

Full Length Research Paper

# Synthesis, characterization and biological activity of new mannich base 1-((4-chlorophenyl)(2,5-dioxopyrrolidin-1-yl) methyl) urea

M. R. Abdullahi<sup>1\*</sup> and S. Rajeswari<sup>2</sup>

<sup>1</sup>Department of Pure and Industrial Chemistry, Bayero University Kano, P. M. B. 3011, Nigeria.

<sup>2</sup>Department of Chemistry, SRM University, Kattankulathur, Tamil Nadu, India.

**A new mannich base 1-((4-chlorophenyl)(2,5-dioxopyrrolidin-1-yl)methyl) urea has been synthesized from the condensation of succinimide, 4-chlorobenzaldehyde and urea. The compound has been characterized on the basis of elemental analysis, FTIR, <sup>1</sup>HNMR <sup>13</sup>C NMR, and Mass spectroscopy. The compound was tested for its antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans* using agar well diffusion method.**

**Key words:** Mannich base, succinimide, antimicrobial.

## INTRODUCTION

Mannich reaction is one of the most fundamental and important C–C bond forming reactions in organic synthesis. It is a three-component condensation between compounds containing an active hydrogen i.e. compound capable of supplying hydrogen atom, with an aldehyde and primary or secondary amine (Tamil et al., 2011). The reaction involves the elimination of water molecule and leads to the formation of compound called Mannich base.

The formation of both C–C and C–N bonds in this amino methylation process makes the Mannich reaction an extremely useful synthetic transformation. Mannich bases have wide application in the area of pharmaceuticals and macromolecular chemistry (Tamil et al., 2011). In Mannich reaction, ammonia or primary or secondary amines are employed for the activation of formaldehyde, tertiary amines lack an N–H proton to form the intermediate imine (Muthumani et al., 2010). The active hydrogen is replaced by amino-methyl group and

form carbon–carbon and carbon–nitrogen bonds. This amino methylation process makes the Mannich reaction an extremely useful synthetic transformation and the Mannich bases are highly reactive because of the basic function which renders the compound soluble in many aqueous solvents (Babu and Pitchai, 2014).

The ligands containing N and O donor atoms possess a number of biological activities such as antibacterial, antifungal, anticancer, anticonvulsant, and anti HIV (Rajeswari et al., 2010a, and Sivakami et al., 2014). Mannich bases have gained importance due to their applications in pharmaceutical chemistry as they are used as local anesthetic, antimalarial, anti-inflammatory, analgesic, antioxidant and antitubercular activities (Sriram et al., 2009).

Mannich bases have also found numerous applications in the treatment of natural macromolecular materials such as leather, paper and textiles, and as additives used by the petroleum industry, water treatment, analytical

\*Corresponding author. Email: [mrabdullahi86@gmail.com](mailto:mrabdullahi86@gmail.com). Tel: +2348039347945.

reagents, cosmetics, dyes, used in the removal heavy metals from effluents. They are also used as powerful pesticides and insecticides apart from other biological applications and these properties are enhanced when ligands form complexes with metals (Tharmaraj et al., 2013).

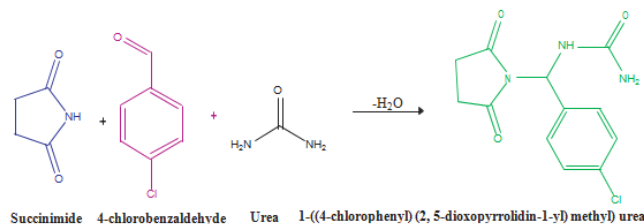
Numerous mannich bases were synthesized, characterized and analyzed for different applications. Mannich base derived from the condensation of succinimide, benzaldehyde and urea together with their metal complexes showed great antimicrobial activities (Rajeswari et al., 2010a). Mannich base 1-(morpholino(phenyl) methyl)pyrrolidine-2,5-dione formed by the direct condensation of morpholine, succinimide, and benzaldehyde has been synthesized and characterized (Rajeswari et al., 2010b). Mannich base 1,3-bis-(morpholin-4-yl-phenyl-methyl)-thiourea derived from the direct condensation of morpholine, benzaldehyde and thiourea have been synthesized and the compound was used to inhibit mild steel corrosion in hydrochloric acid medium to the great extent (DevarajKarthik et al., 2011). The synthesis of novel mannich base and it is metal complexes derived from succinimide 4- methoxy benzaldehyde and thiourea have also been reported and the compounds were screened for anti-microbial activity against *Escherichia coli* and *Bacillus subtilis* bacteria. The compounds were also found to have a significant DNA binding ability (Sivakami et al., 2014). In this Paper, we report the synthesis, characterization and biological activities of new mannich base derived from succinimide, urea and 4-Chloro benzaldehyde.

