SYNTHESIS OF MANNICH BASE DERIVERTIVES AND EXPLORING THEIR BIOLOGICAL ACTIVITIES

Amoateng Isaac Opoku, Yakubu Djakaria, Clement Osei Akoto, PhD.
Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
Faculty of Physical and Computational Sciences
Department of Chemistry
ioamoateng2001@gmail.com, yakubudjakaria@gmail.com, cakoto@hotmail.com

INTRODUCTION

Mannich reaction is:

- a three component one pot reaction
- condensation of an aldehyde(ketone) with a 1^0 or 2^0 amine or ammonia and a non-enolizable aldehyde(ketone) to yield **aminoalkylated derivatives** [1]

NB: They exhibit a variety of biological activities [2]

FIG 1: Carl Ulrich Franz Mannich

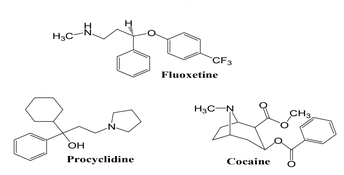


FIG 2: Some known Mannich bases

PROBLEM STATEMENT

The development of **drug resistance** by microorganisms, helminths and the **pharmacokinetic** challenges pose significant barriers to effective treatment.This project serves as a potential solutions to these issues.

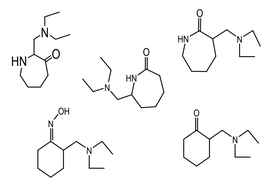


FIG 3: Some synthesized Mannich bases

AIMS AND OBJECTIVES

- Examine the total synthesis of some selected Mannich base derivatives with primary or secondary amines such as methylamine, dimethylamine, and diethylamine with:
  - ❑ Cyclohexanone and formaldehyde.
  - ❑ Azepanone and formaldehyde.
- Evaluating the anti-inflammatory and anthelmintic properties of the various synthesized Mannich bases and their derivatives.

SCHEMATIC REPRESENTATIONS

Oxime Formation and Beckmann rearrangement

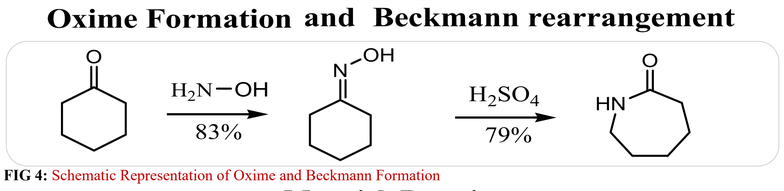


FIG 4: Schematic Representation of Oxime and Beckmann Formation

Mannich Reaction

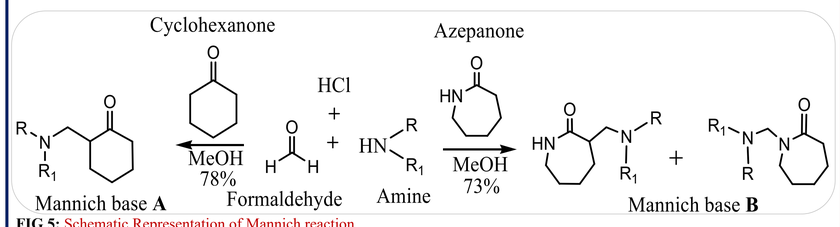


FIG 5: Schematic Representation of Mannich reaction

Oxime Formation and Beckmann Rearrangement

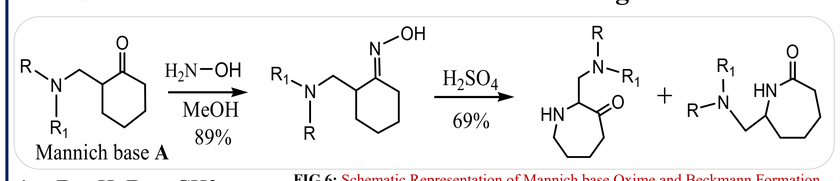


FIG 6: Schematic Representation of Mannich base Oxime and Beckmann Formation

1. **R** = H, $\mathbf{R_1}$ = CH3
2. **R** = CH_3, $\mathbf{R_1}$ = CH3
3. **R** = C_2H_5, $\mathbf{R_1}$ = C2H5

