Review

Advances in synthesis of novel annulated azecines and their unique pharmacological properties

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Abstract: Annulated azecines, mostly partially saturated benzo[*d*]azecine and dibenzo[*c,g*]azecine fusion isomers, constitute a unique class of alkaloids and nature-inspired azaheterocyclic compounds with interesting reactivity, physicochemical and biological properties. Due to difficulties associated with the synthesis of the benzazecine (or bioisosteric) scaffold they are not the focus of organic and medicinal chemists' consideration, whereas it is worth noting the range of their pharmacological activities and their potential application in medicinal chemistry. Herein, we reviewed the synthetic methodologies of arene-fused azecine derivatives known up to date and reported about the progress in disclosing their potential in drug discovery. Indeed, their conformational restriction or liberation drives their selectivity towards diverse biological targets, making them versatile scaffolds for developing drugs, including antipsychotic and anticancer drugs, but also small molecules with potential for anti-neurodegenerative treatments, as the recent literature shows.

Keywords: Benzazecines; aza-Claisen rearrangement; ring-closing metathesis reactions; antipsychotic agents; dopaminergic receptors ligands; anticancer agents.

1. Introduction

Medium-sized azaheterocycles, such as azocines, azonines, azecines and azacycloundecines, are core structures in alkaloids, exhibiting a wide range of bioactivities. In particular, *N*-containing 10-membered cyclic ketone is the core structure alkaloid families of *berberidaceae*, *papaveraceae*, *fumariaceae*, *rutaceae*, *ranunculaceae* and *celandine*, whose representative molecules are cryptopine, muramine, allocryptopine, and protopine (Fig. 1), all being derivatives of 5,6,7,8,13,14-hexahydrodibenzo[*c,g*]azecine.

Protopine and related alkaloids showed diverse pharmacological properties, including inhibition of blood platelet aggregation in rabbit and inhibition of calcium channel influx voltage- and receptor-operated. These compounds

endow antihistaminic, anti-thrombotic, and anti-inflammatory activities [1]. More recently, protopine and cryptopine showed antioxidant activity [2], while muramine inhibited neuroexcitability at low micromolar concentrations, thus gaining potential as anti-epileptic and analgesic agents [3]. Muramine is found in some leafy vegetables and is also used for medicinal purposes.

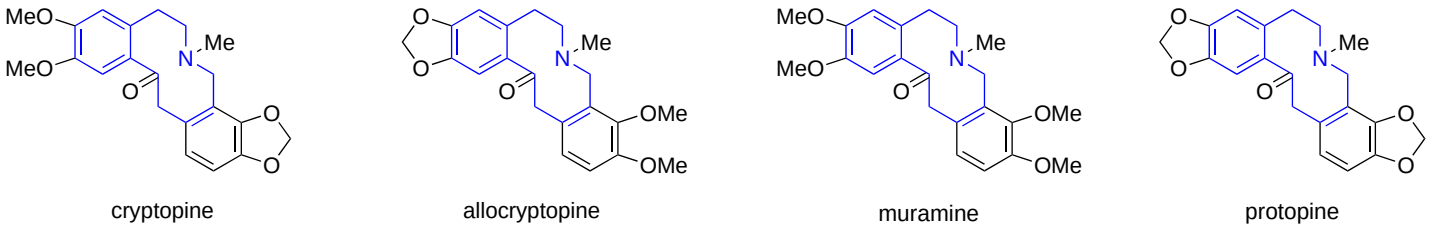


Figure 1. Alkaloids incorporating partially saturated dibenzo[*c*,*g*]azecine.

Some plants use suitable enzymatic systems for the biosynthesis of the benzazecine-containing alkaloids. In the case of *Papaver somniferum*, i.e., the source for the narcotic analgesics morphine and codeine, protopine alkaloids are formed via the 14-hydroxylation of quaternary protoberberine alkaloids, which leads to C–N bond cleavage and formation of a C14 keto moiety. The 14-hydroxylation is catalyzed by (*S*)-*cis*-*N*-methylstylopine 14-hydroxylase (MSH), a member of the CYP82N subfamily, that accepts different quaternary protoberberines (Fig. 2). The allocryptopine, cryptopine and protopine are formed from canadine, sinactine and stylopine, respectively [4].

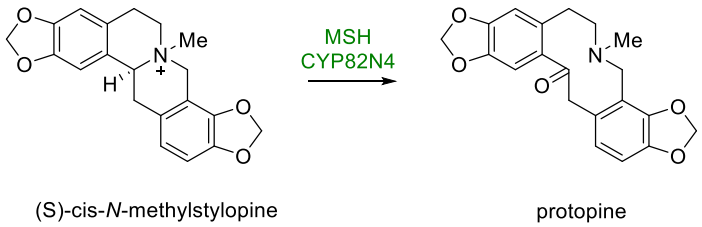


Figure 2. *Papaver somniferum* uses CYP82N4 for the biosynthesis of protopine.

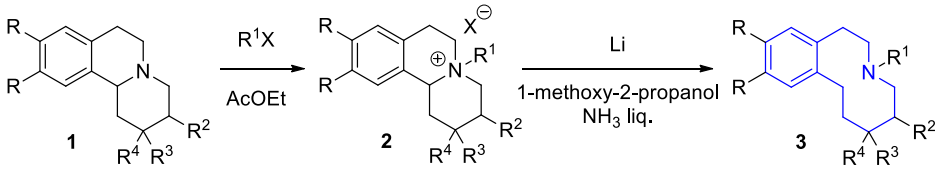
The interest toward this bioactive fused ten-membered azaheterocycle prompted us to systematically review methods for synthesizing the benzazecine moieties, in its different isomeric forms and degrees of saturation, and to explore their application in medicinal chemistry. Herein, we collected protocols for the construction of the benzazecine cycle, highlighting the achievements in (i) C-N and C-C bridging bond cleavage in the corresponding quinolizines and isoquinolizines, (ii) different rearrangements, including the aza-Claisen one and its propargyl evolution, (iii) formation of 10-membered azacycle through cyclization, including ring-closing metathesis. Aiming at investigating the usefulness of the benzazecine moiety in drug design and development, progresses in the knowledge of bioactivity, mechanism of action, pharmacophore and structure–activity relationships (SARs) of its derivatives were examined as thoroughly as

possible in the post-2010 literature, with a special focus on their potential in complex diseases, such as neurologic disorders and cancer.

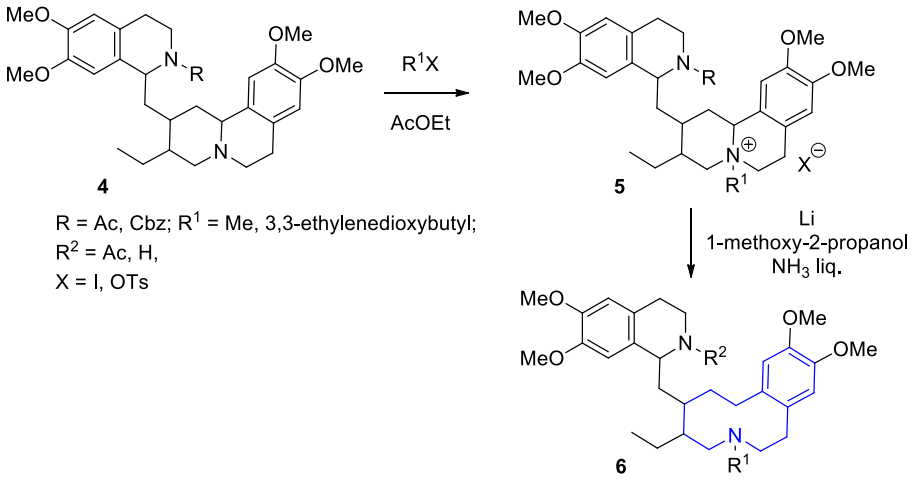
2. Achievements in organic synthesis

2.1. Cleavage of the bridging C-N and C-C bonds

Historically the cleavage of the C-N bridging bond in corresponding compounds was the first and the most reasonable method for the construction of benzazecines. Thus, in late 60s in series of papers devoted to the synthesis of amebicidal active compounds, the Smith's group optimized a new general method for converting benzoquinolizines into benzazecines [5,6]. The protocol included quaternization of the corresponding benzoquinolizines **1** with methyl iodide or 3,3-ethylenedioxy-1-*p*-toluenesulfonate followed by the reduction of the resulting salts **2** with lithium and 1-methoxy-2-propanol in liquid ammonia. The reduction led to the scission of the bridgehead C-N bond providing target 1,2,3,4,5,6,7,8-octahydrobenzo[*d*]azecines **3** in moderate to high yields (Scheme 1). The method turned to be effective for obtaining 1',2'-secoemetine derivatives **4** and showed tolerance of *N*-acetyl group in the reaction conditions.



R = H, OMe; R^1 = Me, 3,3-ethylenedioxybutyl; R^2 = H; iso-butyl; R^3 = R^4 = O, R^3 = H, R^4 = OH
X = I, OTs

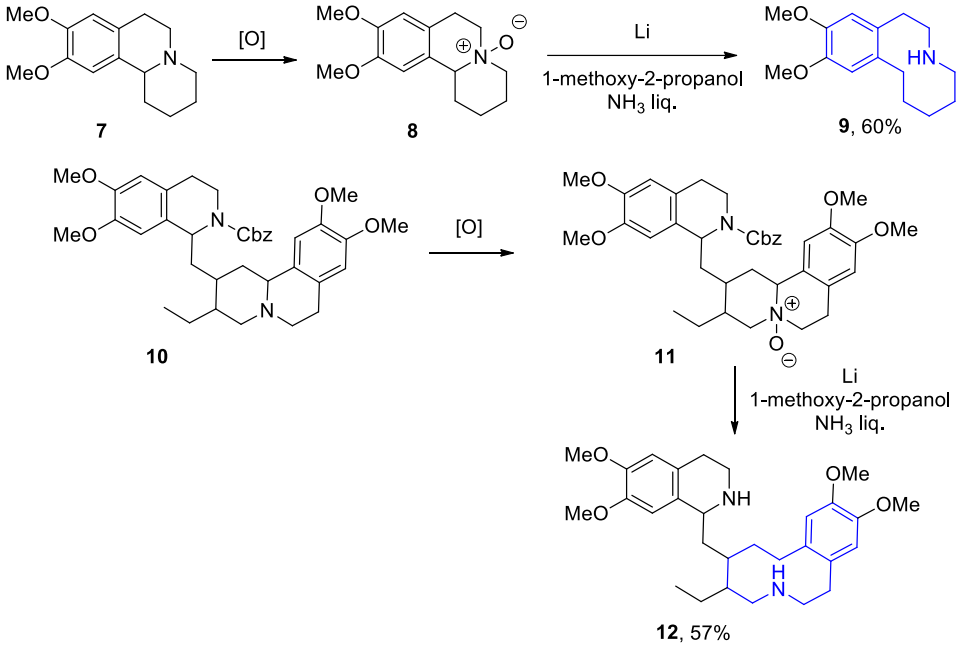


R = Ac, Cbz; R^1 = Me, 3,3-ethylenedioxybutyl;
R^2 = Ac, H,
X = I, OTs

Scheme 1. Synthesis of 1,2,3,4,5,6,7,8-octahydrobenzo[*d*]azecine derivatives **3** and **6** through cleavage of the bridging C-N bond in quaternary ammonium salts **2** and **5**.

Later in 1973, Yardley extended the method and revealed that amine oxides **8**, derived from oxidation of the corresponding tertiary amines **7** with monoperphthalic or *m*-chloroperbenzoic acid (*m*-CPBA), were readily cleaved to

secondary amines **9** through reduction using Li in liquid NH_3 containing 1-methoxy-2-pronanol [7]. The reduction of *N*-oxides to amines proceeds via hydroxylamine intermediate (Scheme 2).

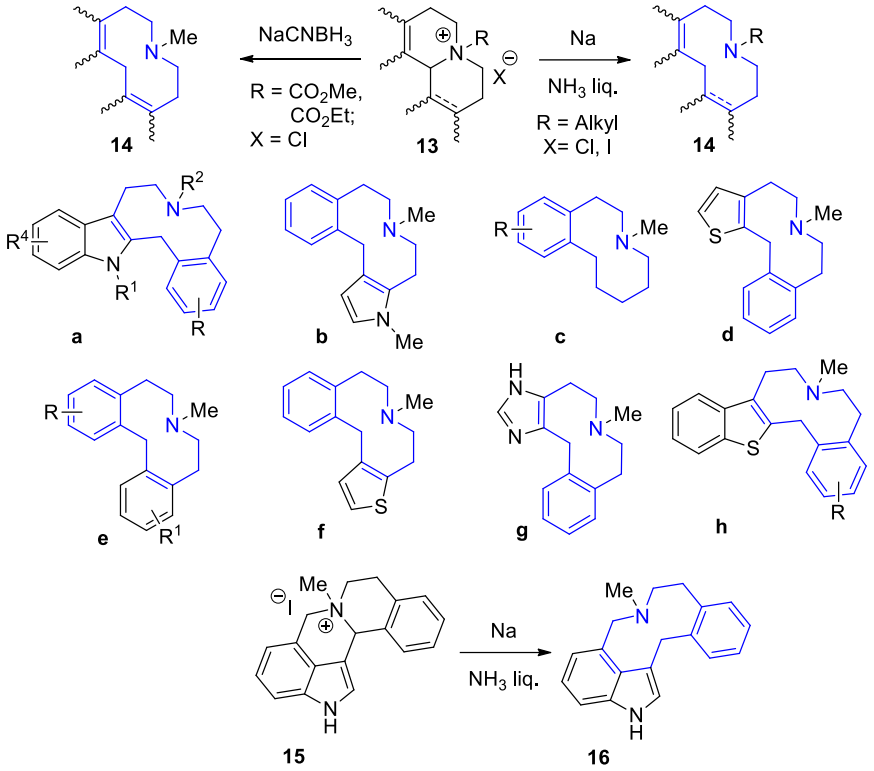


Scheme 2. Cleavage of the bridging C-N bond in tertiary *N*-oxides **11** leading to the benzo[*d*]azecine product **12**.

