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Novel analogues of ketamine and phencyclidine as NMDA receptor antagonists

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ABSTRACT

The identification of structurally novel analogues of ketamine and phencyclidine (PCP), as NMDA receptor antagonists, with low to moderate potency at GluN2A and GluN2B receptors is discussed. In particular, some examples, such as compounds **6** and **10**, shows decreased calculated lipophilicity, when compared to PCP, while retaining moderate activity. Moreover, the germinal aryl amino substituted lactam ring, as exemplified in compounds **7**–**10** and **11**–**13**, constitutes a novel scaffold with potential application in the design of biologically active compounds.

N-Methyl-D-aspartate (NMDA) receptors are glutamate and glycine gated ionotropic receptors highly expressed in the central nervous system (CNS).[1] They are also voltage-gated and opening of their pore allows non-selective cation flux,[2] in particular calcium entry into the cell, which is important in synaptic plasticity, learning and memory.[3] NMDA receptors are heterotetramers of GluN1, GluN2 and GluN3 subunits.[4] The majority of native NMDA receptors exist as heteromeric assemblies containing two glycine-binding GluN1 subunits together with two glutamate-binding GluN2 subunits.[5] GluN1 is coded by a single gene, with at least eight different splice variants; four different GluN2 genes originate GluN2A, GluN2B, GluN2C, GluN2D subunits. The most common receptor forms in the adult CNS are thought to be heterotetramers of two GluN1 and two GluN2A or GluN2B subunits, contributing to a diversity of receptors with differing biophysical and pharmacological properties and specific regional distributions.[6]

Ketamine and phencyclidine (PCP) (Fig. 1) are structurally related arylcycloalkylamine compounds primarily acting at the NMDA receptor pore, as 'open channel' blockers, and therefore defined as uncompetitive antagonists.[7] They are catalogued as dissociative anaesthetics, since they produce an anaesthetic state characterised by profound analgesia, but they also induce dose-dependent side effects such as perceptual abnormalities, disruptions of some aspects of cognitive and sensorimotor functions, mood changes and psychosis-like symptoms reminiscent of those observed in schizophrenia.[8] Ketamine is also used occasionally in the treatment of neuropathic pain conditions.[9] More recently, breakthrough clinical studies have shown safety and efficacy of subanaesthetic doses of ketamine for treatment-resistant major depression.[10] Because of their ability to produce intense psychedelic effects, ketamine and PCP (also known as 'special K' and 'angel dust', respectively, among other street names) are used as recreational drugs, having high risks of developing a psychological addiction.[11] Moreover, chronic ketamine or PCP administration can cause long-term cognitive impairment,[12] which might be due to neuronal cell death or neuronal remodelling.[13]

Ketamine and PCP also affect other neurotransmitter systems beside the NMDA receptor. They are agonists at dopamine D_2 receptors,[14] they interact with 5-HT_2 receptors,[15] mu and kappa opioid receptors,[16] sigma receptors and muscarinic cholinergic receptors.[17] They block HCN1 cation channels,[18] adenosine triphosphate-sensitive potassium channels (K_{ATP}),[19] sodium channels,[20] and nicotinic acetylcholine receptor channels (nAChR).[21] Additionally they inhibit catecholamine uptake,[22] and they interfere with inflammatory mediators such as nitric oxide[23] and NAPDH oxidase.[24] Recently, it has been proposed that the psychotomimetic effects of PCP and ketamine may be mediated by their predominant inhibitory effect on GABAergic interneurons, leading to increased glutamate release.[25] Little has been reported in the literature on synthesis of ketamine and PCP analogues with modified biological profile and physicochemical properties.[26]

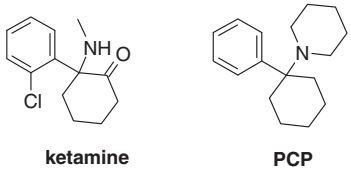

Figure 1. Structures of ketamine and PCP.

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Table 1
Inhibitory effect (pIC_{50}) in GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays for ketamine and PCP

Compd	GluN1/N2A pIC_{50}	GluN1/N2B pIC_{50}	*c* log *P*[29]
Ketamine	5.3(47)	5.9(48)	2.9
PCP	5.9(19)	6.4(19)	5.1

Values are pIC_{50} means from human recombinant GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays. Standard deviations were <0.4 for both compounds. Maximal inhibition was >100% for both compounds. The number of independent experiments is indicated in parenthesis.

