Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (1):
Pg. 01-16

2(3*H*)Pyrrolone – A Biologically Active Scaffold (A Review)

YAKUB ALI[1], MOHAMMAD SARWAR ALAM[1]*, HINNA HAMID[1] and ASIF HUSSAIN[2]

[*a]Department of Chemistry, Faculty of Science, Jamia Hamdard, New Delhi - 110 062, India.
[b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard,
New Delhi - 110 062, India.
*Correspondence author E-mail: msalam@jamiahamdard.ac.in

http://dx.doi.org/10.13005/ojc/300101

(Received: January 25, 2014; Accepted: March 06, 2014)

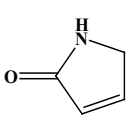
ABSTRACT

Pyrrolones are potent medicinal scaffolds and exhibit a broad spectrum of biological activities. This review throws light on the detailed synthetic approaches which have been used for the synthesis of pyrrolones. This has been followed by an in depth analysis of the pyrrolones with respect to their medicinal significance. This review may help the medicinal chemists to develop new leads possessing pyrrolone nucleus with higher efficacy.

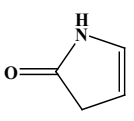
Key words : Pyrrolones, Benzyl Pyrrolone, anti-cancer, anti-inflammatory, anti-microbial activity.

INTRODUCTION

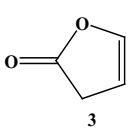
Pyrrolones are the five-membered heterocyclic lactams which are either Δ^3 (**1**) or Δ^4 (**2**) derivatives described by several authors[1,2].



1



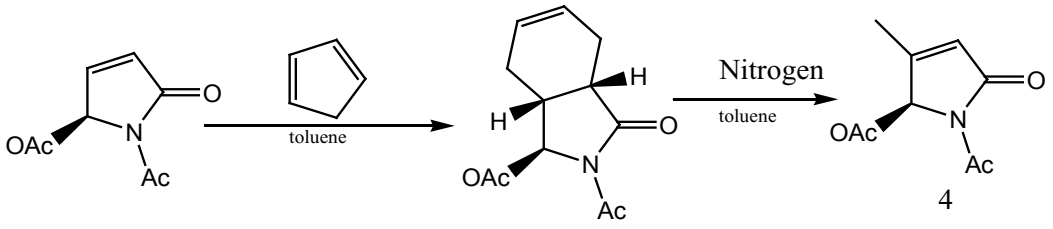
2



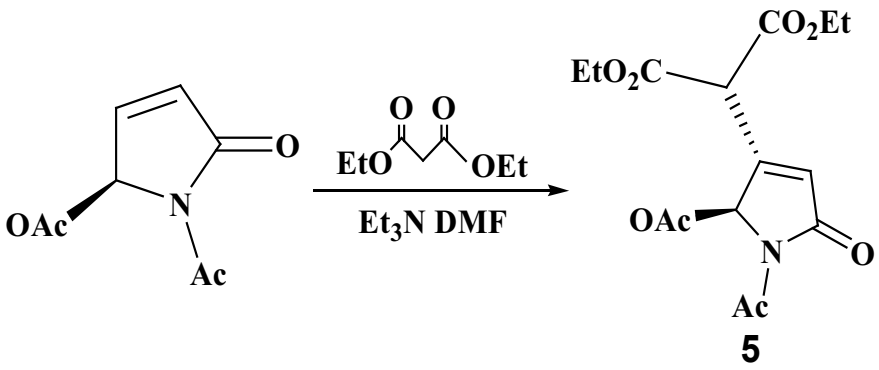
3

These are also known as pyrrolin-2-ones. The γ-lactone ring present in butenolide (**3**) derivatives possess significant reactivity and has been utilized in the synthesis of pyrrolone derivatives with potent biological acitivity[3,4]. Pyrrolone and *N*-benzyl pyrrolone derivatives were reported to have good antifungal, antibacterial and anti-inflammatory activities[5]. Pyrrolones have been proved important as chiral synthons used in the preparation of a variety of bioactive compounds[6]. The frequent use of these compounds as chiral intermediates provides a fast universal method for the determination of absolute configuration.[7] The chemistry of these versatile building blocks has been explored by a number of groups. Because of their multifunctional nature, these heterocycles can take part in several stereo selective transformations like conjugate additions [8,9], cycloadditions[10,11], acyliminium ion chemistry[12] and allylic substitution[13].

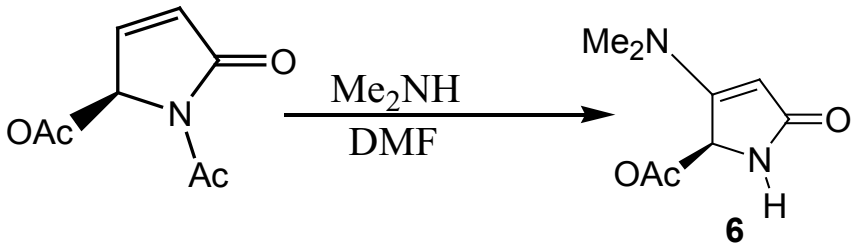
Cycloadditions



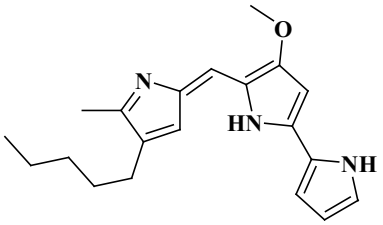
Conjugate additions



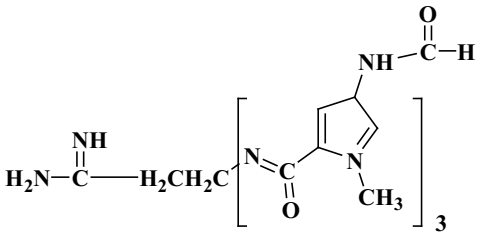
Acyliminium ion



The interest concerning these pyrrolinones is in part due to the presence of pyrrolic systems, which are also present in the natural products[14] *viz* vitamin B_{12}[15], prodigiosin[16], bile-pigments[17] and some antibiotics like distamycin.[18]