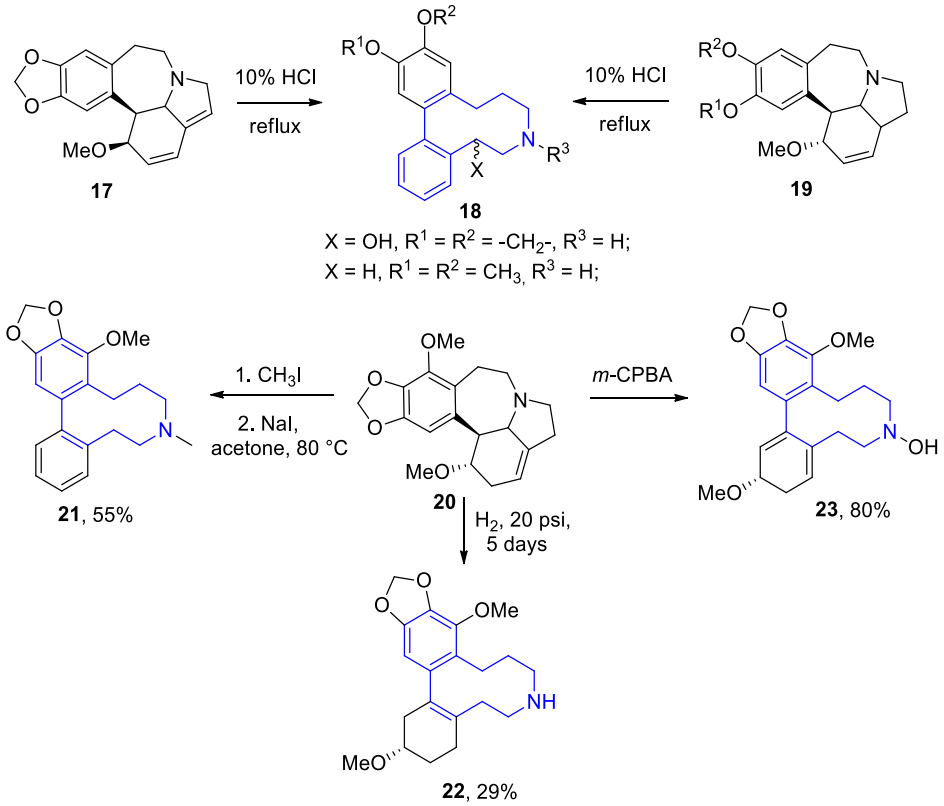
In their research the Lehmann's group also successfully carried out the cleavage of C-N bridging bond via reduction of corresponding quinolizinium salts **13** and skillfully applied it to the synthesis of variously annulated benzo[*d*]azecines **14a-h** (Scheme 3) which exhibited bioactivities, mainly as dopamine antagonists [8-18]. The starting quinolizines were quaternized with alkyl iodide in acetone, followed by the reductive cleavage with Na in liquid ammonia. In some cases, the cleavage of the C-N bond was also achieved through the quaternization with chloroformate esters and subsequent reduction with $NaCNBH_3$ [14, 18] (Scheme 3).

Azepine fragment was also used in the cleavage processes. Thus, demethylation of schellhammeridine **17** by reflux in 10% HCl led not only the expected allyl alcohol but also gave dibenzo[*d,f*]azecine **18** in 13% yield [19]. Under the same conditions comosidine **19** produced dibenzazecine as well as a mixture of alcohols [20]. Dyshomoerythrine **20** was converted to dibenzazecines **21**-**23** by different methods, i.e., via formation of quaternary salt and the subsequent cleavage with sodium iodide and by hydrogenation and under the action of *m*-CPBA [21] (Scheme 4).

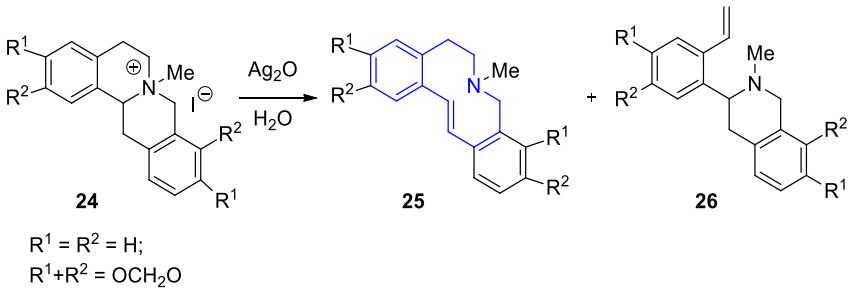
The Hofmann degradation was also employed for the synthesis of benzazecines. The treatment of tetrahydroprotoberberine methyl-iodide **24** with moist silver oxide led to the formation of dibenzo[*c,g*]azecine **25** as a minor product in a low yield of 2% [22]. Later Hofmann degradation applied to stylopine methyl-iodide **24** resulted into the target product **25** in 36% yield [23]. In the same paper cleavage of C-N bond in quaternary salt was accomplished by the action of sodium hydride in DMSO, the yield of azacycle was 70% (Scheme 5).



Scheme 3. Cleavage of the bridging C-N bond in quinolizinium salts **13** and **15** to prepare various benzo[*d*]azecine fused with other arenes (**14a-h** and **16**).

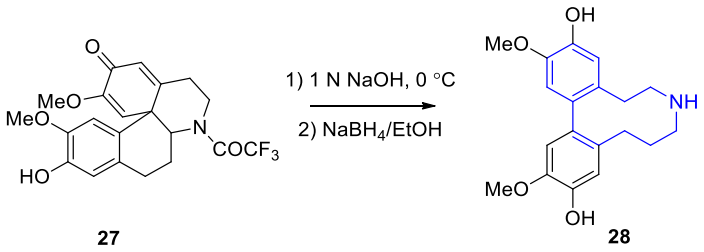


Scheme 4. Cleavage of the bridging C-N bond in pyrroloazepine fragments in **17**, **19** and **20** to achieve the preparation of 5,6,7,8,9,10-hexahydrodibenzo[*d*,*f*]azecines **21**, **22** and **23**.



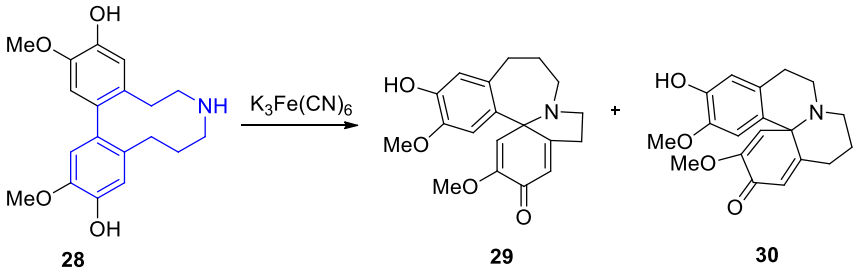
Scheme 5. Cleavage of the bridging C-N bond in quinolizinium methiodides **25**.

The fragmentation process accompanying the formation of the dibenzo[*d,f*]azecine product **28** was observed in the case of prohomoerythrinadienone derivative **27** [24, 25]. The rearrangement in 1N NaOH at 0 °C in MeOH and then the reduction with $NaBH_4$ afforded the target compound **28** in good yields (Scheme 6).



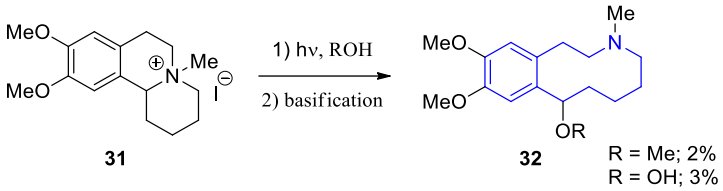
Scheme 6. Cleavage of the bridging C-C bond in quinoline fragment in **27**.

Oxidation of the dibenzo[*d,f*]azecine **28** with $K_3Fe(CN)_6$ in methylene chloride – sodium bicarbonate solution led to a reaction mixture from which dienone (**29**) and homoerysodienone (**30**) were isolated in 45% and 15% yield, respectively [24] (Scheme 7).



Scheme 7. Oxidative transformation of dibenzazecine **28**.

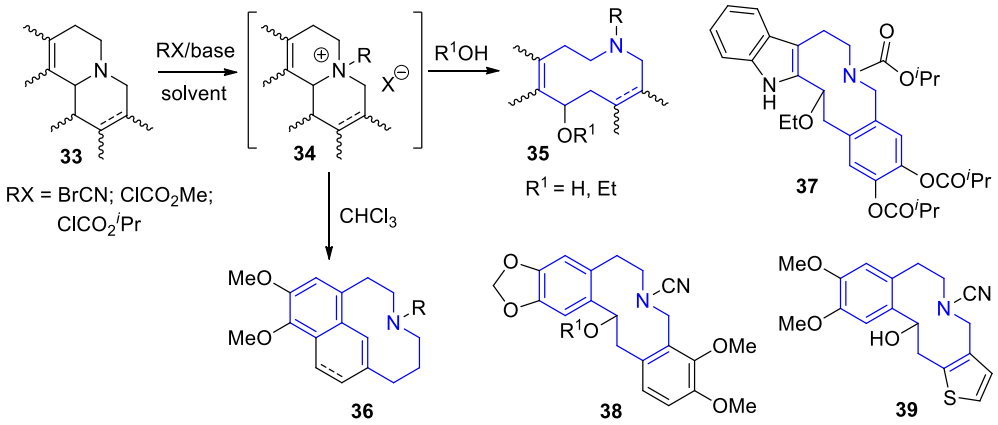
Another version of C-N bridging bond scission in benzo[*a*]quinolizinium salts **31** was described by Bremner [26]. Ultraviolet radiation of the latter in MeOH or acidified water led to the benzo[*d*]azecine derivatives **32** but again in very low yields (2-3%), (Scheme 8).



31 **32**

Scheme 8. Cleavage of the bridging C-N bond in benzoquinolizinium salt **31**.

A number of differently annulated benzazecines **35**-**39** were synthesized by cyanogen bromide or chloroformate esters inducing rupture of C-N bond in corresponding quinolizines derivatives **33** [27-32]. The yields of the transformation were up to 94%. Depending on the solvent, the intermediate quaternary salt **34** underwent nucleophilic substitution leading to solvolysis products or base-induced elimination, affording new double bond in the products (Scheme 9).



33 **34** **35** **37**

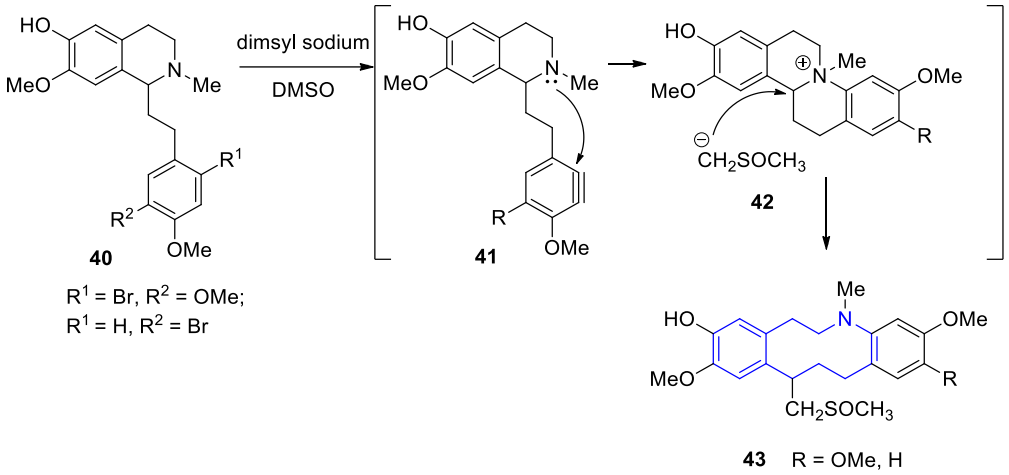
RX = BrCN; $ClCO_2Me$; $ClCO_2{}^iPr$

R^1 = H, Et

36 **38** **39**

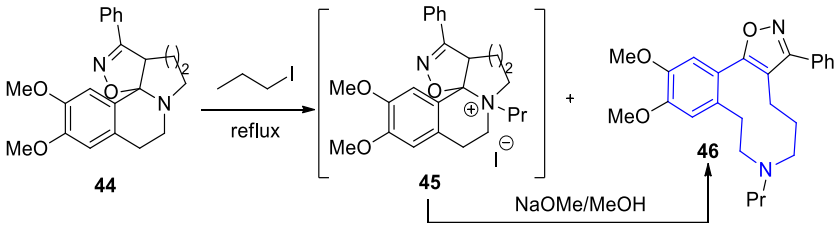
Scheme 9. Cleavage of the bridging C-N bond using cyanogen bromide or chloroformate esters and nucleophiles.

The Kano's group [33, 34] proposed an interesting and elegant solution for furnishing the dibenzo[*b,g*]azecines **43** from 1-halogenephenylethylisoquinolines **40**. When treated with dimesyl sodium **40** generated benzyne intermediate **41** which triggered Michael addition of tertiary amine followed by nucleophilic attack of methylsulfinyl carbanion on the bridged carbon atom in the formed quinolizium salt **42**, the final cleavage of the C-N bond providing azecine cycle **43** (Scheme 10). Later the method was extended to 1-halogenobenzylbenzazepines [35, 36].



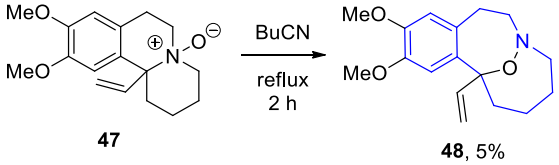
Scheme 10. Cleavage of the bridging C-N bond in quinolizinium salts using methylsulfinyl carbanion as nucleophile.

Fission of C-N bridging bond leading to the formation of benzazecine moiety was also observed in the case of isoxazolo[6',5':3,4]pyrido[2,l-*a*]isoquinoline **44** [37]. Simple heating of the latter with 1-propyl iodide at reflux led to a reaction mixture with benzo[*d*]isoxazolo[5,4-*f*]azecine **46** as a primary component. Subsequent treatment of the resulting mixture with NaOMe/MeOH at 25°C converted the quaternary salt **45** into the target heterocycle **46**. The overall yield of benzazecine **46** was 47% (Scheme 11).



