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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.

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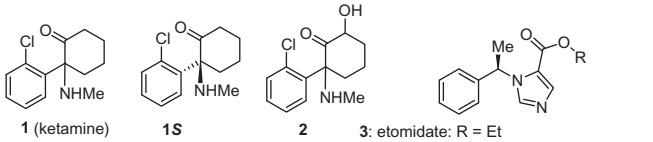
1. Introduction

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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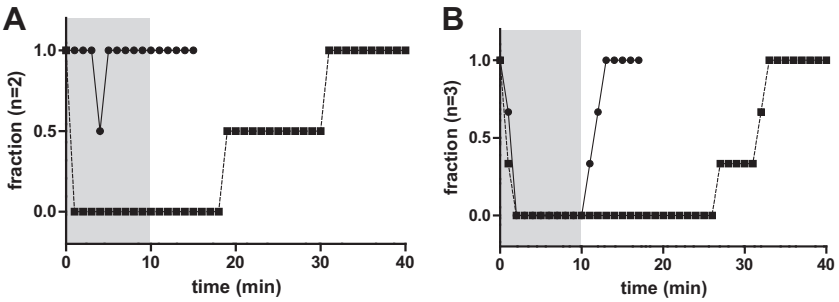


Figure 1. Time-course for anaesthesia (loss and recovery of righting reflex) for compounds **10** (A) and **14** (B). The grey panel shows the duration of drug infusion (measurement taken every minute). ●●●●: test compound. ■■■■: Ketamine.

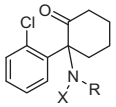
2. Results and discussion

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).

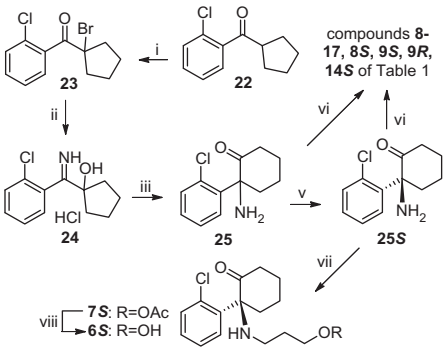
The structures and physicochemical properties of the ketamine analogues prepared are given in Table 1. Their lipophilicities (*c*log*P*) were calculated using ChemBioDraw v12.02 (CambridgeSoft, UK) and pK_a values were calculated using ACD/PhysChem Suite v12; ACD/Labs, Toronto, Canada). Ketamine (**1**) 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

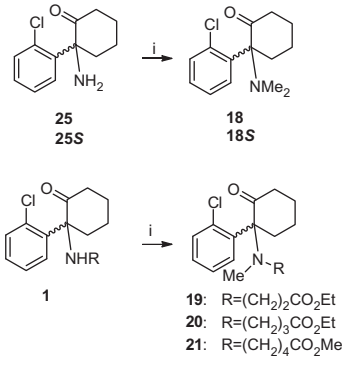


No.	X	R	Purity[a] (%)	*c*log*P*[b]	pK_a[c]
1	H	Me		3.20[d]	7.49
6*S*	H	$(CH_2)_3OH$	97.0	2.85	6.20
7	H	$(CH_2)_3OAc$	97.2	3.76	6.20
7*S*	H	$(CH_2)_3OAc$	95.8	3.76	6.20
8	H	$(CH_2)_2CO_2Et$	97.2	3.93	4.35
8*S*	H	$(CH_2)_2CO_2Et$	99.1	3.93	4.35
9	H	$(CH_2)_2CO_2iPr$	99.0	4.24	4.35
9*S*	H	$CH_2)_2CO_2iPr$	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.

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