## MATERIALS AND METHODS

All the reactants and solvents used for the synthesis of this compound were of analytical grade and commercially available and used without further purification. The melting point of compounds was determined in an open capillary tube using SMP40 melting point apparatus. Elemental micro analysis was carried out with a Carlo Erba 1108 Elemental Analyzer. Mass spectrum was recorded on a Shimadzu 2010s Mass Spectrometer. The IR spectra were recorded on Shimadzu FT-IR instrument using KBr pellets.  $^1\text{H}$  NMR spectrum was recorded using DMSO- $d_6$  as a solvent and TMS as internal standard.  $^{13}\text{C}$  NMR spectrum was recorded in DMSO using a Bruker 500 MHz instrument.

### Synthesis of Mannich base 1-((4-chlorophenyl)(2,5-dioxopyrrolidin-1-yl)methyl) urea (SCBU)

Succinimide, 4-chlorobenzaldehyde and urea were taken in 1:1:1 equimolar ratio. Succinimide and urea were taken in a 250 mL beaker. Sufficient amount of ethanol was added to make the contents a homogeneous solution, and then 4-chlorobenzaldehyde was added slowly in drops with continuous stirring of the solution. A white powdery substance was formed immediately. After 2 weeks, the product was washed several times with distilled water and dried in an air oven at 60°C for 1 hour and recrystallized from ethanol by slow evaporation. The scheme for reaction is given below.



## RESULTS AND DISCUSSION

The analytical and spectral data obtained for the ligand are given below.

Analysis: Calculated for C<sub>12</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>: C 51.16, H 4.29, N 14.92% Found: C 50.97, H 4.28, N 14.87%; FT-IR: (KBr, cm<sup>-1</sup>): 3360 (N-H), 3198-3058 (Aromatic C-H), 2964 (Aliphatic CH), 1699 (succinimide C=O), 1658 (urea C=O), 1175 (C-N-C);  $^1\text{H}$  NMR: (DMSO- $d_6$ ,  $\delta$ , ppm): Multiplet 7.32-7.93 (Aromatic protons), 2.69-2.70 (succinimide CH protons), 5.68-6.0 (NH protons), 2.57 (Methine C-H proton), 10.01 (N-H protons);  $^{13}\text{C}$  NMR: (DMSO- $d_6$ , ppm): 29.5 (CH<sub>2</sub> carbon of the succinimide), 40.0 (Methine carbon), 128.2-137.9 (Aromatic carbon), 156.7 and 179.4 (Urea and succinimide carbon); Mass: Calculated for C<sub>12</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub> m/z = 281.69, found 282 (Tables 1 and 2).

### In vitro antimicrobial activity

The *in vitro* antimicrobial activity of the synthesized compound was tested against one gram negative *Pseudomonas aeruginosa* and one gram positive *Staphylococcus aureus* bacterial pathogens and one mycelial fungal pathogen *Aspergillus niger* and one yeast pathogen *Candida albicans*. These selected pathogenic strains were obtained from Microbiological Division (Jayagen Biologics Analytical Laboratory, Chennai).

### In vitro antibacterial activity

The antibacterial activity was determined by well diffusion methods. About 25 mL of molten nutrient agar was poured into a sterile Petri plate. The plates were allowed to solidify, after which 18 h grown (OD adjusted to 0.6) 100  $\mu\text{L}$  of above said pathogenic bacteria cultures were transferred onto plate and made culture lawn by using sterile L-rod spreader. After five min setting of the pathogenic bacteria, a sterile cork borer was used to make 5 mm well on the agar. The test samples were dissolved in 5% DMSO and loaded in to wells with various concentrations such as 50 g/well, 100 g/well, 150 g/well and 200 g/well. The plates were incubated at 37°C in a 40 W florescent light source ( $\sim 400$  nm) for 24 hrs. The antibacterial activity was determined by measuring the diameter of the zone of inhibition around the well.

**Table 1.** Physical characterization of the ligand.

	Melting point (°C)	Percentage yield (%)	Colour
Ligand	157-160°C	83	White

**Table 2.** Solubility test of the ligand.

Solvent	Water	Ethanol	Methanol	Chloroform	Hexane	DMSO	DMF
Ligand	IS	IS	SS	IS	IS	S	S

**Table 3.** Antibacterial activities of the ligand.

Compound	Zone of Inhibition (mm)				Zone of Inhibition (mm)			
	<i>Pseudomonas aeruginosa</i>				<i>Staphylococcus aureus</i>			
	Concentrations (µg/mL)				Concentrations (ig/mL)			
SCBU C <sub>12</sub> H <sub>12</sub> CIN <sub>3</sub> O <sub>3</sub>	50	100	150	200	50	100	150	200
	6	8	9	10	-	7	8	10

Standard bacterial agent used: Chloramphenicol at 30 µg/ml, ZOI=20 mm.

**Table 4.** Antifungal activities of the ligand (SCBU).

Compound	Zone of Inhibition (mm)				Zone of Inhibition (mm)			
	<i>Aspergillus niger</i>				<i>Candida albicans</i>			
	Concentrations (ig/mL)				Concentrations (ig/mL)			
SCBU C <sub>12</sub> H <sub>12</sub> CIN <sub>3</sub> O <sub>3</sub>	50	100	150	200	50	100	150	200
	-	6	7	8	6	7	7	9

using antibiotic zone scale (Holder and Boyce, 1994). The results for the antibacterial activities are given in Table 3.

