605.2964); IR 2935, 2877, 2777, 1384, 1732, 1616, 1554, 1448, 1264, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84-0.95 (m, 3H, CH_3), 1.30-2.15 (m, 28H, CH, CH_2), 2.41 (t, 2H, O=CCH_2), 2.74 (t, 2H, N-CH_2), 4.11 (t, 2H, OCH_2), 4.23 (t, 2H, OCH_2), 7.58 (t, 2H, ArH), 7.71 (t, 1H, ArH), 8.03 (d, 2H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 2-(4-benzenesulfonyl-furazan-3-yloxy)-1-methyl-ethyl ester (9c). The title compound was obtained starting from **8c** and **4** (light yellow oil, 52.6%). ESI-MS *m/z*: 605.2981 $[M+H]^+$ (Calcd for $C_{30}H_{45}N_4O_7S$ 605.2964); IR 2936, 2877, 2812, 2769, 1385, 1733; 1617, 1556, 1449, 1254, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

0.82-0.99 (m, 6H, CH_3), 1.22-2.00 (m, 24H, CH, CH_2), 2.40 (t, 2H, O=CCH_2), 2.77 (t, 4H, N-CH_2), 4.37 (d, 2H, OCH_2), 4.50 (m, 1H, OCH), 7.63 (t, ArH), 7.77 (t, 1H, ArH), 8.05 (d, 2H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 4-(4-benzenesulfonyl-furazan-3-yloxy)-butyl ester (9d). The title compound was obtained starting from **8d** and **4** (light yellow oil, 61.7%). ESI-MS *m/z*: 619.3139 $[M+H]^+$ (Calcd for $C_{31}H_{47}N_4O_7S$ 619.3121); IR 2927, 2853, 2797, 1361, 1732, 1625, 1554, 1448, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91(t, 3H, CH_3), 1.06-2.17 (m, 30H, CH, CH_2), 2.42 (t, 2H, O=CCH_2), 3.49-3.63 (t, 2H, N-CH_2), 3.79 (t, 2H, OCH_2), 3.96 (t, 2H, OCH_2), 7.13-7.26 (t, 2H, ArH), 7.36 (t, 1H, ArH), 7.61 (d, 1H, ArH), 7.78 (d, 1H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 5-(4-benzenesulfonyl-furazan-3-yloxy)-pentyl ester (9e). The title compound was obtained starting from **8e** and **4** (light yellow oil, 67.5%). ESI-MS *m/z*: 633.3292 $[M+H]^+$ (Calcd for $C_{32}H_{49}N_4O_7S$ 633.3277); IR 2933, 2864, 2767, 1384, 1731, 1615, 1553, 1449, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, CH_3), 1.06-2.17 (m, 32H, CH, CH_2), 2.53 (t, 2H, O=CCH_2), 3.38-3.57 (t, 2H, N-CH_2), 3.77 (t, 2H, OCH_2), 3.88 (t, 2H, OCH_2), 6.90-7.00 (m, 2H, ArH), 7.05(m, 1H, ArH), 7.51(d, 1H, ArH), 7.55(d, 1H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 6-(4-benzenesulfonyl-furazan-3-yloxy)-hexyl ester (9f). The title compound was obtained starting from **8f** and **4** (light yellow oil, 61.4%). ESI-MS *m/z*: 647.3469 $[M+H]^+$ (Calcd for $C_{33}H_{51}N_4O_7S$ 647.3434); IR 2930, 2861, 1361, 1732, 1622, 1557, 1455, 1252, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, CH_3), 1.06-2.17 (m, 34H, CH, CH_2), 2.37 (t, 2H, O=CCH_2), 3.42-3.49 (t, 2H, N-CH_2), 3.83 (t, 2H, OCH_2), 4.01 (t, 2H, OCH_2), 7.48(m, 2H, ArH), 7.53 (m, 1H, ArH), 7.97 (d, 2H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 2-[2-(4-benzenesulfonyl-furazan-3-yloxy)-ethoxy]-ethyl ester (9g). The title compound was obtained starting from **8g** and **4** (light yellow oil, 54.1%). ESI-MS *m/z*: 635.3077 $[M+H]^+$ (Calcd for $C_{31}H_{47}N_4O_8S$ 635.3070); IR 2934, 2871, 1384, 1732, 1618, 1560, 1448, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, CH_3), 0.94-2.67 (m, 30H, CH, CH_2), 3.68-3.75 (m, 2H, OCH_2), 3.76-3.83 (m, 2H, OCH_2), 3.89-3.97 (m, 2H, OCH_2), 4.50-4.64(m, 2H, OCH_2), 7.63 (t, 2H, ArH), 7.76 (t, J = 7.1 Hz, 1H, ArH), 8.01-8.14(d, 2H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 4-(4-benzenesulfonyl-furazan-3-yloxy)-but-2-ynyl ester (9h). The title compound was obtained starting from **8h** and **4** (light yellow oil, 52.5%). ESI-MS *m/z*: 615.2814 $[M+H]^+$ (Calcd for $C_{31}H_{43}N_4O_7S$ 615.2808); IR 2933, 2870, 2813, 2768, 1384, 2167, 1739, 1615, 1446, 1293, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.21-2.17 (m, 26H, CH, CH_2), 2.37 (t, 2H, O=CCH_2), 3.56 (t, 2H, N-CH_2), 4.35(t, 2H, OCH_2), 4.46 (t, 2H, OCH_2), 7.31(m, 2H, ArH), 7.52(m, 1H, ArH), 7.64 (d, 1H, ArH), 7.96 (d, 1H, ArH).

