SUPPORTING INFORMATION

Virtual screening approach to identifying a novel and tractable series of *Pseudomonas aeruginosa* elastase inhibitors

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LIST OF ABBREVIATIONS AND GENERAL EXPERIMENTAL

Abbreviations

AcOH	Acetic acid
Boc	Tert-butyl-carbonyl
COMU	1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethylamine
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl	Hydrochloric acid
HOBt	Hydroxybenzotriazole
H_2SO_4	Sulfuric Acid
MDAP	Mass-Directed Auto Purification
MeOH	Methanol
NaH	Sodium hydride
$NaHCO_3$	Sodiun hydrogen carbonate
NaHMDS	Sodium bis(trimethylsilyl)amide
NH_3	Ammonia
Na_2SO_4	Sodium sulfate
TES	Triethylsilane
TIS	Triisopropylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

General procedures: Reactions were performed under argon using dried glassware and solvents and at room temperature unless otherwise stated. Commercially available reagents and solvents were used as supplied or purified using standard protocols. Reactions were monitored by standard TLC or LC/MS techniques. Chromatography was performed with standard silica columns eluting with solvent combinations as described. ^{1}H spectra were recorded using 500 MHz (Bruker), 400 MHz (Bruker), 400 MHz (Varian) and 300 MHz (Varian) instruments in the deuterated solvents as indicated. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane or alternatively using residual solvent peak as internal standard. Multiplicity is given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or b (broad). Coupling constants (*J*) are reported in Hertz (Hz). Preparative HPLC conditions are individually reported as appropriate. All compounds tested were >95% pure as determined by NMR and LC/MS.

LCMS Instrument-1

Instrument details:

LC: Waters acquity UPLC with binary pump

MS: 3100 SQD module with ESI ionization technique

Method details:

Column: Acquity UPLC BEH C18 (50x2.1) mm; 1.7 um

Mobile phase-A: 0.05% Formic acid in water

Mobile phase-B: 0.05% Formic acid in acetonitrile

Flow rate: 0.6 mL/min

Temperature: 35 °C

Gradient: Time (min)/%B: 0/3, 0.4/3, 3.2/98, 3.8/98, 4.3/3, 4.5,3

LCMS Instrument-2

Instrument details:

LC: Agilent 1290 UPLC with binary pump

MS: 6130A SQD module with ESI ionization technique

Method details:

Column: Acquity UPLC BEH C18 (50x2.1) mm; 1.7 um

Mobile phase-A: 0.1% Formic acid in water

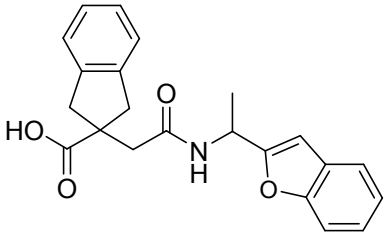
Mobile phase-B: 0.1% Formic acid in acetonitrile

Flow rate: 0.8 mL/min

Temperature: 60 °C

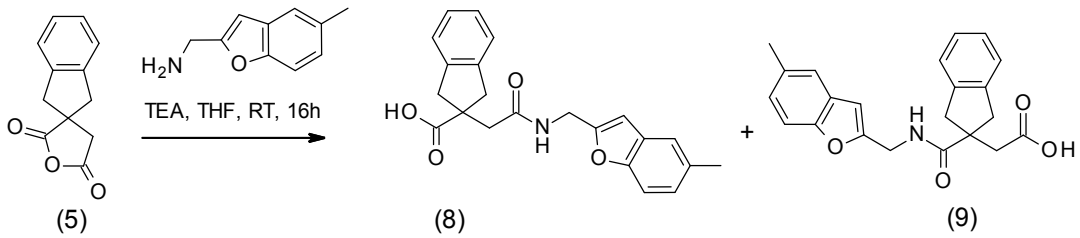
Gradient: Time (min)/%B: 0/2, 0.4/2, 2.2/98, 2.6/98, 2.61/2, 3.0/2

2-(2-((1-(benzofuran-2-yl)ethyl)amino)-2-oxoethyl)-2,3-dihydro-1H-indene-2-carboxylic acid (3)



^{13}C NMR (100 MHz, DMSO-d_6): δ 177.08, 169.47, 159.54, 154.01, 141.18, 128.01, 126.35, 124.32, 124.29, 123.84, 122.76, 120.83, 110.90, 101.82, 50.75, 42.62, 42.17, 42.06, 19.20.
HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1530.

General description of Method A



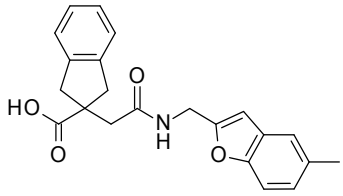
(5) (8) (9)

Scheme S1. Synthesis of compounds (8) and (9)

2-[2-[(5-methylbenzofuran-2-yl)methylamino]-2-oxo-ethyl]indane-2-carboxylic acid (8) and 2-[2-[(5-methylbenzofuran-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (9)

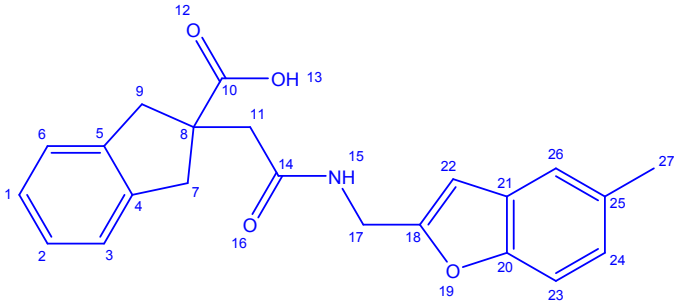
To a stirred solution of 1',3'-dihydro-2H-spiro[furan-3,2'-indene]-2,5(4H)-dione (60 mg, 0.29 mmol) and (5-methylbenzofuran-2-yl)methanamine (112 mg, 0.44 mmol) in THF (5 mL) was added Et_3N (0.09 mL, 0.59 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. After completion disappearance of SM, the reaction mixture was evaporated under reduced pressure. The residue was triturated with DCM (2 mL) and n-pentane (15 mL). The resulting solid was filtered, washed with n-pentane (5 mL) and dried under high vacuum. The solid was further treated with 1*N* HCl (10 mL) for 10 minutes, filtered, washed with water (5 mL) and dried under vacuum to obtain a mixture of the two regioisomers (110 mg) which were separated by SFC [Chiralpak AD-H (30x250 mm), 5 μ; Mobile phase: 60% CO_2 gas, 40% MeOH; Total flow: 70.0 g/min; Back pressure: 100.0 bar; UV: 210 nm] to obtain **8** (15 mg, 14%) as a white solid and **9** (35 mg, 32%) also as a white solid. The structures of 8 and 9 were confirmed by HMBC experiment.

2-[2-[(5-methylbenzofuran-2-yl)methylamino]-2-oxo-ethyl]indane-2-carboxylic acid (8)



M/z 364.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.3 (1H, s), 8.55 (1H, t, *J* = 5.2 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.34 (1H, s), 7.16 (2H, m), 7.12 (2H, m), 7.05 (1H, dd, *J* = 8.4 Hz and 1.2 Hz), 6.58 (1H, s), 4.38 (2H, d, *J* = 5.6 Hz), 3.34 (2H, d, *J* = 16 Hz), 2.89 (2H, d, *J* = 16 Hz), 2.63 (2H, s), 2.37 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.28, 170.30, 155.81, 152.53, 141.28, 131.62, 128.18, 126.26, 124.90, 124.29, 120.52, 110.37, 102.87, 50.92, 42.70, 42.21, 35.88, 20.88. HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1532.

