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DESIGN, SYNTHESIS, AND EVALUATION OF NOVEL PYRAZOLE DERIVATIVES ASPOTENTIAL ANTI-INFLAMMATORY AGENTS

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ABSTRACT

The objective of this research is to develop new substituted pyrazole derivatives with potential anti-inflammatory properties. Many present-day diseases result from infections by pathogenic microorganisms, such as fungi, bacteria, viruses, and rickettsiae. To combat these diseases, potent and broad-spectrum antibiotics have been discovered. Inflammation is a complex process involving various vasoactive, chemostatic, and proliferative agents. Anti-inflammatory drugs primarily work by inhibiting prostaglandin (PG) synthesis at the site of injury. The effectiveness of anti-inflammatory compounds is often correlated with their ability to inhibit cyclooxygenase (COX), a key enzyme in PG synthesis. This study focuses on the synthesis of substituted pyrazoles, which have gained attention due to their diverse biological activities and therapeutic potential. A literature survey highlights the anti-inflammatory properties of substituted pyrazole derivatives. The methodology involves multi-step reactions to synthesize these compounds and characterizing them using various physical and spectral data, including melting points, IR spectra, proton NMR, and mass spectrometry. These newly synthesized pyrazole derivatives hold promise for contributing to the development of novel anti-inflammatory drugs and expanding our understanding of their therapeutic potential.

KEYWORDS: melting points, IR spectra, proton NMR.

INTRODUCTION

Pharmaceutical Chemistry is a multifacetedscience that employs the fundamental principles of chemistry to investigate drugs comprehensively. This field encompasses the study of various

aspects of drugs, including their synthesis, chemical composition, structural characteristics, effects on living organisms, physical and chemical properties, quality control methods, and optimal storage conditions. Within the realm of pharmaceutical sciences, Pharmaceutical Chemistry holds apivotal position, interlinked with related disciplines like Drug Technology, Toxicological Chemistry, Pharmacognosy,and the organization of pharmacy.

Pharmaceutical Chemistry is a specialized science that depends on both chemical disciplines, such as inorganic, organic, analytical, physical, and colloidal chemistry, as well as medico-biological disciplines like pharmacology, physiology, and biological chemistry. This interdisciplinary approach has been instrumental in advancing our understanding of drug mechanisms and development.

The origins of Pharmaceutical Chemistry date back to the 16th century and played a significant role in giving rise to Medicinal Chemistry during the latter half of the 17thcentury. Pharmacists were instrumental in the inception and evolution of pharmaceutical chemistry. According to Burger, Medicinal Chemistry aims to uncover biochemical rationales for drug discovery, driven by the hope of understanding the molecular basis of drug actions.

One of the pivotal moments in the history of Pharmaceutical Chemistry was the introduction of synthetic molecules for medical use in the 19th century, such as chloroform and ether for anesthesia. Among these, phenacetin was among the first drugs designed based on knowledge ofbiochemical transformations.

Pharmaceutical Chemists study the chemical modifications of drug molecules to optimize their therapeutic effects and minimize side effects. Various analytical methods like X-ray analysis, UV spectroscopy, infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) have greatly contributed to the advancement of medicinal chemistry. Moreover, the understanding of drug receptor interactions, pharmacokinetics, and advancements in enzymology have helped scientists hypothesize the mechanisms of action of drug molecules.

Over time, the practice of medicinal chemistry has evolved from empiricalmethods based on the modification of existing drug structures to a moresystematic and rational approach, thanks to developments in molecular biology, physical chemistry, and analytical techniques. This scientific foundation, which includes breakthroughs in molecular biology, high-speed computing, and advanced analytical methods, has ushered in a new era in medicinal

chemistry, allowing for more precise drug design and discovery.

In this context, the study of pyrazoles, which are a class of compounds with a five-membered ring structure containingnitrogen and carbon atoms, has garnered substantial attention due to their diverse biological activities and potential pharmacological applications. These compounds have been widely studied for their activities against variousmicroorganisms, and their pharmacologicalproperties have been investigated.

In summary, Pharmaceutical Chemistry has a rich history and continues to be an ever-evolving field, where interdisciplinary approaches and advances in various scientific disciplines contribute to the development of new drugs, improved therapies, and a deeper understanding of the complex interactions between drugs and living organisms. The study of pyrazoles and their various reactions and properties is a testament to the ongoing exploration of novel chemical entities with potential medical applications.