4-(2-Butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyric acid 2-[4-(4-benzenesulfonyl-

furazan-3-yloxy)phenyl]-ethyl ester (9i). The title compound was obtained starting from **8i** and **4** (light yellow oil, 62.0%). ESI-MS *m/z*: 667.3128 $[M+H]^+$ (Calcd for $C_{35}H_{47}N_4O_7S$ 667.3121); IR 2929, 2875, 1382, 1732, 1615, 1505, 1446, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, CH_3), 1.23~2.09 (m, 26H, CH, CH_2), 2.18 (t, 2H, O=CCH_2), 2.73-2.83 (t, 2H, ArCH_2), 2.96 (t, 2H, N-CH_2), 4.29 (d, 2H, OCH_2), 7.24 (d, 2H, ArH), 7.28 (d, 2H, ArH), 7.66 (t, 2H, ArH), 7.80 (t, 1H, ArH), 8.11 (d, 2H, ArH).

***N*-[2-(4-Benzenesulfonylfurazan-3-yloxy)-ethyl]-4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]-naphthyridin-1-yl)-butyramide (9j)**. The title compound was obtained starting from **8j** and **4** (light yellow oil, 44.4%). ESI-MS *m/z*: 590.2977 $[M+H]^+$ (Calcd for $C_{29}H_{44}N_5O_6S$ 590.2968); IR 3328, 2927, 2854, 1383, 1655, 1615, 1557, 1446, 1223, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_3), 1.05-1.93 (m, 28H, CH, CH_2), 2.36 (t, 2H, NCH_2), 3.69 (d, 2H, O$CH_2$$\underline{CH_2}$), 4.18 (t, 2H, O$CH_2$), 7.39 (d, 2H, ArH), 7.45 (d, 1H, ArH), 7.82-7.88 (t, 2H, ArH), 7.87-7.93 (t, 1H, NH).

