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Synthesis of Ketamine Derivatives by Mannich Reactions

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Abstract: Arylcyclohexylamine Ketamine (HCL) has played an important role in Veterinary and Human Medicine as safe and reliable anesthetic agent but asit produces dysphoria several new derivatives of Ketamine have been synthesized till date. In this Research we have Utilized Mannich reaction to Synthesize The ammonia, primary amine and secondary amine are treated with hydrochloric acid and then added to the formaldehyde. Three novel derivatives were synthesized namely2-(2-chlorophenyl)-6-[(diethyl amino) methyl]-2-(methylamino) cyclohexanone by RXN:102 Mannich Reaction of Ketamine with Di-ethylamine , rxn 113 2-(2chlorophenyl-6-dinitrophenyl hydrazine-methyl2(methylamino) cyclohexanone by Reaction of Ketamine with Di-nitro Phenyl Hydrazine & Rxn: 601. Mannich Reaction of Ketamine with Piperazine to form (2-chlorophenyl)-2-(methylamino)-6-(piperazine -1-yl) methyl cyclohexanone. Other reactions were also undergone to prepare oxazolidine derivatives of ketamine namely Synthesis of ketamine dioxolane derivative:Ketal and Hemiaminal Formation , Rxn: 103 Reaction of Ketamine with Glycerin [6-(2-chlorophenyl)-6-(methylamino)-1, 4-dioxaspiro [4.5] dec-2-yl] methanol and Rxn: 801 Reaction of Ketamine with Ephedrine N ,3,4-trimethyl-2,6 diphenyl-1oxa-4azaspiro [4.5] decan-6-amine derivative was formed. Thin layer chromatography of the synthesized derivatives was performed by using a solvent system of ethyl acetate and chloroform (50:50) and the RF values were calculated. The solubility test proves that compounds obtained from ketamine are polar in nature. All derivatives show similarity in solubility of ketamine. Although the melting points were not exactly comparable to that of ketamine, the range was not more than 5-10°C. This relatively narrow range of melting points proved that these were pure compounds. NMR spectroscopy was performed on all newly synthesized derivatives of ketamine. The notable ones obtained from reactions i.e. Rxn 102, 113, 103, 601and 801. The results of spectroscopy demonstrate that the compounds obtained were completely new species however they were structurally related to ketamine. These derivatives synthesized and confirmed by NMR technology. The derivatives can potentially be formulated for therapeutical purpose. Despite some limitations which are being considered in current drug design, the derivatives have the potential to develop into chemically modified entities that can play a major role in clinical therapeutics. Additional research studies will potentially help to determine the advanced method for high and sophisticated yield of these derivatives. Moreover, synthesis of ketamine metabolites namely N-demethyl compound and N-demethyl-5,6-dehydro analogues is established. However, further studies and modifications of these compounds will open new ventures of drug design and development of clinical implications in health care system.

Keywords: Ketamine, Arylcyclohexamine, Mannich Reaction, Ketal, Hemiaminal, NMR

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1. INTRODUCTION

Ketamine was synthesized in 1962 as PCP derivative Parke-Davis scientist Calvin Stevens. Human Trials began in 1964. Chemically related to phencyclidine (PCP), Ketamine (HCl) is arylcyclohexylamine. It provides dissociative anesthesia with a short time of recovery. In Hypotensive Patients it is a desirable anesthetic agent. As it does not provide muscle relaxation therefore can be given with muscle relaxants. Its Efficacy is offset because it causes dysphoria frequently. It was approved by the FDA in 1972. It is agonist of opiate-receptors and muscarinic acetylcholine-receptors at CNS, Exact MOA is unknown. Synthetically it belongs to Phenyl Cyclohexane (Figure 1). On the basis of mechanism of action, it belongs to N-methyl d-aspartate antagonist. The Ketamine's molecular formula is C13H16ClNO, Molecular mass 237.725 g/mol, CAS ID 6740-88-1, ChemSpider ID 3689, ChEMBL ID 742 and IUPHAR ID 4233. So, we aimed this study is to synthesize new derivatives of ketamine, that should be therapeutically active, safe and efficacious in clinical practice.

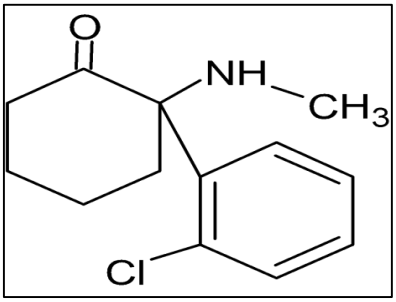


Fig 1. Ketamine is 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone (hydrochloride): It is marketed as Racemic Mixture as it has a chiral center:

It is an organic reaction in which acidic proton placed next to a carbonyl functional group is amino alkylated by a primary or secondary amine or ammonia in the presence of formaldehyde. Mannich Base is the final product of a b-amino carbonyl compound. The chemist Carl Mannich had synthesized mannich bases so the reaction is named after him. (Figure 2)

