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# Recent advances of azomethine ylides for the synthesis of natural and synthetic bioactive pyrrolidines and spiropyrrolidines

Priyankar Paira, *[a] Rinku Chakrabarty, [b] Piyali Deb Barman,[c] Bhagat Singh [d] and Rupankar Paira*[e]

1,3-Dipole-based nitrogen containing carbanion, particularly azomethine ylide, is widely used in cycloaddition reactions. It has important and widespread application not only limited in the synthesis of core structural motifs like pyrrolidine and spiropyrrolidines but also in stereocontrolled dipolarophile for building important classes of heterocyclic compounds. Herein, we will explore the current development of azomethine ylide and all the possible applications of this small but elegant fragment using a green approach. This review article will also covers the application of this super energetic, pharmaceutically important moiety in the field of asymmetric, organocatalytic, and transition metal-catalyzed synthesis processes coupled with a theoretical approach. The development of an environmentally safe multicomponent, tandem synthesis method mediated by azomethine ylide will be discussed in detail in this current review article, which will be important for researchers in the field of organic synthesis, heterocyclic chemistry, and medicinal chemistry.

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[a]*Department of Chemistry, School of Advanced Sciences, Vellore Institute of Technology, Vellore, 632014, Tamilnadu, India. E-mail: priyankar.paira@vit.ac.in*
[b]*Department of Chemistry, Alipurduar University, P. O.-Alipurduar Court, District-Alipurduar, Pin- 36122, West Bengal, India. E-mail: rckncs@gmail.com*
[c]*Chemical Division, Geological Survey of India, Eastern Region, Kolkata 700091, India. E-mail: piyalidebbarman85@gmail.com*
[d]*Eastern New Mexico University, 1500 S Ave K, Portales, NM 88130A, USA. E-mail: bhagatsingh8791@gmail.com*
[e]*Department of Chemistry, Maharaja Manindra Chandra College, 20, Ramkanto Bose Street, Kolkata-700003, India. E-mail: rpaira@mmccollege.ac.in*



**Priyankar Paira**

*Dr Priyankar Paira, MRSC, Associate Professor, VIT, Vellore, Tamilnadu, India, received his PhD degree from the Indian Institute of Chemical Biology (IICB), Jadavpur University, Kolkata. He has carried out his Post Doctoral work under the supervision of Prof. Giorgia Pastorin and Prof. Ang Wee Han from National University of Singapore. His current research focused on bioorganometallic and medicinal chemistry. He has over 100 publications in reputed international journals having citations (3063) and h-Index (29) along with 3 patents. He has successfully completed three SERB projects, two ICMR projects and currently working on one CSIR project. He is associated with professional bodies like ACS, RSC, SBIC, CRSI, CRS, ISCBC, CBS.*

**Rinku Chakrabarty**

*Dr Rinku Chakrabarty embarked on her academic journey at IIEST, Shibpur, India for her PhD under the guidance of Prof. Shyamaprosad Goswami in 2011, focusing on Supramolecular Chemistry, followed by postdoctoral studies at the University of Witwatersrand, Johannesburg, South Africa, where she was involved in the synthesis of rare-earth-based molecular systems as MRI agents. Her passion for academia led her to assume the role of an Assistant Professor in the Department of Chemistry at Alipurduar University. Her research pursuits are centered on nanomaterials, molecular sensing and bioinorganic chemistry, showcasing her unwavering commitment to the advancement of the field of Chemistry.*

## 1. Introduction

Cycloaddition is an important class of pericyclic reactions or chemical processes in which two or more unsaturated molecules (or portions of the same molecule) combine to generate a cyclic adduct. The backbone size of the participants typically characterises cycloadditions; hence, the 1,3-dipolar cycloaddition is a [3 + 2] cycloaddition, and the Diels–Alder reaction is a [4 + 2] cycloaddition. Unsaturated or partially saturated (hetero) cycles with distinct substitution patterns and frequently high stereocontrol are produced by the reaction. For example, there are numerous instances wherein the Diels–Alder reaction results in both heterocyclic and carbocyclic ring systems. Interestingly, [3 + 2] cycloaddition events produce 5-membered ring systems in a manner similar to that of the Diels–Alder reaction, whereas the former produces 6-membered rings. Dipolarophiles and 1,3-dipoles (*cf.* diene and dienophile in the Diels–Alder reaction) are the reactive partners in this reaction pathway. Additionally, these are 4π + 2π processes, where sp and $sp^2$ hybridized entities are generally used, including 1,3-dipoles. The stability of these 1,3-dipoles varies; while certain dipolar species must be used for reactions within 24 hours of production, some can be separated and stored. Others are produced and reacted *in situ* and are highly unstable. One of these $sp^2$-type 1,3-dipoles, azomethine ylides (**1**, **1a**), are planar molecules with four π electrons distributed over the three-atom C–N–C unit. They are made up of one nitrogen atom and two terminal $sp^2$ carbons and exist in two resonating structures (Fig. 1). Many pharmacologically significant heterocyclic compounds are synthesised using this class of potent reagents in [1,3]-dipolar cycloaddition processes.[1]

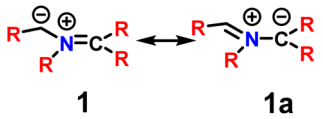



Fig. 1 Resonating structures of azomethine ylide.

[1,3]-Dipolar cycloaddition of azomethine ylides with alkene or alkyne (Fig. 2) is one of the most efficiently used techniques for the synthesis of a variety of pyrrolidine-based (**3**) bioactive compounds, such as organic catalysts, natural alkaloids, and building blocks in organic synthesis.[2] Furthermore, the cycloaddition reaction of non-stabilized azomethine ylides with olefinic dipolarophiles offers a method for the synthesis of

**Piyali Deb Barman**

*Dr Piyali Deb Barman earned her MSc degree in Organic Chemistry from IIT Kharagpur. She carried out her doctoral studies in the application of 1,3-dipolar azomethine ylide cycloaddition reactions as well as in enantioselective total synthesis of bioactive natural products and received her PhD in Organic Chemistry from Jadavpur University in 2014. Presently Dr Deb Barman is employed as a Senior Chemist in the Chemical Division of the Geological Survey of India (GSI), Eastern Region, Kolkata. Her current research is focused on elemental speciation and quantitative analysis of geological materials. She has published in several reputed international journals including Elsevier, Wiley and ACS.*

**Bhagat Singh**

*Dr Bhagat Singh completed his Master of Science in Chemistry at the University of Delhi in 2011. He earned his PhD in 2021 from the Indian Institute of Science Education and Research Kolkata, where his doctoral research focused on aryl carbon–halogen bond functionalization using phenalenyl-based radicals. Following his PhD, Dr Singh held a postdoctoral position at the University of North Carolina at Greensboro, USA (2022–2024). He subsequently pursued a second postdoctoral appointment with the Medicinal Chemistry Team at Wake Forest University, (2024–2025). He is currently undertaking his third postdoctoral position at Eastern New Mexico University, where he has been based since 2025.*

**Rupankar Paira**

*Dr Rupankar Paira earned his Master of Science degree in Organic Chemistry from the Indian Institute of Technology (IIT), Kharagpur. After that, he carried out his doctoral studies on bioactive N-heterocycles and graduated with a PhD degree from Jadavpur University, Kolkata. For his post-doctoral studies, he then went to National University of Singapore (NUS) and Nanyang Technological University (NTU), Singapore and worked on C–H activation chemistry. He is currently employed as an Assistant Professor at Maharaja Manindra Chandra College (affiliated to University of Calcutta). He has received the DST-SERB Young Scientist start-up award (YSS/2014/000877) in 2014, and also a UGC-MRP grant (ROMRP-ERO-CHEM-2015-16-68950) in 2015. He has published in several reputed journals including Elsevier, Wiley, RSC, and ACS.*

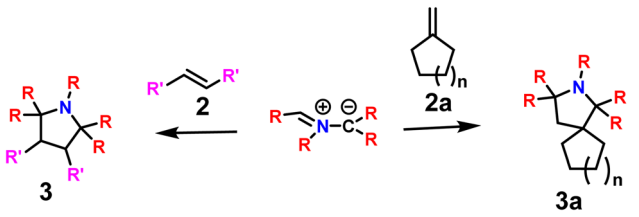



Fig. 2 General cycloaddition process of azomethine ylides.

numerous novel spiroheterocycles (**3a**), having stereoisomers with up to four additional chiral centres.[3–9] Scheme 1 delineates the overall key applications and the key advantages of the application of azomethine ylides. This review article will elucidate the significant uses of this potent moiety, which is primarily crafted in the twenty-first century, for the synthesis of different natural products as well as a number of other bioactive compounds (Table 1).

## 2. Application towards the synthesis of some natural products

### 2.1 (−)-Horsfiline

The plant *Horsfieldia superba* contains the oxindole alkaloid horsfiline (**4**), which is utilized in conventional herbal therapy. It has analgesic properties and has been studied for its synthetic production using simple techniques, as well as for the development of derivatives and analogues that may have better analgesic effects. Using chiral auxiliary-directed δ-face discrimination in an intermolecular [3 + 2] annulation of *N*-methylazomethine ylides with 2-(2-nitrophenyl) acrylate dienophiles **5**, Cravotto *et al.*[10] reported an effective asymmetric method for synthesizing (−)-horsfiline (Fig. 3).

The procedure outlined by Cravotto *et al.* was used to prepare the necessary dipolarophile.[10] Because of the quick availability of the chemicals, the process was straightforward, the reaction conditions were somewhat mild, and the product yields were high. Non-stabilized azomethine ylides were synthesised using the Tsuge route[11] (decarboxylation of R-amino acid iminium salts). Finally, in the presence of a chiral auxiliary-based dipolarophile, the azomethine ylide was reacted and the major product was the desired pyrrolidine (Fig. 4). The potential of the two-step cycloaddition/reductive heterocyclization protocol for the enantioselective synthesis of (−)-horsfiline was demonstrated by this discovery.

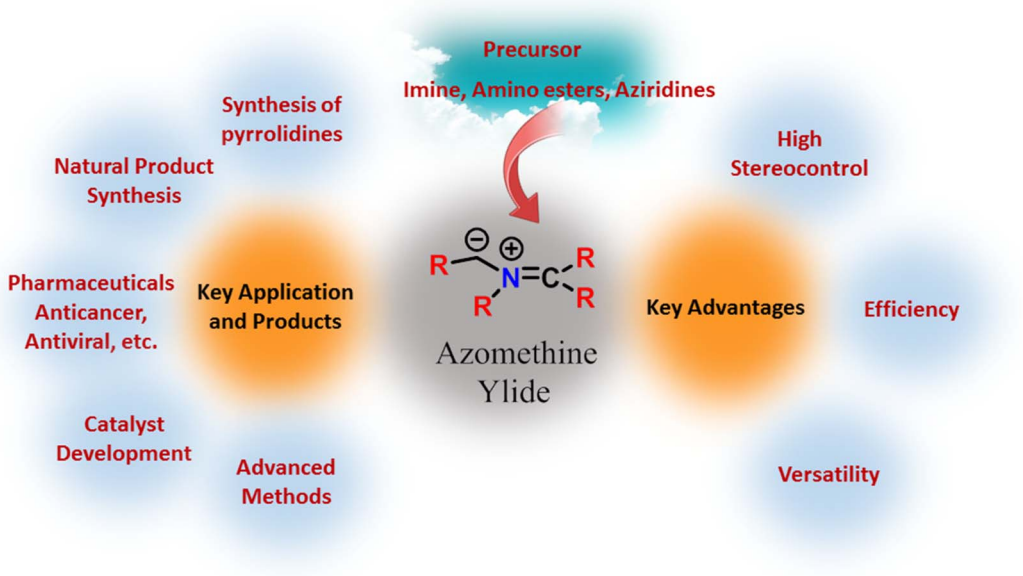
### 2.2 Spirotryprostatin B

The fungus *Aspergillus fumigatus* contains the indole alkaloid spirotryprostatin B (**7**) (Fig. 5). Due to their anti-mitotic qualities, spirotryprostatin B and a number of other indole alkaloids—including spirotryprostatin A, other tryprostatins, and cyclotryprostatins—have gained a lot of attention as potential anti-cancer medications.[12] Therefore, one of the main goals of organic chemists is the complete synthesis of this kind of chemical.

It was expected that an asymmetric [1,3]-dipolar cycloaddition reaction may be used to produce the core pyrrolidine ring in the production of spirotryprostatin B. The reaction of a chiral azomethine ylide (produced by reaction of **9** with **10**) with an oxindolylideneacetate **8** might generate four contiguous stereogenic centers in **11**, which was finally extended to **7** by Williams and co-workers (Fig. 6).[13]

### 2.3 Lamellarin

The alkaloid lamellarin (**12**) (Fig. 7) has a pentacyclic planar chromophore, namely, 6*H*-[1] benzopyrano[4′,3′:4,5]pyrrolo[2,1-




Scheme 1 Schematic representing the overall key applications and the key advantages of the application of azomethine ylides.

Table 1 Summary of the application of azomethine ylide

| S. no. | Compound no. | Reagents and conditions applied | Reference |
|---|---|---|---|
| 1 | **5** | Sarcosine, $(CH_2O)_n$, 3 Å MS, PhMe, reflux | 10 |
| 2 | **6** | $H_2$, 10% Pd/C, MeOH | 10 |
| 3 | **8** | 3A MS, toluene | 13 |
| 4 | **13** | DIPEA, 1,2-dichloroethane, 83 °C, 24 h | 14 |
| 5 | **14** | $AlCl_3$, DCM, rt, 12 h | 14 |
| 6 | **16** | HF·Py, THF, 50 °C | 15 |
| 7 | **20** | $AlMe_3$, toluene, 0 °C | 18 |
| 8 | **22** | *n*-BuLi | 18 |
| 9 | **25** | $N_2H_4 \cdot H_2O$, EtOH, reflux | 20 and 21 |
| 10 | **26** | $AlMe_3$, PhH, 0 °C | 20 and 21 |
| 11 | **28** | *n*-BuLi, −78 °C $H_2O$ | 20 and 21 |
| 12 | **31** | *n*-BuLi, $H_2O$ | 28 |
| 13 | **32** | $CH_2O$, HCl, $CH_3OH$ | 28 |
| 14 | **33** | HCl, mCPBA, heat | 28 |
| 15 | **34** | $Ms_2O$, Py CsOAc, DMF 18-Crown-6, 125 °C, MeOH, $K_2CO_3$ | 28 |
| 16 | **38** | *o*-DCB, 160 °C | 39 |
| 17 | **47** | $PhNHNH_2$, AcOH, 105 °C<br>$NaBH_4$, MeOH, 0 °C to rt | 44 |
| 18 | **52** | Acryloyl chloride, $Et_3N$, DCM | 45 |
| 19 | **59a**, **59b** | ClCbz, $K_2CO_3$, THF<br>Na(Hg), $Na_2HPO_4$ MeOH/THF | 47 |
| 20 | **63** | NBS/$CHCl_3$, heat *t*-butyl chloride, $Et_3N$, 0 °C | 49 |
| 21 | **67** | $Et_3N$, EtOH, RT | 50 |
| 22 | **72** | $NH_2CH_2CO_2H$, toluene<br>Camphor sulfonic acid, heat | 51 |
| 23 | **78** | $NH_2OH$, $^iPr_2NEt$, toluene, heat | 52 |
| 24 | **78** | $Cl \cdot NH_2CH_2CO_2Et$, $^iPr_2NEt$, toluene, heat | 52 |
| 25 | **83** | Sealed tube, heat | 53 |
| 26 | **88** | Toluene, reflux | 54 |
| 27 | **94** | 10 mol% bis-PA<br>Toluene, 3 A MS, 40 °C | 55 |
| 28 | **99** | Glycine, toluene, 110 °C | 58 |
| 29 | **103** | $Cu(MeCN)_4PF_6$, $Et_3N$<br>Ferrocene catalysts | 59 |
| 30 | **108** | Ag(I)F | 64 |
| 31 | **112** | PhMe, heat | 65 |
| 32 | **115** | CsF, THF | 66 |
| 33 | **127** | Cu(I)/DTBM-segphos<br>Toluene, 80 °C | 67 |
| 34 | **130** | Methyl acrylate hydrocinchonine (6 mol%)<br>AgOAc (3 mol%) MS4A, toluene, 0 °C | 68 |
| 35 | **133** | *Tert*-butyl acrylate<br>Ag(I) or Au(I) catalyst<br>Chiral phosphoramidite<br>$Et_3N$, toluene, RT | 69 |
| 36 | **138** | Toluene, heat | 70 |
| 37 | **142** | Bis-phosphoric acid (Bis-PA)<br>3A MS, toluene | 71 |
| 38 | **145** | $Cu(MeCN)_4PF_6$, DBU DCM, −20 °C | 72 |
| 39 | **149** | *N*-Methyl glycine/HCHO<br>Benzene, reflux | 74 |
| 40 | **154** | $CH_3I$, $CHCl_3$, reflux | 75 |
| 41 | **157** | HCHO, PhMe<br>AcOH, reflux | 76 |
| 42 | **160** | $CF_3CO_2H$, DCE, 60 °C<br>3A MS, toluene | 77 |
| 43 | **163** | Bis-phosphoric acid (Bis-PA)<br>3A MS, RT, toluene | 78 |
| 44 | **166** | 90 °C<br>Aqueous media | 79 |
| 45 | **171** | EtOH, AcOH, rt | 80 |
| 46 | **175** | MeCN, reflux | 81 |
| 47 | **183** | [bmin]Br, 100 °C | 82 |

Table 1 (*Contd.*)

| S. no. | Compound no. | Reagents and conditions applied | Reference |
|---|---|---|---|
| 48 | **190** | MeOH, MW, 100 °C | 84 |
| 49 | **194** | EtOH, 30 °C | 85 |
| 50 | **200** | MeOH, reflux | 86 |
| 51 | **205** | MeOH, reflux | 87 |
| 52 | **209** | EtOH | 88 |
| 53 | **213** | MeOH, reflux | 89 |
| 54 | **216** | MeOH, reflux | 90 |
| 55 | **219** | MeOH, heat | 91 |
| 56 | **224** | MeOH, reflux | 93 |
| 57 | **227** | MeOH, reflux | 94 |
| 58 | **229** | D-Proline catalyst | 95 |
| 59 | **233** | MeOH, reflux | 96 |
| 60 | **236** | Dioxane/MeOH, reflux | 97 |
| 61 | **240** | EtOH, reflux | 98 |
| 62 | **242** | ACI/EG, 40 °C | 99 |
| 63 | **246** | MeOH, reflux | 100 |
| 64 | **250** | MeOH, reflux | 101 |
| 65 | **252** | Isatins and sarcosine | 102 |
| 66 | **256** | MeOH, reflux | 103 |
| 67 | **258** | DMF, 70–90 °C | 104 |
| 68 | **262** | MeOH, reflux | 105 |
| 69 | **264** | $Cu(MeCN)_4PF_6$, $Et_3N$ | 106 |
| 70 | **269** | DBU, DCM, room temp | 107 |
| 71 | **271** | DBU | 108 |
| 72 | **274** | EtOH/toluene, 80 °C | 109 |
| 73 | **277** | THF, 80 °C | 110 |
| 74 | **281** | Acetonitrile, reflux | 111 |
| 75 | **285** | MeOH, reflux | 112 |

*a*]isoquinolinone. It can be cytotoxic to prostate cancer cells and to multidrug-resistant tumour cell lines. Therefore, to synthesize this important alkaloid, the solid-phase total synthesis of lamellarin L (**12a**) and lamellarin U (**12b**), the two naturally occurring alkaloids, was proposed by Cironi *et al.* in 2003 (ref. 14) (Fig. 8). Beginning with the Merrifield resin, an *in situ*-generated azomethine ylide **13** was produced from the solid-supported alkyne, which underwent an intramolecular [3 + 2] cycloaddition process to get the products. Cleavage of cycloadduct **14** with aluminium chloride produced **12a** and **12b** in an

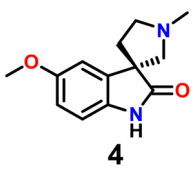



Fig. 3 (–)-Horsfiline.