***N*-[3-(4-Benzenesulfonylfurazan-3-yloxy)-propyl]-4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]-naphthayridin-1-yl)-butyramide (9k**). The title compound was obtained starting from **8k** and **4** (light yellow oil, 47.6%). ESI-MS *m/z*: 604.3133 $[M+H]^+$ (Calcd for $C_{30}H_{46}N_5O_6S$ 604.3124); IR 3333, 2932, 2864, 2766, 1372, 1651, 1620, 1553, 1447, 1354, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, CH_3), 1.23-1.98 (m, 30H, CH, CH_2), 2.36 (t, 2H, NCH_2), 3.23 (d, 2H, NHCH_2), 4.06 (t, 2H, OCH_2), 7.37 (d, 2H, ArH), 7.46 (d, 1H, ArH), 7.89~7.98 (t, 2H, ArH), 8.03 (t, 1H, NH).

***N*-[2-(4-Benzenesulfonylfurazan-3-yloxy)-1-methylethyl]-4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]-naphthyridin-1-yl)-butyramide (9l**). The title compound was obtained starting from **8l** and **4** (light yellow oil, 40.6%). ESI-MS *m/z*: 604.3160 $[M+H]^+$ (Calcd for $C_{30}H_{46}N_5O_6S$ 604.3124); IR 3299, 2928, 2860, 1357, 1668, 1615, 1545, 1446, 1292, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.97 (t, 3H, CH_3), 1.14-1.26 (d, 3H, CH_3), 1.29-2.16 (m, 23H, CH,CH_2), 2.34 (d, 3H, NCH, NCH_2), 2.81 (t, 2H, NCH_2), 2.96-3.09 (t, 2H, NCH_2), 3.37-3.53 (d, 2H, OCH_2), 3.67 (m, 1H, OCH), 7.34-7.40 (t, 2H, ArH), 7.62 (t, 1H, ArH), 7.74 (d, 1H, ArH), 7.82-7.88 (d, 1H, ArH), 8.08 (d, 1H, NH).

1-{4-[2-(4-Benzenesulfonylfurazan-3-yloxy)-ethyl]-piperazin-1-yl}-4-(2-butyldecahydropyrido-[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butan-1-one (9m). The title compound was obtained starting from **8m** and **4** (light yellow oil, 48.4%). ESI-MS *m/z*: 659.3588 $[M+H]^+$ (Calcd for $C_{33}H_{51}N_6O_6S$ 659.3546); IR 2927, 2855, 2807, 1382, 1655, 1446, 1291, 1240, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.89 (d, 3H, CH_3), 1.22-2.13 (m, 26H, CH, CH_2), 2.51 (t, 4H, NH_2), 2.77 (t, 6H, NH_2), 3.63 (t, 4H, O=CNH_2), 4.42-4.73 (t, 2H, OCH_2), 7.44-7.49 (t, 2H, ArH), 7.63 (t, *J* = 7.8 Hz, 1H, ArH), 8.00 (d, 2H, ArH).

General Procedure for the Preparation of 10a-m.

Compound **6** (245 mg, 0. 6 mmol), DMAP (74 mg, 0.26 mmol), and **8a-m** (0.5 mmol) were dissolved in dry CH_2Cl_2 (8 mL), then added dropwise the solution of EDCI (117 mg, 0. 6 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The mixture was stirred at room temperature for 48 h. The reaction mixture was poured into water

and extracted with CH_2Cl_2. The organic layer was collected, dried (over Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography with 10:1 (v/v) CH_2Cl_2-MeOH.

Succinic acid 2-(4-benzenesulfonylfurazan-3-yloxy)-ethyl ester 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10a). The title compound was obtained starting from **8a** and **6** (colorless oil, 55.0%). ESI-MS *m/z*: 677.3204 $[M+H]^+$ (Calcd for $C_{33}H_{49}N_4O_9S$ 677.3176); IR 2931, 2860, 1735, 1618, 1560, 1449, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, CH_3), 1.21-2.09 (m, 30H, CH,CH_2), 2.79 (t, 4H, O=CCH_2), 4.09 (t, 2H, OCH_2), 4.53 (d, 2H, OCH_2), 4.63 (d, 2H, OCH_2), 7.64 (t, 2H, ArH), 7.77 (t, 1H, ArH), 8.07 (d, 2H, ArH).