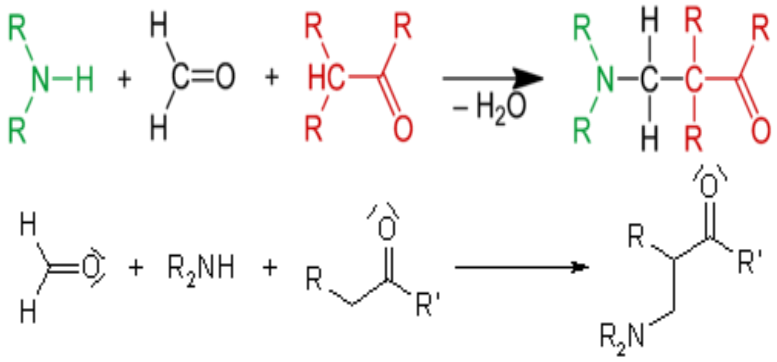


Fig 2. General Scheme of Mannich Reaction

Mannich reaction is a two-step nucleophilic addition reaction. Formation of Schiff base: by the nucleophilic addition of amine to a carbonyl group and then dehydration. During condensation the electrophilic addition of Schiff base with a compound containing acidic proton. Formaldehyde is activated by the presence of amines and enamine is formed. The end product is amino methylated compounds due to the condensation of non-enolizable aldehyde, enolizable carbonyl compound and primary or secondary amine. (Figure 3) In many biosynthetic pathways especially alkaloids Mannich reaction is utilized. It is also used in organic synthesis of natural products example: nucleotides, antibiotics, peptides, plant growth regulators and in polymer chemistry. Examples of Drugs synthesized by Mannich Reaction are mentioned in Figure 4. Rolitetracycline, fluxotiene, tramadol, and tolmetin are medicinal compounds which are synthesized by mannich reaction[2]. Ketal is the functional group which is connected to two R groups with single bonds and with two OR groups given in Figure 5. Ketalization is a reaction which involves the nucleophilic addition of an alcohol to ketone. It is reversible reaction. Figure 6 Figure 6. Nucleophilic attack of a second alcohol molecule to Hemiacetal (or hemiketal) synthesis the Acetal (or Ketal). While the formation of a hemiacetal from an aldehyde and an alcohol (step 1 above) is a nucleophilic addition, the formation of an acetal from a hemiacetal (step 2 above) is a nucleophilic substitution reaction, with the original carbonyl oxygen leaving as a water molecule. Guanadrel is a hypertensive drug which is formed as a result of ketalization. Guanadrel is synthesized by ketalization of cyclohexanone and propanediol. Which is further reacted with phthalimide and S-methylthiourea 3 mentioned in Figure 8. A Heminal is a functional group which is connected to two R groups with single bonds and with a hydroxyl group and amine. It is formed by the reaction of ketone with amine those formed from primary amines are usually unstable. Carbinolamines are readily formed when formaldehyde is reacted with secondary amines.[4] The synthesis of Saxitoxin involves Hemiaminal formation.[5] (Figure 9) Examples of drugs formed as Hemiaminal is the biochemical compounds i.e. glycosylamines or cyclic hemiaminal.

2. MATERIALS & METHODS

The research study was conducted in department of Medicinal Chemistry, Riphah Institute of Pharmaceutical Sciences, Riphah International University, G-7 Islamabad, Pakistan. The ammonia, primary amine and secondary amine are treated with hydrochloric acid and then added to the formaldehyde. Figure 10 Then add the ketonic compound the product will be formed is recrystallized through chloroform or ethanol.[6]

