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RECENT PROGRESS OF THE CHEMISTRY OF AZAAZULENES AND RELATED COMPOUNDS †

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Abstract – This review describes the synthetic methods and reactions of azaazulenes including some of their *dihydro*-, *tetrahydro*-, *oxo*-derivatives and *aromatics- and heterocycles-fused* derivatives and related compounds such as *pyrrolobenzazepines,* and *azepinoindole* derivatives published during 2010 to 2017. The biological and physical properties of azaazulenes and related compounds are also described.

Azaazulenes are a class of the compounds that have been receiving continual interest of chemists for their relationship with the chemistry of azulenes and for remarkable characters about physical and chemical properties as well as biological activities.[1] After being previously reviewed at 2010,[1e] many significant researches were developed in this field. Especially, polycyclic compounds containing azaazulene skeleton, such as pyrrolobenzazepines, azepinoindole-derivatives, and so on, were directed attention from their biological activities and potentialities of drug use.[2] This review covers the recent progress in the chemistry of azaazulenes including some of their *dihydro*-, *tetrahydro*-, *oxo*-derivatives and *aromatics-fused derivatives* and related compounds such as *pyrrolobenzazepines*, and *azepinoindole-derivatives* published during 2010 to 2017.

I. SYNTHESES OF AZAAZULENES

As was mentioned previous review, azaazulene skeletons were fundamentally constructed by the reaction of seven-membered rings, especially reactive troponoids.[1] Palladium-catalyzed amination and successive intramolecular Heck reaction of 2-chlorotropone with 2-bromoaniline gave 5-azabenz[*b*]azulen-6(5*H*)-

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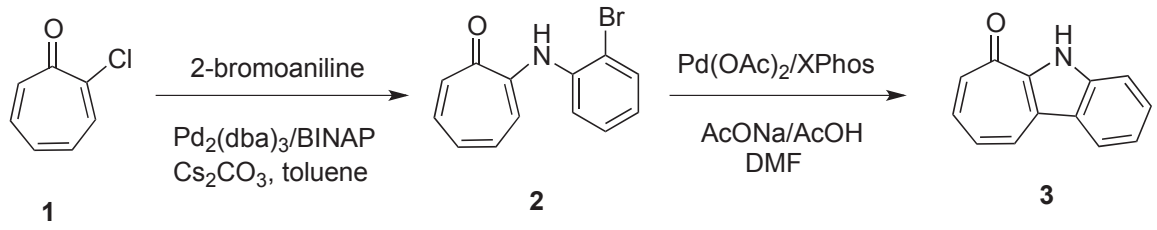
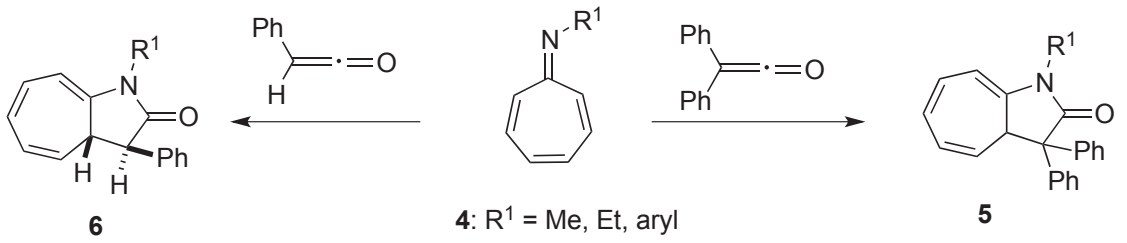
† Dedicated to Prof. Dr. Kiyoshi Tomioka on the occasion of his 70th birthday

one (**3**) (Scheme 1).[3] [8+2]Cycloaddition of 8-azaheptafulvenes (**7**) with ketenes (Scheme 2)[4] or electron-deficient olefins (Scheme 3)[5] gave 1-azaazulene skeletons (**5**, **6**, or **9**, **10**, respectively). Rh(II)-Catalyzed reaction of 8-azaheptafulvenes (**7**) with carbonyl-containing diazo compounds gave tetrahydro-1-azaazulen-2-one derivatives (**12**) (Scheme 4).[6]



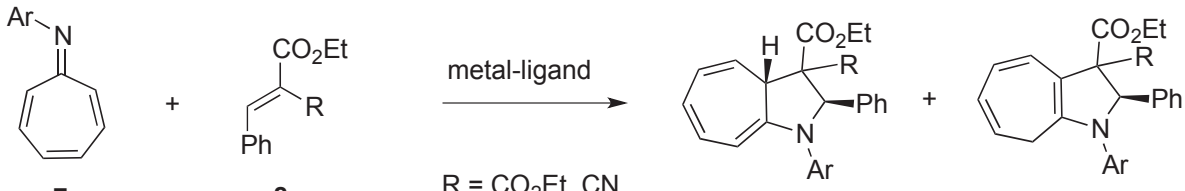
1 **2** **3**

Scheme 1



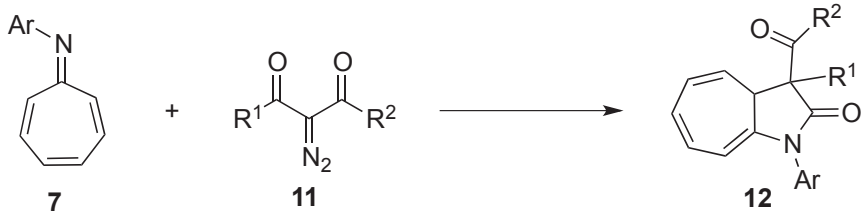
6 **4**: R^1 = Me, Et, aryl **5**

Scheme 2



7 **8** **9** **10**

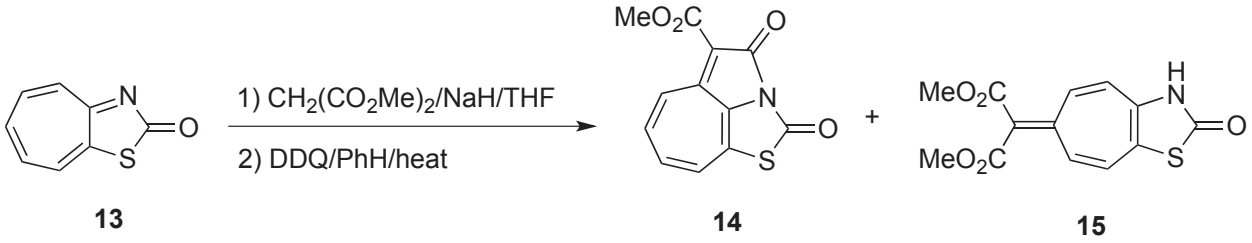
Scheme 3



7 **11** **12**

Scheme 4

Reaction of 1-thia-3-azaazulen-2(1*H*)-one, containing azaheptafulvene moiety, with dimethyl malonate in the presence of NaH followed by DDQ gave **14** in 41% yield together with **15** (33%) (Scheme 5).[7]

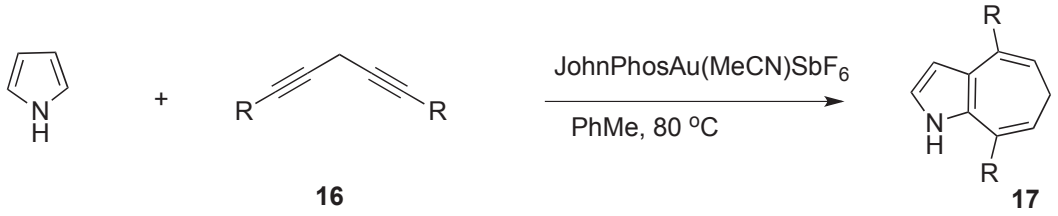


13 **14** **15**

Scheme 5

Annulation of seven-membered ring onto pyrrole, diazole, triazole or indole rings are frequently used synthetic methodology. As building blocks, alkynyl compounds, such as skipped diynes (1,4-diynes), propargyl derivatives, and aryl acetylenes, have been used extensively.

Reaction of pyrrole with skipped diynes bearing electron-donating group (**16**) in the presence of gold catalyst proceeded by a 7-*endo-dig* cyclization to give 1,6-dihydrocyclohepta[*b*]pyrroles (1,6-dihydro-1-azaazulene derivatives) (**17**) in high yields (Scheme 6).[8] Reaction of indoles with skipped diynes gave similar results.[8]

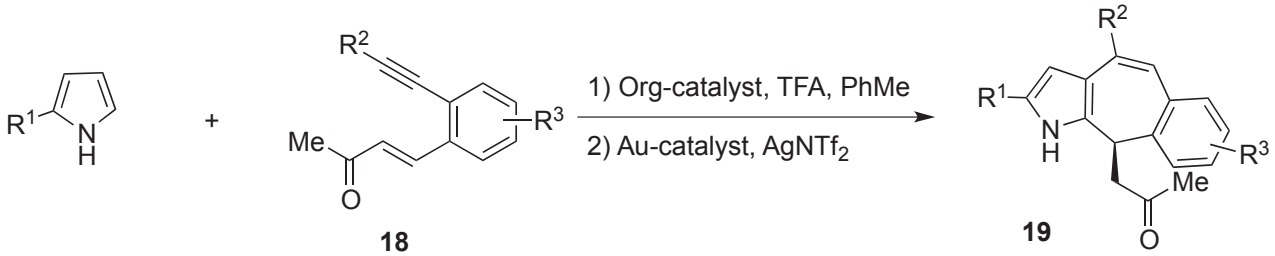


16 **17**

R = Ph (71%), C_6H_4(4-OMe) (80%), C_6H_4(4-Br) 64%),
C_6H_4(4-CN) 32%), C_6H_4(4-Me) (72%), C_6H_4(3-Me) (72%), etc.

Scheme 6

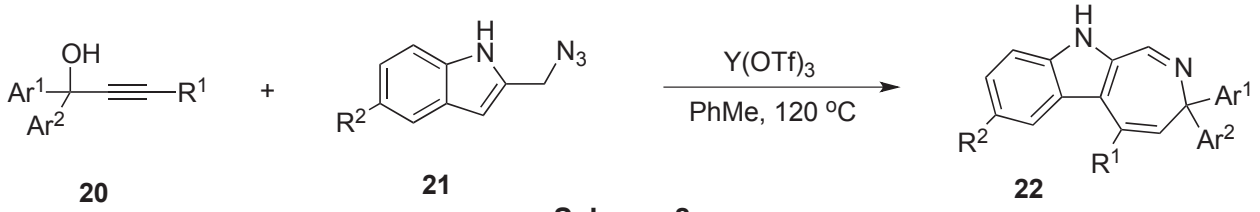
One-pot reaction of pyrroles with **18** under the presence of cinchona-alkaloid-derived amines with TFA and successive addition of Au(I) catalyst and $AgNTf_2$ to access 2,3-annulated pyrrole containing seven-membered rings (**19**) was reported. In the reaction, 6-*endo-dig* cyclization produced spiro-products, and successive [1,2]-migration occurred followed by the Friedel-Crafts-Michael-type reaction of pyrroles with **18** (Scheme 7).[9]



18 **19**

Scheme 7

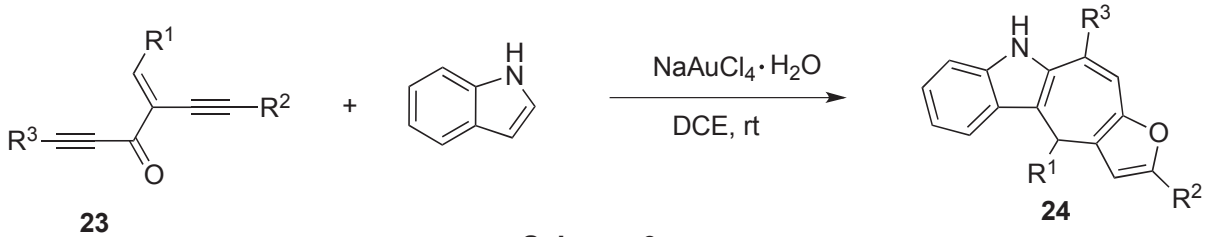
Formation of indole-fused seven-membered *N*-heterocycles (**22**) from alkynol substrate (**20**) with 2-(azidomethyl)-1*H*-indole derivatives (**21**) in the presence of Lewis acid in good yields was reported (Scheme 8).[10] The reaction proceeded *via* Lewis acid catalyzed [4+3]cycloaddition.



20 **21** **22**

Scheme 8

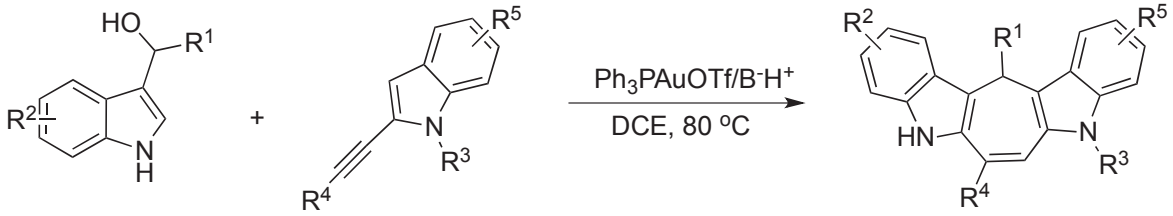
The gold-catalyzed tandem cyclization of 1,2-bis(alkynyl)-2-en-1-ones (**23**) with indoles gave furan–annulated cyclohept[*b*]indoles (fused 1-azaazulene derivatives) (**24**) in one pot *via* a cascade carbonyl-yne cyclization/Friedel-Crafts/indole-yne cyclization sequence (Scheme 9).[11]



23 **24**

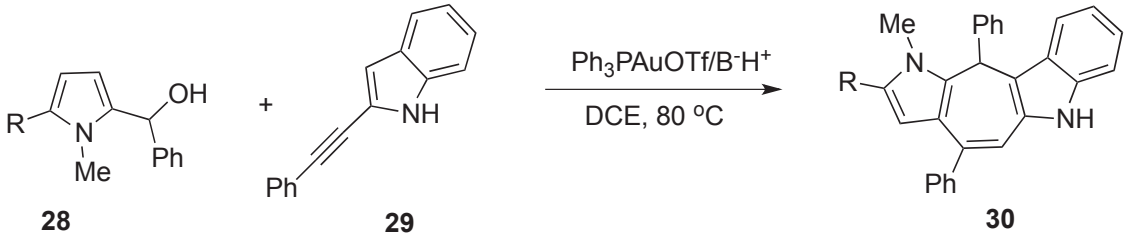
Scheme 9

Patil *et al*. improved above methods, and treated indole derivatives (**25**) with ethynylindoles (**26**) in the presence of Au(I) catalyst/Brønsted acid (B^-H^+), and obtained bis-indole derivatives (**27**) (Scheme 10).[12] Similar treatment of pyrroles (**28**) and ethynylindole (**29**) gave **30** (Scheme 11).[12]



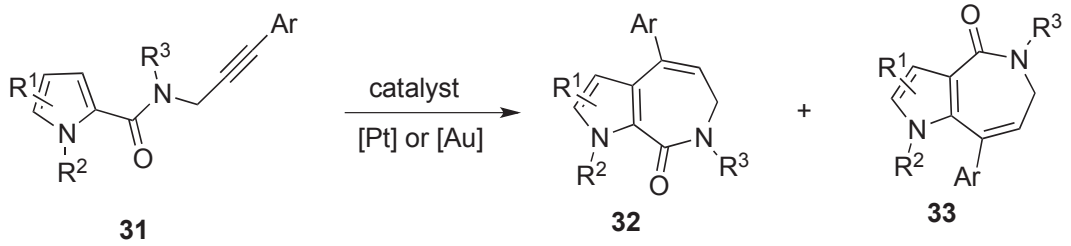
25 **26** **27**

Scheme 10



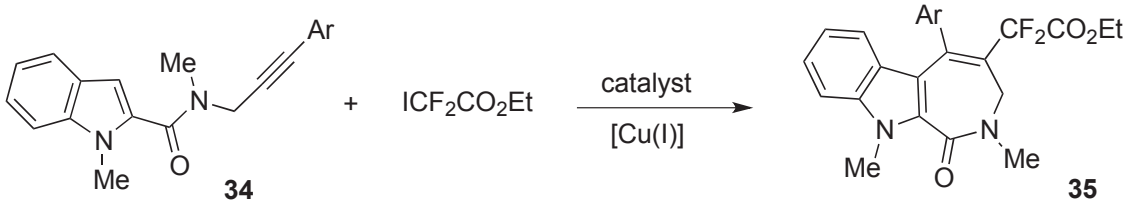
Scheme 11

A variety of novel azepino[3,4-*b*]indol-1-ones (**32**) was produced in a straightforward manner (Scheme 12).[13] The key step was the Pt-catalyzed 7-*endo*-*dig* cyclization process. The formation of the different cyclization products (**33**) strongly depended on the catalyst, solvent, temperature, *N*-protecting group and aryl substituents.



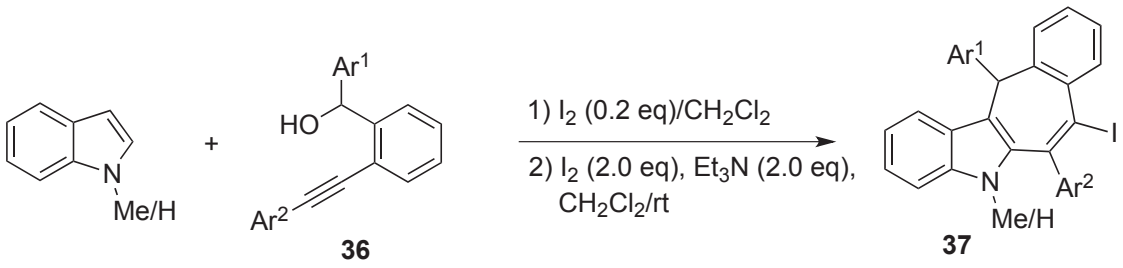
Scheme 12

Diazabenz[*b*]azulenone derivatives (**35**) were produced by a novel copper-catalyzed difluoromethylation of propargyl amide substituted indoles (**34**) with ICF_2CO_2Et *via* radical cascade cyclization process (Scheme 13).[14]



Scheme 13

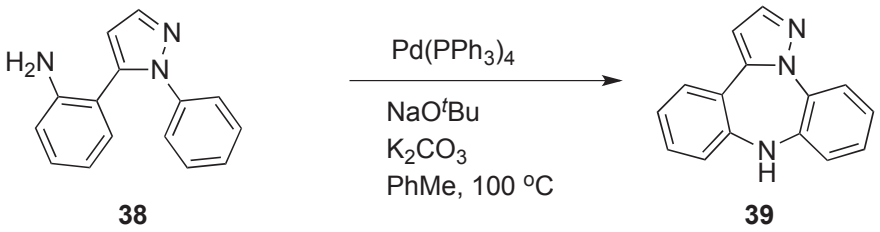
One pot treatment of indoles with 2-alkynyl benzyl alcohols (**36**) with I_2 followed by I_2 and Et_3N caused tandem C-2/C-3 annulated reaction and gave dibenz-1-azaazulenes (**37**) in good yields (Scheme 14).[15]



Scheme 14

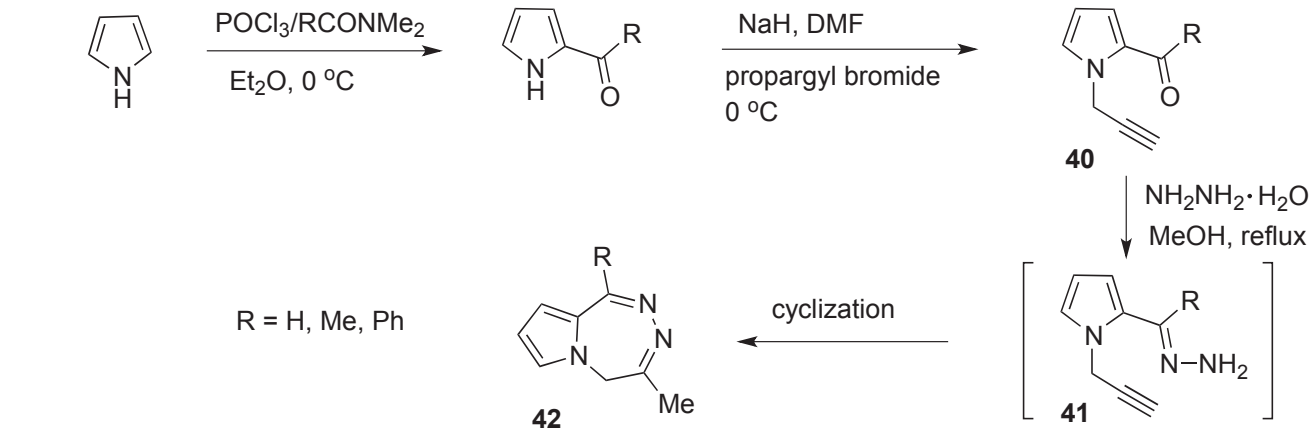
Seven-membered rings containing one more hetero-atoms are interesting motifs for organic synthesis. In addition, seven-membered ring heterocycles fused azoles and aromatics, have found wide spread use in medicinal chemistry due to their diverse biological activity. In this viewpoint, a review about the synthesis of biologically active seven-membered ring heterocycles was reported by Kassiou *et al*.[16]

Synthesis of seven-membered ring heterocycles fused with azoles and/or aromatics have been achieved splendored methodologies.[17] Dominguez *et al*. reported a straightforward entry to pyrazole-fused dibenzo[1,4]diazepines (**39**) using palladium-catalyzed intramolecular *N*-arylation as key step for construction of seven-membered ring (Scheme 15).[17]

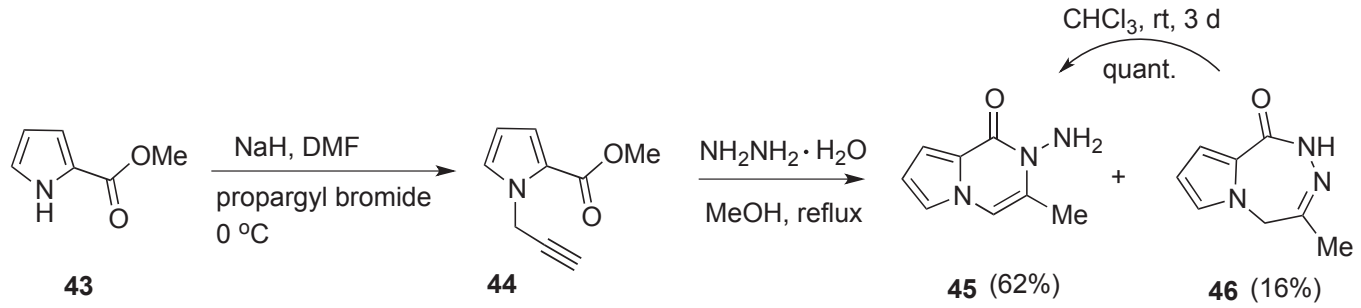


Scheme 15

The pyrrole derivatives having carbonyl groups at the C-2 position were converted to *N*-propargylpyrrole (**40**). The reaction of (**40**) with hydrazine monohydrate resulted in the formation of 3a,6,7-triazaazulene derivatives (**42**) in good yields (Scheme 16).[18] On the other hand, attempted cyclization of pyrrole ester (**44**) gave **45** as the major product, and the seven-membered product (**46**) was formed as the minor product. The compound (**46**) was converted quantitatively to **45** (Scheme 17).[18] Formation mechanism was investigated by experimental and theoretical calculations.

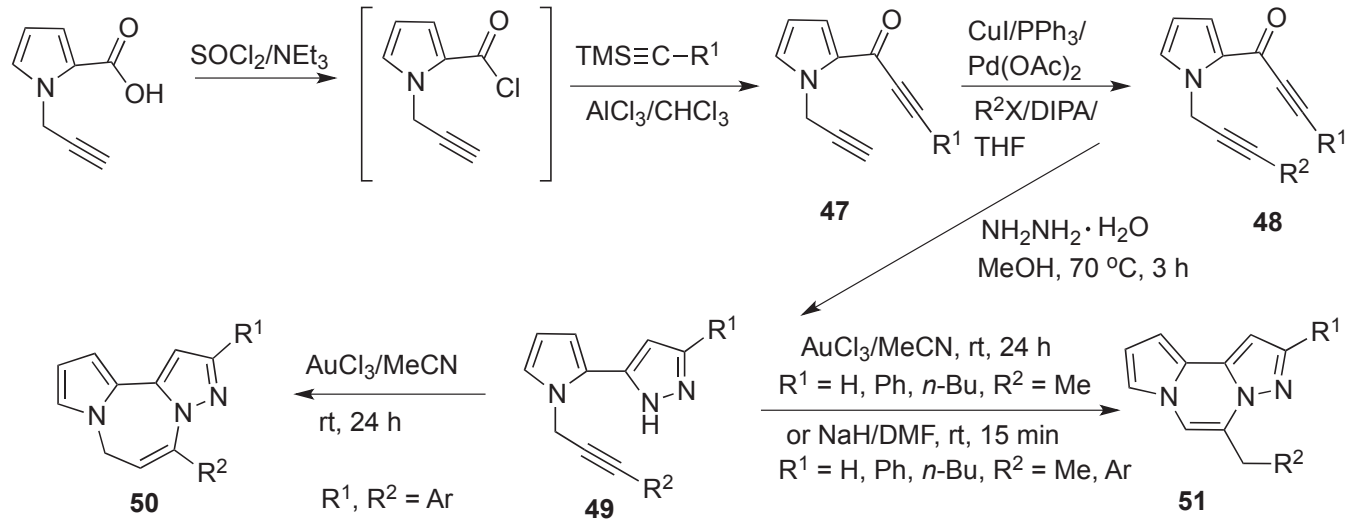


Scheme 16



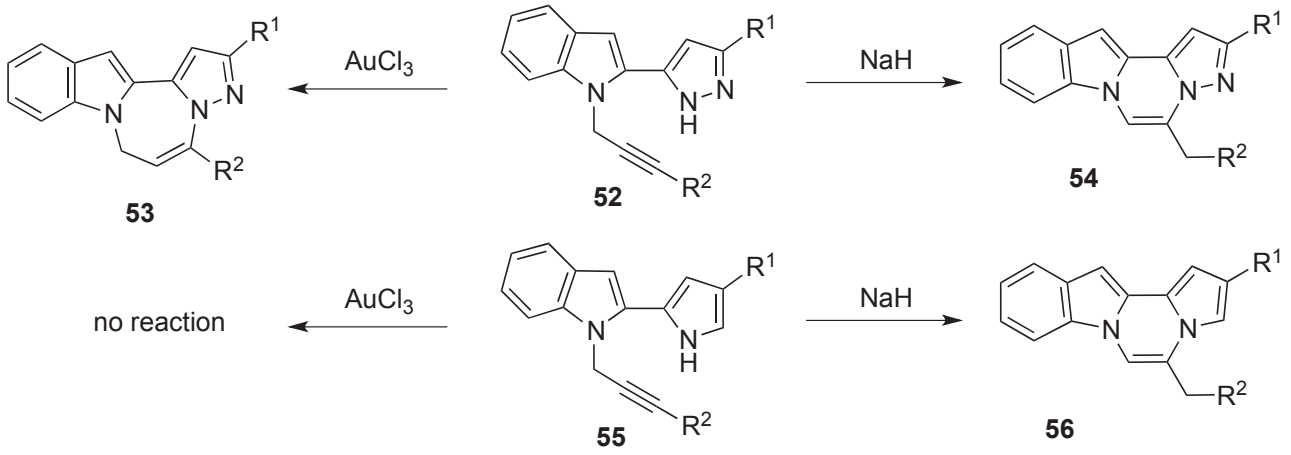
Scheme 17

Treatment of pyrazole-substituted *N*-propargylpyrroles (**49**), synthesized by the sequence of the reactions of pyrrole-derived *α,β*-alkynyl ketones (**47**), with gold catalyst (AuCl and $AnCl_3$) gave 7-*endo-dig* cyclization product (**50**) in excellent yields. According to the substituent (R^1 = H, Ph, *n*-Bu, R^2 = Me), **51** were obtained *via* 6-*exo-dig* cyclization. Treatment of **49** with NaH gave **51** in high yields (Scheme 18).[19]



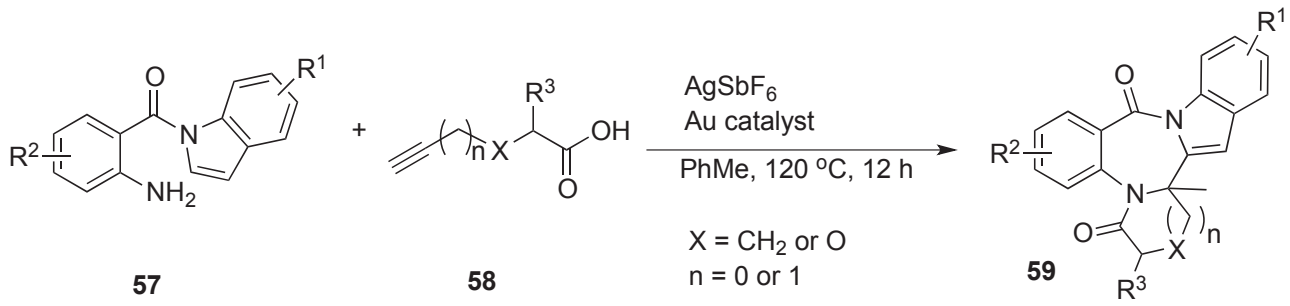
Scheme 18

Similarly as above, treatment of *N*-propargyl-2-(1*H*-pyrazol-5-yl)-1*H*-indoles (**52**) having internal alkynes with gold catalyst gave 7-*endo-dig* cyclization products (**53**), whereas the pyrazoles having a terminal alkyne gave 6-*exo-dig* cyclization products (**54**) exclusively. On the other hand, treatment of **52** with NaH only resulted in the formation of **54** (Scheme 19).[20] Treatment of *N*-propargyl-2-(1*H*-pyrrol-5-yl)-1*H*-indoles (**55**) with NaH gave **56**, but treatment of **55** using gold catalyst (AuCl and $AuCl_3$) gave any trace of 6-*exo-dig* or 7-*endo-dig* cyclization products (Scheme 19).[20]



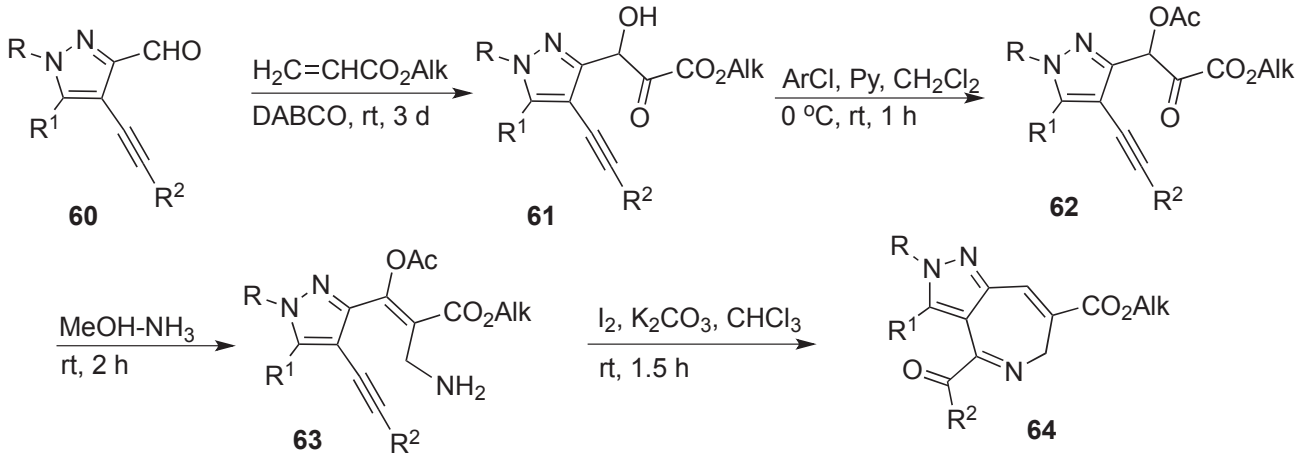
Scheme 19

Aminophenyl group with alkynes are frequently used as scaffoldings for construction for benzo-annulated aza-containing seven-membered rings (benzazepine derivatives). Synthetic methods of benzo[*e*]indolo[1,2-*a*]pyrrolo/pyrido[2,1-*c*][1,4]diazepine-3,9-diones (**59**) were reported by the reaction of the (2-aminophenyl)(1*H*-indol-1-yl)methanone derivatives (**57**) with the carboxylic acids having terminal alkyne (**58**) (for example, 4-pentynoic acid) *via* an $AgSbF_6$/Au-complex catalyzed one pot cascade transformation (Scheme 20).[21] The strategy is tolerant of a broad range of substrates and affords a series of intriguing fused diazepinediones.