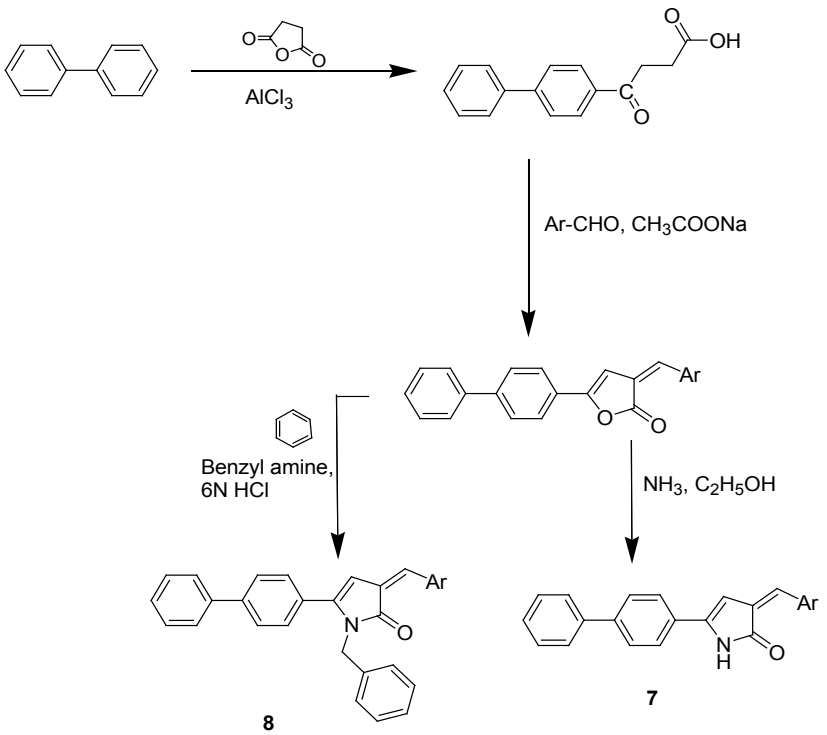
Prodigiosin



Distamycxin

Synthetic methodology of pyrrolinones

Synthesis of pyrrolones & N-benzylpyrrolones from 3-arylidene-5-biphenyl-2(3*H*) furanones

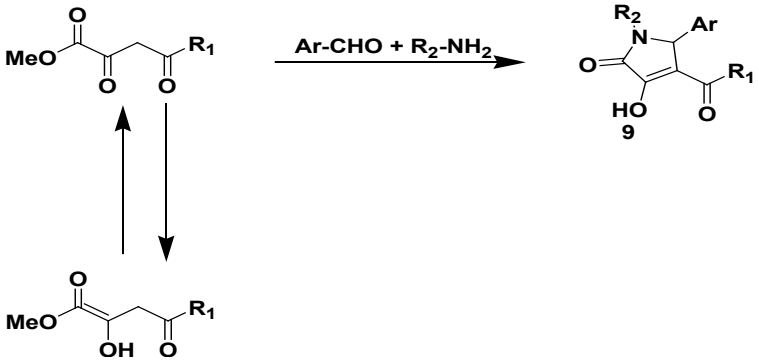


3-Arylidene-5-biphenyl-2(3*H*) pyrrolones (7) have been prepared by treating 3-arylidene-5-biphenyl-2(3*H*) furanones with dry ammonia gas in absolute ethanol. 3-Arylidene-5-biphenyl-1-benzyl-2(3*H*) pyrrolones (**8**) have been reported to be synthesized by reacting appropriate furanones with benzylamine in dry benzene to give [3]-ketobenzylamides which on lacatamization in 6N HCl give N-benzyl-pyrrolones[5].

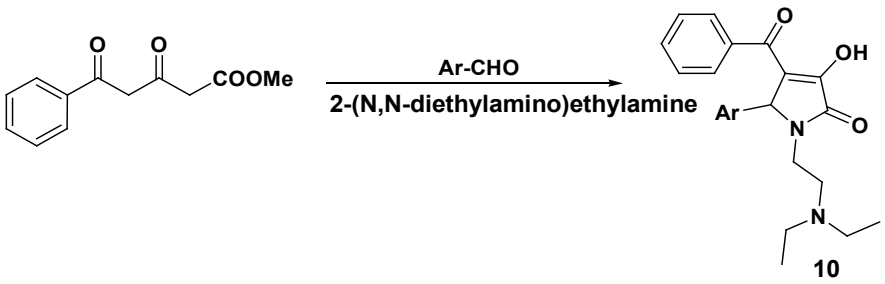
Synthesis of 1-substituted-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones

From ester of pyruvic acid derivatives

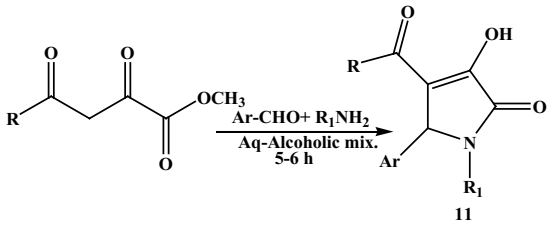
The reaction between equimolar amounts of esters of pyruvic acid with a mixture of aromatic aldehydes and amines gives 1-substituted-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones (**9**)[7, 19,-21].



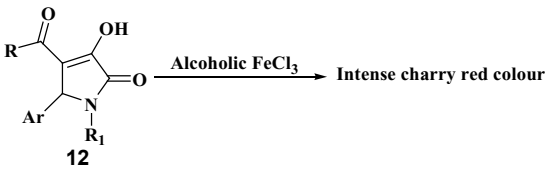
Instead of ester of pyruvic acid derivatives, esters of 4-aryl-2,4-dioxobutanoic acids[22] with aliphatic amines like 2-(N,N-diethylamino)ethylamine and aldehydes in ethanol at room temperature gives good yield.



Reactions conducted in aqueous alcohol mixtures with short time heating gives good yield[7].

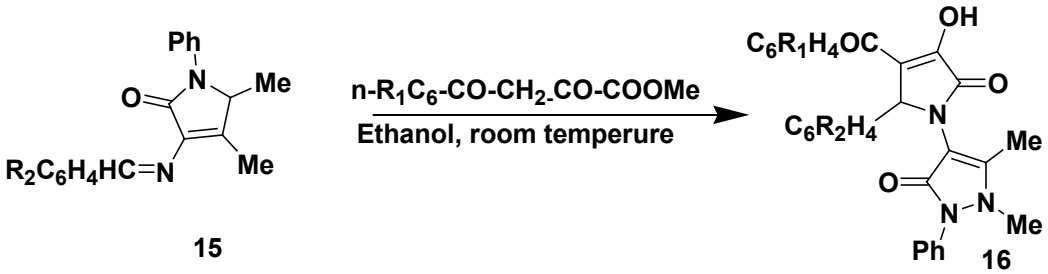


Pyrrolinones so obtained appear as light-yellow crystalline substances insoluble in water and soluble in ethanol, chloroform and DMSO.[20-22]All these compounds develop a characteristic intense cherry-red colour on reacting with an alcoholic solution of iron chloride[37].



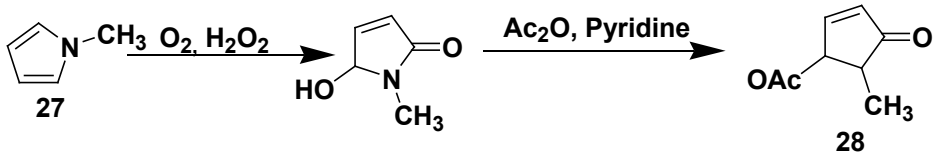
The interaction of benzoylpyruvic acid with mixture of aromatic aldehydes and amines involves several competing reactions. For this reason, the products include both substituted 4-benzoyl-3-hydroxy-2,5-dihydro-2-pyrrolones, benzoylpyruvic acid amides.[23]

1-(4-Antipyryl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones (**16**) have been synthesized by reacting esters of 4-aryl-2,4-dioxobutanoic acids with Schiff bases (**15**), which are obtained by the condensation of aromatic aldehydes with 4-amino antipyrine[22]. To a solution of 0.001 mole of a methyl ester of 4-aryl-2,4-dioxobutanoic acid in ethanol, a mixture of ethanolic solutions of benzaldehyde (0.001 mole) and 4-amino antipyrine (0.001 mole) was added at room temperature. The excess of solvent is distilled off and the product is crystallized from ethyl acetate[22].