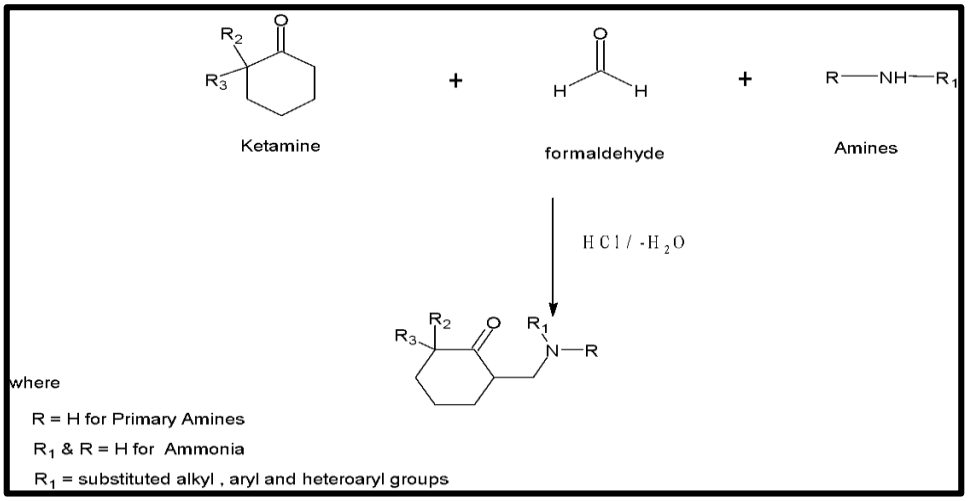


Fig 3: Scheme 1: synthesis of ketamine derivatives

Mannich Reaction of Ketamine conducted by using the Rxn: 102, Rxn: 113, Rxn:601. 1mmol of di-ethylamine HCl (0.73gm) for Rxn:102 (Figure 2) or 1mmole of Di-nitro phenyl hydrazine for Rxn 113 (Figure 3), formaldehyde(0.2ml) and Ketamine (0.274gm) was placed in round bottom flask attached in a reflux condenser, 4ml of 95% ethanol was introduced to which 0.5ml conc HCL was added , and the reaction mixture was refluxed for 2hrs on hot water bath, until the reaction mixture was homogenous, the yellowish solution was filtered through hot water funnel , the filtrate was transferred to 500ml wide mouth conical flask and 500ml acetone was added. For Mannich Reaction of Ketamine with Piperazine Rxn: 601 1mmol of Piperazine (0.86) was added with Methanol and Formaldehyde, Ketamine was added and the reaction mixture was refluxed for 3-4 hrs and then was cooled the final product was filtered given in Figure 3. Synthesis of 2-(2-chlorophenyl)-6-[(diethyl amino) methyl]-2-(methylamino) cyclohexanone mentioned in Figure 11. Synthesis of 2-(2chlorophenyl-6-dinitrophenyl hydrazine-methyl2(methylamino) cyclohexanone elaborated in Figure 4. Whereas, the synthesis of (2-chlorophenyl)-2-(methylamino)-6-(piperazine -1-yl) methyl cyclohexanone given in Figure 5.

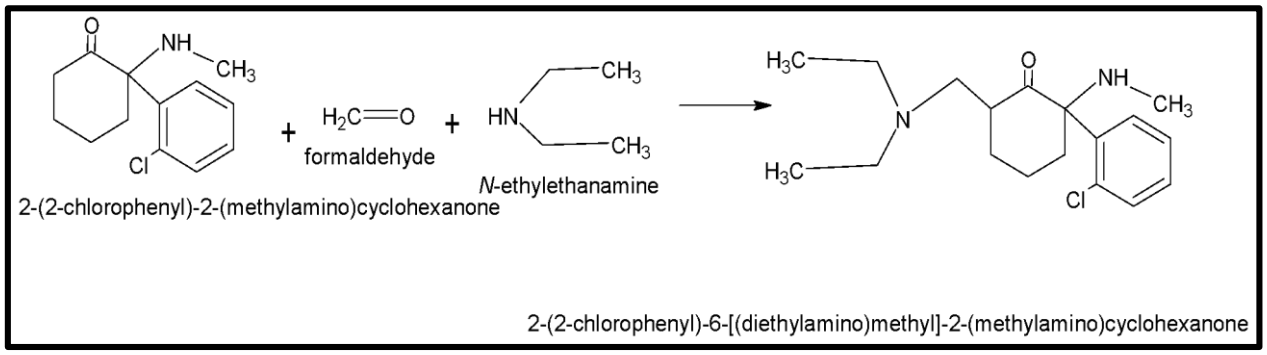


Fig 4. Mannich reaction of Ketamine with diethylamine.

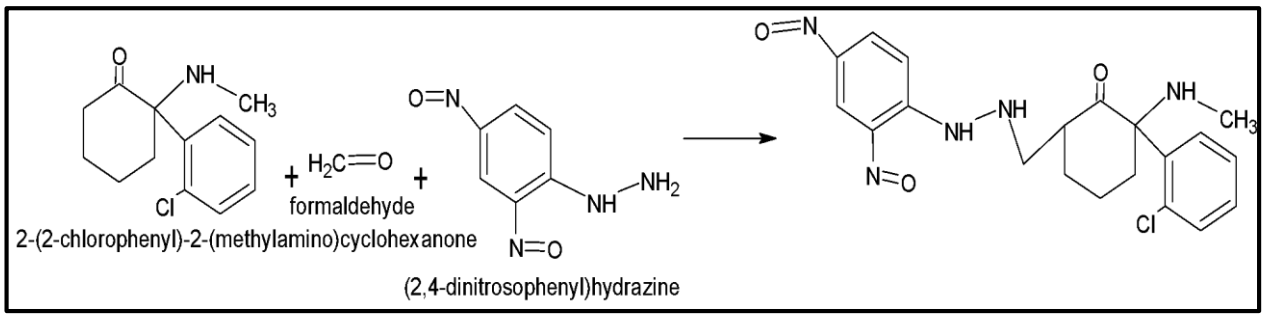
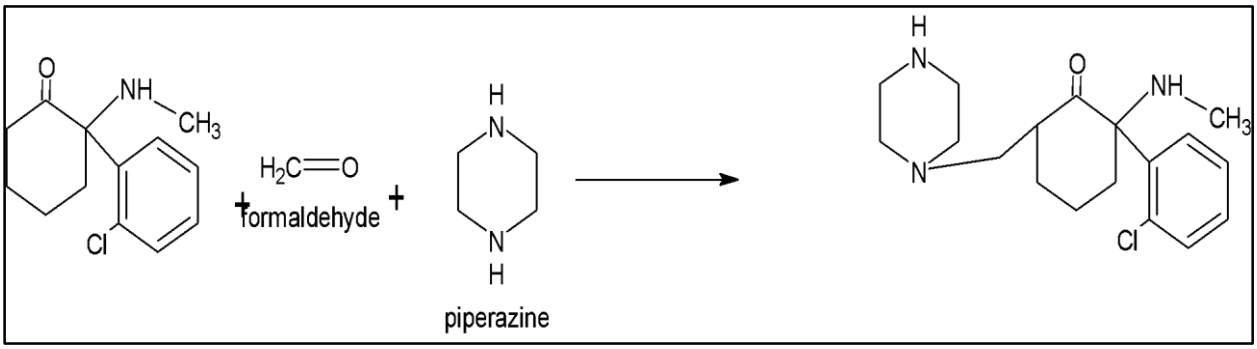


