WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 3, 179-203. Review Article ISSN 2277– 7105

SYNTHESIS, REACTIVITY AND BIOLOGICAL APPLICATIONS OF HALOVINYL ALDEHYDES: A REVIEW

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Article Received on
05 Dec. 2017,

Revised on 26 Dec. 2017,
Accepted on 16 Jan. 2018

DOI: 10.20959/wjpr20183-10699

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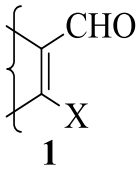
ABSTRACTS

Aim of our review is to provide an overview of the synthesis and diverse synthetic applications of halovinyl aldehydes, ranging from their preparation, transformations and important chemical applications in organic synthesis. These are important synthetic tools in organic synthesis. A large number of research groups have been reported their significant contributions on synthesis and reactivity of halovinyl aldehydes. These become important precursors for construction and development of new types organic derivatives with biological activity.

KEYWORDS: Halovinyl aldehydes, Vilsmeier-Haack's reaction, $DMF/POCl_3$.

INTRODUCTION

Regarding to the practical, economic and environmental issues, development of a clean procedure for the preparation of heterocyclic compounds is a tough challenge in modern heterocyclic chemistry. Halovinyl aldehydes are versatile intermediates in a large number of organic synthesis.[1] The Vilsmeier-Haack's reagent finds many applications in the synthesis of large number of heterocyclic compounds with halovinyl aldehydes moiety.[2]

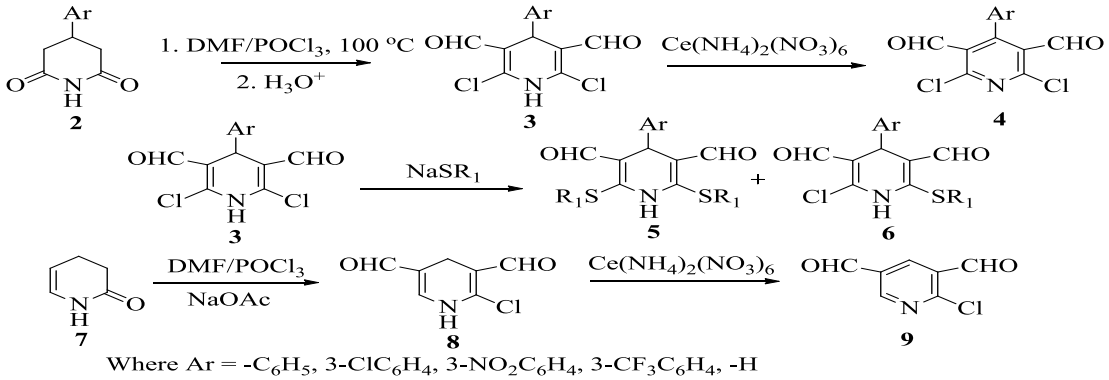


1 Where X= -Cl or -Br

Among heterocyclic compounds, halovinyl (chloro- or bromovinyl) aldehydes have great synthetic utility and hence have attracted by the scientific community, especially researchers involved in the synthetic organic chemistry. Over the past years, halovinyl aldehydes and their derivatives have attracted much attention due to their considerable biological and pharmacological activities as antimicrobial[3,4], anti-fungal[5], antivirus activities[6], anti-malarial[7], antimycotic activity[8], anti-inflammatory and analgesic activity[9,10], inotropic and chronotropic[11] etc. Recent developments in their derivatives such as Schiff's bases[12], pyrazoles[13], 1,2,4-triazole[14], tetrazole[15], benzopyrano fused with benzo-naphthyridinones[16], benzimidazoles[17], pyrido-quinolinones[18], thiazolidinone[19], mercapto/thione-substituted derivatives etc. over the last years. Most reaction types have been successfully applied and used in the production of biological active compounds.

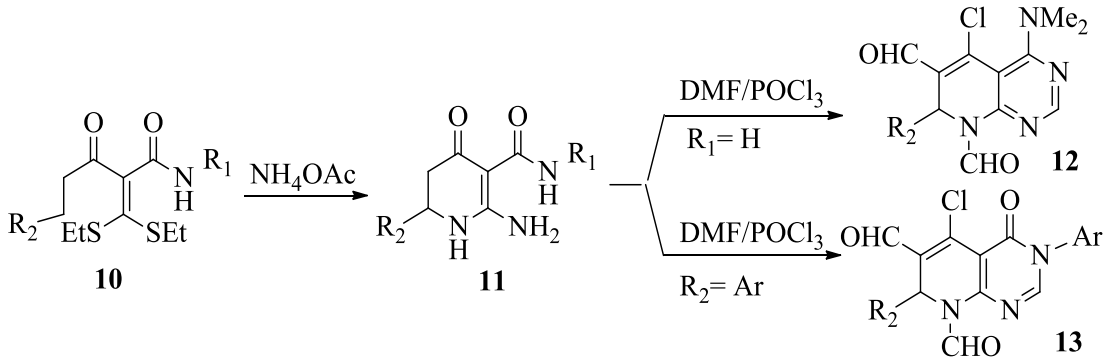
SYNTHESIS OF HALOVINYL ALDEHYDES AND THEIR DERIVATIVES: There have been a number of practically important routes for synthesis of halovinyl aldehyde.

From Piperidine-2,6-dione: Muchowski *et al.* synthesized 2,6-dichloro-4-(substituted phenyl)pyridine-3,5-dicarboxaldehyde **4** from 4-substituted phenyl glutarimides derivatives **2** with Vilsmeier-Haack reagent to give 1,4-dihydro-2,6-dichloro-4-arylpyridine-3,5-dicarboxaldehydes **3** which was oxidized with ceric ammonium nitrate to **4.**[20] Compound **3** reacted with sodium ethane thiolate to give a mixture of 2-(Ethylthio)-6-chloro-4-(substituted phenyl)-l,4-dihydropyridine-3,5-dicarboxaldehyde **5** and 2,6-Bis(phenylthio)-4-(substituted phenyl)-l,4-dihydropyridine-3,5-dicarboxaldehyde **6**. They also extended their work with 2-pyridone. 3,4-dihydro-2-pyridone **7** on treatment with Vilsmeier-Haack reagent gave 2-Chloro-1,4-dihydropyridine-3,5-dicarboxaldehyde **8** and oxidized with CAN to give 2-Chloropyridine-3,5-dicarboxaldehyd **9** (scheme 1).



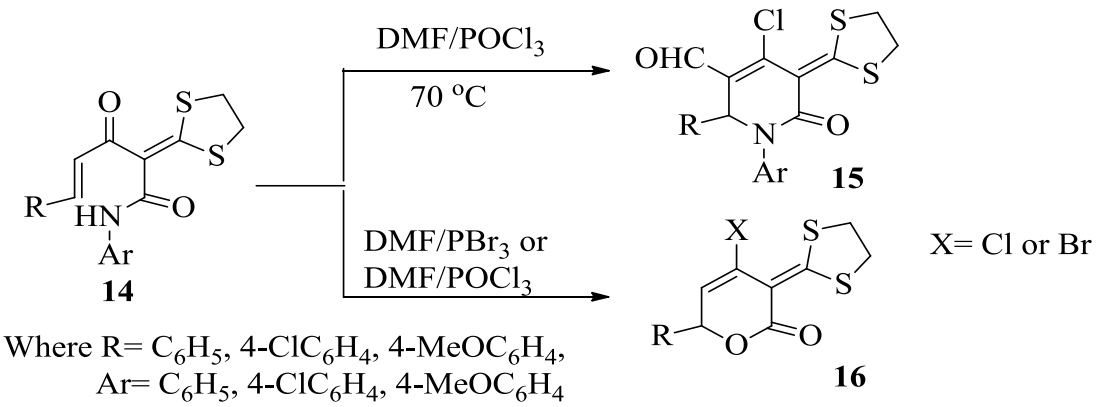
Scheme 1.

From α-Alkenoyl-α-carbamoyl ketene-(S,S)-acetals: An efficient and convenient method was documented regarding the synthesis of highly functionalized dihydropyrido[2,3-d]pyrimidines **11**. Treating α-alkenoyl-α-carbamoyl ketene-(S,S)-acetals **10** with ammonium acetate, followed by treatment with excess of Vilsmeier reagent (DMF/$POCl_3$) to give dihydropyrido-[2,3-d]pyrimidine derivatives, 7,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-ones **12** and 7,8-dihydropyrido[2,3-d]pyrimidines **13** (scheme 2).[21]



Scheme 2.

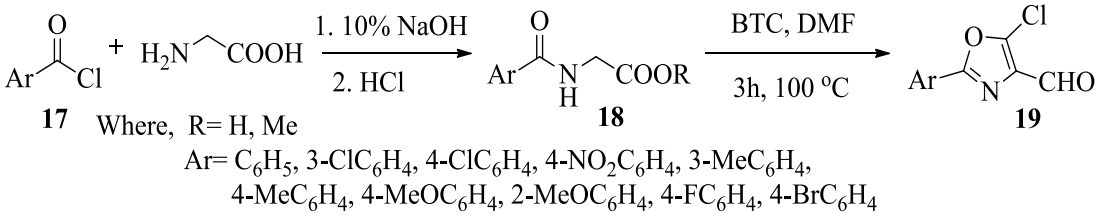
Wang *et al.* developed an efficient method for direct synthesis of polyfunctionalized unsaturated δ-lactones **15** and δ-lactams **16** from the reaction of α-alkenoyl-α-carboxyl/carbamoyl ketene S,S-acetals **14** and Vilsmeier reagents (DMF/ $POCl_3$ or DMF/PBr_3) via a cyclization followed by haloformylation sequence (scheme 3).[22]



Scheme 3.