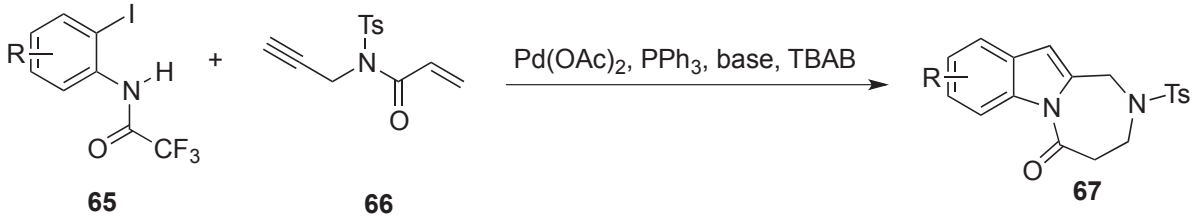
Scheme 20

A straightforward approach to dihydropyrazoro[4,3-*c*]azepines (**64**) *via* I_2-mediated intramolecular hydration in pyrazole-based allylamines (**63**) prepared from Morita-Baylis-Hillman adducts of 4-iodopyrrazolealdehydes was reported (Scheme 21).[22]



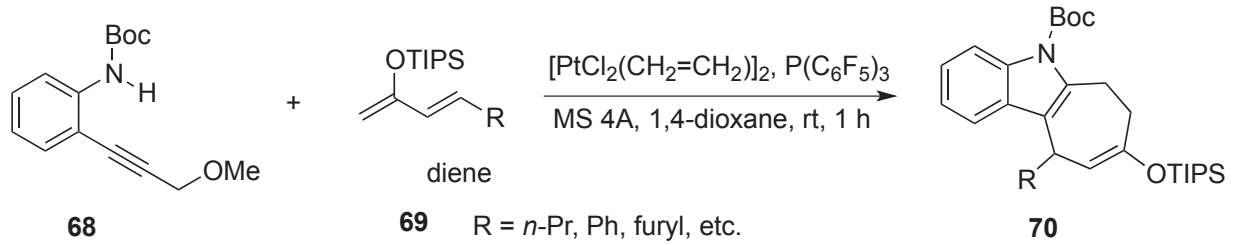
Scheme 21

A straightforward access to tetrahydro[1,4]diazepino[1,2-*a*]indole skeleton was reported, where the reaction proceeded by domino cyclization involving a Pd-catalyzed Sonogashira coupling, indole cyclization, regio- and chemoselective *N*-1 acylation, and 1,4-Michael addition. Thus, treatments of **65** with **66** under the conditions afforded **67** in good yields (Scheme 22).[23]



Scheme 22

Cyclohepta[*b*]indoles (**70**) were synthesized by the reaction of 2-ethynylaniline derivative (**68**) with 1-substituted-2-triisopropylsiloxy-1,3-diene (**69**) in good yields (Scheme 23).[24] The reaction proceeded Pt(II)-catalyzed intermolecular formal [4+3]cycloaddition of α,β-unsaturated carbene complex intermediates with siloxydienes, and would proceed *via* 1,2-alkyl shift of the carbene complex intermediates obtained by [4+2]cycloaddition reaction of the α,β-unsaturated carbene complex intermediates with dienes.

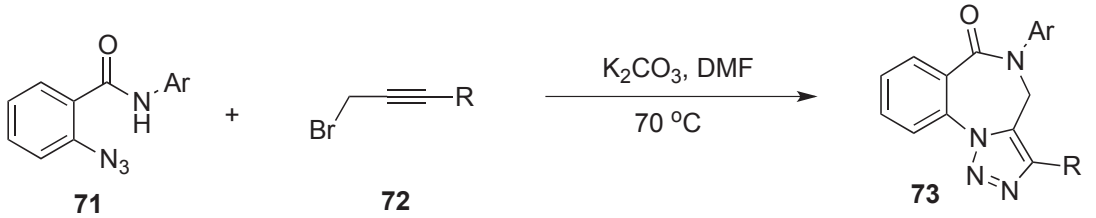


68 **69** R = *n*-Pr, Ph, furyl, etc. **70**

Scheme 23

The 1,4-benzodiazepine core is a common structure to a number of biologically active products and pharmaceutically interesting compounds. Diazole- and triazole-fused benzodiazepine rings have also gained popularity due to their potent biological activity. Therefore, considerable interest has been generated in the development of many efficient synthetic routes to a diverse range fused benzodiazepines. The Huisgen 1,3-dipolar cycloaddition of azides with alkynes have been adopted methods as an excellent synthesis for triazole-fused polycyclic heterocycles.

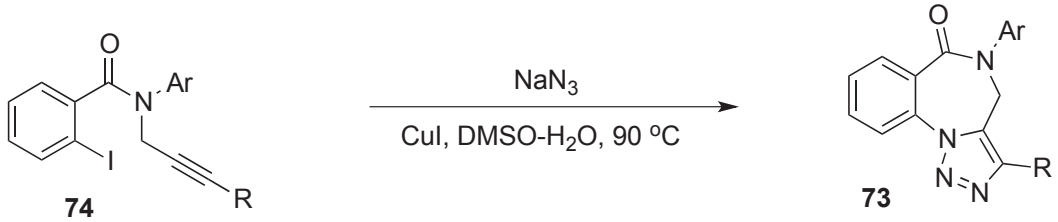
A catalyst-free, one pot synthesis of 1,2,3-triazole-fused 1,4-benzodiazepine derivatives (**73**) from (**71**) with alkynes (**72**) was reported (Scheme 24).[25]



71 **72** **73**

Scheme 24

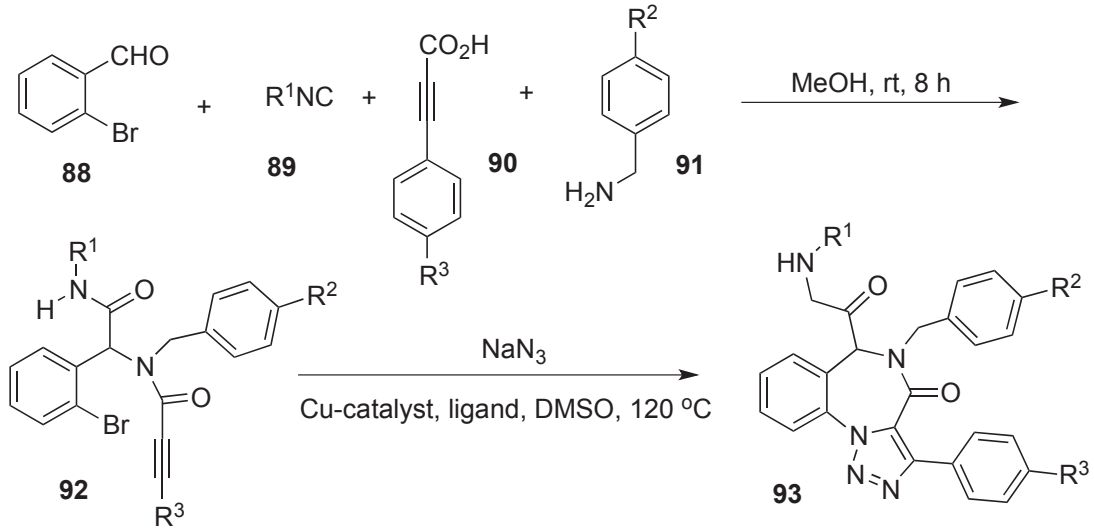
Triazole-fused diazepinones (**73**) were also synthesized from **74** with sodium azide in the presence of CuI in excellent yields (Scheme 25).[26]



74 **73**

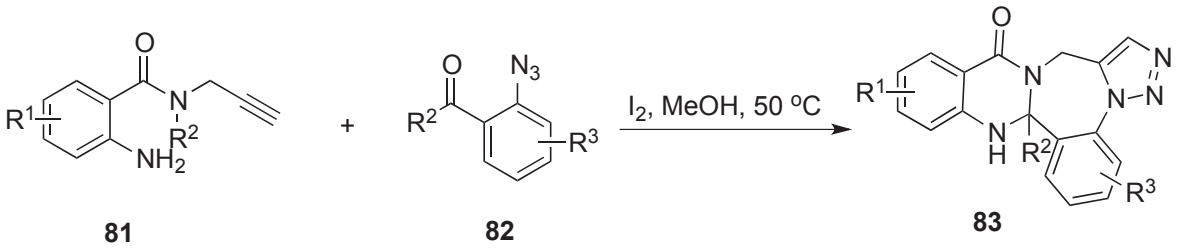
Scheme 25

The methodology for construction of triazolo[1,5-*a*][1,4]benzoazepinones *via* a post-Ugi copper-catalyzed tandem azide-alkyne cycloaddition/Ullmann C-N coupling was reported. Thus, treatment of 4-components (**75**, **76**, **77**, and **77**) in MeOH, followed by with sodium azide in the presence of copper-catalyst produced **80** in good yields (Scheme 26).[27]



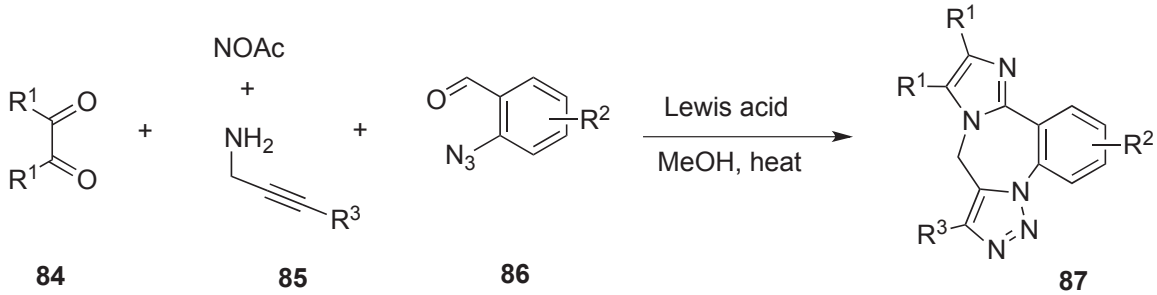
Scheme 26

An operationally simple, one-pot, two-step cascade method for the synthesis quinazolino[1,2,3]triazolo[1,4]benzodiazepinones (**83**) was reported by Kurth *et al*. (Scheme 27).[28]



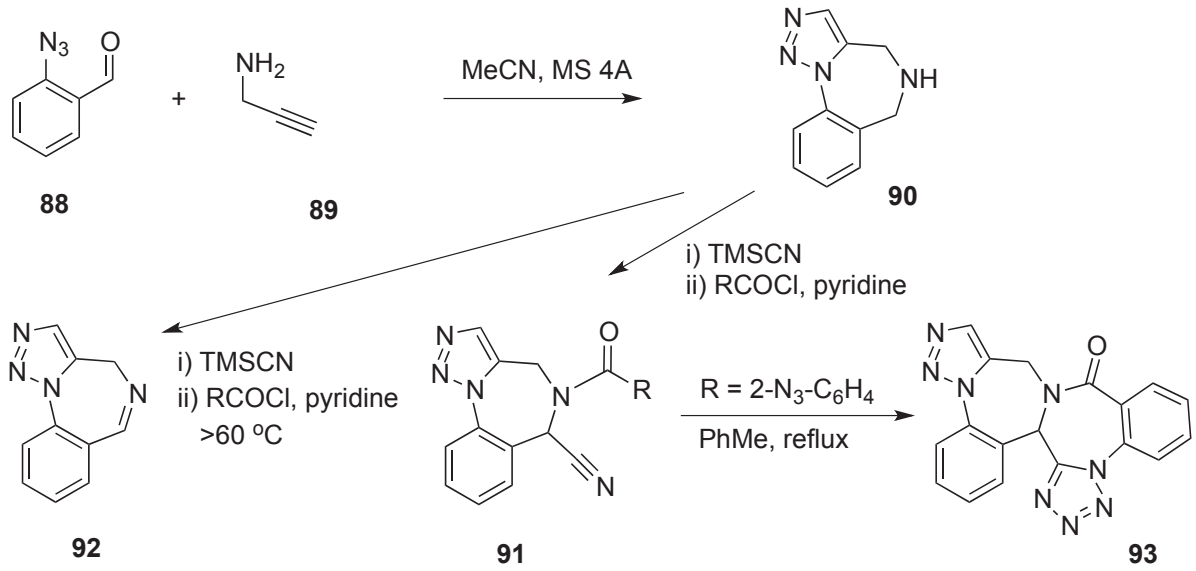
Scheme 27

Kurth *et al*. also reported facile one-pot assembly of imidazotriazolodiazepines (**87**) *via* In(III)-catalyzed multicomponent reactions (Scheme 28).[29]



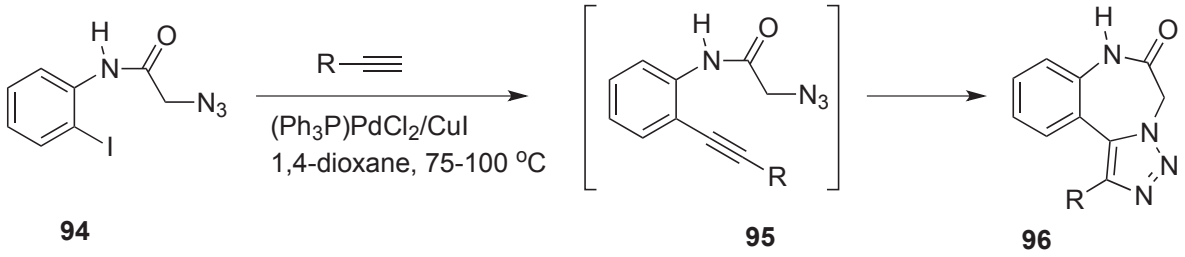
Scheme 28

Martin *et al*. reported the synthesis of a number of diversely substituted 1,2,3-triazole-fused [1,4]benzodiazepines (**90-93**) from **88** with **89** (Scheme 29).[30]



Scheme 29

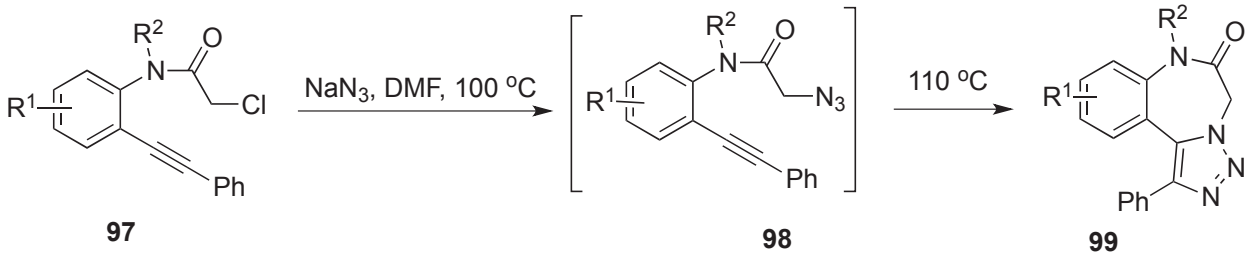
The sequential Sonogashira coupling/Huisgen cycloaddition protocol was frequently adopted as synthetic methodology for the synthesis 1,2,3-triazole-fused benzazepinones. Thus, the synthesis of 1,2,3-triazole-fused [5,1-*d*][1,4]benzodiazepin-2-ones (**96**) from **94** (Scheme 30) was achieved.[31]



R = Ph, CO_2Me, CH_2OH, $(CH_2)_3OH$, CH(OH)Ph

Scheme 30

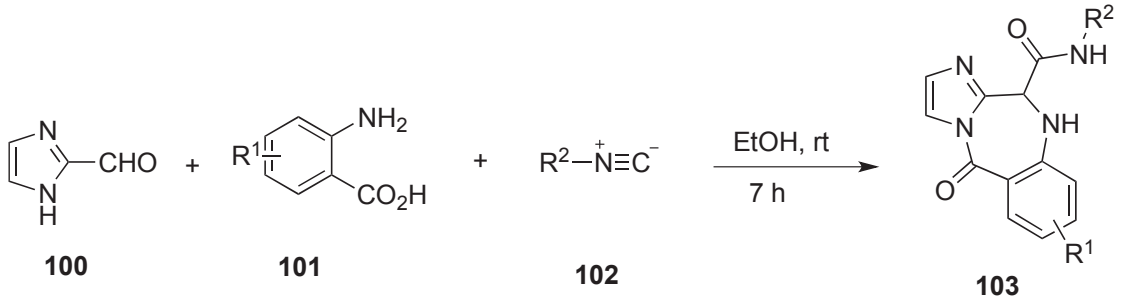
In a similar manner, **99** was synthesized from **97** (Scheme 31).[32]



R^1 = H, Me, fused pyran-2(1*H*)-one; R^2 = Me, Et

Scheme 31

As mentioned above (Scheme 23), Ugi multi-component reaction based route is excellent strategy for the synthesis of heterocyles-fused benzodiazepines. A one-pot synthesis of imidazole-fused benzodiazepines (**103**) was reported (Scheme 32).[33]

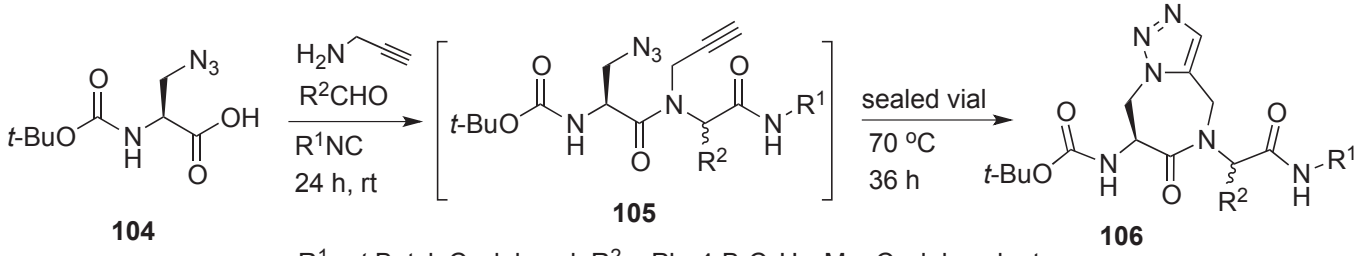


100 **101** **102** **103**

R^1 = H, Me; R^2 = *t*-Bu, *i*-Pr, $(CH_2)_4Me$, Cy, 2-Tol

Scheme 32

Triazoloazepinones (**106**) were also synthesized one-pot Ugi-Huisgen tandem reaction (Scheme 33).[34]

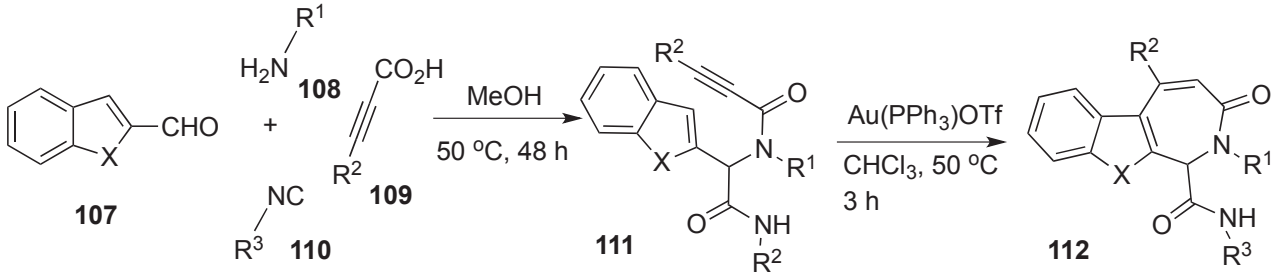


104 **105** **106**

R^1 = *t*-Butyl, Cyclohexyl; R^2 = Ph, 4-BrC_6H_4, Me, Cyclohexyl, etc.

Scheme 33

A post Ugi-late-transition-metal catalyzed intramolecular hydroarylation afforded diversely substituted heterocycles-fused azepinones (**112**) (Scheme 34).[35]



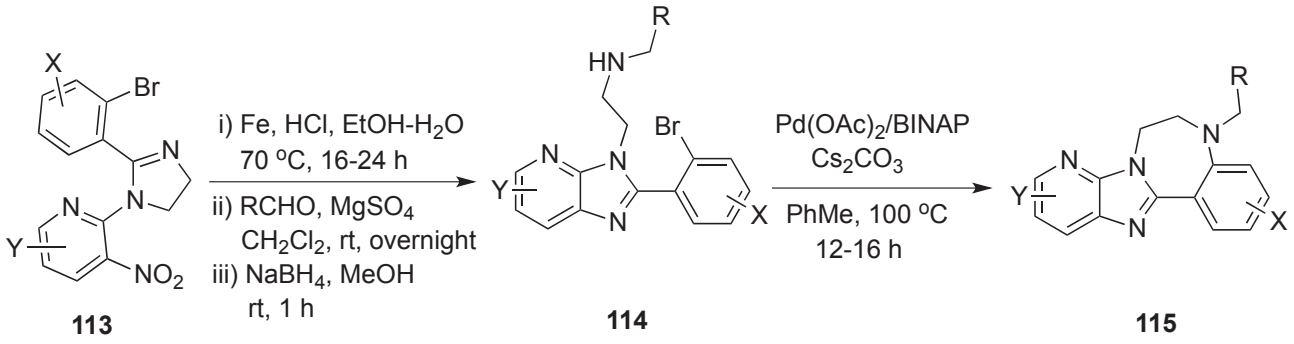
107 **108** **109** **110** **111** **112**

X = NH, NMe, S; R^1 = $CH_2C_6H_4$-*p*-OMe; R^3 = *t*-Bu

Scheme 34

Compounds (**113**), synthesized in five straightforward steps from commercially available 2-bromobenzaldehydes, ethylenediamine and 2-chloro-3-nitropyridines, afforded 6,7-dihydro-

pyrido[3',2':4,5]imidazo[1,2-*d*][1,4]diazepines (**115**) *via* a concise, streamlined, and atom-economical route (Scheme 35).[36]

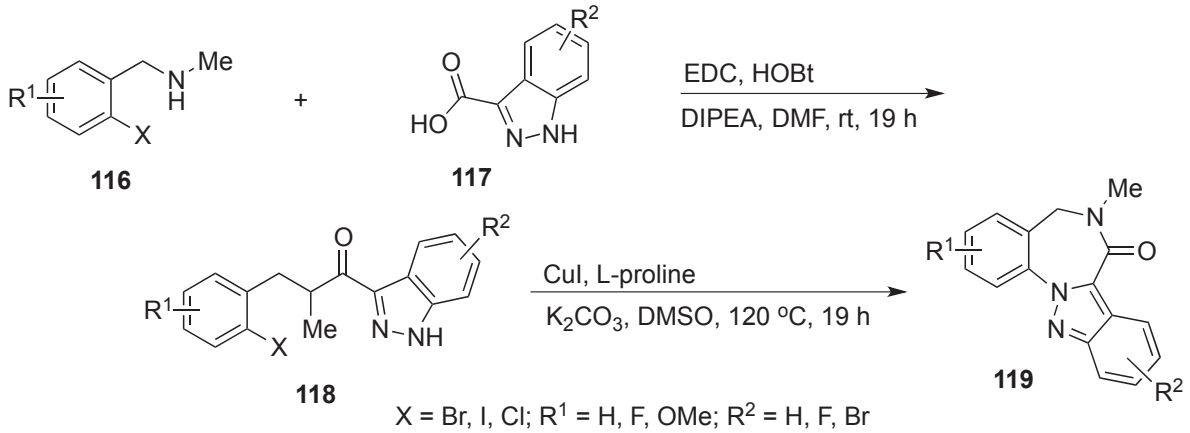


113 **114** **115**

X = H, F, Cl; Y = H, Me, Cl; R = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, *c*-Pr, *c*-Hex

Scheme 35

A variety of compounds (**119**) yielded in good yields by previously reported facile methods (Scheme 36).[37]

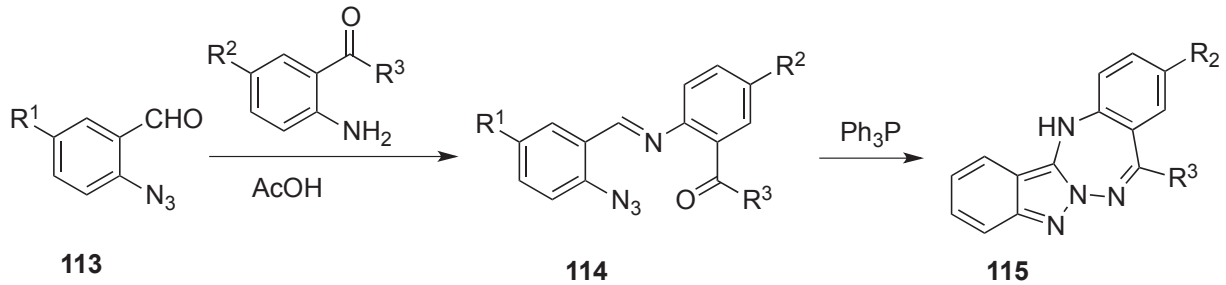


116 **117** **118** **119**

X = Br, I, Cl; R^1 = H, F, OMe; R^2 = H, F, Br

Scheme 36

5*H*-Indazolo[3,2-*b*][1,3,4]benzotriazepines (**122**) were directly prepared by a tandem aza-Wittig cyclization in good yields (Scheme 37).[38]

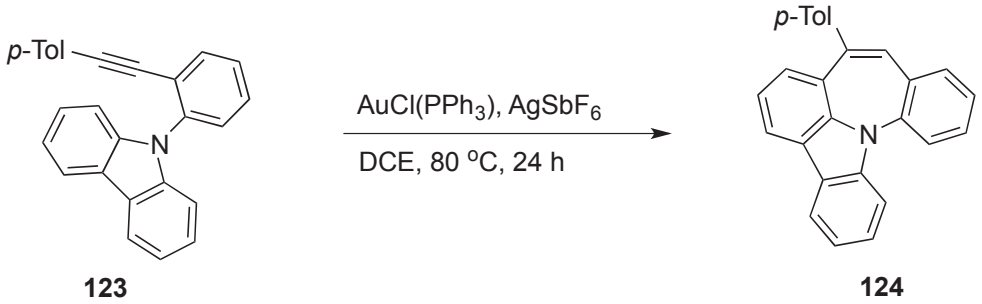


113 **114** **115**

R^1 = H, Cl; R^2 = H, Cl, Br; R^3 = Ph, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$