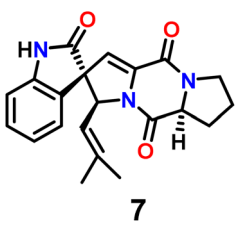



Fig. 5 Spirotryprostatin B.

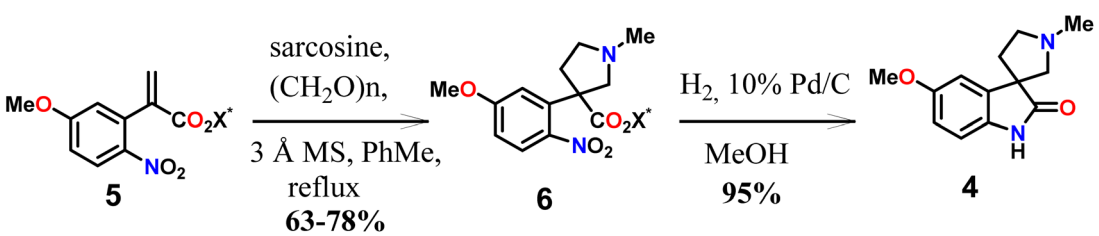



Fig. 4 Synthesis of (–)-horsfiline.

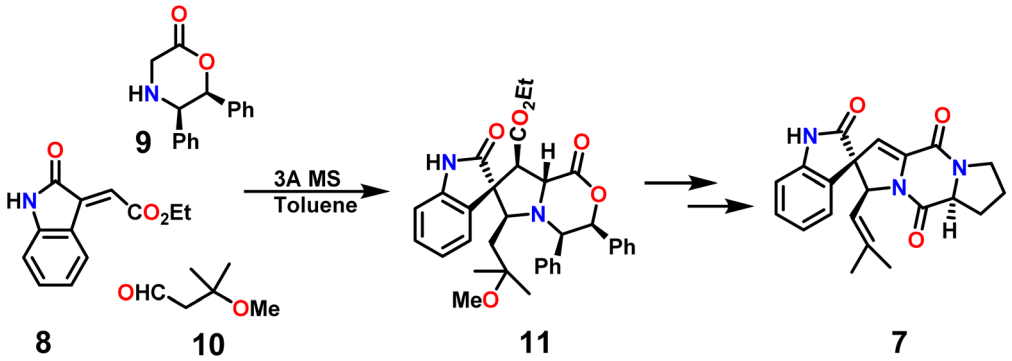



Fig. 6 Synthesis of spirotryprostatin B.

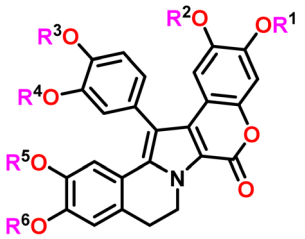



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Fig. 7 Lamellarin.

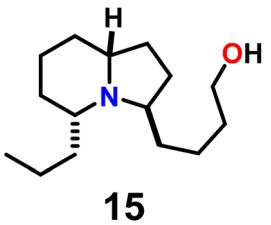

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Fig. 9 Indolizidine 239CD.

overall yield of 10% (R = Me, lamellarin L) and 4% (R = H, lamellarin U), respectively.

### 2.4 Indolizidine 239CD

In order to prepare azomethine ylides for the synthesis of indolizidine 239CD (**15**) (Fig. 9), Pearson *et al.*[15] investigated the utilisation of (2-azaallyl)stannanes **16**. After being treated with HF·pyridine,[16] (2-azaallyl)stannane yielded the extremely uncommon *N*-unsubstituted nonstabilized ylide **17**. Pyrrolidine (**18**) was obtained *via* cycloaddition with phenyl vinyl sulfone as a combination of regio- and stereoisomers (Fig. 10), all of which exhibit the 2,5-*trans* relationship on the pyrrolidine ring, which is a desirable outcome. The penultimate indolizidine 239CD (**15**) was then obtained in a few steps from **18**.

### 2.5 Lapidilectine B

The first member of this class of *Kopsia lapidilecta* alkaloids is known as lapidilectine B (**19**) (Fig. 11).[17] Pearson *et al.* most recently reported the first total synthesis of lapidilectine B (**14**) (Fig. 12).[18] Using stannane **22**, carbonyl compound **20** was converted to cycloadduct **23** in good yield through a one-flask imine formation/cycloaddition process. The desired natural product **19** was then obtained through functional group manipulation.

### 2.6 Lepadiformine

The ambiguity around the true stereostructure of the marine alkaloid lepadiformine[19] (**24**) has hindered its complete synthesis, which will be reported later on, as shown in Fig. 13. Lepadiformine skeleton was first synthesised by Pearson *et al.* using the 2-azapentadienyllithium cycloaddition technique[20,21] (Fig. 14). Amine **26** was produced *via* hydrazinolysis of phthalimide **25**, and it was condensed with ketone **27** to yield imine

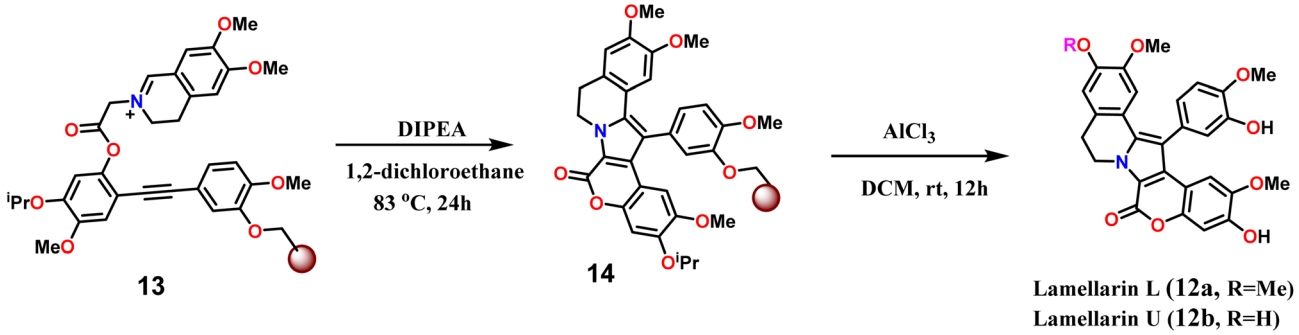


Fig. 8 Synthesis of lamellarin.

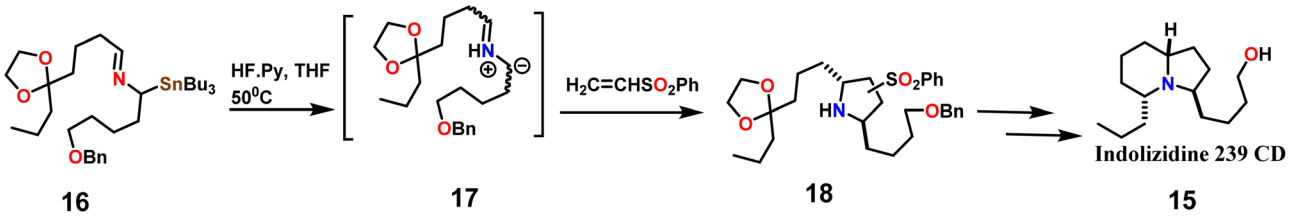


Fig. 10 Synthesis of indolizidine 239CD.

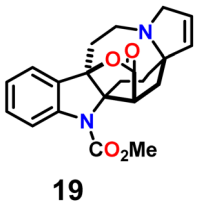


Fig. 11 Lapidilectine B.

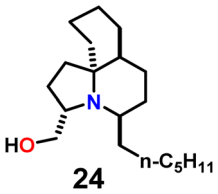


Fig. 13 Lepadiformine.

**28.** Pyrrolidine **29** was synthesised as a single isomer and in good overall yield from phthalimide *via* transmetalation of imine in the presence of phenyl vinyl sulphide. Three of the four potential diastereomers of lepadiformine could be produced at C2 and C13 *via* intramolecular reductive amination, oxidative cleavage of the propenyl side chain, and different functional group modifications. The fourth potential diastereomer was synthesised at those sites by Weinreb[22,23] and Kibayashi,[24] but none of these compounds were able to match the natural product. These findings led to the notion that lepadiformine was epimeric to the synthetic lepadiformine counterpart at the quaternary bridgehead position.[21] This theory has been confirmed through total synthesis by other researchers.[25–27]

### 2.7 Coccinine

Coccinine (**30**) (Fig. 15) is an alkaloid belonging to the 5,11-methanomorphanthridine class of alkaloids. Pearson *et al.*[28] synthesised this compound *via* intramolecular cycloaddition of an *in situ* generated 2-azaallyllithium with vinylsulfide (Fig. 16). Following an aqueous workup, perhydroindole **32** was produced. This was then subjected to a Pictet–Spengler cyclisation to provide the cyclized product **33**. After the sulfoxide was eliminated and the secondary alcohol was inverted, the desired coccinine alkaloid (**30**) was obtained.

This azomethine ylide cycloaddition method has been used to synthesise a number of other alkaloids in addition to the ones already mentioned, like crinine,[29,30] amabiline,[30,31] augustamine,[30,31] and 6a-epipretazettine.[32]

### 2.8 Mubironine C

*Dendrobium nobile* produces the sesquiterpenoid alkaloid dendrobine (**25**, Fig. 17), which is the main alkaloidal component of the Chinese folk remedy "Chin-Shih-Hu".[33–36] Although it is not mechanistically related to picrotoxinin, this lactonic tetracycle has analgesic, antipyretic, and convulsant properties.[37,38] There are also closely related congeners from comparable orchid species that differ more infrequently in the methanolysis of the lactone, as in mubironine C (**37**), or more frequently in the oxidation at the 2-position, as in dendrine (**36**).

Dendrobium Snowflake "Red Star" is the source of the alkaloid mubironine C. Trauner and colleagues devised the synthesis pathway by using an intramolecular 1,3-dipolar cycloaddition of an unstabilized azomethine ylide to detach the pyrrolidine ring. Their synthesis procedure started with *R*-carvone and proceeded in seven steps to the cyclisation precursor, which produced deoxymubironine C when it reacted with *N*-methylglycine *via* 1,3-dipolar cycloaddition (Fig. 18).[39]

### 2.9 Aspidospermidine

With over 250 naturally occurring alkaloids, the *Aspidosperma* alkaloids (Fig. 19) are the biggest family of monoterpene indole alkaloids.[40] They have been utilized in conventional therapies,

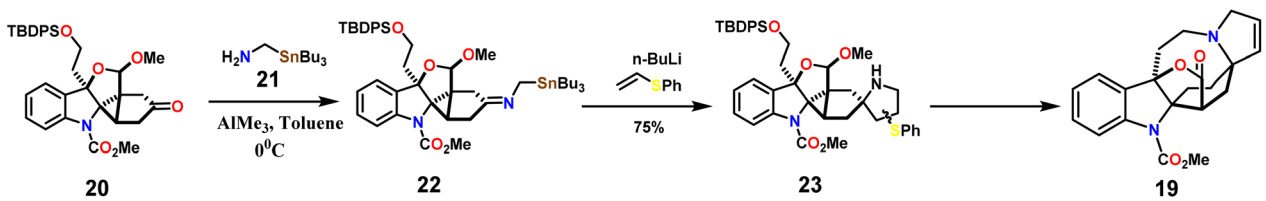


Fig. 12 Synthesis of lapidilectine B.

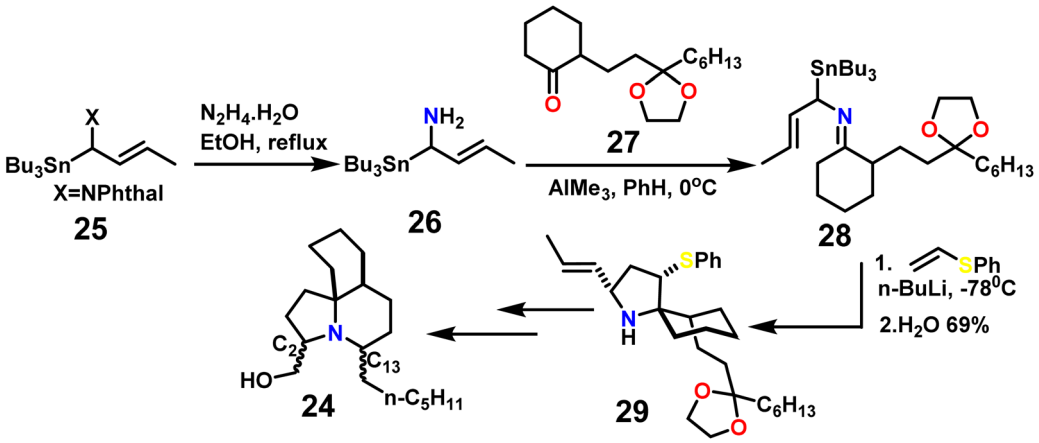


Fig. 14 Synthesis of lepadiformine.

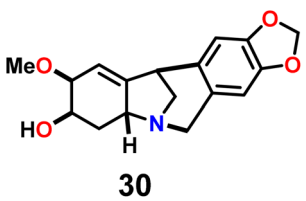


Fig. 15 Coccinine.

including anti-inflammatory and anti-cancer medications, and exhibit a range of biological actions.[41–43] This big family's parent chemical is pentacyclic aspidospermidine (**41**).

Its synthesis was started by alkylating δ-valerolactam **44** (Fig. 20) to yield lactam **46**. Tricyclic ketone **47** was produced through a reductive Michael addition/[3 + 2]cyclo-addition cascade catalysed by an iridium catalyst. Ultimately, the complete synthesis of aspidospermidine (**41**) was achieved after Fischer indole cyclisation, followed by $NaBH_4$ reduction.[44]

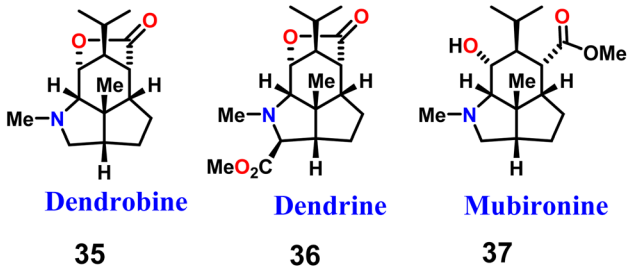


Fig. 17 Structures of mubironine and the related alkaloids.

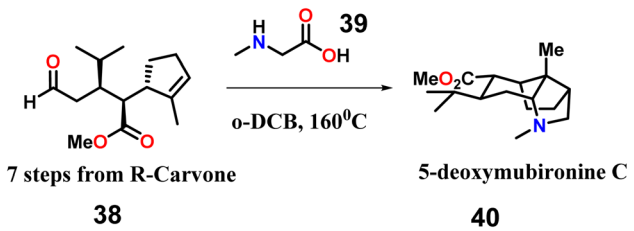


Fig. 18 Synthesis of deoxymubironine C.

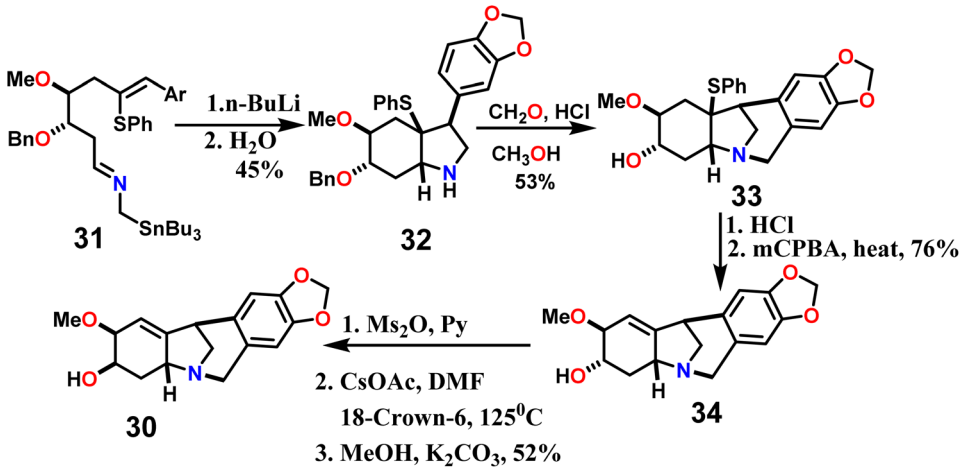


Fig. 16 Synthesis of coccinine.

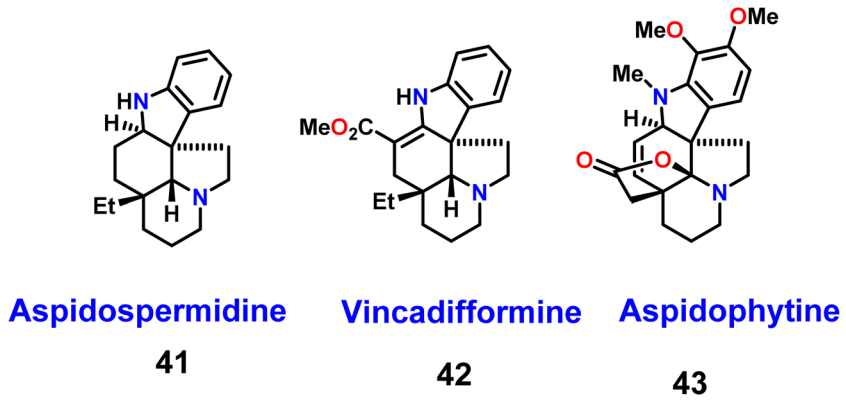


Fig. 19 *Aspidosperma* alkaloids.

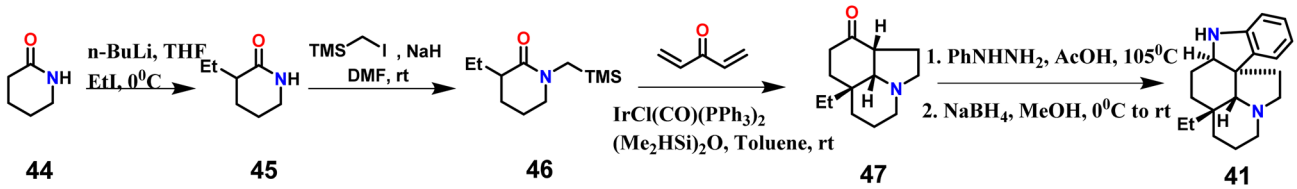


Fig. 20 Synthesis of the *Aspidosperma* alkaloids.