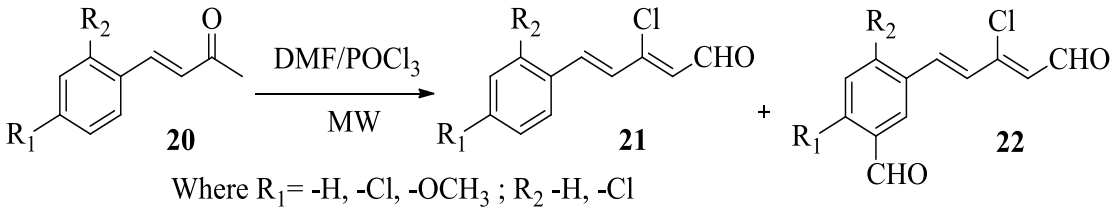
From Substituted N-arylglycine: Weike Su *et al.* developed a method for synthesis of 5-chloro-2-aryloxazole-4-carbaldehyde **19** from substituted N-arylglycine **18** on reaction with the Vilsmeier reagent. Compound **18** was prepared by reaction of solution of glycine in 10%

NaOH with substituted benzoyl chloride, followed by acidification with concentrated HCl (scheme 40).[23]



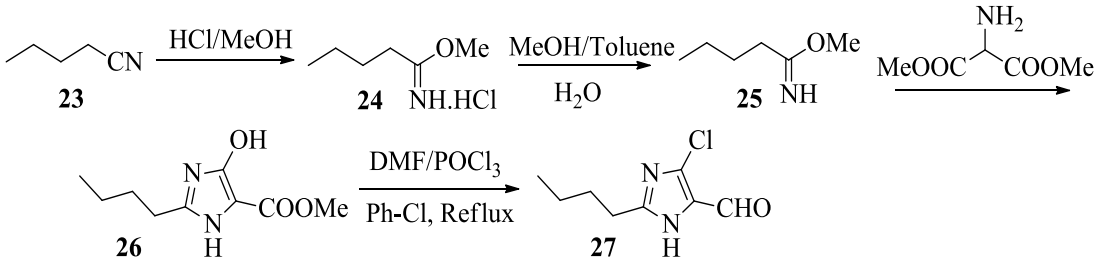
Scheme 4.

From Benzalacetone: Perumal *et al.* synthesized 3-chloro-5-arylpenta-2,4-dien-1-als 2**1** and 3-chloro-(5-formylaryl) penta-2,4-dien-1-als **22** by reaction of disubstituted benzalacetone **20** with Vilsmeier-Haack's reagent under microwave irradiation for a short time (scheme 5).[24]



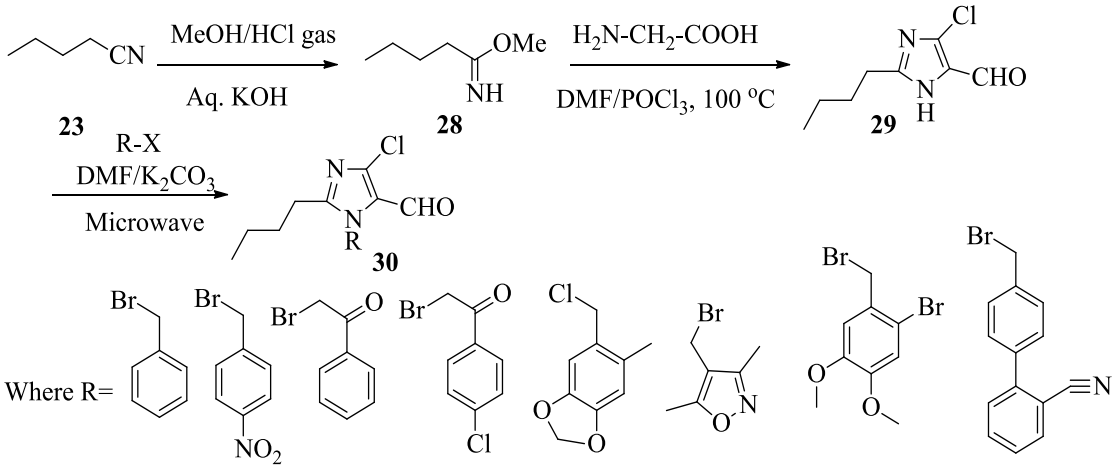
Scheme 5.

From Methyl Pentanimidate: A novel method for synthesis of 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde **27**, a key intermediate of Losartan was reported by Xiang *et al.*[25] Methyl pentanimidate **24** was reacted with dimethyl 2-aminomalonate in methanol to produce methyl-2-butyl-3H-imidazole-4-hydroxy-5-carboxylate **26**, which reacted with $POCl_3$/DMF to give 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde **27**. This pyazoline compound with chlorovinyl aldehyde moiety was treated with 5-(4-(bromomethyl)biphenyl-2-yl)-1-trityl-1H-tetrazole by N-alkylation, reduction reaction and deprotection of triphenylmethyl group to give Losartan in three steps (scheme 6).



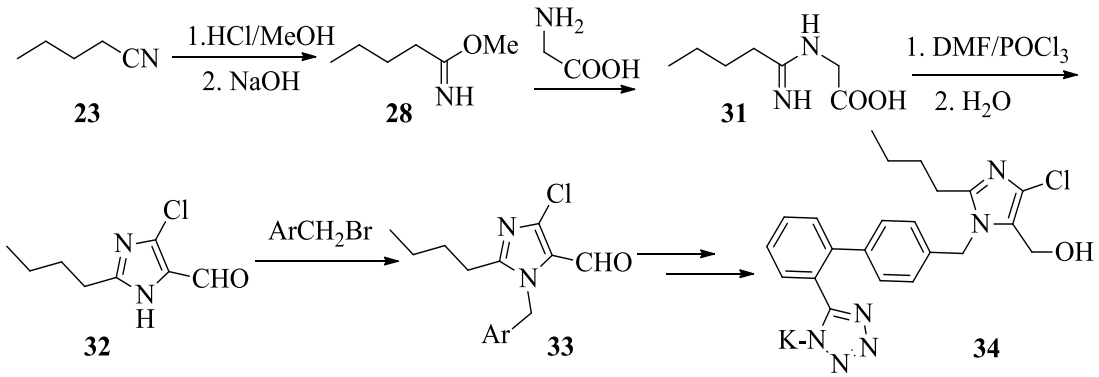
Scheme 6.

Gaonkar *et al.* synthesized a series of N-substituted 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde derivatives **30** from 2-Butyl-5-chloro-3H-imidazole-4-carbaldehyde **29** upon microwave irradiation and synthesized compounds exhibited moderate to good anti-inflammatory activity in the range 23–46%.[26] Compound with isoxazole substituent of the imidazole derivative 4, showed maximum inhibition of oedema (46%) (scheme 7).



Scheme 7.

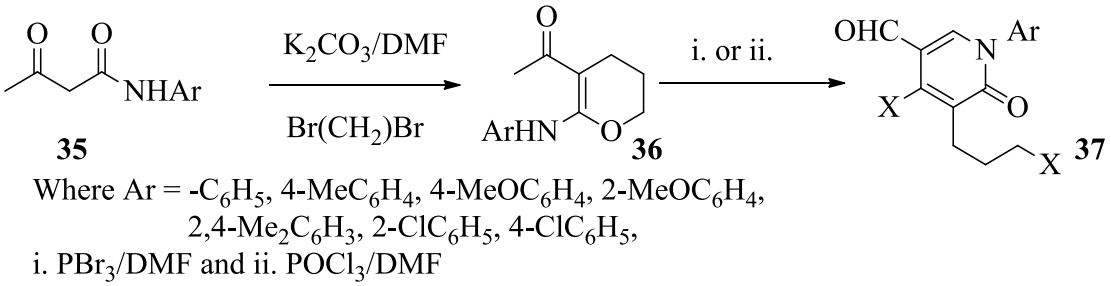
A key step in the synthesis of Merck's Losartan potassium is the regioselective N-alkylation of 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde **32** using either 4-bromobenzyl bromide or 4-arylbenzyl bromide.[27] Efficient one-pot procedures for the synthesis of aldehyde 2-butyl-4-chloro-1H-imidazole-5-carbaldehyde **32** by reaction of 2-pentanimidamidoacetic acid **31** with $POCl_3$/DMF have been developed and optimized. 2-pentanimidamidoacetic acid **31** were synthesized in stepwise manner (scheme 8).



Scheme 8.

From Substituted N-phenyl-3-Oxobutanamide: Dewen *et al.* synthesized a series of substituted 2-arylamino-3-acetyl-5,6-dihydro-4H-pyrans **36** on reaction of substituted-N-

phenyl-3-oxobutanamide **35** with anhydrous potassium carbonate in dimethyl formamide followed by addition of 1,3-dibromopropane.[28] The compound **36** with Vilsmeier-Haack reagent (PBr_3/DMF or $POCl_3$/DMF) at 80°C gave highly substituted pyridin-2(1H)-ones **37** with halovinyl aldehyde moiety (scheme 9).