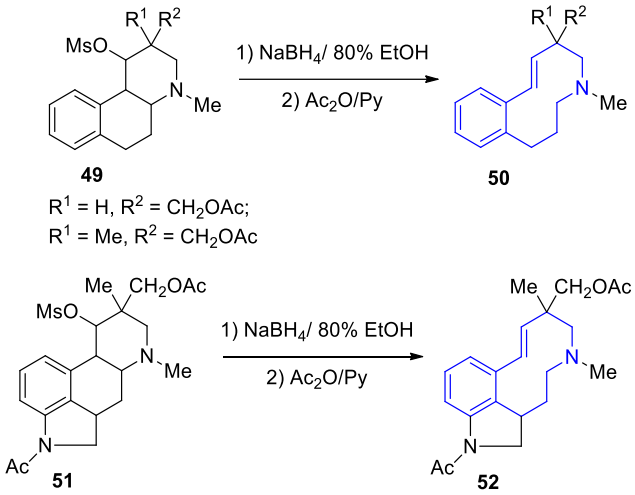
Scheme 11. Cleavage of the bridging C-N bond in quinolizinium salts **45** using NaOMe/MeOH.

The attempt to conduct Meisenheimer rearrangement for 11b-vinylbenzoquinolizine *N*-oxide **47** in boiling dry butyronitrile provided the target benzo[*d*]azecine **48** in just 5% yield [38] (Scheme 12).



Scheme 12. Cleavage of the bridging C-N bond via the transformation of quinolizine *N*-oxide **47**.

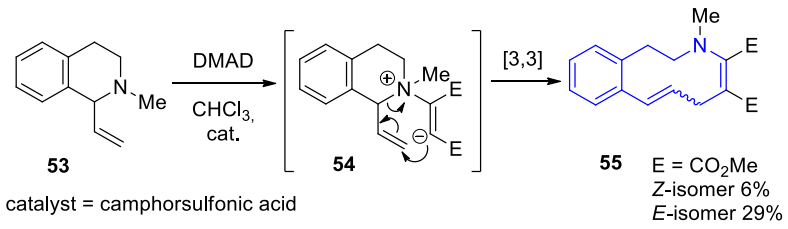
When developing a total synthesis towards the ergot alkaloids (±)-chanoclavine-I and (±)-isochanoclavine-I, Ninomiya and co-workers observed the cleavage of the C-C bridging bond in octahydrobenzo[*f*]quinolines **49** and **51** to afford the benzo[*f*]azecines **50** and **52** [39]. The starting octahydrobenzo[*f*]quinolines **49** and **51** were treated with $NaBH_4$ in 80% EtOH, the subsequent reacetylation of the crude product led to the formation of benzo[*e*]azecines **50** and **52** in moderate yields. The reaction conditions were found to be suitable for the ring-opening in ergoline derivative affording the target compound in 59% yield (Scheme 13).



Scheme 13. Cleavage of the bridging C-C bond in quinolone fragments in **49** and **51** to achieve the preparation of the benzo[*e*]azecine derivatives **50** and **52**, respectively.

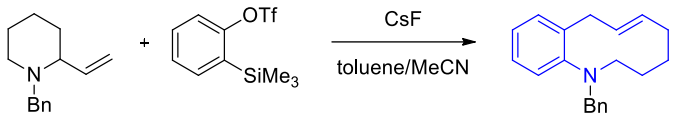
2.2. Aza-Claisen rearrangement

Inspired by a new technique of ring expansion of cyclic allylic amines by four atoms, previously suggested by Vedejs [40], Vernon and co-workers demonstrated that the same principle, based on Michael addition/aza-Claisen rearrangement sequence, could be applied to 1-vinyl substituted tetrahydroisoquinoline **53** [41]. Thus, the interaction of **53** with dimethylactylenedicarboxylate (DMAD) in freshly distilled chloroform in the presence of a catalytic amount of camphorsulfonic acid led to the formation of 1,2,3,6-tetrahydrobenzo[*d*]azecine diesters **55** in 6% (*Z*-isomer) and 29% (*E*-isomer) yields (Scheme 14).



Scheme 14. Synthesis of 1,2,3,6-tetrahydrobenzo[*d*]azecine **55** from 1-vinyl-1,2,3,4-tetrahydroisoquinoline **53**.

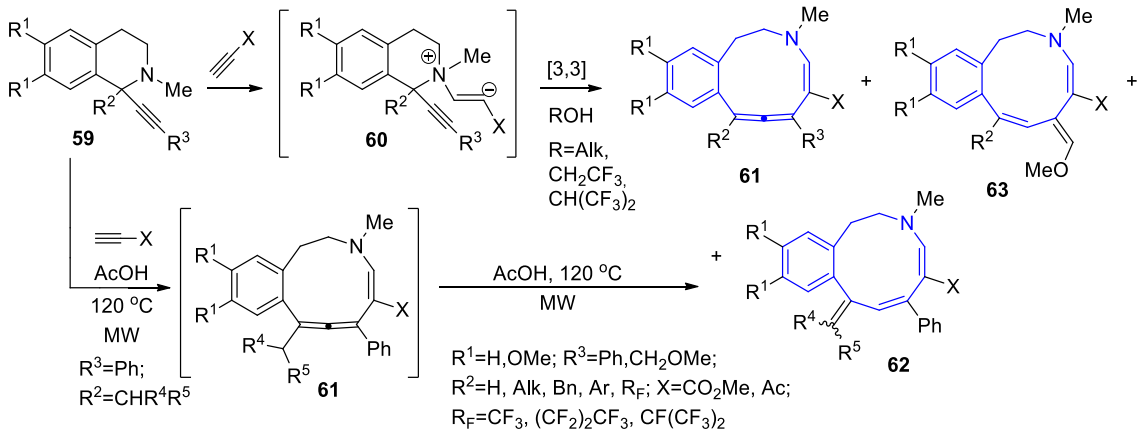
Later the above-mentioned method was extended by an interesting version of charge-accelerated aza-Claisen reaction [42]. It was demonstrated that in the reaction with cyclic amines, instead of stable alkynes, *in situ* generated benzynes could be used. The modified method afforded (*E*)-1-benzyl-1,2,3,4,5,8-hexahydrobenzo[*b*]azecine **58** in 28% yield through the reaction of 2-vinyl *N*-benzylpiperidine **56** with benzyne precursor **57** (Scheme 15).



Scheme 15. Synthesis of the benzo[*b*]azecine derivative **58** from 2-vinylpiperidine **56**.

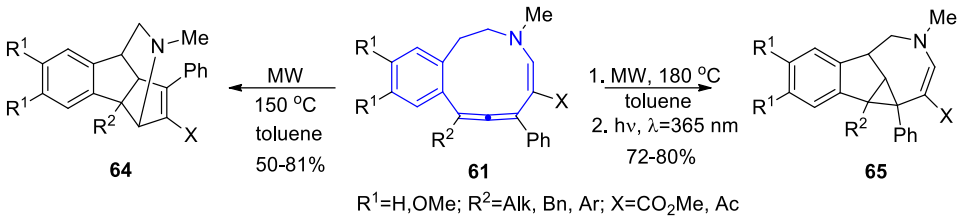
2.3. *N*-propargyl aza-Claisen rearrangement

A further development of the aza-Claisen rearrangement in the synthesis of more planar and rigid benzazecines was applied in Michael addition/*N*-propargyl aza-Claisen rearrangement cascade which was realized in reactions of 1-alkynyl substituted 1,2,3,4-tetrahydroisoquinolines **59** with terminal electron-deficient alkynes in fluorinated alcohols [43-46] (Scheme 16). This approach deserves a special attention as benzazecines **61** synthesized by this methodology possess unique allene moiety and proved to be promising for studying their chemical properties and biological activities [46-48]. Thus, by varying the reaction conditions (solvents, especially) or substituents in the reactants, the process could be directed to the formation of 8-ylidene decorated benzo[*d*]azecines **62** [49] and 6-methoxymethylylidene analogues **63** [50] (Scheme 16). It was also demonstrated that these compounds could be obtained straight from allene substituted benzazecines **61**.



Scheme 16. Synthesis of benzo[*d*]azecines from 1-alkynyl-1,2,3,4-tetrahydroisoquinolines **59** and electron-deficient alkynes.

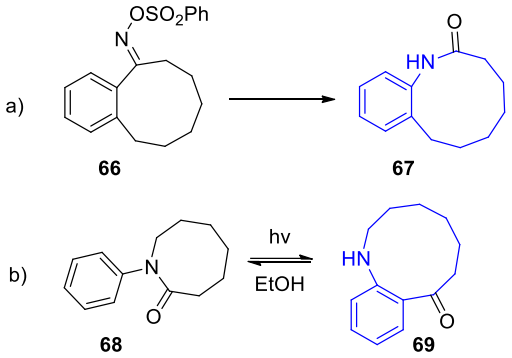
Benzazecines bearing allene fragment **61** turned out to be rather reactive heterocyclic compounds that made possible to study their thermal transformation [51] (Scheme 17) and other properties of the target products **64** and **65** [52, 53] in the reactions, as well as compare and evaluate their inhibition activity against human acetyl- and butyrylcholinesterase (*h*AChE, *h*BChE) [53, 54].



Scheme 17. Thermal transformations of allene benzo[*d*]azecines **61**.

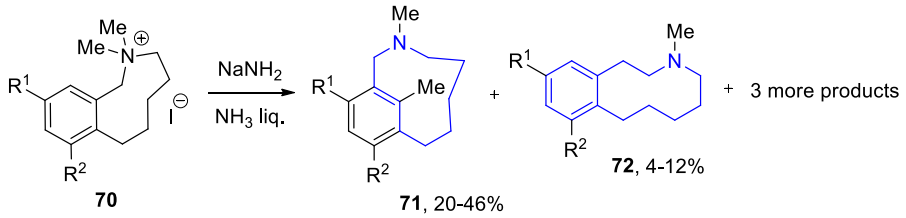
2.4. Other rearrangements

Other rearrangements towards the synthesis of diversely annulated benzazecines have been explored. Thus, the Beckmann rearrangement of the benzenesulphonate of 1-benzocyclononenone oxime **66** led to the formation of octahydro-1-benzazecin-2-one **67** [55-57] (Scheme 18a). Octahydro-1-benzazecin-8-one **69** was prepared through irradiation-assisted rearrangement of 1-phenylazocan-2-one **68** in 83% yield [58, 59] (Scheme 18b).



Scheme 18. Bekmann rearrangement and synthesis of benzazecinones **67** and **69**.

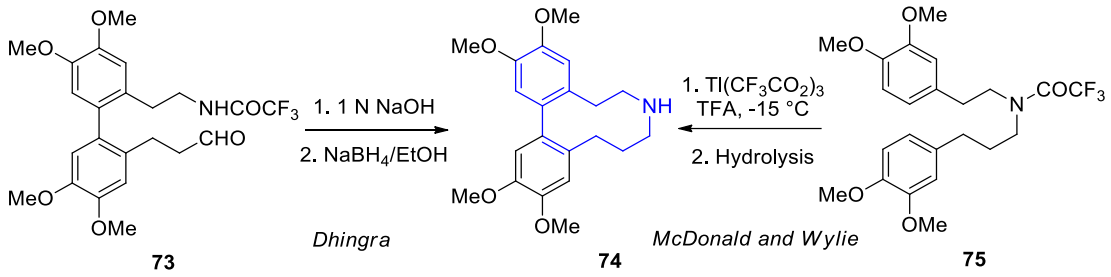
Two types of benzazecines were obtained from hexahydro-2-benzazoninium iodides **70** via the Sommelet-Hauser and the Stevens rearrangements [60]. The starting methiodides **70** were treated with sodium amides in liquid ammonia leading to complex reaction mixtures from which benzo[*c*]azecines **71** were isolated in 20-46% yield and benzo[*d*]azecines **72** in 4-12% yields, respectively (Scheme 19).



Scheme 19. Synthesis of benzazecines through rearrangements of benzazoninium salts **70**.

2.5. Cyclization

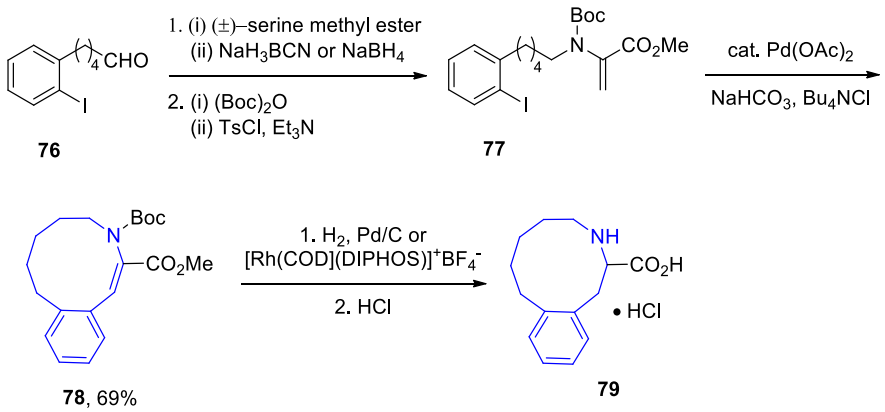
One example of cyclization of aldehyde-amide leading to 5,6,7,8,9,10-hexahydrodibenzo[*d,f*]azecine **74** was described by Dhingra and co-workers [25]. Cyclization of the starting compound **73** under the action of methanolic sodium hydroxide proceeded smoothly to generate intermediate imine which was reduced by $NaBH_4$ to give final compound **74** (Scheme 20).



Scheme 20. Synthesis of hexahydrodibenzo[*d,f*]azecine **74** from the noncyclic aldehyde-amide.

McDonald and Wylie suggested the ring closure based on oxidative coupling of phenolic ether **75** [61], which treated with $Tl(CF_3COO)_3$-TFA at -15 °C provided the formation of **74** (60% yield); the hydrolysis of **74** afforded the free base (Scheme 20).

In 2002, Gibson and co-workers designed and developed the route to the synthesis of the conformationally constrained analogues of phenylalanine, including the new ten-membered ring analogue **79**, called Xic [62]. The route presented a sequence of reactions in which the key step for the construction of the ring was the Heck cyclization. Reductive amination of starting aldehyde **76** with (±)-serine methyl ester followed by Boc protection and introduction of a C=C double bond using TsCl provided the Heck substrate **77**. Cyclization of the latter with $Pd(OAc)_2$ resulted in the formation of 3-(*tert*-butyl) 2-methyl (*Z*)-5,6,7,8-tetrahydrobenzo[*d*]azecine-2,3(4*H*)-dicarboxylate **78**. The subsequent hydrogenation and hydrolysis of compound led to target Xic **79** (Scheme 21).



