Supporting Information for

Original article

Discovery of novel KRAS–PDEδ inhibitors with potent activity in patient-derived human pancreatic tumor xenograft models

Long Chen[a,†], Jing Zhang[b,†], Xinjing Wang[c,d,†], Yu Li[a], Lu Zhou[e], Xiongxiong Lu[c,d,*], Guoqiang Dong[a,*], Chunquan Sheng[a,*]

[a]*School of Pharmacy, Second Military Medical University, Shanghai 200433, China*

[b]*Department of Pathology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China*

[c]*Department of General Surgery, Pancreatic Disease Center, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai 200025, China*

[d]*Research Institute of Pancreatic Diseases, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China*

[e]*Department of Medicinal Chemistry, School of Pharmacy, Fudan University, Shanghai 201203, China*

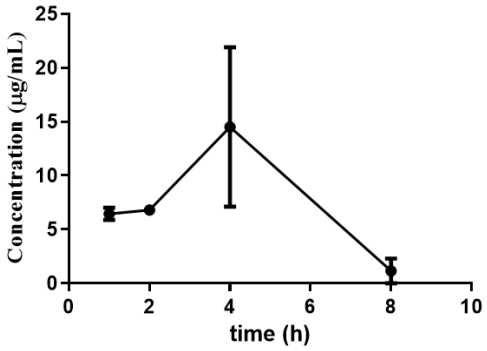
[†]These authors made equal contributions to this work.

Received 19 April 2021; received in revised form 3 July 2021; accepted 5 July 2021

*Corresponding authors. Tel./fax: +86 21 6437 0045 671003 (Xiongxiong Lu), +86 21 8187 1242 (Guoqiang Dong), +86 21 8187 1239 (Chunquan Sheng).

E-mail addresses: simone515night@126.com (Xiongxiong Lu), gdong@smmu.edu.cn (Guoqiang Dong), shengcq@smmu.edu.cn (Chunquan Sheng).

Table of contents



T_{max}	4	h
C_{max}	15.50	μg/mL
$AUC_{(0-t)}$	59.23	h·μg/mL

Figure S1 Pharmacokinetic study of **36l** *in vivo via* intraperitoneal administration at 100 mg/kg in ICR mice. Left: plasma drug concentration–time profile of **36l**. Right: Calculated bioavailability of **36l**. AUC: area under curve.

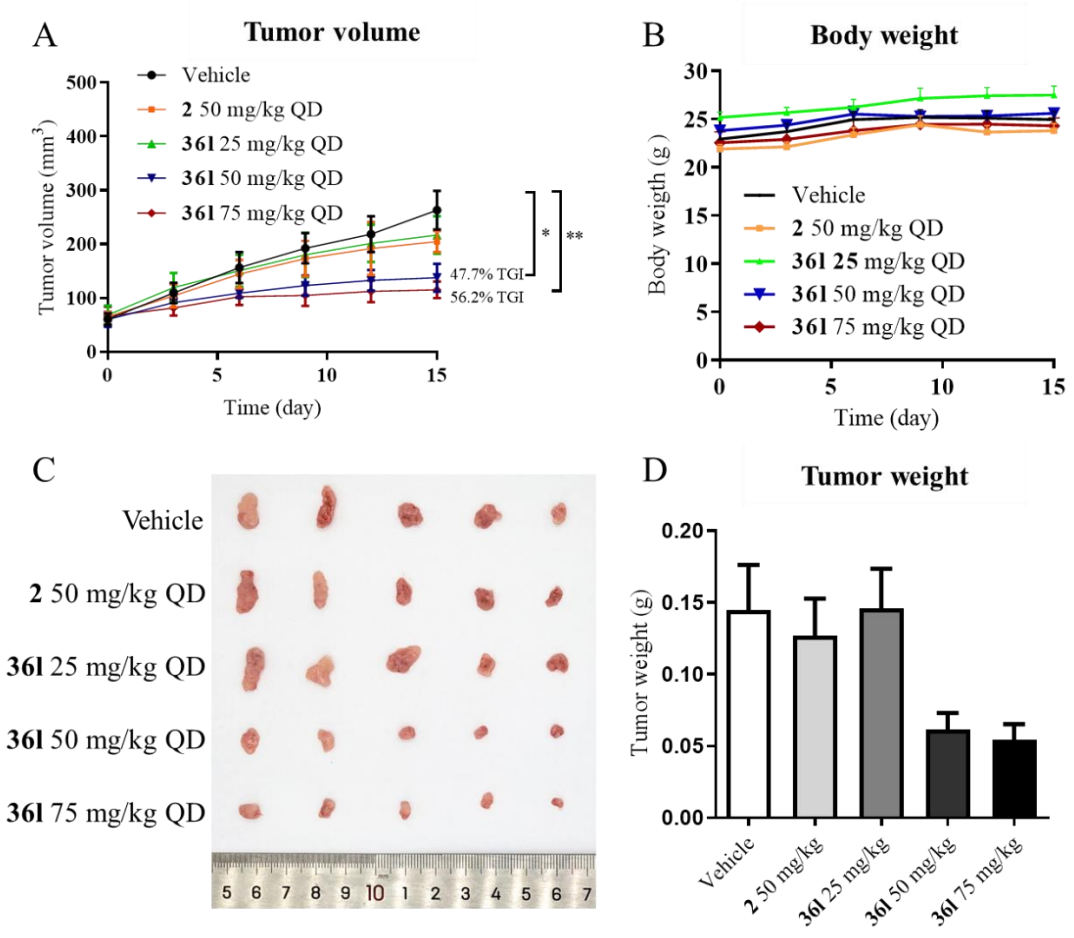
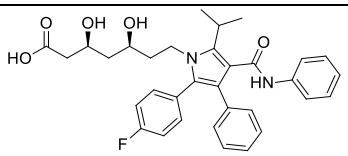
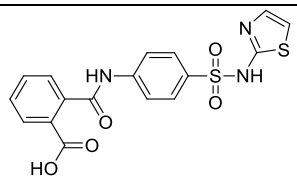
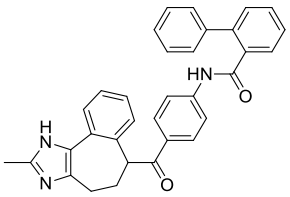
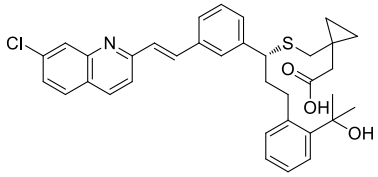
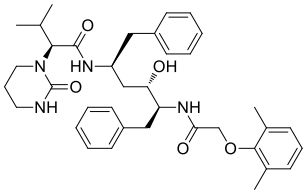
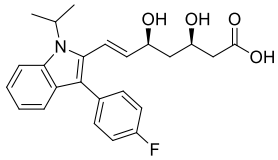
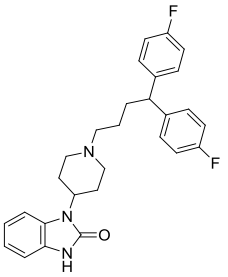
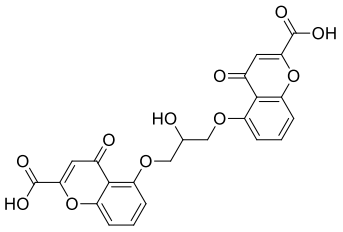
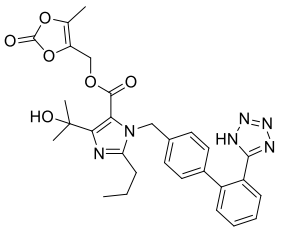
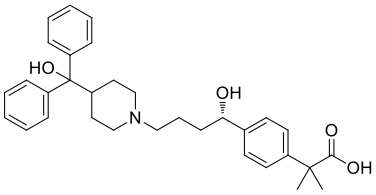
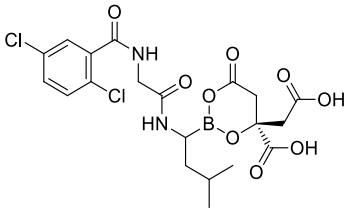
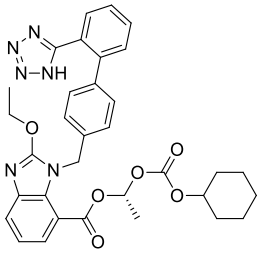
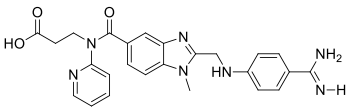
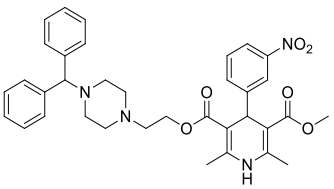
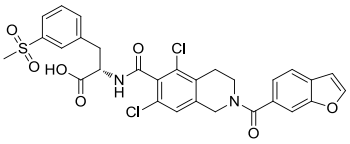
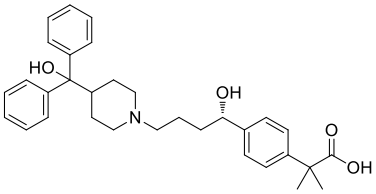
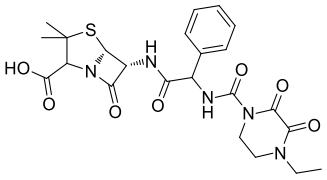
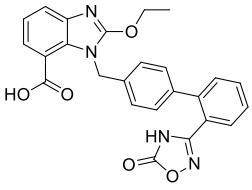
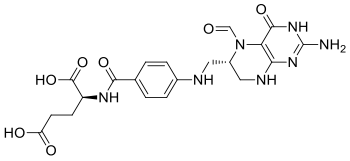
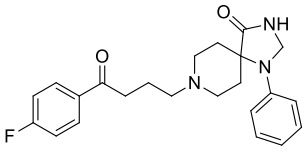
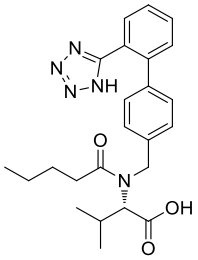
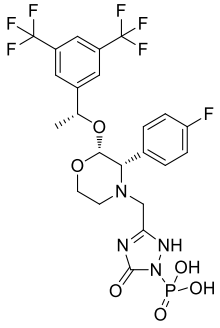
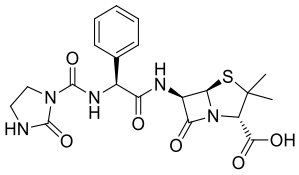
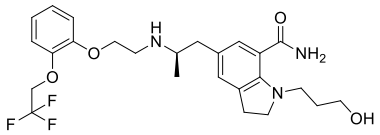
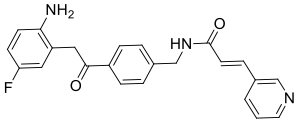
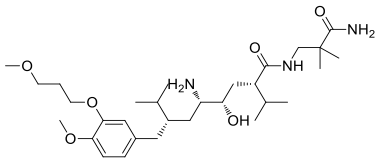
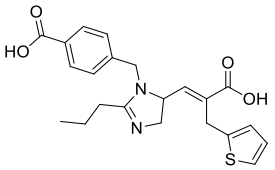
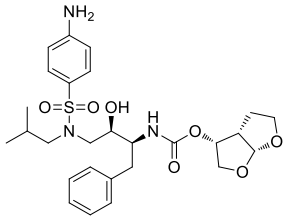
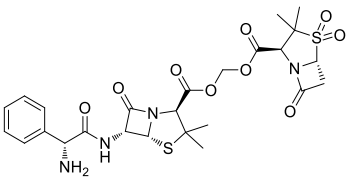
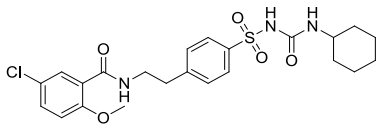
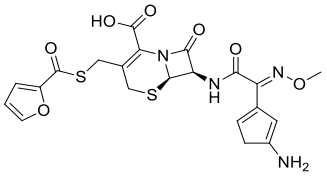
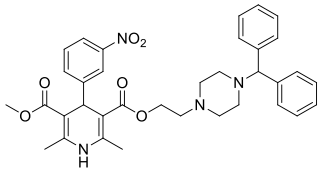