### 2.10 Pregnane (modified hybrid)

Using this method, Fedotcheva and associates created a modified hybrid using steroid pregnane as a chiral auxiliary. Starting with megestrol acetate (**49**), the study produced all of the novel hybrid compounds by modifying the C-3 pregnane position. An initial acryloylation produced **50**, which yielded **51** on stereoselective cycloaddition with stabilised *N*-metalated azomethine

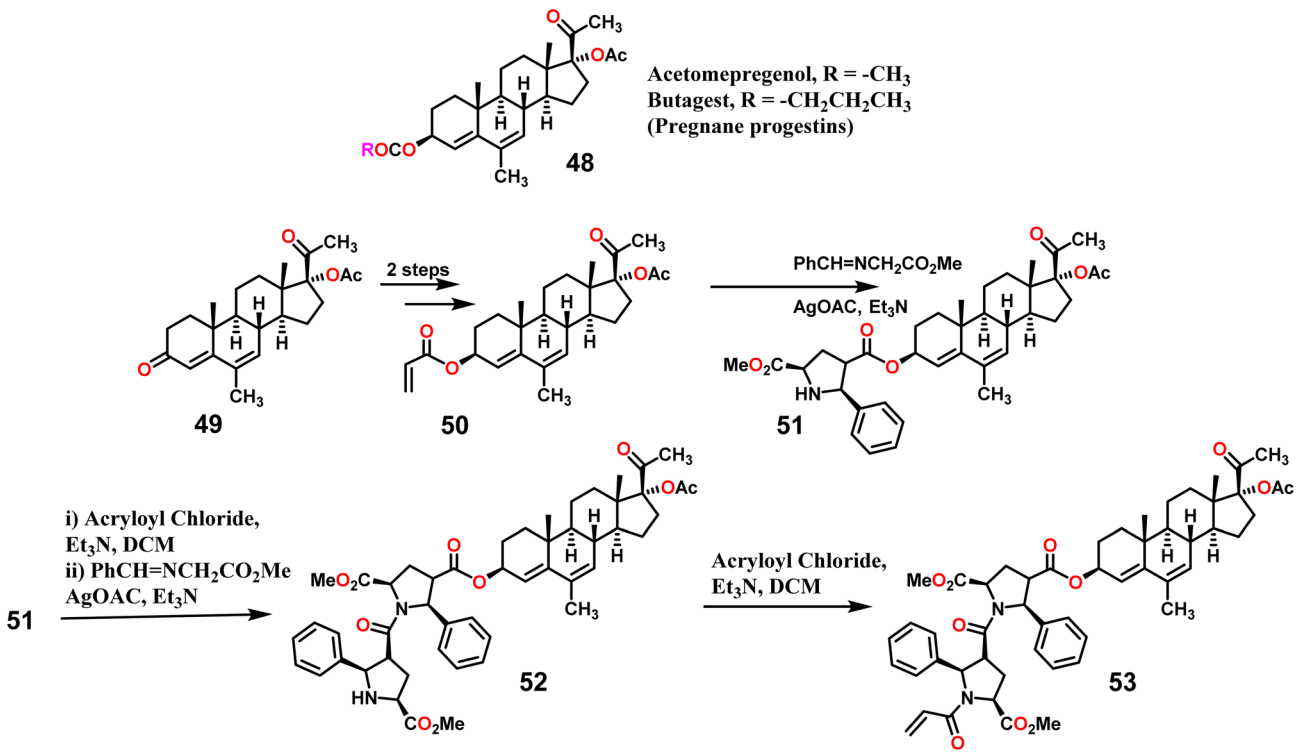


Fig. 21 Synthesis of pregnane (modified hybrid).

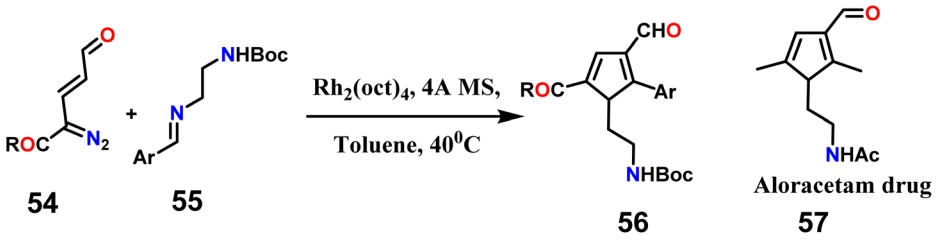


Fig. 22 Synthesis of the aloracetam analogue (modified hybrid).

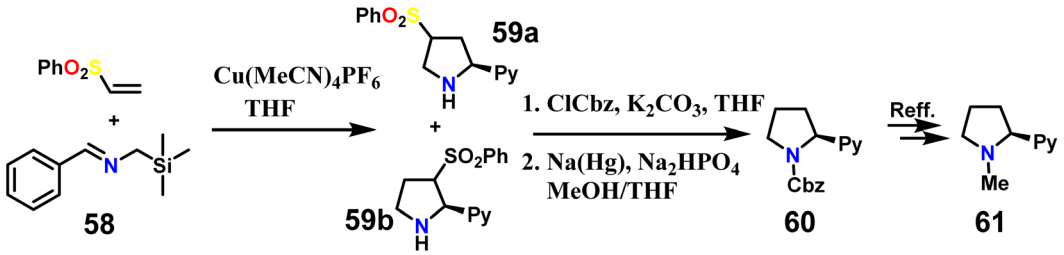


Fig. 23 Synthesis of nicotine.

ylide. On further repetition of these two steps, **52** was produced, which was again arylated to **53** (Fig. 21). The hybrids showed micromolar cytotoxic activity against breast carcinoma MCF-7 cell culture and human cervical epithelioid cancer HeLa cell culture in both natural and estradiol-stimulated forms. When compared with the hormonal tumour cells under study, the majority of hybrid chemicals were found to be less harmful to human skin fibroblasts (HSF).[45]

### 2.11 Aloracetam analogue (modified hybrid)

Mandal *et al.* reported the use of a novel class of enal-functionalized azomethine ylides (**54**, EAYs) in 2024 for the synthesis of an aloracetam analogue (Fig. 22). The Rh-catalyzed [3 + 2] annulation of ylide with *N*-alkyl imines (**55**) yielded tetrasubstituted *N*-alkyl pyrrole-3-carbaldehyde derivatives (**56**). Notably, despite the side chain's competing NH-insertion reaction, the *N*-Boc-protected 1,2-ethylenediamine-derived aldimine was able to provide pyrrole **56**, an analogue of the medication aloracetam (**57**), in 49% yield.[46]

### 2.12 Nicotine

The direct enantioselective synthesis of α-hetero-arylpyrrolidines using the [3 + 2] cycloaddition of hetero-arylsilylimines with activated alkenes has been demonstrated as a feasible and effective process by Javier and coworkers in 2014. With a broad range of azomethine precursors and di-polarophiles, strong enantioselectivity and moderate-to-high diastereoselectivity have been achieved using $Cu(CH_3CN)_4PF_6$ as the catalyst system. The cycloaddition of azomethine precursors **56**, with phenyl vinyl sulfone, also showed remark-able reactivity, yielding a mixture of both regioisomers **59a** and **59b** in 88% yield (Fig. 23),[47] which were then converted to **60**, the known precursor[48] for α-nicotine **61**.

### 2.13 Tetrazomine

Scott *et al.* described the synthesis (Fig. 24) of the powerful antitumor antibiotic tetrazomine for the first time in 2002. To obtain tetracyclic intermediate essential for the synthesis of tetrazomine, the synthetic protocol began with an anisole-derivative, **62**, to produce the allylic amine precursor **63**. An azomethine ylide was then created and utilised in an effective [1,3]-dipolar cycloaddition to give **64**, which lead to tetrazomine **65** in eight additional steps.[49]

### 2.14 Lamellarin skeleton

A novel, all-encompassing pathway (Fig. 25) to 1,2-diaryl-substituted pyrrolo[2,1-*a*]isoquinoline (**68**) has been estab-lished through the 1,5-dipolar electrocyclization processes of

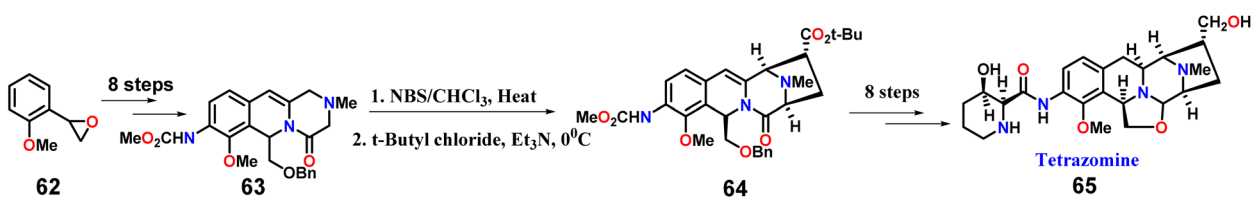


Fig. 24 Synthesis of tetrazomine.

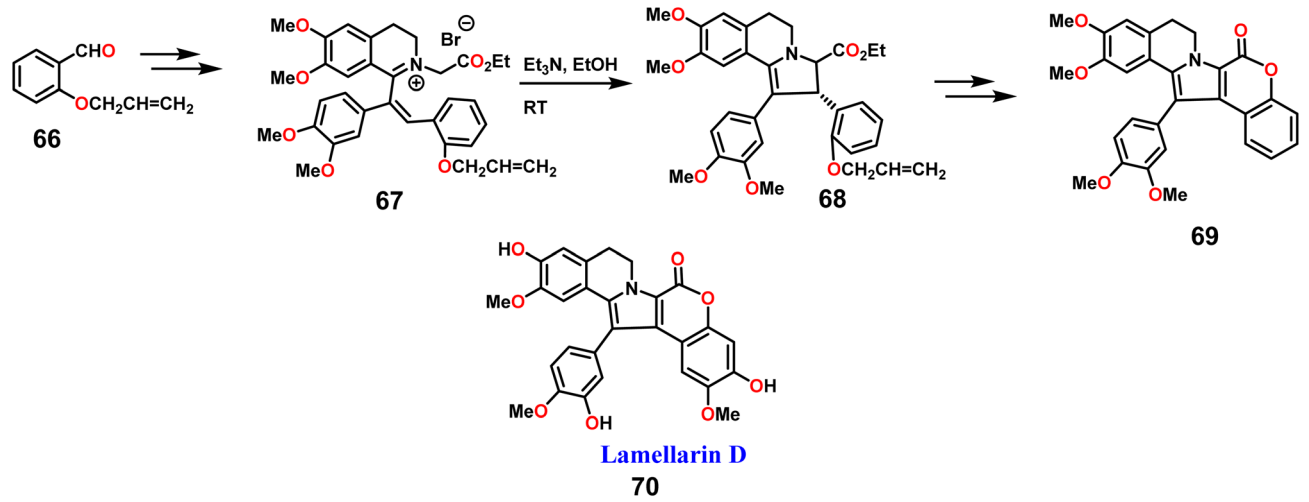


Fig. 25 Synthesis of the lamellarin skeleton.

azomethine ylide (**67**), which is obtained from easily accessible stilbenic acid (**66**). The lamellarin skeleton (**69**) was subsequently constructed from **68**.[50]

### 2.15 Aspidospermine, aspidospermidine, and quebrachamine

Through a tandem cyclization/cycloaddition cascade reaction, Coldham *et al.* reported the synthesis of three new rings while maintaining total control over stereochemistry and regiochemistry (Fig. 26). The protocol began with the conversion of a dibromoketone (**71**) into a precursor of a cyclic azomethine ylide (**72**). The formation of a cyclic azomethine ylide followed by an intramolecular cycloaddition onto the tethered alkene yielded the tricycle (**73**). This tricycle then further extrapolated to aspidospermine (**74**), aspidospermidine (**75**), and quebrachamine (**76**).[51]

### 2.16 Stemona alkaloid cores

In 2010, Burrell *et al.* demonstrated the synthesis (Fig. 27) of the stenine and neostenine core ring systems, which may be accomplished using the chemistry of cascade condensation, cyclisation, and cycloaddition. The study began with propyl nitrile (**77**), which was converted into an acyclic aldehyde (**78**). The stemona alkaloid cores (**79**, **80**) with an azepine ring bonded to a pyrrolidine and a cyclohexane ring were then produced from **78**.[52]

### 2.17 Quinocarcin core

In 2011, Huck *et al.* investigated whether azomethine ylides could be produced from **82**, through iminium salt, **83**. He described a catalyst-free dehydration method (Fig. 28) that produced *anti*- and *syn*-cycloadducts that included the quinocarcin core (**81**) and thereby unveiled a novel synthetic approach that enables access of hemiaminals **84** and **85** to yield highly functionalised cycloadducts.[53]

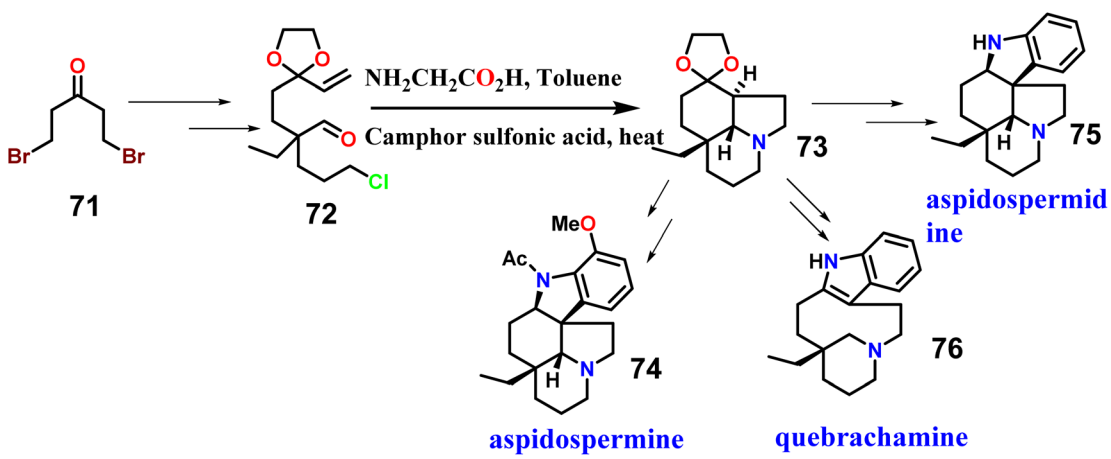


Fig. 26 Synthesis of aspidospermine, aspidospermidine, and quebrachamine.

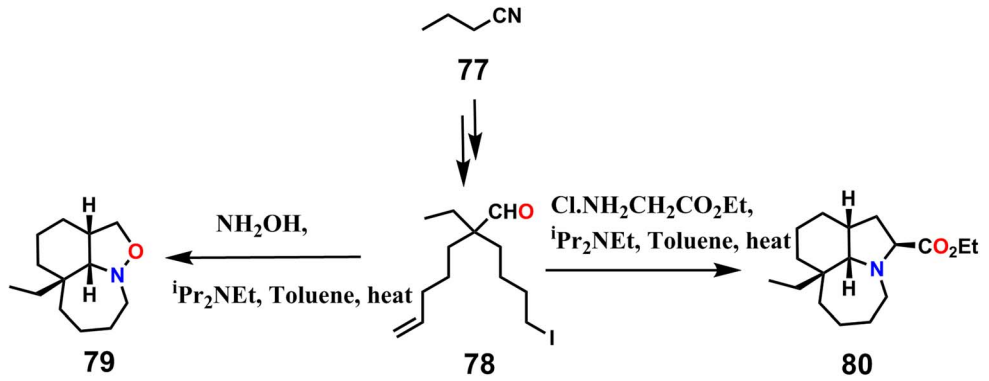


Fig. 27 Synthesis of *Stemona* alkaloid.

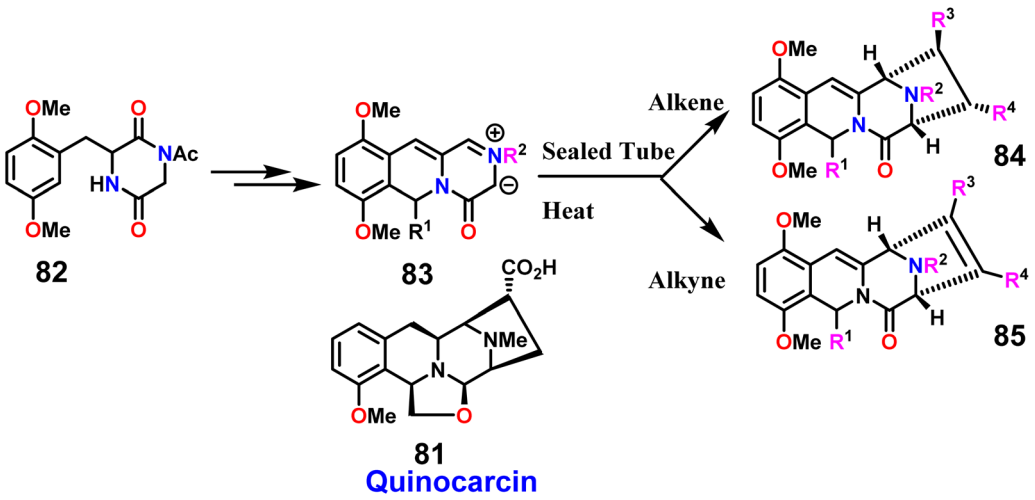


Fig. 28 Synthesis of the quinocarcin core.

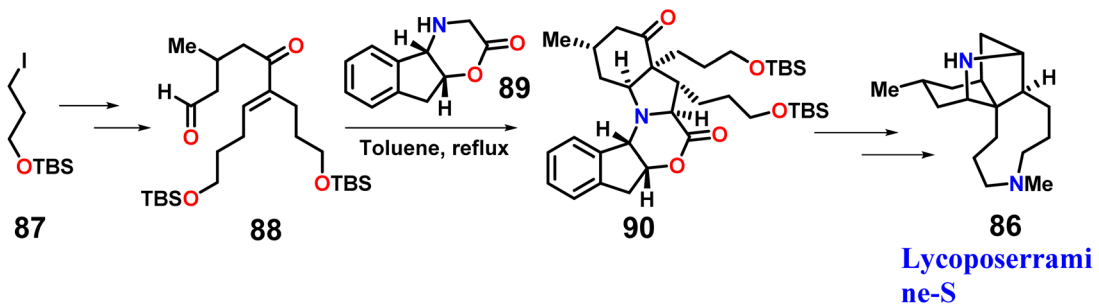


Fig. 29 Synthesis of lycoposerramine-S.

