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Structure–activity relationships for ketamine esters as short-acting anaesthetics

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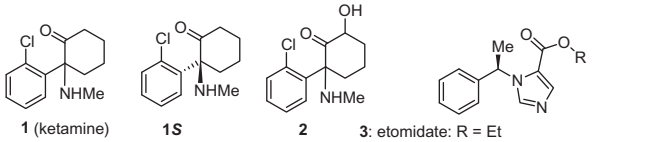
ABSTRACT

A series of aliphatic esters of the non-opioid anaesthetic/analgesic ketamine were prepared and their properties as shorter-acting analogues of ketamine itself were explored in an infused rat model, measuring the time after infusion to recover from both the anaesthetic (righting reflex) and analgesic (response to stimulus) effects. The potency of the esters as sedatives was not significantly related to chain length, but Me, Et and i-Pr esters were the more dose potent (up to twofold less than ketamine), whereas n-Pr esters were less potent (from 2- to 6-fold less than ketamine). For the Me, Et and i-Pr esters recovery from anaesthesia was 10–15-fold faster than from ketamine itself, and for the n-Pr esters it was 20–25-fold faster than from ketamine. A new dimethylamino ketamine derivative (homoketamine) had ketamine-like sedative effects but was slightly less potent than, but ester analogues of homoketamine had very weak sedative effects.

1. Introduction

Racemic (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (ketamine; **1**; Fig. 1) is an effective and widely-used non-opioid anaesthetic/analgesic.[1,2] With respect to its analgesic activity it is thought to act primarily at *N*-methyl-D-aspartate (NMDA) receptors as a non-competitive antagonist of the calcium channel pore, but also has effects on a wide variety of other muscarinic and monoaminergic receptors.[3] Ketamine's major advantages over opioids are a lack of respiratory depression or hyperalgesic effects (it also has a primary role in pain management as an 'antihyperalgesic' or 'tolerance-protective' compound[4]), and an absence of longer-term effects such as increased tolerance and immune suppression. Ketamine is normally used as the (cheaper) racemate, but more recently the more active (*S*)-enantiomer (**1*S***) has begun to be employed. (*S*)-Ketamine has similar pharmacological, analgesic and anaesthetic properties to the racemate, but is about twice as potent.[5]



1 (ketamine) **1*S*** **2**

3: etomidate: R = Et
4: MOC-etomidate: R = $(CH_2)_2CO_2Me$
5: MOC-etomidateacid: R = $(CH_2)_2CO_2H$

The most clinically significant adverse effect of **1** is its hallucinogenic properties which, together with its relatively long half-life (2–3 h) means that it is normally administered together with sedative or hypnotic drugs like midazolam and/or propofol to control the prolonged period of post-anesthesia hallucinations.[6,7] While the (*S*)-enantiomer (**1*S***) has somewhat faster elimination than the racemic material,[6] there is still a need for analogues with much shorter half-lives to avoid the concomitant use of sedatives/hypnotics.

The limited structure–activity relationships of analogues of **1** have shown that its anaesthetic effects are related closely to its physicochemical properties, with its (more polar) secondary 6-hydroxy metabolite (**2**) having no anaesthetic properties.[8] This suggested to us that an ester with similar lipophicity to 1 might retain desirable anaesthetic properties, but would be rapidly hydrolysed by serum esterases to the corresponding very polar and thus non-anaesthetic ionised acid. This concept has been applied successfully to the sedative-hypnotic drug etomidate (**3**) which, as a concomitant very potent inhibitor of 11β-hydroxylase, has the side-effect of prolonged adrenocortical suppression. Development of the shorter-acting ester derivative methoxycarbonyl-etomidate (MOC-etomidate; **4**)[9] which is readily hydrolysed to the inactive acid **5** (Fig. 1) resulted in faster recovery from both hypnosis and adrenal suppression. A similar strategy has also been followed in the development of the fast-acting analgesic opioid remifentanil, where a ester moiety is rapidly hydrolysed to an inactive carboxylic acid metabolite.[10]

Abbreviations: DCM, dichloromethane; LRR, loss of righting reflex; NMDA, *N*-methyl-D-aspartate; PWR, pedal withdrawal reflex score.

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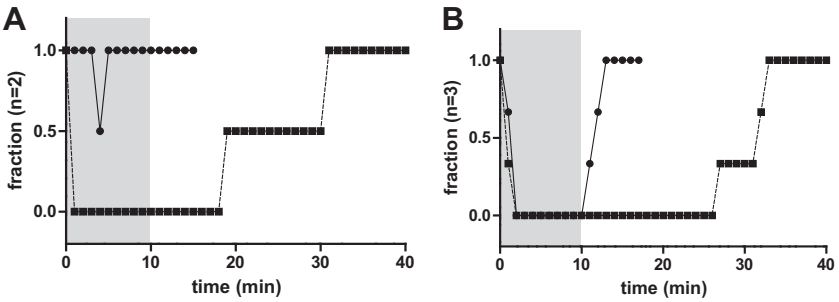


Figure 1. Time-course for anaesthesia (loss and recovery of righting reflex) for compounds **10** (A) and **14** (B). The grey panel shows the duration of drug infusion (measurement taken every minute). ●●●●: test compound. ■■■■: Ketamine.

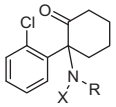
2. Results and discussion

2.1. Chemistry

The compounds of interest were prepared from norketamine (**25**), which was in turn prepared from commercially available (2-chlorophenyl)(cyclopentyl)methanone (**22**) following a reported procedure[11] (Scheme 1). Bromination of **22** with $CuBr_2$ gave the bromide **23**, which was converted to the imine **24** with NH_4OH/NH_3, and thermal rearrangement of the hydrochloride salt of **24** in Dowtherm A gave racemic norketamine (**25**). Resolution of this via the L-(*R*,*R*)-(+)-tartaric acid salts gave (**25*S***). Acetates **7** and **7*S*** of Table 1 were prepared by reaction of amines **25** or **25*S***, respectively, with 3-bromopropyl acetate, and NaOH hydrolysis of **7*S*** gave alcohol **6*S***. Similar reaction of **25** or **25*S*** with the appropriate alkyl halides $Br(CH_2)_nCO_2(CH_2)R$ and conversion of the products to the hydrochloride salts with HCl gas (Scheme 1) gave compounds **8**–**17** of Table 1. The 'homoketamines' **18** and **18*S*** were obtained by treating a methanolic solution of norketamines **25** and **25*S*** successively with sodium cyanoborohydride and then formaldehyde for 24 h (Scheme 2). Finally, compounds **19**–**21** were obtained by reaction of ketamine ester **1** with sodium cyanoborohydride and then formaldehyde for 24 h (Scheme 2).

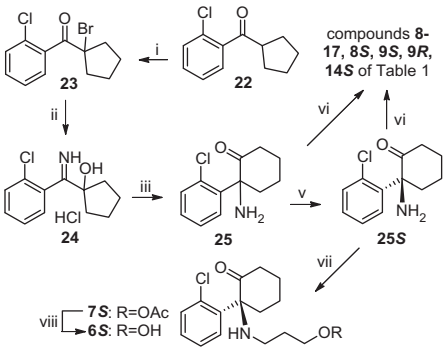
The structures and physicochemical properties of the ketamine analogues prepared are given in Table 1. Their lipophilicities (*c*log*P*) were calculated using ChemBioDraw v12.02 (CambridgeSoft, UK) and pK_a values were calculated using ACD/PhysChem Suite v12; ACD/Labs, Toronto, Canada). Ketamine (**1**) has a measured[12] aqueous pK_a of 7.49 and a calculated clogP of 2.22. The closest match to this were the acetates (**7**, **7*S***), which were evaluated since acetate hydrolysis to the more polar alcohols is known to be reasonably rapid in blood.[13] Next closest in physicochemical properties were the C4 methyl esters (**14**, **14*S***). The esters overall