METHODOLOGY

I. Preparation of 3-Methyl-Pyrazole-5-One (Ia)

Materials

- Ethylacetoacetate (1.3 ml, 0.01 mol)
- Hydrazine hydrate (0.5 ml, 0.01 mol)
- Round bottom flask
- Stirring apparatus
- Filtration setup
- Alcohol for recrystallization
- Melting point apparatus

1. Into a clean, dry round bottom flask,introduce ethylacetoacetate (1.3 ml, 0.01 mol).
2. Add hydrazine hydrate (0.5 ml, 0.01 mol) drop by drop with constant stirring at room temperature.
3. Allow the reaction mixture to cool at room temperature.
4. Filter and dry the solid that forms.
5. Recrystallize the product from alcohol.
6. Record the melting point (222- 224°C) and calculate the percentageyield (70%).

II. Preparation of 3-Methyl-1-Phenyl-Pyrazole-5-One (Ib)

MATERIALS

- Redistilled ethylacetoacetate (1.3 ml, 0.01 mol)
- Phenyl hydrazine (1.8 ml, 0.01 mol)
- Large evaporating dish
- Boiling water bath
- Fuming chamber
- Ether
- Filtration setup
- Hot water for recrystallization
- Melting point apparatus

1. Mix redistilled ethylacetoacetate (1.3 ml, 0.01 mol) and phenyl hydrazine (1.8 ml, 0.01 mol) in a large evaporating dish.
2. Heat the mixture on a boiling water bath in a fuming chamber for about 2 hours with constant stirring.
3. Allow the syrup to cool, then add 25ml of ether and stir vigorously.
4. Filter and wash the solid that formsto remove impurities.
5. Recrystallize the product from hot water.
6. Record the melting point (125- 127°C) and calculate the percentageyield (70%).

III. Preparation of 6-Amino-4-(2- Chlorophenyl)-3-Methyl-1,4- Dihydropyrano [2,3-c]Pyrazole-5-Carbonitrile (IId)

Materials

- 3-Methyl-pyrazole-5-one (Ia) (0.98gm, 0.01 mole)
- Melanonitrile (0.6 ml, 0.01 mole)
- 2-Chloro benzaldehyde (1.4 ml, 0.01 mole)
- Round bottom flask
- Alcohol (10-15 ml)
- Piperidine
- Methanol for recrystallization
- Melting point apparatus

1. Introduce 3-Methyl-pyrazole-5-one (Ia) (0.98 gm, 0.01 mole) into a clean, dry round bottom flask and dissolve in alcohol (10-15 ml).
2. Add melanonitrile (0.6 ml, 0.01 mole) and 2-chloro benzaldehyde (1.4 ml, 0.01 mole)

with constant stirring.

3. Slowly add 5 to 6 drops of piperidine and continue stirring for 2 hours.
4. Collect the solid product (IId) and recrystallize it from methanol.
5. Record the melting point (240- 242°C) and calculate the percentageyield (64%).

IV. Synthesis of Remaining Compounds(IIa-o)

- The remaining compounds (IIa-o) were synthesized following the same procedure as described above, and they were recrystallized using methanol. The percentage yields ranged between 60-80%.

V. Preparation of 4-(2-Chlorophenyl)-3- Methyl-6-{[(1E)-Phenyl Methylene] Amino}-1,4-Dihydropyrano [2,3-c]Pyrazole-5-Carbonitrile (IIId).

- Similar to the synthesis of IId,starting with 6-amino-4-(2-Chlorophenyl)-3-Methyl-1,4-Dihydropyrano [2,3-c] Pyrazole-5-Carbonitrile (IId) as a precursor.

VI. Synthesis of Remaining Compounds(IIIa-o)

- The remaining compounds (IIIa-o) were synthesized following the same procedure as described above, and they were recrystallized using methanol. The percentage yields ranged between 30-50%.

MATERIALS

- Round bottom flasks
- Alcohol for dissolving and recrystallization
- Glacial acetic acid
- Crushed ice for quenching reactions
- Filtration setup
- Melting point apparatus

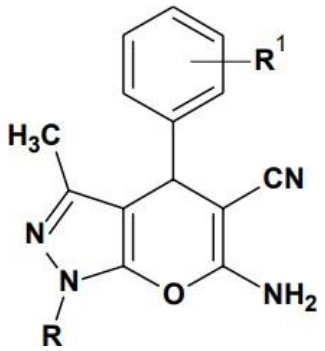
Spectral Data

- Spectral data for each compound, including IR, 1HNMR, and Mass Spectra, were collected and analyzed to confirm the chemicalstructures and purity.

