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Review

Azomethine Ylides—Versatile Synthons for Pyrrolidinyl-Heterocyclic Compounds

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Abstract: Azomethine ylides are nitrogen-based three-atom components commonly used in [3+2]-cycloaddition reactions with various unsaturated 2π-electron components. These reactions are highly regio- and stereoselective and have attracted the attention of organic chemists with respect to the construction of diverse heterocycles potentially bearing four new contiguous stereogenic centers. This review article complies the most important [3+2]-cycloaddition reactions of azomethine ylides with various olefinic, unsaturated 2π-electron components (acyclic, alicyclic, heterocyclic, and exocyclic ones) reported over the past two decades.

Keywords: cycloaddition; azomethine ylide; pyrrolidine; spiro-compound

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1. Introduction

The three-atom component (TAC) is an organic species that is represented by zwitterionic octet structures and undergoes [3+2]-cycloadditions with an unsaturated 2π-electron component in a one-step reaction, often in an asynchronous and symmetry-conducive fashion, via a thermal six-electron Hückel aromatic transition state. The formal charges are lost in the [3+2→5] cycloaddition (Figure 1) [1]. Recently, studies based on molecular electron density theory (MEDT) have suggested that the compounds involved in these reactions do not have a polar nature but a diradical, pseudoradical, or carbenoid nature. Therefore, the use of the term "1,3-dipole" is unjustified and should be replaced with "three-atom component". It was also recommend that the designation of "dipolarophile" should be replaced with "unsaturated 2π-electron component", and "1,3-dipolar cycloaddition" with "[3+2]-cycloaddition" [2].

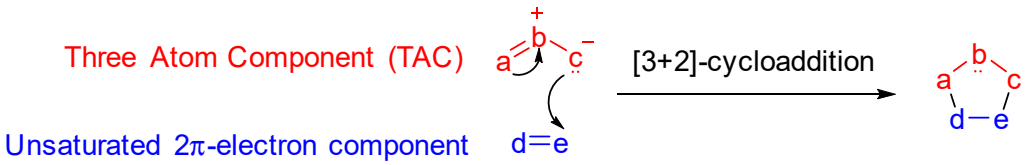


Figure 1. Historical Huisgen's view on the [3+2]-cycloaddition reaction.

While there is a mechanistic spectrum of this reaction from a synchronous one-step process to a stepwise overall transformation (including radical pathways), to avoid mechanistic digressions that may not have chemical or stereochemical consequences, in this synthetic review article, we will refer to the azomethine ylide reaction as a pericyclic cycloaddition. [3+2]-Cycloadditions of azomethine ylide with homomultiple and heteromultiple unsaturated 2π-electron components have been extensively used to produce a wide range of

heterocycles [3]. There are several methods for the formation of azomethine ylides, including the thermolysis or photolysis of readily prepared aziridines, the dehydrohalogenation of immonium salts, and proton abstraction from imine derivatives of α-amino acids [3]. They are often generated in situ because of their high reactivity and/or transient existence; however, in some cases, stabilized ylides have been isolated and used further [4–6].

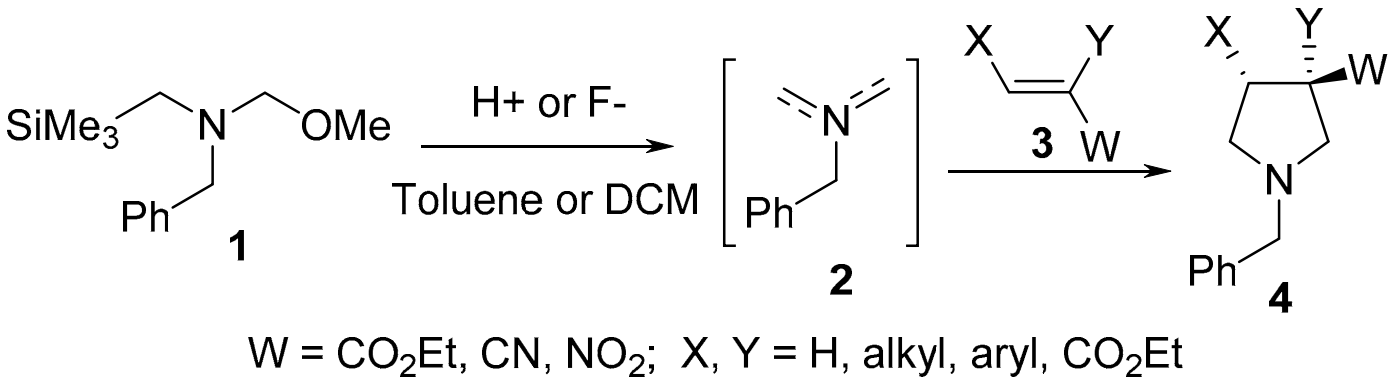
The synthesis of five-membered heterocyclic systems through azomethine ylides is one of the most adopted, efficient, and powerful approaches. Since the first report of successful the enantioselective [3+2]-cycloaddition of an azomethine ylide in 1991 [7], there has been tremendous progress in the chemistry regarding azomethine ylides. Azomethine ylides are extensively used in the synthesis of various heterocyclic systems such as pyrrolidines, pyrrolizidines, indolizidines, piperidines, oxazolidines, spiroindoles, spiropyrrolidines, and spiropiperidines, but they are also used for the total synthesis of complex natural products as well as bioactive compounds [8–15]. In recent years, the [3+2]-cycloaddition reaction has been extensively studied for the synthesis of heterocycles using different synthetic strategies [16,17]. In addition, the reaction is also investigated to understand the related reactivity, reaction conditions, intermediates, etc. [18,19].

This review article deals with the [3+2]-cycloaddition reaction of azomethine ylides with an unsaturated carbon–carbon bond (in either acyclic, alicyclic, heterocyclic, or exocyclic systems) that leads to the formation of pyrrolidinyl-containing analogs reported in the last two decades and their biological applications. This review article is intended to be a critical resource for the researchers involved or interested in azomethine ylides-mediated heterocyclic synthesis. It is also hoped that this review article will inspire chemists in this area of research.

2. Acyclic Unsaturated 2π-Electron Components

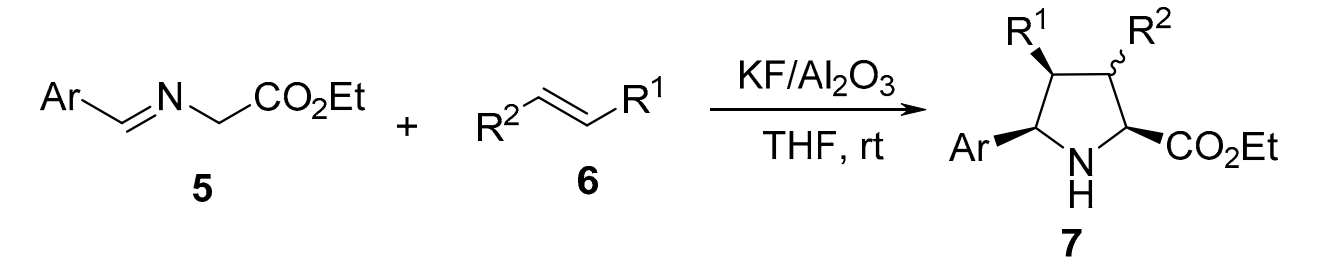
2.1. Intermolecular Cycloaddition Reaction of Azomethine Ylides to Acyclic Unsaturated 2π-Electron Components (Alkenes)

Unstabilized azomethine ylide **2** derived from benzyl(methoxymethyl)(trimethylsilylmethyl) amine **1** undergoes a [3+2]-cycloaddition reaction with electron-deficient alkenes **3** under continuous flow conditions in the presence of catalytic trifluoroacetic acid, thereby affording the corresponding pyrrolidines **4** (Scheme 1) [20].



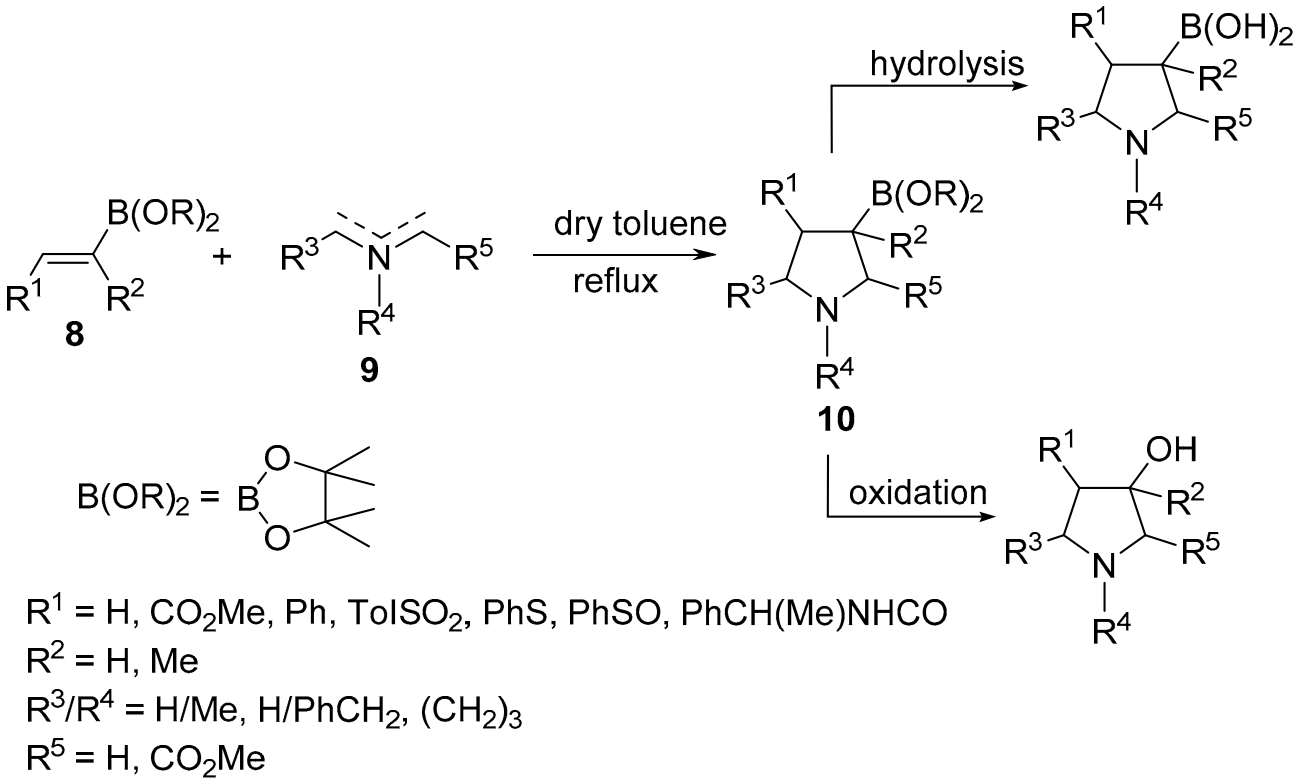
Scheme 1. Synthesis of pyrrolidines **4**.

Azomethine ylides generated via the deprotonation of α-imino-esters **5** undergo a [3+2]-cycloaddition reaction with unsaturated 2π-electron components **6** in the presence of the eco-friendly supported solid-base catalyst KF/Al_2O_3 to yield the corresponding pyrrolidines **7** with high regio- and diastereoselectivity (Scheme 2) [21].



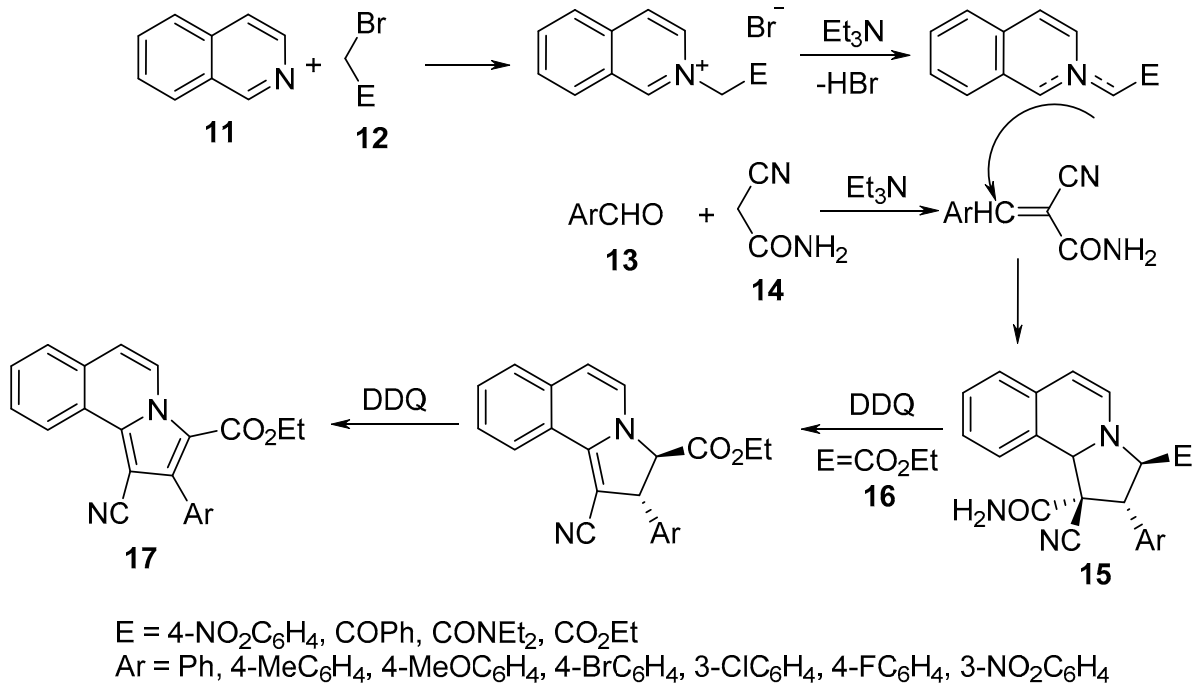
Scheme 2. Synthesis of pyrrolidines **7**.

Belfaitah et al. reported the cycloaddition reaction of azomethine ylides **9** with alkenyl boronates **8** to obtain the 3-boronic-ester-substituted pyrrolidines **10** (Scheme 3) [22].



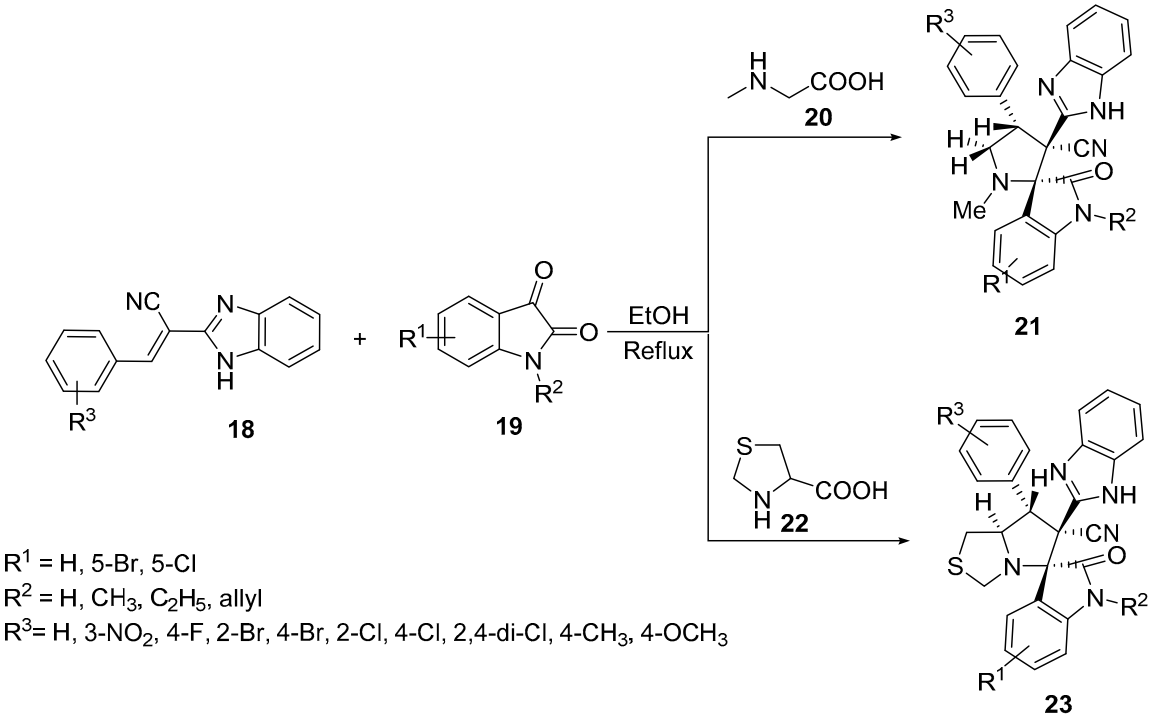
Scheme 3. Synthesis of 3-boronate pyrrolidines **10**.

Pyrrolo[2,1-*a*]isoquinolines **15** were obtained through a sequential one-pot, two-step tandem reaction of isoquinoline **11**, *α*-halogenated methylenes **12**, aromatic aldehydes **13**, and cyanoacetoamide **14** in the presence of triethylamine as a basic catalyst and 2,4-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidizing agent. The transformation was assumed to take place through [3+2]-cycloaddition of *N*-substituted carbonylmethyleneisoquinolinium bromide (formed via the reaction of isoquinoline **11** and **12**) with arylidene cyanoacetamide (formed via the condensation of cyanoacetamide **14** with aromatic aldehyde **13**) [23]. In the case of the ethyl bromoacetate **16** derivative, the formation of pyrrolo[2,1-*a*]isoquinolines **17** was observed probably due to DDQ oxidation (Scheme 4) [23].



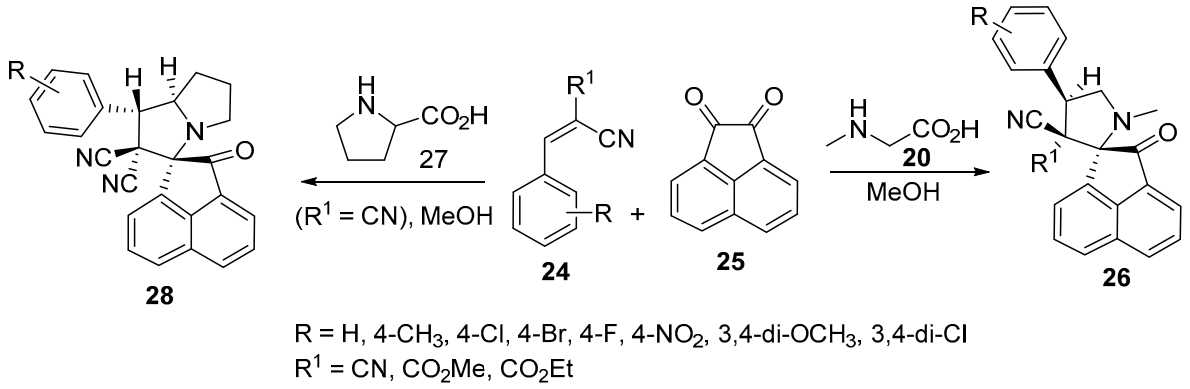
Scheme 4. Synthesis of pyrrolo[2,1-*a*]isoquinolines **15/17**.

Spiro[indoline-3,2′-pyrrolidines] **21** were prepared by the [3+2]-cycloaddition reaction of benzoimidazol-2-yl-3-phenylacrylonitriles **18** with azomethine ylides, which was generated in situ from the condensation of isatin **19** and sarcosine **20** in refluxing ethanol. Similarly, spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles] **23** were formed by using thioproline **22** as a secondary amino acid (Scheme 5) [24].



Scheme 5. Synthesis of spiro[indoline-3,2′-pyrrolidines] **21** and spiro[indoline-3,5′-pyrrolo[1,2-c]thiazoles] **23**.

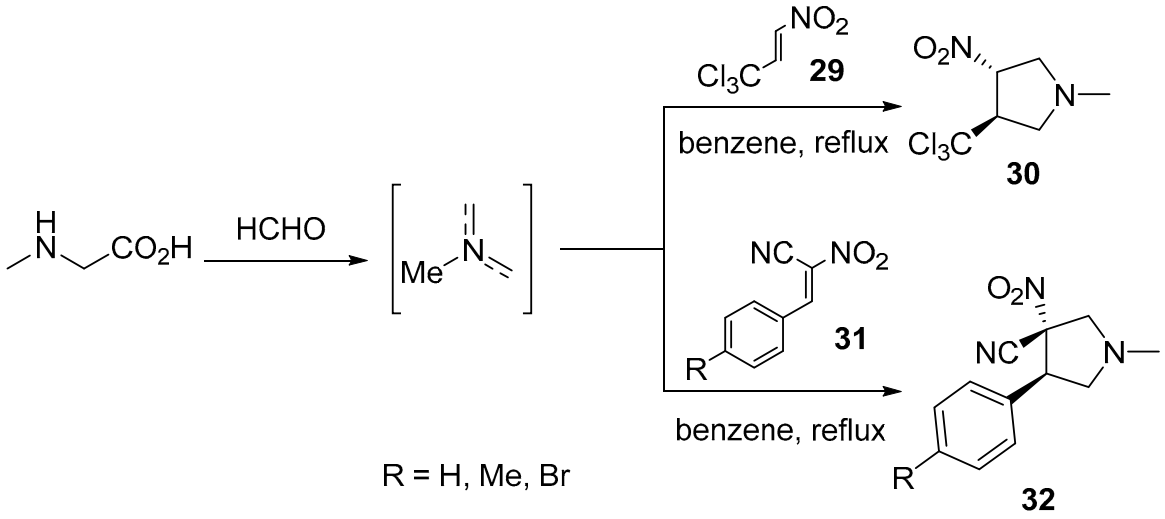
The chemistry was extended further to obtain spiro[acenaphthylene-1,2′-pyrrolidines] **26** and spiro[acenaphthylene-1,2′-pyrrolizidines] **28** possessing a cyano group from the azomethine ylides (generated from acenaphthenequinone **25**) with α-amino acids (sarcosine **20** and proline **27**) and Knoevenagel adducts **24** (Scheme 6) [25].



Scheme 6. Synthesis of spiro[acenaphthylene-1,2′-pyrrolidines] **26** and spiro[acenaphthylene-1,2′-pyrrolizidines] **28**.

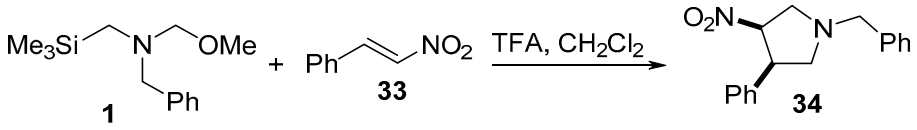
2.2. Nitroalkenes

Nitroalkenes are reactive, unsaturated 2π-electron components that are intensively used in cycloaddition reactions by various researchers [26]. 3-Nitro-4-(trichloromethyl) pyrrolidine **30** was obtained through the cycloaddition of trans-3,3,3-trichloro-1-nitroprop-1-ene **29** with azomethine ylide (obtained from the condensation of paraformaldehyde and sarcosine in refluxing benzene). Quantum chemical calculations (DFT, M062X/6-311G(d)) explained the reaction pathway [27]. Analogously, 3-nitro-4-arylpyrrolidine-3-carbonitriles **32** were obtained through the cycloaddition of the azomethine ylide with (2*E*)-3-phenyl-2-nitroprop-2-enenitriles **31** [28] (Scheme 7).



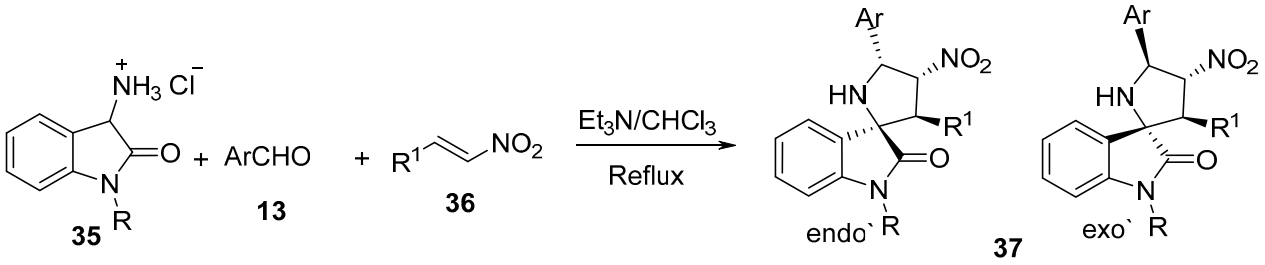
Scheme 7. Synthesis of 3-nitro-4-(trichloromethyl)pyrrolidine **30** and 3-nitro-4-arylpyrrolidine-3-carbonitriles **32**.

Trans-3-nitropyrrolidine **34** was prepared by reacting *trans*-1-nitro-2-phenylethylene **33** with *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine **1**, which is an azomethine ylide equivalent, in the presence of trifluoroacetic acid in dichloromethane. Some of the synthesized **34** revealed promising inhibitory properties as Na^+ channel blockers, which are useful in the treatment of ischemic stroke (Scheme 8) [29].



Scheme 8. Synthesis of trans-3-nitropyrrolidine **34**.

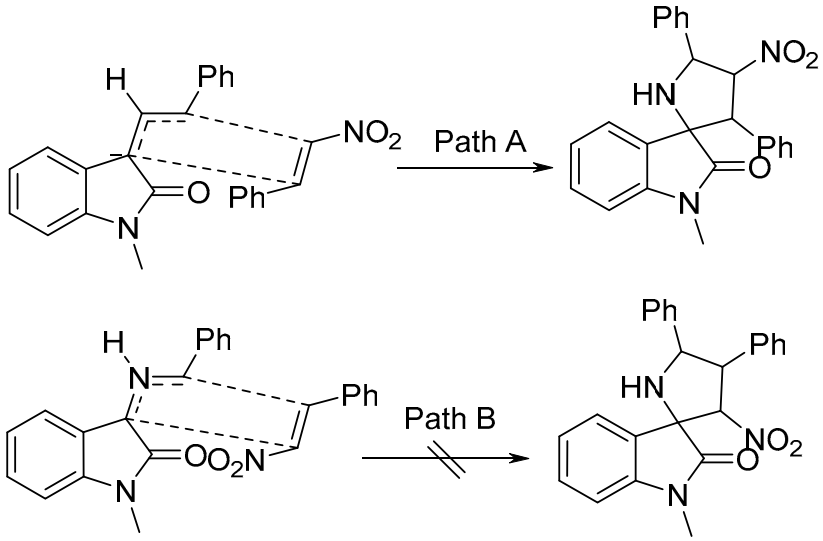
Another set of spiro compounds, spiro[pyrrolidine-2,3′-oxindoles] **37,** were regioselectively synthesized by a multicomponent reaction of azomethine ylides, generated in situ from 3-aminoindoline-2-ones hydrochloride **35**, with aldehydes **13** and (*E*)-nitroalkenes **36** (Scheme 9) [30].



R = H, Me, Bn; Ar = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$F_3CC_6H_4$, 1-naphthyl, 2-thienyl, $CH_3(CH_2)_2$, cyclohexyl;
R^1 = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$F_3CC_6H_4$, 2- naphthyl, 2-thienyl

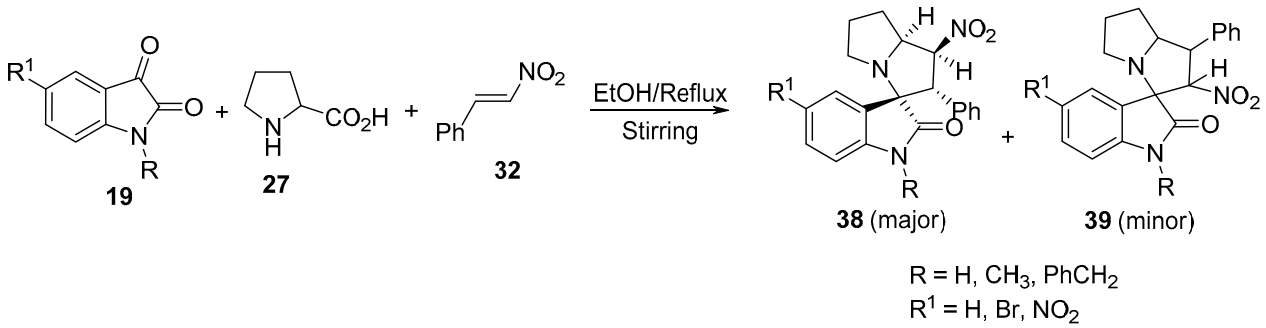
Scheme 9. Synthesis of spiro[pyrrolidin-2,3′-oxindoles] **37**.

It was assumed that, based on the secondary orbital interaction (SOI) of the electron-poor nitroalkenes **36** with the azomethine ylide, Path A was exclusively followed, as the *endo*-transition state in the reaction sequence was more energetically favorable (Scheme 10) [30].



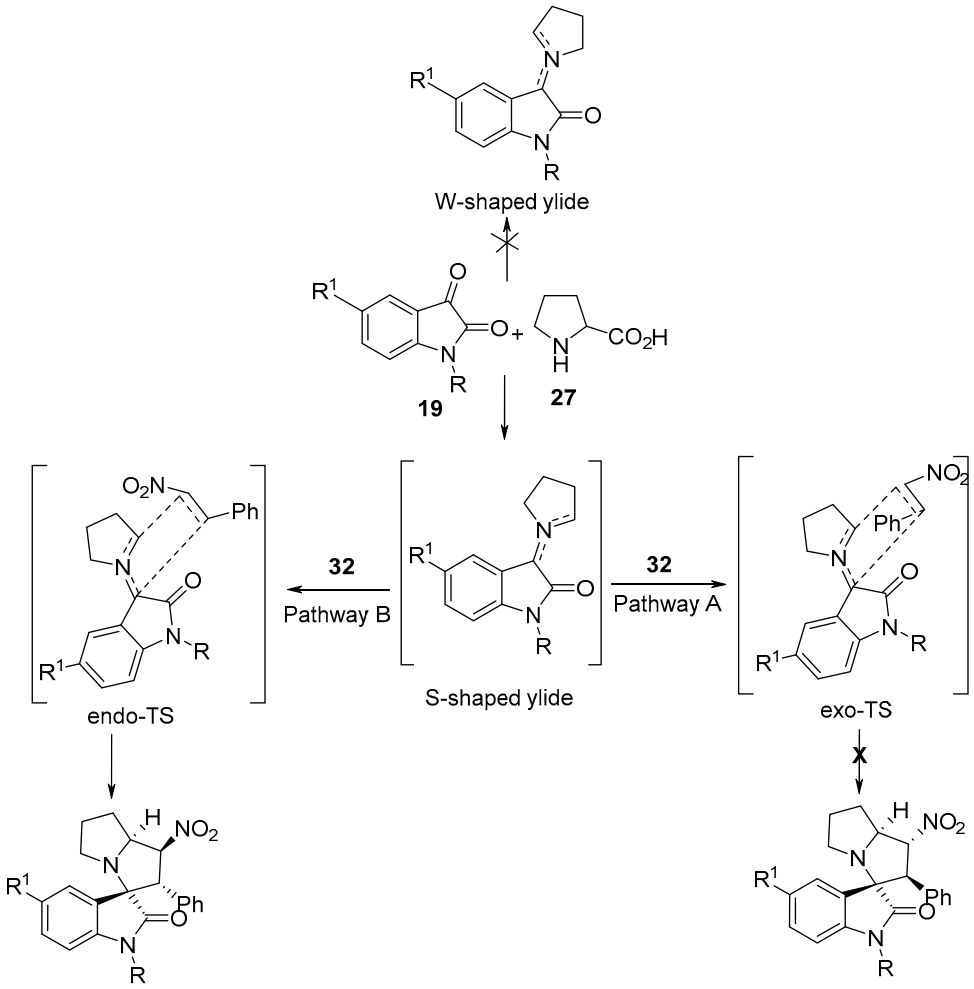
Scheme 10. Proposed mechanism for the cycloaddition of azomethine ylide (via endo′-transition state).

Spirooxindolo-nitropyrrolizines **38** (major product) and **39** (minor product) were obtained from the cycloaddition reaction of azomethine ylides, generated in situ from isatin **19**, with proline **27** and (*E*)-*ß*-nitrostyrene **32** (Scheme 11) [31]. A significant inversion in the regioselectivity was observed when the polar [3+2]-cycloaddition of the azomethine ylides was attempted with trans-β-nitrostyrene instead of (*E*)-1-phenyl-2-nitropropene.



Scheme 11. Synthesis of spirooxindolo-nitropyrrolizines **38** and **39**.

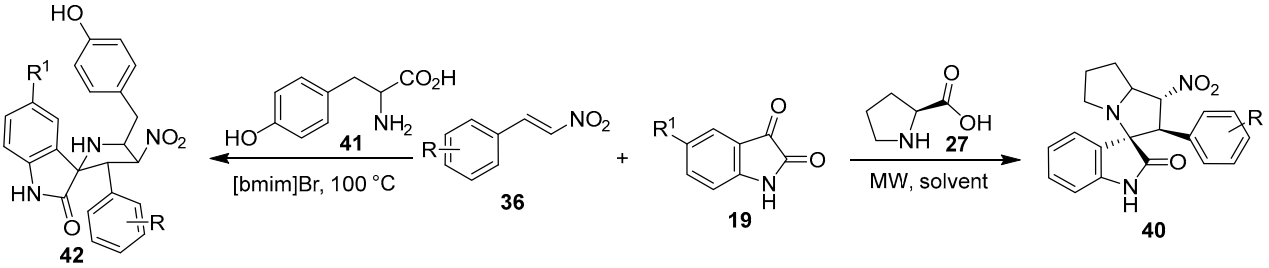
It was assumed that the reaction proceeds through *S*-shaped ylide with a cycloaddition via the endo-transition state (pathway B), yielding cycloadducts **38**, and not the exo-transition state (pathway A). Computational studies (Gaussian 03) of the transition states (Density Functional Theory (DFT), B3LYP, and 6-31G(d,p) basis set) confirmed these assumptions (Scheme 12) [31].



Scheme 12. Proposed mechanism for the cycloaddition of the azomethine ylides with nitrostyrene.

A series of spiro[indoline-3,3′-pyrrolizin]-2-ones **40** with potential anti-amyloidogenic properties useful against Alzheimer's disease were obtained by the microwave-assisted cycloaddition of nitroalkenes **36** and azomethine ylides (generated from isatin **19** and *L*-proline **27**) [32]. Analogously, spirooxindole-pyrrolidines **42** were obtained by the reaction of tyrosine **41** in an ionic liquid [bmim]Br at 100 °C. Promising antiproliferation

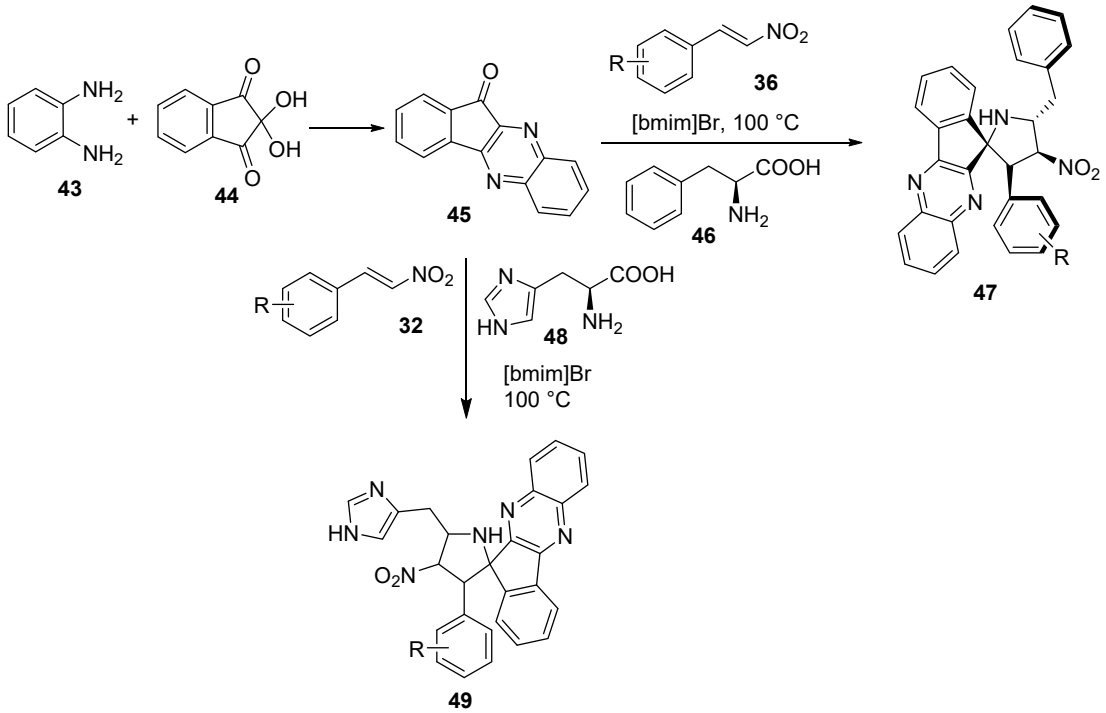
properties were observed for some of the synthesized compounds (**42**) against human A549 (adenocarcinoma basal epithelial) and Jurkat (*T*-cell lymphoma) cell lines (MTT assay) using Camptothecin as a positive control; the compounds exhibited a safe response against the non-cancer cell lines MCF-10 (normal breast) and PCS-130-010 (lung smooth muscle). Caspase-dependent apoptosis (especially caspase-3) was mentioned as the mode of action for the observed antiproliferative activity (Scheme 13) [33].



R = H, 4-Me, 4-OMe, 2,4-$(OMe)_2$, 2,5-$(OMe)_2$, 2,6-$(OMe)_2$, 3,4-$(OMe)_2$, 4-OH-3-OMe, 4-Cl, 4-Br, 3-NO_2
R^1 = H, OCF_3

Scheme 13. Synthesis of spiro-indolines **40**, **42**.

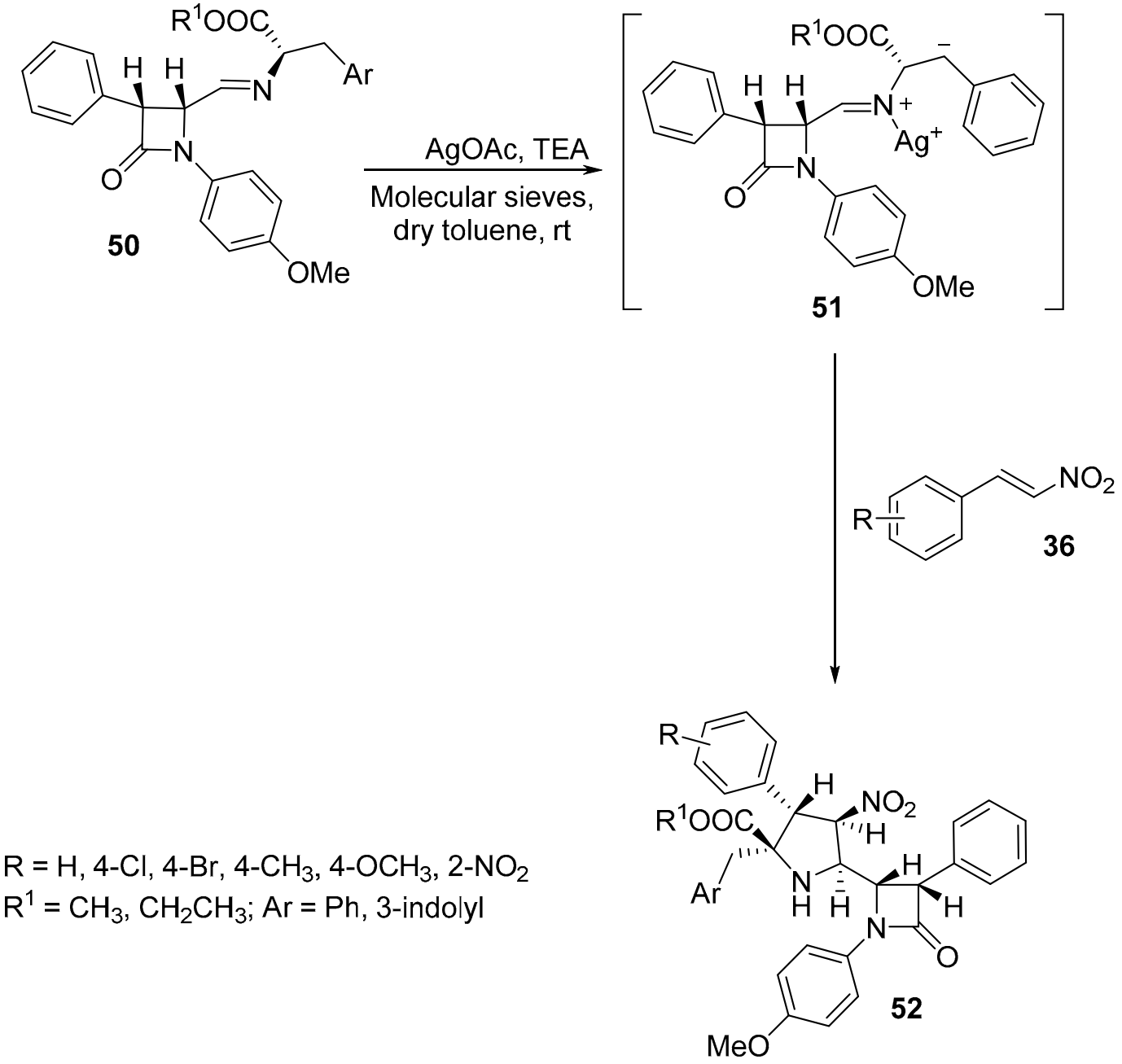
Ionic liquid chemistry was utilized to prepare 4′-nitrospiro[indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidines] **47** by the cycloaddition reaction of nitroalkenes **36** with azomethine ylide (generated from indenoquinoxalinone **45** and *L*-phenylalanine **46**) in an ionic liquid [bmim]Br. Some of the synthesized agents revealed antimycobacterial properties (*Mycobacterium tuberculosis* H37Rv) with an efficacy comparable to that of ethambutol (reference standard) [34]. Similarly, spiro compounds **49** were obtained by using *L*-histidine **48** instead of *L*-phenylalanine **46** in this reaction. Some of the synthesized compounds revealed cholinesterase (acetylcholinesterase and butyrylcholinesterase)-inhibitory properties with considerable efficiencies relative to Galantamine (Scheme 14) [35].



R = H, 4-Br, 2-Cl, 4-Cl, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-F, 4-F, 3-NO_2, 2-furanyl, 2-pyridinyl

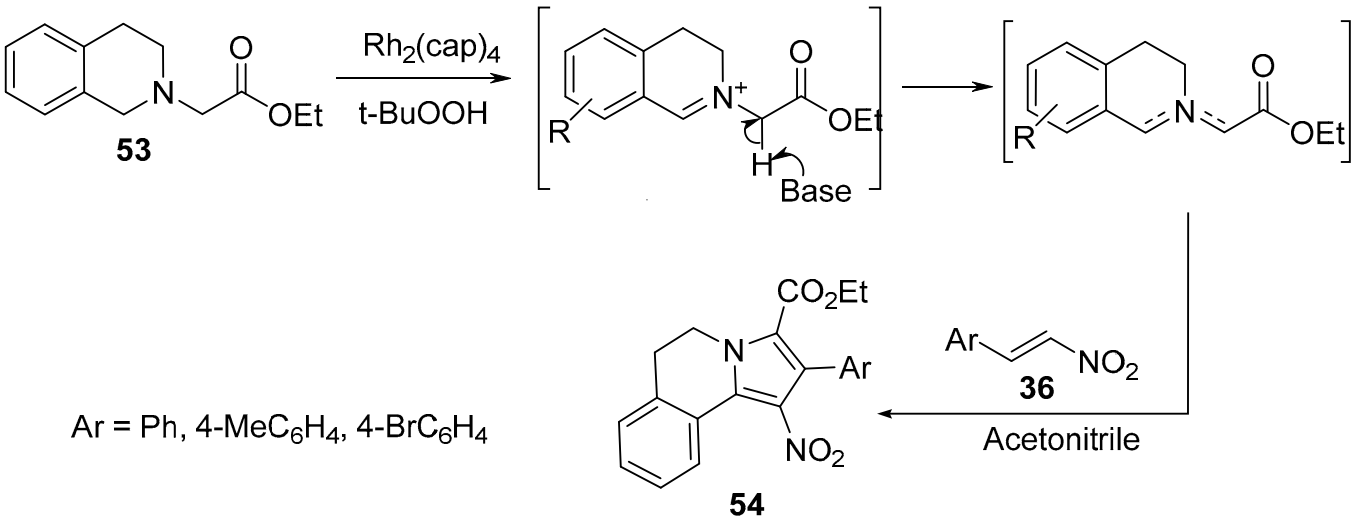
Scheme 14. Synthesis of 4′-nitrospiro[indeno[1,2-b]quinoxaline-11,2′-pyrrolidines] **47**, **49**.

Pyrrolidinyl *ß*-lactams **52** were prepared as single diastereomers by the reaction of azomethine ylides **51**, generated from β-lactam imines of α-amino ester **50**, with nitrostyrenes **36** in the presence of silver acetate and triethylamine (Scheme 15). This reaction is an example of [3+2]-cycloaddition reaction via *N*-metallo azomethine ylide [36].



Scheme 15. Synthesis of pyrrolidinyl β-lactams **52**.

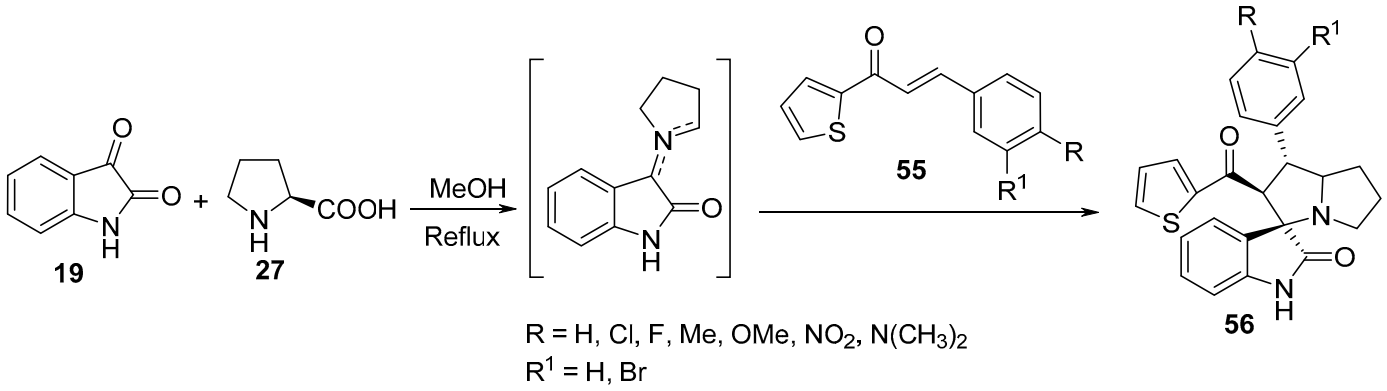
3,4-Dihydropyrrolo[2,1-*a*]isoquinolines **54** were obtained by the [3+2]-cycloaddition reaction of nitroalkenes **36** with an azomethine ylide that was efficiently generated via the dirhodium(II)caprolactamate [$Rh_2(cap)_4$] catalyzed oxidation of tetrahydroisoquinoline **53** (Scheme 16). Doyle's oxidative protocol was used to generate azomethine ylides, which were further trapped in situ via [3+2]-cycloaddition [37].



Scheme 16. Synthesis of pyrrolo[2,1-*a*]isoquinolines **54**.

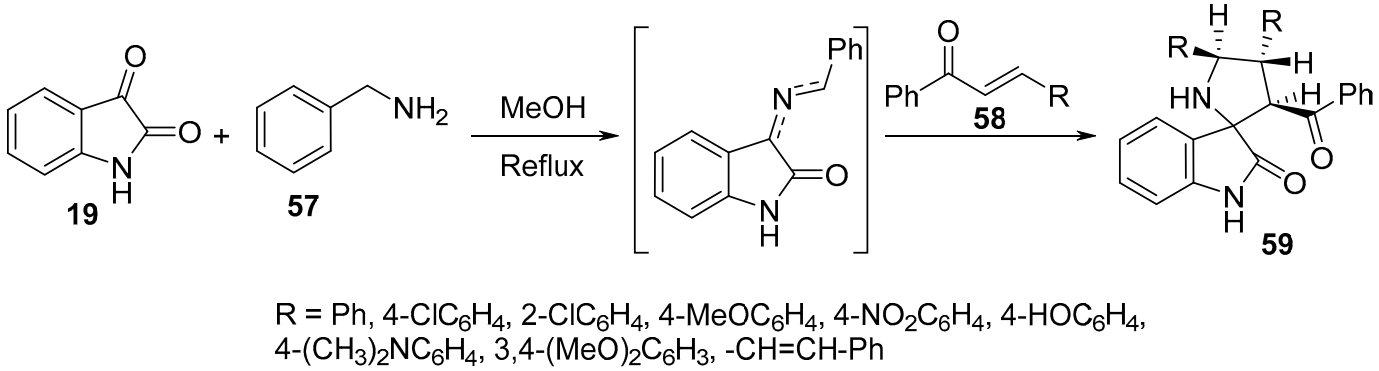
2.3. α,β-Unsaturated Polarophiles

Spiro[3*H*-indole-3,3′-[3*H*]pyrrolizin]-2-ones **56** were synthesized by the cycloaddition reaction of (*E*)-3-aryl-1-(thiophen-2-yl)-prop-2-en-1-ones **55** with azomethine ylide generated in situ from the condensation of isatin **19** with *L*-proline **27** (Scheme 17). Some of the synthesized spiroindoles **56** showed potential antibacterial activity against *Staphylococcus aureus* and *Salmonella typhi* (relative to Streptomycin) and antifungal activity against *Candida albicans* (relative to Amphotericin B) [38].



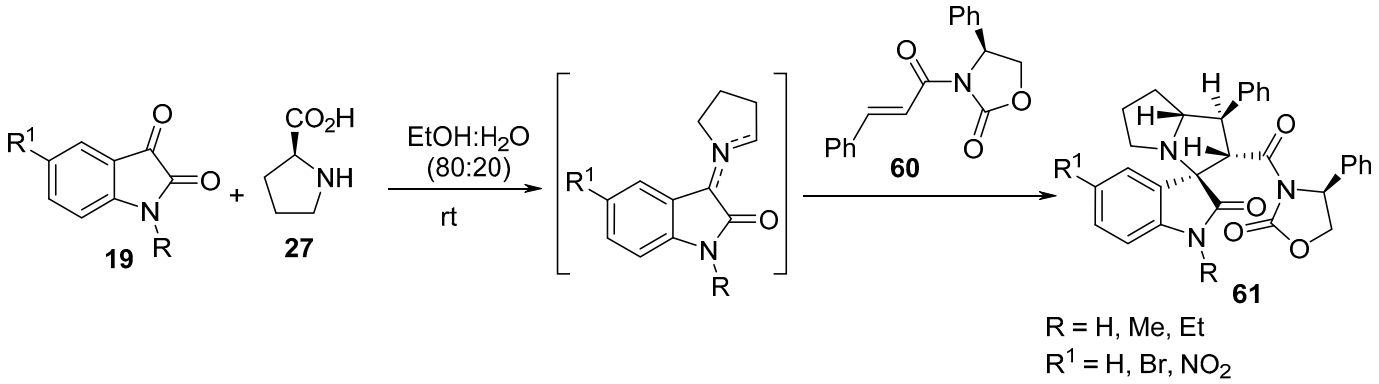
Scheme 17. Synthesis of spiro[3H-indole-3,3′-[3H]pyrrolizin]-2-ones **56**.

Spiro[pyrrolidine-2,3′-indolin]-2′-ones **59** were synthesized by the multi-component cycloaddition reaction of chalcones **58** and an azomethine ylide formed from the condensation of isatin **19** and benzylaminemine **57**. Few of the synthesized spiro-analogs **59** revealed potent inhibitory advanced glycation end (AGE) product formation in a bovine serum albumin (BSA)-glucose assay that was higher than that of aminoguanidine (standard reference). The occurrence of AGE is related to hyperglycemia observed as a complication of diabetes (Scheme 18) [39].



Scheme 18. Synthesis of spiro[pyrrolidine-2,3′-indolin]-2′-ones **59**.

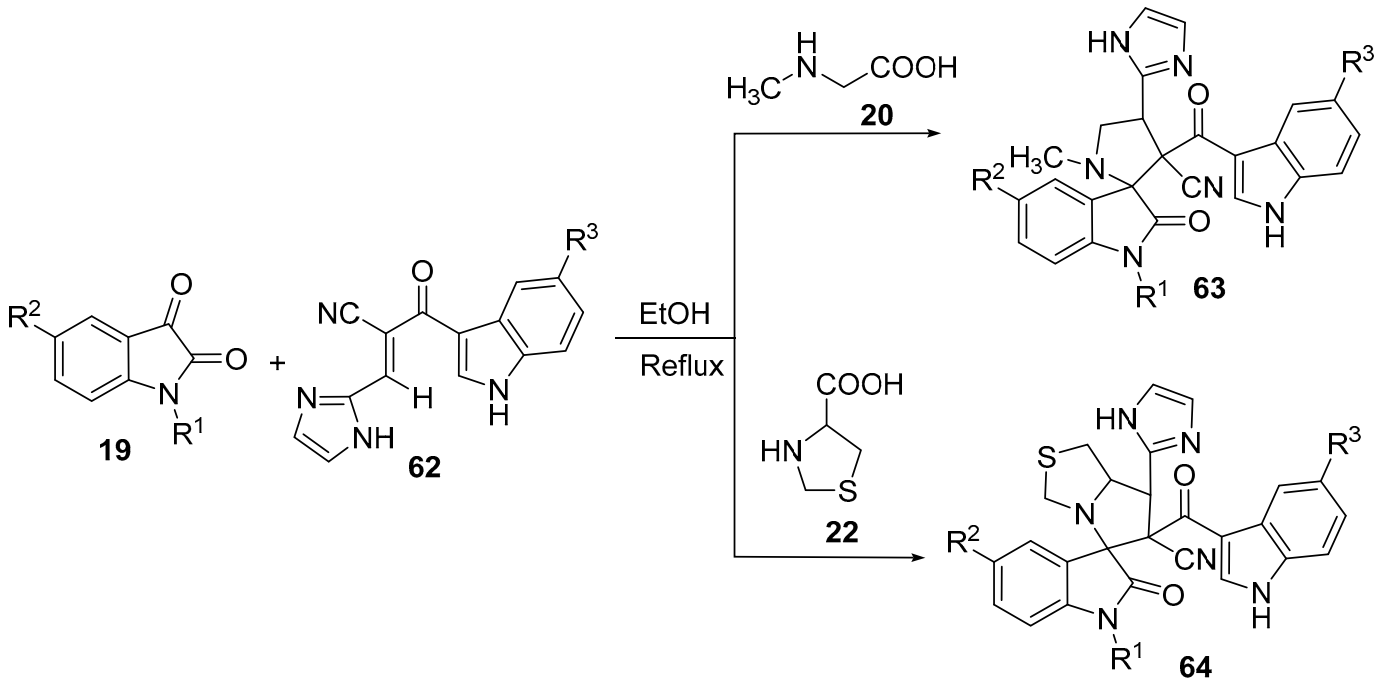
Taghizadeh et al. reported an efficient and greener multicomponent protocol for the synthesis of regio-, diastereo-, and enantioselective spiro-oxindolopyrrolizidines **61** from optically active cinnamoyl oxazolidinone **60** and azomethine ylides that were formed from the condensation reaction of isatin **19** and *S*-proline **27** (Scheme 19) [40].