Table 1
Physiciochemical properties of ketamine esters

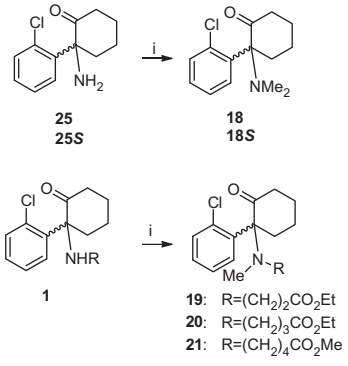


No.	X	R	Purity[a] (%)	*c*log*P*[b]	pK_a[c]
1	H	Me		3.20[d]	7.49
6*S*	H	$(CH_2)_3OH$	97.0	2.85	6.20
7	H	$(CH_2)_3OAc$	97.2	3.76	6.20
7*S*	H	$(CH_2)_3OAc$	95.8	3.76	6.20
8	H	$(CH_2)_2CO_2Et$	97.2	3.93	4.35
8*S*	H	$(CH_2)_2CO_2Et$	99.1	3.93	4.35
9	H	$(CH_2)_2CO_2iPr$	99.0	4.24	4.35
9*S*	H	$CH_2)_2CO_2iPr$	99.5	4.24	4.35
9*R*	H	$CH_2)_2CO_2iPr$	99.5	4.24	4.35
10	H	$(CH_2)_2CO_2nPr$	99.0	4.46	4.35
11	H	$(CH_2)_3CO_2Et$	95.3	4.29	5.86
12	H	$(CH_2)_3CO_2iPr$	98.4	4.60	5.86
13	H	$(CH_2)_3CO_2nPr$	97.2	4.82	5.85
14	H	$(CH_2)_4CO_2Me$	99.1	3.74	6.29
14*S*	H	$(CH_2)_4CO_2Me$	97.0	3.74	6.29
15	H	$(CH_2)_4CO_2Et$	94.4	4.27	6.29
16	H	$(CH_2)_4CO_2iPr$	97.6	4.58	6.29
17	H	$(CH_2)_4CO_2nPr$	95.4	4.80	6.29
18	Me	Me	98.5	3.49	5.86
18*S*	Me	Me	99.7	3.49	5.86
19	Me	$(CH_2)_2CO_2Et$	93.0	4.40	4.77
20	Me	$(CH_2)_3CO_2Et$	94.0	4.29	5.51
21	Me	$(CH_2)_4CO_2Me$	94.8	4.04	5.74

[a] Purity by reverse-phase HPLC.
[b] *c*log *p* calculated using ChemBioDraw Ultra v12.02.
[c] pK_a calculated using ACD/PhysChem Suite v12.
[d] pK_a Measured value from Ref. 9.



Scheme 1. Reagents and conditions: (i) $CuBr_2$, EtOAc, reflux, 3 h; (ii) (a) NH_3/NH_4OH, 25 °C, 5 days; (b) HCl_g, isopropanol/diethyl ether, 0 °C, 3 h; (iii) dowtherm A, 200 °C, 12 min; (v) L-(*R*,*R*)-(+)-tartaric acid, Me_2CO, 3x crystallisation; (vi) $Br(CH_2)_nCO_2R$ (R = Me, Et, iPr, nPr), KI, K_2CO_3, MeCN; (vii) $Br(CH_3)_2OAc$, KI, K_2CO_3, MeCN; (viii) 0.2 N NaOH, MeCN, 25 °C, 2 h.



Scheme 2. Reagents and conditions: (i) $NaCNBH_3$, HCHO, AcOH, MeOH, 25 °C, 24 h.

showed a range of both pK_a values (from 4.35 to 6.29) and lipophilicities (from 2.77 to 3.92), so that any dependency of activity on these parameters could be evaluated.

2.2. Biology

The compounds were evaluated for their ability to anaesthetise rats when administered by continuous intravenous infusion, with the results given in Tables 2 and 3. Compounds were administered so as to initially deliver 20 mg/kg/min (weight-adjusted flow) to uniform pedal withdrawal reflex score (PWR = 1), then titrated to maintain loss of righting reflex (LRR) for 10 min. The PWR is a standardised response to a stimulus, and is a measure of analgesic effect. LRR is a measure of anaesthetic hypnotic effect. Following an initial single-animal exploratory study, three rats were used in a confirmatory study, with each group of rats also acting as their own ketamine control. Data were collected on time (seconds), and total dose of drug (mg/kg), to achieve LRR and a PWR = 1. Also recorded were the times (in seconds, from cessation of the infusion) to recovery of righting reflex (RRR) (recovery from the hypnotic anaesthesia effect), and time to normalisation of the PWR (loss of analgesic effect). Full definitions of LRR and PWR are given

Table 2
Anaesthetic effects of ketamine esters in a rat infusion study, compared head-to-head each time to racemic ketamine (**1**) as a positive control

No.	LRR[a]		PWR = 1[b]		RRR[c]	Walk[d]
	Time[e] (sec)	Dose[f] (mg/kg)	Time[e] (sec)	Dose[f] (mg/kg)	Time[e] (sec)	Time[e] (sec)
1	69 ± 7	23 ± 2	84 ± 4	28 ± 2	874 ± 81	1384 ± 374
6*S*	59 ± 9	21 ± 3	102 ± 16	34 ± 4	341 ± 60	588 ± 108
1	59 ± 5	20 ± 2	93 ± 8	31 ± 2	863 ± 153	1918 ± 518
7*S*	81 ± 10	26 ± 3	104 ± 7	34 ± 1	566 ± 30	983 ± 93
1	77 ± 10	27 ± 4	95 ± 13	38 ± 10	1602 ± 549	2536 ± 250
8	135 ± 61	48 ± 23	154 ± 68	55 ± 25	177 ± 51	253 ± 68
1	53 ± 1	20 ± 1	73 ± 3	26 ± 1	1315 ± 215	2163 ± 722
8*S*	171 ± 54	59 ± 19	185 ± 55	62 ± 20	62 ± 8	80 ± 8
1	62 ± 7	22 ± 2	71 ± 9	24 ± 3	760 ± 144	1100 ± 144
9	103 ± 17	33 ± 6	127 ± 13	37 ± 6	83 ± 19	153 ± 33
1	65 ± 10	30 ± 4	77 ± 12	34 ± 4	900 ± 60	1200 ± 180
9*S*	222 ± 18	74 ± 9	247 ± 13	84 ± 4	15 ± 15	224 ± 90
1	53	24	69	26	1170	1629
9*R*	170	71	190	82	0	900
1	51 ± 3	18 ± 1	63 ± 3	21 ± 1	1060 ± 221	1500 ± 5
10	404 ± 196	131 ± 62	420 ± 180	136 ± 67	0	0
1	59 ± 6	17 ± 2	76 ± 7	24 ± 4	1523 ± 131	2122 ± 131
11	70 ± 6	24 ± 2	137 ± 14	44 ± 5	95 ± 12	170 ± 17
1	69 ± 7	23 ± 2	84 ± 4	28 ± 2	874 ± 81	1384 ± 374
12	125 ± 21	42 ± 9	192 ± 47	66 ± 17	37 ± 22	110 ± 45
1	69 ± 7	23 ± 2	84 ± 4	28 ± 2	874 ± 81	1384 ± 374
13	329 ± 106	137 ± 48	558 ± 42	209 ± 20	10 ± 5.5	65 ± 33
1	70 ± 28	20 ± 5	81 ± 23	22 ± 4	1104 ± 95	1462 ± 113
14	92 ± 14	34 ± 7	124 ± 21	44 ± 10	99 ± 16	126 ± 32
1	55 ± 2	20 ± 1	72 ± 2	25 ± 1	1286 ± 127	1740 ± 282
14*S*	107 ± 9	36 ± 3	130 ± 10	44 ± 34	95 ± 18	900 ± 30
1	56 ± 6	17 ± 2	76 ± 7	23 ± 4	1523 ± 131	2122 ± 107
15	97 ± 8	34 ± 4	172 ± 36	57 ± 12	134 ± 22	112 ± 18
1	54	19	66	22	1281	1499
16	122	38	122	38	180	320
1	65 ± 10	23 ± 3	77 ± 12	26 ± 4	900 ± 60	1200 ± 180
17	271 ± 97	82 ± 34	277 ± 97	83 ± 34	45 ± 15	90 ± 30
1	56	19	60	21	480	900
18	125	43	130	43	1500	1740
1	53	20	69	21	1170	1620
18*S*	94	32	103	35	880	1215
1	60	21	69	25	1230	1475
19	280	95	290	99	0	0
1	75	25	86	29	1500	1920
20	600	196	600	196	0	0
1	57	20	82	28	2040	2340
21	420	145	435	148	0	201

[a] LRR: (loss of righting reflex) assesses anaesthetic hypnotic effect. Righting reflex is considered absent when the animal fails to right from a position of dorsal recumbency to a position of sternal recumbency on three attempts performed in rapid succession.
[b] PWR (pedal withdrawal reflex) assesses analgesic effect, and is conducted by a 1-second application of firm constant pressure (for rats, firm digital pressure) over the forepaw of the animal. A PWR = 1 (a flicker of response) indicates a satisfactory level of analgesia (nociception).
[c] RRR (recovery of righting reflex; ability to right from dorsal recumbency).
[d] Walk (ability to sustain independent locomotion).
[e] Time: the time from onset of the infusion of drug to achieve LRR or PWR = 1, or the time from the end of the infusion of drug to achieve RRR or walk.
[f] Dose: the total drug administered to achieve LRR or PWR = 1. Where no errors are given (compounds **9*R***, **18**, **18*S***, **19** and **21**) the results are from a single animal.