### 2.18 Lycoposerramine-S

The complete synthesis of lycoposerramine-S (**86**) from the known alkyl iodide **87** was described (Fig. 29) by Fukuyama and coworkers in 2012. They have achieved total synthesis in 14 stages. The azomethine ylide precursor **88** was first produced from **87** and reacted with **89**, which upon 5-*exo-trig* radical cyclisation and intramolecular 1,3-dipolar cycloaddition simply produced the desired polycycle **90**, which finally led to the production of lycoposerramine-S (**86**), in a few steps.[54]

### 2.19 18-Epispirotryprostatin A and 9,18-bis-epispirotryprostatin A

Cheng *et al.* (2011) have shown (Fig. 30) a 1,3-dipolar cycloaddition reaction between azomethine ylides and methyl 2-(2-nitro-phenyl)acrylate (**94**) that produces highly enantioenriched pyrrolidine derivatives (**95**). The cycloaddition was catalysed by

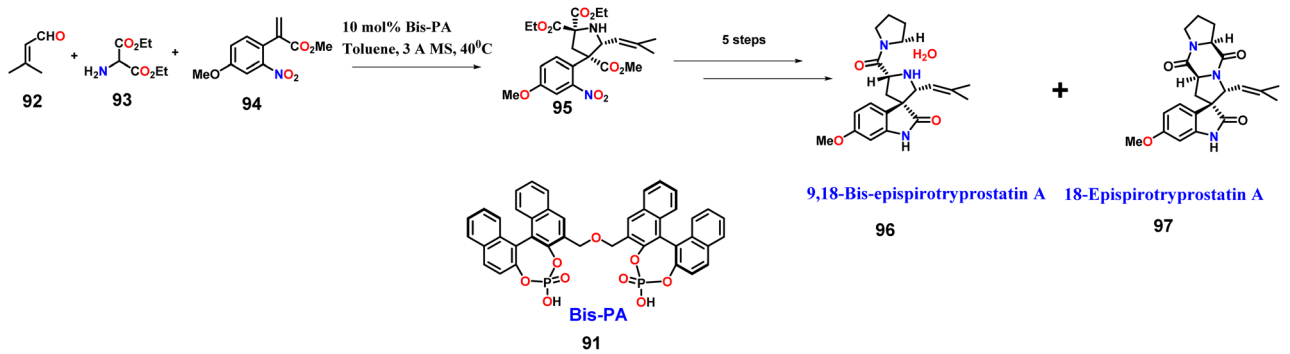


Fig. 30 Synthesis of the diastereoisomers of spirotryprostatin A.

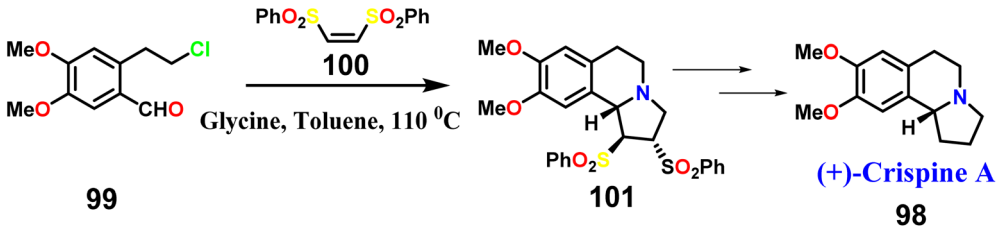


Fig. 31 Synthesis of the diastereoisomers of crispine A.

a bis-phosphoric acid derivative (**91**). The application of this process was demonstrated by the synthesis of diastereoisomers of spirotryprostatin A (**96** and **97**).[55]

### 2.20 (±)-Crispine A

In order to synthesise (±)-crispine A (**98**), Coldham *et al.* (2009)[58] utilised a cascade pathway of condensation–cyclization–cycloaddition process. The aldehyde (**99**) required for this method was first easily produced in two steps by following the described protocol.[56,57] After that, glycine and phenyl vinyl sulfone were initially used in the cascade chemistry; however the resultant mixture of two isomers produced the required cycloadduct in a low yield. Therefore, using the highly active bis-sulfone (**100**) as a dipolarophile, we performed the crucial step. In this instance, an enhanced yield (70%) of the intended product **101** was attained (Fig. 31), which was used to synthesize alkaloid crispine A in a few steps.[58]

### 2.21 Spirotryprostatin A analogue

Waldmann and coworkers, in 2011, synthesised the polycyclic spirotryprostatin scaffold (**102**) containing the 3,30-pyrrolidinyl-spirooxindole core in a highly enantioselective and high-yielding manner (Fig. 32). The cycloaddition step was facilitated by copper/ferrocene dual catalysis, which involved an isatin-type dipolarophile (**103**), to yield spiropyrrolidine **105**. The spirotryprostatin A analogue was then produced from **103** in a few steps. The synthesis is effective and very useful and provides easy access to a range of compounds inspired by natural products.[59]

### 2.22 Epibatidine

In 1992, Daly *et al.* isolated epibatidine (**106**), a novel alkaloid with the 7-aza-bicyclo[2.2.1]heptane ring system and a 6-chloro-3-pyridyl substituent in *exo* orientation,[60] from the skin extracts of Equadorian poison frogs, *Epipedobates tricolour*. It has been

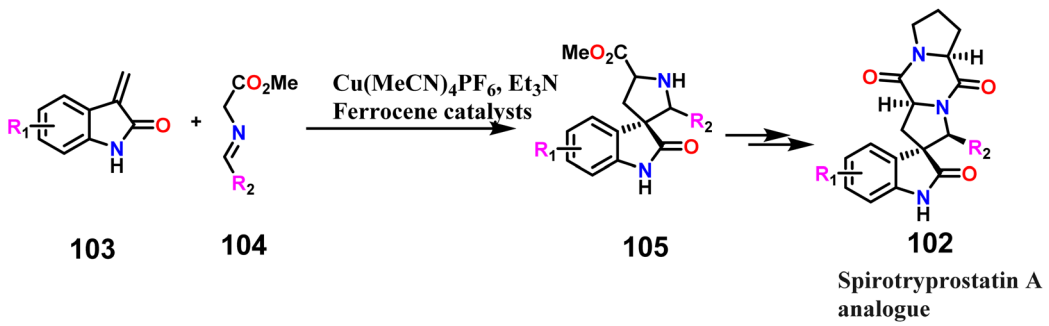


Fig. 32 Synthesis of the spirotryprostatin A analogue.

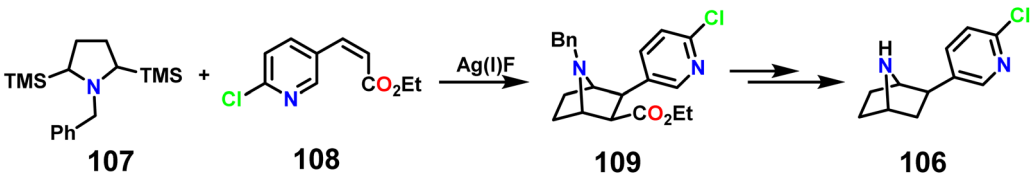


Fig. 33 Synthesis of epibatidine.

demonstrated to have 200–500 times the nonopiod analgesic activity of morphine. According to recent research, epibatidine is a very strong agonist of the acetylcholine receptors and has been implicated in the mediation of a number of human illnesses, including Parkinson's and Alzheimer's.[61–63] Therefore, to address this growing attention, its synthesis was attempted by Pandey and coworkers in a stereoselective fashion using the crucial step of [3 + 2] cycloaddition of azomethine ylide (Fig. 33). The methodology involves the use of a silver-catalysed cycloaddition step with a pyridine derivative (**108**) and an azomethine ylide generated *in situ* from **107**. The cycloadduct (**109**) was then extended to **106** in a few steps. This method has opened up the possibility of using it to synthesise the different analogues of **106** and homoepibatidine.[64]

### 2.23 Homoerythrina alkaloids

Pearson *et al.* described the synthesis (Fig. 34) of the demethoxy derivative of the homoerythrina skeleton (**110**) in 2007, as well as other synthetic attempts aimed at the complete synthesis of homoerythrina alkaloids. The study began with a monoprotected diol (**111**), which was converted to **112**, in a few steps for a tandem *N*-alkylation/azomethine ylide [3 + 2] cycloaddition reaction. The effective synthesis of the alkaloids' A–C rings is the crucial aspect of the syntheses. This crucial step involves *N*-alkylation with **113**, followed by the intramolecular cycloaddition of a tethered dipolarophile (**112**), yielding the demethoxy derivative of the homoerythrina skeleton (**110**).[65]

### 2.24 Rolipram

A novel method for the enantioselective synthesis of 1,3,4-trisubstituted and 1,4-disubstituted pyrrolidin-2-one derivatives was described by Olano and coworkers in 2001. The authors synthesized Fischer alkoxy alkenyl carbene complexes (**115**) from the different derivatives of menthol, which underwent 1,3-dipolar cycloaddition with functionalised azomethine ylides (**116**) to produce cycloadducts (**117**) as chelated tetracarbonyl Fischer carbene complexes. The cycloadducts then underwent oxidation and further transformations, which makes pyrrolidin-2-ones easily accessible. Using this methodology, the authors easily showcased (Fig. 35) its implication by producing the anti-inflammatory and depressive medication rolipram (**114**) in four steps with an overall yield of 20%.[66]

## 3. Application towards the synthesis of some synthetic bioactive pyrrolidines

Apart from the naturally occurring pyrrolidine and spiropyrrolidine-based products, azomethine ylide-mediated

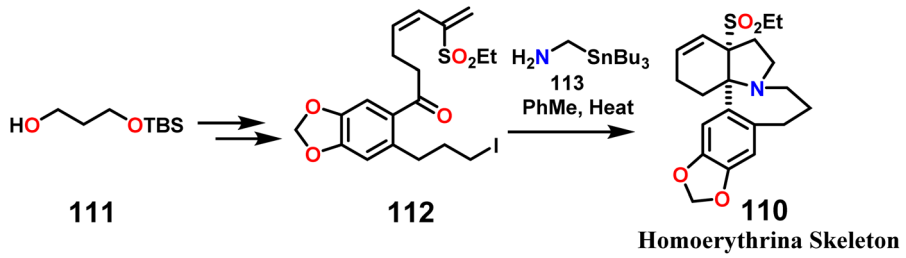


Fig. 34 Synthesis of the homoerythrina skeleton.

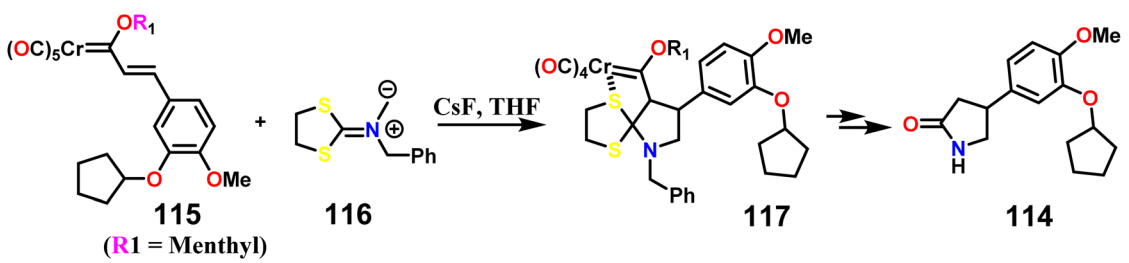


Fig. 35 Synthesis of rolipram.

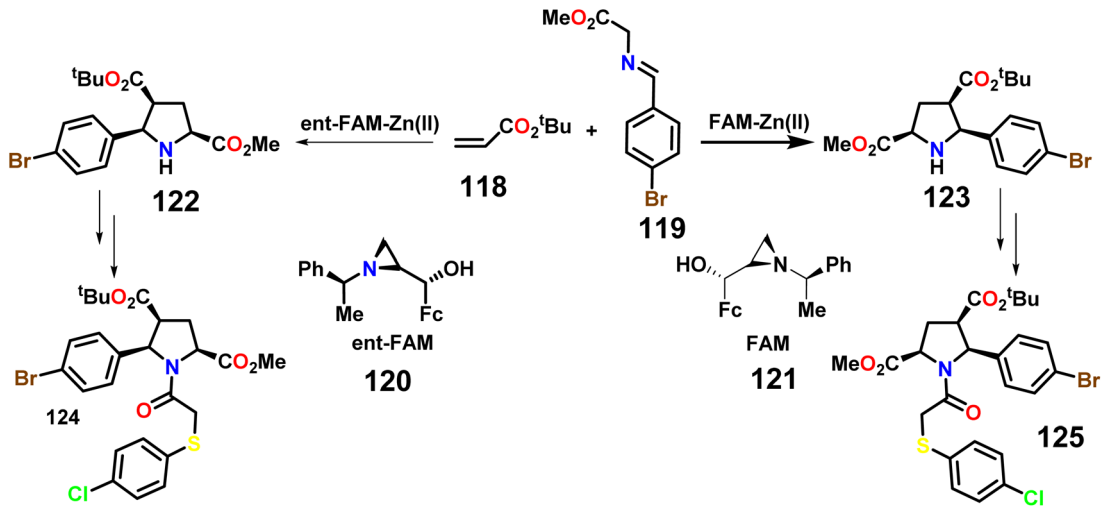


Fig. 36 Synthesis of the enantiomerically pure pyrrolidine derivatives with potential antithrombin activity.

cycloadditions also provide a simple and modular pathway to highly substituted and enantiomerically enriched lab-grown pyrrolidines and spiropyrrolidines of immense biological significance. These synthetic molecules are generally produced from azomethine ylides of imines or isatins with dipolarophiles, such as acrylates or maleimides.[2–9] Aryl-based dipolarophiles have been of keen interest to a number of potentially active research groups in recent years.

For example, Ayan *et al.* (2013) described (Fig. 36) the development of a successful synthetic route for phenylpyrrolidines (**122**, **123**) using enantiopure organocatalysts (**120**, **121**). These pyrrolidines were then converted into putative chiral ligands (**124**, **125**) using a structure-based methodology.

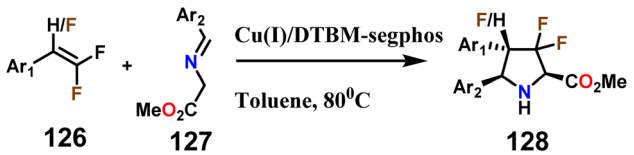


Fig. 37 Synthesis of the antifungal fluorinated pyrrolidines.

The usefulness of this chemical class for the development of selective thrombin inhibitors is indicated by the bioinformatic approaches used to clarify the ligand–enzyme interactions between well-defined pyrrolidines **124** and **125** and the thrombin/trypsin pair.[67]

Also, very recently in 2022, Teng and coworkers created a variety of new chiral 3,3-diuoro- and 3,3,4-triuoropyrrolidinyl derivatives (**128**) by asymmetrically adding arylated azomethine (**126**) ylides to less-active 1,1-*gem*-difluoro/1,1,2-trifluorostyrenes (**126**) *via* a Cu(I)-catalyzed 1,3-dipolar cycloaddition (Fig. 37). High yields (up to 96% yield), stereoselectivity (up to >20 : 1 dr and 97% ee), and a wide substrate scope (55 instances) are characteristics of this technology. Antifungal experiments were used to assess the biological activity of these recently synthesised compounds, and some of these fluorinated pyrrolidines showed excellent antifungal activity against *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Pestalotiopsis*, and brown-rot fungi.[68]

Apart from these, uses of heteroaryl-substituted azomethine ylides have also been reported. Using AgOAc and hydrocinchonine (**129**), Xie and colleagues, in 2008, created an operationally straightforward catalytic system. In this

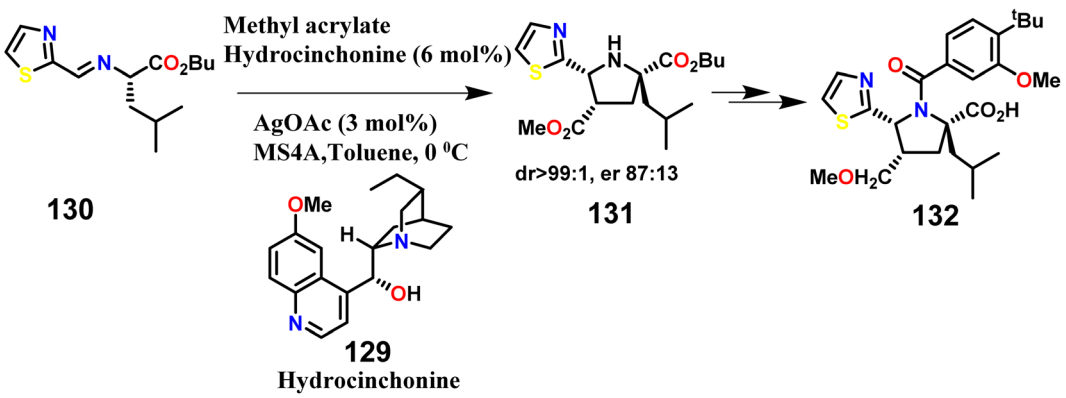


Fig. 38 Synthesis of the HCV polymerase inhibitors.

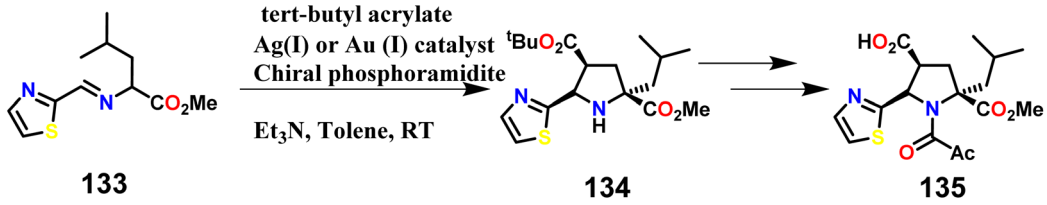


Fig. 39 Synthesis of the second-generation inhibitor of hepatitis C virus.