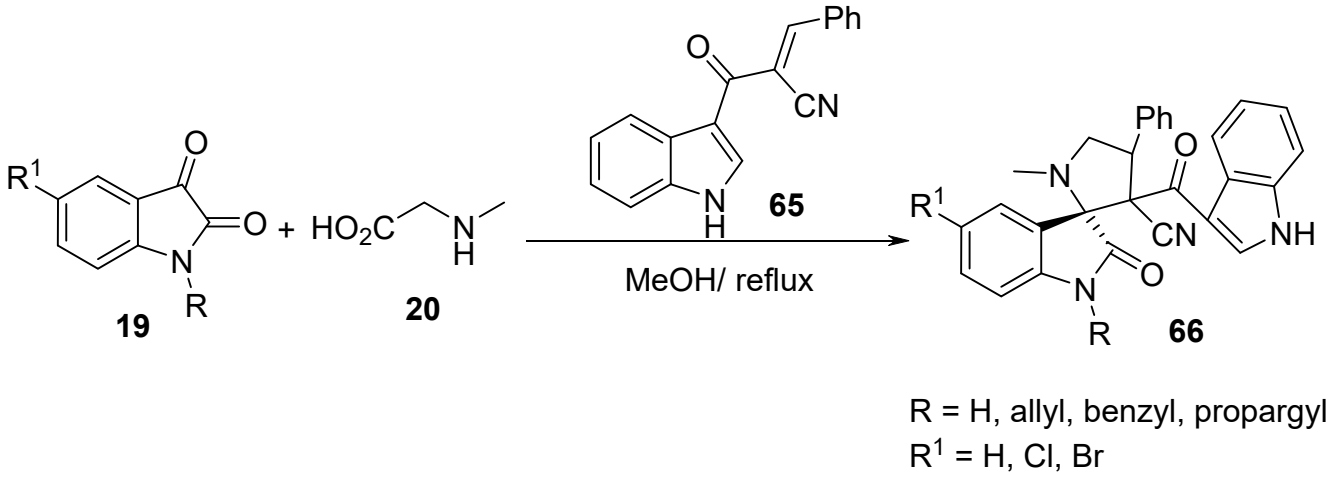
Scheme 19. Synthesis of the spiro-oxindolopyrrolizidines **61**.

Spiro[indoline-3,2′-pyrrolidines] **63** were prepared by the reaction of compound **62** containing an *α*,*β*-unsaturated ketone function with azomethine ylides obtained from isatin **19** and sarcosine **20**, while spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles] **64** was obtained from a similar reaction that involved thioproline **22** instead of sarcosine **20** (Scheme 20). Some of the synthesized spiro-compounds, **63** and **64,** revealed anticancer properties against the A549 lung cancer cell line (MTT assay) [41,42] and spiro-compound **63** also showed antimicrobial activity against Gram-positive (*Micrococcus luteus*, *Enterobacter aerogenes*, *Staphylococcus aureus* and *Staphylococcus aureus* "MRSA-methicillin resistant") and Gram-negative (*Salmonella typhimurium*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Shigella flexneri*) bacterial strains and fungi (*Malassesia pachydermatis*, *Candida albicans*) relative to Streptomycin and Ketoconazole (used as antibacterial and antifungal standard references, respectively) [42].

Spiropyrrolidine-oxindoles **66** were prepared in appreciable yields by the cycloaddition reaction of the unsaturated 2π-electron component (*E*)-2-(1*H*-indole-3-carbonyl)-3-phenylacrylonitrile **65** and azomethine ylides obtained from the condensation of isatin **19** and sarcosine **20** (Scheme 21) [43].

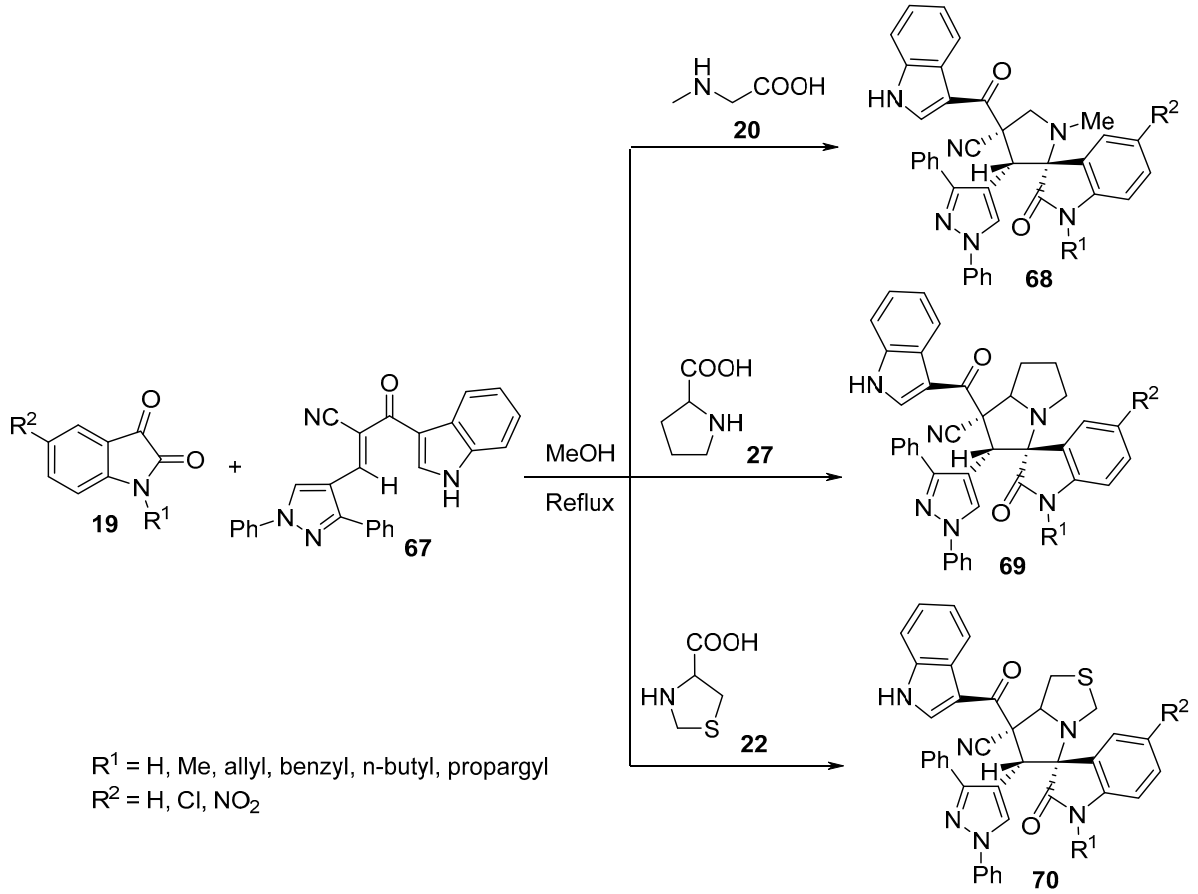


Scheme 20. Synthesis of spiro[indoline-3,2′-pyrrolidines] **63** and spiro[indoline-3,5′-pyrrolo[1,2-c]thiazoles] **64**.



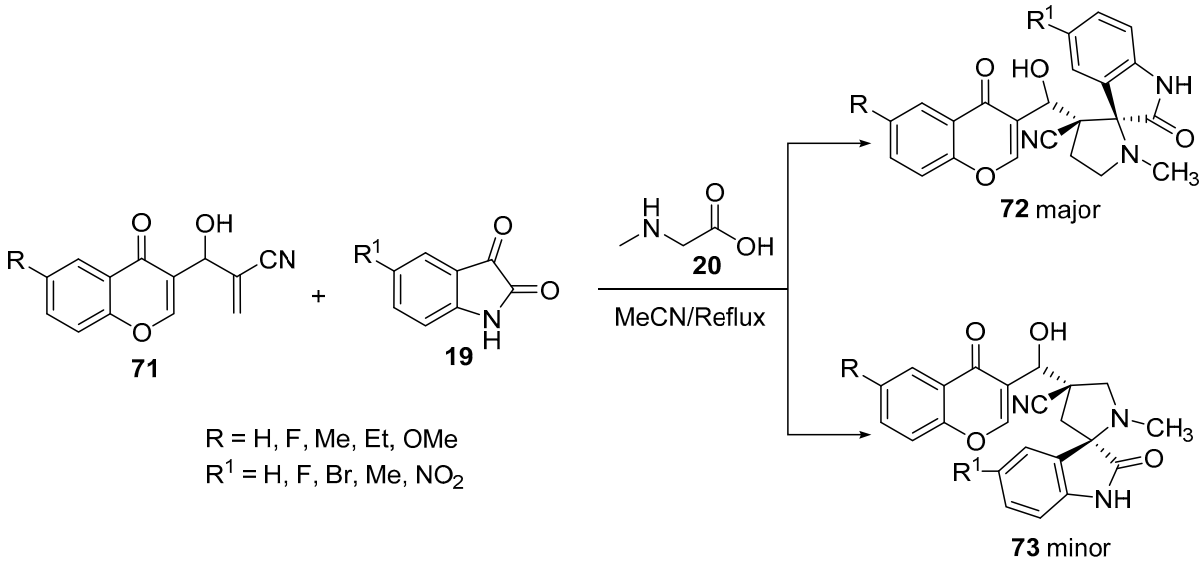
Scheme 21. Synthesis of spiropyrrolidine-oxindoles **66**.

Similarly, spiropyrrolidine–oxindoles **68**–**70** were obtained from the reaction of enone **67** with azomethine ylides derived from isatin **19** and *α*-amino acids (sarcosine **20**, proline **27** or thioproline **22**). Among all the synthesized compounds, some showed antimicrobial properties against Gram-positive and Gram-negative bacterial as well as fungal strains using Streptomycin and Ketconazole as standard references (Scheme 22) [44].



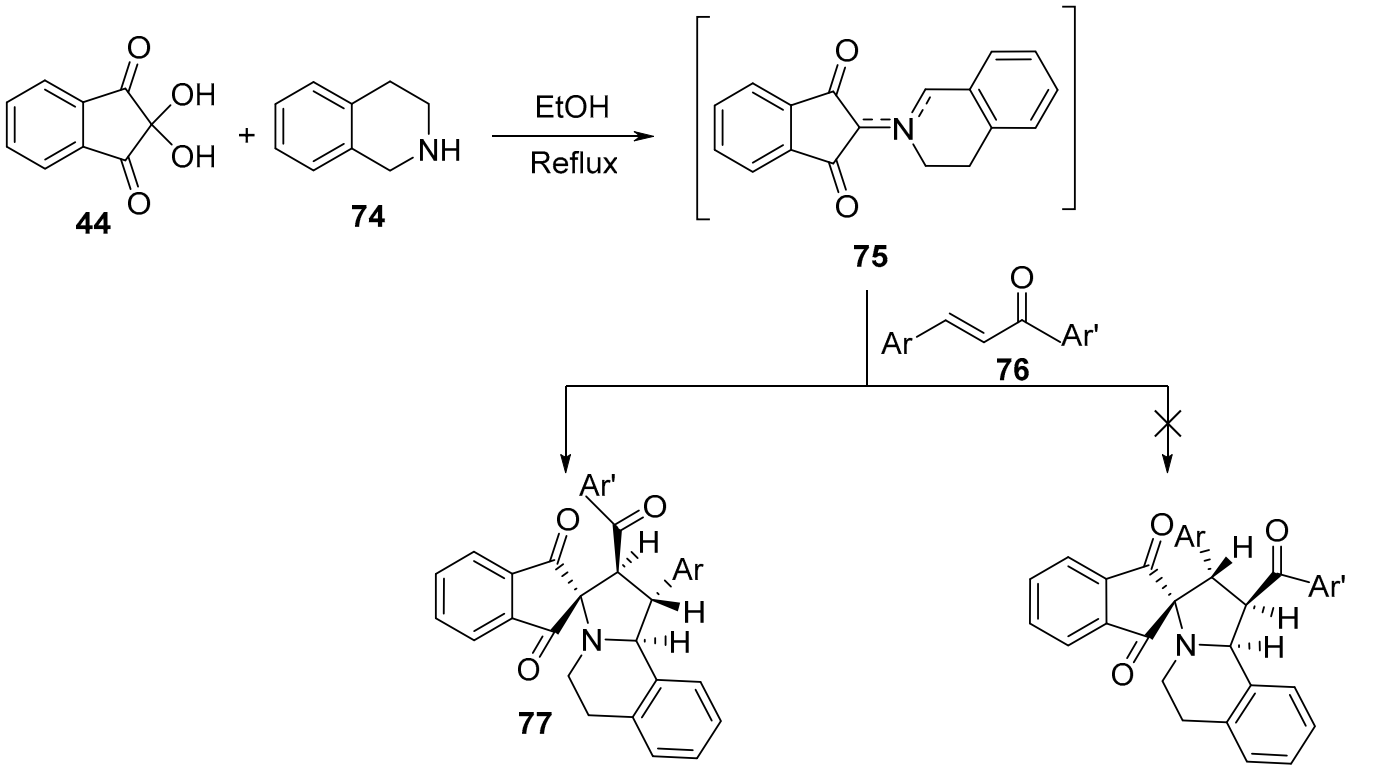
Scheme 22. Synthesis of spiropyrrolidine-oxindoles **68**–**70**.

The unsaturated 2π-electron component, 2-[hydroxyl(4-oxo-4*H*-chromen-3-yl)methyl] acrylonitrile **71,** was synthesized by the Baylis–Hillman reaction of chromene-3-aldehyde, treated with the azomethine ylides (from isatin **19** and sarcosine **20**), which afforded the corresponding regioselective spiro[pyrrolidine-oxindoles] **72** and **73** as major and minor products, respectively (Scheme 23) [45].



Scheme 23. Synthesis of spiro[pyrrolidine-oxindoles] **73**, **74**.

A convenient method for the selective construction of spiroindane-1,3-diones **77** relies upon the generation of unstabilized azomethine ylides from the initial condensation between ninhydrin **44** and 1,2,3,4-tetrahydroisoquinoline **74.** Subsequent azomethine ylide cycloaddition onto the conjugated double bond of chalcone **76** was exploited, giving target cycloadducts with good yields (77–94%) and diastereoselectivity (Scheme 24) [46].

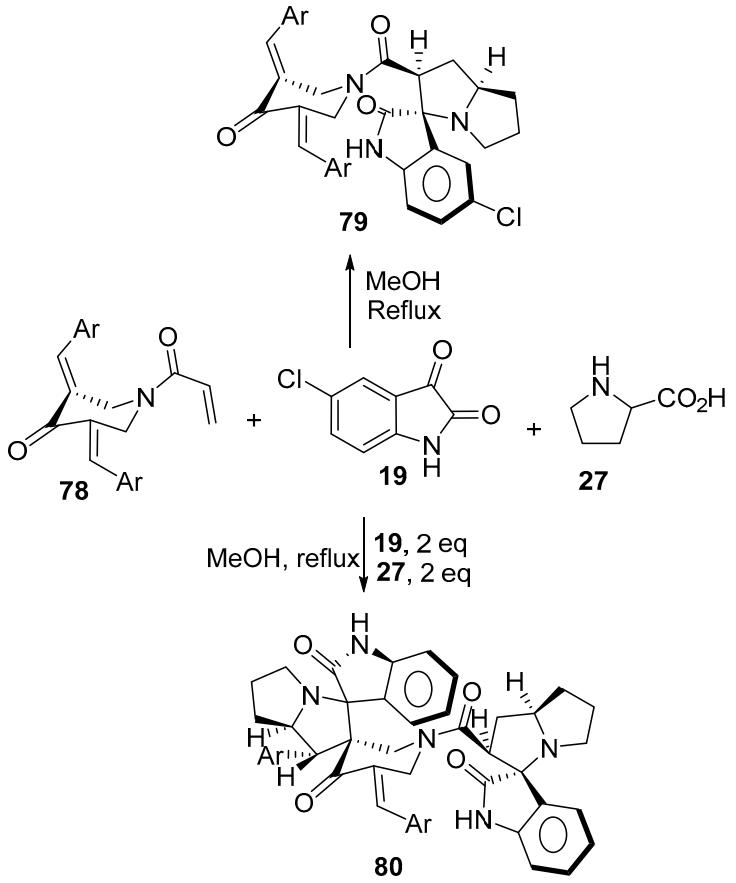


Ar = Ph, 4-CNC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$
Ar' = Ph, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 4-MeOC$_6$H$_4$

Scheme 24. Synthesis of spiroindane-1,3-diones **77**.

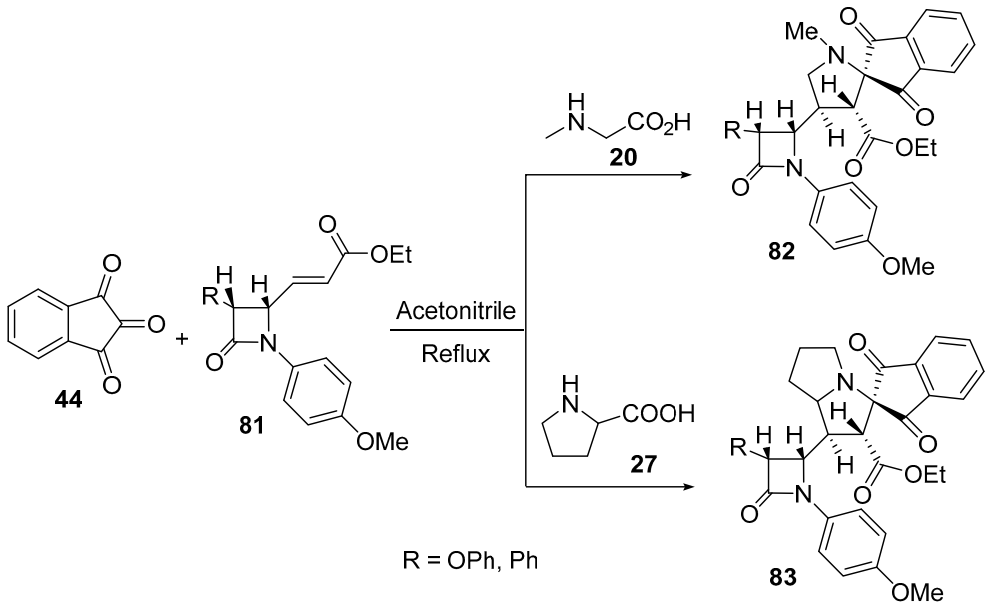
The reaction of azomethine ylide generated from 5-choloroisatin **19** and *L*-proline **27** as well as 1-acryloyl-4-piperidinones **78** yielded the corresponding spirooxindole-pyrrolizines **79** (yield 62–84%). Some of the synthesized cycloadducts **79** displayed cholinesterase-inhibitory properties (acetylcholinesterase and butyrylcholinestrase) with potency relative to Galantamine [47]. When the reaction was conducted in a 1:2:2 molar ratio of 1-acryloyl-4-piperidinones **78,** isatin **19,** and *L*-proline **27,** respectively, the bisspiropyrrolizines **80** were formed instead (yield 53–74%). It was found that most of the mono-spiropyrrolizines **79** (obtained using a 1:1:1 molar ratio of the reactants in yields of 73–84%) revealed higher cholinesterase enzyme (acetylcholinesterase and butyrylcholinestrase)-inhibitory activity than the bisspiropyrrolizine derivatives **80** (Scheme 25) [48].

The reaction of 3-(3-phenylazetidin-2-yl) acrylates **81** with azomethine ylide formed by the condensation of ninhydrin **44** and amino acids (sarcosine **20**/*L*-proline **27**) afforded the corresponding spiroindanopyrrolidines **82** and spiroindanopyrrolizines **83** (Scheme 26). The synthesized cycloadducts **82** and **83** showed antibacterial properties against *Proteus mirabilis*, *Proteus vulgaris*, *Salmonella typhi*, and *Staphylococcusi aureus* relative to Tetracycline (standard reference drug) [49].



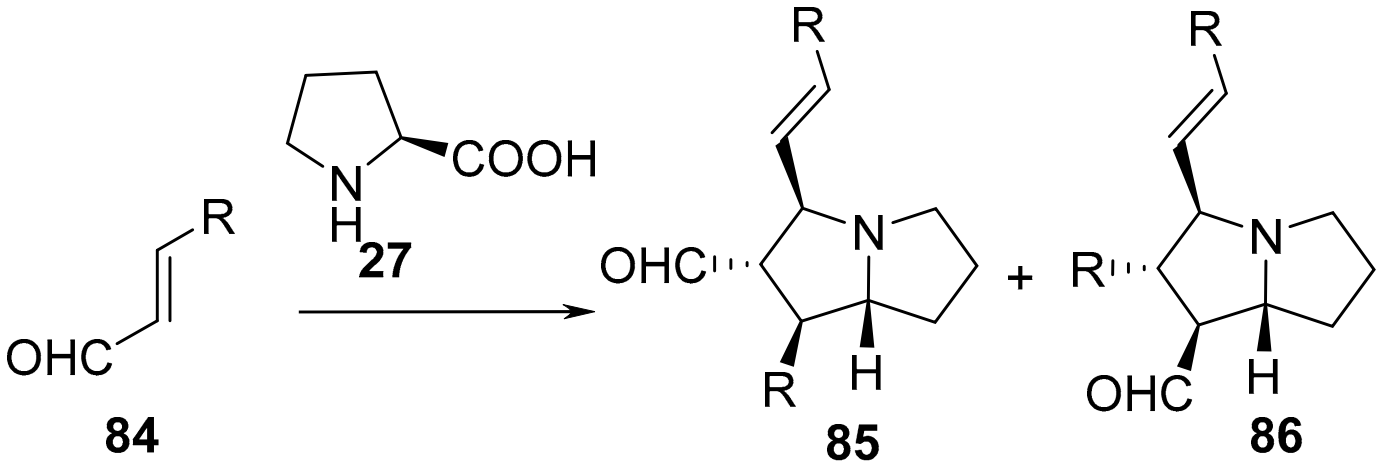
Ar = Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 2-FC_6H_4, 3-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 1-naphthyl

Scheme 25. Synthesis of mono-spiropyrrolizines **79** and bisspiropyrrolizines **80**.



Scheme 26. Synthesis of spiroindanopyrrolidines **82** and spiroindanopyrrolizines **83**.

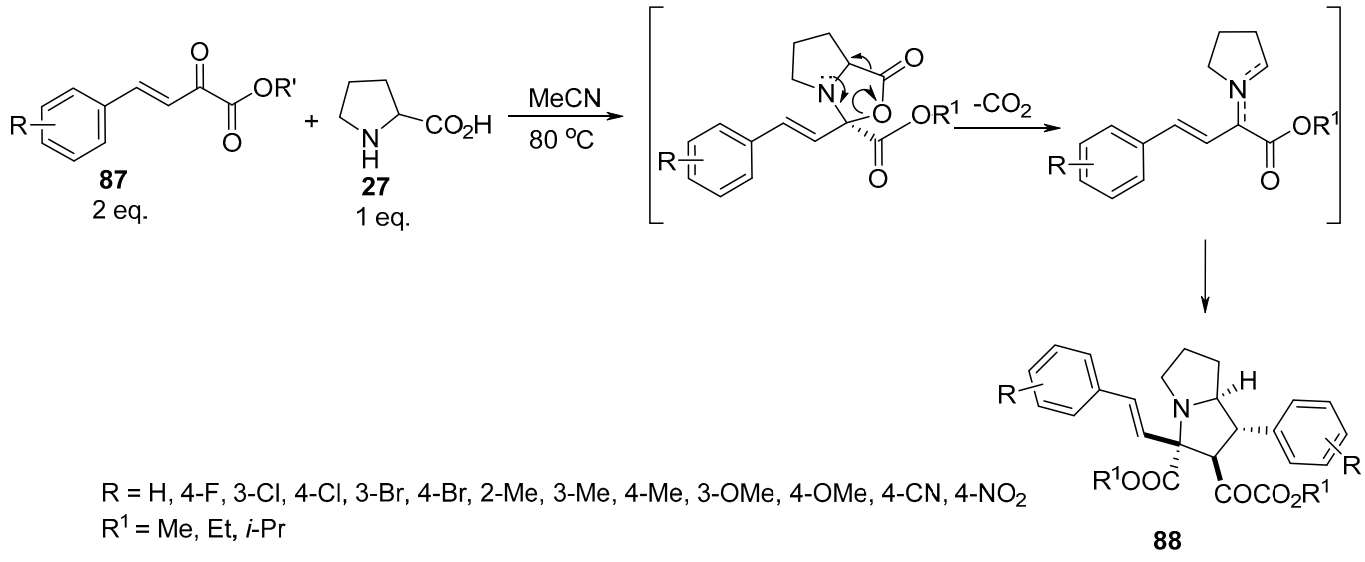
Cycloaddition of cinnamaldehydes **84** with azomethine ylides, generated from another cinnamaldehyde molecule **84** and *L*-proline **27**, afforded hexahydro-1*H*-pyrrolizines **85** and **86** in different ratios depending on the heating method (conventional heating, 25–80 °C vs. with microwave technique) and the solvent used (MeCN, DMF, toluene, CH_2Cl_2, DMSO) (Scheme 27) [50].



R = Ph, 2-furanyl, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$

Scheme 27. Synthesis of hexahydro-1*H*-pyrrolizines **85** and **86**.

Pyrrolizidines of type **88** were obtained by reacting β,γ-unsaturated α-keto esters of type **87** with proline **27** in a 2:1 molar ratio. The reaction was assumed to proceed via the formation of azomethine ylides by the condensation of the starting unsaturated esters of type **87** with amino acid **27**, which, in turn, interacted with another molecule of **87** to ultimately yield pyrrolizidines of type **88** (Scheme 28) [51].

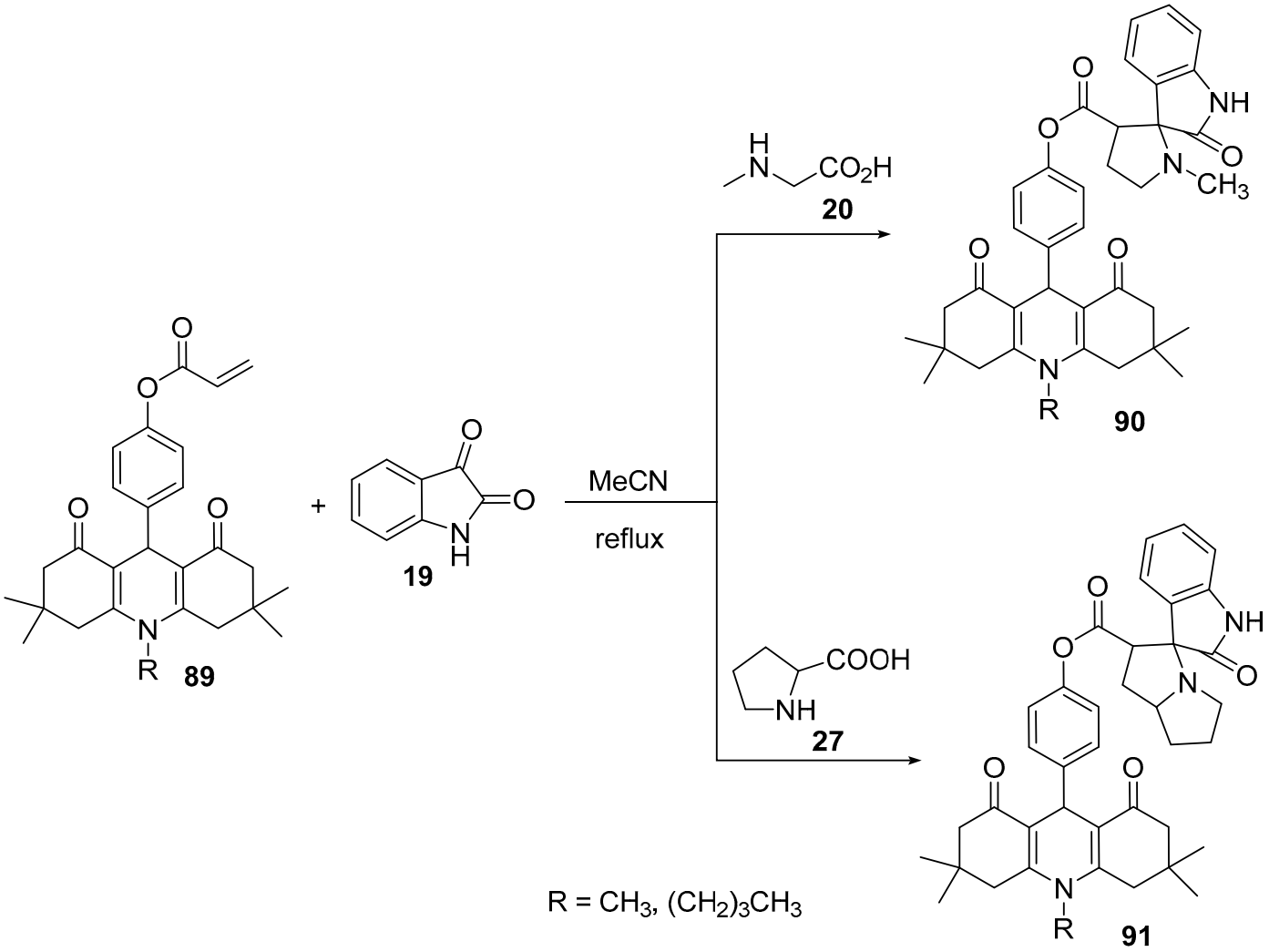


R = H, 4-F, 3-Cl, 4-Cl, 3-Br, 4-Br, 2-Me, 3-Me, 4-Me, 3-OMe, 4-OMe, 4-CN, 4-NO_2
R^1 = Me, Et, *i*-Pr

Scheme 28. Synthesis of pyrrolizidines **88**.

2.4. Acrylates

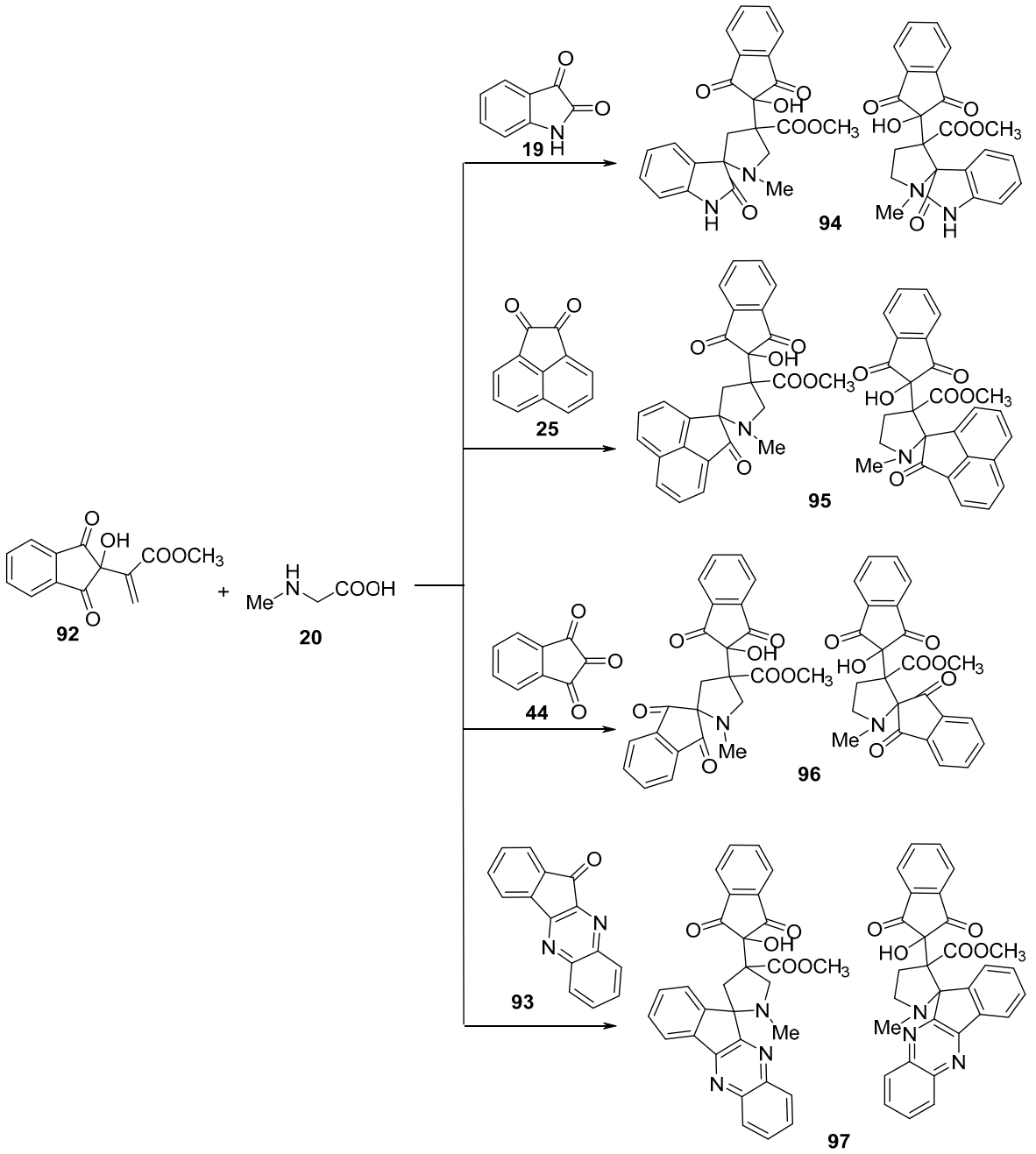
The reaction of *O*-acryloylacridinediones **89** with azomethine ylides, generated from isatin **19** and secondary amino acids (sarcosine **20**/proline **27**), afforded the corresponding spiro-pyrrolidines **90** and spiro-pyrrolizidines **91** (Scheme 29) [52].



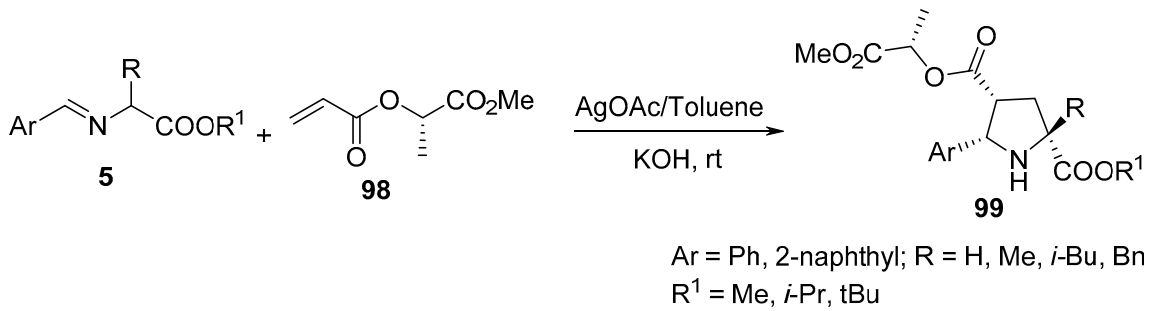
Scheme 29. Synthesis of spiro-pyrrolidines/pyrrolizidines **90/91**.

Spiropyrrolidines **94**–**97** were obtained via the reaction of methyl 2-(1*H*-inden-2-yl)acrylate **92** with azomethine ylides generated in situ by reacting ketones (isatin **19**, acenaphthenequinone **25**, ninhydrin **44,** or 11*H*-indeno[1,2-*b*]quinoxaline-11-one **93**) with sarcosine **20** (Scheme 30) [53].

The reaction of methyl lactate acrylates of type **98** with azomethine ylides, generated from imino-esters **5** in the presence of silver acetate and KOH, gave chiral proline derivatives of type **99** (Scheme 31) [54].

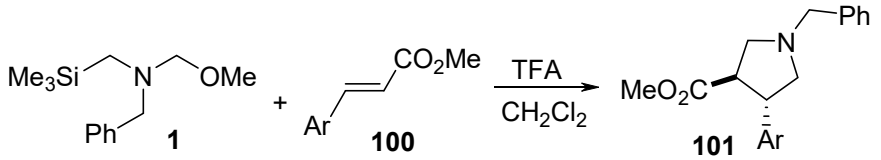


Scheme 30. Synthesis of spiropyrrolidines **94**–**97**.



Scheme 31. Synthesis of chiral prolines **99**.

The reaction of *trans* arylacrylates **100** with the azomethine ylide, formed from benzyl-(methoxymethyl)[(trimethylsilyl)methyl]amine **1** in the presence of a catalytic amount of trifluoroacetic acid, afforded the corresponding *trans* pyrrolidine derivatives **101** (Scheme 32) [55].



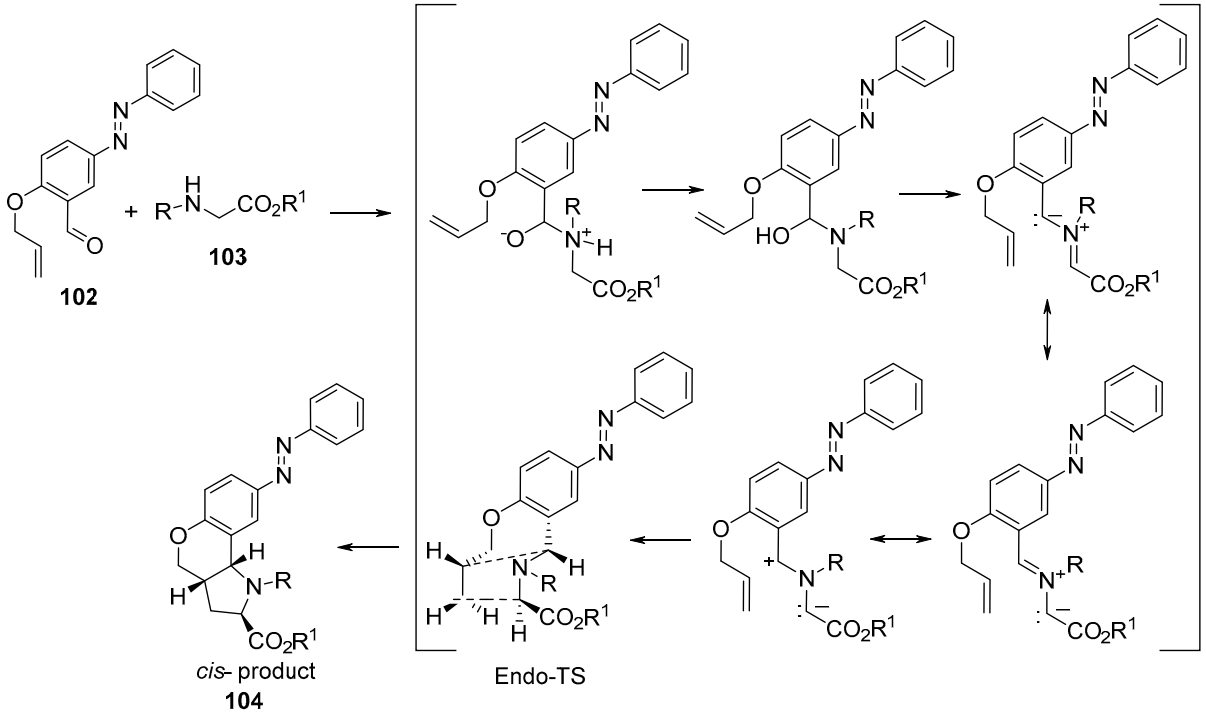
Ar = Ph, 2-FC_6H_4, 4-FC_6H_4, 2,4-$F_2C_6H_3$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 32. Synthesis of trans pyrrolidines **101**.

2.5. Intramolecular Cycloaddition Reaction of Azomethine Ylides with Acyclic Unsaturated 2π-Electron Components

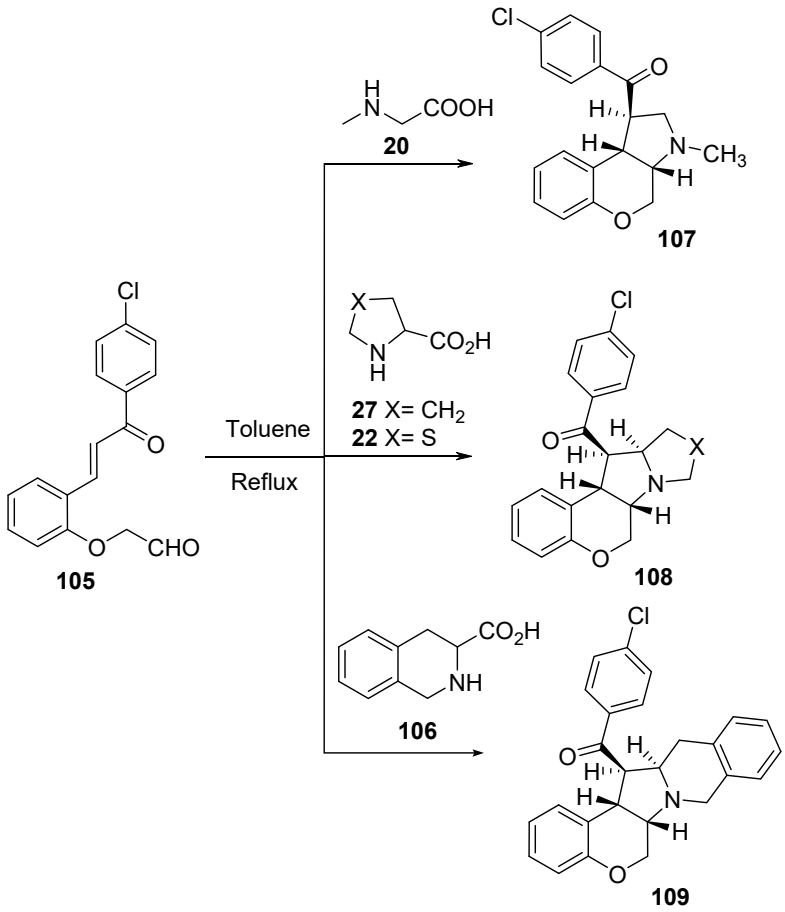
2.5.1. Acyclicunsaturated 2π-Electron Components Containing Olefinic and Aldehyde Groups

Azomethine ylides (formed via the reaction of α-amino esters **103** with *O*-allyl-5-phenyldiazenylsalicylaldehyde **102**) underwent intramolecular [3+2]-cycloaddition under microwave conditions, affording the 8-phenyldiazenylchromeno[4,3-*b*]pyrrolidines **104** (Scheme 33). The synthesized compounds showed antibacterial activity against Gram-positive (*Streptococcus pneumoniae*, *Clostridium tetani*, and *Bacillus subtilis*) and Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae*, and *Escherichia coli*), fungi (*Aspergillus fumigatus* and *Candida albicans*), and mycobacteria (*M. Tuberculosis* H37RV) relative to the antibacterial (Ampicillin, Norfloxacin, Chloramphenicol, Ciprofloxacin), antifungal (Griseofulvin, Nystatin), and antimycobacterial (Metronidazole) standard references used [56].



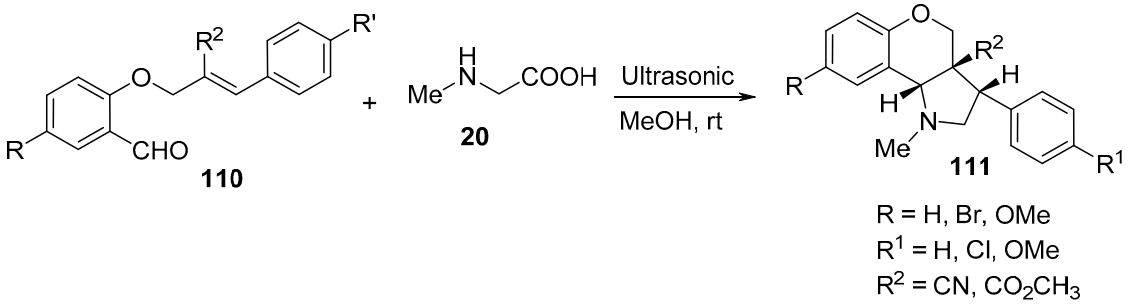
Scheme 33. Synthesis of 8-phenyldiazenylchromeno[4,3-*b*]pyrrolidines **104**.

The intramolecular cycloaddition reaction of azomethine ylides, formed from alkenyl aldehyde **105** and secondary amino acids (sarcosine **20**, *L*-proline **27**, thioproline **22,** and tetrahydroisoquinoline-3-carboxylic acid **106**), afforded the corresponding chromenopyrrole derivatives **107**–**109** (Scheme 34). The synthesized compounds showed promising antibacterial (against *S. aureus*, *B. subtilis* "Gram-positive"; *S. pneumoniae*, *E. coli*, and *Shigella* sp., *S. typhi* "Gram-negative") and antifungal (against *Trichoderma* sp., *Aspergillus* sp. and *C. albicans*) activities against the references Tetracycline and Carbendazim (antibacterial and antifungal standard references, respectively) [57].



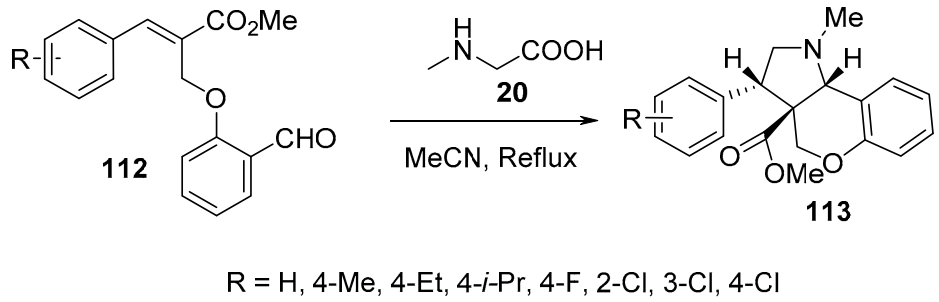
Scheme 34. Synthesis of chromenopyrrole-containing compounds **107**–**109**.

The intramolecular cycloaddition of *O*-allyl salicylaldehydes **110** and sarcosine **20** under ultrasonic irradiation in methanol at room temperature yielded the corresponding chromeno[4,3-*b*]pyrroles **111** (Scheme 35) [58].



Scheme 35. Synthesis of chromeno[4,3-*b*]pyrroles **111**.

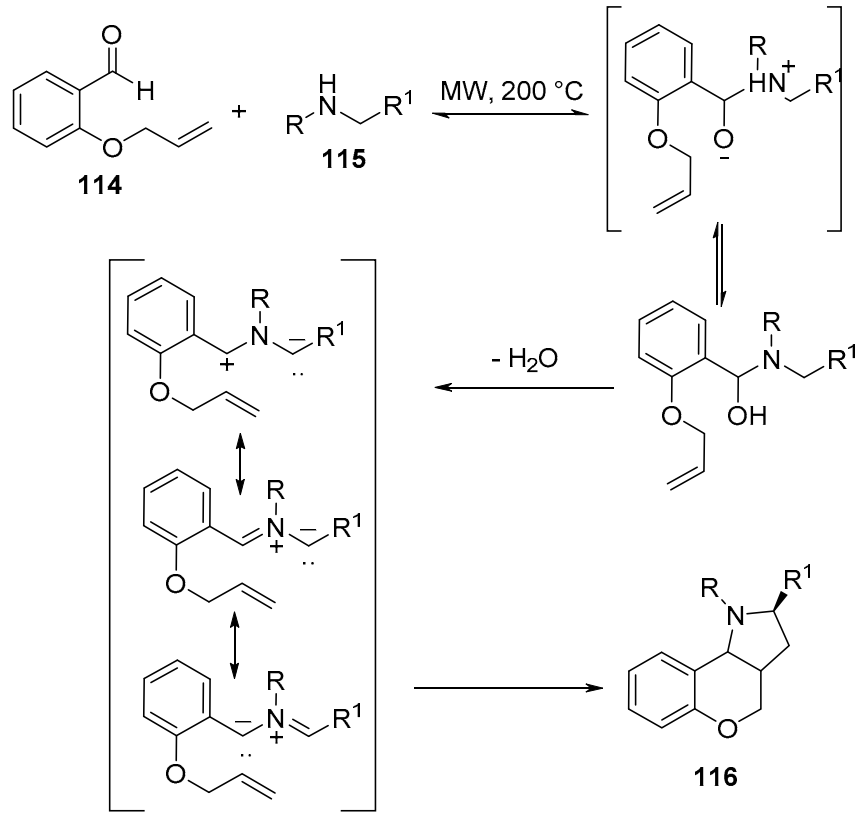
Chromeno[4,3-*b*]pyrrolidines **113** were obtained in a highly regio- and stereoselective manner by the intramolecular cycloaddition of *O*-allylic salicylaldehydes **112** and sarcosine **20** (Scheme 36) [59].



R = H, 4-Me, 4-Et, 4-*i*-Pr, 4-F, 2-Cl, 3-Cl, 4-Cl

Scheme 36. Synthesis of chromeno[4,3-*b*]pyrrolidines **113**.

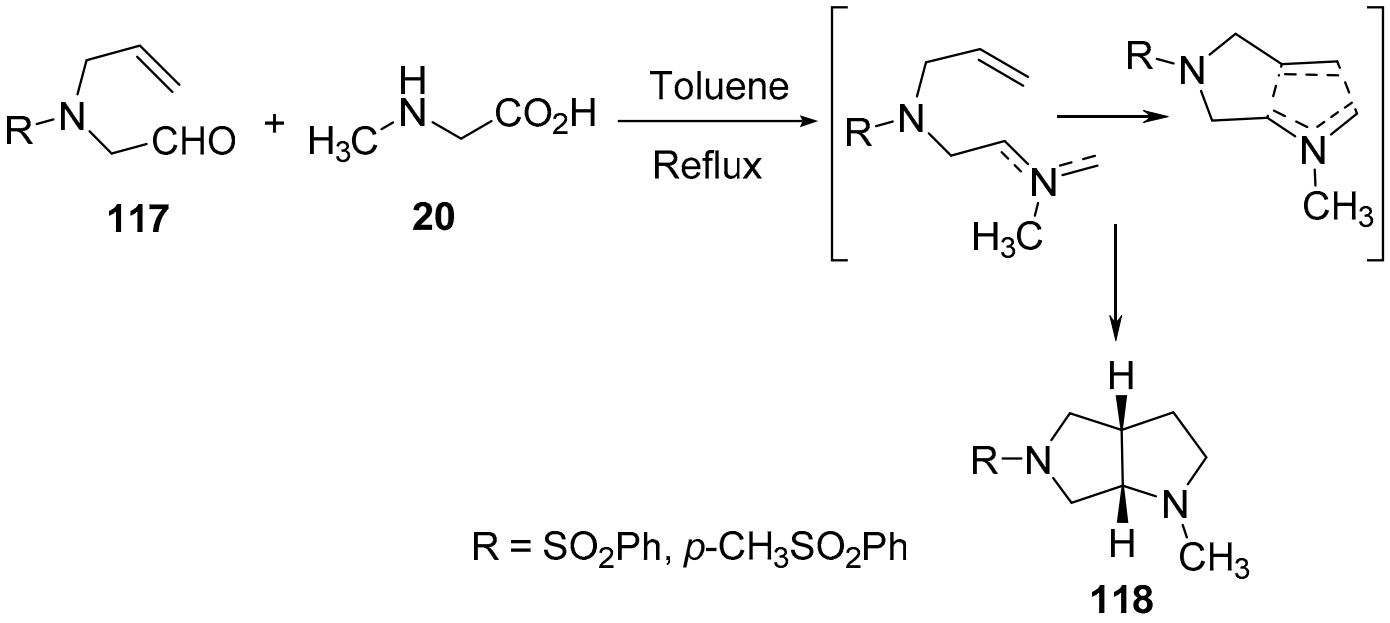
Similarly, hexahydrochromeno[4,3-*b*]pyrroles **116** were obtained via intramolecular [3+2]-cycloaddition of *O*-allylic salicylaldehyde **114** and amines **115** under microwave conditions (Scheme 37) [60].



R = benzyl, ethyl, n-butyl, iso-propyl, 1-adamantyl, ter-butyl
R^1 = CN, CO_2Et, CO_2Pri, CO_2But, $CONMe_2$, $CONPri_2$, CON(Et)Ts

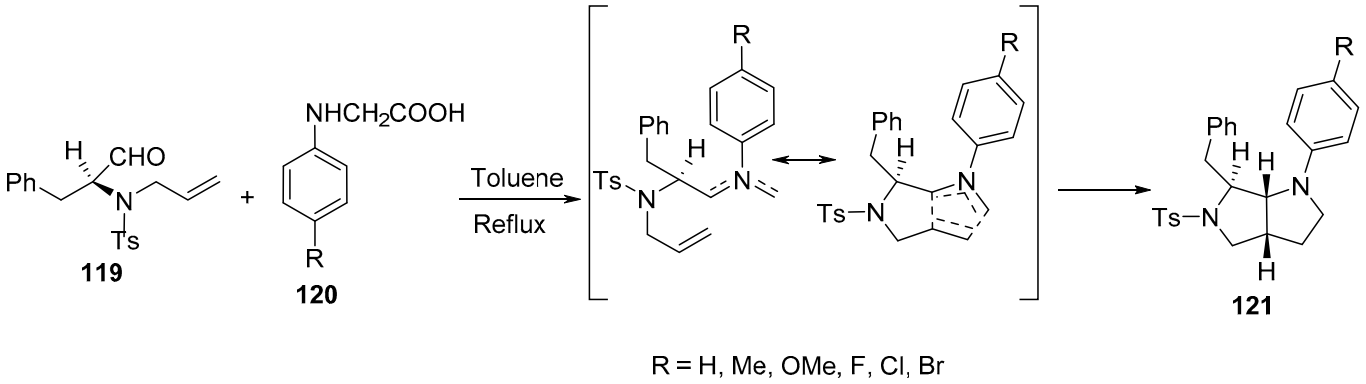
Scheme 37. Synthesis of hexahydrochromeno[4,3-*b*]pyrroles **116**.

