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'SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF MORPHOLINE MANNICH BASE DERIVATIVE

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ABSTRACT:

In this research work we have synthesized some new 3-[morpholino -4- yl]- N- phenyl-3-sustituted propanamide derivatives were synthesized with help of Mannich reaction, Here, we have synthesized 5 Mannich bases using various aldehydes and TLC was Done for the Compounds later those are sent for IR and NMR Spectroscopy for characterization of functional groups present in the synthesized samples. Later the synthesized compounds are screened for Anti-microbial activity under this; the Anti-bacterial activity is seen for both the gram positive as well as gram negative against Staphylococcus aureus and EshericiaColi respectively. With help of the cup plate method and the result was compared against the standard drug ciprofloxacin. For Anti-Fungal activity the organism used was aspergillus Niger with help of the cup plate method and was compared against the standard using the Clotrimazole. The entire synthesized compound shows good yield and good Anti-microbial activity. C4 compound, the derivative of p- dimethyl amino benzaldehyde was found with greater activity among all compounds and it shows the similar action with the standard drug.

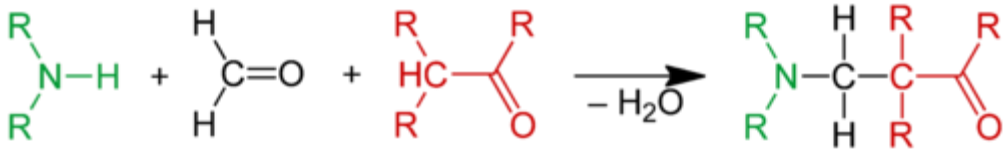
Keywords: Morpholine, Mannich base, antimicrobial activity, synthesis

INTRODUCTION:

Medicinal chemistry is an interdisciplinary field of study aspects of organic chemistry. It is concerned with discovery, design synthesis and interactions of a pharmaceutical agent with the body and medicinal chemistry is mainly concerned with small organic molecules both natural and synthetic. Compounds in clinical use are primarily small organic compounds, organ metallic compounds, biopharmaceuticals and inorganic compounds used in medicine as therapeutics.

Mannich Reaction:

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.



The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol). The Mannich reaction is also considered a condensation reaction. In the Mannich reaction, primary or secondary amines or ammonia, are employed for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α- Chasidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocyclic such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gamine derivatives.

Mannich bases are the end products of Mannich reaction and are known as beta-amino ketone carrying compounds. Mannich reaction is a carbon-carbon bond forming nucleophilic addition reaction and is a key step in synthesis of a wide variety of natural products, pharmaceuticals, and so forth. Mannich reaction is important for the construction of nitrogen containing compounds.

There is a number of amino alkyl chain bearing Mannich bases like fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, and so forth with high curative value. The literature studies enlighten the fact that Mannich bases are very reactive and recognized to possess potent diverse activities like anti-inflammatory, anticancer, antifilarial, antibacterial, antifungal, anticonvulsant, anthelmintic, antitubercular, analgesic, anti-HIV, antimalarial, antipsychotic, antiviral activities and so forth. The biological activity of Mannich bases is mainly attributed to α, β-unsaturated ketone which can be generated by deamination of hydrogen atom of the amine group.

Anti-Microbial Activity:

Antibacterial:

The discovery, development and use of antibacterial during the 20th century has reduced mortality from bacterial infections. Antibacterial are among the most commonly used drugs . As a consequence of widespread use of antibacterial, there has been an accelerated emergence of antibiotic resistant pathogens, resulting in a serious threat to global public health. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibacterial. Possible strategies towards this objective include increased sampling from diverse environments and application of metagenomics to identify bioactive compounds produced by currently unknown and uncultured microorganisms as well as the development of small-molecule libraries customized for bacterial targets

Antifungal:

Antifungal are used to kill or prevent further growth of fungi. In medicine, they are used as a treatment for infections such as athlete's foot, ringworm and thrush and work by exploiting differences between mammalian and fungal cells. They kill off the fungal organism without dangerous effects on the host. Unlike bacteria, both fungi and humans are eukaryotes. Thus, fungal and human cells are similar at the molecular level, making it more difficult to find a target for an antifungal drug to attack that does not also exist in the infected organism. Consequently, there are often side effects to some of these drugs. Some of these side effects can be life-threatening if the drug is not used properly.

As well as their use in medicine, antifungal are frequently sought after to control mold growth in damp or wet home materials. Sodium bicarbonate (baking soda) blasted on to surfaces acts as an antifungal. Another antifungal serum applied after or without blasting by soda is a mix of hydrogen peroxide and a thin surface coating that neutralizes mold and encapsulates the surface to prevent spore release. Some paints are also manufactured with an added antifungal agent for use in high humidity areas such as bathrooms or kitchens. Other antifungal surface treatments typically contain variants of metals known to suppress mold growth e.g. pigments or solutions containing copper, silver or zinc. These solutions are not usually available to the general public because of their toxicity.

Materials & methods:

Mannich base is the final product of beta amino carbonyl compound synthesized generally with basic amine, carbonyl Compound and formaldehyde here in this reaction we used morpholine, Acetanilide and various aldehydes respectively. To carry out the Mannich reaction

General reaction:

Here in this general reaction 0.1M of Morpholine, 0.1M of Acetanilide and 0.1 of Aldehydes (Aromatic/Allyl/Alkyl) was refluxed for 6hrs in the presence of methanol as solvent and the product that obtained was poured in Ice cold water and stir well, the obtained product was filtered, Dried and recrystallized with methanol. The Obtained products were monitored for thin layer chromatography. Later on, those products were screened for Anti-Microbial Activity Both Anti-Bacterial as well as Antifungal Activity.