76 **77** **78**, 69% **79**

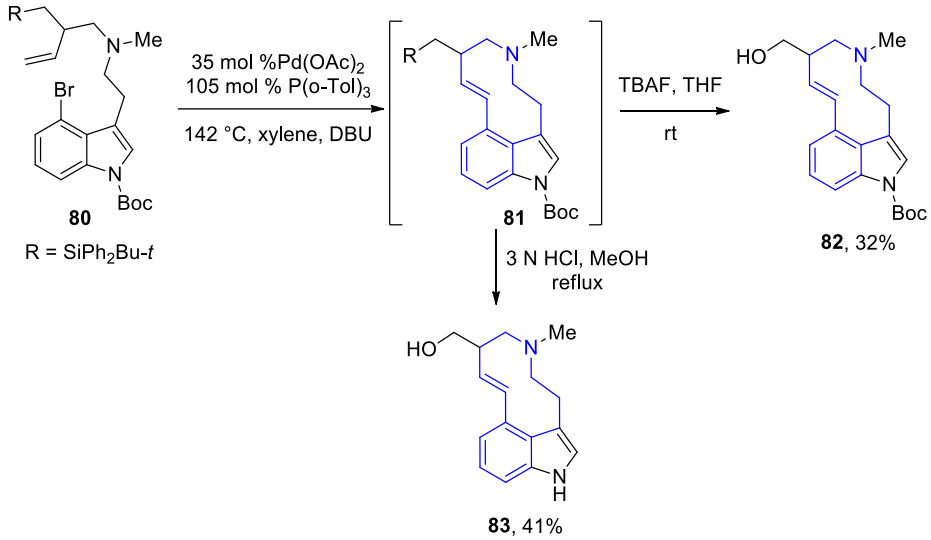
254

Scheme 21. Synthesis of benzazecine **78** through the intramolecular Heck cyclization reaction. 255

256

In 2003, Kalinin et al. also demonstrated the possibility of constructing a benzazecine moiety via the intramolecular Heck cyclization [63]. The Heck reaction of indole **80** using $Pd(OAc)_2$, P(*o*-Tol)$_3$, DBU in xylene at 142 °C provided a mixture of isomers where trans-10-membered compound **81** was a major product. Deprotection with HCl or TBAF provided the target compounds **82** and **83** in 32 % and 41 % yields, respectively (Scheme 22). 257 258 259 260

261



80 **81** **82**, 32% **83**, 41%

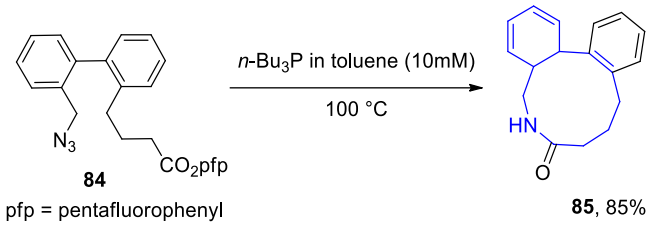
262

Scheme 22. Synthesis of benzazecines through the intramolecular Heck cyclization reaction. 263

264

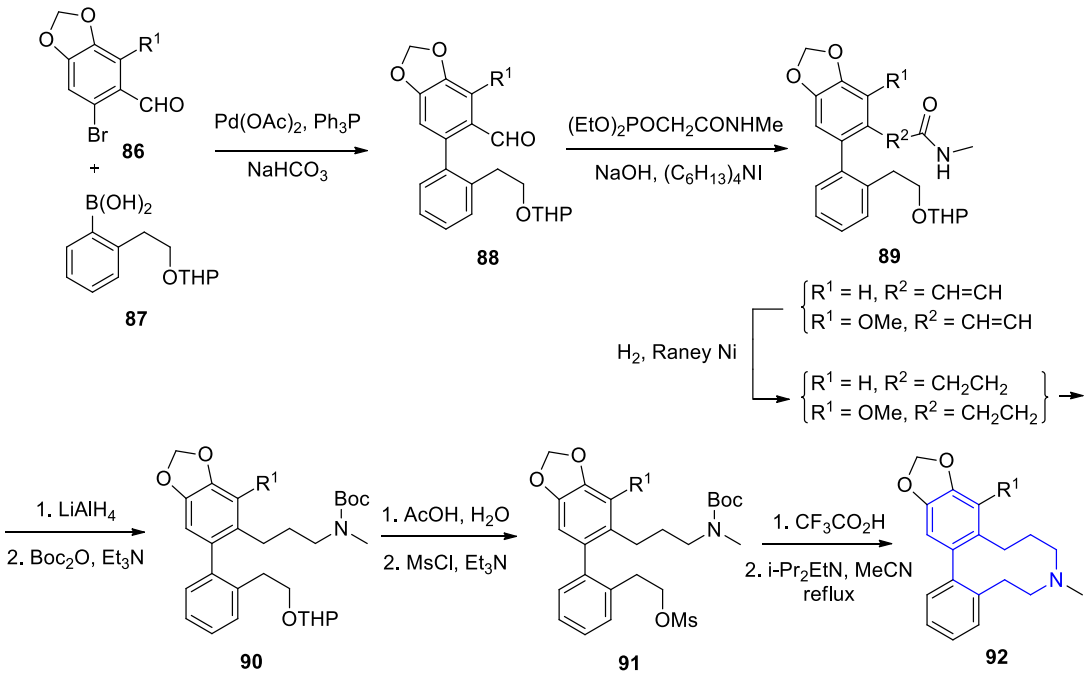
An intramolecular Staudinger–aza-Wittig reaction of ω-azido pentafluorophenyl ester **84** was successfully applied for the synthesis of dibenzo[*c,e*]azecine **85** [64]. The reaction proceeded under high-dilution conditions at elevated temperature with the use of *n*-Bu_3P as a reagent (Scheme 23). 265 266 267

268



Scheme 23. Synthesis of dibenzo[*c,e*]azecine **85** via the intramolecular Staudinger–aza-Wittig reaction.

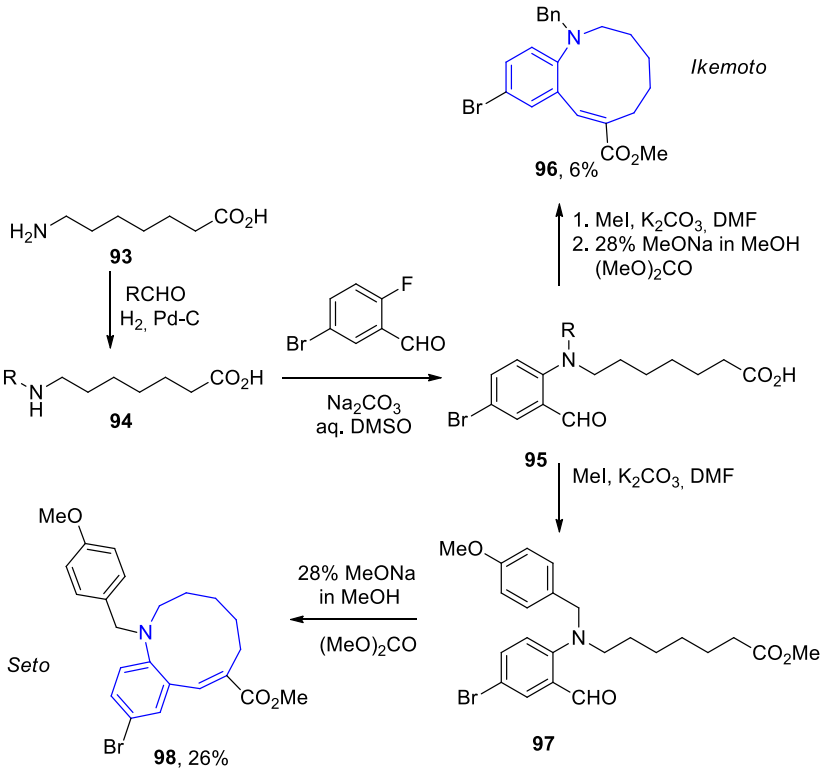
The racemic hexahydrodibenz[*d,f*]azecines **92** were synthesized via intramolecular mesyloxy displacement in dilute solution [65]. Suitable disubstituted biphenyl derivatives **91** required for the final aza-ring closure were obtained through a sequence of reactions which included the Suzuki-Miyaura coupling of benzene derivatives **86** and **87** (Scheme 24), chain extension with diethyl *N*-methylphosphonoacetamide, two reduction processes (the double carbon-carbon bond and amide fragment) followed by Boc protection of resulting secondary amines, cleavage of the tetrahydropyranyl group and *O*-mesylation. Removal of the Boc group by using trifluoroacetic acid led to intermediate secondary amines, whose treatment with Hunig's base in refluxing acetonitrile resulted into ring closure to form dibenzazecines **92** (Scheme 24).



Scheme 24. Synthesis of 5,6,7,8,9,10-hexahydrodibenzo[*d,f*]azecine **92** via the cyclization of secondary amine.

In 2004, Ikemoto and co-workers demonstrated that intramolecular Claisen-Schmidt type condensation of certain *o*-formylaniline-acid could lead to benzo[*b*]azecine ring **96** [66]. First, reaction of amino acid **94** prepared by reductive amination of compound **93** with benzaldehyde and Pd-C/H_2, with 5-bromo-2-fluorobenzaldehyde produced *o*-formylaniline-acid **95**. The latter was esterified with methyl iodide in the presence of K_2CO_3 then treated with the

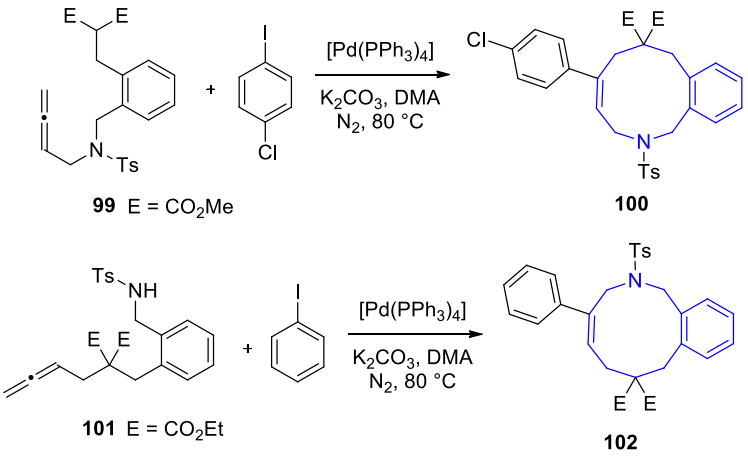
combination of alcoholate and dimethyl carbonate in one-pot. Benzo[*b*]azecine **96** was obtained in poor yield of 6% (Scheme 25).



Scheme 25. Synthesis of benzo[*b*]azecines via the Claisen-Schmidt type condensation reaction.

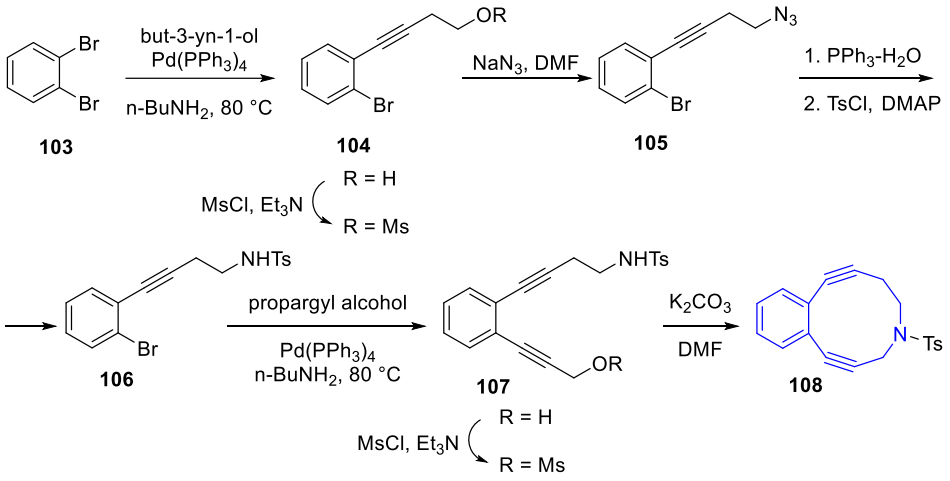
The same principle for the construction of benzazecine moiety **98** was used by Seto et al. [67]. Unlike the Ikemoto's synthetic route, esterification and cyclization were performed as two separate steps resulting in only 26% yield of the target compound **98** (Scheme 25).

Benzazecines **100** and **102** were synthesized in high yields, 82% and 83% respectively, through Pd-catalyzed coupling cyclization reaction of functionalized allenes **99**, **101** with organic halides [68]. The reactions feature high regio- and stereoselectivity leading to only *E*-isomer (Scheme 26).



Scheme 26. Synthesis of benzazecines via Pd-catalyzed coupling cyclization reaction.

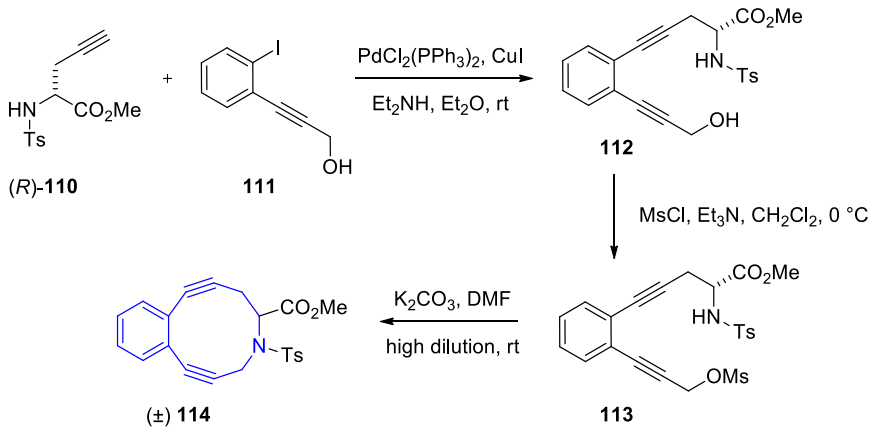
The Basak's group developed the synthesis of diyne benzo[*e*]azecine **108** starting from 1,2-dibromobenzene **103** where Pd-catalyzed Sonogashira coupling was a key step [69]. First, 1,2-dibromobenzene **103** was monocoupled with homopropargyl alcohol, intermediate ynol **104** was converted to azide **105**, whose subsequent reduction followed by *N*-tosylation led to sulfonamide **106**. The second coupling with propargyl alcohol and *O*-mesylation produced benzene derivative **107** which finally underwent intramolecular *N*-alkylation under high dilution to give benzazecine **108** in 80% yield (Scheme 27). The authors showed that the synthesized benzazecine was stable at room temperature and underwent the Bergman cyclization to tetrahydrobenzoisoquinoline **109** after being refluxed in $CHCl_3$ for three days (Scheme 28).