Bicyclic pyrrolo[3,4-*b*]pyrroles **118** were obtained by the intramolecular cyclization of the generated azomethine ylides from aldehydes **117** and sarcosine **20** under refluxing conditions in toluene (Scheme 38) [61].



Scheme 38. Synthesis of pyrrolo[3,4-*b*]pyrroles **118**.

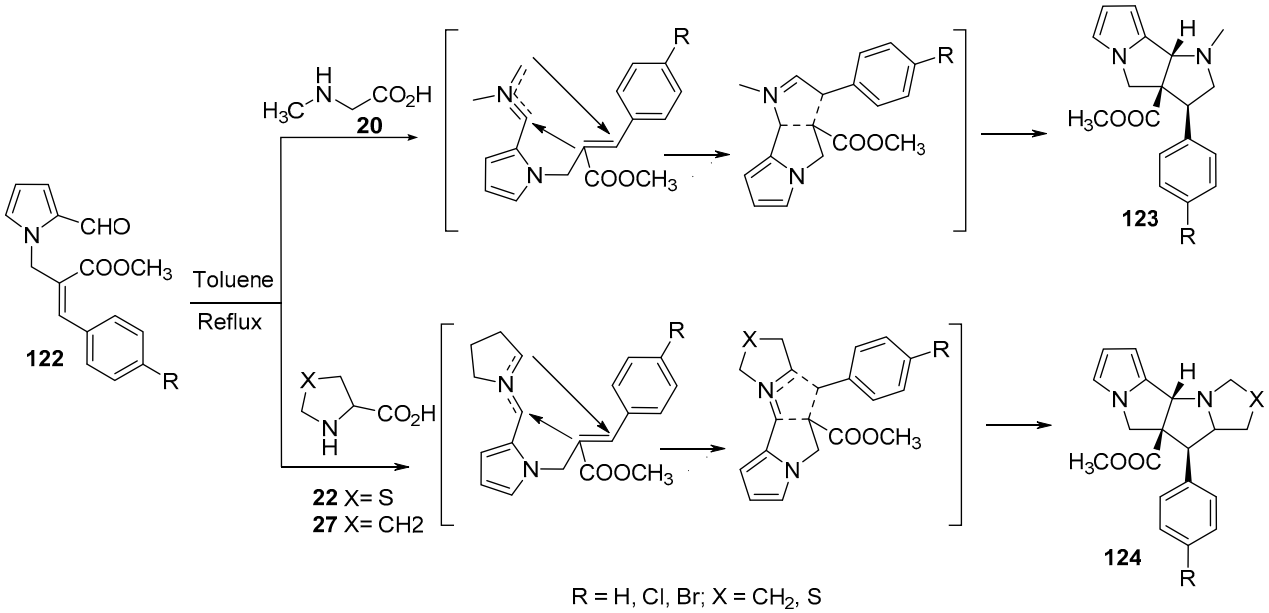
Octahydropyrrolo[3,4-*b*]pyrroles **121** with various substituents in their aromatic rings were synthesized by the intramolecular cycloaddition of azomethine ylides, which was formed from the reaction of alkenyl aldehyde **119** with *N*-aryl glycines **120** (Scheme 39) [62].



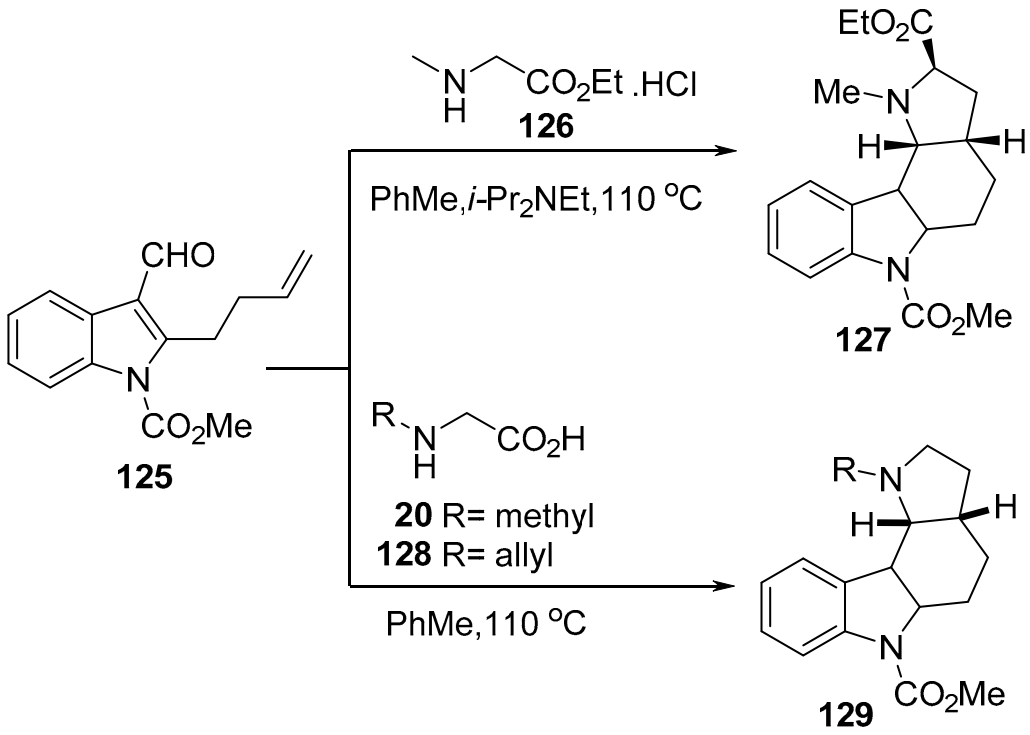
Scheme 39. Synthesis of octahydropyrrolo[3,4-*b*]pyrroles **121**.

The condensation of *N*-alkenyl aldehydes **122** with *α*-amino acids (sarcosine **20**, thioproline **22** and proline **27**) generated azomethine ylides, which underwent an intramolecular cycloaddition reaction yielding the corresponding polycyclic compounds **123** and **124** (Scheme 40) [63].

Similarly, the intramolecular reaction of azomethine ylide obtained from 2-butenylindole-3-carboxaldehyde **125** with *N*-methyl glycine ethyl ester hydrochloride **126** gave the indole-containing alkaloid **127**. Whereas its reaction with *N*-methyl glycine **20** or *N*-allyl glycine **128** gave the corresponding indole heterocycles of type **129** (Scheme 41) [64].

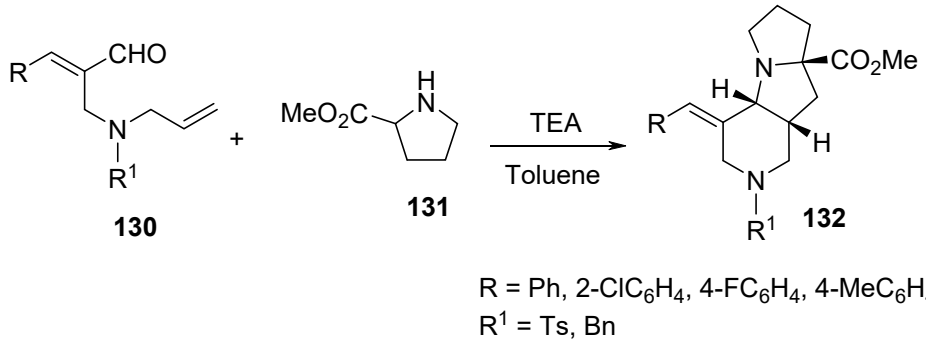


Scheme 40. Synthesis of polycyclic compounds **123** and **124**.



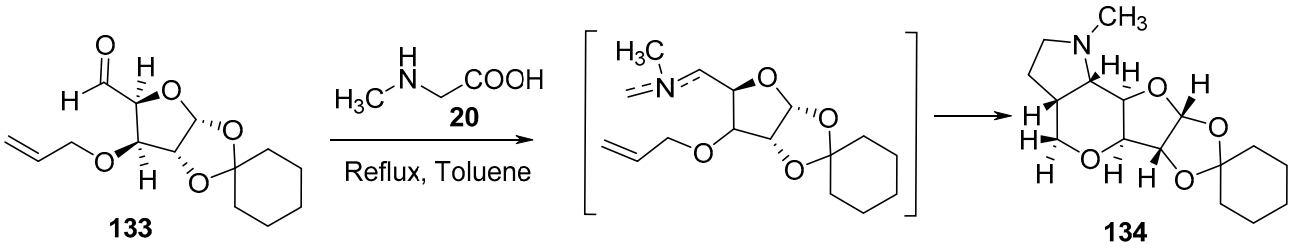
Scheme 41. Synthesis of indole-containing heterocycles **127** and **129**.

Another example of intramolecular cycloaddition was the reaction of (*E*)-2-{[allyl(benzyl) amino]methyl} cinnamaldehydes **130** with proline methyl ester hydrochloride **131** under microwave conditions, which afforded the pyrido[3,4-*b*]pyrrolizines **132** (Scheme 42) [65].



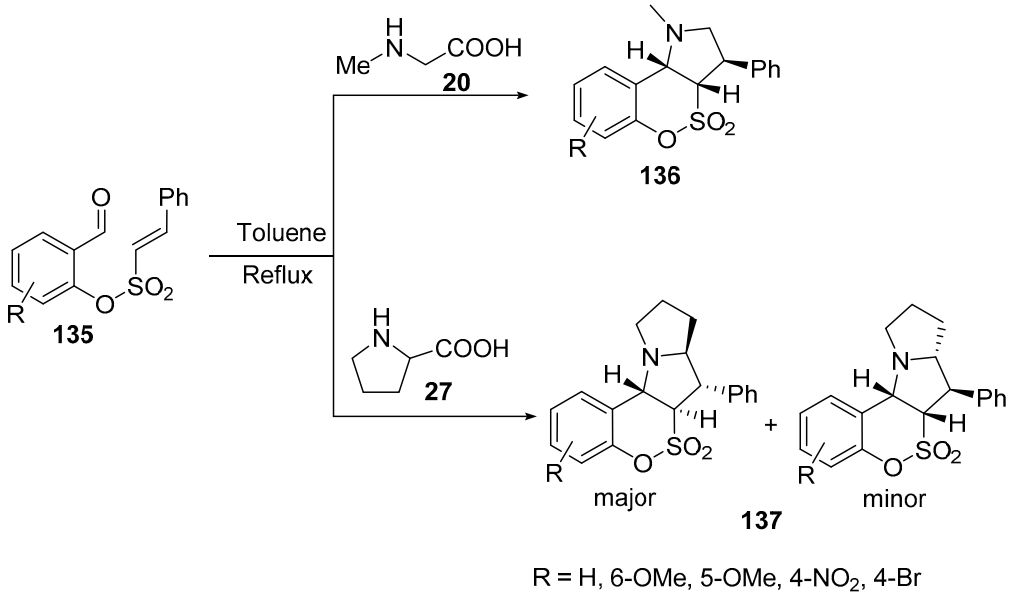
Scheme 42. Synthesis of pyrido[3,4-*b*]pyrrolizines **132**.

By using 1,2-*O*-cyclohexylidine-3-*O*-allyl-*α*-*D*-xylopentadialdo-1,4-furanose **133** (sugar-derived aldehyde) in a reaction with sarcosine **20,** furopyranopyrrolidine of type **134** was formed with high diastereoselectivity (Scheme 43) [66].



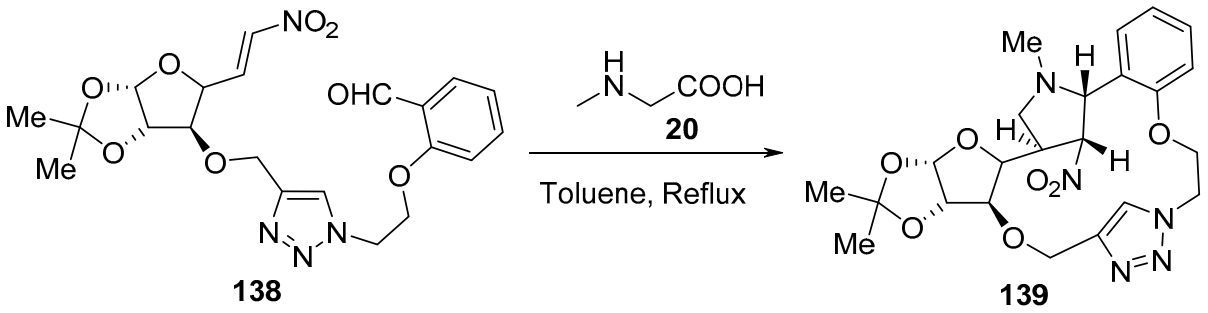
Scheme 43. Synthesis of furopyranopyrrolidine **134**.

The intramolecular [3+2]-cycloaddition of azomethine ylides, generated from 2-formylphenyl-(*E*)-2-phenylethenesulfonates **135** and sarcosine **20,** afforded the corresponding [1,2]oxathiino[4,3-*b*]pyrroles **136**. However, the reaction of derivative **135** with *L*-proline **27** gave the corresponding [1,2]oxathiino[3,4-*b*]pyrrolizines **137** as *trans–trans* (major) and *cis–trans* (minor) isomers (Scheme 44) [67].



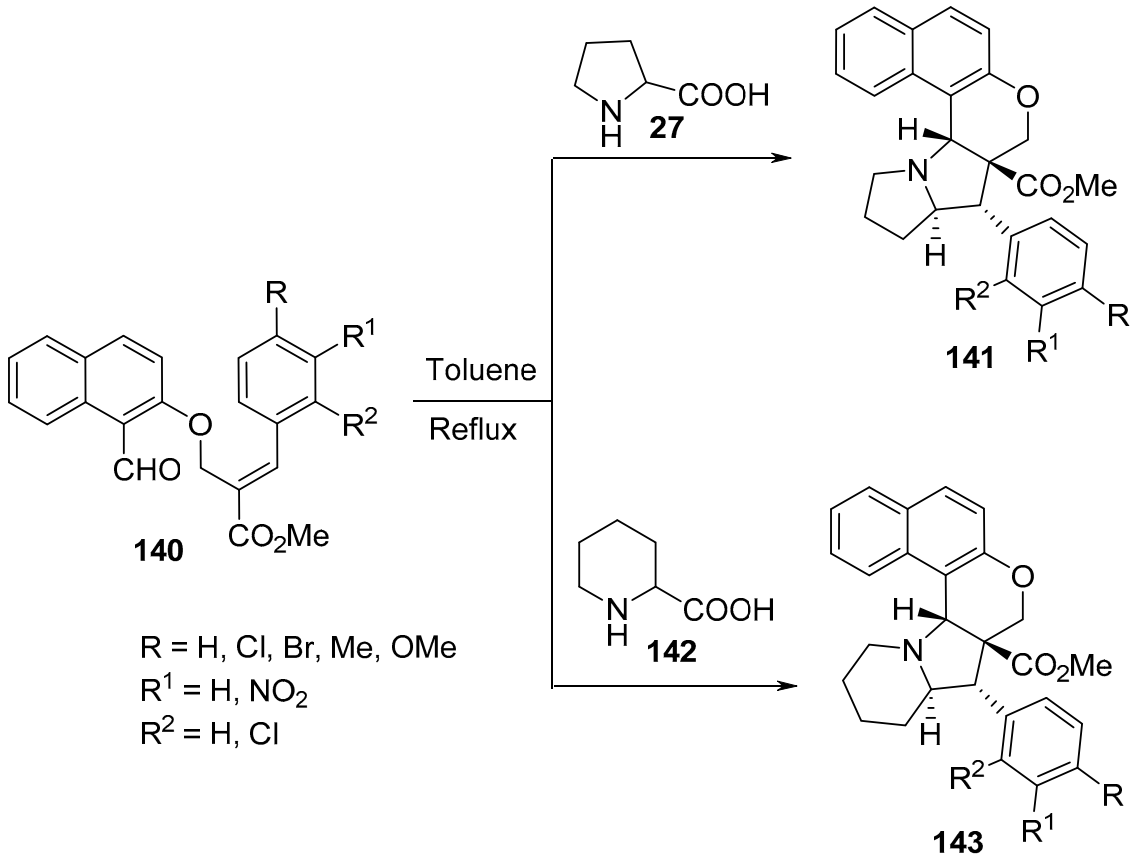
Scheme 44. Synthesis of benzo[*e*][1,2]oxathiino[4,3-*b*]pyrrole-4,4-dioxides **136** and benzo[*e*][1,2]oxathiino[3,4-*b*]pyrrolizine-6,6-dioxides **137**.

Scheme 45 shows an interesting example of a macrocycle of type **139** formation via the intramolecular cycloaddition of an azomethine ylide generated from a triazole-linked glycol-nitroalkenyl aldehyde derivative **138** and sarcosine **20** [68].



Scheme 45. Synthesis of macrocycle **139**.

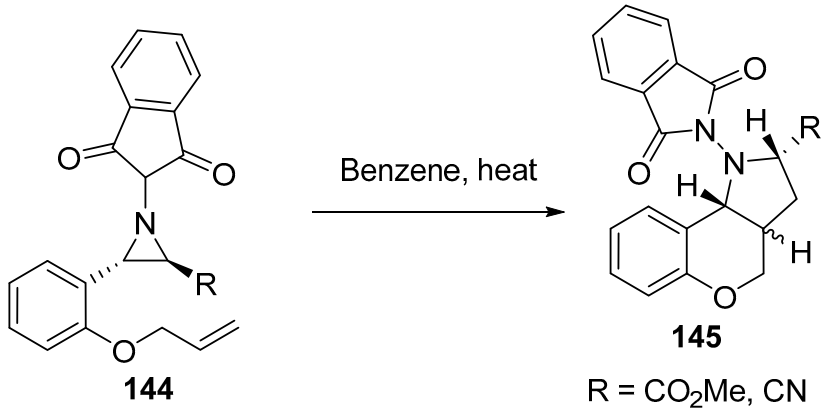
Polycyclic naphtho[2,1-*b*]pyrano-pyrrolizidine and indolizidine derivatives **141** and **143** were synthesized by the intramolecular [3+2]-cycloaddition of azomethine ylides generated from naphtho-*O*-alkenyl aldehydes **140** and *α*-amino acids (*L*-proline **27** or *DL*-pipecolinic acid **142)** (Scheme 46) [69].



Scheme 46. Synthesis of naptho-pyrano-pyrrolizidines/indolizidines **141** and **143**.

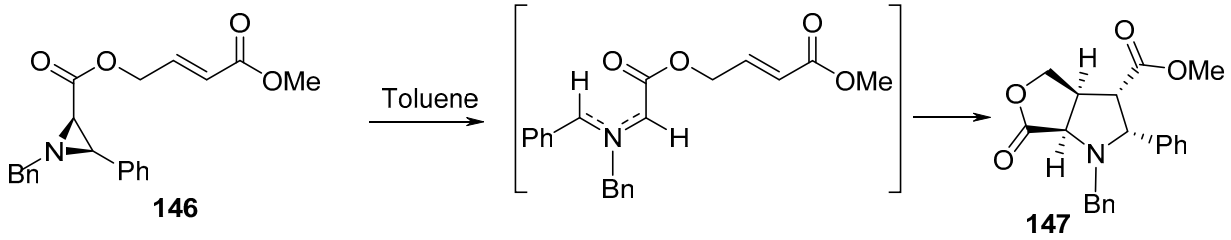
2.5.2. Acyclic Unsaturated 2π-Electron Components Containing Olefinic Linkage and Azirdine

Scheme 47 shows the thermolysis of aziridines **144** that led to the in situ formation of azomethine ylides, which underwent intramolecular cycloaddition, thus affording *N*-phthalimidopyrrolidine derivatives **145** as a mixture of two diastereoisomers [70].



Scheme 47. Synthesis of *N*-phthalimidopyrrolidines **145**.

Another bicyclic system of γ-lactone **147** was created by the intramolecular [3+2]-cycloaddition of azomethine ylide generated via the thermolysis of aziridine derivative **146** in refluxing toluene (Scheme 48) [71].

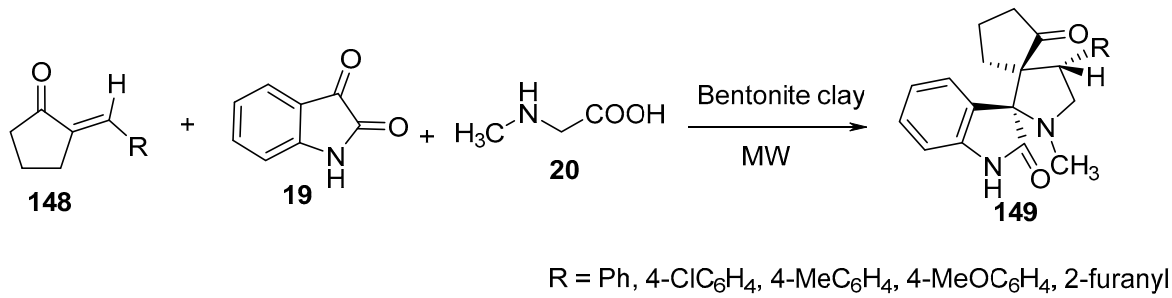


Scheme 48. Synthesis of bicyclic γ-lactone **147**.

3. Exocyclic, Unsaturated 2π-Electron Components

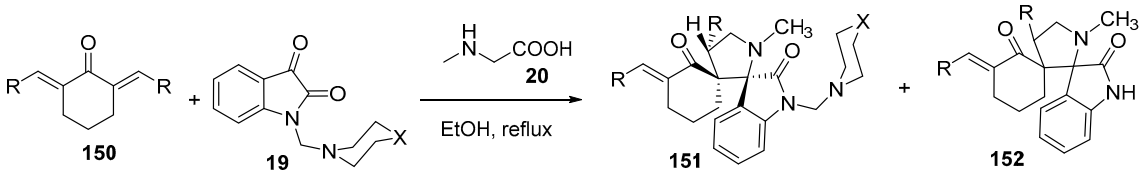
3.1. Cycloalkanones

The exocyclic olefinic linkage is a reactive, unsaturated 2π-electron component intensively used in [3+2]-cycloaddition reactions forming various heterocycles [72–76]. For example, the cycloaddition of azomethine ylide (formed from isatin **19** and sarcosine **20**) with 2-arylidene-1-cyclopentanones **148** in the presence of bentonite clay under microwave conditions afforded dispiropyrrolidinyl-oxindoles **149** (Scheme 49) [77].



Scheme 49. Synthesis of dispiropyrrolidinyl-oxindoles **149**.

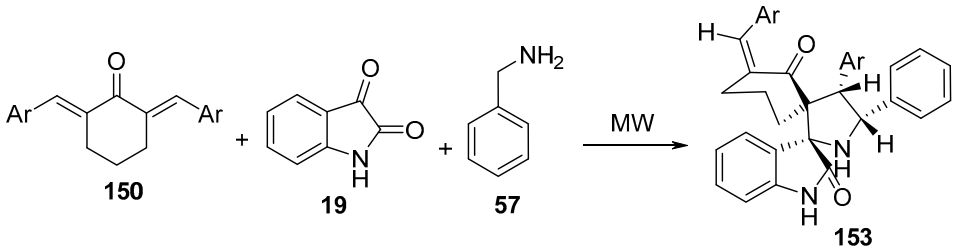
Similarly, dispiro[cyclohexane-1,3′-pyrrolidine-2′,3″-[3*H*]indoles] **151** and **152** were obtained by the cycloaddition reaction of azomethine ylides (generated from isatin derivative **19** and sarcosine **20**) with 2*E*,6*E*-bis(arylidene)-1-cyclohexanones **150** (Scheme 50). Some of the synthesized compounds demonstrated antitumor properties against liver (HEPG2), cervical (HELA), and prostate (PC3) cancer cell lines while using Doxorubicin as a standard reference in an SRB assay [78].



R = Ph, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 4-FC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 2-thienyl, 5-methyl-2-furanyl
X = CH$_2$, O, NCH$_3$

Scheme 50. Synthesis of dispiro[cyclohexane-1,3′-pyrrolidine-2′,3″-[3*H*]indoles] **151** and **152**.

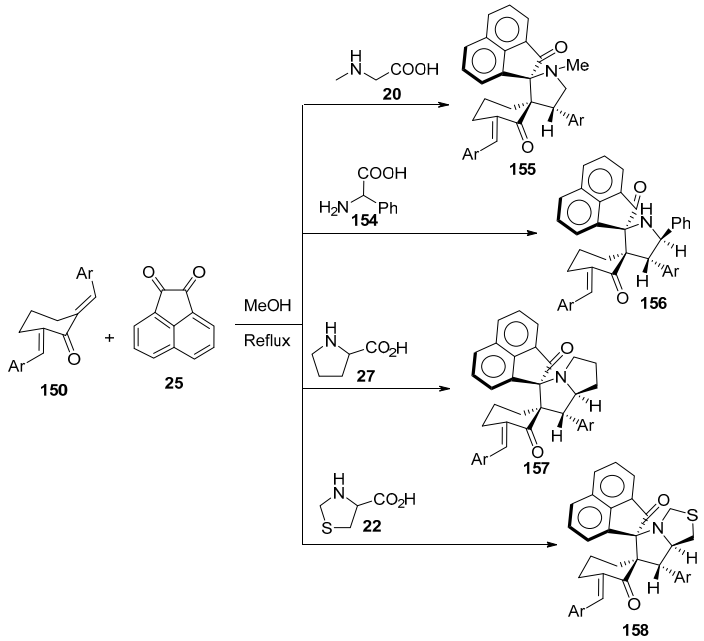
Azomethine ylide formed from the condensation of benzylamine **57** and isatin **19** also underwent a cycloaddition reaction with 2,6-bis(ylidene)cyclohexanones **150** under solvent-free conditions using microwave irradiation, thereby affording the dispiro-oxindole **153** with high regioselectivity (Scheme 51) [79].



Ar = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Scheme 51. Synthesis of dispiro-oxindoles **153**.

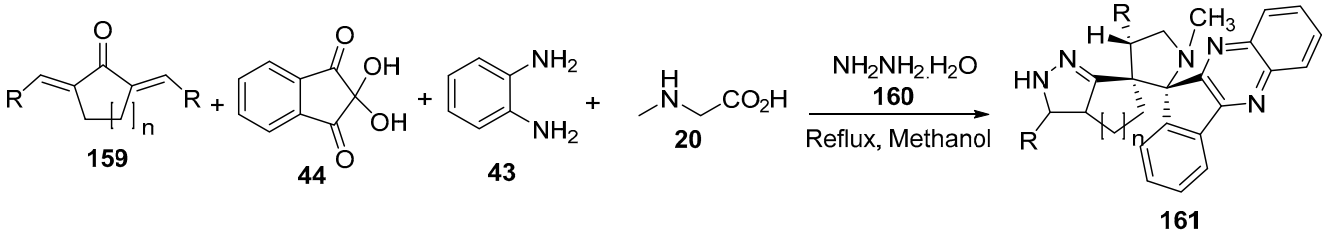
Azomethine ylides derived from acenaphthenequinone **25** and *α*-amino acids (sarcosine **20**, phenylglycine **154**, proline **27,** or thioproline **22**) afforded the corresponding spirocyclohexanones **155–158** upon reaction with 2,6-bis(ylidene)cyclohexanones **150** in refluxing methanol [80] (Scheme 52). Some of the synthesized spiro compounds revealed activity against *Mycobacterium tuberculosis* H37Rv (MTB) relative to Ethambutol and Pyrazinamide [80].



Ar = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-FC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 1-naphthyl

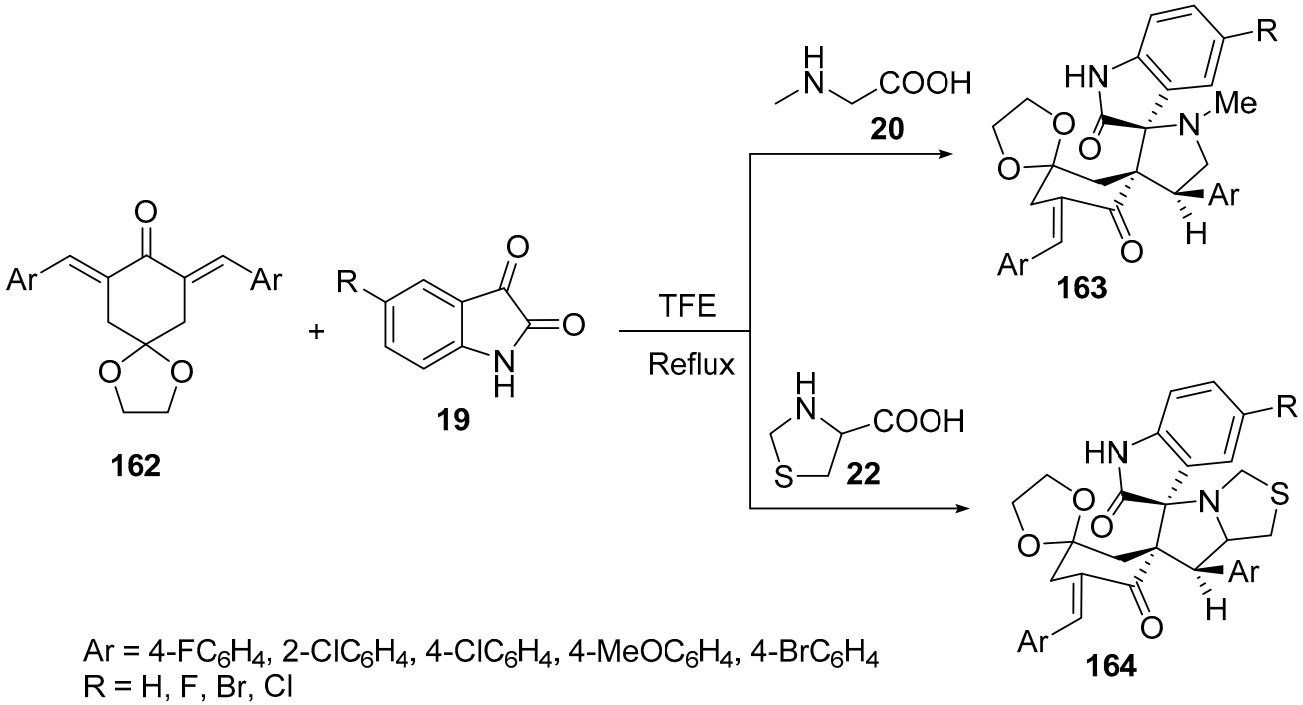
Scheme 52. Synthesis of spirocyclohexanone **155–158**.

A one-pot, five-component reaction of azomethine ylide (formed from ninhydrin **44**, *o*-phenylenediammine **43**, and sarcosine **20**) with bis(ylidene)cycloalkanones **159** in the presence of hydrazine hydrate **160** in refluxing methanol regioselectively afforded the corresponding spiro-indenoquinoxaline-pyrrolidines **161** at a high yield (Scheme 53) [81].



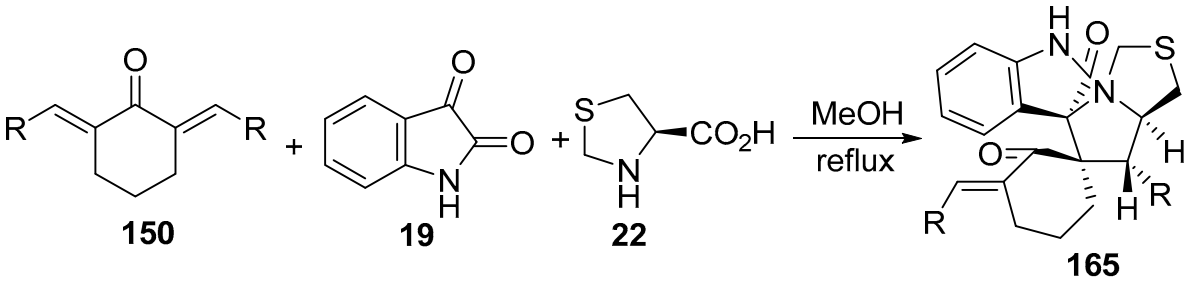
Scheme 53. Synthesis of spiro-indenoquinoxaline pyrrolidines **161**.

Trispiropyrrolidines/thiapyrrolizidines **163** and **164** were synthesized through the reaction of 7,9-bis[(*E*)-ylidene]-1,4-dioxa-spiro[4,5]decane-8-ones **162** and azomethine ylides (formed from isatin **19** and sarcosine **20** or thioproline **22**) in 2,2,2-trifluoroethanol (TFE) (Scheme 54). Some of the products showed anti-fungal properties (against *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323) and antimycobacterial properties against *M. tuberculosis* H37Rv relative to the standard references Nysyatin, Greseofulvin (antifungal), and Isoniazid (antimycobacterial) [82].



Scheme 54. Synthesis of trispiropyrrolidines/thiapyrrolizidines **163**, **164**.

Analogously, dispiro compounds of type **165** were synthesized by the reaction of 2,6-bis(ylidene)cyclohexanones **150** with azomethine ylide (formed from *L*-thioproline **22** and isatin **19**) in refluxing methanol. Some of the synthesized derivatives revealed promising antiproliferative properties (apoptotic mechanism) against the MCF7 (breast) and K562 (leukemia) cell lines (WST-1 assay) relative to 5-Fluorouracil (standard reference drug) (Scheme 55) [83].

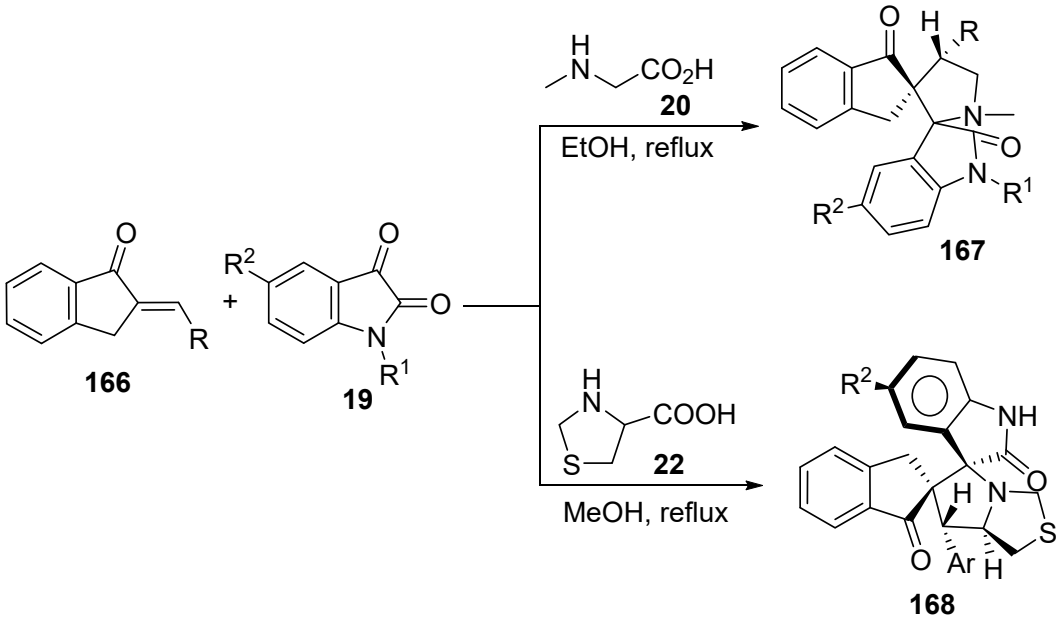


R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 3-MeC_6H_4, 3-FC_6H_4, 3-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 3-$NO_2C_6H_4$, 4-BrC_6H_4, 4-FC_6H_4, 2-thienyl, 2-naphthyl

Scheme 55. Synthetic route towards dispiro[cyclohexane-1,6′-pyrrolo[1,2-*c*].thiazole-5′,3″-indoline]-2,2″-diones **165**.

3.2. Indanones and Indanediones

A series of dispiro compounds of type **167** were regioselectively synthesized by the cycloaddition of 2-(ylidene)-1-indanones **166** with azomethine ylides (formed from isatin derivatives **19** with sarcosine **20**) in refluxing ethanol. Promising anti-inflammatory properties were exhibited by the synthesized compounds (via a rat carrageenan paw edema assay) relative to Indomethacin (standard reference drug) [84]. Antiproliferative properties were also revealed by some of the synthesized derivatives against human metastatic melanoma cells (GaLa, LuPiCi, and LuCa), with a potency relative to that of Doxorubicin (SRB assay) (Scheme 56) [85]. In an analogous reaction, by using *L*-thioproline **22** instead of sarcosine **20,** spiro-pyrrolothiazolyloxindole derivatives of type **168** were obtained. Some of these compounds showed activities against *Mycobacterium tuberculosis* H37Rv relative to Ethambutol (standard reference) [86].



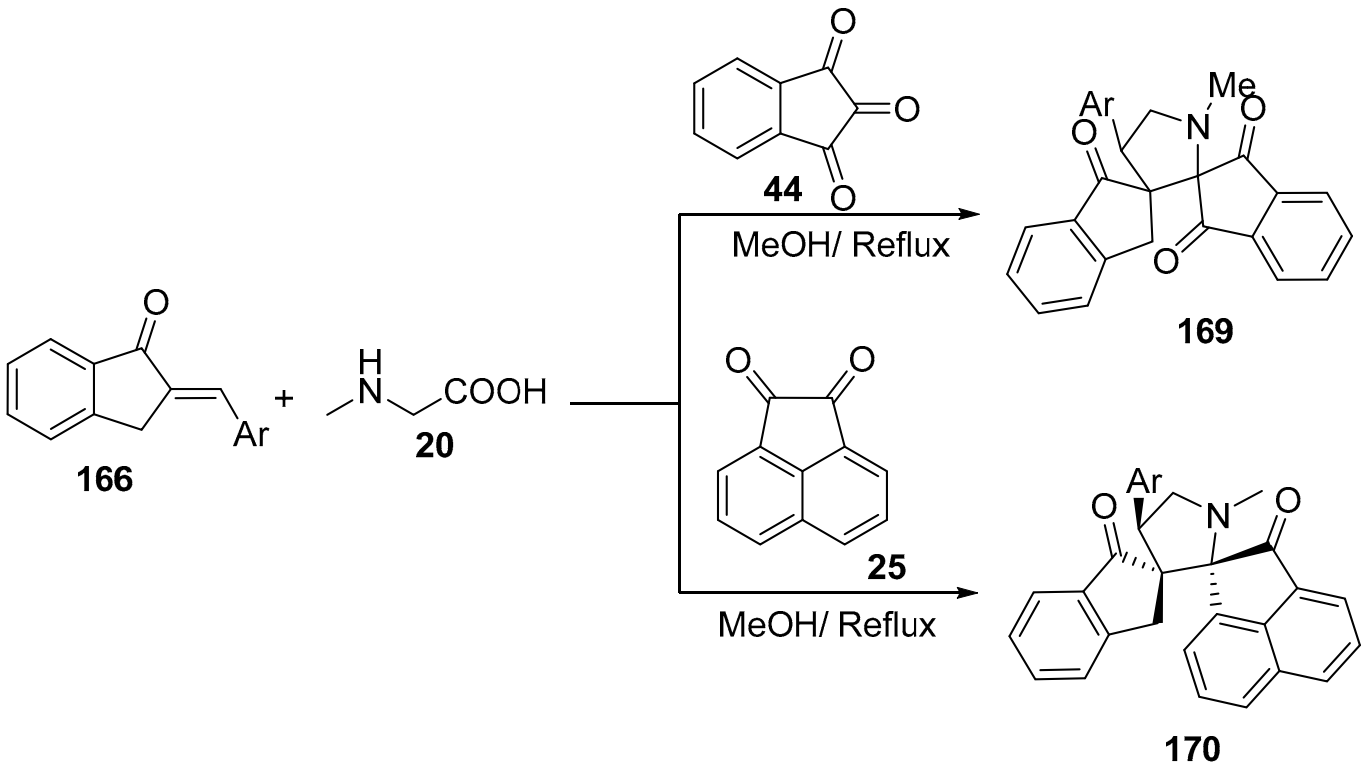
R = Ph, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2,3-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-$Me_2NC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 2-furanyl

R^1 = H, Me, CH_2(1-piperidinyl), CH_2(4-morpholinyl)

R^2 = H, Cl, NO_2

Scheme 56. Synthetic route towards dispiro compounds **167** and **168**.

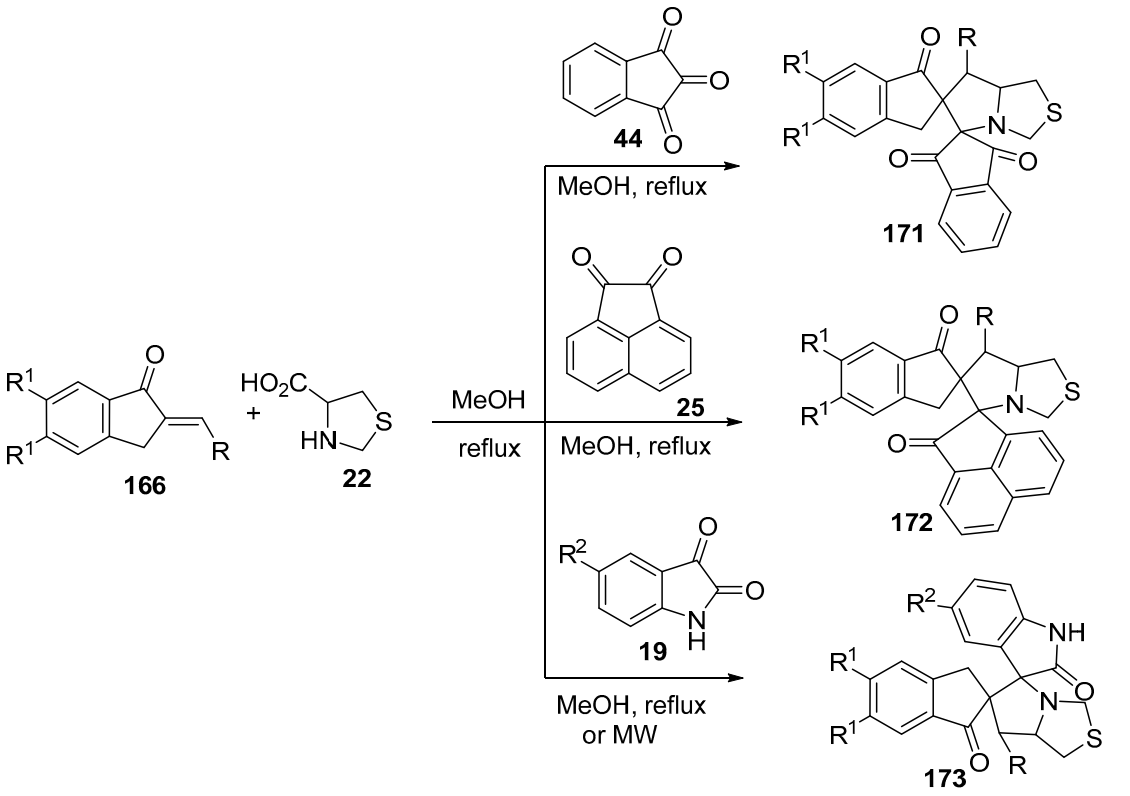
Other dispiropyrrolidines of type **169** were synthesized by the cycloaddition of azomethine ylide (formed from ninhydrin **44** and sarcosine **20)** with 2-(arylidene)-1-indanones **166** (Scheme 57). When acenaphthenequinone **25** was used instead of ninhydrin **44** in this reaction, dispiropyrrolidines of type **170** were formed in a highly regio- and stereoselective manner. Some of the synthesized derivatives—**169** and **170** showed antimycobacterial properties against *M. tuberculosis* H37Rv and INH resistant *M. tuberculosis* strains relative to Isoniazid and Ethambutol (standard reference drugs) [87,88].



Ar = Ph, 5-(4-fluorophenyl)pyridinyl, 4-chlorophenyl, 4-bromophenyl, 4-carboxyphenyl, 3-nitrophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 4-carboxyphenyl, 3-nitrophenyl, benzo[*d*][1,3]dioxolyl, 4-dimethylaminophenyl, 2,5-dimethoxyphenyl, 1-[4-(piperidine-1-yl)phenyl], 1-[4-(morpholine-1-yl)phenyl]

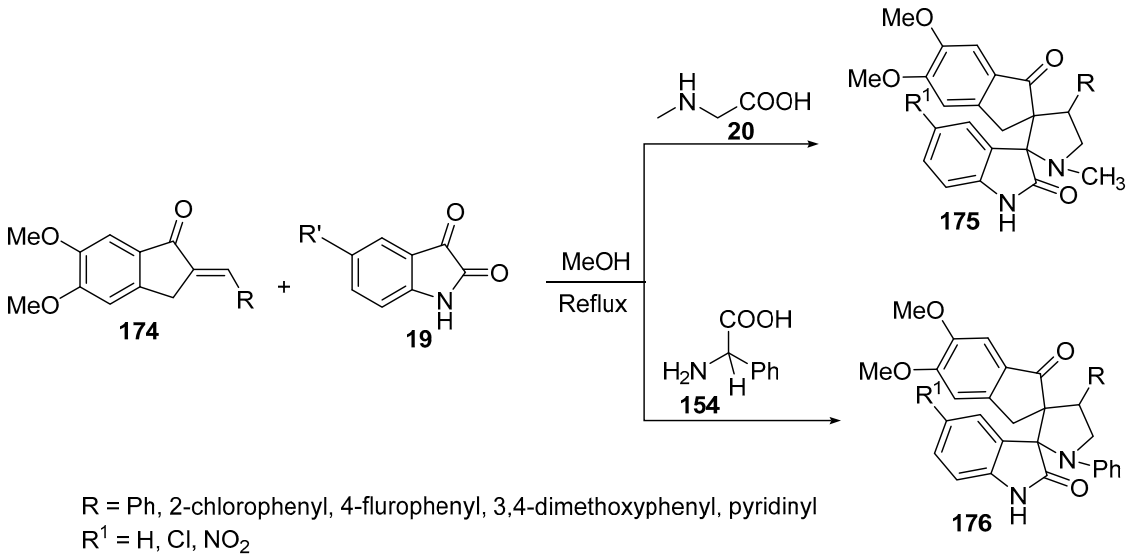
Scheme 57. Synthesis of dispiropyrrolidines **166** and **167**.

Dispiropyrrolidines **171** and **172** were obtained by the cycloaddition of 2-(ylidene)-1-indanones **166** with azomethine ylides (obtained through the condensation of *L*-thioproline **22** with ninhydrin/acenaphthenequinone **44/25**) in refluxing methanol. Some of the synthesized compounds showed promising in-vitro antimycobacterial properties against *M. tuberculosis* H37RV relative to Cycloserine [89]. Analogously, pyrrolothiazolyloxindoles of type **173** were obtained when isatin **19** was used instead of ninhydrin **44** or acenaphthenequinone **25** in this reaction. Some of the isatin-derived compounds of type **173** exhibited inhibitory properties toward acetylcholinesterase that could be useful for Alzheimer's disease therapy (Scheme 58) [90].



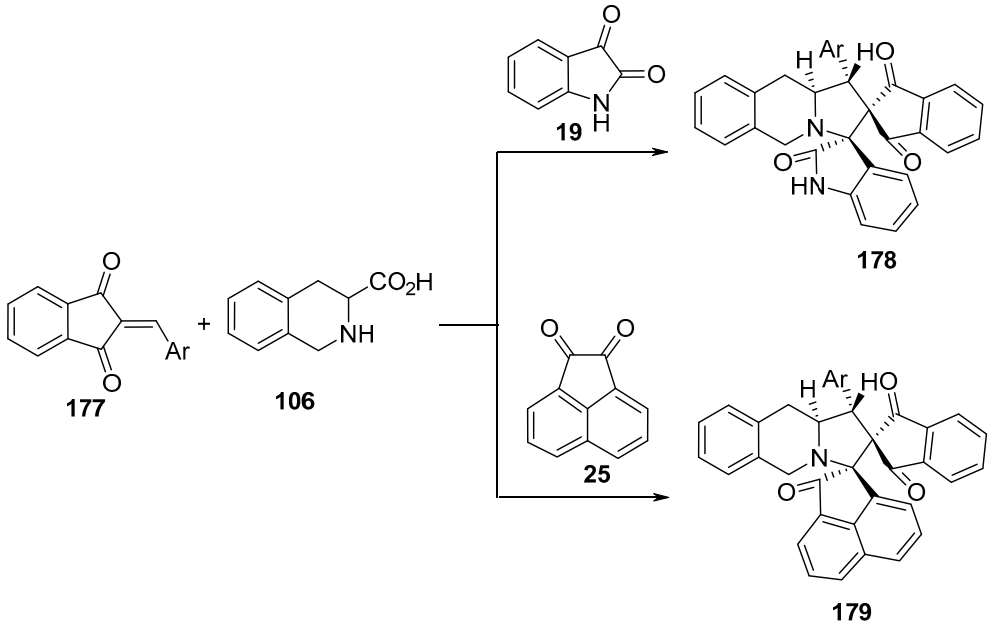
Scheme 58. Synthetic route towards dispiro compounds **171**–**173**.

By reacting 5,6-dimethoxy-2-(arylidene)-1-indanone **174** and isatin **19** with sarcosine **20** or phenylglycine **154**, spiropyrrolidines **175** and **176**, respectively, were obtained (Scheme 59). Some of these compounds showed inhibitory activities toward acetylcholinesterase [91].



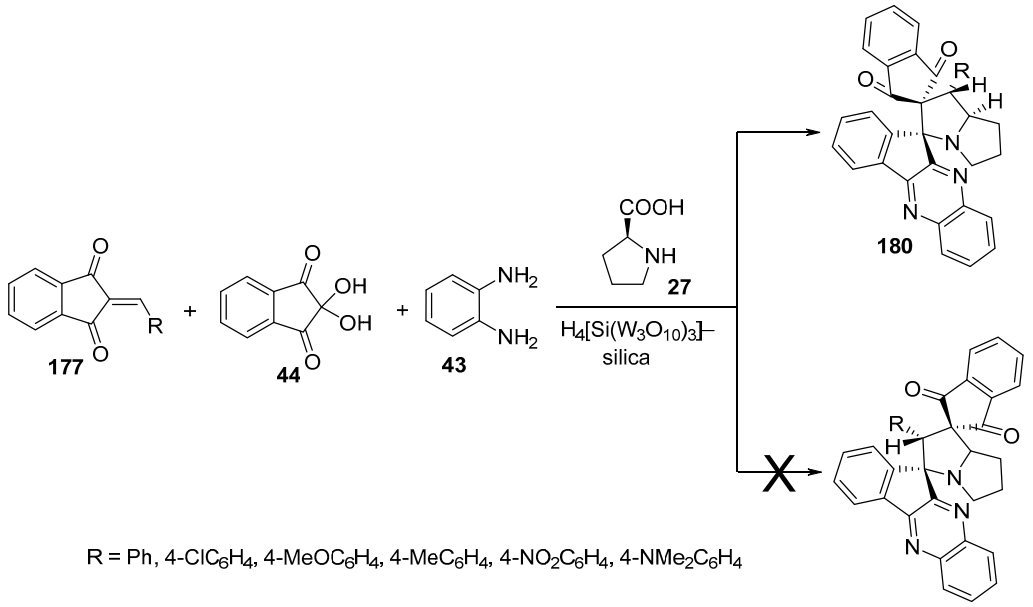
Scheme 59. Synthesis of spiropyrrolidines **175** and **176**.

TiO_2–silica was used as an efficient solid-supported catalyst for the cycloaddition reaction of 2-arylidene-1,3-indanediones **177** with the corresponding azomethine ylides generated from tetrahydroisoquinoline-3-carboxylic acid **106** and isatin derivative **19** or acenaphthenequinone **25** to afford the corresponding dispiropyrroloisoquinolines **178** and **179** (Scheme 60) [92].



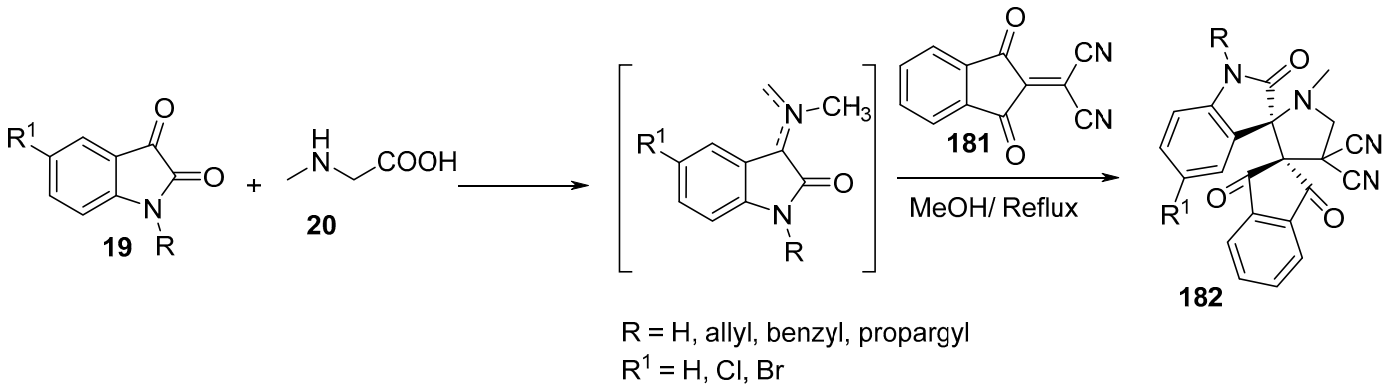
Scheme 60. Synthesis of dispiropyrroloisoquinolines **178** and **179**.