Scheme 37

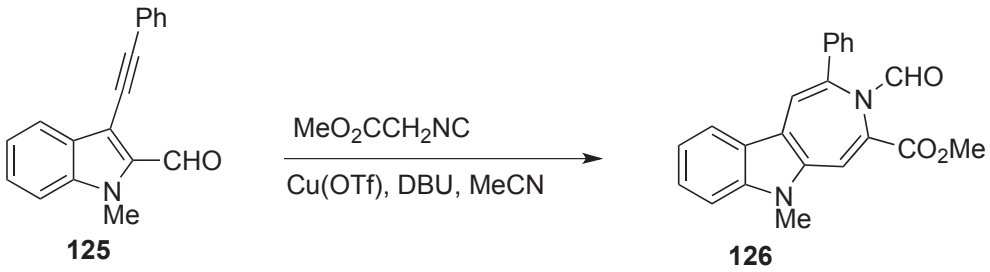
The creation of a new π-conjugated system (**124**), having 3a-azaazulene skeleton, was achieved by cationic Au(I)-catalyzed 7-*endo*-*dig*-selective cycloisomerization of carbazole-based substrates (**123**) (Scheme 38).[39]



123 **124**

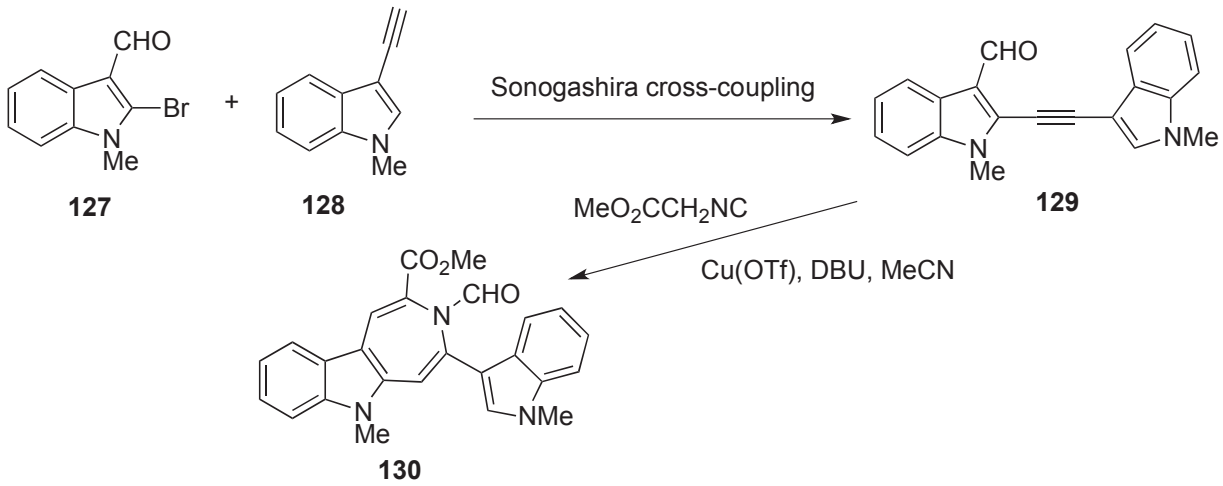
Scheme 38

Kneovenagel condensation of 3-alkyny-2-formylindoles (**125**) or 2-alkynyl-3-formylindoles (**129**) with isocyanoacetates, followed by copper-catalyzed 7-*endo*-selective annulation afforded azepinoindoles (**126** or **130**, respectively) (Scheme 39, 40).[40]



125 **126**

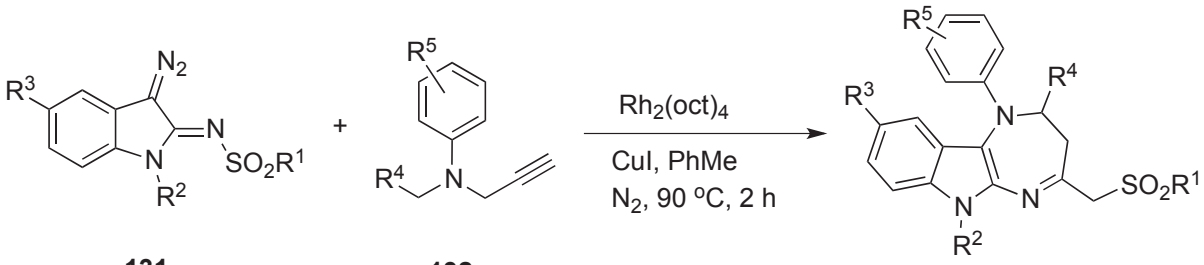
Scheme 39



127 **128** **129** **130**

Scheme 40

Rhodium-catalyzed reaction of diazoindolin-2-imines with alkynes or 1,3-dienes caused interesting cycloaddition. Tetrahydro[1,4]diazepino[2,3-*b*]indoles (**133**) were prepared by the rhodium-catalyzed reactions of 3-diazoindolin-2-imines (**131**) with *N*-alkyl-*N*-propargylanilines (**132**) (Scheme 41).[41] 3-Diazoindolin-2-imine acted as precursors of α-imino rhodium carbenes in the transformations.

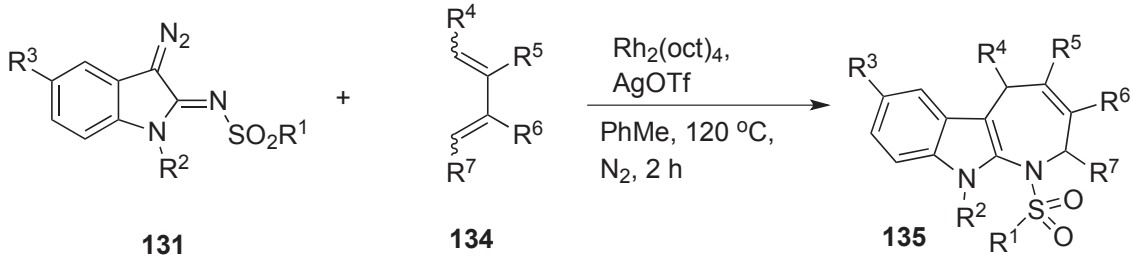


131 **132** **133**

$Rh_2(oct)_4$ = dirhodium(II) tetraoctanoate
R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, β-Np, Me;
R^2 = Et, Bn; R^3 = MeO, Br; R^4 = H, Et; R^5 = 4-MeO, 4-Br, 3-Me

Scheme 41

Azepino[2,3-*b*]indoles (**135**) were regioselectively prepared through rhodium-catalyzed formal aza [4+3]cycloaddition between 3-diazoindolin-2-imines (**131**) and 1,3-dienes (**134**) (Scheme 42).[42]

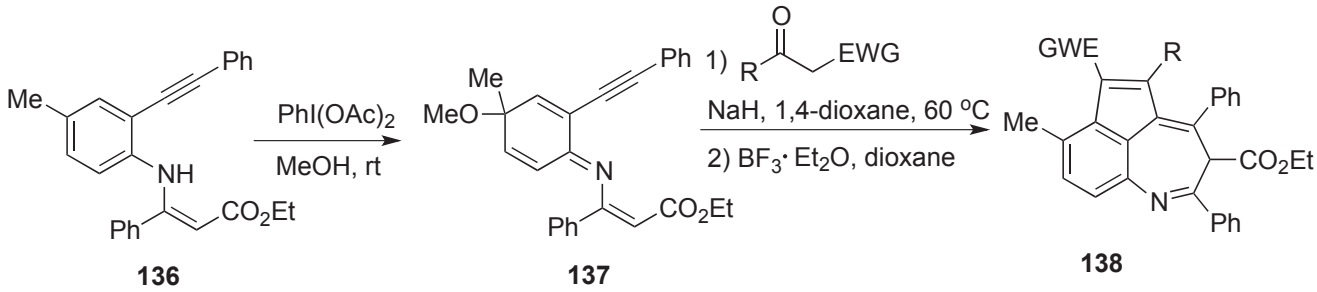


131 **134** **135**

R^1 = Ph, 4-ClC_6H_4, Me; R^2 = H, Me, Bn, Allyl, i-Pr; R^3 = H, MeO, F, Cl, Br;
R^4 = H; R^5 = H, Me; R^6 = H, Me; R^7 = H, Me, Ph, OTMS

Scheme 42

The oxidative dearomatization of β-enamino esters (**136**) followed by base-promoted tandem Michael addition/polycyclization and successive an acid-catalyzed aromatization resulted in the formation of 6(8*H*)-azacyclohept[*cd*]indenes (**138**) (Scheme 43).[43] The nonaromatic structure of the Michael adducts might be essential to the realization of the 7-*end*-*dig* cyclization.

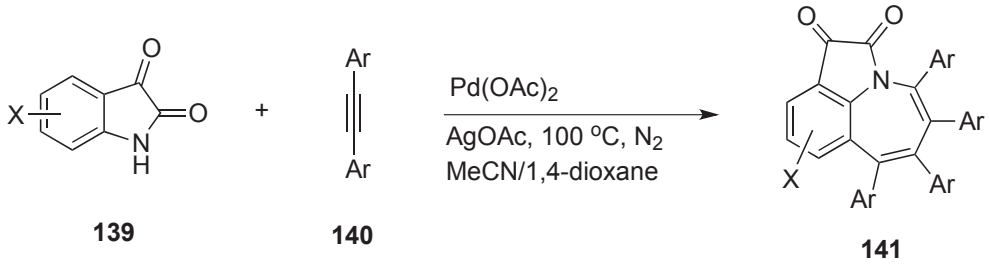


136 **137** **138**

EWG = CO_2Me, CO_2Et, MeCO, PhCO, SO_2Me

Scheme 43

Direct Pd(II)-catalyzed oxidative cycloaddition through C-H/N-H activation of readily available isatins (**139**) and alkynes (**140**) achieved construction of benzazepines (**141**) (Scheme 44).[44] The versatility of the Pd-catalyzed oxidative cycloaddition can be exploited in chemoselective transformation to access various frameworks with high degrees of molecular complexity.

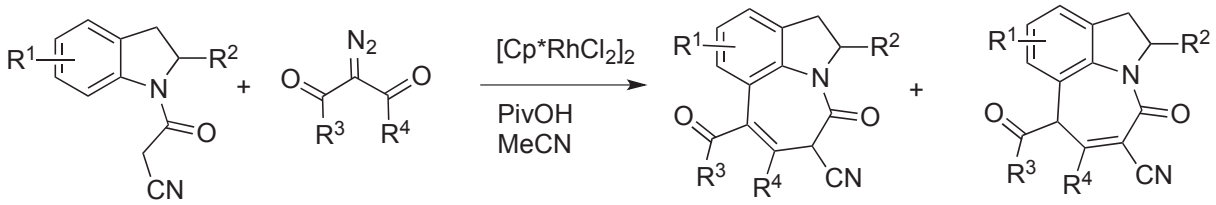


139 **140** **141**

X = Me, *i*-Pr, *t*-Bu, *n*-C_7H_{16}, OMe, F, Cl, Br

Scheme 44

Tandem Rh(III)-catalyzed C-H activation of 3-(indolin-1-yl)-3-oxopropanenitriles (**142**) with diazo compounds (**143**) and cyclization leading to seven-membered ring scaffolds (**144** and **145**) proceeded efficiently (Scheme 45).[45]

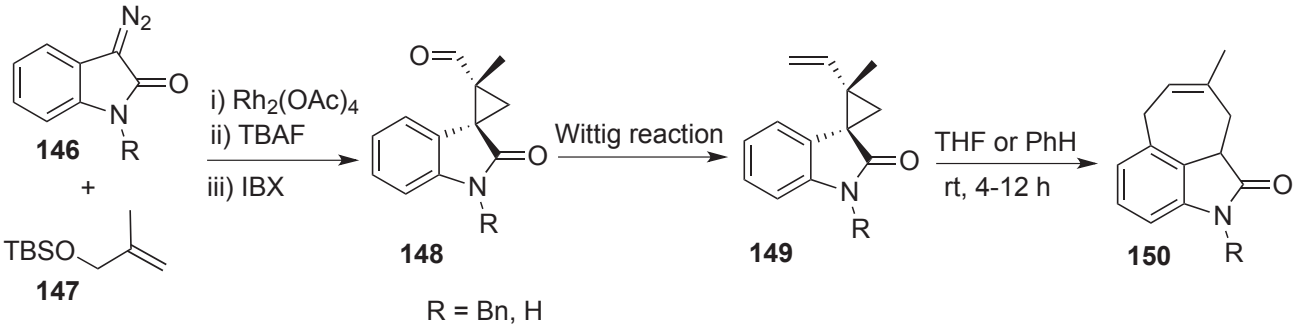


142 **143** **144** **145**

R^1 = H, Me, OMe, Cl, F, CO_2Me, NO_2; R^2 = H, Me; R^3 = OMe, OEt, O-*t*-Bu, O-Allyl; R^4 = Me, Et, Ph

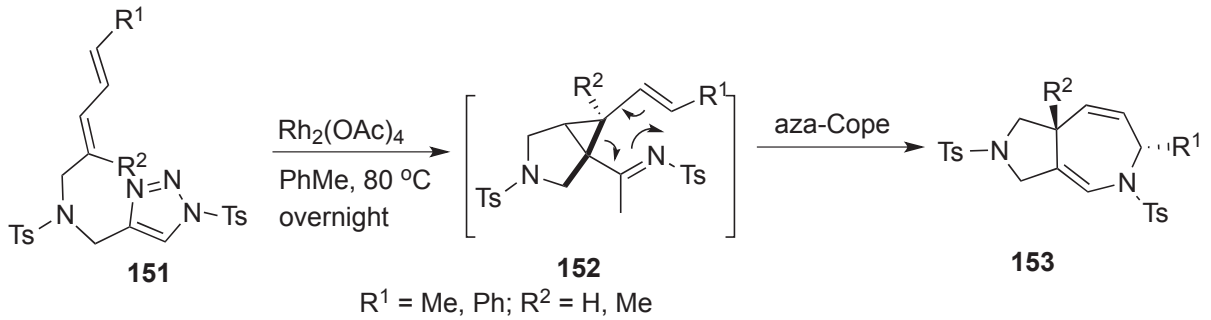
Scheme 45

Evidence an enzyme-catalyzed [3,3]-sigmatropic rearrangement of the dimethallylltryptophan synthase was exhibited. Formation of **150** from **149**, being supposed the bioinspired system by Gaich *et al*., was accomplished by chemically feasible Cope rearrangement to the 4-position of indole nucleus (Scheme 46).[46]



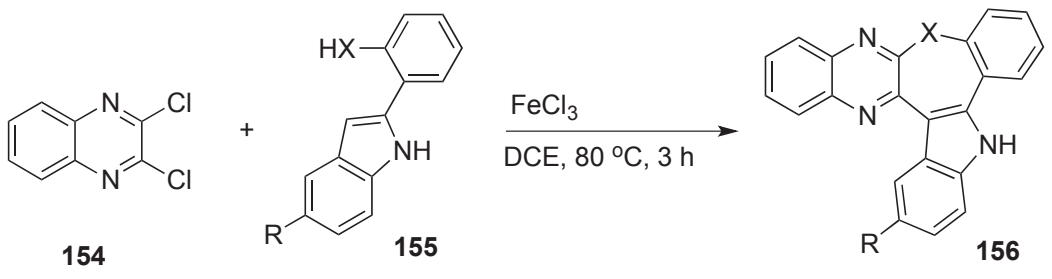
Scheme 46

An efficient protocol was proposed for fast entry to dihydroazepines (**153**) from various dienyltriazoles (**151**). The reaction proceeds through a carbine generation-cyclopropanation-aza-Cope rearrangement cascade driven by strain release of 3-membered ring (Scheme 47).[47]



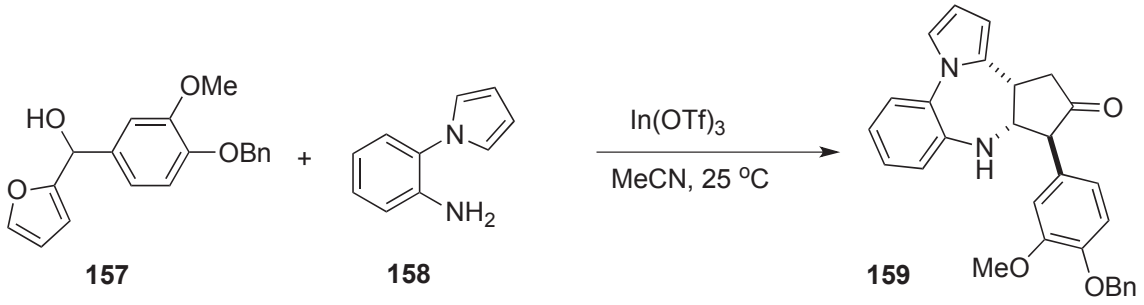
Scheme 47

Coupling reactions are frequently used to prepare the fused aromatics. Various pyrroloazepine derivatives (**156**) were synthesized using one pot reaction of 2,3-dichloroquinoxalline (**154**) with 2-(1*H*-indol-2-yl)aniline (**155**) in the presence of $FeCl_3$ (Scheme 48).[48]



Scheme 48

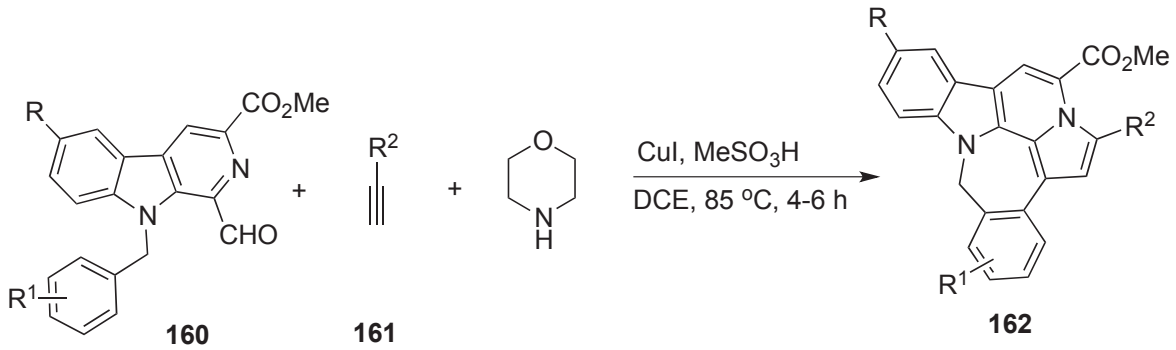
2-Furylcarbinols (**157**) underwent a smooth aza-Piancatelli rearrangement followed by Friedel-Crafts alkylation with a bifunctional substrate, (1*H*-pyrrol-1-yl)aniline (**158**), in the presence of $In(OTf)_3$ to afford corresponding pyrrolo[1,2-*d*]benzodiazepine derivatives (**159**) in good yield (Scheme 49).[49]



157 **158** **159**

Scheme 49

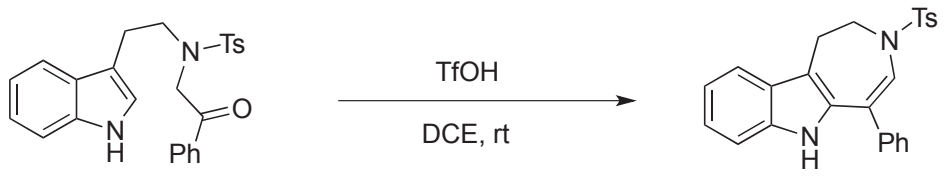
A triple cooperative catalysis-mediated cascade approach for the synthesis of *β*-carboline-fused benzazepines (**162**) *via* an intramolecular C_{sp}^2-C_{sp}^2 Friedel-Crafts arylation was reported (Scheme 50).[50] The protonation of tertiary amine followed by a 1,3-H-shift would offer an imine intermediate which underwent nucleophilic attack of the C_{sp}^2-H of the electron-rich arene system in highly concerted manner to produce polycyclic *β*-carbolines.



160 **161** **162**

Scheme 50

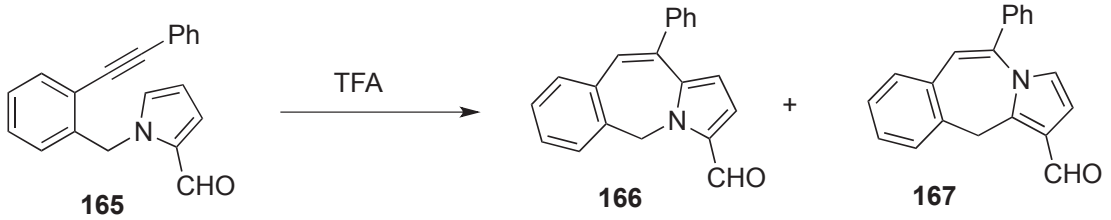
A mild and efficient approach to azepino[4,5-*b*]indole derivatives (**164**), in the presence of a catalytic amount of TfOH (Scheme 51).[51] The simple and straightforward process of indole-fused heterocycles would be useful for organic synthesis and medicinal chemistry.



163 **164**

Scheme 51

11-Aryl-5*H*-benz[*e*]pyrrolo[1,2-*a*] azepine-1-carbaldehydes (**166**) were obtained as major products at 90 °C as a result of intramolecular 7-*endo-dig* cyclization, while 6-*endo-dig* closure by electrophilic addition of nitrogen of pyrrole to a vinyl cation generated under acidic medium followed by domino rearrangement process was shown at 40 °C in some cases, resulting in 5-aryl-11*H*-benz[*d*]pyrrolo[1,2-*a*]-azepine-1-carbaldehydes (**167**) along with the former products (Scheme 52).[52] Two distinctive modes of cyclization were revealed to depend on the reaction temperature in the process of acid-catalyzed intramolecular alkyne carbonyl metathesis.

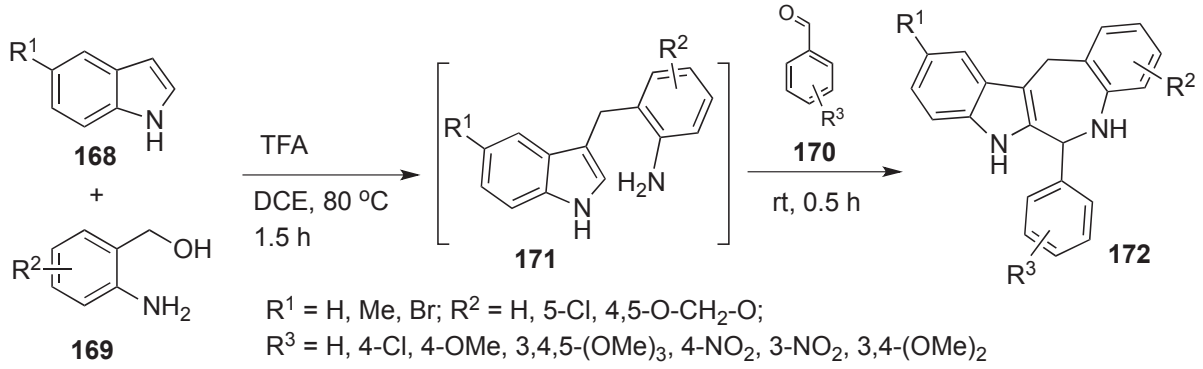


165 **166** **167**

90 °C	80%	0%
40 °C	34%	50%

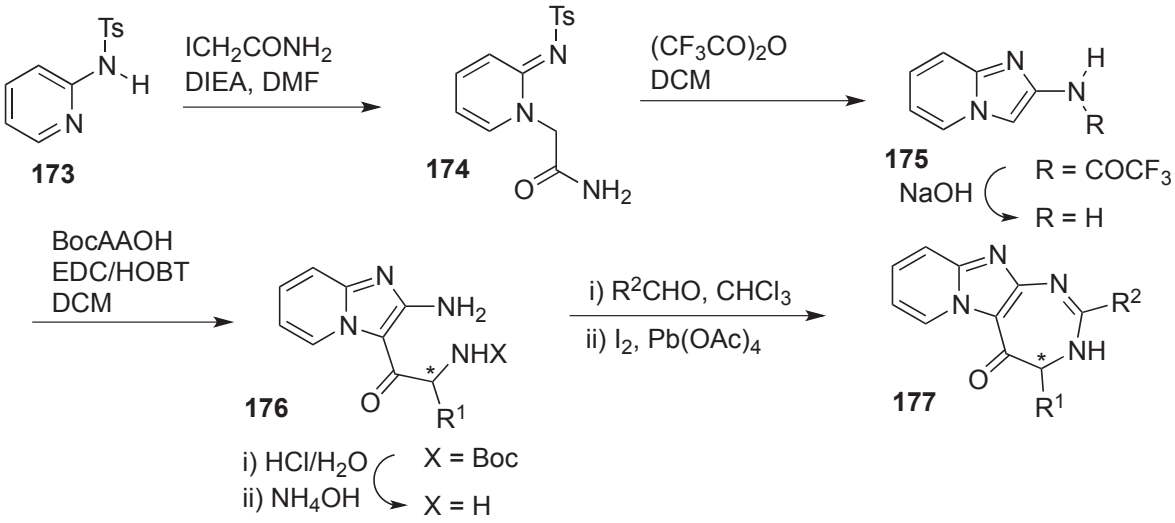
Scheme 52

A one-pot three component tandem intra molecular hydroamination reaction involving indoles (**168**), 2-aminobenzyl alcohols, and benzaldehydes proceeded and gave dibenzo[1,4]diazaazulene derivatives (**172**) *via* 7-*endo-dig* Pictet-Spengler cyclization (Scheme 53).[53]



Scheme 53

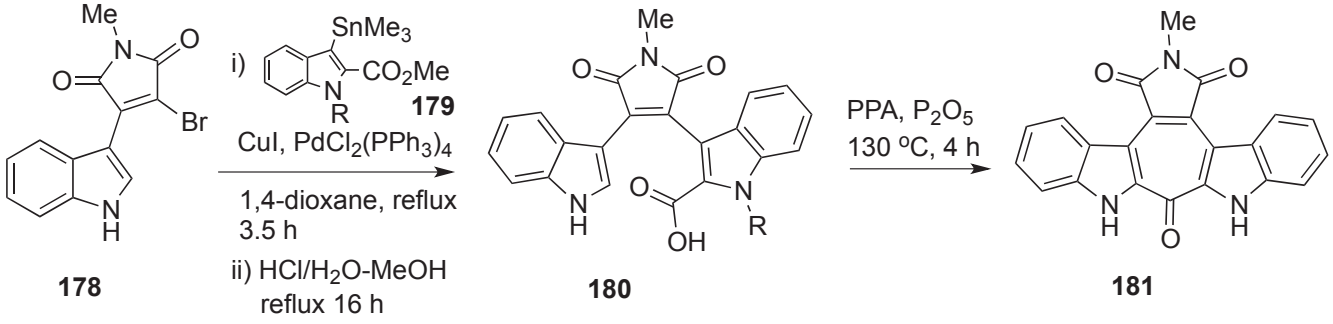
Imidazo[1,2-*a*]pyridine-fused [1,3]diazepin-5-ones (**177**) were synthesized in four steps with moderate overall yields (Scheme 54).[54] The key step consists of a selective C-acylation reaction of accessible 2-amino-imidazo[1,2-*a*]pyridine (**175**) at C-3.