Succinic acid 3-(4-benzenesulfonylfurazan-3-yloxy)-propyl ester 4-(2-butyldecahydropyrido-[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10b). The title compound was obtained starting from **8b** and **6** (colorless oil, 57.4%). ESI-MS *m/z*: 691.3604 $[M+H]^+$ (Calcd for $C_{34}H_{51}N_4O_9S$ 691.3332); IR 2922, 2850, 1736, 1618, 1578, 1448, 1384; 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, CH_3), 1.24-2.03 (m, 32H, CH, CH_2), 2.81 (t, 4H, O=CCH_2), 4.07 (t, 2H, OCH_2), 4.32 (t, 2H, OCH_2), 4.53 (t, 2H, OCH_2), 7.65 (t, 2H, ArH), 7.78 (t, 1H, ArH), 8.08 (d, 2H, ArH).

Succinic acid 2-(4-benzenesulfonylfurazan-3-yloxy)-1-methyl-ethyl ester 4-(2-butyldecahydropyrido-[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10c). The title compound was obtained starting from **8c** and **6** (colorless oil, 54.8%). ESI-MS *m/z*: 691.3401 $[M+H]^+$ (Calcd for $C_{34}H_{51}N_4O_9S$ 691.3332); IR 2927, 2858, 1735, 1622, 1581, 1448, 1384, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88-1.06 (m, 6H, CH_3), 1.23-2.24 (m, 30H, CH, CH_2), 2.57-2.79 (t, 4H, O=CCH_2), 4.1 (t, 2H, OCH_2), 4.23 (d, 2H, OCH_2), 4.51 (m, 1H, OCH), 7.61 (t, ArH), 7.78 (t, 1H, ArH), 8.02 (d, 2H, ArH).

Succinic acid 4-(4-benzenesulfonylfurazan-3-yloxy)-butyl ester 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10d). The title compound was obtained starting from **8d** and **6** (colorless oil, 65.6%). ESI-MS *m/z*: 705.3522 $[M+H]^+$ (Calcd for $C_{35}H_{53}N_4O_9S$ 705.3489); IR: 2929, 2851, 1719, 1626, 1572, 1452, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_3), 1.31-2.12 (m, 34H, CH, CH_2), 2.81 (t, 4H, O=CCH_2), 4.12 (t, 2H, OCH_2), 4.20 (d, 2H, OCH_2), 4.47 (d, 2H, OCH_2), 7.65 (t, 2H, ArH), 7.78 (t, 1H, ArH), 8.07 (d, 2H, ArH).

Succinic acid 5-(4-benzenesulfonylfurazan-3-yloxy)-pentyl ester 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10e). The title compound was obtained starting from **8e** and **6** (colorless oil, 72.7%). ESI-MS *m/z*: 719.3703 $[M+H]^+$ (Calcd for $C_{36}H_{55}N_4O_9S$ 719.3645); IR 2929, 2857, 1735, 1618, 1553, 1449, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, CH_3), 1.32-2.10 (m, 36H, CH, CH_2), 2.62-2.79 (m, 4H, O=CCH_2), 4.02-4.07 (t, 4H, OCH_2), 4.36 (d, 2H, OCH_2), 7.56 (t, 2H, ArH), 7.70 (t, 1H, ArH), 7.99 (d, 2H, ArH).

Succinic acid 6-(4-benzenesulfonylfurazan-3-yloxy)-hexyl ester 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10f). The title compound was obtained starting from **8f** and **6**

(colorless oil, 62.3%). ESI-MS *m/z*: 733.3624 $[M+H]^+$ (Calcd for $C_{37}H_{57}N_4O_9S$ 733.3802); IR 2927, 2861, 1736, 1618, 1551, 1449, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, CH_3), 1.12-2.18 (m, 28H, CH, CH_2), 2.36-2.85 (m, 10H, N-CH, N-CH_2), 2.79 (m, 4H, O=CCH_2), 4.02 (t, 2H, OCH_2), 4.24 (t, 4H, OCH_2), 7.55 (t, 2H, ArH), 7.71 (t, 1H, ArH), 7.99 (d, 2H, ArH).