Proton, Carbon assignment and key HMBC correlations of Compound 8



Exact Mass: 363.15

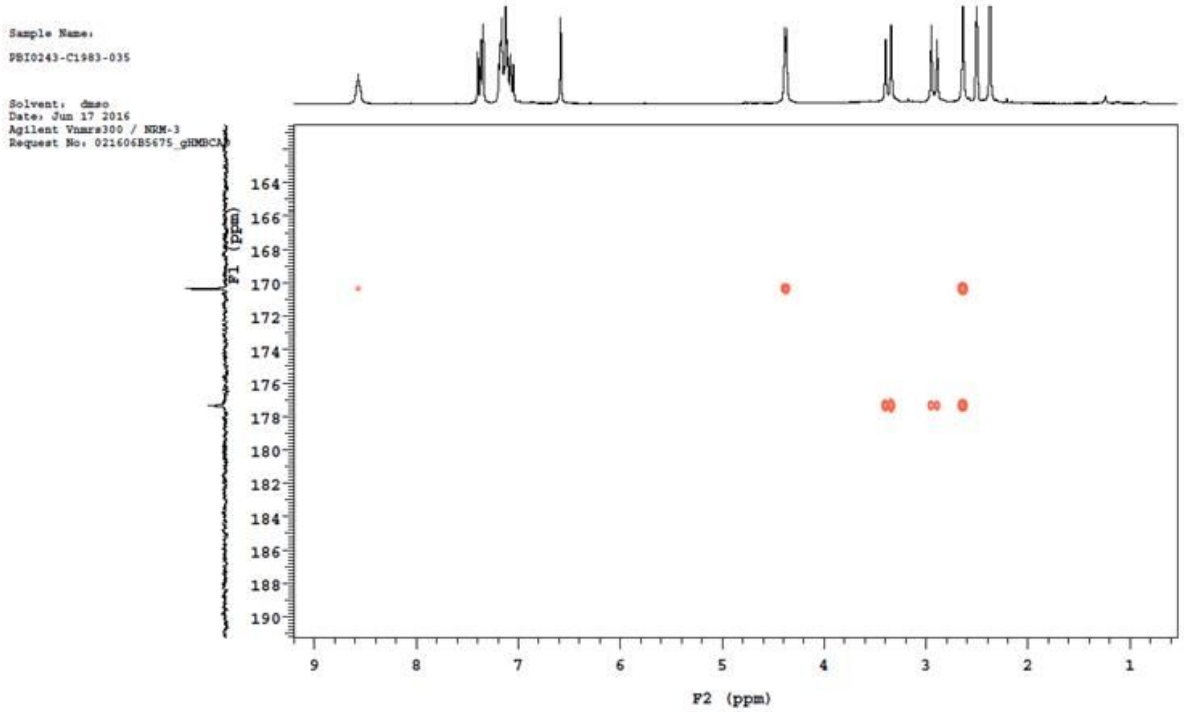
Atom No	Type of Atom	^{1}H Chemical shift (ppm) Coupling constant (J)	^{13}C chemical shift (ppm)
1,2	CH	7.12 (m, 2H)	126.29
3,6	CH	7.16 (m, 2H)	124.29
4,5	C	-	141.28
7,9	CH_2	2.89, 3.34 (d, 16Hz, 4H)	42.21
8	C	-	50.92
10	C	-	177.28
11	CH_2	2.63 (s, 2H)	42.70
12	O	-	
13	OH	12.3 (s, 1H)	-
14	C	-	170.30
15	NH	8.55 (t, 5.2Hz, 1H)	-
16	O	-	-
17	CH_2	4.38 (d, 5.6Hz, 2H)	35.88
18	C	-	155.81
19	O	-	-
20	C	-	152.53
21	C	-	128.18
22	CH	6.58 (s, 1H)	102.87
23	CH	7.37 (d, 8.4Hz, 1H)	110.37
24	CH	7.05 (dd, 8.4Hz, 1.2Hz, 1H)	124.90
25	C	-	131.62
26	CH	7.34 (s, 1H)	120.52
27	CH_3	2.37 (s)	20.88

Key correlations:

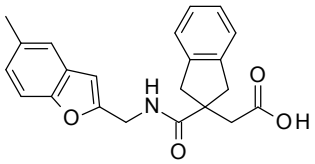
- In HMBC experiment H7, H9 (2.89 ppm & 3.34 ppm) and H11 (2.63 ppm) protons showing connectivity to C10 (177.28 ppm) carbon.

- In HMBC experiment H11(2.63 ppm), H15 (8.55 ppm) and H17 (4.38 ppm) protons showing connectivity to C14 (170.30 ppm) carbon.

Here three methylene groups showing connectivity to acid carbonyl.

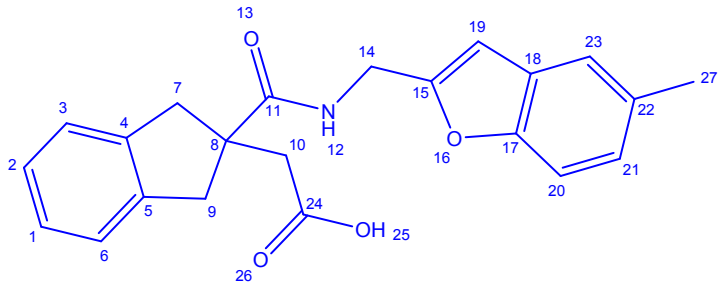


2-[2-[(5-methylbenzofuran-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (9)



M/z 364.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.2 (1H, bs), 8.44 (1H, t, J = 5.6 Hz), 7.35 (1H, d, J = 8 Hz), 7.29 (1H, s), 7.18 (2H, m), 7.12 (2H, m), 7.03 (1H, dd, J = 8.4 Hz, J = 1.6 Hz), 6.46 (1H, d, J = 0.8 Hz), 4.39 (2H, d, J = 5.2 Hz), 3.40 (2H, d, J = 16.0 Hz), 2.94 (2H, d, J = 16.0 Hz), 2.72 (2H, s), 2.36 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.94, 172.67, 156.33, 152.43, 141.15, 131.55, 128.27, 126.35, 124.67, 124.40, 120.32, 110.33, 102.26, 51.47, 42.31, 41.73, 36.71, 20.88. HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1532.

Proton, Carbon assignment and key HMBC correlations of Compound 9



Exact Mass: 363.15

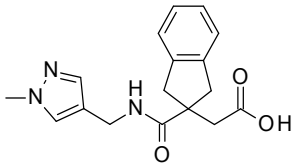
Atom No	Type of Atom	^{1}H Chemical shift (ppm) Coupling constant (J)	^{13}C chemical shift (ppm)
1,2	CH	7.12 (m, 2H)	126.35
3,6	CH	7.18 (m,2H)	124.40
4,5	C	-	141.15
7,9	CH_2	2.94, 3.40 (d, 16Hz, 4H)	42.31
8	C	-	51.47
10	CH_2	2.72 (s, 2H)	41.73
11	C	-	174.94
12	NH	8.44 (t, 5.6Hz, 1H)	-
13	O	-	-
14	CH_2	4.39 (d, 5.2Hz, 2H)	36.71
15	C	-	156.33
16	O	-	-
17	C	-	152.43
18	C	-	128.27
19	CH	6.46 (d, 0.8Hz, 1H)	102.26
20	CH	7.35 (d, 8Hz, 1H)	110.33
21	CH	7.03 (dd, 8.4Hz, 1.6Hz, 1H)	124.67
22	C	-	131.55
23	CH	7.29 (s,1H)	120.32
24	C	-	172.67
25	OH	12.2 (broad peak, 1H)	-
26	O	-	-
27	CH_3	2.36 (s, 3H)	20.88

Key correlations:

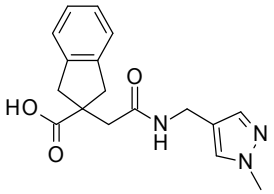
- In HMBC experiment H7, H9 (2.94 ppm & 3.40 ppm), H10 (2.72 ppm), H12 (8.44 ppm) and H14 (4.39 ppm) protons showing connectivity to C11(174.94 ppm) carbon.

- In HMBC experiment H10 (2.72 ppm) protons showing connectivity to C24 (172.67 ppm) carbon.

Here one methylene group showing connectivity to acid carbonyl.



(10)



(12)

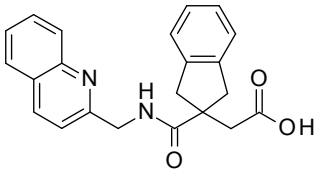
2-[2-[(1-methylpyrazol-4-yl)methylcarbamoyl]indan-2-yl]acetic acid (10) and 2-[2-[(1-methylpyrazol-4-yl)methylamino]-2-oxo-ethyl]indane-2-carboxylic acid (12)

Method A was used as described above for compounds **8** and **9** using (1-methylpyrazol-4-yl)methanamine as amine.

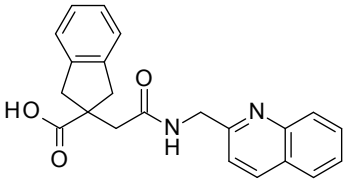
2-[2-[(1-methylpyrazol-4-yl)methylcarbamoyl]indan-2-yl]acetic acid (10)
M/z 314.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 11.90 (1H, bs), 8.45 (1H, bs), 7.41 (1H, s), 7.22 (1H, s), 7.18-7.16 (2H, m), 7.13-7.08 (2H, m), 4.07 (2H, d, J = 5.6 Hz), 3.74 (3H, s), 3.35 (2H, d, J = 16.0 Hz), 2.91 (2H, d, J = 16.0 Hz), 2.61 (2H, s).

2-[2-[(1-methylpyrazol-4-yl)methylamino]-2-oxo-ethyl]indane-2-carboxylic acid (12)
M/z 314.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.05 (1H, bs), 8.22 (1H, bs), 7.49 (s, 1 H), 7.26 (1H, s), 7.17-7.14 (2H, m), 7.12-7.09 (2H, m), 4.04 (2H, d, J = 5.6 Hz), 3.76 (3H, s), 3.36 (2H, obs), 2.88 (2H, d, J = 16.0 Hz), 2.55 (2H, s). HRMS anal. calcd for $C_{17}H_{20}O_3N_3$ $[M+H]^+$: 314.1499, found 314.1489.

2-(2-((quinolin-2-ylmethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (11) and 2-[2-oxo-2-(2-quinolylmethylamino)ethyl]indane-2-carboxylic acid (13)



(11)



(13)

Method A was used as described above for compounds **8** and **9** using quinol-2-ylmethanamine as amine.

2-(2-((quinolin-2-ylmethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (11)

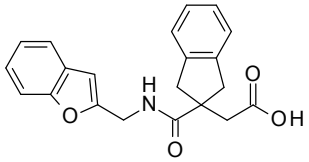
M/z 361.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.11 (1H, bs), 8.50 (1H, bs), 8.25 (1H, d), 7.95-7.92 (2H, m), 7.74 (1H, m), 7.57 (1H, m), 7.38 (1H, d, J = 8.9 Hz), 7.24-7.21 (2H, m), 7.17-7.13 (2H, m), 4.54 (2H, d, J = 6.0 Hz), 3.50 (2H, d, J = 16.4 Hz), 3.01 (2H, d, J = 16.4 Hz), 2.77 (2H, s). HRMS anal. calcd for $C_{22}H_{21}O_3N_2$ $[M+H]^+$: 361.1547, found 361.1539.