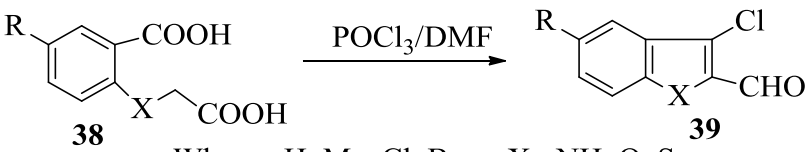


Where Ar = -C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2,4-$Me_2C_6H_3$, 2-ClC_6H_5, 4-ClC_6H_5,

i. PBr_3/DMF and ii. $POCl_3$/DMF

Scheme 9.

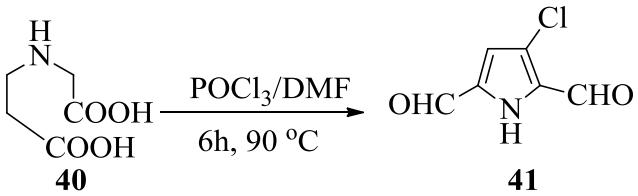
From Substituted Benzoic Acids: Perumal *et al.* synthesized a series of fused heterocycles indole **39** with halovinyl aldehyde moiety by the one-pot reaction of various substituted 2-[(carboxymethyl)amino]benzoic acids **38** using Vilsmeier reagent (DMF/$POCl_3$) in good yields.[29] Oxygen and sulphur analogous of compound also showed smooth reaction.



Where= H, Me, Cl, Br X= NH, O, S

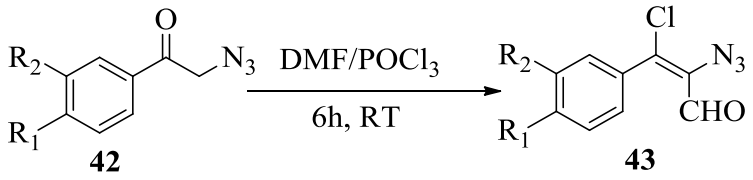
Scheme 10.

They also tested reaction of Vilsmeier reagent (DMF/$POCl_3$) with N-(carboxymethyl)-β-alanine **40** to give 3-Chloro-1H-pyrrole-2,4-dicarboxaldehyde **41** (scheme 11).



Scheme 11.

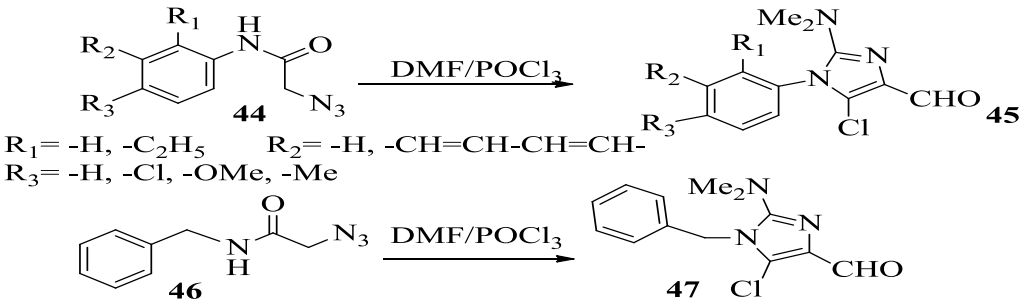
From 2-Azidoacetophenones: Perumal and co-workers have reported the synthesis of α-azido-β-chlorovinyl aldehydes **43** by the treatment of 2-azidoacetophenones **42** with excess of Vilsmeier reagent (scheme 12).[30]



Where R_1= H, Me, Cl, Br, Ph. R_2= H, Me

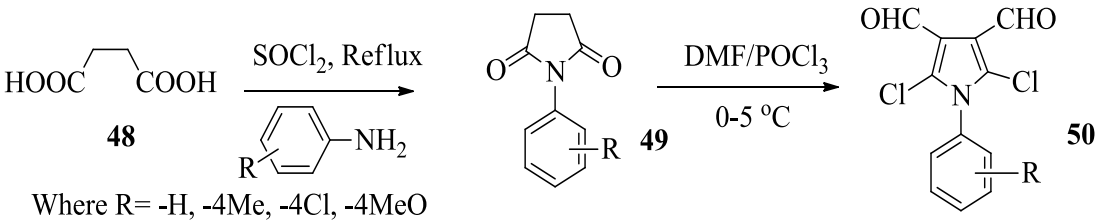
Scheme 12.

They also extend their work and synthesized 5-chloro-2-(dimethylamino)-1-phenethyl-1H-imidazole-4-carbaldehyde **45** and 1-benzyl-5-chloro-2-(dimethylamino)-1H-imidazole-4-carbaldehyde **47** from 2-azido-N-(2-phenylethyl)acetamide **44** and 2-azido-N-(phenylmethyl)acetamide **46** with Vilsmeier reagent respectively (scheme 13).



Scheme 13.

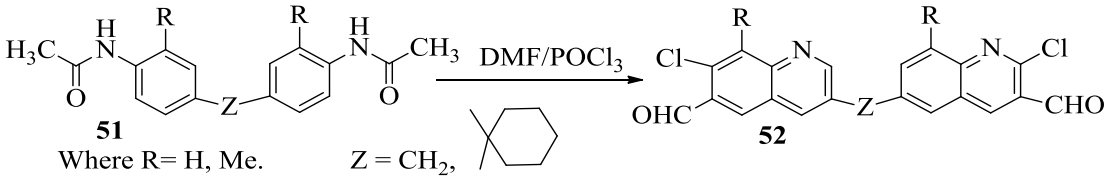
From Succinic Acid: Rajput *et al.* synthesized N-substituted phenyl succinimides **49** from succinic acid **48** and thionyl chloride followed by addition of substituted anilines in benzene.[31] These on treatment with Vilsmeier-Haack reagent gave 2,5-dichloro-3,4-diformyl (N-substituted phenyl) pyrroles **50**. They tested their microbial activity against bacteria (scheme 14).



Scheme 14.

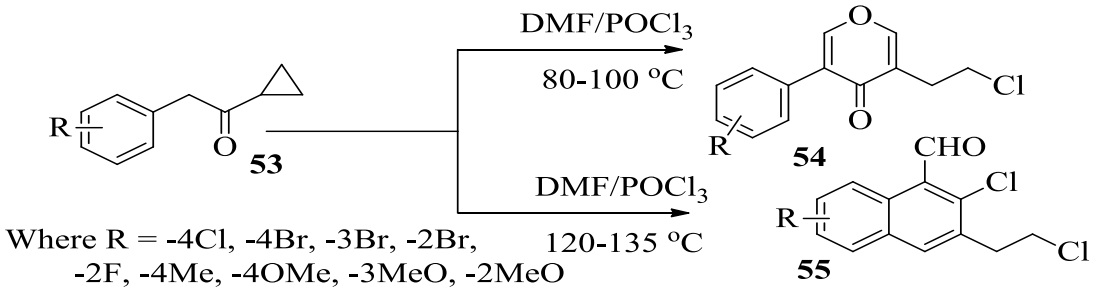
Synthesis of Bis-quinoline with Halovinyl Aldehyde moiety: Parsania *et al.* synthesized 7-chloro-3-ethyl-8-methylquinoline-6-carbaldehyde-2-chloro-8-methylquinoline-3-carbaldehyde **52** from N,N'-[methylene bis-(2-methyl-4,1-phenylene)] diacetamide **51** via

Vilsmeier–Haack reaction (scheme 15).[32] These compounds were possess moderate to good anti-bacterial and anti-fungal activities.



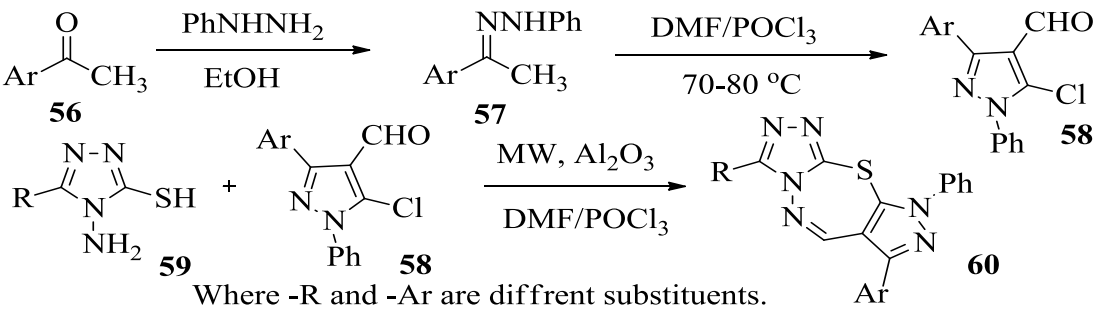
Scheme 15.

From 1-Cyclopropyl-2-arylethanones: Min Shi *et al.* developed an efficient method to synthesized 3-(2-chloroethyl)-5-aryl-4H-pyran-4-ones **54** and 2-chloro-3-(2-chloroethyl)-1-naphthaldehydes **55** from the Vilsmeier-Haack reaction of 1-cyclopropyl-2-arylethanones **53** at different temperature (scheme 16).[33] This reaction proceeds via sequential enolization, ring opening, haloformylation, and intramolecular nucleophilic cyclization or Friedel-Crafts alkylation reactions to produce **54** or **55**.