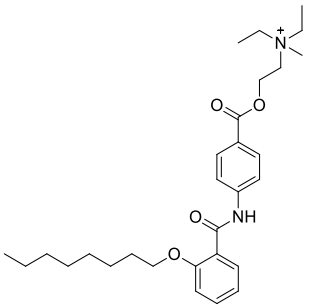
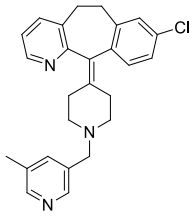
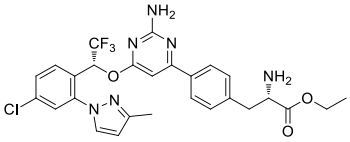
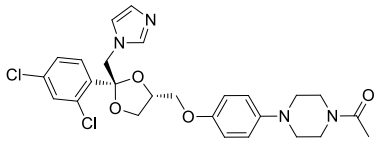
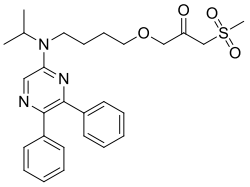
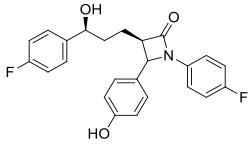
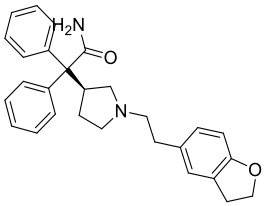
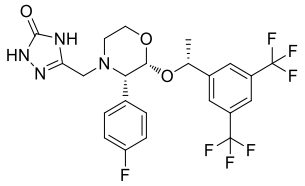
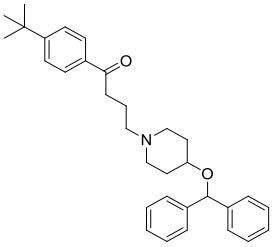
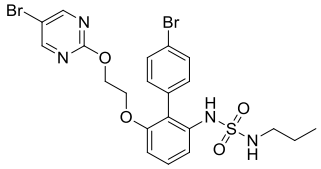
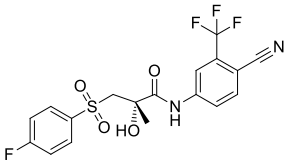
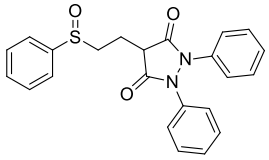
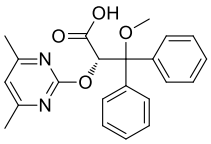
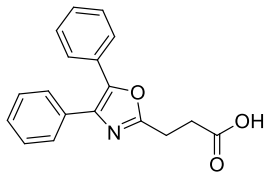
Figure S2 The *in vivo* efficacy antitumor of **36l** and positive drug **2** in the xenograft model. The pancreatic cancer cell Mia PaCa-2 was selected to establish the mouse xenograft model. The mice were respectively treated with the saline, **2** (50 mg/kg, QD) and **36l** (25, 50 and 75 mg/kg, QD) intraperitoneally until the endpoint. (A) Effect of **36l** on tumor volume growth in the xenograft model. (B) Change in the body weight of nude mice treated with compound vehicle, **2** and **36l**. (C) Respective image of tumor treated with vehicle, **2** and **36l**. (D) Weight of the tumor treated with vehicle, **2** and **36l**. Data expressed as the mean ± standard deviation. **P* < 0.05, ***P* < 0.01.

