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Advances in the Synthesis and Pharmacological Applications of Heterocyclic Scaffolds: Benzoxepine and Benzothiepine Derivatives

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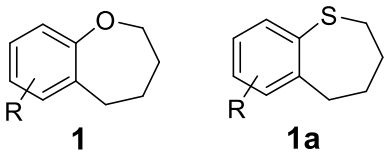
ABSTRACT:

Paul Cagniant first reported the synthesis of benzoxepine which was named as homochroman **1.**[1] Since then a large number of substituted benzoxepine derivatives were prepared by various synthetic routes, the significant being **(i)** By rearrangement of anisylidine flavone epoxides;[2] **(ii)** From dihydrobenzofuran-3-one;[3] **(iii)** By PARHAM Cyclialkylation;[4,5] **(iv)** From aryl oxazolines;[6] **(v)** By ring closure of Isoprenyl terminal epoxides;[7]



1 **1a**

Homochroman (1-Benzoxepine and 1-Benzothiepine)

(vi) By photocycloaddition of Benzo[*b*]furan derivatives to alkenes;[8] and several other synthetic routes not being employed in common practice. The thia analog is known as benzothiepine **1a**.

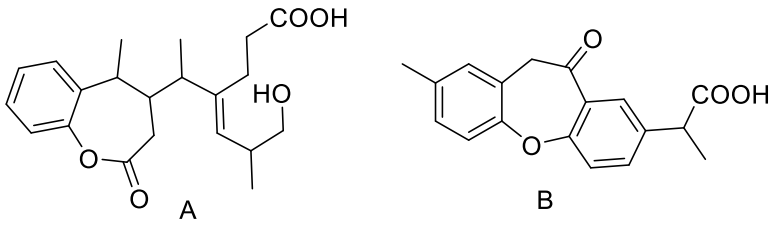
A review on Benzoxepines has described the synthetic routes reported in literature till 1990.[9,10] The present review describes the synthetic routes, reactions, the naturally occurring 1-Benzoxepines, its derivatives and their pharmacological significance.

Keywords: Benzoxepine and Benzothiepine, synthetic routes, reactions, pharmacological significance.

INTRODUCTION

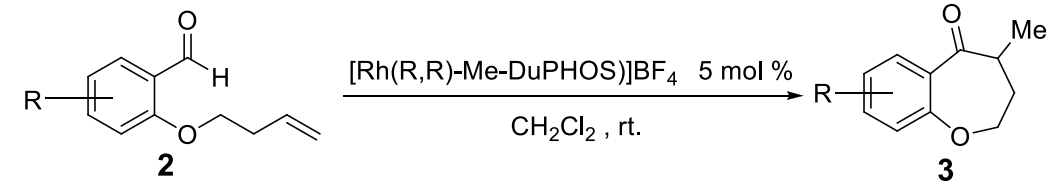
Neuroinflammation, driven by the way microglia cells change their state, plays a key role in the start and worsening of various brain diseases and disorders affecting nervous system function. Conditions like multiple sclerosis, demyelinating diseases, Parkinson's disease, and stroke are examples of such ailments, and unfortunately, effective treatments are currently lacking[11,12]. Microglia are the resident immune cells of the central nervous system (CNS). Besides a resting state, they can activate into two main functional types: M1 and M2 phenotypes[13]. The M1

microglia are pro-inflammatory; they release substances like tumour necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β). These molecules can break down the blood-brain barrier (BBB) and weaken the protective myelin sheath around nerve fibers. This damage leads to demyelination, intensifies inflammation, and impairs the ability of nerves to transmit signals[14]. In contrast, M2 microglia are anti-inflammatory, secreting cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10). These cells are crucial for repairing damaged nerve tissues[15]. Consequently, managing neuroinflammatory disorders can be improved by influencing microglia polarization, essentially guiding them to shift from the M1 state towards the M2 state[16]. PKM2 is a protein kinase and transcriptional coactivator that is essential for controlling the rate of glycolysis, a key energy-producing pathway[17]. Research has shown that when PKM2 is activated, it boosts the production of IL-1β by M1 microglia, which in turn amplifies neuroinflammation[18]. This suggests that reducing PKM2 activity might help suppress M1 polarization. Indeed, studies have indicated that disruptions in glycolysis can trigger polarization responses in BV2 microglia cells[19]. Marine organisms have recently garnered significant attention as a rich source for discovering new drugs[20]. Interestingly, Kathir's research highlighted substantial anti-inflammatory properties in a tetrahydrobenzo-[c]oxepin analogue (compound A, Fig. 1) derived from the mangrove *Rhizophora annamaloyana*[21] Building upon this benzoxepine scaffold, recent structural optimizations have been conducted. For instance, the synthetic compound 2-(8-methyl-11-oxo-10,11-dihydrodibenzo-[b,f]oxepin-2-yl)propanoic acid (compound B)[22].



SYNTHETIC ROUTES

1. By Rh-Catalyzed Intramolecular Olefin Hydroacylation: Intramolecular hydroacylation of alkenal **2** prepared from salicyldehyde derivative with 5 mol.%[Rh((R,R)-Me-DuPHOS)]BF_4 in methylene chloride led to formation of benzoxepine derivatives **3** in 80-95% yield with % ee 94 to 98% as shown in Scheme **1.**[23]

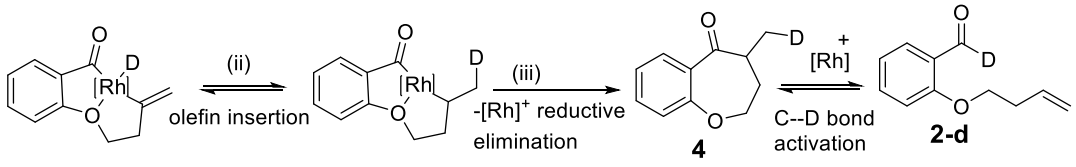


R=H, 5-F, 5-Cl, 5-Me, 5-OMe, 3-OMe

Yield 80-95%
e.e. 94-98%

Scheme 1

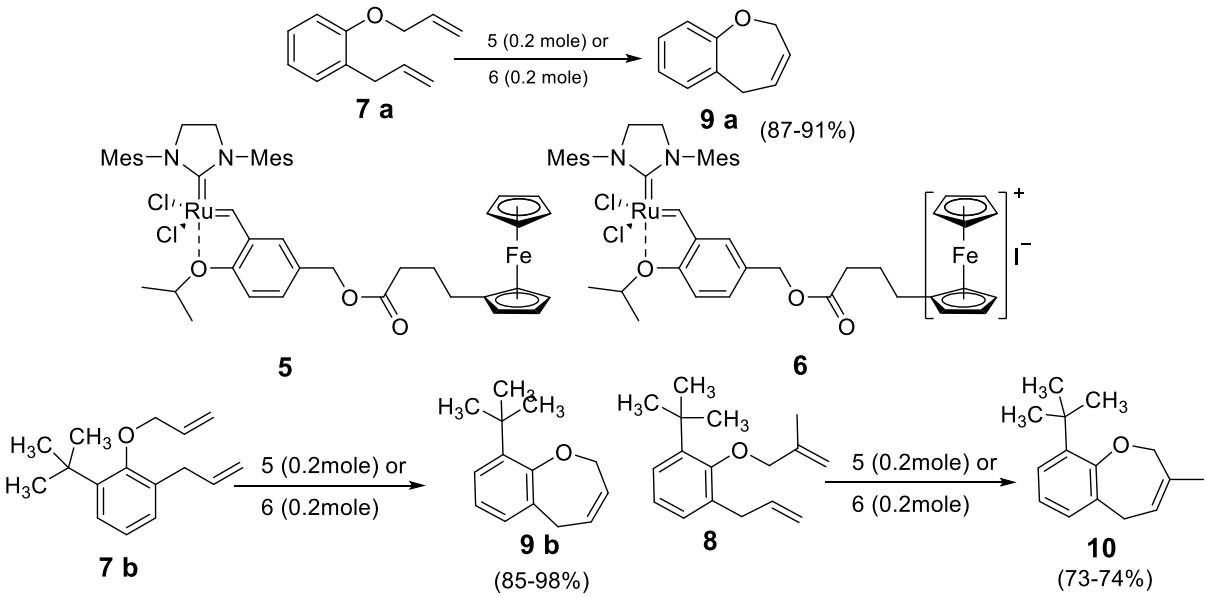
The preliminary studies by Dong et al[23] concerning machanism of this asymmetric hydroacylation have been carried out to ascertain incorporation of Deuterium with no scrambling. The Deuterium labelled **2-d** undergoes hydroacylation by the well established steps i.e C-D bond activation, Olefin insertion and reduction elimination to produce seven membered ring ketone as shown in Figure 1.



Catalyst : [Rh{ (R,R)-Me-DuPHOS}]BF_4

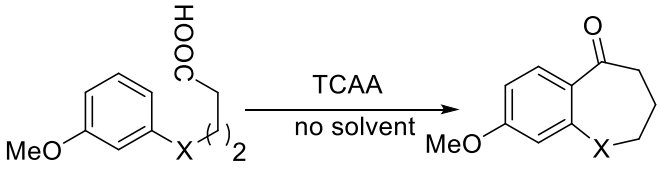
Figure 1

2. By Ring Closing Metathesis with Ferrocene Tagged Ru Catalysts: Ferrocene tagged Ru catalysts **5** & **6** have been employed for ring closing metathesis of Diallylethers **7** & **8** to yield benzoxepine derivatives **9** & **10** respectively as shown in Scheme **2** in excellent yields.[24]



Scheme 2

3. By Friedel-Crafts Cyclization with Trichloroacetic Anhydride : Intramolecular Friedel-Crafts cyclization of 4-(3-Methoxyphenoxy)- butanoic acid and 4-(3-Methoxyphenylthio)-butanoic acids **11** & **12** with trichloroacetic anhydride in absence of any solvent, resulted in the formation of 8-Methoxy-3,4-dihydro-1-benzoxepin-5(2*H*)-one **13** & 8-methoxy-3,4-dihydro-1-benzothiepin-5(2*H*)-one **14** respectively as shown in Scheme **3**.[25]

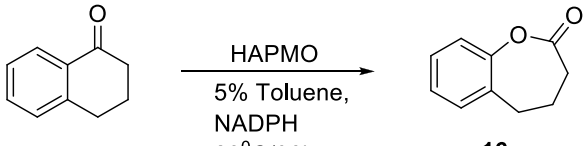


11, X=O
12, X=S

Scheme 3

13, X=O (72%)
14, X=S (71%)