Scheme 27. Synthesis of diyne benzazecine **108**.

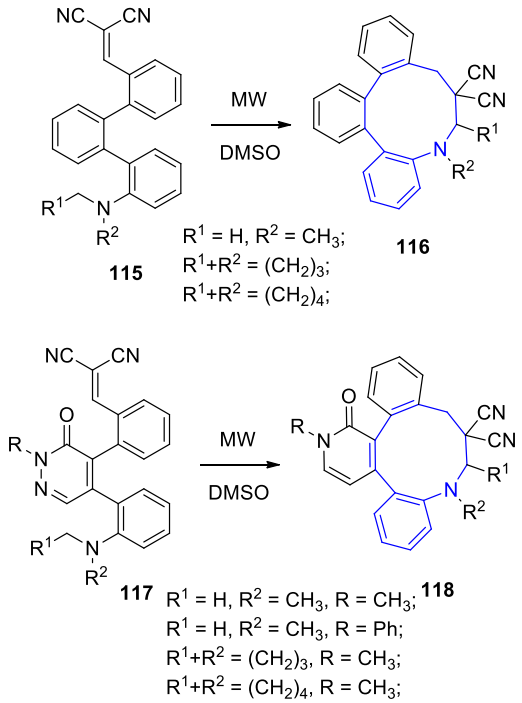
Scheme 28. The Bergman cyclization of diyne benzazecine **109**.

Rutjes and co-workers expanded the above-mentioned idea and prepared 10-membered cyclic enediyne-containing amino acid **114** from propargylglycine **110** and aryliodide **111** [70]. Coupling of enantiopure *N*-tosyl-protected propargylglycine methyl ester (*R*)-**110** with aryliodide **111** led to cyclic enediynes (*R*)-**112**, *O*-mesylation of which with methanesulfonyl chloride afforded the substrate **113** ready for cyclization. Treatment of highly diluted solutions (6 mM) of mesylate in DMF with potassium carbonate (5 equiv.) provided racemic benzazecine **114** in 75% (Scheme 29). The authors also demonstrated cycloaromatization of benzazecine analogous in Scheme 28.



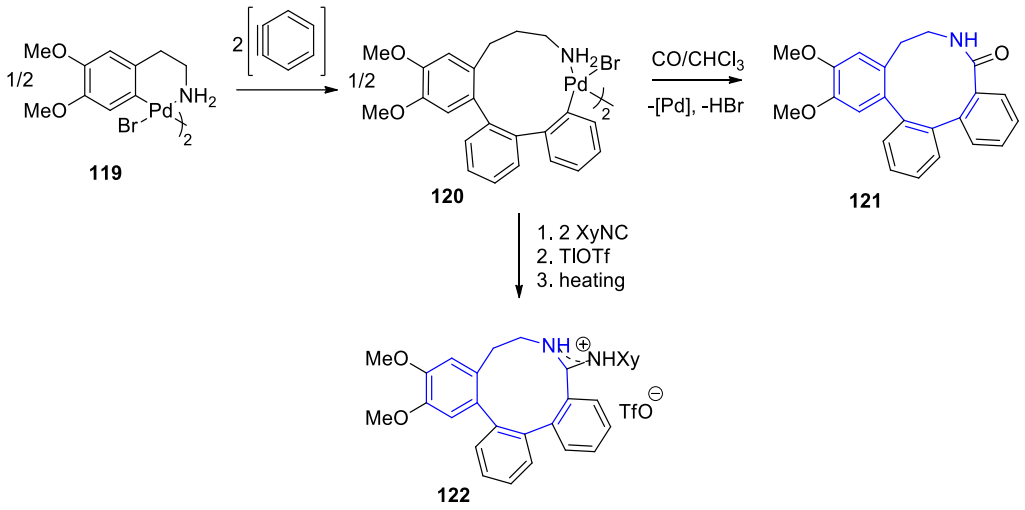
Scheme 29. Synthesis of racemic diyne benzazecine **114**.

Mátyus and co-workers reported a microwave-assisted synthesis of tribenzo[*b,d,f*]- and pyridazino[*d*]dibenzo[*b,f*]azecines **116** and **118**, exploiting the so-called "tert-amino effect" [71]. The desired compounds were obtained via an ''open-vessel'' microwave-assisted cyclization of corresponding triphenyl or biphenyl-pyridazine compounds **115**, **117** possessing a vinyl and a *tert*-amino group (Scheme 30).



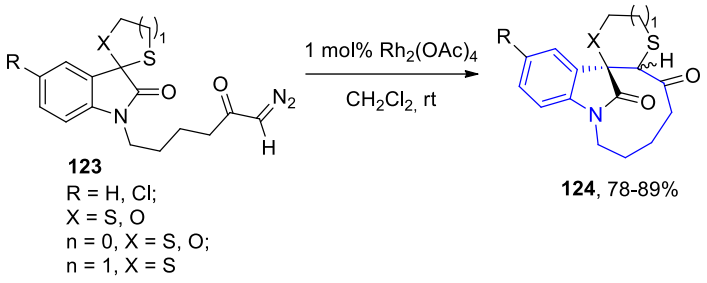
Scheme 30. Synthesis of condensed dibenzazecines via the MW-assisted cyclization reaction.

Vicente and co-workers described benzyne-benzyne-RNC or CO triple sequential insertion into the Pd-C bond of *ortho*-palladated derivative of homoveratrylamine which allowed to obtain tribenzo[*c,e,g*]azecine **121** and **122** in moderate yields (47% and 65%, respectively) [72] (Scheme 31).



Scheme 31. Synthesis of tribenzo[*c,e,g*]azecine.

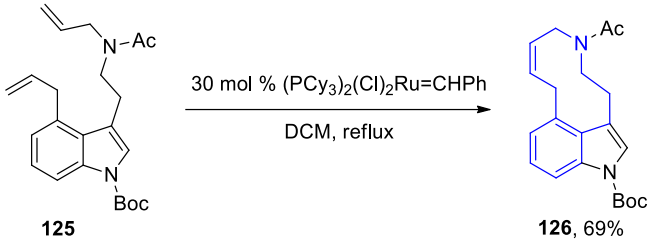
Interesting macrocyclic spiro-1,4-dithianes, -1,4-oxathianes and -1,4-dithiepanes incorporating the benzazecine moiety **124** were obtained by a rhodium(II) acetate-catalyzed synthesis from thiol-protected diazocarbonyl compounds **123** [73]. The cyclization proceeded through the formation of intramolecular sulfonium ylides followed by a Stevens rearrangement. It was mentioned that 1,3-dithiolanes, in general, afforded a single diastereomer, whereas 1,3-oxathiolanes led a single product or a mixture of diastereomers. 1,3-Dithianes produced only a mixture of diastereomers (Scheme 32).



Scheme 32. Synthesis of condensed benzazecines via Rh(II) acetate catalyzed reaction.

2.6. Ring-closing metathesis reactions

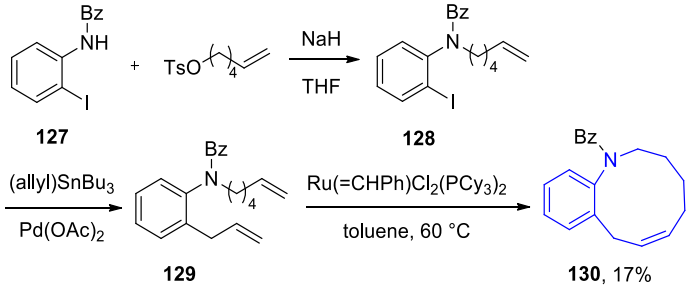
In 2003, ring-closing metathesis (RCM) protocol was applied for the construction of benzazecine fragment [63]. RCM precursor was treated with the first-generation catalyst [$(PCy_3)_2(Cl)_2Ru$=CHPh] in refluxing CH_2Cl_2 to afford *tert*-butyl (*Z*)-10-acetyl-9,10,11,12-tetrahydroazecino[4,5,6-*cd*]indole-2(6*H*)-carboxylate derivative **126** in 69% yield as a single (*Z*)-isomer (Scheme 33).



125 **126**, 69%

Scheme 33. Synthesis of condensed tetrahydroazecino[4,5,6-*cd*]indole **126** via ring-closing metathesis reaction.

RCM was also exploited at the key stage in the synthesis of the benzazecine derivative **130** [74]. Alkylation *N*-2-iodophenylbenzamide **127** with 1-hex-5-enyl *p*-toluenesulfonate followed by Stille cross-coupling with allyltributyltin provided the diene derivative which underwent RCM mediated by Grubb's catalyst. Despite all attempts to optimize the reaction conditions the target benzo[*b*]azecine **130** was obtained in small yield (17%) in a reaction time of one week. The alkene fragment in the azecine ring possesses *Z*-geometry (Scheme 34).



127 **128** **129** **130**, 17%

Scheme 34. Synthesis of benzo[*b*]azecine **130** via ring-closing metathesis reaction.

3. Pharmacology of diverse benzazecine derivatives

The unique pharmacological properties of diverse synthetic annulated benzazecine derivatives (mostly as benzo[*d*]azecine fusion isomers) and bioisosteric analogs, as well as unprecedented bioactivities of benzazecine-containing alkaloids, have been studied over time. Some of the most investigated synthetic biologically active annulated azecines appeared in literature in 2000 as dopamine receptor antagonists, and therefore as potential antipsychotic agents, but other important properties have been disclosed for applications in the treatments of cancers and neurologic disorders (Fig. 3). In Table 1 the structures of pharmacologically noteworthy synthetic benzo[*d*]azecine (or 3-benzazecine) derivatives, with different degrees of saturation and diverse substituents, are shown along with their validated biological targets and potential pharmacological applications. More detailed information about drug design, SARs, pharmacophores and pharmaceutical development is given in the following sections. Evidence about recently disclosed bioactivities associated to natural benzazecine-containing alkaloids is highlighted in the last section.

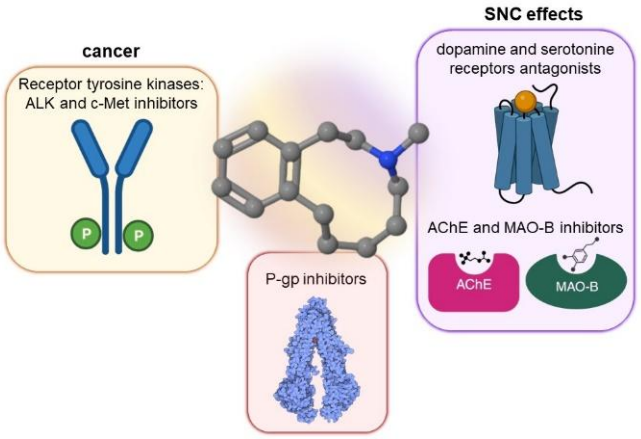
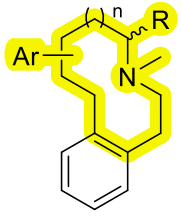
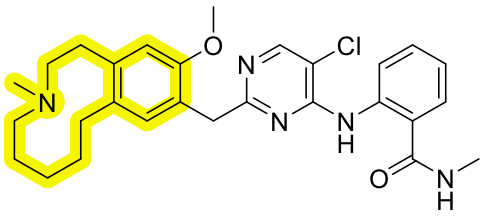
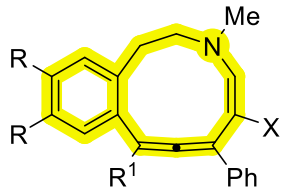


Figure 3. The benzo[*d*]azecine scaffold is found in molecules targeting multiple biological systems, including SNC (e.g., dopamine and serotonin receptors for psychosis, AChE and MAO-B for neurodegeneration), tyrosine kinase receptors involved in cancer, and P-glycoprotein (P-gp) efflux pumps responsible for multidrug resistance (MDR).

Table 1. Chemical structure, biological target and determined mechanism of action of synthetic benzo[*d*]azecine derivatives of potential pharmacological interest. [a]

Structure	Biological target(s) [b]	Mechanism of action and pharmacology
 Ar = aryl R = -CH_3, -CH_2OH, -COOH n= 1, 2	DA and 5-HT receptors	Aryl-substituted 1,2,3,4,5,6,7,8-octahydro-3-methylbenzo[*d*]azecine derivatives (section 3.1) act as mixed 5-HT and DA receptors antagonists to treat psychotic disorders (reff. 8, 12, 14, 15, 17, 18, 81).
	c-Met and ALK kinase	The incorporation of 2,4-diaminopyrimidine skeleton of tyrosine kinase inhibitors into the 1,2,3,4,5,6,7,8-octahydro-3-methylbenzo[*d*]azecine moiety (section 3.2) confers to the molecule anticancer activity (ref. 85).

 R = H, OMe R^1= Me, i-Pr, Ph X = CO_2Me, Ac	P-gp, ChEs and/or MAOs	C6-C8 allene-containing benzo[*d*]azecine enamino derivatives (sections 3.2 and 3.3) show activity as inhibitors of P-gp and ChEs and/or MAOs involved in neurodegeneration (reff. 47, 50, 53, 54).

[a] The benzazecine motif is highlighted in yellow. [b] Abbreviations: 5-hydroxytryptamine (5-HT); dopamine (DA) Mesenchymal epithelial transition growth factor (c-Met); Anaplastic lymphoma kinase (ALK); P-glycoproteins (P-gp); cholinesterases (ChEs); monoamine oxidases (MAOs).

3.1 Antipsychotic agents

The first study was carried out by Lehman et al. in 2000. They synthesized a new heterocyclic system incorporating the structures of 5-hydroxytryptamine (5-HT) and β-phenylethylamine (DA) in order to target with a single molecule both 5-HT and DA receptors (Fig. 4) [8]. In fact, mixed D_2/5-HT_{2A} receptor antagonists (like risperidone and clozapine) lead to the so-called 'atypical neuroleptics', more effective than the traditional neuroleptics in treating the symptoms of psychoses, causing less extra-pyramidal side effects. As a result of the merging strategy, LE300 (**132**) proved to be a potent D_1 antagonist and a moderate D_2 and 5-HT_{2A} antagonist, whereas the conformationally restricted quinolizidine was devoid of any activity.

