Review

4,5,6,7-Tetrahydroindol-4-Ones as a Valuable Starting Point for the Synthesis of Polyheterocyclic Structures

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Abstract: This review focuses on the synthesis of polyheterocyclic structures with a variety of medicinal and optoelectronic applications, starting from readily available 4,5,6,7-tetrahydroindol-4-one analogs. First, routes toward the 4,5,6,7-tetrahydroindol-4-one starting materials are summarized, followed by synthetic pathways towards polyheterocyclic structures which are categorized based on the size and attachment point of the newly formed (hetero)cyclic ring.

Keywords: pyrrole; indolone; polyheterocycle; natural product; biological activity; optoelectronics

1. Introduction

Pyrrolo[1,2-a]pyridine-3,4-diones, such as 4,5,6,7-tetrahydroindol-4-one 1 and their derivatives are important structural motifs found in a variety of drugs, for example the FDA approved antipsychotic molindone 2 used to treat schizophrenia [1], the GABA A agonist CP-409,092 3 for the treatment of anxiety [2], and the potent heat shock protein 90 (Hsp90) inhibitor 4 for cancer treatment [3] (Figure 1). Examples of natural occurrence of 1 derivatives are scarce. However, the pyrrolo fused scalarane sesterterpenoid 5 has been isolated from sponges [4]. Furthermore, dehydrogenation of the 4,5,6,7-tetrahydroindol-4-one structure gives rise to a 4-hydroxy-indole moiety which is found in many bioactive alkaloids such as psilocin and its precursor psilocybin 6 [5] and FDA approved drugs, for example the non-selective beta blocker pindolol 7 [6].

Figure 1. 4,5,6,7-tetrahydroindol-4-one 1 motif in drug design and natural products.
Due to the presence of the pyrrole and ketone functionality, 4,5,6,7-tetrahydroindol-4-one analogs have received considerable attention for the synthesis of complex polyheterocyclic structures with a variety of medicinal and optoelectronic applications. This review will focus on the synthesis of polyheterocyclic structures starting from 4,5,6,7-tetrahydroindol-4-one analogs. First, routes toward the 4,5,6,7-tetrahydroindol-4-one motif are summarized, followed by synthesis of polyheterocyclic structures which are categorized based on the size and attachment point of the newly formed (hetero)cyclic ring.

2. Synthesis of 4,5,6,7-Tetrahydroindol-4-One Analog

The synthesis of the 4,5,6,7-tetrahydroindol-4-one motif 1 was first reported in 1928 by Nenitzescu and Scortzbanu, starting from condensation of 1,3-cyclohexadiones 8 with a-aminocarboxyls 9 in a [2+3] fashion (Scheme 1) [7]. Since many a-aminoaldehydes 9 (R3 = H) and a-aminoketones 9 (R3 ≠ H) self-condense easily, precursors have been used to form a-aminocarboxyl 9 building blocks in situ. Nenitzescu and Scortzbanu therefore introduced the amine functionality by reduction of oximes 10 with zinc as described in the classical Knorr pyrrole synthesis [8]. Later on, these a-aminocarboxyl building blocks 9 have been synthesized from various other precursors. Thus, a-hydroxy ketones 11 have been condensed with ammonium acetate [9]. The aldehyde or ketone functionality can be formed from a-aminocetals 12 [10,11] and a-azidocetals 13 (aza-Wittig reaction) [12], oxidation of a-aminoalcohols 14 [13–16], or from dehydration of amino acids 15 [17,18]. Stetter and Siehnhold reported the synthesis of 1 starting from alkylation of 1,3-cyclohexadiene 8 with phenacyl bromide 16 (X = Br, R2 = Ph, R3 = H) followed by a Paal-Knorr pyrrole synthesis of triketone 17 with primary amines [19]. Over the years, many modifications have been applied of this [4+1] strategy including different a-haloketones 16 and different nitrogen sources, such as fixation of atmospheric nitrogen [20] and in situ generation of ammonia from decomposition of urea in deep eutectic solvents [21]. Likewise, one-pot [2+2+1] procedures with a-haloketones 16, 1,3-diketones 8 and primary amines catalyzed by heterogeneous acids have been developed [22,23]. Instead of a-haloketones, ary1 glyoxals 16 (X = O) have been used for the synthesis of 3-hydroxy-substituted pyrroles 1 (R3 = OH) [24]. 4-Oxotetrahydrobenzofurans 18 are accessible from condensation of 1,4-diketones 17 and are transformed into their 4-oxotetrahydroindole analogs 1 with primary amines [25]. Next, addition of enehydroxamines 19 onto alkynes 20 gives O-vinylhydroxyaminic 21, which can undergo a [3+3]-sigmatropic rearrangement followed by an intramolecular condensation to obtain the 4,5,6,7-tetrahydroindol-4-one structure 1 similar to a Trofimov reaction [26,27]. Furthermore, direct intramolecular and intermolecular metal-catalyzed cyclization between β-enameinone 22 and alkynes 20 has been reported [28,29] as well as a Cu-catalyzed 5-exo-dig annulation of alkylene-tethered enaminones [30]. Ceric (IV) ammonium nitrate (CAN) oxidative coupling of 22 with vinyl ethers 23 affords structural motif 1 and is an attractive strategy toward N-aryl 2,3-unsubstituted tetrahydroindol-4-ones [31]. Furthermore, azirines are interesting building blocks for pyrroles [32]. 2H-Azirines 24 are prepared from isoxazoles 25 [33] or generated in situ from a-azidochalcones 26 [34]. The final example uses C-H insertion of a-imino rhodium carbeneoids accessible from N-sulfonyl-1,2,3-triazoles 27 into 1,3-cyclohexanediiones 8 [35].
3. Synthesis of [1,2]-Fused Polyheterocyclic Structures