4. By Enzymatic Baeyer–Villiger Oxidation of Benzo Annelated Ketones: The bio-catalyst 4-Hydoxy acetophenone monooxygenase (HAPMO) was isolated from *Pseudomonas Fluorescence* ACB. HAPMO catalyzed oxidation of 1- Tetralone **15** in presence of toluene and NADPH at 20^0 C for 96 hours resulted in the formation of 1-Benzoxepin-2-one **16** as shown in Scheme **4**.[26]

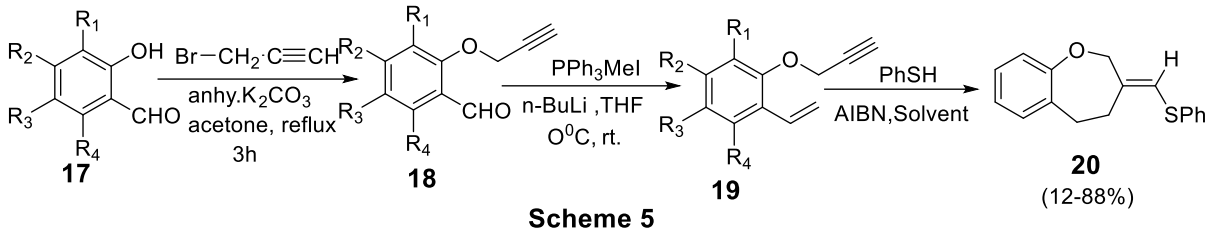


15

Scheme 4

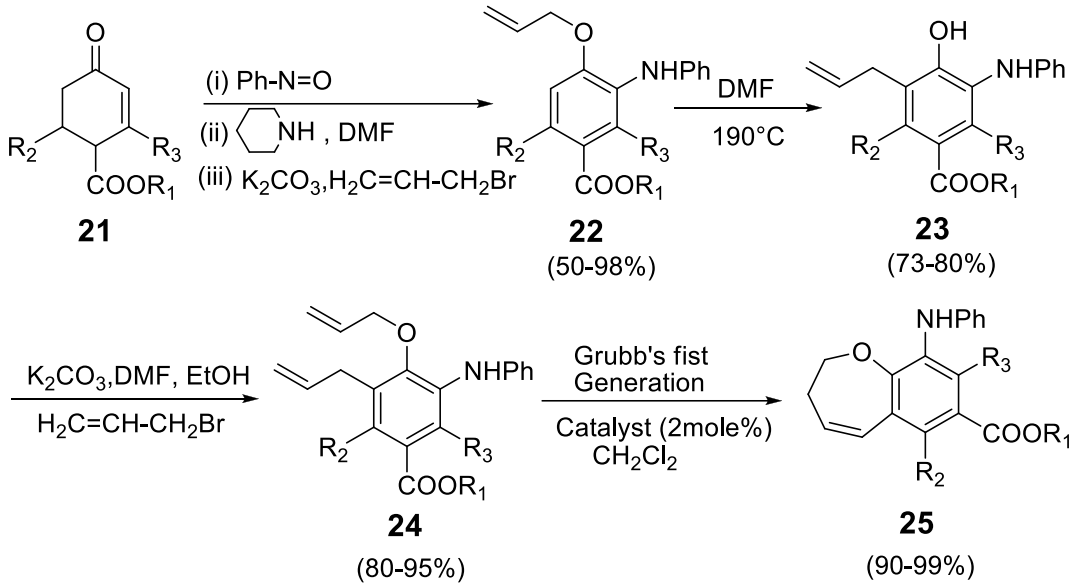
16
(26%)

5. Wittig Olefination & Thiol Mediated 7-Endo-Trig Radical Cyclization Reaction in the Synthesis of Benzoxepine Derivatives: The radical precursors **19** were prepared in good yield by the wittig reaction of the substrate **18** which in turn were obtained from 2-Hydroxy benzaldehyde derivatives **17** with propargyl bromide as shown in Scheme **5**. Substrate **19** on radical cyclization in the presence of thiophenol (1.5 eq.) and A1BN (1.5 eq.) as radical initiator yielded Benzoxepine derivatives **20** as shown in Scheme **5**.[27] The best yields were obtained by using benzene as a solvent.



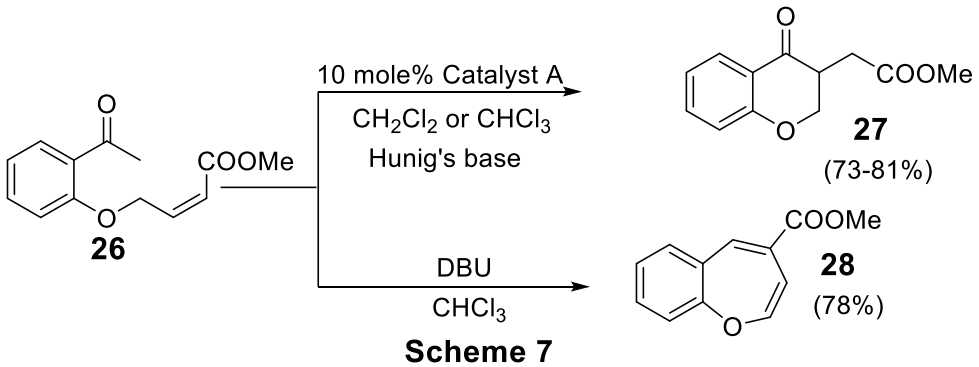
Scheme 5

6. One Pot Synthetic Approach for Synthesis of Benzo[*b*]oxepines using RCM α, β- unsaturated keto esters **21** on reaction with nitrosobenzene & allyl bromide afforded Olefin **22** according to the procedure of Rama Chary ***et. al.***[28] Olefin **22** on further reaction with DMF at 190^{0}C led to formation of substituted phenyl derivative **23** in good yields. Allylation of **23** with allyl bromide in DMF afforded functionalized dienes **24** in excellent yields. Further RCM reaction of **24** with Grubb's first generation catalyst (2 mol%) in Methylene Chloride and base afforded Benzo[*b*]oxepine derivatives **25** in excellent yields as shown in Scheme- **6**.[29]



Scheme 6

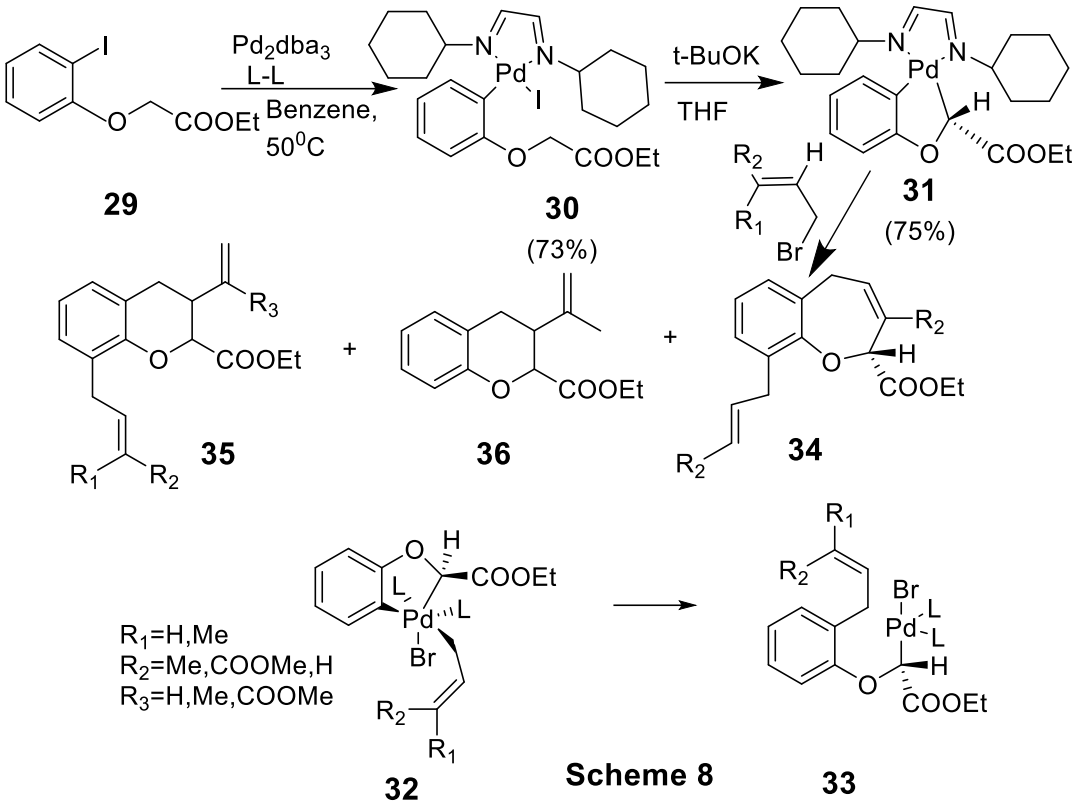
7. By Intramolecular Stellar Reaction: The Intramolecular Stellar reaction[17/30] leading to formation of Chroman-4-one derivatives **27** in presence of a catalyst has been achieved in good yields as shown in Scheme- **7**. Thus the reaction of salicylaldehyde derived substrate **26** with 10 mol % catalyst led to formation of Chromanone derivatives **27** in good yields. However if the reaction of **26** is carried out in presence of strong bases, Benzoxepine derivatives **28** are formed as shown in Scheme- **7**.[31]



Scheme 7

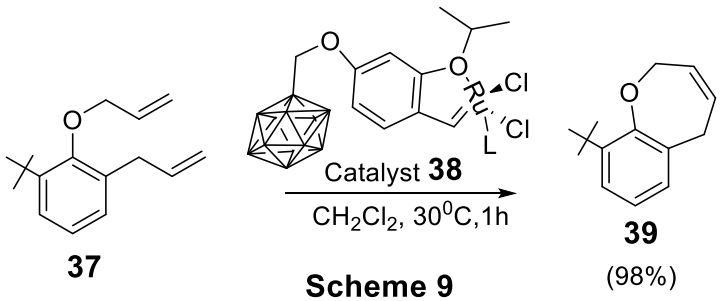
8. Synthesis of Benzoxepine Derivative by use of Allyl Palladium (IV) Intermediate: Aryl iodide derivative **29** on reaction with *N,N*- Dicyclohexyl ethylenediimine legand gave intermediate **30** in presence of benzene as a solvent in good yields. **30** on further treatment with potassium *tert.* butoxide resulted in the formation of the stable palladacycle