Synthesis of an enantioselective enzymatic transesterification

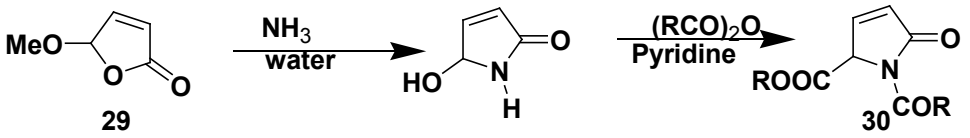
N-Methyl derivatives of Δ^3-pyrrolinones have been synthesized from pyrroles using an enantioselective enzymatic transesterification[33]. N-Methyl pyrrolinone (28) have been synthesized by photo-oxidation of N-methylpyrrole (27) followed by esterification. Subsequent enzymatic resolution by *Candida antarctica* mediated transesterification has been reported.



27 28

Synthesis of N-acyl derivatives of Δ^3-pyrrolinones from methoxy furanones

N-Acyl derivatives of Δ^3-pyrrolinones (**30**) have been reported to be synthesized from 5-methoxy-3-furan-2-one (**29**) using an enantioselective enzymatic transesterification.[33]

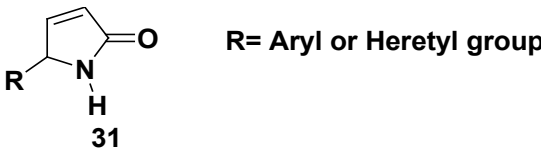


29 30

Synthesis of C-5 substituted –δ^3-pyrrolin-2-ones

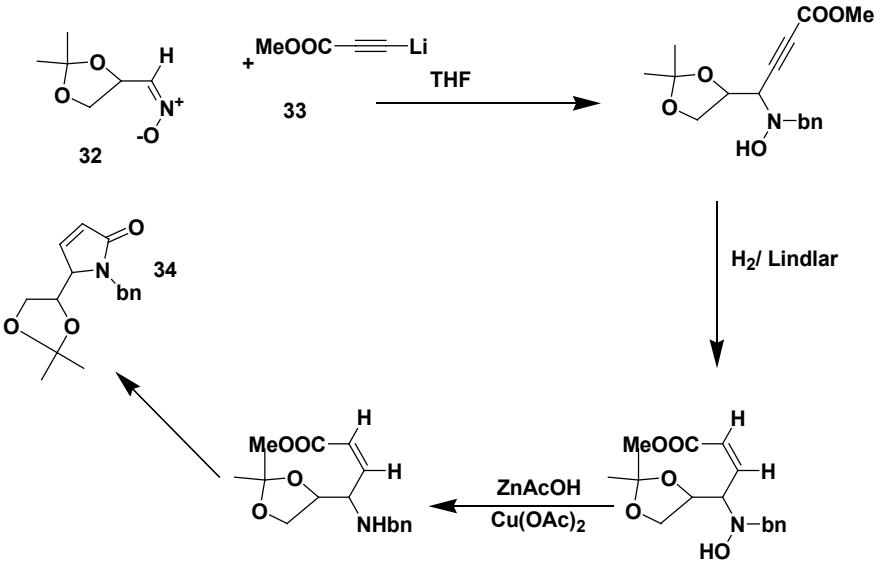
From nitrone

C-5 substituted-δ^3-pyyrollinones (**31**)have been synthesized from nitrones[17].



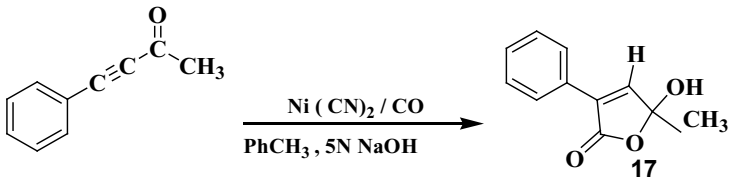
31

The addition of lithium propiolate (**33**) to nitrone (**32**) takes place with complete *syn* selectivity and in quantitative yield to afford the prop-2-ynyl hydroxylamine.[34,35]



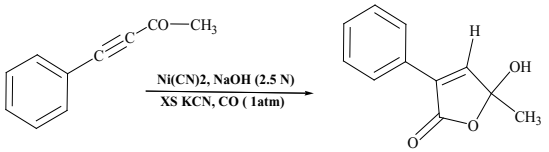
Synthesis of unsaturated hydroxy-butyrolactones under phase transfer conditions

Unsaturated hydroxy-butyrolactones or 2-alkylidene-3-ketocarbocyclic acids (**17**) can be synthesized by carbonylation of α-ketoalkynes in the presence of $Ni(CN)_2$ under phase-transfer conditions[24].



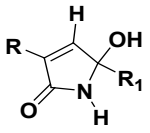
17

By changing the reaction conditions it is possible to obtain hydroxyl-butyrolactams (**18**) in good yields[25].

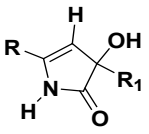


18

However the formation of hydroxylactams by hydrocyanation of α-ketoalkynes in water under mild conditions, it is possible to obtain hydroxyl butyrolactams (**19**) and (**20**)[26]



19

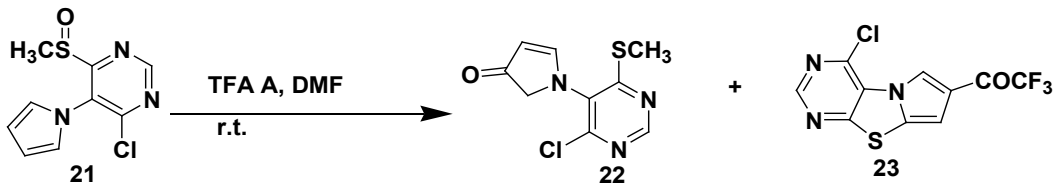


20

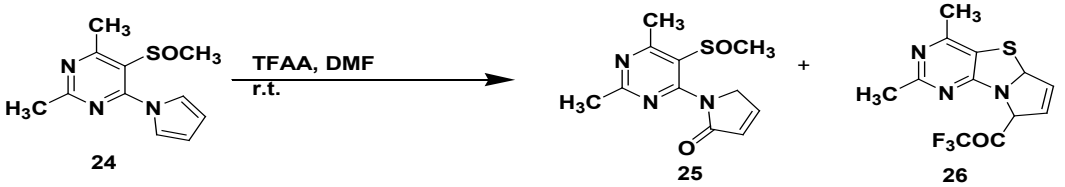
Synthesis of Δ^3 and Δ^4-pyrrolinones by oxidation of pyrrole

Using sulfoxide electrophillic sulfenylation:

Δ^3 Pyrrolinones with very small amounts of Δ^4 isomer can be obtained by the oxidation of pyrrole[25] during sulfoxide electrophilic sulfenylation (SES). Sulfoxide electrophilic sulfenylation (SES) is a useful technique for the synthesis of heterocycles. Pyrrole-containing sulfoxides have been exploited for intramolecular sulfenylation to form a wide variety of N,S-heterocycles. Typical (SES) reaction conditions *via* two possible reaction pathways accounts for pyrrolinones formation during SES cyclization.[27-29] Upon treatment with trifluro acetic acid (TFAA) (DMF, room temperature) compound (21) produced the expected SES product only as minor product(23) and the major product was the pyrrolinones (22). Similarly compound (24) produced a mixture of pyrrolinones (25) and (26) SES cyclization product[30-32].