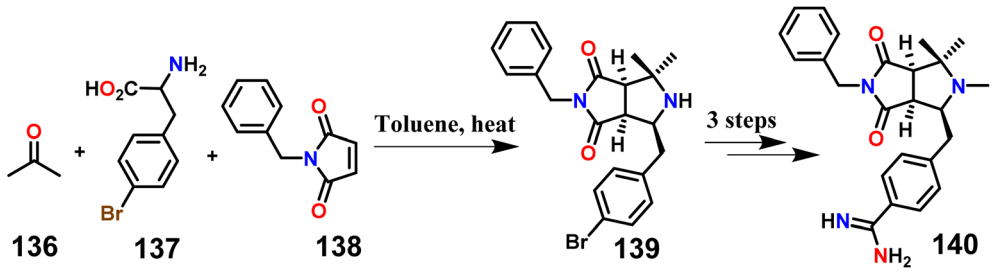


Fig. 40 Synthesis of the selective thrombin inhibitors.

methodology, thiazole-based azomethine ylide was prepared from **130** and reacted with methylacrylate to yield pyrrolidine core **131**, which was extended to **132**, a HCV polymerase inhibitor. This asymmetric synthesis was also performed in multikilogram scale (Fig. 38).[69]

Later in 2011, a similar report was published by Cossío and coworkers, where enantioselective 1,3-dipolar cycloaddition involving a leucine-derived iminoester (**133**) and *tert*-butyl acrylate was used to synthesise a second-generation inhibitor of hepatitis C virus (Fig. 39). Using chiral phosphoramidites or chiral BINAP in the presence of silver(I) and gold(I) catalysts in this reaction, pyrrolidine (**134**) was produced in high yields. When extended, the hepatitis C virus inhibitor (**135**) was synthesised in four steps under optimal reaction conditions, resulting in a 63% overall yield and 99% ee. DFT simulations also supported the origin of the chiral gold(I) catalyst's enantioselectivity, with one of the gold atoms and the nitrogen atom of the thiazole moiety forming a stabilising coulombic connection.[70]

Similar aryl-based azomethine ylides can also be generated *in situ* and be further reacted in the medium to produce the desired pyrrolidine core. For example, the 1,3-dipolar cycloaddition between an *N*-substituted maleimide (**138**) and an azomethine ylide, which is made *in situ* using the decarboxylative technique from a carbonyl compound (**136**) and an a-amino acid (**137**), is a crucial step in the synthesis of pyrrolidine, **139**, which in three steps yields **140**, a new class of nonpeptidic, active, and selective thrombin inhibitor (Fig. 40). The compounds were also tested for activity against the related serine protease trypsin in biological assays.[71]

Another three-component reaction involving aldehydes (**141**), amino-esters (**142**), and substituted alkyl (**143**) catalysed by phosphoric acid was reported in 2011 by Tu and coworkers, which was used to create a number of novel chiral 2,5-dihydropyrrole derivatives (**144**) with strong enantioselectivity. High enantioselectivity (up to 98% ee), atom economy, a wide range of substrate tolerance, and operational simplicity are the main characteristics of this method, which make it easy and

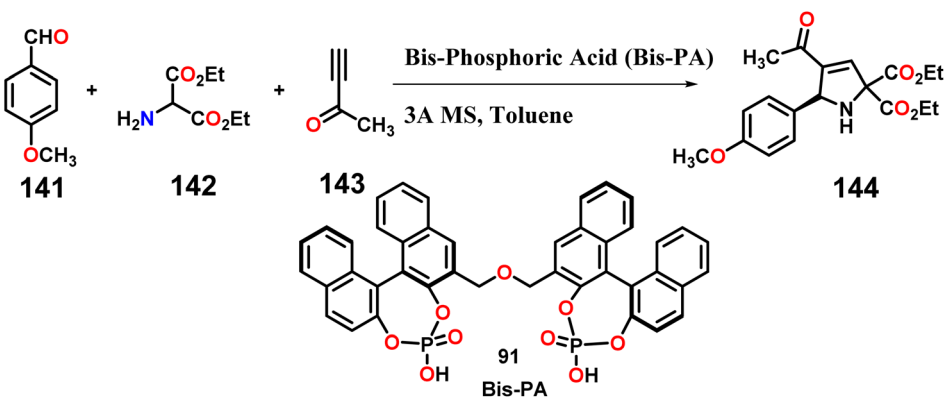


Fig. 41 Synthesis of the anticancer pyrrolidines.

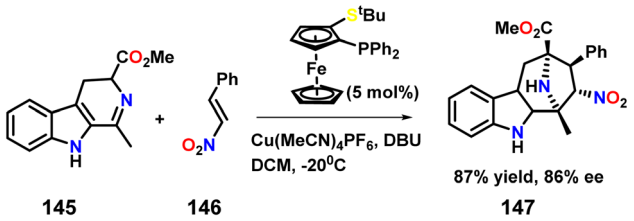


Fig. 42 Synthesis of a novel hedgehog-signaling inhibitor.

simple to obtain biologically significant chiral 2,5-dihydropyrroles. Furthermore, a number of compounds with effective cytotoxicity to the cancer cell line MCF7 have been identified as a result of the initial assessment of the cytotoxic activity of this class of chiral 2,5-dihydropyrrole derivatives (Fig. 41).[72]

Another interesting case of aryl-substituted azomethine ylide was reported (Fig. 42) by Waldmann and coworkers in 2013, where an effective ferrocene/Cu dual catalysis led to highly diastereoselective and enantioselective [3 + 2] cycloaddition process of 1,3-fused cyclic azomethine ylides (**145**) with nitroalkenes (**146**) to yield azabicyclo-octanes (**147**). In their report, an S-shaped azomethine ylide was successfully employed in an enantioselective catalytic method for the first time. The authors also investigated their hedgehog-signaling inhibitory activities and found them to be highly potent.[73]

Apart from aryl-substituted azomethine ylides, the utilization of other categories of such 1,3-dipoles has also been reported. For example, Hanessian *et al.* in 2005 described a synthetic route for a peptide-linked pyrrolidine in an enantiopure form (Fig. 43). The process began with R-amino aldehyde (**148**) originating from L-leucine, which led to the azomethine ylide precursor **149**. A subsequent 1,3-dipolar addition then produced pyrrolidine **150**, which was further elaborated to link a dipeptide to achieve the intended prototype pseudopeptide inhibitor **151**. Its inhibitory activity against BACE1, an enzyme implicated in the cascade of events leading to plaque formation in Alzheimer's disease, was found and later further tuned with pyrrolidinone analogues, which showed low nanomolar inhibition.[74]

Another interesting case was reported by Menon and coworkers in 2013, where cationic fullerene–s-triazine conjugates were synthesized (Fig. 44), which may cleave supercoiled DNA when exposed to photoirradiation and NADH. Starting from a triazine (**152**), the azomethine ylide precursor **153** was achieved in a few steps, which upon cycloaddition with C60 produced the fullerene conjugate (**154**). Further reaction with MeI led to the production of cationic fullerene–*s*-triazine, **155**. The mechanism of fullerene-conjugate binding over the minor groove of DNA was further comprehended through computational modeling. The docked conformation was found to be in good agreement with the obtained experimental data. In the area of DNA cleavage by this new class of fullerene–*s*-triazine derivatives, this discovery presents intriguing opportunities.[75]

Also, macrolides can be functionalized with the help of azomethine ylides to produce bioactive pyrrolidines. For example, Gu *et al.* reported (Fig. 45) a stereoselective route towards novel antibacterial agents *via* an azomethine ylide in 2004.[76] In this process, the macrolide **156** was first converted to **157**, which then underwent (3 + 2) cycloaddition intramolecularly to yield **158**.

## 4. Application towards the synthesis of some synthetic bioactive spiropyrrolidines

Bioactive spiropyrrolidines are often produced by using 1,3-dipolar cycloaddition of azomethine ylides with an exocyclic double/triple bond. Pairing an isatin derivative and an α-amino acids or an amine is quite common and effective. In a single

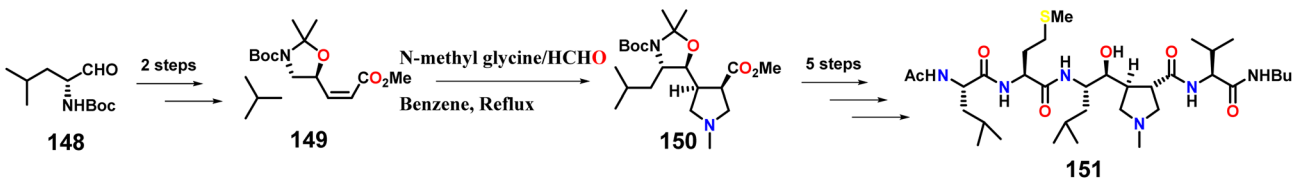


Fig. 43 Synthetic route for a BACE1 inhibitor.

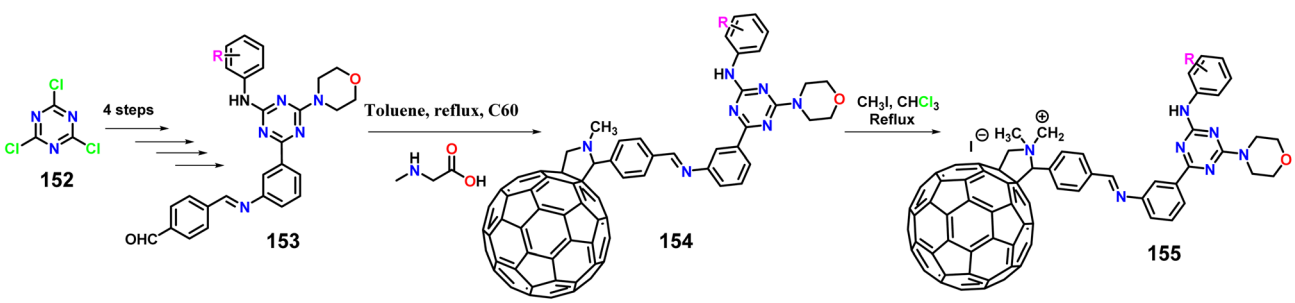


Fig. 44 Synthesis of the cationic fullerene–*s*-triazine conjugate DNA binder.

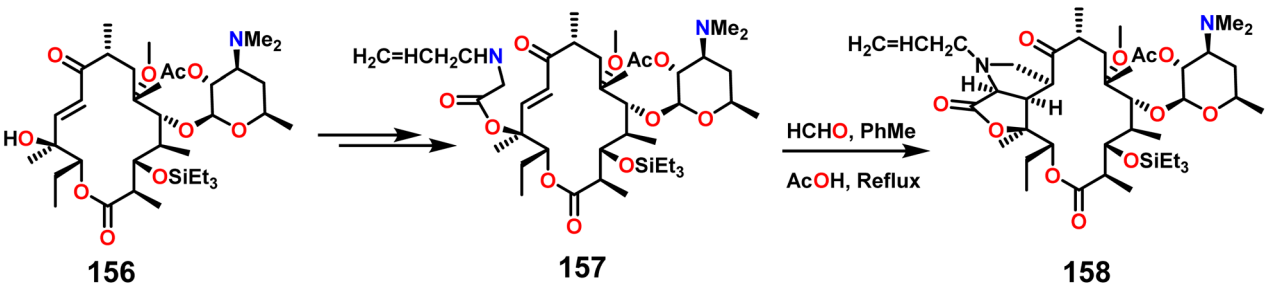


Fig. 45 Synthesis of the novel macrolide antibacterial agents.

step, azomethine ylide forms highly functionalized spiro-pyrrolidine frameworks *via* cycloaddition to electron-deficient alkenes as a reactive dipole.

### 4.1 Isatin-based azomethine ylides

In 2013, an effective three-component reaction (Fig. 46) of isatin (**159**), amino-ester (**160**) and alkyne (**161**) was reported by Shi and coworkers to produce a 2,5-dihydropyrrole scaffold based on spiro-oxindole (**162**) with potential bioactivity. This procedure is the first 1,3-dipolar cycloaddition of electron-deficient alkynes with azomethine ylides generated from isatin. It offers a simple way to obtain structurally diverse 2,5-dihydropyrroles based on spiro-oxindole in high yields (up to 99%). Additionally, sixteen compounds with promising cytotoxicity to MCF-7 cells were discovered *via* bio-screening of novel spiro-dihydropyrroles.[77]

However, the employment of alkenyl dipolarophiles to synthesize bioactive scaffolds is much more abundant than that of alkenyl dipolarophiles. In this context, another interesting report was published in the previous year by the same group, where they had utilized alkene (**164**), instead of alkyne. They reported an organocatalytic 1,3-dipolar cycloaddition of isatin (**163**)/amino-ester (**160**)-based azomethine ylides (Fig. 47), which has been used to establish the catalytic asymmetric construction of a biologically significant spiro[pyrrolidin-3,2′-oxindole] scaffold (**165**) with contiguous quaternary stereogenic centres in excellent stereoselectivities (up to >99 : 1 d.r., 98% ee). In order to comprehend the stereochemistry, theoretical calculations were also carried out on the reaction's transition state. Using these spiro[pyrrolidin-3,2′-oxindole], preliminary bioassays demonstrated that a number of compounds exhibited considerable cytotoxicity to SW116 cells.[78]

Galvis *et al.* (2013) replaced aliphatic alkene dipolarophiles with its aryl variant and developed a highly regio- and stereoselective method for the synthesis of a 20-membered library of spirooxindole 1′-nitro pyrrolizidines (**169**) in aqueous media through the 1,3-dipolar cycloaddition of azomethine ylides (Fig. 48). The ylides are produced *in situ via* a decarboxylative

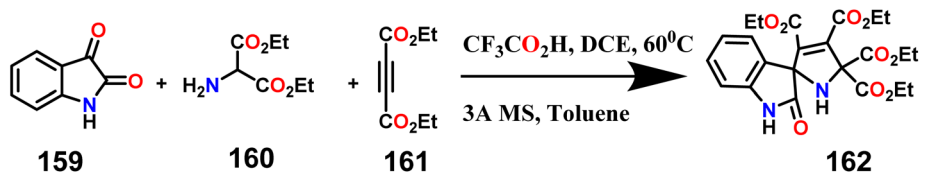


Fig. 46 Synthesis of the 2,5-dihydropyrrole scaffolds.

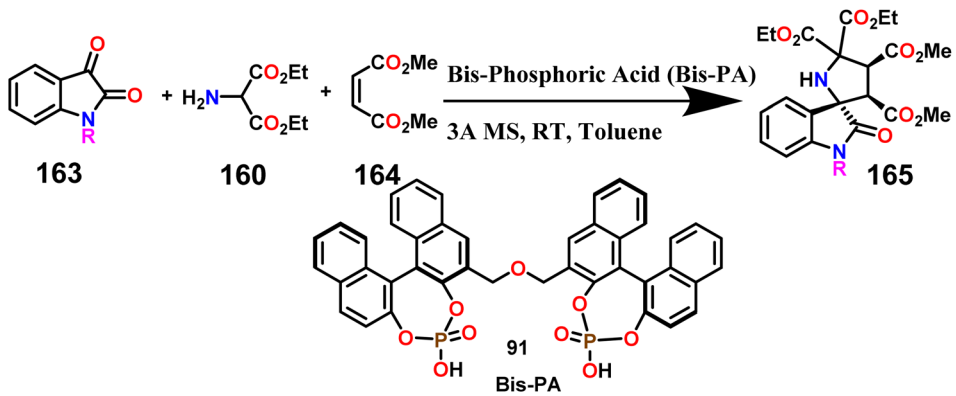


Fig. 47 Organocatalytic synthesis of the spiro[pyrrolidin-3,2′-oxindole] scaffolds.

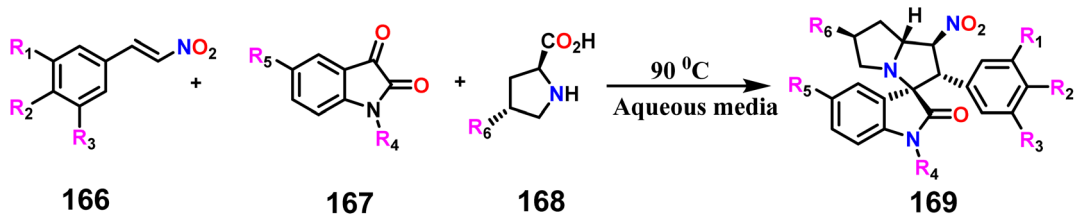


Fig. 48 Synthesis of spirooxindole 1′-nitro pyrrolizidines.

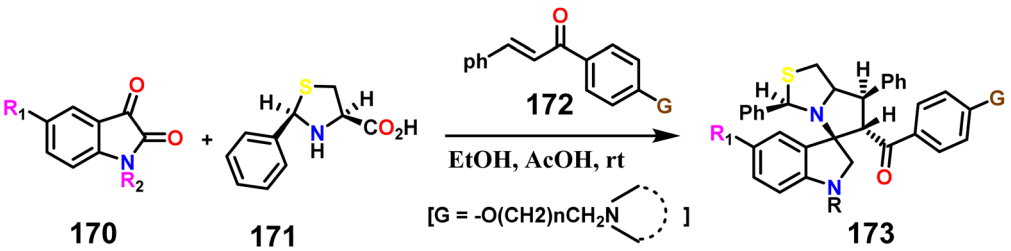


Fig. 49 Synthesis of spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles].

route from a common set of diverse isatins (**167**) and L-proline derivatives (**168**) and reacted with substituted β-nitrostyrenes (**166**). The products were tested with Zebrafish embryos to determine their ADME properties and $LC_{50}$. They were also subjected to computational studies to (i) determine the ADME properties using Lipinski's rule, (ii) screen the toxicological profile, and (iii) forecast the synthetic compounds' ability to pass through the blood–brain barrier (BBB).[79]

In the same year, Kumar *et al.* reported an easy-to-follow and regioselective protocol for the efficient synthesis of a novel series of spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazoles] (**173**) in good yield (65–85%) from the reactions of isatins (**170**), thioprolene (**171**) (Fig. 49) and substituted chalcones (**172**) using a catalytic amount of acetic acid as a catalyst in ethanol at room temperature. The anti-proliferative properties of all the synthesized compounds were evaluated *via* MTT assay against three breast cancer cell lines: MDA-MB-231, T47D, and MCF-7. The majority of the substances that were synthesised exhibited notable anti-cancer properties.[80]

Similar reaction with thioprolene was also reported in 2016 by Cao and coworkers to synthesize a new class of isoxazole-functionalised spiropyrrolidine-fused oxindoles (**179–181**)

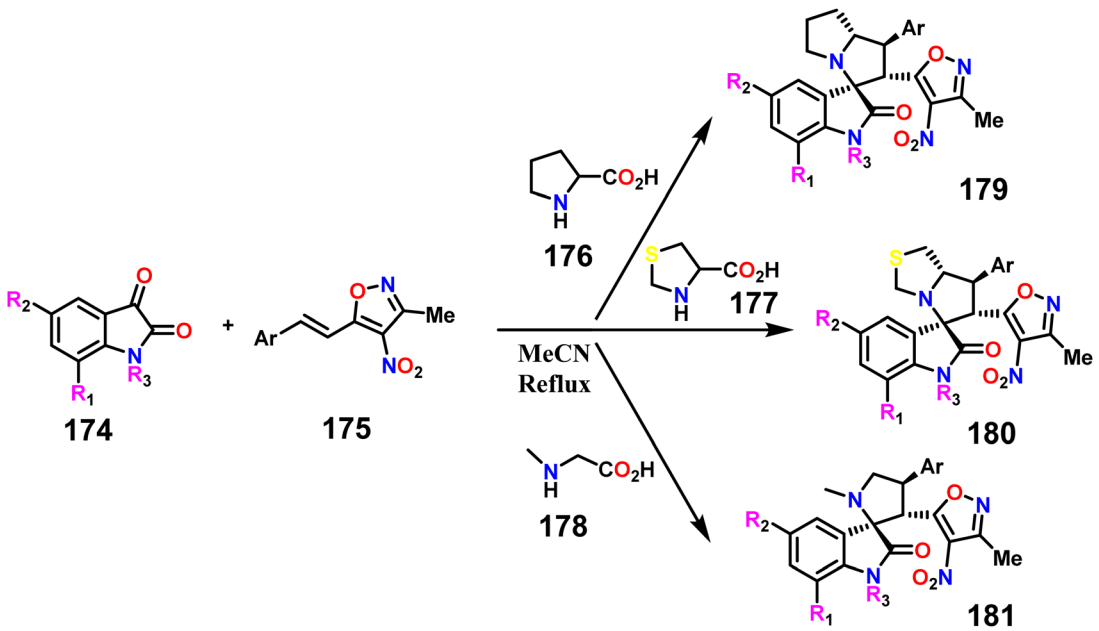


Fig. 50 Synthesis of the isoxazole-functionalised spiropyrrolidine-fused oxindoles.