31. **31** on treatment with substituted aryl bromide in acetonitrile or dichloro ethane resulted in the formation of Benzoxepine derivatives **34** alongwith Benzopyran derivatives **35** & **36** as shown in the Scheme **8**.[32]



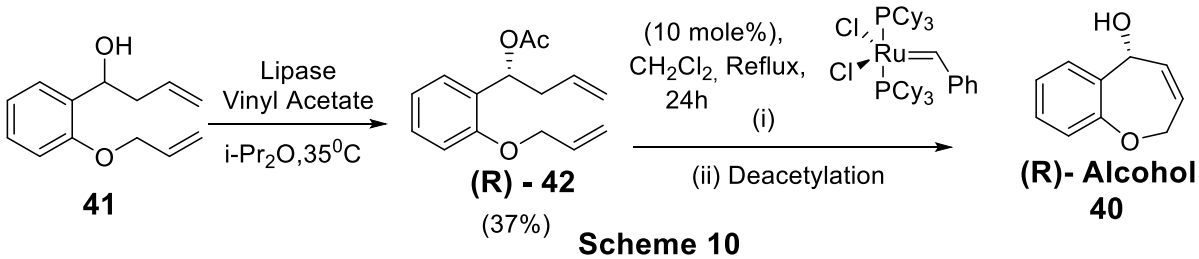
Scheme 8

9. Synthesis of Benzoxepine Derivatives by RCM Reaction with Ruthenium Carbene Complexes : Ru carbene catalyst **38** has been employed for RCM reaction of **37** in presence of CH_2Cl_2 to afford Benzoxepine derivative **39** in 98% yield as exhibited in Scheme **9**.[33]



Scheme 9

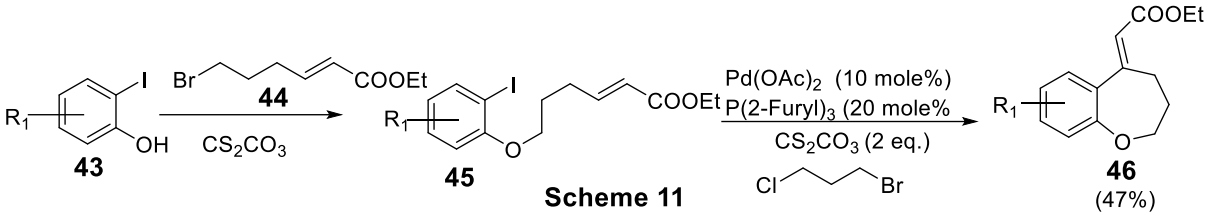
10. Synthesis of Enantiomerically pure Benzoxepine Derivatives via Enzyme Catalyzed and RCM Reaction : Synthesis of R-2,5-dihydro-2*H*-benzo[*b*]oxepin-5-ol **40** was accomplished from Racemic 1-[2-(allyloxy)phenyl]prop-2-en-1-ol **41** by transesterification with catalyst Novozym 435 using vinyl acetate (1.5equiv) as an acyl donor and further RCM reaction of (R)-(-)-1-[2-(allyloxy)phenyl]prop-2-en1-ol **42** with Grubbs 1st generation catalyst as exhibited in Scheme **10**.[34]



Scheme 10

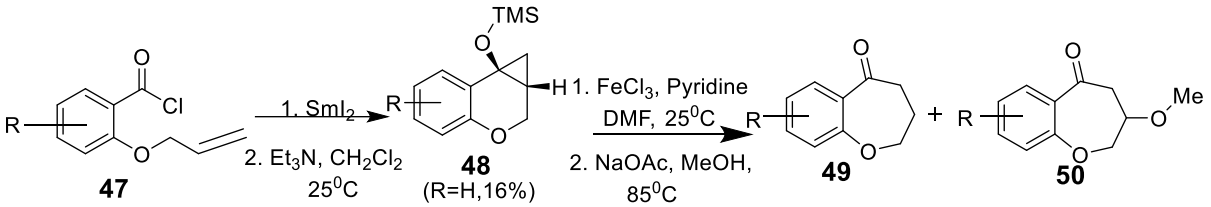
11. Synthesis of Benzoxepines via a Domino Ortho-Alkylation / Heck Coupling Reaction: 2-Iodophenols **43** on reaction with bromo-hexenoic acid-ethyl ester **44** and CS_2CO_3 (2 eq.) in dry CH_3CN resulted in the formation of Iodo

ester **45.** **45** on Intramolecular Heck reaction with $Pd(OAc)_2$ and $P(2\text{-Furyl})_3$ afforded Benzoxepine derivative **46** in 47% yield as shown in Scheme **11**.[35]



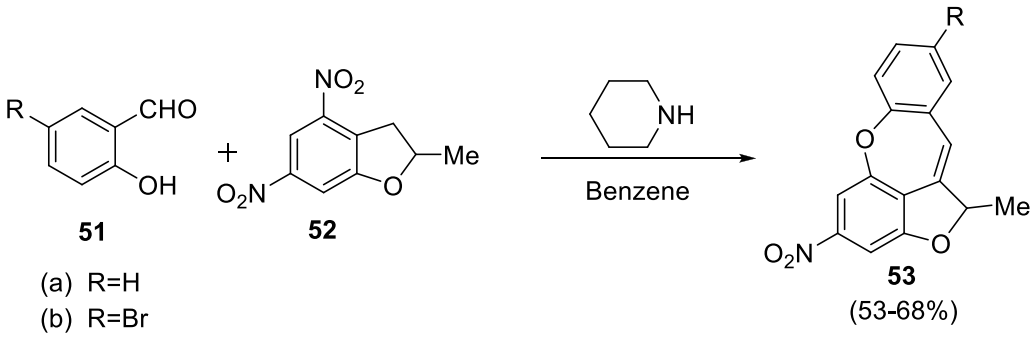
Scheme 11

12.By Oxidative Ring Opening Reactions of Cyclopropanol Derivatives : SmI_2 reduction followed by silylation of Ortho Allyloxybenzoyl Chloride **47** afforded Cyclopropyl trimethyl silyl ether **48**. $FeCl_3$ promoted regioselective ring opening reaction of **48** afforded ring expanded Benzoxepinones **49** & **50** as shown in Scheme **12**.[36]



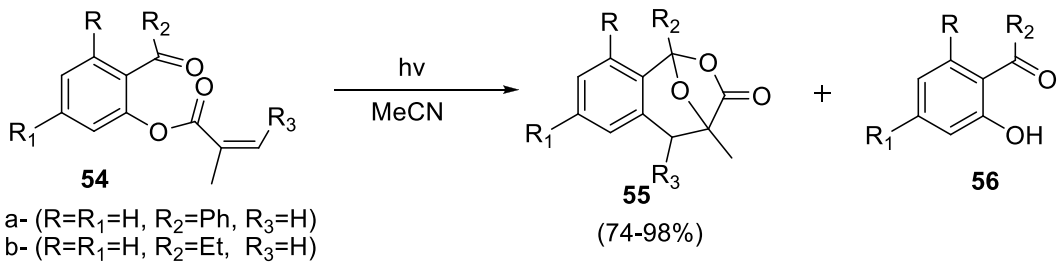
Scheme 12

13. Synthesis of Benzoxepine Derivatives by Knoevenagel Condensation : The reaction of Salicylaldehyde derivative **51** with 2 Methyl-4,6-dinitro-2,3-dihydro-benzofuran **52** in presence of piperidine leads to Knoevenagel condensation followed by intramolecular nucleophilic substitution of the nitro group further leading to formation of Benzo[*b*]furo[4,3,2-*ef*]-1-benzoxepine derivative **53** as shown in Scheme **13**.[37]



Scheme 13

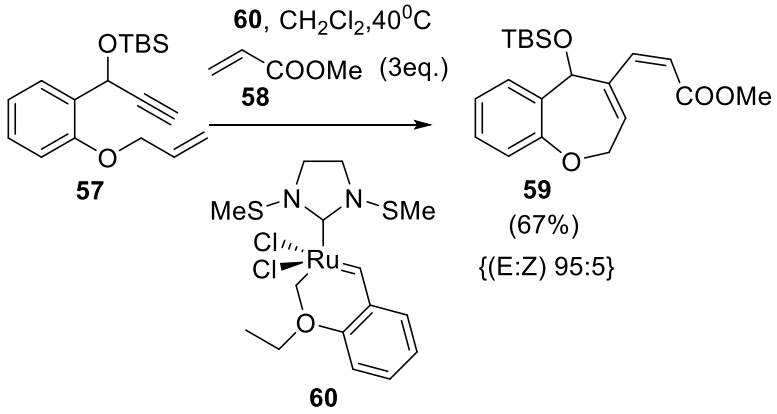
14. Synthesis of Benzoxepines by Intramolecular Photocyclization of 2-Acylphenyl Methacrylates : Irradiation of 2-Acylphenylmethacrylates **54** in acetonitrile with high pressure Hg lamp under Argon leads to formation of 4,5-Dihydro-1,4-epoxy-2-benzoxepin-3(1*H*)-ones **55** in high yields along with small amounts of 2 Acylphenols **56** as shown in Scheme **14**.[38]



Scheme 14

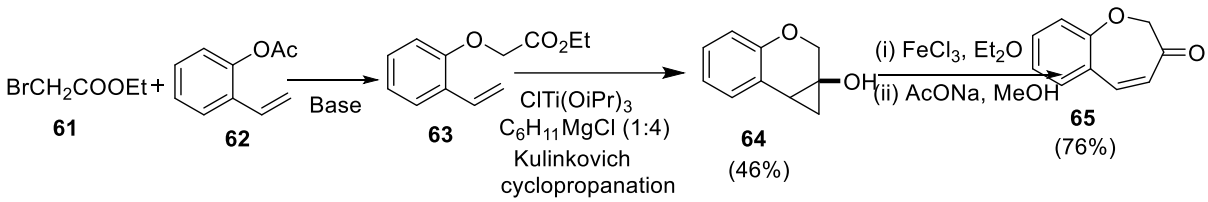
15. Synthesis of Benzoxepines by Selective Domino Ring-Closing Metathesis (RCM) – Cross Metathesis (CM); Metathesis process between Enynes and Electron Deficient Alkenes: The Ring Closing Metathesis (RCM)

and Cross Metathesis (CM) between enynes **57** and Methylacrylate **58** (3 eqvi.) resulted in the formation of cross metathesis product Benzoxepine derivatives **59** (E:Z >95:5). The use of catalyst **60** (10 mol %) in Dichloromethane at 40^0C afforded the best result as shown in Scheme **15**.[39]