21 **22** **23**

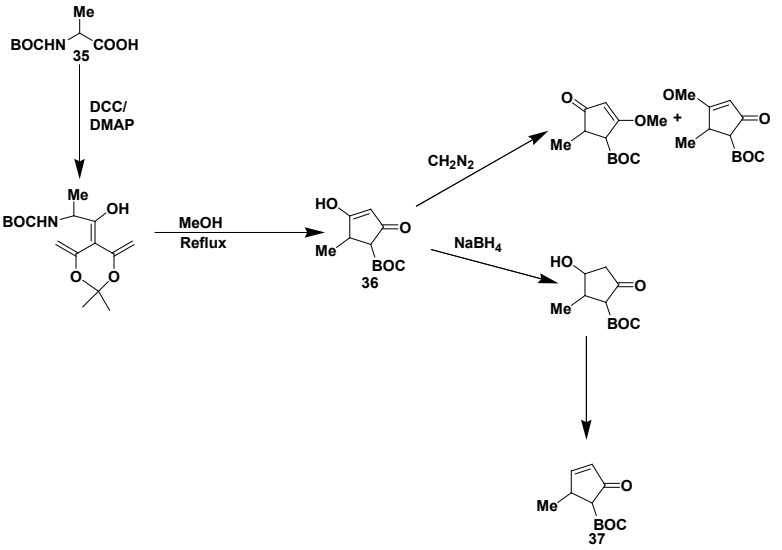


24 **25** **26**

The selective hydrogenation of the triple bond was achieved in 1 hr at ambient temperature and 1 atm pressure using the lindlar catalyst. The corresponding allylhydroxylamine was obtained in quantitative yields[36]. Further deoxygenation of hydroxylamine was accomplished with Zn-Cu catalyst in acetic acid as a solvent. Under these conditions, resulting allylamine could not be isolated since it cyclized spontaneously to the pyrrolin-2-one (**34**) which was obtained in 84% yield after purification by column chromatography[37]. This is a straight forward method of preparing enantiomerically pure ´[3]-pyrrolin-2-ones which can serve as templates for the construction of a number of highly functionalized 2-pyrrolidones and pyrrolidines. The latter has attracted much attention due to their ability to act as selective glycosidase inhibitors with a variety of therapeutic effects [38-42].

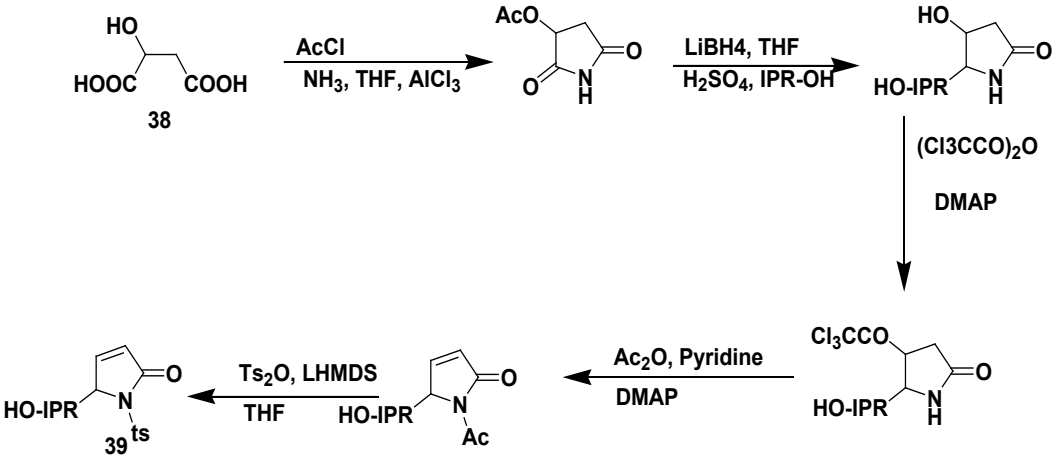
From N-boc protected amino acids

N-boc protected 5-methyl-[3]-pyrrolinone (**37**) has been synthesized from N-boc protected amino acids (**35**) by Jouin[42] and further improved by Ma[43]. (5S)-N-tert-butoxycarbonyl-4-hydroxy-5-methyl-3-pyrroli-2-one (**36**) was synthesized from N-boc protected L-alanine and meldrum's acid which was then reduced with $NaBH_4$[44] and hydroxyl group of resulting compound was eliminated to get N-boc protected 5-methyl-pyrrolinone[44-45].



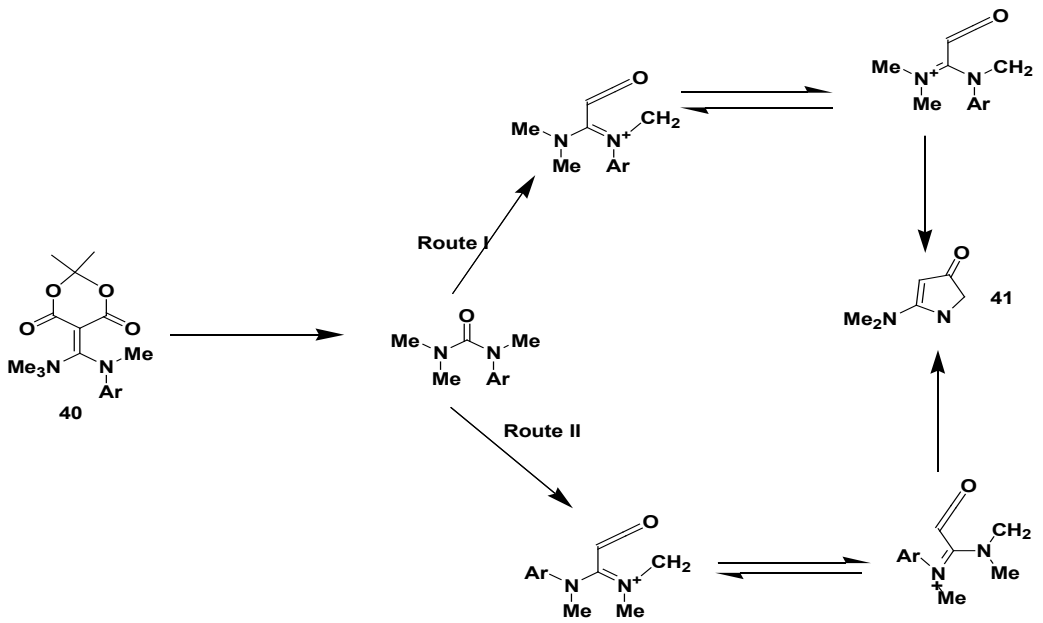
From (S)-malic acid

5-Isopropoxy-δ_3-pyrrolin-2-ones (**39**) can be obtained *via* stereo-selective synthetic route starting from (S)-malic acid (**38**)[43,45].