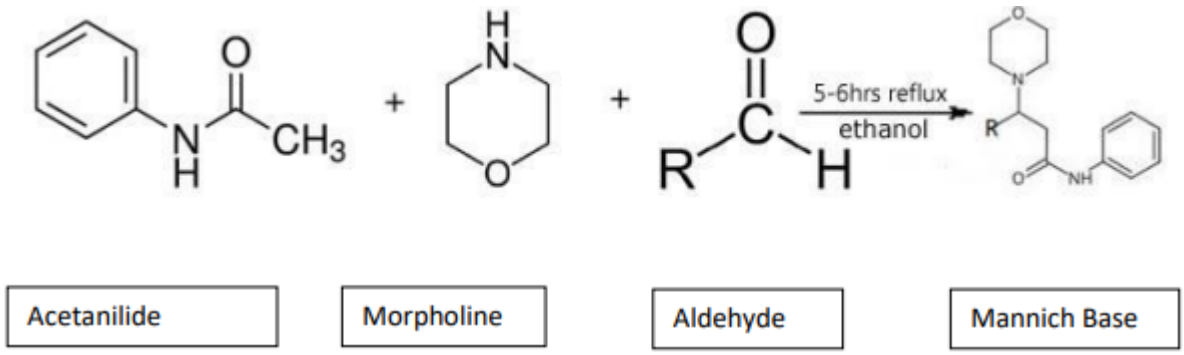
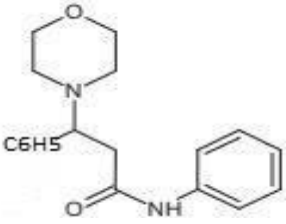
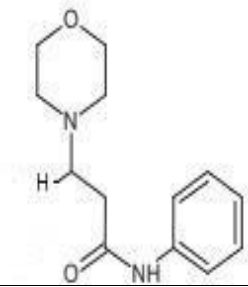


Table 1: List of synthesized compounds.

Compound	Product	Aldehydes used(R)	Structure of compound	Product IUPAC name
1	C1	Benzaldehyde		3-[morpholino -4- yl]- N- phenyl-3-phenyl propanamide
2	C2	Formaldehyde		3-[morpholino -4- yl]- N- phenyl-3- propanamide

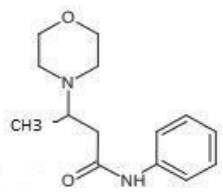
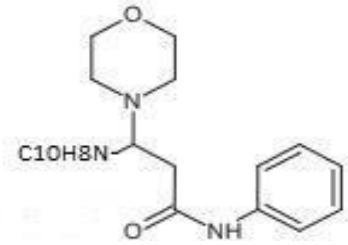
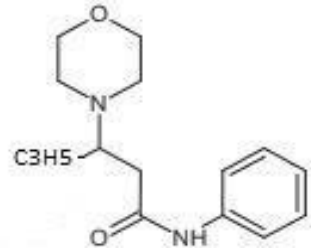
3	C3	Acetaldehyde		3-[morpholino - 4- yl]- N- phenyl- 3-methyl propanamide
4	C4	N, N Para dimethylamino benzaldehyde		3-[morpholino - 4- yl]- N- phenyl- 3-[4-N,N- dimethyl] phenyl propanamide
5	C5	Crotonaldehyde		3-[morpholino - 4- yl]- N- phenyl- 3-[1-propenyl] propanamide

Table 2: Physical properties of synthesized compounds.

COMPOUND	MOLECULAR FORMULA	%YIELD	MELTING POINT	SOLUBILITY
C1	$C_{19}H_{22}O_2N_2$	65.1%	132^{O}C	Soluble in Methanol, DMSO & chloroform
C2	$C_{13}H_{18}O_2N_2$	72%	118^{O}C	Soluble in Methanol, DMSO & chloroform & insoluble in water
C3	$C_{14}H_{20}O_2N_2$	68%	120^{O}C	Soluble in Methanol, DMSO & chloroform & insoluble in water
C4	$C_{21}H_{24}O_2N_3$	84%	135^{O}C	Soluble in Methanol, DMSO & chloroform & insoluble in water
C3	$C_{15}H_{22}O_2N_2$	75%	125^{O}C	Soluble in Methanol, DMSO & chloroform & insoluble in water

RESULTS AND DISCUSSION:

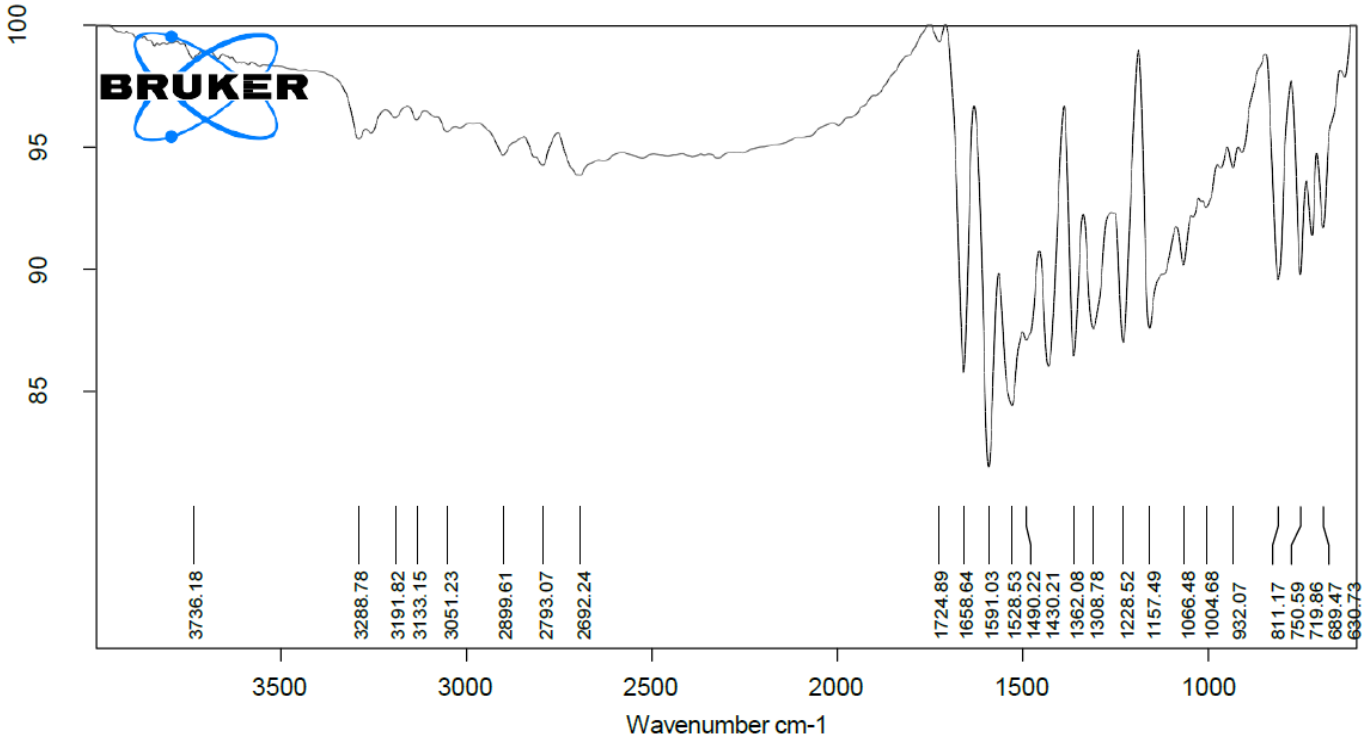
Table 3: Spectral data of synthesized compounds.