Table 3
Head-to-head ratios of the anaesthetic properties of ketamine esters to ketamine

No.	LRR[a]		PWR = 1[b]		RRR[c]	Walk[d]
	Time[e]	Dose[f]	Time[e]	Dose[f]	Time[e]	Time[e]
6*S*	0.86	0.91	1.21	1.21	0.39	0.42
7*S*	1.37	1.30	1.12	1.10	0.65	0.51
8	1.75	1.78	1.62	1.45	0.11	0.10
8*S*	3.22	2.95	2.53	2.38	0.05	0.04
9	1.66	1.50	1.79	1.54	0.11	0.14
9*S*	3.41	2.46	3.14	2.47	0.02	0.19
9*R*	3.20	2.96	2.75	3.15	NA[g]	0.06
10	7.92	7.28	6.67	6.48	NC[h]	NC[h]
11	1.19	1.41	1.80	1.83	0.062	0.08
11*S*	3.23	2.95	2.53	2.38	0.05	0.04
12	1.81	1.83	2.29	2.36	0.042	0.08
13	4.77	5.95	6.64	7.46	0.012	0.05
14	1.31	1.70	1.53	2.00	0.090	0.086
14*S*	1.94	1.80	1.81	1.76	0.07	0.51
15	1.73	2.00	2.26	2.48	0.09	0.05
16	2.26	2.00	1.85	1.73	1.78	1.17
17	4.17	3.56	3.60	3.19	0.05	0.08
18	2.23	2.26	2.17	2.05	3.12	1.88
18*S*	1.77	1.60	1.49	1.67	0.75	0.75
19	4.67	4.50	4.20	3.96	NC[h]	NC[h]
20	8.00	7.84	6.98	6.76	NC[h]	NC[h]
21	7.37	7.25	5.30	5.29	NC[h]	0.09

[a-f] As for Table 2.
[g] NA: not active.
[h] NC: not calculable.

in the ∗∗Experimental Section. For the ketamine standard, the average values of the parameters measured over the different experiments are given in Table 4. Given the complexity of the experimental protocol, the pre-sedation data (time and total dose for LRR; Table 2) are very consistent, with ranges of only 1.5-fold. The consistency of the post-sedation recovery times are expectedly lower, with ranges of about 2.5-fold.

Representative plots of compound performance—each compared with their ketamine control—are presented in Figures 1 and 2. As illustrations we have chosen an ultra-rapidly metabolised, relatively non-potent compound (**10**), and more potent compound (**14**). Loss of righting are shown in Figure 1a and b, respectively, and pedal withdrawal scoring shown in Figure 2a and b. Figure 3 depicts a scatter-plot of effective potency (dose [mg/kg] to loss of righting reflex) versus duration (time to return of righting reflex) for all compounds.

Table 4
Average parameters determined for the ketamine standard

Property	Average	Range
Time to achieve LRR (sec)	61 ± 8	51–75
Total dose to LRR (mg/kg)	21 ± 7	17–27
Time to PWR = 1 (sec)	76 ± 9	60–95
Total dose to PWR = 1 (mg/kg)	26 ± 4	21–34
Time to RRR (sec)	1212 ± 318	863–2040
Time to walking (sec)	1709 ± 400	1100–2340

2.3. Structure–activity relationships

The acetate **7*S*** was the most potent of the compounds studied (about as potent as ketamine), but showed only moderately faster recoveries (1.5- to 2-fold) than ketamine itself. This is most likely not due to slow acetate hydrolysis, but to the fact that the alcohol product **6*S*** is itself a potent hypnotic/analgesic (the most potent of the compounds evaluated here), even though it was no more polar (*c*log*P* 2.10) than **7*S*** itself.

However, the norketamine esters proved to be a more useful class. The more potent compounds (up to twofold less dose-potent than ketamine itself) **8**, **9**, **11**, **12**, **14**, **15** and **16** comprised a series of esters with chain lengths across the whole range studied (thus the full range of pK_as) and a variety of Me, Et and iPr esters. In contrast, compounds **10**, **13** and **17** (from 2- to 6-fold less potent than ketamine) also contained a wide range of different chain lengths, but were all n-Pr esters, and at the higher end of the lipophilicity range. Thus the potency of the esters was more dependent on the nature of the ester functionality than its separation from the amine moiety. Since dose-potency and rapidity of recovery from both LRR and PWR are broadly reciprocal, it is not surprising that the norketamine esters resulting in fastest recovery (20–25-fold faster than ketamine) are in each case the same n-Pr esters **10**, **13** and **17**.

The bulk of the norketamine esters explored were racemic, but in three cases the *S*-enantiomers were also evaluated (**8*S***, **9*S***, and **14*S***), since (*S*)-ketamine (**1*S***) is known to be as active but about twice as potent as its racemate [5]. However two of the *S*-enantiomer esters (**8*S***, **9*S***) while they were active, were only half as potent as the corresponding racemates and showed faster recoveries, suggesting more rapid hydrolysis of the *S*-enantiomer esters. The **9*R*** enantiomer was also prepared and had similar potencies and kinetics of recovery to **9*S***. The third pair (**14**/**14*S***) had broadly equivalent properties.

We also prepared the tertiary amine **18** ('homoketamine'), which has not been previously reported. The racemic compound **18** exhibited ketamine-like sedative effects but was slightly less potent than ketamine, with a duration of action somewhat longer than the average value for ketamine. The (*S*)-enantiomer **18*S*** was somewhat more dose-potent than racemic **18** but had broadly similar sedative properties. These thus seemed good targets for ester formation, and the corresponding esters **19**–**21** were prepared and exploratory studies were done (mostly by single-animal

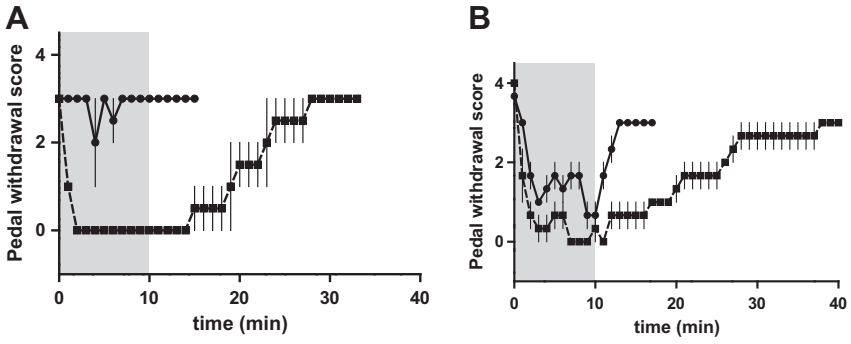


Figure 2. Time-course for analgesia (pedal withdrawal reflex score) with representative compounds. Loss and recovery of pedal withdrawal reflex for compounds **10** (A) and **14** (B). The grey panel shows the duration of drug infusion (measurement taken every minute). Error bars are SEM. ●●●●: Test compound. ■■■■: Ketamine.

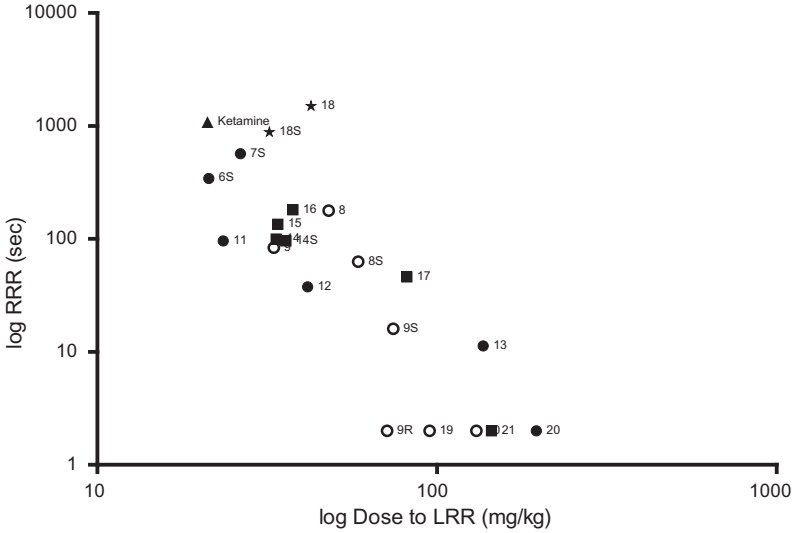


Figure 3. Effective potency versus duration for all compounds. Plot (log 10) of effective potency (dose [mg/kg] to LRR) versus duration (time to RRR) for studied compounds. The alkyl chain length of compounds is denoted by symbol: ★ = C1; ○ = C2; ● = C3; ■ = C4; ▲ = ketamine.

evaluations). The racemic C2 ethyl ester **19** was about as potent as the n-Pr norketamine esters above, but had a very weak sedative effect, with very rapid recovery. Longer chain lengths were explored with the C3 ethyl and C4 methyl esters **20** and **21**, but these were even less potent, with very poor sedative activity. There was no clear effect of pK_a on anaesthetic activity, although the weakest bases (compounds **8**–**10**, **19**) were among the least potent of the norketamine esters.