Table S1 Structures and inhibitory rates to PDEδ of inhibitors at 5 μmol/L.

Num	Structure	Inhibitory rate (%)	Num	Structure	Inhibitory rate (%)
1		62	**2**		15.3
3		11.2	**4**		30.5
5		35.4	**6**		23.7

7		42.1	**8**		31.8
9		43.7	**10**		34.1
11		32.5	**12**		45.6
13		21.3	**14**		38.2
15		42.1	**16**		34.2
17		6.5	**18**		39.5
19		48.0	**20**		54.0

21		39.2	**22**		40.2
23		38.6	**24**		23.2
25		32.4	**26**		32.9
27		15.2	**28**		7.4
29		4.2	**30**		43.7
31		35.3	**32**		15.3

33		35.0	**34**		46.3
35		9.1	**36**		14.2
37		31.5	**38**		11.0
39		36.3	**40**		43.2
41		12.1	**42**		34.4
43		30.0	**44**		9.4
45		45.3	**46**		37.6

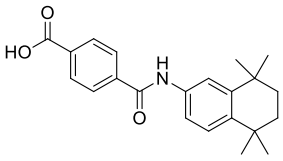
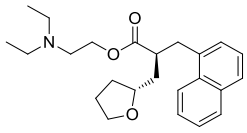
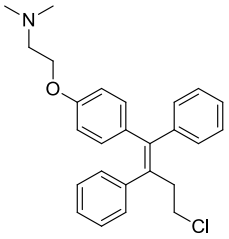
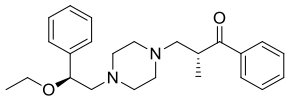
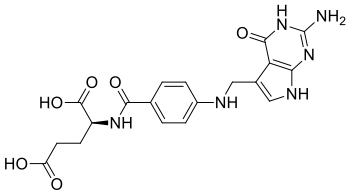
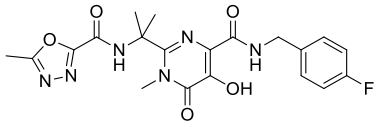
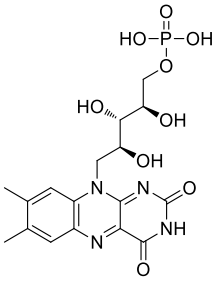
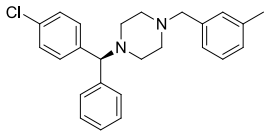
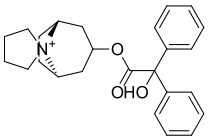
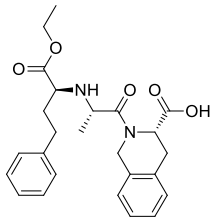
47		2.6	**48**		37.0
49		6.2	**50**		12.9
51		25.8	**52**		21.6
53		6.9	**54**		36.6
55		46.6	**56**		41.1

Table S2 Determination of the solubility of **36l** and **2**.

	Concen-tration	Absorbance (**36l**)	Absorbance (**2**)
Standard solution in ACN	1.000	> 1	> 1
	0.500	> 1	> 1
	0.250	0.710	0.845
	0.125	0.377	0.484
	0.0625	0.209	0.140
Saturated solution in PBS		0.932	0.041
Solubility (mmol/L)		0.626	0.030

Table S3. Caco-2 permeability assay of **36l**

Compd.	Papp (10^{-6} cm/s)		Recovery %		P_{app}
	A to B	B to A	A to B	B to A	
Atenolol	0.38	0.36	92.7	92.3	Low
36l	2.83	6.80	47.4	69.0	Moderate

Synthesis of compounds 22b–22e

4-Chloro-*N*-(2,3-dihydro-1*H*-inden-5-yl)butanamide (22b). The compound (654 mg, 55.2% yield) was synthesized by the protocol of **22a** with 2,3-dihydro-1*H*-inden-5-amine **21b** (370 mg, 5 mmol) and 4-chlorobutyryl chloride (850 mg, 1.2 eq, 6 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 (s, 1H), 7.22 (s, 1H), 7.14 (s, 2H), 3.66 (t, 2H, J = 6.1 Hz), 2.83-2.90 (m, 4H), 2.53 (t, 2H, J = 7.3 Hz), 2.15–2.23 (m, 2H), 2.01–2.10 (m, 2H).

4-Chloro-*N*-(naphthalen-2-ylmethyl)butanamide (22c). The compound (680 mg, 52.1% yield) was synthesized by the protocol of **22a** with naphthalen-2-ylmethanamine **21c** (790 mg, 5 mmol) and 4-chlorobutyryl chloride (850 mg, 1.2 eq, 6 mmol). ^{1}H NMR (300 MHz, DCCl3) δ 7.98–8.01 (m, 1H), 7.86–7.90 (m, 1H), 7.80–7.83 (m, 1H), 7.49–7.58 (m, 2H), 7.42–7.44 (m, 2H), 5.74 (s, 1H), 4.89 (d, 2H, J = 5.2 Hz), 3.6 (t, 2H, J = 5.7 Hz), 2.36 (t, 2H, J = 5.3 Hz), 2.09–2.18 (m, 2H).

4-Chloro-*N*-cyclohexylbutanamide (22d). The compound (610 mg, 60.1% yield) was synthesized by the protocol of **22a** with cyclohexanamine **21d** (500 mg, 5 mmol) and 4-chlorobutyryl chloride (850 mg, 1.2 eq, 6 mmol). ^{1}H NMR (300 MHz, DCCl3) δ 5.47 (s, 1H), 3.72–3.82 (m, 2H), 3.62 (t, 1H, J = 6.3 Hz), 2.34 (t, 2H, J = 7.3 Hz), 2.08–2.16 (m, 2H), 1.89–1.94 (m, 2H), 1.59–1.75 (m, 3H), 1.30–1.44 (m, 2H), 10.7–1.23 (m, 3H).

4-Chloro-*N*-cyclopentylbutanamide (22e). The compound (590 mg, 62.3% yield) was synthesized by the protocol of **22a** with cyclopentanamine **21e** (450 mg, 5 mmol) and 4-chlorobutyryl chloride (850 mg, 1.2 eq, 6 mmol). ^{1}H NMR (300 MHz, DCCl3) δ 5.51 (s, 1H), 4.14–4.25 (m, 1H), 3.60 (t, 1H, J = 6.2 Hz), 2.33 (t, 2H, J = 7.4 Hz), 2.08–2.14 (m, 2H), 1.95–2.01 (m, 2H), 1.58–1.68 (m, 4H), 1.30–1.41 (m, 2H), 10.7–1.23 (m, 3H).

Synthesis of compounds 33b–33o

***N*-(4-Chlorobenzyl)aniline (33b).** The compound (930 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and 4-chlorobenzaldehyde **31b** (700 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37 (s, 4H), 7.00–7.06 (m, 2H), 6.48–6.55 (m, 3H), 6.28 (t, 1H, J = 5.9 Hz), 4.25 (d, 2H, J = 5.9 Hz).

***N*-(2-Bromobenzyl)aniline (33c).** The compound (1070 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and 2-bromobenzaldehyde **31c** (920 mg, 5 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.61 (dd, 1H, J = 0.9, 7.9 Hz), 7.36–7.38 (m, 1H), 7.30–7.33 (m, 1H), 7.17–7.20 (m, 1H), 7.03–7.06 (m, 2H), 6.51–6.54 (m, 3H), 6.30 (t, 1H, J = 6.0 Hz), 4.28 (d, 2H, J = 6.0 Hz).