compound	IR spectra data	1HNMR spectra data
C1	2793 (CH str in phenyl ring), 1658 (NHCO), 1362 (C-N), 1228 (C-O), 1154 (C-C)	7.7-7.4(5H,Ar-H),7.25-7.13(1H,NH), 3.56-3.97(4H,O-CH2- morpholine), 2.50-2.34(4H,N-CH2-morpholine, 1.23-1.12(1H,CH)
C2	2801 (CH str in phenyl ring), 1658 (NHCO), 1312 (C-N), 1251 (C-O), 1592(C-C)	7.7-7.4(5H,Ar-H),7.25-7.13(1H,NH), 3.86-3.56(4H,O-CH2- morpholine), 2.50-2.34(4H,N-CH2-morpholine, 2.23-1.12(2H,CH2)
C3	2793 (CH str in phenyl ring), 1660 (NHCO), 1364(C-N), 1112 (C-O), 1166 (C-C)	7.7-7.4(5H,Ar-H),7.25-7.13(1H,NH), 3.56-3.97(4H,O-CH2- morpholine), 2.50-2.34(4H,N-CH2-morpholine, 1.23-1.12(1H,CH)
C4	2316 (CH str in phenyl ring), 1658 (NHCO), 1313 (C-N), 1252 (C-O), 1035 (C-C)	7.7-7.4(5H,Ar-H),7.25-7.13(1H,NH), 3.56-3.97(4H,O-CH2- morpholine), 2.50-2.34(4H,N-CH2-morpholine, 1.23-1.12(1H,CH)
C5	2316 (CH str in phenyl ring), 1658 (NHCO), 1313 (C-N), 1252 (C-O), 1035 (C-C)	7.7-7.4(5H, Ar-H),7.25-7.13(1H, NH), 3.56-3.97(4H, O-CH2- morpholine), 2.50-2.34(4H, N-CH2-morpholine, 1.23-1.12(1H, CH)

Anti-Microbial Activity:

	Anti Bacterial Activity Zone of Inhibiton (mm)		Anti Fungal Activity Zone of inhibition(mm)
Compound	Gram +ve (st. aureus)	Gram -ve (E. coli)	Apergillus niger
C1	9	4	9
C2	6	8	0
C3	11	10	12
C4	18	15	19
C5	14	12	17
Control	0	0	0
Standard	19(Ciprofloxacin)	17(Ciprofloxacin)	21 (clotrimazole)

C1-IR SPECTRA



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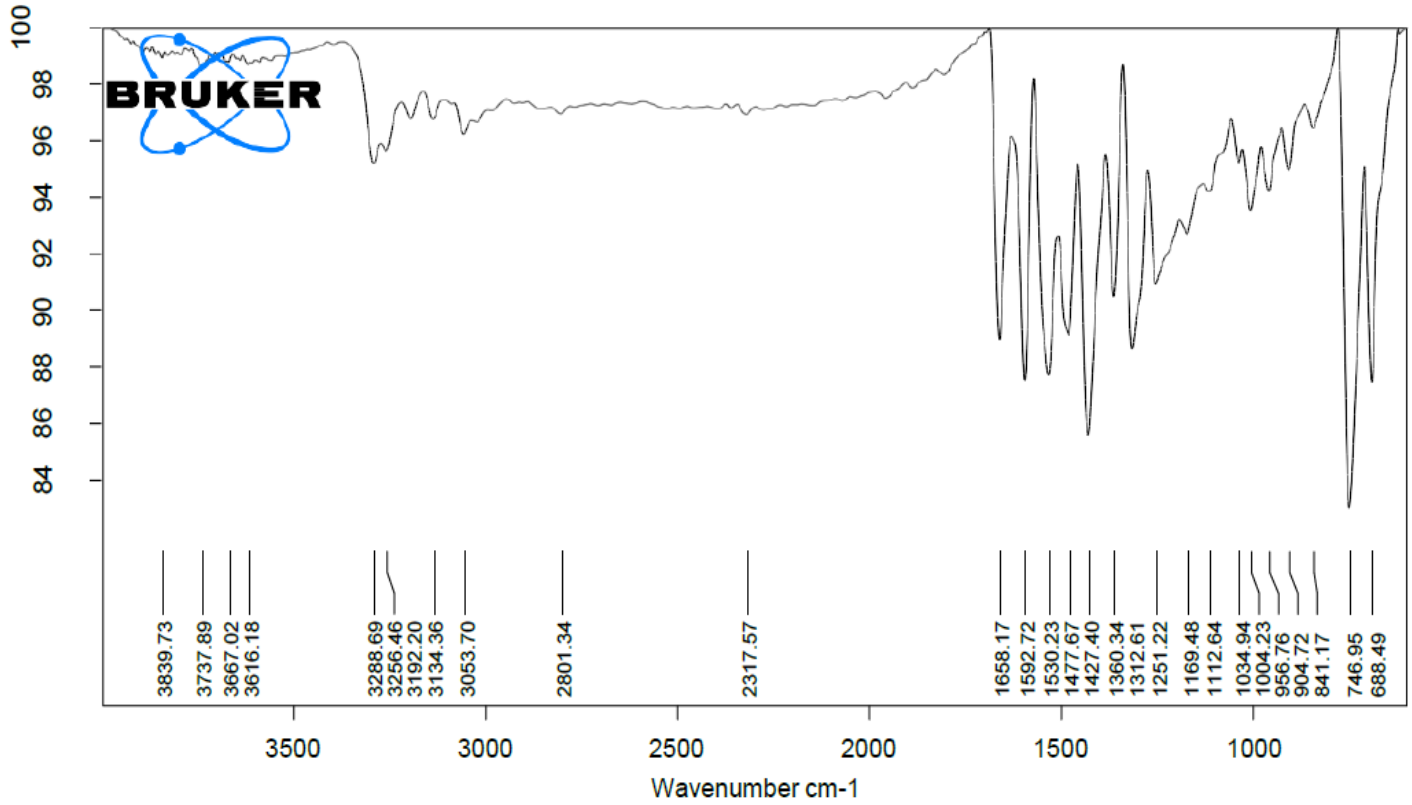