2.4. Conclusions

The above results show that short-chain aliphatic ester analogues of ketamine broadly retain its desirable anaesthetic and analgesic activities, yet are metabolised to the more polar and inactive acids sufficiently rapidly to minimise the drawbacks of ketamine itself in this capacity. While the structure activity relationships for the ester were not straightforward, the results suggest that the n-propyl esters, and the *S*-enantiomers tend to be less potent; likely due to their more rapid hydrolysis.

3. Experimental

3.1. Chemistry

All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Reactions requiring anhydrous conditions were performed under nitrogen atmospheres. Reactions were monitored by thin layer chromatography (TLC) on preloaded silica gel F254 plates (Sigma–Aldrich) with a UV indicator. Column chromatography was performed with Merck 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H and 101 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ or $(CD_3)_2SO$. The chemical shifts are reported in parts per million (δ) downfield using tetramethylsilane ($SiMe_4$) as internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), br (broad), m (multiplet), and q (quartet). Coupling constants (J values) were measured in hertz (Hz). All LC/MS data were gathered by direct injection of methanolic solutions into a Surveyor MSQ mass spectrometer using an atmospheric pressure chemical ionisation (APCI) with a corona voltage of 50 V and a source temperature of 400 °C. High-resolution electrospray ionisation (HRESIMS) mass spectra were determined on a Bruker micrOTOFQ II mass spectrometer. Final products were analysed by reverse-phase HPLC (Alltima C18 5 μm column, 150 mm × 3.2 mm; Alltech Associated, Inc., Deerfield, IL) using an Agilent HP1100 equipped with a diode array detector. The mobile phase was 80% MeCN/20% H_2O (v/v) in 45 mM HCO_2NH_4 at pH 3.5 and 0.5 mL/min. The purity was determined by monitoring at 272 nm and was ⩾95% for final products unless otherwise stated. Enantiomeric purity was analysed by chiral HPLC (Chiralcel OJ-H column, 0.46 cm × 45 cm). The mobile phase was 85% hexanes/15% EtOH with a flow rate of 0.6 mL/min. The purity was determined by monitoring at 254 and 280 nm and was ⩾95% unless otherwise stated. The final product purity was also assessed by combustion analysis carried out in the Campbell Micro analytical Laboratory, University of Otago (Dunedin, New Zealand). Melting points were determined on an Electrothermal 2300 Melting Point Apparatus and are uncorrected. DCM refers to dichloromethane, DMF refers to *N*,*N*-dimethylformamide, EtOAc refers to ethyl acetate, EtOH refers to ethanol.

3.1.1. 3-((1-(2-Chlorophenyl)-2-oxocyclohexyl)amino)propyl acetate hydrochloride (7) (Scheme 1)

(2-Chlorophenyl)(cyclopentyl)methanone (**22**) (10 g, 48.0 mmol) was dissolved in EtOAc (100 mL) followed by addition of Cu(II)Br_2 (27 g, 120.9 mmol). The solution was refluxed for 3 h and cooled to 25 °C. The solid was filtered and the filtrate was evaporated under reduced pressure. Some solid began to form while evaporating solvent under reduced pressure. DCM (100 mL) was added to the solid formed and solution cooled to 0 °C in an ice bath. After standing for 10 min. the solution was filtered and the filtrate concentrated under reduced pressure to obtain (1-bromocyclopentyl)(2-chlorophenyl)methanone[14] (**23**) as a yellow oil (12.3 g, 89%). ^{1}H NMR ($CDCl_3$) δ 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 7.43 (dd, J = 7.9, 1.3 Hz, 1H), 7.37 (td, J = 7.4, 1.8 Hz, 1H), 7.30 (td, J = 7.4, 1.3 Hz, 1H), 2.45–2.27 (m, 4H), 2.09–2.01 (m, 2H), 1.89–1.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.47, 138.87, 130.83, 130.55, 130.16, 128.33, 126.49, 74.29, 40.42, 23.26. MS m/z 289.3 ($M2H^+$, 24 %) 207.4 ($M-Br^-$, 100%).

Ammonium hydroxide (200 mL) was cooled to 0 °C in an ice bath and was saturated with NH_3 gas for 5 min. The solution was added to a flask containing **23** (12.74 g, 44.5 mmol) and stirred vigorously at 25 °C for 5 days. The brown clumps formed were separated from the solvent and resuspended in hexanes (150 mL). After stirring in hexanes for 4 h, the precipitate formed was filtered

and dried to obtain **24** (8.15 g, 81%) as a pale yellow solid. This was suspended in 8 mL of 2-propanol and cooled to 0 °C in an ice bath. HCl gas was bubbled through the solution for 2 min. and Et_2O (16 mL) was added. Upon standing at 0 °C for 3 h a pale yellow precipitate was formed which was filtered, dried under vacuum to obtain 1-((2-chlorophenyl)(imino)methyl)cyclopentanol[15] (**24**) as the HCl salt (7.21 g). ^{1}H NMR ($CDCl_3$) δ 14.05 (br, 1H), 12.28 (br, 1H), 7.61–7.32 (m, 4H), 2.23 (br, 2H), 1.98 (m, 4H), 1.69 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 195.76, 132.74, 131.42, 130.57, 128.99, 128.85, 126.82, 85.56, 38.78, 23.85 (two Peaks overlapping). MS *m*/*z* 224.4 (MH^+).

To Dowtherm A (142 mL) heated to 200 °C was added in portions **24** (18 g, 69.2 mmol). The heating was continued for 12 min. and cooled to 0 °C in an ice bath. The reaction mixture along with precipitate formed was poured into diethyl ether (500 mL) and allowed to stand overnight. The white precipitate formed was filtered and washed with Et_2O (100 mL). The precipitate was dissolved in water (200 mL) and neutralized with 2 N NaOH. The water layer was extracted with DCM (3 × 100 mL), dried over Na_2SO4 and solvent evaporated. The residue obtained was purified by passing through a short silica gel column eluting with DCM (100%) to 10% MeOH/DCM to give racemic 2-amino-2-(2-chlorophenyl)cyclohexanone.[15] (norketamine) (**25**) (9.2 g, 59%). ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.39–7.33 (m, 2H), 7.26 (td, *J* = 7.6, 1.6 Hz, 1H), 2.79–2.72 (m, 1H), 2.63–2.56 (m, 1H), 2.51–2.43 (m, 1H), 2.08–2.0 (m, 1H), 1.88 (br, 1H), 1.81–1.75 (m, 2H), 1.72–1.63 (m, 1H).

A solution of racemic **25** (200 mg, 0.89 mmol), 3-bromopropyl acetate[16] (194 mg, 1.07 mmol), KI (45 mg, 0.27 mmol), K_2CO_3 (371 mg, 2.7 mmol) was dissolved in MeCN (5 mL). The reaction mixture was heated to reflux for 24 h. After completion of reaction the reaction mixture was cooled to room temperature and solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexanes, EtOAc/hexanes (40%). The solvent was evaporated under reduced pressure to obtain the desired product as yellow oil (173 mg, 59%). The yellow oil was dissolved in Et_2O (5 mL) and was cooled to 0 °C in an ice bath. Dry HCl gas was bubbled through the solution at 0 °C for 2 min. The solvent was evaporated under reduced pressure to obtain a yellow solid. The yellow solid was taken up in EtOAc (1 mL) and sonicated at 25 °C for 2 min. The white precipitate formed was diluted with EtOAc (5 mL) and filtered, washed with EtOAc and dried under vacuum to give racemic **7** as the HCl salt (107 mg, 33%), mp 180–183 °C.^{1}H NMR ($CDCl_3$) δ 11.71 (br, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.09 (br, 1H), 7.58 (m, 1H), 7.46 (d, *J* = 4.0 Hz, 2H), 4.15 (m, 1H), 4.08 (m, 1H), 3.81 (dm, *J* = 12.0 Hz, 1H), 3.19 (br, 1H), 2.74 (d, *J* = 12.0 Hz, 1H), 2.68–2.60 (m, 2H), 2.47 (br, 1H), 2.28 (t, *J* = 14 Hz, 1H), 2.12 (br, 2H), 2.09 (s, 3H), 1.84 (br, 2H), 1.54 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 206.20, 171.04, 135.14, 132.56, 132.34, 131.79, 129.16, 128.92, 77.49, 62.22, 41.87, 40.63, 40.01, 29.91, 25.84, 21.82, 21.02. MS *m*/*z* 324.2 (MH^+). Anal. Calcd for $C_{17}H_{23}Cl_2NO_3$: C, 56.67; H, 6.43; N, 3.89; Cl, 19.68. Found: C, 56.49; H, 6.61; N, 3.69.