***N*-(3-Bromobenzyl)aniline (33d).** The compound (950 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and 3-bromobenzaldehyde **31d** (920 mg, 5 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.40 (d, 1H, J = 8.1 Hz), 7.36 (d, 1H, J = 7.5 Hz), 7.27 (t, 1H, J = 8.1 Hz), 7.02-7.04 (m, 2H), 6.55 (d, 2H, J = 8.1 Hz), 6.51 (t, 1H, J = 7.0 Hz), 6.29 (t, 1H, J = 5.9 Hz), 4.27 (d, 2H, J = 5.9 Hz).

***N*-((1*H*-Imidazol-4-yl)methyl)aniline (33e).** The compound (565 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and 1*H*-imidazole-4-carbaldehyde **31e** (480 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.06 (t, 2H, J = 7.9 Hz), 6.92 (s, 2H), 6.63 (d, 2H, J = 8.1 Hz), 6.55 (t, 1H, J = 7.2 Hz), 6.01 (t, 1H, J = 5.6 Hz), 4.22 (t, 2H, J = 4.0 Hz).

***N*-(Thiophen-2-ylmethyl)aniline (33f).** The compound (820 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and thiophene-2-carbaldehyde **31f** (560

mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45–7.47 (m, 1H), 7.31–7.33 (m, 1H), 7.01–7.09 (m, 3H), 6.60 (d, 2H, J = 7.7 Hz), 6.51 (t, 1H, J = 7.3 Hz), 6.05 (t, 1H, J = 5.8 Hz), 4.22 (d, 2H, J = 6.2 Hz).

***N*-(Thiophen-3-ylmethyl)aniline (33g).** The compound (795 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and thiophene-3-carbaldehyde **31g** (560 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34–7.36 (m, 1H), 7.02–7.08 (m, 3H), 6.94–6.97 (m, 1H), 6.62 (d, 2H, J = 7.5 Hz), 6.54 (t, 1H, J = 7.2 Hz), 6.22 (t, 1H, J = 5.6 Hz), 4.43 (d, 2H, J = 5.9 Hz).

***N*-(Pyridin-2-ylmethyl)aniline (33h).** The compound (745 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and picolinaldehyde **31h** (535 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51–8.52 (m, 1H), 7.68–7.74 (m, 1H), 7.35 (d, 1H, J = 7.9 Hz), 7.21–7.25 (m, 1H), 7.01–7.06 (m, 2H), 6.49–6.57 (m, 3H), 6.33 (t, 1H, J = 6.0 Hz), 4.34 (d, 2H, J = 6.0 Hz).

***N*-(Pyridin-4-ylmethyl)aniline (33i).** The compound (780 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and isonicotinaldehyde **31i** (535 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (d, 2H, J = 5.3 Hz), 7.34 (d, 2H, J = 5.3 Hz), 7.03 (t, 1H, J = 7.1 Hz), 6.49–6.54 (m, 3H), 6.38 (d, 1H, J = 5.9 Hz), 4.31 (d, 2H, J = 5.9 Hz).

***N*-(Quinolin-6-ylmethyl)aniline (33j).** The compound (940 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and quinoline-6-carbaldehyde **31j** (785 mg, 5 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.84–8.85 (m, 1H), 8.29–8.31 (m, 1H), 7.98 (d, 1H, J = 8.8 Hz), 7.90 (s, 1H), 7.77 (dd, 1H, J = 2.0, 8.8 Hz), 7.49 (q, 1H, J = 4.2

Hz), 7.01–7.04 (m, 2H), 6.59–6.61 (m, 2H), 6.50 (d, 1H, *J* = 7.4 Hz), 6.40 (s, 1H), 4.45 (s, 2H).

***N*-(Quinolin-3-ylmethyl)aniline (33k).** The compound (925 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and quinoline-3-carbaldehyde **31k** (785 mg, 5 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.24 (s, 1H), 7.96 (dd, 1H, *J* = 8.0, 47.7 Hz), 7.69–7.72 (m, 1H), 7.57 (t, 1H, *J* = 7.2 Hz), 7.04 (t, 2H, *J* = 7.8 Hz), 6.63 (d, 2H, *J* = 7.9 Hz), 6.52 (t, 2H, *J* = 7.2 Hz), 6.38 (d, 1H, *J* = 5.5 Hz), 4.48 (d, 2H, *J* = 5.5 Hz).

***N*-(Cyclohexylmethyl)aniline (33l).** The compound (840 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and cyclohexanecarbaldehyde **31l** (560 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.03 (t, 2H, *J* = 7.7 Hz), 6.53 (d, 2H, *J* = 8.1 Hz), 6.46 (t, 1H, *J* = 7.3 Hz), 5.54 (t, 1H, *J* = 5.5 Hz), 2.81 (t, 2H, *J* = 6.1 Hz), 1.78 (d, 2H, *J* = 13.1 Hz), 1.64–1.70 (m, 4H), 1.47–1.56 (m, 1H), 1.11–1.25 (m, 2H), 0.86–0.97 (m, 2H).

***N*-(Cyclopentylmethyl)aniline (33m).** The compound (745 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and cyclopentanecarbaldehyde **31m** (490 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6 DMSO-d_6) δ 7.02 (t, 2H, *J* = 7.9 Hz), 6.52 (d, 2H, *J* = 7.9 Hz), 6.46 (t, 1H, *J* = 7.5 Hz), 5.50 (t, 1H, *J* = 5.0 Hz), 2.86 (t, 2H, *J* = 6.6 Hz), 2.04–2.14 (m, 1H), 1.70–1.75 (m, 2H), 1.45–1.59 (m, 4H), 1.17–1.23 (m, 2H).

***N*-(Cyclobutylmethyl)aniline (33n).** The compound (720 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and cyclobutanecarbaldehyde **31n** (420 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.02 (t, 2H, *J* = 7.8 Hz), 6.52 (d, 2H, *J* =

7.8 Hz), 6.46 (t, 1H, *J* = 7.4 Hz), 5.44 (t, 1H, *J* = 5.3 Hz), 2.98 (t, 2H, *J* = 6.2 Hz), 2.51–2.56 (m, 1H), 1.97–2.07 (m, 2H), 1.78–1.88 (m, 2H), 1.62–1.73 (m, 2H).

***N*-(Cyclopropylmethyl)aniline (33o).** The compound (685 mg) was synthesized by the protocol of **33a** with aniline **32** (465 mg, 5 mmol) and cyclopropanecarbaldehyde **31o** (350 mg, 5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.04 (t, 2H, *J* = 7.4 Hz), 6.56 (d, 2H, *J* = 7.8 Hz), 6.49 (t, 1H, *J* = 7.4 Hz), 5.56 (t, 1H, *J* = 5.7 Hz), 2.86 (t, 2H, *J* = 5.7 Hz), 1.97-1.07 (m, 1H), 0.42–0.48 (m, 2H), 0.17–1.22 (m, 2H).

Synthesis of compounds 34b–34o

***N*-(4-Chlorobenzyl)-4-hydroxy-*N*-phenylbutanamide (34b).** The compound (125 mg, 13.7% yield) was afforded by the protocol of **34a** with **33b** (650 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and γ-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, $DCCl_3$) δ 7.31–7.37 (m, 3H), 7.18 (dd, 4H, *J* = 8.4, 33.8 Hz), 6.95–6.98 (m, 2H), 4.83 (s, 2H), 3.62 (t, 1H, *J* = 5.8 Hz), 3.25–3.31 (m, 2H), 2.22 (t, 2H, *J* = 7.2 Hz), 1.78–1.86 (m, 2H).