The four-component reaction of 2-arylidene-1,3-indanediones **177**, ninhydrin **44**, *o*-phenylenediamine **43**, and *L*-proline **27**, proceeding via an azomethine intermediate and in the presence of heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica as a catalyst in refluxing acetonitrile, afforded the dispiroindenoquinoxaline-pyrrolizidines **180** (Scheme 61) [93].



Scheme 61. Synthesis of dispiroindenoquinoxaline-pyrrolizidine **180**.

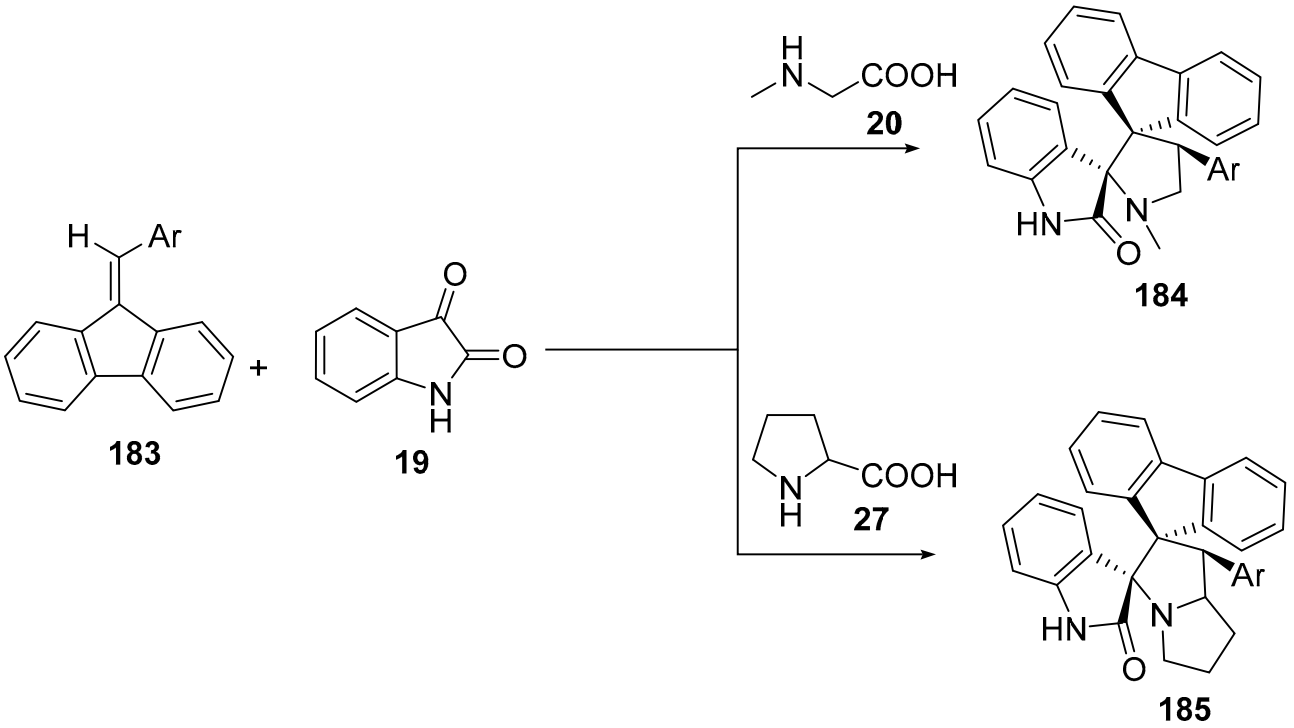
Dispiro compounds of type **182** were synthesized by the reaction of the generated azomethine ylides (from isatin **19** and sarcosine **20**) with 2-(1,3-dioxo-indan-2-ylidene) malononitrile **181** (Scheme 62) [43].



Scheme 62. Synthesis of spiroindane-1,3-diones **182**.

3.3. Fluorenes

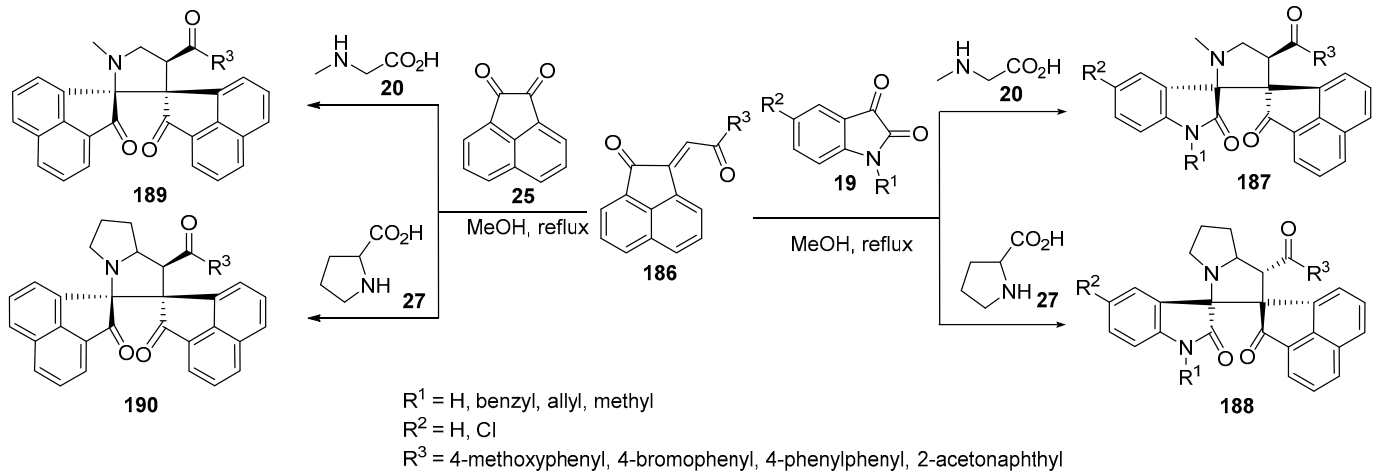
The solvent-free reaction of (*E*)-arylidenefluorenes **183** with isatin **19** and sarcosine **20** or proline **27,** under microwave conditions, afforded the corresponding dispiro-oxindoles **184** and **185**, respectively (Scheme 63) [94].



Scheme 63. Synthesis of dispiro-oxindoles **184** and **185**.

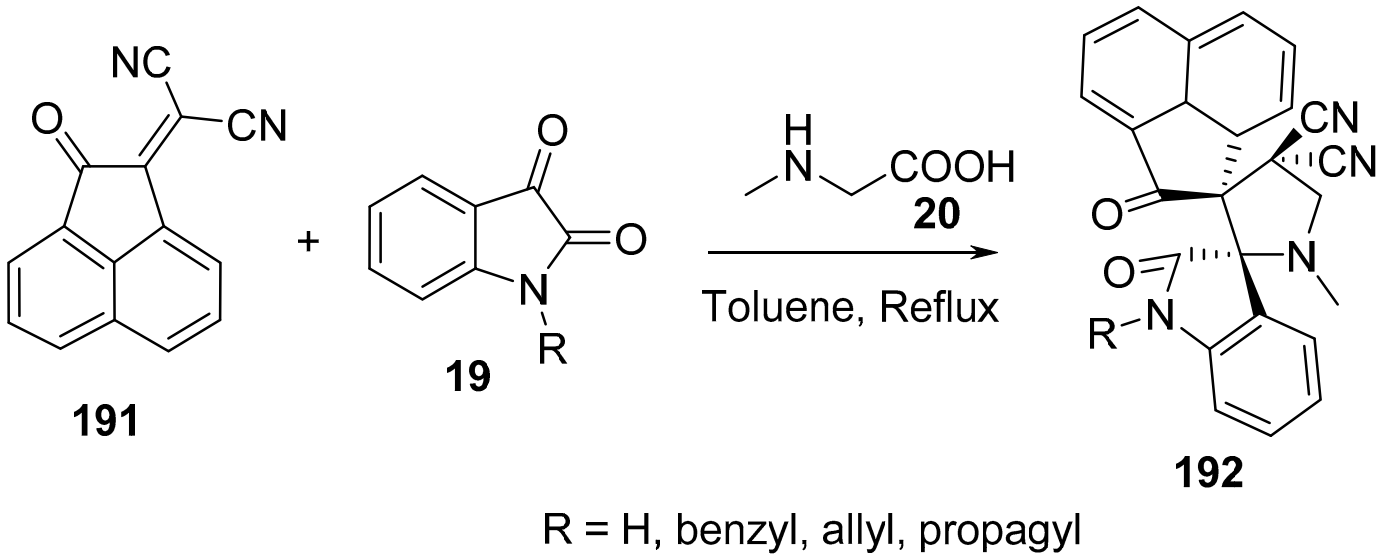
3.4. Acenaphthenes

The reaction of acenaphthenone-2-ylidene ketones of type **186** with azomethine ylides formed from the condensation of isatin **19** or acenaphthenequinone **25** and secondary amino acids (sarcosine **20** or *L*-proline **27**) in refluxing methanol afforded the corresponding spirooxindoles **187**–**190** (Scheme 64) [95].



Scheme 64. Synthesis of spirooxindoles **187**–**190**.

Similarly, 2-oxo-(2*H*)-acenaphthylen-1-ylidene-malononitrile **191** afforded the corresponding dispiropyrrolidine-oxindoles **192** by its reaction with isatin **19** and sarcosine **20** in refluxing toluene (Scheme 65) [96].

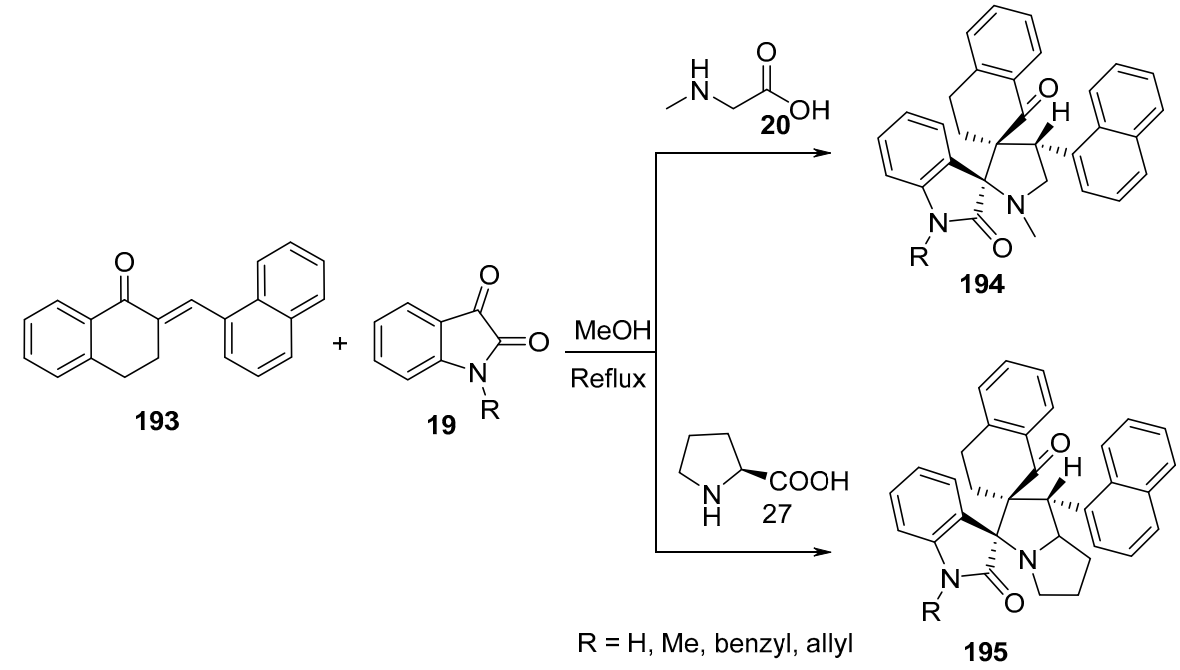


Scheme 65. Synthesis of dispiropyrrolidine-oxindoles **192**.

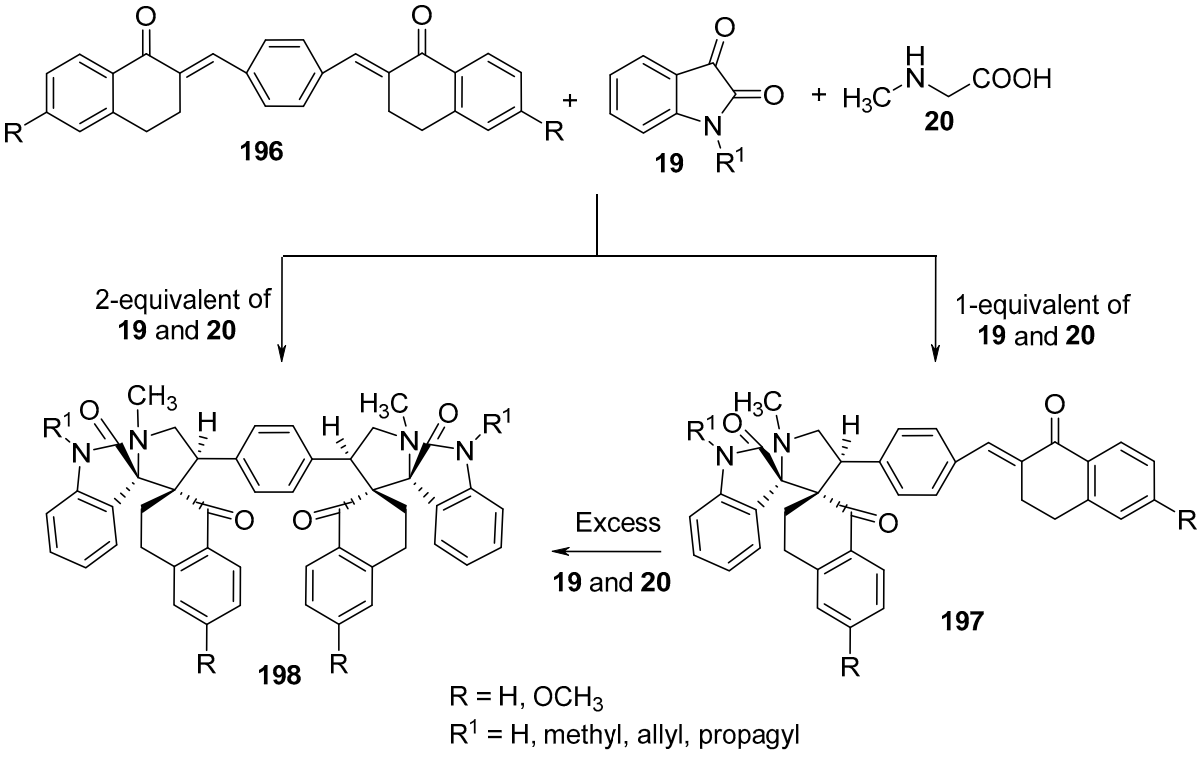
3.5. Tetralones

Dispiro-oxindolopyrrolidine/pyrrolizidines **194** and **195** were synthesized via the cycloaddition of (*E*)-1-naphthylidene-1-tetralone **193** with the corresponding azomethine ylides generated from isatin **19** and sarcosine **20** or *L*-proline **27** (Scheme 66) [97].

Further, the cycloaddition of 1,4-bis(3′,4′-dihydro-1′-oxonaphthalen-2′-ylidene)benzene derivative **196** with azomethine ylides (from isatin **19** and sarcosine **20**) in a 1:2 molar ratio afforded the corresponding tetraspiro-bisoxindolopyrrolidine **198**. With a 1:1 ratio of the reactants, mono derivatives of type **197** were formed, which, in the presence of an excess of isatin **19** and sarcosine **20,** afforded bisoxindolopyrrolidines **198** [98] (Scheme 67).



Scheme 66. Synthesis of dispiro-oxindolopyrrolidine/pyrrolizidines **194** and **195**.

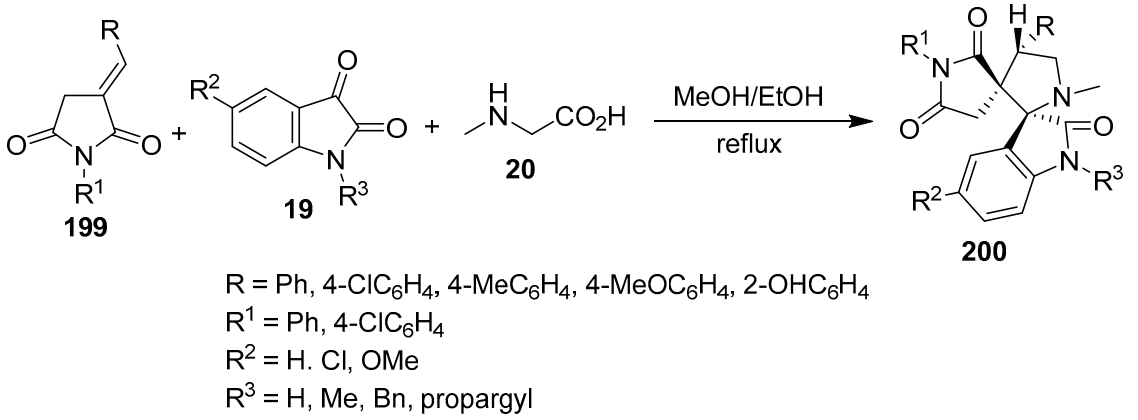


Scheme 67. Synthesis of tetraspiro-bisoxindolopyrrolidines **198**.

3.6. Pyrrolidine-2,5-diones

Dispiropyrrolidines of type **200** were prepared regioselectively by the cycloaddition of 3-(ylidene)pyrrolidine-2,5-diones **199** with azomethine ylide (formed from condensation of sarcosine **20** and isatin **19**) in refluxing alcohol. Promising cholinesterase (acetylcholinesterase and butyrylcholinesterase) inhibitory properties were observed for some of the synthesized compounds (relative to Donepezil, used as the standard reference) that

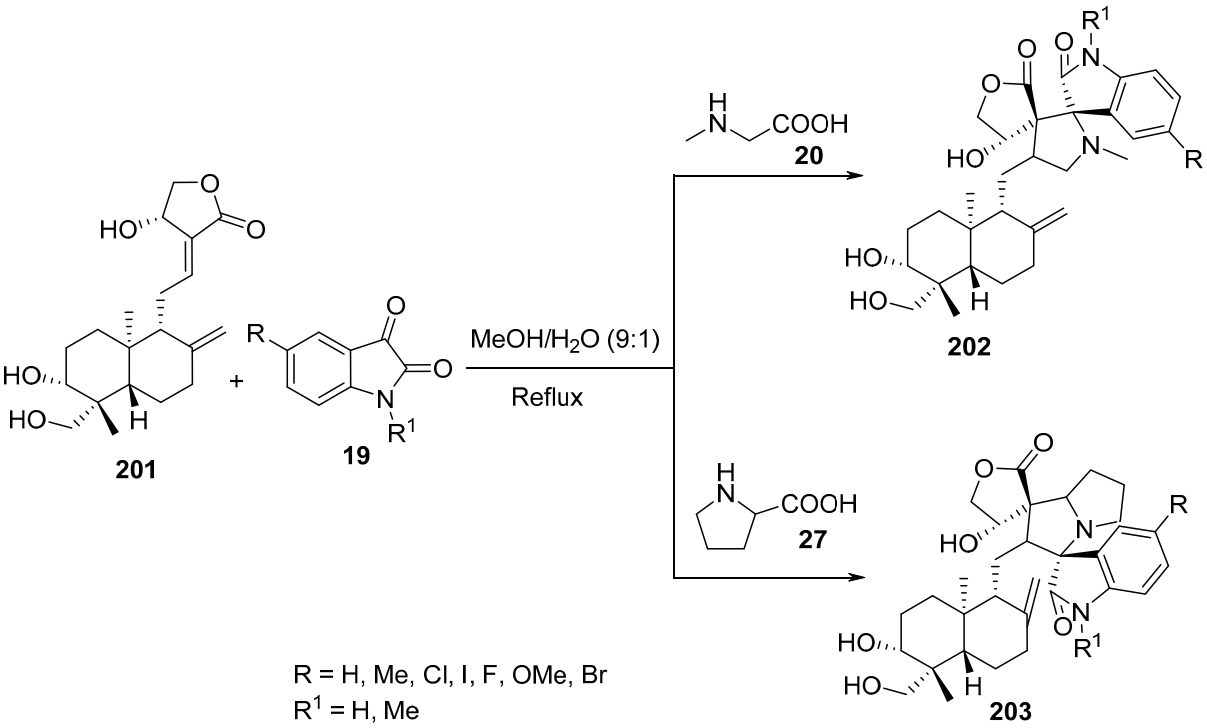
are of potential importance for fighting Alzheimer's disease (Scheme 68) [99]. Some of the synthesized **200** also revealed antibacterial activities against *Bacillus subtilis* NCIM 2718, *Staphylococcus aureus* NCIM5021, *Salmonella typhi* NCIM2501, *Pseudomonas aeruginosa* NCIM 5029, and *Proteus vulgaris* NCIM2813 relative to Ampicillin [100].



Scheme 68. Synthetic route towards dispiro[indoline-3,2′-pyrrolidine-3′,3″-pyrrolidines] **200**.

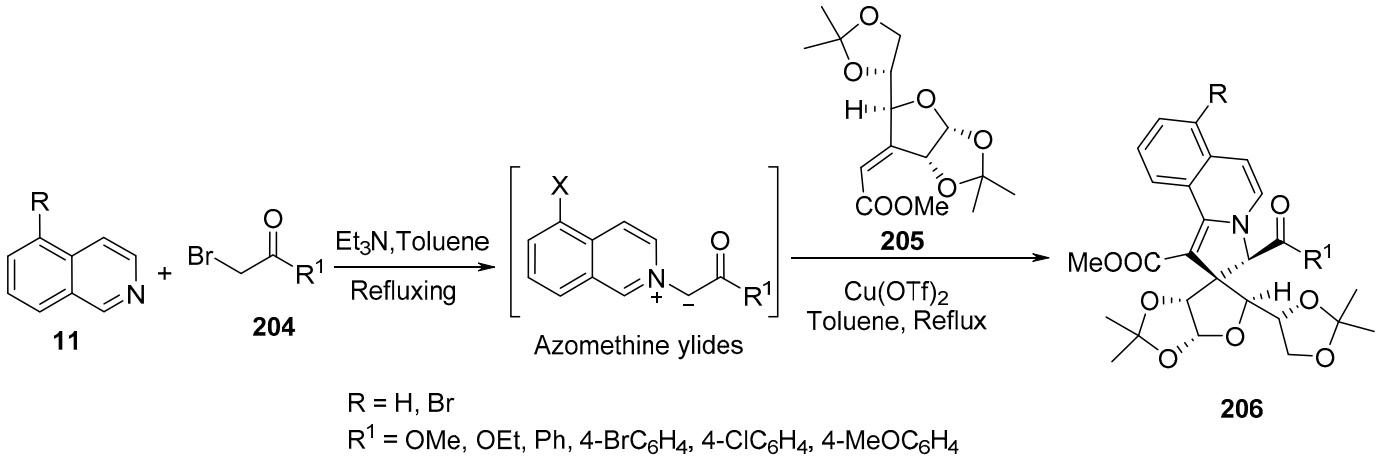
3.7. Lactones

Dispiropyrrolidino/pyrrolizidino-oxindoles **202** and **203** were obtained through the cycloaddition of *α*,*ß*-unsaturated-*γ*-lactone **201** with isatin **19**/sarcosine **20** or isatin **19**/proline **27** reagent systems (Scheme 69) [101].



Scheme 69. Synthesis of dispiropyrrolidino/pyrrolizidino-oxindoles **202** and **203**.

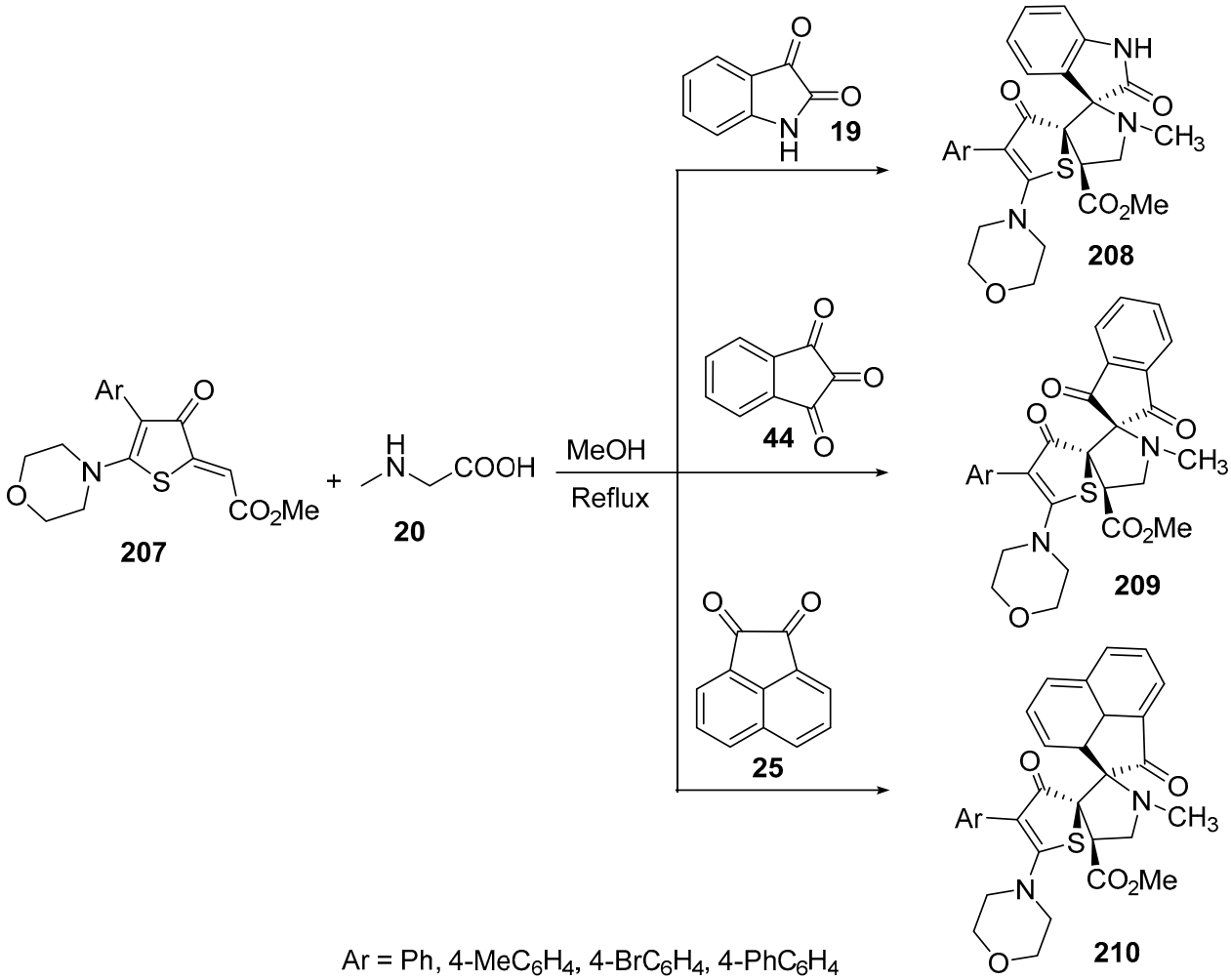
Glycospiro-2,3-dihydropyrrolo[2,1-*a*]isoquinolines **206** were synthesized by the reaction of 3-deoxy-3-*C*-[(*Z*)-(methoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-*α*-*D*-glucofuranose **205** with isoquinoline-based azomethine ylide formed from isoquinolines **11** and alkyl bromoacetates or 2-bromoacetophenones **204** in the presence of $Cu(OTf)_2$–Et_3N as a catalyst (Scheme 70) [102].



Scheme 70. Synthesis of glycospiro-2,3-dihydropyrrolo[2,1-*a*]isoquinolines **206**.

3.8. Thiophenones

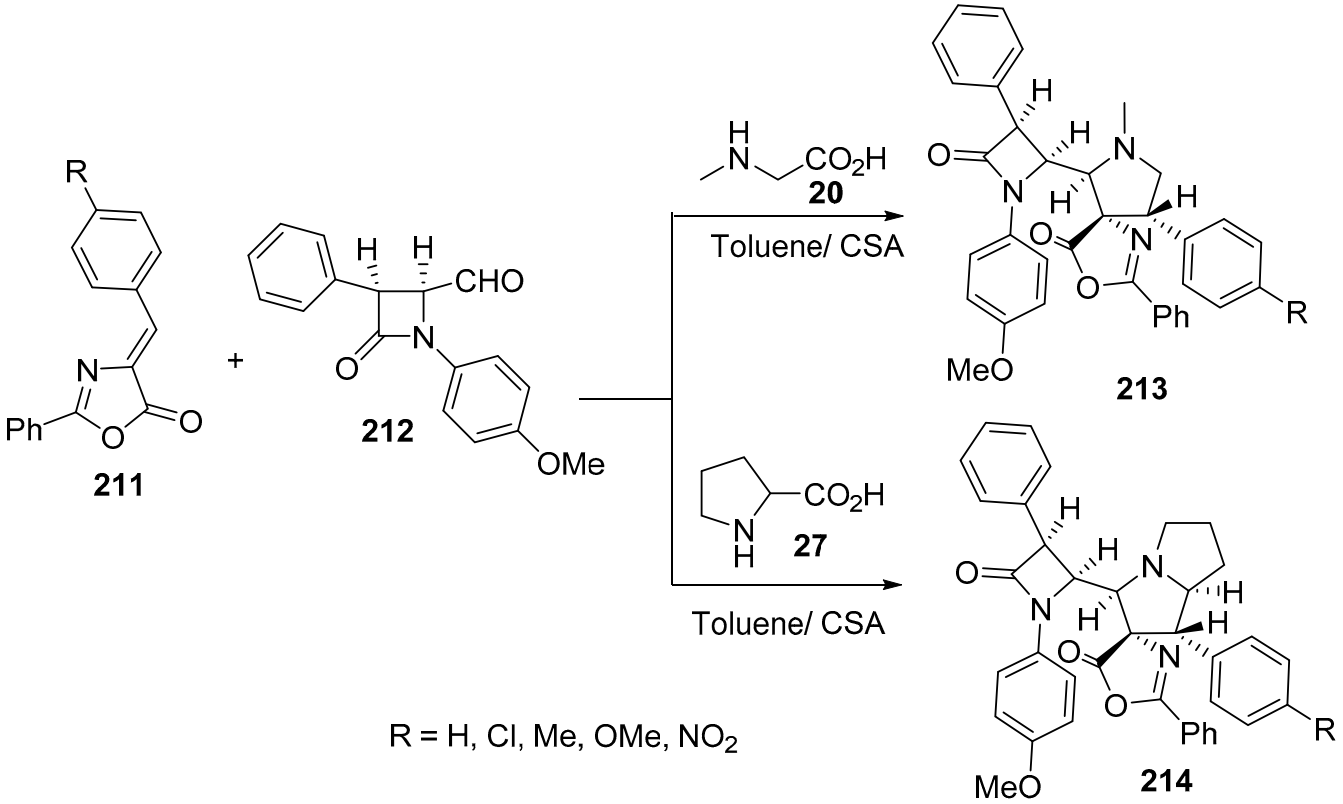
The reaction of 2-(ylidene)thiophen-3-ones **207** with various azomethine ylides generated from sarcosine **20** and different ketones (isatin **19**, ninhydrin **44** or acenaphthoquinone **25**) afforded the corresponding dispiropyrrolidine containing-thiophenones **208**–**210** in good yields (Scheme 71) [103].



Scheme 71. Synthesis of dispiropyrrolidine containing-thiophenones **208**–**210**.

3.9. Oxazolones

The reaction of 4-ylidene-5-(4*H*)-oxazolones **211** with azomethine ylide derived from *cis*-4-formyl-2-azetidinone **212** and sarcosine **20** or pyrrolidine **27**, in the presence of camphor sulphonic acid (CSA) as a catalyst, afforded the corresponding spiro[3.4′]-(oxazol-5′-one)-pyrrolidines **213** and spiro[3.4′]-(oxazol-5′-one)-pyrrolizidines **214**, respectively (Scheme 72) [104].

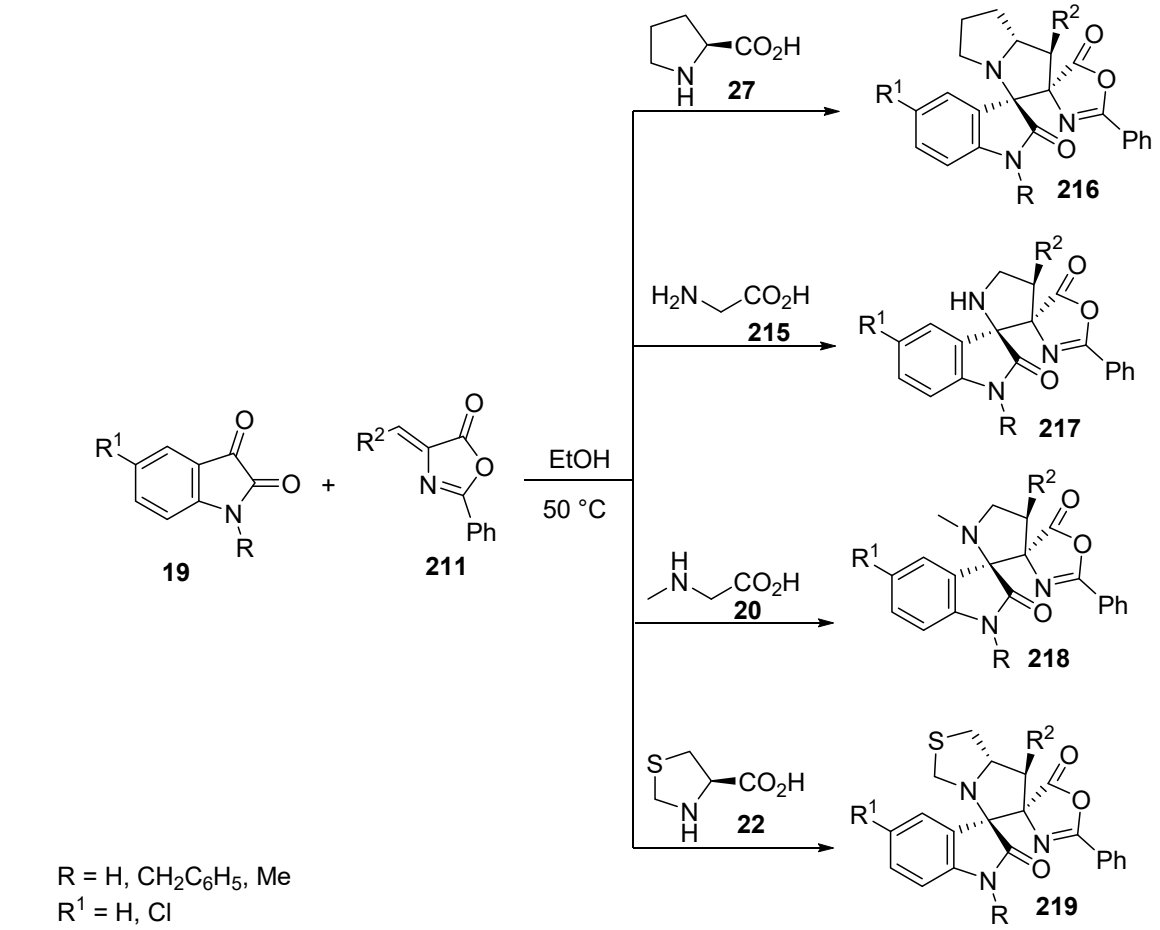


Scheme 72. Synthesis of spiro[3.4′]-(oxazol-5′-one)-pyrrolidines **213** and spiro[3.4′]-(oxazol-5′-one)-pyrrolizidines **214**.

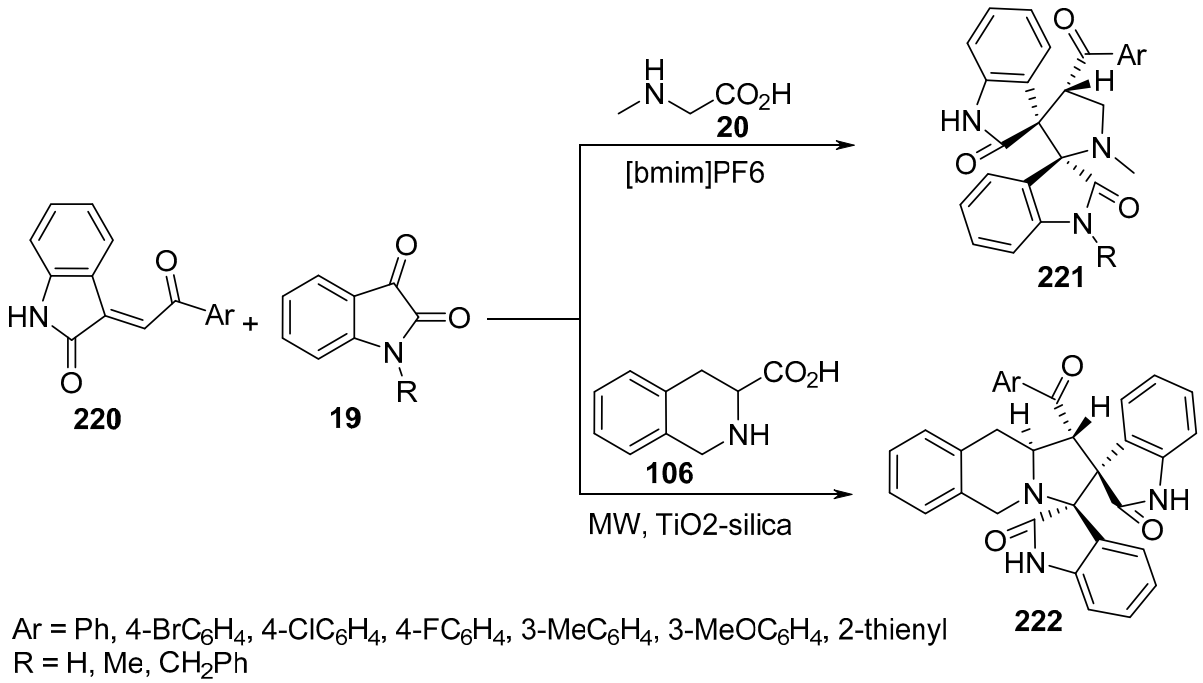
Spiro-compounds of types **216**–**219** were obtained via the cycloaddition reaction of 4-ylidene-5-oxazolones **211** and azomethine ylides (generated from isatin **19** and the appropriate α-amino acids). Some of the synthesized compounds showed considerable antitumor properties against breast cancer (MCF7, MDA-MB-231, and MDA-MB-468) and hepatocellular (HepG2, HCCC-9810, and HuH7) cell lines (MTT assay) relative to Gefitinib and Sorafenib (standard references) (Scheme 73) [105].

3.10. Indoles

The azomethine ylide (formed from isatin **19** and sarcosine **20**) underwent cycloaddition with 3-aroylmethyleneindol-2-ones **220** under green chemistry conditions in an ionic liquid ([bmim]PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate) to afford the corresponding dispiropyrrolidine-bisoxindoles **221** [106]. TiO_2–silica was also used as a solid-supported catalyst under microwave conditions for the synthesis of dispiropyrroloisoquinolines **222** via the three-atom component cycloaddition reaction of azomethine ylide (generated from tetrahydroisoquinoline-3-carboxylic acid **106** and isatin **19**) with **220** [92] (Scheme 74).

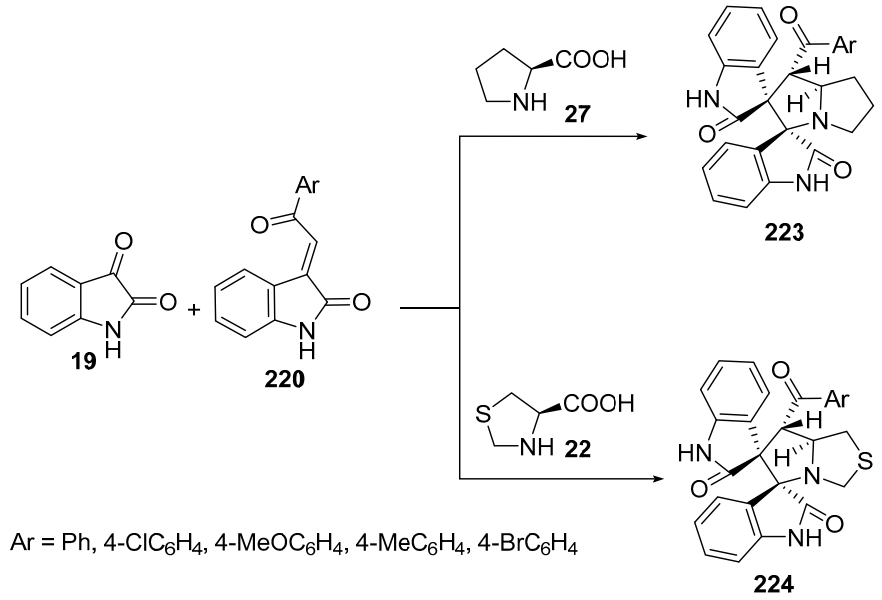


Scheme 73. Synthetic route towards spiro-compounds **216**–**219**.



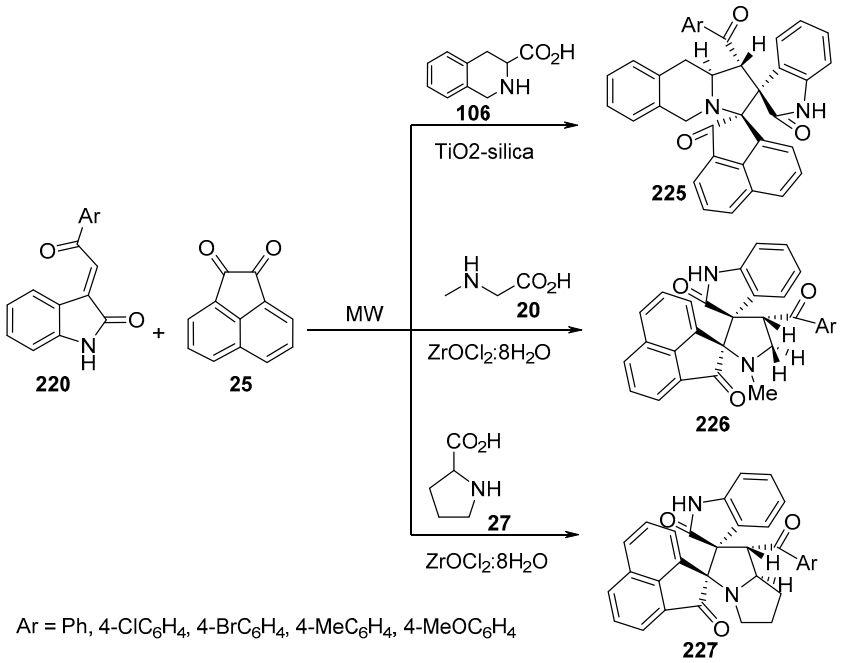
Scheme 74. Synthesis of dispiropyrrolidines **221** and **222**.

Dispiro-oxindolopyrrolizidines **223** and dispiro-oxindolothienopyrroles **224** could also be obtained by the reaction of azomethine ylides (generated from isatin **19** with *L*-proline **27** or *R*-thioproline **22**) with 3-aroylmethyleneindol-2-ones **220** under ultrasonication conditions in the presence of silica as a catalyst (Scheme 75) [107].



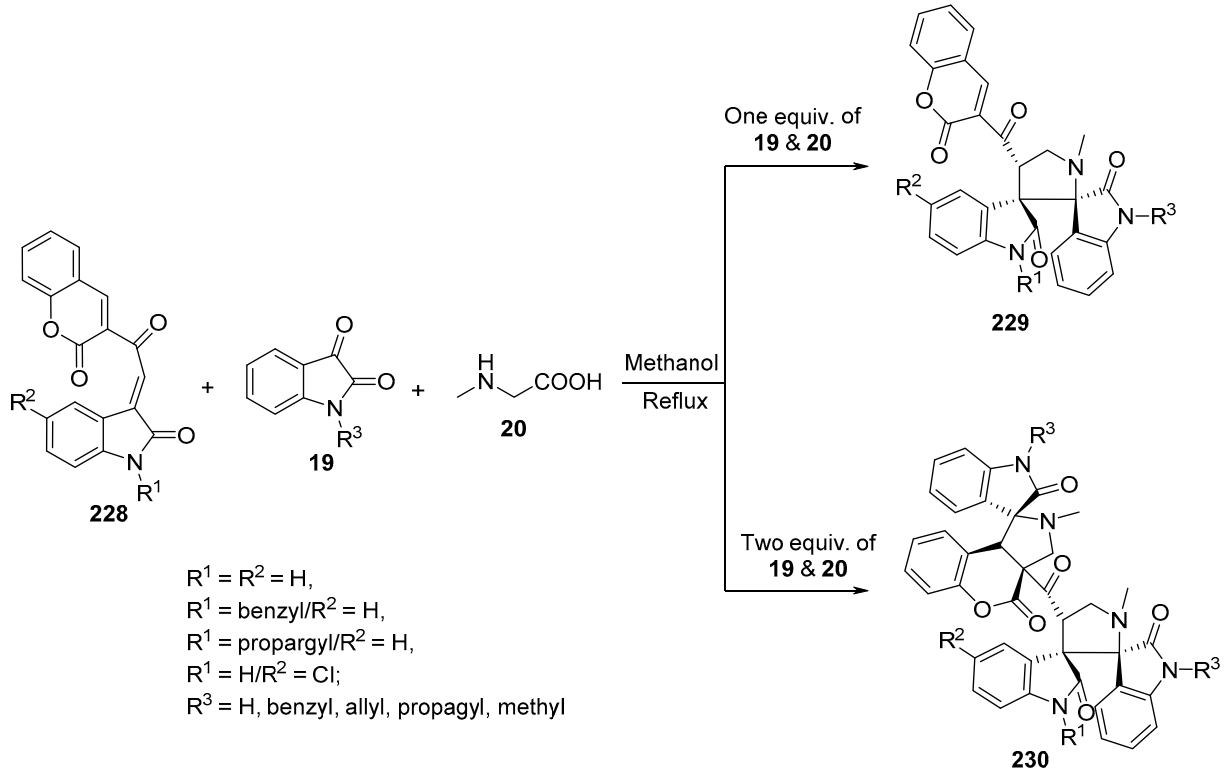
Scheme 75. Synthesis of dispiro-oxindolopyrrolizidines **223** and dispiro-oxindolothienopyrroles **224**.

Similarly, the cycloaddition reaction of 3-aroylmethyleneindol-2-ones **220** with azomethine ylide (formed from tetrahydroisoquinoline-3-carboxylic acid **106** and acenaphthenequinone **25**) using TiO_2–silica as a solid-supported catalyst under microwave conditions yielded dispiropyrroloisoquinoline **225** [92]. Ball-clay-supported zirconium oxychloride octahydrate was also used as a catalyst in the cycloaddition reaction of azomethine ylides (generated from acenaphthenequinone **25** and sarcosine **20** or *L*-proline **27**) to produce spiro-oxindolopyrrolidine **226** and spiro-oxindolopyrrolizidine **227**, respectively (Scheme 76) [108].



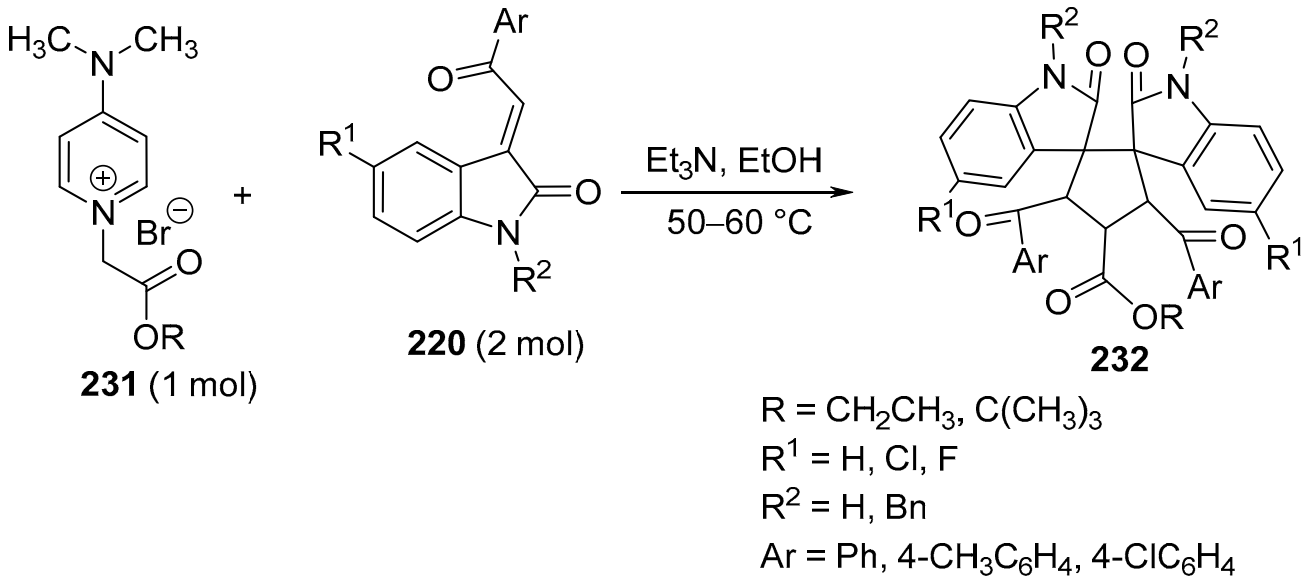
Scheme 76. Synthesis of spiropyrrolidines **225**–**227**.

Spiro-oxindoles of type **229** were obtained by reacting isatin **19**, sarcosine **20**, and 3-[2-oxo-ethylidene]indolin-2-one **228** in equimolar quantities whereas spiro-oxindole derivatives of type **230** were formed when isatin **19** and sarcosine **20** were used at a two-fold degree of molar excess over acceptor **228** (Scheme 77) [109].



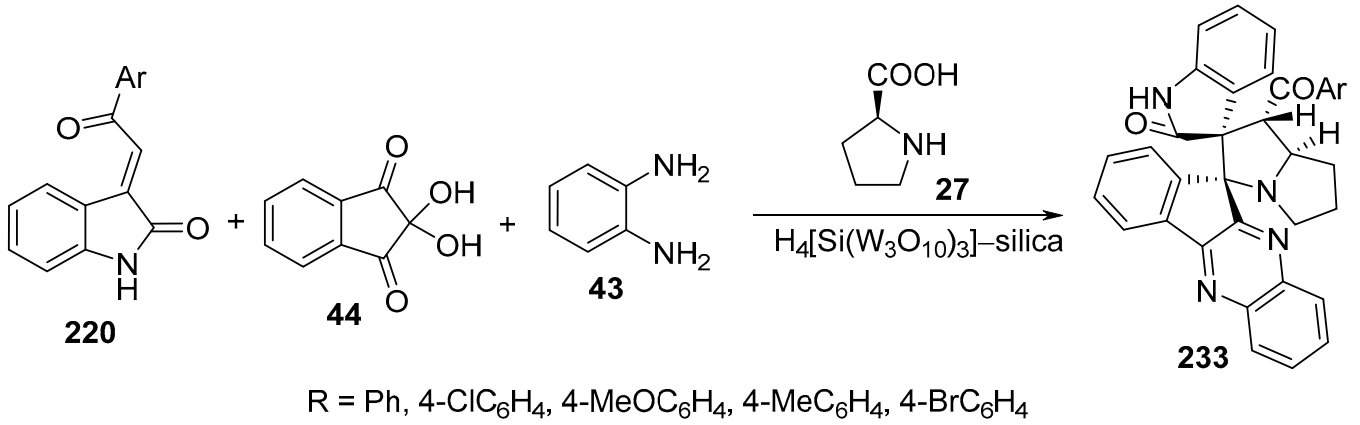
Scheme 77. Synthesis of spiropyrrolidinyl-oxindoles **229** and **230**.

Another dispirocyclopentanebisoxindole **232** can be obtained by the cycloaddition of azomethine ylides generated from 4-dimethylamino-1-alkoxycarbonylmethylpyridinium bromide **231** and aroylmethyleneindol-2-one **220** (Scheme 78) [110].



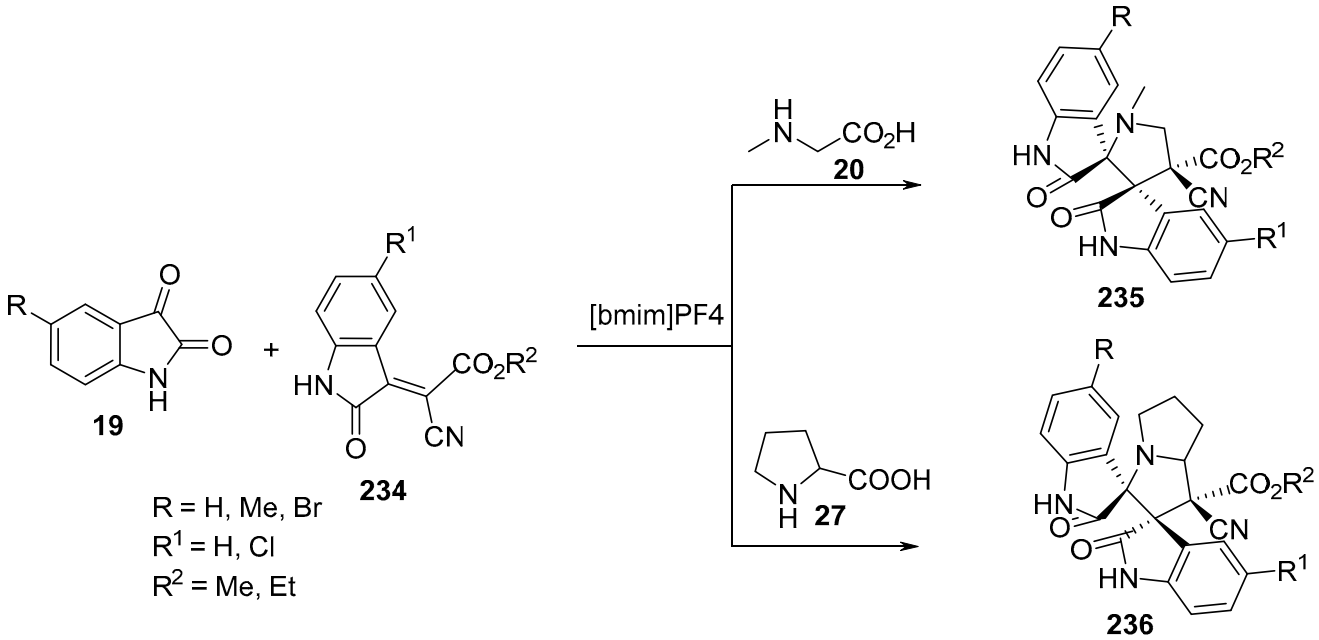
Scheme 78. Synthesis of dispirocyclopentanebisoxindole **232**.