REACTION MECHANISMS

Beckmann Rearrangement [1]

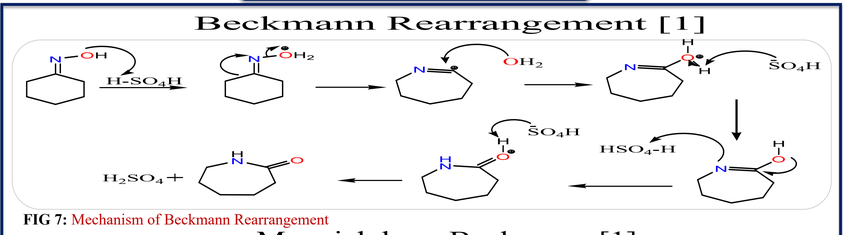


FIG 7: Mechanism of Beckmann Rearrangement

Mannich base Beckmann [1]

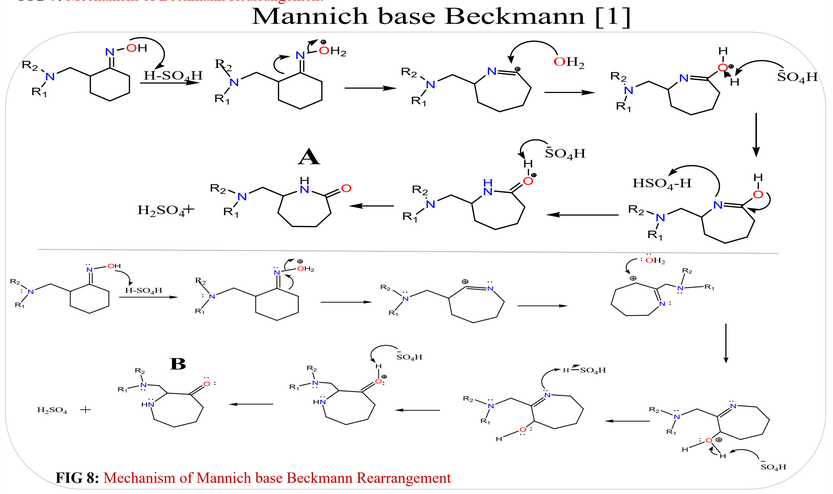
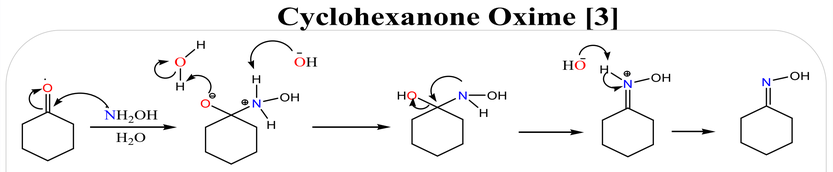


FIG 8: Mechanism of Mannich base Beckmann Rearrangement

Cyclohexanone Oxime [3]