3.1.2. (*S*)-3-((1-(2-Chlorophenyl)-2-oxocyclohexyl)amino)propyl acetate hydrochloride (7*S*) (Scheme 1)

Resolution of norketamine was achieved by following a published procedure.[16] A solution of racemic **25** (13.2 g, 59.1 mmol) in MeOH (33 mL) was treated with L-(*R*,*R*)-(+)-tartaric acid (8.9 g, 59.1 mmol) in MeOH (118 mL). The reaction mixture was stirred overnight at 25 °C and filtered to remove any solid impurities. The filtrate was evaporated and the white solid obtained washed with 2-butanone (264 mL). The solid was suspended in acetone (1750 mL) and heated to reflux until most of the solid was dissolved. The solution was cooled to room temperature and allowed to stand for 2 days. The crystals formed were filtered and recrystallized two additional times in acetone (1750 and 800 mL, respectively) to obtain (*S*)-2-amino-2-(2-chlorophenyl)cyclohexanone (**25*S***) as the tartrate salt, mp: 190–191 °C. ^{1}H NMR (DMSO-d_6) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 4.21 (s, 2H), 2.78–2.70 (m, 1H), 2.32 (dt, *J* = 15.1, 4.4 Hz, 1H), 1.96–1.81 (m, 3H), 1.73–1.60 (m, 2H), one proton submerged with DMSO-d_6 peak; ^{13}C NMR (DMSO-d_6) δ 208.6, 173.320, 131.96, 130.28, 129.1 (2), 128.93, 127.09, 71.93, 64.84, 38.31, 37.5, 25.79, 20.84. MS *m*/*z* 224.2 (MH^+).

The (*S*)-norketamine tartrate salt was dissolved in water (200 mL), neutralized with 2 N NaOH. Extraction with DCM (3 × 100 mL) gave the free base of **25*S*** (4.96 g) as a pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.70 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38–7.31 (m, 2H), 7.28–7.23 (m, 1H), 2.79–2.71 (m, 1H), 2.63–2.56 (m, 1H), 2.51–2.43 (m, 1H), 2.08–2.02 (m, 1H), 1.89–1.74 (m, 3H), 1.71–1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 212.75, 140.49, 133.02, 131.0, 128.97, 128.32, 127.20, 66.42, 41.25, 38.98, 28.32, 22.16. MS *m*/*z* 224.2 (MH^+).

A solution of **25*S*** (1 g, 4.47 mmol) was treated with 3-bromopropyl acetate, KI and K_2CO_3 in MeCN as above to give a crude product that was purified by column chromatography on silica gel eluting with hexanes, EtOAc/hexanes (40%) to give a yellow oil (695 mg, 48%). This dissolved in Et_2O (20 mL), cooled to 0 °C in an ice bath and treated with dry HCl gas at 0 °C for 2 min. The precipitate formed was filtered, resuspended in EtOAc (20 mL), stirred for 10 min at room temperature and filtered to give **7*S*** as the HCl salt (512 mg, 29%), mp 169–172 °C. ^{1}H NMR ($CDCl_3$) δ 11.87 (br, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.62–7.54 (m, 1H), 7.48 (d, *J* = 3.8 Hz, 2H), 7.39 (br, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.83 (dm, *J* = 14.4 Hz, 1H), 3.11–3.02 (m, 1H), 2.75 (d, *J* = 12.5 Hz, 1H), 2.70–2.61 (m, 1H), 2.51 (br, 1H), 2.32 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 11.1 Hz, 1H), 2.05 (br, 1H), 1.99–1.88 (m, 2H), 1.83 (d, *J* = 14.5 Hz, 2H), 1.76–1.61 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.41, 173.07, 135.21, 132.58, 132.06, 131.67, 129.34, 128.99, 73.20, 60.57, 43.59, 40.82, 39.62, 33.65, 29.68, 26.07, 22.27, 21.77, 14.31. MS *m*/*z* 352.2 (MH^+). Anal. Calcd for $C_{19}H_{27}Cl_2NO_3$: C, 58.77; H, 7.01; N, 3.61; Cl, 18.26. Found: C, 58.81; H, 7.1, N, 3.51; Cl, 18.31.

3.1.3. (*S*)-2-(2-Chlorophenyl)-2-(3-hydroxypropylamino)-cyclohexanone hydrochloride (6*S*)

(Scheme 1). A solution of the HCl salt of **7*S*** (360 mg, 1.11 mmol) in 0.2 N NaOH (20 mL)/MeCN (2 mL) was stirred at 25 °C for 2 h, then the reaction mixture was made acidic (pH 2–3) by addition of 1.25 N HCl in MeOH. The solvent was evaporated under reduced pressure and the white solid obtained was suspended in MeCN (20 mL) and stirred for 2 h at 25 °C, then filtered and the filtrate dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a colourless viscous oil that was suspended in EtOAc (20 mL) and sonicated for 2 min. The white solid formed was filtered to obtain (*S*)-2-(2-chlorophenyl)-2-(3-hydroxypropylamino)cyclohexanone hydrochloride (**6*S***) (263 mg, 74%), mp 187–190 °C. ^{1}H NMR ($CDCl_3$) δ 10.82 (br, 1H), 8.72 (br, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.59–7.54 (m, 1H), 7.49–7.44 (m, 2H), 3.97–3.93 (m, 1H), 3.79 (t, *J* = 9.3 Hz, 1H), 3.66 (d, *J* = 12.1 Hz, 1H), 3.21 (br, 1H), 2.85 (br, 1H), 2.70 (d, *J* = 12.8 Hz, 1H), 2.60 (td, *J* = 13.1, 6.0 Hz, 1H), 2.39–2.22 (m, 2H), 2.09–2.0 (m, 2H), 1.92–1.79 (m, 3H), 1.58 (q, *J* = 13.8 Hz, 1H); MS *m*/*z* 282.5 (MH^+). Anal. Calcd for $C_{15}H_{21}Cl_2NO_2$: C, 56.61; H, 6.65; N, 4.40. Found: C, 55.21; H, 6.70; N, 4.37.

3.1.4. General procedure for synthesis of N-alkylated norketamine esters (Scheme 1)

A solution of racemic **25** or **25*S*** (1 equiv), the appropriate alkyl halide (1.2 equiv or 6 equiv in case of ethyl-3-bromo propionate), KI (0.3 equiv) and K_2CO_3 (3 equiv) was dissolved in MeCN

(4.5 mL/mmol). The solution was heated to 80 °C in a sealed tube for 24 h (72 h in case of ethyl-3-bromo propionate). The reaction mixture was cooled to room temperature and solvent evaporated. The residue was purified by column chromatography on silica gel eluting with hexanes, EtOAc/hexanes (20–35%). The solvent was evaporated and the HCl salts of the amines were prepared as above with dry HCl gas, followed by evaporation under reduced pressure to dryness. The crude products were taken up in EtOAc (2 mL), sonicated at 25 °C for 2 min, then diluted with EtOAc (10 mL), filtered, washed with EtOAc and dried under vacuum to obtain the pure HCl salts. The following compounds were prepared according to this general procedure:

3.1.5. Ethyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)propanoate hydrochloride (8)

From racemic **25** and ethyl 3-bromopropionate (33% yield), mp 199–202 °C. ^{1}H NMR ($CDCl_3$) δ 12.24 (br, 1H), 8.13 (d, J = 8.0 Hz, 2H), 7.61–7.54 (m, 1H), 7.49 (d, J = 3.8 Hz, 2H,), 4.23 (q, J = 7.2 Hz, 2H), 3.78 (dm, J = 14.3 Hz, 1H), 3.59–3.45 (m, 1H), 3.25 (q, J = 5.4 Hz, 1H), 2.73 (br, 2H), 2.68–2.54 (m, 2H), 2.23 (td, J = 13.7, 2.5 Hz, 1H), 2.14–2.02 (m, 1H), 1.89–1.82 (m, 2H), 1.65–1.59 (m, 1H), 1.28 (t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 206.10, 171.94, 135.27, 132.57, 132.40, 131.85, 129.05, 128. 57, 73.42, 61.67, 40.30, 39.71, 39.63, 30.38, 29.93, 21.86, 14.18; MS m/z 324.2 (MH^+). Anal. Calcd for $C_{17}H_{23}Cl_2NO_3$: C, 56.67; H, 6.43; N, 3.89; Cl, 19.68. Found: C, 56.65; H, 6.57; N, 3.89; Cl, 19.90.