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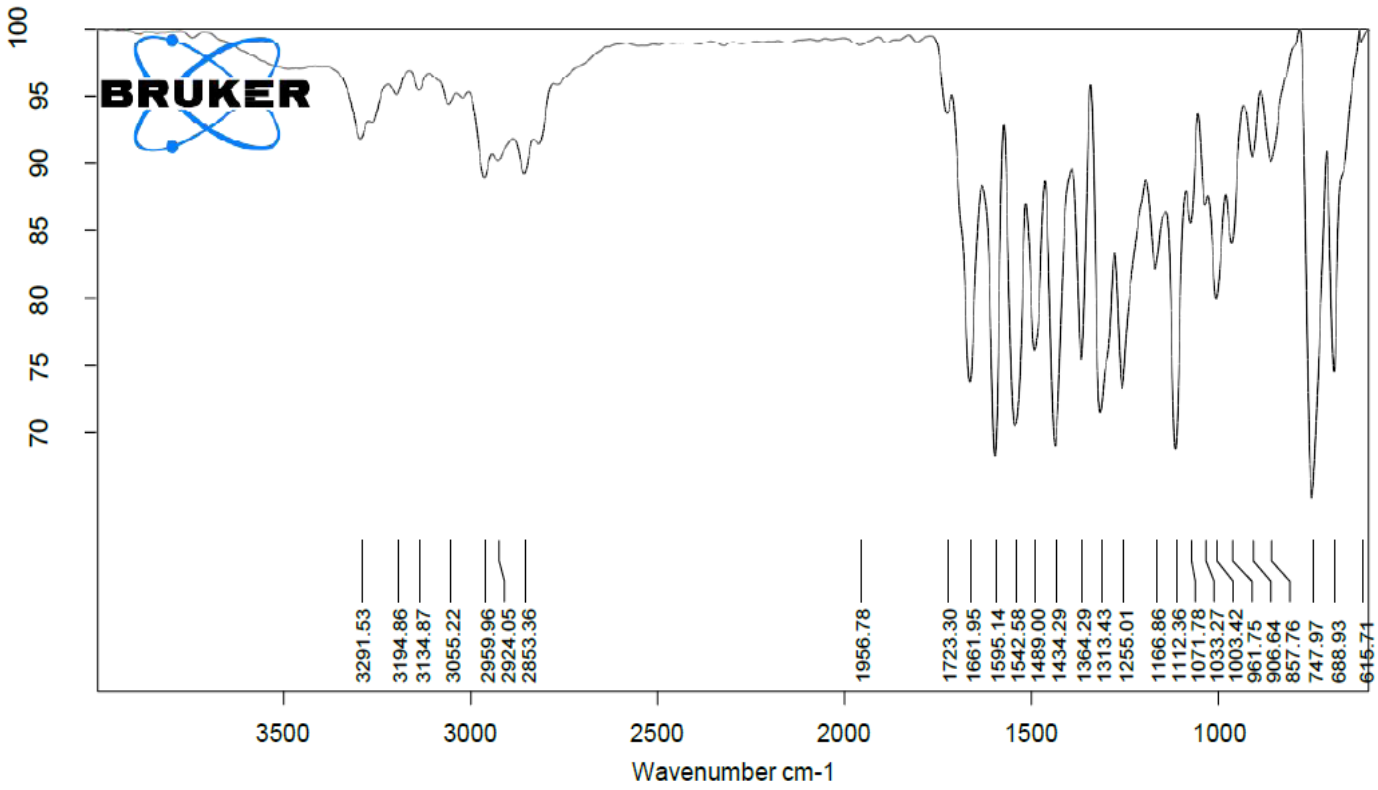

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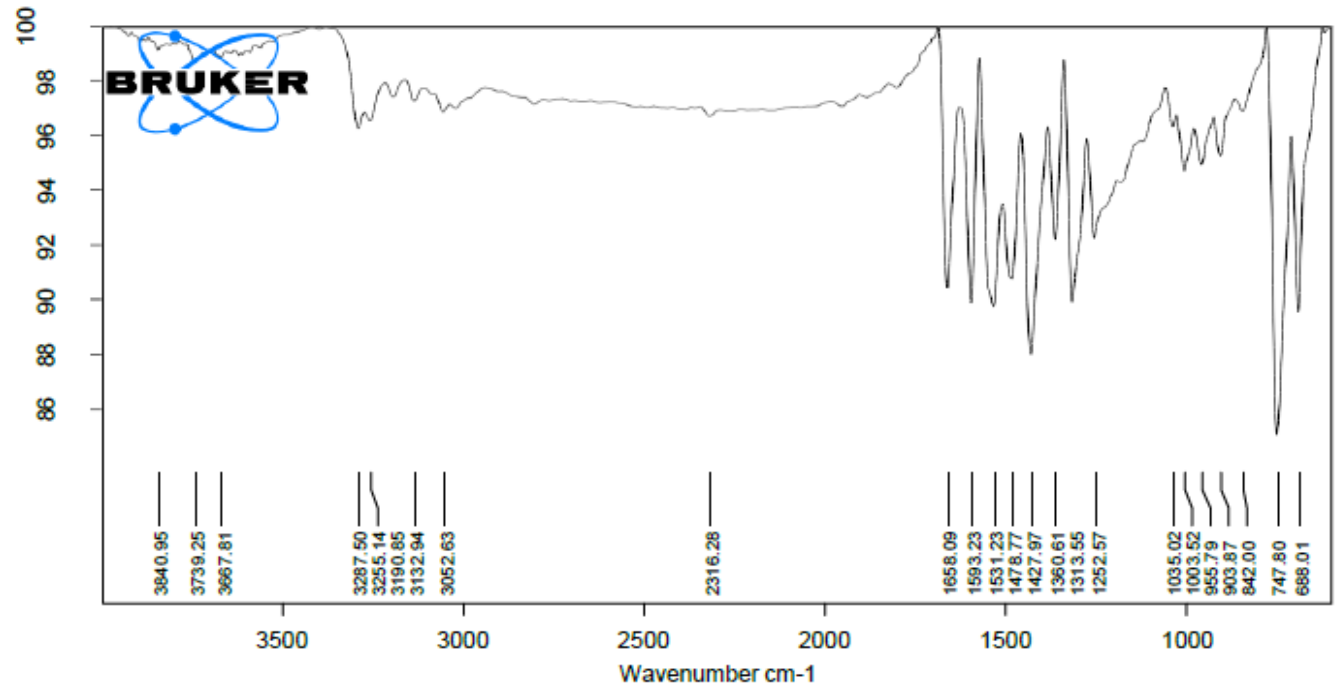