R^1 = CH_2Ph, Me, CH(Me)OBn; R^2 = H, *p*-$NO_2C_6H_4$, Ph, *o*-,*m*-, *p*-MeC_6H_4, *i*-Bu, 3-Py

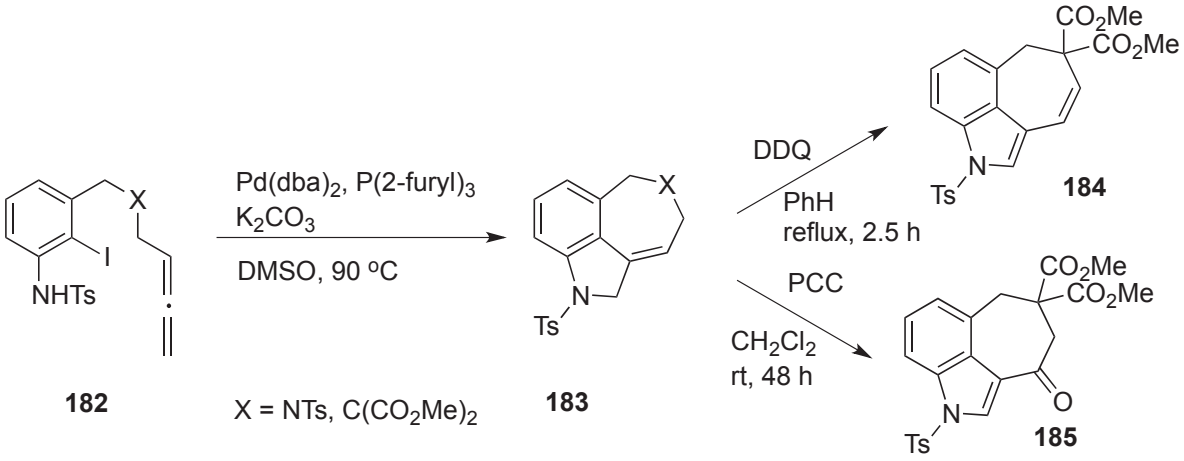
Scheme 54

N-Methyloxoarcyriaflavin (**181**) was synthesized in only few efficient steps involving a Pd-catalyzed Stille cross-coupling reaction of **178** with **179**, and successive electrophilic cyclization (Scheme 55).[55]



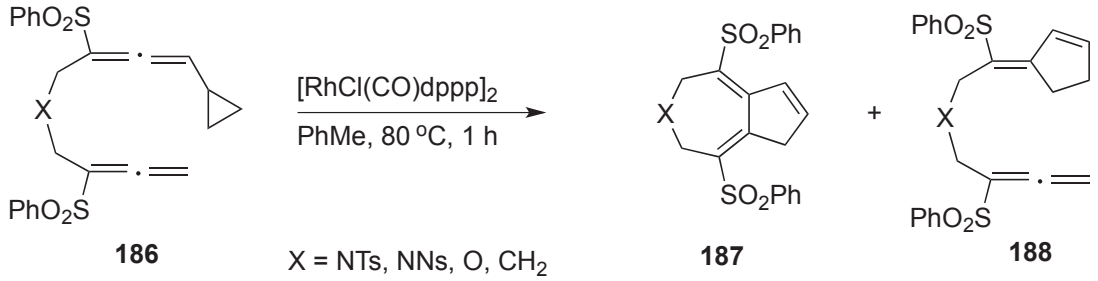
Scheme 55

A Pd-catalyzed reaction of allenes tethered to *o*-iodoaniline derivatives (**182**) at the *meta*-position proceeded in cascade cyclization by intramolecular Heck insertion of allene-allylic amination and afforded 2-benz[*cd*]azulene derivatives (**183**) in moderate to excellent yields (Scheme 56).[56]



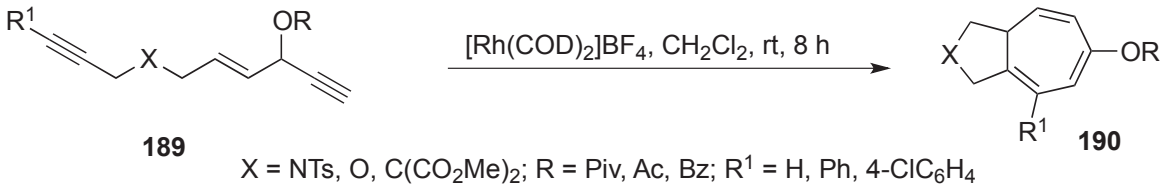
Scheme 56

The Rh(I)-catalyzed intramolecular [5+2-2]-type cycloisomerization of allene-allenylcyclopropanes (**188**) was reported. In the reaction, ethylene was liberated, and tetrahydroazulenes (**187**) were produced (Scheme 57).[57]

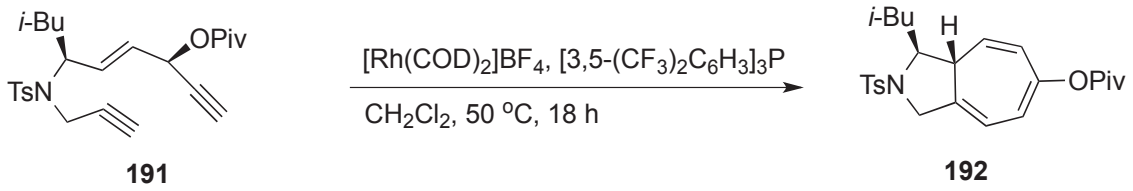


Scheme 57

A conceptually novel Rh-catalyzed intramolecular [5+2]cycloaddition reaction of 3-acyloxy-1,4-enynes with tethered alkyne (**189**) was appeared. In the reaction, tetrahydroazulene skeletons (**190**) were obtained with concomitant 1,2-migration **(190)** (Scheme 58).[58] The chirality of compounds (**191**), which were available in an optically pure form, can be transferred to significantly bicyclic products (**192**) (Scheme 59).[59]



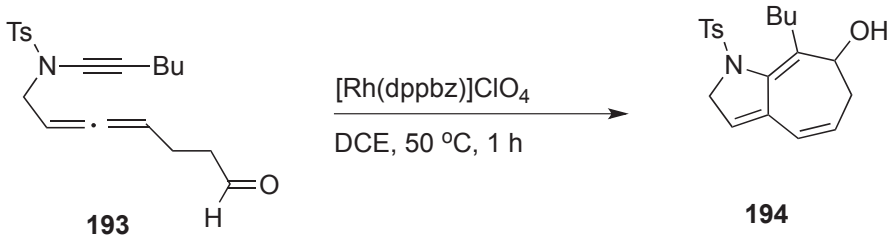
Scheme 58



191 **192**

Scheme 59

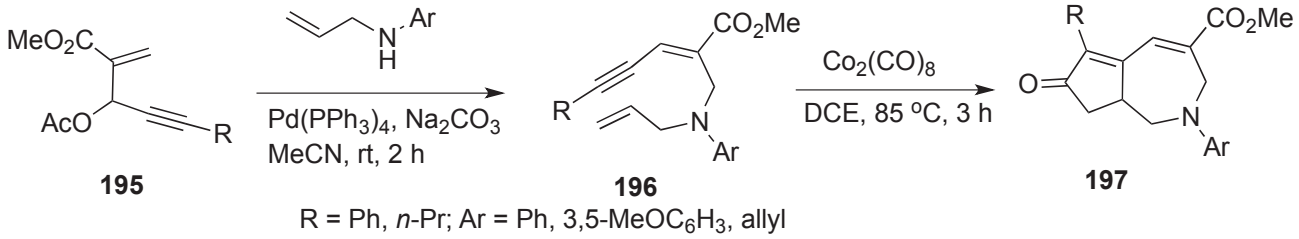
Rh(I)-Catalyzed [2+2+2]cyclization of allenynes (**193**) afforded 1-azaazulene derivative (**194**) in 71% yield (Scheme 60).[60]



193 **194**

Scheme 60

An efficient approach for the construction of bicyclic fused cyclopentanones starting Morita-Baylis-Hillman (MBH) acetates was reported using a two-step reaction sequence involving allylic substitution and Pauson-Khand reaction. Thus, the reaction of MBH-acetates (**195**) with allylamines under the conditions gave **196**, and successive reaction gave **197** (Scheme 61).[61]

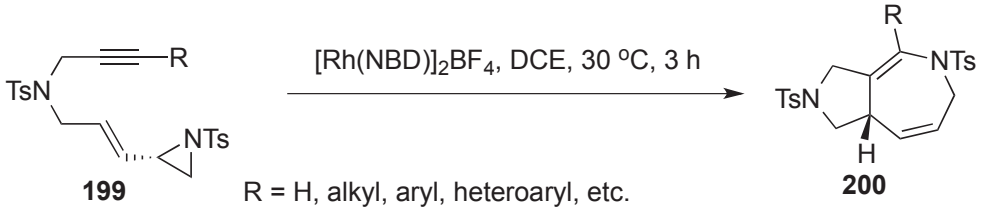


195 **196** **197**

R = Ph, *n*-Pr; Ar = Ph, 3,5-$MeOC_6H_3$, allyl

Scheme 61

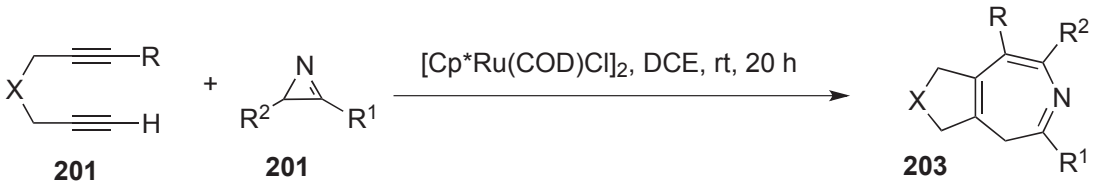
Reactions of vinyl aziridine-alkyne substrates (**199**) underwent *via* Rh-catalyzed intramolecular formal hetero [5+2]cycloaddition, and gave fused 2,5-dihydroazepines (**200**) in excellent yields (Scheme 62).[62] The chirality of vinyl aziridine-alkyne substrates can be completely transferred to the cycloadducts.



199 R = H, alkyl, aryl, heteroaryl, etc. **200**

Scheme 62

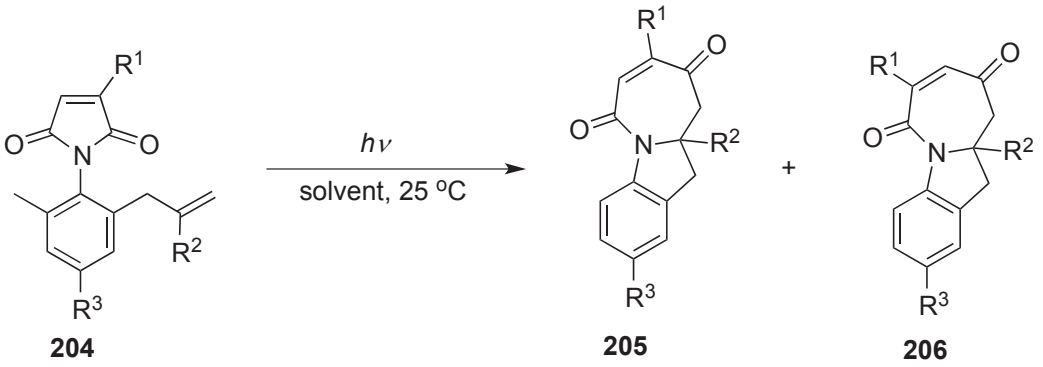
The formation of fused azepine skeletons by a ruthenium-catalyzed [3+2+2]cycloaddition reaction of 2*H*-azirines with diynes was reported. Thus, treatment of diynes (**201**) with 2*H*-azirines (**201**) under the conditions resulted in the formation of fused azepine derivatives (**203**) (Scheme 63).[63]



X = NTs, O, CR'_2; R = H, Me; R^1 = Ph, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, etc.;
R^2 = Ph, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 2-$MeOC_6H_4$

Scheme 63

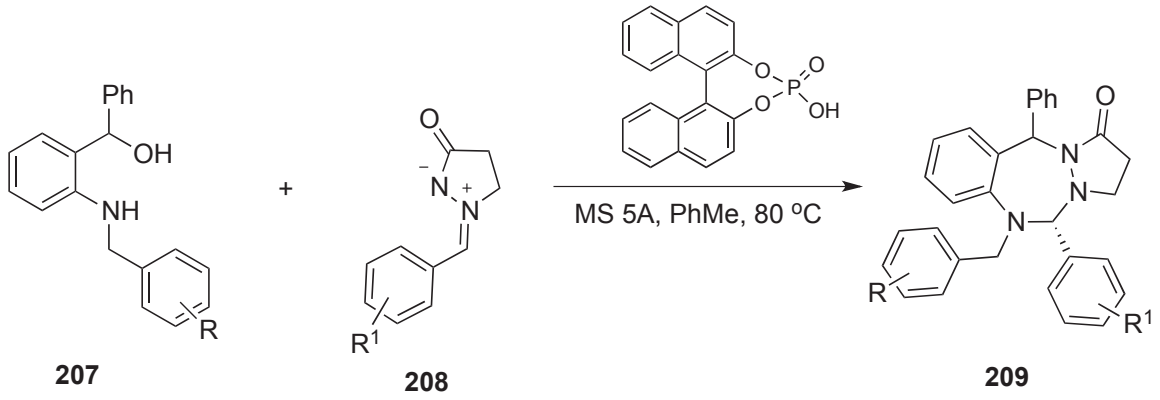
Photochemical transformations offer a powerful tool in organic chemistry that provide rapid access to complex and unique structure containing compounds. Raghnathan *et al*. reported synthesis and atropselective [5+2]photocycloaddition of atoropisomeric maleimides. Thus, direct irradiation of **204** yielded azepinone derivatives (**205**, **206**) (Scheme 64).[64]



R^1 = H, Me, Br, Ph, OMe, CF_3; R^2 = H, Me; R^3 = H, Me

Scheme 64

The reaction of *o*-aminobenzyl alcohols or *o*-hydroxybenzyl alcohols with *N*,*N'*-cyclic azomethine imines under Brønsted acid catalyst underwent [4+3]cycloaddition to give seven-membered ring containing heterocycles. Thus treatment of **207** with **208** under the conditions yielded **209** in good yields and excellent diastreoselectivities (Scheme 65).[65]

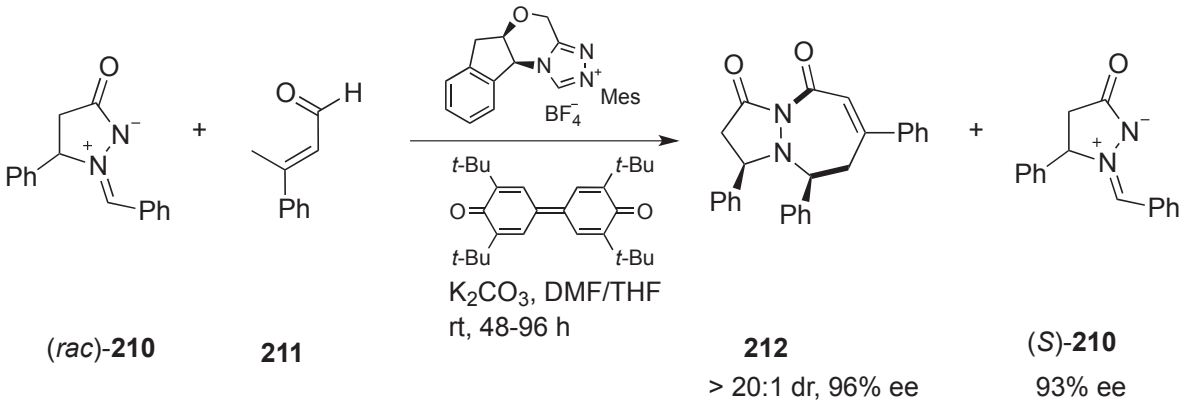


207 **208** **209**

R = *p*-OMe, *m*-OMe; R^1 = H, *o*-OMe, *m*-OMe, *p*-OMe

Scheme 65

Oxidative catalytic remote activation of enals affords 1,4-dipolarophile intermediate that react with 1,3-dipolar azomethine imines to generate dinitrogen-fused seven-membered heterocyclic products with high optical purities. Treatment of racemic azomethine imine substrate (**210**) with enals (**211**) under the conditions gave the seven-membered [3+4]-adducts (**212**) with excellent diastereoselectivity and high optical purities (Scheme 66).[66]

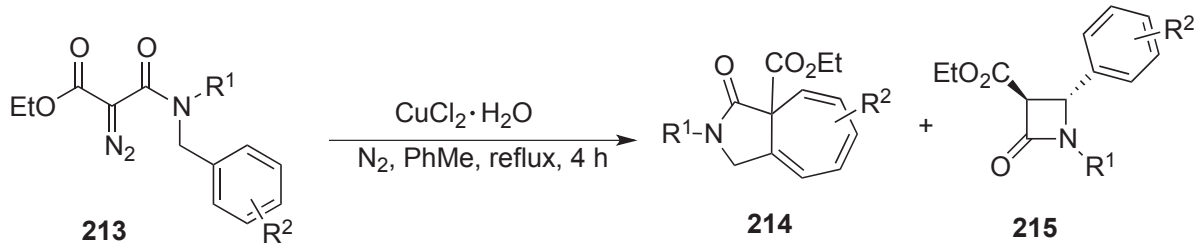


(*rac*)-**210** **211** **212** (*S*)-**210**

> 20:1 dr, 96% ee 93% ee

Scheme 66

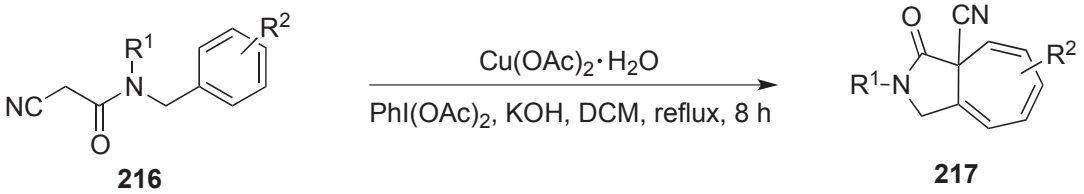
The reaction of carbenes provide a powerful tool to construct synthetically and biologically important organic compounds *via* intramolecular insertion. The copper-catalyzed reaction of ethyl diazoamidoacetates (**213**) generated both cyclohepta[*c*]pyrrolones (Buchner products) (**214**) and *β*-lactams (**215**) (Scheme 67).[67]



R^1 = Bn, Me, *n*-Pr, *i*-Pr, *t*-Bu; R^2 = H, 4-Me, 4-Cl,3,-Cl, 2-Cl, 4-F, 4-Br, 4-OMe

Scheme 67

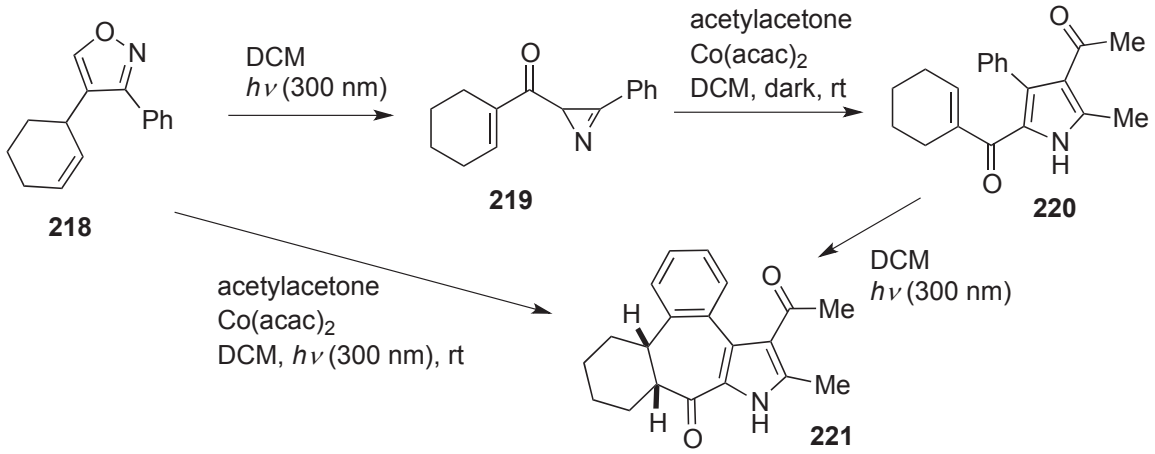
Iodonium ylides, generated *in situ* from *N*-benzyl-2-cycnoacetoamides (**216**) and $PhI(OAc)_2$ in the presence of base, underwent intramolecular Buchner reaction under catalysis from $Cu(OAc)_2 \cdot H_2O$, affording seven-membered ring products (**217**) (Scheme 68).[68]



R^1 = Bn, 4-Cl-Bn, 4-MeO-Bn, *t*-Bu, Cy; R^2 = H, Me, Bn, Cy, Br, CN, *i*-Pr, OMe, SMe, etc.

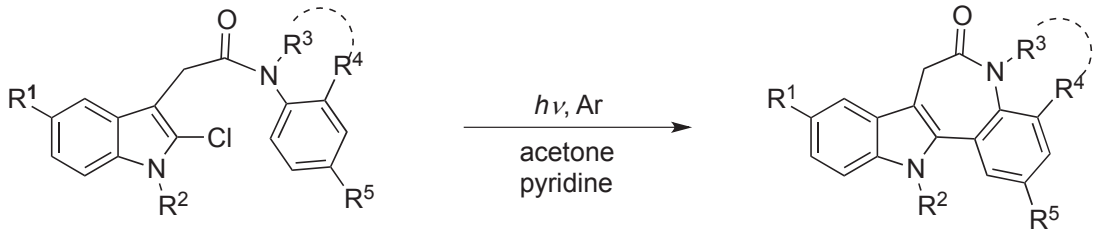
Scheme 68

A photochemically induced vinylogous Nazarov-type cyclization of isoxazoles (**218**) formed cycloheptanone derivatives (**221**) (Scheme 69).[69] The reaction can be included in a three-step cascade consisting a photochemical isoxazole-azirine ring contraction, Co(II)-catalyzed ring expansion, and photochemical cyclization.



Scheme 69

An efficient synthesis of paullone and kenpaullone derivatives (**223**) by photocyclization of **222** were reported (Scheme 70).[70]



222 **223**

R^1 = H, Br; R^2 = H, Boc, Ac, Me, Bn; R^3 = H, Me, Boc; R^4 = H; R^5 = H, OMe; R^4-R^5 = $(CH_2)_3$

Scheme 70

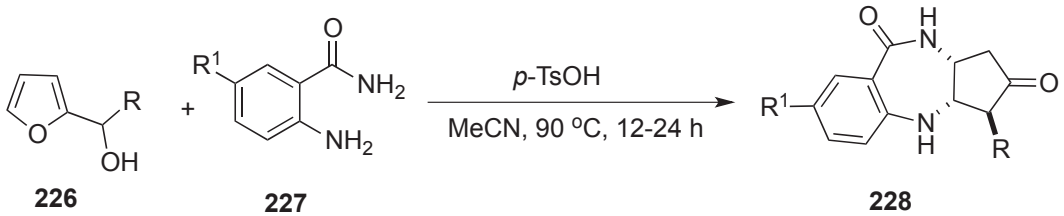
A paper about a protocol based on *N*-bromosuccinimide-induced cycloisomerization appeared to prepare tricyclic azepino[4,5-*b*]indoles (**225**) from simple *β*-enamino esters or *β*-enaminones containing an indole unit (**224**) (Scheme 71).[71] A mechanism, involving a sequence of Pictet-Spengler cyclization, an aziridine ring formation, and a regioselective C-N bond cleavage, was proposed to account for the seven-membered ring formation and the migration of electron-withdrawing group.

224 **225**

R = H, Me, OMe, Cl; R^1 = H, Me, Bn; R^2 = Me, Et, $(CH_2)_2CO_2Me$;
EWG = CO_2Me, COMe, COAr

Scheme 71

For the construction of 1,4-diazepin-5-ones, a *para*-toluenesulfonic acid catalyzed domino aza-Piancatelli rearrangement/Michel reaction was presented. The method proceeded well in the presence of various furfurylcarbinols and *o*-aminobenzamides to give cyclopentanone fused 1,4-benzdiazepin-5-ones (**228**) (Scheme 72).[72]

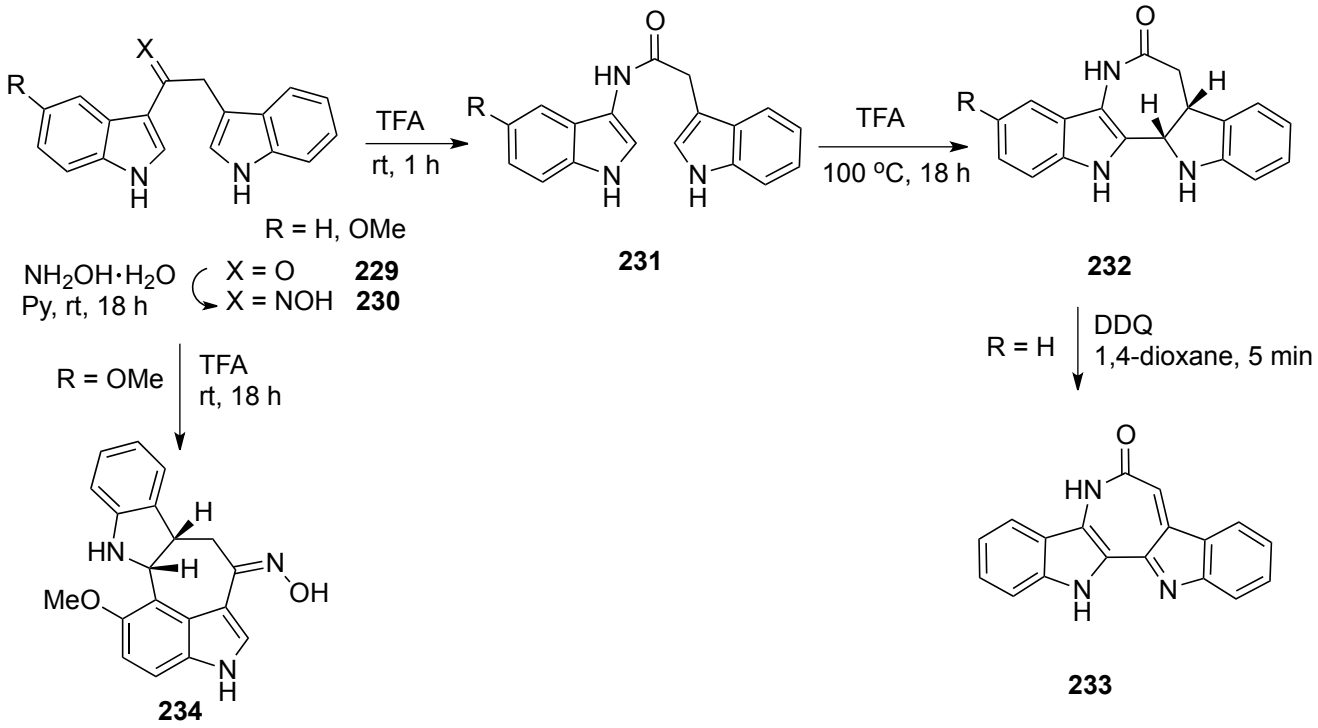


226 **227** **228**

R = Ph, allyl, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 3,4-$(MeO)_2C_6H_3$; R^1 = H, Br

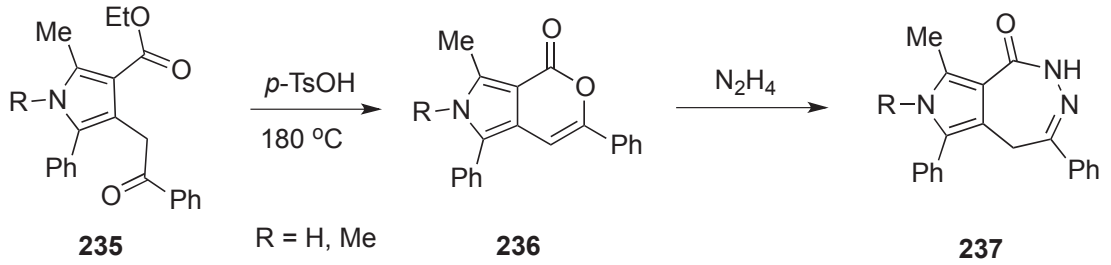
Scheme 72

Iheyamines A and B, which are alkaloids having unique azepinobisindole scaffold, were isolated from the ascidian *Polycitorella* sp. Collected off Iheya island, Okinawa, and recently completed a total synthesis of iheyamine A (*vide infra*, Scheme 109).[119] In connection with the research of the synthesis of iheyamine A, Sperry *et al*. found interesting intramolecular Mannich cyclization. The (*E*)-oxime (**230**, R=H) underwent Beckmann rearranegement to give the bisindolylacetamide (**231**, R=H) followed by an intramolecular Mannich cyclization affording 2-(indolin-2-yl)indole (**232**, R=H). However, **232** could not be converted into azepinobisindole core of iheryamine alkaloids. Treatment of **232** with DDQ gave **233**, including diazaazulenone skeleton. The (*E*)-oxime (**230**, R=OMe) did not undergo Beckmann rearrangement, but instead an intramolecular Mannich cyclization whereby the electron rich C-4 site attacked the intermediate iminium ion, generating **234** bearing the heterocyclic framework of the slime mold pigment arcyriacyanin A (Scheme 73).[73]



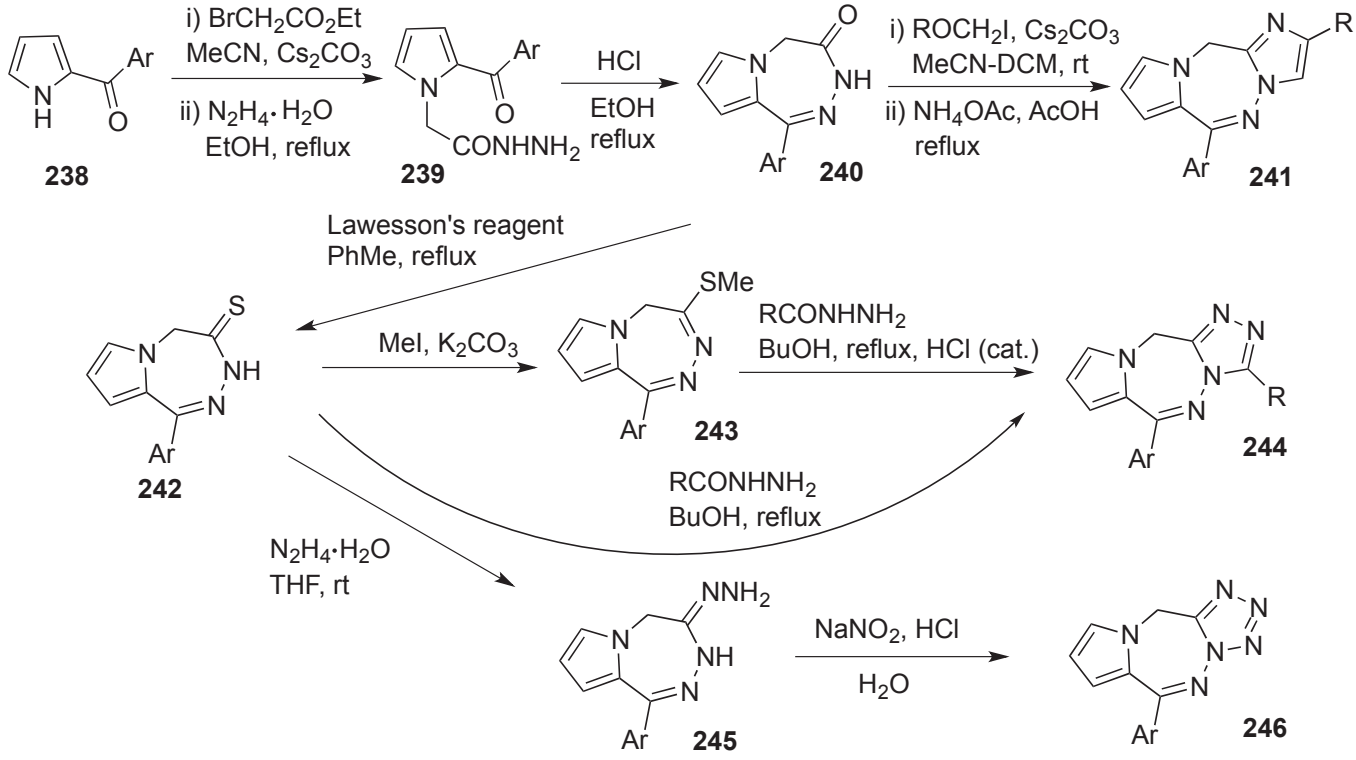
Scheme 73

A simple method for preparing 2,5,6-triazaazulenone (**237**) by the cyclization pyrrole polycarbonyl compounds using hydrazine was reported (Scheme 74).[74]



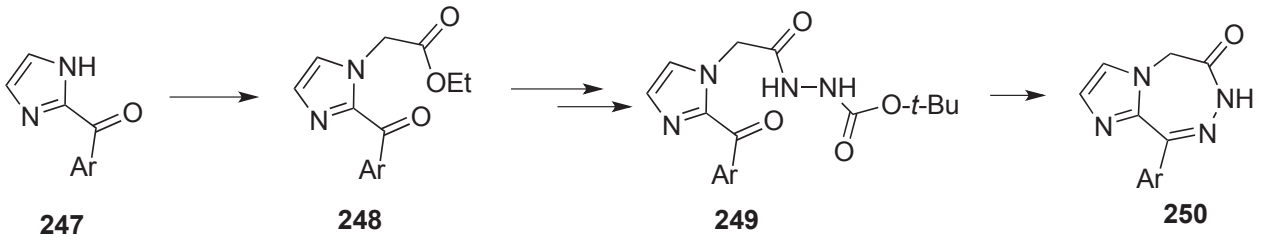
Scheme 74

The synthesis of three new ring systems, pyrrolotriazepine condensed with an imidazole, a triazole or a tetrazole ring, appeared (Scheme 75).[75] 1-Aryl-3*H*-pyrrolo[2,1-*d*][1,2,5]triazepin-4(5*H*)-one (**240**) was prepared form aroyl pyrrole (**238**) as the starting material for the synthesis of new tricyclic systems. Compounds (**241**) were prepared from **240** in two steps. Compounds (**244**) also prepared from **240**. The carbonyl group of **240** was converted into thiocarbonyl moiety by using Lawesson's reagent leading to pyrrolotriazepinethiones (**242**). Compounds (**244**) were prepared from **242** by treatment with acyl hydrazides in refluxing butanol in medium to excellent yields. In certain cases, an alternate approach proved to be more efficient: Formation of **243** and subsequent treatment with acyl hydrazides afforded **244**. Reaction of **242** with hydrazine hydrate resulted in **245**, and successive treatment of **245** with $NaNO_2$ gave **246**.