3.1.6. (*S*)-Ethyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl) amino) propanoate hydrochloride (s-C2Et) (8*S*)

From **25*S*** and ethyl 3-bromopropanoate (54%), mp 208–210 °C. ^{1}H NMR ($CDCl_3$) δ 12.08 (br, 1H), 8.25 (br, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.61–7.56 (m, 1H), 7.49 (br, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.76 (dm, J = 14.3, 3.2 Hz, 1H), 3.55–3.46 (m, 1H), 3.28 (q, J = 9.97 Hz, 1H), 2.75–2.56 (m, 4H), 2.26 (td, J = 14.14 Hz, 1H), 2.08 (br, 1H), 1.90–1.78 (m, 2H), 1.61 (br, 1H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.35, 172.38, 135.08, 132.39, 132.33, 131.71, 128.91, 128.27, 73.32, 61.75, 40.08, 39.57, 29.91, 29.89, 21.69, 14.02 (1C overlapping). MS m/z 324.2 (MH^+). HRMS calculated for $C_{17}H_{23}ClNO_3$ (MH^+) 324.1361, found 324.1370.

3.1.7. *Iso*-Propyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)propanoate hydrochloride (9)

From racemic **25** and isopropyl 3-bromopropanoate (48%), mp 203–205 °C. ^{1}H NMR ($CDCl_3$) δ 12.0 (br, 1H), 8.27 (br, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.61–7.55 (m, 1H), 7.49 (br, 2H), 5.13–5.04 (m, 1H), 3.79 (dm, J = 14.3 Hz, 1H), 3.52–3.44 (m, 1H), 3.28 (br, 1H), 2.74 (br, 2H), 2.65–2.56 (m, 2H), 2.24 (td, J = 13.8 Hz, 3.2 Hz, 1H), 2.07 (br, 1H), 1.89–1.78 (m, 2H), 1.65–1.62 (m, 1H), 1.26 (d, J = 5.01 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 206.57, 172.2, 135.23, 132.63, 132.49, 131.84, 129.07, 129.03, 73.51, 69.86, 40.23, 39.85, 30.27, 30.08, 21.93, 21.84. MS m/z 338.2 (MH^+). Calculated for $C_{18}H_{25}ClNO_3$ (MH^+) 338.1517, found 338.1529.

3.1.8. (*S*)-Isopropyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)propanoate hydrochloride (s-C2iPr) (9S)

From **25*S*** and isopropyl 3-bromopropanoate (29%), mp 208–211 °C. ^{1}H NMR ($CDCl_3$) δ 12.22 (br, 1H), 8.14 (dbr, J = 8.1 Hz, 2H), 7.61–7.55 (m, 1H), 7.49 (br, 2H), 5.12–5.06 (m, 1H), 3.79 (dm, J = 14.4 Hz, 1H), 3.52–3.43 (m, 1H), 3.26 (q, J = 11.9 Hz, 1H), 2.71 (br, 2H), 2.67–2.55 (m, 2H), 2.21 (td, J = 14.1, 3.3 Hz, 1H), 2.07 (br, 1H), 1.89–1.78 (m, 2H), 1.63 (br, 1H), 1.27 (app. dd, J = 4.93, 1.25 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 206.62, 172.23, 135.24, 132.62, 132.48, 131.84, 129.08, 128.42, 73.48, 69.86, 40.24, 39.87, 30.28, 30.09, 21.93, 21.87, 21.84. MS m/z 338.2 (MH^+). HRMS calculated for $C_{18}H_{25}ClNO_3$ (MH^+) 338.1517, found 338.1524.

3.1.9. (*R*)-Isopropyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)amino)propanoate hydrochloride (r-C2iPr) (9R)

From **25*R*** and isopropyl 3-bromopropanoate (29%), mp 216–219 °C. ^{1}H NMR ($CDCl_3$) δ 12.20 (br, 1H), 8.14 (dbr, J = 8.1 Hz, 2H), 7.60–7.56 (m, 1H), 7.49 (br, 2H), 5.14–5.04 (m, 1H), 3.80 (dm, J = 13.6 Hz, 1H), 3.51–3.44 (m, 1H), 3.26 (br, 1H), 2.73 (br, 2H), 2.64–2.56 (m, 2H), 2.21 (t, J = 13.2 Hz, 1H), 2.06 (br, 1H), 1.89–1.79 (m, 2H), 1.64 (br, 1H), 1.26 (app. dd, J = 4.81, 1.40 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 206.71, 172.36, 135.23, 132.67, 132.51, 131.85, 129.11, 128.39, 73.5, 69.94, 40.24, 39.95, 30.26, 30.13, 21.95, 21.89, 21.85. MS m/z (MH^+). HRMS calculated for $C_{18}H_{25}ClNO_3$ (MH^+) 338.1517, found 338.1521.

3.1.10. *n*-Propyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)propanoate hydrochloride (10)

From racemic **25** and propyl 3-bromopropanoate (44%) mp 163–165 °C. ^{1}H NMR ($CDCl_3$) δ 11.68 (br, 1H), 8.69 (br, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.61–7.54 (m, 1H), 7.49 (br, 2H), 4.07 (t, J = 6.8 Hz, 2H), 3.74 (dm, J = 14.3 Hz, 1H), 3.53–3.43 (m, 1H), 3.38 (br, 1H), 2.81–2.71 (m, 3H), 2.64–2.57 (m, 1H), 2.35 (td, J = 13.8, 3.2 Hz, 1H), 2.07 (br, 1H), 1.92–1.80 (m, 2H), 1.68–1.54 (m, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.03, 172.0, 135.28, 132.48, 132.37, 131.84, 128.99, 128.6, 73.4, 67.22, 40.31, 39.57, 30.28, 29.9, 21.9, 21.81, 10.42. MS m/z 338.2 (MH^+). HRMS calculated for $C_{18}H_{25}ClNO_3$ 338.1517, found 338.1526.

3.1.11. Ethyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)amino)butanoate hydrochloride (11)

From racemic **25** and ethyl 4-bromobutanoate (37% yield), mp 186–189 °C. ^{1}H NMR ($CDCl_3$) δ 11.14 (br, 1H), 9.14 (br, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.62–7.49 (m, 1H), 7.45 (d, J = 3.8 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.75 (dm, J = 14.4 Hz, 1H), 3.38–3.26 (m, 1H), 2.75–2.64 (m, 2H), 2.64–2.58 (m, 1H), 2.43–2.26 (m, 2H), 2.45–2.28 (m, 2H), 2.14–2.07 (m, 1H), 1.98(br, 2H), 1.91–1.79 (m, 1H), 1.58–1.44 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 206.03, 173.16, 135.11, 132.76, 132.08, 131.61, 129.19, 129.02, 73.17, 61.04, 43.54, 40.86, 40.00, 32.24, 29.72, 21.64, 14.27. MS m/z 338.2 (MH^+). Anal. Calcd for $C_{18}H_{25}Cl_2NO_3$: C, 57.76; H, 6.73; N, 3.74; Cl, 18.94. Found: C, 57.55; H, 6.92; N, 3.64; Cl, 18.73.

