International Journal of Engineering Science Invention (IJESI)
ISSN (Online): 2319-6734, ISSN (Print): 2319-6726
www.ijesi.org ||Volume 12 Issue 3 March 2023 || PP 15-20

"Design, synthesis, characterization and biological activity of acetophenone hetrocycle via novel mannich base MCR ."

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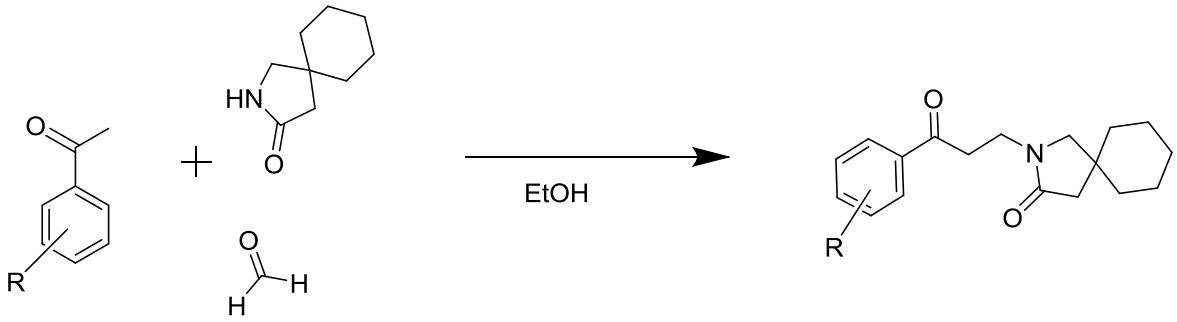
ABSTRACT:
In this work ,Newly Fifteen-Compounds synthesized by Mannich base Multicomponent reaction .The synthesized compounds were characterized by using FT-IR, H^1-NMR , C^{13}-NMR And Mass Spectrometry .The final compounds were evaluated for their Antibacterial activities using Agar-wel Diffusion method. The tested compounds show good to moderate activity with Inhibition zone value between 8 to 22 mm, when compared to reference Ampicilin and Ciprofloxacin. Among them compounds 4c and 4o show most promoting activity against E.coli, B.cereus and B.substilis.

***KEYWORDS**: Acetophenone , Antibacterial activity, gabapentin lacatam,Mannic base ,Multicomponent reactions,.*

Date of Submission: 06-03-2023 Date of Acceptance: 19-03-2023

General Scheme:



R=3CH3,3CF3,3I,3NO2, 3OCH3,4OH,2OCH3,2OH,
2CH3,2CF3,2NO2,3H,3F,2OC2H5,2Br

I. INTRODUCTION :

The derivatives of C- Mannich base play an imperative role in a diverse fields, such as organic synthesis , medicinal chemistry, and agrochemistry.[1] The Gabapentin lactam linked C-C mannich base scaffolds is widespread in a range of effective agrochemicals, and pharmaceuticals. For example, C-C products analog and derivatives have been exhibited to bear a array of pharmacological and biological properties such as Antibacterial,[2] antifungal,[3] Antitubercular, Anticancer,[4] Antiinflammtory, antianalgesic, Anticonvulsant, antidepressant, anti-HIV, and Antidiabetic.[5-7] Gabapentin lactam linked C-C mannich base has become a advantageous structure among the several types of organic compounds since the first isolation from natural indigo dye, . Because of the wide spectrum of functions in materials, pigments, pharmaceuticals, agrochemicals, and fragrances, Mannich product chemistry has fascinated extensive attentions from scientific society in the last few decades.[8]

Multicomponent reactions (MCRs) are single-pot transformations utilizing more than two starting components, Gabapentin lactam are a unique class of Nitrogen and carbonyl containing heterocyclic compounds with vital Medicinal activities. This molecular diversity offers a spacious range of pharmacological properties.[10] In consideration of auspicious properties of Acetophenone scaffolds Gabapentin lactam, and formaldehyde, the design and construction of new functionalized hybrid skeletons, which bearing all these three moieties may emerge as an crucial device in the organic synthesis.