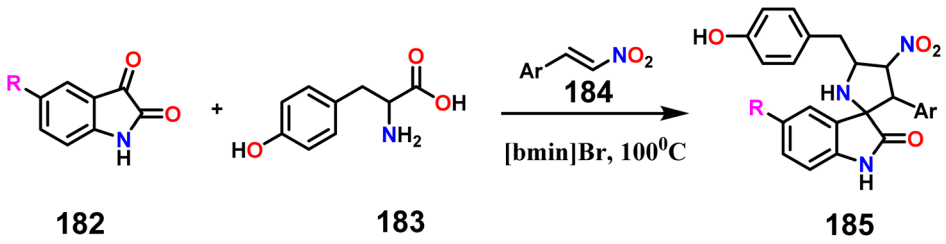


Fig. 51 Synthesis of 3-(aryl)-5-(4-hydroxybenzyl) spiro[indoline-3′,2-pyrrolidin]-2′-ones.

without the use of a catalyst (Fig. 50). The reaction was done between substituted isatins (**174**), isoxazole derivative (**175**) and L-proline (**176**)/thioprolene (**177**)/*N*-methylglycine (**178**) in acetonitrile under refluxed conditions at 80 °C (Fig. 50). The synthesised products were also shown to be highly effective against all the tested cancer cell lines, such as lung (A549), prostate (PC-3), and leukaemia (K562) cancer cells.[81]

Later in 2019, Kumar *et al.* described the synthesis of several 3-(aryl)-5-(4-hydroxybenzyl)spiro[indoline-3′.2-pyrrolidin]-2′-ones (**185**) in excellent yields (88–94%) in just one hour using [3 + 2] cycloaddition reactions of substituted isatins (**182**), tyrosine (**183**), and nitrostyrenes (**184**) in the presence of ionic liquid ([bmim]Br) at 100 °C (Fig. 51). The anti-cancer activity of the cycloadducts (**185**) against the lung cancer cell line A549 was found to be nearly identical to that of the reference medication, camptothecin.[82]

In the same year, Biju *et al.* constructed a unique spiro(-oxindole-3,2′-pyrrolidine) scaffold (**188**) with a broad range of biological activity. The traditional 1,3-dipolar cycloaddition reaction of azomethine ylide, made *in situ* from isatin (**186**)/*N*-methylglycine (**178**), with heterocyclic ylidenes (**187**) has been used to create a number of these compounds with heterocyclic rings joined to the pyrrolidine unit (Fig. 52). Cell toxicity and anticancer efficacy of these entitied were assessed and it has been found that, by activating the pro-apoptotic genes p53 and caspase 7, they demonstrated strong anticancer action while remaining non-cytotoxic up to 100 mg $ml^{-1}$.[83]

There have also been reports on the intramolecular cyclisation of azomethine ylides that allow the targeted synthesis of structurally complex and highly functionalised spiro-oxindoles (**193**), particularly access to octahydropyrrolo[2,3-*c*]pyrrol-4-ones and octahydro-pyrrolo[2,3-*c*]pyridine-4-ones, in extremely effective 5-step sequences (Fig. 53). The reaction began with arene **189** and was converted to the precursor **190**, which upon treatment with isatin **191** yielded cycloadduct **192** and was further extended to highly functionalised spiro-oxindoles (**193**). The synthesized spiro-oxindoles demonstrated high potency in the wild-type osteosarcoma SJSA-1 cell line proliferation experiment.[84]

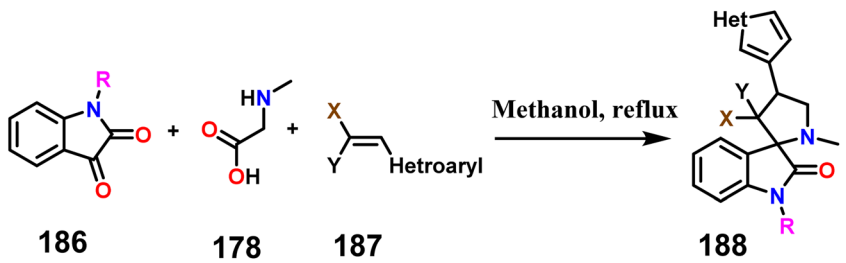


Fig. 52 Synthesis of spiro(oxindole-3,2′-pyrrolidine).

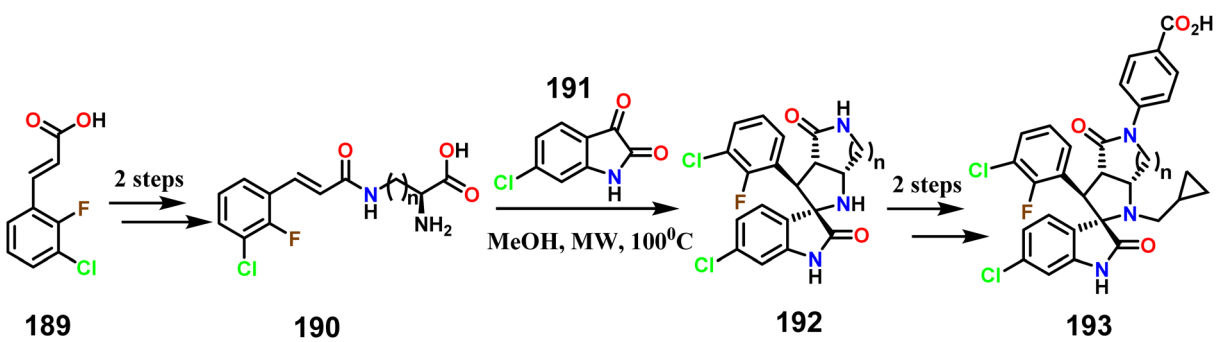


Fig. 53 Intramolecular cyclisation of azomethine ylides.

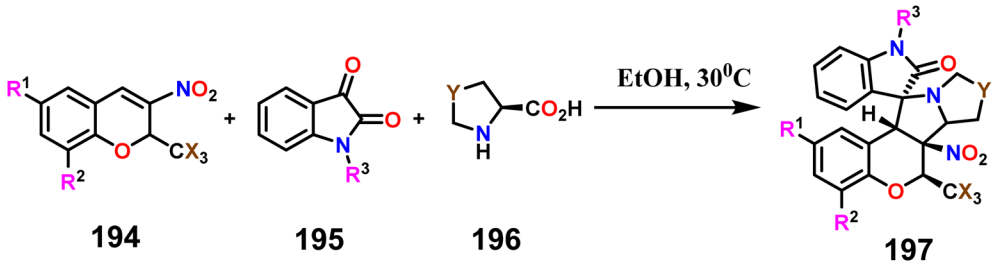


Fig. 54 Synthesis of spiro[chromeno(thia)pyrrolizidine-oxindoles].

Later in 2021, Kutyashev *et al.* demonstrated the three-component reaction of 3-nitro-2-(trifluoro(trichloro)methyl)-2*H*-chromenes (**194**) with azomethine ylides produced *in situ* from isatins (**195**) and L-(thia)proline (**196**) in EtOH at 30 °C to regio- and stereoselectively produce (trifluoro(trichloro)methyl)-substituted spiro[chromeno(thia)pyrrolizidine-oxindoles] (**197**) in high yields (Fig. 54). The resulting compounds showed strong cytotoxic effect against RD human embryonic rhabdomyosarcoma cells and HeLa human cervical carcinoma cells.[85] All the candidates showed high selectivity for cancer cells, and cytotoxicity testing showed that each drug's $IC_{50}$ exhibited low toxicity to normal human dermal fibroblasts (HDF). The low micromolar cytotoxic activity and selectivity of these spirooxindole analogues make them promising anticancer medicines, particularly for the targeted destruction of cervical cancer cells with little adverse effects on healthy tissues.

Around the same time in 2021, Aziz *et al.* reported two new spirooxindole compounds (**202**, **203**) that target the p53–MDM2 relationship, which inhibits Bcl-2 signalling. Aziz *et al.* used an effective synthetic approach (Fig. 55), *i.e.*, by enabling an aldol condensation reaction between *N*-methyl-2-acetylpyrrole (**198**) and substituted benzaldehydes (**199**) to produce corresponding *N*-methyl pyrrole chalcones (**200**) regio- and stereoselectively. The required spirooxindole derivatives (**202**, **203**) were then formed by subjecting these chalcones to a one-pot cycloaddition reaction with 5-chloroisatine (**201**) and sarcosine (**178**)/thioproline (**177**). These compounds demonstrated significant anticancer effects through Bcl2 signalling and the p53–MDM2 interaction, respectively.[86]

In another report, almost simultaneously, researchers demonstrated a new class of pyrooxindole derivatives (**207**) with thiochromene (**205**) dipolarophiles. According to Barakat *et al.*, **206** was condensed with different isatin derivatives (**204**) to produce azomethine ylides. The required spirooxindole derivatives were then formed through a 1,3-dipolar cycloaddition process with different chalcones that included thiochromene scaffolds (Fig. 56). Promising results from the anti-cancer assay made them excellent candidates for further research. These entities are most effective against breast cancer (MCF-7) and cervical cancer (HeLa) cell lines.[87]

In the following year, Mayakrishnan *et al.* described a very effective and eco-friendly *in situ* 1,3-dipolar cycloaddition procedure (Fig. 57) to create new spirooxindole hybrids (**210**, **211**). This synthetic approach involved the one-pot reaction of 5-bromoisatine derivatives (**208**) with quinoline-indole-based chalcones (**209**) in the presence of thioproline (**177**) or sarcosine (**178**). These hybrids are very effective in blocking the Bcl-2 receptor, which was further supported by molecular docking experiments. They also demonstrated significant cytotoxic action against HepG-2 cell lines.[88]

Independently, around the same time in 2022, a novel set of spirooxindole derivatives was created by Rajaraman *et al.*, who

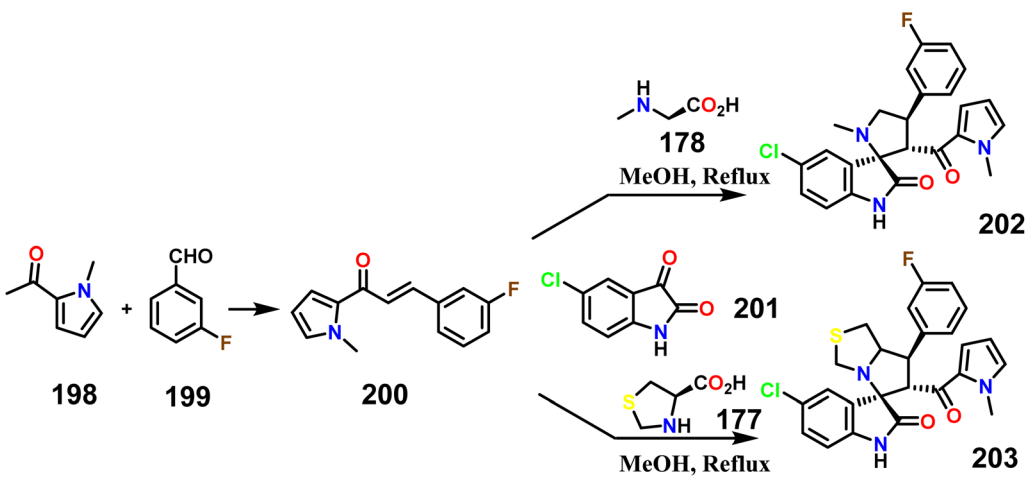


Fig. 55 Synthesis of the anticancer spirooxindoles.

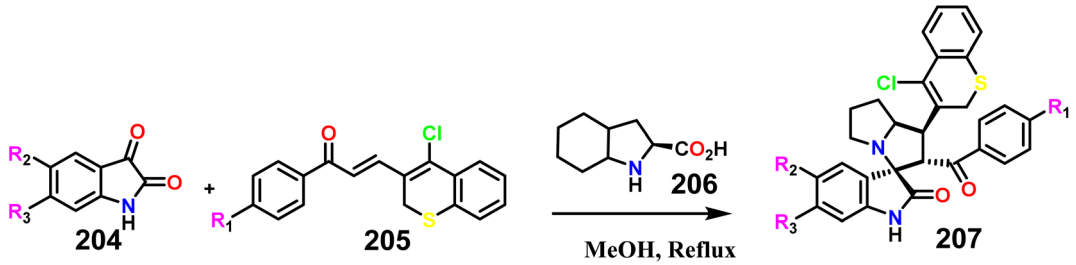


Fig. 56 Synthesis of the thiochromone-based pyrooxindoles.

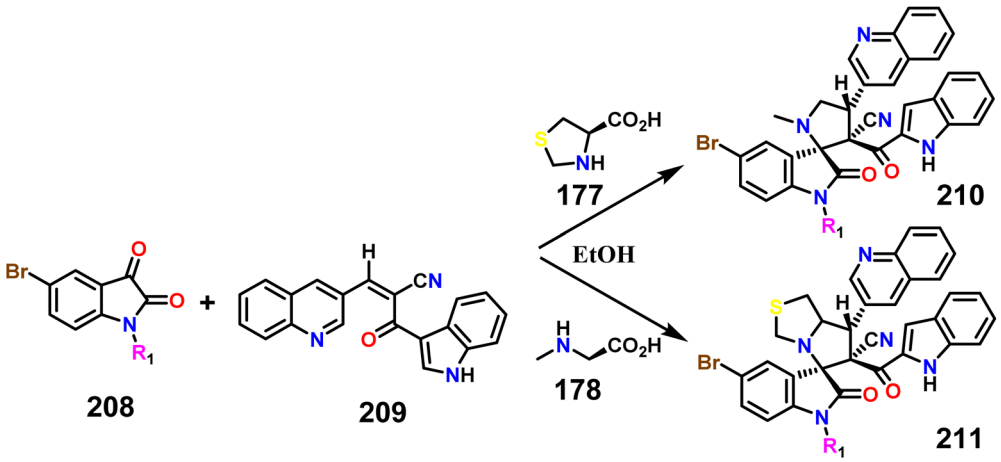


Fig. 57 Synthesis of the quinoline-indole-based spirooxindole hybrids.

also assessed the compounds' antioxidant capacity against superoxide and hydroxyl radicals. As part of the synthetic approach, isatin (**159**) and 2-(piperazin-1-yl)ethanamine (**212**) underwent decarboxylative condensation to produce an azomethine ylide precursor (**213**), which *in situ* produced reactive azomethine ylide intermediates, that also underwent a 1,3-dipolar cycloaddition reaction (Fig. 58) with different chalcones (**214**) to create the target spirooxindole derivatives (**215**). The antitumor effectiveness of these entities against KB oral cancer cells was determined to be promising. This spirooxindole scaffold's overall ability to target malignancies that begin in the epithelium is also promising, as they also maintained negligibly harmful effects on non-cancer cells even at high doses. This information suggests a lot of room for additional structural and preclinical development.[89]

Another similar chalcone-based dipolarophile was used by Zhao *et al.* to create a new class of spirooxindole derivatives (**218**) that include pyrrolothiazolidine (Fig. 59). Using chloroisatin (**191**) and thioproline amino acid (**177**), azomethine ylides were produced at the start of the synthesis. These intermediates were *in situ* exposed to a [3 + 2] cycloaddition process with different chalcones (**216**), producing the desired spirooxindole derivatives (**217**). Using peptide coupling reagents, such as HATU/DIEPA, the nitro group on the benzene ring was later reduced to an amine, which was further linked with acid-linker derivatives (**218**). These entities demonstrated significant inhibitory action against MDM2 and HDAC. Additionally, they

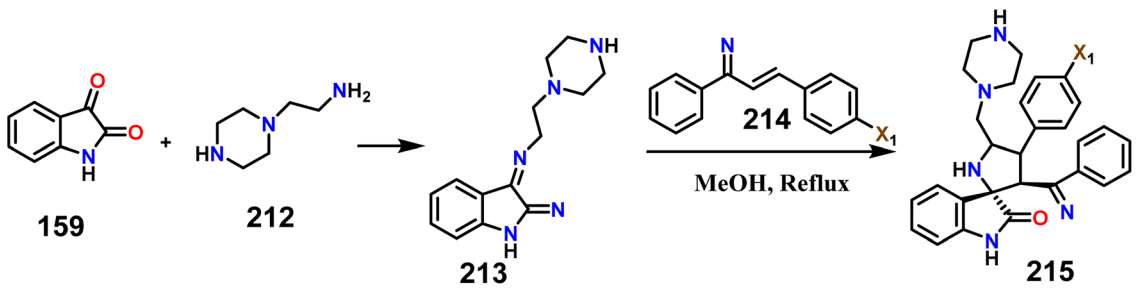


Fig. 58 Synthesis of the antitumor spirooxindoles.

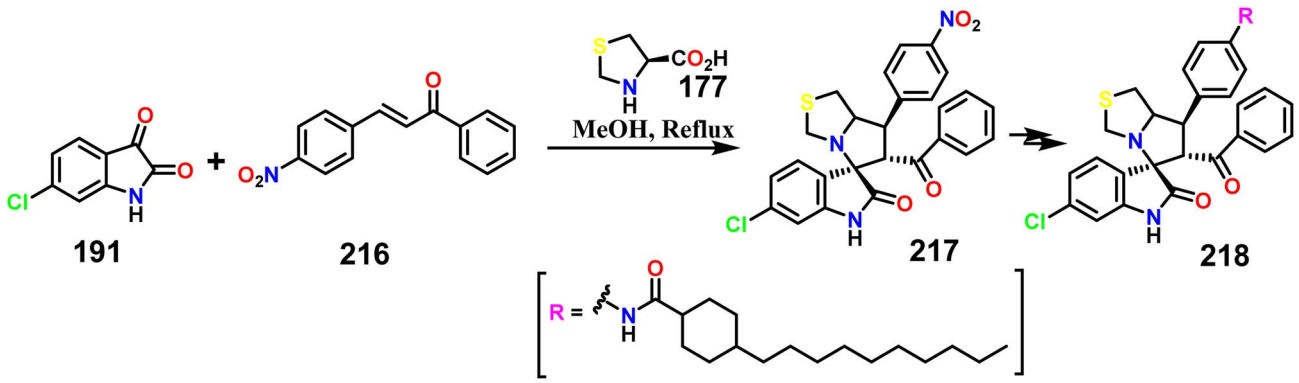


Fig. 59 Synthesis of the anticancer spirooxindoles.