Mannich base Oxime

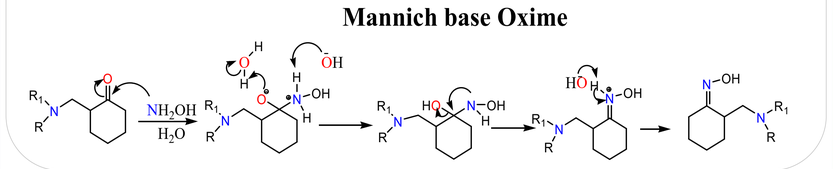
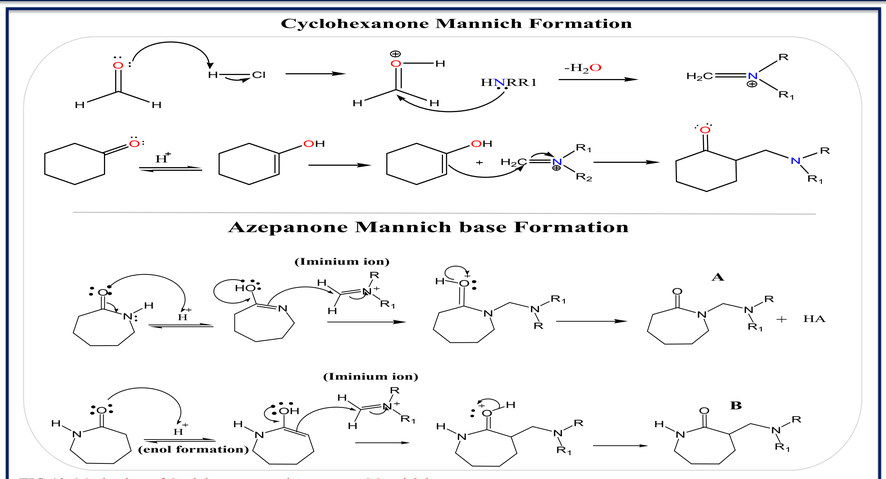


FIG 9: Mechanism of Cyclohexanone and Mannich base Oxime

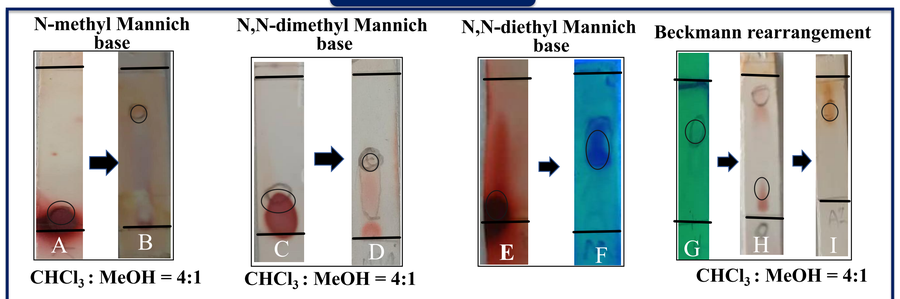
Cyclohexanone Mannich Formation

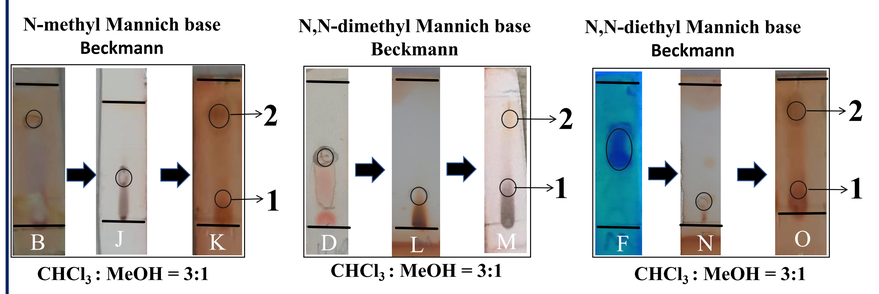


Azepanone Mannich base Formation

FIG 10: Mechanism of Cyclohexanone and Azepanone Mannich base

TLC RESULTS





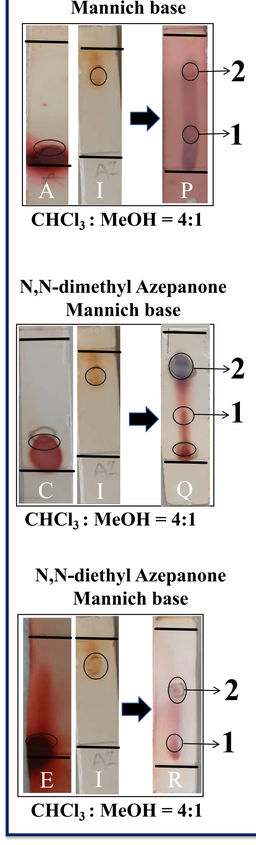


Table 1: TLC Analysis and Retardation Factors (R_f)