3.1.12. *Iso*propyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)butanoate hydrochloride (12)

From racemic **25** and *iso*propyl 4-bromobutanoate[17] (24% yield), mp 167–169 °C. ^{1}H NMR ($CDCl_3$) δ 11.41 (br, 1H), 8.94 (br, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.68–7.50 (m, 1H), 7.45 (d, J = 3.9 Hz, 2H), 4.99 (m, 1H), 3.79 (dm, J = 14.4 Hz, 1H), 3.31–3.21 (m, 1H), 2.75–2.68 (m, 1H), 2.66–2.59 (m, 2H), 2.58–2.49 (m, 1H), 2.42–2.48 (m, 1H), 2.34 (t, J = 10.8 Hz, 2H), 2.11–1.98 (m, 2H), 1.84 (d, J = 10.2 Hz, 2H), 1.58–1.46 (m, 1H), 1.22 (dd, J = 6.28, 2.2 Hz, 6H) ; ^{13}C NMR ($CDCl_3$) δ 206.29, 173.46, 135.04, 132.84, 132.13, 131.62, 129.08, 129.06, 73.11, 68.81, 43.70, 40.84, 40.21, 32.79, 29.90, 21.91, 21.68. MS m/z 352.2 (MH^+). Anal. Calcd for $C_{19}H_{27}Cl_2NO_3$: C, 58.77; H, 7.01; N, 3.61. Found: C, 58.57; H, 7.2; N, 3.54.

3.1.13. *n*-Propyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)butanoate hydrochloride (13)

From racemic **25** and *n*-propyl 4-bromobutanoate (19%), mp 160–161 °C. ^{1}H NMR ($CDCl_3$) δ 11.10 (br, 1H), 9.23 (br, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.59–7.52 (m, 1H), 7.44 (d, J = 5.1 Hz, 2H), 4.01 (t, J = 6.8 Hz, 2H), 3.76 (dm, J = 14.4 Hz,1H), 3.39–3.28 (m, 1H), 2.70 (t, J = 7.8 Hz, 1H), 2.66 (t, J = 6.9 Hz, 1H), 2.62–2.54 (m, 1H), 2.51 (td, J = 7.0, 2.8 Hz, 2H), 2.47–2.41 (m, 1H), 2.39–2.30 (m, 1H), 2.15–2.06 (m, 1H), 2.0 (br, 1H), 1.85 (td, J = 8.0, 3.9 Hz, 2H), 1.57–1.66 (m, 2H), 1.50 (q, J = 14.4 Hz, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.92, 173.47, 135.12, 132.78, 132.05, 131.59, 129.23, 129.0, 73.16, 66.62, 43.54, 40.86, 39.99, 32.19,

29.77, 22.0, 21.78, 21.70, 10.48. MS *m*/*z* 352.2 (MH^+). Anal. Calcd for $C_{19}H_{27}Cl_2NO_3$: C, 58.77; H, 7.01; N, 3.61; Cl, 18.26. Found: C, 58.88; H, 7.15; N, 3.51; Cl, 18.28.

3.1.14. rac-Methyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)pentanoate hydrochloride (14)

From racemic **25** and ethyl 5-bromopentanoate, followed by purification by preparative HPLC (41%). ^1H NMR ($CDCl_3$) δ 7.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.31 (dt, *J* = 7.8, 7.6, 1.5 Hz, 1H), 7.25–7.21 (m, 1H), 3.64 (s, 3H), 2.77–2.69 (m, 1H), 2.55–2.42 (m, 2H), 2.36–2.30 (m. 1H), 2.26 (t, *J* = 7.4, 2H), 2.09–1.73 (m, 7H), 1.66–1.58 (m, 2H), 1.55–1.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 205.35, 173.0, 134.5, 131.86, 131.45, 131.09, 128.38, 72.56, 59.91, 51.21, 42.96, 40.13, 39.18, 32.75, 29.14, 25.58, 21.54, 13.71. MS *m*/*z* 338.2 (MH^+).

3.1.15. (*S*)-Methyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)pentanoate hydrochloride (14*S*)

From **25*S*** and ethyl 5-bromopentanoate (42%), mp (MeOH/EtOAc) 188–191 °C, ^1H NMR ($CDCl_3$) δ 7.52 (dd, *J* = 7.82, 1.68 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.31 (dt, *J* = 7.8, 7.60, 1.45 Hz, 1H), 7.23 (dt, *J* = 8.0; 1.7 Hz, 1H), 3.65 (s, 3H), 2.76–2.68 (m, 1H), 2.55–2.42 (m, 2H), 2.36–2.30 (m, 1H), 2.26 (t, *J* = 7.4 Hz, 2H), 2.08–1.74 (m, 7H), 1.66–1.58 (M, 2H), 1.57–1.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 206.14, 173.65, 135.12, 132.56, 132. 2, 131.75 (2C), 129.1, 73.27, 60.54, 51.87, 43.66, 40.75, 33.34, 29.87, 26.14, 22.1, 14.35. MS *m*/*z* 338.2 (MH^+). Analysis calculated for $C_{18}H_{25}Cl_2NO_3$: C, 57.8; H, 6.7, Cl, 18.9, N, 3.7; found C, 57.7, H, 6.8 Cl, 18.9 N, 3.7.

3.1.16. rac-Ethyl 5-((1-(2-chlorophenyl)-2-oxocyclohexyl)-amino)pentanoate hydrochloride (15)

From racemic **25** and ethyl 5-bromopentanoate (29%), mp 169–172 °C. ^1H NMR ($CDCl_3$) δ 11.87 (br, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.62–7.54 (m, 1H), 7.48 (d, *J* = 3.8 Hz, 2H), 7.39 (br, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.83 (dm, *J* = 14.4 Hz, 1H), 3.11–3.02 (m, 1H), 2.75 (d, *J* = 12.5 Hz, 1H), 2.70–2.61 (m, 1H), 2.51 (br, 1H), 2.32 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 11.1 Hz, 1H), 2.05 (br, 1H), 1.99–1.88 (m, 2H), 1.83 (d, *J* = 14.5 Hz, 2H), 1.76–1.61 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.41, 173.07, 135.21, 132.58, 132.06, 131.67, 129.34, 128.99, 73.20, 60.57, 43.59, 40.82, 39.62, 33.65, 29.68, 26.07, 22.27, 21.77, 14.31. MS *m*/*z* 352.2 (MH^+). Anal. Calcd for $C_{19}H_{27}Cl_2NO_3$: C, 58.77; H, 7.01; N, 3.61; Cl, 18.26. Found: C, 58.81; H, 7.1, N, 3.51; Cl, 18.31.

3.1.17. *Iso*propyl 5-((1-(2-chlorophenyl)-2-oxocyclohexyl)amino)pentanoate hydrochloride (16)

From racemic **25** and *iso*propyl 5-bromovalerate (40%), mp 161–163 °C. ^1H NMR ($CDCl_3$) δ 11.04 (br, 1H), 8.78 (br, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.59–7.53 (m, 1H), 7.47 (br, 2H), 5.01–4.92 (m, 1H), 3.74 (dm, *J* = 14.4 Hz, 1H), 3.29–3.21 (m, 1H), 2.73 (d, *J* = 12.2 Hz, 1H), 2.64 (td, *J* = 13.3 Hz, 6.3, 1H), 2.54–2.42 (m, 2H), 2.26–2.21 (m, 2H), 2.10–1.99 (m, 2H), 1.94–1.83 (m, 2H), 1.78 (d, *J* = 17.6 Hz, 1H), 1.71–1.47 (m, 3H), 1.20 (dd, *J* = 6.3, 1.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 205.7, 172.68, 135.18, 132.61, 132.13, 131.72, 129.26, 129.04, 73.25, 67.95, 43.66, 40.80, 39.76, 33.95, 29.78, 26.12, 22.25, 21.97, 21.8. MS *m*/*z* 366.2 (MH HRMS calculated for $C_{20}H_{29}ClNO_3$ (MH^+) 366.1830, found 366.1842.

3.1.18. *n*-Propyl 5-((1-(2-chlorophenyl)-2-oxocyclohexyl)amino)pentanoate hydrochloride (17)

From racemic **25** and propyl 5-bromopentanoate (45 %), ^1H NMR ($CDCl_3$) δ 11.23 (br, 1H), 8.49 (br, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.59–7.52 (m, 1H), 7.46 (br, 2H), 4.0 (t, *J* = 6.8 Hz, 2H), 3.76 (dm, *J* = 14.3 Hz, 1H), 3.24–3.18 (m, 1H), 2.74 (br, 1H), 2.69–2.61 (m, 1H), 2.46 (t, *J* = 14.0 Hz, 2H), 2.29 (td, *J* = 7.5, 2.9 Hz, 2H), 2.04–1.95 (m, 1H), 1.92–1.89 (m, 1H), 1.87–1.83 (m, 1H), 1.79 (dbr, *J* = 15.3 Hz, 1H), 1.73–1.57 (m, 5H), 1.54–1.47 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.98, 173. 29, 135.14, 132. 6, 132.19, 131.74, 129.17, 129.08, 73.28, 66.31, 43.68, 40.77, 39.88, 33.58, 29.85, 26.16, 22.16, 22.06, 21.81, 10.5. MS *m*/*z* 366.2 (MH^+). HRMS calculated for $C_{20}H_{29}ClNO_3$ (MH^+) 366.1830, found 366.1839.