The cycloaddition of aroylmethyleneindol-2-one **220** with azomethine ylide formed from indenoquinoxaline-11-one (generated in situ from ninhydrin **44** and *o*-phenylenediamine **43**) and *L*-proline **27** was catalyzed by eteropolyacid $H_4[Si(W_3O_{10})_3]$–silica and afforded the corresponding dispiroindenoquinoxaline-pyrrolizidine **233** (Scheme 79) [91].



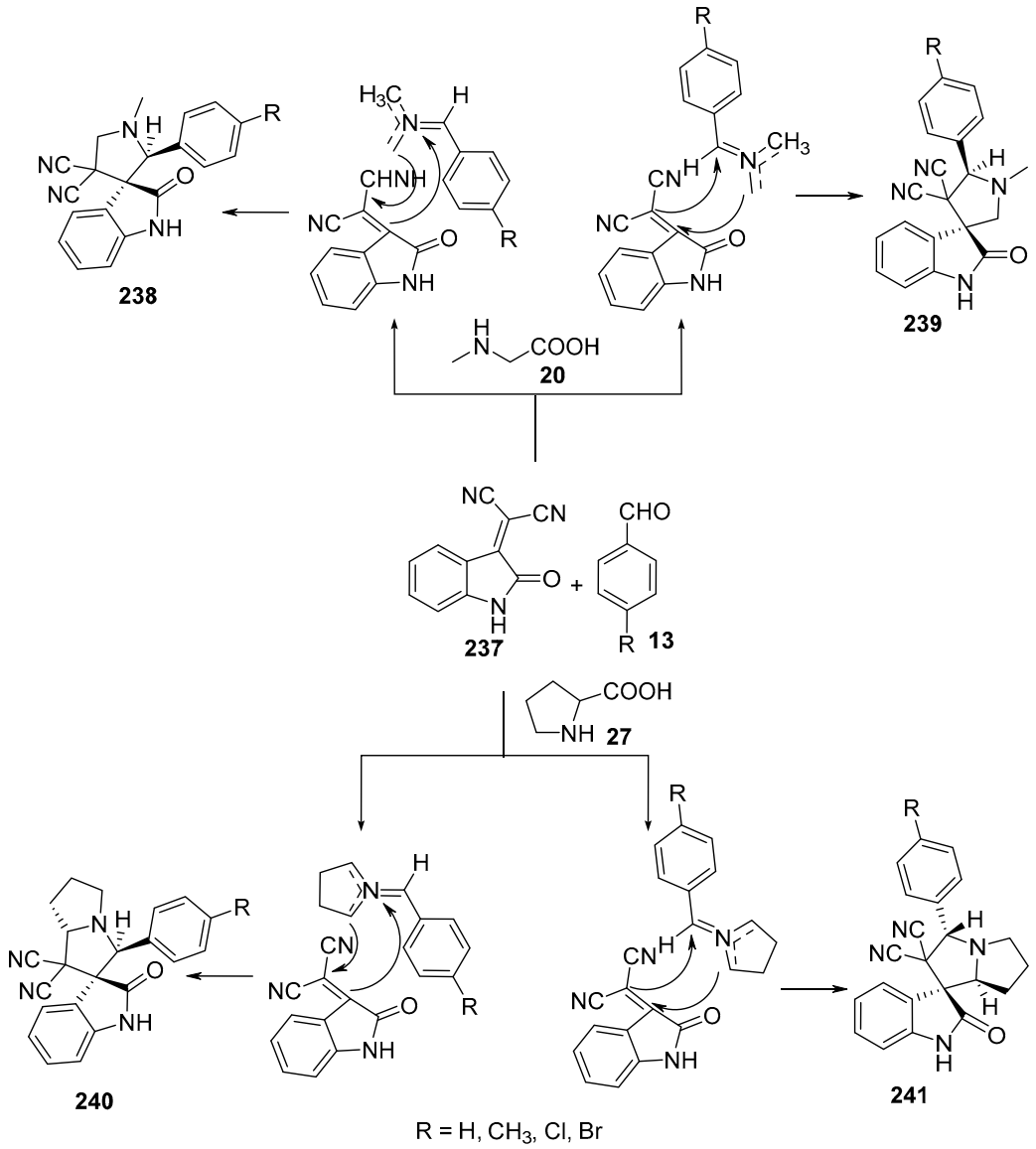
Scheme 79. Synthesis of dispiroindenoquinoxaline-pyrrolizidine **233**.

The reaction of azomethine ylides—formed from the condensation of isatin **19** and sarcosine **20** or proline **27** in an ionic liquid [bmim] BF_4 (without using any catalyst)—with 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **234** yielded the corresponding dispiropyrrolidine-bisoxindole **235** and dispiropyrrolizidine-bisoxindole **236**, respectively (Scheme 80) [111].



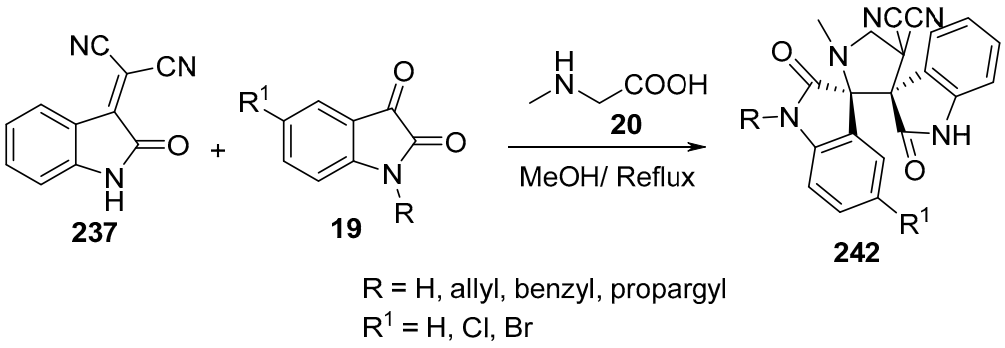
Scheme 80. Synthesis of dispiropyrrolidine-bisoxindoles/dispiropyrrolizidine-bisoxindoles **235/236**.

Spiropyrrolidine/spiropyrrolizine-oxindoles **238**–**241** were synthesized by a multi-component cycloaddition reaction of 2-oxo-(3*H*)-indol-3-ylidine-malononitrile **237** with azomethine ylides (generated from aromatic aldehyde **13** and sarcosine **20** or *L*-proline **27**) in refluxing toluene containing molecular sieves (3 Å) (Scheme 81) [112].



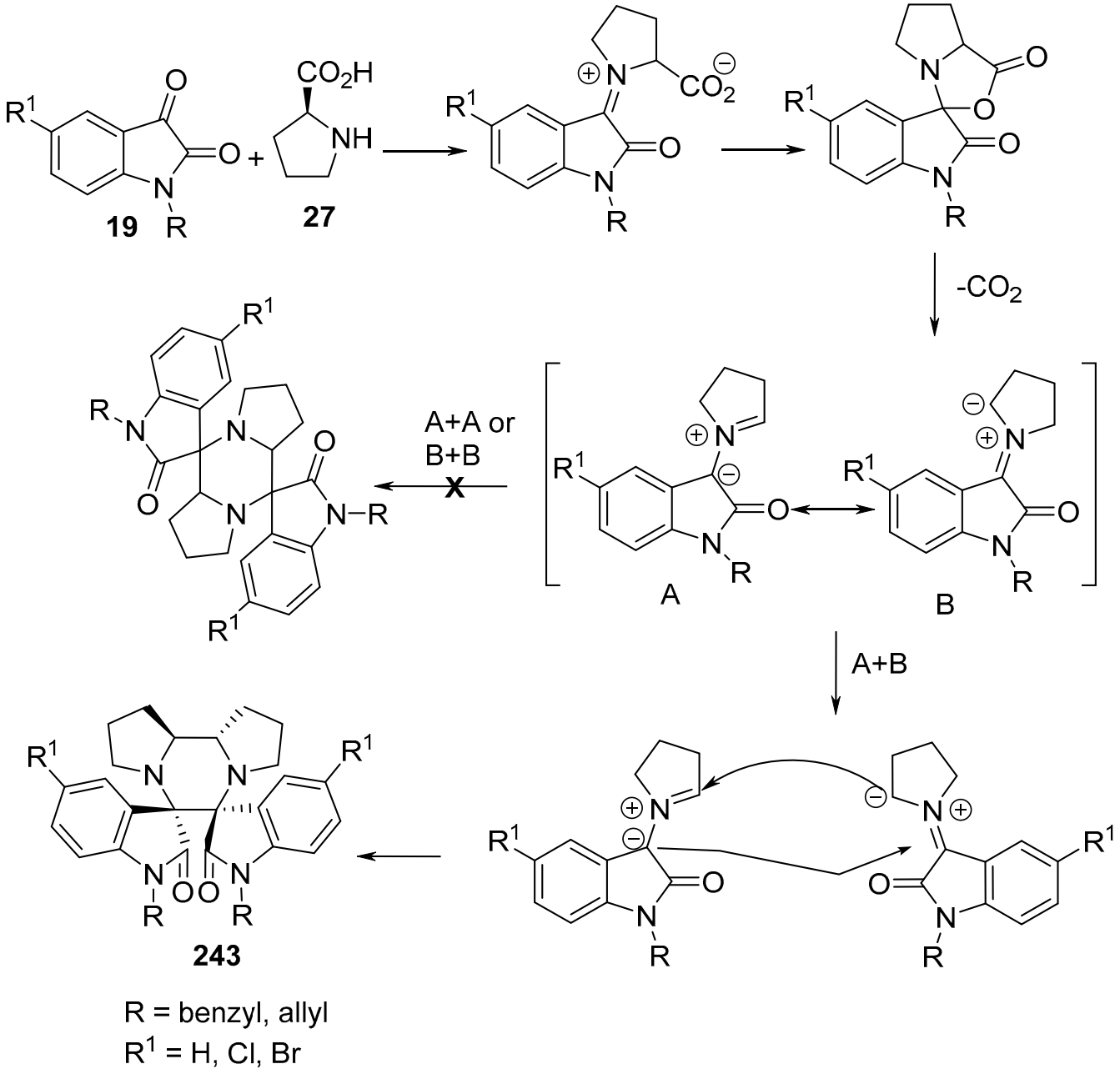
Scheme 81. Synthesis of spiropyrrolidine/spiropyrrolizine-oxindoles **238**–**241**.

In addition, dispiropyrrolidine-bisoxindole derivatives of type **242** were obtained from a three-atom component reaction of isatin **19**, sarcosine **20**, and isatylidene malononitrile **237** with high regioselectivity (Scheme 82) [43].



Scheme 82. Synthesis of dispiropyrrolidine-bisoxindole **242**.

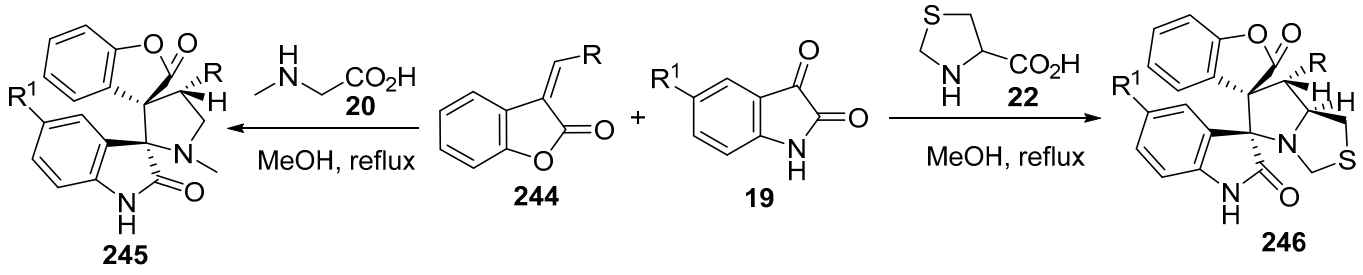
Dispiro-oxindoles of type **243** were obtained by the dimerization of in situ generated azomethine ylides (A and B) via A+B pathways. X-Ray studies supported the postulated structures of type **243** (Scheme 83) [113].



Scheme 83. Synthesis of dispiro-oxindole **243**.

3.11. Benzofuran-2-ones

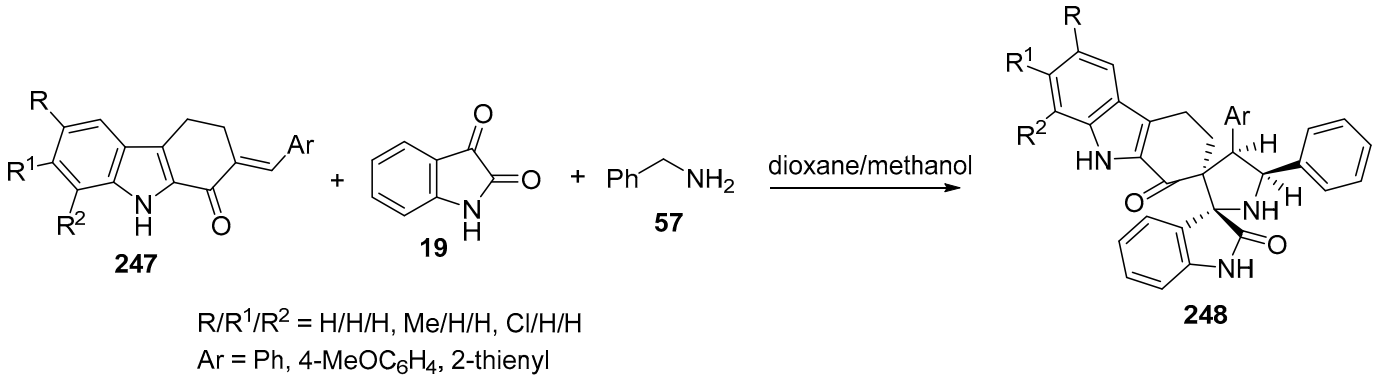
Dispiro-oxindolopyrrolidine **245** and dispiro-oxindolopyrrolothiazole **246** were obtained by a multi-component reaction of 3-(ylidene)benzofuran-2-one **244** with isatin **19** and the appropriate *α*-amino acid (sarcosine **20** or thioproline **22**, respectively) in refluxing methanol. Some of the synthesized compounds revealed promising antimycobacterial (*M. tuberculosis* H37Rv) properties relative to pyrazinamide (standard reference) (Scheme 84) [114].



Scheme 84. Synthetic route towards dispiro-oxindolopyrrolidine **245** and dispiro-oxindolopyrrolothiazole **246**.

3.12. Keto-Carbazoles

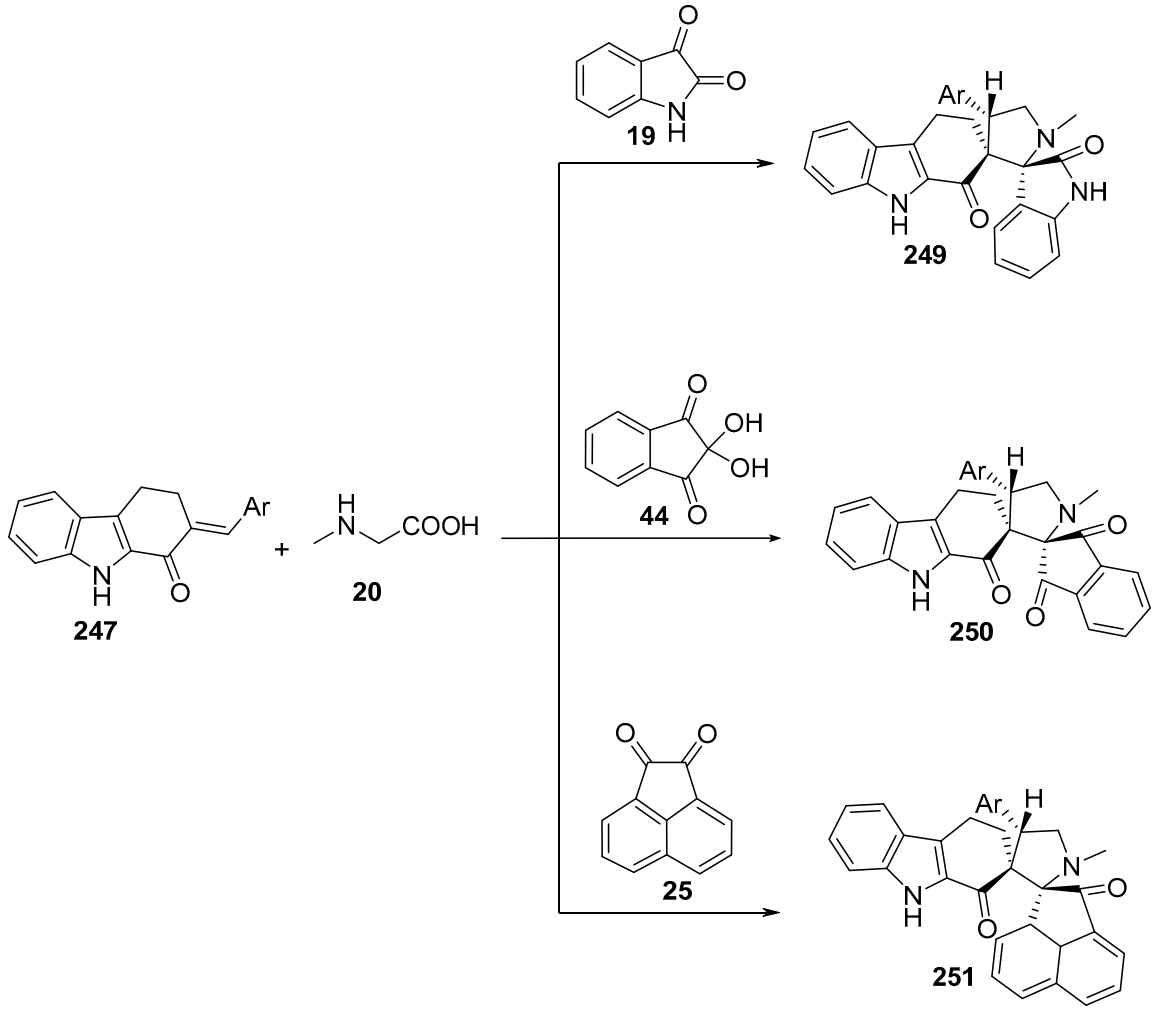
Dispiro[carbazole-2,3′-pyrrolo-2′,3″-indole] derivatives of type **248** were synthesized regio- and stereoselectively by the reaction of 2-ylidene-1*H*-carbazol-1-one **247** and in situ-generated azomethine ylide (formed from isatin **19** and benzylamine **57**). Some of the obtained compounds revealed antiproliferative properties (MTT assay) via apoptosis induction against MCF7 (breast) and A-549 (lung) cancer cell lines relative to Cisplatin (Scheme 85) [115].



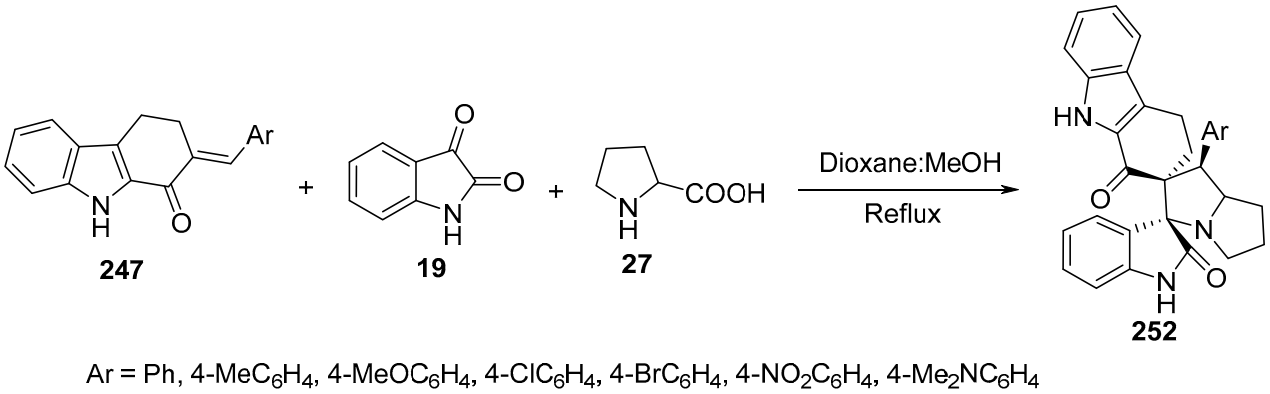
Scheme 85. Synthesis of dispiro[carbazole-2,3′-pyrrolo-2′,3″-indoles] **248**.

The reaction of (*E*)-2-arylidine-1-ketocarbazole **247** with various azomethine ylides generated from sarcosine **20** and di/tri ketone (isatin **19**, ninhydrin **44**, acenathenequinone **25**) under microwave irradiation afforded the corresponding ketocarbazolodispiropyrrolidines **249**–**251** (Scheme 86). Some of the synthesized compounds showed antimicrobial properties against *Proteus vulgaris*, *Proteus mirabilis*, *Staphylococcus aureus*, and *Salmonella typhi* relative to Tetracycline [116].

Similarly, dispiro-oxindolopyrrolizidines of type **252** were prepared by reacting (*E*)-2-arylidine-1-ketocarbazole **247** with the azomethine ylide formed from isatin **19** and proline **27** (Scheme 87). Some of the products showed antimicrobial activities against human pathogens (*Proteus vulgaris*, *Proteus mirabilis*, *Staphylococcus aureus*, and *Salamonella typhi*) relative to Tetracycline and acted as inhibitors of plant fungal pathogen mycelial growth (*Fusarium oxysporum* and *Macrophomena phaseolina*) relative to the standard reference—Carbendazim [117].



Scheme 86. Synthesis of ketocarbazolodispiropyrrolidines **249**–**251**.

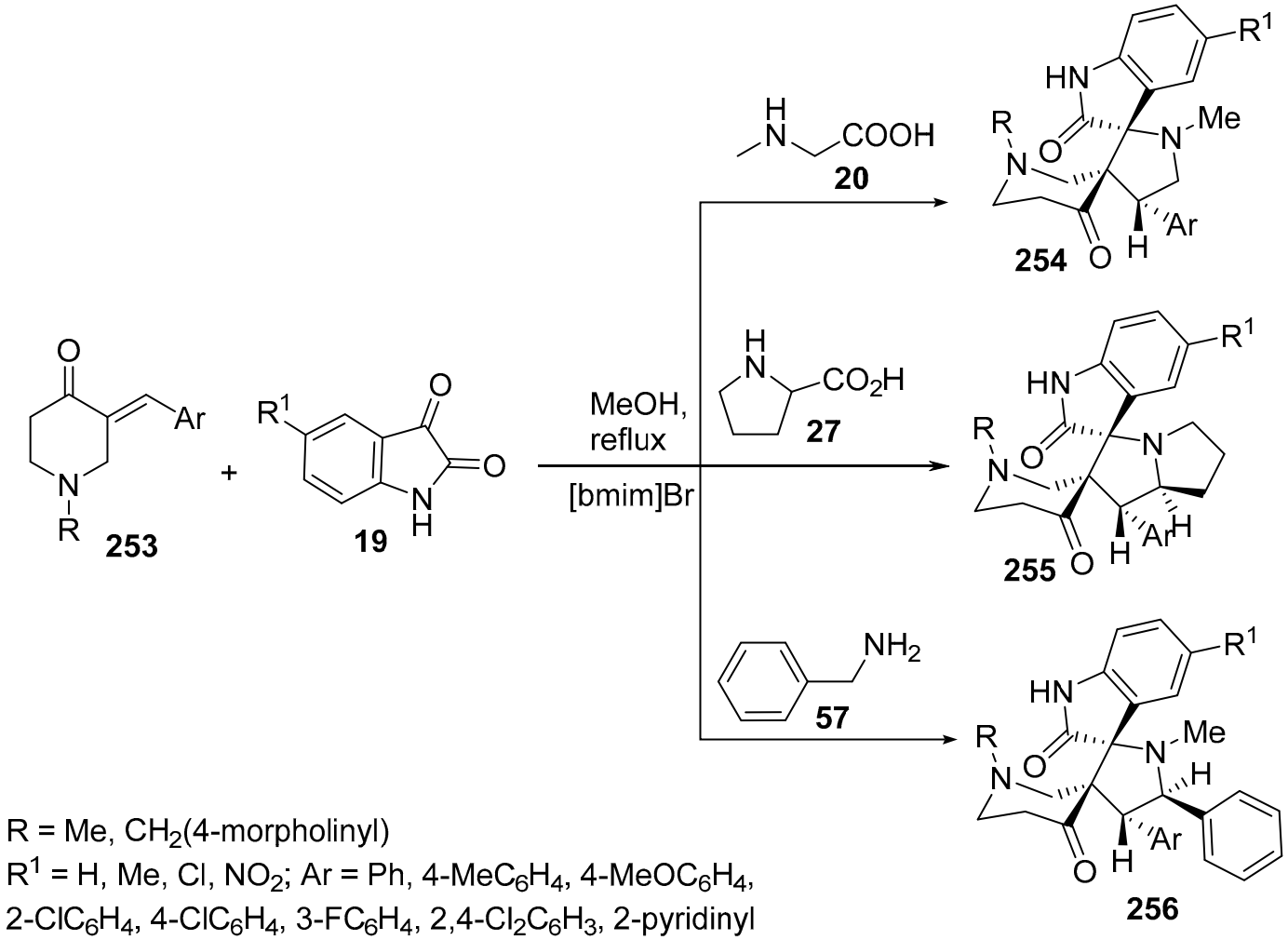


Scheme 87. Synthesis of dispiro-oxindolopyrrolizidines **252**.

3.13. Piperidones

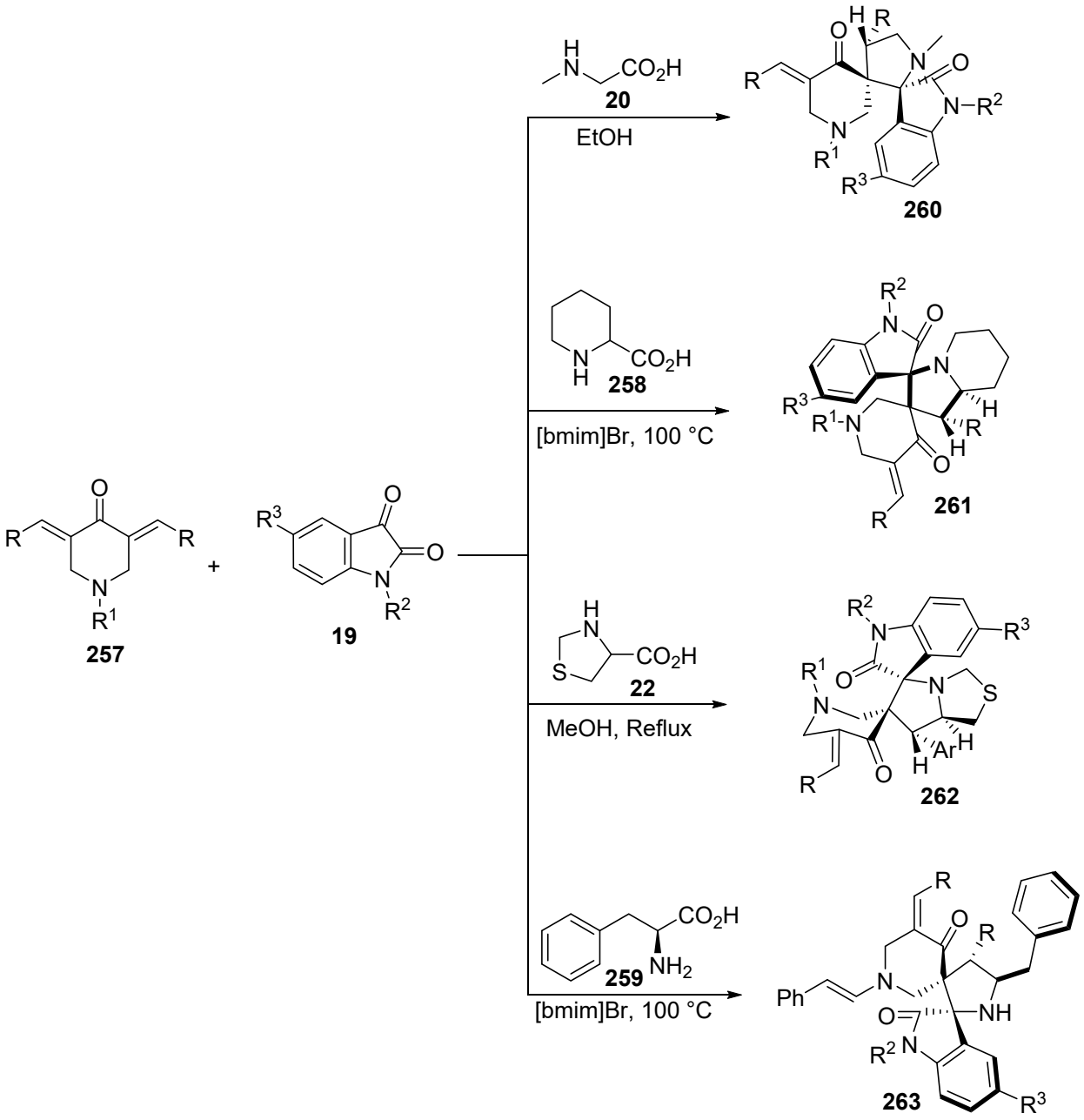
The reaction of isatin **19** with various amines (sarcosine **20**, proline **27,** and benzylamine **57**) in refluxing methanol or in ionic liquid [bmim]Br generated the corresponding azomethine ylides that was added to 3-(arylidene)-4-piperidones **253** to form the corresponding spiropiperido-pyrrolizines/pyrrolidines **254**–**256** (Scheme 88). Some of the products showed activities against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug

resistant *M. tuberculosis* (MDR-TB), and *Mycobacterium smegmatis* (MC2) relative to ethambutol and pyrazinamide (standard references) [118], and also had acetyl- and butyryl-cholinesterase inhibitory properties (of potential use against Alzheimer's disease) relative to galantamine [119].



Scheme 88. Synthesis of spiropiperido-pyrrolizines/pyrrolidines **254**–**256**.

A variety of dispiro-heterocycles of types **260**–**263** were obtained via azomethine ylide intermediates (formed from isatin **19** and sarcosine **20**, piperidine-2-carboxylic acid **258**, thioproline **22,** or 2-amino-3-phenylpropanoic acid **259**) in a reaction with 3,5-bis(ylidene)-4-piperidone **257** (Scheme 89). Some of the synthesized analogs revealed considerable antiproliferation properties against a variety of tumor cell lines [120–123]. Promising anti-inflammatory properties were also exhibited by some of the synthesized compounds (50 mg/kg) in a rat model of carrageenan-induced paw edema (anti-edematous test) relative to indomethacin (10 mg/kg) [120,124]. Some derivatives of compound **262** showed activities against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB) relative to ethambutol and pyrazinamide (standard references) [125], and had antifungal properties against *Candida albicans* ATCC 10231 with high inhibition of the fungal hyphae relative to fluconazole (standard reference drug) [126].



R = Ph, 2-BrC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 2-FC_6H_4, 4-FC_6H_4, 2,4-$Cl_2C_6H_3$, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$^{i}PrC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2,4-$MeO_2C_6H_3$, 3-$NO_2C_6H_4$, 2-thienyl, 5-methyl-2-furanyl, 3-pyridinyl

R^1 = Me, Et

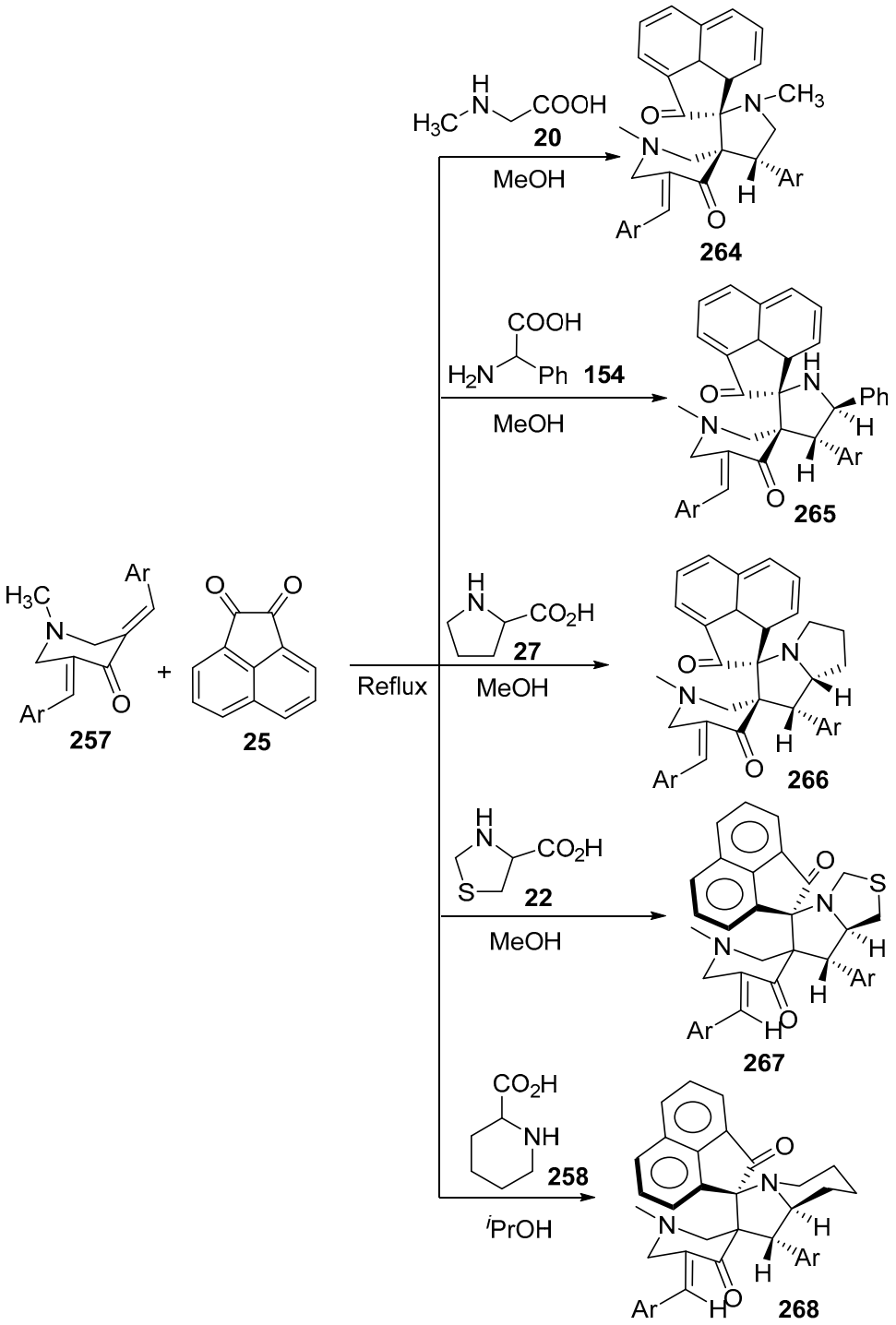
R^2 = H, Me, CH_2(1-piperidinyl), CH_2(4-moroholinyl)

R^3 = H, Cl, OMe, OCF_3

Scheme 89. Synthesis of spiropyrrolidines **260**–**263**.

Similarly, the reaction of 3,5-bis(ylidene)-4-piperidone **257** with a series of azomethine ylides generated from acenaphthenequinone **25** and *α*-amino acids (sarcosine **20**, phenylglycine **154**, proline **27**, thioproline **22,** or piperidine-2-carboxylic acid **258**) afforded the corresponding spiropiperidone-containing compounds **264**–**268** (Scheme 90). Some of these derivatives revealed promising activities against *Mycobacterium tuberculosis* H37Rv (MTB),

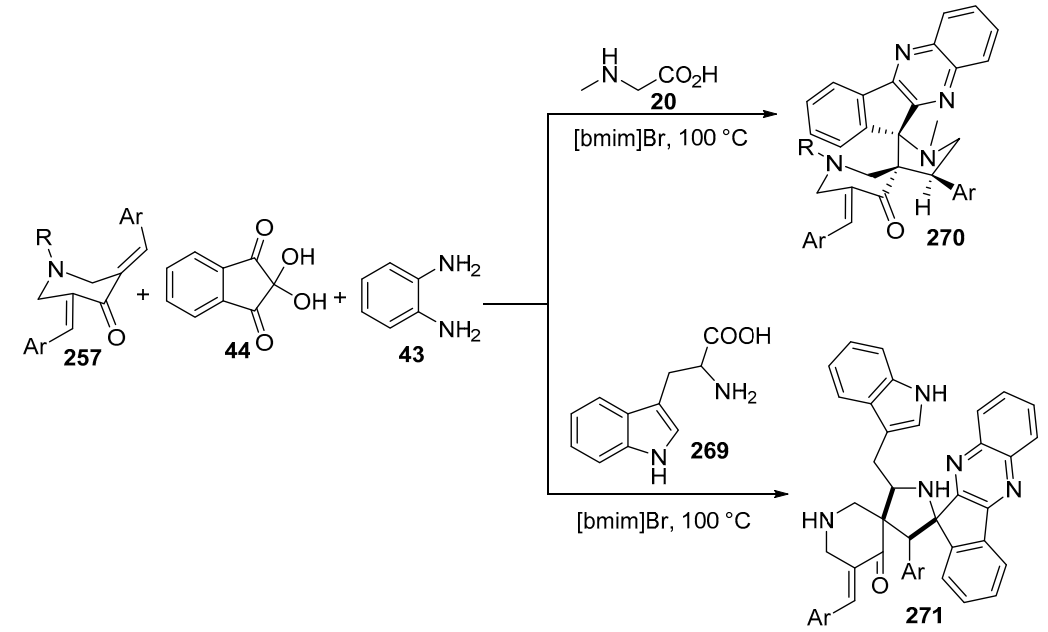
multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), and *Mycobacterium smegmatis* relative to Isoniazid [127]. Another group of the synthesized spiro-heterocycles **267** and **268** showed acetylcholine (AChE)-inhibitory properties relative to Donepezil HCl [128].



Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-FC_6H_4, 2-BrC_6H_4, 3-FC_6H_4, 2-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 1-naphthyl

Scheme 90. Synthesis of spiropiperidone-containing compounds **264**–**268**.

A multicomponent reaction of 3,5-bis[(*E*)-ylidene]-4-piperidone **257**, ninhydrin **44**, *o*-phenylenediamine **43**, and *α*-amino acid (sarcosine **20** or *L*-tryptophan **269**) in 1-butyl-3-methylimidazoliumbromide ([BMIm]Br) used as an ionic liquid produced the corresponding dispiro compounds **270** and **271** [129,130] (Scheme 91). Significant acetylcholinesterase-(AChE) and butyrylcholinesterase (BChE)-inhibitory properties were shown by some of the synthesized compounds relative to galantamine (standard reference) [130].

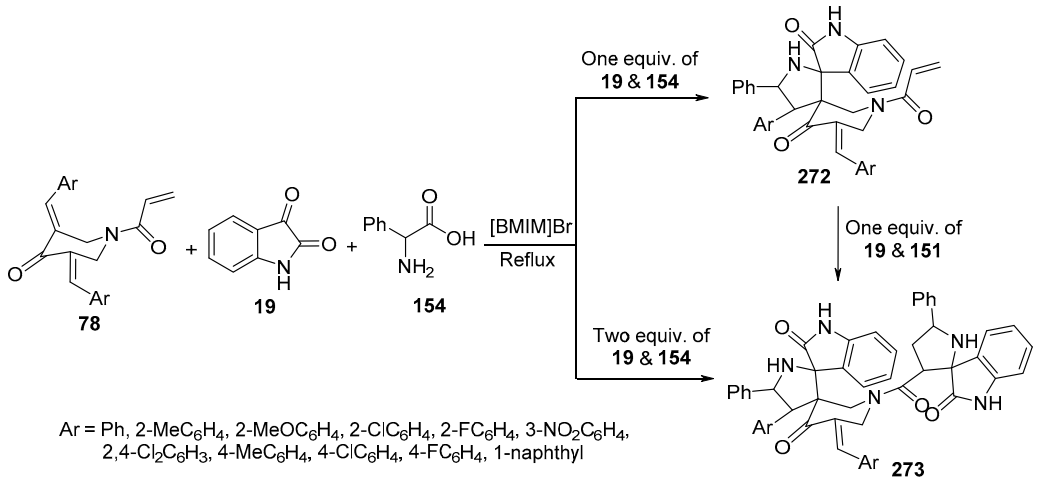


R = H, Me, $CH_2C_6H_5$

Ar = H, Ph, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$^{i}PrC_6H_4$, 4-$Me_2NC_6H_4$, 3-$NO_2C_6H_4$, 2-thienyl, 1-naphthyl

Scheme 91. Synthesis of dispiro compounds **270** and **271**.

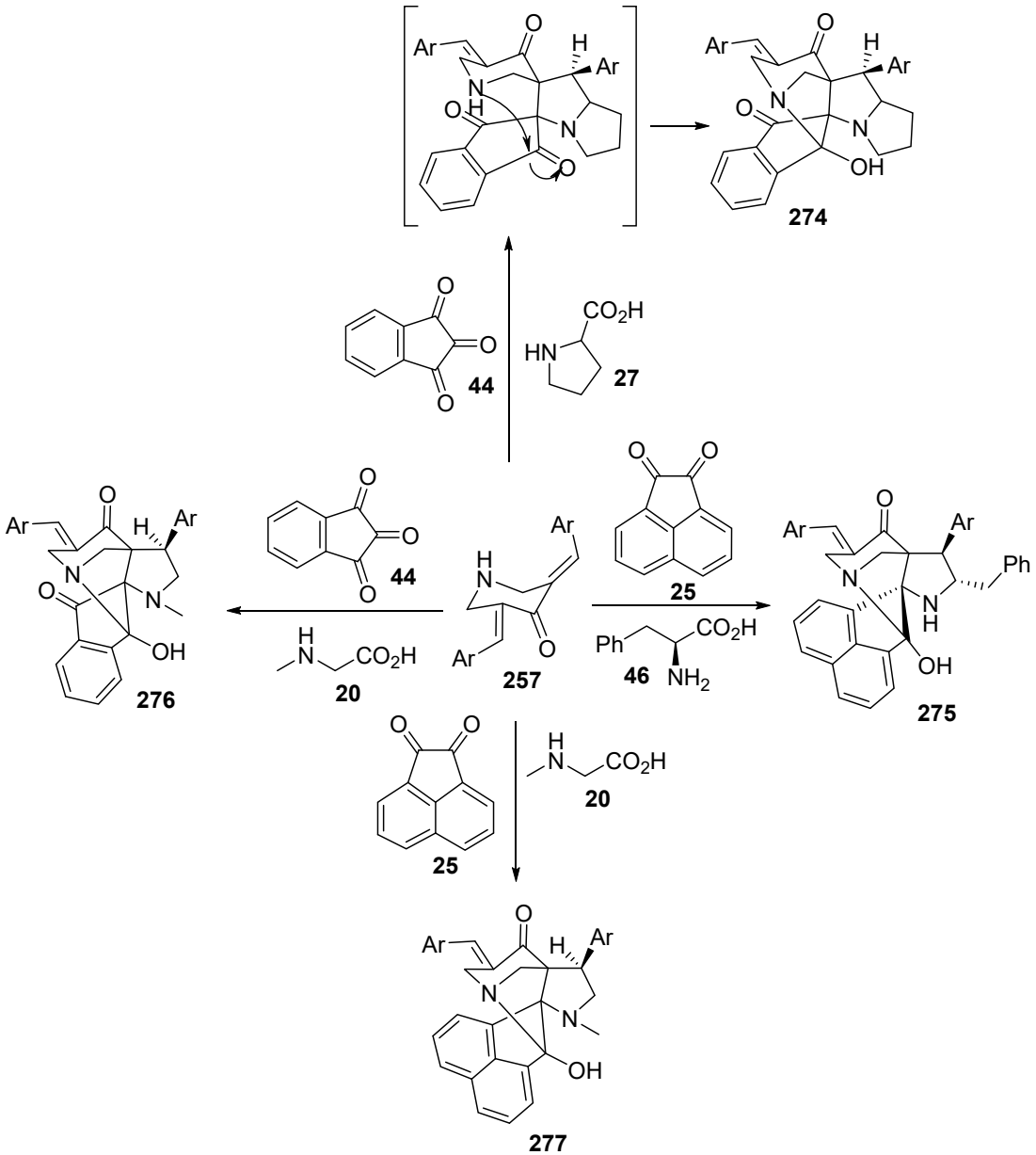
Mono-spiropyrrolidines of type **272** were synthesized by the reaction of 1-acryloyl-3,5-bis(ylidene)-4-piperidinone **78** with azomethine ylide generated from isatin **19** and phenylglycine **154** from equimolar amounts of the reactants. Meanwhile, bisspiropyrrolidine derivatives of type **273** were formed using two equivalents, namely, isatin **19** and phenylglycine **154** (Scheme 92). Some of the synthesized compounds showed promising AChE- and BChE-inhibitory properties relative to Galanthamine [131].



Ar = Ph, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2-ClC_6H_4, 2-FC_6H_4, 3-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 1-naphthyl

Scheme 92. Synthesis of mono-spiropyrrolidines **272** and bisspiropyrrolidines **273**.

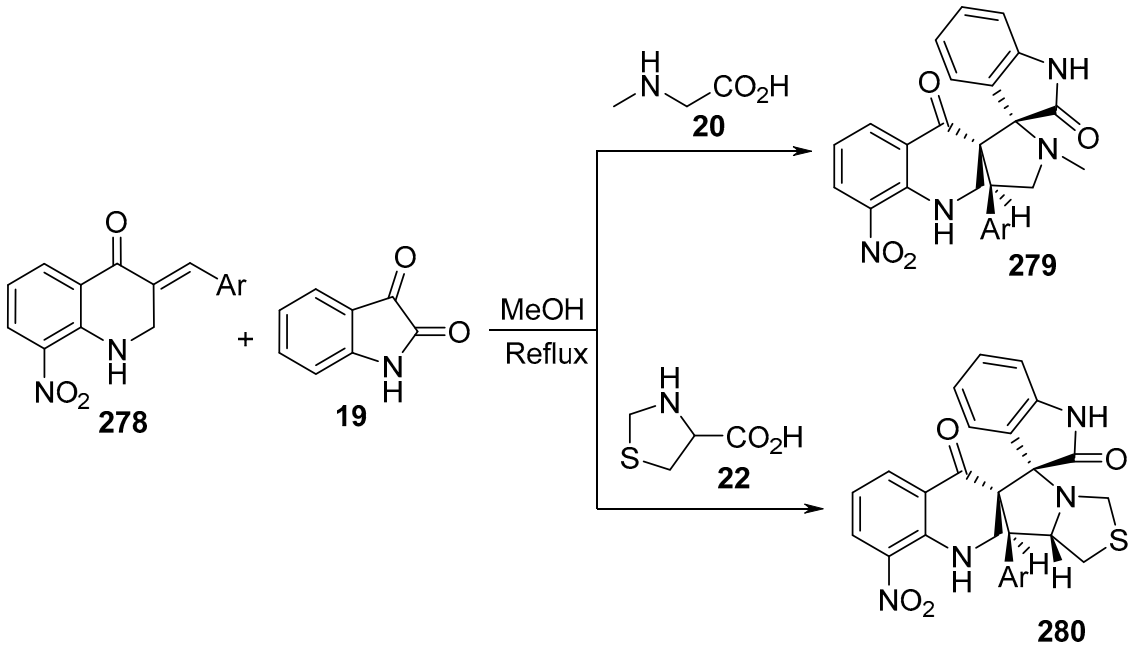
Finally, the reaction of 3,5-bis(ylidene)-4-piperidone **257** with azomethine ylide formed from ninhydrin **44** and proline **27** in refluxing methanol afforded diazahexacycle **274** [132]. Similarly, **275**–**277** were obtained by the reaction of **257** with another azomethine ylides generated from ninhydrin **44** or acenaphthenequinone **25** with sarcosine **20** or *L*-phenylalanine **45** (Scheme 93) [133,134]. Some of the derivatives of type **274** exhibited inhibitory activities toward AChE relative to Donepezil HCl [132].



Scheme 93. Synthesis of diazahexacycles **274**–**277**.

3.14. Quinolones

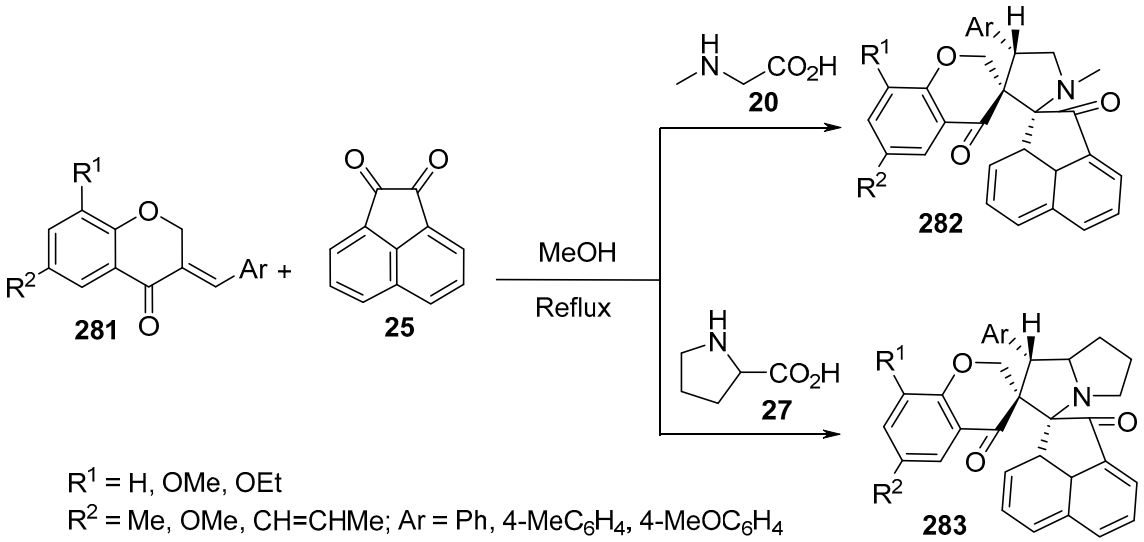
Spiropyrrolidines **279** and **280** were synthesized by the reaction of (*E*)-3-(ylidene)-4-quinolone **278** with azomethine ylides formed from isatin **19** and sarcosine **20** or thioproline **22** (Scheme 94) [135].



Scheme 94. Synthesis of spiropyrrolidines **279** and **280**.

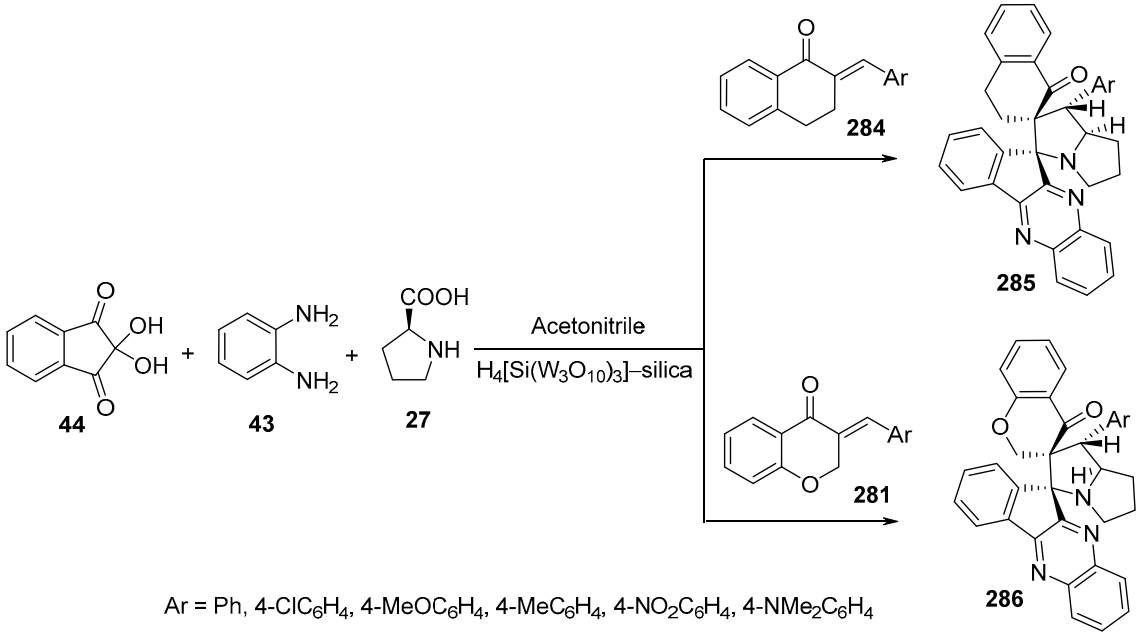
3.15. Chromanones

The reaction of (*E*)-3-arylidene-4-chromanone of type **281** with azomethine ylides formed from acenaphthenequinone **25** and sarcosine **20** or proline **27** afforded spiropyrrolidines **282** and **283**, respectively, with high regioselectivity (Scheme 95) [136].



Scheme 95. Synthesis of spiropyrrolidines **282** and **283**.