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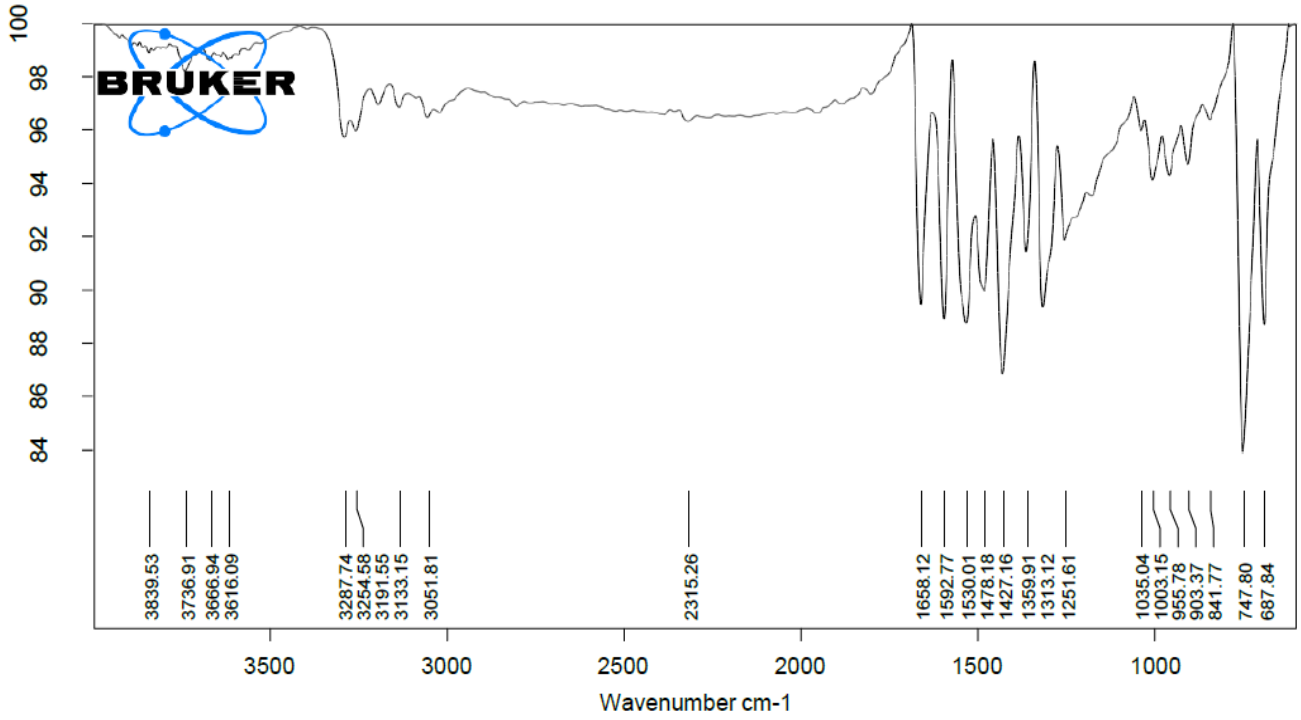

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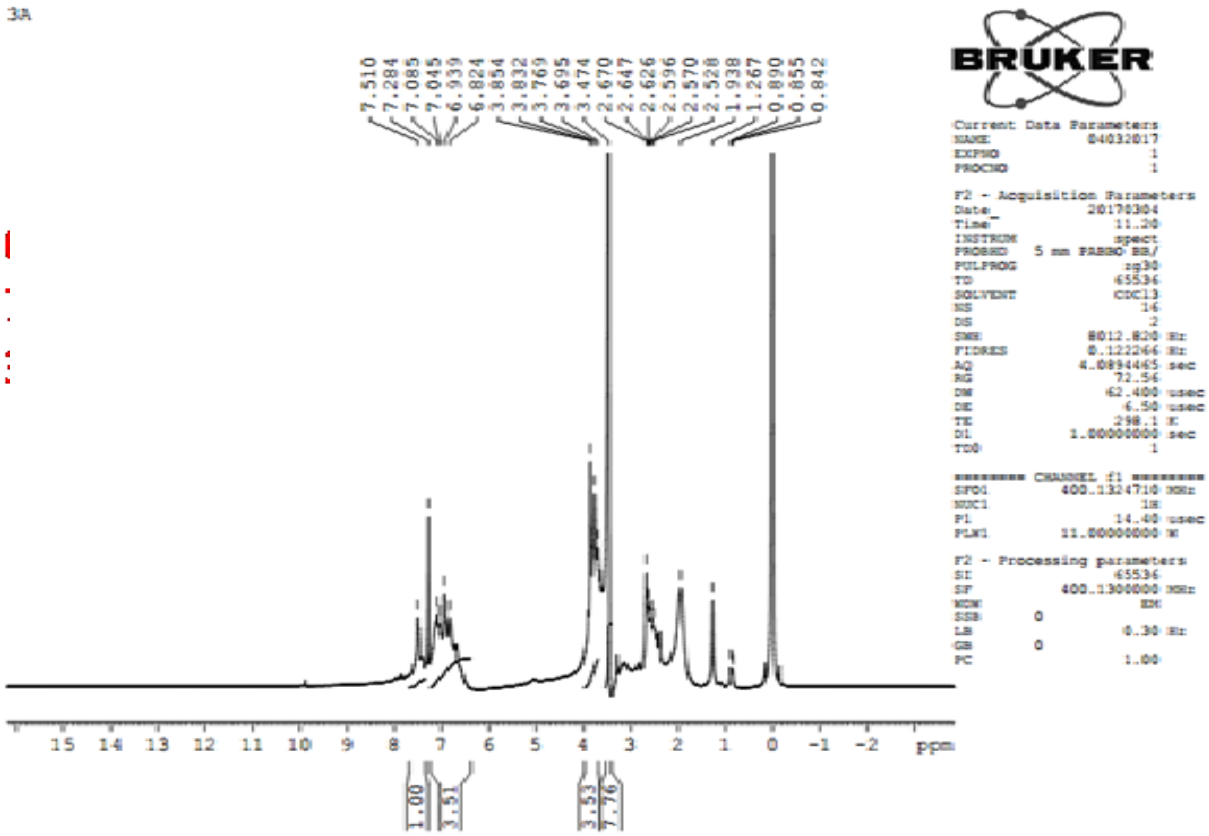