***N*-(2-Bromobenzyl)-4-hydroxy-*N*-phenylbutanamide (34c).** The compound (130 mg, 12.5% yield) was afforded by the protocol of **34a** with **33c** (780 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and γ-butyrolactone (510 mg, 5 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.55 (d, 1H, *J* = 8.0 Hz), 7.38 (t, 3H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.3 Hz), 7.27-7.31 (m, 3H), 7.18 (t, 1H, *J* = 7.5 Hz), 4.93 (s, 2H), 4.36 (t, 2H, *J* = 5.0 Hz), 3.30–3.31 (m, 1H), 2.16 (t, 2H, *J* = 6.5 Hz), 1.63–1.68 (m, 2H).

***N*-(3-Bromobenzyl)-4-hydroxy-*N*-phenylbutanamide (34d).** The compound (125 mg, 12.0% yield) was afforded by the protocol of **34a** with **33d** (780 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 5 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37–7.42 (m, 4H), 7.21–7.32 (m, 2H), 7.15–7.21 (m, 3H), 4.83 (s, 2H), 3.34 (t, 1H, J = 6.7 Hz), 3.28 (t, 2H, J = 6.3 Hz), 2.10 (t, 2H, J = 7.0 Hz), 1.57–1.66 (m, 2H).

***N*-((1*H*-Imidazol-4-yl)methyl)-4-hydroxy-*N*-phenylbutanamide (34e).** The compound (63 mg, 8.1% yield) was afforded by the protocol of **34a** with **33e** (520 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 20:80). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.26–7.40 (m, 5H), 6.86 (s, 2H), 4.82 (s, 2H), 4.36 (br, 1H), 3.25-3.30 (m, 2H), 2.06 (t, 2H, J = 7.1 Hz), 1.57–1.66 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(thiophen-2-ylmethyl)butanamide (34f). The compound (90 mg, 10.9% yield) was afforded by the protocol of **34a** with **33f** (520 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43–7.46 (m, 1H), 7.28–7.40 (m, 3H), 7.13–7.18 (m, 3H), 6.93–6.95 (m, 1H), 4.81 (s, 2H), 4.35 (t, 2H, J = 5.1 Hz), 3.25–3.31 (m, 2H), 2.06 (t, 2H, J = 6.9 Hz), 1.58–1.67 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(thiophen-3-ylmethyl)butanamide (34g). The compound (92 mg, 11.1% yield) was afforded by the protocol of **34a** with **33g** (520 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and

purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30–7.42 (m, 4H), 7.13 (d, 2H, J = 7.2 Hz), 6.87–6.89 (m, 1H), 6.79 (br, 1H), 4.96 (s, 2H), 4.35 (t, 1H, J = 4.4 Hz), 3.24–3.28 (m, 2H), 2.04 (t, 2H, J = 7.4 Hz), 1.56–1.65 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(pyridin-2-ylmethyl)butanamide (34h). The compound (85 mg, 10.5% yield) was afforded by the protocol of **34a** with **33h** (550 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and γ-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 0:100). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (d, 1H, J = 3.1 Hz), 7.69–7.72 (m, 1H), 7.31–7.36 (m, 3H), 7.26–7.28 (m, 3H), 7.19–7.21 (m, 1H), 4.89 (s, 2H), 4.32 (t, 1H, J = 5.0 Hz), 3.26–3.27 (m, 2H), 2.11 (t, 2H, J = 6.2 Hz), 1.58–1.63 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(pyridin-4-ylmethyl)butanamide (34i). The compound (80 mg, 9.9% yield) was afforded by the protocol of **34a** with **33i** (550 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and γ-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 0:100). ^{1}H NMR (300 MHz, $DCCl_3$) δ 8.44 (d, 2H, J = 4.5 Hz), 7.26–7.32 (m, 3H), 7.11 (d, 2H, J = 4.5 Hz), 6.99–7.02 (m, 2H), 4.83 (s, 2H), 3.55 (t, 2H, J = 6.0 Hz), 2.22 (t, 2H, J = 6.8 Hz), 1.76–1.85 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(quinolin-6-ylmethyl)butanamide (34j). The compound (90 mg, 9.4% yield) was afforded by the protocol of **34a** with **33j** (700 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and γ-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 0:100). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (d, 1H, J = 4.2 Hz), 8.29 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.8 Hz),

7.71 (s, 1H), 7.62 (d, 1H, *J* = 9.6 Hz), 7.47–7.51 (m, 1H), 7.19–7.37 (m, 5H), 5.05 (s, 2H), 4.38 (t, 1H, *J* = 5.1 Hz), 3.28–3.30 (m, 2H), 2.14 (t, 2H, *J* = 6.7 Hz), 1.62–1.71 (m, 2H).

4-Hydroxy-*N*-phenyl-*N*-(quinolin-3-ylmethyl)butanamide (34k). The compound (95 mg, 9.9% yield) was afforded by the protocol of **34a** with **33k** (700 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 0:100). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (d, 1H, *J* = 1.9 Hz), 8.10 (s, 1H), 7.95 (dd, 2H, *J* = 8.4, 22.9 Hz), 7.68–7.73 (m, 1H), 7.53–7.58 (m, 1H), 7.21–7.38 (m, 5H), 5.08 (s, 2H), 4.42 (br, 1H), 3.33 (t, 2H, *J* = 6.1 Hz), 2.16 (t, 2H, *J* = 6.7 Hz), 1.64–1.73 (m, 2H).

***N*-(Cyclohexylmethyl)-4-hydroxy-*N*-phenylbutanamide (34l).** The compound (105 mg, 12.7% yield) was afforded by the protocol of **34a** with **33l** (570 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41–7.45 (m, 2H), 7.30–7.35 (m, 1H), 7.24–7.26 (m, 2H), 4.29 (t, 1H, *J* = 4.4 Hz), 3.49 (t, 2H, *J* = 7.1 Hz), 3.22–3.24 (m, 2H), 1.95–2.00 (m, 2H), 1.55–1.62 (m, 7H), 1.29–1.35 (m, 1H), 1.05–1.12 (m, 3H), 0.81–0.92 (m, 2H).

***N*-(Cyclopentylmethyl)-4-hydroxy-*N*-phenylbutanamide (34m).** The compound (100 mg, 12.8% yield) was afforded by the protocol of **34a** with **33m** (525 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.44 (t, 2H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.3 Hz), 7.27 (d, 2H, *J* = 7.6 Hz),

4.34 (t, 1H, *J* = 4.9 Hz), 3.60 (d, 2H, *J* = 7.8 Hz), 3.22-3.28 (m, 2H), 1.96–2.03 (m, 2H), 1.84–1.92 (m, 1H), 1.42–1.62 (m, 8H), 1.11–1.19 (m, 2H).

***N*-(Cyclobutylmethyl)-4-hydroxy-*N*-phenylbutanamide (34n).** The compound (100 mg, 13.5% yield) was afforded by the protocol of **34a** with **33n** (485 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (t, 2H, *J* = 7.4 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 7.20 (d, 2H, *J* = 7.3 Hz), 4.30 (t, 1H, *J* = 4.9 Hz), 3.67 (d, 2H, *J* = 7.6 Hz), 3.19–3.25 (m, 2H), 2.25–2.35 (m, 1H), 1.90–1.96 (m, 2H), 1.80–1.84 (m, 2H), 1.68–1.76 (m, 2H), 1.49–1.59 (m, 4H).

***N*-(Cyclopropylmethyl)-4-hydroxy-*N*-phenylbutanamide (34o).** The compound (90 mg, 12.9% yield) was afforded by the protocol of **34a** with **33o** (440 mg, 3 mmol), trimethylaluminum (2 mol/L in toluene, 3 mL) and *γ*-butyrolactone (510 mg, 6 mmol) and purified by flash column chromatography (hexane/ethyl = 40:60). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 (t, 2H, *J* = 7.2 Hz), 7.36 (t, 1H, *J* = 7.2 Hz), 7.29 (d, 2H, *J* = 7.3 Hz), 4.33 (t, 1H, *J* = 4.5 Hz), 3.47 (d, 2H, *J* = 7.1 Hz), 3.22-3.31 (m, 2H), 1.98 (t, 2H, *J* = 6.6 Hz), 1.55–1.61 (m, 2H), 0.80–0.88 (m, 1H), 0.34–0.36 (m, 2H), 0.01–0.02 (m, 2H).