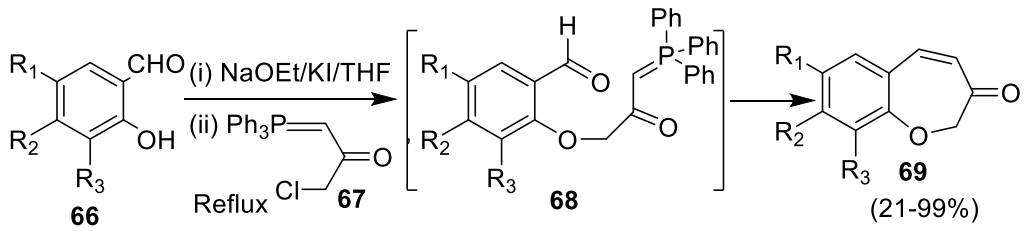
Scheme 15

16. Synthesis of Benzoxepines by Intramolecular Cyclopropanation, Oxidation and Dehydrochlorination : The basic condensation of Ethyl bromo acetate **61** and 2-Vinyl phenol acetate **62** led to formation of Ether **63** . The cyclopropanation with Chloro titanium triisopropoxide and 4 eq. of Grignard reagent (Cyclohexyl Magnesium Chloride) known as Kulinkovich Cyclopropanation led to formation of *cis* fused cyclopropanol derivative **64**. Saegusa oxidation and dehydrohalogenation of **64** afforded Benzoxepinone derivative **65** in good yield as shown in Scheme **16**.[40]



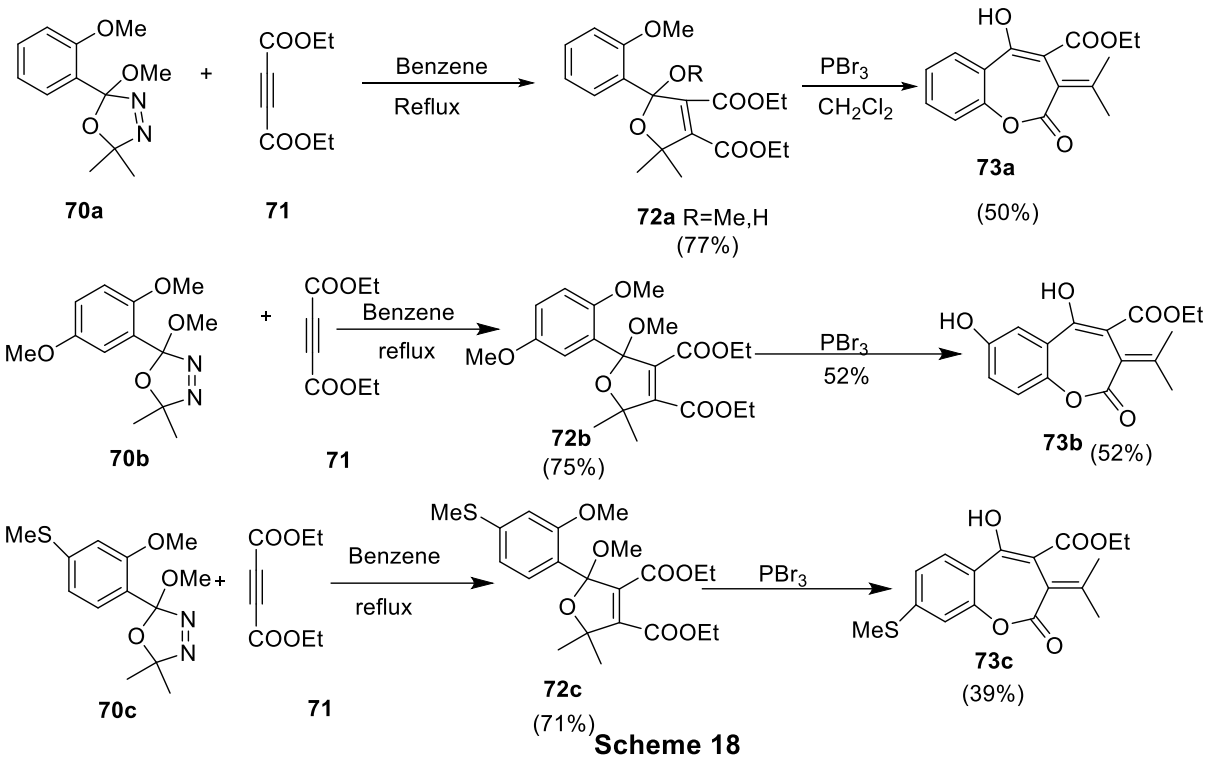
Scheme 16

17. Synthesis of 1-Benzoxepine derivatives via Tandem S_N2 /Wittig Reaction: The base catalyzed condensation reaction of salicyladehyde derivative **66** with Triphenyl chloro acetonyl phosphorane **67** in presence of Sodium Methoxide led to formation of intermediate **68**. Intramolecular cyclization via Wittig Olefination between tethered triphenylacetophosphorane and the benzoyl group in **68** afforded highly functionalized Benzoxepine derivative **69** in moderate to high yields as shown in Scheme **17**.[41]



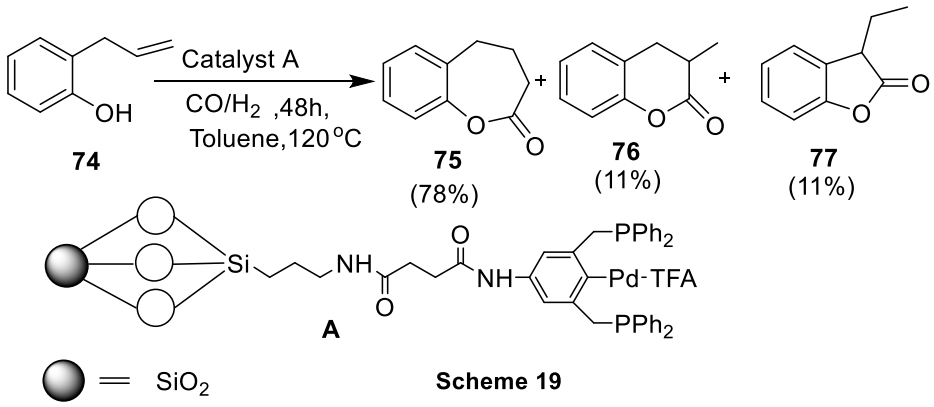
Scheme 17

18. Synthesis of 1-Benzoxepine Derivatives via Rearrangement of Dihydrofurans: Oxadiazolines **70 (a-c)** on heating with diethyl acetylenedicarboxylate **71** afforded adduct **72(a-c)**. Adduct **72(a-c)** is formed by [3+2] cycloaddition of carbonyl ylide derived from **70(a-c)**. **72(a-c)** on treatment with PBr_3 (5 eqiv.) undergoes rearrangement to form 1-benzoxepine derivatives **73(a-c)** as exhibited in Scheme **18**.[42]



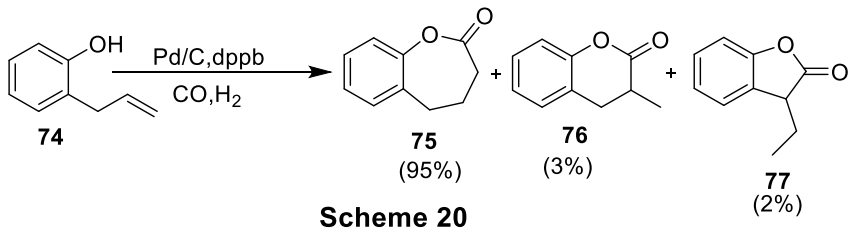
Scheme 18

19. Synthesis of 1-Benzoxepine derivatives by Cyclocarbonylation reaction of 2-Allylphenols: Intramolecular cyclocabonylation of 2-Allylphenol **74** was accomplished by treatment of 2-Allylphenol **74** with 1:1 mixture of CO/H_2 in toluene at 120^0C in the presence of Palladium (II) tridentate diphosphinoaryl legand catalyst immobilized on Silica (A). Benzoxepine derivative **75** was obtained in excellent yield and in 78% selectively as exhibited in Scheme **19**. Small amount of 6 & 5 membered ring Lactones **76** & **77** respectively were also formed during the course of Cyclocarbonylation reaction.[43]



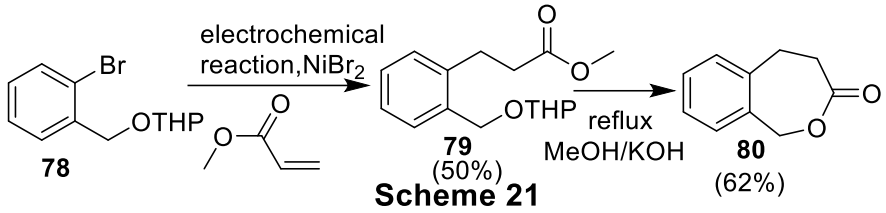
Scheme 19

20. Synthesis of 1-Benzoxepine derivatives by Cyclocarbonylation reaction using Pd/C-1,4-bis(diphenylphosphine) butane: Cyclocarbonylation of 2-Allylphenol **74** using catalytic amount of Pd/C (5 wt.% of Pd) & dppb using 1:5 mixture of $CO:H_2$ in methylene chloride resulted in the formation of 1-Benzoxepine derivative **75** in excellent yield alongwith 6 membered & 5 membered lactones **76** & **77** as minor products as shown in Scheme **20**.[44]



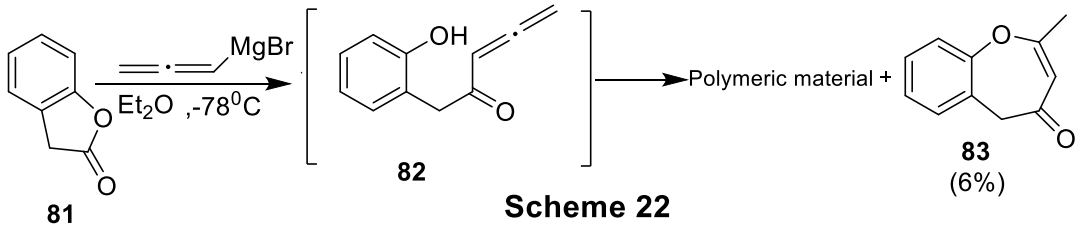
Scheme 20

21. Synthesis of Benzoxepine derivatives by nickel-catalyzed electrochemical arylation and reduction of α,β unsaturated esters : Orthobromo anisole or its THP derivative **78** on treatment with methylacrylate in presence of nickel bromide was subjected to electrochemical reaction leading to formation of ester **79**. The THP protected ester **79** on treatment with MeOH/KOH at reflux resulted in the formation of Benzoxepine derivative **80** in 62% yield as exhibited in Scheme **21**.[45] The final product **80** corresponds to endo-cyclization mode.