Scheme 16.

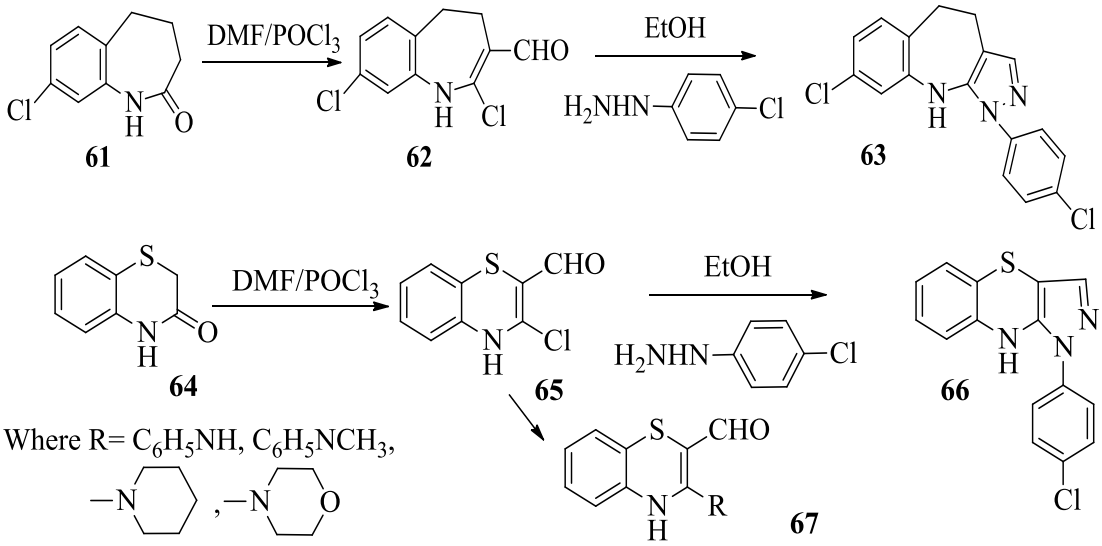
Synthesis of Thiadizapine fused with 1,2,4-triazole: On microwave irradiation, 5-substituted-4-amino-1,2,4-triazole-3-thiol **59** underwent ring closure with pyrazole containing halovinyl aldehyde **58** afforded thiadizapine **60**. Similarly 1,2,4-triazole coupled with halovinyl aldehyde 98 resulted in thiadizapine derivatives (scheme 17).[34]



Scheme 17.

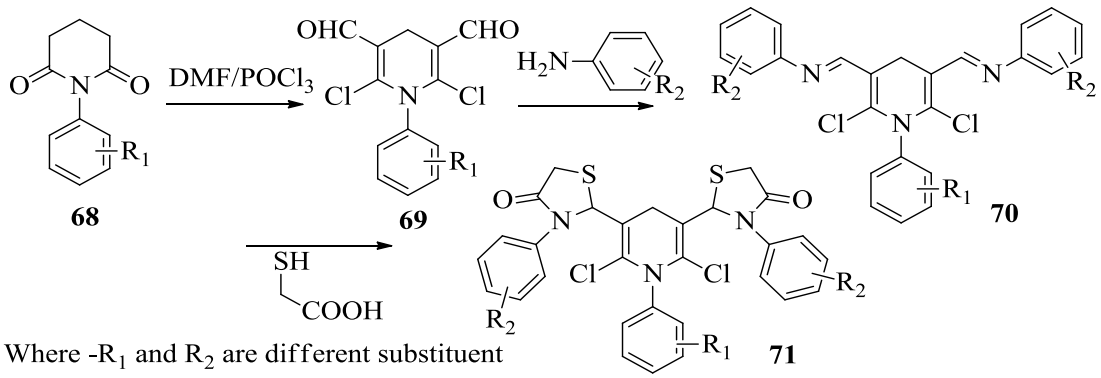
Synthesis of Pyrazole fused with Benzazepine: The reaction of 8-chloro 1,3,4,5-tetrahydro-2H-benzazepin-2-one **61** with DMF/ $POCl_3$ gave 2,8-dichloro-4,5-dihydro-1H-1-benzazepine-3-carbaldehyde **62**, which on reaction with 4-chloro phenyl hydrazine gave 8-chloro-1-(4-chlorophenyl)-1,4,5,10-tetrahydropyrazolo[3,4b][1] benzazepine **63** (scheme 18).[35]

They also extended Vilsmeier-Haack reaction with 2H-1,4-benzothiazin-3(4H)-one **64** giving 3-chloro-2-formyl-1,4-benzothiazine **65**. This compound **65** was attacked various nucleophiles to give fused heterocycles 1-(4-chlorophenyl)-1,9-dihydropyrazolo[4,3-b][1,4]benzothiazine **66** and 3-substituted-4H-1,4-benzothiazine-2-carbaldehyde **67**.



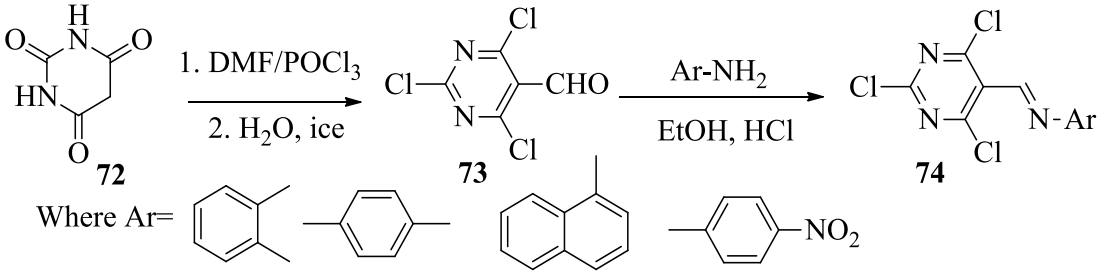
Scheme 18.

Synthesis of Thiazolidin-2-one Containing Heterocycles: Rajput *et al.* synthesized a series of 4-thiazolidinones derivatives from halovinyl aldehydes and tested their biological activities[36]. 1-substituted phenylpiperidine-2,6-dione **68** gave 2,6-dichloro-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde **69** on treatment with Vilsmeier-Haack reagent. Compound **69** treated with substituted anilines to give (2,6-dichloro-1-(N-substituted phenyl-1,4-dihydropyridine-3,5-diyl)bis(methanylylidene)dianiline **70**, which on cyclocondensation with thioglycolic acid yielded 4-(2,6-dichloro-5-(4-oxo-3-phenylthiazolidin-2-yl)-1-phenyl-1,4-dihydropyridin-3-yl)-3-phenylthiazolidin-2-one **71** in anhydrous $ZnCl_2$ in dry 1,4-dioxane (scheme 19).[36] Synthesized title compounds have been screened for their *in vitro* anti-microbial and anti-fungal activities against *B. subtilis S. aureus E. coli, P. aeroginosa* and *A. niger*.



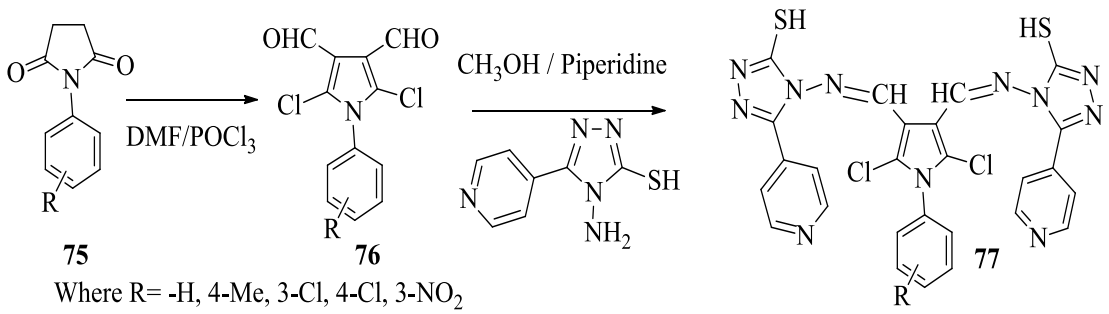
Scheme 19.