Fig 5. Mannich Reaction of Ketamine with Di-nitroPhenylhydrazine



2-(2-chlorophenyl)-2-(methylamino)cyclohexanone
2-(2-chlorophenyl)-2-(methylamino)-
6-(piperazin-^{1}-ylmethyl) cyclohexanone

Fig 6. Mannich Reaction of Ketamine with Piperazine.

Synthesis of ketamine dioxolane derivative:Ketal and Hemiaminal FormationThe ketamine was treated with glycerin to synthesize the derivatives of 1, 3-dioxolane. The product 1, 3-dioxolane will be recrystallized through chloroform or ethanol given in Figure 4. Synthesis of [6-(2-chlorophenyl)-6-(methylamino)-1, 4-dioxaspiro [4.5] dec-2-yl] methanol (Rxn: 103) 1mmol of Ketamine was placed in round bottom flask with (0.092gm) of Glycerine, few drops of concentrated HCl were added while methanol was taken as solvent mixture, The Reaction mixture was mixed for few hours and allowed to stay and cool for 12-24hrs. White Crystalline product was formed mentioned in Figure 5.

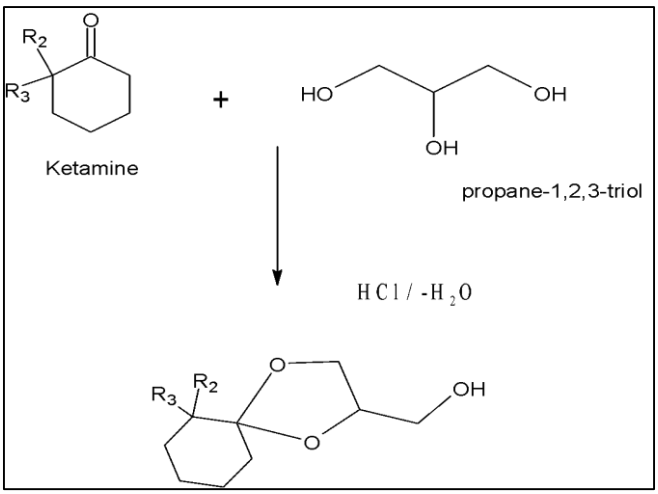


Fig 7. Synthesis of derivatives of 1,3-dioxolan.

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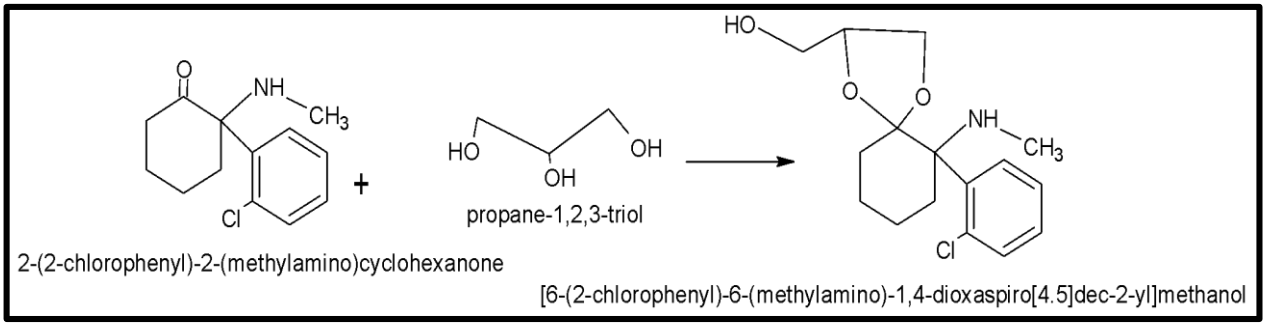
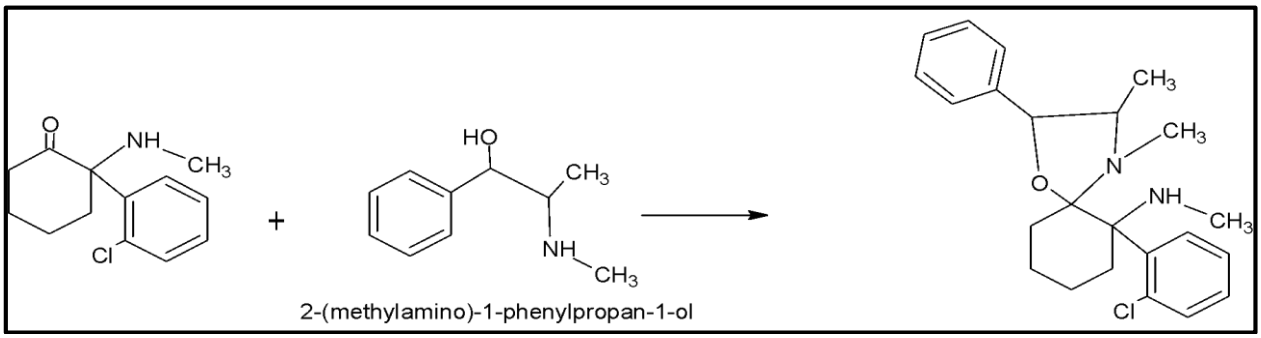