Succinic acid 2-[2-(4-benzenesulfonylfurazan-3-yloxy)-ethoxy]ethyl ester 4-(2-butyldecahydro-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10g). The title compound was obtained starting from **8g** and **6** (colorless oil, 57.2%). ESI-MS *m/z*: 721.3470 $[M+H]^+$ (Calcd for $C_{35}H_{53}N_4O_{10}S$ 721.3438); IR 2939, 2869, 1735, 1615, 1549, 1448, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_3), 1.23-2.20 (m, 32H, CH, CH_2), 3.77-3.83 (t, 4H, O=CCH_2), 3.92 (t, 2H, OCH_2), 4.10 (t, 2H, OCH_2), 4.28 (d, 2H, OCH_2), 4.57 (d, 2H, OCH_2), 7.63 (t, 2H, ArH), 7.77 (t, 1H, ArH), 8.07 (d, 2H, ArH).

Succinic acid 4-(4-benzenesulfonylfurazan-3-yloxy)-but-2-ynyl ester 4-(2-butyldecahydropyrido-[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10h). The title compound was obtained starting from **8h** and **6** (colorless oil, 56.3%). ESI-MS *m/z*: 701.3211 $[M+H]^+$ (Calcd for $C_{35}H_{19}N_4O_9S$ 701.3176); IR 2927, 2850, 2163, 1736, 1618, 1550, 1449, 1280, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, CH_3), 1.21-2.09 (m, 28H, CH, CH_2), 2.37 (t, 2H, N-CH_2), 2.67 (t, 4H, O=CCH_2), 4.14 (t, 2H, OCH_2), 4.78 (d, 2H, OCH_2), 5.09 (d, 2H, OCH_2), 7.66 (t, 2H, ArH), 7.80 (t, 1H, ArH), 8.10(d, 2H, ArH).

Succinic acid 2-[4-(4-benzenesulfonylfurazan-3-yloxy)-phenyl]-ethyl ester 4-(2-butyldecahydro-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10i). The title compound was obtained starting from **8i** and **6** (colorless oil, 52.2%). ESI-MS *m/z*: 753.2241 $[M+H]^+$ (Calcd for $C_{39}H_{53}N_4O_9S$ 753.3489); IR 2926, 2850, 1734, 1617, 1551, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, CH_3), 1.21-2.26 (m, 28H, CH, CH_2), 2.35(t, 2H, N-CH_2), 2.69 (t, 4H, O=CCH_2), 2.98 (t, 2H, Ar-CH_2), 4.13 (d, 2H, OCH_2), 4.30 (d, 2H, OCH_2), 7.16-7.35 (m, 4H, ArH), 7.66 (t, 2H, ArH), 7.80 (t, 1H, ArH), 8.11 (d, 2H, ArH).

***N*-[2-(4-Benzenesulfonylfurazan-3-yloxy)-ethyl]-succinamic acid 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10j)**. The title compound was obtained starting from **8j** and **6** (colorless oil, 43.0%). ESI-MS *m/z*: 676.1356 $[M+H]^+$ (Calcd for $C_{33}H_{50}N_5O_8S$ 676.3335); IR 2918, 2848, 1698, 1556, 1504, 1457, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 0.90 (t, 3H, CH_3), 1.30-2.29 (m, 30H, CH, CH_2), 2.49-2.61 (t, 4H, O=CCH_2), 3.51 (m, 2H, O$CH_2$$\underline{CH_2}$), 4.07 (t, 2H, O$CH_2$), 4.53 (d, 2H, O$CH_2$), 7.64 (t, 2H, ArH), 7.75 (t, 1H, ArH), 8.06 (d, 2H, ArH), 8.09 (s, 1H, NH).