Synthesis of Schiff's bases of 2,4,6-trichloropyrimidine: This method included reaction of barbituric acid **72** on with Vilsmeier reagent ($DMF/POCl_3$) to give 2,4,6-trichloropyrimidine-5-carbaldehyde **73**, which treated with substituted anilines in ethanol in acidic condition gave Schiff's bases with 2,4,6-trichloropyrimidine moiety **74** (scheme 20).[37]



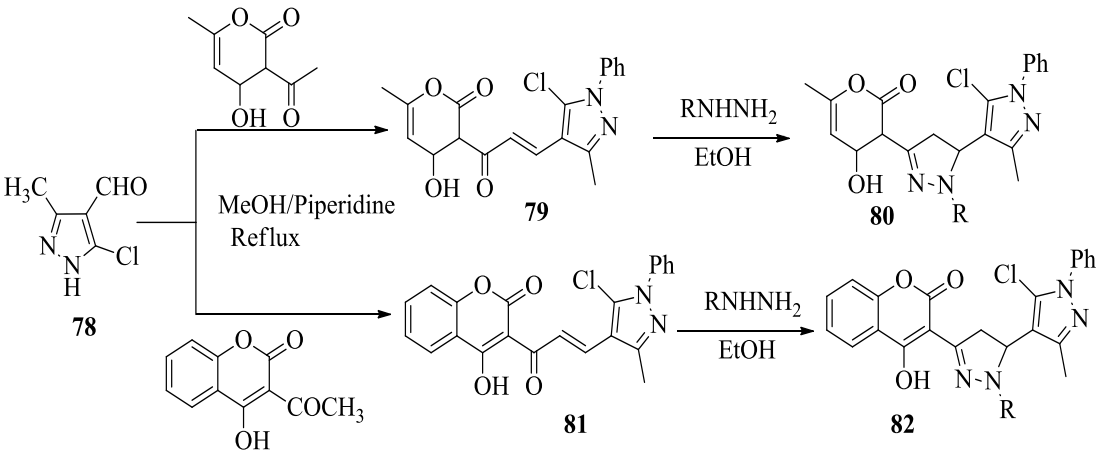
Scheme 20.

Synthesis of Schiff's bases with 1,2,4-triazole moiety: Rajput *et al.* synthesized a series of halovinyl aldehydes derivatives (2,5-dichloro-1-(substituted phenyl)-pyrrole-3,4-dicarbaldehyde) **76** using Vilsmeier-Haack reaction from cyclic imides **75**. These compounds **76** were condensed with 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol afforded a series of new Schiff's bases **77** (scheme 21).[38]



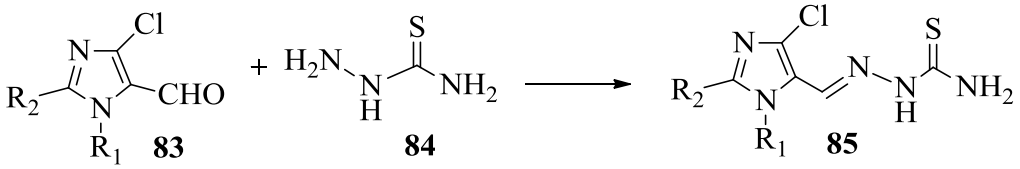
Scheme 21.

Synthesis of fused Bipyrazole: Siddiqui *et al.* reported reaction of 5-Chloro-3-methyl-1-phenylpyrazole-4-carbaldehyde **78** with 3-acetyl-4-hydroxy-6-methyl-3,4-dihydro-2H-pyran-2-one and 3-acetyl-4-hydroxy-2H-chromen-2-one via Claisen-Schmidt condensation to afford heterochalcones **79** and **81** which undergo facile cyclisation with hydrazine or phenyl hydrazine to give 3,5-heteroaryl-2-pyrazolines **80** and **82** respectively (scheme 22).[39] The newly synthesized heterochalcones and pyrazolines have been screened for their anti-bacterial activity.



Scheme 22.

Synthesis of Schiff's bases with Imidazole Ring: Chornous *et al.* synthesized a series of thiosemicarbazones derivatives with imidazole ring **85** from condensation of 4-chloro-1H-imidazole-5-carbaldehydes **83** with thiosemicarbazide **84** (scheme 23).[40] Synthesized compounds were possess high activity against *S. aureus*, *E. coli*, *C. albicans* and *M. tuberculosis* strains.

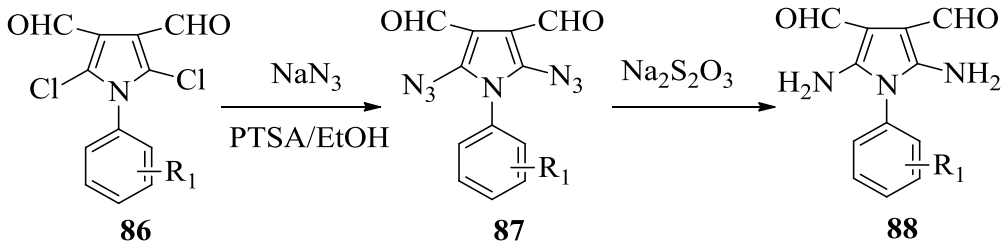


Where R_1= Me, Ph, 2-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4 4-MeC_6H_4.
R_2= -H, -OMe, -Cl, $-NH_2$, $-N_3$, 2-ClC_6H_4, 3-$NO_2C_6H_4$

Scheme 23.

Synthesis of 2,5-diamino-3,4-diformy pyrrole: Rajput *et al.* synthesized a series of 2,5-diazo-1-(N-substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde **87** by treating halovinyl aldehyde derivatives **86** with Vilsmeier-Haack reagent. These compounds **87** were reduced to

2,5-diamino-1-(N-substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde **88** from sodium dithionate in methanol (scheme 24).[41] The synthesized series of compound was tested for anti-bacterial and anti-fungal activity.

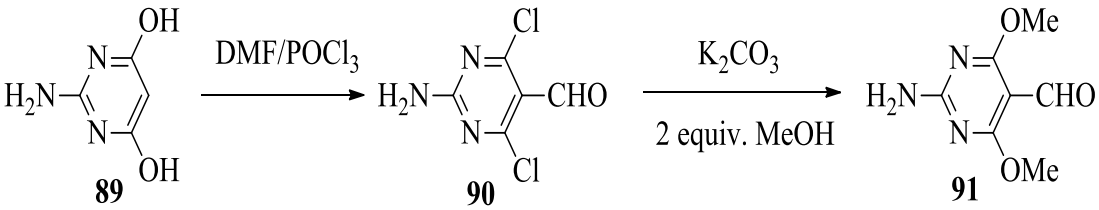


86 **87** **88**

Where R_1= 4-OMe, 3,4-Me_2, 3,4-$(Cl)_2$, 3,5-$(Cl)_2$

Scheme 24.

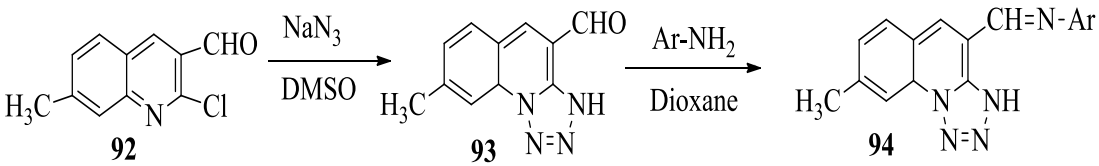
Synthesis of 2-Amino-5-formyl-4,6-dimethoxypyrimidine: Yong-jin *et al.* synthesized 2-aminopyrimidines with halovinyl aldehyde moiety **90** in excellent yield. 4,6-dihydroxy-2-aminopyrimidines **89** on reaction with DMF/$POCl_3$ gave 2-Amino-4,6-dichloro-5-formylpyrimidine **90**, which on treatment with potassium carbonate and methanol gave 2-Amino-5-formyl-4,6-dimethoxypyrimidine **91** (scheme 25).[42]



89 **90** **91**

Scheme 25.

Synthesis of Quinoline bearing Tetrazole: Halo-formylation of m-methylacetanilide gave 2-chloro-3-formyl-7-methylquinoline **92**, which on treatment with sodium azide in DMSO gave 4–formyl-8-methyltetrazolo[1,5-a]quinoline **93** as a key intermediate.[43] Subsequent condensation of **93** with various aromatic amines gave compounds **94** (scheme 26). And have been evaluated for their anti-inflammatory and anti-microbial activities.

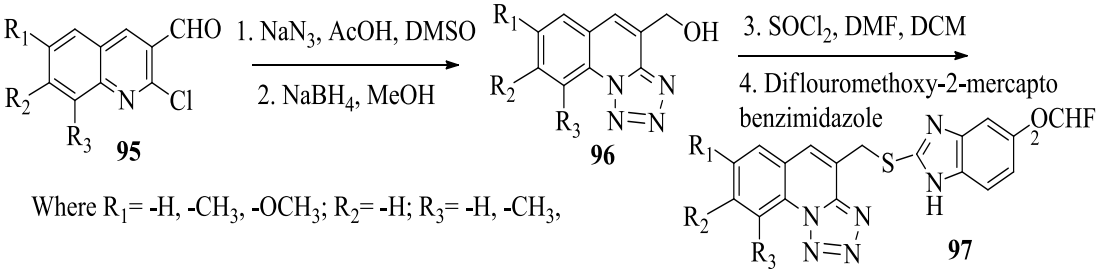


92 **93** **94**

Where Ar= 16 various substituted anilines

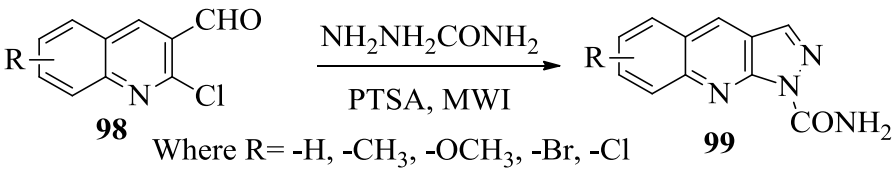
Scheme 26.