Scheme 75

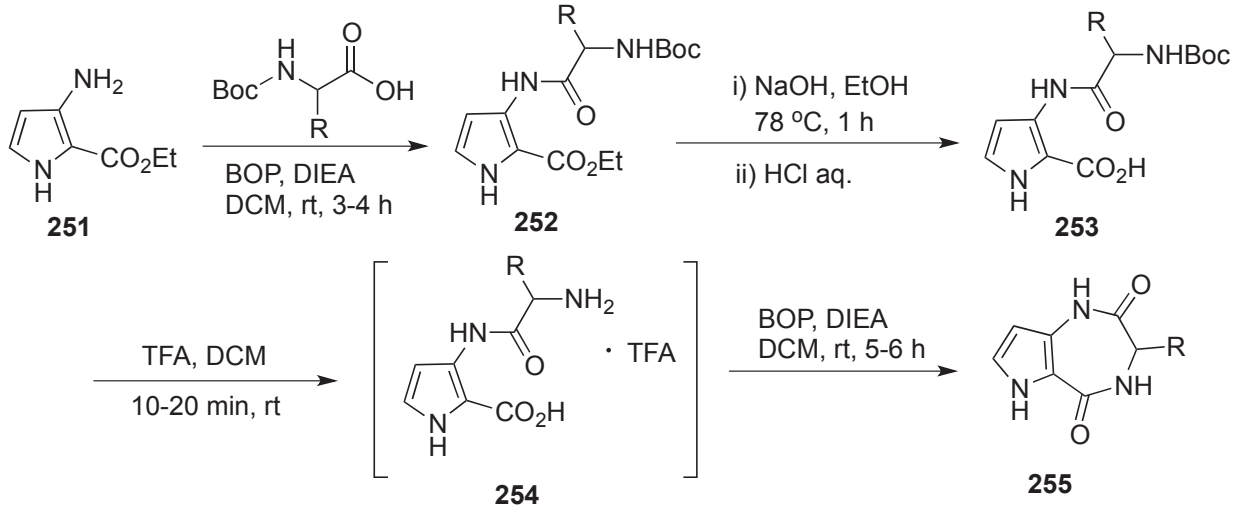
5*H*-Imidazo[2,1-*d*][1,2,5]triazepin-6-ones (**250**), structural analogues of **240**, were synthesized efficiently (Scheme 76).[76]



Scheme 76

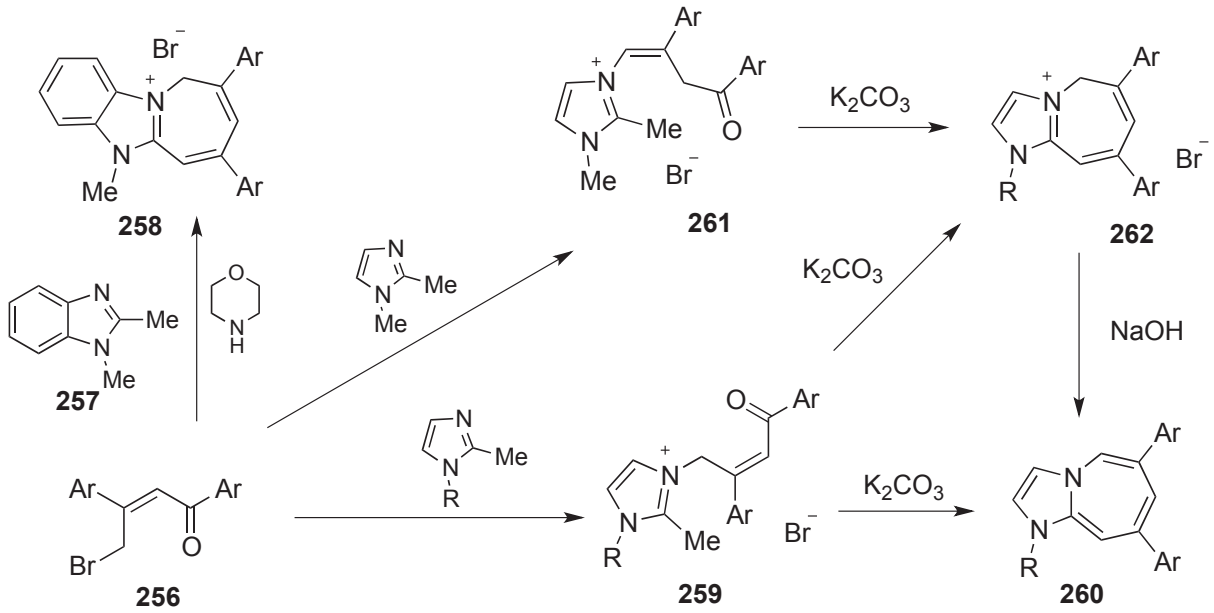
Individual reports about the synthesis of polyazaazulene skeletons occurred passim.

As a part of researches of pyrrolo[3,2-*d*][1,3]oxazine-2,4-dione, Lisowski *et al*. reported about synthesis of pyrrolo[3,2-*e*][1,4]diazepine-2,5-diones. Pyrrolo[3,2-*d*][1,3]oxazine-2,4-dione reacted with alanine and gave 1,4,7-trimetyl derivative of **255**, but the reaction were limited. To overcome the limited reactivity of [3,2-*d*][1,3]oxazine-2,4-dione, they reported alternative route to produce non protected pyrrolo[3,2-*e*][1,4]diazepine-2,5-diones (**255**). A sequence of treatment of amino ester (**251**) with protected amino acids, hydrolysis, intramolecular coupling in the presence of DIEA and BOP, afforded **255** in good yields (Scheme 77).[77]



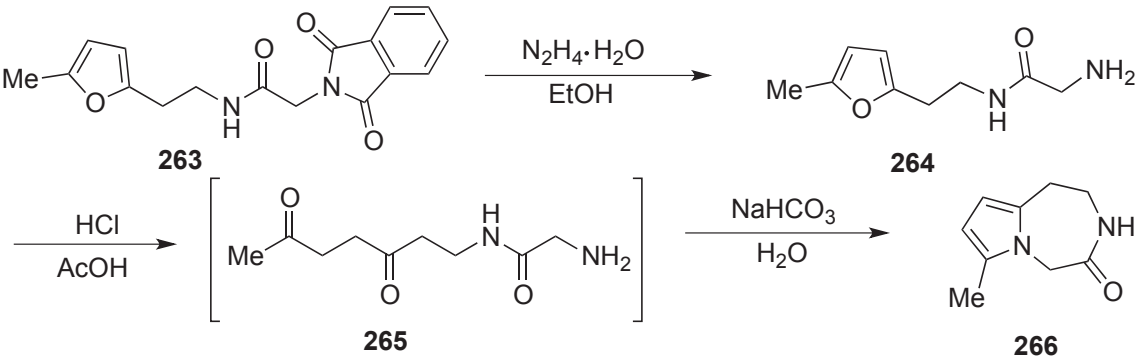
Scheme 77

Although many studies about imidazo[1,2-*a*]azepine condensed systems were carried out, there are few reports for the synthetic studies concerning the unsaturated compounds in azepine ring. Potikha *et al*. reported the synthesis of 5,10-dihydroazepino[1,2-*a*]benzimidazolium bromides (**258**), 1*H*-imidazo[1,2-*a*]azepines (**262**) and (**260**) by the reaction of *γ*-bromodypnones (**256**) with benzimidazoles or imidazoles (Scheme 78).[78]



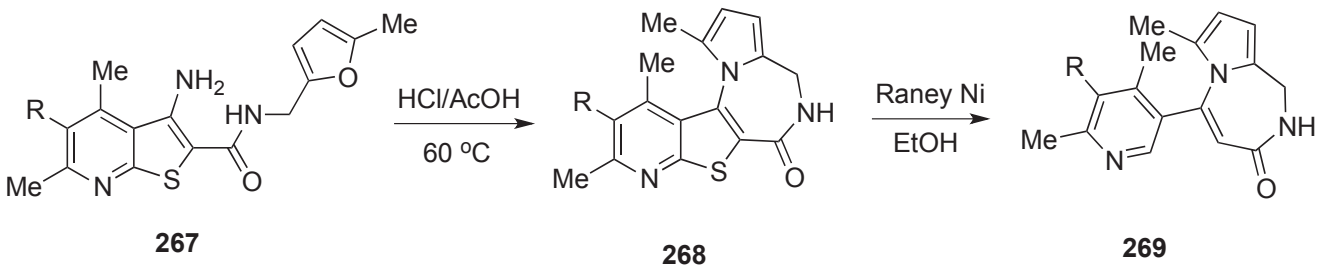
Scheme 78

For the construction of pyrrolodiazepines, uses of the Paar-Knorr reaction were little. Nevertheless, a simple preparation method of pyrrolo[1,2-*d*][1,4]diazepinones was reported. Opening of furan ring of **264** and successive Paar-Knorr-type recyclization gave pyrrolo[1,2-*d*][1,4]diazepinones (**266**) (Scheme 79).[79]



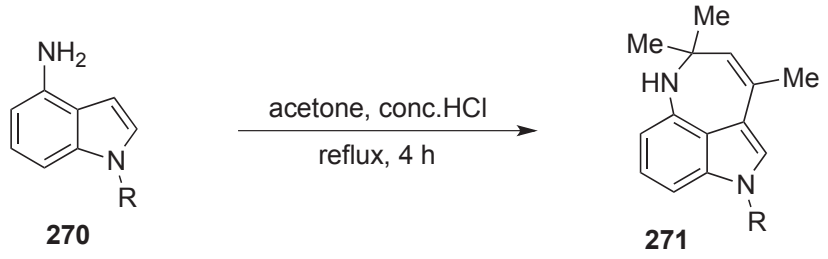
Scheme 79

Desulfurization of thiophene-fused tetracyclic systems (**268**) using Raney nickel gave pyrrolo[1,2-*a*][1,4]diazepinones (**269**) (Scheme 80).[80]



Scheme 80

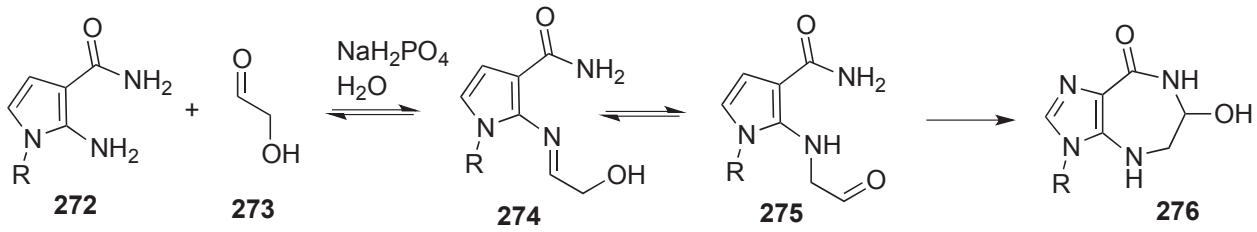
Unexpected regioselectivity for the Skraup-Doebner-Von Miller reaction occurred during the synthesis of quinolone from 4-aminoindoles (**270**), and gave azepino[4,3,2-*cd*]indoles (**271**) (Scheme 81).[81]



270 **271**

Scheme 81

Azepinomycin (**276**), a guanine deaminase inhibitor isolated from the culture filtrate of *Streptomyces* sp., was synthesized by an amino-imidazole tethering strategy that uses an Amadori rearrangement, which coupled glycol aldehyde (**273**) to 5-amino-imidazole-4-carboxamide (**272**) (Scheme 82).[82]

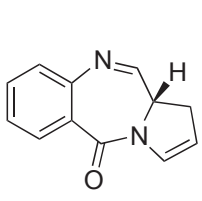


272 **273** **274** **275** **276**

R = H, ribosyl

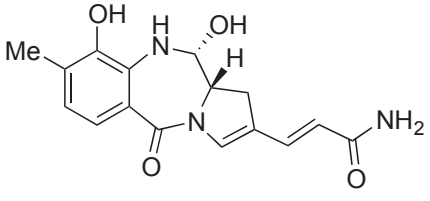
Scheme 82

The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) (**277**) are a group of potent antitumor antibiotics agents, gene regulators, and DNA probes based on the naturally occurring anthramycin family, the best known member of which is anthramycin itself (**278**) (Figure 1). From the interest to the potentialities of PBDs pharmacological, clinical uses, many investigations about PBDs and related compounds were reported, and outstanding reviews appeared up to recently.[2] Although many investigations were reported, only few examples were described here.



277

PBD core structure

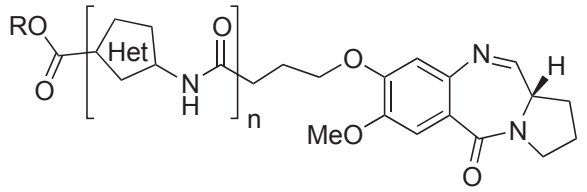


278

anthramycin

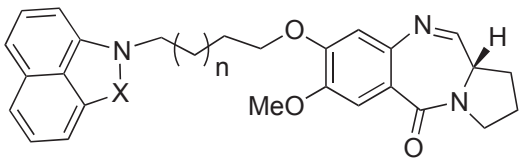
Figure 1

As investigation of the binding of nuclear factor Y to invert CCAAT boxes within the promoter region of DNA topoisomerase IIα, PBD C8 conjugates consisting of one PBD unit attached to tri-heterocyclic polyamides (**279**) were synthesized (Figure 2).[83] A series of benzo[*cd*]indol-2(1*H*)-one-PBD conjugates (**280**), linking the C-8 position with a benzo[*cd*]indol-2(1*H*)-one moiety through different alkane spacers, were synthesized as potential anticancer agents (Figure 2).[84]



Het = pyrrole, imidazole, thiazole; R = Me, Et; n = 2,3

279

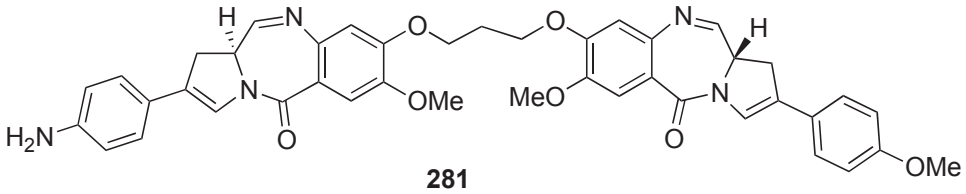


X = CO, C=C(CN)$_2$, SO$_2$

280

Figure 2

Kolakowski *et al*. reported efficiently synthesize both symmetric and non-symmetrical PBD dimers, such as **281** (Figure 3).[85] The dimers were shown potent cytotoxicity in the nanomolar to picomolar range against a number of cancer cell lines.



281

Figure 3

An investigation of a new series of 10-substituted 2-hydroxy-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-diones (**282**) as angiotensin converting enzyme inhibiter was reported (Figure 4).[86]

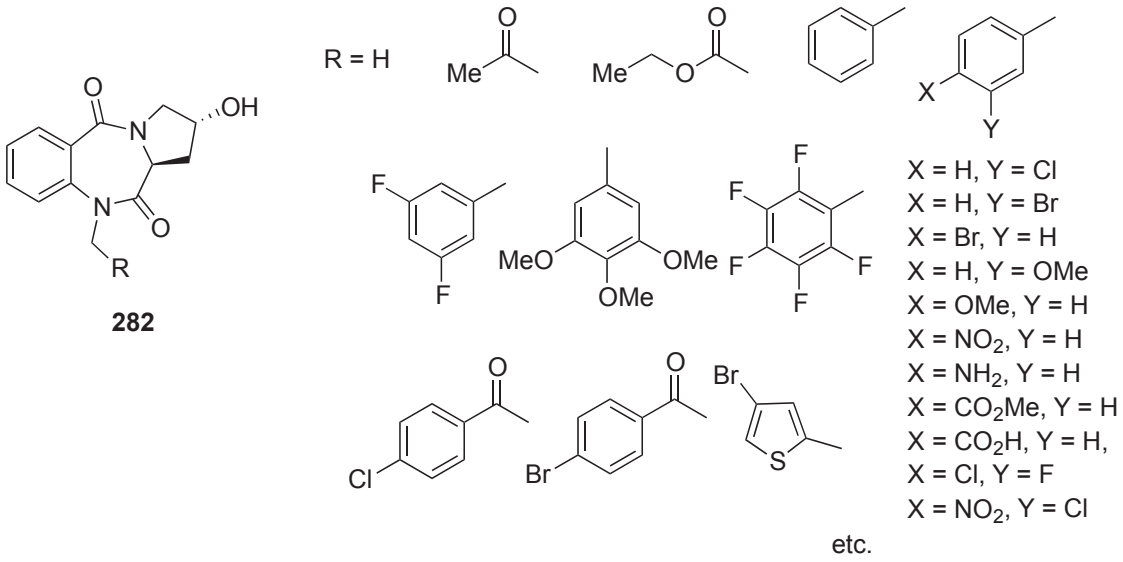
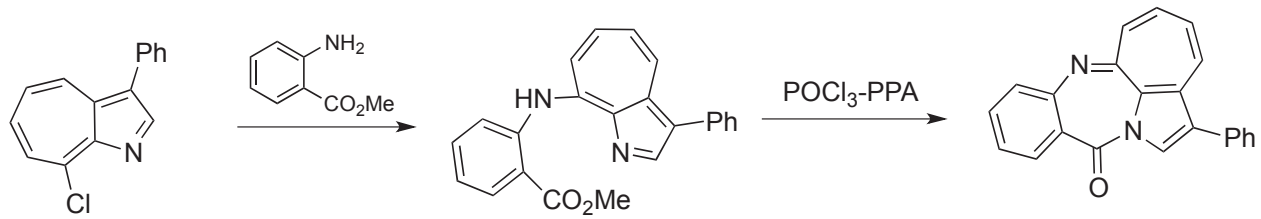


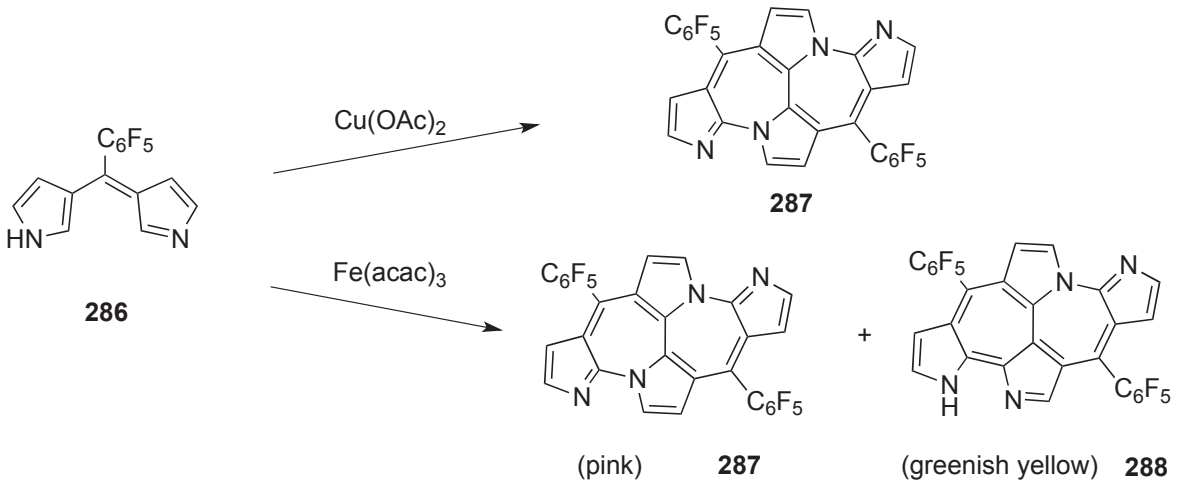
Figure 4

Seven-membered ring fused pyrrolo[2,1-*c*][1,4]benzodiazepine (**285**) was synthesized by Friedel-Crafts-type intramolecular cyclization of **284** (Scheme 83).[87] Compound (**285**) showed a strong cytotoxicity against HeLa-S3 cells (IC_{50}=0.54 μM).



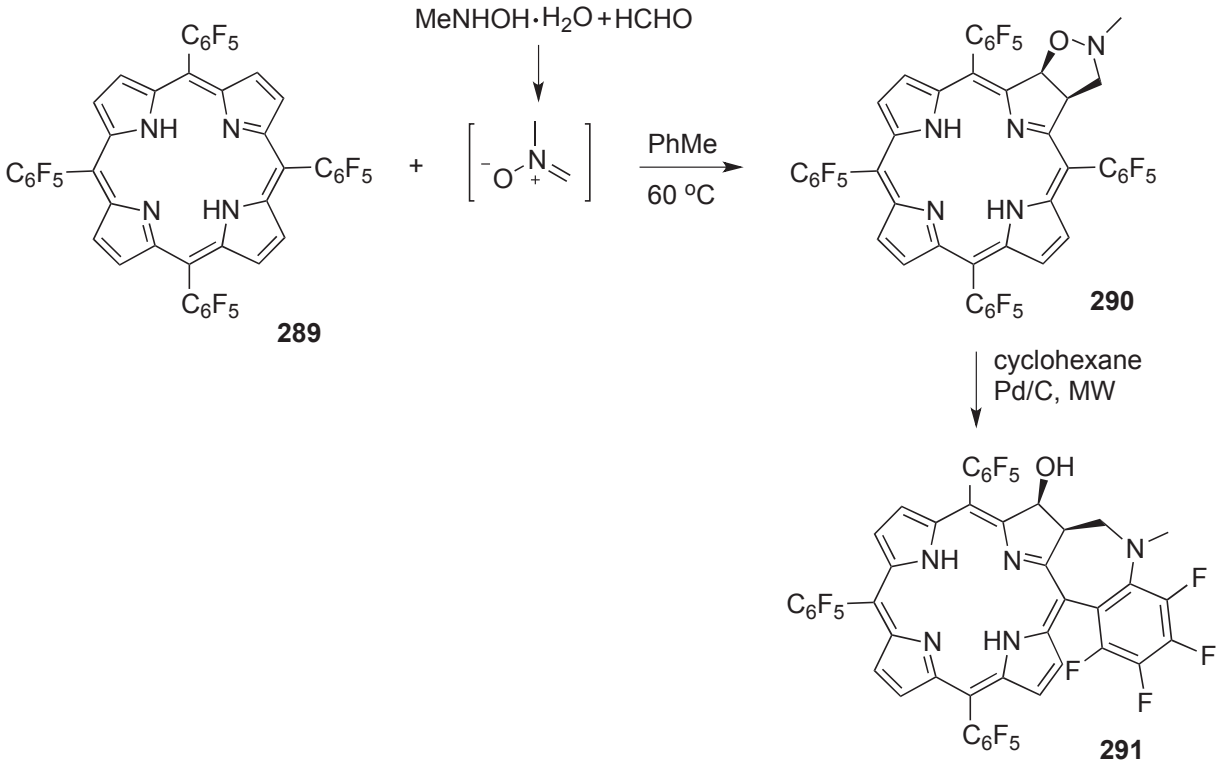
Scheme 83

Macrocycles containing azaazulene moiety are attractive for their structural interests. Metal assisted cyclodimerization of doubly *N*-confused dipyrrins into polycyclic systems containing azaazulene structures was reported. Thus, doubly *N*-confused dipyrrin (**286**), which derived from 3,3'-dipyrromethane by oxidation with DDQ, reacted with metal salts gave **287** and **288** (Scheme 84).[88] Single crystal X-ray structure analysis showed that **287** and **288** have planar conformation, and spectroscopic characterization and computational studies support as nonbenzenoid aromatic molecules.