N-containing heterocyclic compounds are attracting increases significance among the synthetic organic in the light of history owing of their abundance in various naturally occur product and the application in chemistry, material and biological science. [11-14]

In this study, we report the three-component Mannich reaction of variety of acetophenones with gabapentin lactam. we aim to synthesis of a number of Mannich bases derived from substituted acetophenones, then these compounds were characterized by FT-IR, 1H NMR spectra and their most probable antimicrobial test.

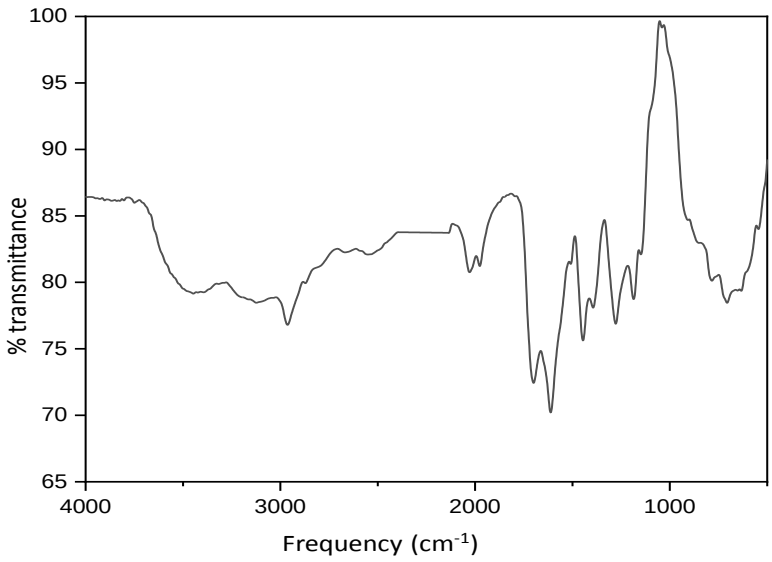
II. MATERIAL AND METHODS

All the chemicals were purchased from Sigma Aldrich and Thermo Fisher Scientific. Melting points were determined (uncor- rected) in open capillary tubes. The reaction progress was evaluated by thin layer chromatography (TLC) using Merck precoated silica gel plates (F254). The infrared (IR) spectra were recorded on Shimadzu Fourier transform infrared (FTIR) spectrophotometer using potassium bromide pellets. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on AMX-40 0, Bruker-40 0 liquid-state NMR spectrometer using tetramethyl silane as the internal standard. Chemical shifts were recorded as δ(ppm). The spin multiplicities are noted by symbols, s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Mass spectra were measured on an LCMS-2010A.