Physical Data

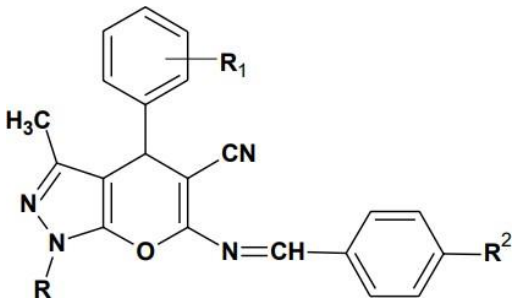
- The physical characterization data for each synthesized compound, including molecular formula, molecular weight, melting point, and percentage yield, were recorded and presented in tables.

Table 1: Physical data of synthesized compounds (IIa-o).



S.No	Compound code	R	R1	Molecular Formula	Mol.Wt	Melting point	Yield (%)
1	IIa	H	4-OH	C14H12N4O2	268	210-212 ^{0}C	60
2	IIb	H	3,4-di-OCH3	C16H16N4O3	312	188-190 ^{0}C	68
3	IIc	H	2-NO2	C14H11N5O3	297	230-232 ^{0}C	72
4	IId	H	2-Cl2	C14H11ClN4O	287	240-242 ^{0}C	64
5	IIe	H	4-F	C14H11FN4O	270	230-232 ^{0}C	75
6	IIf	C6H5	H	C20H16N4O	328	140-144 ^{0}C	65
7	IIg	C6H5	4-OH	C20H16N4O2	344	194-196 ^{0}C	67
8	IIh	C6H5	4-OCH3	C21H18N4O2	358	170-174 ^{0}C	70
9	IIi	C6H5	3,4-di-OCH3	C22H20N4O3	388	130-132 ^{0}C	78
10	IIj	C6H5	3,4,5-tri-OCH3	C23H22N4O4	418	160-162 ^{0}C	65
11	IIk	C6H5	2-NO2	C20H15N5O3	373	135-137 ^{0}C	66
12	II l	C6H5	3-NO2	C20H15N5O3	373	188-190 ^{0}C	78
13	IIm	C6H5	2-Cl2	C20H15ClN4O	363	142-145 ^{0}C	77
14	IIn	C6H5	3-Cl2	C20H15ClN4O	363	160-163 ^{0}C	69
15	IIo	C6H5	4-F	C20H15FN4O	346	168-170 ^{0}C	70

Table 2: Physical characteristic data of synthesized compounds (IIa-o).



S.No	Compound code	R	R1	R2	Molecular Formula	Mol. Wt.	Melting point	Yield (%)
1	IIIa	H	4-OH	OH	C21H16N4O3	372	175-180 ^{0}C	30
2	IIIb	H	3,4-di-OCH3	H	C23H20FN4O3	400	160-162 ^{0}C	42
3	IIIc	H	2-NO2	H	C21H15N5O3	385	210-212 ^{0}C	35
4	IIId	H	2-Cl2	H	C21H15ClN4O	375	180-183 ^{0}C	30
5	IIIe	H	4-F	OH	C21H15FN4O2	374	185-187 ^{0}C	45
6	IIIf	C6H5	H	H	C27H20N4O	416	160-164 ^{0}C	48
7	IIIg	C6H5	4-OH	H	C27H20N4O2	432	280-285 ^{0}C	42

8	IIIh	C6H5	4-OCH3	OH	C28H22N4O3	462	215-217 ^{0}C	38
9	IIIi	C6H5	3,4-di-OCH3	H	C29H24N4O3	476	160-162 ^{0}C	32
10	IIIj	C6H5	3,4,5 tri-OCH3	OH	C30H26N4O5	552	225-227 ^{0}C	40
11	IIIk	C6H5	2-NO2	H	C27H19N5O3	461	210-212 ^{0}C	42
12	III l	C6H5	3-NO2	H	C27H19N5O3	461	145-148^{0}C	44
13	IIIm	C6H5	2-Cl2	H	C27H19ClN4O	451	120-125 ^{0}C	40
14	IIIn	C6H5	3-Cl2	OH	C27H19ClN4O2	464	178-180 ^{0}C	45
15	IIIo	C6H5	4-F	OH	C27H19FN4O2	450	206 -208 ^{0}C	46

RESULTS AND DISCUSSION

Spectral Data

In this study, the synthesized compounds (Ia, Ib, IId, IIi, IIIi, and IIIn) were characterized using various spectroscopic techniques, including infrared (IR) and proton nuclear magnetic resonance (1H- NMR) spectroscopy. The spectral data provided valuable insights into the chemical structure of these compounds.

IR Spectra

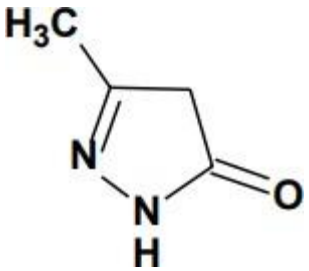
The IR spectra of the compounds revealed several key functional groups and characteristic absorption bands. Notably,the following bands were observed.