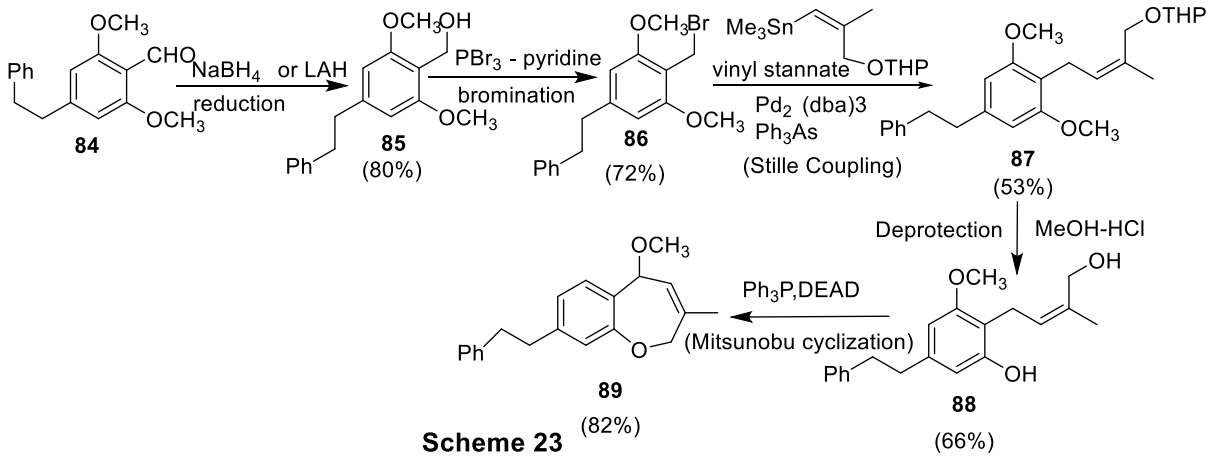
Scheme 21

22. Synthesis of Benzoxepine derivatives from Ortho-Hydroxy Benzyl Ketones: Benzofuranone derivative **81** on treatment with allenyl magnesium bromide in ether at -78^0 C did not lead to formation of expected allenyl ortho hydroxy benzyl ketone **82**. In addition to the polymeric material, Benzoxepine derivative **83** was formed in low yield as exhibited in Scheme **22**.[46]



Scheme 22

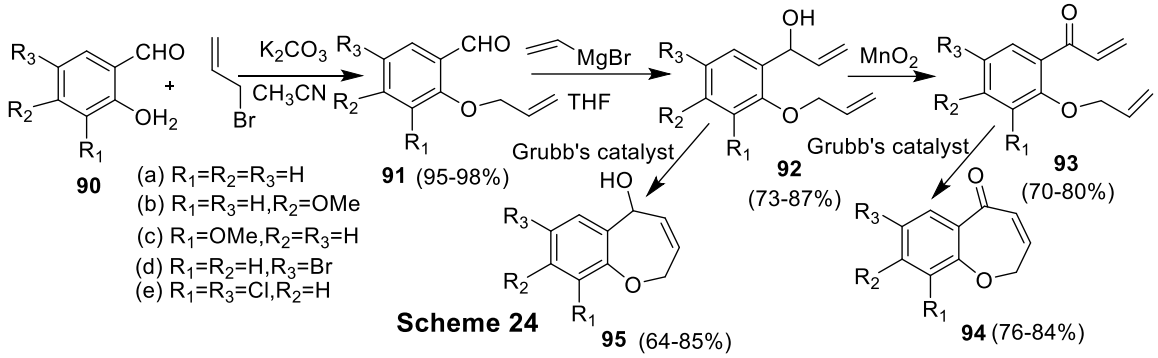
23. Synthesis of 1-Benzoxepine Derivatives by Stille Coupling and Mitsunobu Cyclization :2,6-Dimethoxy-4-(phenylethyl)benzaldehyde **84**. The benzaldehyde **84** was converted to corresponding Benzyl bromide **86** by first reduction with $NaBH_4$ or $LiAlH_4$ into alcohol **85** followed by bromination with PBr_3- Pyridine. Stille coupling of **86** with Vinyl Stannane derivatives using $Pd_2(dba)_3$ and Ph_3As led to formation of coupling product **87** which was converted to corresponding diol **88** by acidic deprotection with MeOH-HCl. Mitsunobu cyclization of **88** by treatment with Ph_3P and DEAD afforded 1-Benzoxepine derivative **89** as exhibited in Scheme **23**.[47]



Scheme 23

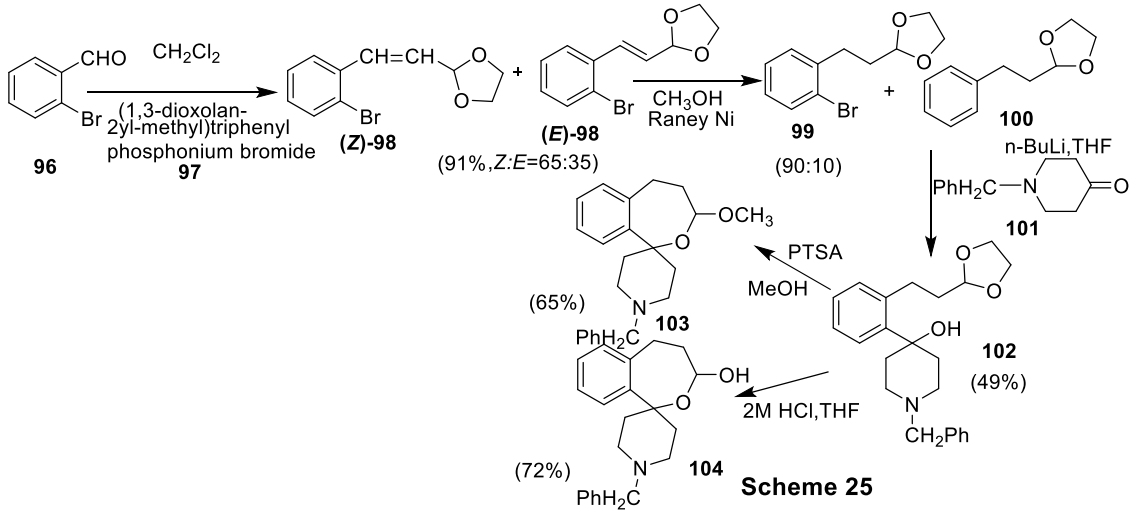
24. Synthesis of 1-Benzoxepine Derivatives from Salicylaldehyde by using Ring Closing Metathesis: Salicylaldehydes **90** on reaction with allyl bromide resulted in the formation of Allyloxy benzaldehydes **91** in excellent yield. Further treatment of **91** with Vinyl magnesium bromide resulted in the formation of 2-Allyloxyaryl-2-propen-1-ols **92** in excellent yield. Oxidation of **92** with MnO_2 in CH_2Cl_2 afforded 2-Allyloxyaryl-2-propen-1-ones **93** in very good yield. The treatment of **93** with Grubb's catalyst (second generation) in CH_2Cl_2 afforded 2*H*-1-benzoxepin-5-ones **94** in very good yields. In order to synthesize 2*H*-1-benzoxepin-5-ols **95**, **92** was treated with

Grubb's catalyst (second generation) in $CHCl_3$ at room temperature to yield alcohol **95** in very good yield as shown in Scheme **24**.[48]



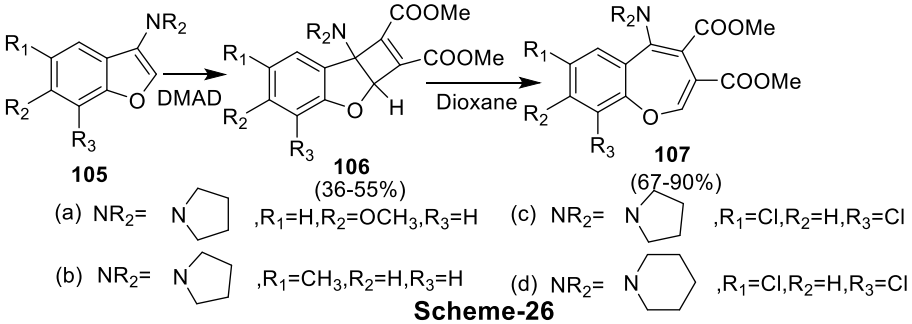
Scheme 24

25. Synthesis of 2-Benzoxepine Derivatives by means of Wittig Reaction and Cyclization of Hydroxyacetal with PTSA : Wittig- Horner-Emmons reaction of 2-Bromobenzaldehyde **96** with Wittig reagent (1,3-Dioxolan-2-ylmethyl)triphenyl phosphonium bromide **97** afforded 2-Bromo cinnamic aldehyde acetal **98** as a mixture of *Z&E* isomers in the ratio of 65:35. The hydrogenation of **98** with Raney nickel in methanol resulted in the formation of (2-Bromophenyl)-propionaldehyde acetal **99** alongwith debrominated by product **100** which was separated by flash chromatography. **99** on further treatment with n-Butyl Lithium and 1-Benzyl piperidin-4-one **101** led to formation of Hydroxy acetal **102**. Cyclization of Hydroxy acetal **102** with PTSA afforded Spirocyclic Oxepine derivative **103** in good yield. However cyclization of **102** with the aqueous HCl in THF yielded Benzoxepine derivative **104** in good yield as shown in Scheme **25.**[49]