2-[2-oxo-2-(2-quinolylmethylamino)ethyl]indane-2-carboxylic acid (13)

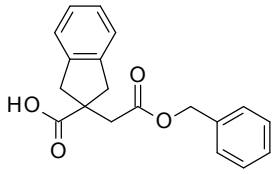
M/z 361.3 $[(M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.85 (1H, bs), 8.31 (1H, d, J = 8.4 Hz), 7.95 (2H, d, J = 8.8 Hz), 7.75 (1H, td, J = 8.4 Hz, J = 1.6 Hz), 7.58 (1H, t, J = 8.4 Hz), 7.43 (1H, d, J = 8.8 Hz), 7.19-7.16 (2H, m), 7.13-7.10 (2H, m), 4.51 (2H, d, J = 6.0 Hz), 3.38 (2H, d, J = 16.4 Hz), 2.94 (2H, d, J = 16.4 Hz), 2.67 (2H, s). HRMS anal. calcd for $C_{22}H_{21}O_3N_2$ $[M+H]^+$: 361.1547, found 361.1537.

General description of Method B

2-(2-{[(1-Benzofuran-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetic acid (16)

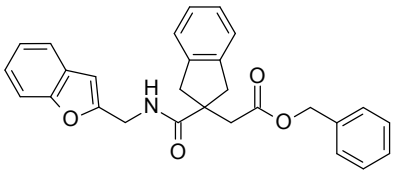


a. **2-[2-(Benzyloxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylic acid**



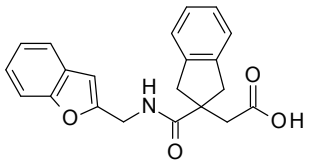
A mixture of 1,3-dihydrospiro[indene-2,3'-oxolane]-2',5'-dione (500 mg, 2.5 mmol) and benzyl alcohol (400 mg, 3.7 mmol) in toluene (2 mL) was heated at 100°C under argon overnight. The cooled solution was diluted slowly with cyclohexane (5 mL) and filtered, washing with cyclohexane then drying under vacuum to afford a white solid (0.54 g, 70%). M/z 311.3 $(M+H)^+$.

b. Benzyl 2-(2-{[(1-benzofuran-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetate



A solution of 2-[2-(benzyloxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylic acid (50 mg, 0.16 mmol) and diisopropylethylamine (62 mg, 0.48 mmol) in DMF was treated with HATU (73 mg, 0.19 mmol). After 15 minutes (1-benzofuran-2-yl)methanamine hydrochloride (44 mg, 0.24 mmol) was added. After 1.25 hours the mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined extracts were dried (Na_2SO_4) and evaporated affording a brown oil (100 mg). M/z 440.5 $(M+H)^+$.

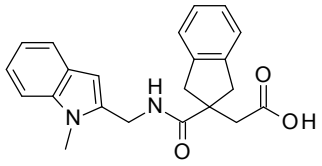
c. 2-(2-{[(1-Benzofuran-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetic acid (16)



A solution of benzyl 2-(2-{[(1-benzofuran-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetate (100 mg) in EtOAc (5 mL) was hydrogenated overnight over 10% palladium on charcoal (20 mg). The mixture was heated to 50°C and hydrogenated for a further 8 hours. The mixture was filtered and evaporated affording a yellow oil (100 mg) which was purified

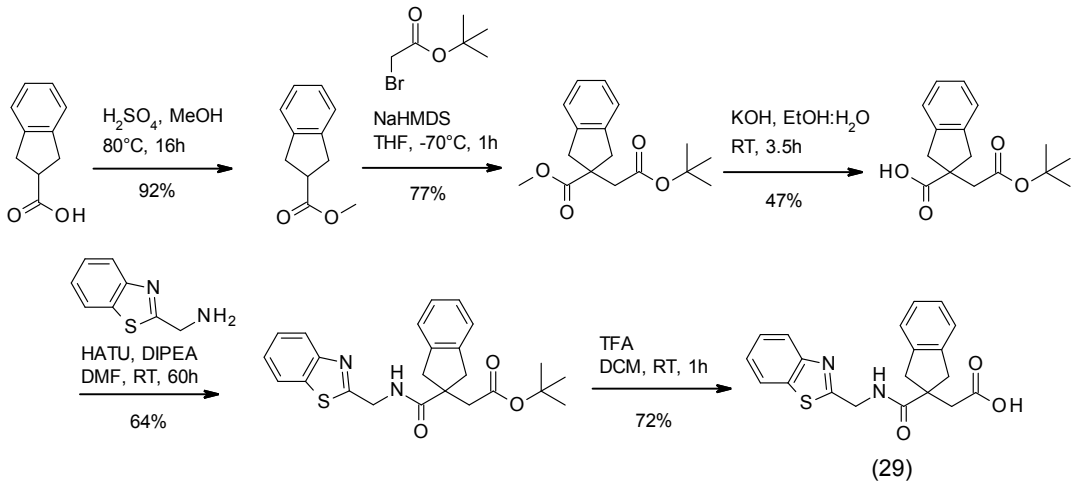
by chromatography on silica eluting with 0-40% EtOAc in cyclohexane affording the title compound as a colourless oil (32 mg, 57% yield over 2 steps). M/z 350.4 $(M+H)^+$. ^{1}H NMR (d6-DMSO) δ 8.45-8.35 (1H, bs), 7.50 (2H, t), 7.25-7.15 (4H, m), 7.15-7.00 (2H, m), 6.55 (1H, s), 4.43 (2H, d), 3.42 (2H, d, J = 16 Hz), 2.97 (2H, d, J = 16 Hz), 2.72 (2H, s).

2-[2-[(1-methylindol-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (26)



Method B was used as described for compound **16**, using (1-methylindol-2-yl)methanamine as the amine. M/z 363.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (1H, bs), 7.45 (1H, d, J = 7.2 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.15-7.07 (5H, m), 6.98 (1H, t, J = 7.2 Hz), 6.31 (1H, s), 4.48 (2H, d, J = 4.8 Hz), 3.65 (3H, s), 3.40 (2H, d, J = 16.0 Hz), 2.94 (2H, d, J = 16.0 Hz), 2.49-2.44 (2H, bs). HRMS anal. calcd for $C_{22}H_{21}O_3N_2$ $[M-H]^-$: 361.1547, found 361.1555.

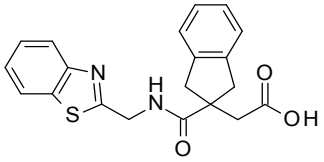
General description of Method C



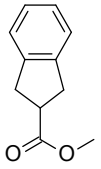
Scheme S2. Synthesis of compound (29)

2-(2-{[(1,3-Benzothiazol-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetic acid (29)

.

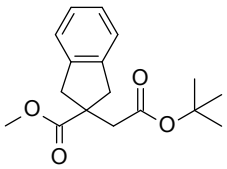


a. Methyl indane-2-carboxylate



To a stirred solution of 2,3-dihydro-1H-indene-2-carboxylic acid (20 g, 123 mmol) in MeOH (200 mL) was added con. H_2SO_4 (10 mL, 185 mmol) dropwise at room temperature and stirred at 80 °C for 16 h. The reaction mixture was evaporated. The residue was dissolved in water (100 mL) and extracted with EtOAc (2x100 mL). The organic layer was washed with sat. sodium bicarbonate, brine, dried (Na_2SO_4) and evaporated, affording a light brown oil (20 g, 92%). M/z 177.1 $(M+H)^+$.

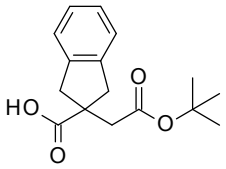
b. Methyl 2-[2-(*tert*-butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylate



A solution of commercially available methyl 2,3-dihydro-1H-indene-2-carboxylate (4.53 g, 25.7 mmol) in THF (100 mL) was treated with a solution of sodium hexamethylsilazide in THF (1M, 38.6 ml, 38.8 mmol) dropwise at -70° C under nitrogen. After 0.25 hours, *tert*-butyl bromoacetate (5.7 mL, 38.6 mmol) was added dropwise, ensuring the internal temperature did not rise above -60° C. After the addition was complete the mixture was allowed to warm to room temperature over 0.5 hours then quenched with saturated aqueous

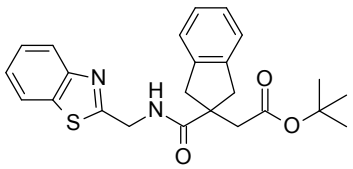
ammonium chloride solution (150 mL). The mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated affording the crude product (11.2 g) which was chromatographed on silica eluting with 0-40% EtOAc in hexane affording methyl
2-[2-(*tert*-butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylate as a yellow oil (5.7 g, 77%).
M/z 291.4 $(M+H)^+$ and M/z 235.3 $(M+H)^+$ (loss of *iso*butene)

c. 2-[2-(*tert*-Butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylic acid



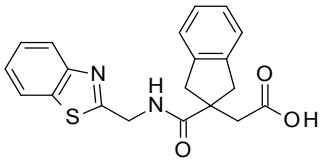
A solution of methyl 2-[2-(tert-butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylate (4.0 g, 13.8 mmol) in EtOH/H_2O (80 mL/40 mL) was treated with KOH (4.3 g, 75.8 mmol). After 3.5 hours the mixture was diluted with water and washed with diethyl ether. The aqueous phase was acidified to pH 3 with solid citric acid monohydrate and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated affording the crude product as a solid (3.7 g). This was redissolved in chloroform, filtered and evaporated to give
2-[2-(*tert*-butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylic acid as a white solid (1.76 g, 47%).
M/z 277.3 $(M+H)^+$

d. *tert*-Butyl 2-(2-{[(1,3-benzothiazol-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetate



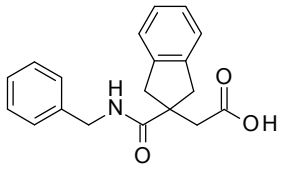
A solution of 2-[2-(*tert*-butoxy)-2-oxoethyl]-2,3-dihydro-1H-indene-2-carboxylic acid (530 mg, 1.92 mmol), HATU (876 mg, 2.3 mmol) and DIPEA (1.34 mL, 7.7 mmol) in DMF (10 mL) was stirred for 0.25 hours then 1,3-benzothiazol-2-ylmethanamine (350 mg, 1.74 mmol) was added. The mixture was stirred for 2.5 days then evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous sodium bicarbonate solution, water and brine, then the organic extract was dried (Na_2SO_4) and evaporated affording the crude product (628 mg). This was chromatographed on silica eluting with 0-100% EtOAc in hexane affording *tert*-butyl
2-(2-{[(1,3-benzothiazol-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetate as a white solid (520 mg, 64%).
M/z 423.2 $(M+H)^+$

e. 2-(2-{[(1,3-Benzothiazol-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)aceti c acid (29)



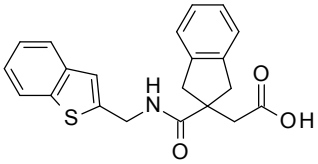
A solution of *tert*-butyl
2-(2-{[(1,3-benzothiazol-2-yl)methyl]carbamoyl}-2,3-dihydro-1H-inden-2-yl)acetate (520 mg, 1.23 mmol) in DCM (20 mL) was treated with TFA (2 mL). After 0.75 hours a further portion of TFA (1 mL) was added. The mixture was stirred overnight then evaporated, azeotroping twice with toluene. The residue was chromatographed on silica eluting with 0-100% EtOAc in hexane affording an oil which was dissolved in acetonitrile/water and lyophylised affording the title compound as a white solid (327 mg, 72%). M/z 367.4 $(M+H)^+$. ^{1}H NMR (d6-DMSO) δ 8.80-8.70 (1H, t), 8.05 (1H, d), 7.92 (1H, d), 7.50 (1H, t), 7.40 (1H, t), 7.20 (2H, m), 7.15 (2H, m), 4.67 (2H, d), 3.45 (2H, d, J = 16 Hz), 3.00 (2H, d, J = 16 Hz), 2.75 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.35, 172.37, 171.96, 152.64, 140.97, 134.60, 126.42, 125.99, 124.84, 124.44, 122.24, 122.10, 51.22, 42.19, 41.76, 41.48. HRMS anal. calcd for $C_{20}H_{19}O_3N_2S$ $[M+H]^+$: 367.1111, found 367.1102.

2-[2-(benzylcarbamoyl)indan-2-yl]acetic acid (21)

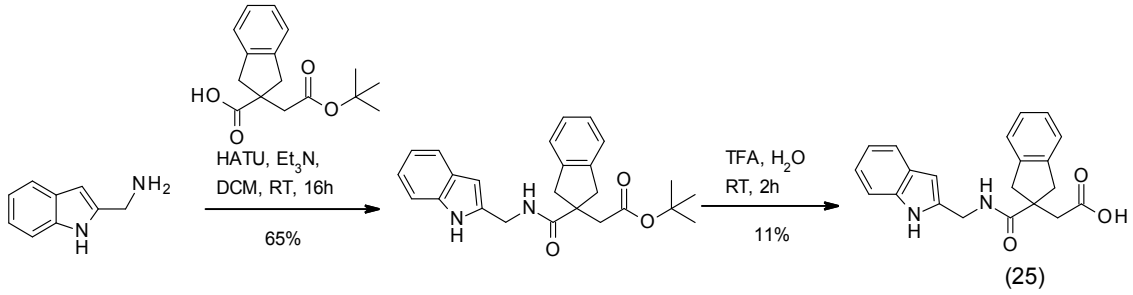


Method C was used as described for compound **29**, using benzylamine as the amine.
M/z 310.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.05 (1H, bs), 8.20 (1H, m), 7.28-7.10 (9H, m), 4.28 (2H, d, J = 5.4 Hz), 3.40 (2H, d, J = 16.3 Hz), 2.94 (2H, d, J = 16.3 Hz), 2.72 (2H, s). HRMS anal. calcd for $C_{19}H_{20}O_3N$ $[M+H]^+$: 310.1438, found 310.1427.

2-[2-(benzothiophen-2-ylmethylcarbamoyl)indan-2-yl]acetic acid (24)

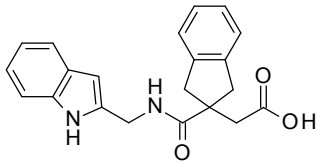


Method C was used as described above for compound **29**, using benzothiophen-2-ylmethanamine as the amine.
M/z 366.5 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 8.50 (1H, bs), 7.86 (1H, d), 7.71 (1H, d), 7.31 (2H, m), 7.19 (2H, m), 7.14 (3H, m), 4.53 (2H, d), 3.42 (2H, d, J = 16 Hz), 2.97 (2H, d, J = 16 Hz), 2.71 (2H, s). HRMS anal. calcd for $C_{21}H_{20}O_3NS$ $[M+H]^+$: 366.1158, found 366.1147.



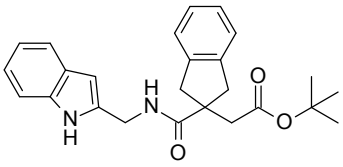
Scheme S3. Synthesis of compound (25)

2-[2-(1H-indol-2-ylmethylcarbamoyl)indan-2-yl]acetic acid (25)



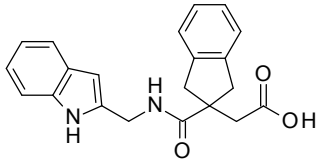
Method C was used as described for compound **29**, using 1H-indol-2-ylmethanamine as the amine.

a. Tert-butyl 2-[2-(1H-indol-2-ylmethylcarbamoyl)indan-2-yl]acetate



To a stirred solution of (1H-indol-2-yl)methanamine (50 mg, 0.34 mmol) in DCM (10 mL) was added triethylamine (0.14 mL, 1.02 mmol), 2-(2-(tert-butoxy)-2-oxoethyl)-2,3-dihydro-1H-indene-2-carboxylic acid (114 mg, 0.41 mmol) and HATU (195 mg, 0.51 mmol). The reaction mixture was stirred for 16 hours and then partitioned between DCM (50 mL) and water (30 mL). The organic layer was separated, washed with water and brine then dried (Na_2SO_4) filtered and evaporated to give a solid. This was purified by chromatography (12 g silica cartridge, gradient 10% - 15% EtOAc/petroleum ether) to yield tert-butyl 2-(2-(((1H-indol-2-yl)methyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetate (90 mg, 65%) as a white solid. M/z 405.54 $(M+H)^+$.

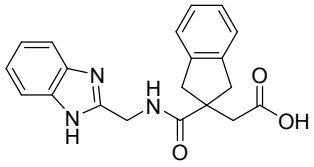
b. 2-[2-(1H-indol-2-ylmethylcarbamoyl)indan-2-yl]acetic acid (25)



A solution of tert-butyl 2-(2-(((1H-indol-2-yl)methyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetate (100 mg, 0.24 mmol) in TFA/H_2O (2 mL, 95:5) was stirred for 1.5 hours and the solvent was evaporated to give an oil. This was purified by preparative HPLC [YMC 18 (150*25 mm), 10 u, Mobile phase: A: 0.1% Formic Acid in H_2O, B: MeCN] to obtain **25** (9.5 mg, 11%) as a white solid. M/z 349.3 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 10.95 (1H, bs), 8.62 (1H, bs), 7.39 (1H, d, J = 8 Hz), 7.30 (1H, d, J = 8 Hz), 7.20-7.18 (2H, m), 7.14-7.11 (2H, m),

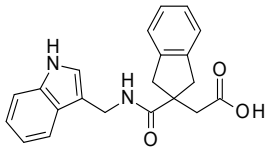
6.99 (1H, t, J = 8 Hz), 6.91 (1H, t, J = 8 Hz), 6.15 (1H, s), 4.44 (2H, d, J = 5.2 Hz), 3.43 (2H, d, J = 16 Hz), 2.95 (2H, d, J = 16 Hz), 2.65 (2H, s).

2-(2-(((1H-benzo[d]imidazol-2-yl)methyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (27)



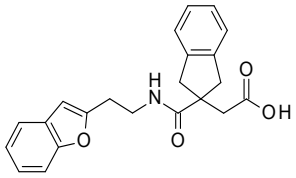
Method C was used as described for compound **29**, using (1H-benzo[d]imidazol-2-yl)methanamine hydrochloride as the amine. M/z 350 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.46 (2H, bs), 8.48 (1H, t), 7.55-7.50 (2H, m), 7.23-7.17 (4H, m), 7.16-7.12 (2H, m), 4.52 (2H, d), 3.48 (2H, d), 2.97 (2H, d), 2.72 (2H, s). HRMS anal. calcd for $C_{20}H_{20}O_3N_3$ $[M+H]^+$: 350.1499, found 350.1490.