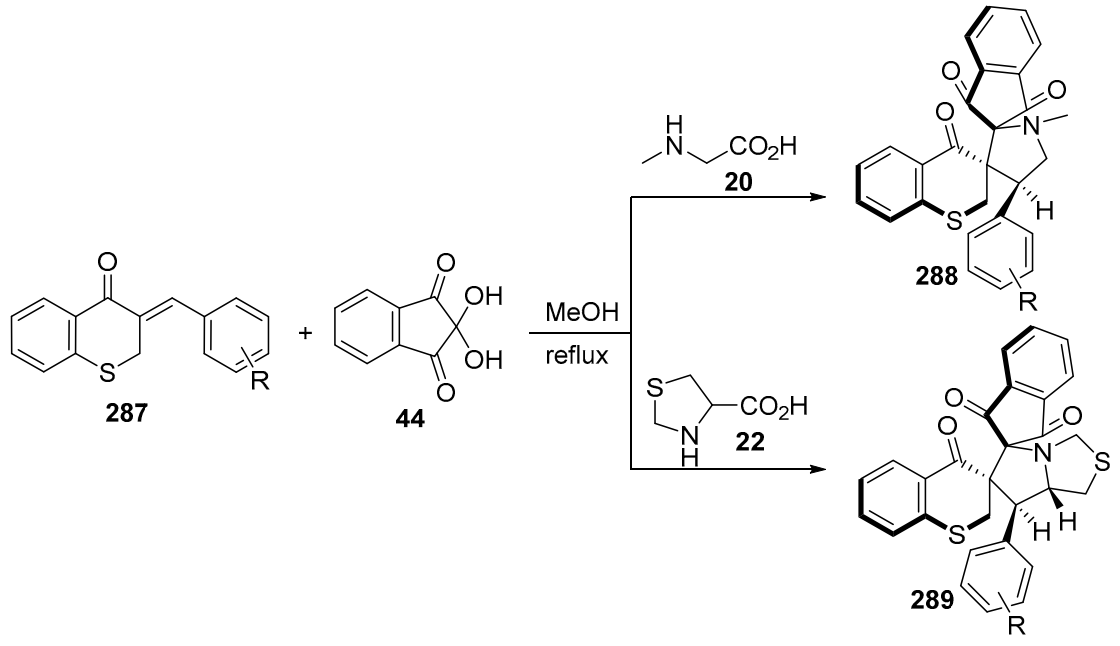
A multi-component reaction of 2-ylidene-tetrahydronaphthalene-1-one **284** or (*E*)-3-ylidene-4-chromanone **281** with azomethine ylide formed from indenoquinoxaline-11-one (generated from ninhydrin **44** and *o*-phenylenediamine **43**) and *L*-proline **27** afforded, in the presence of heteropolyacid $H_4[Si(W_3O_{10})_3]$-silica as a catalyst in refluxing acetonitrile, the corresponding dispiroindenoquinoxaline-pyrrolizidines **285** and **286**, respectively (Scheme 96) [93].



Scheme 96. Synthesis of dispiroindenoquinoxaline-pyrrolizidines **285** and **286**.

3.16. Thiochromanones

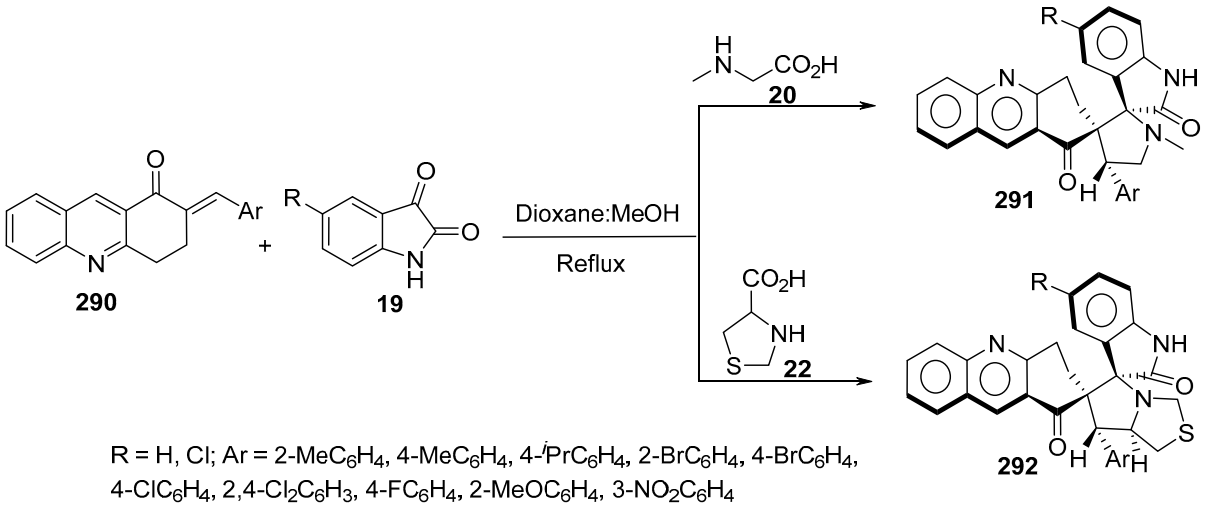
Dispiro[indene-2,2′-pyrrolidine-3′,3″-thiochromanes] **288** were obtained by reacting 3-arylidenethiochroman-4-one **287** with azomethine ylide (obtained from ninhydrin **44** and sarcosine **20**) in refluxing methanol. When thioproline **22** was used instead of sarcosine **20**, the corresponding dispiro derivatives of type **289** were obtained. Some of the synthesized pyrrolizidines revealed antimycobacterial properties (*Mycobacterium tuberculosis* H37Rv) relative to Cycloserine and Pyrimethamine (standard references). Additionally, mild antiproliferative properties against CCRF-CEM (leukemia), HT29 (ovarian), and MCF7 (breast) cancer cell lines relative to Doxorubicin (MTT assay) were observed (Scheme 97) [137].



Scheme 97. Synthetic route towards dispiro-containing compounds **288** and **289**.

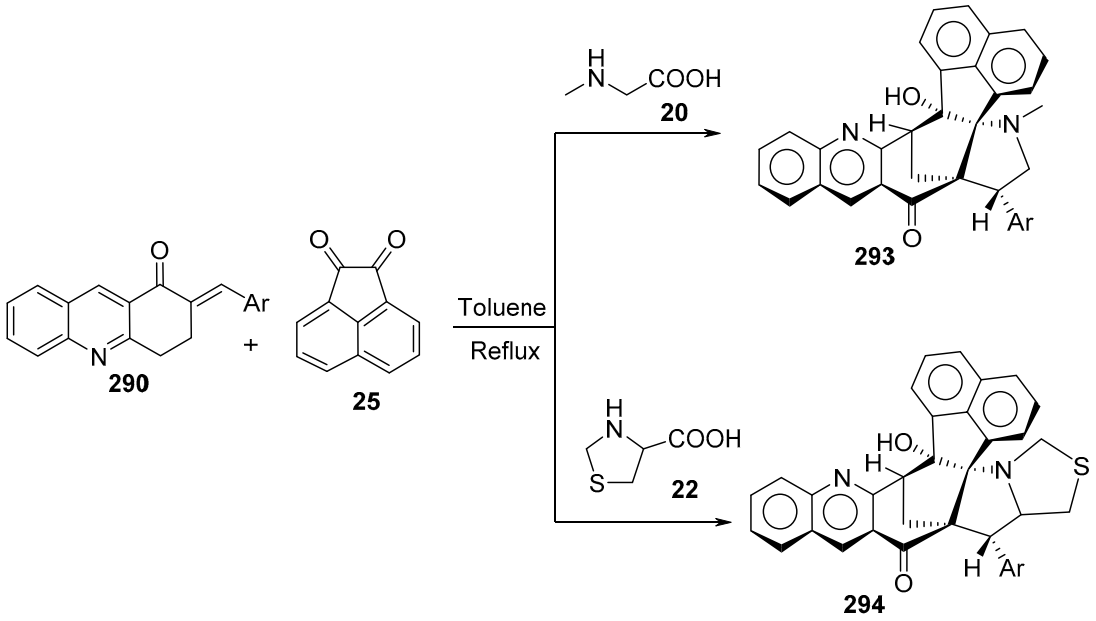
3.17. Acridinones

The reaction of (*E*)-2-(arylidene)-3,4-dihydro-1(2*H*)-acridinones **290** with azomethine ylides formed from the condensation of isatin **19** and sarcosine **20** or thioproline **22** in refluxing dioxane/methanol afforded the corresponding dispirooxindolyl-[acridine-2′,3-pyrrolidine/thiapyrrolizidine]-1′-ones **291** and **292**, respectively (Scheme 98) [138].



Scheme 98. Synthesis of dispirooxindolyl-[acridine-2′,3-pyrrolidine/thiapyrrolizidine]-1′-ones **291** and **292**.

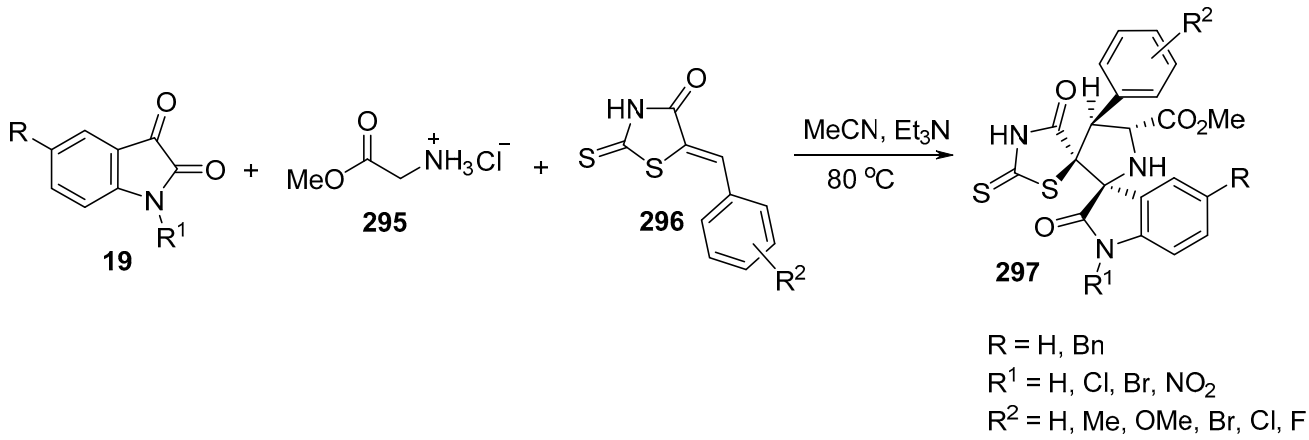
Naphtho[1′,8′:1,2,3]pyrrolo[3′,2′:8,8*a*]azuleno[5,6-*b*]quinolin-14-one **293** and naphtho [1′,8′:1,2,3]thiazolo[3″,4″:1′,5′]pyrrolo[3′,2′:8]-azuleno-[5,6-*b*]quinolin-18-one **294** were obtained by reacting (*E*)-2-(arylidene)-3,4-dihydro-1(2*H*)-acridinone **290** with azomethine ylides generated from acenaphthoquinone **25** with sarcosine **20** or thioproline **22** in refluxing toluene, respectively (Scheme 99) [139].



Scheme 99. Synthesis of naphtho[1′,8′:1,2,3]pyrrolo[3′,2′:8,8*a*]azuleno[5,6-*b*]quinolin-14-ones **293** and naphtho[1′,8′:1,2,3]thiazolo[3″,4″:1′,5′]pyrrolo[3′,2′:8]azuleno-[5,6-*b*]quinolin-18-ones **294**.

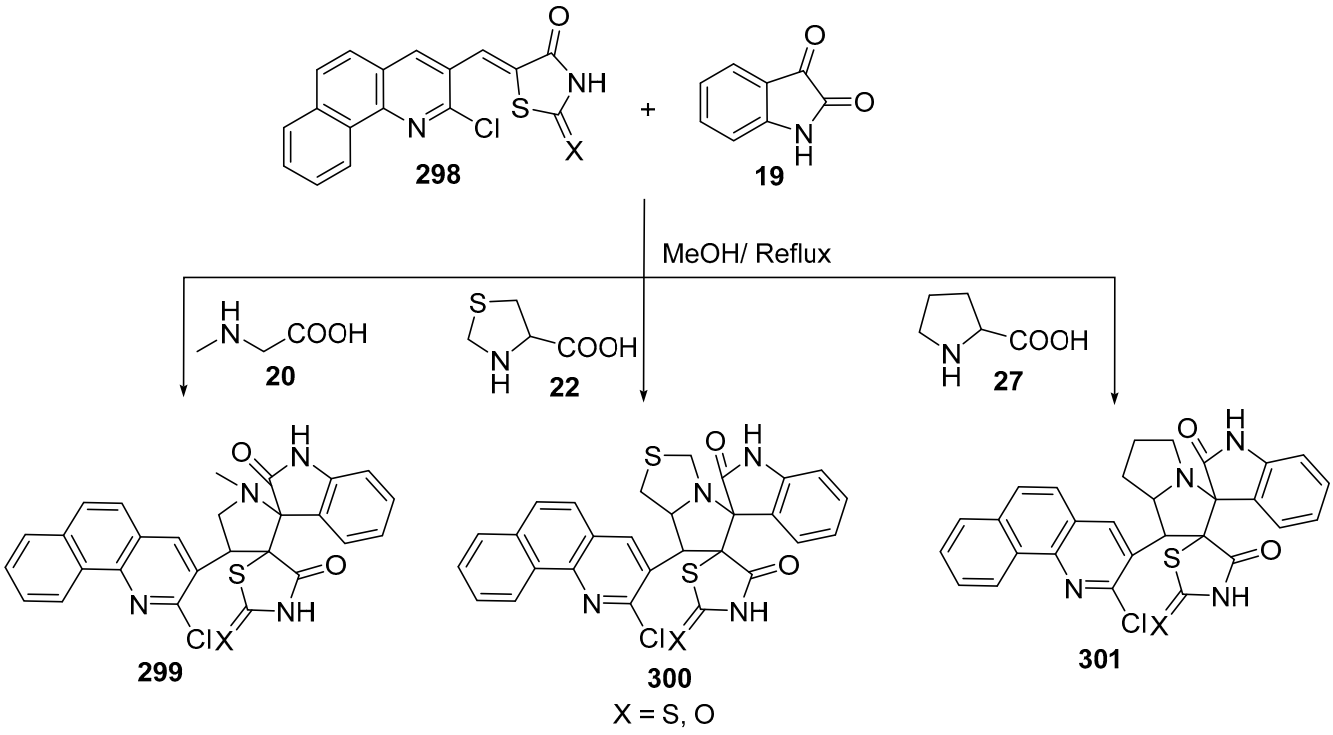
3.18. Thiazolidinones

A series of dispiro[indoline-3,2′-pyrrolidine-3′,5″-thiazolidines] of type **297**, which are potential *α*-amylase inhibitors (useful for type-2 diabetes mellitus), were obtained through the cycloaddition of azomethine ylide (generated from glycine methyl ester **295** and isatin **19**) and 5-arylidine-2-thioxothiazolidin-4-one **296** (Scheme 100) [140].



Scheme 100. Synthesis of dispiro[indoline-3,2′-pyrrolidine-3′,5″-thiazolidines] **297**.

Another group of benzo[*h*]quinolinyl dispiro-compounds **299**–**301** was obtained by reacting [5-(2′-chlorobenzo[*h*]quinolin-3′-yl)methylidene]-thiazolidin-2,4-dione/2-thioxothiazolidin-4-one **298** with various azomethine ylides formed from isatin **19** and different amino acids (sarcosine **20**, thioproline **22,** or *L*-proline **27**) (Scheme 101) [141].

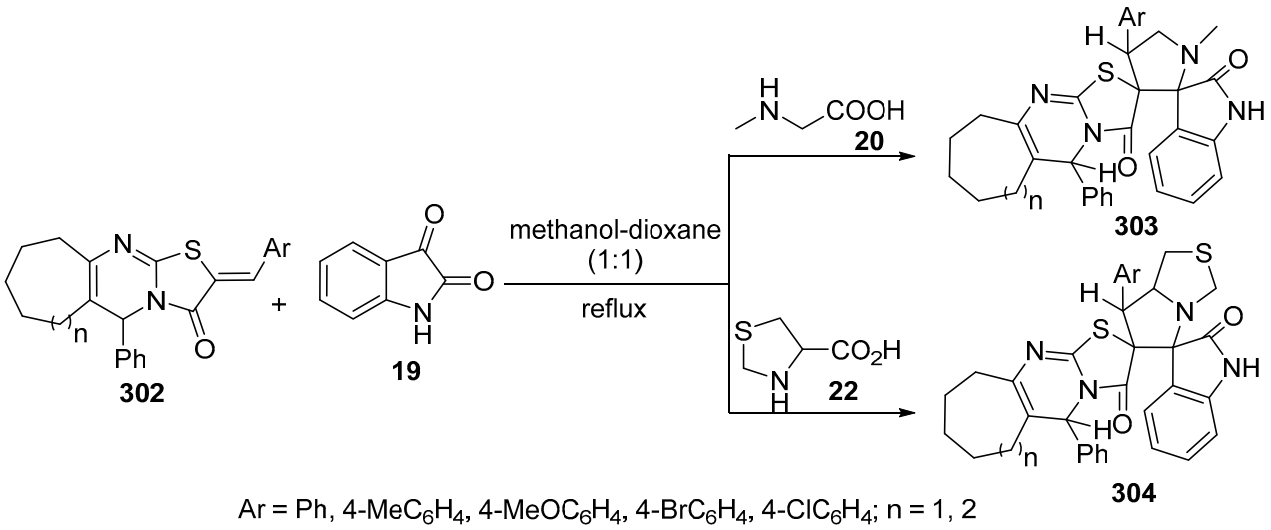


Scheme 101. Synthesis of benzo[*h*]quinolinyl dispiro-compounds **299**–**301**.

3.19. Thiazolo[3,2-a]pyrimidine-3-ones

Various (*E*)-arylmethylene-octahydro/decahydro cycloalka[*d*]thiazolo[3,2-*a*]pyrimidine-3-ones of type **302** reacted smoothly with azomethine ylides formed from isatin **19** and

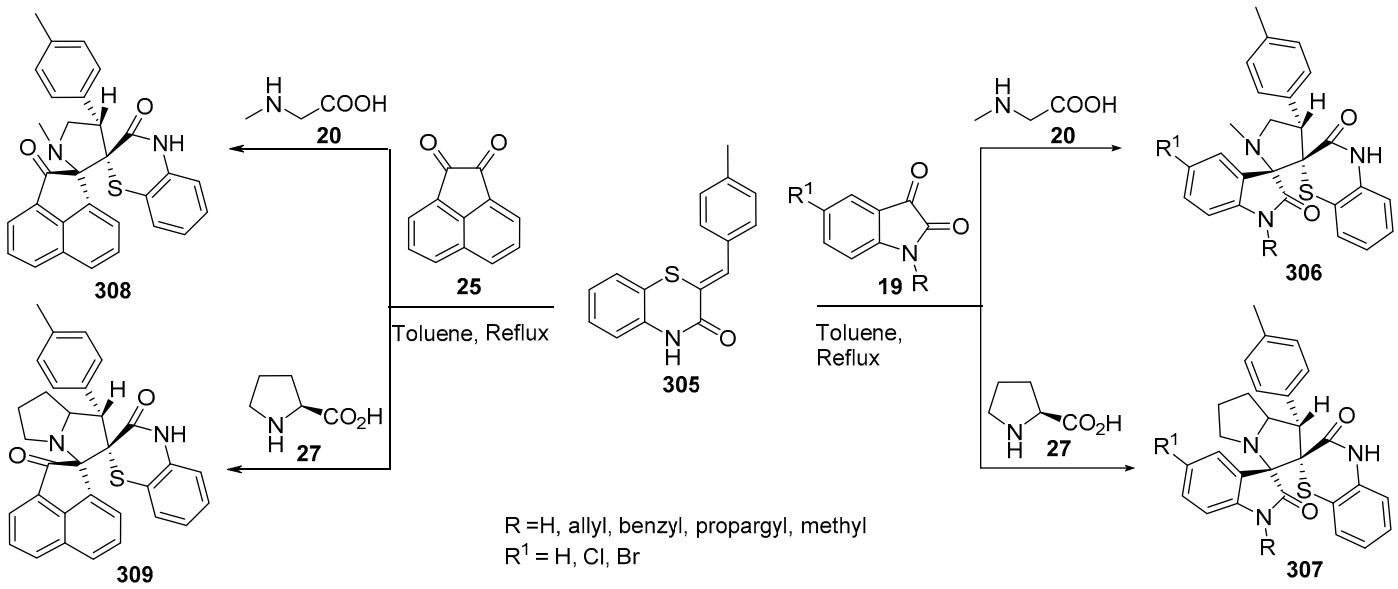
sarcosine **20** or thioproline **22** in a refluxing methanol-dioxane (1:1) mixture, thereby affording the corresponding spiro-oxindoles **303** and **304**, respectively (Scheme 102) [142].



Scheme 102. Synthesis of spiro-oxindoles **303** and **304**.

3.20. Benzo[1,4]thiazines

Spiro-oxindoles **306** and **307** and spiro-acenaphthylen-1-ones **308** and **309** were synthesized via a multicomponent reaction of 2-(4-methylbenzylidene)-4*H*-benzo[1,4]thiazin-3-one **305** and azomethine ylides derived from isatin **19** or acenaphthenequinone **25** with sarcosine **20** or *L*-proline **27** in refluxing toluene (Scheme 103) [143].



Scheme 103. Synthesis of spiro-oxindoles and spiro-acenaphthylen-1-ones **306**–**309**.

4. Cyclic Unsaturated 2π-Electron Components

4.1. Non-Aromatic Cyclc 2π-Electron Components

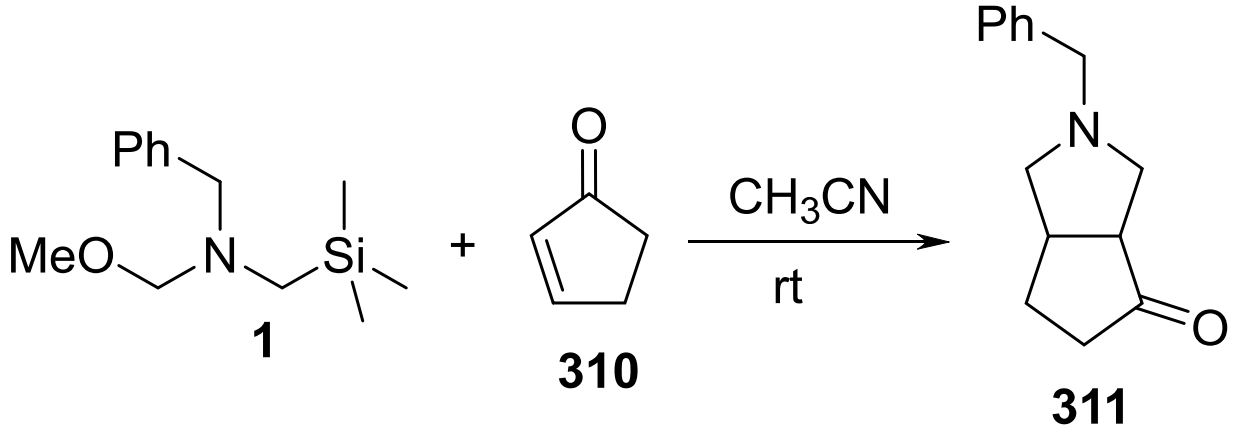
4.1.1. Alicyclic Unsaturated 2π-Electron Components

Intermolecular Cycloaddition Reactions

- Cyclopentenone

The reaction of azomethine ylide generated from benzyl(methoxymethyl)(trimethylsily lmethyl)amine **1** with cyclopentenone **310** afforded bicyclic ketone **311** via an addition to

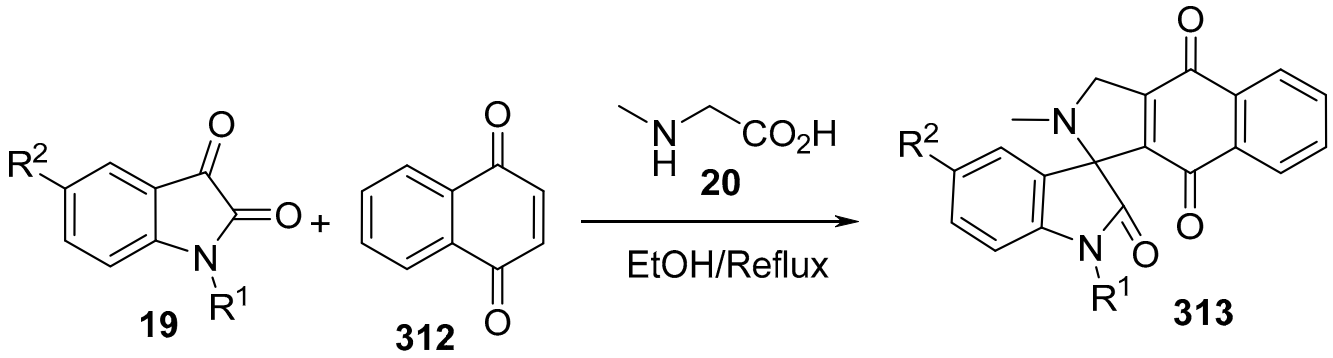
the *C*2-*C*3 unsaturated linkage. Some analogs of **307** exhibited histamine H_3 receptor antagonists that are responsible for the production and regulation of histamine and other neurotransmitters (Scheme 104) [144].



Scheme 104. Synthesis of bicyclic ketone **311**.

- 1,4-Naphthoquinone

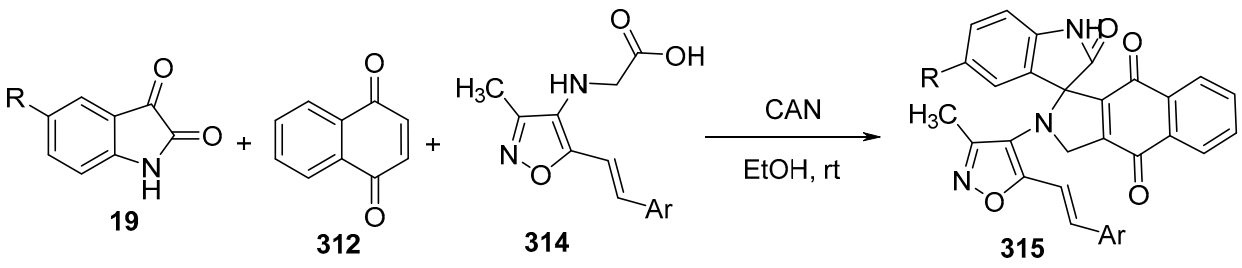
Spirooxindoles of type **313** were obtained by the cycloaddition of azomethine ylides, formed from isatin **19** and sarcosine **20**, with 1,4-naphthoquinone **312** in refluxing ethanol (Scheme 105). Some of the synthesized compounds showed antibacterial activities against *Staphylococcus aureus*, *S. aureus* (MRSA), *Enterobacter aerogens*, *Micrococcus luteus*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Salmonella typhimurium*, and *Salmonella paratyphi-B*, and antifungal activities against *Malassesia pachydermatis*, *Candida albicans*, and *Botyritis cinerea* relative to Streptomycin and Ketoconazole (standard references) [145].



R^1 = H, Me, Et, propagyl, propenyl, benzyl, butyl, hexyl, acetyl
R^2 = H, Me, Cl, Br, I

Scheme 105. Synthesis of spiro-indoles **313**.

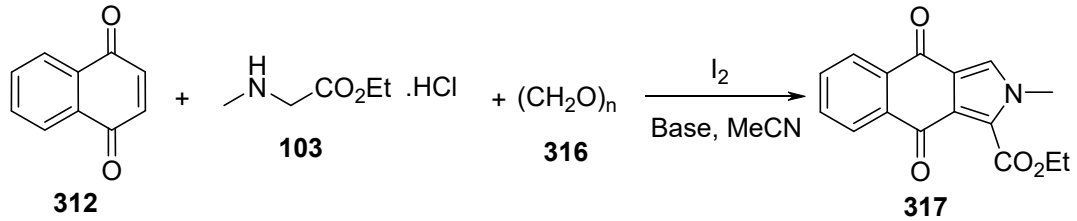
Further spiro[benzo[*f*]isoindole-1,3′-indolines] of type **315** were synthesized by the cycloaddition of azomethine ylides (formed from isatin **19** and 2-(3-methyl-5-styrylisoxazol-4-ylamino)acetic acids **314**) and 1,4-naphthoquinone **312** using ceric ammonium nitrate (CAN) as a catalyst (Scheme 106). Some of the products showed anti-inflammatory (determined via rat carrageen paw edema assay) and analgesic (determined via acetic acid writing protocol) properties relative to Ibuprofen and Diclofenac as references, respectively [146].



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 2-OHC_6H_4
R = H, Cl, OMe, Me

Scheme 106. Synthesis of spiro[benzo[f]isoindole-1,3′-indolines] **315**.

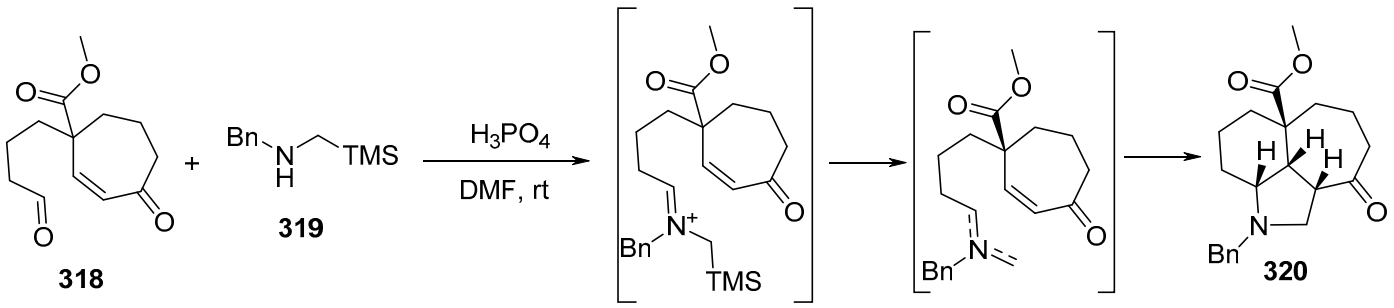
Tricyclic benzo[*f*]isoindole-4,9-dione-1-carboxylate **317** was obtained by reacting 1,4-naphthoquinone **312** with azomethine ylide generated from sarcosine ethyl ester hydrochloride **103** and paraformaldehyde **316** in the presence of iodine and sodium bicarbonate as a base in refluxing acetonitrile (Scheme 107) [147].



Scheme 107. Synthesis of benzo[*f*]isoindole-4,9-dione-1-carboxylate **317**.

Intramolecular Cycloaddition Reactions

The azatricyclic [6-5-7] ring system **320** was created via the intramolecular [3+2]-cyclo addition reaction of azomethine ylide generated from aldehyde **318** and *N*-(trimethylsilyl) methyl iminium salt **319** in the presence of a catalytic amount of phosphoric acid in DMF as a solvent (Scheme 108) [148].

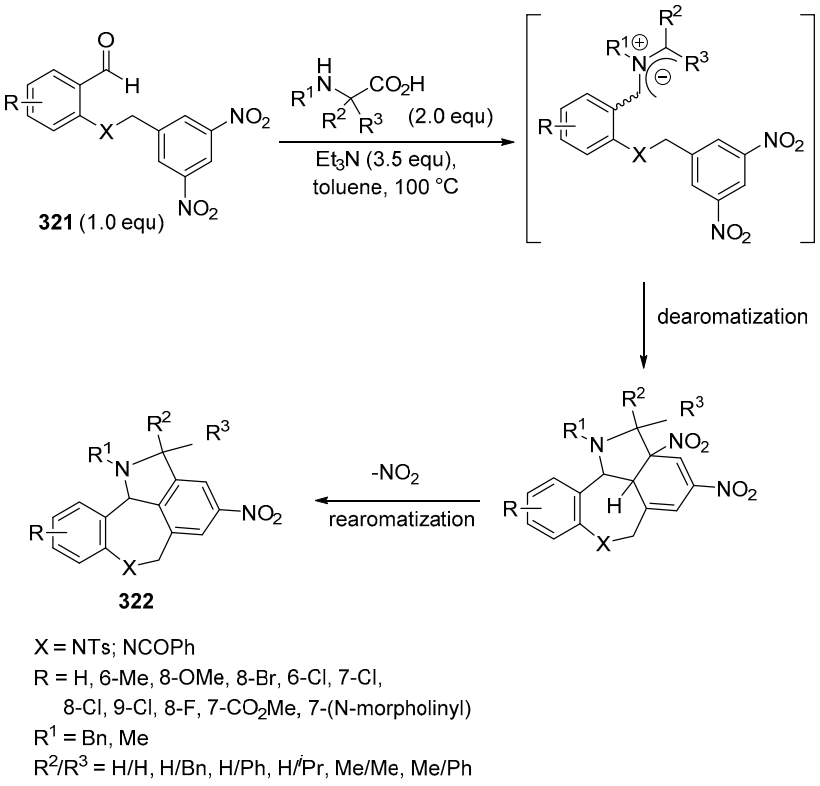


Scheme 108. Synthesis of azatricyclic [6-5-7] ring system **320**.

4.2. Aromatic Cyclic Unsaturated 2π-Electron Components

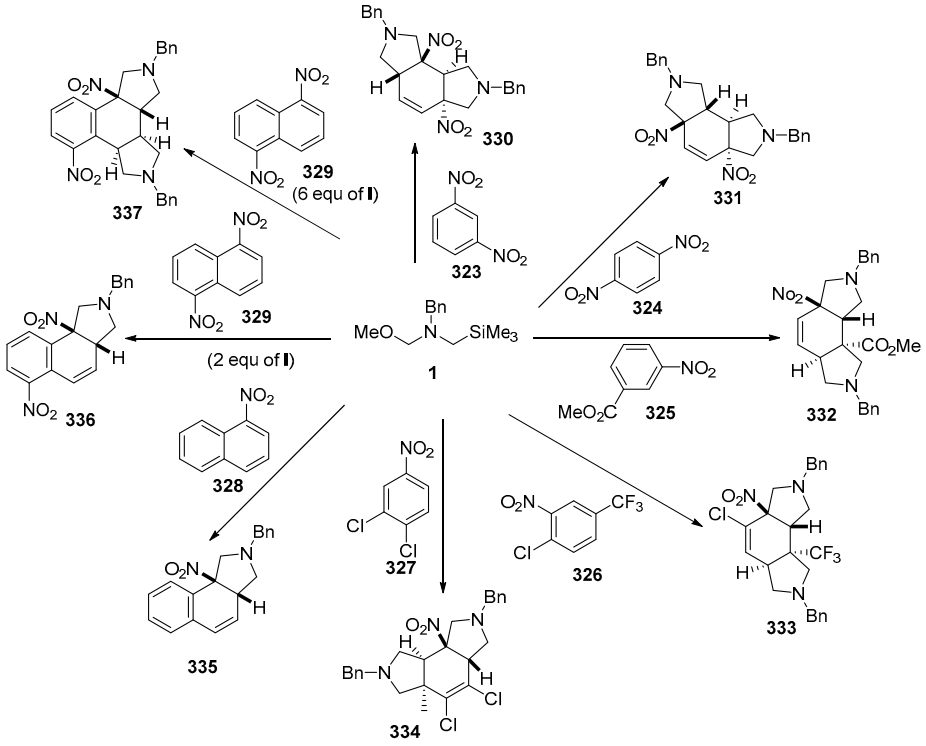
Azomethine ylide's cycloaddition to aromatic 2π-electron components (aromatic or heteroaromatic) was reviewed in [149].

A series of benzoazepine-fused isoindolines of type **322** were obtained through thermal azomethine ylide-based cycloaddition of benzaldehydes bearing 3,5-dinitrophenyl **321** and N-substituted α-amino acids. The reaction was assumed to proceed through a regioselective dearomatizing [3+2] cycloaddition with the removal of HNO_2, thus yielding the aromatic final product **322** (Scheme 109) [150].



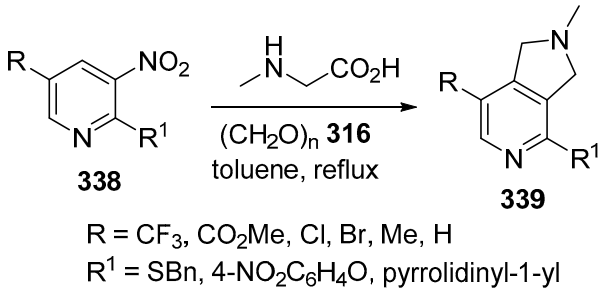
Scheme 109. Synthesis of benzoazepine-fused isoindolines **322**.

Nitro-substituted benzenes **323**–**329** underwent [3+2] cycloaddition of azomethine ylide derived from (*N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzylamine) **1,** affording the pyrrolidinyl cycloadducts **330**–**337** (Scheme 110) [151].



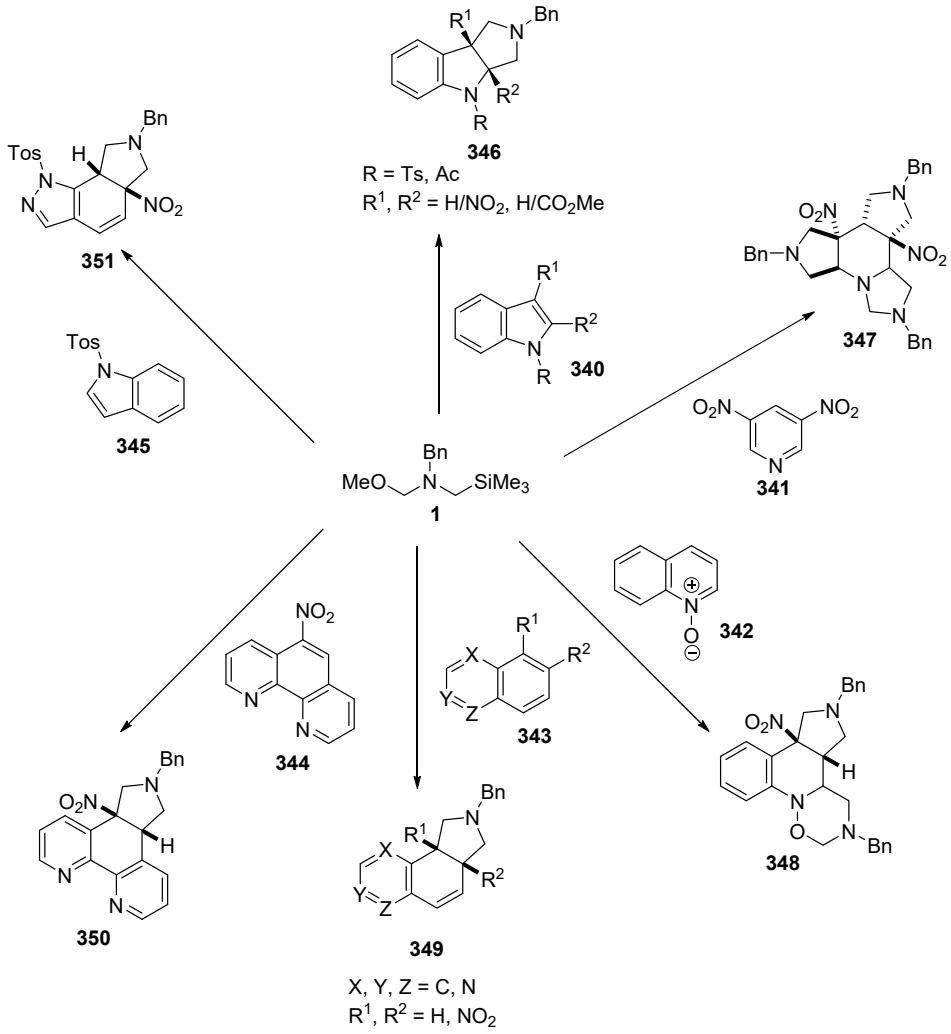
Scheme 110. Synthesis of pyrrolidinyl cycloadducts **330**–**337**.

Pyrrolo[3,4-*c*]pyridines **339** were obtained through azomethine ylide's (formed from sarcosine and paraformaldehyde **316**) cycloaddition with 3-nitropyridines **338** in refluxing toluene (Scheme 111) [152].

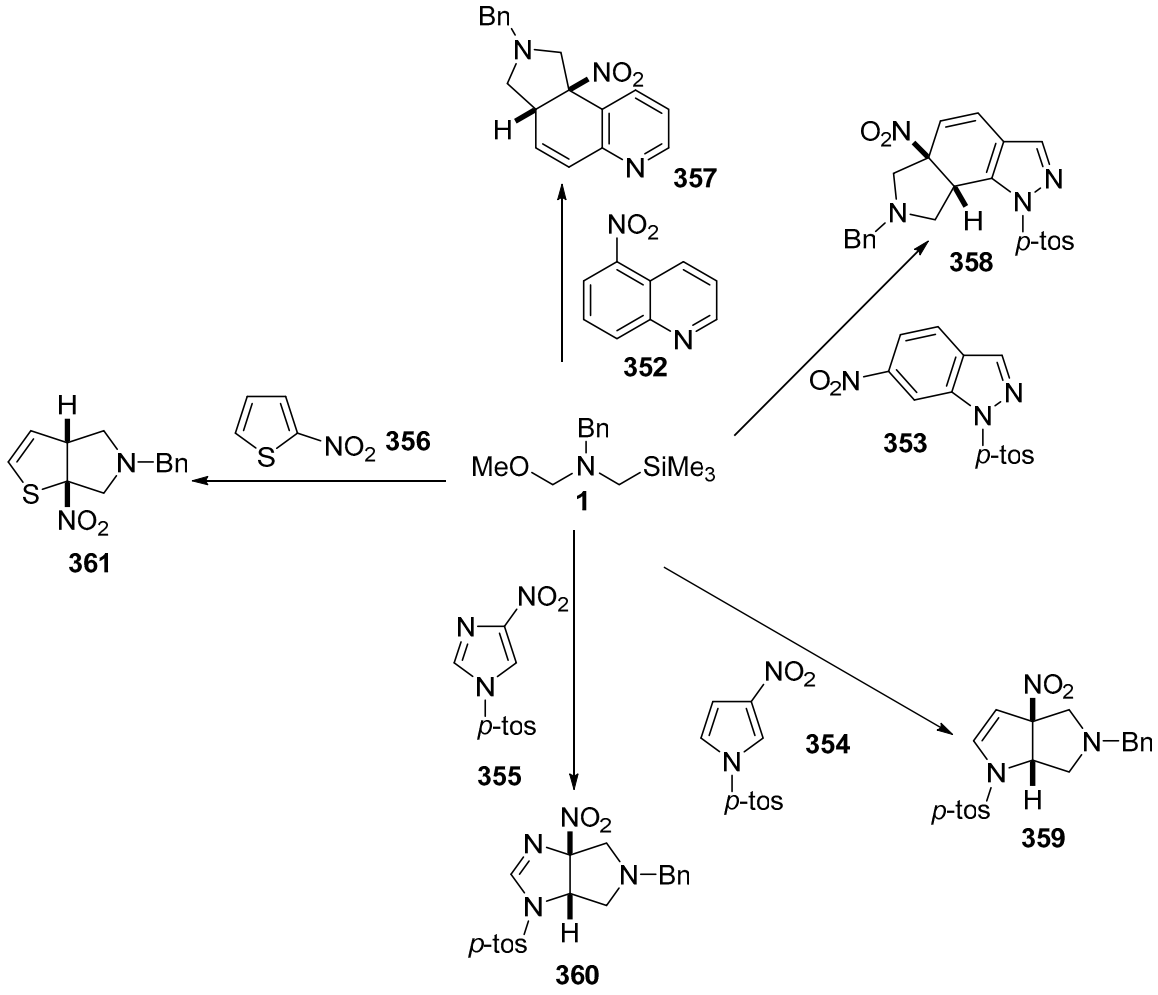


Scheme 111. Synthesis of pyrrolo[3,4-*c*]pyridines **339**.

Analogously, heterocyclic compounds bearing nitro groups **340**–**345** and **352**–**356** underwent a cycloaddition reaction with azomethine ylide derived from (*N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzylamine) **1**, affording the pyrrolidinyl-containing analogs **346**–**351** and **357**–**361** (Schemes 112 and 113) [151,153].

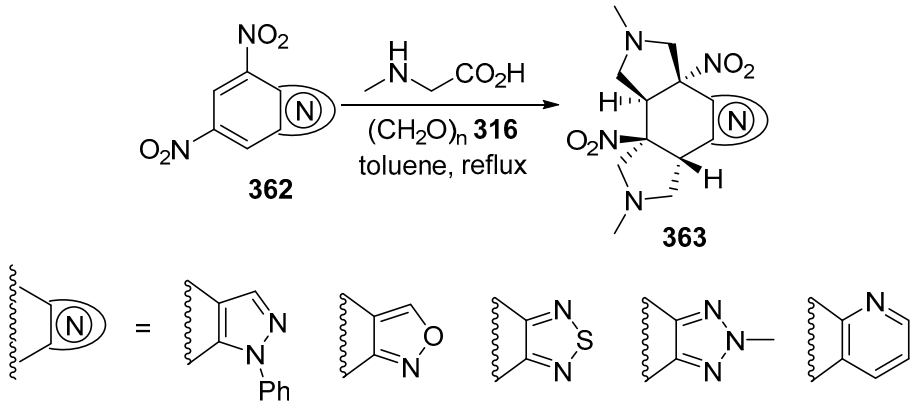


Scheme 112. pyrrolidinyl-fused heterocycles **346**–**351**.



Scheme 113. pyrrolidinyl-fused heterocycles **357**–**361**.

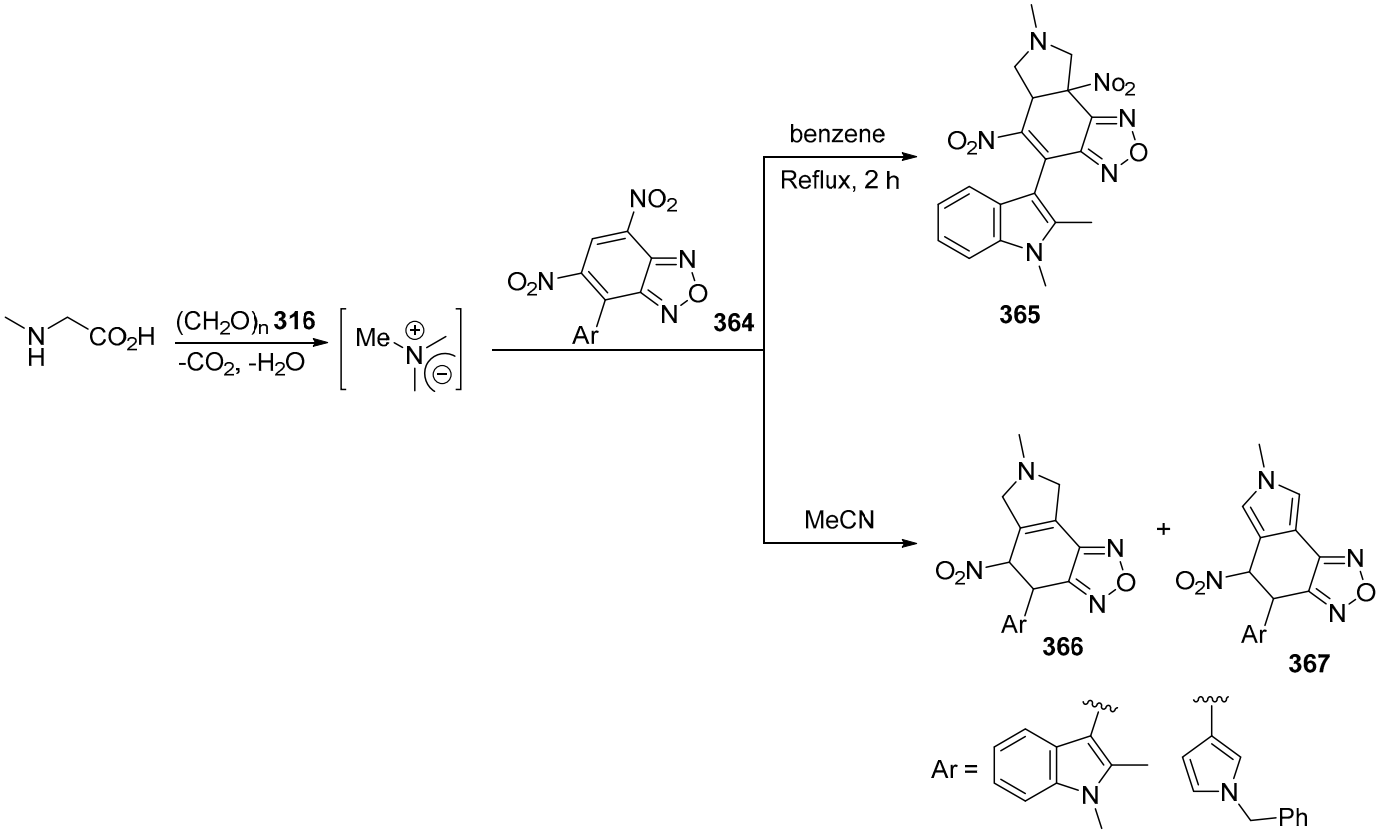
Double cycloadducts of type **363** were obtained through azomethine ylide (formed from sarcosine and paraformaldehyde **316**) with meta-dinitro-containing nitrogenous heterocycles **362** in refluxing toluene (Scheme 114) [154].



Scheme 114. Synthesis of double cycloadducts **363** from meta-dinitro-containing nitrogenous heterocycles of type **362**.

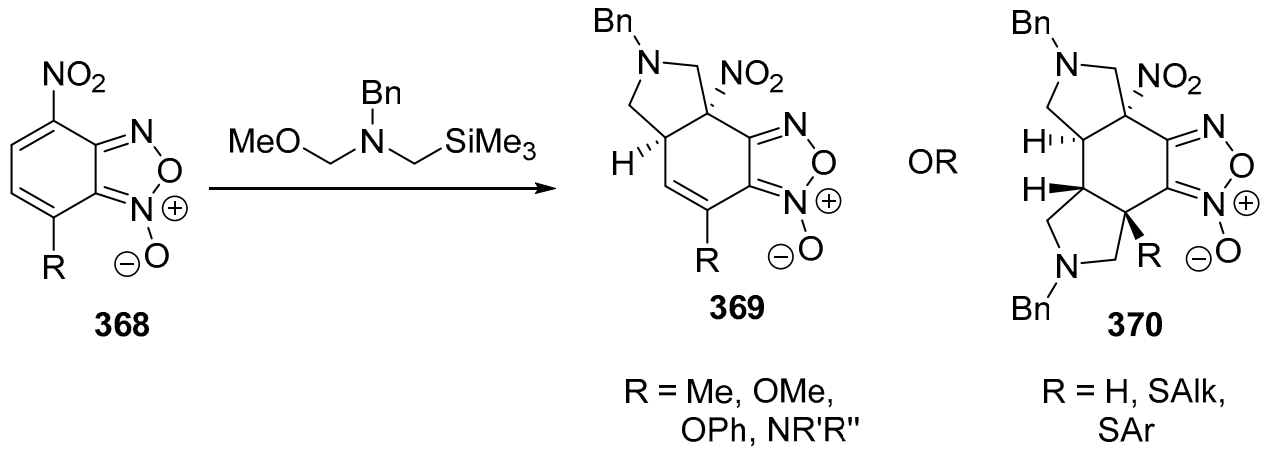
4-Chloro-5,7-dinitro-4-benzofurazan bearing indolyl heterocycle **364** underwent azomethine ylide (formed from the condensation of sarcosine and paraformaldehyde **316**) cycloaddition in refluxing benzene, affording the corresponding tetrahydro-5*aH*-[1,2,5]oxa-diazolo[3,4-

e]isoindole **365**. Alternatively, conducting the reaction in refluxing MeCN afforded a mixture of **366** and **367**. Similarly, analogs with a pyrrolidinyl function (**366** and **367**) were obtained upon reacting the appropriate analog of **365** in MeCN at room temperature (in the darkness) (Scheme 115) [155].



Scheme 115. Synthesis of [1,2,5]oxa-diazolo[3,4-*e*]isoindole **365**–**367**.

The cycloaddition reaction of azomethine ylide derived from (*N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzylamine) with 4-nitrobenzofuroxan **368** afforded either mono **369** or bis **370** cycloadducts based via the substitution of the starting benzofuroxan at the 7-position (Scheme 116) [156].

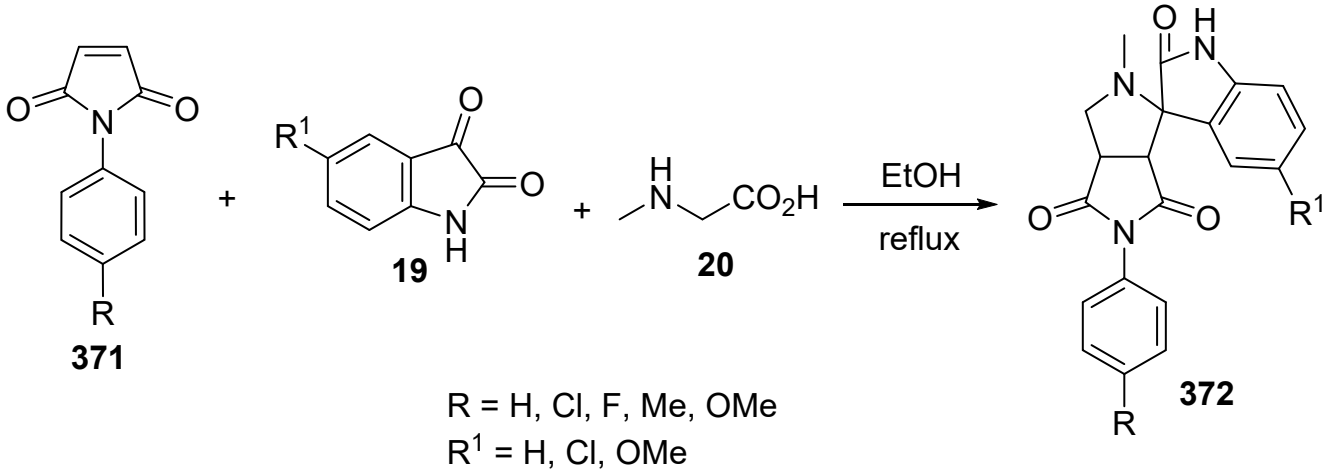


Scheme 116. Synthesis of mono-**369** or biscycloadducts **370** of 4-nitrobenzofuroxans.