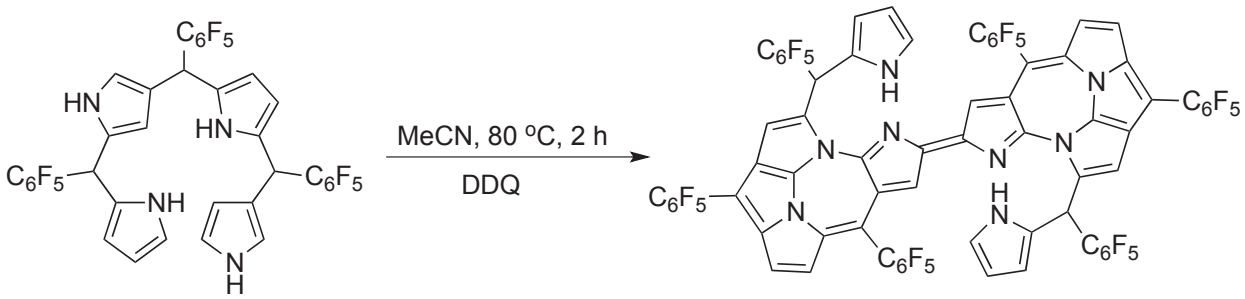
Scheme 84

The microwave-assisted catalytic hydrogenation of the isoxazolidine-fused *meso*-tetrakis-(pentafluorophenyl)cholin (**290**) afforded directly a mono-annulated cholin with a singular 1-methyl-2,3-dihydro-1*H*-benzo[*b*]azepine ring (**291**) that resulted from the cleavage of the isoxazolidine N-O bond followed by an intramolecular nucleophilic aromatic substitution of an *o*-F atom (Scheme 85).[89]



Scheme 85

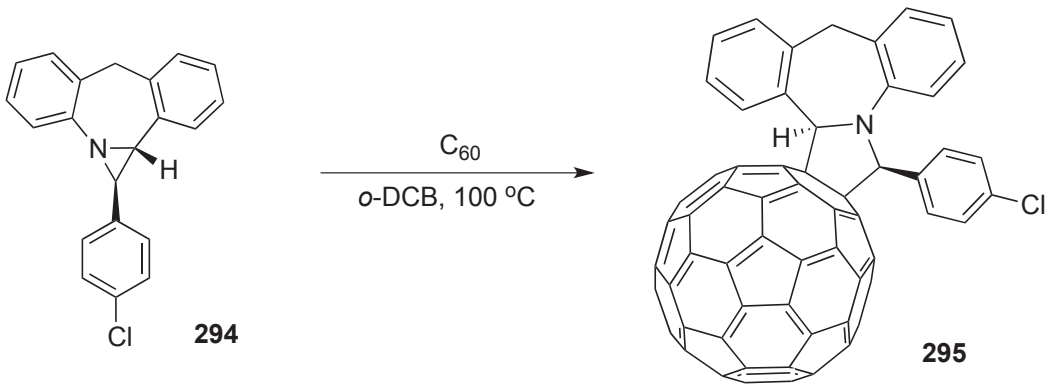
The oxidation of *N*-confused bilan (**292**) with 3.0 equiv of DDQ in MeCN gave the compound (**293**) together with a C-N fused tetrapyrrin that bears a 5,5,5-tricyclic ring (Scheme 86).[90]



292 **293**

Scheme 86

In the investigation of the synthesis and reaction of 7,11b-dihydro-1*H*-azirino[1,2-*a*]dibenzo[*c*,*f*]azepine (**294**), fulleropyrrolidine (**295**) was synthesized by the reaction of **294** with fullerene C_{60} (Scheme 87).[91]



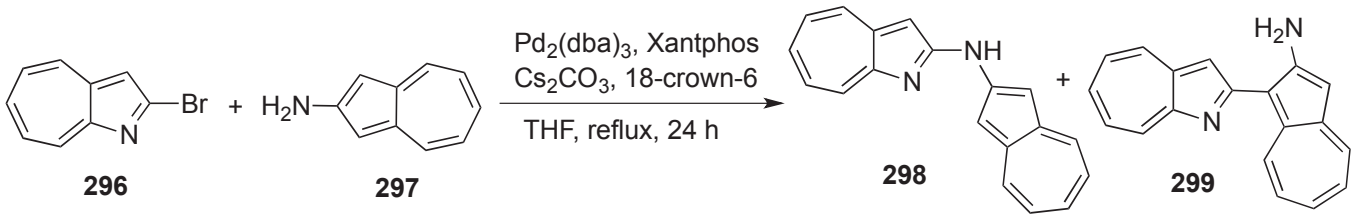
294 **295**

Scheme 87

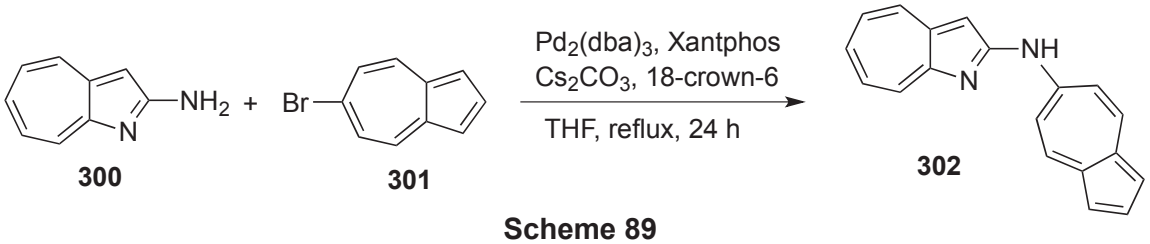
II. REACTIONS AND SOME PROPERTIES

Cross-couplings of nucleophile and electrophile using transition metal catalysts are essentially important and widely applicable methods for precise syntheses. As for azaazulene chemistry, the methods such as Suzuki coupling, Hartwig-Buchwald reaction, etc. were extensively exploited.

Under Hartwig-Buchwald reaction conditions, treatment of 2-bromo-1-azaazulene (**296**) with 2-aminoazulene (**297**) gave Hartwig-Buchwald type product (**298**) together with 1-(1-azaazulen-2-yl)-2-aminoazulene (**299**) as C-C coupling compound (Scheme 88).[92] Whereas, treatment of 2-amino-1-azaazulene (**300**) with 6-bromoazulene (**301**) under similar conditions resulted in only Hartwig-Buchwald type product (**298**) (Scheme 89).[92]

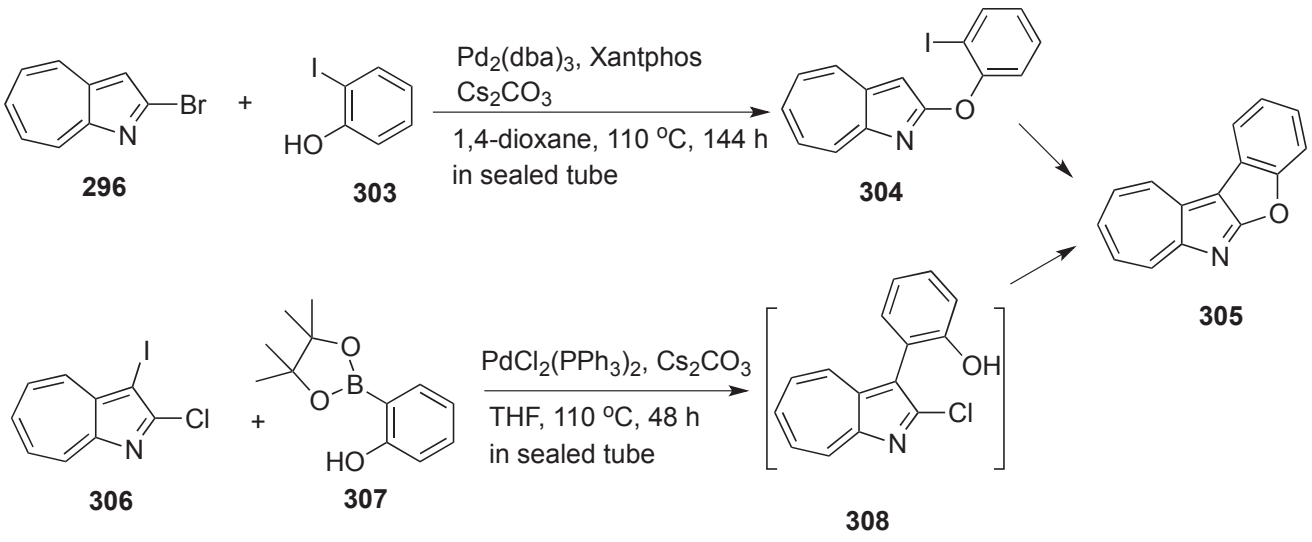


Scheme 88



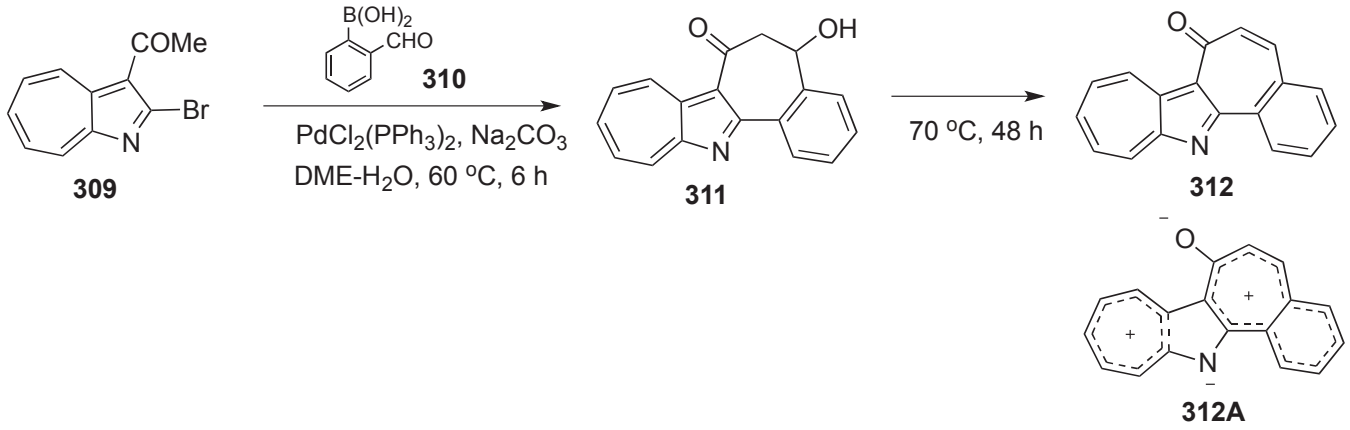
Scheme 89

Treatment of **296** with **303** under the conditions of Hartwig-Buchwald type hetroarylation in a sealed tube proceeded domino-reaction of Hartwig-Buchwald type *O*-arylation/C-C coupling to give benzofuran-fused 1-azaazulene (**305**) together with Hartwig-Buchwald type hetroarylation product (**304**). Compound (**304**) converted to **305** under the same conditions. Compound (**305**) was also obtained domino Suzuki coupling/Hartwig-Buchwald coupling reaction of **306** with **307**. In the reaction, the intermediate (**308**) was not isolated (Scheme 90).[93]



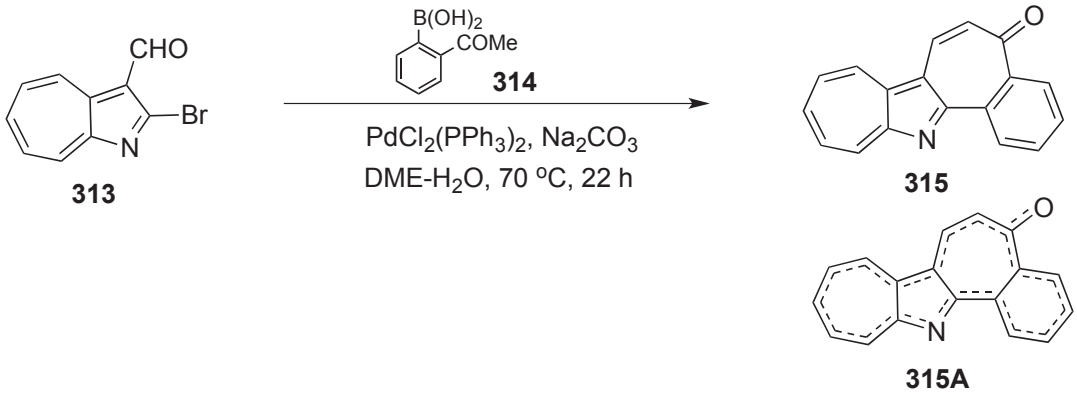
Scheme 90

Domino Suzuki coupling/aldol condensation of **309** with **310** afforded tetracyclic compound (**312**). Spectroscopic studies and theoretical calculations suggested that the structure of **312** has ionic character (**312A**) (Scheme 91).[94]



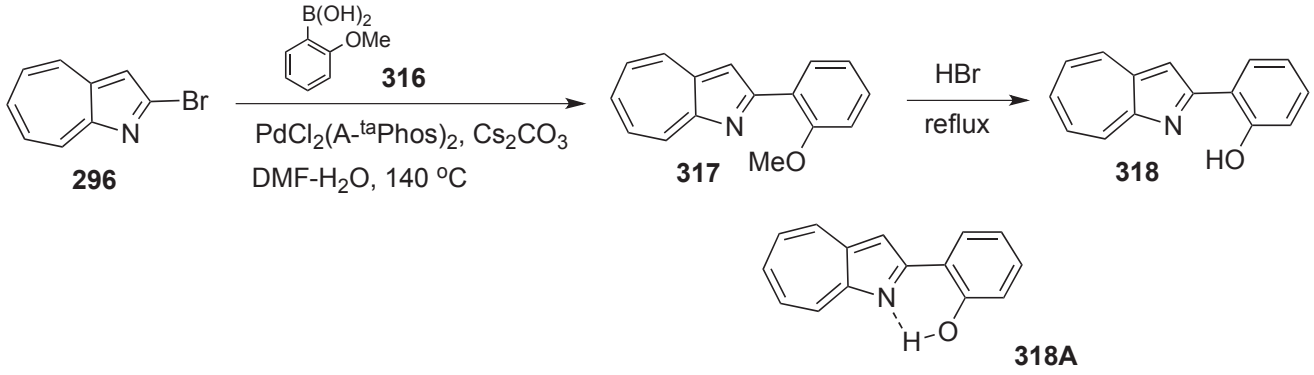
Scheme 91

Similar tandem Suzuki coupling/aldol condensation of **313** with **314** afforded tetracyclic compound (**315**). In the reaction, corresponding intermediate was not isolated. Spectroscopic studies and theoretical calculations suggested that the structure of **315** has peripheral conjugated structure (**315A**) (Scheme 92).[94]



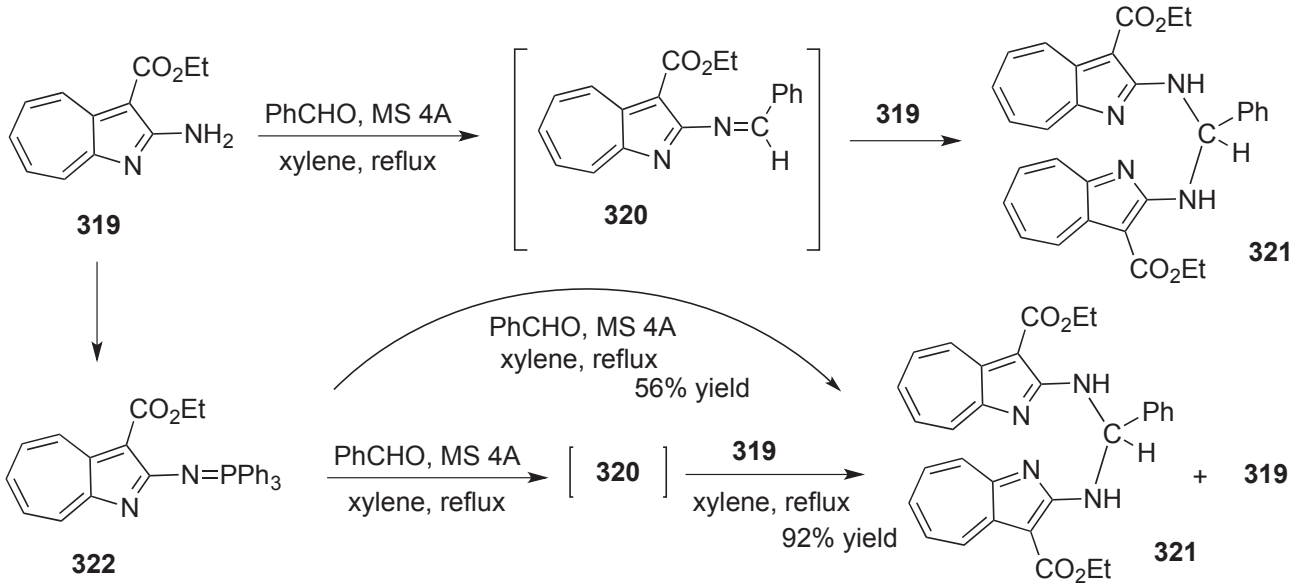
Scheme 92

Oda *et al*. investigated about the synthesis, molecular structures, and some properties of 2-(2-hydroxyphenyl)-1-azaazulene (**318**). Suzuki coupling of **296** with **316** gave **317**, and successive hydrolysis gave **318** (Scheme 93).[95] X-Ray structure analysis and spectroscopic studies of **318** showed that the molecular is co-planar and has intramolecular hydrogen bond between the phenolic hydrogen atom and nitrogen atom of the azaazulenyl nitrogen (**318A**).



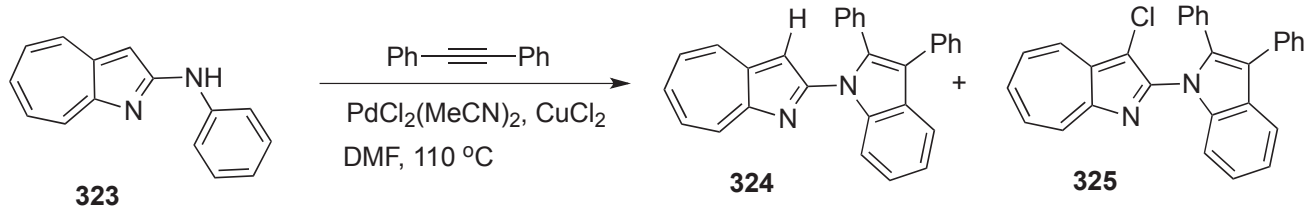
Scheme 93

Attempts for the synthesis of (1-azaazulen-2-yl)imine (**320**) by the reaction of 2-amino-1-azaazulene (**319**) with benzaldehyde resulted in the formation of bis[(1-azaazulen-2-yl)amino]phenylmethane (**321**), and the imine (**320**) could not isolated (Scheme 94).[96] Aza-Wittig reaction of [(1-azaazulen-2-yl)imino]triphenylphosphorane (**322**) with benzaldehyde again resulted in the formation of **321**. The results suggested that the produced imine (**320**) is rather reactive and subsequent reactions of **321** with **319** and/or **322** proceeded (Scheme 94).[96]



Scheme 94

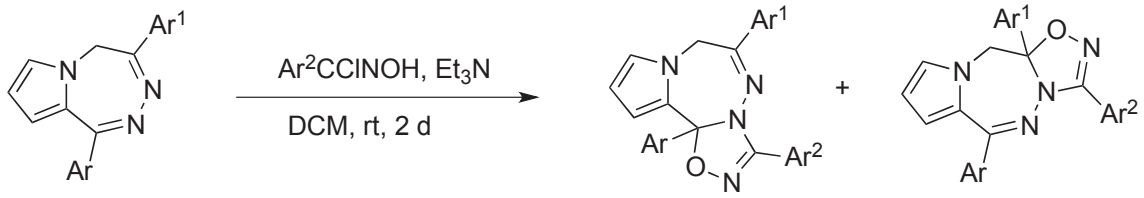
Cycloaddition reaction of 2-phenylamino-1-azaazulene (**323**) with diphenylacetylene in the presence of a Pd(II)-catalyst and a Cu salt gave indole-substituted 1-azaazulenes (**324** and **325**) (Scheme 95).[97] The cycloaddition occurred preferentially at the aniline moiety and not reacted at C-3 of azaazulene.



323 324 325

Scheme 95

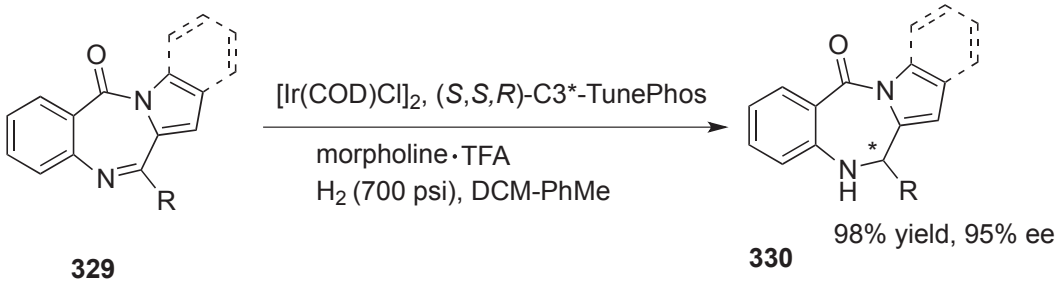
Dipolar cycloaddition reaction of 5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (**326**) with nitrile oxide, generated from *N*-hydroxyarylcarboxaimidoyl chlorides with Et_3N *in situ*, were investigated, and two oxadiazole-fused regioisomers (**327** and **329**) were obtained in high yields (Scheme 96).[98] The structures were unambiguously proved by X-ray structure analysis.



326 327 328

Scheme 96

Highly enantioselective Ir-catalyzed hydrogenation of seven-membered cyclic imines of benzodiazepinones (**329**) and benzodiazepines was achieved and highly optical pure compounds (**330**) were obtained (Scheme 97).[99]

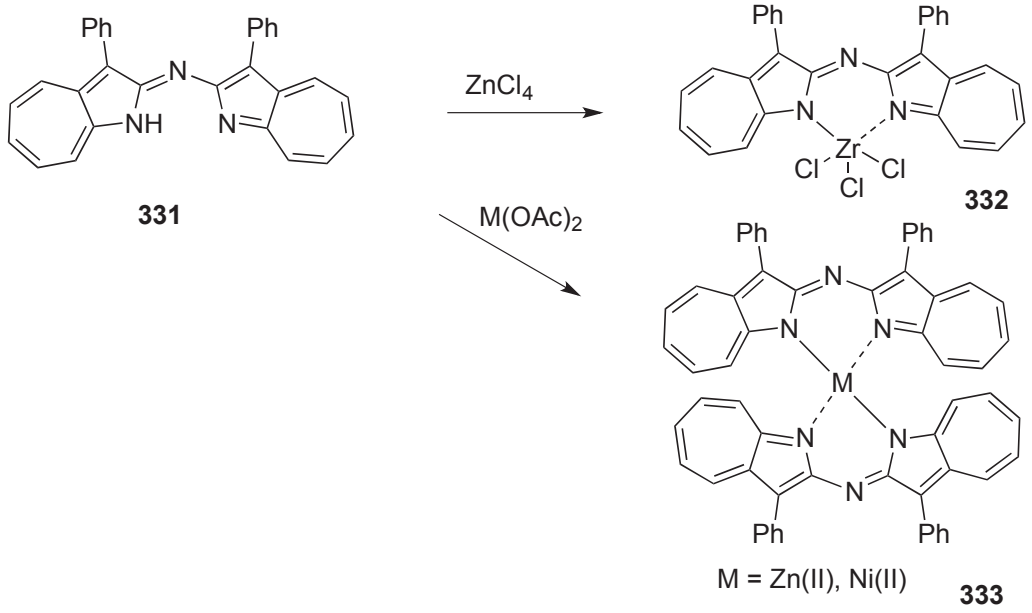


329 330

Scheme 97

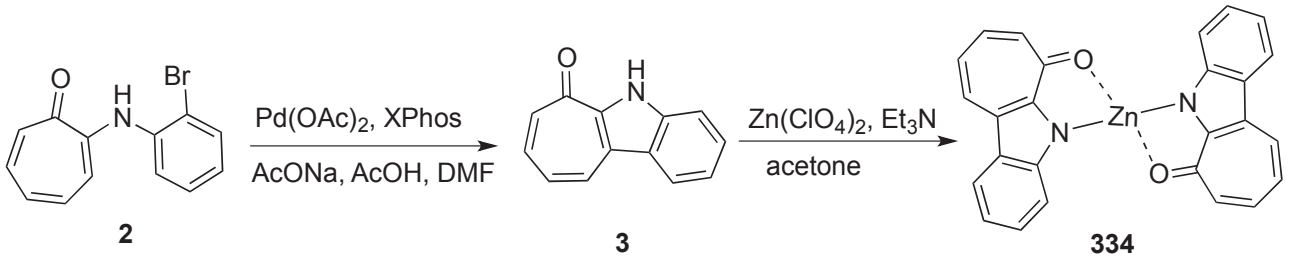
Azadipyrrins were attracted for interests that the structures could lead modified aza-BODIPY dyes. Di(1-azaazulen2-yl)amines can tautomerize to the compound (**331**) containing aza-dipyrrin structures. Examination of metal-complex formation of the compound (**331**), produced by the Hartwig-Buchwald coupling reaction of 2-amino-1-azulenes with 2-halo-1-azaazules, was performed, and complexes (**332**, **333**) were obtained. The absorption spectra of longest wavelength appeared at around 635 nm (log ε ~4.3)

(Scheme 98).[100] Resemble investigation and complexation of di(1-azaazulen2-yl)(2-pyridyl)amine with metal was reported by Oda *et al*.[101]



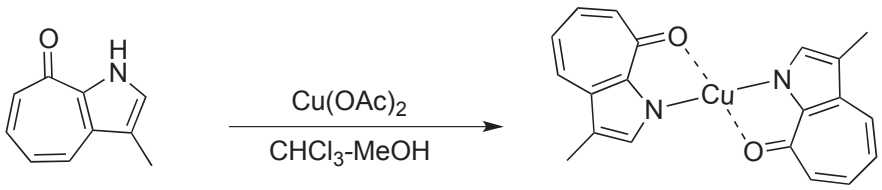
Scheme 98

Oda *et al*. investigated the synthesis and electrochemiluminescence (ECL) properties of Zn(II) complex of indolo[2,3-*b*]tropone ligand (**334**) (Scheme 99).[3] A distinct blue-green ECL emission from the compound (**334**) was observed during electrochemical reduction in DMSO at rt when benzoyl peroxide was used as coreactant. The ECL emission was almost identical to the photoluminescence spectrum of **334**.



Scheme 99

Kubo *et al*. reported the crystal structure of 3-methylpyrrolo[2,3-*b*]tropone (**335**) and its Cu(II) complexes (**336**) using X-ray crystal structure analysis (Scheme 100).[102] The structure of **335** exists in the crystal in the keto form rather than in the enol form. Pyrrolotropone (**336**) formed a 2:1 complex with Cu(II), and the Cu(II) ion has a tetragonal environment formed by two tropone *O*-atoms and two pyrrole *N*-atoms.



335 **336**

Scheme 100

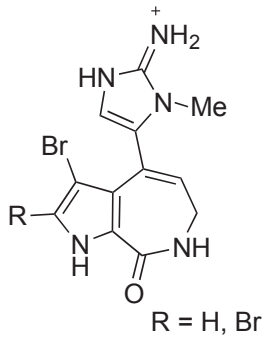
III. NATURAL PRODUCTS AND TOTAL SYNTHESIS

The chemistry of marine natural products has grown enormously, because they have been the source of highly interesting bioactive compounds.[103] Alkaloids containing azaazulene skeletons (pyroroazepines, pyrorobenzazepines, etc.) are especially interesting.

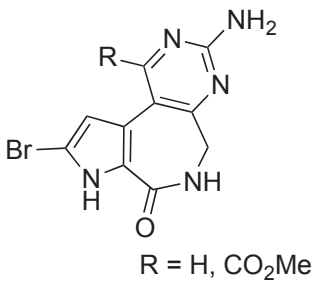
From Indonesian marine sponge *Stylissa* sp., compounds (**337**, **338**) were isolated along with eight known metabolites (Figure 5).[104] These compounds were tested for their cytotoxicity against mouse lymphoma cell line L5187Y, and the compound (**337**, R=Br) showed significant *in vitro* activity with EC_{50} value of 3.5 μg/mL.

Tsukamoto *et al*. isolated spongiacidin C (**339**) from the marine sponge *Stylissa massa*, collected at North Sulawesi, Indonesia, as the first USP7 (a deubiquitylating enzyme hydrolyzing the isopeptide bond at the C-terminus of ubiquitin) inhibitor from natural source (Figure 6).[105] Inhibitory activity of **339** against USP7 was IC_{50}=3.8 μM.

Capon *et al*. isolated callyspongisines A-D (**340**-**343**) along with known two co-metabolites (hymenialdisine and 2-bromoaldisine) from an Australian marine sponge, *Callyspongia* sp (Figure 7).[106] The callyspongisines proved to be non-cytotoxic against a range of prokaryotic, eukaryotic and mammalian cell lines.

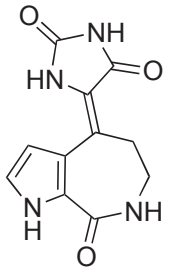


337



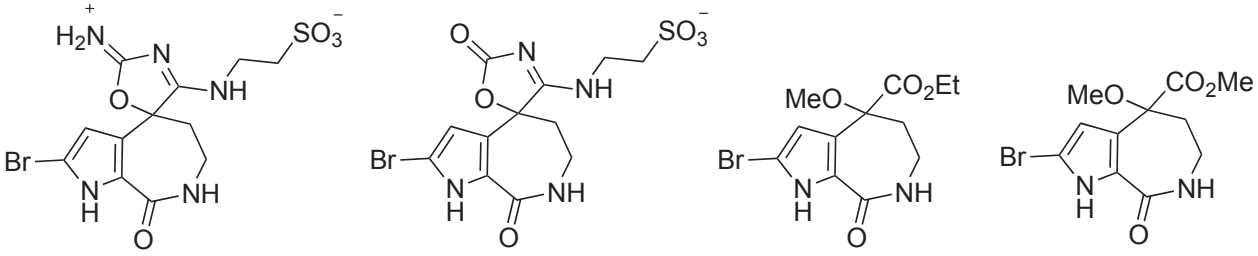
338

Figure 5



339

Figure 6

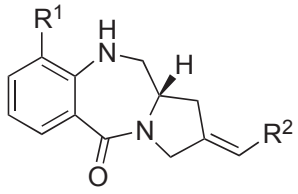


340 **341** **342** **343**

Figure 7

New anthramycin-type analogues, designated usabamycin A-C (**344**), were isolated from cultures of *Streptmyces* sp. NPS853, a bacterium found in marine sediments (Figure 8).[107] Usabamycins showed weak inhibition of HeLa cell growth and selective inhibition of serotonin 5-HT_{2B} uptake inhibitory activities with moderate *in vitro* potency.