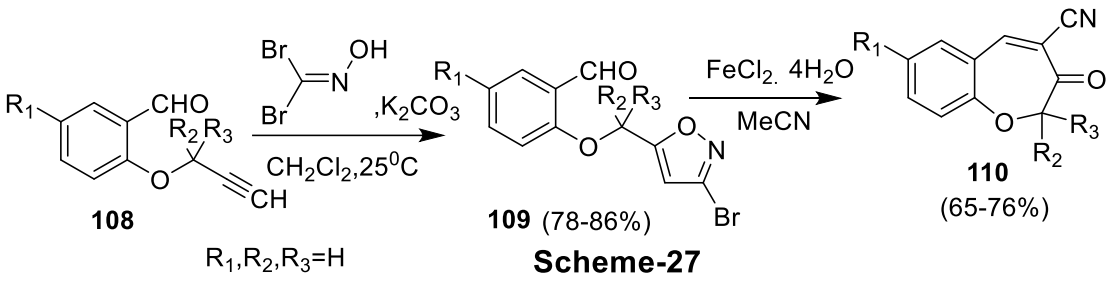
Scheme 25

26. Synthesis of 1-Benzoxepine Derivatives by (2+2) Cycloaddition of Benzofuran-3-(2*H*)-one enamines with DMAD: Cycloaddition reaction of Pyrolidine & Morpholine enamines of substituted Benzofuran-3-(2*H*)ones **105** with DMAD at 0^0C resulted in the formation of cyclobutene adduct **106**. Cyclobutene adduct **106** on thermal isomerization in Dioxane afforded 1-Benzoxepine derivative **107** as exhibited in Scheme **26**.[50]



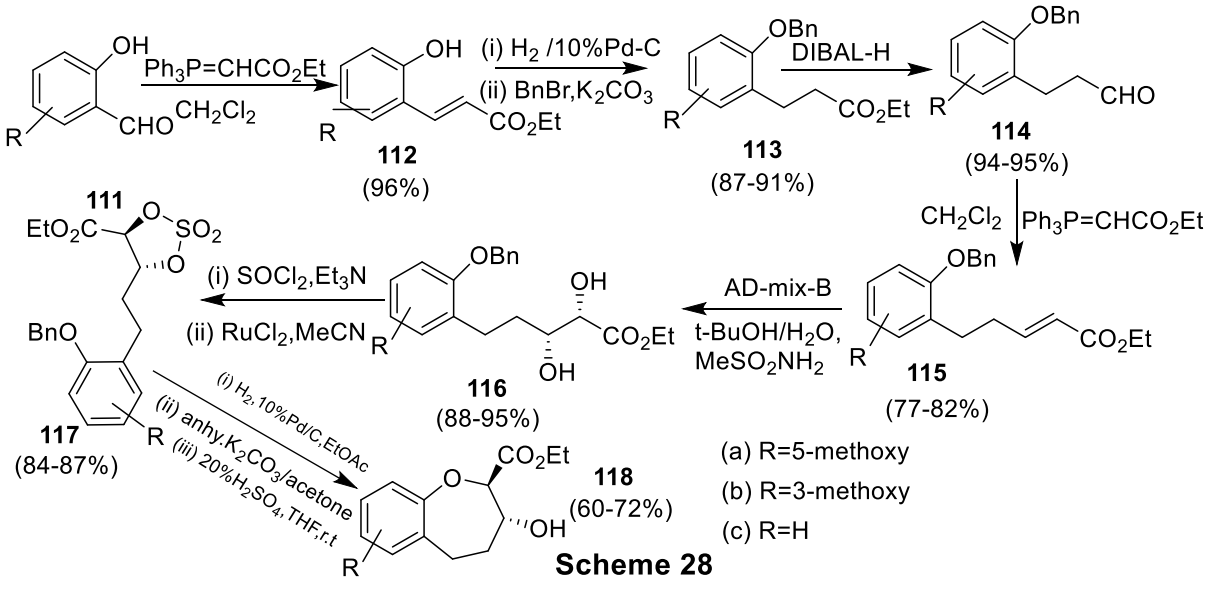
Scheme-26

27. Synthesis of 1-Benzoxepines by Tandem ring-opening/cyclocondensation of 3-Bromoisooxazoles: Aldehydes containing 3-Bromoiso oxazole **109** were prepared from acetylinic aldehydes **108** by reaction with dibromo oxime in presence of K_2CO_3. Tandem ring-opening/cyclization with $FeCl_2.4H_2O$ in MeCN resulted in the formation of 1-Benzoxepine derivatives **110** in good yield as shown in Scheme **27**.[51]



Scheme-27

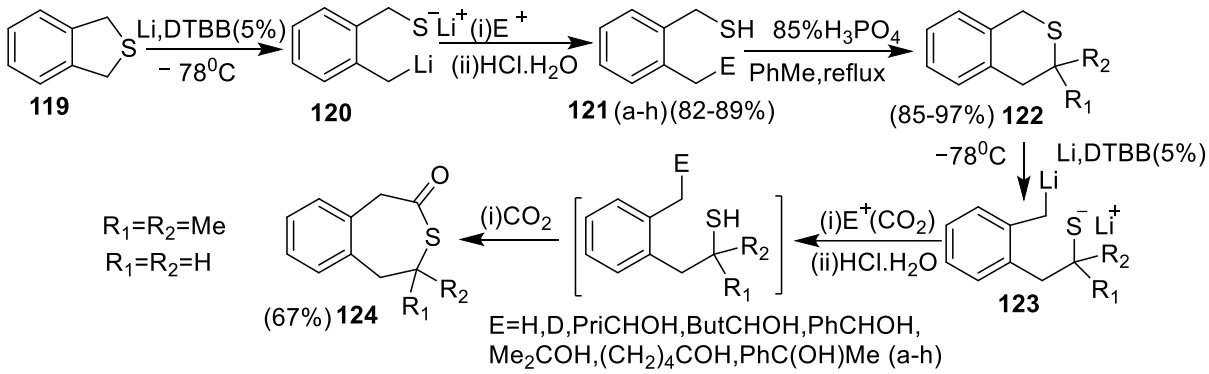
28. Asymmetric Synthesis of 2,3 Disubstituted 1-Benzoxepines: 2,3-Disubstituted 1-Bezoxepines **118** can be synthesized by Sharpless asymmetric dihydroxylation of *trans α,β*-unsaturated esters & phenoxide ion mediated intramolecular 7- *endo-tet* S_N2 carbocyclization of *syn*-2,3-dihydroxy esters derived cyclic sulphates. 2-Hydroxy benzaldehyde derivatives **111** were used as starting materials. The Wittig olefination of **111** with (Ethoxy carbonyl methylene)triphenyl phosporanes afforded the corresponding (*E*)-cinnamate esters in high yield. Hydrogenation of **112** with 10% Pd/C followed by benzylation with benzyl bromide and anhydrous K_2CO_3 yielded **113** in high yield. Reduction of **113** with DIBAL-H afforded corresponding aldehydes **114** in excellent yields. **114** on treatment with (Ethoxy carbonyl methylene)triphenyl phosphorane resulted in the formation of corresponding (*E*)-unsaturated esters **115**. Sharpless asymmetric dihydroxylation with AD-mix-beta in tBuOH and water resulted in the formation of enantiomerically pure Dihydroxy derivatives **116** in very good yields. Treatment of diols **116** with Thionyl chloride & Triethyl amine afforded cyclic sulphides, which on further oxidation with $NaIO_4$ and $RuCl_3$ afforded cyclic sulphates **117** in very good yields. Debenzylation with H_2 and 10% Palladium Charcol and treatment with anhydrous K_2CO_3 in dry acetone and ultimately with 20% H_2SO_4 in THF afforded Benzoxepine derivatives **118** in good yields, as shown in Scheme **28.**[52]



Scheme 28

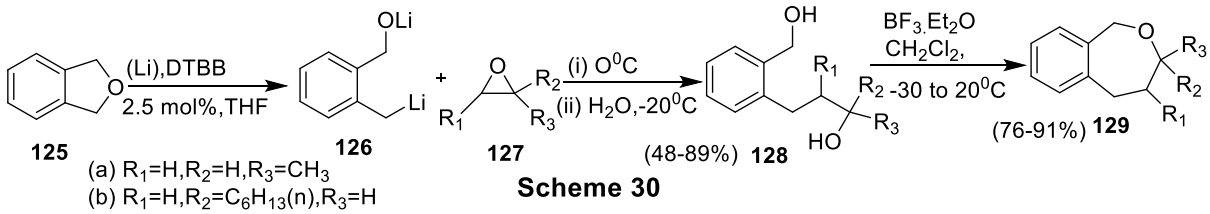
29. Synthesis of Benzothiepine Derivatives from Thiophthalan: 3-Benzothiepine derivatives **124** were synthesized by reductive opening of Thiophthalan **119**. The reaction of thiophthalan 119 with an excess of Lithium

powder and a catalytic amount of DTBB at -78^{0}C led to a solution of Dianion intermediate **120** which on hydrolysis with water and HCl led to formation of functionalized thiols **121**. Treatment of compound **121** with 85% phosphoric acid in refluxing toluene resulted in the formation of isothiochroman **122** in excellent yields. The reductive opening of isothiochromans **122** with lithium powder and catalytic amount of DTBB 5% led to formation of corresponding Dianion intermediate **123** which on carbonation with CO_2 and Hydrolysis with HCl & water led to formation of 3-Benzothiepine derivative **124** as shown in Scheme **29**.[53]



Scheme 29

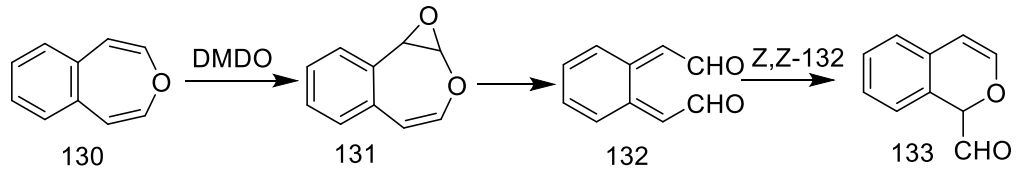
30. Synthesis of Benzoxepine by Dehydration of 1,6-Diols using $BF_3.OEt_2$ as a Catalyst: Dianions **126** derived from Phthalan **125** on treatment with epoxides **127** resulted in the formation of Diols **128** in good yields. **128** undergoes cyclodehydration in presence of $BF_3.OEt_2$ resulting in the formation of Benzoxepine **129** in very good yield as depicted in Scheme **30**.[54]