- Compound Ib displayed an aromaticCH stretching band at 3030 cm-1 and a CO absorption band at 1800 cm-1.
- Compounds IId, IIi, IIIi, and IIIn exhibited characteristic CN stretching absorption bands at 2191cm-1, 2193 cm-1, 2150 cm-1, and 2160 cm-1, respectively.
- Compound IId demonstrated NH and NH2 stretching bands at 3630 cm-1 and 3387 cm-1, while compound IIi exhibited an NH2 stretching band at 3333 cm-1.
- Compound IIIn displayed an OHstretching band at 3204 cm-1.

  These IR spectra data provided evidence of the presence of specific functional groups within the compounds and served as a useful tool for structural characterization.

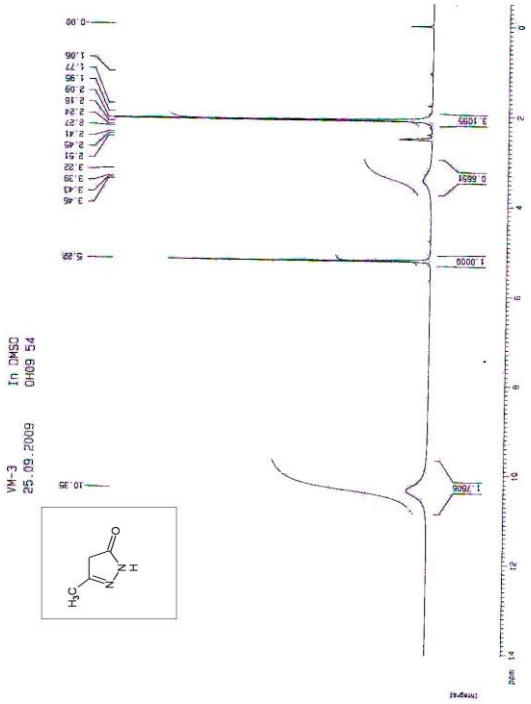
SPECTRAL DATA

Compound Ia



1 HNMR spectra

Value	Nature of segment	Type
10.3-10.4, 2H	BroadSinglet	2H of OH and NH
5.2-5.3, 1H	Singlet	H of -CH=
2.0-2.1, 3H	Singlet	3H of CH3



1H-NMR Spectra

The 1H-NMR spectra of the compounds further elucidated their chemical structure. Key proton signals were identified, and chemical shifts were recorded. The following observations were made.

- Compound Ia exhibited a singlet between 5.2-5.3 ppm for one protonof CH= and singlets at 2.0-2.1 ppmand 10.3-10.4 ppm for three protonsof CH3 and two protons of OH and -NH groups, respectively.
- Compound Ib showed a multiplet between 7.1-7.9 ppm for five protons of an aromatic ring, and singlets at 2.1-2.0 ppm and 3.4-3.5 ppm for three protons of CH3 and two protons of CH2, respectively.
- Compound IIId displayed a multiplet between 7.2-8.2 ppm for four protons of an aromatic ring, a singlet at 2.0-2.2 ppm for three protons of CH3, and a broad singlet at 10.8-11.2 ppm for one proton of -NH group.
- Compound IIi exhibited a singlet at4.7-4.8 ppm, 4.6-6.7 ppm, and 1.9- 2.0 ppm for two protons of NH2, one proton of pyran CH, and three protons of CH3, respectively.

These 1H-NMR spectra data provided detailed information about the chemical environment of the protons in each compound and aided in structural confirmation.

Mass Spectrometry (LCMS)