Fig 8. Dioxolan derivative of Ketamine with Glycerine



N,3,4-trimethyl-2,6-diphenyl-1-oxa-4-azaspiro[4.5]decan-6-amine

Fig 9. Reaction of Ketamine with Ephedrine.

Synthesis of N ,3,4-trimethyl-2,6 diphenyl-1oxa-4azaspiro [4.5] decan-6-amine (Rxn: 801) 1mmol of Ephedrine was taken in a Round bottom flask with methanol and formaldehyde. Ketamine 1mmol was added and refluxed for 3-4 hrs. The reaction mixture was allowed to stay and cool for 12-24hrs Crystalline product was filtered out illustrated in Figure 7.

3. RESULTS

Derivatives of ketamine were yielded through a series of chemical reactions known as Mannich reactions. Other reactions were also undergone to prepare oxazolidine derivatives of ketamine. The derivatives of ketamine were tested for their chemical Characterizations. From the data obtained for melting points of the derived compounds, it can be interpreted that some derivatives of ketamine show similarity in melting points. Although the melting points were not exactly comparable to that of ketamine, the range was not more than 5-10°C. This relatively narrow range of melting points proved that these were pure compounds given in Table 1.

Table 1. Melting Point Test for derivatives of ketamine

Ligand	Melting Point Range (C^0)
Ketamine	254 C°
Rx-102	Decompose
Rx-113	Decompose
Rx-106	Decompose
Rx-601	225-250
Rx-801	230-240

Additionally, not all compounds were found to have melting points. For instance, some of the derived products from Rxn 102, 113, 106 decomposed at nonspecific temperature.

Table 2. Thin layer Chromatography

Compound	Rf Values
Ketamine	0.99
Rx-102	0.88
Rx-113	1.3
Rx-103	0.77
Rx-601	0.85
Rx-801	0.54

To determine Rf values, ethyl acetate and chloroform were used. Although, Rf values of compounds obtained were quite variable, however they were found to give a single spot on TLC plates. Therefore, indicating that all compounds formed were pure. As a comparison to the Rf value of ketamine which was 1.0cm, all compounds showed different values of Rf. For example, Rxn 102 and 103 along with the series 601and 801 illustrate lower values of Rf. (Table 2) The solubility test proves that compounds obtained from ketamine are polar in nature. All derivatives show similarity in solubility of ketamine. As demonstrated by the ability of being freely soluble in polar solvents as ethanol, methanol and water. They are partially soluble in chloroform. Furthermore, it is also justified from the results that all compounds are generally insoluble in non-polar solvents such as acetone, hexane and toluene used in the test. (Table 2) NMR spectroscopy was performed on all newly synthesized derivatives of ketamine. The notable ones obtained from reactions i.e. Rxn 102, 113, 103, 601 and 801. The results of spectroscopy demonstrate that the compounds obtained were completely new species however they were structurally related to ketamine.

Rxn: 102

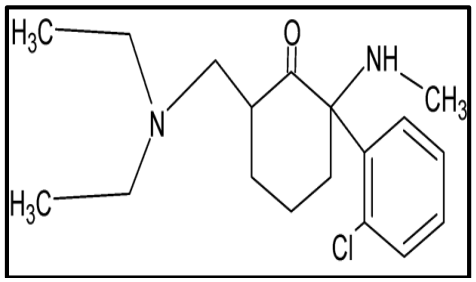


Figure 11. 2-(2-chlorophenyl)-6- [(diethyl amino) methyl]-2-(methylamino) cyclohexanone

Table 3. C13- NMR Spectra of Rx-102

Ligand	C13- NMR Spectra	
	Rx-102	GAM-1 (Ketamine)
C-1	209.11	208.36
C-2	70.1	73.68
C-3	39.48	37.52
C-4	21.79	22.82
C-5	28.03	28.05
C-6	38.58	37.52
C-1'	137.8	135.9
C-2'	133.69	133.93
C-3'	131.17	133.35
C-4'	128.66	133.32
C-5'	126.62	127.8
C-6'	129.38	129.26
N-CH3	29.08	31.05
R1 CH2	11.29	
R2 N(C2H5)	42.23	