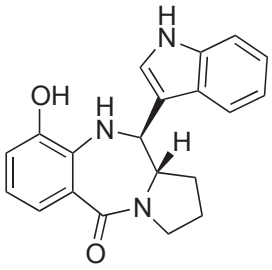
Breinbauer and Zechner *et al*. reported the biosynthesis of tilivalline (**345**) and showed that this nonribosomal peptide assembly pathway initially generates tilimycin (**346**), a simple pyrrolobenzodiazepine with cytotoxic properties (Figure 9).[108]



usabamaycin A: R^1 = OCMe, R^2 = Et
usabamaycin B: R^1 = OMe, R^2 = Me
usabamaycin C: R^1 = H, R^2 = Et

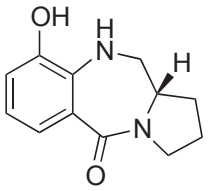
344

Figure 8



tilivalline

345

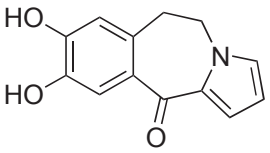


tilimycin

346

Figure 9

A new tricyclic alkaloid named portulactone (**347**) together with eight known compounds were isolated from aerial parts of *Portulaca oleracea* L (Figure 10).[109] Compound (**347**) showed dose-dependent scavenging activities against DPPH (2,2-diphenyl-1-picryl-hydrazyl) free radical, with EC_{50} value of 14.36 μM.

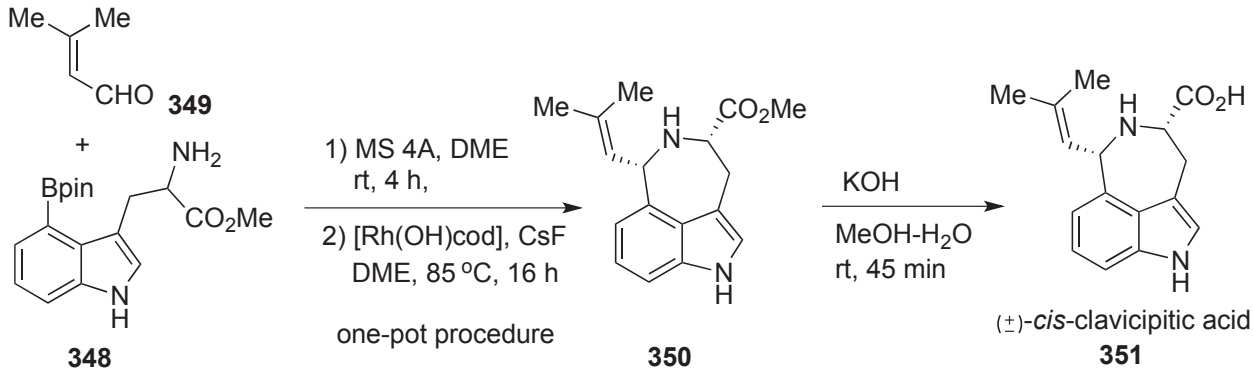


portulactone

347

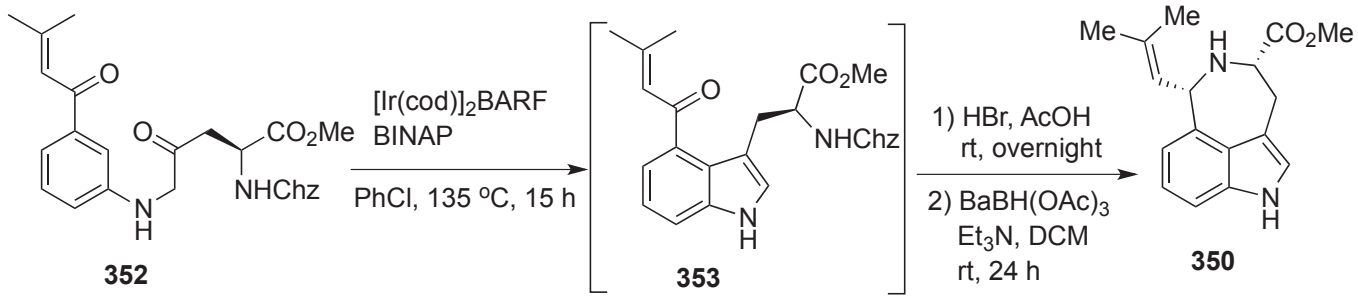
Figure 10

Clavicipitic acid (**351**) is an ergot alkaloid biosynthesis derailment product and was isolated from the Claviceps strain SD58 and from *Claviceps fusiformis*. Piersanti *et al*. reported the concise total synthesis of **351** in only four total steps from 4-boronate indole (**348**) and **349** with high diastreoselectivity (Scheme 101).[110] The synthesis was achieved using a selective Friedel-Crafts alkylation and an unprecedented intramolecular Rh(I)-catalyzed imine hydroarylation reaction via a one-pot procedure.



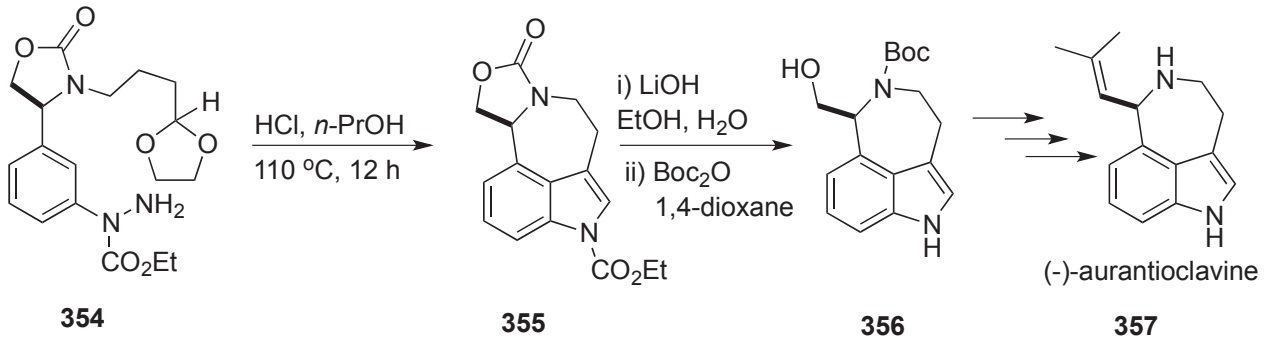
Scheme 101

Shibata *et al*. also synthesized **350** by Ir-catalyzed reaction and intramolecular reductive amination of **352**, which was synthesized from asparagine (Scheme 102).[111]



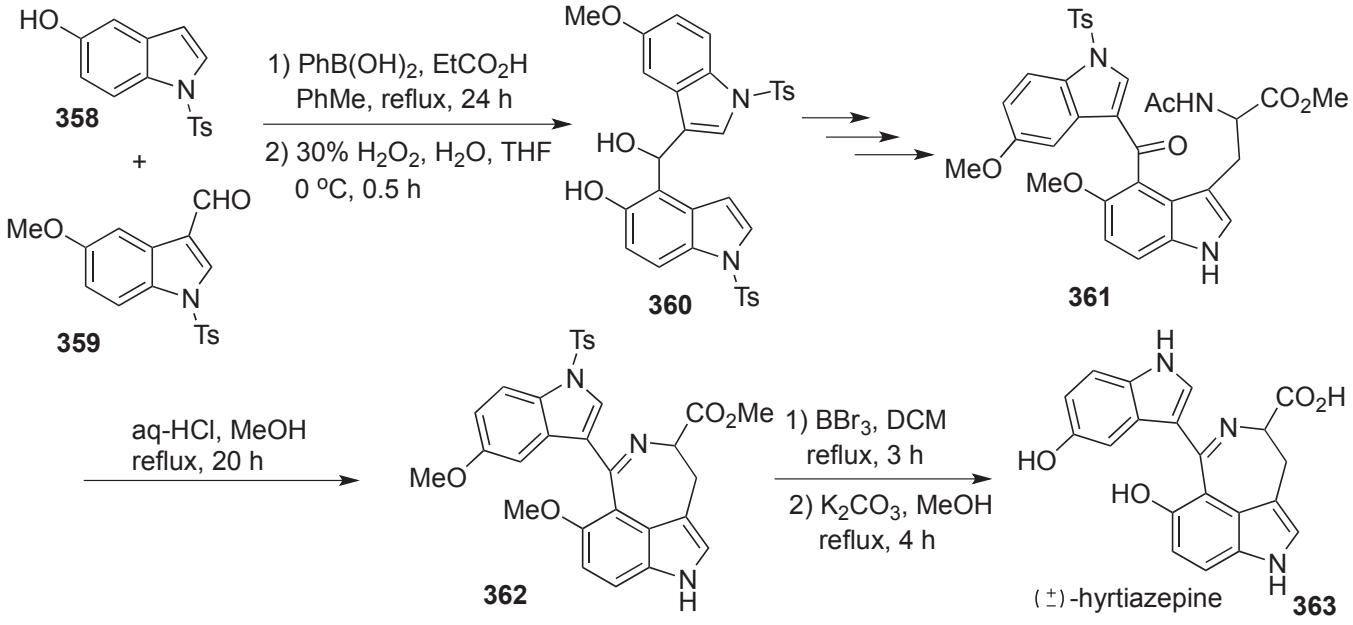
Scheme 102

A concise total synthesis of (-)-aurantioclavin (**357**) appeared. For the formation of 3,4-fused tricyclic indoles, a sequence of the reaction conceptually new synthetic approach was presented, where aryl hydrazides (**354**) with ketone or aldehyde containing side chains linked to the *meta*-position of the aromatic ring undergo acid-promoted intramolecular Fischer indole synthesis (Scheme 103).[112]



Scheme 103

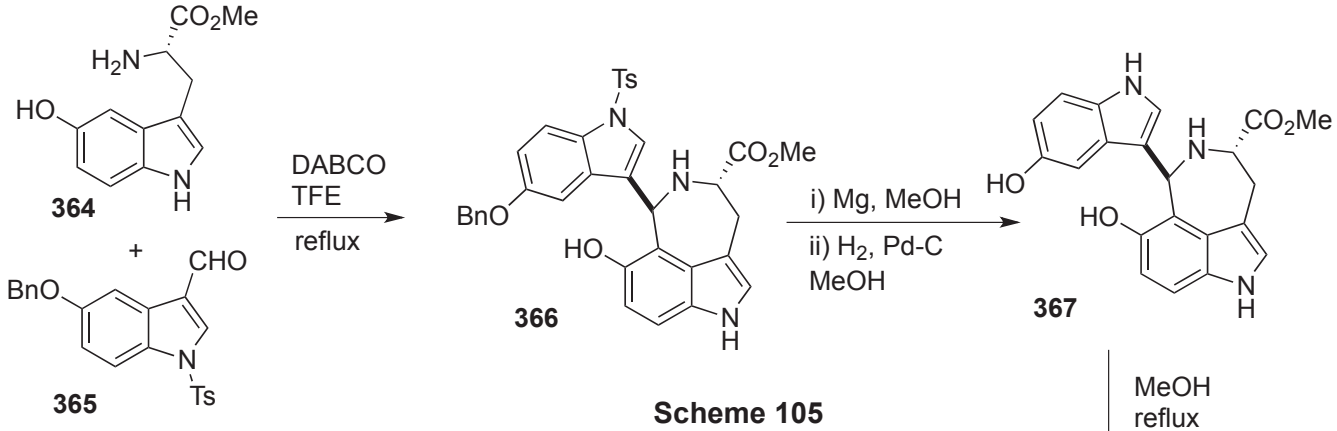
Hyrtiazepine (**363**), azepinoindole alkaloid and a family of bisindole natural products, was initially isolated from marine sponge *Hyrtios erectus*. Ito *et al*. reported the total synthesis of **363** by the *ortho*-selective α-hydroxyalkylation of **358** with **359** and the intramolecular imination of **362** (Scheme 104).[113]



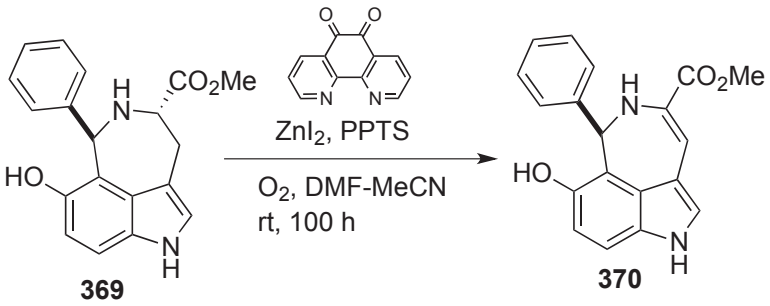
Scheme 104

Abe *et al*. investigated a biomimetic approach by constructing the azepinoindole core (**368**) in one-pot manner. Treatment of the indoles (**364** and **365**) in one-pot using DABCO and TFE, where a biomimetic

approach employed a C-4 Pictet-Spengler reaction, afforded a precursor (**366**). Deprotection of Ts and Bn from **366** gave **367**. The attempts for the synthesis of hyrtiazepine from **367** employing the oxidation conditions were failed, where 5-hydroxyindole was mainly obtained *via* Mannich type fragmentation. Compound (**368**), the framework present in azepinoindole alkaloids such as fargesine and cimitripazepine, was produced by the treatment of **367** in refluxing MeOH (Scheme 105).[114] For the purpose of the imine formation, compound (**369**) was synthesized and oxidized. When the Stahl's oxidation conditions was employed to **369**, unexpected enamine formation occurred and **370** was obtained (Scheme 106).[114]

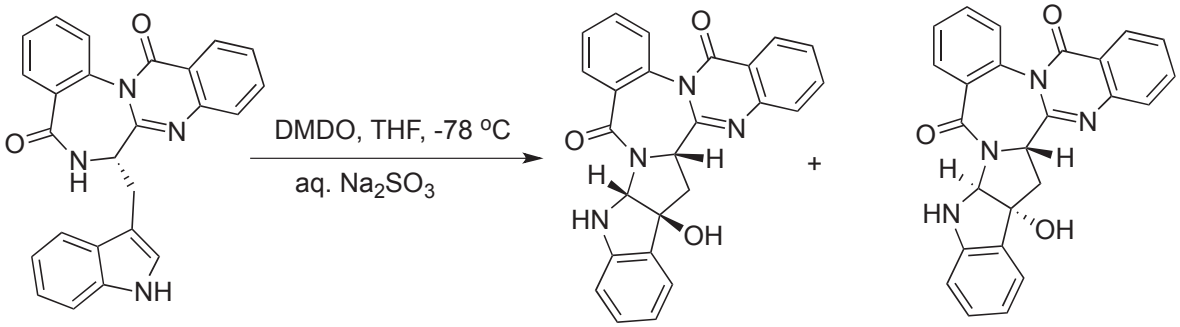


Scheme 105



Scheme 106

Quinazolinone alkaloid asperlicin C (**371**) and E (**372**) are two non-peptidal antagonists of the gastrointestinal hormone neurotransmitter cholecystokinin (CCK), which were isolated from the fermentation broths produced by *Asperbillus alliaceus*. Huang *et al*. reported a highly enantioselective synthesis of (-)-asperlicin C (**371**) and the transformation of **371** to (+)-asperlicin E (**372**) and its diastereomer (**373**) (Scheme 107).[115]



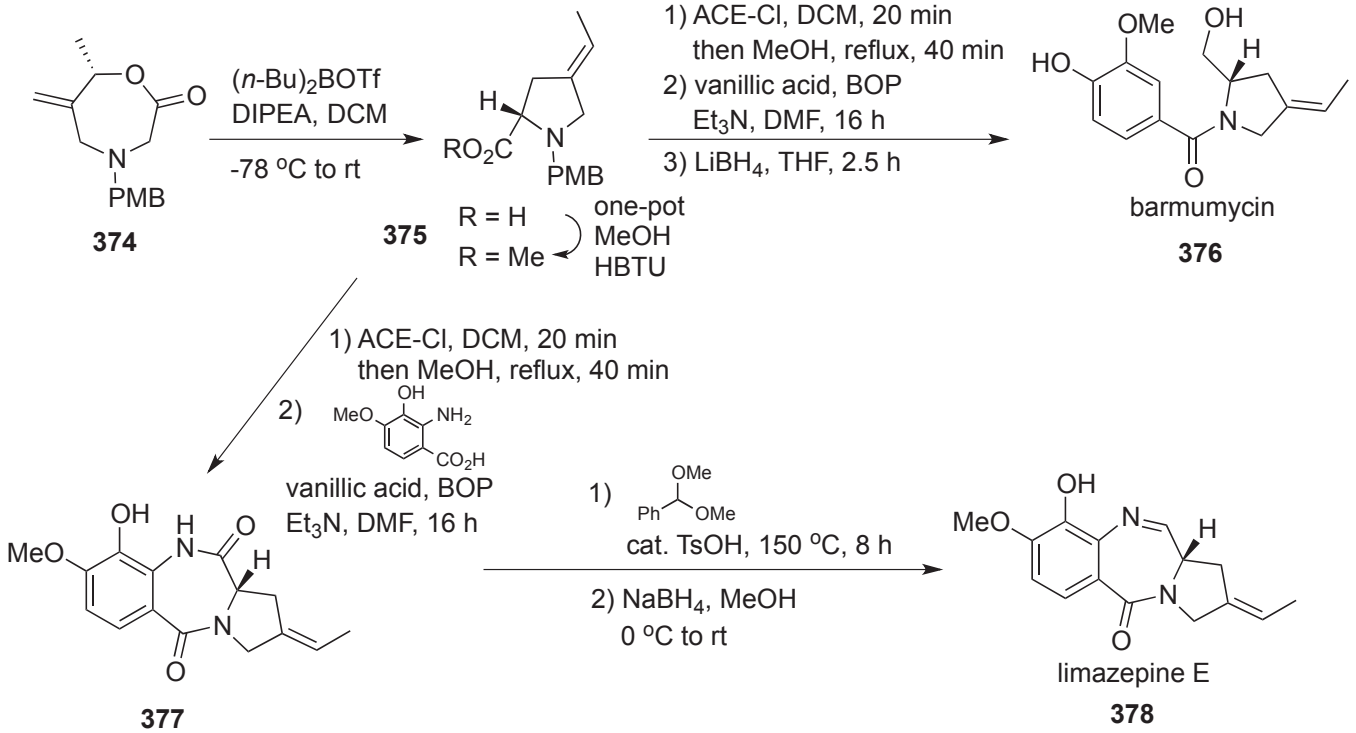
asperlicin C
371

asperlicin E
372

2,3-di-*epi*-asperlicin E
373

Scheme 107

Barmumycin (**376**) was isolated from the marine actinomycete *Streptomyces* sp. BOSC-022A. Limazepine E (**378**) was isolated from a culture broth of *Micrococcus* sp. strain ICBB 8177 and belong to the PBD class of natural products. Ireland-Claisen rearrangement of seven-membered lactone (**374**), synthesized from (*S*)-ethyl lactate, produced (*E*)-ethylidene proline (**375**). Barmumycin (**376**) was easily obtained from **375**. Total synthesis of limazepine E (**378**) was achieved as shown in the Scheme 108.[116]

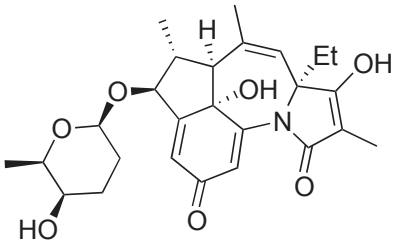


Scheme 108

Tetrapetalone A was isolated from *Streptomyces* sp. USF-4727. Wood *et al*. reported the total synthesis of (-)-tetrapetalone A and C (**379** and **380**) (Figure 11).[117] A key azepine intermediate was derived by the

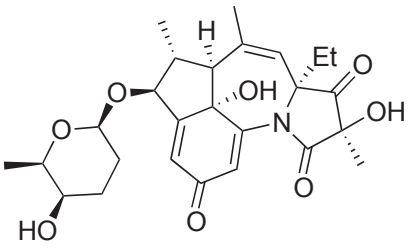
sequence of reactions which involves initial assembly of masked *N*-aryltetramic acid which is advanced *via* a highly selective conjugate addition/intramolecular Friedel-Crafts acylation.

Total synthesis of the hexacyclic system of trigonoliimine A (**381**) (Figure 12) was achieved by Hao *et al*. in four steps from *N*-phthalolyl 6-OMe-tryptamine.[118]



(+)- or (-)-tetrapetalon A

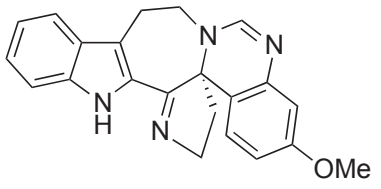
381



(+)- or (-)-tetrapetalon C

382

Figure 11

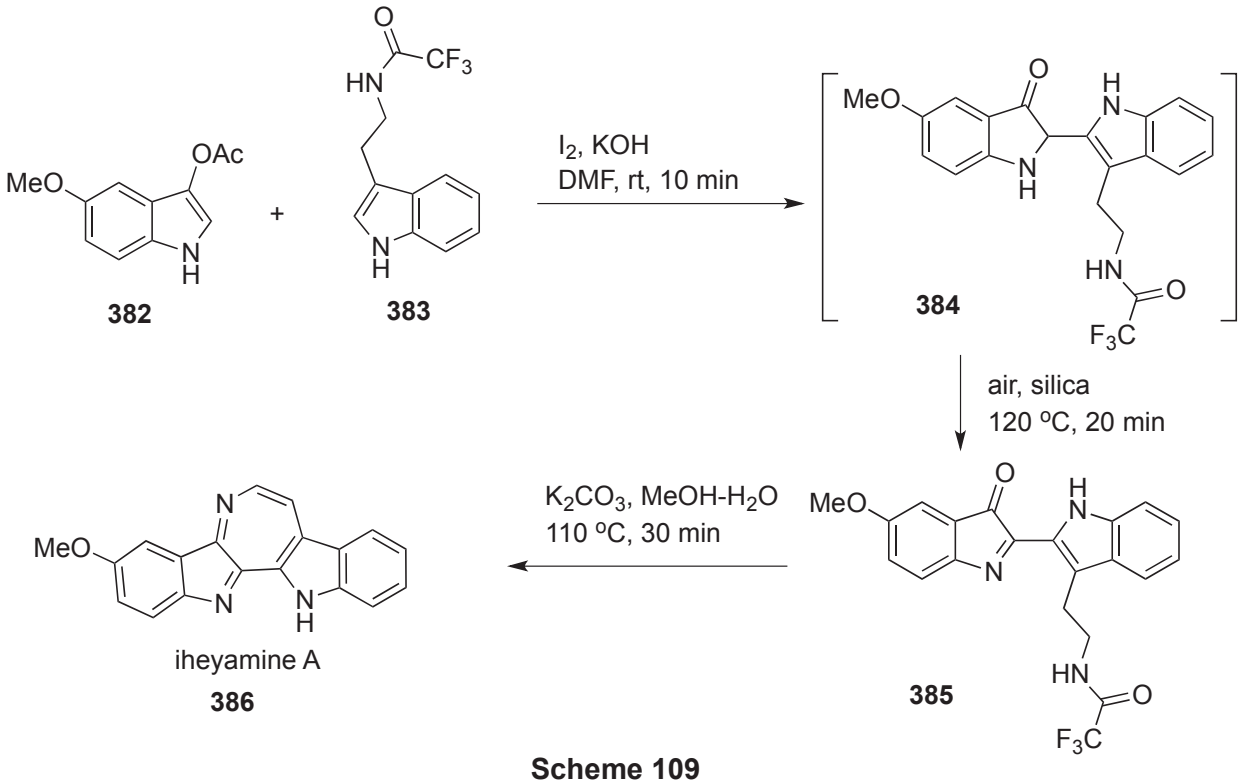


trigonoliimine A

383

Figure 12

The total synthesis of iheyamin A was reported by Sperry *et al*. Intermoleculer cross-Mannich reaction between **382** with **383** gave unsymmetrical 2,2-bisindole (**385**). The pivotal deprotonation-cyclization-aromatization sequence proceeded to give iheyamine A (**386**) (Scheme 109).[119]



Scheme 109

IV. BIOLOGICAL ACTIVITIES AND PHARMACOROGY

Azaazulenes and polycyclic compounds containing azaazulene and/or azepine skeleton, such as pyrrolobenzazepines, azepinoindole-derivatives, and so on, were directed attention from their biological activities and potentialities of drug use, especially antitumor antibiotics.[2a-2c,2e] Pyrrolobenzodiazepines (PBDs) have been investigated as potential anticancer agents, actually, the best known PBD dimer SJG-136 has completed Phase II clinical trials in patients with leukaemia and ovarian cancer.[2c]

Non-symmetrical PBD dimer (**281**), reported by Kolakowski *et al*., showed potent cytotoxicity against a number of cancer cell lines (786-0: IC_{50}=0.5 nM, Caki-1: IC_{50}=0.2 nM, HEL92.1.7: IC_{50}=0.024 nM, HL60cy: IC_{50}=0.013 nM, MCF-7: IC_{50}=1 nM, TF-1a: IC_{50}=1 nM).[85]

PBD C8 conjugates consisting of one PBD unit attached to tri-heterocyclic polyamides (**279**) were evaluated for *in vitro* cytotoxicity in the National Cancer Institute 60-cell-line panel. Compound (**279**: Py-Py-Im-PBD) exhibited the lowest average GI_{50} value (1.5 nM).[83]

A Series of benz[*cd*]indol-2(1*H*)-one-PBD conjugates (**280**) was evaluated in human cell lines, and compound (**280**: X = SO_2) exhibited strong cytotoxicity (A549: IC_{50}=1.05 nM, A431: IC_{50}=1.72 nM, Colo-205: IC_{50}=1.21 nM, PC-3: IC_{50}=1.52 nM).[84]

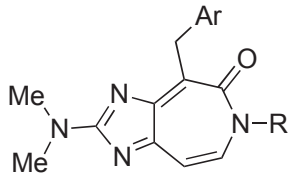
10-Substituted 2-hydroxy-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-diones (**282**) as angiotensin converting enzyme (ACE) inhibiter were screened, and compound (**282**: R=4-bromothiophen-2-yl; IC_{50}=0.272 μM) emerged as most active non-carboxylic acid ACE inhibitor with minimal toxicity comparable to clinical drugs Lisinopril, Benazepril, and Ramipril.[86]

Many investigation about cytotoxicity against diverse cancer cell lines, such as HeLa, BT-474, RT-474, HepG2, HCT-116, L5178Y, and so on. Cytotoxic activities of fused 1-azaazulene derivatives against HeLa S3 cells were investigated, and some compounds showed cytotoxic activities (e.g., **285**: IC_{50}=0.54 μM, **311**; IC_{50}=10.5 μM, 312; IC_{50}=3.2 μM, **315**; IC_{50}=4.6 μM).[87,94] Qinoxaline-fused dibenzo-1,6-diazaazulenes showed strong cytotoxic activities (**156** (R=H): HeLa; IC_{50}=7 μM, BT-474; IC_{50}=7.6 μM, MCF-7; IC_{50}=23.3 μM; **156** (R=Me): HeLa; IC_{50}=10 μM, BT-474; IC_{50}=11.6 μM, MCF-7; IC_{50}=0.9 μM,).[48]

Natural products containing azaazulene skeletons showed bioactivities severally. Spongiacidin C (**339**) showed inhibitory activity of against USP7 (IC_{50}=3.8 μM). Usabamycins A-C (**344**) have only weak cytotoxic activities against HeLa cells (IC_{50}>100 μM), but **344** showed serotonin 5-HT2B uptake inhibitory activities with moderate in vitro potency (usabamycin A: IC_{50}=12.4 μM, usabamycin B: IC_{50}=8.45 μM, usabamycin C: IC_{50}=8.24 μM).