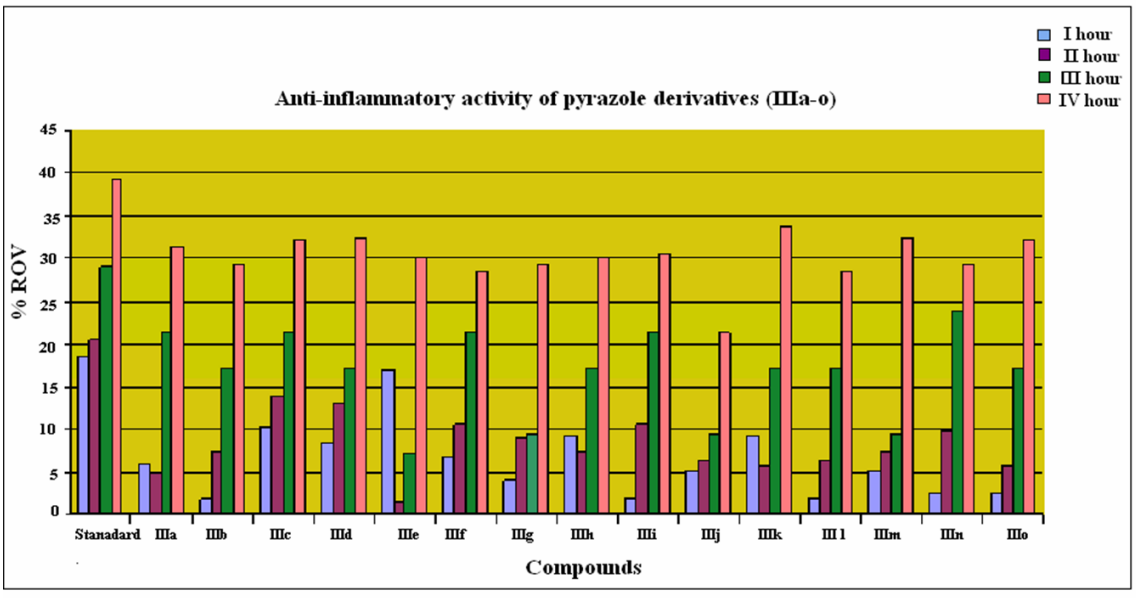
Molecular weight determination using LCMS confirmed the molecular weights of the synthesized compounds as follows: Ia (99), Ib (175), IId (288), IIi (387), IIIi (475), and IIIn (464). Molecular ion peaks were observed at these respective masses, validating the molecular weightassignments.

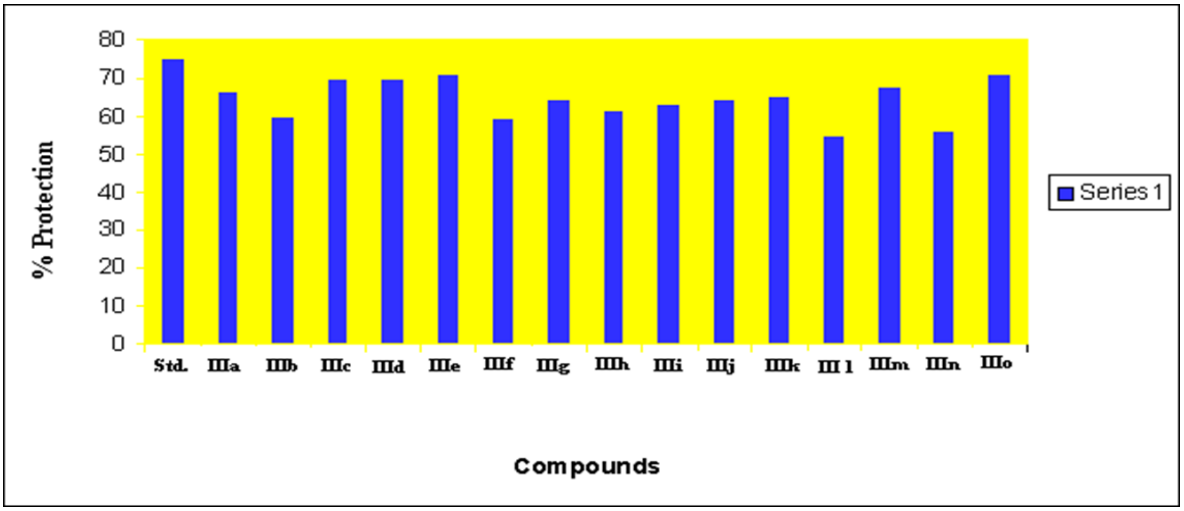
The presence of M+1 peaks in some compounds indicated the potential presenceof nitrogen or oxygen isotopes, while compounds IId and IIIn showed M+2 peaksdue to chlorine isotopes.

Anti-Inflammatory Activity

In vivo anti-inflammatory activity was evaluated using the Carrageenan-induced rat paw edema model. The study involved several groups of rats treated with different compounds, including a control group, a standard drug (Ibuprofen) group, and groups treated with the synthesized compounds (IIIa to IIIo).

The results indicated a significant reduction in paw edema volume in the treated groups compared to the control group. Percentage reduction in edema volume was calculated, demonstrating the anti-inflammatorypotential of the compounds. This reductionsuggests that the synthesized compounds may have anti-inflammatory properties, making them potential candidates for further investigation as anti-inflammatory agents.





Graph showing In-vitro anti-inflammatory activity of pyrazole derivatives (IIIa-o).