4.3. Heterocyclic Unsaturated 2π-Electron Components

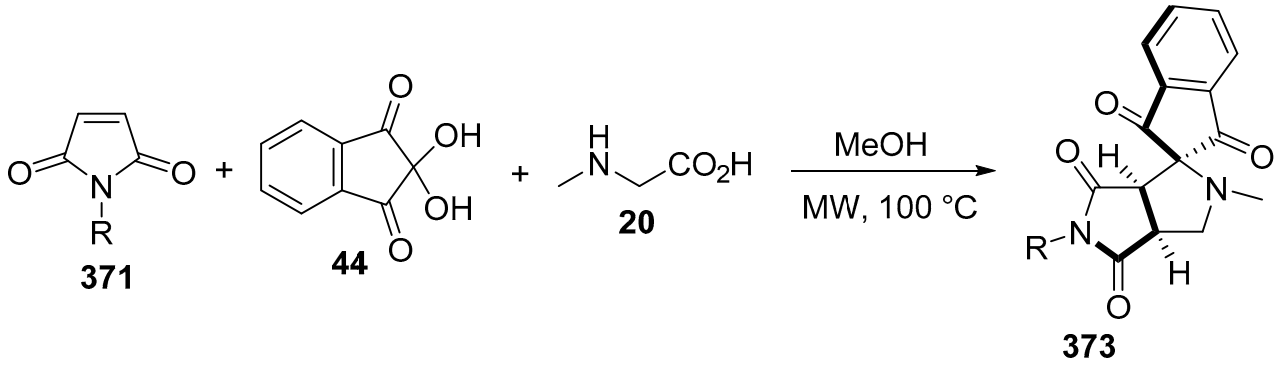
4.3.1. Maleimides

Spiro[3*H*-indole-3,2′(1′*H*)-pyrrolo[3,4-*c*]pyrroles] of type **372** were obtained in good yields by the cycloaddition of azomethine ylide (formed from sarcosine **20** and isatin **19**) to the *C*3-*C*4 unsaturated bond of maleimide **371**. Some of the synthesized compounds revealed promising to moderate antiproliferative properties against HEPG2 (liver), HCT116 (colon), and MCF7 (breast) cancer cell lines (SRB technique) relative to Doxorubicin (standard reference drug) (Scheme 117) [157].



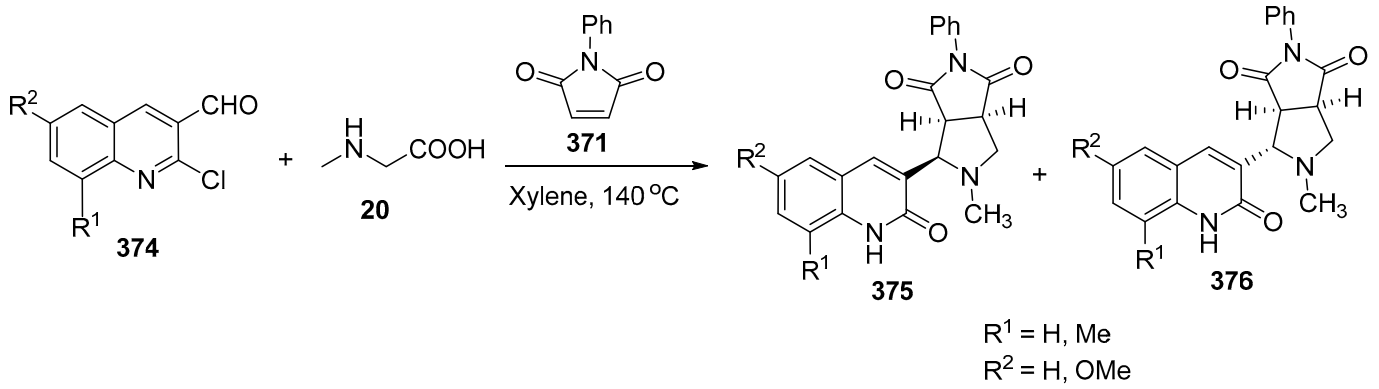
Scheme 117. Synthetic route towards spiro[3*H*-indole-3,2′(1′*H*)-pyrrolo[3,4-*c*]pyrroles] **372**.

A microwave-assisted multi-component reaction of maleimide **371** with azomethine ylide produced from sarcosine **20** and ninhydrin **44** stereoselectively afforded spiro[indene-2,1′-pyrrolo[3,4-*c*]pyrroles] **373**. Some of the products showed promising antimycobacterial (*M. tuberculosis* H37Rv) properties relative to Cycloserine (Scheme 118) [158].



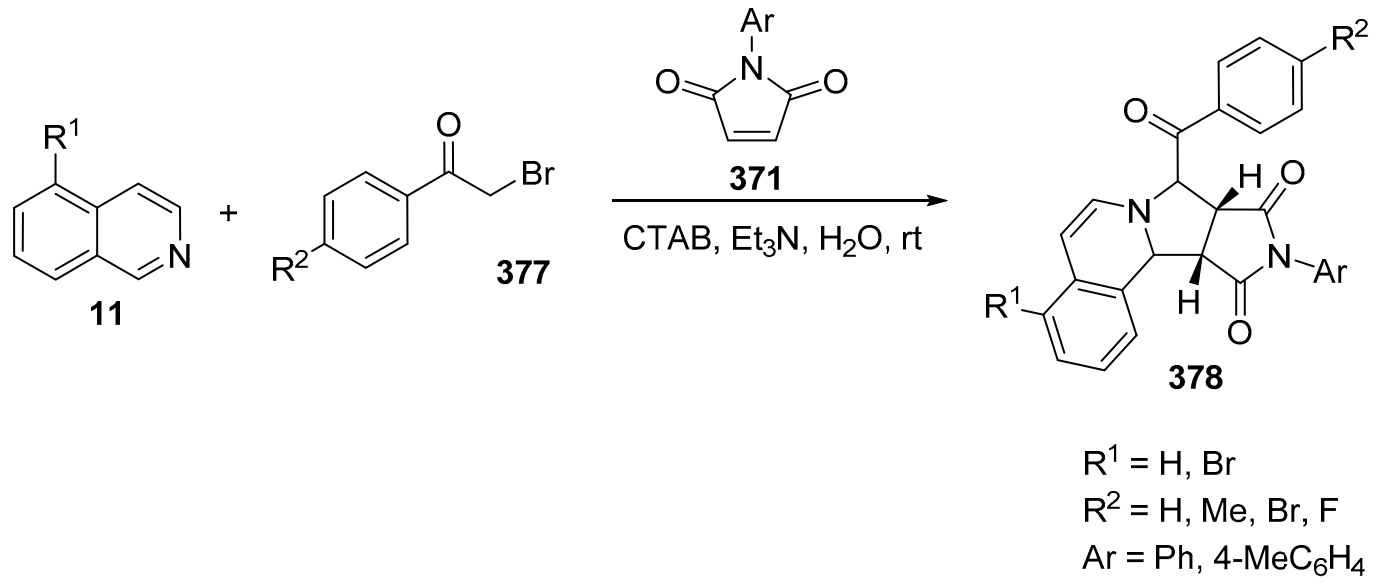
Scheme 118. Synthetic route towards spiro[indene-2,1′-pyrrolo[3,4-*c*]pyrroles] **373**.

In another reaction of *N*-phenylmaleimide **371** with azomethine ylides generated from 2-chloro-quinoline-3-carbaldehydes **374** and sarcosine **20**, two isomeric cycloadducts, namely, 1,4-diaza-bicyclo[3.3.0]octanes **375** and **376,** were formed (Scheme 119) [159].



Scheme 119. Synthesis of the two isomeric cycloadducts 5-(2-chloroquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octanes **375** and **376**.

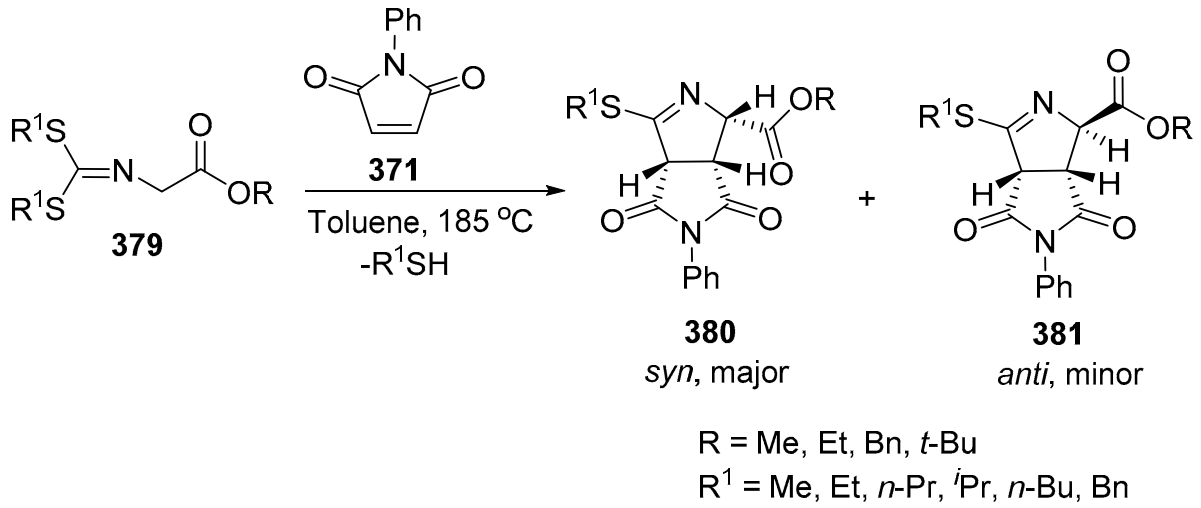
Tetracyclic pyrroloisoquinolines of type **378** were synthesized by the reaction of azomethine ylides, formed from isoquinolines **11** and phenacyl bromide **377**, with *N*-arylmaleimides **371** in the presence of cetyl trimethyl ammonium bromide (CTAB) (Scheme 120) [160].



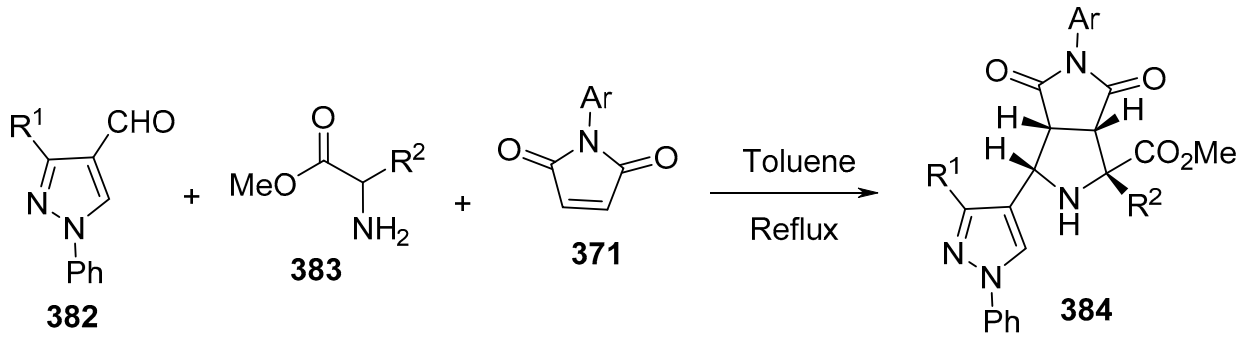
Scheme 120. Synthesis of pyrroloisoquinolines **378**.

Bicyclic hexahydropyrrolo[3,4-*c*]pyrrole-1-carboxylates **380** and **381** were obtained by reacting *N*-phenylmaleimide **371** with a series of azomethine ylides generated in situ from sulfanyl-substituted imines of glycine esters **379** (Scheme 121) [161]. Some of the synthesized diastereomeric compounds showed antioxidant activity relative to Nordihydroguaiaretic acid and Trolox [161].

Another reaction of maleimide **371** with pyrazole-4-carbaldehyde **382** and *α*-amino acid ester **383**, proceeding via azomethine intermediates in refluxing toluene, afforded the corresponding pyrazolylpyrrolopyrrole **384** (Scheme 122) [162].

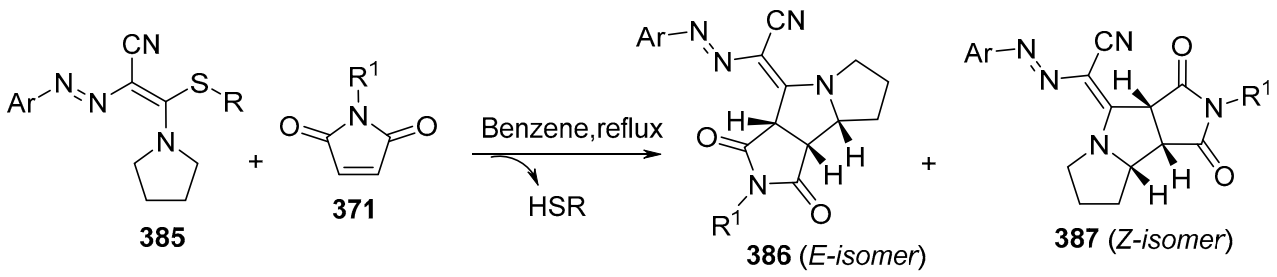


Scheme 121. Synthesis of hexahydropyrrolo[3,4-*c*]pyrrole-1-carboxylates **380** and **381**.



Scheme 122. Synthesis of pyrazolylpyrrolopyrroles **384**.

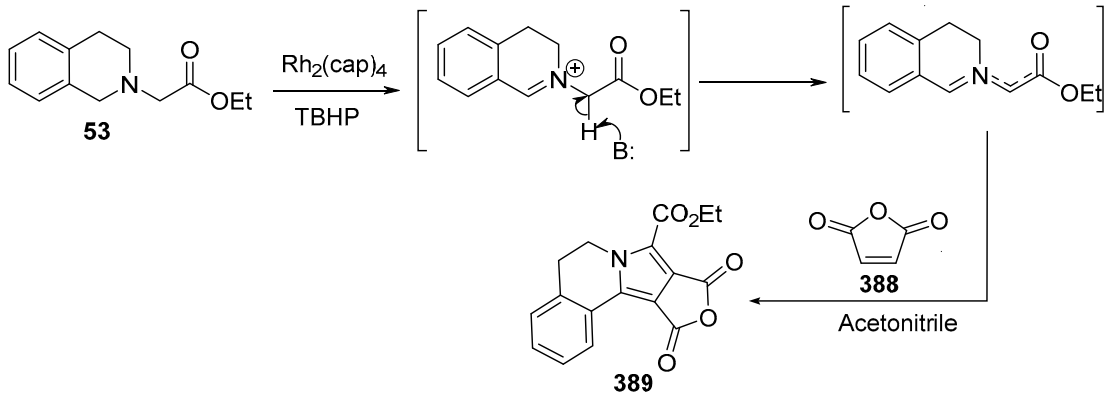
Isomeric pyrrolo[3,4-*a*]pyrrolizines **386** and **387** were synthesized by the cycloaddition of maleimide **371** with azomethine ylides formed from 3-alkylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)acrylonitriles of type **385** in refluxing benzene (Scheme 123) [163].



Scheme 123. Synthesis of pyrrolo[3,4-*a*]pyrrolizines **386**, **387**.

4.3.2. Maleic Anhydride

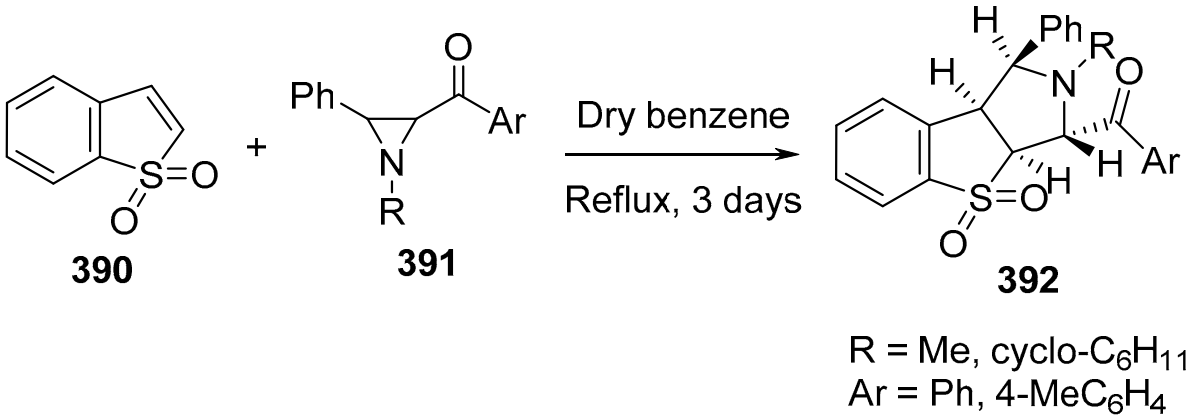
3,4-Dihydropyrrolo[2,1-*a*]isoquinoline **389** was obtained through the reaction of maleic anhydride **388** with azomethine ylide formed via the oxidation of tetrahydroisoquinoline **53** by dirhodium(II)caprolactamate [$Rh_2(cap)_4$] in the presence of *tert*-butyl hydroperoxide (TBHP) (Scheme 124) [37].



Scheme 124. Synthesis of 3,4-dihydropyrrolo[2,1-*a*]isoquinoline **389**.

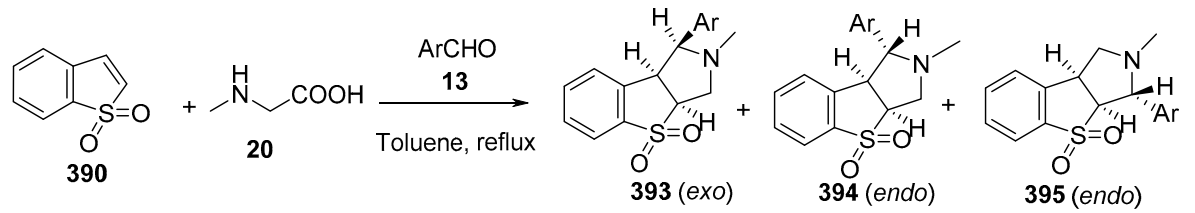
4.3.3. Benzo[b]thiophene-1,1-dioxide

The reaction of benzo[*b*]thiophene-1,1-dioxide **390** with a thermally generated azomethine ylide from aziridines **391** in refluxing dry benzene afforded the cycloadducts of type **392** (Scheme 125) [164].



Scheme 125. Synthesis of cycloadducts **392**.

Three isomeric cycloadducts, **393**–**395**, were obtained by reacting benzo[*b*]thiophene-1,1-dioxide **390** with azomethine ylides generated from sarcosine **20** and aldehydes **13** in refluxing toluene (Scheme 126) [164].

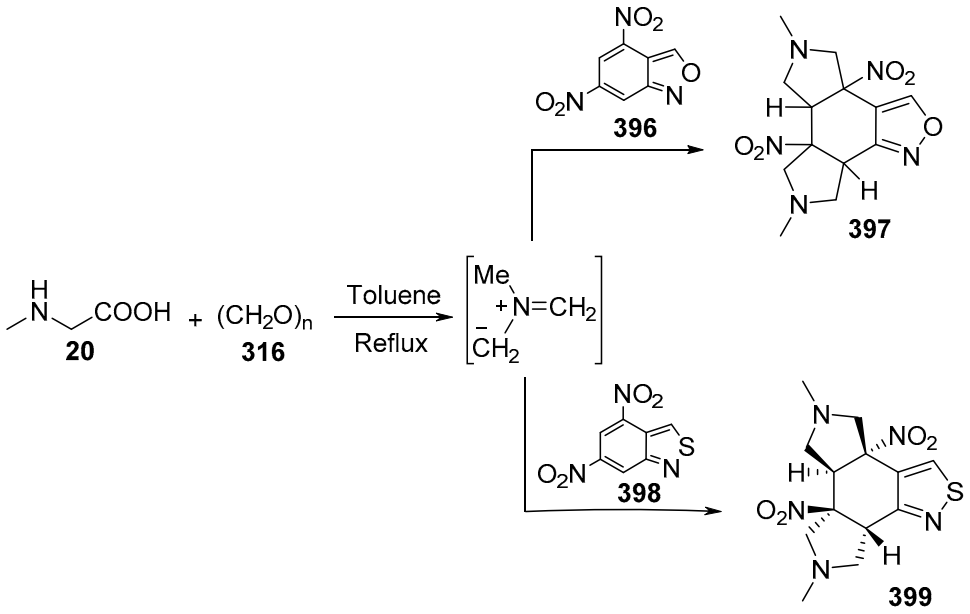


Ar = Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3,5-$(MeO)_2C_6H_3$, 4-BrC_6H_4

Scheme 126. Synthesis of cycloadducts **393**–**395**.

4.3.4. Benzo[*c*]isoxazole and Benzo[*c*]isothiazole

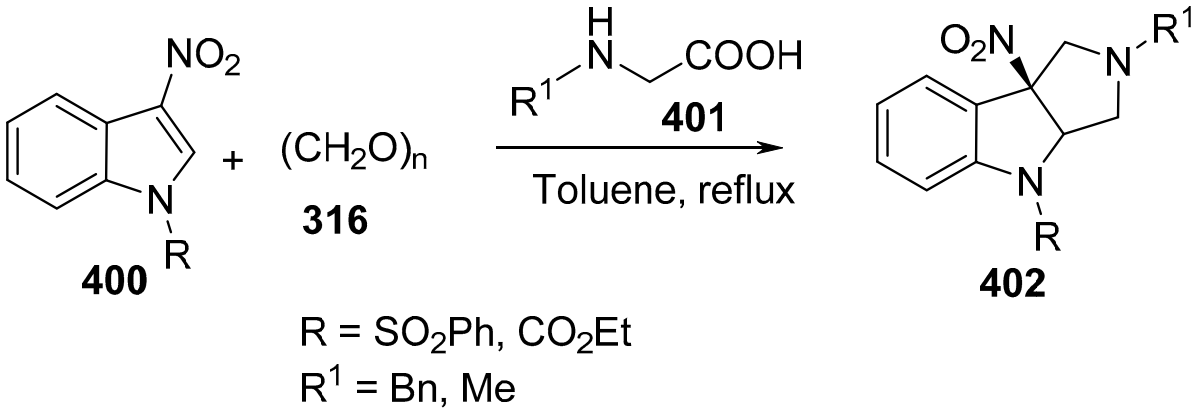
Decahydroisoxazolo[3,4-*e*]pyrrolo[3,4-*g*]isoindole **397** and its isothiazolo-derivative **399** were synthesized by the [3+2]-cycloaddition of benzo[*c*]isoxazole **396** and benzo[*c*]isothiazole **398**, respectively, to azomethine ylide generated from sarcosine **20** and paraformaldehyde **316** in toluene under reflux conditions (Scheme 127) [165].



Scheme 127. Synthesis of decahydroisoxazolo[3,4-*e*]pyrrolo[3,4-*g*]isoindole **397** and decahydroisothiazolo[3,4-*e*]pyrrolo[3,4-*g*]isoindole **399**.

4.3.5. Indoles

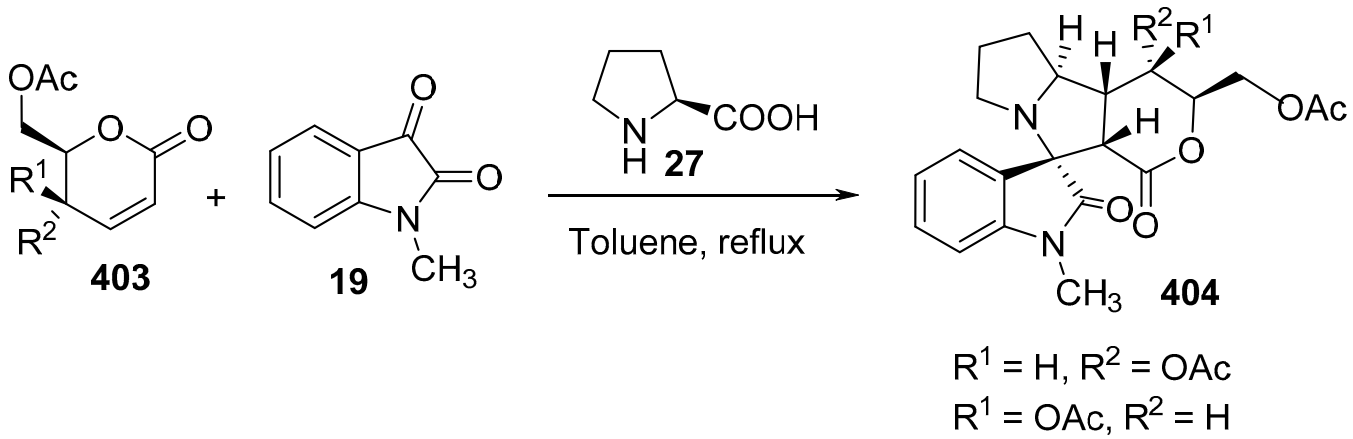
Hexahydropyrrolo[3,4-*b*]indoles of type **402** were synthesized by reacting 3-nitroindoles of type **400** with azomethine ylides formed from *α*-amino acids (sarcosine **20** or *N*-benzylglycine **401**) and paraformaldehyde **316** (Scheme 128) [166].



Scheme 128. Synthesis of hexahydropyrrolo[3,4-*b*]indoles **402**.

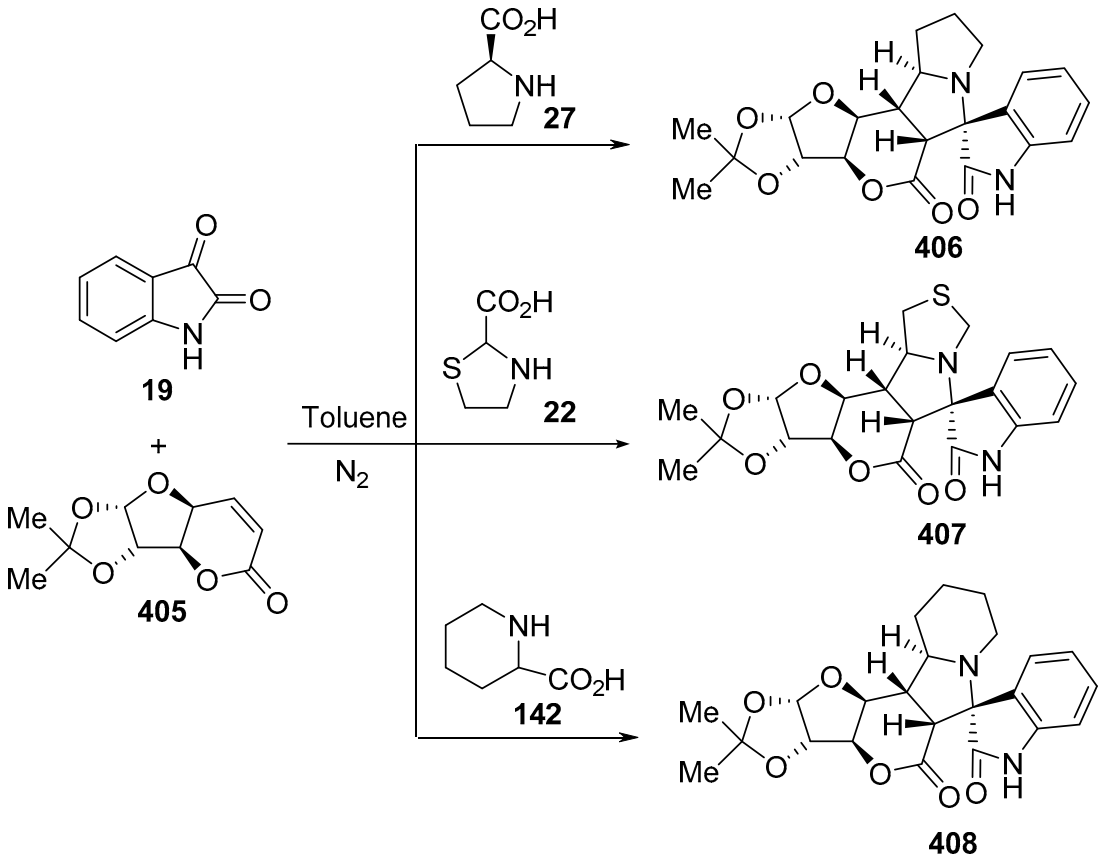
4.3.6. Lactones

The reaction of *α*,*β*-unsaturated lactones of type **403** with azomethine ylide formed from *N*-methyl isatin **19** and proline **27** in refluxing toluene afforded the corresponding pyrrolidinyl-spirooxindole lactones of type **404** in high yield (Scheme 129) [167].



Scheme 129. Synthesis of pyrrolidinyl-spirooxindole lactones **404**.

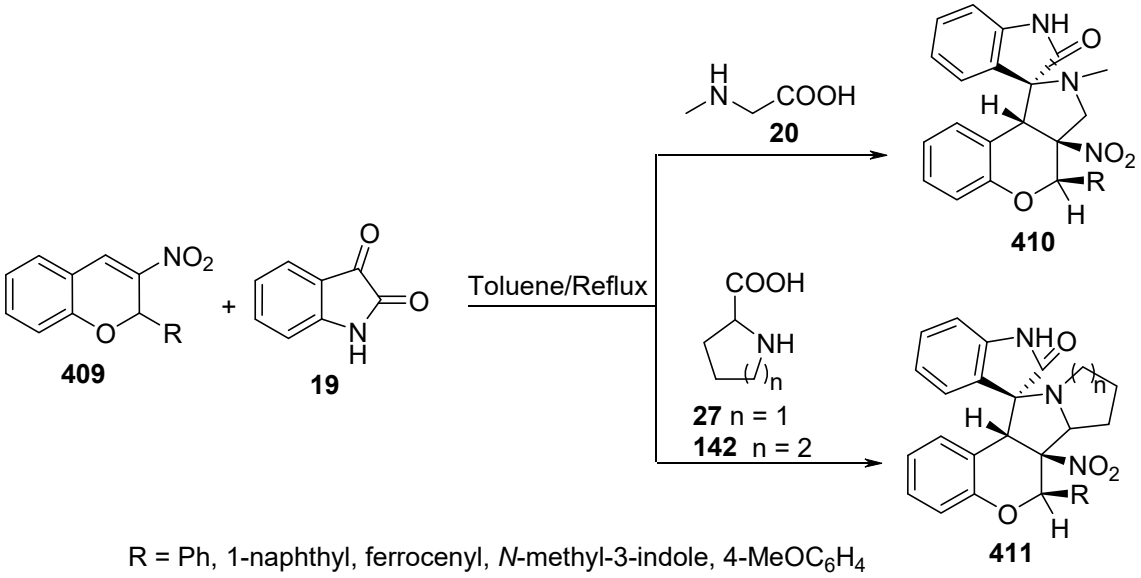
Another glucosyl *α,ß*-unsaturated-7,3-lactone **405** reacted with azomethine ylides generated from isatin **19** and secondary amino acids (proline **27**, thioproline **22** or pipacolinic acid **142**) in refluxing dry toluene under N_2 (inert atmosphere) to produce glucosylspirooxindoles **406**–**408** in a highly regio- and stereoselective manner (Scheme 130) [168].



Scheme 130. Synthesis of glucosyl-spirooxindoles **406**–**408**.

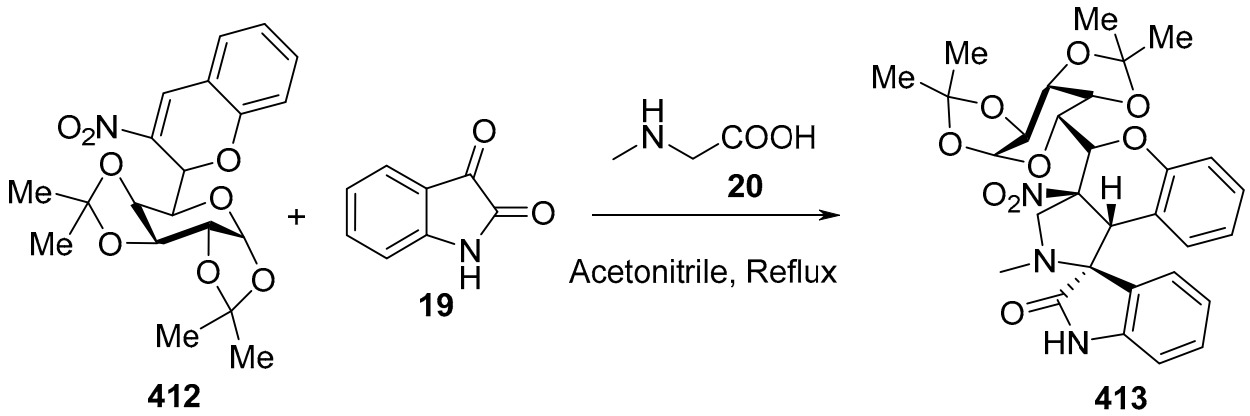
4.3.7. Chromenes

3-Nitrochromenes of type **409** underwent a reaction with azomethine ylides formed from isatin **19** and amino acids (sarcosine **20**, proline **27,** or pipacolinic acid **142**) in refluxing toluene to afford the corresponding spiropyrrolidine/spiro-pyrrolizidine/spiroindolizidine-oxindoles **410** and **411** (Scheme 131) [169].



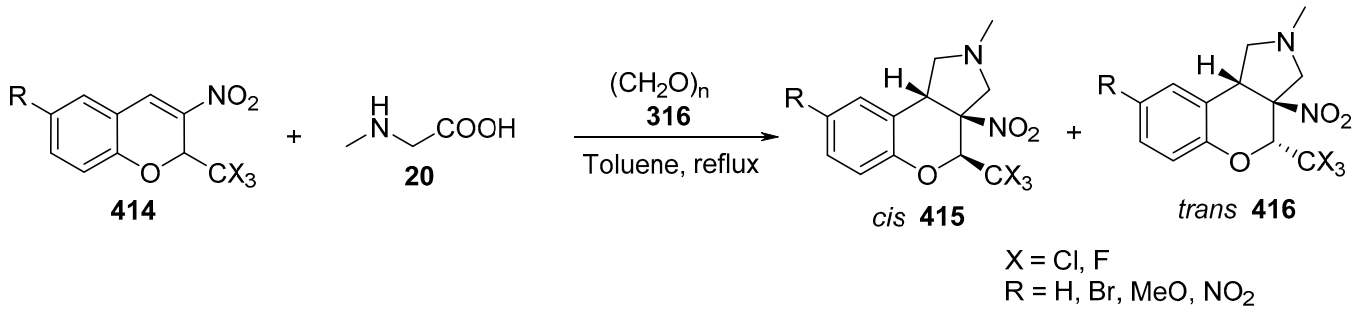
Scheme 131. Synthesis of spiropyrrolidine/spiropyrrolizidine/spiroindolizidine-oxindoles **410** and **411**.

Spiropyrrolidine-oxindole carbohydrate **413** was synthesized by the reaction of glycol 3-nitrochromene **412** with azomethine ylide formed from isatin **19** and sarcosine **20** in refluxing acetonitrile (Scheme 132) [170].



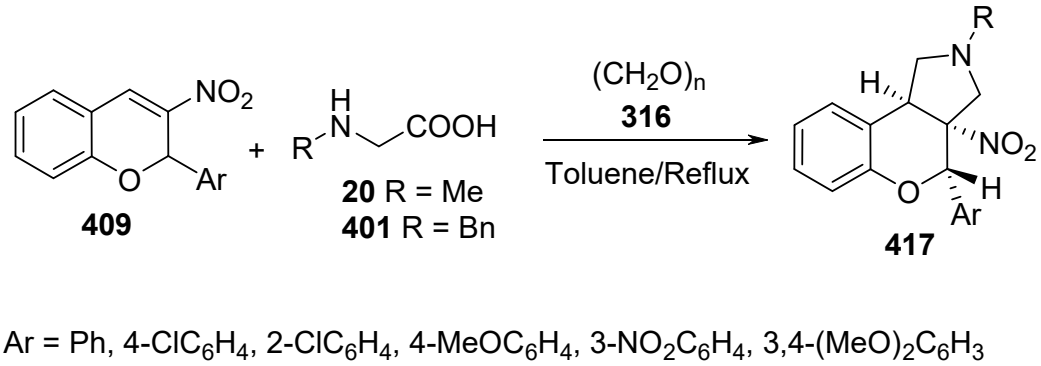
Scheme 132. Synthesis of spiropyrrolidine-oxindole carbohydrate **413**.

Isomeric benzopyrano[3,4-*c*]pyrrolidines **415** and **416** were obtained via the cycloaddition of 3-nitro-2-trihalomethyl-2*H*-chromenes **414** to azomethine ylide generated from sarcosine **20** and paraformaldehyde **316** in refluxing toluene (Scheme 133) [171].



Scheme 133. Synthesis of benzopyrano[3,4-*c*]pyrrolidines **415** and **416**.

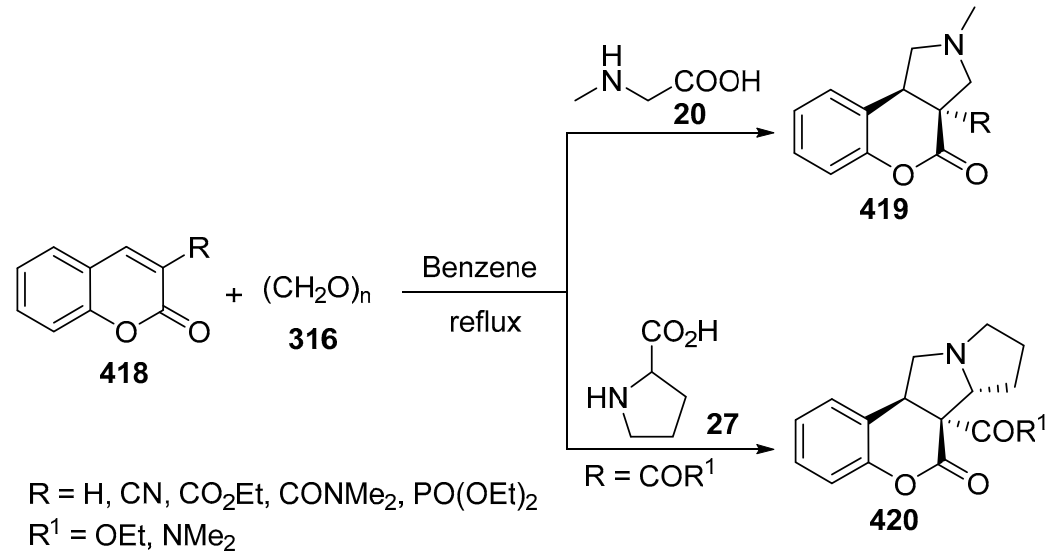
However, the reaction of 2-aryl-3-nitrochromenes **409** with azomethine ylides formed from paraformaldehyde **316** and sarcosine **20** or *N*-benzyl-glycine **401** in toluene under refluxing conditions afforded the corresponding 3*a*-nitro-4-aryl benzopyrano[3,4-*c*]pyrrolidines of type **417** in high yields. Further, ^{1}H,^{1}H-NOE spectroscopic studies supported the structure of **417** (Scheme 134) [172].



Scheme 134. Synthesis of 3*a*-nitro-4-aryl benzopyrano[3,4-*c*]pyrrolidines **417**.

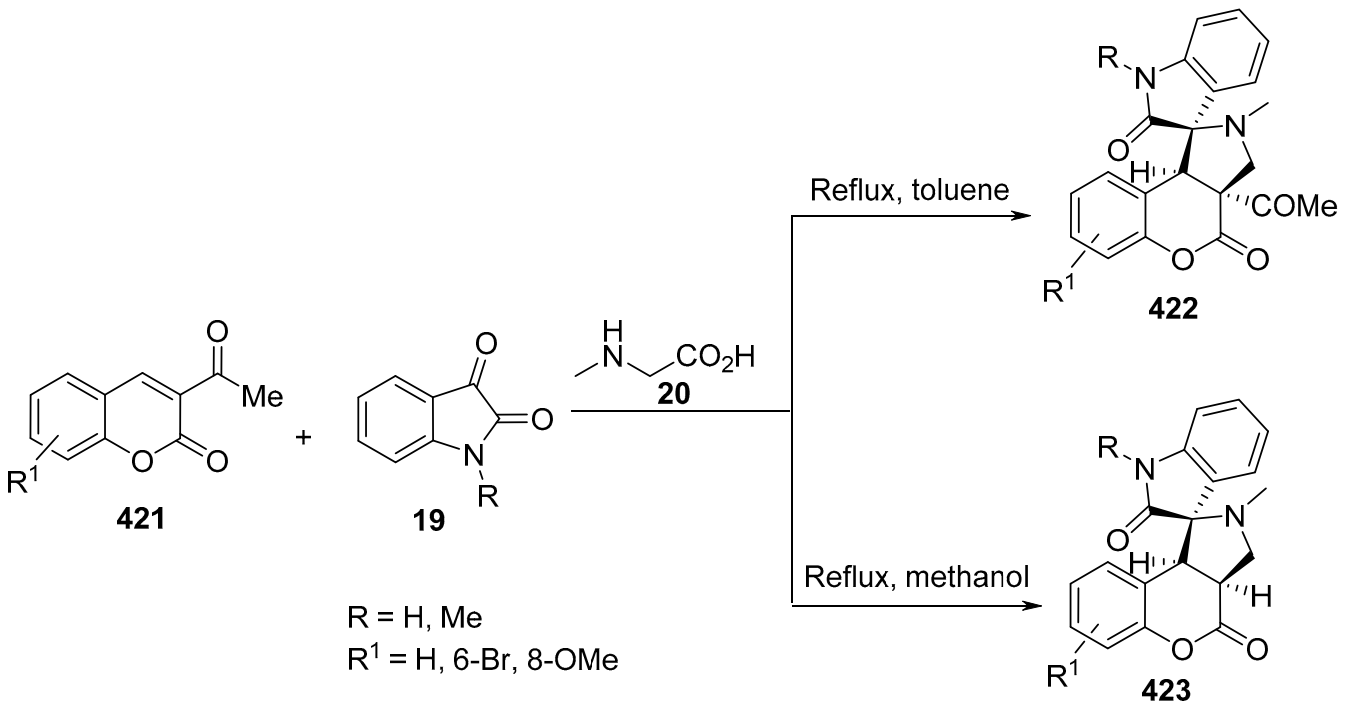
4.3.8. Coumarins

A cycloaddition strategy for the synthesis of [1]-benzopyrano[3,4-*c*]pyrrolidines **419** and **420** was based on the reaction of 3-substituted coumarins of type **418** and in situ-generated azomethine ylides formed from sarcosine **20** or proline **27** with paraformaldehyde **316** in refluxing benzene (Scheme 135) [173,174].



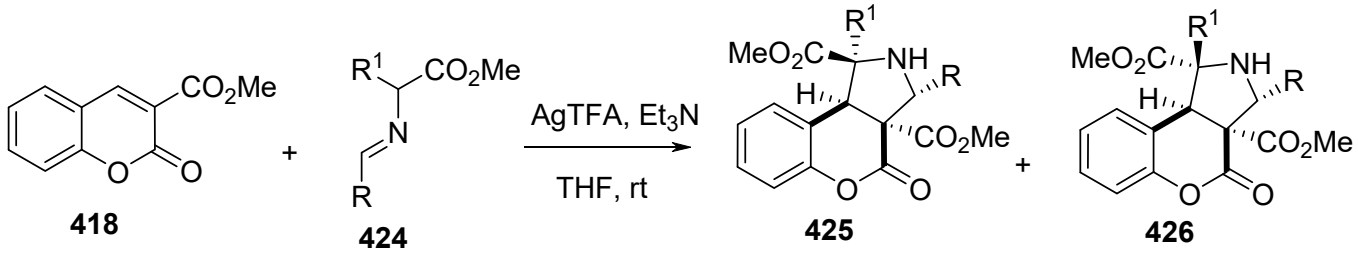
Scheme 135. Synthesis of [1]-benzopyrano[3,4-*c*]pyrrolidines **419**, **420**.

The reaction of 3-acetyl-2*H*-chromen-2-one **421** with azomethine ylides generated from isatin **19** and sarcosine **20** in refluxing toluene afforded the corresponding chromeno[3,4-*c*]spiropyrrolidine-oxindoles of type **422**, while the analogous reaction in methanol gave chromeno[3,4-*c*]spiropyrrolidine-oxindole derivatives of type **423** (Scheme 136) [175].



Scheme 136. Synthesis of chromeno[3,4-*c*]spiropyrrolidine-oxindoles **422** and **423**.

Mixtures of isomeric benzopyrano[3,4-*c*]pyrrolidines **425** and **426** were obtained from the reaction of coumarin **418** with azomethine ylides formed from *α*-iminoester **424** in the presence of silver(I)-trifluoroacetate (AgTFA) in tetrahydrofuran at room temperature (Scheme 137) [176].



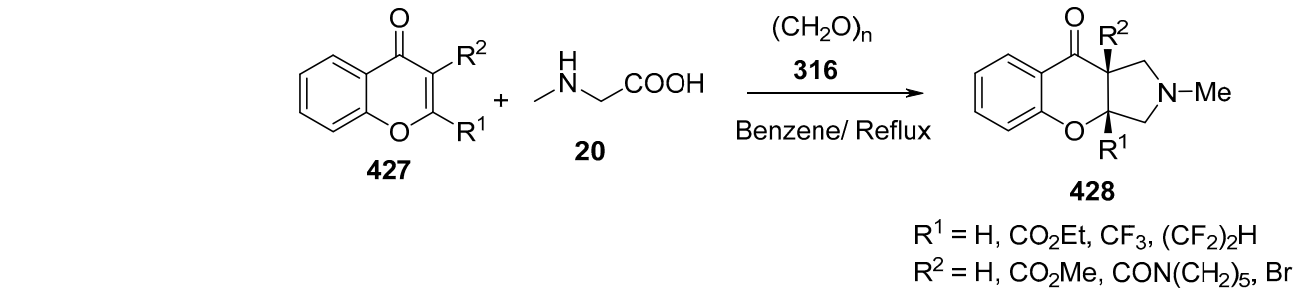
R = Ph, 4-BrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 2-FC_6H_4, 4-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-MeOC_6H_4, 2-naphthyl, 3-MeO-4-benzyloxyC_6H_3, 2-furanyl, 5-benzodiozole, ^{t}Bu, pentanyl

R^1 = H, Me, ^{i}Pr, Ph

Scheme 137. Synthesis of benzopyrano[3,4-*c*]pyrrolidines **425** and **426**.

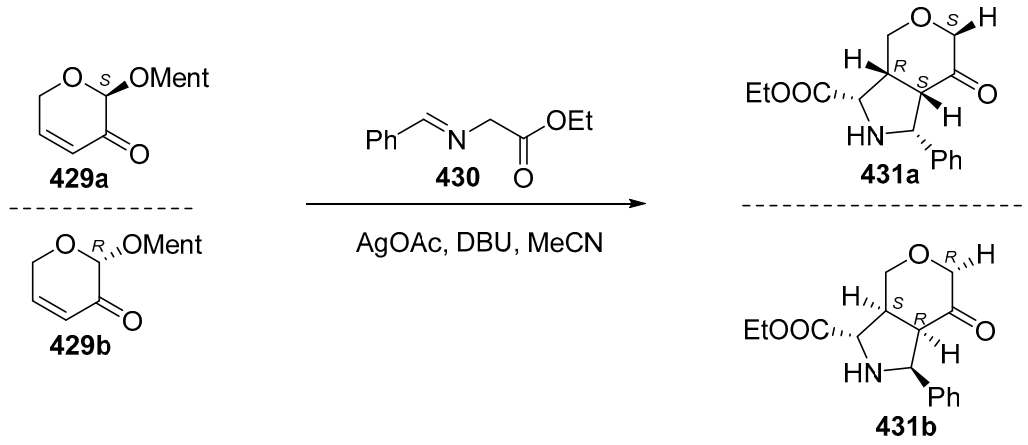
4.3.9. Chromones

Benzopyranopyrrolidine derivatives of type **428** were synthesized by the cycloaddition of 3-substituted chromones of type **427** with azomethine ylide generated from sarcosine **20** and paraformaldehyde **316** in benzene under refluxing conditions (Scheme 138) [177].



Scheme 138. Synthesis of benzopyranopyrrolidines **428**.

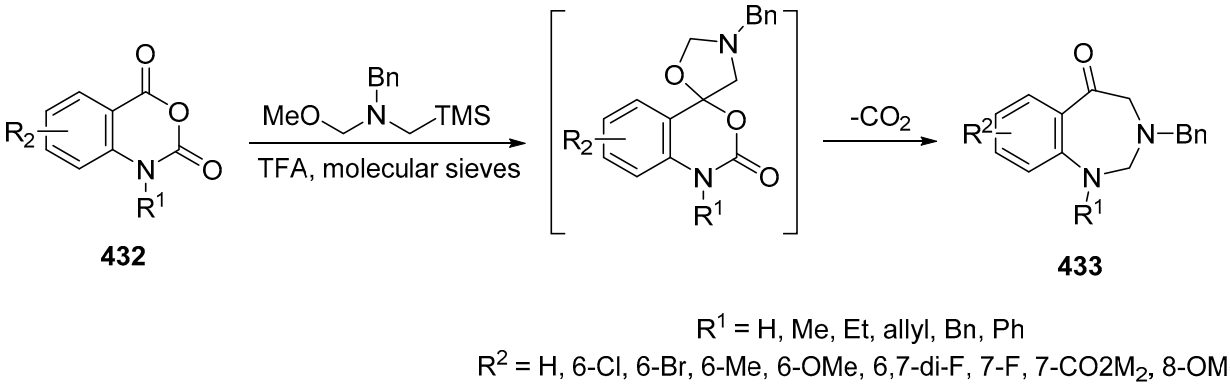
Udry et al. described the synthesis of enantiomerically pure cycloadducts (**431a**, **431b**) from stabilized azomethine ylides of type **430** and sugar-derived enones (**429a** and **429b**) through the [3+2]-cycloaddition reaction in the presence of silver acetate (AgOAc) and DBU in acetonitrile. The cycloadducts were further used to synthesize enantiomeric polyhydroxyalkylpyrrolidines as potential *β*-galactofuranosidase inhibitors (Scheme 139) [178].



Scheme 139. Synthesis of enantiomeric pyrrolidines **431**.

4.3.10. Isatoic Anhydride

1,3-Benzodiazepin-5-ones of type **433** were obtained through azomethine ylide (formed from (*N*-(methoxymethyl)-*N*-(trimethylsilyl-methyl)-benzylamine) **1** cycloaddition to isatoic anhydride **432** in trifluoroacetic acid in the presence of molecular sieves (4 Å) (Scheme 140) [179].



Scheme 140. Synthesis of 1,3-benzodiazepin-5-one **433**.

5. Conclusions and Outlook

Among various methods, the [3+2]-cycloaddition reaction of azomethine ylides is one of the most adopted protocols for the formation of pyrrolidine and pyrrole systems. The chemistry of azomethine ylides has progressed significantly in the last two decades. Azomethine ylides have been used for the synthesis of many stereoselective natural products, core ring systems of natural products, and several bioactive molecules containing multiple chiral centers. The cycloaddition of a three-atom component to an appropriate unsaturated substrate, namely, the unsaturated 2π-electron component, is the most embraced approach to the synthesis of five-membered heterocyclic compounds. By using various unsaturated 2π-electron components in reaction with in situ-generated azomethine ylides, a plethora of pyrrolidinyl-containing heterocycles can be obtained in a highly regio- and stereoselective manner. As a result of intermolecular cycloadditions, one new ring with a defined stereochemistry is formed; however, when the three-atom component and the substrate are part of the same molecule, the cycloaddition is intramolecular and leads to a more complex molecular architecture that is difficult to access by other routes, namely, through the use of new bicyclic systems.

This review summarizes the synthesis of some of the most important compounds resulting from the [3+2]-cycloaddition reactions of azomethine ylides with various olefinic (acyclic, alicyclic/heterocyclic, and exocyclic) unsaturated 2π-electron components and highlights their potential therapeutic significance. We believe the compiled subject will develop interest within this field among the research community and encourage them to develop a wider variety of asymmetric [3+2]-cycloaddition reaction strategies for the synthesis of complex molecules.