COMPOUNDS	RETARDATION FACTORS (R_f)
A (N-methylamine)	**0.15**
B ((2-(N-methylamino)methyl)cyclohexanone)	**0.75**
C (N,N-dimethylamine)	**0.27**
D ((2-(N,N-dimethylamino)methyl)cyclohexanone)	**0.52**
E (N,N-diethylamine)	**0.20**
F ((2-(N,N-diethylamino)methyl)cyclohexanone)	**0.56**
G (Hydroxylamine)	**0.68**
H (Cyclohexanone oxime)	**0.29**
I (Azepan-2-one)	**0.72**
J ((2-(N-methylamino)methyl)cyclohexanone oxime)	**0.43**
K (N-methyl Mannich base Beckmann)	SPOT 1: **0.31** SPOT 2: **0.85**
L ((2-(N,N-dimethylamino)methyl)cyclohexanone oxime)	**0.31**
M (N,N-dimethyl Mannich base Beckmann)	SPOT 1: **0.32** SPOT 2: **0.90**
N ((2-(N,N-diethylamino)methyl)cyclohexanone oxime)	**0.28**
O (N,N-diethyl Mannich base Beckmann)	SPOT 1: **0.21** SPOT 2: **0.83**
P (N-methyl Azepanone Mannich base)	SPOT 1: **0.39** SPOT 2: **0.76**
Q (N,N-dimethyl Azepanone Mannich base)	SPOT 1: **0.47** SPOT 2: **0.80**
R (N,N-diethyl Azepanone Mannich base)	SPOT 1: **0.35** SPOT 2: **0.64**

FT-IR RESULTS

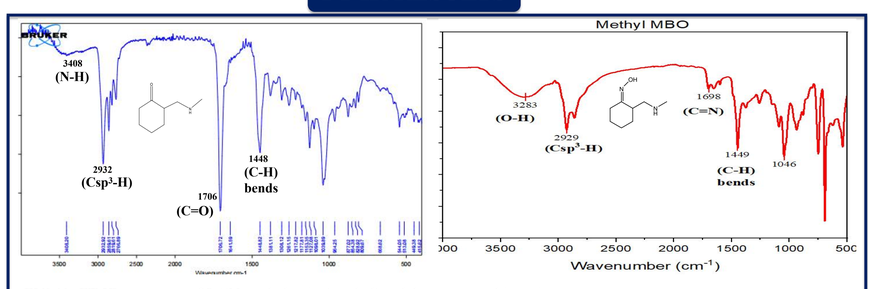


FIG 11: FT-IR spectrum of 2-((N-methylamino)methyl)cyclohexanone and its oxime

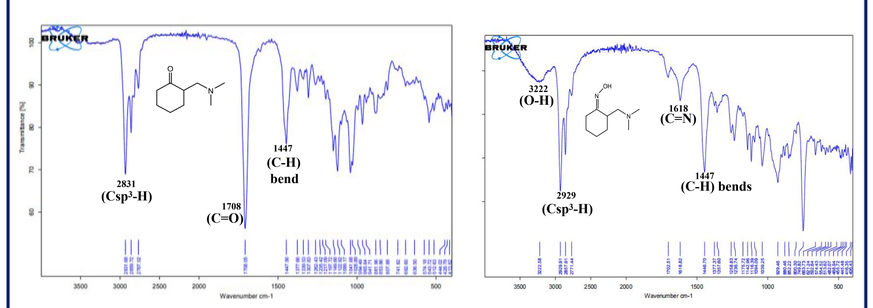


FIG 12: FT-IR spectrum of 2-((N,N-dimethylamino)methyl)cyclohexanone and its oxime