The NMR spectra indicate structural relations of ketamine to the derivative obtained from Rxn 102. Results show that the obtained compound is altogether a new entity with basic structure related to ketamine, the parent drug. The difference is shown by a spectrum at 11.29 which is the R1 CH2 group, absent in ketamine itself. (Table No.3,4)

Table 4. Proton NMR Spectra of Ligand (GAM-1) and Rx102

Ligand	Proton(ppm,J)	Proton(ppm,J)
	RX-102	GAM-1 (Ketamine)
C-1	----------	----------
C-2	----------	----------
C-3	2.56td,3.4dm(13HZ)	2.28td (14.2,3.8HZ),3.52dm (14.2Hz)
C-4	1.52m,1.80m	1.58m , 1.86m
C-5	1.82m,1.97m	1.85m , 2.06m
C-6	2.60td(10.6Hz),2.64dm(10.0Hz)	2.59td (12.8 , 6.0 Hz) ,2.69dm (12.8 Hz)
C-1'	----------	----------
C-2'	----------	----------
C-3'	7.45m	7.49m
C-4'	7.38m	7.47m
C-5'	7.52ddd	7.56ddd (8.3,6.5,2.0 Hz)
C-6'	8.0d	8.02d (8.3Hz)
N-CH3	2.02singlet	2.53 singlet
R1 CH2	1.59d	
R2 N(C2H5)	2.44m,3.03m	
CH2-CH3	1.42t	

Rxn: 113

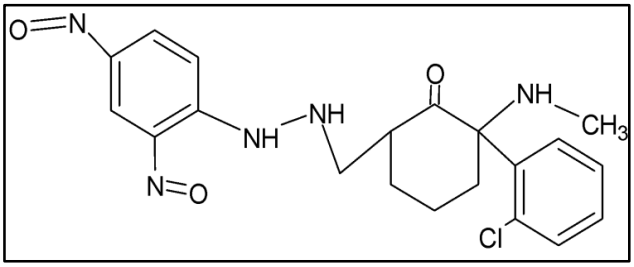


Fig 2. Ketamine reaction with Di-nitro Phenyl Hydrazine.

The compound derived from ketamine by rxn 113 was quite different from the parent molecule. The NMR spectra show significant alkyl chains of R4, R6, R7 and R8 at 175.9, 136.21, 116.37 and 123.57 respectively. These chains are originally not present in ketamine. (Table 5,6) Moreover, R5 NH at 21.15 also interpreted in NMR data is of significance. Another nitrogen group, NH-NH is seen at 25.5. The two nitrogen groups substituted in the newly synthesized compound of which ketamine itself is devoid of, proves the derived substance is a new entity altogether.

Table 5: C13- NMR Spectra of Rx-113

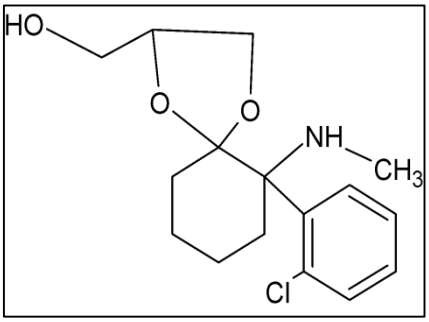
Ligand	C13- NMR Spectra	
	Rx-113	GAM-1(Ketamine)
C-1	209.13	208.36
C-2	70.6	73.68
C-3	39.72	37.52
C-4	21.87	22.82
C-5	28.58	28.05
C-6	38.56	37.52
C-1'	134.05	135.9
C-2'	131.36	133.93
C-3'	130	133.35
C-4'	129.82	133.32
C-5'	126.96	127.8
C-6'	129.25	129.26
N-CH3	28.83	31.05
R4	175.9	
R5 NH	21.15	
R6	136.21	
R7	116.37	
R8	123.57	
NH-NH	25.5	

However, this derivative is comparable to the parent compound as demonstrated by remaining data. Therefore, it is structurally related but with significant modifications in the structure.

Table 6: Proton- NMR Spectra of Rx-113

Ligand	Proton(ppm,J)	Proton(ppm,J)
	RX-113	GAM-1 (Ketamine)
C-3	1.73td, 1.78dm	2.28td (14.2,3.8HZ),3.52dm (14.2Hz)
C-4	1.80m, 2.06m	1.58m , 1.86m
C-5	2.43td , 2.40dm	1.85m , 2.06m
C-6	2.86td, 2.01dm	2.59td (12.8 , 6.0 Hz) ,2.69dm (12.8 Hz)
C-3'	7.27m	7.49m
C-4'	7.35m	7.47m
C-5'	7.37 ddd	7.56ddd (8.3,6.5,2.0 Hz)
C-6'	8.2d	8.02d (8.3Hz)
N-CH3	2.5singlet	2.53 singlet
R-NH-CH2	2.83q	
NH-NH-R	2.15d,	
R-NH	9.10 singlet 11.0singlet	