Shingare *et al.* have reported the conversion of 2-chloroquinoline-3-carbaldehydes **95** into tetrazolo[1,5-a]quinoline-4-carbaldehyde **96** on treatment with sodium azide, reduction to the corresponding alcohol derivatives. Compound **96** on conversion to chlorides with thionyl chloride and coupling with 5-(difluoromethoxy)-1H-benzo[d]imidazole-2-thiol gave 4-((5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolones derivatives **97** (scheme 27).[44] All the compounds were screened for anti-bacterial activities against *B. subtilis, S. aureus, E. coli* and *S. aboney*.



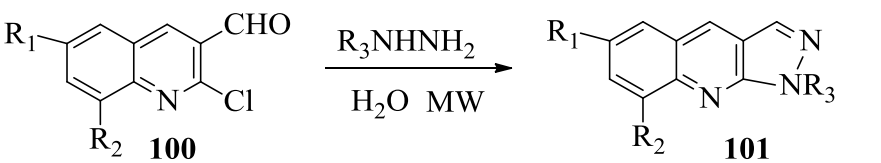
Scheme 27.

Synthesis of Quinolines bearing Pyrazole: T Selvi *et al.* synthesized a series of quinolines bearing pyrazole moiety **99** from condensation of various 2-Chloro-3-formylquinolines with semicarbazide **98** (scheme 28).[45] These compounds have been screened for their anti-microbial activities.



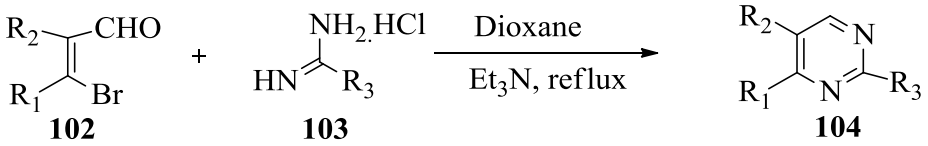
Scheme 28.

Similarly, Mane *et al.* developed convenient and eco-friendly water-mediated synthetic method for quinolines carrying pyrazole **101** from condensation of 2-chloro-3-formyl quinolines **100** and substituted hydrazine on microwave irradiation (scheme 29).[46]



Scheme 29.

Synthesis of Trisubstituted Pyrimidines: Jun Lin *et al.* synthesized a series of 2,3,6-trisubstituted pyrimidines **104** from cyclocondensation of bromovinyl aldehydes **102** with amidine hydrochlorides **103** using dioxine in the presence of Et_3N in excellent yield (scheme 30).[47]

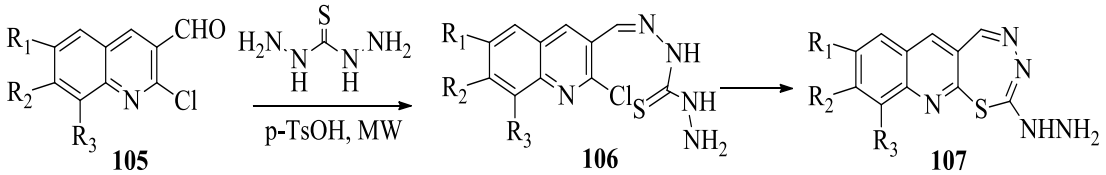


102 **103** **104**

Where R_1= aryl, cycloalkyl. R_2= H, cycloalkyl. R_3= H, Me, aryl

Scheme 30.

Synthesis of Quinolines bearing Thiadiazepine: Naik *et al.* developed a simple efficient and environmentally benign method for the synthesis of 2-hydrazino-[1,3,4]thiadiazepino[7,6-b]quinolines **107** under microwave irradiation conditions from 2-chloro-3-formyl-quinoline **105** and carbidimide in presence of p-TsOH and DMF (scheme 31).[48]

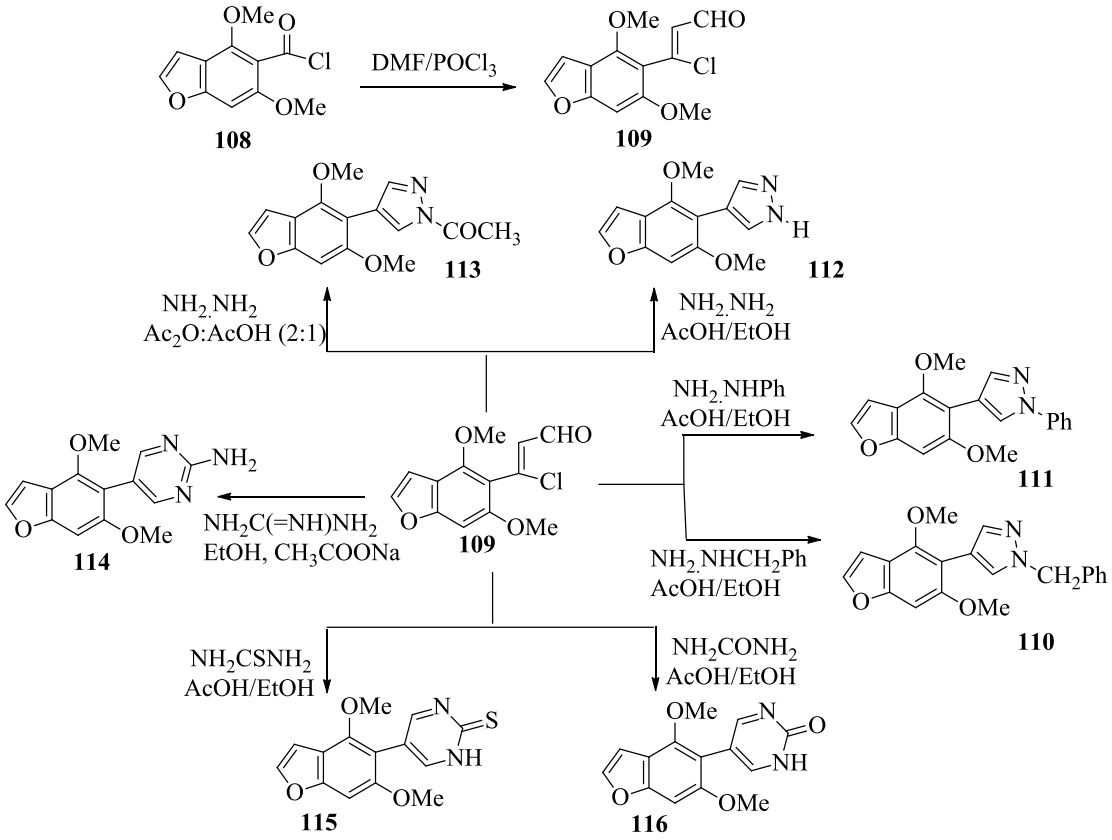


105 **106** **107**

Where R_1= -H, -CH_3, Cl, -OCH_3, R_2= -H, -CH_3, -OCH_3, R_3= -H, -CH_3, -OCH_3.

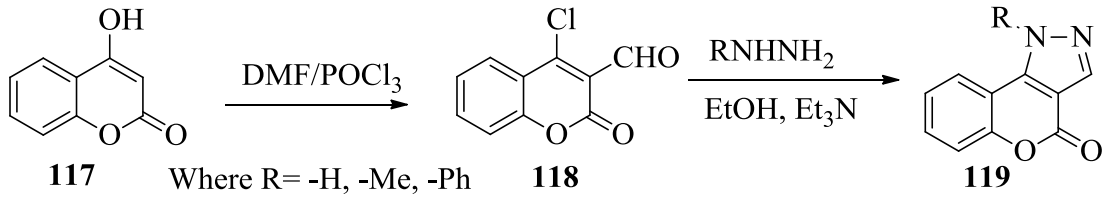
Scheme 31.

Synthesis of differently Substituted Benzofurans: Mandour *et al.* synthesized 3-chloro-3-(4,6-dimethoxybenzofuran-5-yl)propenal **109** from 1-(4,6-dimethoxybenzofuran-5-yl)ethanone **108** on Vilsmeier-Haack reaction. compound **109** on reaction with hydrazine hydrate, phenyl hydrazine and benzyl hydrazine hydrochloride resulted in the formation of pyrazole derivatives **110, 111, 112** and **113.**[49] Similarly reaction of compound **109** with guanidine, thiourea and urea **114, 115** and **116** led to the formation of the pyrimidine derivatives respectively (scheme 32). Synthesized compounds were tested for their anti-inflammatory, analgesic and anti-convulsant activities.



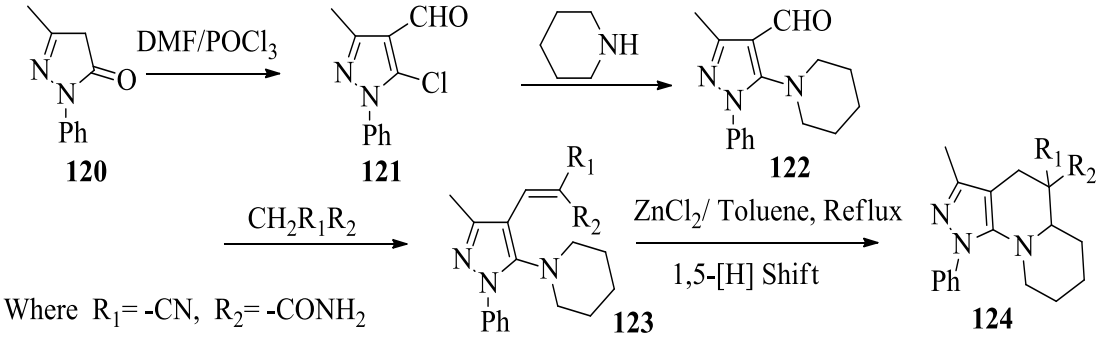
Scheme 32.