Synthesis of compounds 35b–35o

***N*-(4-Chlorobenzyl)-4-oxo-*N*-phenylbutanamide (35b).** The compound (88 mg, 58.5% yield) was afforded by the protocol of **35a** with **34b** (152 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25).^{1}H NMR (600 MHz, $DCCl_3$) δ 9.82 (s, 1H), 7.35–7.37 (m, 3H), 7.19 (dd, 4H, *J* =

8.3, 35.3 Hz), 7.03–7.06 (m, 2H), 4.84 (s, 2H), 2.79 (t, 2H, *J* = 6.5 Hz), 2.35 (t, 2H, *J* = 6.5 Hz).

***N*-(2-Bromobenzyl)-4-oxo-*N*-phenylbutanamide (35c).** The compound (98 mg, 56.8% yield) was afforded by the protocol of **35a** with **34c** (175 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25). ^{1}H NMR (600 MHz, $DCCl_3$) δ 9.81 (s, 1H), 7.46 (d, 1H, *J* = 7.9 Hz), 7.28–7.36 (m, 4H), 7.24–7.27 (m, 1H), 7.13 (d, 2H, *J* = 7.3 Hz), 7.08 (d, 1H, *J* = 7.3 Hz), 5.03 (s, 2H), 2.80 (t, 2H, *J* = 6.3 Hz), 2.41 (t, 2H, *J* = 6.3 Hz).

***N*-(3-Bromobenzyl)-4-oxo-*N*-phenylbutanamide (35d).** The compound (105 mg, 60.8% yield) was afforded by the protocol of **35a** with **34d** (175 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25). ^{1}H NMR (300 MHz, $DCCl_3$) δ 9.80 (s, 1H), 7.34–7.38 (m, 5H), 7.05–7.14 (m, 4H), 4.83 (s, 2H), 2.78 (t, 2H, *J* = 6.6 Hz), 2.35 (t, 2H, *J* = 6.6 Hz).

***N*-((1*H*-Imidazol-4-yl)methyl)-4-oxo-*N*-phenylbutanamide (35e).** The compound (74 mg, 57.6% yield) was afforded by the protocol of **35a** with **34e** (130 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 60:40). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.31–7.43 (m, 5H), 6.91 (s, 2H),4.84 (s, 2H), 2.60 (t, 2H, *J* = 6.7 Hz), 2.30 (t, 2H, *J* = 6.7 Hz).

4-Oxo-*N*-phenyl-*N*-(thiophen-2-ylmethyl)butanamide (35f). The compound (84 mg, 61.5% yield) was afforded by the protocol of **35a** with **34f** (138 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25). ^{1}H NMR (300 MHz, $DCCl_3$) δ 9.76 (s, 1H), 7.30–7.35 (m, 3H),

7.19–7.21 (m, 1H), 7.01–7.04 (m, 2H), 6.94–6.98 (m, 2H), 4.82 (s, 2H), 2.73 (t, 2H, *J* = 6.3 Hz), 2.30 (t, 2H, *J* = 6.3 Hz).

4-Oxo-*N*-phenyl-*N*-(thiophen-3-ylmethyl)butanamide (35g). The compound (87 mg, 63.7% yield) was afforded by the protocol of **35a** with **34g** (138 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25). ^{1}H NMR (300 MHz, $DCCl_3$) δ 9.80 (s, 1H), 7.21 (d, 1H, *J* = 5.0 Hz), 7.07–7.10 (m, 2H), 6.86–6.89 (m, 1H), 6.79 (d, 1H, *J* = 3.0 Hz), 4.99 (s, 2H), 2.77 (t, 2H, *J* = 6.5 Hz), 2.33 (t, 2H, *J* = 6.5 Hz).

4-Oxo-*N*-phenyl-*N*-(pyridin-2-ylmethyl)butanamide (35h). The compound (78 mg, 58.2% yield) was afforded by the protocol of **35a** with **34h** (135 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 25:75). ^{1}H NMR (300 MHz, $DCCl_3$) δ 9.69 (s, 1H), 8.38 (d, 1H, *J* = 4.3 Hz), 7.55–7.57 (m, 1H), 7.19–7.30 (m, 4H), 7.12–7.14 (m, 2H), 7.04–7.06 (m, 1H), 4.94 (s, 2H), 2.69 (t, 2H, *J* = 6.7 Hz), 2.34 (t, 2H, *J* = 6.7 Hz).

4-Oxo-*N*-phenyl-*N*-(pyridin-4-ylmethyl)butanamide (35i). The compound (76 mg, 56.7% yield) was afforded by the protocol of **35a** with **34i** (135 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 25:75).^{1}H NMR (300 MHz, $DCCl_3$) δ 9.76 (s, 1H), 8.48 (d, 2H, *J* = 5.0 Hz), 7.29–7.36 (m, 3H), 7.07–7.14 (m, 4H), 4.83 (s, 2H), 2.76 (t, 2H, *J* = 6.9 Hz), 2.35 (t, 2H, *J* = 6.9 Hz).

4-Oxo-*N*-phenyl-*N*-(quinolin-6-ylmethyl)butanamide (35j). The compound (87 mg, 54.7% yield) was afforded by the protocol of **35a** with **34j** (160 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography

(hexane/ethyl = 25:75).^{1}H NMR (300 MHz, $DCCl_3$) δ 9.81 (s, 1H), 8.87 (d, 1H, J = 3.6 Hz), 8.08 (d, 1H, J = 8.1 Hz), 8.03 (d, 1H, J = 8.5 Hz), 7.61 (s, 1H), 7.58 (d, 1H, J = 8.9 Hz), 7.47–7.51 (m, 1H), 7.27–7.34 (m, 3H), 7.05–7.08 (m, 2H), 5.05 (s, 2H), 2.80 (t, 2H, J = 6.2 Hz), 2.38 (t, 2H, J = 6.2 Hz).

4-Oxo-*N*-phenyl-*N*-(quinolin-3-ylmethyl)butanamide (35k). The compound (90 mg, 56.6% yield) was afforded by the protocol of **35a** with **34k** (160 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 25:75).^{1}H NMR (300 MHz, $DCCl_3$) δ 9.65 (s, 1H), 8.72 (d, 1H, J = 1.7 Hz), 8.10 (s, 1H), 7.94 (dd, 2H, J = 8.8, 19.7 Hz), 7.71 (t, 1H, J = 6.8 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.25–7.40 (m, 5H), 5.06 (s, 2H), 2.67 (t, 2H, J = 6.4 Hz), 2.35 (t, 2H, J = 6.4 Hz).

***N*-(Cyclohexylmethyl)-4-oxo-*N*-phenylbutanamide (35l).** The compound (84 mg, 61.5% yield) was afforded by the protocol of **35a** with **34l** (138 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25).^{1}H NMR (600 MHz, $DCCl_3$) δ 9.77 (s, 1H), 7.42 (t, 2H, J = 7.7 Hz), 7.35 (t, 1H, J = 7.3 Hz), 7.20 (d, 2H, J = 7.3 Hz), 3.56 (d, 2H, J = 7.3 Hz), 2.71 (t, 2H, J = 6.5 Hz), 2.31 (t, 2H, J = 6.5 Hz), 1.65–1.69 (m, 4H), 1.61 (br, 1H), 1.45–1.48 (m, 1H), 1.13–1.16 (m, 3H), 0.94–0.99 (m, 2H).