2-[2-(1H-indol-3-ylmethylcarbamoyl)indan-2-yl]acetic acid (31)



Method C was used as described above for compound **29**, using 1H-indol-3-ylmethanamine as the amine. M/z 349.5 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 8.81 (1H, bs), 7.49 (1H, d), 7.32 (1H, d), 7.14 (6H, m), 6.94 (1H, m), 4.42 (2H, d), 3.38 (2H, d, J = 16 Hz), 2.92 (2H, d, J = 16 Hz), 2.56 (2H, s). HRMS anal. calcd for $C_{21}H_{21}O_3N_2$ $[M+H]^+$: 349.1547, found 349.1535.

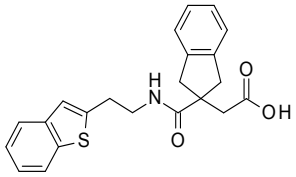
2-[2-[2-(benzofuran-2-yl)ethylcarbamoyl]indan-2-yl]acetic acid (32)



Method C was used as described for compound **29**, using 2-(benzofuran-2-yl)ethanamine as the amine. M/z 364.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.00 (1H, bs), 7.87 (1H, m), 7.53-

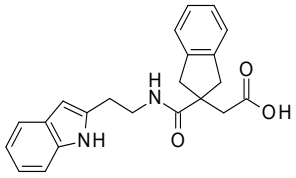
7.46 (2H, m), 7.23-7.09 (6H, m), 6.53 (1H, s), 3.43-3.29 (4H, m), 2.93-2.87 (4H, m), 2.64 (2H, s). HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1530.

2-[2-[2-(benzothiophen-2-yl)ethylcarbamoyl]indan-2-yl]acetic acid (33)



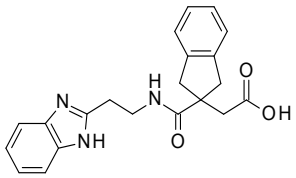
Method C was used as described for compound **29**, using 2-(benzothiophen-2-yl)ethanamine as the amine. M/z 380.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.02 (1H, bs), 7.85 (2H, m), 7.72 (1H, m), 7.30 (2H, m), 7.20-7.08 (5H, m), 3.35 (4H, m), 2.99 (2H, m), 2.92 (2H, d, J = 16 Hz), 2.62 (2H, s). HRMS anal. calcd for $C_{22}H_{22}O_3NS$ $[M+H]^+$: 380.1315, found 380.1305.

2-[2-[2-(1H-indol-2-yl)ethylcarbamoyl]indan-2-yl]acetic acid (34)



Method C was used as described for compound **29**, using 2-(1H-indol-2-yl)ethanamine as the amine. M/z 363.5 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 10.95 (1H, s), 8.15 (1H, bs), 7.39 (1H, d, J = 7.2 Hz), 7.26 (1H, d, J = 7.2 Hz), 7.14-7.09 (4H, m), 6.97 (1H, m), 6.92 (1H, m), 6.10 (1H, s), 3.40-3.31 (4H, m), 2.91 (2H, d, J = 16.2 Hz), 2.84 (2H, m), 2.61 (2H, s). HRMS anal. calcd for $C_{22}H_{23}O_3N_2$ $[M+H]^+$: 363.1703, found 363.1692.

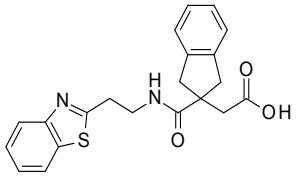
2-[2-[2-(1H-benzimidazol-2-yl)ethylcarbamoyl]indan-2-yl]acetic acid (35)



Method C was used as described for compound **29**, using 2-(1H-benzimidazol-2-yl)ethanamine as the amine. M/z 364.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.1 (1H, bs), 7.90

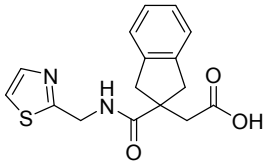
(1H, m), 7.45 (2H, m), 7.19-7.08 (6H, m), 3.48 (2H, m), 3.34 (2H, m), 2.92 (4H, m), 2.65 (2H, s). HRMS anal. calcd for $C_{21}H_{22}O_3N_3$ $[M+H]^+$: 364.1656, found 364.1648.

2-[2-[2-(1,3-benzothiazol-2-yl)ethylcarbamoyl]indan-2-yl]acetic acid (36)

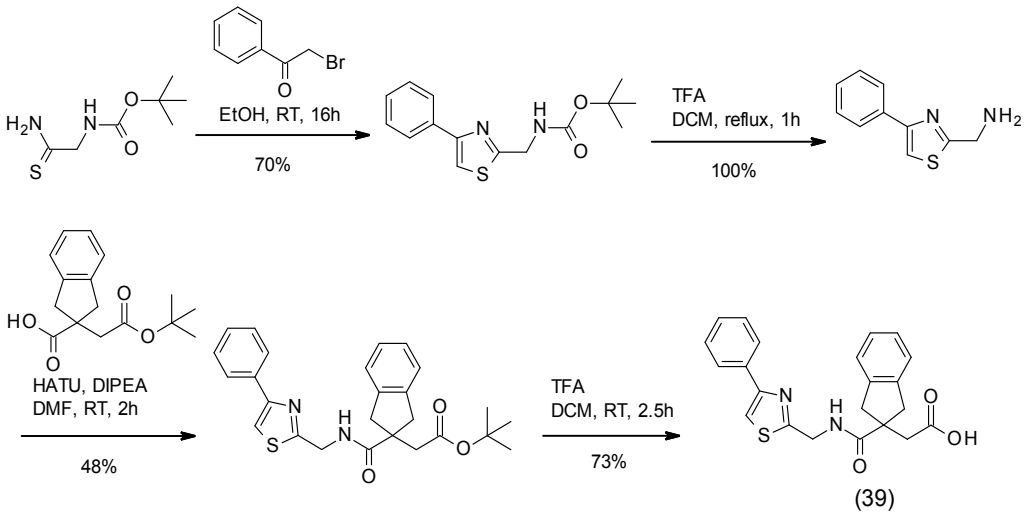


Method C was used as described above for compound **29**, using 2-(benzo[d]thiazol-2-yl)ethan-1-amine as the amine. M/z 381.4 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.00 (1H, bs), 8.03 (1H, m), 7.91 (2H, m), 7.48 (1H, m), 7.40 (1H, m), 7.15 (2H, m), 7.10 (2H, m), 3.51 (2H, m), 3.36 (2H, d, J = 16.2 Hz), 3.21 (2H, m), 2.92 (2H, d, J = 16.2 Hz), 2.65 (2H, s). HRMS anal. calcd for $C_{21}H_{21}O_3N_2S$ $[M+H]^+$: 381.1267, found 381.1259.

2-(2-((thiazol-2-ylmethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (37)

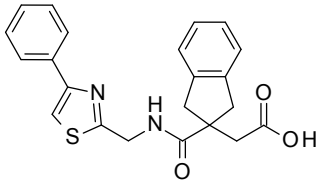


Method C was used as described for compound **29**, using 2-(aminomethyl)thiazole as the amine. M/z 317.3 $(M+H)^+$. ^1H NMR (d6-DMSO) δ 12.06 (1H, bs), 8.69 (1H, bs), 7.68 (1H, d), 7.58 (1H, d), 7.22-7.18 (2H, m), 7.15-7.10 (2H, m), 4.54 (2H, d), 3.43 (2H, d), 2.98 (2H, d), 2.72 (2H, s). HRMS anal. calcd for $C_{16}H_{17}O_3N_2S$ $[M+H]^+$: 317.0954, found 317.0948.

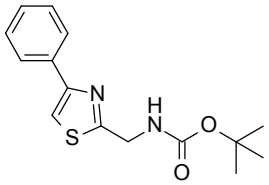


Scheme S4. Synthesis of compound (39)

2-[2-[(4-phenylthiazol-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (39)

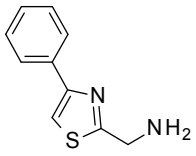


a. Tert-butyl N-[(4-phenylthiazol-2-yl)methyl]carbamate



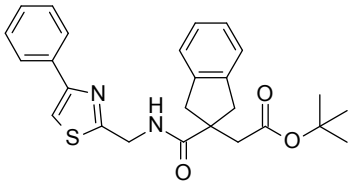
A solution of 2-bromo-1-phenyl-ethanone (1.99 g, 10 mmol) and tert-butyl (2-amino 2-thioxoethyl)carbamate (1.90 g, 10 mmol) in EtOH (50 mL) was stirred for 16 h. The solution was evaporated and the resulting residue diluted in water (25 mL) and extracted with EtOAc (2 x 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated affording a pale yellow solid. Recrystallisation from MeCN (13 mL) afforded a colourless solid (2.03 g, 70%). M/z 235 $(M+H\text{-}tBu)^+$.

b. (4-phenylthiazol-2-yl)methanamine trifluoroacetate



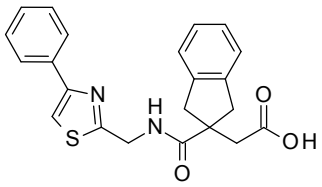
TFA (5 mL) was added to a solution of tert-butyl N-[(4-phenylthiazol-2-yl)methyl]carbamate (2.03 g, 6.99 mmol) in DCM (10 mL). The resulting solution was heated to reflux for 1 h. The cooled solution was evaporated, redissolved in MeOH (5 mL) and applied to SCX-2 cartridge (20 g). The cartridge was washed with MeOH (50 mL) then the product eluted with 2M NH_3 in MeOH (50 mL). The solution was evaporated affording a white solid (1.33 g, 100%). M/z 174 $(M+H-NH_3)^+$.

c. Tert-butyl 2-[2-[(4-phenylthiazol-2-yl)methylcarbamoyl]indan-2-yl]acetate



HATU (160 mg, 0.420 mmol) and DIPEA (0.18 mL, 1.05 mmol) were added to a solution of (4-phenylthiazol-2-yl)methanamine (83 mg, 0.438 mmol) and 2-(2-(tert-butoxy)-2-oxoethyl)-2,3-dihydro-1H-indene-2-carboxylic acid (97 mg, 0.35 mmol) in DMF (2 mL). The resulting mixture was stirred for 2 h, diluted with water (3 mL) and saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with DCM (6 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The resulting pale yellow oil was chromatographed on silica eluting with 5-30% EtOAc in hexane affording a white solid (75 mg, 48%). M/z 449 $(M+H)^+$.