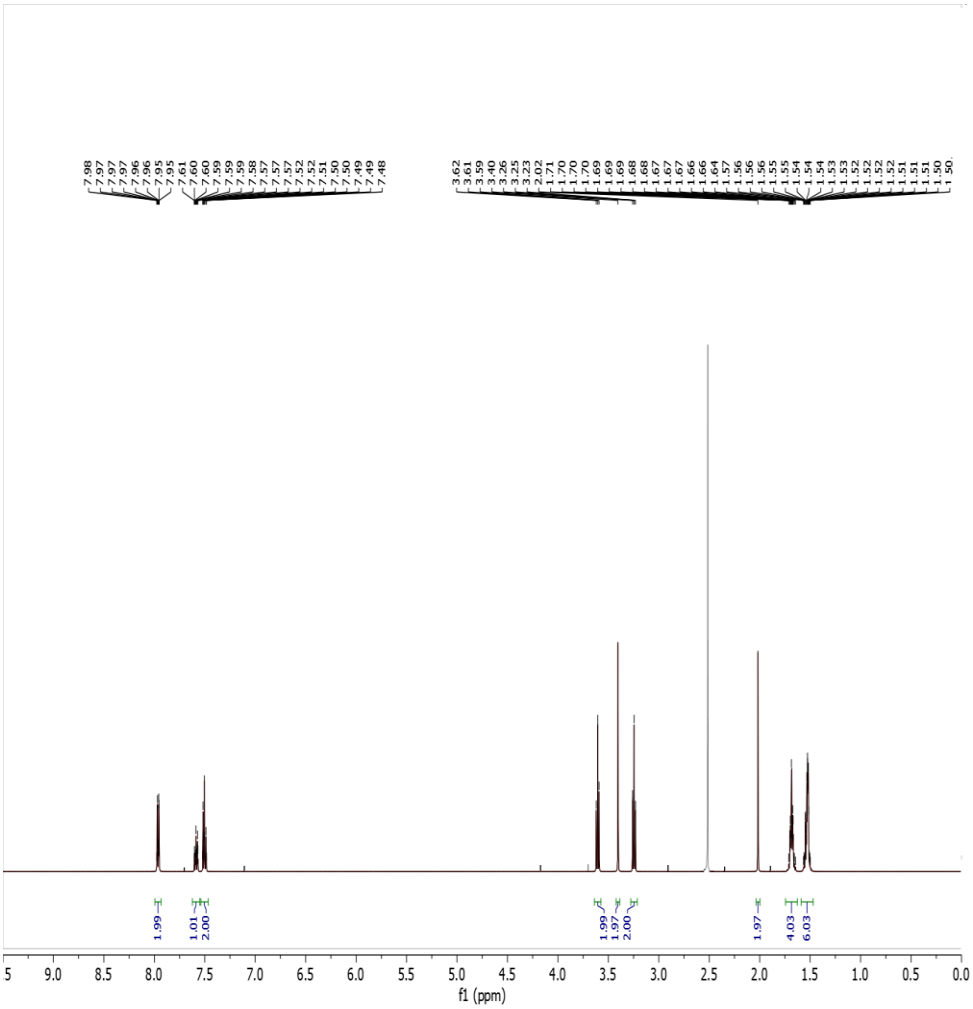
II.1 Synthesis of compounds 2-(3-oxo-3-phenylpropyl)-2-azaspiro[4.5]decan-3-one
To a solution of ethanol, add ketone (0.0036 mole) , Gabbapentin lactum -hydrochloric acid (0.0036mole) and formaldehyde (0.0036 mole) few drop of concentrate acid. Reflux the reaction mass till completion of reaction checking on TLC, filter and concentrate the volume evaporate the solvent through rotavapour and get sticky material.

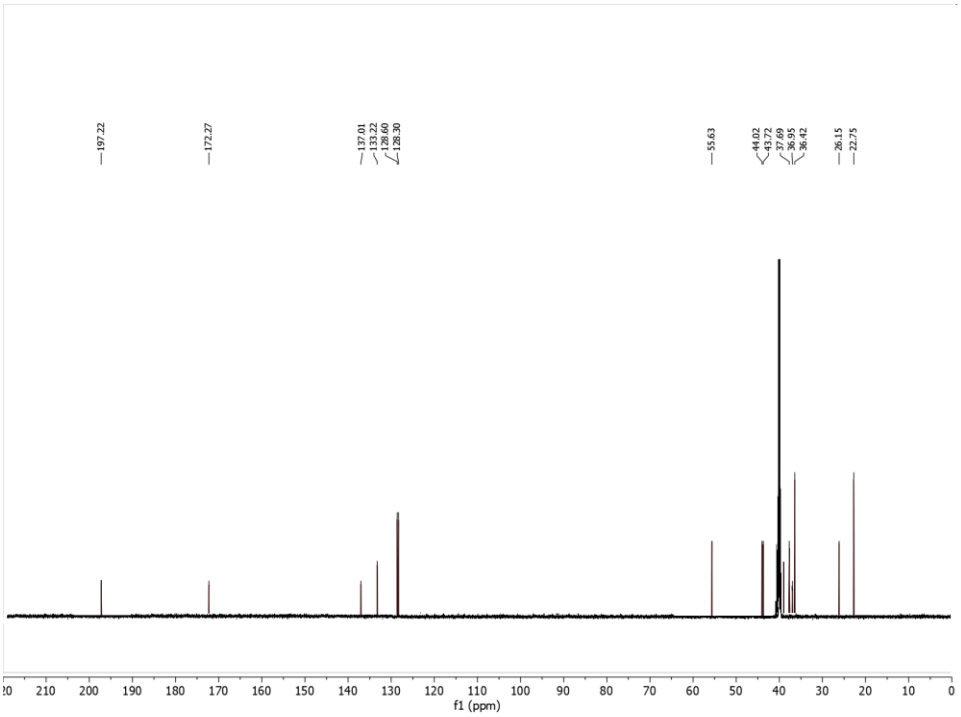
II.2CHEMISTRY: Charactrization-IR, NMR, MASS
A new series of Substituted-2-(3-oxo-3-phenylpropyl)-2-azaspiro[4.5]decan-3-one analogs and some derived spiro systems have been synthesized in good yields using the synthetic route outlined in scheme.