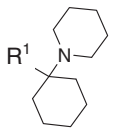


Figure 2. General structure of derivatives **1–6**.

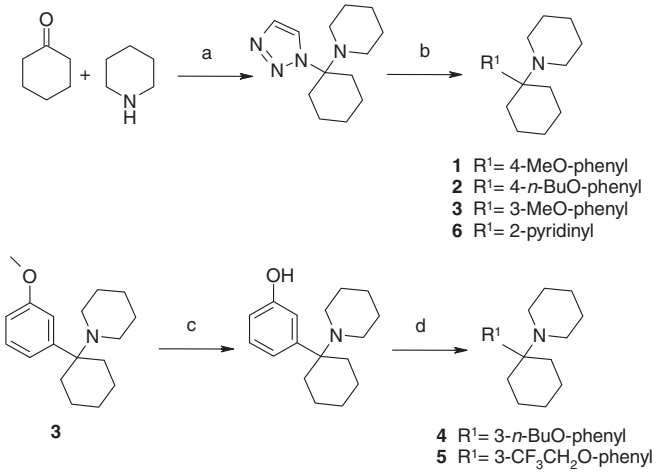
The present study describes the design, the synthesis and the biological evaluation of novel ketamine and PCP analogues. The aim of this study was to find NMDA pore blockers with equivalent or slightly increased potency and/or reduced lipophilicity with respect to ketamine and PCP through exploration of the aryl moiety and (oxo)cyclohexyl ring.

The functional activity of ketamine and PCP, as well as those of the compounds described below, was tested on recombinant human GluN1/N2A and GluN1/N2B receptors, transiently expressed in U2-OS cells using BacMam methodology.[27] Compound modulation of intracellular calcium levels in U2-OS cells expressing GluN1/N2A or GluN1/N2B receptor was assessed using FLIPR/Ca^{2+} methodology.[28] Both ketamine and PCP showed moderate potencies at both receptors, with slight preference for the GluN1/N2B over the GluN1/N2A combination (Table 1).

An initial focused exploration, aimed at maintaining potency at GluN1/N2A and GluN1/N2B targets, was directed towards the modulation of the aryl moiety of PCP (Fig. 2).

PCP analogues **1–6** were prepared following the synthetic route outlined in Scheme 1.

The first step was the in situ preparation of a key intermediate obtained through the reaction of cyclohexanone with piperidine in the presence of 1,2,3-triazole in toluene at 130 °C.[30]



Scheme 1. Reagents and conditions: (a) 1,2,3-Triazole, toluene, 130 °C, 12 h; (b) aryl magnesium bromide or aryl lithium, THF, −78 °C→rt, 1–4 h; (c) BBr_3, −78→0 °C, DCM, 3 h; (d) K_2CO_3, NaI, alkyl bromide or iodide, DMF, 80–120 °C, 1–3 h.

Table 2
Inhibitory effect (pIC_{50}) in GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays for PCP analogues **1**, **2** and **4–6** modified at the aryl moiety

Compd	R^1	GluN1/N2A pIC_{50}	GluN1/N2B pIC_{50}	*c* log *P*
1	4-Methoxy-phenyl	4.8(6)	5.4(6)	5.0
2	4-Butyloxy-phenyl	<4.3(7)	<4.3(7)	6.6
4	3-Butyloxy-phenyl	4.7(2)	5.7(2)	6.6
5	3-(2,2,2-Trifluoro ethyloxy)-phenyl	4.5(1)	5.3(2)	5.8
6	2-Pyridinyl	5.1(5)	5.6(5)	3.6

Values are pIC_{50} means from human recombinant GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays. Standard deviations were <0.27 for all tested compounds, except compound **1** which had 0.48 and 0.45, respectively, as SD value. Maximal inhibition was 94–100% for all listed compounds. The number of independent experiments is indicated in parenthesis.

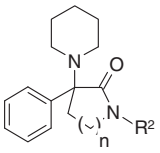


Figure 3. General structure of derivative **7–10**.