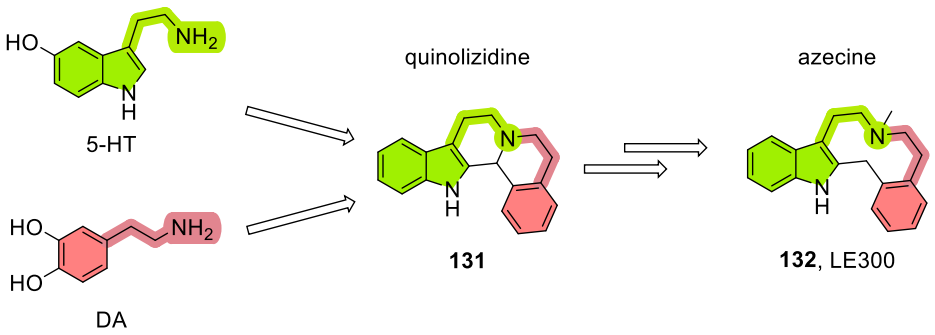
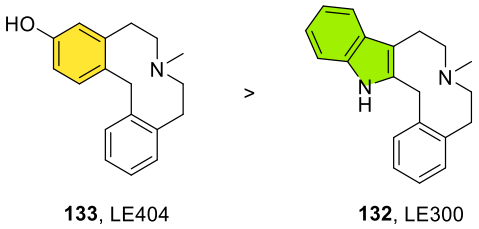


Figure 4. The conformational liberation that derives from the C-N bond cleavage of quinolizidines is responsible for the pharmacological activity of the azecine LE300 compound (**132**) as dopaminergic and serotoninergic antagonist.

Surprisingly, the conformational liberation, that derives from the cleavage of the C-N bond, disclosed the potential of the resulting 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-benzo[7,8]azecino[5,4-*b*]indole (**132**) that acted as dopaminergic and serotoninergic receptor ligands (K_i = 0.08 nM *vs* D_1 receptor, 6.0 nM *vs* D_2 receptor, 20.0 nM *vs* 5-HT_{2A} receptor). It is noteworthy that, unlike the many cases in which conformation restriction increases the potency of a ligand by stabilizing a favorable binding conformation and reducing the entropic penalty on binding to the target [75-77], in this case a conformational liberation proved to be beneficial.

In the first decade of the XXI century intensive SAR investigations were performed by the same research group in order to identify the pharmacophore of this new class of ligands, including variations in ring size [78], de-indolization of the structure [10], insertion of an additional oxygen atom [79, 80] and changing one of the aromatic moieties (e.g., indole replaced by benzene, thiophene, and 1-methyl-1*H*-pyrrole) and its location with respect to each other at the central alicyclic ring [12]. These studies resulted in the identification of a dibenzo[*d,g*]azecin-3-ol, LE404 (**133**), which displayed low nanomolar affinities for all dopamine receptor subtypes and subnanomolar affinity toward the D_1 receptor in radioligand binding experiments (Fig. 5).



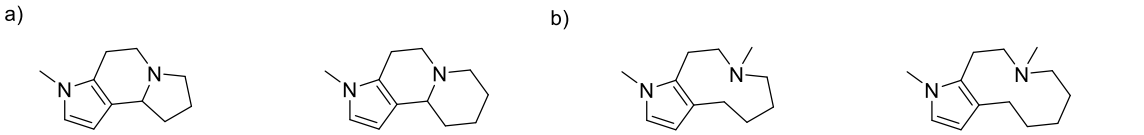
133, LE404 **132**, LE300

Affinities for Human Cloned Dopamine Receptors Radioligand Binding Data (*Ki* nM)

cmpd	*h*D_1	*h*D_{2L}	*h*D_4	*h*D_5
LE300	**1.9**	44.7	109	**7.5**
LE404	**0.39**	17.5	11.3	**1.5**

Figure 5. Dibenzo[*d,g*]azecin-3-ol (**133**, LE404) has affinity for all human dopamine receptor subtypes compared to LE300.

Here we want to highlight the progresses in understanding and exploiting the pharmacological potential of this class of molecules. In 2010, Rostom [81] deprived LE300 of the phenyl rings, and replaced the indole with 1-methyl-1*H*-pyrrole moiety together with a constriction of the ten-membered azecine to the nine-membered azonine ring, in an attempt to estimate the influence of such a structural variation on the biological activities. The pyrrolo[2,3-*g*]indolizine **134** and the pyrrolo[3,2-*a*]quinolizine **135** were devoid of any activity at the 5-HT_{2A} receptor, as assessed by using the rat-tail artery model. In contrast, the corresponding pyrrolo[2,3-*d*]azonine **136** and pyrrolo[2,3-*d*]azecine **137** showed partial agonistic activity at the same receptor (Fig. 6).



pyrrolo[2,3-*g*]indolizine **134** — pyrrolo[3,2-*a*]quinolizine **135** — no activity at 5-HT_{2A}

dimethylpyrrolo[2,3-*d*]azonine **136** — dimethylpyrrolo[2,3-*d*]azecine **137** — partial agonistic activity at 5-HT_{2A}

Figure 6. Structural modification of LE300 (**132**) and relative activity *vs* 5-HT_{2A} receptor. The structural modifications are shown that led to (a) inactive compounds or to (b) partial agonists at 5-HT_{2A} receptor.

In the same year, Enzensperger *et al.* [78] studied arylalkylamine-, β-carboline-, quinolizine- and azecine-derived compounds and their interaction with the ionotropic 5-HT_3 receptor. Even though 5-HT_3 receptor antagonists, such as

sertrons, are commonly used in the treatment of gastrointestinal disorders, other investigations suggest that 5-HT_3 receptor antagonists have potential as centrally acting drugs (e.g., anxiolytic, antidepressive and procognitive effects).

The [^{14}C] guanidinium experiments on N1E-115 cells showed that among all investigated classes of compounds, 3-substituted dibenzo[*d,g*]azecines displayed the strongest channel blocking effect at 100 µM. The order of effectiveness is 3-methoxy and 3-hydroxy dibenzo[*d,g*]azecines (**138**), being as effective as tropisetron (positive control), followed by the corresponding indole derivatives (**140**) and the unsubstituted dibenzo- derivatives which lacked selectivity at the 5-HT_3 receptor (Fig. 7).

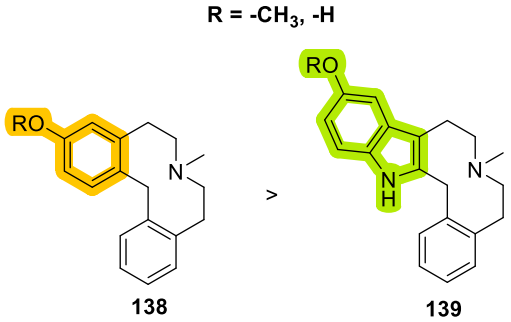


Figure 7. Selectivity of dibenzo[*d,g*]azecine derivatives (**138**) and their indole-fused analogs (**139**) at 5-HT_3 receptor.

Lehmann *et al.* [14] changed the annulation pattern of the heterocycles in LE300 (**132**), rearranging the indolo[3,2-*f*]benzazecine skeleton of the parent compound to indolo[4,3a,3-*ef*]benzazecine (Fig. 8, **140**), indolo[4,3a,3-*fg*]benzazacycloundecene (**141**) and to indolo[2,3-*f*]benzazecine (**142**). The most constrained compound (**140**) was inactive, the benzo-azacycloundecene (**141**) showed antagonistic properties (functional Ca^{2+} assay) with nanomolar affinities (radioligand binding) for all dopamine receptor subtypes, whereas the indolo[2,3-*f*]benzazecine (**142**) displayed a selectivity profile similar to **141**, but with lower affinities. The authors concluded that modifying the annulation pattern of LE300 does not lead to significant changes in the affinities for the different DA receptors. Compounds **141** and **142** remain indeed as active as DA antagonists. However, decreasing the flexibility of the structure and decreasing the distances between nitrogen and the aromatic moieties both showed negative effects on the affinities which can lead to activity loss, as in the case of compound **140**.

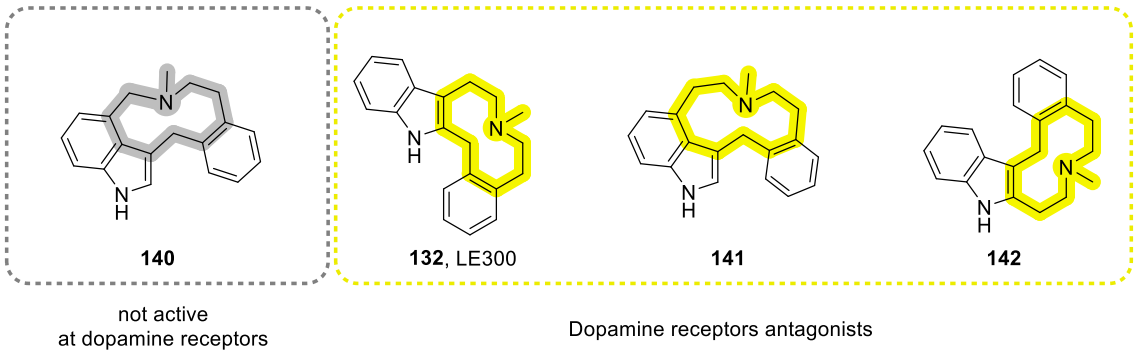


Figure 8. Changes in the annulation pattern of LE300 (**132**) do not lead to significant changes in the affinities and activities for the different dopamine receptors, except for compound **140**.

The cleavage of the central C-N bond of tetrahydroprotoberberines made by Schulze *et al.* [82] to synthesize the dibenzo[*c*,*g*]azecine analog resulting in a sharp decrease of the affinities, as assessed by radioligand binding assay, for all DA receptor subtypes (Fig. 9). At the same time, they observed some changes in the selectivity at the DA receptor subtypes by the enlargement of tetrahydroprotoberberines (THPBs) ring B or C. In particular, the expansion of the C-ring leads to higher selectivity towards D_4 receptor, while the expansion of the other central ring (B) led to compounds with much lower affinities for all DA receptor subtypes.

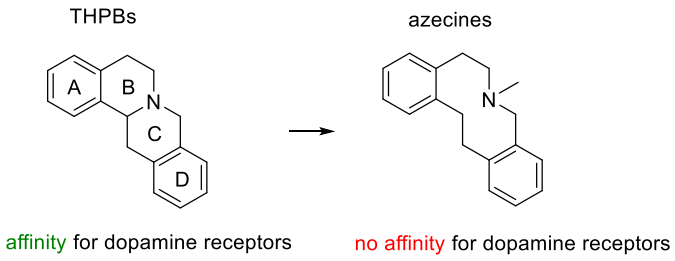


Figure 9. Cleavage of the C-N bond in THPBs causes a dramatic loss of affinity to dopamine receptors.

Robaa *et al.* [15] prepared and tested racemic and enantiopure 8-substituted derivatives of the lead DA receptor antagonist LE 300 (Fig. 10). Indolobenzazecine derivatives bearing at C8 three different substituents (R = Me, CH_2OH and COOH) were prepared as α- and β-isomers (with the substituents pointing below and above the indole ring plane in **143** and **144**, respectively). All tested compounds showed antagonistic properties in the functional Ca^{2+} assay. While α-8-methylbenzindoloazecine was almost as active as the lead LE300 (**132**), β-8-methylbenzindoloazecine exhibited at least 100-fold reduction in affinities for all the dopamine receptors. A similar but less pronounced difference was observed between the α and β 8-hydroxymethylindolobenzazecine: α-8-hydroxymethylbenzindoloazecine was more active than the β-enantiomer (but less active than α-8-methyl), while β-8-hydroxymethylbenzindoloazecine showed a 10-fold reduction in affinities for all dopamine receptors. The group did not manage to accomplish separation of enantiomers of the carboxylic acid derivative racemic mixture, which showed a pronounced decrease in the affinities for all DA receptors.

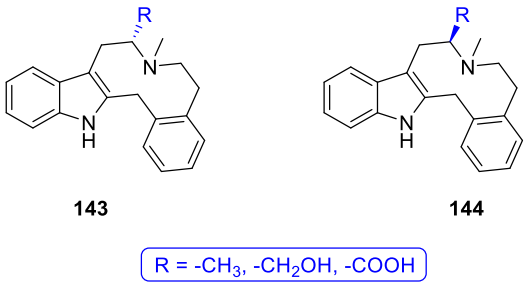
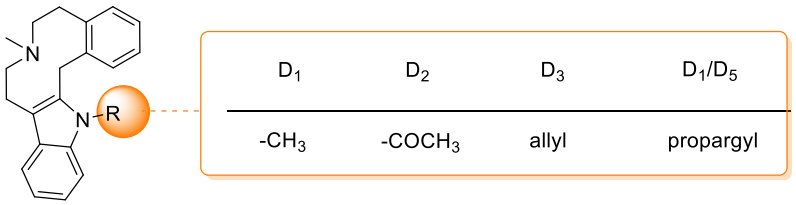


Figure 10. 8-substituted derivatives of the lead dopamine receptor antagonist LE 300.

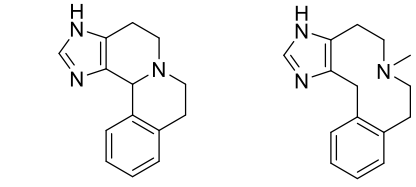
To elucidate the effect of indole-*NH* substitution, Robaa *et al.* [16] synthesized eleven new *N*14-substituted 7-methyl-6,7,8,9,14,15-hexahydro-5*H*-benzo[7,8]azecino[5,4-*b*]indoles (Fig. 11, **145**) and their affinities for all DA receptors were determined by radioligand binding assays. An inverse relation was observed between chain length and affinity, the optimal binding affinity being achieved with a methyl group (Fig. 11). Compared with the lead LE300, the indole-*NH* methylated compound showed a 5–15-fold decrease in affinity for all DA receptor subtypes, except for D_1. Longer alkyl chains and bulky substituents were unfavorable. In fact, the *N*14-octyl derivative showed the lowest affinities among all tested compounds. Moreover, the increased alkyl chain length parallels increased cytotoxicity. Modified alkyl chains follow the same trend (for example the fluoroethyl derivative exhibited affinities similar to the ethyl one, the cyclopropylmethyl derivative generally showed affinities similar to the *N*14-propyl derivative). Moreover, *N*-acetyl, *N*-allyl and *N*-propargyl compounds showed increased affinity towards D_2, D_3 and D_1/D_5 receptors respectively. The shift in selectivity for the *N*-propargyl compound with respect to the *N*-allyl one is explained in terms of additional stacking interactions, hydrogen bond between the terminal alkyne-*H* and the receptor counterpart and steric bulk. In summary, it appeared that indole-*NH* is not involved in a hydrogen bond and that the enhancing effect of methyl substitution on the affinities is rather caused by steric factors.