Rxn: 103



Rxn 103 yielded a new compound, which is structurally quite easily compared with ketamine as derived by NMR spectrum for all carbons. The difference in structure of this newly synthesized compound was the addition of a glycerol group in the molecule as indicated by peak at 64.18. (Table No.7,8)

Fig 3. [6-(2-chlorophenyl)-6-(methylamino)-[1], 4-dioxaspiro [4.5] dec-2-yl] methanol

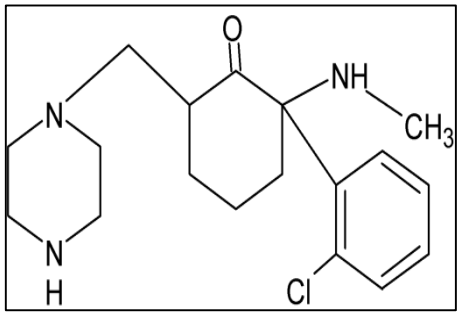
Table 7. C13- NMR Spectra of Rx-103

Ligand	C13- NMR Spectra	
	Rx-103	GAM-1(Ketamine)
C-1	205.29	208.36
C-2	72.71	73.68
C-3	40.24	37.52
C-4	21.69	22.82
C-5	28.5	28.05
C-6	38.52	37.52
C-1'	135.32	135.9
C-2'	132.04	133.93
C-3'	131.94	133.35
C-4'	131.8	133.32
C-5'	128.6	127.8
C-6'	128.72	129.26
N-CH3	29.47	31.05
R3 (glycerol)	64.18	

Table 8. Proton- NMR Spectra of Rx-103

Ligand	Proton(ppm,J)	Proton(ppm,J)
	RX-103	GAM-1 (Ketamine)
C-3	2.44 td	2.28td (14.2,3.8HZ),3.52dm (14.2Hz)
C-4	1.53m	1.58m , 1.86m
C-5	1.97m	1.85m , 2.06m
C-6	2.65dm , 3.45m	2.59td (12.8 , 6.0 Hz) ,2.69dm (12.8 Hz)
C-3'	7.3m	7.49m
C-4'	7.43m	7.47m
C-5'	7.48ddd	7.56ddd (8.3,6.5,2.0 Hz)
C-6'	7.9d	8.02d (8.3Hz)
N-CH3	2.4singlet	2.53 singlet
-OCH2-CH2	3.4 t	
CH2-CH2OH	3.3q , 9.53m	
CH2OH-CH2	2.52t10.49	

Rxn: 601



2-(2-chlorophenyl)-2-(methylamino) cyclohexanone
2-(2-chlorophenyl)-2-(methylamino)-
6-(piperazin-[1]-ylmethyl) cyclohexanone

Fig 4. The compound derived from ketamine by rxn 601.

The compound derived from ketamine by rxn 601 was quite different from the parent molecule. The NMR spectra show significant alkyl chains of RCH2Nand CH2CH2N at 19.32and 43.79 respectively. These chains are originally not present in ketamine. (Table No.10,11)

Table 9. C13- NMR Spectra of Rx-601

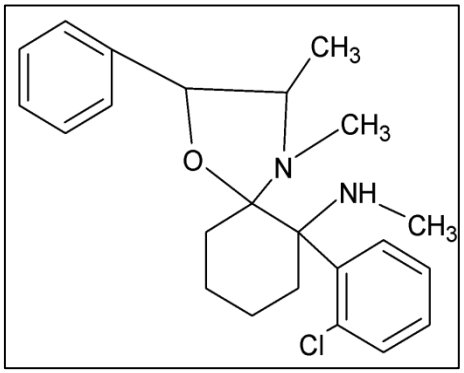
Ligand	C13- NMR Spectra	
	Rx-601	GAM-1(Ketamine)
C-1	208.45	208.36
C-2	73.60	73.68
C-3	37.49	37.52
C-4	22.79	22.82
C-5	28.00	28.05
C-6	40.74	37.52
C-1'	135.86	135.9
C-2'	133.80	133.93
C-3'	133.34	133.35
C-4'	133.11	133.32
C-5'	129.56	127.8
C-6'	129.69	129.26
N-CH3	30.97	31.05
R-CH2-N	19.32	
CH2-CH2-N	43.79	

Table 10. Proton- NMR Spectra of Rx-601

Ligand	Proton(ppm,J)	Proton(ppm,J)
	RX-601	GAM-1 (Ketamine)
C-1	----------	----------
C-2	----------	----------
C-3	1.73td, 1.78dm	2.28td (14.2,3.8HZ),3.52dm (14.2Hz)
C-4	1.80m, 2.06m	1.58m , 1.86m
C-5	2.43td , 2.40dm	1.85m , 2.06m
C-6	2.86td, 2.01dm	2.59td (12.8 , 6.0 Hz) ,2.69dm (12.8 Hz)
C-1'	----------	----------
C-2'	----------	----------
C-3'	7.59m	7.49m
C-4'	7.5m	7.47m
C-5'	7.6ddd	7.56ddd (8.3,6.5,2.0 Hz)
C-6'	7.9d	8.02d (8.3Hz)
N-CH3	2.52 singlet	2.53 singlet
R-CH2*-N	2.36 singlet	
C-a	2.53t	
C-b	2.55t	

However, this derivative is comparable to the parent compound as demonstrated by remaining data. Therefore, it is structurally related but with significant modifications in the structure.