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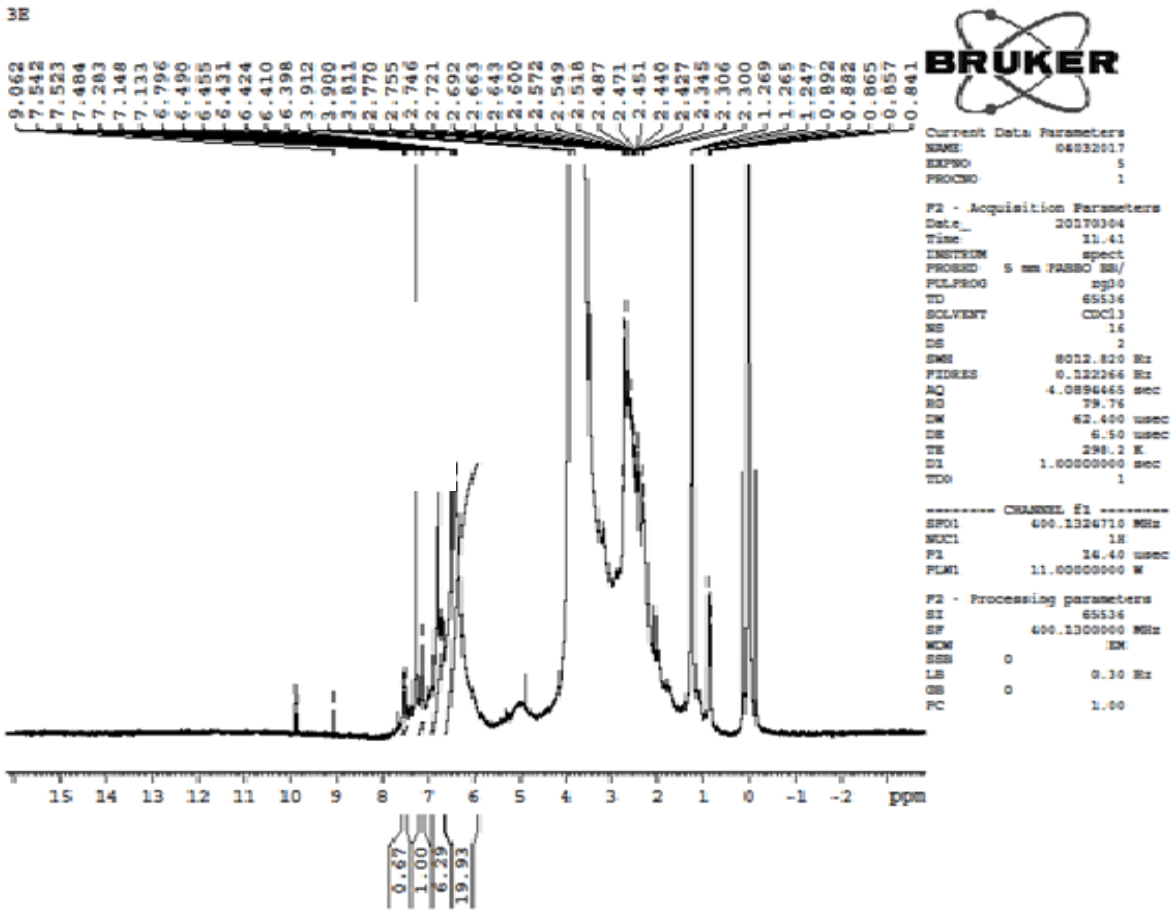
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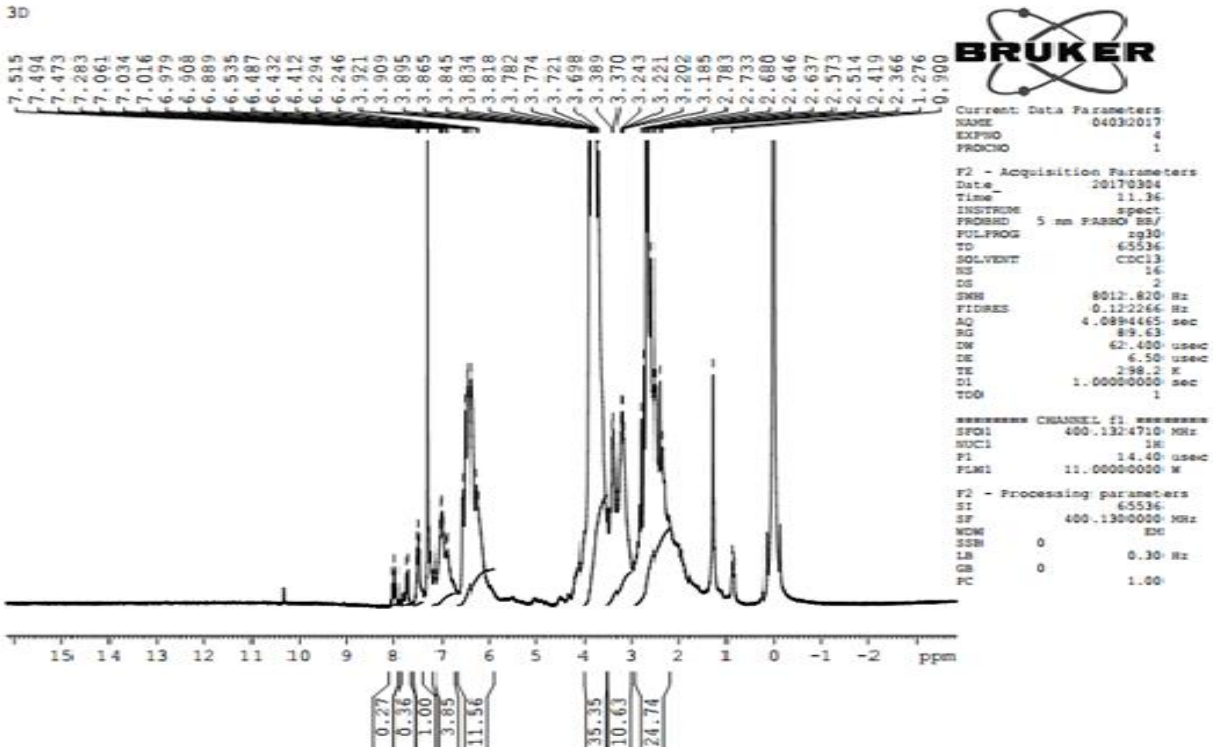
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