3.1.19. 2-(2-Chlorophenyl)-2-(dimethylamino)cyclohexanone hydrochloride(18) (Scheme 2)

Racemic **25** (200 mg, 0.9 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C in an ice bath. Acetic acid (0.2 mL, 3.6 mmol) and $NaCNBH_3$ (112 mg, 1.8 mmol) was added to the above solution and stirred at 0 °C for 5 min. Formaldehyde (37% in H_2O, 2.2 mmol) was added at 0 °C and reaction mixture allowed to stir at 25 °C for 24 h. The reaction mixture was quenched with $NaHCO_3$ and diluted with water. The aqueous layer was extracted with DCM (3 × 20 mL), washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the product as yellow oil. The yellow oil was dissolved in Et_2O (5 mL), cooled to 0 °C in an ice bath and treated with HCl gas for 1 min. Solvent was evaporated and the residue was resuspended in EtOAc (2 mL) and sonicated. The precipitate formed was diluted with EtOAc (10 mL) and filtered, dried to give **18** as the HCl salt (155 mg, 60%), mp 192–194 °C. ^1H NMR ($CDCl_3$) δ 12.38 (br, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.62–7.58 (m, 1H), 7.52 (br, 2H), 3.39 (d, *J* = 12.4 Hz, 1H), 3.07 (s, 3H), 2.78 (s, 3H), 2.72–2.59 (m, 2H), 2.44 (td, *J* = 13.5, 3.2 Hz, 1H), 2.05–1.97 (m, 1H), 1.90–1.81 (m, 2H), 1.46 (t, *J* = 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 205.07, 135.99, 132.76, 132.62, 132.35, 128.89, 128.71, 42.11, 40.37, 39.36, 37.3, 29.25, 22.18. MS *m*/*z* 252.1 (MH^+).

3.1.20. (*S*)-2-(2-Chlorophenyl)-2-(dimethylamino)cyclohexanone hydrochloride(18*S*)

From **25*S*** following the procedure for **18**, (42%). ^1H NMR ($CDCl_3$) δ 12.45 (br, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.62–7.58 (m, 1H), 7.51 (br, 2H), 3.39 (d, *J* = 12.8 Hz, 1H), 3.08 (s, 3H), 2.78 (s, 3H), 2.72–2.59 (m, 2H), 2.44 (t, *J* = 13.5 Hz, 1H), 2.02–1.97 (m, 1H), 1.90–1.81 (m, 2H), 1.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 205.05, 135.06, 133.93, 131.7, 130.09, 129.04, 126.67, 42.0, 39.45, 38.53, 29.42, 22.48. MS *m*/*z* 252.1 (MH^+). HRMS calculated for $C_{14}H_{19}ClNO$ (MH^+) 252.1150, found 252.1156.

3.1.21. Ethyl 3-((1-(2-chlorophenyl)-2-oxocyclohexyl)(methyl)amino)propanoate (19)

From reductive methylation of **8**, (97 %). ^1H NMR ($CDCl_3$) δ 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.36–7.33 (m, 1H), 7.30 (td, *J* = 7.9, 1.4 Hz, 1H), 7.25–7.21 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.11–3.04 (m, 1H), 2.97–2.90 (m, 1H), 2.80–2.73 (m, 1H), 2.58 (t, *J* = 6.7 Hz, 2H), 2.49–2.45 (m, 2H), 2.43 (s, 3H), 2.05–1.91 (m, 2H), 1.89–1.72 (m, 2H), 1.65–1.56 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.1, 172.7, 138.0, 134.07, 131.68, 129.86, 18.64, 126.65, 74.58, 60.37, 47.76, 41.19, 36.97, 36.14, 34.73, 27.28, 22.33, 14.27. MS *m*/*z* 338.5 (MH^+). HRMS calculated for $C_{18}H_{25}ClNO_3$ (MH^+) 338.1517, found 338.1514.

3.1.22. Ethyl 4-((1-(2-chlorophenyl)-2-oxocyclohexyl)(methyl)amino)butanoate hydrochloride (20)

From reductive methylation of **11** (97%). Mixture of rotamers. ^1H NMR ($CDCl_3$) δ 11.97 (br, 1H), 11.79 (br, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.64–7.46 (m, 6H), 4.12–4.04 (m, 4H), 3.96 (t, *J* = 9.3 Hz, 1H), 3.69 (d, *J* = 14.8 Hz, 1H), 3.47 (1H), 3.25 (d, *J* = 14.5 Hz, 1H), 3.16 (s, 3H), 2.78 (br, 6H), 2.69–2.55 (m, 5H), 2.48–2.34 (m, 3H), 2.14 (br, 3H), 1.97 (br, 3H), 1.84 (br, 5), 1.48–1.39 (m, 2 H), 1.31–1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 205.26, 204.28, 172, 136.05, 135.91, 133.57, 132.87, 132. 77,

132.65, 132.55, 132.11, 129.2, 128.53, 127.69, 60.85, 53.32, 52.16, 42.65, 41.99, 37.37, 37.17, 36.59, 35.39, 31.49, 29.16, 22.22, 22.13, 20.64, 20.55, 14.3 (some C not seen for both rotamers). MS *m*/*z* 352.2 (MH^+). HRMS calculated for $C_{19}H_{27}ClNO_3$ (MH^+) 352.1674, found 352.1687.

3.1.23. Methyl 5-((1-(2-chlorophenyl)-2-oxocyclohexyl)(methyl)amino)pentanoate (21)

From reductive methylation of **14**, (97 %). ^1H NMR ($CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 2H), 7.38–7.29 (m, 2H), 3.66 (s, 3H), 2.83 (br, 2H), 2.61–2.57 (m, 3H), 2.49 (br, 3H), 2.30 (t, J = 7.1 Hz, 2H), 2.10–1.94 (m, 3H), 1.88–1.77 (m, 3H), 1.62–1.59 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 206.75, 173.94, 134.77, 133.19, 132.01, 131.14, 130.12, 127.44, 52.02, 51.62, 41. 63, 37.0, 35.86, 33.66, 28.04, 27.07, 22.58, 22.27 (1C overlapping). MS *m*/*z* 352.2 (MH^+). HRMS calculated for $C_{19}H_{27}ClNO_3$ (MH^+) 352.1674, found 352.1683.

3.2. Biological activity

3.2.1. General

All animal experiments were conducted at the Ruakura Research Centre, Hamilton, New Zealand, using experimental protocols reviewed and approved by the Ruakura Animal Ethics Committee (ethics ref 12604). Following acquisition of baseline physiologic parameters (heart rate, respiratory rate, PWR, and righting reflex (RR)) adult female Sprague-Dawley rats of approximately 350–450 g were put under non-traumatic restraint and the marginal vein of the tail was cannulated. Ketamine or an experimental compound at 10 mg/ml was administered via a minibore extension tube adequately secured to the tail. Infusions were commenced at a rate (weight-adjusted) to deliver 20 mg/kg/min initially (continued until the pedal withdrawal reflex score PWR = 1), then were reduced to a rate of 6.7 mg/kg/min. Infusion rate was then titrated in an up-and-down fashion to maintain dorsal recumbency and a PWR = 1 to 10 min before cessation. Three rats were used in each study, with each group of rats also acting as their own ketamine control. The order of study drug administration was determined by prior odds/evens randomisation with a recovery interval of at least one hour afforded between experiments. PWR and RR were recorded at 1 min intervals throughout. The times from cessation of infusion to return of righting reflex (RRR), and from cessation of infusion to the animals displaying independent locomotion (walk) were recorded.

3.2.2. Pedal withdrawal reflex (PWR) scoring

Nociceptive testing in animals was conducted via 1 sec application of constant pressure (firm digital pressure) over the forepaw of the animal. Pedal withdrawal reflex testing is primarily used to assess analgesic effect, and responses are graded accordingly: 0, absent; 1, flicker; 2, moderate withdrawal; 3, fast withdrawal; 4, Fast withdrawal with cry/preceding apnoea (modified from Ref. 18).

3.2.3. Loss of righting reflex (LRR)

This is primarily used to assess anaesthetic hypnotic effect. Righting reflex is judged absent when the rat fails to right from a position of dorsal recumbency to a position of sternal recumbency on three attempts performed in rapid succession. Dose to LRR is termed effective potency.

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