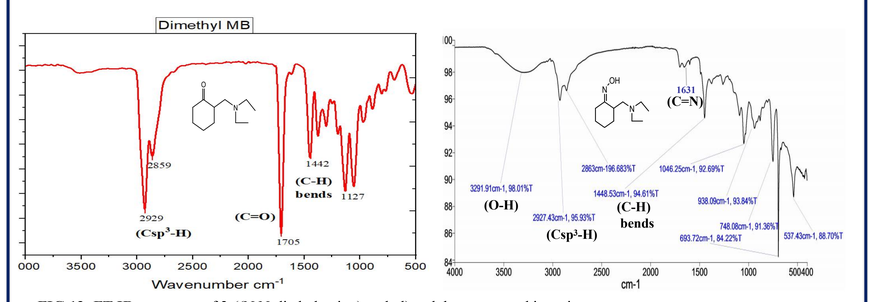


FIG 13: FT-IR spectrum of 2-((N,N-diethylamino)methyl)cyclohexanone and its oxime

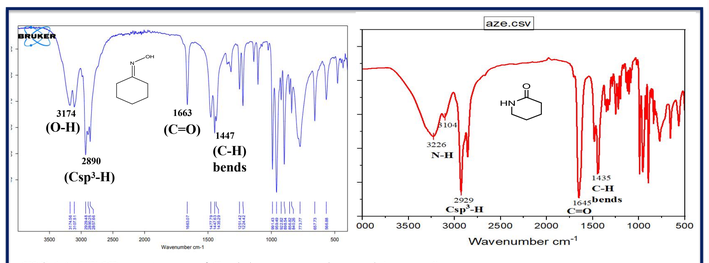


FIG 14: FT-IR spectrums of Cyclohexanone oxime and Azepan-2-one

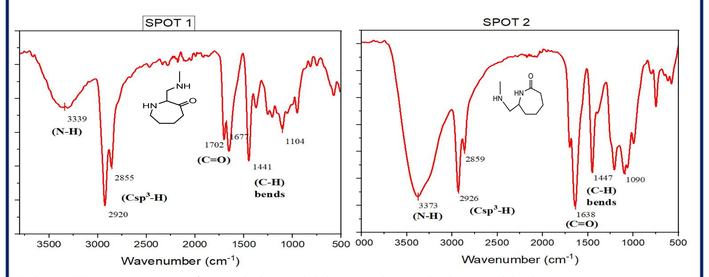


FIG 15: FT-IR spectrums of N-methyl Mannich base Beckmann **SPOT 1** and **SPOT 2**