Synthesis of isomeric pyrrolones by flash vacuum pyrrolysis of bis aminomethylene derivatives of meldrum's acid

Under flash vacuum pyrrolysis[46,47] (FVP) conditions (600°C, 0.005 Torr) bis-amino methylene derivatives of meldrum's acid (40) were transformed into mixtures of the pyrrolones[42]. FVP provides a simple and direct synthetic route to 1-substituted-3-hydroxypyrroles and their tautomers i.e. 1*H*-pyrrol-3-(2*H*)-ones. Its mechanism was investigated by Brown and Eastwood[57] and more recently by Wentrum *et al.*[49].

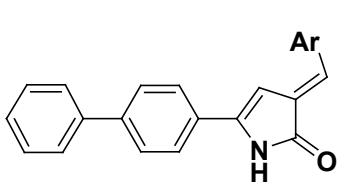


Spectral Properties

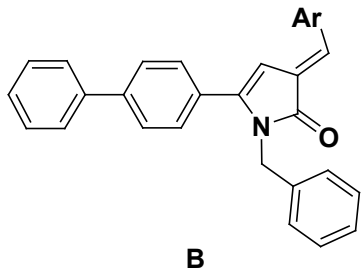
Circular dichroism (CD) spectra

In case of the simple 3-pyrrolin-2-ones bearing no substituents on the olefinic bond, the maximum of the π-π* cotton effect is observed at λ_{max} 200 nm. The maximum of the π-π * cotton effect is seen at longer wavelength, around 230 nm, where the UV spectrum displays a broad shoulder. The 3-pyrrolin-2-ones with an oxygen substituent at C (5) generally display much stronger cotton effects than those containing alkyl group. A methoxy substituent at C(3) shifts the positions of the π-π * band to λ_{max} 230 nm, as does tosyl substitution at N^1. 3-Pyrrolin-2-ones with an imide-type group (R^2 = acyl) display an additional cotton effect at 280 nm, presumably due to a second π-π * transition. Such double π-π * cotton effects are observed at 250 nm in a saturated imides[43] and result from the transitions involving combinations of the carbonyl n orbitals of opposite symmetry. This cotton effect however is much smaller than the n-π* cotton effects caused primarily by the α,β-unsaturated lactam chromophore[49-52].

Spectral data of representative compounds



A



B

^{1}H NMR: In structure A, the chemical shift (δ) value at 6.44-6.95 ppm confirmed the presence of proton at C-4 of pyrrolone ring. Also, the chemical shift ranging between 7.39- 7.68 showed the presence of olefinic proton at C-3 position. Both these peaks appeared as singlet which further evidenced that these are not aromatic protons. The proton attached to N of pyrrolone ring generally appeared at δ = 7.92-8.10. The formation of benzyl pyrrolones (structure B) could be confirmed by disappearance of -NH proton and appearance of a sharp singlet at δ = 4.74-4.88. (methylene proton). IR: The IR spectra of structure A showed the absorption bands at 1680-1710 cm^{-1} due to the stretching vibrations of the lactam carbonyl groups[21]. MS: Generally, the mass spectra 3(H)-pyyrolin-2-ones showed peaks at M^+ and M^+- Ar with high intensities[26].

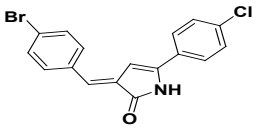
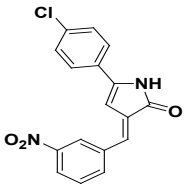
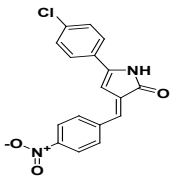
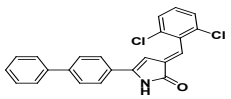
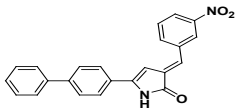
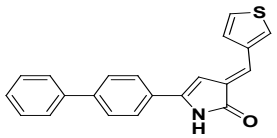
Biological Action

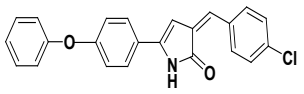
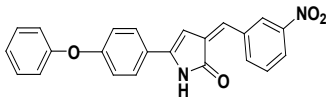
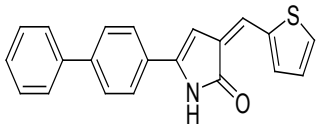
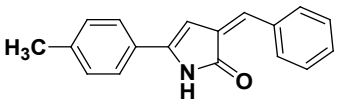
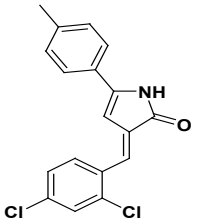
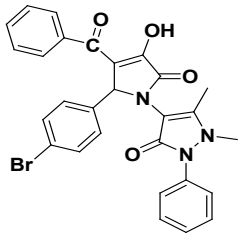
Various types of pharmacological activities shown by pyrrolinones are as follows

Antimicrobial activity

A series of 5-aryl-4-acyl-1-(N,N-dimethylaminoethyl)-3-hydroxy-3-pyrrolin-2ones were found to show weak bacteriostatic activity[55]. Also various compounds of type 1-substituted-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones and derivatives were found to be bacteriostatic against *Staphylococcus aureus* and *Escherichia coli*[40]**.** **3**-Arylidene-4-(biphenyl)- 2(3H)-pyrrolones [5], 3-Arylidene-5-(substituted)- 2(3H)-pyrrolones[57], 3-Arylidene-5-(4-phenoxy phenyl)-2(3H)-pyrrolones[58] and 3-Arylidene-5-(4-Methyl)- 2(3H)-pyrrolones[59] were found to have good antimicrobial activity.

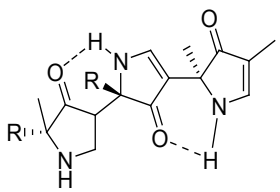
List of compounds showing anti microbial activity

Compound	Antifungal activity	Anti-bacterial activity	Reference
	*Rhizopus oryza* (6.25 MIC, μg mL^{-1}).	*E. coli, P. aeruginosa* (6.25 MIC, μg mL^{-1}).	56
	*C. albicans A. niger* (6.25 MIC, μg mL^{-1}).		56
	*Rhizopus oryza* (6.25 MIC, μg mL^{-1}).	*Pseudomonas aeruginosa* (6.25 MIC, μg mL^{-1})	56
	*Candida albicans* (2 MIC, μg mL^{-1})		5
	*Candida albicans* (2 MIC, μg mL^{-1})		5
	*Candida albicans* (2 MIC, μg mL^{-1})		5

	*Candida albicans* (10 MIC, µg mL^{-1})		57
	*Candida albicans* (10 MIC, µg mL^{-1})		57
	*Candida albicans* (10 MIC, µg mL^{-1})		5
	*Candida albicans* (15 MIC, µg mL^{-1})		58
	*Candida albicans* (25 MIC, µg mL–1)	*Pseudomonas aeruginosa* (50 MIC, µg mL–1)	58
		*Escherichi coli,* (62 MIC, µg mL–1) *Staphylococcus aureus* (500 MIC, µg mL–1)	55

Antiviral activity

A number of synthesized pyrrolinones has shown antiviral activity. N-methylated-3,5-linked bis-pyrrolin-4-ones derivatives have been found to be orally bioavailable inhibitors of the HIV-1 protease[60-63].