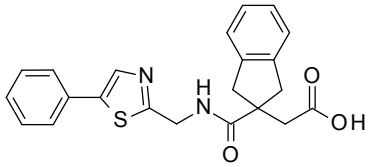
d. 2-[2-[(4-phenylthiazol-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (39)



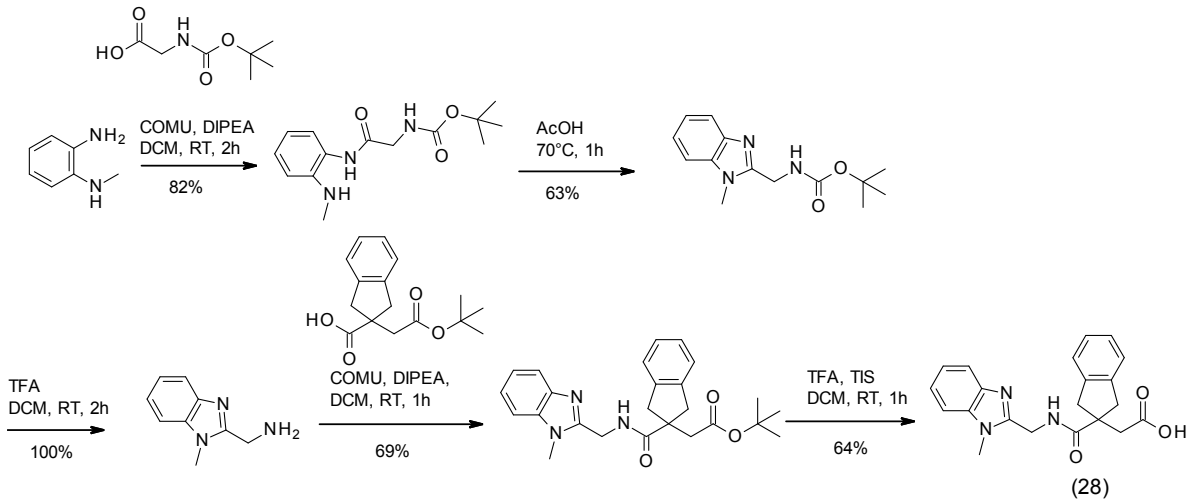
TFA (1 mL) was added to a solution of tert-butyl 2-[2-[(4-phenylthiazol-2-yl)methylcarbamoyl]indan-2-yl]acetate (215 mg, 0.479 mmol) in DCM (2 mL). The reaction

mixture was stirred for 2.5 h, cooled, evaporated and azeotroped with toluene (2 x 5 mL). The residue was purified by preparative HPLC (MDAP) affording the title product as a white solid (137 mg, 73%). M/z 393.2 $(M+H)^+$. ^{1}H NMR (d6-DMSO) δ 12.1 (1H, bs), 8.71 (1H, bs), 7.99 (3H, m), 7.49-7.11 (7H, m), 4.60 (2H, d, *J* = 6 Hz), 3.48 (2H, d, *J* = 16 Hz), 2.98 (2H, d, *J* = 16 Hz), 2.72 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.22, 172.39, 170.47, 153.58, 141.04, 134.13, 128.73, 127.87, 126.40, 125.85, 124.41, 114.03, 51.22, 42.23, 41.57, 41.20. HRMS anal. calcd for $C_{22}H_{21}O_3N_2S$ $[M+H]^+$: 393.1267, found 393.1259.

2-[2-[(5-phenylthiazol-2-yl)methylcarbamoyl]indan-2-yl]acetic acid (38)

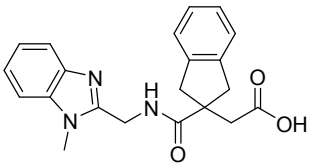


The title product was prepared following the procedure described for compound **39** using 2-(aminomethyl)-5-phenylthiazole as the amine in step-c. M/z 393.3 $(M+H)^+$. ^{1}H NMR (d6-DMSO) δ 12.13 (1H, bs), 8.67 (1H, s), 8.03 (1H, s), 7.59 (2H, m), 7.42 (2H, m), 7.35 (1H, m), 7.20 (2H, m), 7.12 (2H, m), 4.52 (2H, d, *J* = 6 Hz), 3.45 (2H, d, *J* = 16 Hz), 2.99 (2H, d, *J* = 16 Hz), 2.71 (2H, s). HRMS anal. calcd for $C_{22}H_{21}O_3N_2S$ $[M+H]^+$: 393.1267, found 393.1258.

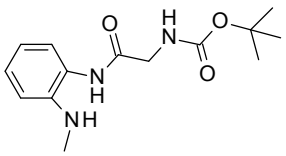


Scheme S5. Synthesis of compound (28)

2-(2-(((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (28)

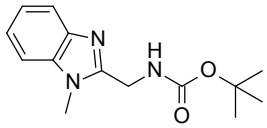


a. tert-butyl (2-((2-(methylamino)phenyl)amino)-2-oxoethyl)carbamate



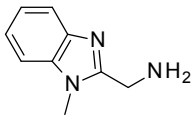
To a solution of Boc-Gly-OH (3.26 g, 18.6 mmol) in DCM (150 mL) were added COMU (8.78 g, 20.5 mmol), DIPEA (7.14 mL, 41.0 mmol) and N-methylbenzene-1,2,-diamine (2.50 g, 20.5 mmol) and the mixture stirred for 2 h. It was then washed with water, dried (Na_2SO_4) and evaporated to afford an oil. Chromatography on silica gel (0-100% EtOAc in isohexane) gave a cream foam (4.29 g, 82%). M/z 280 $(M+H)^+$.

b. tert-butyl ((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)carbamate



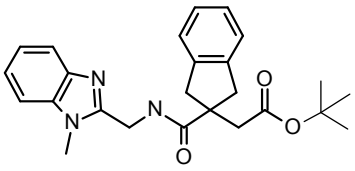
A mixture of tert-butyl (2-((2-(methylamino)phenyl)amino)-2-oxoethyl)carbamate (4.29 g, 15.4 mmol) in AcOH (100 mL) was stirred at 70 °C for 1h, then cooled and evaporated to dryness. The residue was redissolved in EtOAc, washed with saturated aq $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated to dryness. The resulting solid was triturated with Et_2O/isohexane (1:5) and isohexane, then dried in vacuo to afford a cream solid (2.53 g, 63%). M/z 262 $(M+H)^+$.

c. (1-methyl-1H-benzo[d]imidazol-2-yl)methanamine



A mixture of tert-butyl ((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)carbamate (2.53 g, 9.68 mmol) in TFA (20 mL) and DCM (80 mL) was stirred for 2 h and evaporated to dryness. The solution was applied to an SCX-2 cartridge (75 g, prewashed with DCM). The cartridge was washed with MeOH then the product eluted with 2M NH_3 in MeOH. Evaporation of this filtrate gave a brown solid (1.63 g, 100%). M/z 162 $(M+H)^+$.

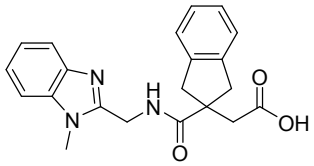
d. Tert-butyl 2-[2-[(1-methylbenzimidazol-2-yl)methylcarbamoyl]indan-2-yl]acetate



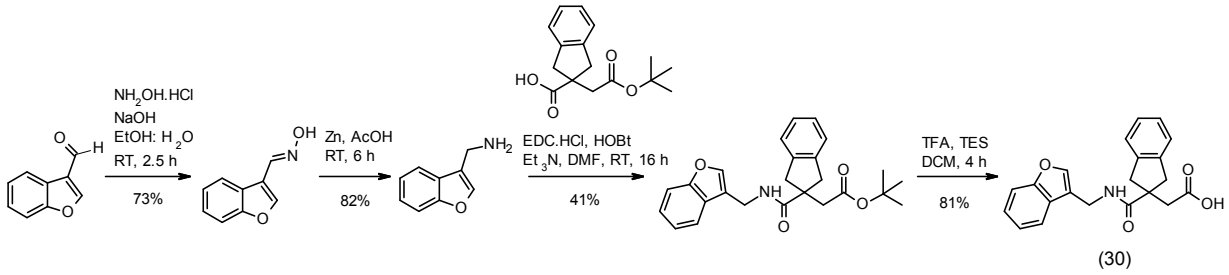
To a solution of 2-(2-(tert-butoxy)-2-oxoethyl)-2,3-dihydro-1H-indene-2-carboxylic acid (300 mg, 1.09 mmol) and COMU (514 mg, 1.2 mmol) in DCM (10 mL) was added DIPEA (418 µL, 2.4 mmol). The mixture was stirred for 10 minutes then (1-methyl-1H-benzo[d]imidazol-2-yl)methanamine (193 mg, 1.2 mmol) was added. The mixture was stirred for 1 h then diluted with DCM (10 mL) and washed with water (10 mL). The organic extract was dried (Na_2SO_4),

filtered and evaporated. The residue was purified by chromatography on silica eluting with 5% MeOH in EtOAc to afford an off-white solid (314 mg, 69%). M/z 420 $(M+H)^+$.