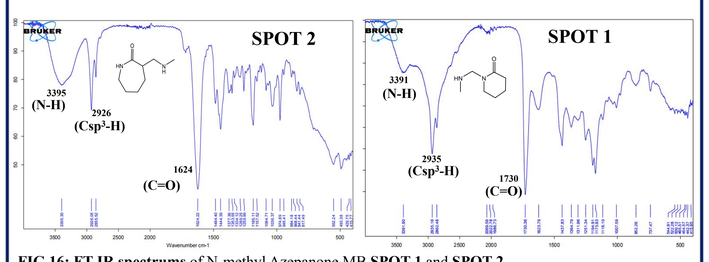


FIG 16: FT-IR spectrums of N-methyl Azepanone MB **SPOT 1** and **SPOT 2**

IN VITRO ANTI-INFLAMMATORY ASSAY

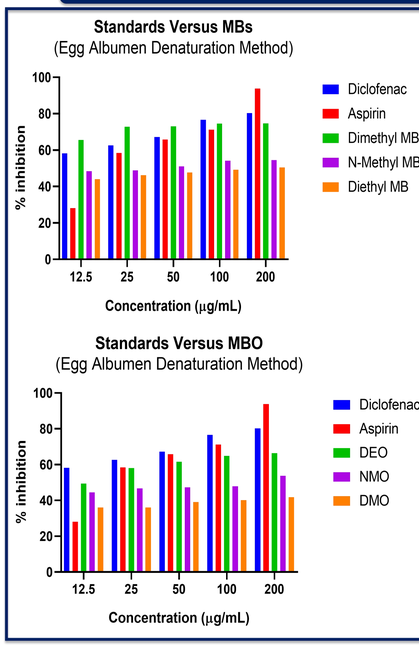


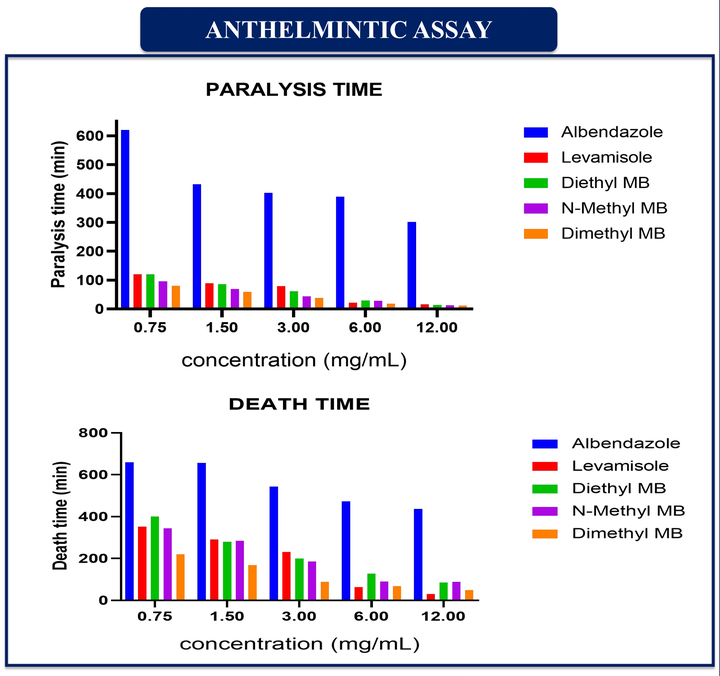
Table 2: Compounds and their IC_{50} values

COMPOUNDS	IC_{50} (µg/mL)
Diclofenac	**21.61 ± 0.10**
Aspirin	**46.38 ± 0.08**
Dimethyl MB	**24.72 ± 0.89**
N-Methyl MB	**38.15 ± 0.54**
Diethyl MB	**57.28 ± 0.65**

Table 3: Compounds and their IC_{50} values

COMPOUNDS	IC_{50} (µg/mL)
Diclofenac	**21.61 ± 0.10**
Aspirin	**46.38 ± 0.08**
Dimethyl MBO	**55.33 ± 0.29**
N-Methyl MBO	**86.85 ± 0.97**
Diethyl MBO	**69.41 ± 0.48**

ANTHELMINTIC ASSAY



FURTHER WORKS

1. Evaluate the anti-inflammatory and anthelmintic assays
2. Further purification of the synthesized product using column chromatography and HP-LC
3. Further characterization of the synthesized products using FT-IR both ^{1}H-NMR and ^{13}C-NMR

CONCLUSION

Series of Mannich base derivatives of Cyclohexanone and Azepanone were synthesized, some showed promising anthelmintic and anti-inflammatory activities, indicating potential as lead compounds for further drug development.

REFERENCES

1. Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. (2018); Chem. Rev. 2011, 111, 3076. (b) Toure, B. B.; Hall, D. G. Chem. Rev. 2009, 109, 4439
2. Kharb, R., Sharma, P.C., & Yar, M.S. (2010); Pharmacological significance of Mannich bases, Der Chemica Sinica, 1(3), 24-28
3. Parker, W. L., & Ttimm, D. L. (1965); Studies on the Reaction of Hydroxylamine with Cyclohexanone. The Journal of Organic Chemistry, 30(5), 1557-1560