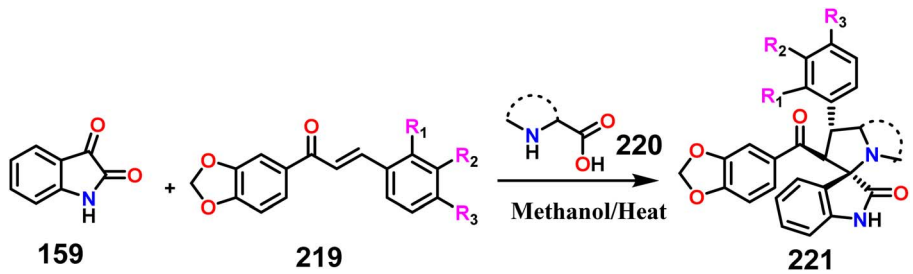


Fig. 60 Synthesis of the anti-diabetic spirooxindoles.

outperformed the reference medications SAHA and Nutlin-3 in terms of efficacy, exhibiting strong antiproliferative activities against MCF-7 cell lines. These studies were further confirmed by molecular docking investigations that showed specific inhibition against HDAC1 and HDAC2 and therefore may be considered for the development of viable anti-cancer drugs in the near future.[90]

Nivetha *et al.* found that the 1,3-dipolar cycloaddition reaction between the chalcone dipolarophiles (**219**) and the azomethine ylide dipole, which is created *in situ* by the reaction of amino acids (**220**) and isatin (**159**), can be performed in a highly stereoselective three-component manner (Fig. 60) to produce pyrrolidine-based spirooxindoles (**221**). Following the creation of spirooxindole derivatives, the authors used the enzymes α-glucosidase and α-amylase to investigate the derivatives' antidiabetic qualities. Their substantial inhibitory effect against enzymes α-glucosidase and α-amylase was further confirmed by molecular docking tests.[91]

Interestingly, in the following year, Alshahrani *et al.* used another type of chalcone with benzimidazole link (**222**) as the dipolarophile and described the synthesis of a new class of spirooxindole compounds (**223**). These cycloadducts were created regio- and stereoselectively in a one-pot [3 + 2] cycloaddition process (Fig. 61), where azomethine ylides were generated *in situ* from 5-chloroisatin (**201**) and (2*S*)-octahydro-1*H*-indole-2-carboxylic acid (**206**). On biological assessment, these compounds demonstrated excellent anticancer activity with considerably lower $IC_{50}$ (mM) values.[92]

In the same year, Islam *et al.* employed phenylimidazole-based chalcones (**224**) as dipolarophiles and reacted with *in situ* generated azomethine ylide from isatin (**159**) and L-thioproline (**177**) to construct (Fig. 62) a novel series of spirooxindole derivatives with a spiro[3*H*-indole-3,20-pyrrolidin]-2(1*H*)-one framework (**225**). Upon investigation of their potential as MDM2 inhibitors and *in vitro* anti-tumorigenic activity on different cell lines, many of these entities were found to be

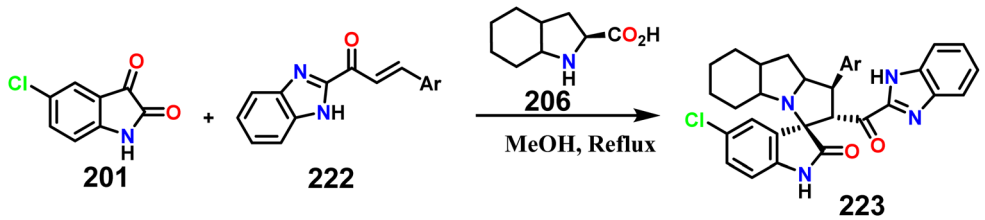


Fig. 61 Synthesis of the benzimidazole-based spirooxindoles.

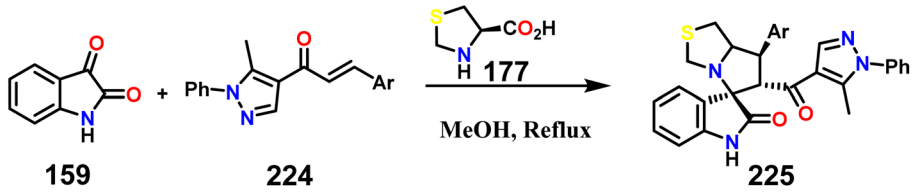


Fig. 62 Synthesis of phenylimidazole-based spirooxindoles.

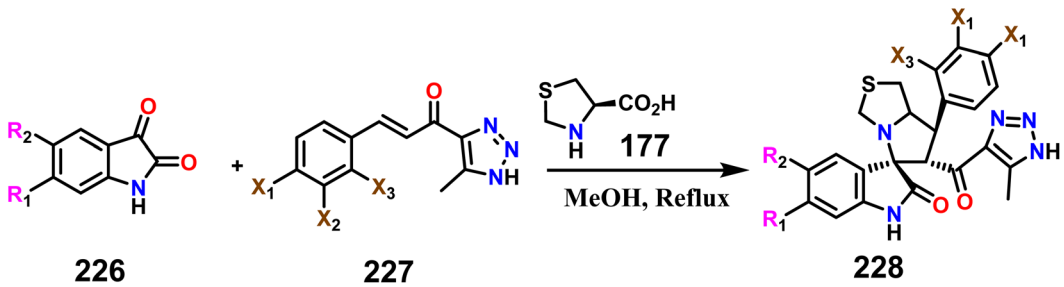


Fig. 63 Synthesis of the triazole–spirooxindole derivatives.

highly active against A549 lung cancer cells and to have strong cytotoxic activity against A2780 ovarian cancer cells. Some of them have also shown efficacy against MDA-MB-453 breast cancer cells, demonstrating their potential, particularly in multi-target cancer treatment approaches, as evidenced by the modest $IC_{50}$ values in the micromolar range, selectivity against cancer cells and ability to restore p53 tumour suppression.[93]

In order to explore more complex dipolarophiles, very recently, triazine-based chalcones (**227**) were utilized by Shawish *et al.* to construct triazole–spirooxindole derivatives (**228**). The azomethine ylides, which were produced *in situ* by the decarboxylative condensation of isatin derivatives (**226**) with thioproline (**177**), were reacted with the aforementioned chalcones to produce cycloadducts (Fig. 63). The authors then investigated their anticancer properties using HepG2 and MDA-MB-231 cell lines and found them to be effective cytotoxic agents against these cell lines. The good binding interactions of these adducts in the EGFR active site were further confirmed by 60-hour molecular docking experiments, suggesting the possibility of dual inhibition. Due to their significant selectivity and structural flexibility, these spirooxindoles may lead to the potential development of EGFR inhibitors in anticancer therapy.[94]

Abdessadak *et al.* have attempted to carry out a D-proline catalysed reaction between acrolein (**230**) and a thiophene-linked imine diester (**229**). The reaction led to the formation of thiophene-linked pyrrolidines (**231**), which was further extended to **232**, in a few steps (Fig. 64). The final product was examined in the search for substances that are effective against hepatitis C virus. Additionally, molecular docking simulations were used to assess the antiviral activity of the pyrrolidine against cyclophilin A, the co-factor that causes hepatitis C virus. These simulations revealed interesting interactions and a high C-score, which were further validated by molecular dynamics simulations that showed stability over a 100-ns simulation period. Additionally, compared with the hepatitis C virus inhibitor, the *cis*-cycloadduct pyrrolidine shows advantageous drug-like characteristics and a superior ADMET profile.[95]

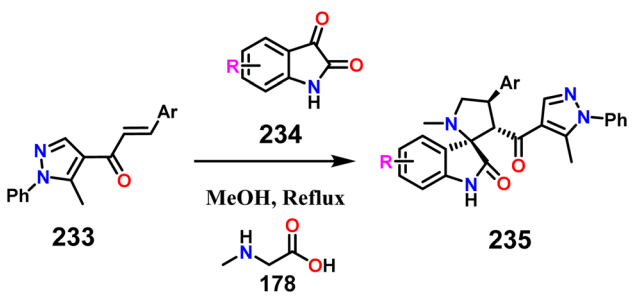


Fig. 65 Synthesis of the pyrazole-linked spirooxindoles.

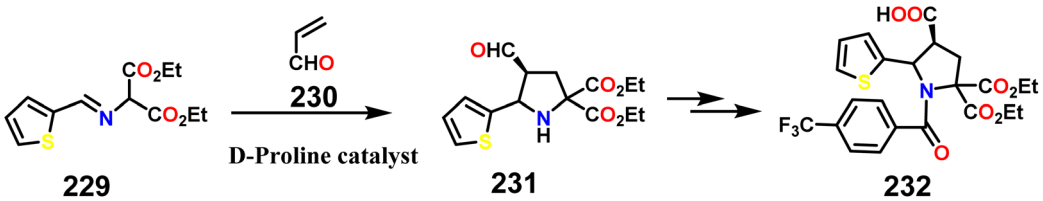


Fig. 64 Synthesis of the triazole-spirooxindole derivatives.

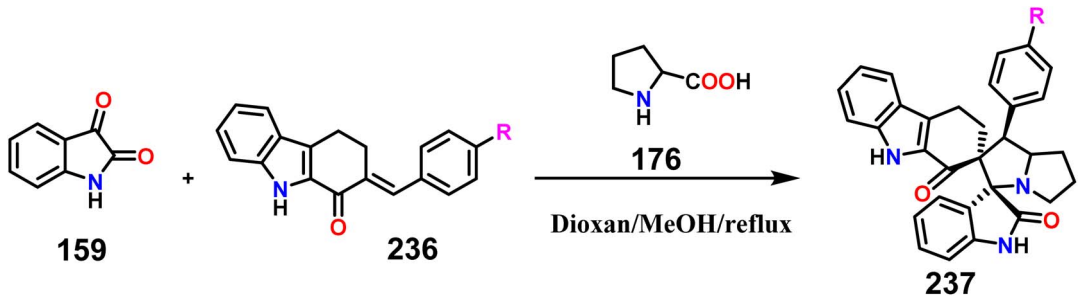


Fig. 66 Synthesis of the antifungal and antibacterial dispirooxindolopyrrolizidines.

In this context, most recently, Islam *et al.* reported a new series of spirooxindoles to target bacteria and non-small cell lung cancer (Fig. 65). This novel family of pyrazole-linked spirooxindoles (**235**) was inspired by the fusion of some structural elements from marine anticancer and antibacterial drugs.[96] Cycloadducts were produced from a chalcone-based dipolarophile (**233**) *via* reaction with azomethine ylides, generated *in situ* from isatins (**234**) and sarcosine (**178**). Upon biological investigation, these entities have shown strong antibacterial and anticancer properties against *Staphylococcus aureus* and non-small cell lung carcinoma (NSCLC), respectively, having low $IC_{50}$ values with tumor-specific cytotoxicity. These results received further support from docking experiments that revealed strong intercalative binding within DNA strands.

Some recent reports focused on the application of the exocyclic variants of spiropyrrolidines. For example, Periyasami *et al.* described a reaction between dipolarophile (*E*)-2-arylidine-1-ketocarbazole (**236**) and azomethine ylide derived from proline (**176**) and isatin (**159**), which produced di-spirooxindolopyrrolizidine derivatives (**237**) demonstrating antifungal and antibacterial properties (Fig. 66).[97]

Later Huang *et al.* deduced a productive method for the 1,3-dipolar cycloaddition of isatin-derived exocyclic dipolarophiles (**240**) with 1,3-dipoles derived from 1,2,3,4-tetrahydroisoquinoline (**239**) and isatin derivatives (**238**). Excellent yields of the expected di-spirooxindoles (**241**) with strong regio- and stereoselectivities were obtained from this three-component process (Fig. 67). Additionally, many of these cycloadducts were found to demonstrate promising cytotoxicity to HepG2 cells.[98]

Within a couple of years, through the use of an environmentally friendly deep eutectic solvent, Sathi *et al.* described the regio- and diastereospecific syntheses (Fig. 68) of new biologically relevant thiazolo[3,2-*b*]indole derivatives (**245**). The [3 + 2] cycloaddition reaction was done between a thiazolidine dipolarophile (**242**) and azomethine ylides, obtained from isatins (**243**) and different amino acids (**244**). These entities were then investigated for their potential to inhibit MDM2-p53 *via* molecular docking and *in vitro* investigations and found to have promising inhibitory properties.[99]

In this context, an interesting seven-membered azepane-based exocyclic dipolarophile (**246**) was described by Kumar *et al.*, which was used in a one-pot [3 + 2] cycloaddition procedure to design and synthesise a novel spirooxindole derivative with a pyrrolidine motif. These chalcones were reacted with an azomethine ylide [produced *in situ* by the decarboxylative condensation of isatin (**159**) with phenylglycine (**247**)] afforded **248**. As shown in Fig. 69, this method effectively produced the intended new bis-spirooxindole derivatives (**248**). These products were then tested for their antiproliferative potential and were found to have strong activity with low $IC_{50}$ values. Their potency was also found to be increased over time, suggesting a potential cumulative or delayed mode of action. According to these findings, more pharmacokinetic and structural optimisation would be required to attain adequate potency and selectivity for anticancer treatment.[100]

In the following year, Al-Majid *et al.* adopted the (3 + 2) cycloaddition reaction to synthesise a new series of di-

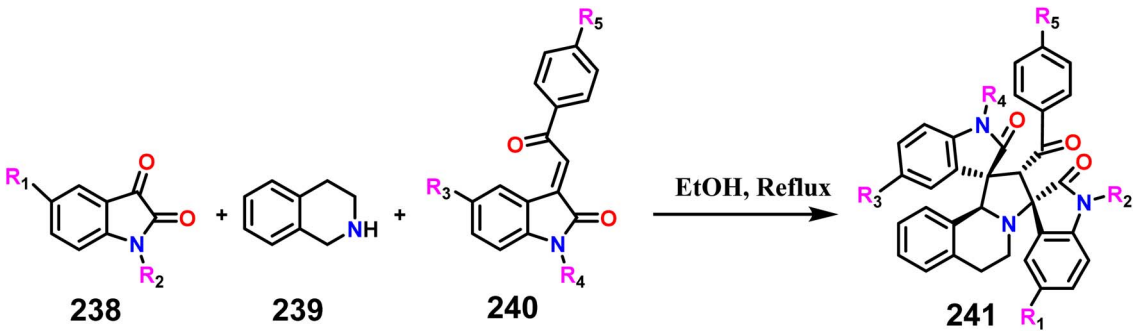


Fig. 67 Synthesis of di-spirooxindoles.

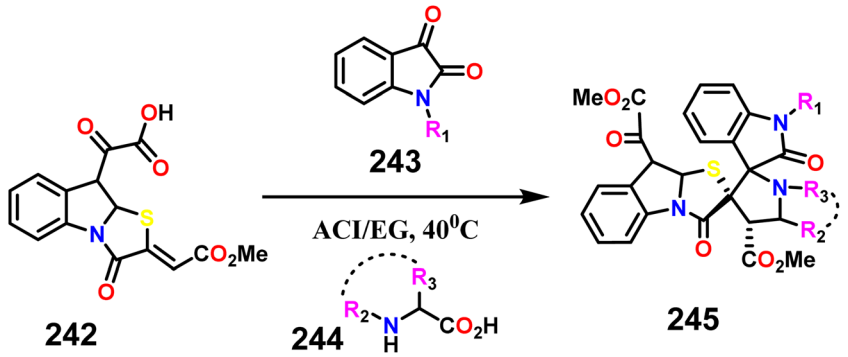


Fig. 68 Synthesis of the MDM2-p53 inhibiting di-spirooxindoles.

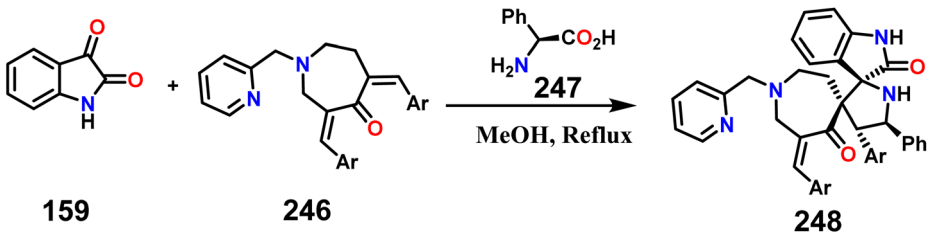


Fig. 69 Synthesis of the anticancer bis-spirooxindoles.

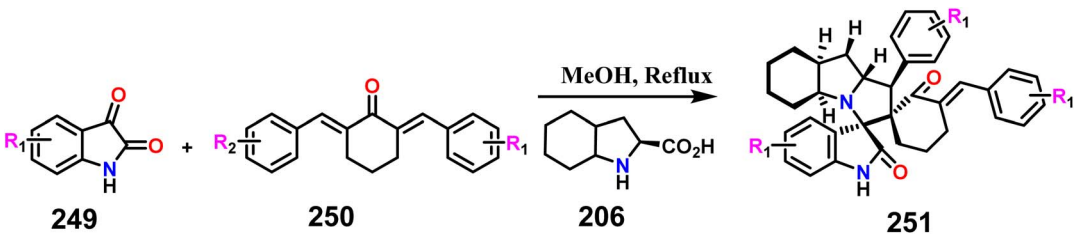


Fig. 70 Synthesis of the anticancer bis-spirooxindoles.

spirooxindole derivatives with a cyclohexanone moiety in a single pot. As shown in Fig. 70, this procedure involved *in situ* reaction of isatins (**249**) with (2*S*)-octahydro-1*H*-indole-2-carboxylic acid (**206**) to produce azomethine ylides, which were subsequently reacted with cyclohexanone-based chalcones (**250**) to produce di-spirooxindole derivatives (**251**). The synthesised di-spirooxindole derivatives showed high activity with an $IC_{50}$ value in the low micromolar range, and all of the investigated compounds have shown significant anti-proliferative capabilities against PC3 human prostate cancer cell lines. Some of them also demonstrated significant cytotoxicity in cervical (HeLa) and triple-negative breast carcinoma (MDA-MB-231) cancer cell lines. Additionally, these substances demonstrated a high degree of cytotoxic selectivity between normal and malignant cells at comparable dosages. The strong affinity and selectivity for tumor-related targets may be due to the structural stiffness of the di-spirooxindole structure. The practical significance of this scaffold for investigating additional anticancer medications is demonstrated by the possible dual antitumor effects in a number of malignancies.[101]

A similar investigation was done by Fawazy *et al.* in 2021, where a novel series of alkylsulfonyl-substituted di-spirooxindole derivatives (**254**) showing anti-SARS-CoV-2 characteristics was successfully developed and synthesised (Fig. 71). Azomethine ylides, which were produced *in situ* from isatins (**253**) and sarcosine (**178**), were used in the 1,3-dipolar cycloaddition with 1-(alkylsulfonyl)-3,5-bis(ylidene)-piperidin-4-ones (**252**) to accomplish the synthesis. These substances showed

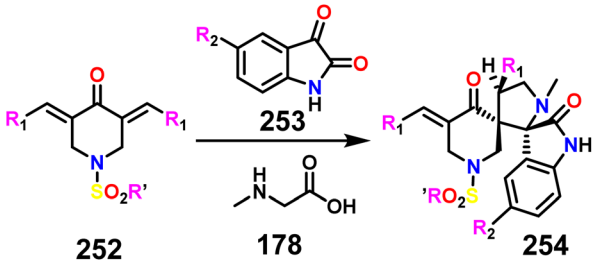


Fig. 71 Synthesis of di-spirooxindoles for multi-target treatment.