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References

1. Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: Hoboken, NJ, USA, 1984; Volume 1, Chapter 1; pp. 3–5.
2. Rios-Gutierrez, M.; Domingo, L.R. Unravelling the mysteries of the [3+2] cycloaddition reactions. *Eur. J. Org. Chem.* **2019**, *2019*, 267–282. [CrossRef]
3. William Lown, J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: Hoboken, NJ, USA, 1984; Volume 1, Chapter 6; pp. 657, 726.
4. Coldham, I.; Hufton, R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005**, *105*, 2765–2809. [CrossRef] [PubMed]
5. Song, G.; Chen, D.; Su, Y.; Han, K.; Pan, C.-L.; Jia, A.; Li, X. Isolation of Azomethine Ylides and Their Complexes: Iridium(III)-Mediated Cyclization of Nitrone Substrates Containing Alkynes. *Angew. Chem. Int. Ed.* **2011**, *50*, 7791–7796. [CrossRef] [PubMed]
6. Lee, D.J.; Han, H.S.; Shin, J.; Yoo, E.J. Multicomponent [5+2] Cycloaddition Reaction for the Synthesis of 1,4-Diazepines: Isolation and Reactivity of Azomethine Ylides. *J. Am. Chem. Soc.* **2014**, *136*, 11606–11609. [CrossRef]
7. Molteni, G.; Silvani, A. Spiro-2-oxindoles via 1,3-dipolar cycloadditions. A decade update. *Eur. J. Org. Chem.* **2021**, *2021*, 1653–1675. [CrossRef]
8. Adrio, J.; Carretero, J.C. Stereochemical diversity in pyrrolidine synthesis by catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Comm.* **2019**, *55*, 11979–11991. [CrossRef]
9. Bdiri, B.; Zhao, B.-J.; Zhou, Z.-M. Recent advances in the enantioselective 1,3-dipolar cycloaddition of azomethine ylides and dipolarophiles. *Tetrahedron Asymm.* **2017**, *28*, 876–899. [CrossRef]
10. Tang, S.; Zhang, X.; Sun, J.; Niu, D.; Chruma, J.J. 2-Azaallyl Anions, 2-Azaallyl Cations, 2-Azaallyl Radicals, and Azomethine Ylides. *Chem. Rev.* **2018**, *118*, 10393–10457. [CrossRef]

11. Dondas, H.A.; de Gracia Retamosa, M.; Sansano, J.M. Current Trends towards the Synthesis of Bioactive Heterocycles and Natural Products Using 1,3-Dipolar Cycloadditions (1,3-DC) with Azomethine Ylides. *Synthesis* **2017**, *49*, 2819–2851. [CrossRef]
12. Meyer, A.G.; Ryan, J.H. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides with Carbonyl Dipolarophiles Yielding Oxazolidine Derivatives. *Molecules* **2016**, *21*, 935. [CrossRef]
13. Fang, X.; Wang, C.-J. Catalytic asymmetric construction of spiropyrrolidines via 1,3-dipolar cycloaddition of azomethine ylides. *Org. Biomol. Chem.* **2018**, *16*, 2591–2601. [CrossRef] [PubMed]
14. Arrastia, I.; Arrieta, A.; Cossio, F.P. Application of 1,3-Dipolar Reactions between Azomethine Ylides and Alkenes to the Synthesis of Catalysts and Biologically Active Compounds. *Eur. J. Org. Chem.* **2018**, *2018*, 5889–5904. [CrossRef] [PubMed]
15. Wei, L.; Chang, X.; Wang, C.-J. Catalytic Asymmetric Reactions with N-Metallated Azomethine Ylides. *Acc. Chem. Res.* **2020**, *53*, 1084–1100. [CrossRef] [PubMed]
16. Verma, S.; George, J.; Singh, S.; Pardasani, P.; Pardasani, R. [3+2] Cycloaddition reactions of thioisatin with thiazolidine-2-carboxylic acid: A versatile route to new heterocyclic scaffolds. *Org. Med. Chem. Lett.* **2011**, *1*, 6. [CrossRef] [PubMed]
17. Lashgari, N.; Ziarani, G.M. Synthesis of heterocyclic compounds based on isatin through 1,3-dipolar cycloaddition reactions. *ARKIVOC* **2012**, *2012*, 277–320. [CrossRef]
18. Padwa, A.; Pearson, W.H. (Eds.) The chemistry of heterocyclic compounds. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; John Wiley & Sons: Hoboken, NJ, USA, 2002; Volume 59.
19. Martina, K.; Tagliapietra, S.; Veselov, V.V.; Cravotto, G. Green protocols in heterocycle syntheses via 1,3-dipolar cycloadditions. *Front. Chem.* **2019**, *7*, 95. [CrossRef]
20. Grafton, M.; Mansfield, A.C.; Fray, M.J. [3+2] Dipolar cycloadditions of an unstabilised azomethine ylide under continuous flow conditions. *Tetrahedron Lett.* **2010**, *51*, 1026–1029. [CrossRef]
21. Boruah, M.; Konwar, D.; Sharma, S.D. KF/Al2O3 mediated 1,3-dipolar cycloaddition of azomethine ylides: A novel and convenient procedure for the synthesis of highly substituted pyrrolidines. *Tetrahedron Lett.* **2007**, *48*, 4535–4537. [CrossRef]
22. Belfaitah, A.; Isly, M.; Carboni, B. 1,3-Dipolar cycloadditions of azomethine ylides to alkenylboronic esters. Access to substituted boron analogues of β-proline and 3-hydroxypyrrolidines. *Tetrahedron Lett.* **2004**, *45*, 1969–1972. [CrossRef]
23. Han, Y.; Hou, H.; Fu, Q.; Yan, C.-G. One-pot two-step tandem reactions for selective synthesis of pyrrolo[2,1-a]isoquinolines and dihydro-, tetrahydro-derivatives. *Tetrahedron* **2011**, *67*, 2313–2322. [CrossRef]
24. Poomathi, N.; Mayakrishnan, S.; Muralidharan, D.; Perumal, P.T. A facile access to novel spiroxindole fused pyrrolidine and thiazolo pyrrolidine benzimidazole derivatives via 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2015**, *56*, 721–726. [CrossRef]
25. Dandia, A.; Jain, A.K.; Laxkar, A.K.; Bhati, D.S. A highly efficient protocol for the regio- and stereo-selective synthesis of spiro pyrrolidine and pyrrolizidine derivatives by multicomponent reaction. *Tetrahedron Lett.* **2013**, *54*, 3180–3184. [CrossRef]
26. Aksenov, A.V.; Aksenov, D.A.; Arutiunov, N.A.; Aksenov, N.A.; Aleksandrova, E.V.; Zhao, Z.; Du, L.; Kornienko, A.; Rubin, M. Synthesis of Spiro [indole-3, 5′-isoxazoles] with Anticancer Activity via a Formal [4+1]-Spirocyclization of Nitroalkenes to Indoles. *J. Org. Chem.* **2019**, *84*, 7123–7137. [CrossRef] [PubMed]
27. Żmigrodzka, M.; Sadowski, M.; Kras, J.; Dresler, E.; Demchuk, O.M.; Kula, K. Polar [3+2] cycloaddition between N-methyl azomethine ylide and trans-3, 3, 3-trichloro-1-nitroprop-1-ene. *Sci. Radices* **2022**, *1*, 26–35. [CrossRef]
28. Żmigrodzka, M.; Dresler, E.; Hordyjewicz-Baran, Z.; Kulesza, R.; Jasiński, R. Synthesis and chemical properties of 3-alkoxycarbonylchromones and 3-alkoxalylchromones. *Chem. Heter. Comp.* **2017**, *53*, 1161–1162. [CrossRef]
29. Seki, M.; Tsuruta, O.; Tatsumi, R.; Soejima, A. Synthesis and biological evaluation of pyrrolidine derivatives as novel and potent sodium channel blockers for the treatment of ischemic stroke. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4230–4234. [CrossRef]
30. Sun, H.; Wang, X.; Chen, Y.; Ouyang, L.; Liu, J.; Zhang, Y. Efficient construction of highly functionalized endo′-selective spiro[pyrrolidin-2,3′-oxindoles] via a regioselective 1,3-dipolar cycloaddition reaction between 3-amino oxindoles as azomethine ylide precursors and nitroalkenes. *Tetrahedron Lett.* **2014**, *55*, 5434–5438. [CrossRef]
31. Alimohammadi, K.; Sarrafi, Y.; Tajbakhsh, M.; Yeganegi, S.; Hamzehloueian, M. An experimental and theoretical investigation of the regio- and stereoselectivity of the polar [3+2] cycloaddition of azomethine ylides to nitrostyrenes. *Tetrahedron* **2011**, *67*, 1589–1597. [CrossRef]
32. De Silva, N.H.; Pyreddy, S.; Blanch, E.W.; Hügel, H.M.; Maniam, S. Microwave-assisted rapid synthesis of spirooxindole-pyrrolizidine analogues and their activity as anti-amyloidogenic agents. *Bioorg. Chem.* **2021**, *114*, 105128. [CrossRef]
33. Kumar, R.S.; Almansour, A.I.; Arumugam, N.; Mohammad, F.; Kotresha, D.; Menéndez, J.C. Spirooxindole-pyrrolidine heterocyclic hybrids promotes apoptosis through activation of caspase-3. *Bioorg. Med. Chem.* **2019**, *27*, 2487–2498. [CrossRef]
34. Arumugam, N.; Almansour, A.I.; Kumar, R.S.; Alaqeel, S.I.; Krishna, V.S.; Sriram, D. Anti-tubercular activity of novel class of spiropyrrolidine tethered indenoquinoxaline heterocyclic hybrids. *Bioorg. Chem.* **2020**, *99*, 103799. [CrossRef] [PubMed]
35. Almansour, A.I.; Arumugam, N.; Kumar, R.S.; Kotresha, D.; Manohar, T.S.; Venketesh, S. Design, synthesis and cholinesterase inhibitory activity of novel spiropyrrolidine tethered imidazole heterocyclic hybrids. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126789. [CrossRef] [PubMed]
36. Arumugam, N.; Raghunathan, R. Synthesis of highly functionalized β-lactam substituted pyrroloisoquinoline and indolizinoindole system by sequential intermolecular 1,3-dipolar cycloaddition reaction and Pictet-Spengler cyclization. *Tetrahedron* **2010**, *66*, 969–975. [CrossRef]

37. Wang, H.-T.; Lu, C.-D. Synthesis of 3,4-dihydropyrrolo[2,1-a]isoquinolines based on [3+2] cycloaddition initiated by Rh2(cap)4-catalyzed oxidation. *Tetrahedron Lett.* **2013**, *54*, 3015–3018. [CrossRef]
38. Thangamani, A. Regiospecific synthesis and biological evaluation of spirooxindolopyrrolizidines via [3+2] cycloaddition of azomethine ylide. *Eur. J. Med. Chem.* **2010**, *45*, 6120–6126. [CrossRef]
39. Kaur, A.; Singh, B.; Vyas, B.; Silakari, O. Synthesis and biological activity of 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-one derivatives as novel potent inhibitors of advanced glycation end product. *Eur. J. Med. Chem.* **2014**, *79*, 282–289. [CrossRef]
40. Taghizadeh, M.J.; Arvinnezhad, H.; Samadi, S.; Jadidi, K.; Javidan, A.; Notash, B. Synthesis of new enantiomerically pure spirooxindolopyrrolizidines via a three-component asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides derived from isatin. *Tetrahedron Lett.* **2012**, *53*, 5148–5150. [CrossRef]
41. Arun, Y.; Saranraj, K.; Balachandran, C.; Perumal, P.T. Novel spirooxindole–pyrrolidine compounds: Synthesis, anticancer and molecular docking studies. *Eur. J. Med. Chem.* **2014**, *74*, 50–64. [CrossRef]
42. Arun, Y.; Bhaskar, G.; Balachandran, C.; Ignacimuthu, S.; Perumal, P.T. Facile one-pot synthesis of novel dispirooxindole-pyrrolidine derivatives and their antimicrobial and anticancer activity against A549 human lung adenocarcinoma cancer cell line. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1839–1845. [CrossRef]
43. Lakshmi, N.V.; Thirumurugan, P.; Perumal, P.T. An expedient approach for the synthesis of dispiropyrrolidine bisoxindoles, spiropyrrolidine oxindoles and spiroindane-1,3-diones through 1,3-dipolar cycloaddition reactions. *Tetrahedron Lett.* **2010**, *51*, 1064–1068. [CrossRef]
44. Kathirvelan, D.; Haribabu, J.; Reddy, B.S.R.; Balachandran, C.; Duraipandiyan, V. Facile and diastereoselective synthesis of 3,2′-spiropyrrolidineoxindoles derivatives, their molecular docking and antiproliferative activities. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 389–399. [CrossRef] [PubMed]
45. Yuvaraj, P.; Reddy, B.S.R. Synthesis of 3-spiropyrrolidine-3-spirooxindoles from Baylis–Hillman adducts of chromone with azomethine ylides via [3+2] cycloaddition reaction. *Tetrahedron Lett.* **2013**, *54*, 821–827. [CrossRef]
46. Sarrafi, Y.; Hamzehlouian, M.; Alimohammadi, K.; Khavasi, H.R. Regioselective synthesis of novel spiroindane-1,3-diones through 1,3-dipolar cycloaddition reactions. *Tetrahedron Lett.* **2010**, *51*, 4734–4737. [CrossRef]
47. Kia, Y.; Osman, H.; Kumar, R.S.; Murugaiyah, V.; Basiri, A.; Perumal, S.; Razak, I.A. A facile chemo-, regio- and stereoselective synthesis and cholinesterase inhibitory activity of spirooxindole-pyrrolizine-piperidine hybrids. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2979–2983. [CrossRef] [PubMed]
48. Kia, Y.; Osman, H.; Kumar, R.S.; Murugaiyah, V.; Basiri, A.; Perumal, S.; Wahab, H.A.; Bing, C.S. Synthesis and discovery of novel piperidone-grafted mono- and bis-spirooxindole-hexahydropyrrolizines as potent cholinesterase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 1696–1707. [CrossRef] [PubMed]
49. Arumugam, N.; Periyasami, G.; Raghunathan, R.; Kamalraj, S.; Muthumary, J. Synthesis and antimicrobial activity of highly functionalised novel β-lactam grafted spiropyrrolidines and pyrrolizidines. *Eur. J. Med. Chem.* **2011**, *46*, 600–607. [CrossRef]
50. Hong, B.-C.; Liu, K.-L.; Tsai, C.-W.; Liao, J.-H. Proline-mediated dimerization of cinnamaldehydes via 1,3-dipolar cycloaddition reaction with azomethine ylides. A rapid access to highly functionalized hexahydro-1H-pyrrolizine. *Tetrahedron Lett.* **2008**, *49*, 5480–5483. [CrossRef]
51. Kang, T.-R.; Cheng, Y.; He, L.; Ye, J.; Liu, Q.-Z. Facile synthesis of highly functional pyrrolizidine derivatives from β,γ-unsaturated α-keto esters and proline via a tandem cycloaddition. *Tetrahedron Lett.* **2012**, *53*, 2552–2555. [CrossRef]
52. Rajesh, R.; Suresh, M.; Selvam, R.; Raghunathan, R. Synthesis of acridinedione derived mono spiro-pyrrolidine/pyrrolizidine derivatives–a facile approach via intermolecular [3+2] cycloaddition reaction. *Tetrahedron Lett.* **2014**, *55*, 4047–4053. [CrossRef]
53. Ramesh, E.; Kathiresan, M.; Raghunathan, R. Solvent-free microwave-assisted conversion of Baylis–Hillman adducts of ninhydrin into functionalized spiropyrrolidines/pyrrolizidines through 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2007**, *48*, 1835–1839. [CrossRef]
54. Nájera, C.; de Gracia Retamosa, M.; Sansano, J.M. 1,3-Dipolar cycloadditions of azomethine ylides with chiral acrylates derived from methyl (S)- and (R)-lactate: Diastereo- and enantioselective synthesis of polysubstituted prolines. *Tetrahedron Asymmetry* **2006**, *17*, 1985–1989. [CrossRef]
55. Ujjainwalla, F.; Warner, D.; Snedden, C.; Grisson, R.D.; Walsh, T.F.; Wyvratt, M.J.; Kalyani, R.N.; MacNeil, T.; Tang, R.; Weinberg, D.H.; et al. Design and syntheses of melanocortin subtype-4 receptor agonists. Part 2: Discovery of the dihydropyridazinone motif. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4023–4028. [CrossRef] [PubMed]
56. Parmar, N.J.; Pansuriya, B.R.; Barad, H.A.; Kant, R.; Gupta, V.K. An improved microwave assisted one-pot synthesis, and biological investigations of some novel aryldiazenyl chromeno fused pyrrolidines. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4075–4079. [CrossRef] [PubMed]
57. Purushothaman, S.; Prasanna, R.; Niranjana, P.; Raghunathan, R.; Nagaraj, S.; Rengasamy, R. Stereoselective synthesis of hexahydro-3-methyl-1-arylchromeno[3,4-b]pyrrole and its annulated heterocycles as potent antimicrobial agents for human pathogens. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7288–7291. [CrossRef] [PubMed]
58. Ramesh, E.; Raghunathan, R. A facile synthesis of chromeno[4,3-b]pyrroles derived from allyl derivatives of Baylis–Hillman adducts through intramolecular 1,3-dipolar cycloaddition using ultrasonication. *Tetrahedron Lett.* **2008**, *49*, 1125–1128. [CrossRef]
59. Bakthadoss, M.; Sivakumar, N.; Sivakumar, G.; Murugan, G. Highly regio- and stereoselective synthesis of tricyclic frameworks using Baylis–Hillman derivatives. *Tetrahedron Lett.* **2008**, *49*, 820–823. [CrossRef]

60. Pospíšil, J.; Potáček, M. Microwave-assisted solvent-free intramolecular 1,3-dipolar cycloaddition reactions leading to hexahydrochromeno[4,3-b]pyrroles: Scope and limitations. *Tetrahedron* **2007**, *63*, 337–346. [CrossRef]
61. Poornachandran, M.; Raghunathan, R. Synthesis of pyrrolo[3,4-b]pyrroles and perhydrothiazolo[3′,4′-2,3]pyrrolo[4,5-c]pyrroles. *Tetrahedron* **2008**, *64*, 6461–6474. [CrossRef]
62. Poornachandran, M.; Raghunathan, R. A novel diastereoselective 1,3-dipolar cycloaddition approach to cis-fused bispyrrolidines. *Tetrahedron Asymmetry* **2008**, *19*, 2177–2183. [CrossRef]
63. Kathiravan, S.; Ramesh, E.; Raghunathan, R. Synthesis of pyrrolo[2,3-a]pyrrolizine and pyrrolizine[2,3-a]pyrrolizine derived from allyl derivatives of Baylis–Hillman adducts through intramolecular 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2009**, *50*, 2389–2391. [CrossRef]
64. Coldham, I.; Dobson, B.C.; Franklina, A.I.; Fletcher, S.R. Synthesis of tetracyclic indole-containing ring systems by intramolecular cycloadditions of azomethine ylides. *Tetrahedron Lett.* **2007**, *48*, 873–875. [CrossRef]
65. Mishra, A.; Rastogi, N.; Batra, S. 2-(N-Allylaminomethyl)cinnamaldehydes as substrates for syntheses of aza-polycycles via intramolecular cycloaddition reactions. *Tetrahedron* **2012**, *68*, 2146–2154. [CrossRef]
66. Sirisha, N.; Raghunathan, R. Stereoselective synthesis of novel glyco-pyrano pyrrolidines/pyrrolizidines/indolizidines through intramolecular [3+2] cycloaddition approach. *Tetrahedron Lett.* **2010**, *51*, 2515–2518. [CrossRef]
67. Ghandi, M.; Taheri, A.; Bozcheloei, A.H.; Abbasi, A.; Kia, R. Synthesis of novel tricyclic and tetracyclic sultone scaffolds via intramolecular 1,3-dipolar cycloaddition reactions. *Tetrahedron* **2012**, *68*, 3641–3648. [CrossRef]
68. Rao, J.N.S.; Raghunathan, R. One-pot sequential azide–alkyne/intramolecular azomethine ylide 1,3-dipolar cycloaddition strategy for the synthesis of carbohydrate grafted macrocycles. *Tetrahedron Lett.* **2015**, *56*, 2669–2673. [CrossRef]
69. Kathiravan, S.; Vijayarajan, D.; Raghunathan, R. Novel synthesis of naphtho[2,1-b]pyrano pyrrolizidines and indolizidines through intramolecular 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2010**, *51*, 3065–3070. [CrossRef]
70. Pankova, A.S.; Voronin, V.V.; Kuznetsov, M.A. Intramolecular cycloaddition of N-phthalimidoaziridines to double and triple carbon–carbon bonds. *Tetrahedron Lett.* **2009**, *50*, 5990–5993. [CrossRef]
71. Shishido, Y.; Ito, F.; Morita, H.; Ikunaka, M. Stereoselective synthesis of a novel 2-aza-7-oxabicyclo[3.3.0]octane as neurokinin-1 receptor antagonist. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6887–6890. [CrossRef]
72. Girgis, A.S.; Farag, H.; Ismail, N.S.M.; George, R.F. Synthesis, hypnotic properties and molecular modeling studies of 1,2,7,9-tetraaza-spiro[4.5]dec-2-ene-6,8,10-triones. *Eur. J. Med. Chem.* **2011**, *46*, 4964–4969. [CrossRef]
73. Girgis, A.S.; Ismail, N.S.M.; Farag, H.; El-Eraky, W.I.; Saleh, D.O.; Tala, S.R.; Katritzky, A.R. Regioselective synthesis and molecular modeling study of vasorelaxant active 7,9-dioxa-1,2-diaza-spiro[4.5]dec-2-ene-6,10-diones. *Eur. J. Med. Chem.* **2010**, *45*, 4229–4238. [CrossRef]
74. Girgis, A.S.; Barsoum, F.F.; Samir, A. Regioselective synthetic approaches towards 1,2,8,9-tetraazadispiro[4.1.4.2]trideca-2,9-dien-6-ones of potential antimicrobial properties. *Eur. J. Med. Chem.* **2009**, *44*, 2447–2451. [CrossRef] [PubMed]
75. Mishriky, N.; Girgis, A.S.; Hosni, H.M.; Farag, H. Regio- and stereoselective synthesis of spiro[1-benzothiepine-4(5H),3′(3H)-pyrazol]-5-ones. *J. Heterocycl. Chem.* **2006**, *43*, 1549–1556. [CrossRef]
76. Hegab, M.I.; Girgis, A.S.; Ahmed-Farag, I.S. Novel regioselective synthesis of 3′H, 4H-spiro[chromene-3,2′-[1,3,4]thiadiazol]-4-one containing compounds. *J. Heterocycl. Chem.* **2006**, *43*, 1237–1242. [CrossRef]
77. Sridhar, G.; Gunasundari, T.; Raghunathan, R. A greener approach for the synthesis of 1-N-methyl-(spiro[2.3′]oxindolespiro[3.2″]/spiro[2.3′]indan-1,3-dionespiro[2.2″])cyclopentanone-4-aryl pyrrolidines. *Tetrahedron Lett.* **2007**, *48*, 319–322. [CrossRef]
78. George, R.F.; Ismail, N.S.M.; Stawinski, J.; Girgis, A.S. Design, synthesis and QSAR studies of dispiroindole derivatives as new antiproliferative agents. *Eur. J. Med. Chem.* **2013**, *68*, 339–351. [CrossRef]
79. Jayashankaran, J.; Manian, R.D.R.S.; Venkatesan, R.; Raghunathan, R. A regioselective synthesis of dispiro[oxindole-cyclohexanone]pyrrolidines and dispiro[oxindole-hexahydroindazole]pyrrolidines by sequential 1,3-dipolar cycloaddition and annulation through a microwave induced solvent-free approach. *Tetrahedron* **2005**, *61*, 5595–5598. [CrossRef]
80. Kumar, R.R.; Perumal, S.; Manju, S.C.; Bhatt, P.; Yogeeswari, P.; Sriram, D. An atom economic synthesis and antitubercular evaluation of novel spiro-cyclohexanones. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3461–3465. [CrossRef]
81. Gavaskar, D.; Raghunathan, R.; Babu, A.R.S. An expedient one-pot sequential five-component synthesis of highly substituted spiro-pyrrolidine heterocycles. *Tetrahedron Lett.* **2014**, *55*, 2217–2220. [CrossRef]
82. Dandia, A.; Singh, R.; Joshi, J.; Kumari, S. An eco-compatible synthesis of medicinally important novel class of trispiroheterocyclic framework using 2,2,2-trifluoroethanol as a reusable medium. *J. Fluor. Chem.* **2013**, *156*, 283–289. [CrossRef]
83. Lotfy, G.; Said, M.M.; El Ashry, E.H.; El Tamany, E.H.; Al-Dhfyan, A.; Abdel Aziz, Y.M.; Barakat, A. Synthesis of new spirooxindole-pyrrolothiazole derivatives: Anti-cancer activity and molecular docking. *Bioorg. Med. Chem.* **2017**, *25*, 1514–1523. [CrossRef]
84. Girgis, A.S. Regioselective synthesis of dispiro[1H-indene-2,3′-pyrrolidine-2′,3″-[3H]indole]-1,2″(1″H)-diones of potential anti-tumor properties. *Eur. J. Med. Chem.* **2009**, *44*, 91–100. [CrossRef] [PubMed]
85. Girgis, A.S.; Panda, S.S.; Srour, A.M.; Farag, H.; Ismail, N.S.M.; Elgendy, M.; Abdel-Aziz, A.K.; Katritzky, A.R. Rational design, synthesis and molecular modeling studies of novel anti-oncological alkaloids against melanoma. *Org. Biomol. Chem.* **2015**, *13*, 6619–6633. [CrossRef] [PubMed]
86. Prasanna, P.; Balamurugan, K.; Perumal, S.; Yogeeswari, P.; Sriram, D. A regio- and stereoselective 1,3-dipolar cycloaddition for the synthesis of novel spiro-pyrrolothiazolyloxindoles and their antitubercular evaluation. *Eur. J. Med. Chem.* **2010**, *45*, 5653–5661. [CrossRef] [PubMed]

87. Wei, A.C.; Ali, M.A.; Yoon, Y.K.; Ismail, R.; Choon, T.S.; Kumar, R.S.; Arumugam, N.; Almansour, A.I.; Osman, H. Antimycobacterial activity: A facile three-component [3+2]-cycloaddition for the regioselective synthesis of highly functionalised dispiropyrrolidines. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4930–4933. [CrossRef]
88. Wei, A.C.; Ali, M.A.; Yoon, Y.K.; Ismail, R.; Choon, T.S.; Kumar, R.S. A facile three-component [3+2]-cycloaddition for the regioselective synthesis of highly functionalised dispiropyrrolidines acting as antimycobacterial agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1383–1386. [CrossRef] [PubMed]
89. Wei, A.C.; Ali, M.A.; Yoon, Y.K.; Choi, S.B.; Osman, H.; Masand, V.H.; Choon, T.S. Antimycobacterial activity and in silico study of highly functionalised dispiropyrrolidines. *Med. Chem. Res.* **2015**, *24*, 818–828. [CrossRef]
90. Ali, M.A.; Ismail, R.; Choon, T.S.; Kumar, R.S.; Osman, H.; Arumugam, N.; Almansour, A.I.; Elumalai, K.; Singh, A. AChE inhibitor: A regio- and stereo-selective 1,3-dipolar cycloaddition for the synthesis of novel substituted 5,6-dimethoxy spiro[5.3′]-oxindolespiro-[6.3″]-2,3-dihydro-1H-inden-1″-one-7-(substituted aryl)-tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 508–511. [CrossRef]
91. Ali, M.A.; Ismail, R.; Choon, T.S.; Yoon, Y.K.; Wei, A.C.; Pandian, S.; Kumar, R.S.; Osman, H.; Manogaran, E. Substituted spiro [2.3′]oxindolespiro[3.2″]-5,6-dimethoxy-indane-1″-one-pyrrolidine analogue as inhibitors of acetylcholinesterase. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7064–7066. [CrossRef]
92. Babu, A.R.S.; Raghunathan, R. TiO2–silica mediated one pot three component 1,3-dipolar cycloaddition reaction: A facile and rapid synthesis of dispiro acenaphthenone/oxindole [indanedione/oxindole] pyrroloisoquinoline ring systems. *Tetrahedron* **2007**, *63*, 8010–8016. [CrossRef]
93. Babu, A.R.S.; Raghunathan, R. Heteropolyacid–silica mediated [3+2] cycloaddition of azomethine ylides–a facile multicomponent one-pot synthesis of novel dispiroheterocycles. *Tetrahedron Lett.* **2006**, *47*, 9221–9225. [CrossRef]
94. Jayashankaran, J.; Manian, R.D.R.S.; Raghunathan, R. A facile synthesis of novel dispiroheterocycles through solvent-free microwave-assisted [3+2] cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2004**, *45*, 7303–7305. [CrossRef]
95. Lanka, S.; Thennarasu, S.; Perumal, P.T. Facile synthesis of novel dispiroheterocylic derivatives through cycloaddition of azomethine ylides with acenaphthenone-2-ylidine ketones. *Tetrahedron Lett.* **2012**, *53*, 7052–7055. [CrossRef]
96. Dandia, A.; Jain, A.K.; Bhati, D.S. Direct construction of novel dispiro heterocycles through 1,3-dipolar cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2011**, *52*, 5333–5337. [CrossRef]
97. Saravanan, P.; Pushparaj, S.; Raghunathan, R. An expedient approach for the synthesis of naphthyl dispiro pyrrolidine/pyrrolizidine through 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2013**, *54*, 3449–3452. [CrossRef]
98. Rajesh, R.; Raghunathan, R. Regio- and stereoselective synthesis of novel tetraspiro-bispyrrolidine and bisoxindolopyrrolidine derivatives through 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2010**, *51*, 5845–5848. [CrossRef]
99. Youssef, M.A.; Panda, S.S.; El-Shiekh, R.A.; Shalaby, E.M.; Aboshouk, D.R.; Fayad, W.; Fawzy, N.G.; Girgis, A.S. Synthesis and molecular modeling studies of cholinesterase inhibitor dispiro[indoline-3,2′-pyrrolidine-3′,3″-pyrrolidines]. *RSC Adv.* **2020**, *10*, 21830–21838. [CrossRef]
100. Karthikeyan, K.; Kumar, P.M.S.; Doble, M.; Perumal, P.T. Synthesis, antibacterial activity evaluation and QSAR studies of novel dispiropyrrolidines. *Eur. J. Med. Chem.* **2010**, *45*, 3446–3452. [CrossRef]
101. Hazra, A.; Paira, P.; Sahu, K.B.; Naskar, S.; Saha, P.; Paira, R.; Mondal, S.; Maity, A.; Luger, P.; Weber, M.; et al. Chemistry of andrographolide: Formation of novel di-spiropyrrolidino and di-spiropyrrolizidino-oxindole adducts via one-pot three-component [3+2] azomethine ylide cycloaddition. *Tetrahedron Lett.* **2010**, *51*, 1585–1588. [CrossRef]
102. Barman, P.D.; Sanyal, I.; Mandal, S.B.; Banerjee, A.K. Cu(OTf)2-promoted efficient synthetic route towards glycospiro-pyrrolo[2,1-a]isoquinolines. *Tetrahedron Lett.* **2014**, *55*, 5648–5651. [CrossRef]
103. Moghaddam, F.M.; Khodabakhshi, M.R.; Ghahremannejad, Z.; Foroushani, B.K.; Ng, S.W. A one-pot, three-component regiospecific synthesis of dispiropyrrolidines containing a thiophenone ring via 1,3-dipolar cycloaddition reactions of azomethine ylides. *Tetrahedron Lett.* **2013**, *54*, 2520–2524. [CrossRef]
104. Arumugam, N.; Jayashankaran, J.; Manian, R.D.R.S.; Raghunathan, R. A novel access to highly functionalised β-lactams by regio- and stereoselective 1,3-dipolar cycloaddition reaction. *Tetrahedron* **2005**, *61*, 8512–8516. [CrossRef]
105. Dong, H.; Song, S.; Li, J.; Xu, C.; Zhang, H.; Ouyang, L. The discovery of oxazolones-grafted spirooxindoles via three-component diversity oriented synthesis and their preliminary biological evaluation. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3585–3591. [CrossRef] [PubMed]
106. Jain, R.; Sharma, K.; Kumar, D. Ionic liquid mediated 1,3-dipolar cycloaddition of azomethine ylides: A facile and green synthesis of novel dispiro heterocycles. *Tetrahedron Lett.* **2012**, *53*, 1993–1997. [CrossRef]
107. Babu, A.R.S.; Raghunathan, R. Ultrasonic assisted-silica mediated [3+2] cycloaddition of azomethine ylides–a facile multicomponent one-pot synthesis of novel dispiroheterocycles. *Tetrahedron Lett.* **2007**, *48*, 6809–6813. [CrossRef]
108. Babu, A.R.S.; Raghunathan, R. ZrOCl2·8H2O mediated microwave induced [3+2] cycloaddition of azomethine ylides–a facile one-pot synthesis of novel dispiroheterocycles. *Tetrahedron Lett.* **2007**, *48*, 305–308. [CrossRef]
109. Lanka, S.; Thennarasu, S.; Perumal, P.T. Stoichiometry-controlled cycloaddition of azomethine ylide with dipolarophiles: Chemoselective and regioselective synthesis of bis- and tris-spirooxindole derivatives. *Tetrahedron Lett.* **2014**, *55*, 2585–2588. [CrossRef]

110. Lu, L.-J.; Fu, Q.; Sun, J.; Yan, C.-G. Synthesis of complex dispirocyclopentanebisoxindoles via cycloaddition reactions of 4-dimethylamino-1-alkoxycarbonylmethylpyridinium bromides with 2-oxoindolin-3-ylidene derivatives. *Tetrahedron* **2014**, *70*, 2537–2545. [CrossRef]
111. Dandia, A.; Jain, A.K.; Laxkar, A.K.; Bhati, D.S. Synthesis and stereochemical investigation of highly functionalized novel dispirobisoxindole derivatives via [3+2] cycloaddition reaction in ionic liquid. *Tetrahedron* **2013**, *69*, 2062–2069. [CrossRef]
112. Ghandi, M.; Yari, A.; Rezaei, S.J.T.; Taheri, A. Synthesis of novel spiropyrrolidine/pyrrolizine-oxindole scaffolds through 1,3-dipolar cycloadditions. *Tetrahedron Lett.* **2009**, *50*, 4724–4726. [CrossRef]
113. Mamari, K.A.; Ennajih, H.; Zouihri, H.; Bouhfid, R.; Ng, S.W.; Essassi, E.M. Synthesis of novel dispiro-oxindoles via 1,3-dipolar cycloaddition reactions of azomethine ylides. *Tetrahedron Lett.* **2012**, *53*, 2328–2331. [CrossRef]
114. Mhiri, C.; Boudriga, S.; Askri, M.; Knorr, M.; Sriram, D.; Yogeeswari, P.; Nana, F.; Golz, C.; Strohmann, C. Design of novel dispirooxindolopyrrolidine and dispirooxindolopyrrolothiazole derivatives as potential antitubercular agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4308–4313. [CrossRef] [PubMed]
115. Murali, K.; Sparkes, H.A.; Prasad, K.J.R. Regio- and stereoselective synthesis of dispirooxindole-pyrrolocarbazole hybrids via 1,3-dipolar cycloaddition reactions: Cytotoxic activity and SAR studies. *Eur. J. Med. Chem.* **2018**, *143*, 292–305. [CrossRef] [PubMed]
116. Periyasami, G.; Raghunathan, R.; Surendiran, G.; Mathivanan, N. Regioselective synthesis and antimicrobial screening of novel ketocarbazolodispiropyrrolidine derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 959–966. [CrossRef]
117. Periyasami, G.; Raghunathan, R.; Surendiran, G.; Mathivanan, N. Synthesis of novel spiropyrrolizidines as potent antimicrobial agents for human and plant pathogens. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2342–2345. [CrossRef] [PubMed]
118. Kumar, R.R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines. *Eur. J. Med. Chem.* **2009**, *44*, 3821–3829. [CrossRef] [PubMed]
119. Basiri, A.; Abd Razik, B.M.; Ezzat, M.O.; Kia, Y.; Kumar, R.S.; Almansour, A.I.; Arumugam, N.; Murugaiyah, V. Synthesis and cholinesterase inhibitory activity study of new piperidone grafted spiropyrrolidines. *Bioorg. Chem.* **2017**, *75*, 210–216. [CrossRef] [PubMed]
120. Girgis, A.S. Regioselective synthesis and stereochemical structure of anti-tumor active dispiro[3H-indole-3,2′-pyrrolidine-3′,3″-piperidine]-2(1H),4″-diones. *Eur. J. Med. Chem.* **2009**, *44*, 1257–1264. [CrossRef]
121. Girgis, A.S.; Panda, S.S.; Shalaby, E.M.; Mabied, A.F.; Steel, P.J.; Hall, C.D.; Katritzky, A.R. Regioselective synthesis and theoretical studies of an anti-neoplastic fluoro-substituted dispirooxindole. *RSC Adv.* **2015**, *5*, 14780–14787. [CrossRef]
122. George, R.F.; Panda, S.S.; Shalaby, E.M.; Srour, A.M.; Ahmed Farag, I.S.; Girgis, A.S. Synthesis and molecular modeling studies of indole-based antitumor agents. *RSC Adv.* **2016**, *6*, 45434–45451. [CrossRef]
123. Girgis, A.S.; Panda, S.S.; Aziz, M.N.; Steel, P.J.; Hall, C.D.; Katritzky, A.R. Rational design, synthesis, and 2D-QSAR study of anti-oncological alkaloids against hepatoma and cervical carcinoma. *RSC Adv.* **2015**, *5*, 28554–28569. [CrossRef]
124. Kumar, R.S.; Antonisamy, P.; Almansour, A.I.; Arumugam, N.; Periyasami, G.; Altaf, M.; Kim, H.-R.; Kwon, K.-B. Functionalized spirooxindole-indolizine hybrids: Stereoselective green synthesis and evaluation of anti-inflammatory effect involving TNF-α and nitrite inhibition. *Eur. J. Med. Chem.* **2018**, *152*, 417–423. [CrossRef] [PubMed]
125. Karthikeyan, S.V.; Bala, B.D.; Raja, V.P.A.; Perumal, S.; Yogeeswari, P.; Sriram, D. A highly atom economic, chemo-, regio- and stereoselective synthesis and evaluation of spiro-pyrrolothiazoles as antitubercular agents. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 350–353. [CrossRef] [PubMed]
126. Lawson, S.; Arumugam, N.; Almansour, A.I.; Kumar, R.S.; Thangamani, S. Dispiropyrrolidine tethered piperidone heterocyclic hybrids with broad-spectrum antifungal activity against *Candida albicans* and *Cryptococcus neoformans*. *Bioorg. Chem.* **2020**, *100*, 103865. [CrossRef] [PubMed]
127. Kumar, R.R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. A highly atom economic, chemo-, regio- and stereoselective synthesis, and discovery of spiro-pyrido-pyrrolizines and pyrrolidines as antimycobacterial agents. *Tetrahedron* **2008**, *64*, 2962–2971. [CrossRef]
128. Sivakumar, S.; Kumar, R.R.; Ali, M.A.; Choon, T.S. An atom economic synthesis and AChE inhibitory activity of novel dispiro 7-aryltetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole and 4-aryloctahydroindolizine N-methylpiperidin-4-one hybrid heterocycles. *Eur. J. Med. Chem.* **2013**, *65*, 240–248. [CrossRef]
129. Rajesh, S.M.; Bala, B.D.; Perumal, S. Multi-component, 1,3-dipolar cycloaddition reactions for the chemo-, regio- and stereoselective synthesis of novel hybrid spiroheterocycles in ionic liquid. *Tetrahedron Lett.* **2012**, *53*, 5367–5371. [CrossRef]
130. Arumugam, N.; Almansour, A.I.; Kumar, R.S.; Kotresha, D.; Saiswaroop, R.; Venketesh, S. Dispiropyrrolidinyl-piperidone embedded indeno[1,2-b]quinoxaline heterocyclic hybrids: Synthesis, cholinesterase inhibitory activity and their molecular docking simulation. *Bioorg. Med. Chem.* **2019**, *27*, 2621–2628. [CrossRef]
131. Kia, Y.; Osman, H.; Kumar, R.S.; Basiri, A.; Murugaiyah, V. Synthesis and discovery of highly functionalized mono- and bis-spiro-pyrrolidines as potent cholinesterase enzyme inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1815–1819. [CrossRef]
132. Kumar, R.S.; Ali, M.A.; Osman, H.; Ismail, R.; Choon, T.S.; Yoon, Y.K.; Wei, A.C.; Pandian, S.; Manogaran, E. Synthesis and discovery of novel hexacyclic cage compounds as inhibitors of acetylcholinesterase. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3997–4000. [CrossRef]

133. Arumugam, N.; Almansour, A.I.; Kumar, R.S.; Perumal, S.; Ghabbour, H.A.; Fun, H.-K. A 1,3-dipolar cycloaddition-annulation protocol for the expedient regio-, stereo- and product-selective construction of novel hybrid heterocycles comprising seven rings and seven contiguous stereocentres. *Tetrahedron Lett.* **2013**, *54*, 2515–2519. [CrossRef]
134. Kumar, R.S.; Osman, H.; Perumal, S.; Menéndez, J.C.; Ali, M.A.; Ismail, R.; Choon, T.S. A facile three-component [3+2]-cycloaddition/annulation domino protocol for the regio- and diastereoselective synthesis of novel penta- and hexacyclic cage systems, involving the generation of two heterocyclic rings and five contiguous stereocenters. *Tetrahedron* **2011**, *67*, 3132–3139. [CrossRef]
135. Chandraprakash, K.; Sankaran, M.; Uvarani, C.; Shankar, R.; Ata, A.; Dallemer, F.; Mohan, P.S. A strategic approach to the synthesis of novel class of dispiroheterocyclic derivatives through 1,3 dipolar cycloaddition of azomethine ylide with (E)-3-arylidene-2,3-dihydro-8-nitro-4-quinolone. *Tetrahedron Lett.* **2013**, *2011*, 3896–3901. [CrossRef]
136. Augustine, T.; Kanakam, C.C.; Vithiya, S.M.; Ramkumar, V. A facile entry into a novel class of dispiroheterocyclic framework through 1,3-dipolarcycloaddition of azomethine ylides with 3-arylidene-4-chromanones as dipolarophiles. *Tetrahedron Lett.* **2009**, *50*, 5906–5909. [CrossRef]
137. Bharkavi, C.; Kumar, S.V.; Ali, M.A.; Osman, H.; Muthusubramanian, S.; Perumal, S. A facile stereoselective synthesis of dispiro-indeno pyrrolidine/pyrrolothiazole–thiochroman hybrids and evaluation of their antimycobacterial, anticancer and AchE inhibitory activities. *Bioorg. Med. Chem.* **2016**, *24*, 5873–5883. [CrossRef] [PubMed]
138. Maheswari, S.U.; Perumal, S.; Almansour, A.I. A facile regio- and stereoselective synthesis of novel dispirooxindolyl-[acridine-2′,3-pyrrolidine/thiapyrrolizidine]-1′-ones via 1,3-dipolar cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2012**, *53*, 349–353. [CrossRef]
139. Maheswari, S.U.; Perumal, S. An expedient domino three-component [3+2]-cycloaddition/annulation protocol: Regio- and stereoselective assembly of novel polycyclic hybrid heterocycles with five contiguous stereocentres. *Tetrahedron Lett.* **2013**, *54*, 7044–7048. [CrossRef]
140. Toumi, A.; Boudriga, S.; Hamden, K.; Sobeh, M.; Cheurfa, M.; Askri, M.; Knorr, M.; Strohmann, C.; Brieger, L. Synthesis, antidiabetic activity and molecular docking study of rhodanine-substitued spirooxindole pyrrolidine derivatives as novel α-amylase inhibitors. *Bioorg. Chem.* **2021**, *106*, 104507. [CrossRef]
141. Kumar, G.S.; Satheeshkumar, R.; Kaminsky, W.; Platts, J.; Prasad, K.J.R. A facile regioselective 1,3-dipolar cycloaddition protocol for the synthesis of new class of quinolinyl dispiro heterocycles. *Tetrahedron Lett.* **2014**, *55*, 5475–5480. [CrossRef]
142. Poornachandran, M.; Raghunathan, R. Synthesis of dispirooxindolecycloalka[d]pyrimidino[2,3-b]thiazole pyrrolidine/thiapyrrolizidine ring systems. *Tetrahedron* **2006**, *62*, 11274–11281. [CrossRef]
143. Lakshmi, N.V.; Tamilisai, R.; Perumal, P.T. A facile synthetic approach to novel spiro-oxindoles/acenaphthylen-1-ones containing benzo[1,4]thiazin-3-one ring via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2011**, *52*, 5301–5307. [CrossRef]
144. Santora, V.J.; Covel, J.A.; Hayashi, R.; Hofilena, B.J.; Ibarra, J.B.; Pulley, M.D.; Weinhouse, M.I.; Sengupta, D.; Duffield, J.J.; Semple, G.; et al. A new family of H3 receptor antagonists based on the natural product Conessine. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1490–1494. [CrossRef] [PubMed]
145. Bhaskar, G.; Arun, Y.; Balachandran, C.; Saikumar, C.; Perumal, P.T. Synthesis of novel spirooxindole derivatives by one pot multicomponent reaction and their antimicrobial activity. *Eur. J. Med. Chem.* **2012**, *51*, 79–91. [CrossRef] [PubMed]
146. Rajanarendar, E.; Ramakrishna, S.; Reddy, K.G.; Nagaraju, D.; Reddy, Y.N. A facile synthesis, anti-inflammatory and analgesic activity of isoxazolyl-2,3-dihydrospiro[benzo[f]isoindole-1,3′-indoline]-2′,4,9-triones. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3954–3958. [CrossRef]
147. Huang, H.-M.; Gao, J.-R.; Hou, L.-F.; Jia, J.-H.; Han, L.; Ye, Q.; Li, Y.-J. The first iodine improved 1,3-dipolar cycloaddition: Facile and novel synthesis of 2-substituted benzo[f]isoindole-4,9-diones. *Tetrahedron* **2013**, *69*, 9033–9037. [CrossRef]
148. Ma, D.; Cheng, H.; Huang, C.; Xu, L. Synthesis of the azatricyclic ACD ring system of calyciphylline A-type Daphniphyllum alkaloids via a nonstabilized azomethine ylide generated by desilylation. *Tetrahedron Lett.* **2015**, *56*, 2492–2495. [CrossRef]
149. Ryan, J.H. 1,3-Dipolar cycloaddition reactions of azomethine ylides with aromatic dipolarophiles. *ARKIVOC* **2015**, *46*, 160–183. [CrossRef]
150. Wales, S.M.; Rivinoja, D.J.; Gardiner, M.G.; Bird, M.J.; Meyer, A.G.; Ryan, J.H.; Hyland, C.J.T. Benzoazepine-fused isoindolines via intramolecular (3+2)-cycloadditions of azomethine ylides with dinitroarenes. *Org. Lett.* **2019**, *21*, 4703–4708. [CrossRef]
151. Lee, S.; Chataigner, I.; Piettre, S.R. Facile dearomatization of nitrobenzene derivatives and other nitroarenes with *N*-benzyl azomethine ylide. *Angew. Chem. Int. Ed.* **2011**, *50*, 472–476. [CrossRef]
152. Bastrakov, M.A.; Fedorenko, A.K.; Starosotnikov, A.M.; Shakhnes, A.K. Nitropyridines as 2π-partners in 1,3-dipolar cycloadditions with N-methyl azomethine ylide: An easy access to condensed pyrrolines. *Molecules* **2021**, *26*, 5547. [CrossRef]
153. Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I.; Piettre, S.R. Aromatic C=C bonds as dipolarophiles: Facile reactions of uncomplexed electron-deficient benzene derivatives and other aromatic rings with a non-stabilized azomethine ylide. *Chem. Eur. J.* **2013**, *19*, 7181–7192. [CrossRef]

154. Bastrakov, M.A.; Starosotnikov, A.M.; Pechenkin, S.Y.; Kachala, V.V.; Glukhov, I.V.; Shevelev, S.A. Double 1,3-dipolar cycloaddition of N-methyl azomethine ylide to meta-dinitrobenzene annelated with nitrogen aromatic heterocycles. *J. Heterocycl. Chem.* **2010**, *47*, 893–896. [CrossRef]
155. Semenyuk, Y.P.; Kochubei, A.S.; Morozov, P.G.; Burov, O.N.; Kletskii, M.E.; Kurbatov, S.V. [3+2] Cycloaddition reactions to indolyl- and pyrrolyl derivatives of dinitrobenzofurazan. *Chem. Heterocycl. Compd.* **2015**, *50*, 1731–1740. [CrossRef]
156. Starosotnikov, A.M.; Bastrakov, M.A.; Kachala, V.V.; Fedyanin, I.V.; Shevelev, S.A.; Dalinger, I.L. Unusual pericyclic reactivity of 4-nitrobenzofuroxans in 1,3-dipolar cycloaddition with N-benzyl azomethine ylide—A new example of multiple C–C-bond forming transformations. *ChemistrySelect* **2018**, *3*, 9773–9777. [CrossRef]
157. Girgis, A.S.; Stawinski, J.; Ismail, N.S.M.; Farag, H. Synthesis and QSAR study of novel cytotoxic spiro[3H-indole-3,2′(1′H)-pyrrolo[3,4-c]pyrrole]-2,3′,5′(1H,2′aH,4′H)-triones. *Eur. J. Med. Chem.* **2012**, *47*, 312–322. [CrossRef] [PubMed]
158. Bharkavi, C.; Kumar, S.V.; Ali, M.A.; Osman, H.; Muthusubramanian, S.; Perumal, S. One-pot microwave assisted stereoselective synthesis of novel dihydro-2′H-spiro[indene-2,1′-pyrrolo-[3,4-c]pyrrole]-tetraones and evaluation of their antimycobacterial activity and inhibition of AChE. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3071–3075. [CrossRef]
159. Nyerges, M.; Pintér, Á.; Virányi, A.; Blaskó, G.; Tőke, L. Synthesis of pyrrolo[3,4-c]quinolines by 1,5-electrocyclisation of non-stabilised azomethine ylides. *Tetrahedron* **2005**, *61*, 8199–8205. [CrossRef]
160. Mondal, S.; Maity, A.; Paira, R.; Banerjee, M.; Bharitkar, Y.P.; Hazra, A.; Banerjee, S.; Mondal, N.B. Efficient synthesis of novel tetrahydropyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline derivatives via a simple and convenient MCR in aqueous micellar system. *Tetrahedron Lett.* **2012**, *53*, 6288–6291. [CrossRef]
161. Georgiou, D.; Toutountzoglou, V.; Muir, K.W.; Hadjipavlou-Litina, D.; Elemes, Y. Synthesis of sulfur containing dihydro-pyrrolo derivatives and their biological evaluation as antioxidants. *Bioorg. Med. Chem.* **2012**, *20*, 5103–5109. [CrossRef]
162. Quiroga, J.; Gálvez, J.; Pérez, A.; Valencia, A.; Abonia, R.; Insuasty, B. Catalyst free three-component synthesis of (±)-pyrazolylpyrrolopyrroles by 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2011**, *52*, 5471–5473. [CrossRef]
163. Belskaya, N.P.; Bakulev, V.A.; Deryabina, T.G.; Subbotina, J.O.; Kodess, M.I.; Dehaen, W.; Toppet, S.; Robeyns, K.; Meervelt, L.V. 3-Alkylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)-acrylonitriles as masked 1,3-dipoles. *Tetrahedron* **2009**, *65*, 7662–7672. [CrossRef]
164. Malatesti, N.; Boa, A.N.; Clark, S.; Westwood, R. 1,3-Dipolar cycloaddition reactions of benzo[b]thiophene 1,1-dioxide with azomethine ylides. *Tetrahedron Lett.* **2006**, *47*, 5139–5142. [CrossRef]
165. Konstantinova, L.S.; Bastrakov, M.A.; Starosotnikov, A.M.; Glukhov, I.V.; Lysov, K.A.; Rakitin, O.A.; Shevelev, S.A. 4,6-Dinitrobenzo[c]isothiazole: Synthesis and 1,3-dipolar cycloaddition to azomethine ylide. *Mendeleev Commun.* **2010**, *20*, 353–354. [CrossRef]
166. Roy, S.; Kishbaugh, T.L.S.; Jasinski, J.P.; Gribble, G.W. 1,3-Dipolar cycloaddition of 2- and 3-nitroindoles with azomethine ylides. A new approach to pyrrolo[3,4-b]indoles. *Tetrahedron Lett.* **2007**, *48*, 1313–1316. [CrossRef]
167. Rao, J.N.S.; Raghunathan, R. An expedient diastereoselective synthesis of pyrrolidinyl spirooxindoles fused to sugar lactone via [3+2] cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2012**, *53*, 854–858. [CrossRef]
168. Prasanna, R.; Purushothaman, S.; Raghunathan, R. Synthesis of glucosylspiro-oxindole derivatives via one-pot three-component cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2014**, *55*, 6631–6634. [CrossRef]
169. Rao, J.N.S.; Raghunathan, R. An expedient synthesis of pyrrolidinyl spirooxindole grafted 3-nitrochromanes through 1,3-dipolar cycloaddition reaction of azomethine ylides. *Tetrahedron Lett.* **2013**, *54*, 6568–6573. [CrossRef]
170. Rao, J.N.S.; Raghunathan, R. A facile synthesis of glyco 3-nitrochromane hybrid pyrrolidinyl spiro heterocycles via [3+2] cycloaddition of azomethine ylides. *Tetrahedron Lett.* **2015**, *56*, 2276–2279. [CrossRef]
171. Korotaev, V.Y.; Barkov, A.Y.; Moshkin, V.S.; Matochkina, E.G.; Kodess, M.I.; Sosnovskikh, V. Ya. Highly diastereoselective 1,3-dipolar cycloaddition of nonstabilized azomethine ylides to 3-nitro-2-trihalomethyl-2H-chromenes: Synthesis of 1-benzopyrano[3,4-c]pyrrolidines. *Tetrahedron* **2013**, *69*, 8602–8608. [CrossRef]
172. Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M. 3-Nitrochromene derivatives as 2π components in 1,3-dipolar cycloadditions of azomethine ylides. *Tetrahedron* **2006**, *62*, 8720–8730. [CrossRef]
173. Moshkin, V.S.; Sosnovskikh, V.Y.; Röschenthaler, G.-V. Synthesis of benzopyranopyrrolidines via 1,3-dipolar cycloaddition of nonstabilized azomethine ylides with 3-substituted coumarins. *Tetrahedron* **2013**, *69*, 5884–5892. [CrossRef]
174. Moshkin, V.S.; Sosnovskikh, V.Y.; Slepukhin, P.A.; Röschenthaler, G.-V. 1,3-Dipolar cycloadditions of nonstabilised azomethine ylides at 3-substituted coumarins: Synthesis of 1-benzopyrano[3,4-c]pyrrolidines. *Mendeleev Commun.* **2012**, *22*, 29–31. [CrossRef]
175. Ghandi, M.; Taheri, A.; Abbasi, A. A facile synthesis of chromeno[3,4-c]spiropyrrolidine-oxindoles via 1,3-dipolar cycloadditions. *Tetrahedron* **2010**, *66*, 6744–6748. [CrossRef]
176. Potowski, M.; Golz, C.; Strohmann, C.; Antonchick, A.P.; Waldmann, H. Biology-oriented synthesis of benzopyrano[3,4-c]pyrrolidines. *Bioorg. Med. Chem.* **2015**, *23*, 2895–2903. [CrossRef]
177. Sosnovskikh, V.Y.; Kornev, M.Y.; Moshkin, V.S.; Buev, E.M. Substituted chromones in [3+2] cycloadditions with nonstabilized azomethine ylides: Synthesis of 1-benzopyrano[2,3-c]pyrrolidines and 1-benzopyrano[2,3-c:3,4-c′]dipyrrolidines. *Tetrahedron* **2014**, *70*, 9253–9261. [CrossRef]

178. Oliveira, U.; Guillermo, A.; Repetto, E.; Vega, D.R.; Varela, O. Synthesis of Enantiomeric Polyhydroxyalkylpyrrolidines from 1,3-Dipolar Cycloadducts. Evaluation as Inhibitors of a β-Galactofuranosidase. *J. Org. Chem.* **2016**, *81*, 4179–4189. [CrossRef] [PubMed]
179. D'Souza, A.M.; Spiccia, N.; Basutto, J.; Jokisz, P.; Wong, L.S.-M.; Meyer, A.G.; Holmes, A.B.; White, J.M.; Ryan, J.H. 1,3-Dipolar cycloaddition-decarboxylation reactions of an azomethine ylide with isatoic anhydrides: Formation of novel benzodiazepinones. *Org. Lett.* **2011**, *13*, 486–489. [CrossRef] [PubMed]