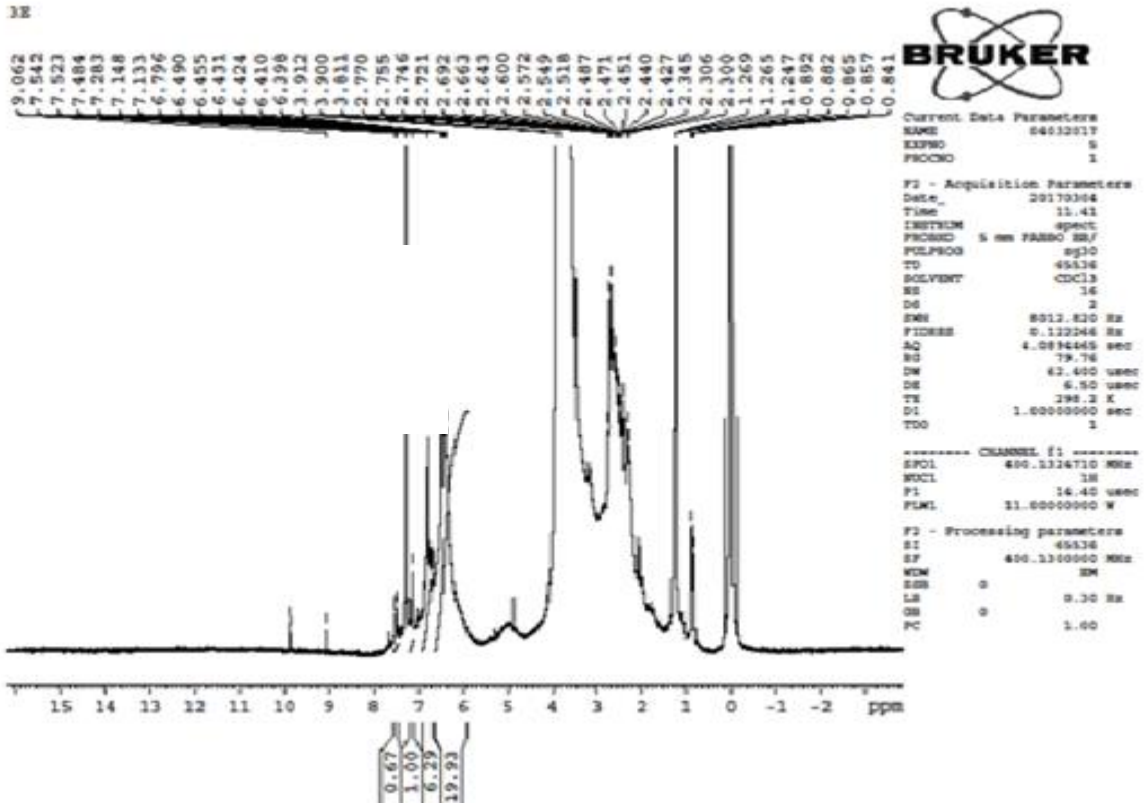
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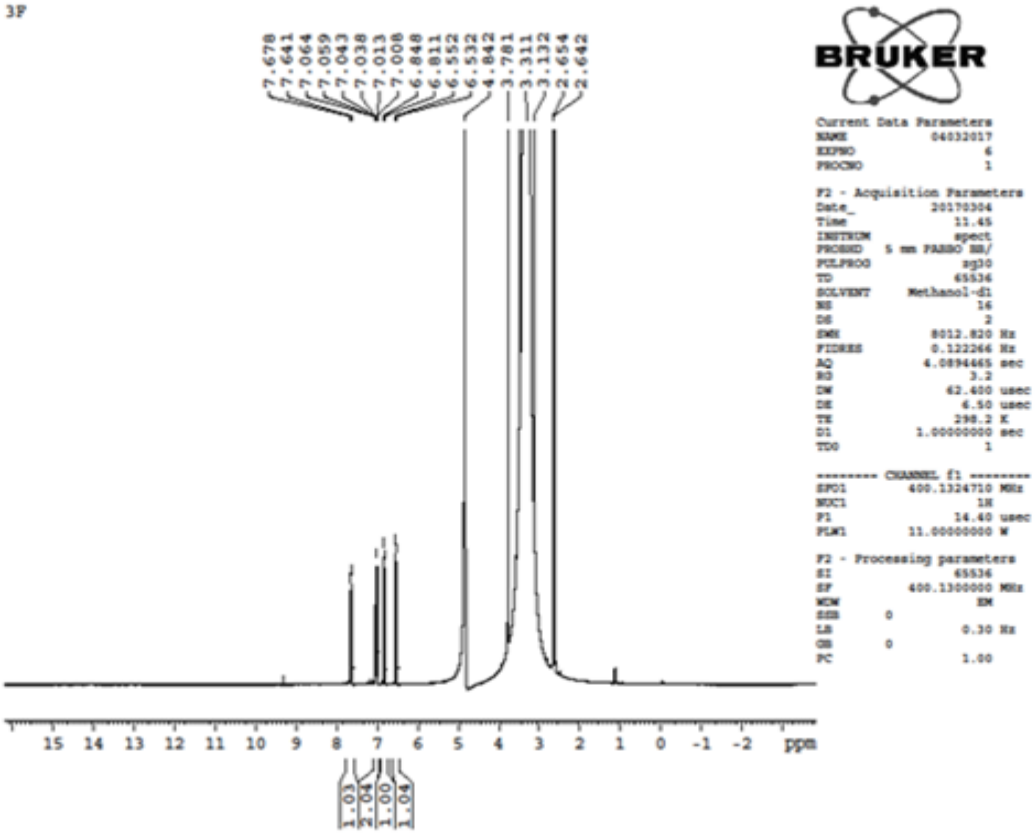
C5-NMR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Conclusion;