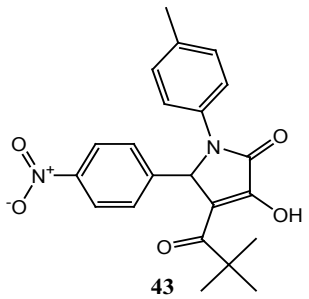


3,4 - linked poly pyrroline-4-one

42

Antitumour activity

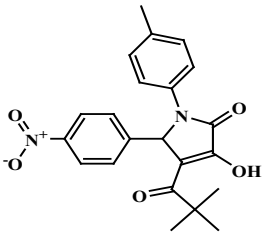
The compound 3-hydroxy-5-nitrophenyl-4-pivaroyl-2,5-dihydro-2-pyrrolone (43) exhibits antitumour activity[19]and inhibited the growth of lung cancer (Tumour Growth = 45%) and CNS cancer (Tumour Growth = 33%)[19].



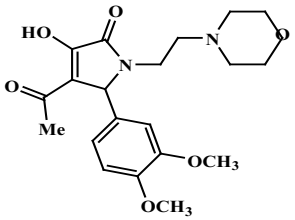
43

Nootropic / Antiamnesic activity

The compounds 3-hydroxy-5-nitro phenyl-4-pivaroyl-2,5-dihydro-2-pyrrolones (44)[19] and 4-Acetyl-5-(3,4-dimethoxy-phenyl)-3-hydroxy-1-1(2-piperidin-1-ylethyl)-2,5-dihydro-2-pyrrolones (45)[63] were found to have antiamnesic activity. The drugs were characterized by the ability to eliminate amnesia, increase the latent period and change the number of animals in the test group visiting a dark compartment of the experimental box. The time of stay in the light and dark compartments was determined three minutes after drug injection[19]. All synthesized compounds favored recovery of the memory trace in the test rats, as evidence by a drop in the number of animals visiting the dark compartment and the time of stay there[66].



44

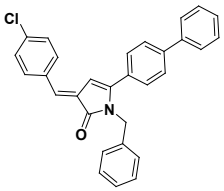
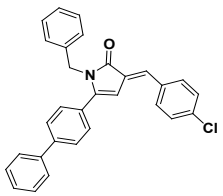


45

Anti-inflammatory activity

2-Arylidene-4-biphenyl-but-3-en-4-olides and their corresponding pyrrolones and N-benzyl-pyrrolones[4] (Table 1), 2-Arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides and their corresponding pyrrolones and N-benzyl-pyrrolones[58] (Table 2) were found to exhibit anti-inflammatory activity. A series of 3-Arylidene-5-(substituted aryl)-1-benzyl-2(3*H*)-pyrrolones were also found to have promising anti-inflammatory activity[57] (Table 3). But the anti-inflammatory activity decreased by the substitution of oxygen atom of butenolide ring with NH (pyrrolones), while substitution of oxygen atom with benzylamine moiety (N-benzyl-pyrrolones) markedly increased the activity. A series of 3-arylidene-5-(4-chloro-phenyl)-2(3H)-benzyl pyrrolones were found to show promising anti-inflammatory activity[67]. (Table4).

Table 1: Anti-inflammatory activity of 2-Arylidene-4-biphenyl-but-3-en-4-olides and their corresponding pyrrolones and N-benzyl-pyrrolones

Compound	% inhibition
	55 at 3 h
	62 at 3h

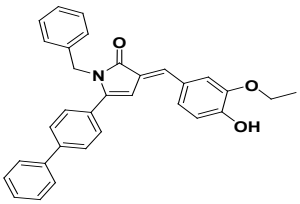
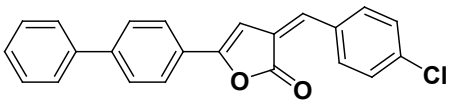
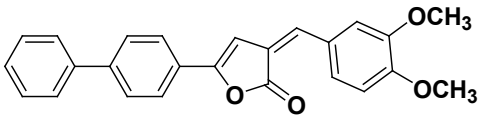
	55.2 at 3h
	52.5 at 3h
	54.2 at 3h

Table 2: Anti-inflammatory activity of 2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides and their corresponding pyrrolones and N-benzyl-pyrrolones

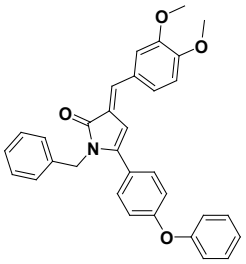
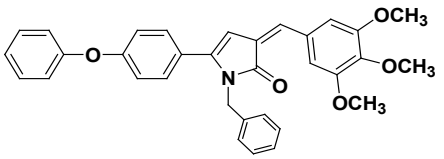
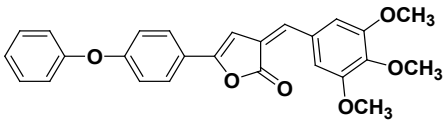
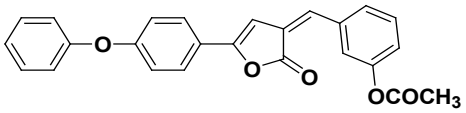
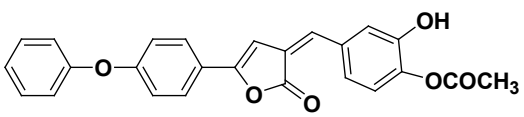
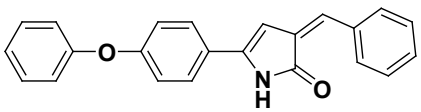
Compound	% Inhibition
	51
	58
	45.6
	48.38
	45.6
	19.35

Table 3: Anti-inflammatory activity of 3-Arylidene-5-(substituted aryl)-1-benzyl-2(3H)-pyrrolones

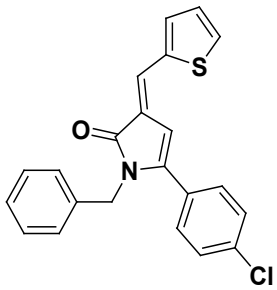
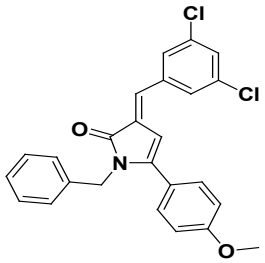
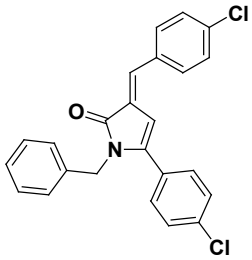
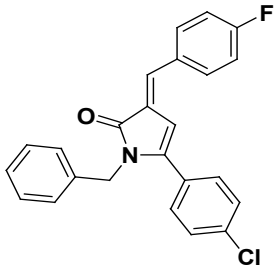
Compound	% Inhibition
	54.83
	61.31