Synthesis of Coumarin fused with Pyrazole: 4-hydroxycoumarin **117** gave 4-Chloro-3-coumarincarbaldehyde **118** in DMF/$POCl_3$, which reacted with nitrogen-containing nucleophiles leading to the corresponding substituted chromen-[4,3-c]pyrazol-4-ones **119** (scheme 33) and these compounds were evaluated for possible anti-oxidant activities.[50]



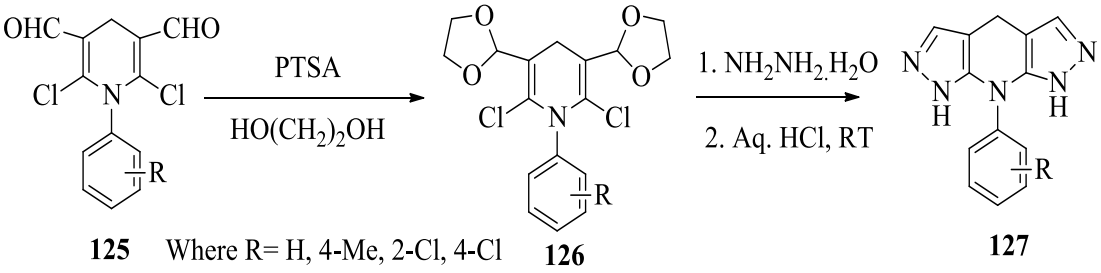
Scheme 33.

Synthesis of Quinolizine fused with Pyrazole: Prajapati *et al.* synthesized 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde **121** from chloroformylation of pyrazolone **120** under Vilsmeier conditions.[51] The Knovenagel condensation of 5-tert-amino-3-methyl-1-phenylpyrazolone-4-carboxal-dehyde **122** with active methylene compounds such as malononitrile and cyanoacetamide followed by cyclisation using anhydrous zinc chloride gave compounds **124** (scheme 34).



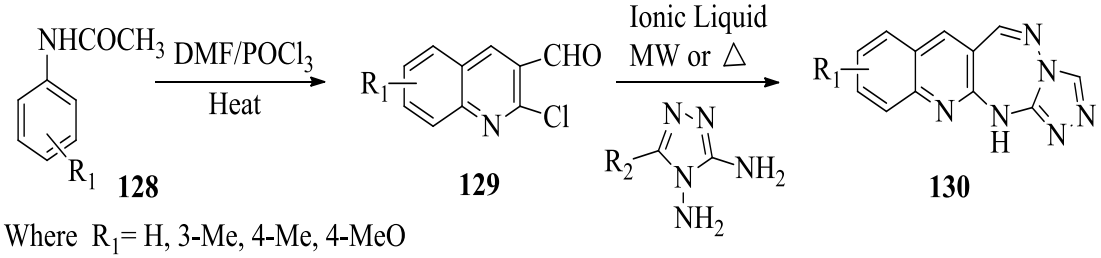
Scheme 34.

Synthesis of Pyridine fused with Pyrazole: Rajput *et al.* synthesized 8-(N-substituted phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]-pyridines **127** from 3,5-di(1,3-dioxolan-2-yl)-2,6-dihydrazinyl-1-phenyl-1,4-dihydropyridine **126,** which was synthesized on refluxing 2,6-dichloro-1-(N-substituted phenyl)-1,4-dihydropyridine-3,5-dicarbaldehyde **125** in ethylene glycol and PTSA (scheme 35).[52]



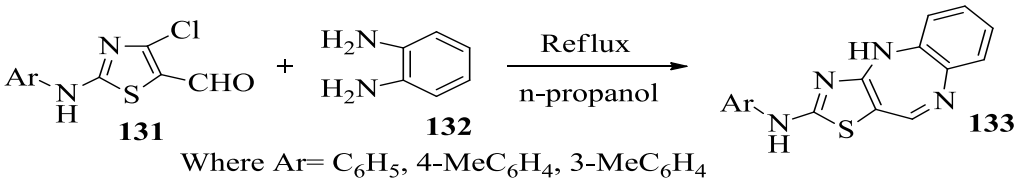
Scheme 35.

Synthesis of Quinolines fused with Pyrazole: M Gupta synthesized 9-substituted-3-aryl-5H,13-H-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines **130** from 2-chloro-3-formylquinolines **129** and 5-aryl-3,4-diamino-1,2,4-triazoles in ionic liquid under microwave heating (scheme 36).[53] These compounds have been screened for anti-fungal activity.



Scheme 36.

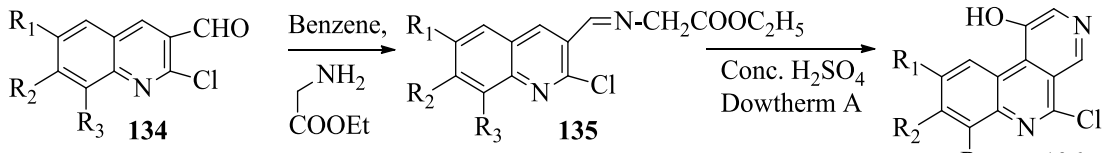
Synthesis of Thiazole fused with Diazepine: Rajput *et al.* synthesized N-phenyl-4H-benzo[b]thiazolo[4,5-e][1,4]diazepin-2-amine **133** by refluxing 4-chloro-2-(phenylamino)thiazole-5-carbaldehyde **131** and 1,2-diamino benzene **132** in n-propanol and tested their anti-microbial activity (scheme 37).[54]



Where Ar= C_6H_5, 4-MeC_6H_4, 3-MeC_6H_4

Scheme 37.

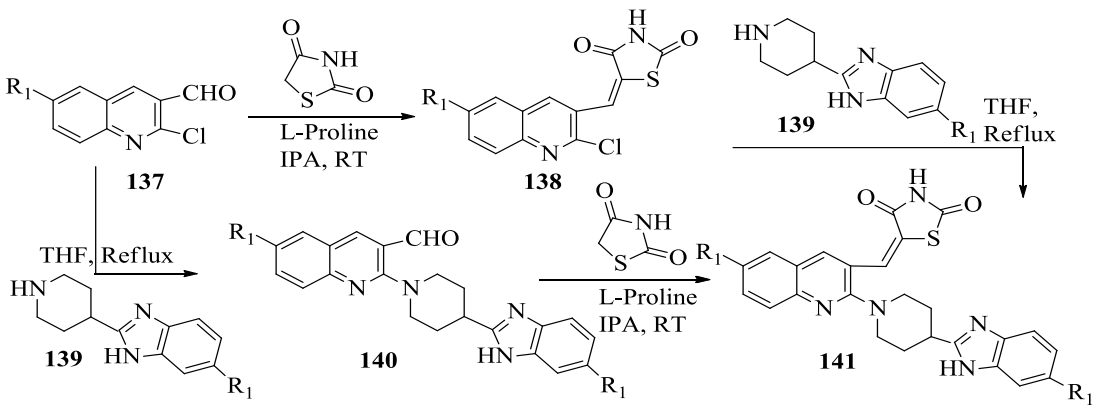
Synthesis of Benzo-naphthyridines: Multisubstituted quinoline with halovinyl moiety **134** on condensation with glycine ethyl ester has provided the imines **135** which on cyclisation in acidic medium furnished the 1-hydroxy-5-chloro-benzo[f][2,7]naphthyridines **136** (scheme 38).[55]



Where R_1= -H, -CH_3; R_2= -H, -CH_3, -OMe, -CH=CH-CH=CH-
R_3= H, -CH_3, -CH=CH-CH=CH-

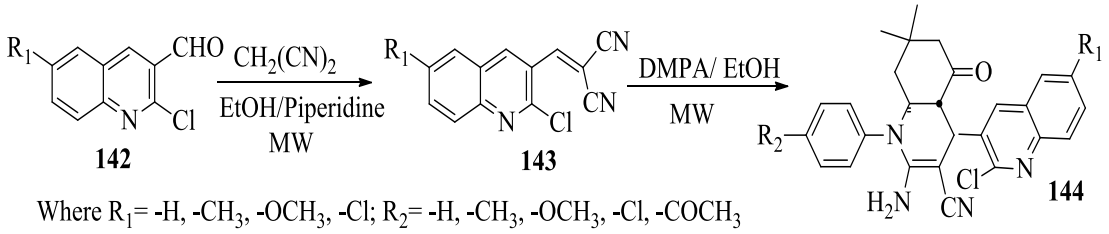
Scheme 38.

Synthesis of Quinolines bearing Piperidines: Condensation between 2-chloro,3-formyl quionoline **137** with an active methylene group containing 2,4-thazolidinedione gave 5-((2-(4-(1H-benzoimidazol-2-yl)piperidino)-quinolin-3-yl)methylene)thiazolidine-2,4-dione **138** in isopropyl alcohol using *l*-proline which on reaction with 2-(piperidino)-1H-benzoimidazole 3 and 4-thazolidinedione gave compounds **141** (scheme 39).[56]



Scheme 39.