Seratamine A analogues (**387**) (Figure 13) were synthesized by Liu *et al*. and cytotoxicity against cancer cell lines (HCT-116, HepG2, BGC-823, A549, and A2780) were evaluated. Compounds (**387**: R=Me,

Ar=3,5-$(Me)_2C_6H_3$; **387**: R=CH_2Ph, Ar=Ph) exhibited most potent cytotoxicity which were better than ceratamine A against A549.[120]



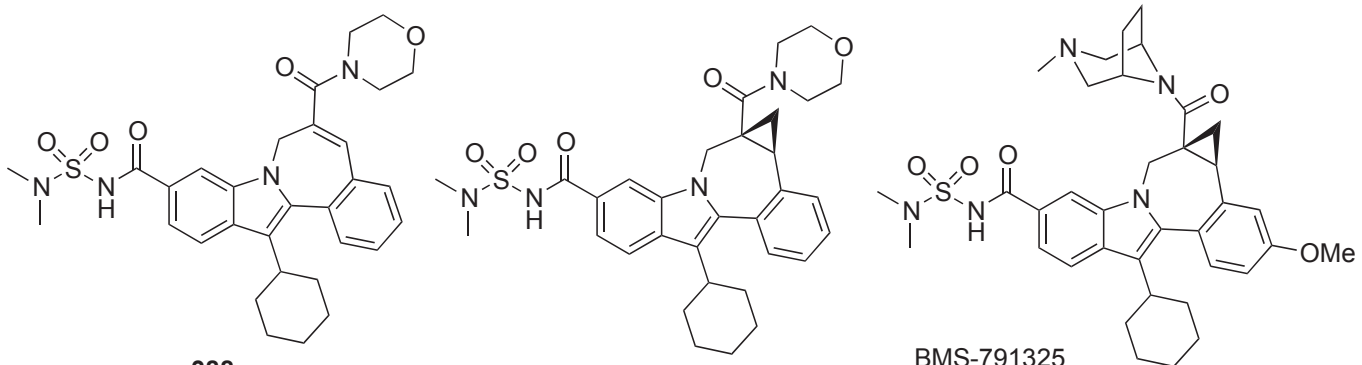
387

ceratramine A analogues

R = Me, Et, CH_2Ph
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-EtC_6H_4, 4-$(Me)_2NC_6H_4$, 4-$MeO_2CC_6H_4$, 4-$MeOC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, 3,5-$(Me)_2C_6H_3$, Py

Figure 13

Pursuits of allosteric inhibitor of the Hepatitis C virus NS5B polymerase have been elucidated vigorously. Structure-activity relationship studies that resulted in the optimization of the activity of member of a class of cyclopropyl-fused indolobenzaepine HCV NS5B polymerase inhibiters were reported. A series of alkyl bridged piperazine carboxamides was of particular interest, and compound BMS-791325 (**390**) was found to have distinguishing antiviral, safety, and pharmacokinetic properties. The introduction of cyclopropyl moiety into indolobenzazepines of the type (**388**) associated with improvements in potency. To investigate this position, analogues of **388** and their related cyclopropyl derivatives were prepared. Finally, compound (**390**) was selected as clinical candidate for the treatment of HCV infection. Compound (**390**) evaluated currently in Phase II studies in combination with the NS5A inhibitor daclatasvir and the HCV protease inhibitor asunaprevir in an all-oral regimen in treatment–naive patients infected with genotypes 1 and 4 (Figure 14).[121]

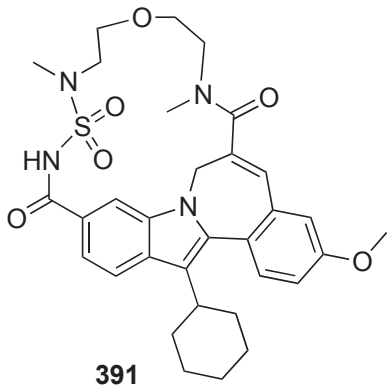


388 **389** BMS-791325 **390**

Figure 14

A structure-based macrocyclization strategy led to the discovery of potent and selective inhibitors of HCV NS5B polymerase devoid of the undesirable features characterizing non-macrocyclic analogues, and culminated in the discovery of the candidate (**391**) (Figure 15),[122] which was characterized by high

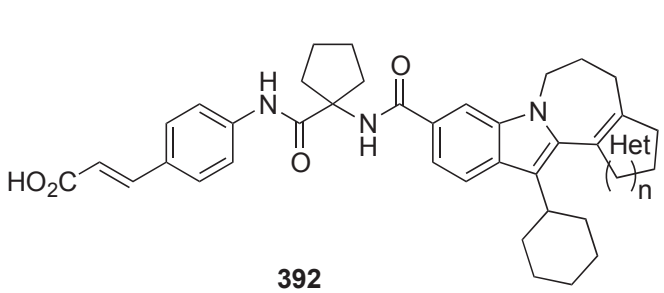
affinity for and persistent binding to NS5B polymerase, encouraging *in vivo* properties in preclinical species. In a Phase Ib trial with HCV genotype 1-infected patients, **391** was considered to be safe and well tolerated and demonstrated potent antiviral activity.



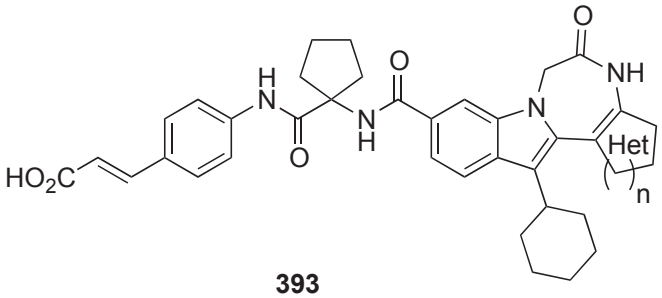
391

Figure 15

Structure-activity relationship (SAR) studies on a series of heteroaryl-fused tetracyclic indole-based inhibitors of the HCV NS5B polymerase were reported by Ding *et al*. A number of the derivatives were synthesized, and pyridine-fused analogues displayed excellent potency against both HCV 1a and HCV 1b genotypes, with (**392**: Het=Py; IC_{50}=30 nM; EC_{50}=9 nM, **393**: Het=Py; IC_{50}=24 nM; EC_{50}=12 nM) against 1b (Figure 16).[123]



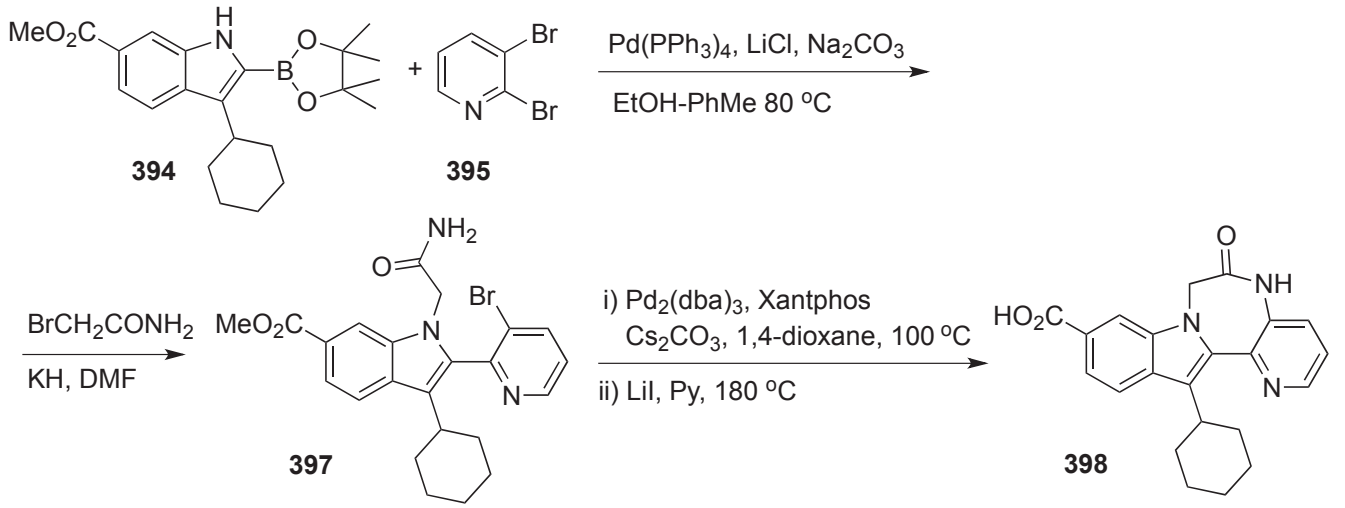
392



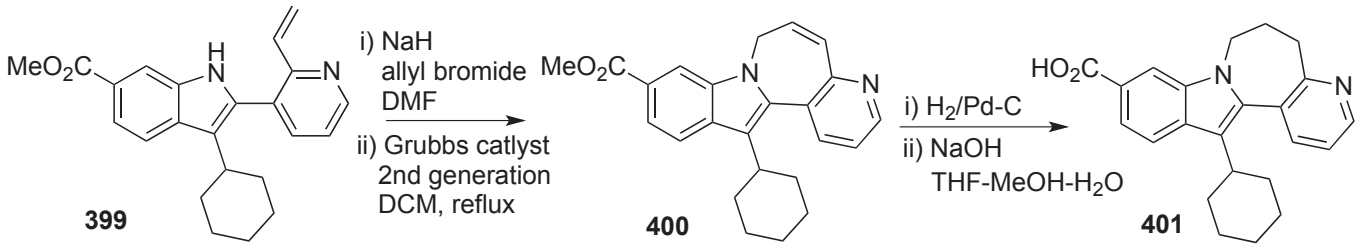
393

Figure 16

General synthetic approaches of a series of tetracyclic indole ring systems, heteroaryl-fused 6*H*-azepino[1,2-*a*]indoles and 4-oxo-1*H*-[1,4]diazepino[1,7-*a*]indoles, were investigated (Schemes 110 and 111).[124] Pyridino-fused systems (**397**) and (**401**) exhibited the activity against the HCV NS5B 1b genotypes (**397**: IC_{50}=0.28 μM; EC_{50}=1.8 μM, **401**: IC_{50}=0.45 μM; EC_{50}=0.52 μM).



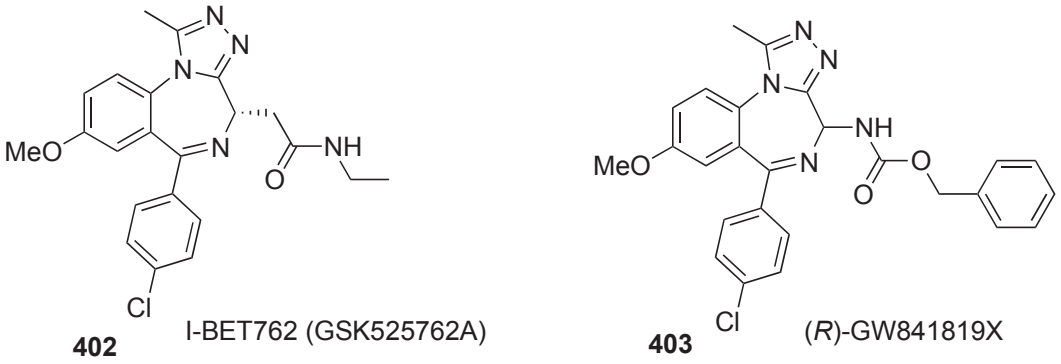
Scheme 110



Scheme 111

The 1,4-benzodiazepine scaffold has attracted attention in the field of epigenetics, with the discovery of a class of potent small molecule inhibitors of the interaction between Bromo and Extra-Terminal (BET) bromodomain proteins and their acetylated histone substrates. Rapid success has been achieved with the BET family of bromodomains, and a number of potent and selective probes has been reported. These compounds have enabled linking of the BET bromodomains with diseases, including cancer and inflammation, suggesting that bromodomains are druggable targets. Conway *et al*. reviewed the biology of the bromodomains and discussed the SAR for the existing small probes, including **402** and **403**, and so on.[125]

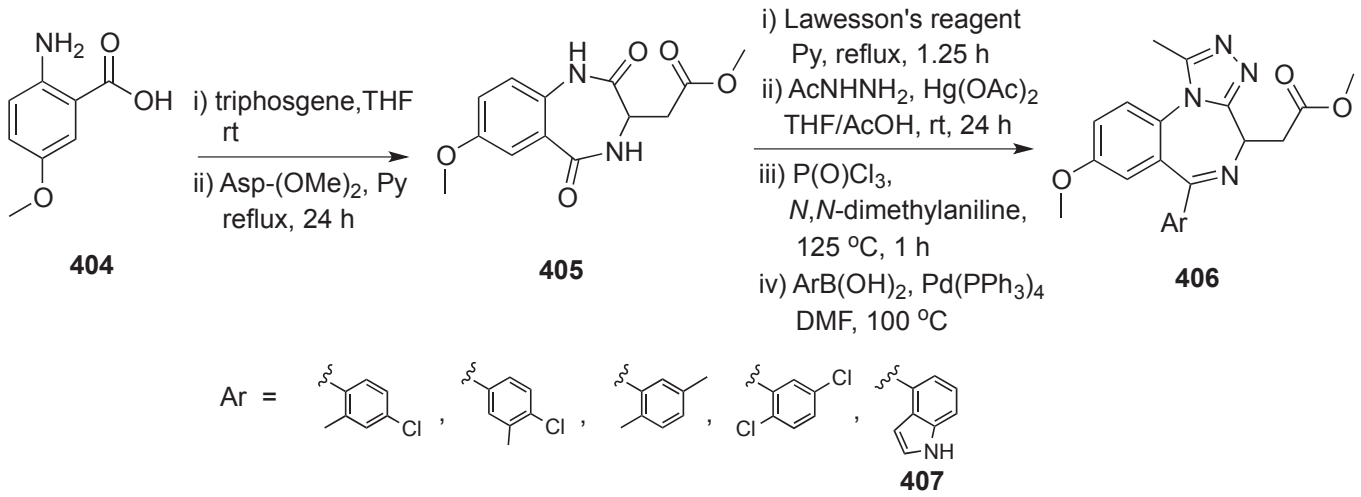
The optimized lead compound I-BET762 (**402**) is currently being evaluated in Phase I clinical trial for treatment of human cancer by Zhao *et al*.[126] Mirguet *et al*. investigated the discovery and SAR of potent benzodiazepine inhibitors that disrupt the function of the BET family of bromodomains (BRD2, BRD3, and BRD4). They evaluated I-BET762 (**402**) in a Phase I/II clinical trial for nuclear protein in testis (NUT) midline carcinoma and other cancers.[127]



402 **403**

Figure 17

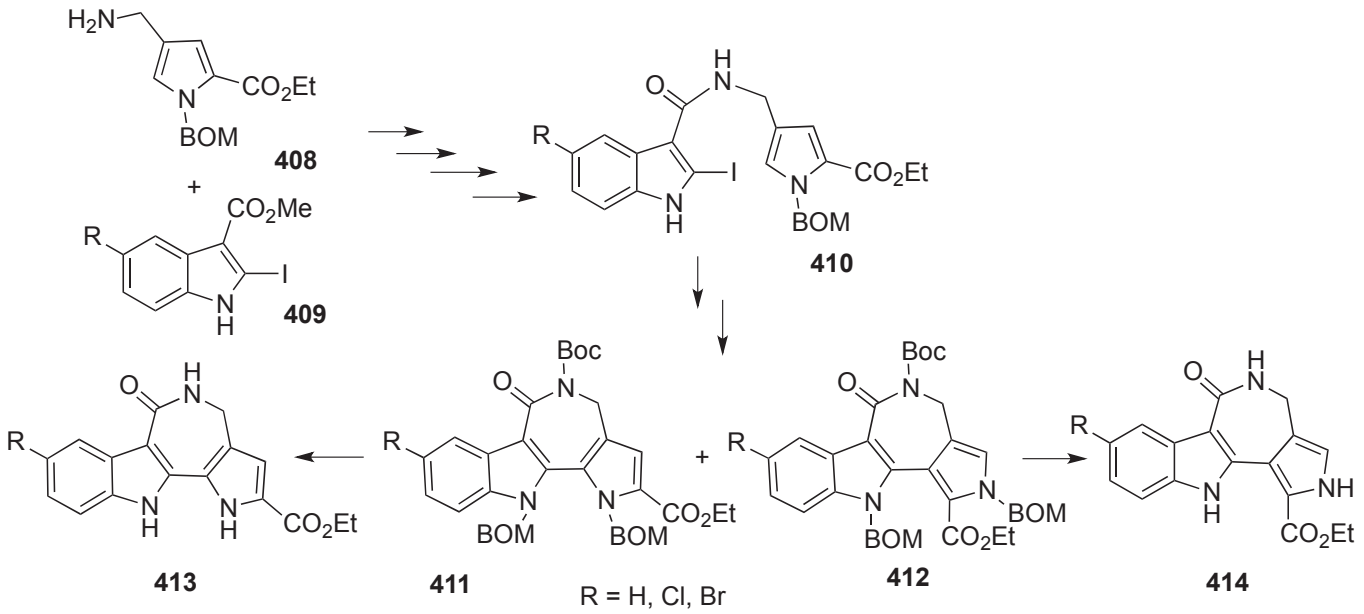
Ciulli *et al*. investigated new synthetic routes developed toward a range of substituted analogues of BET bromodomain inhibitors I-BET762/JQ1 based on the triazolo-benzodiaepine scaffold. Thus, they synthesized triazolo-benzodiazepines (**406**) from 2-amino-5-methoxybenzoic acid (**404**) (Scheme 112).[128] an indole analogue (**407**) was highly potent and displayed a marked BD2 selectivity profile by exploiting the asparatate/histidine substitution in the bromodomain BC loop.



404 **405** **406** **407**

Scheme 112

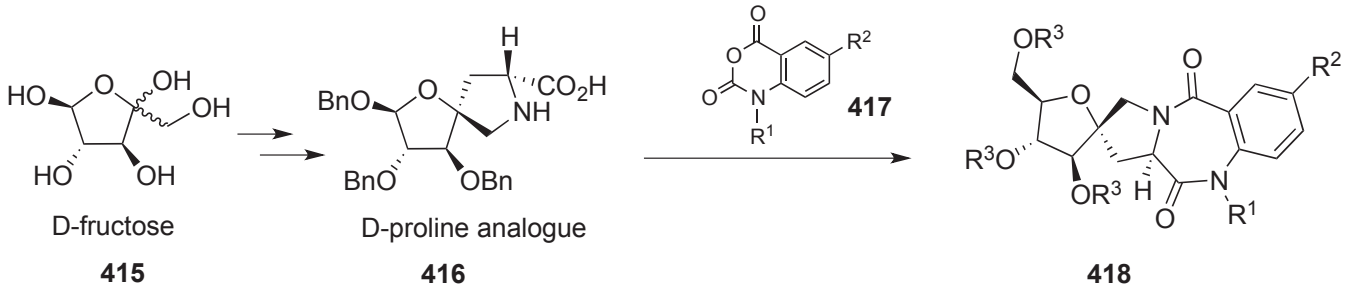
Fousters *et al*. synthesized 1*H*-pyrrole annulated indoloazepinone scaffolds (**413** and **414**), via sequential amide conjugation of appropriate indole (**409**) and pyrrole precursors (**408**) and intramolecular Heck coupling reaction (Scheme 113).[129] Obtained products displayed no significant antiproliferative activity against MCF-7 cancer cells. Compound (**414**: R=H) exhibited selective TAK1 kinase inhibitory activity.



Scheme 113

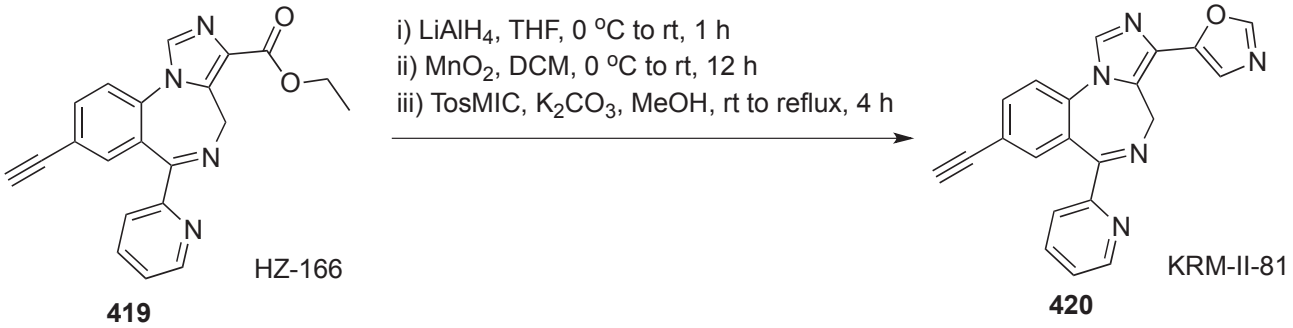
The gamma-amino butyric acid A ($GABA_A$) receptor is a heteropentameric chloride ion channel. The $GABA_A$ receptors ($GABA_AR$) are responsible for a myriad of brain functions. Positive allosteric modulators (PAMs) and negative allosteric modulators (NAMs) act on the benzodiazepine site of the $GABA_AR$ which can change the conformation of the receptor to inhibit or excite the neurons associate with the ion channel. Benzodiazepines, β-carbolines, and other class of readily target the $GABA_A$ receptors. Recently, Cook *et al*. reviewed about the updated pharmacophore the alpha 5 $GABA_A$ benzodiazepine receptor model.[2e]

Araujo *et al*. reported the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (**418**) derived from spiro bicyclic D- or L-proline analogues (**416**) containing a D- or L-fructose moiety (**415**) (Scheme 114).[130] Molecular modeling calculations and DNMR studies showed that **418** exhibit a rigid (*P*)- and (*M*)-helical conformation, respectively. The biological activity of the library is far from that of classical $GABA_A$ modulators.



Scheme 114

Schkeryantz *et al*. synthesized 1,3-oxazole KRM-II-81 (**420**) from HZ-166 (**419**) and characterized as $GABA_A$ receptor ligand (Scheme 115).[131] The oxazole (**420**) represents a unique and promising lead compound with attributes that include a desirable $\alpha2/\alpha3$-$GABA_AR$ selective profile, low molecular weight (MW=351), superb lipophilicity (clogP=2.3), good pH=7 solubility (by light scattering), excellent total exposure in plasma and brain, and favorable measured fraction unbound in plasma and brain (26% and 18%, respectively), leading to *in vivo* activity in preclinical rodent models of anxiety.



Scheme 115

Cook *et al*. synthesized and characterized some bioisosteric analogues of XHeII-053 as $GABA_A$ receptor ligand, and found that oxadiazole (**421**) was clearly $\alpha3$ benzazepine/GABAergic receptor subtype selective ligand at pharmacologically relevant dose (approximately 100 nM) and much more stable on human liver microsomes than HZ-166 (**419**) (Figure 18).[132] The ligand oxadiazole (**421**) has been evaluated in the light dark paradigm and clearly is an anxiolytic, wherein this ligand was anxiolytic with less sedative properties, *in vivo*, as compared to diazepam in this paradigm.

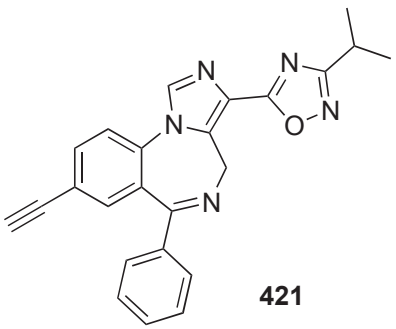
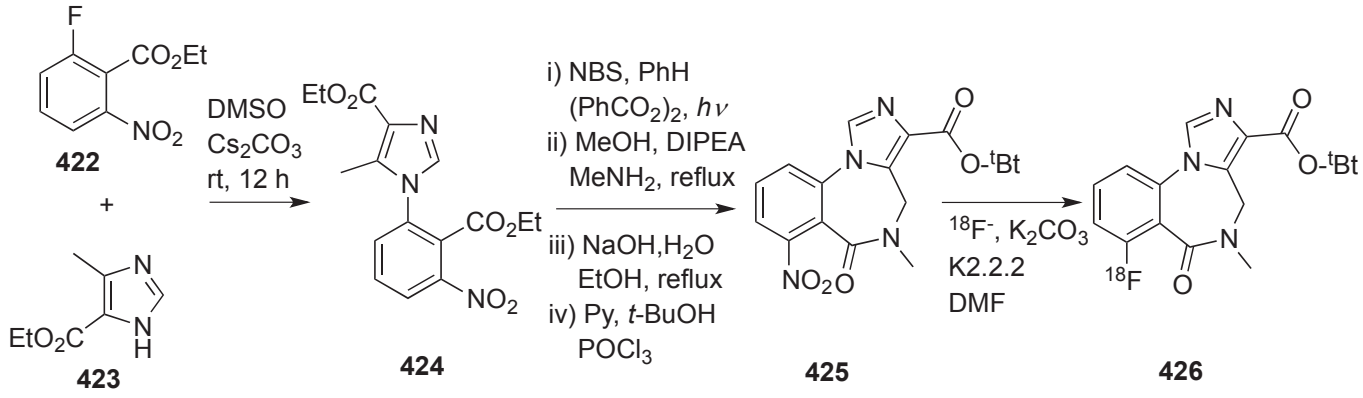


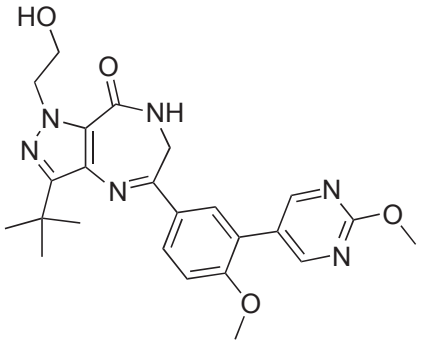
Figure 18

Jackson *et al*. made direct comparison between the currently known F-18 labelled $GAVA_A$ radio tracer and their synthesized novel imidazobenzodiazepine ligands, such as compound (**426**) (Scheme 116).[133] Eleven of the novel compounds, where **426** was contained, assessed suitable *in vivo* assessment as proton emission tomography (PET).



Scheme 116

In the investigation for the pursuit of potent selective bioavailable phosphodiesterase 2 (PDE2) inhibitors, Plummer *et al*. synthesized and evaluated the pyrazolodiazepinone PDE2 inhibitor (**427**) (Figure 18).[134] Compound (**427**) was >1000-fold selective for PDE2 over recombinant, full length PDEs 1B, 3A, 3B, 4A, 4B, 4C, 7A, 7B, 8A, 8B, 9, 10, and 11. Compound (**427**) also retained excellent PDE2 selectivity (241-fold to 419-fold) over the remaining recombinant, full length PDEs 1A, 4D, 5, and 6. Compound (**427**) demonstrated significant *in vivo* activity 1 and 3 h after a single dose in a rat model of osteoarthritis pain.



427

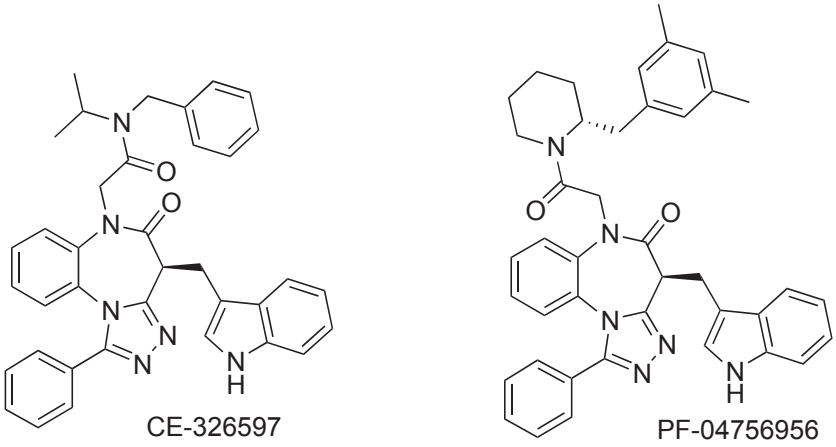
PDE2 IC_{50} = 3.3 nM
PDE4B IC_{50} = 562 nM
selectivity PDE4/PDE2 = 168
HLM $t_{1/2}$ (min) = 6.9

Figure 19

Cameron *et al*. reported the synthesis and SARs of triazolobenzobenzodiazepinone chlolecyctonkinin-1 receptor (CCK1R) antagonists. Their synthesized compound CE-326597 (**428**) (Figure 20) demonstrated sustained food intake efficacy in rodents with complete gallbladder refilling 24 h after dosing. PK studies with **428** to access intestinal systemic exposure suggested that efficiency is primarily derived from activation of the intestinal CCK1 receptors. Unfortunately, **428** demonstrated in sufficient efficacy for the treatment of either diabetes or obesity after 12 weeks of dosing in a Phase II clinical trial.[135]

Cameron *et al*. synthesized PF-04756956 (**429**) (Figure 20), which is a potent CCK1R agonist and demonstrated robust weight loss in a diet-induced obese rat model with systemic exposure.[136]

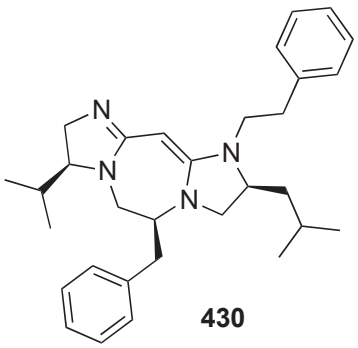
Miller *et al*. defined the mechanism of binding activity of two triazolobenzodiazepines, CE-326597 (**428**) and PF-04756956 (**429**). These ligands exhibited cooperativity with benzodiazepine binding across the CKK1R homodimeric complex, resulting in their ability to inhibit only a fraction of the saturable binding of a benzodiazepine radioligand, unlike other small molecular antagonist and agonist of this receptor.[137]



428 **429**

Figure 20

Diimidazole-fused diazepines (**430**) were synthesized from reduced tripeptides (Figure 21).[136] *In vitro* screening with radioligand competition binding assays demonstrated variable affinity for μ(MOR), δ(DOR), and κ(KOR) opioid receptors across the series, with the diimidazodiazepine (**430**) displaying good affinity for DOR and KOR. Central (icv), intraperitoneal (ip) or oral (po) administration of **430** produced dose-dependent, opioid-receptor mediated antinociception in the mouse. Only trace amounts of **430** was found in brain up to 50 min later, suggesting poor BBB penetration and possible peripherally activity. Central administration did not produce locomotor effects. These diazahetrocyclic mixed activity opioid receptor agonists may hold potential as new analgesics with fewer labilities of use.



430

in vitro	*in vivo*
μ=KI: 721 nM κ=KI: 23 nM δ: KI=32 nM	-ED_{50}=5.09 mg/kg, i.p. (tail withdrawat test) -ED_{50}=0.07 mg/kg, i.p. (acetic acid writhing assay)

Figure 21

CONCLUSION

In the recent studies about azaazulenes, pyrrolobenzazepines (PBDs), azepinoindole-derivatives, and so on, some new synthetic methods were evolved, and a lot of novel compounds having various patterns of the azaazulene, pyrorobenzazepine, and their analogous skeletons were produced. In addition, their biological activities and pharmaceutical pursuits are prominent. I wish that the investigations of these region develop and go far towards the evolvement of medicinal researches.

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