IR:



NMR:


7.98 7.97 7.97 7.97 7.96 7.96 7.95 7.95 7.61 7.60 7.60 7.59 7.59 7.59 7.58 7.57 7.57 7.52 7.51 7.50 7.50 7.49 7.49 7.48
3.62 3.61 3.59 3.59 3.40 3.26 3.25 3.23 2.02 1.71 1.70 1.70 1.70 1.69 1.69 1.69 1.68 1.68 1.67 1.67 1.67 1.66 1.66 1.66 1.64 1.57 1.56 1.56 1.56 1.55 1.55 1.54 1.54 1.54 1.53 1.53 1.52 1.52 1.52 1.51 1.51 1.51 1.50 1.50
1.99
1.01
2.00
1.99
1.97
2.00
1.97
4.03
6.03
5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data of $C_{18}H_{23}NO_2$ (4l) are in agreement with the proposed structures of all newly synthesized compounds. In the IR spectrum of intermediate sharp str. bands around at cm^{-1} - 1600 -1800 (ketone), 1695 (amide), 1600 (benzene), 1200-1300 (C-N), 1660 (C=C), 2900 (sp3 -CH), 1000-1100 (C-C),1480 (-CH bending) ^{1}H-NMR (ppm) =7.95-7.98 d (2H, 7.6 Hz),7.50-7.60 m (3H, 7.6 Hz),3.62 t (2H, J=7.1 Hz),3.41 S (2H , J=7.1 Hz), 3.26 t (2H,J=6.9Hz),2.03 S (2H, J=6.9Hz),1.51-169 m (10H, J=6.9Hz). ^{13}CNMR δ ppm =197 (C=O),172 (-amide),128-137 (-aromatic carbon), 55,45 (–CH2-) , 37(4^{0}C),22-36 (-CH2- in cyaclohexane) .The mass spectrum of showed a molecular ion peak at MS (ESI) m/z:285.

TABLE:I PHYSICAL DATA OF COMPOUNDS:

Sr.No.	Compounds Library	R	% Yields	M.P (±5) ^{0}C	M.F
1	4a	$3CH_3$	77	230	$C_{19}H_{25}NO_2$
2	4b	$3CF_3$	70	223	$C_{19}H_{22}F_3NO_2$
3	4c	$3NO_2$	73	270	$C_{18}H_{22}N2O_4$
4	4d	3I	62	267	$C_{18}H_{22}INO_2$
5	4e	$3OCH_3$	57	246	$C_{19}H_{25}NO_3$
6	4f	3OH	64	232	$C_{18}H_{23}NO_3$
7	4g	$2OCH_3$	65	280	$C_{19}H_{25}NO_3$
8	4h	2OH	63	244	$C_{18}H_{23}NO_3$
9	4i	$2CH_3$	72	222	$C_{19}H_{25}NO_2$
10	4j	$2CF_3$	63	235	$C_{19}H_{22}F_3NO_2$
11	4k	$2NO_2$	50	211	$C_{18}H_{22}N_2O_4$
12	4l	3H	66	250	$C_{18}H_{23}NO_2$
13	4m	3F	50	257	$C_{18}H_{22}FNO_2$
14	4n	$2OC_2H_5$	69	238	$C_{20}H_{27}NO_3$
15	4o	2Br	58	245	$C_{18}H_{22}BrNO_2$