e. 2-(2-(((1-methyl-1H-benzo[d]26midazole-2-yl)methyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid (28)

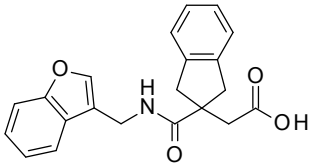


TFA (5 mL) was added to a solution of tert-butyl 2-[2-[(1-methylbenzimidazol-2-yl)methylcarbamoyl]indan-2-yl]acetate (140 mg, 0.334 mmol) and TIS (0.15 mL) in DCM (10 mL). The reaction mixture was stirred for 1 h, and then evaporated to dryess, azeotroping with toluene. The residue was purified by MDAP to give the title product as an off-white solid (77 mg, 64%). M/z 364.1 $(M+H)^+$. ^{1}H NMR (d6-DMSO) δ 12.28 (1H, bs), 8.35 (1H, t), 7.58 (1H, d), 7.53 (1H, d), 7.25 (1H, t), 7.22-7.17 (3H, m), 7.14-7.11 (2H, m), 4.58 (2H, d), 3.71 (3H, s), 3.44 (2H, d), 2.94 (2H, d), 2.72 (2H, s). HRMS anal. calcd for $C_{21}H_{22}O_3N_3$ $[M+H]^+$: 364.1656, found 364.1646.

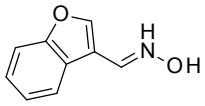


Scheme S6. Synthetic scheme for compound (30)

2-[2-(benzofuran-3-ylmethylcarbamoyl)indan-2-yl]acetic acid (30)

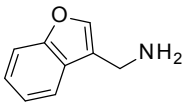


a. Benzofuran-3-carbaldehyde oxime



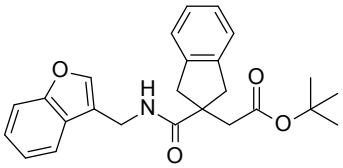
To a solution of benzofuran-3-carbaldehyde (100 mg, 0.68 mmol) in EtOH:H_2O (4 mL, 1:1) was added hydroxylamine hydrochloride (71 mg, 1.02 mmol) and sodium hydroxide (137 mg, 3.42 mmol) stirred for 2.5 h.The reaction mixture was cooled to 0°C and acidified with 1N HCl to pH~2. The resulting precipitate was filtered, washed with water and then dried under vacuum to obtain an off-white solid (80 mg, 73%). M/z 162.3 $(M+H)^+$.

b. Benzofuran-3-ylmethanamine



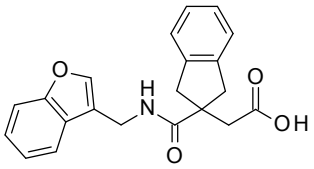
To a stirred solution of benzofuran-3-carbaldehyde oxime (80 mg, 0.49 mmol) in AcOH (2 mL) was added zinc (49 mg, 0.74 mmol) and the mixture was stirred for 6 h. The reaction mixture was diluted with cold water (5 mL) and basified with ammonium hydroxide to pH~9 and then extracted with EtOAc (2x 30 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent remove evaporated to give a pale brown oil (60 mg, 82%). M/z 148.3 $(M+H)^+$.

c. **tert-butyl 2-[2-(benzofuran-3-ylmethylcarbamoyl)indan-2-yl]acetate**

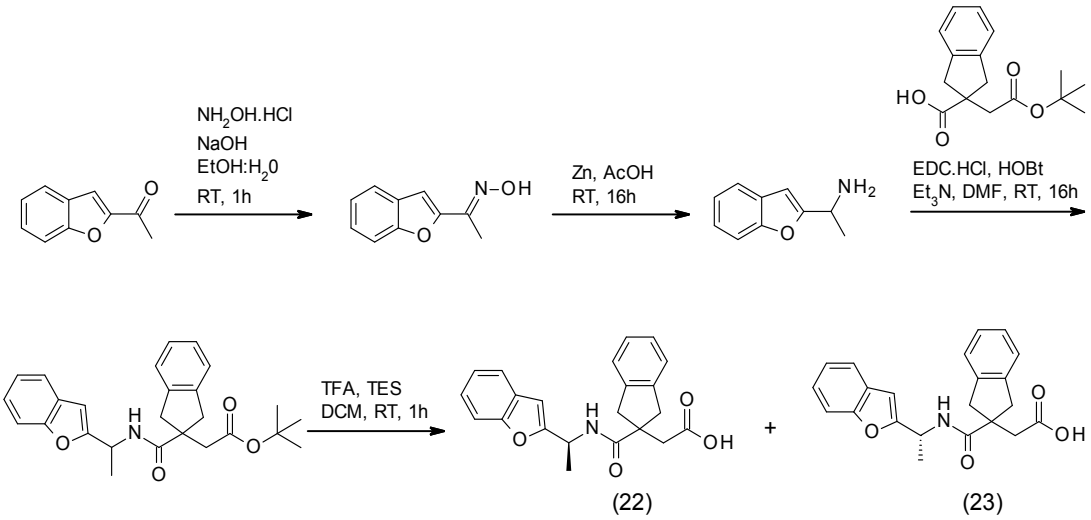


Method C was used as described for compound **29**, using benzofuran-3-ylmethanamine as the amine. Tert-butyl 2-[2-(benzofuran-3-ylmethylcarbamoyl)indan-2-yl]acetate was purified by Preparative TLC (using 15% EtOAc/ petroleum ether), affording a brown oil (56 mg, 41%). M/z 406.52 $(M+H)^+$.

d. 2-[2-(benzofuran-3-ylmethylcarbamoyl)indan-2-yl]acetic acid (30)

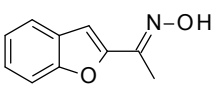


To a stirred solution of tert-butyl 2-(2-((benzofuran-3-ylmethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetate (50 mg, 0.12 mmol) in DCM (2 mL) was added TFA:TES (0.8 mL, 5:1). The reaction mixture was stirred for 4 hours and the solvent was evaporated. The residue was treated with cold water (5 mL), then basified with lithium hydroxide monohydrate to pH~9, washing with diethyl ether (2x 20 mL). The aqueous phase was then acidified with 1*N* HCl to pH~2 and stirred for 5 minutes. The resulting precipitate was filtered, washed with water and dried under vacuum to yield 2-(2-((benzofuran-3-ylmethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid as an off white solid (35 mg, 81%). M/z 350.46 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (1H, bs), 8.37 (1H, bs), 7.49 (1H, dd, J = 10.8 Hz, J = 8.4 Hz), 7.25-7.12 (6H, m), 6.55 (1H, s), 4.42 (2H, d, *J* = 5.6 Hz), 3.42 (2H, d, *J* = 16.5 Hz), 2.97 (2H, d, *J* = 16.5 Hz), 2.73 (2H, s). HRMS anal. calcd for $C_{21}H_{20}O_4N$ $[M+H]^+$: 350.1387, found 350.1377.



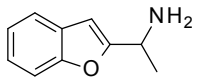
Scheme S7. Synthetic scheme for compounds (22) and (23)

a. 1-(benzofuran-2-yl)ethanone oxime



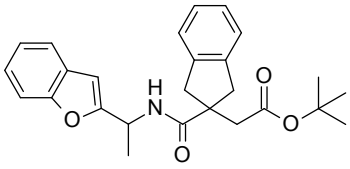
A solution of 1-(benzofuran-2-yl)ethan-1-one (1 g, 6.24 mmol), hydroxylamine hydrochloride (0.7 g, 9.98 mmol) in EtOH:H_2O (4 mL: 0.5 mL) was treated portionwise with solid sodium hydroxide (1.3 g, 33.4 mmol). The resulting mixture was treated with additional water (5 mL) and EtOH (5 mL) and stirred for 1 h. The reaction mixture was then cooled to 0°C and acidified with 1*N* HCl to pH ~2. The resulting precipitate was filtered, washed with water and dried under vacuum to obtain a mixture of (E)-1-(benzofuran-2-yl)ethan-1-one oxime and (Z)-1-(benzofuran-2-yl)ethan-1-one oxime (1 g, 93%) as an off-white solid. M/z 176.3 $[M+H]^+$.

b. 1-(benzofuran-2-yl)ethanamine



To a stirred solution of a mixture of (E)-1-(benzofuran-2-yl)ethan-1-one oxime and (Z)-1-(benzofuran-2-yl)ethan-1-one oxime (500 mg, 2.85 mmol) in AcOH (10 mL) was added Zn (930 mg, 65.3 mmol) and the mixture stirred for 16 h. It was then diluted with cold water (5 mL), treated with ammonium hydroxide to pH~9 and the extracted with EtOAc (2x30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to give the title compound as a pale yellow oil (180 mg, 39%). M/z 162.3 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 7.58-7.44 (m, 2 H), 7.22-7.15 (m, 2 H), 4.10-4.00 (m, 1 H), 1.99 (br s, 2 H), 1.28 (d, J = 6.8 Hz, 1 H).