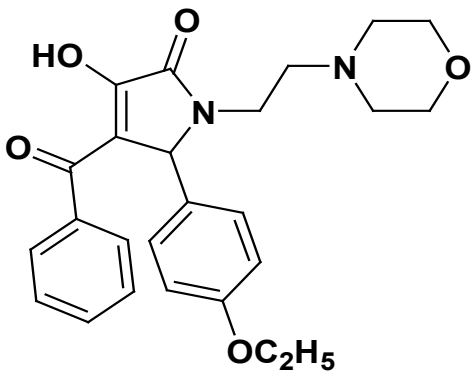
Table 4: Anti-inflammatory activity of 3-arylidene-5-(4-chloro-phenyl)-2(3H)-benzyl pyrrolones

Compound	% Inhibition
	88.88
	89.50

Analgesic activity

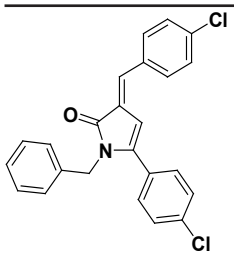
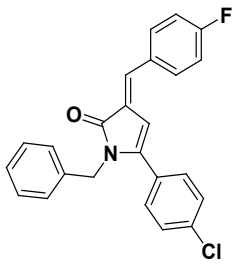
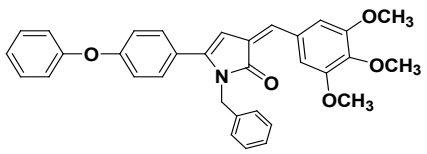
A series of 3-Arylidene-4-(4-phenoxy-phenyl)1-benzyl-2-(3H) pyrrolones 57 and 3-Arylidene-4-(4-chloro -phenyl)1-benzyl-2-(3H) pyrrolones65 were found to have promising analgesic activity.

The compounds of type 3-hydroxy-1,5-diaryl-4-pivaloyl-2,5-dihydro-2-pyrrolones and their derivatives were found to have potent analgesic activity[63].

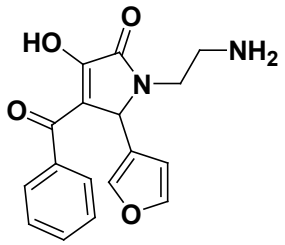


46

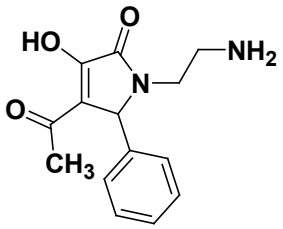
Table 5: Analgesic activity of pyrrolones

Compound	Inhibition
	57.83
	59.03
	51.33

A series of disubstituted-1-(2-amino ethyl)-3-hydroxy-3-pyrroline-2-ones and their derivatives have been reported to posses showed analgesic activity.[66]



47



48

CONCLUSION

It may be concluded that pyrrolones and N benzyl pyrrolones exhibit a broad spectrum of biological activities like anti-inflammatory, anticancer, antibacterial, antifungal, antiviral, analalegic and anti-HIV activities. Thus the pyrrolone scaffold still remains as therapeutic target for the development of new leads in the modern medicinal chemistry. The physical, chemical and the pharmacokinetic properties of pyrrolones still maintains the importance of this moiety inspite of the rising levels of drug resistance in today's era.

REFERENCES

1. Langenbeck, W.; Boser, H., *Chem. Ber.,* 84, 526 (1951): Grab, C. A.; Anklihelv, P., *Chim. Acta*., **32**: 2010 (1949).
2. Bordner, J.; Rpoport, H., *J. Org. Chem*., **30**, 3824 (1965): Atkinson, J. H.; Johnson, A. W., *J. Chem. Soc*., 5999 (1965).
3. Awad, W. I.; Hashem, A. I.; El-Badry, K., *Ind. J. Chem*., **13**, 1139 (1975).
4. Khattab, S. A.; Honsy, M., *Ind. J. Chem*., 19B, 1038 (1980).
5. Khan, M. S.Y.; Husain, A., *Pharmazie*, 57(7), 448-452 (2002).
6. Casiraghi, G.; Spanu, P., Rassu, G ; PINNA, L.; Ulgheri, F. *J. Org. Chem.,* **59**, 2906 (1994).
7. Gawronski, J. K.; Oeveran van, A.; Deen Van Deer, H.; Leung, C. W.; Feringa, B. L., *J. Org. Chem*., **61**, 1513 (1996).
8. Jimenez, M. D.; Ortega, R.; Tito, A.; Farina F., *Heterocycles*, **27**, 73 (1988).
9. Koot, W. J.; Hiemstra, H.; Speckamp, W. N., *Tetrahedron:Asymmetry*, **4**, 1941 (1993).
10. Koot, W. J.; Hiemstra, H.; Speckamp, W. N., *J. Org. Chem*., **57**, 1059 (1992).
11. Cooper, D. M.; Grigg, R.; Hargreaves, S.; et al., *Tetrahedron*, **51**, 7769 (1995).
12. Koot, W. J.; Hiemstra, H.; Speckamp, W. N., *Tetrahedron Lett.*, **3**, 7969 (1992).
13. Cuiper, A. D.; Kellog, R. M.; Feringa, B.L., *Chem. Commun*., 655 (1998).
14. Birchall, G. R.; Hughes, C. G.; Rees, A. H., *Tetrahedron Lett.*, 4879 (1970).
15. Bonnet, J. R.; Canon, J. R.; Clark, A. W.; Johnson, A. W.; et al., *J. Chem. Soc*., 1158 (1957).
16. Raport, H; Holden, K. G., *J. Am. Chem. Soc*., 84: 635 (1962).
17. Salmon, M.; Diaz, E.; Rock, M. C.; Fensalu, C., *Org. Magn. Reson.*, 126 (1976).
18. Grehn, L.; Ragnarsson, U., *J. Org. Chem*.**, 46**: 3492 (1981).
19. Koz'minykh, V. O.; Lgidov, N. M.; Zykova, S. S.; *et al., Pharma. Chem. J*., 36(4): 188-191 (2002).
20. Gein, V. L.; Kasimova, N. N.; Voronina, E. V.; Gein, L. F., *Pharma. Chem. J*., **35**(3): 151-154 (2001).
21. Gein, V. L.; Gein, L. F.; Porseva, N. Yu.; Voronina, E. V.; et al., *Pharma. Chem. J*., **32**(9): 477 (1998).
22. Gein, V. L.; Pitirimova, S. G.; Voronina, E. V.; et