Here in this project, we have synthesized 5 new Mannich bases with Morpholine and Acetanilide by changing the Aldehyde Derivatives. Among all the compounds Compound C4 was found to begreater yield. the functional groups are determined in IR spectra In the biological screening of thecompound the compound R4 the derivative of 2,4 di methyl amino benzaldehyde was found withthe greater activity among all compounds and it shows the similar action with the standard drug Among all aldehyde derivatives the Aromatic aldehyde groups show higher activity than allylic aldehyde derivatives than Aliphatic aldehyde compounds. In the future investigation this project we can identify the compounds with NMR Spectroscopy and the screening the compounds with wide number of Microbial organisms.

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References:

1. Bauer, A.W., Kirby, W.M., Sherris, J.C., Truck, J.C.M., 1966. Am. Clin. Pathol. 9 (5), 493–496.
2. Borenstein, M.R., Doukas, P.H., 1987. J. Pharm. Sci. 76, 300–302.
3. Jamal Abdul Nasser, A., Idhayadhulla, A., Kumar, R.S., Selvin, J., 2009. Indian J. Heterocyclic Chem. 18, 399–400.
4. Sarangapani, M., Reddy, V.M., 1994. Indian J. Pharm. Sci. 56, 174– 177.
5. Mannich, C., Krosche, W., 1912. Arch. Pharm. (Weinheim) 250, 647– 667.
6. J. A. Gautier, M. Miocque, D. Q. Quan, C. r. Acad. Sci. 258 (1964) 3731.
7. E. Comanita, I. Popovici, B. Comanita, Gh. Roman, Bul. Inst. Politehn. Iasi. XLII (XLVI) (1996) 135 C.A. 128 (1998) 140496.
8. M. Tramontini, L. Angiolini, Tetrahedron 46 (1990) 1791.
9. I. Popovici, E. Comanita, Gh. Roman, B. Comanita, Acta Chim. Slov. 43 (1999) 413.
10. U. R. Kalkote, D. D. Goswami, Aust. J. Chem. 30 (1977) 1947.
11. Konkel, M. J.; Packiarajan, M.; Chen, H.; Topiwala, U. P.; Jimenez, H.; Talisman, I. J.; Coate, H.; Walker, M. W. Bioorg. Med. Chem. Lett., 2006, 16, 3950.
12. Gursoy, A.; Karali, N.; Buyuktimakin, S.; Demirayak, S.; Ekinci, A. C.; Ozer, H. Farmaco, 1996, 39, 5072.
13. Selvam, P.; Chandramohan, M.; DeClercq, E.; Witvrouw, M.; Pannecouque, C. Eur. J. 11. Pharm. Sci., 2001, 14, 313.
14. Pandeya, S. N.; Yogeswari, P.; Sriram, D.; DeClercq, E.; Pannecouque, C.; Witvrouw, M. Chemotherapy, 1999, 45, 192.
15. Teitz, Y.; Ronen, D.; Vansover, A.; Stematsky, T.; Rigg, J. L. Antiviral Res., 1994, 24, 215.
16. Daisley, R. W.; Shah, V. K. J. Pharm. Sci., 1984, 73, 407.
17. Piscopo, B.; Diumo, M. V.; Godliardi, R.; Cucciniello, M.; Veneruso, G. Bol. Soc. Ital. Biol. Sper., 1987, 63, 827.

18. M.N. Ibrahim and S.A.E. Sharif, E-J. Chem., 4, 531 (2007).
19. J.T. Leonard, L. Jeyaseeli, O.S. Rajesh, K. Murugesh, R. Sivakumar and V. Gunasekaran, Asian J. Chem., 18, 1104 (2006).
20. B. Lingappa, K.S. Girisha, B. Kalluraya, N.S. Rai and N.S. Kumari, Indian J. Chem., 47B, 4448 (2008).
21. S. Joshi, A.D. Manikpuri and P. Tiwari, Bioorg. Med. Chem. Lett., 17, 645 (2006).
22. S. Mitsumori, H. Zhang, P.H.Y. Cheong, K. Houk, F. Tanaka and C.F. Barbas, J. Am. Chem. Soc., 128, 1040 (2006).
23. Gol'tsova, L. V.; Lezna, V. P.; Kuz'min, V. I.; Simrnov, L. D. Izv. Akad. Nauk SSSR Ser. Khim. 1984, 1660; Chem. Abstr. 1985, 102, 6156.
24. Dyumaev, K. M.; Lokhov, R. E. Zh. Org. Khim. 1972, 416; Chem. Abstr. 1972, 76, 126728.
25. Rechert, B. ln Die Mannich Reaction; Springer Verlag: Berline, 1959.
26. Peter, S. A Guidebook to Mechanism in Organic Chemistry, 6th ed.; Longman Scientific Technical: New York, 1995; p 165.
27. Bogatsky, A. V.; Lukyanenko, N. G.; Pastushok, V. N.; Kostyanovsky, R. G. Dokl. Acad. Nauk SSSR. 1982, 265, 619; Chem. Abstr. 1982, 97, 216146c.
28. ramontini, M.; Angliolini, L. Mannich Base: Chemistry and Uses; CRC Press: Boca Raton, 1994; pp 17-20.
29. Tramontini, M.; Angliolini, L. Tetrahedron 1990, 46.
30. Marvel CS and heris GS. Orgonic synthesis collective volume-1.2nd Ed.john wiley &sons, new york 423, 1941.
31. Krishna, R.; pande, B.R.; Bharthwal, S.P.; Parmer, s,s.eur.J.Med.chem. 15,567, 1980.
32. Singh,A.; Rathod,S.; Berad, B.N.; patil, S.D.; Dosh, A.G. orient.J.CHEM. 16,315, 2000.