c. Tert-butyl 2-[2-[1-(benzofuran-2-yl)ethylcarbamoyl]indan-2-yl]acetate



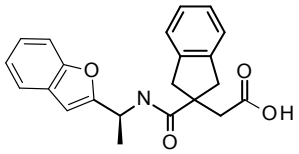
To a stirred solution of 2-(2-(tert-butoxy)-2-oxoethyl)-2,3-dihydro-1H-indene-2-carboxylic acid (200 mg, 0.72 mmol) in DMF (10 mL) was added Et_3N (0.3 mL, 2.16 mmol), EDC. HCl (208 mg, 1.08 mmol) and HOBt (146 mg, 1.08 mmol) and stirred for 10 minutes. Then 1-(benzofuran-2-yl)ethan-1-amine (117 mg, 0.72 mmol) was added and the mixture stirred for 16 h. The reaction mixture was diluted with cold water (15 mL) and extracted with EtOAc (30 mL). The organic layer was separated, washed with water (2x10 mL), dried over Na_2SO_4,

filtered to obtain tert-butyl 2-[2-[1-(benzofuran-2-yl)ethylcarbamoyl]indan-2-yl]acetate (220 mg, 73%) as an off-white solid. M/z 420.4 $[M+H]^+$.

d. 2-[2-[[(1S*)-1-(benzofuran-2-yl)ethyl]carbamoyl]indan-2-yl]acetic acid (22) and 2-[2-[[(1R*)-1-(benzofuran-2-yl)ethyl]carbamoyl]indan-2-yl]acetic acid (23)

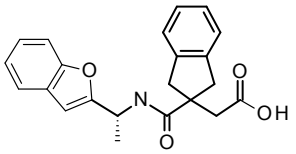
To a stirred solution of tert-butyl 2-(2-((1-(benzofuran-2-yl)ethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetate (300 mg, 0.71 mmol) in DCM (30 mL) was added TFA:TES (5:1, 3 mL) at 0°C and the mixture was stirred for 1 h. The mixture was evaporated and the residue was triturated with diethyl ether (10 mL) to obtain an off-white solid. This was purified by preparative HPLC [ATLANTIS T3 (250x19 mm), 5 u; Mobile phase: A: 0.1% Formic Acid in H_2O, B: MeCN] to obtain racemic 2-(2-((1-(benzofuran-2-yl)ethyl)carbamoyl)-2,3-dihydro-1H-inden-2-yl)acetic acid as a white solid (180 mg, 70%) which was further purified by chiral SFC [Chiralcel OX-H (4.6x250 mm), 5 u; Mobile phase: 80% CO_2 gas, 20% (0.5% DEA in MeOH)] to obtain **22 (**45 mg) and **23** (35 mg) as white solids in the order of elution.

2-[2-[[(1S*)-1-(benzofuran-2-yl)ethyl]carbamoyl]indan-2-yl]acetic acid (22)



M/z 364.4 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 12.18 (1H, bs), 8.14 (1H, d, J = 8.1 Hz), 7.55-7.49 (2H, m), 7.27-7.11 (6H, m), 6.60 (1H, s), 5.20-5.12 (1H, m), 3.43 (2H, d, J = 16 Hz), 2.95 (2H, dd, J = 16 Hz, J = 3 Hz), 2.73 (2H, s), 1.46 (3H, d, J = 6.9 Hz). HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1532.

2-[2-[[(1R*)-1-(benzofuran-2-yl)ethyl]carbamoyl]indan-2-yl]acetic acid (23)



M/z 364.5 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.20 (1H, bs), 8.46 (1H, bs), 7.55 (1H, dd, J = 8.4 Hz, J = 1.2 Hz), 7.49 (1H, d, J = 8 Hz), 7.27-7.11 (6H, m), 6.61 (1H, s), 5.20-5.13 (1H, m), 3.43 (2H, d, J = 16.4 Hz), 2.96 (2H, dd, J = 16.4 Hz, J = 4.8 Hz), 2.69 (2H, s), 1.46 (3H, d, J = 6.8 Hz). HRMS anal. calcd for $C_{22}H_{22}O_4N$ $[M+H]^+$: 364.1543, found 364.1531.

Fluorometric LasB inhibition assay

A fluorometric assay was performed using purified LasB enzyme (0.5 ng/well, purified and provided by Charles River Laboratories) in 50 mM Tris-HCl pH7.4, 2.5 mM $CaCl_2$, 0.01% of Triton X100 in 96-well black microtiter plates. Fluorogenic substrate Abz-Ala-Gly-Leu-Ala-p-Nitro-Benzyl-Amide (250 µM, Ex: 340 nm, Em: 415 nm, from Peptides International) was used and its hydrolysis followed at wavelength 430 nm (every 60 seconds over 30 min) at 37°C using a Perkin Elmer Envision UV fluorescence plate reader (Program: Ex: 320 nm, Em: 430 nm). Hydrolysis rate data and the percentage of LasB inhibition were determined first at a single dose of inhibitors (30 µM) and then the best compounds were tested at a range of concentrations (from 0.012 to 200 µM, compound dilution performed in dimethyl sulfoxide, DMSO) in order to determine IC_{50}. The IC_{50} values were converted to K_i using the standard Cheng-Prusoff equation:

$K_i = IC_{50} / (1+([S]/K_m)$

where [S] is the substrate concentration: 250 µM and K_m is the Michaelis constant: K_m value for LasB is 214 µM. Means of K_i values from multiple independent experiments were presented.

ECR elastolytic assay

To determine LasB elastase activity and assess compound inhibition, an overnight culture of *P. aeruginosa* strain PAO1 was diluted in LB medium. After reaching an OD_{600nm} of 0.6, this culture was diluted 1:100 and incubated for an additional 24 h in a 37°C shaking incubator. The culture supernatant was recovered by centrifugation and filtered through a 0.22 µm filter. This supernatant was dialysed (filtration molecules < 20 kDa) into a 50 mM Tris-HCl pH 7.4, 2.5 mM $CaCl_2$ solution at 4°C under agitation for 24 h. The dialysed supernatant, supplemented with Triton X100 (final concentration of 0.01%), was then mixed 1:1 with 2X ECR suspension, resulting in a final concentration of 10 mg/mL ECR in presence of DMSO (positive control) and/or different concentrations of compounds (range from 3.1 to 100 µM, compound dilution

performed in DMSO). As a negative control, the dialysed supernatant was replaced by Tris-HCl solution (50 mM Tris-HCl pH 7.4, 2.5 mM $CaCl_2$). The mixed reaction was then incubated for 16h in a 37°C shaking incubator. The supernatant was recovered by centrifugation and the release of congo-red dye was measured by its absorbance at 495 nm ($OD4_{95nm}$) at endpoint using Perkin Elmer Ensight Multimode plate reader.

The percentage of LasB inhibition was determined using the following equation:

((OD_{495nm} value of positive control – OD_{495nm} value of negative control) – (OD_{495nm} value of treated supernatant – OD_{495nm} value of negative control)) / (OD_{495nm} value of positive control – OD_{495nm} value of negative control) x 100.

Means of percentage of inhibition values from multiple independent experiments were presented.

Fluorometric ACE inhibition assay

A fluorometric assay was performed using rabbit ACE metalloenzyme (14.3 ng/well) in 100 mM Tris HCl (pH7), 50 mM NaCl, 10 µM $ZnSO_4$ buffer in 96-well black microtiter plates. Fluorogenic substrate Abz-FRK (DNP)-P (10 µM, Ex: 320 nm, Em: 420 nm) was used and its hydrolysis followed at wavelength 430 nm (every 30 seconds over 5 min) at 37°C using a Perkin Elmer Envision UV fluorescence plate reader (Program: Ex: 320 nm, Em: 430 nm). Hydrolysis rate data in the presence of a range of inhibitor concentrations (0.4 to 200 µM, diluted in dimethyl sulfoxide, DMSO) were determined.

X-ray crystallography

Purified LasB protein (provided by Charles River Laboratories) was concentrated to 10 mg/mL and co-crystallisation set up in hanging drops at 20°C with 0.1M MOPS pH 6.5 and 1.3-1.8M ammonium sulphate. Drops consisted of 1 µL well solution and 1 µL concentrated LasB protein previously incubated on ice for 1-2 hours with 1 mM ligand.

Table S1. Data collection and refinement statistics.

Parameter	LasB:**29**
X-ray source	ESRF, beamline ID30A-1

Wavelength (Å)	0.977170
Data collection temp (K)	100
Space group	$P2_12_12_1$
Cell dimensions (Å)	44.122; 51.260; 120.708
subunits/asymmetric unit	1
Matthews coefficient ($Å^3$ Da^{-1})	2.07
Solvent content (%)	40.7
Resolution limits (Å)[a]	47.23-1.75 (1.78-1.75)
No. of reflections measured[a]	176579 (9370)
No. of unique reflections[a]	28269 (1500)
Completeness (%)[a]	99.5 (98.0)
R_{merge} (%)[a,b]	11.7 (97.1)
Multiplicity[a]	6.2 (6.2)
I/σ(I)[a]	11.9 (2.0)
Wilson B factor ($Å^2$)	5.67
R_{cryst} (%)[a,b]	17.6 (54.9)
R_{free} (%)[a,b]	23.4 (50.3)
Protein atoms	2302
Ligand atoms	31
Water molecules	134
Avg B factor ($Å^2$)	18.2
RMSD bond length (Å)	0.008
RMSD bond angle (°)	1.456

[a]Data in parentheses refer to results for the highest-resolution shell.

[b]$R_{merge} = \Sigma_h\Sigma_i|I_{i,h} - \bar{I}_h|/\Sigma_h\Sigma_i I_{i,h} \times 100$. $R_{cryst}(R_{free}) = \Sigma_h||F_{h,obs}| - |F_{h,calc}|/\Sigma_h||F_{h,obs}| \times 100$.