III. RESULTS AND DISCUSSION:

In an extension of our study of the Mannich coupling reaction, we conducted reactions of formaldehyde, NH group and aromatic ketones (acetophenone), in the presence of acid catalyst . To optimize the reaction conditions, the reaction of gabapentin lactam, formaldehyde and acetophenone was performed. A

series of novel Mannich bases 2-(3-oxo-3-phenylpropyl)-2 azaspiro[4.5]decan-3-one was synthesized and evaluated for the antimicrobial activity. Acetophenone- gabapentin lactam was synthesized and studied for the antimycobacterial activity. The antimycobacterial activity of the test compounds was evaluated against the standard strain of E.coli, B.cereus and B.substilis. Ampicillin , Ciprofloxacin were used as standards. The results exposed the fact that the compounds4c,4j,4k,4m and 4o exhibited good activity. [14-16]

The classical Mannich reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis because of its atom economy advantages and application in biologically active molecule syntheses.[16-21] However, a three-component condensation between structurally diverse substrates containing at least one acidic hydrogen atom, an aldehyde component and an amine reagent leads to Mannich bases. This multicomponent reaction usually occurs under acid catalysis, although catalysis is not mandatory.[14] The mannich base products 2-(3-oxo-3-phenylpropyl)-2 azaspiro[4.5]decan-3-one derivative was prepared according to the reported procedure which was further utilized as a building block to synthesize various acetophenone derivatives substituted either at the benzene function or fused to the gabapentin back bone.A Synthesis of Mannich bases of gabapentin lactam by the reaction of gabapentin lacatam, formaldehyde and acetophenone in EtOH at Reflux condition in 54–64% yields. The ^{1}H NMR spectrum of compound 4l NMR (ppm) =7.95-7.98 d (2H, 7.6 Hz),7.50-7.60 m (3H, 7.6 Hz),3.62 t (2H, J=7.1 Hz),3.41 S (2H , J=7.1 Hz), 3.26 t (2H,J=6.9Hz),2.03 S (2H, J=6.9Hz),1.51-169 m (10H, J=6.9Hz). while, the IR spectrum of compound 3 showed NH function absorption band at 3387 cm-1. In addition to, absorption bands at 1600 -1800 (ketone), 1695 (amide), 1600 (benzene), 1200-1300 (C-N), 1660 (C=C), 2900 (sp3 -CH), 1000-1100 (C-C),1480 (-CH bending).

IV. ANTIBACTERIAL SCREENING:

TABLE: 2 ANTIBACTERIAL ACTIVITIES

Antibacterial Activity			
	Inhibition zone (mm)		
	Gram negative		Gram positive
Compounds	***E.coli***	***B.cereus***	***B.substilis***
4a	12	13	12
4b	18	19	-
4c	20	22	21
4d	12	11	-
4e	16	14	15
4f	15	15	-
4g	17	16	14
4h	12	13	-
4i	17	16	14
4j	20	18	18
4k	19	18	16
4l	13	11	-
4m	19	18	17
4n	15	14	14
4o	21	23	22
Ampicillin	30	31	23
Ciprofloxacin	37	33	29

AGAR-WELL DIFFUSION METHOD:

Simple susceptibility screening test using agar-well diffusion method as adapted earlier was used. Each microorganism was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately to 10^6 colony forming unit (cfu)/mL. They were ''flood-inoculated'' onto the surface of MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI)and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 mL of the extract substances was delivered into the wells. The plates were incubated for 18 h at 35 C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 mg) and Ciprofloxacine (5 mg) were used as standard drugs. Ethanols were used as solvent controls. [22-23]

V. CONCLUSION:

Substituted acetophenone manic base scaffolds were synthesized by MCR and their compounds were confirmed by spectroscopic data. The synthesized compounds were screening in vitro biological evaluation as antibacterial activity. The results of newer Substituted acetophenone-gabapentin manic base scaffolds reported good to moderate activity with compare to reference compounds. The compounds 4c and 4o exhibited potent antibacterial activity.

DECLARATION OF COMPETING INTEREST
The authors declare no conflict of interest.

Acknowledgements:
We gratefully acknowledge the generous support provided by the Department of Chemistry, Veer Narmad South Gujarat University for providing essential facilities and Government Science college laboratories, Vankal , Surat, for antimicrobial activity.

Supplementary materials
Supplementary material associated with this article can be found, in the online version .

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