145

Figure 11. The substitution at the *N*-indole of LE300 modulate the affinity and selectivity for DA receptors.

Lehman *et al.* [17] synthesized two heterocyclic rings, namely the imidazo[4',5':3,4]pyrido[2,1-*a*]isoquinoline (Fig. 12, **146**) and the imidazo[4,5-*f*][3]benzazecine derivative (Fig. 12, **147**), by changing the biogenic amines from tryptamine to histamine. Radioligand binding studies at human DA receptors showed a submicromolar affinity towards D_1 and D_5 receptors of the imidazo-benzazecine but not of the isoquinoline. Both compounds were less affine compared to LE300.



146 **147**

no affinity at D receptors

submicromolar affinity at D1 and D5 receptors

Figure 12. Histamine-derived benzazecine compounds.

Abdel-Fattah *et al.* [18] tried to modulate the selectivity/affinity profiles of lead azecine derivatives LE 300 towards DA receptors by replacing the indole moiety with a thiophene or benzothiophene ring, inspired by the advantageous bioisosteric replacement of benzene in clozapine benzene with thiophene in olanzapine, which proved to be responsible for the increased affinities and slightly different selectivity profile of the latter compared to the former. The thieno[2,3-*g*]azecine (**148**, Table 2) was shown to have the best selectivity towards the D_5 receptor subtype with D_1/D_5 selectivity index of 20, while its regioisomer thieno[3,2-*g*]azecine (**149**, Table 2) with a reversed thiophene position, prefers the D_1 subtype over the D_5 subtype, with a D_5/D_1 selectivity index of 3.3.The benzothieno-benzazecine analog (**150**, Table 2) showed a unique high affinity pattern towards D_2 and D_5 receptors with *K*i values of 1.5 and 1.9 nM respectively.

Starting from the parent compound **132** (LE300, Fig. 13), the following SARs for aryl-substituted 1,2,3,4,5,6,7,8-octahydro-3-methylbenzo[*d*]azecine derivatives as DA/5-HT receptors' antagonists can be inferred from the literature: (i) the azecine moiety is essential for the activity, because more constrained derivatives (e.g., quinolizidines) are devoid of any activity; (ii) even variations of the ring size are detrimental for affinities [8, 14], while some substitutions (i.e. 8-methyl-) are tolerated [15]; (iii) removal of one phenyl ring changes the activity from antagonistic to partial agonistic [81]; (iv) *N*-indole substituted derivatives achieve lower affinities for all D-receptor subtypes compared to the parent **132** (LE300) [16]; (v) activity and selectivity at different D and 5-HT receptor subtypes can be tuned by replacing indole with other aromatic or heteroaromatic rings [12, 17, 18, 81].

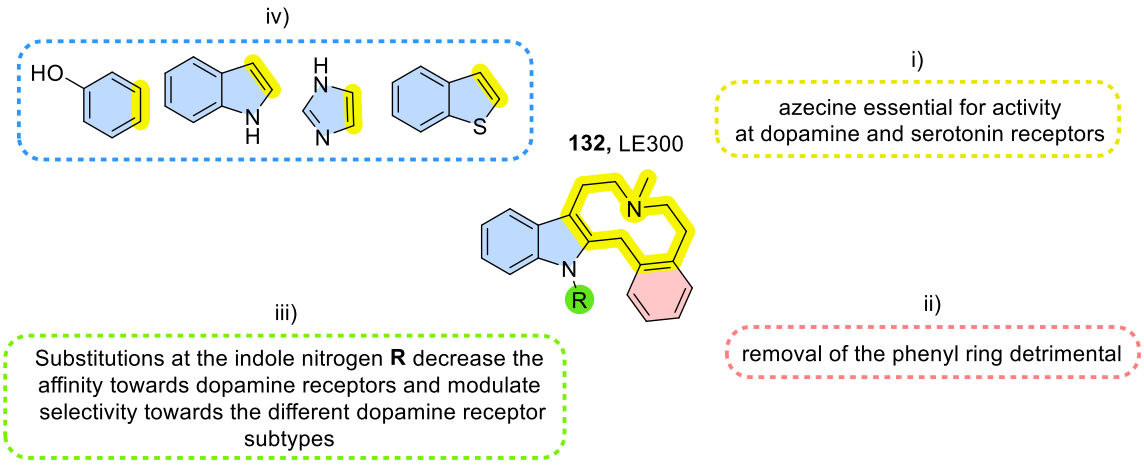
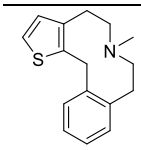
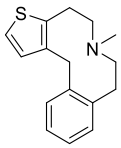
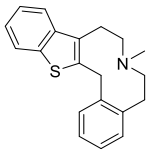


Figure 13. Pictorial SARs of annulated azecine derivatives as dopamine/serotonin receptors' antagonists compared to the parent compound LE300.

Seeling *et al.* synthesized some ester derivatives of the parent compound LE404, since it showed a rapid loss of activity likely due to its rapid metabolism [83]. With increasing the size of the ester moiety, the affinity for the individual receptors was reduced, according to the radioligand binding studies, while small esters show a too rapid hydrolysis rate. *In vivo* experiments showed that the isobutyric ester has by far the largest therapeutic index. To evaluate whether the effect was based on the ester derivative or on the compound resulting from ester cleavage, the rate of hydrolysis was assessed by incubating the ester with porcine liver esterase. The lowest tested enzyme activity (0.125 U) resulted in a half-life of 31 min. In three animal models a maximum effect was achieved in the range of 90 to 150 min. In test solutions with an enzyme activity of 0.125 U, the ester derivative concentration decreased to 9.8 % in 120 min, whereas the parent compound increased, so the observed effect on the rats was based solely on the last one. The isobutyric

ester was regarded as a prodrug of LE404. In another study, Seeling *et al*. [84] tested different esters to evaluate their stability in physiological media. All derivatives were stable in simulated gastric and intestinal fluid. The ester derivative with the slower esterase cleavage was again the isobutyric ester (90 min, half-life), whilst the carbamate derivatives showed no esterase cleavage, their hydrolysis being catalyzed by cholinesterases. Moreover, the carbonate synthesized had the longest half-life in vitro (131 min).

Table 2. Binding affinities of thieno-azecine fusion isomers for cloned human dopamine receptors.

Compounds	Binding affinities (K_i ± SEM [nM]) for cloned human dopamine receptors
 **148**	**D_1 = 60 ± 4.2**; D_2 = 45 ± 2.7; D_3 = 24 ± 1.5; D_4 = 188 ± 17; **D_5 =3 ± 1.7**
 **149**	**D_1 = 4 ± 0.4**; D_2 = 190 ± 2.7; D_3 = 87 ± 6; D_4 = 99 ± 21; **D_5 = 15 ± 3.2**
 **150**	D_1 = 40 ± 1.5; **D_2 = 1.5 ± 0.02**; D_3 = 18 ± 2; D_4 = 72 ± 7; **D_5 = 1.9 ± 0.5**

3.2 Anticancer activity

Zhang *et al.* [85] developed a series of new 2,4-diarylaminopyrimidine analogues (DAAPalogues) by incorporating the dopamine D_1/D_5 receptor ligand motif, i.e., a C^1-substituted-N^3-benzazepine or a benzazecine, into the classical 2,4-diaminopyrimidine skeleton of tyrosine kinase inhibitors, in continuation with their effort on repurposing a typical G-protein coupled receptor (GPCR) agonist/antagonist motif into kinase inhibitors scaffolds. The anaplastic lymphoma kinase (ALK) and mesenchymal epithelial transition growth factor (c-Met) inhibitor crizotinib (PF2341066) approved by FDA in 2011 for patients with advanced or metastatic ALK-positive nonsmall cell lung cancer (NSCLC) was used as starting point, to which the benzazepine and the benzazecine cores were attached. Compared to crizotinib which showed an IC_{50} value of 2.4 nM at the ALK and 28 nM at the c-Met, the benzazecine derivative **151** (Fig. 14) achieved an IC_{50} value of 17 nM at the ALK and 710 nM at the c-Met with an inverted selectivity and a much higher selectivity ratio.

Atypical molecular scaffolds containing a more rigid benzazecine motif were synthesized by Titov *et al.* [47]. In particular, 10,11-dimethoxy-3-benzazecine, incorporating the C6=C7=C8 allene system and an enamine fragment in α-position relative to the allene (Fig. 14) proved to be highly potent inhibitors of the P-glycoprotein (P-gp) efflux pump associated with multidrug resistance (MDR) in cancer cells. The methyl carboxylate derivative **153** (Fig. 14) proved to be a single-digit nanomolar inhibitor of P-gp (IC_{50} 4.2 nM), with significant MDR reversal activity in doxorubicin-

resistant tumor cells and negligible cytotoxicity at 100 µM in MCF7 (breast) and HepG2 (liver) cancer cells. Compound **153** proved to significantly increase the antitumor potency of doxorubicin in multidrug-resistant tumor cell lines.

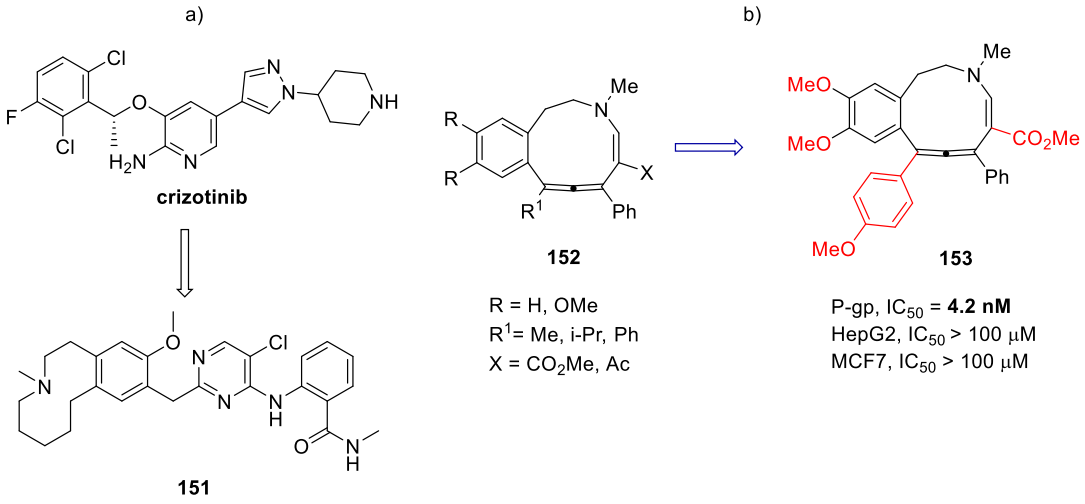


Figure 14. Anticancer activity of benzazecines. (a) 2,4-diarylamino pyrimidine derivative compound **151** as potent anaplastic lymphoma kinase inhibitor, (b) 3-benzazecine-based cyclic allene derivatives as highly potent P-gp inhibitors synergistically improving the in-vitro antitumor activity of doxorubicin in multidrug-resistant tumor cells.

The SARs of this class of newly synthesized P-gp inhibitors are illustrated in Fig. 15 (**154**). 10,11-dimethoxy derivatives proved to be five-to-tenfold more potent inhibitors than the related unsubstituted compounds. Compounds with methoxycarbonyl esters in C5 were always more potent than the respective ketone derivatives, while molar volume was found to be correlated to pIC_{50}. Molecules bearing bulkier substituents in C8 (R^1, Fig. 15) resulted in stronger van der Waals interactions or additional aromatic π–π interactions and higher pIC_{50}s.

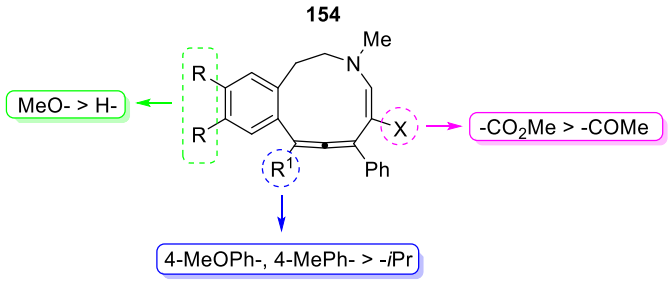


Figure 15. SARs of 3-benzazecine-based cyclic allene derivatives as potent P-glycoprotein inhibitors.

3.3 Activity against target enzymes of neurodegeneration

The activity of the above allene derivatives of 3-benzazecines was also tested against human cholinesterases [53]. Among them, compound **155** (Fig. 16) resulted a moderately potent reversible inhibitor of *h*AChE (IC_{50} = 14 µM), which is a target enzyme for drugs used in the symptomatic treatment of mild-to-moderate dementias related to Alzheimer disease (AD), a selective inhibitor of monoamine oxidase B (IC_{50} = 7.1 µM) and a weak inhibitor of $Aβ_{40}$ self-aggregation. Microwave-assisted thermal rearrangement of allene 3-benzazecines led to *N*-bridged cyclopenta[*a*]indene

derivatives. Some of them proved to be very potent BChE inhibitors and effective in neuroprotection from glutamatergic excitotoxic insult. Given its low intrinsic cytotoxicity and good in-vitro brain penetration, compound **155** was proposed as a multitarget hit for the treatment of AD-related dementias.

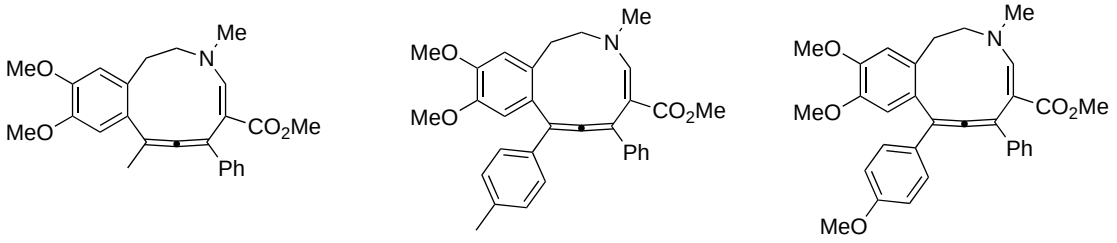
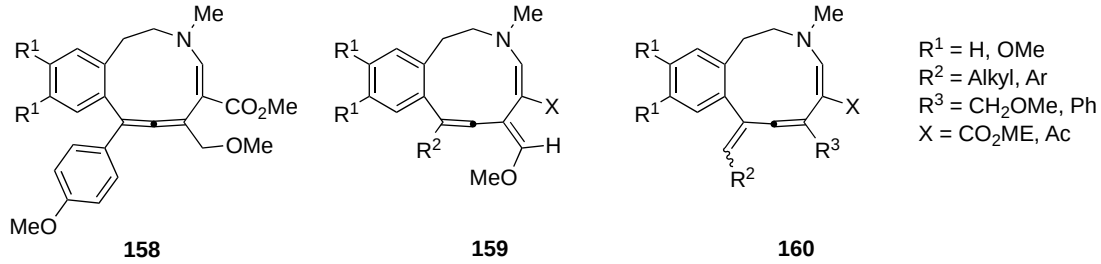


Figure 16. Allene 3-benzazecine derivatives (**155**-**157**).