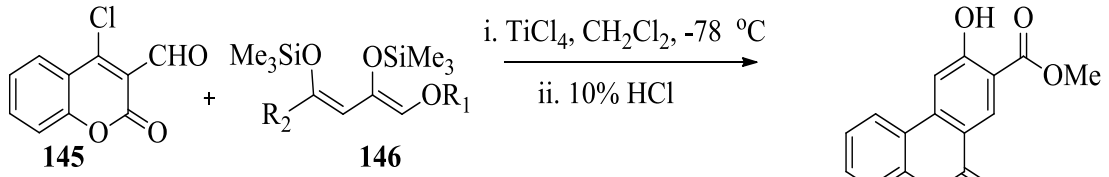
Using 2-chloro,3-formyl quinolone **142**, Patel *et al.* synthesized [(2-chloro-3-quinolyn)methylene)methane-1,1-dicarbonitrile **143,** which gave 3-arylamino-5,5-dimethyl-cyclohex-2-en-1-one **144** under microwave irradiation catalysed by DMAP in short time with high yield (scheme 40).[57] Synthesized compounds showed good anti-bacterial and anti-fungal activities.



Where R_1= -H, -CH_3, -OCH_3, -Cl; R_2= -H, -CH_3, -OCH_3, -Cl, -$COCH_3$

Scheme 40.

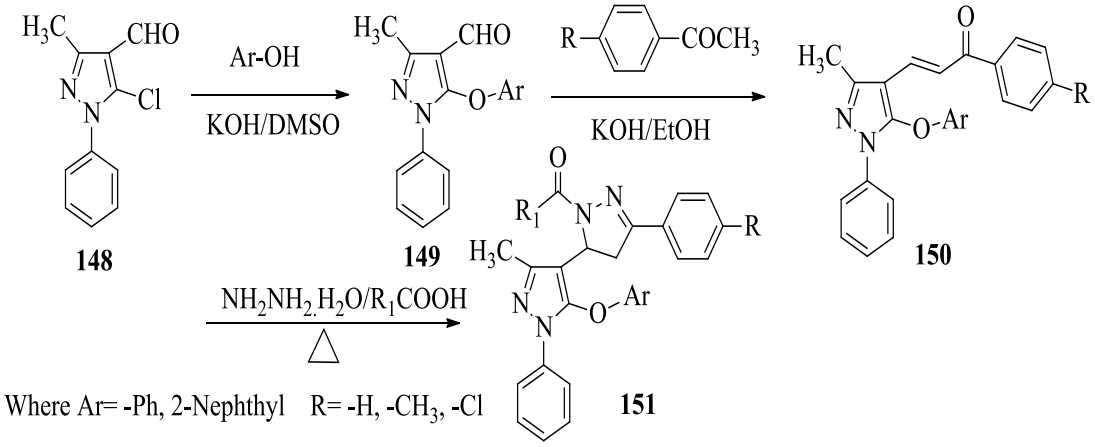
Synthesis of Benzo-chromenones: Iaroshenko *et al.* reported a new synthesis of functionalized 9-hydroxy-6H-benzo[c]chromen-6-ones **147** based on the cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes **146** with 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **145** (scheme 41).[58]



Where R_1= -Me, -Et, -CH_2CH_2OMe, -iPr, -tBu
R_2= -H, -Me, -Et, -nPr, -nPent, -nHex, -nDec, -Cl, -OMe,
-CH_2Ph, -CH_2CH_2Ph, -$CH_2CH_2CH_2Ph$,-$CH_2CH_2CH_2Cl$

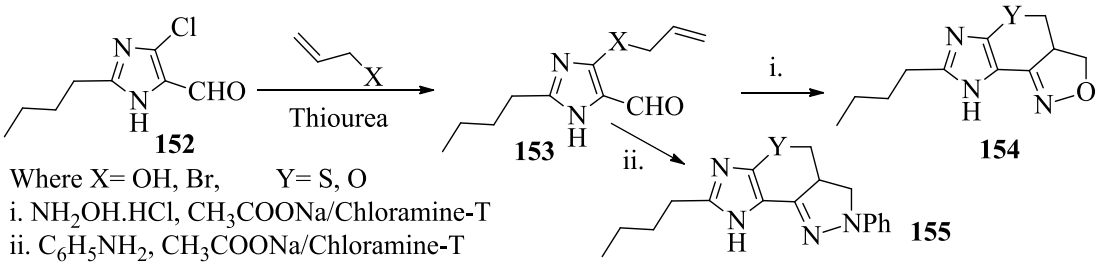
Scheme 41.

Synthesis of Pyrazolyl Pyrazole: Kalluraya *et al.* synthesized substituted 1-acetyl/propyl-3-aryl-5-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-pyrazolines **151** by condensing The 3-(5-aryloxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-aryl-2-propen-1-one **150** and hydrazine hydrate. Compound **150** were prepared 5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-carboxaldehyde **148** and phenol/β-naphthol followed by treatment with suitable substituted acetophenone (scheme 42).[59] The synthesized compounds were showed good analgesic and anti-inflammatory activity.



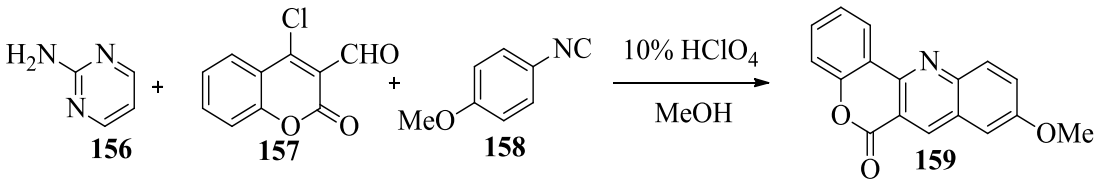
Scheme.[42]

Synthesis of Tricyclic Heterocycles: Rai *et al.* prepared tricyclic heterocycles **154** and **155** from 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde **152** by substituting the chlorine atom and then converting aldehyde function into 1,3-dipole cycloaddition reaction using Chloramine-T (scheme 43).[60]



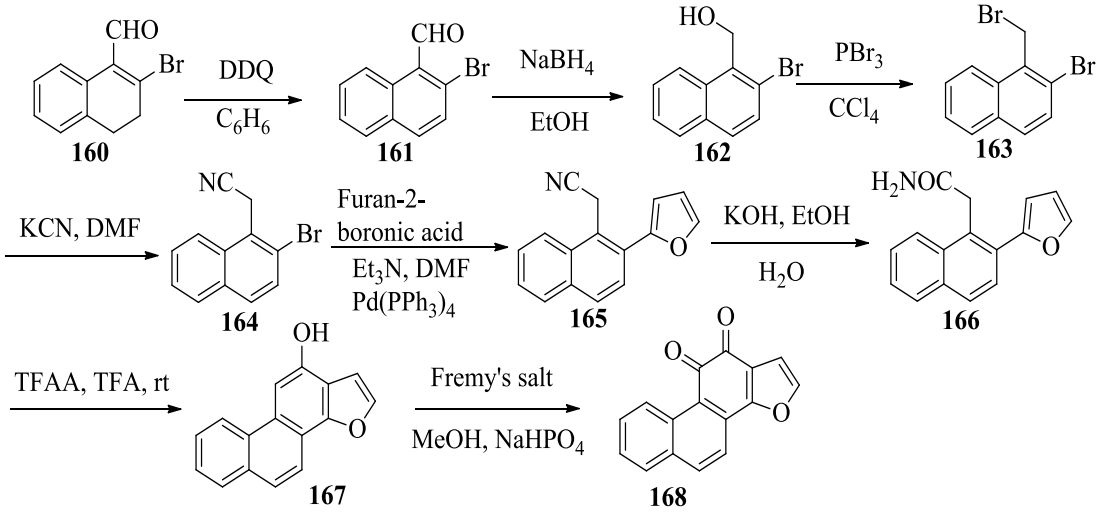
Scheme 43.

Synthesis of Quinolines with Chromenone: Reaction of aryl isocyanides **158** with 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **157** and pyrimidin-2-amine **156** lead to chromeno[4,3-b]quinolin-6-ones **159** in good yields (scheme 44).[61]



Scheme 44.

Synthesis of Furoquinone Diterpenoids: Kar *et al.* described the synthesis of phenanthro[1,2-b]furan-10,11-dione **168**, a furoquinone diterpenoids, starting from 2-bromo-3,4-dihydro-1-naphthaldehyde **160** in series of reaction shown below (scheme 45).[62]



Scheme 45.

CONCLUSION

Halovinyl aldehydes have wide range of synthetic utility in organic chemistry due to the presence of an electrophilic aldehydic carbon and a labile halogen atom. Numerous fused heterocyclic compounds synthesized by using halovinyl aldehydes. Their biological and medicinal importance is also explained. This survey is attempted to summarize the synthetic methods and reactions of halovinyl aldehydes during last year's.

ACKNOWLEDGEMENT

One of the authors is thankful to Council of Scientific and Industrial Research (CSIR), New Delhi for providing financial support.

CONFLICT OF INTERESTS

Declared None.

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