### ***In vitro* antifungal activity**

The agar plug of mycelia fungal inoculum was placed onto the potato dextrose agar individually. Whereas, yeast pathogen at the inoculum concentration of  $5 \times 10^5$  cfu was swabbed using sterile cotton swabs. The wells were made using sterile cork borer (5 mm). The given sample was loaded as 50 g/well, 100 g/well, 150 g/well and 200 g/well concentration. The plates were incubated at 35°C and observed after 48 and 72 h. The inhibition zones were read at the point of complete inhibition of growth (ZOI). The results for the antifungal activities are given in Table 4. From the results of antibacterial activity, the ligand was found to be active against the tested microbes. The activity of the compound increases with increase in concentrations, but the ligand showed no

activity at lower concentration (50 ig/mL) against *S. aureus*. The overall activities of both the ligand was found to be lower than that of the Chloramphenicol at 30 µg/ml which was used as standard, with inhibition zone of 20 mm.

The results for the antifungal activities reveals that both the ligand shows no activity at lower concentration against *A. niger*, but was found to show some activity against *C. albicans*. The overall activities of both the ligand was also found to be lower than that of the standard, Clotrimazole at 30 µg/ml with inhibition zone of 24 mm.

### **Conclusion**

A new mannich base have been synthesized and characterized by spectral techniques and the compound have been evaluated for its antibacterial and antifungal activities and the compound showed lower activity against the tested microorganisms and also lower activity when compared with selected drugs used for the study.

## CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

## REFERENCES

- Babu K, Pitchai P (2014) An innovative synthesis of new mannich base, its metal complexes and their antibacterial studies, international journal of pharmaceutical, chemical and biological sciences, IJPCBS 4(2):256-261 ISSN: 2249-9504.
- DevarajKarthik D, Tamilvendan G Venkatesa P (2011) Study on the inhibition of mild steel corrosion by 1,3-bis-(morpholin-4-yl-phenyl-methyl)-thiourea in hydrochloric acid medium. Journal of Saudi Chemical Society 18:835-844.
- Sriram D, Banerjee D, Yogeeswari P (2009). "Efavirenz Mannich bases: synthesis, anti-HIV and antitubercular activities," Journal of Enzyme Inhibition and Medicinal Chemistry 24(1):1-5.
- Tamil D, Vendan S, Rajeswari S, Ilavenil K, Chakkaravarthy G, Venkatesa P (2011) Syntheses, spectral, crystallographic, antimicrobial, and antioxidant studies of few Mannich bases. Medicinal Chemistry Research 21(12):4129-4138.
- Holder A, Boyce ST (1994) Agar well diffusion assay testing of bacterial susceptibility to various antimicrobials in concentrations non-toxic for human cells in culture. Burns 20:426-429.
- Sivakami M, Natarajan B, Vijayachandrasakar M, Rajeswari S (2014) Evaluation of DNA Binding and Cytotoxic activity of a new Mannich base and its Metal Complexes. (IJIRSE) International Journal of Innovative Research in Science and Engineering ISSN (Online) 2347-3207
- Muthumani P, Neckmohammed R, Meera S, Venkataraman N, Chidambaranathan P, Devi CA, Suresh K (2010) Synthesis and evaluation of anticonvulsant and antimicrobial activities of some Mannich bases of substituted aminophenol and acetophenone. International Journal of Pharmaceutical and Biomedical Research 1(3):78- 86. ISSN No: 0976-0350
- SaravanaBhava P, Tharmaraj P, Muthuraj V, Umadevi M (2013) Synthesis, characterization and biological activities of transition metal chelates of 2-aminothiazole-derived Mannich bases, IOSR Journal of Engineering (IOSRJEN) ISSN: 2278-8719 Vol. 3, Issue 3 (April. 2013), pp. 18-27.
- Rajeswari S, Tamilvendan DG, Venkatesa P (2010a) 1-[(2,5-dioxopyrrolidin-1-yl)(phenyl)methyl] urea and 1-[(2,5-dioxopyrrolidin-1-yl)(phenyl)methyl] thiourea and its transition metal (II) complexes: Synthesis, structural characterization and antimicrobial study. <https://www.tsijournals.com/articles/125dioxopyrrolidin1ylphenylmethyl-urea-and-125dioxopyrrolidin1ylphenylmethyl-thiourea-and-its-transitionmetal-ii-complexes.pdf>
- Rajeswari S, Venkatesa Prabhu G, Tamilvendan D, Ramkumar V (2010b) Spectroscopic Studies and Crystal Structure of 1-(Morpholino (Phenyl) Methyl) Pyrrolidine 2,5-Dione. Springer J Chem Crystallogr (2010) 40:437-442 DOI 10.1007/s10870-009-9674-1.