SUMMARY AND CONCLUSION

The objective of this research was to synthesize pyrazole-substituted derivatives and investigate their anti-inflammatory activity. The study revealed that these compounds exhibited significant anti- inflammatory activity. The presence ofstrong electron-withdrawing groups such as Cl and NO2 at ortho positions and OH and F at para positions was associated with good activity. Conversely, the presence of mild electron-donating groups, such as OCH3,resulted in moderate activity. Compounds with NO2 and Cl at meta positions showed less significant activity compared to those with para substitution.

The findings indicate that pyrazole moieties, when appropriately modified, can serve as effective anti-inflammatory agents. The synthesized compounds were screened for both in-vivo and in-vitro anti-inflammatory activities, demonstrating their potential in mitigating inflammation. This study suggests that pyrazoles can be a valuable resource for further research and development, with the potential to yield more potent and specific anti-inflammatory compounds while minimizing toxicity.

While some compounds exhibited promising activity at low dosage levels, it is crucial to emphasize that there is no completely safe drug. Medications have the power to alter physiological processes, and they come with both benefits and risks. To fully harness the benefits of these compounds, it is essential to consider their potential effects and seek realistic standardsof harmlessness.

Moving forward, further research, including molecular modeling, may contribute to the development of even better drugs. Compounds synthesized for biological testing might not always become new drugs, but they serve as valuable models for testing hypotheses and expanding our understanding of anti-inflammatory mechanisms. This research opens the door to exploring the possibilities of pyrazole-based compounds for future drug development, aiming for improved efficacy and safety in anti-inflammatory treatments.

REFERENCES

1. Paget GE, Barnes JM, Laurence DR, Bachrach AC. New Yark Academic Press, 1983; 1.
2. Bakr FAW, Hatem AA, Essam MA.Euro J Med Chem, 2008.
3. Hutter R, Kratzer. J Chem Ber, 2014. 1959; 92: 2014.
4. Finar IL, Lord GH. J Chem Soc, 1957; 3314.
5. Caton MPL, Jones DH, Slack R and woolridge KRH. J Chem Soc, 1964; 446.
6. Olah GA, Narang SC, Fung AP. J OrgChem, 1981; 46: 2706.
7. Hutter R, Schafer O, Justus JP. LiebigsAnn Chem, 1955; 593: 200.
8. Lipp, Dallacker F, Justus MS. LiebigsAnn Chem, 1958; 618: 11.
9. Finely JH and Volpp GP. J Het Chem, 1969; 6: 841.
10. Pino P, Piacent F, Fatti G. Gazz Chimital, 1960; 90: 356.
11. Bheemasankar Rao CH, Subba Raju GV. J Ind Chem Soc, 1986; 25(B): 400-03.
12. Ellis GP, Thomas IL. J Chem Soc Perkin Trans, 1973; I: 2781.
13. Mustafa A, Hismat OH. Chem Abstr, 1966; 65: 3823.
14. Aziz G, Nosseir MH. Ind J Chem, 1976; 12: 1-4.
15. Thakare VG, Wadodkar KH. Ind J Chem, 1986; 25(B): 610-12.
16. Wadodkar KN. Synthesis in heterocyclic compound, Ph.D. thesis, Nagpur University, Nagpur, 1977.
17. Mustafa A, Fleifel AM. J Org Chem, 1950; 24: 1740.
18. Osaman AM, Maghuraby MA. J Ind Chem Soc, 1977; L4: 394-98.
19. Ingle VN. J Ind Chem Soc, 1986; L13: 823-24.
20. Sachchar SP, Singh AK. J Ind Chem Soc, 1985; 12: 142-46.
21. Franco C, Simone C, Daniela S, Adriana B, Bruna B, Paola C, AriannaG, Matilde Y, Francisco O. Euro J of Med Chem, 2009; 30: 1-5.
22. Bakavoli M, Bagherzadeh G, MaryamV, Ali S, Mehdi PMM, Pordeli P, Maryam A. Euro J of Med Chem, 2009; 30: 1-4.
23. Floa FB, Adel SG. Euro J of MedChem, 2009; 44: 2172-77.