***N*-[3-(4-Benzenesulfonylfurazan-3-yloxy)-propyl]-succinamic acid 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10k)**. The title compound was obtained starting from **8k** and **6** (colorless oil, 44.7%). ESI-MS *m/z*: 690.0312 $[M+H]^+$ (Calcd for $C_{34}H_{52}N_5O_8S$ 690.3492); IR 2934, 2867, 1648, 1618, 1560, 1448, 1283, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, CH_3), 1.30-2.29 (m, 32H, CH, CH_2), 2.34-2.48 (t, 4H, O=CCH_2), 3.55(m, 2H, NH-$\underline{CH_2}$), 4.09 (t, 2H, OCH_2), 4.50 (d, 2H, OCH_2), 7.61 (t, 2H, ArH), 7.75(t, 1H, ArH), 8.02(d, 2H, ArH), 8.05(s, 1H, NH).

***N*-[2-(4-Benzenesulfonylfurazan-3-yloxy)-1-methyl-ethyl]-succinamic acid 4-(2-butyldecahydro-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10l)**. The title compound was obtained starting from **8l** and **6** (colorless oil, 44.9%). ESI-MS *m/z*: 690.0156 $[M+H]^+$ (Calcd for $C_{34}H_{52}N_5O_8S$ 690.3492); IR 2926, 2859, 1649, 1618, 1554, 1448, 1281, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, CH_3), 1.31 (t, 3H, CH_3), 1.40-2.29 (m, 28H, CH, CH_2), 2.46 (t, 4H, O=CCH_2), 3.23 (m, 2H, NH$\underline{CH_2}$), 4.09 (t, 2H, OCH_2), 4.45 (d, 2H, OCH_2), 7.64 (t, 2H, ArH), 7.76 (t, 1H, ArH), 8.01 (d, 2H, ArH), 8.06(s, 1H, NH).

4-{4-[2-(4-Benzenesulfonylfurazan-3-yloxy)-ethyl]-piperazin-1-yl}-4-oxo-butyric acid 4-(2-butyldecahydropyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)-butyl ester (10m). The title compound was obtained starting from **8m** and **6** (colorless oil, 55.8%). ESI-MS *m/z*: 745.3127 $[M+H]^+$ (Calcd for $C_{37}H_{57}N_6O_8S$ 745.3914); IR 2930, 2861, 1648, 1618, 1553, 1449, 1290, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 0.95 (t, 3H, CH_3), 1.23-2.12 (m, 30H, CH, CH_2), 2.74-2.85 (t, 4H, O=CCH_2), 2.86-2.94 (t, 4H, N-CH_2), 3.63 (t, 6H, N-CH_2), 4.09 (t, 2H, OCH_2), 4.56 (t, 2H, OCH_2), 7.63 (t, 2H, ArH), 7.78 (t, 1H, ArH), 8.06 (d, 2H, ArH).

Anticancer activity study (MTT assay)

Human HCC HepG2, Bel-7402, SMMC-7721 cells at 10^4 cells per well were cultured in 10% FBS DMEM and a 37 °C incubator with 5% CO_2 in 96-well flat-bottom microplates overnight. The cells were incubated in triplicate with, or without, different concentrations of each test compound for 72 h. During the last 4 h incubation, 30 μL of tetrazolium dye (MTT) solution (5 $mg \cdot mL^{-1}$) was added to each well. The resulting MTT-formazan crystals were dissolved in 150 μL DMSO, and absorbance was measured spectro-photometrically at 570 nm using an ELISA plate reader. The inhibition induced by each test compound at the indicated concentrations was expressed as a percentage ((1 – the optical density ratio of the treatment to vehicle control) × 100%). The IC_{50} value is calculated by Käber method as following:

IC_{50}= Xm-I(P-(3-Pm-Pn)/4).

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