Scheme 30

REACTIONS OF BENZOXEPINES AND BENZOTHIEPINES

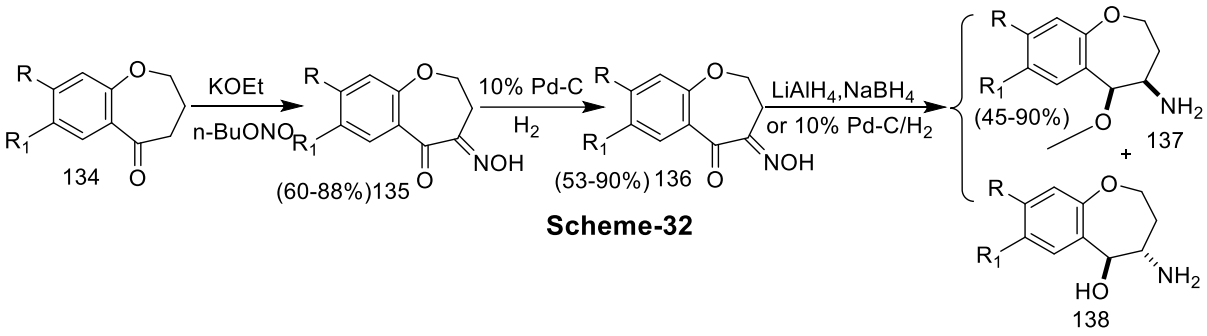
1. Rearrangement and Ring Contraction Reactions: The reaction of 4,5- Benzoxepine **130** with dimethyl dioxirane (DMDO) resulted in the formation of 4,5-Benzoxepin-2,3oxide **131**. The concerted ring opening reaction of **131** could possibly result in the formation of *Z,Z*-132 which undergoes concerted ring closure to form 1*H*-2Benzopyran-1-Carboxaldehyde **133** as shown in Scheme **31**.[55]



Scheme 31

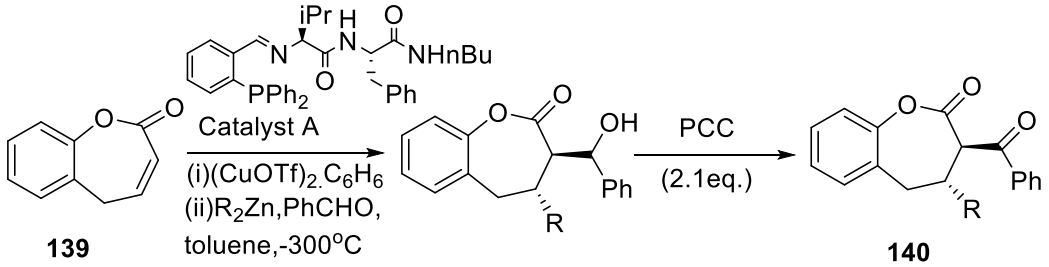
2. Chemo and Stereoselective Synthesis of *cis*-and *trans*-Amino Alcohols from 1-Benoxepine-5-ones: 1-Benzoxepin-5-one derivatives **134** on nitrosation with n-butyl nitrile and potassium ethoxide resulted in the formation of oximino ketone **135**. Catalytic reduction of **135** in the presence of 10% Pd/C and H_2 resulted in the formation of α-aminoketones **136**. Further reduction of α-aminoketones **136** in the presence of LAH, $NaBH_4$ or 10% Pd/C led to formation of a mixture of *cis* and *trans* amino alcohols **137** & **138**. However both chemo selectivity and stereo

selectivity was accomplished by reduction of α-aminoketones **136** with $LiAl(t\text{-}BuO)_3H$ resulting in the formation of exclusively *trans* amino alcohols **138** in good yields as shown in Scheme **32**.[56]



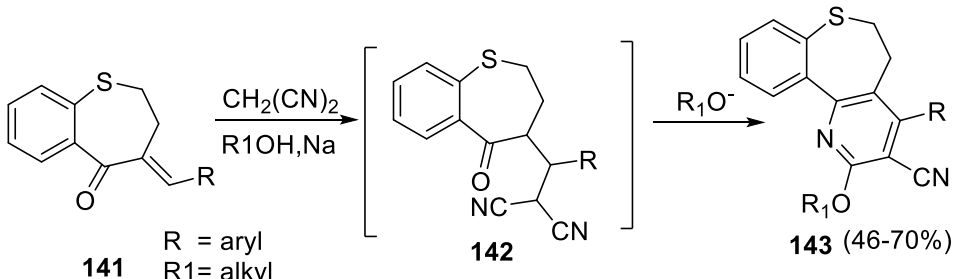
Scheme-32

3. Synthesis of 1-Benzoxepine Derivatives by Cu Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Lactones: Cu catalyzed asymmetric conjugate additions of Dimethylzinc and Diethylzinc to Benzoxepin-2-one derivative **139** resulted in the formation of chiral secondary alcohol which on further oxidation with PCC [Pyridinium Chloro Chromate(2.1eq.)] resulted in the formation of Diketone **140** (94-98% ee) as exhibited in Scheme **33**.[57]



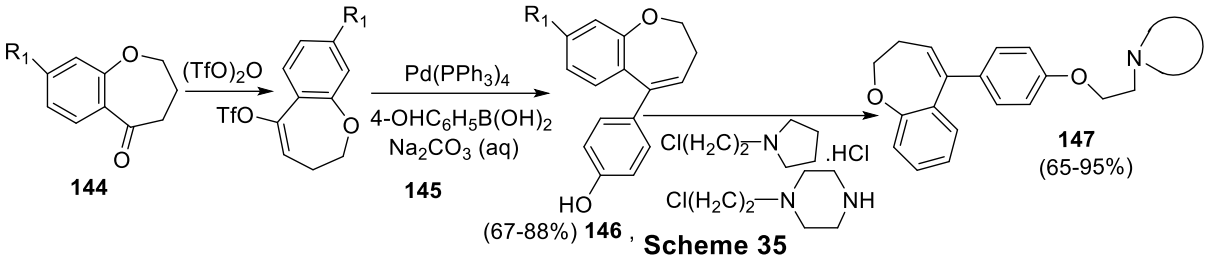
Scheme 33

4. Michael Addition Reaction of Benzothiepine Derivatives with Malononitrile: The reaction of 4-Arylmethylene-3,4-dihydro-[1]-benzothiepin-5(2*H*)-ones **141** with malononitrile in alcohols in the presence of Na afforded 2-alkoxy-4-aryl-5,6-dihydro[1]-benzothiepino[5,4-*b*]pyridine-3-carbonitrile **143** via intermediate formation of acyclic adduct **142**. The formation of **143** from **141** can be explained by Michael addition reaction rather than expected knoevenagel condensation as exhibited in Scheme **34**.[58]



Scheme 34

5. Suzuki Reaction of Benzoxepine Derivatives: 1-Benzoxepin-5-one derivatives **144** were converted to the Triflate by treatment with Triflic anhydride to form triflate derivatives **145**. **145** were subjected to Suzuki reaction by coupling with 4-hydroxy phenyl boronic acid and tetra phenyl phosphino palladium resulting in the formation of 5-aryl benzoxepines **146** which on further treatment with pyrolidine and piperidine hydrochlorides in presence of anhydrous K_2CO_3 and acetone resulted in the formation of ether derivatives **147**. **147** were used for docking study of a series of benzoxepine derived estrogen receptor modulator as shown in Scheme **35**.[59]



Scheme 35

NATURALLY OCCURRING BENZOXEPINES AND RELATED COMPOUND

Two novel fungal antibiotics isolated from fermentation of A *Pterula* species containing benzoxepine ring system are chlorinated derivatives. These compounds are Pterulinic acid **148** and Pterulone **149**. Both these compounds interfere with the NADH: ubiquinone oxidoreductase and also inhibit the respiration of Eucaryotes.Pterulinic acid **148** exhists as a mixture of two inseperable mixture of [*Z&E*] isomers as shown in Fig. **2**.[60]

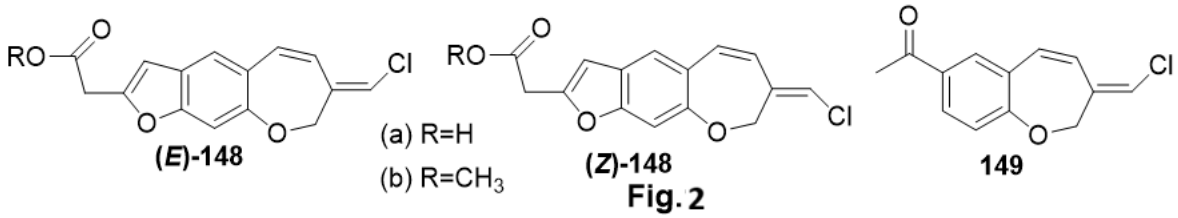
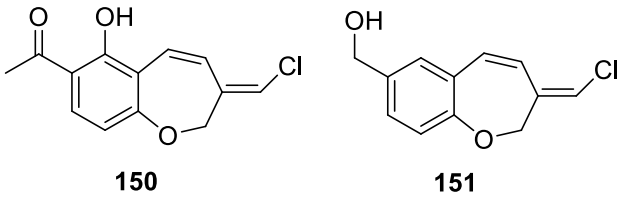
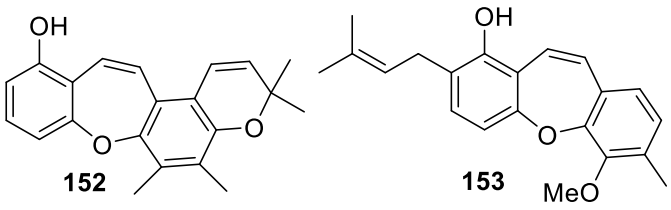


Fig. 2

In addition to fungal metabolites Pterulone **148** and Pterulinic acid **149**, two oter fungal metabolites containing 1-benzoxepine ring system in them were isolated from the fungus *Mycena galopus*. The biological activity of these new metabolites **150** and **151** have yet to be ascertained.[61]



Two new antimicobacterial Dibenzo[*b,f*]oxepines named as Bauhinoxepin A **152** and Bauhinoxepin B **153**, were isolated from the root extract of *Bauhinia saccoclyx* (Family Leguminosae) both Bauhinoxepins **152** & **153** exhibited antimalarial and antimicrobial activities.[62]