24. Babasaheb PB, Gawande SS, Bodane RG, Gawande NM, Khobragade NC. Bioorg and Med Chem, 2009; 17: 8168- 73.
25. El-Shimaa MN Abdel- Hafez, Gamal El-Din AA, Abuo-Rahma, Mohamed AA, Mohamed FR, Hassan HF. Bioorg and Med Chem, 2009; 17: 3829-37.
26. Bruno O, Brullo C, Francesco B, Schenone S, Spisani S, Maria SF, Katia V, Elisabetta B, Vigilio B, Giorgio C, Massimiliano T. Bioorgand Med Chem, 2009; 17: 3379-87.
27. Sureshbabu D, Edward JV, Ashton T H. Tetrahedron Letters, 2009; 50: 291-94.
28. Porter J, Payne A, Ben de Candole, Daniel F, Hutchinson B, Trevitt G, James T, Edwards C, Watkins C, Whitcombe I, Jeremy D, Stubberfield C. Bioorg and Med Chem Letters, 2009; 19: 230-33.
29. Mohammad A, Abdul RB, Fareeda A,Amir A. Euro J of Med Chem, 2009; 44(1): 417-25.
30. Guiping O, Chen Z, Xue JC, Bao S, Pinaki SB, Yang S, Jin LH, Xue W, DeYH, Zeng S. Bioorg Med Chem, 2008;16: 9669-9707.
31. Nada M A, Hamdi MH, Nadia GK andOmar AM. Molecules, 2008; 13: 1011-24.
32. Khan R, Imam UM, Sultan AM, Mahammad MH and Rabiul Islam Md.Bangladesh J Pharmacol, 2008; 3: 27- 35.
33. Adnan AB, Hayam MA, Yasser SAG,Alaa El-Din AB, Azza B. Euro J of Med Chem, 2008; 43: 456-63.
34. Om Prakash, Rajesh Kumar, SehrawatR. Euro J Med Chem, 2008; 42(6): 868-72.
35. Gupta S, Ligia MR, Ana PE, Ana MF,Sao JNS, Nazareth N, Honorina C, Marta PN, Fernandes E, Madalena P, Nuno MFSA, Natercia B. Euro J Med Chem,2008; 43: 771-80.
36. David K, Uros G, Anton M, Dahmann G, Stanovnik B, Jurij S. Tetrahedron, 2007; 63:11213-222.
37. Nesrin GK, Samiye Y, Kupeli E, Salgin U, Ozen O, Gulberk U, Yesilada E, Kendi E, Akgul Y and Altan BA. Bioorg and Med Chem, 2007; 15: 5775-86.
38. Xia Y, Dong ZW, Zhao BX, Xiao G, Meng N, Shin DS and Miao JY. Bioorg and Med Chem, 2007; 15: 6893-99.
39. Olga B, Brullo C, Francesco B, Angelo R, Schenone S, Mario SF, Katia V and Susanna S. Bioorg and Med Chem Letters, 2007; Vol 17: 3696-3701.
40. Pande PS and Wadodkar KN. Ind J Het Chem 2007; 17: 19-22.
41. Jagadhani SG, Kale SB, ChaudharyCS, Sangle MD, Randhavane PV and Karale BK. Ind J Het Chem, 2007; 16:255-58.
42. Subash MS, Hengmiao C, Kristin ML,Shavnya A, Martha LM, Bryson R, Jason D, Li C, Robert JR, David AK, Li J, Burton HJ, Carl BZ, Donald WM, Carol FP, Scott BS,

Annette MS, David MG, Hickmann A, Michelle LH and Michael PL. Bioorg and Med Chem Letters, 2006; 16: 1202-06.