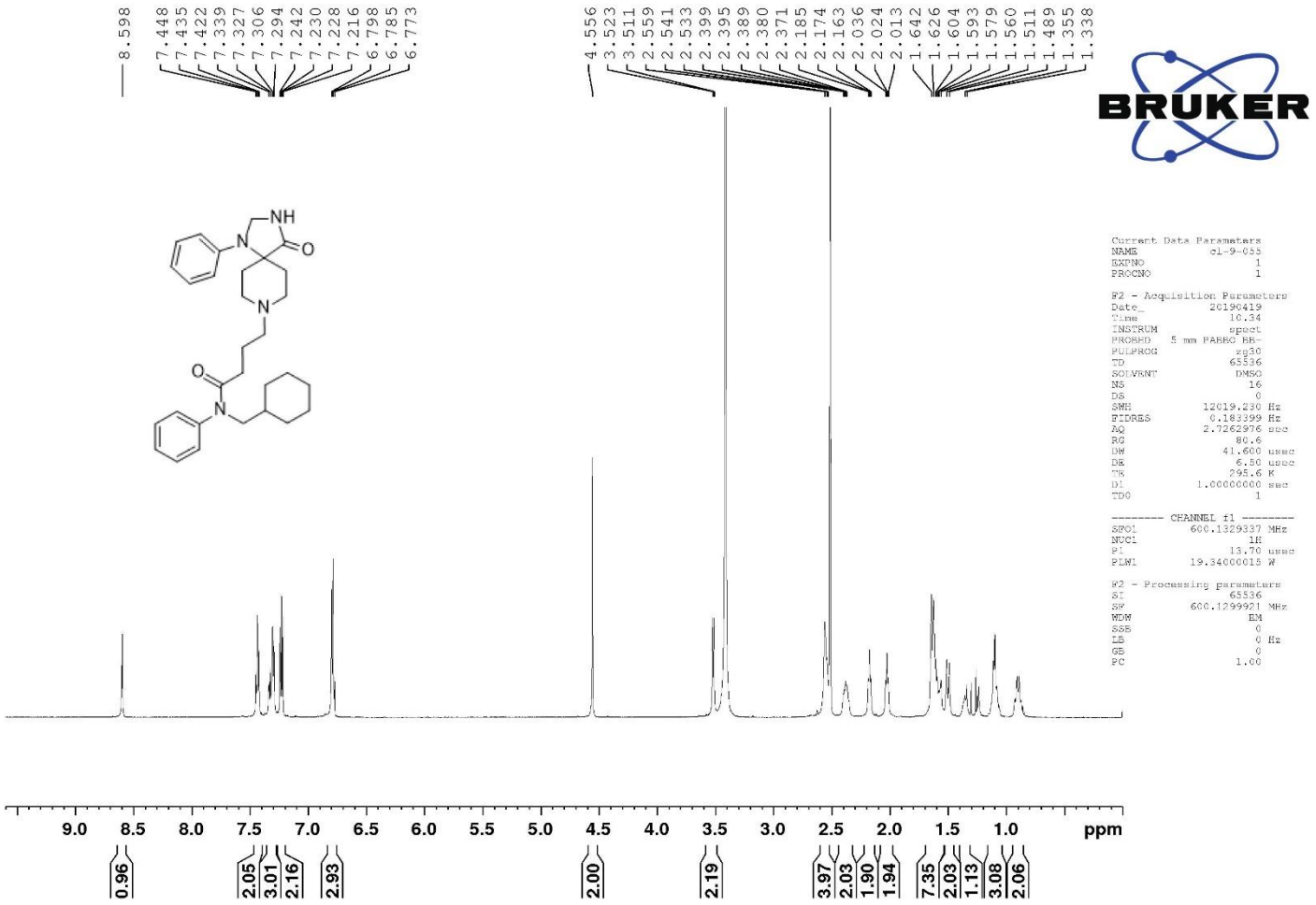
***N*-(Cyclopentylmethyl)-4-oxo-*N*-phenylbutanamide (35m).** The compound (77 mg, 59.4% yield) was afforded by the protocol of **35a** with **34m** (131 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25).^{1}H NMR (300 MHz, $DCCl_3$) δ 9.78 (s, 1H), 7.35–7.45 (m, 3H),

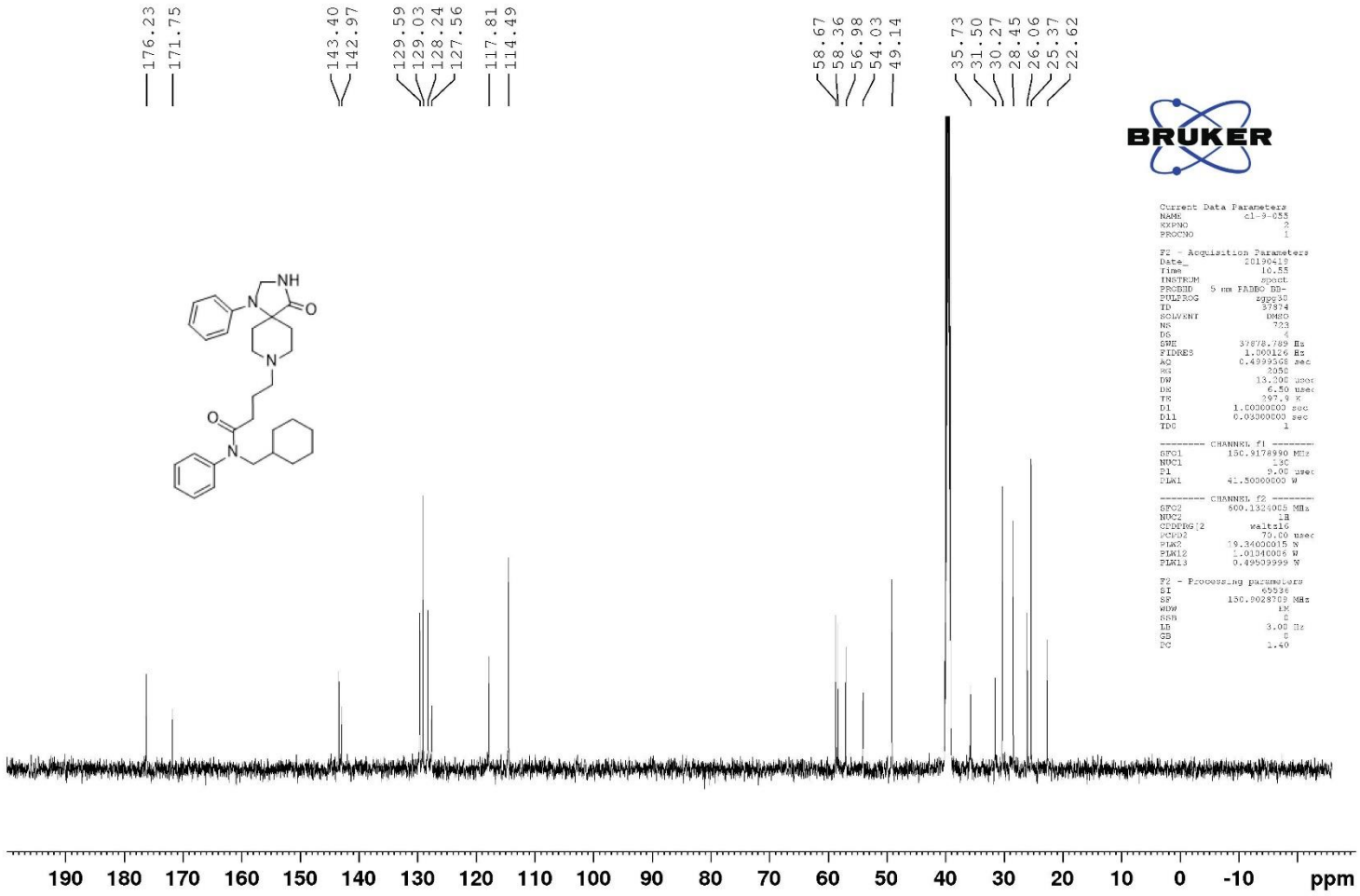
7.23 (d, 2H, *J* = 7.3 Hz), 3.68 (d, 2H, *J* = 7.6 Hz), 2.72 (t, 2H, *J* = 6.5 Hz), 2.30 (t, 2H, *J* = 6.5 Hz), 1.96–2.03 (m, 1H), 1.48–1.66 (m, 6H), 1.18–1.27 (m, 2H).