The triazolyl intermediate so obtained was not isolated but rather was added to a solution of 4-methoxyphenylmagnesium bromide to obtain compound **1**.[31] Similarly the use of 4-(butyloxy)phenyl magnesium bromide and the use of 3-methoxyphenylmagnesium bromide afforded compounds **2** and **3**, respectively. Compound **3** was then dealkylated using boron tribromide at low temperature and alkylated with butylbromide or 2-iodo-1,1,1-trifluoroethane affording compounds **4** and **5**, respectively. 2-Pyridinyllithium, obtained in situ through bromine–lithium exchange, afforded compound **6**.

Modification of the aryl group of PCP resulted in a loss of functional activity with respect to PCP itself (Table 2). Replacement of phenyl group in PCP with 2-pyridinyl gave compound **6** with the highest activity at the targets GluN1/N2A and GluN1/N2B and reduced lipophilicity among the series.[32]

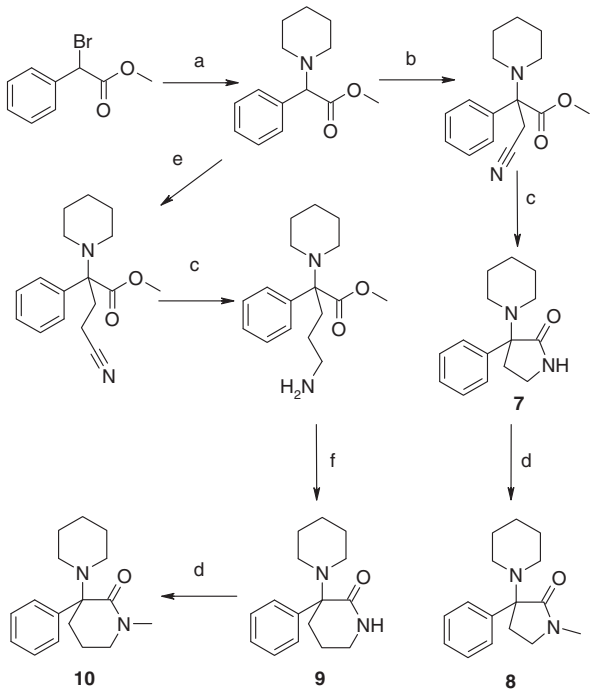
In a separate exploration aimed at reducing lipophilicity, an amide functionality was introduced in the cyclohexyl ring of PCP thus providing lactam derivatives **7–10** (Fig. 3).

Compounds **7–10** were prepared following the synthetic route outlined in Scheme 2.

Substitution of commercially available methyl bromo(phenyl)acetate with piperidine gave the corresponding α-amino ester. Alkylation with iodoacetonitrile using butyl lithium as base gave the corresponding quaternary cyano derivative.[33]

Reduction of the cyano group was achieved with Raney Nickel at five atmospheres overnight.[34] Under these conditions, cyclisation to the five-membered ring derivative **7** was obtained spontaneously.[35]

Similarly, α-alkylation of the piperidinyl acetate intermediate with 3-bromopropanenitrile[36] was performed in order to prepared the six-membered ring derivatives **9** and **10**. When α-alkylation was attempted by the use of acrylonitrile and potassium *tert*-butoxide, the desired quaternary intermediate was obtained in a lower yield. In this case reduction of the cyano group performed as described above did not yield spontaneous cyclisation to the desired six-membered ring derivative **9**. Instead, cyclisation was achieved using acidic conditions and high temperature on the isolated bis-aminoester intermediate.[37] Selective methylation of the



Scheme 2. Reagents and conditions: (a) Piperidine, rt, Et_2O, 20 h; (b) ICH_2CN, DIPA, *n*-BuLi in *n*-hexane 1.6 M, −78 °C, THF, 2 h; (c) Raney Nickel, hydrogen, rt, 5 atm, MeOH, overnight; (d) MeI, KOH, TBAB, 0 °C→rt, THF, 1 h; (e) $Br(CH_2)_2CN$, DIPA, *n*-BuLi in *n*-hexane 1.6 M, −78→−30 °C, THF, 3 h; (f) AcOH, 110 °C, 7 h.

Table 3
Inhibitory effect (pIC_{50}) in GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays for PCP analogues **7–10** comprising lactam ring

Compd	R^2	*n*	GluN1/N2A pIC_{50}	GluN1/N2B pIC_{50}	*c* log *P*
7	H	1	4.2(3)	4.6(2)	2.2
8	Me	1	3.6(2)	4.3(1)	2.9
9	H	2	3.8(3)	4.6(4)	2.8
10	Me	2	<3.6(4)	5.5(4)	3.5

Values are pIC_{50} means from human recombinant GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays. Standard deviations were <0.11 for all tested compounds, except compound **7** which had 0.28 and 0.39, respectively, as SD value. Maximal inhibition was 80–100% for all listed compounds. The number of independent experiments is indicated in parenthesis.

secondary amide groups of **7** and **9** gave the desired compounds **8** and **10**, respectively.