Molecules able to elude or inhibit P-gp efflux pumps may have higher potential in crossing the blood–brain barrier (BBB). Indeed, in addition to its role in MDR associated to limited success of anticancer chemotherapeutics, P-gp efflux pumps may limit the brain disposition of drugs. 4'-Me (Fig. 16, **156**) and 4'-OMe-phenyl allene methoxycarbonyl esters (**157**) proved to be very potent inhibitors of P-gp (IC_{50}s equal 13 and 4.2 nM for **156** and **157**, respectively), which led to assume their central nervous system (CNS) uptake. Titov *et al.* [54] found that compound **157** is a selective inhibitor of AChE, with IC_{50} of about 5 μM. The allene subset of the CO_2Me esters proved to be generally more potent as inhibitors than the COMe ketone derivatives. The congeners bearing the electron-donating (ED) groups Me and OMe were found more active than those bearing the electron-withdrawing (EWG) substituents Cl and NO_2 in *para*-position of the 8-phenyl group. An *in vitro* screening of 3-benzazecines with cyclic allene moiety (**158**) and exocyclic double bond (**159**, **160**) for their potential inhibitory activities against human AChE and BChE and MAOs A and B [50] showed that the allene compounds were more potent than the corresponding -ylidene ones as selective AChE inhibitors (Fig. 17).



- AChE inhinbitor (Ki = 4.9 μM)
- improved solubility

Figure 17. Structures of 3-benzazecines with intramolecular allene moiety (**158**) and exocyclic double bond (**159**, **160**).

Comprehensive scheme of the chemical modifications of the allene 3-benzazecine scaffold and its changing in biological activity is depicted in Fig. 18.

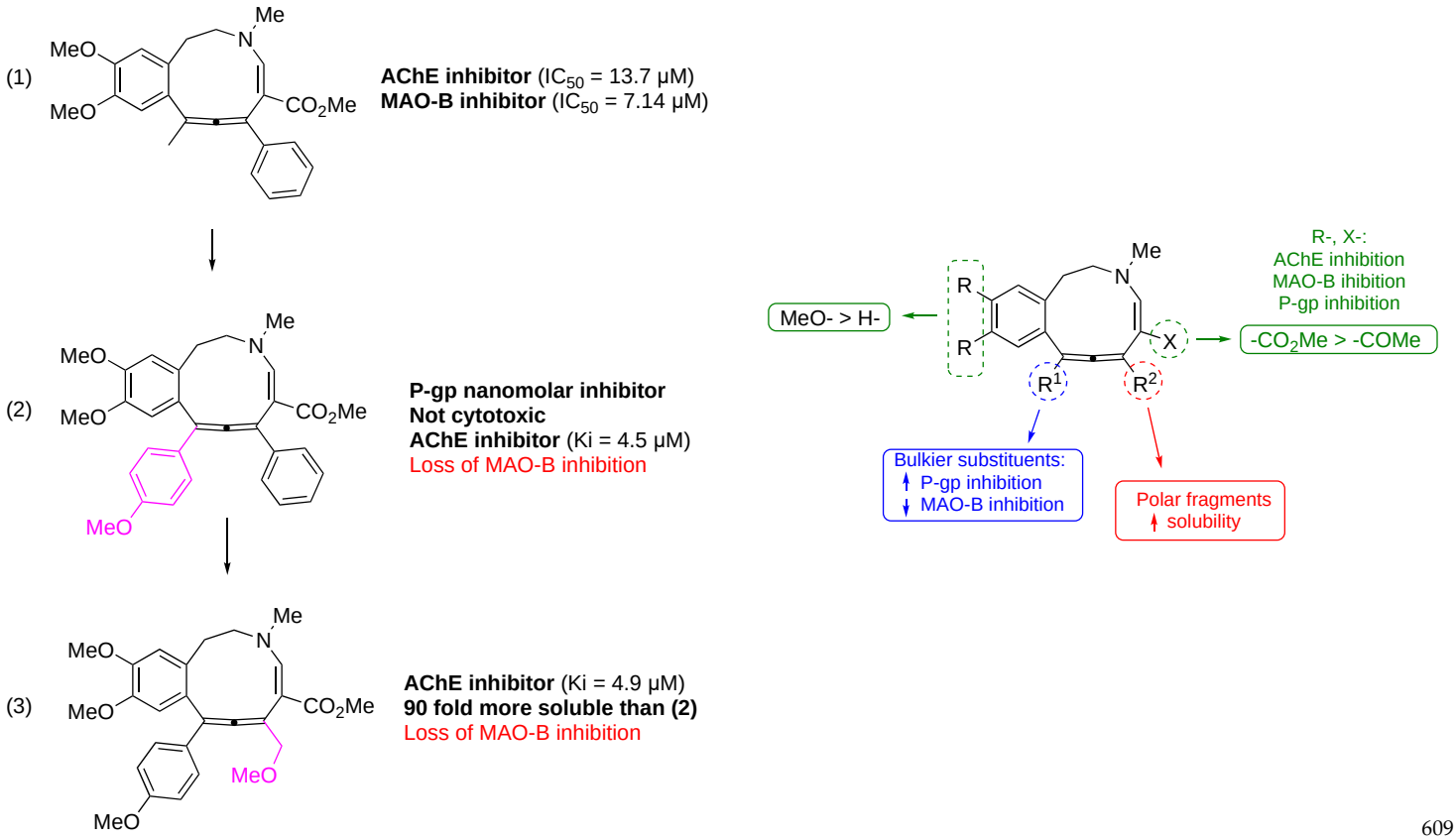


Figure 18: Summary of chemical modification and biological activity of the cyclic allene benzo[*d*]azecine scaffold.

3.4 Other activities of benzazecine-containing alkaloids

The isolation of compounds from plants of the family of Amaryllidaceae, led to the identification of cripowellins showing multiple biological activities (Fig.19) [86, 87, 88, 89]. 4,8-Dimethoxy-cripowellin C (**161**), 4,8-dimethoxy-cripowellin D (**162**), 9-methoxy-cripowellin B (**163**), 4-methoxy-8-hydroxy-cripowellin B (**164**) and cripowellin C (**167**) proved to be endowed with cytotoxic, antimicrobial, radical scavenging, and anti-inflammatory activities [86,87].

Other works [88, 89] highlighted the potential of cripowellins in targeting specific stages of the malaria parasite's life cycle. Cripowellins A and B were found to induce reversible cytostasis in the ring stage of *Plasmodium falciparum*, effectively pausing the development of the parasites during this early stage of their intraerythrocytic life cycle. This effect was observed within the first 24 hs of treatment, indicating that these compounds can halt the progression of the parasite without killing it at this stage. In contrast to their effects on the ring stage, cripowellins A and B exhibited cytotoxic effects on the trophozoite and schizont stages of the parasite.

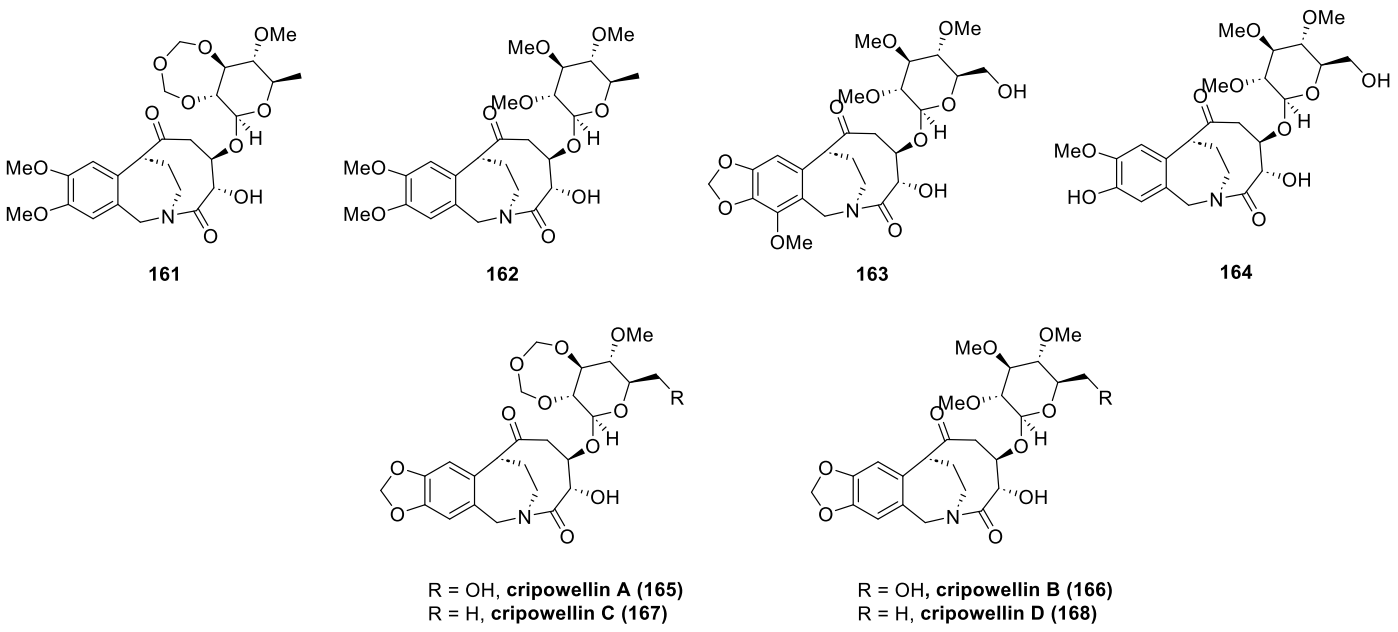


Figure 19. Crypowellins are alkaloids exhibiting a wide range of biological activities.

The study demonstrated that cripowellin B specifically disrupts the transcriptional program necessary for the progression of *P. falciparum* through its intraerythrocytic life cycle. After the removal of the drug, the treated parasites were able to re-enter transcriptional progression, indicating that the effects of cripowellins are reversible. Compounds **165**-**168** exhibited potent antiplasmodial activity by inhibiting *P. falciparum* strains growth [90], with IC_{50} values ranging from 11 to 260 nM.

4. Concluding remarks

A major purpose of this review was the evaluation and updating of synthesis methods, reactivity and medicinal chemistry of annulated azecine derivatives, mostly partially saturated benzo[*d*]azecines and dibenzo[*c,g*]azecines, that is a rare class of alkaloids and nature-inspired compounds. Due to difficulties associated with the synthesis of the benzazecine scaffold and bioisosteric analogs, this class of molecules is still rather underexploited in drug discovery. Herein, we reviewed several synthetic routes, including C-C and C-N bond cleavage, aza-Claisen rearrangements and ring closing metathesis, which lead to original bioactive annulated azecine derivatives.

The limited use of benzazecine moieties in the medicinal chemistry landscape is also reflected in the lack of preclinical data and in their absence in drugs available on the market. Despite being underexploited, annulated azecines proved to be endowed with diverse pharmacological properties. It is noteworthy that the degree of saturation of the azecine nucleus and its fusion isomerism with the arene ring drive the selectivity of benzazecine analogs towards diverse biological targets. Indeed, azecine-containing compounds proved to act as dopamine and serotonin receptors' modulators, antipsychotics, antimicrobial and anticancer agents, whereas more rigid and planar benzo[*d*]azecines incorporating endocyclic allene or conjugated diene were shown by us to inhibit P-gp and enzymes implicated in neurodegeneration, such as MAO B and AChE.

Considering their ascertained pharmacological properties, arene-fused azecines would deserve higher consideration in drug design. It is likely that progresses in synthetic methods and in-silico target-based approaches would help to exploit the medicinal potential of this class of medium-sized azaheterocyclic compounds.

5. Abbreviations.

Ac – Acetyl

AChE – Acetylcholinesterase

AD - Alzheimer's Disease

ALK – Anaplastic lymphoma kinase

BChE – Butyrylcholinesterase

Boc – *tert*-Butoxycarbonyl

Bz – Benzoyl

Cbz – Benzyloxycarbonyl

m-CPBA – *m*-Chloroperbenzoic acid

CHEs – Cholinesterases

Cy – Cyclohexyl

DBU – 1,8-Diazabyciclo[5.4.0]undec-7-ene

DCM – Dichloromethane

DMA – *N*,*N*-Dimethylacetamide

DMAP – 4-Dimethylaminopyridine

DMF – *N*,*N*-Dimethylformamide

DMSO – Dimethylsulphoxide

DA – Dopamine

P-gp – P-glycoproteins

5-HT – 5-Hydroxytryptamine

C-Met – Mesenchymal epithelial transition growth factor

Ms – Methanesulphonyl

MSH – (*S*)-*cis*-*N*-methylstylopine 14-hydroxylase

MW – Microwave irradiation

MAO – Monoamine oxidase

Py – Pyridine

RCM – Ring-closing metathesis

SARs – Structure–activity relationships

TBAF – Tetrabutylammonium fluoride

Tf – Trifluoromethanesulfonyl

TFA – Trifluoroacetic acid

THF – Tetrahydrofurane

THP – Tetrahydropyranyl

o-Tol – *o*-Toluyl

Ts – *p*-Toluenesulphonyl

TsO – *p*-Toluenesulfonate

Xy – 2,6-Dimethylphen-1-yl (*m*-Xylen-1-yl)

Author Contributions: Conceptualization, A.A.T. and C.D.A.; methodology and software, A.V.L., F.S., A.A.T. and R.P.; data curation, A.V.L., F.S., A.A.T., R.P., M.d.C. and M.C; writing—original draft, A.V.L., F.S., A.A.T. and R.P.; review and editing, A.A.T and C.D.A.; supervision, A.V.V., L.G.V. and C.D.A. All authors have read and agreed to the published version of the manuscript.

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