Rxn: 801



N ,3,4-trimethyl-2,6 diphenyl-1oxa-4azaspiro [4.5] decan-6-amine

Fig 5. New compounds yielded through Rxn 801.

Rxn 801 yielded a new compound, which is structurally quite easily compared with ketamine as derived by NMR spectrum for all carbons. The difference in structure of this newly synthesized compound was the addition of an ephedrine group in the molecule. Table No.11)

Table 11. C13- NMR Spectra of Rx-801

Ligand	C13- NMR Spectra	
	Rx-801	GAM-1(Ketamine)
C-1	208.372	208.36
C-2	73.64	73.68
C-3	40.74	37.52
C-4	22.79	22.82
C-5	27.99	28.05
C-6	37.46	37.52
C-1'	135.87	135.9
C-2'	133.87	133.93
C-3'	133.34	133.35
C-4'	133.19	133.32
C-5'	126.99	127.8
C-6'	129.34	129.26
N-CH3	31.5	31.05
R-CH-N	61.47	
R-CH-O	71.77	
CH2-CH3	10.01	
N-CH3*	31.02	
C-a	141.37	
C-b	129.73	
C-c	129.55	
C-d	128.97	

4. DISCUSSION

Ketamine metabolites have antidepressant efficacy in preclinical studies and broader clinical relevance than previously been considered. [6-8] The overall, pharmacological target deconvolution of ketamine and its metabolites will provide insight critical to the development of new pharmacotherapies that possess the desirable clinical effects of ketamine, but limit undesirable side effects. Additionally, two optical isomers of S(+) ketamine and R(-) ketamine, 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone ketamine have their particular therapeutical properties. [1] The pharmacological effects of this drug are mediated by N-methyl-d-aspartate (NMDA), opioid, muscarinic and different voltage-gated receptors. Clinically, the anesthetic potency of the S(+)-isomer is approximately three to four times that of the R(-)-isomer, which is attributable to the higher affinity of the S(+)-isomer to the phencyclidine binding sites on the NMDA receptors. Moreover, the combination of ketamine with midazolam can be extremely useful and safe for sedation and pain relief in intensive care patients, especially during sepsis and cardiovascular instability.[9] In the treatment of chronic pain ketamine is effective as a potent analgesic or substitute together with other potent analgesics, whereby it can be added by different methods.[10] There are some important patient side-effects, however, that limit its use, whereby psycho-mimetic side-effects are most common.[11] The Synthesis of carbon-14 labeled ketamine and norketamine, having anesthetic effect and inhibits cerebral NMDA receptors. [12] Norketamine is a major circulating metabolite of ketamin. A nasal spray formulation of esketamine, the S enantiomer of ketamine, is under development for the management of treatment-resistant depression. [13] To assess the pharmacokinetic properties, ketamine and norketamine were prepared separately from commercially available through a five-step sequence with the

quaternary carbon of the cyclohexyl ring. Chiral resolution of ketamine and chiral column separation of norketamine resolved/separated the (S)-enantiomers from (R)-enantiomers.[14] In addition of that convenient method to synthesize ketamine metabolite dehydronorketamine-d, started from commercially production of deuterium labeled bromochlorobenzene. The Key steps include Grignard reaction, regioselective hydroxybromination, Staudinger reduction, and dehydrohalogenation.[15,16] The effects of ketamine and its enantiomers before considering underlying mechanisms including N-Methyl-D-Aspartate receptor antagonism,[17,18] γ -aminobutyric acid-ergic interneuron inhibition, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor activation, brain-derived neurotrophic factor and tropomyosin kinase B signaling ,[19,20,21] mammalian target of rapamycin complex [1] and extracellular signal-regulated kinase signaling, inhibition of glycogen synthase kinase-3 and inhibition of lateral habenula bursting, alongside potential roles of the monoaminergic and opioid receptor systems.[22,23]

5. CONCLUSION

All the derivatives were synthesized and confirmed by NMR technology. The newly formed derivatives can potentially be formulated for therapeutical purpose. Despite some limitations which are being considered in current drug design, this class of drugs and its derivatives has the potential to progress into chemical modifications for newer drugs and that may play a major role in clinical therapeutics. Additional research studies will potentially help to determine the acanced method for the synthesis of these derivatives with high yield and purity. Moreover, synthesis of ketamine metabolites namely N-demethyl compound and N-demethyl-5,6-dehydro analogues is established. However, further studies and modifications of these compounds will open new ventures of drug design and development of clinical implications in health care system.

6. AUTHORS' CONTRIBUTIONS STATEMENT

This work was carried out in collaboration among all authors. Syed Muzzammil Masaud, Ghulam Abbas Miana and Taha Nazir designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Saeed Ur Rasheed and Ishtiaq Rabi managed the analyses of the study. Hassan Imran and Nida Taha managed the literature searches. All authors read and approved the final manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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