***N*-(Cyclobutylmethyl)-4-oxo-*N*-phenylbutanamide (35n).** The compound (75 mg, 61.2% yield) was afforded by the protocol of **35a** with **34n** (124 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25).^{1}H NMR (300 MHz, $DCCl_3$) δ 9.79 (s, 1H), 7.33–7.45 (m, 3H), 7.18 (d, 2H, *J* = 7.3 Hz), 3.78 (d, 2H, *J* = 7.8 Hz), 2.73 (t, 2H, *J* = 6.5 Hz), 2.40–2.51 (m, 1H), 2.30 (t, 2H, *J* = 6.5 Hz), 1.90–1.97 (m, 2H), 1.78–1.87 (m, 2H), 1.60–1.70 (m, 2H).

***N*-(Cyclopropylmethyl)-4-oxo-*N*-phenylbutanamide (35o).** The compound (70 mg, 60.6% yield) was afforded by the protocol of **35a** with **34o** (116 mg, 0.5 mmol) and Dess-Martin reagent (425 mg, 1 mmol) and purified by flash column chromatography (hexane/ethyl = 75:25).^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.48 (t, 2H, *J* = 7.1 Hz), 7.34–7.41 (m, 3H), 3.48 (d, 2H, *J* = 7.1 Hz), 2.56 (t, 2H, *J* = 6.4 Hz), 2.22 (t, 2H, *J* = 6.4 Hz), 0.80–0.88 (m, 1H), 0.32–0.38 (m, 2H), 0.00–0.04 (m, 2H).

Representative NMR, HRMS and HPLC data of 36l.




176.23
171.75
143.40
142.97
129.59
129.03
128.24
127.56
117.81
114.49
58.67
58.36
56.98
54.03
49.14
35.73
31.50
30.27
28.45
26.06
25.37
22.62
BRUKER
Current Data Parameters
NAME cl-9-055
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190418
Time 10.55
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 37874
SOLVENT DMSO
NS 723
DS 4
SWH 37878.789 Hz
FIDRES 1.000126 Hz
AQ 0.4999508 sec
RG 2050
DW 13.200 usec
DE 6.50 usec
TE 297.8 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 150.9178990 MHz
NUC1 13C
P1 9.00 usec
PLW1 41.50000000 W
CHANNEL f2
SFO2 600.1324005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 19.34000015 W
PLW12 1.01340006 W
PLW13 0.49509999 W
F2 - Processing parameters
SI 65536
SF 150.9028709 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

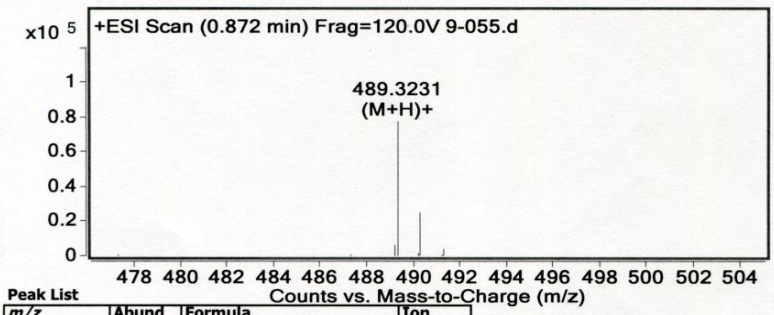
Qualitative Analysis Report

Data Filename	9-055.d	**Sample Name**	
Sample Type	Sample	**Position**	P2-B1
Instrument Name	Instrument 1	**User Name**	
Acq Method	TEST-POS-WL.m	**Acquired Time**	7/16/2019 4:45:40 PM
IRM Calibration Status	Some Ions Missed	**DA Method**	SERUM-POS-19MIN.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
120	0	ESI



Peak List

m/z	Abund	Formula	Ion
489.3231	77243.6	C30 H41 N4 O2	(M+H)+

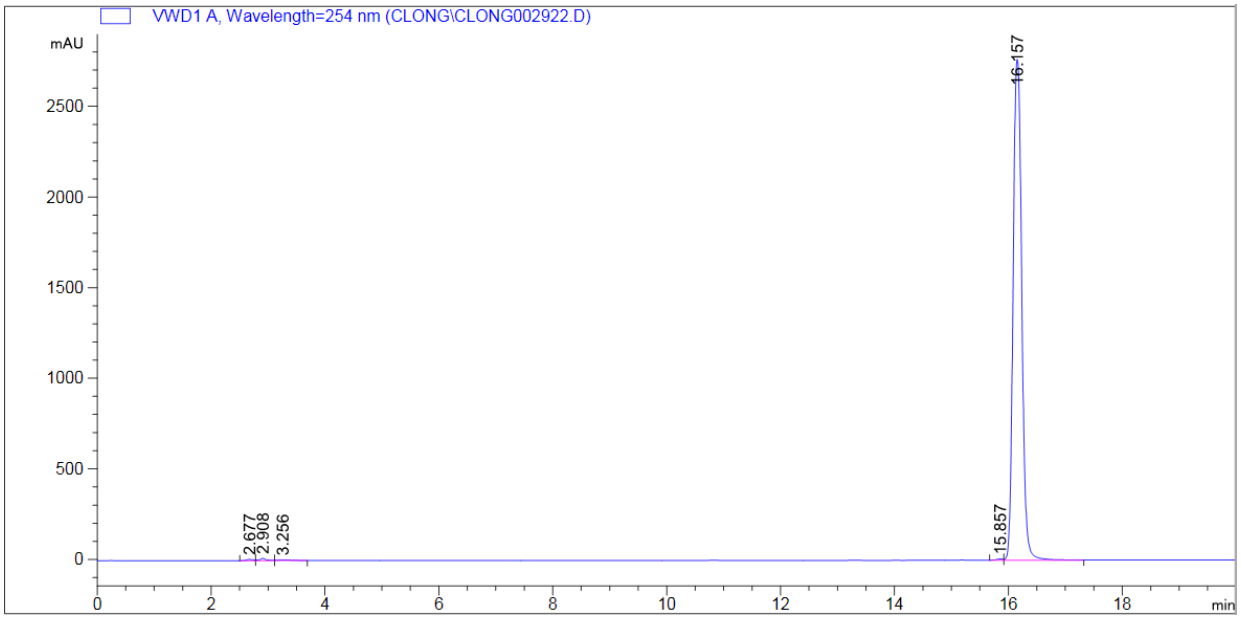
Formula Calculator Element Limits

Element	Min	Max
C	0	100
H	0	150
O	2	2
N	4	4

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C30 H40 N4 O2	TRUE	488.3158	488.3151	-1.4	C30 H41 N4 O2	98.02

--- End Of Report ---


VWD1 A, Wavelength=254 nm (CLONG\CLONG002922.D)
mAU
2500
2000
1500
1000
500
0
2.677
2.908
3.256
15.857
16.157
0
2
4
6
8
10
12
14
16
18
min