43. Subash MS, Kristin ML, Shavnya A, Martha LM, Bryson R, Cheng H, Robert JR, David AK, Li J, Burton HJ,Carl BZ, Donald WM, Carol FP, ScottBS, Annette MS, David MG, SuzanneSt. Denis, Hickmann A, Michelle LH and Michael PL. Bioorg and Med Chem Letters, 2006; 16: 288-92.
44. Wageeh SE, Momen AAK and EmamMH. Ind J Het Chem, 2006; 45(B):2091- 98.
45. Vartale SP, Jadhav JS, Kale MA and Kuberkar SV. Ind J Het Chem, 2006; 16: 163-66.
46. Moh Amir, Agarwal HK, Jadhav SA and Kumar H. Ind J Het Chem, 2006; 16: 175-78.
47. Surkhan R, Nagarajan G, Balasubramaniam V, Suganthi K and Velrajan G. Ind J Het Chem, 2005; 14: 201-04.
48. Wadhan SA, Wadodkar KN and PandePS. Ind J Het Chem, 2005; 15: 11-14.
49. Ezawa M, Garvey DS, Janero DR, Khanapur SP, Leets LG, Martino A, Ranatunge RR, Schwalb DJ and Young DV. Letters in Drug Design and Discovery, 2005; 2: 40-43.
50. Rossella F, Fedele M, Franco C, Bolasco A, Daniela S, Paola C, Cristiano F and Giovanni S. Bioorg and Med Chem Letters, 2005; 15: 4632-35.
51. Akihiko T, Oyamada Y, Keiko O, Hideo T, Motoji K, Masaaki W and Jun-ichi Y. Bioorg and Med ChemLetters, 2005; 15: 4299-4303.
52. Hyun JP, Lee K, Su JP, Bangle A, Jong CL, Hee YC and Kee- In Lee. Bioorg and Med Chem Letters, 2005; 15: 3307-12.
53. Bhat BA, Dhar KL, Puri SC, Saxena AK, Shanmugavel M and Qazi GN. Bioorg and Med Chem Letters, 2005; 15: 2097-2102.
54. El-Saied AA, Mohamed AEB and Mohamed AB. Ind J Chem, 2004; 43(B): 1355- 59.
55. Solanki PR and Wadodkar KN. Ind J Het Chem, 2003; 13: 135-38.
56. Giuseppe D, Maggio B, Salvatore P, Demetrio R, Domenico S, Migliara O,Antonella C, Vincenza MCC, Maria AR. II Farmaco, 1998; 53: 350-56.
57. Sachchar SP, Singh AK. J Ind Chem Soc, 1985; L12: 142-46.
58. Sirrewiberg WE. Chem abstr, 1978; 89.
1. 59. Desai NC, Trivadi PB, Unnadevi NK,Dave AM, Bhat KN. Ind J Chem, 1993;32(B): 760.
59. Ead HA, Hassanun HM, Abdullah MA. Arch pharma, 1991; 324: 35-37.
60. Sachchar SP, Singh AK. J Ind ChemSoc, 1985; L13: 242-46.
61. Ritch S, Horsfall JC. Chem Abstr, 1952; 56: 11543.
62. Mitra P, Nayak A. J Ind Chem Soc,1982; L9: 1005.

63. Parvati M, Mitra AG. J Ind Chem Soc, 1981; L 8: 695-69.
64. Sadasiva M, Rao R. J Ind Chem Soc,1982; L9: 1104.
65. Nayak A, Mitra AS. J Ind Chem Soc,1980; L7: 643-45.
66. Tiwari N, Dwivedi B, Nizamuddin.Bol Chem Farm, 1989; 128: 332-35.
67. Mohanty SK, Sridhar R. J Ind ChemSoc, 1977; 15:1146.
68. Mazahir K, Sharma R and Misra P. IndJ Chem, 2002; 41(B): 427.
69. Sachchar SP, Singh AK. J Ind Chem Soc, 1985; L11: 142-46.
70. Frangly AM, Chaban I, Khalil MA, Behkit AA. Arch Pharma, 1990; 325(5): 311- 15.
71. Coli B, Silerstrint. Exp Med Therap, 1957.
72. Saragan S, Somashekara S. J Ind Chem Soc, 1976; L3: 21-26.
73. Froesch ER, Wolaogel M. Mol Pharmacol, 1967; 3: 429-42.
74. Brunner HR, Eichenberger K. Experimentia, 1966; 22: 208.
75. Smith DL, Forist AA. J Med Chem,1965; 8: 350.
76. Arya VP, Grewal RS. Experentia1967; 23: 824.
77. Sweeny MJ, Dais FA. Cancer Res, 1973; 33: 2619.
78. Chasin M, Harris DH. Bio ChemPharmacol, 1972; 21: 2443.
79. Navinson T, Scholten H. A Chem SocAbstr, 1972; 52: 78-79.
80. Kerdawy MM, Agemy AA. Acta PolPharm, 1975; 7: 105.
81. Wrezicino U. Acta Pol Pharm, 1975;30: 433.
82. Gover RK, Moore JD. PhytoPathology, 1962; 52: 876.
83. Nayak A, Das S. J Ind Chem Soc, 1977; 54: 485.
84. Philip E, Deutsch. Chem Abstr, 1957; 51: 11383.
85. Bilgin AA, Palaska E, Sunal R. Arzneimittel for shcung, Oct 1993; 43(10): 1041.
86. Thangam C and Dhananjayan R.Indian J Pharmacology, 2003; 35: 388.
87. Cotran RS, Kurma V, Collins T and Robbins. Pathological basis of disease 6th ed. W B Saunder's Company 2001.
88. Kavimani S, Vetrichelvan T and Nagarajan NS. Indian Drugs, 2002; 99(3): 161.
89. Shivaji B, Tapas KS, Suvra M, Prabhash CD and Sridhar S. Ind J Pharmac, 2000; 32: 21.
90. Nivsarkar M, Mukherjee M, Patel M, Padh H and Bapu C. Indian Drugs, 2002; 39(5): 290.
91. Yamamoto and Gaynor 2006. Journalof Clinical Investigation, 107: 13.