Heliannuols, a family of allelochemicals of sunflower origin (*Helianthus annuus*L.) contains 4-Tetrahydrobenzo[*b*]oxepines Heliannuol A **154**, Heliannuol B **155**, Heliannuol C **156**, Heliannuol D **157** [Fig.3]. These compounds were found to be potent growth inhibitors of Cress (Lepidium sativum L) and Oat (Avna sativa L).[63]

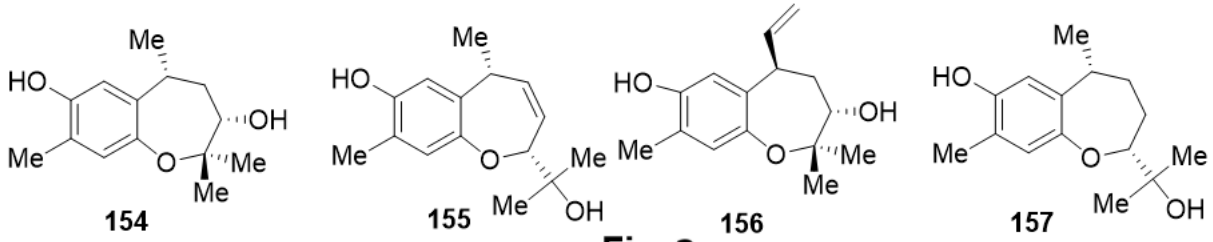
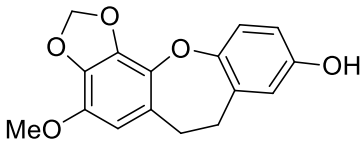


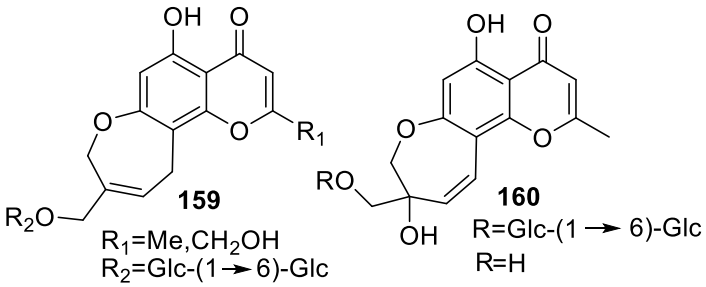
Fig. 3

Pholidota chinensis (Orchidaceae) named Shi-Xian-To in china, a medicinal plant is widely distributed in south east in china. The plant has been widely used as remedy for chronic bronchitis, toothache and duodenal ulcer. The ethanol extract of the whole plant led to isolation of 1-Benzoxepine derivative **158** named as **Bulbophylol B** alongwith eight known Dihydrophenanthrene derivatives and two new stilbene derivatives.[64]

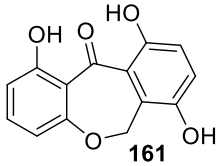


158

The dried tubers of ***Eranthis cilicica*** (Family Ranunculaceae) were extracted with hot methanol resulting in isolation of a mixture of Chromone and two Benzoxepine derivatives after column chromatography. The structure elucidation after 1D & 2D NMR resulted in structural elucidation of two Benzoxepine derivatives as 8,11-Dihydro-5-hydroxy-2,9-dihydroxymethyl-4*H*-pyrano[2,3-*g*][1]benzoxepin-4-one **159** and 9-[(O-β-D-Glucopyranosyl)oxy]methyl-8,11-dihydro-5,9-dihydroxy-2-methyl-4*H*-pyrano[2,3-*g*] [1]-benzoxepin-4-one **160**.[65]

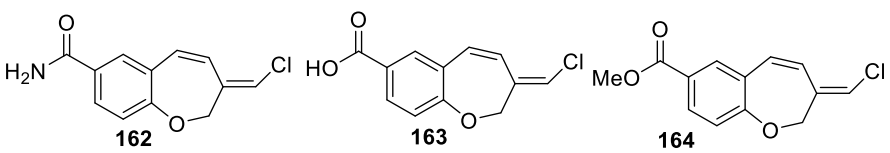


Leptosphraerin D **161** isolated from the cultures of Ascomycete fungus *Leptosphraeria* species alongwith dihydroxy benzoic acid derivatives and spiro furan derivatives. The structure of Leptosphraerin D **161** was assigned on the basis of HRESIMS, ^{1}H NMR & ^{13}C NMR spectra to be Dibenzo[*b,e*]oxepin-11(6*H*)-one.[66]



161

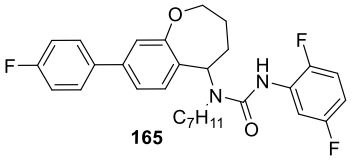
Chemical investigation of compounds isolated from culture BCC 18689 of the fungus *Favolaschia tonkinensis* contained 3 mono chlorinated 2,3-Dihydro-1-benzoxepine derivatives **162**,**163**,**164**. All the three compounds displayed cytotoxic activity against KB cells and NCI-H 1877 with compounds **162** and **163** having IC_{50} values of 0.78 and 11.66 µg/ml.[67]



162 **163** **164**

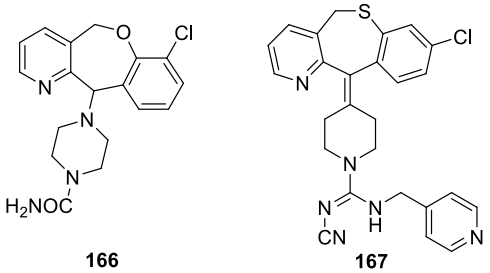
PHARMACEUTICAL SIGNIFICANCE & FUTURE PROSPECTS

N^2-(2,4-Difluorophenyl) - N^1 - 8 - (4-fluorophenyl) - 2,3,4,5 - tetrahydro-1-benzoxepin-5-yl-N^1-n-heptyl urea **165** was found to be very active on both the inhibition of aortic ACAT and the inhibition of rat cholesterol intestinal absorption.[68]



165

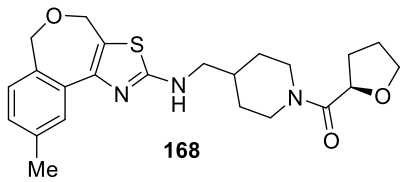
Benzoxepines & Benzothiepines containing piperidine and piperazine ring at the C-6 carbon atom, **166** &**167** were found to be potent inhibitors of Farnesyl protein transferase synthesis in vitro.[69]



166 **167**

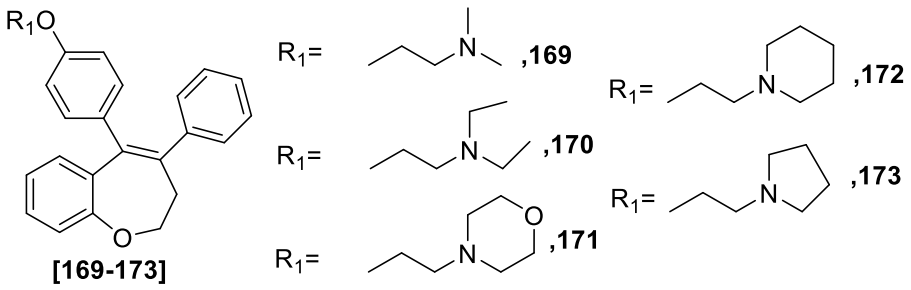
Several pyridines, pyridones & pyrans fused to benzothiepine exhibited potential anticancer and anti HIV activity. Some of these compounds exhibited good anticancer activity comparable to 5-Fluoro deoxy uridine used as a reference compound and moderate anti HIV activity in comparision with AZT.[70]

{4[(9-Methyl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]-azulen-2-ylamino)methyl]piperidin-1-yl}-((R)–tetrahydrofuran-2-yl)-methanone **168** synthesized from p-cresol in six steps was shown to completely inhibit feeding induced by a selective NPY5 (Neuro peptide Y5) agonist (i.c.v) in rats. This class of compound is capable of delivering potent and selective orally and centrally bioavailable NPYY5 receptor antagonists.



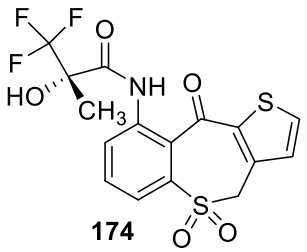
168

A novel molecular scaffold for modulation of estrogen receptor was prepared from 2,3,4,5 Tetra hydro-1-benzoxepine derivatives. The compounds **169-173** prepared from the traditional triphenyl ethylene structure of Tamoxifen analogs by incorporation of N isomerically constrained heterocyclic ring system and by variation of basic side chain systems alongwith introduction of aromatic ring substituent. The compounds **169-173** demonstrated competitive estrogenic receptor binding and exhibit antiestrogenic potency by later inhibition of the proliferation of human MCF-7 breast cancer cells, the unsubstituted benzoxepine estrogenic receptor scaffold acts better than Tamoxifen with lower cytotoxicity.



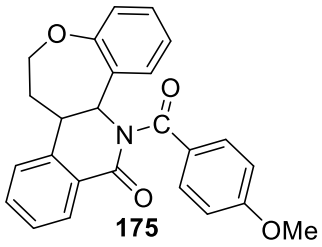
[169-173]

A novel K^+ channel agonist **174** has been used for the treatment of variety of disorders and has been found to be useful therapeutic agent for both acute and chronic condition involving nociceptive sensitization of afferent neurons. **174** enhances A-type K^+ channel activity. **174** has also been found to be a promising agent for treatment of a number of disorders better associated with afferent neuron hyper excitability which includes urinary bladder disfunction induced by spinal cord injury.



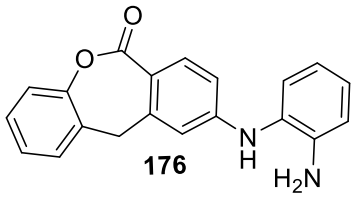
174

Benz[*b*]oxepine derivative **175** synthesized by Cho et.al.has been shown to possess potent cytotoxicity and Topoisomerase 1 inhibitory activity. A surflex-DOC-docking study was performed to eventualize the Topoisomerase 1 activity of **175**.



175

N-substituted 11*H*-Dibenzo[*b,f*]oxepin-10-ones **176** synthesized from 2-substituted phenol derivatives were found to be p-38 inhibitors. The p-38 mitogen activated protein (MAP) kinase is the key enzyme in anti-inflammatory diseases due to its involvement in the biosynthesis of pro inflammatory cytokines such as TNF-α and IL-1β.[71]



176

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