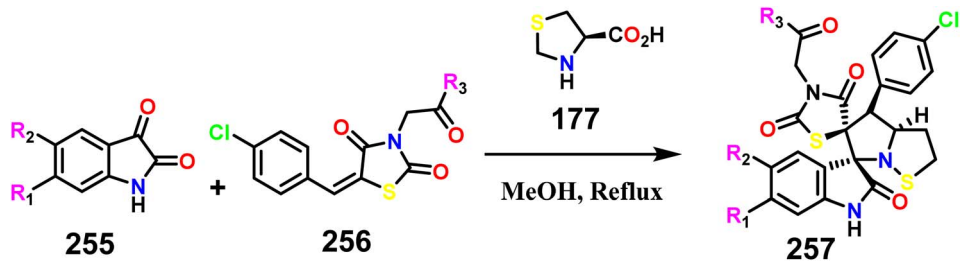


Fig. 72 Synthesis of the anticancer bis-spirooxindole derivatives.

a favourable selectivity index towards normal RPE1 cells while being tested for activity against a number of human cancer cell lines, including MCF7, HCT116, A431, and PaCa2. The di-spirooxindole derivatives were assessed for their antiviral, anticancer, and cholinesterase-inhibiting properties and were found to demonstrate strong potency. Furthermore, a small number of the analogues demonstrated significant dual activity against both BChE and AChE and therefore hold great promise as multi-target treatments for viruses, cancer, and neurological illnesses.[102]

Also, very recently in 2024, Nafie *et al.*, in search of a possible anti-breast cancer drugs, created a novel family of di-spirooxindole hybrids (**257**) based on pyrrolidinyl-bis-spirooxindole (Fig. 72). Here, the azomethine ylides were produced from isatins (**256**) and thioprolene (**177**) and then reacted with thiazolidine-based dipolarophiles (**256**) to produce cycloadducts. The entities showed good anticancer activity, with low $IC_{50}$ values. They were shown to have strong cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells. Additionally, compounds containing alaninate moieties showed good efficacy against HeLa and MDA-MB-231 cancer cell lines.[103]

This 1,3-dipolar cycloaddition was also explored in sugar-based systems. For example, the reaction of uracil polyoxin C (UPoC)-derived azomethine ylides for obtaining analogues of nikkomycin is notable in this context, where the thermal reactions of uracil polyoxin C (UPoC) (**258**) with isatin **159** in the presence of *N*-methylmaleimide (NMM) **259** resulted in good yields of polyoxin cycloadducts **260** and **261** (Fig. 73).[104]

The have also been reports on steroid-based systems. For example, modified bis-spiropyrrolidine derivatives of oestrone steroid **263** were synthesised by reacting (*Z*)-16-arylidene-estrone derivatives **262** as 2π components with azomethine ylides (Fig. 74).[105] Three distinct sets of circumstances were used to conduct the reactions. Additionally, innovative bis-spiro oxindole/pyrrolidine **267** has been synthesised in moderate yields using 2,5-bis(arylmethylidene)-cyclopentanone **265** as a dipolarophile.

### 4.2 Non-isatin-based azomethine ylides

Among non-isatin-based azomethine ylides, Waldman's report may be cited here. Using 1–3 mol% of a chiral catalyst produced

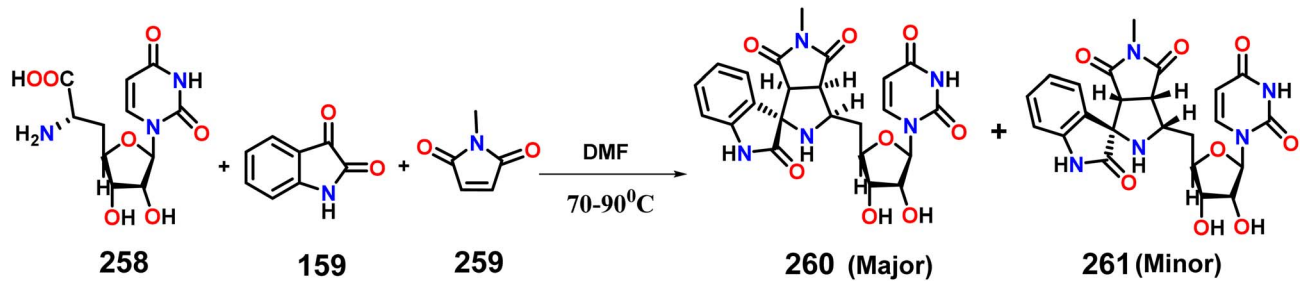


Fig. 73 Reaction of the polyoxin C (UPoC)-derived azomethine ylides.

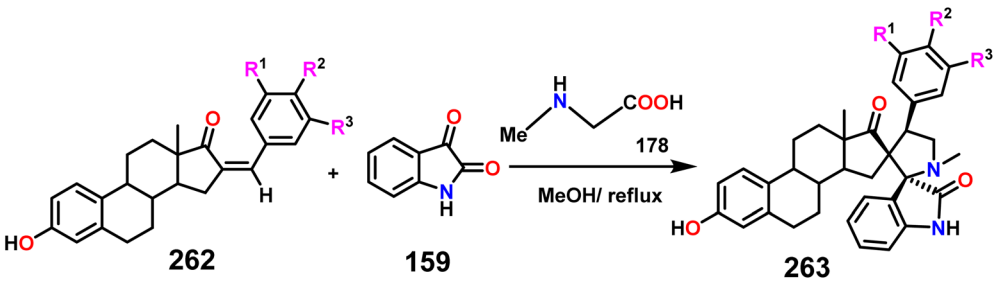


Fig. 74 Synthesis of a steroid-based bis-spiropyrrolidine.

from an *N*,*P*-ferrocenyl ligand (**266**) and $CuPF_6(CH_3CN)_4$, Waldman and colleagues reported a highly enantioselective synthesis of 3,3′-pyrrolidinyl spirooxindoles (**267**) (Fig. 75) inspired by natural products. This was accomplished by an asymmetric Lewis acid-catalyzed 1,3-dipolar cycloaddition of an azomethine ylide, generated *in situ* from **265**, to a substituted 3-methylene-2-oxindole (**264**). It was discovered that the cycloadduct interfered with the p53-MDM2 interaction, causing mitotic arrest.[106]

Later, in 2021, the potential of a novel series of nitroisoxazole-based spiro[pyrrolidin-3,20-oxindoles] (**270**) with a $-CF_3$ moiety as dual inhibitors of GPX4 and MDM2 was assessed by Liu *et al.* In this reaction, 3-methyl-4-nitro-5-styrylisoxazole (**269**) and 6-chloro-isatin imine (**268**) (Fig. 76) reacted in a basic medium of DBU to produce cycloadducts. Adducts were targeted for their potential application in breast cancer owing to their potent dual inhibitory activities against GPX4 and MDM2. They induced ferroptosis and apoptosis in MCF-7 cells by suppressing the MDM2-mediated degradation of

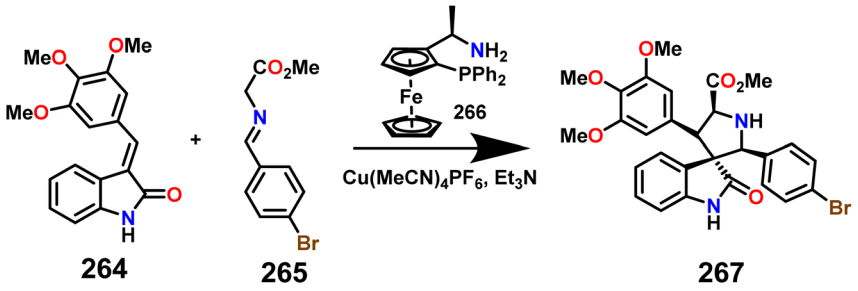


Fig. 75 An enantioselective synthesis of 3,3′-pyrrolidinyl spirooxindoles.

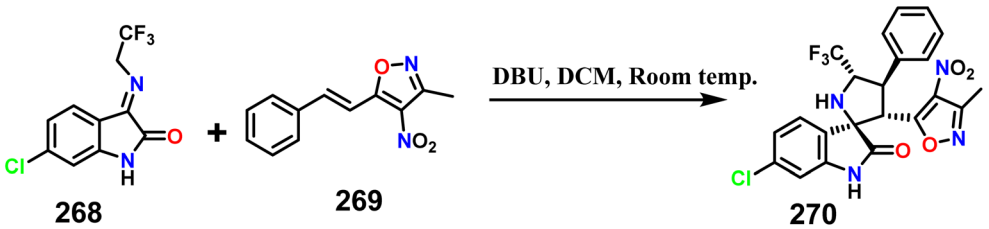


Fig. 76 Synthesis of the nitroisoxazole-based spiro[pyrrolidin-3,20-oxindoles].

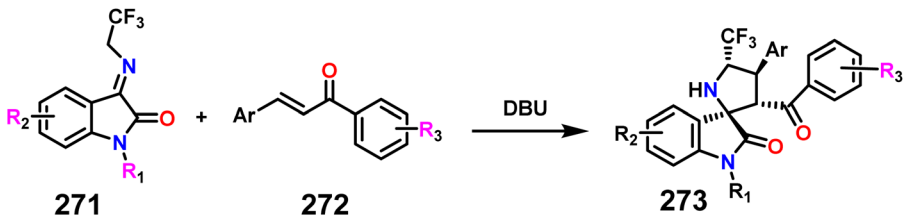


Fig. 77 Synthesis of the CF3-substituted pyrrolidinyl spirooxindoles.

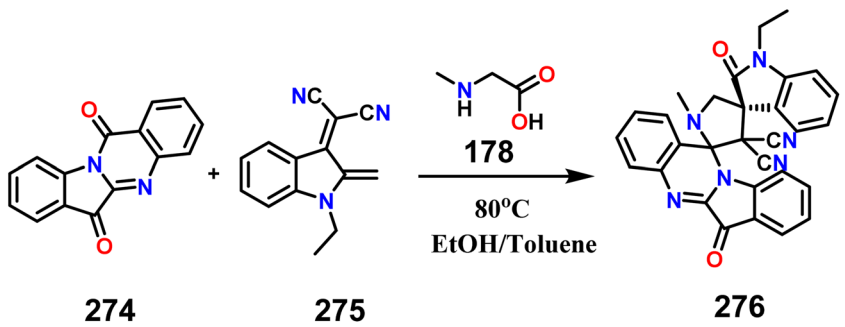


Fig. 78 Synthesis of antibacterial oxindoles.

p53 and lowering GPX4 expression. Lipid peroxidation, caspase-9 processing, and ROS generation were all involved in the process.[107]

A similar DBU-enabled reaction was recently reported by Zhou *et al.* to successfully design and synthesise a novel series of CF3-substituted pyrrolidinyl spirooxindoles (**273**) with exceptional diastereoselective 1,3-dipolar [3 + 2] cyclo-addition of *N*-2,2,2-triuoroethylisatin-based ketimines (**271**) with chalcones (**272**) (Fig. 77). Using MTT assay, the synthesised compounds' anticancer activity was evaluated *in vitro* against human gastric cancer SCG7901 cells. Many of them showed cytotoxicity, with moderate $IC_{50}$ values. The biological evidence supports the phenotypic significance of the $-CF_3$ motif and spirooxindole scaffold, despite the fact that they are not sub-micromolar.[108]

In another interesting report by Leena *et al.*, dispiropyrrolidineoxindoles (**276**) were synthesised from tryptanthrin (**274**) and isatilidenes (**275**) (Fig. 78) *via* [3 + 2] cycloaddition of azomethine ylide units. A thorough *in vitro* evaluation against ESKAPE pathogens and clinically relevant drug-resistant MRSA/VRSA strains showed the antibacterial properties of these compounds. The findings demonstrated that the bromo-substituted dispiropyrrolidineoxindole had good selectivity and a strong case against *S. aureus* ATCC 29213.[109]

Very recently, Pan *et al.* reported a three-component [3 + 2] azomethine ylide cycloaddition approach using benzofuran-based dipolarophiles (**277**), ninhydrin (**278**) and sarcosine (**178**) to create a spiro-pyrrolidine molecule based on benzofuran (**279**) (Fig. 79). With a wide variety of substrates, excellent yields, and simple operation under mild circumstances, this reaction can quickly produce potentially beneficial compounds. These spiro-heterocyclics also demonstrated outstanding anti-tumor capabilities.[110]

Ninhydrin was also used by Ren and coworkers to produce a novel series of spirooxindole–indenoquinoxaline compounds

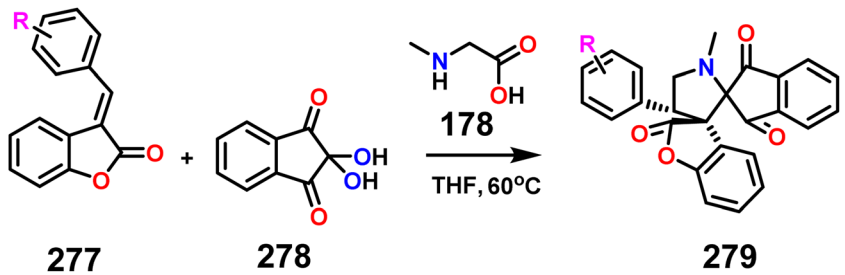


Fig. 79 Synthesis of the antitumor benzofuran scaffolds.

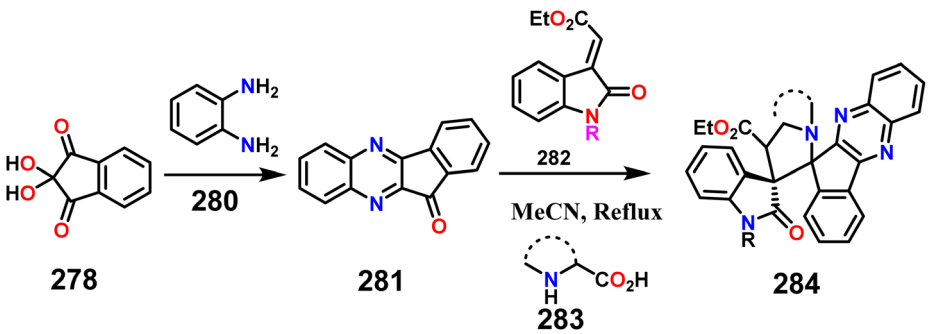


Fig. 80 Synthesis of spirooxindole–indenoquinoxaline.

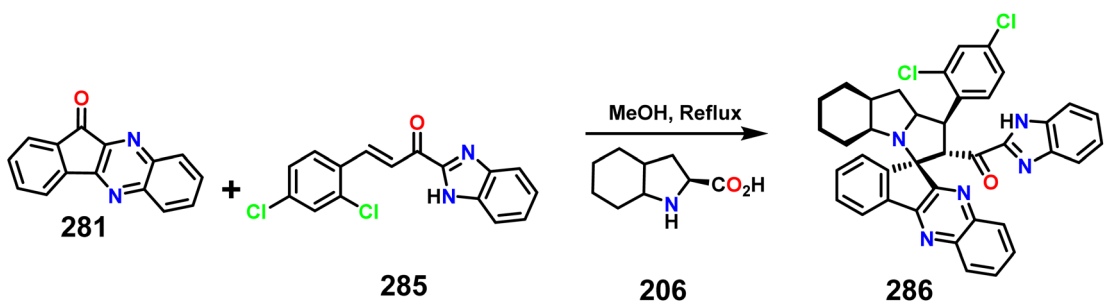


Fig. 81 Synthesis of spiro-indeno[1,2-*b*]quinoxaline.

(**284**) that function as tryptophanyl-tRNA synthetase (TrpRS) inhibitors. However, in this case, an indeno-quinoxalinone (**281**) was first produced from ninhydrin and orthophenylene diamine (**280**). The ketone was then further used to produce azomethine ylides from amino acids (**283**). Finally, through a 1,3-dipolar cycloaddition reaction with **282** (Fig. 80), dispirocycloadducts were produced. Through *in vitro* tests against a variety of Gram-positive and Gram-negative bacterial strains as well as diffuse large B-cell lymphoma (DLBCL) cell lines, these drugs' biochemical TrpRS inhibitory activity was assessed, and they showed excellent antibacterial activity against *Staphylococcus aureus*. Some of them also demonstrated significant anti-proliferative activities against DLBCL cell lines in cancer models, where they can serve as a tool compound for the discovery of dual antibacterial and anticancer agents.[111]

The same indeno-quinoxalinone (**281**) was used by Barakat *et al.*, where a novel series of spiro-indeno[1,2-*b*]quinoxaline derivatives (**286**) (Fig. 81) with a benzimidazole moiety was logically developed and synthesised. The imidazolyl chalcones (**285**) were reacted in a one-pot, multicomponent [3 + 2] cycloaddition process with the indeno-quinoxalinone (**281**) and octahydroindole-2-carboxylic acid (**206**). Upon testing their anticancer potential in human lung cancer cells, they have shown significantly high activity, suggesting significant selectivity towards cancer cells. Such a selectivity is consistent with earlier observations of spirooxindole compounds that contain indenoquinoxaline and benzimidazole moieties. Significantly, at concentrations that were effective for A549 cells, normal cardiovascular fibroblasts did not show significantly reduced viability, demonstrating excellent selectivity against CDK2 and pointing to its potential as an anti-lung cancer medication.[112]

## 5. Conclusion

In this review article, we have focused on exploring recent impacts of azomethine ylide chemistry for the strategic synthesis of pyrrolidine and spiropyrrolidine derivatives, which are important structural motifs in many natural and synthetic bioactive molecules. Azomethine ylides' inherent reactivity as adaptable 1,3-dipoles permits extremely effective and stereocontrolled [3 + 2] cycloaddition reactions with a wide range of dipolarophiles, facilitating the quick building of structurally varied and stereochemically complicated heterocycles. Also, significant advancements have been made in asymmetric, organocatalytic, and transition-metal-catalyzed processes to improve regio-, chemo-, and enantioselectivity control. These, coupled with computational research and mechanistic understanding, have facilitated researchers in the logical design of substrates and catalysts, increasing the accuracy and range of these transformations. Of note, atom economy and operational simplicity have also been enhanced by the development of multicomponent, tandem, and environmentally safe synthetic methods, which are consistent with the concepts of sustainable and green chemistry. All of these developments have made it easier to synthesise complex natural products and pharmacologically active compounds, demonstrating the critical role of azomethine ylides in contemporary synthetic and medicinal chemistry. The major challenges of the application of azomethine ylides include the control of stereoselectivity and regioselectivity issues. It also deals with the limited confined space of dipolarophiles, which are in general very reactive in nature. Therefore, there is an urgent need for a specific generation method to restrict the application of harsh chemicals and to get rid of unwanted side products. In a nutshell, regio- and stereoselectivity issues, limited dipolarophile scope, the need for harsh reaction conditions like high temperature, the incorporation of stabilizing group, catalyst specificity, and related competing reactions like proton transfer reaction, condensation reaction *etc.*, are the major limitations of the application and challenges of azomethine ylides. These limitations may be overcome by further investigation into their reactivity in conjunction with cutting-edge catalytic systems, which will open up new possibilities for the effective synthesis of intricate nitrogen-containing frameworks with increased biological potential.

## Conflicts of interest

There are no conflicts to declare.

## Abbreviations

| | |
|---|---|
| MCF-7 | Breast cancer cell line |
| MDA-MB-231 | Breast cancer cell line |
| T47D | Breast cancer cell line |
| A549 | Lung cancer cell line |
| PC-3 | Prostate cancer cell line |
| K562 | Leukaemia cancer cell line |
| SJSA-1 | Wild-type osteosarcoma cell line |
| HeLa | Cervical cancer cell line |
| HepG-2 | Hepatocellular carcinoma |
| KB | Oral cancer cell line |
| MDA-MB-453 | Breast cancer cell line |
| NSCLC | Non-small cell lung carcinoma |
| HCT116 | Colon cancer cell line |
| A431 | Human epidermoid carcinoma cell line |
| PaCa2 | Epithelial cell line |

## Data availability

No new data was generated.

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