Table 3 reports functional activity of compounds **7–10** in GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays.

Replacement of the cyclohexyl ring with pyrrolidinone or piperidinone led, in all cases, to substantial loss of functional activity when compared to PCP, the most active derivative being compound **10** which showed a one log unit loss at the GluN1/N2B receptor.

An exploration strategy similar to that reported above for PCP was also designed and implemented for ketamine as depicted in Figure 4.

Ketamine is less lipophilic in comparison with PCP but it also shows lower GluN2A/2B antagonist activity (Table 1). Therefore, also in this case, a focused exploration aimed at further decreasing lipophilicity whilst maintaining or increasing activity at the two targets GluN1/N2A and GluN1/N2B was planned. To this purpose, compounds **11–13** (Table 4) were then designed comprising a lactam system in place of the metabolically more labile cyclohexanone system.

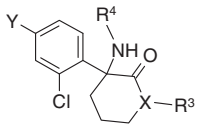


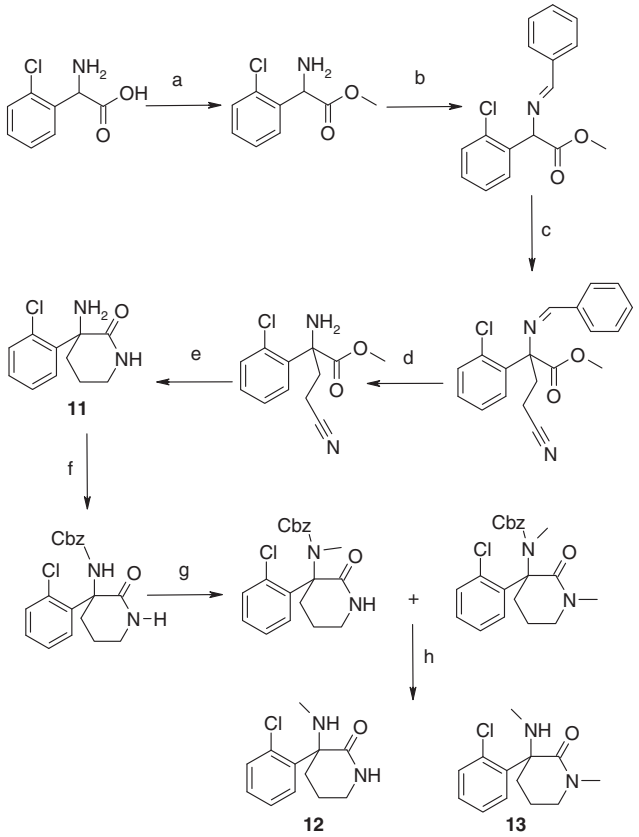
Figure 4. General structure of derivatives **11–14**.

Table 4
Inhibitory effect (pIC_{50}) in GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays for ketamine analogues **11–14** comprising lactam ring

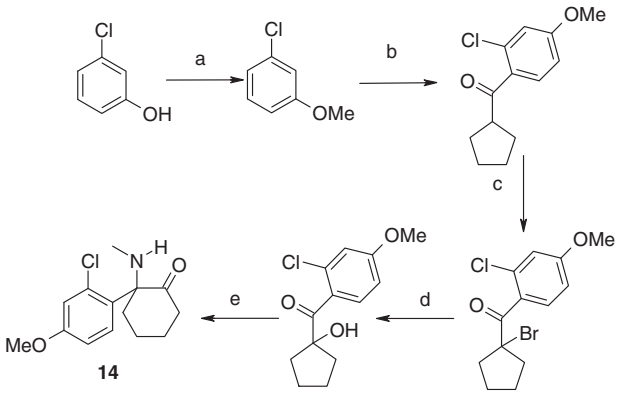
Compd	X	Y	R^3	R^4	GluN1/N2A pIC_{50}	GluN1/N2B pIC_{50}	*c* log *P*
11	N	H	H	H	<4.3(5)	<4.3(5)	1.3
12	N	H	H	Me	<3.6(4)	4.4(2)	1.8
13	N	H	Me	Me	<3.6(4)	<3.6(4)	2.4
14	C	OMe	H	Me	4.7(3)	5(4)	3.0

Values are pIC_{50} means from human recombinant GluN1/N2A and GluN1/N2B FLIPR/Ca^{2+} assays. Standard deviations were <0.3 for all tested compounds. Maximal inhibition was 80–100% for all listed compounds. The number of independent experiments is indicated in parenthesis.