al., *Pharma. Chem. J.*, **31**(11): 603 (1997).
23. Bezmaternykh, E. N., *Author's abstract of Cand. Sci. Chem.* Thesis [in Russia], Perm (2000).
24. Arzoumanian, H.; Magali, J.; Didier, N.; Cabrera, A.; Garcia, J. L.; Rosas, N., *Organometallics*, **14**: 5438 (1995).
25. Arzoumanian, H.; Magali, J.; Didier, N.; Cabrera, A.; Garcia, J. L.; Rosas, N., *Organometallics*, in press.
26. Rosas, N.; Chavez, M. I.; Garcia, J. L.; Sharma, P.; *et al., Analytical Sci.*, **14**: 585-588, june (1998).
27. Xia Shao; Kohrt, J.; Dallas, K. Bates, Dept. of Chem., Michigan Tech. Univ., Houghton, MI, 49931, ECHET96 Article 005: Masaru Tada.
28. Gilchrist, T. L.; John Wiley and Sons, *Heterocyclic Chemistry*, 2nd edition , New York, 207 (1992).
29. Epstein, W. W.; Sweat, F. W., *Chem. Rev.*, **67**: 247 (1967).
30. Yamanaka, H.; Abe, H.; Sakamoto, T., *Chem. Pharm. Bull.*, **25**: 3334 (1977).
31. Bates, D. K.; Habib, Q. A., *J. Heterocycl. Chem.*, **32**: 1447 (1995): Bates, D. K.; Tafel, K. A., *J. Org. Chem.*, **59**: 8076 (1994): Tafel. K. A.; Bates, D. K., *J. Org. Chem.*, **57**: 3676 (1992).
32. Russell, G. A.; Mikol, G., *J. Mechanisms of Molecular Migrations*; Thyagarajan, B. S. Ed.; Interscience Publishers: New York, **1**: 157-207 (1968).
33. Deen van der, H.; Cuiper, A. D.; Hof, R. P.; et al., *J. Am. Chem. Soc.*, **118**: 3801 (1996).
34. Merino, P.; Anono, S.; Castilloo, E.; Merchan, F.; Tajero, T., *Tetrahedron:Asymmetry*, 7 (1996).
35. Merchan, F.; Merino, P.; Tajero, T., *Theochem.*, **34**: 321(1996).
36. Merchan, F.; Merino, P.; Tajero, T., *Departmento de Quimica*, ICMA, *Universidad de Zaragoza*, CSIC, Zaragoza, Spain.
37. Winchester, B.; Fleet, G. W., *J. Glycobiol.*, **2**: 199 (1992).
38. Fleet, G. W. J., *Top. Med. Chem.*, 65, 149 (1988): Legler, G., *Adv. Carbohydr. Chem. Biochem.*, **48**: 319 (1990).
39. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P., *Chem. Rev.*, **95**: 1677 (1995).
40. Spanu, P.; Rassu, G.; Ulgheri, F.; Zanardi, F.; et al., *Tetrahedron Lett.*, **52**: 4829 (1996): Poli, G.; Cioli, F.; Maccagni, E.; et al., *Tetrahedron Lett.*, **36**: 8669 (1995).
41. A. Vandana, Y. Yadav and D. Kishore, *Orient J. Chem.,* **29**(4): 1643-1646 (2013).
42. Jouin, P.; Castro, B., *J. Chem. Soc., Perkin Trans.*, 1: 1177 (1987).
43. Ma, D.; Ma, J.; Ding, W.; Dai, L., *Tetrahedron:Asymmetry*, **7**: 2365 (1996).
44. Decico, C. P.; Grover, P., *J. Org. Chem.*, **61**: 3534 (1996).
45. Mattern, R. H., *Tetrahedron Lett.*, **37**: 291 (1996).
46. Hopman, J. C. P.; Hiemstra, H.; Speckamp, W. N., *Chem. Communi.*, 617 (1995).
47. Mcnab, H.; Jones, R. A.; Monahan, L, C., *in Pyrroles Part-2; New York*, 525 (1992).
48. Mcnab, H.; Gaber, A. M, *Synthesis*, 2059 (2001).
49. Wentrup, C.; Rao, V. V. R.; Frank, W.; et al., *J. Org. Chem.*, **64**: 3608 (1999).
50. Rassu, G.; Casiraghi, G.; Spanu, P.; pinna, l.; Fava, G. G.; *et al.*, *Tetrahedron:Asymmetry*, 3: 1035 (1992).
51. Nikitin, K. V.; Andyukhova, N. P., *Mendeleev Commun.*, **4**: 168-170 (1999); C.A., **131**(18): 243131w (1999).
52. Kateva, A. V.; Gein, L. F.; Gein, V. L.; Aliev, Z. G., *Russ. J. Gen. Chem.*, **69**(4): 668-669 (1999): C.A., **131**(24): 322498z (1999).
53. Liu, X.; Zang, L.; Van der Schyf, C. J.; et al., *Chem. Res. Toxicol.*, **12**(6): 508-512 (1999): C.A., 131(7), 84260u (1999).
54. Gein, V. L.; Shumilovskikh, E. V.; Andreichikov, Yu. S.; et al., *Khim.- Farm. Zh.*, 30(12), 37-40 (1996).
55. Gein, V. L.; Popov, A. V.; Kolla, V. E.; et al., *Khim.- Farm. Zh.*, **27**(5): 42 (1993).
56. Gein, V. L., Kasimova, N.N., Voronina, E.V.Gein., L.F, Pharm.; Chem., 5 31-34 (2001).
57. Khan, M. S. Y.; Husain, A., Sharma., S., *Ind. J. Chem.*, 41(B), 2160-2171 (2002).
58. Husain, A., Khan, M. S., A., Hasan, S.M., Alam, M. M., *Eur. J. Med,* **40**(12): 1394-404 (2005).
59. Husain, A., Hasan, S.M., L., Sukhibir., Alam, M. M., *Ind. J. Chem.*, **68**(4): 536-538 (2006).
60. Smith, A. B.; Favor, D. A.; Sprengeler, P. A.; et al., *Bioorg. Med. Chem.*, **7**(1): 9-22 (1999).

61. Polonski, t.; Milewska, M. J.; Gdaniee, M., *J. Org. Chem.*, **58**: 3134 (1993).
62. Koot, W. J.; Hiemstra, H.; Speckamp, W. N., *Chem. Communi.*, 156 (1993).
63. Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tajero, T., *Synth. Communi.*, **24**: 2537 (1994).
64. Gein, V. L., Yushkow, V.V.; Kasimova, N.N., Shuklina, M. S.; Vasilenia., M. Yu., *Pharm.; Chem.,* **39**: 33-39 (2005).
65. R. Moradivalikbani, Y. Hozhiboevy and Z. Heidarhezhad, *Orient J. Chem.*, **29**(4): 1647-1650 (2013).
66. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P., *Chem. Rev.*, **95**: 1677 (1995).
67. Alam, M. M., Hussain, A., Hasan, S. M., Suruchi, Anwer, T., *Eur. J. Med.* **44**(6): 2636-2642, (2009).
68. Gein, V. L., Yushkow, V.V.; Kasimova, N.N., Shuklina, M. S.; Vasilenia., M. Yu., *Pharm.; Chem.,* **39**: 484-487 (2005).