Compounds **11–13** were prepared as depicted in Scheme 3. The methyl ester of commercially available amino(2-chlorophenyl)acetic acid was easily obtained. Protection of the amino functionality was carried out through imine formation.[38] Alkylation was performed by the use of acrylonitrile with potassium *tert*-butoxide as base.[39] When alkylation was attempted on the



Scheme 3. Reagents and conditions: (a) $SOCl_2$, MeOH, rt, overnight; (b) NaOMe, PhCHO, MeOH, rt, overnight; (c) CH_2CHCN, KBu^tO, Bu^tOH, rt, overnight; (d) HCl 6 M, Et_2O, rt, 4 h; (e) $CoCl_2$, $NaBH_4$, MeOH, 100 °C, MW, 20 min for two cycles; (f) $NaHCO_3$, CbzCl, THF, rt, overnight; (g) MeI, NaH, DMF, 0 °C→rt, overnight; (h) TFA, 50 °C, overnight, HPLC purification.



Scheme 4. Reagents and conditions: (a) K_2CO_3, MeI, DMF, rt, overnight; (b) cyclopentanecarbonyl chloride, $AlCl_3$, *n*-hexane, 40 °C, 5 h; (c) Br_2, 1,4-dioxane, rt, 2 h; (d) KOH, MeOH, rt, 2 h; (e) $MeNH_2$, MW, 165 °C, 30 min.

benzyloxycarbonyl or *tert*-butyloxycarbonyl amino protected analogues using either acrylonitrile or allylbromide, the reaction did not work and the targeted quaternary protected α-amino esters were not obtained. The α-alkylated imino ester was then deprotected. The formation of the six-membered ring in compound **11** was achieved by the use of dichlorocobalt and sodium borohydride.[40] In order to obtain mono-methylation of the primary amino group, it was first necessary to protect it using benzyloxycarbonylchloride.

Methylation using methyl iodide and sodium hydride gave a mixture of compounds: one compound methylated only at the Cbz-protected N-atom, and a bis-methylated one, which were separated through HPLC purification to afford compounds **12** and **13** after removal of the protecting group.

The biological evaluation of compounds **11–13** showed that a piperidinone in place of the cyclohexanone was not tolerated since, in all cases, a substantial drop of functional activity at both GluN1/N2A and GluN1/N2B targets was observed when compared to ketamine.

Finally, while maintaining the cyclohexanone moiety of ketamine, the introduction of a methoxy substituent on the aromatic ring was evaluated.

To this purpose compound **14**, bearing a methoxy group at the aromatic ring, was then prepared following the synthetic route depicted in Scheme 4.

Commercially available 3-chlorophenol was methylated. Then, the formation of the ketone was achieved through a Friedel–Crafts acylation, at 40 °C using aluminium chloride as Lewis acid.[41] After bromination, the α-bromoketone intermediate was transformed into the α-hydroxyketone.[42] Treatment of a suitable α-hydroxyketone with an amine has long been known to induce the 1,2-shift of an alkyl or aryl substituent to form an isomeric product of the imino intermediate.[43]

Rearrangement using methylamine led indeed to the formation of the desired methyl amino cyclohexanone derivative **14**. The presence of the methoxy group in **14** was tolerated, showing appreciable activity, in particular in the GluN1/N2B assay (Table 4) when compared with ketamine.

In summary, the identification of structurally novel analogues of ketamine and PCP with low to moderate potency at GluN2A and GluN2B receptors was described. In particular, some examples, such as compounds **6** and **10**, showed decreased calculated lipophilicity, when compared to PCP, while retaining moderate activity. Selected compounds from this series deserve to be explored for their pharmacokinetic properties and selectivity, prior to further SAR expansion and refinement.

Moreover, the geminal aryl amino substituted lactam ring, as exemplified in compounds **7–10** and **11–13**, constitutes a novel scaffold with potential application in the design of biologically active compounds.

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