3.1. Five-Membered Rings

3.1.1. Electrophilic Aromatic Substitution

Electrophilic aromatic substitution (EAS) onto pyrroles readily occurs at the C-2 position. Sechi et al. N-alkylated pyrrole 1 with acrylonitrile to obtain 28 followed by basic hydrolysis to 9 and polyphosphoric acid (PPA) mediated intramolecular Friedel-Crafts acylation to afford polyheterocyclic structure 30 in an overall yield of 45% (Scheme 2 Route A) [36]. Interestingly, Wolff-Kishner reduction of 30 in diethylene glycol (DEG) was selective for one ketone functionality, leading to 31 in 22% yield. Later, an alternative, albeit less efficient route toward 30 was disclosed starting with an EAS on 1 with chlorosulfonyl isocyanate to introduce a 2-nitrile group which afforded ester 32 upon hydrolysis in 30% yield over two steps (Scheme 2 route B) [37]. N-Alkylation with ethyl acrylate followed by Dieckmann condensation to 33 and decarboxylation eventually produced tricycle 30 in an overall yield of 15%.
Scheme 2. EAS onto pyrrole to obtain [1,2]-fused five-membered rings.

In 1995, Edstrom et al. examined the oxidation of similar structures (Scheme 3) [38]. 34 was previously synthesized using 1,3-cyclohexadiones 8 and proline derivatives of 15 according to the strategy depicted in Scheme 1 [17]. Treatment of 34 with excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform at 80°C afforded 35, which upon mild basic hydrolysis formed 36 in 56% yield over two steps. Limiting the amount of oxidant at room temperature and shorter reaction time provided a mixture of 37, 35 and starting material 34. Furthermore, by trapping the cationic intermediate with methanol, 38 was isolated which was used later on in the total synthesis of mitomycin C analog 39 in nine more steps [39].

Scheme 3. Oxidation of 34 under various conditions.

In 2017, Zhao et al. reported the synthesis of N-allenamides and pyrroles (Scheme 4) [40]. Under gold 42 catalysis, N-alkynylpyrrole bearing a benzyloxy group at the propargylic position 40 was converted into the corresponding allenepyrrrole 41, expelling benzaldehyde 43. Next, the electrophilic gold species 42 activates the allene moiety for an intramolecular EAS on the C-2 of the pyrrole to obtain polycyclic spiro structure 44 in 95% yield.

Scheme 4. Synthesis of N-(allenyl)pyrrole 42 and subsequent EAS.
3.1.2. C-H Activation

Interest in C-H activation of pyrroles and indoles has increased over the years. This is due to the “atom economic” nature and the need for less reactive starting materials with a C-H bond instead of for example a C-X bond with X being a (pseudo)halide. Challenges are the inertness of the stronger C-H bonds compared to C-X bonds used in traditional metal-catalyzed cross-coupling reactions. Furthermore, the only small differences in C-H bond strengths lead to regioselectivity issues [41]. However, it should be noted that the electron rich nature of pyrrole already activates C-H bonds toward electrophilic metal species with the 2-position being more nucleophilic compared to the 3-position (as observed in classical EAS reactions due to better stabilization of the Wheland-type intermediate). Moreover, intramolecular reactions have less regioselectivity issues due to a limited degree of freedom. Chang et al. reported a Pd-catalyzed cyclization of N-(2-halobenzyl)-substituted 4,5,6,7-tetrahydro-4-indolone 45 which afforded a condensed pyrroloindole structure 46 via tandem activation of benzyl halide and the pyrrolic C-H bond (Scheme 5) [42].

![Scheme 5. Tandem activation of benzyl halide and pyrrole 45 toward 46.](image)

For inactivated C-H bonds, a directing group (DG) is typically employed to ensure both reactivity and regioselectivity. A pyrimidine (Pym) group onto the N1-position of pyrrole 47 is often used to direct the transition metal to the C2-H bond. Wang et al. disclosed a Mn-catalyzed alkenylation of N-DG indoles with allenes 48 (Scheme 6) [43]. Surprisingly, the strong nucleophilicity of the C-Mn bond leads to 1,4-migration of the directing group (Smiles rearrangement) with subsequent intramolecular substitution of the N-Mn onto the ester to stereoselectively afford a cyclized product. An extensive scope was made including various indoles, pyrroles, isoquinolin-1(2H)-ones and pyridine-2(1H)-ones as well as different directing groups and allenes with varying yields of 33–96%. In the context of this review, 47 was alkenylated with 48 to intermediate 49 followed by Smiles rearrangement and subsequent intramolecular substitution onto the ester, to provide 50 in 67% yield.

![Scheme 6. Mn-catalyzed alkenylation of 47 and subsequent Smiles rearrangement.](image)

3.2. Six-Membered Rings

3.2.1. Substitution

[1,2]-Annulated six-membered rings with the pyrrole moiety 52 have been synthesized via an intramolecular oxidative radical substitution of pyrroles bearing primary N-alkyl iodides 51 to aromatic carbon nuclei using dicumyl peroxide (DCP), acting both as radical initiator and oxidant (Scheme 7) [44]. Furthermore, Beckmann rearrangement on the oxime analogs 52 afforded conformationally restricted azepinepyrroloisoquinolinones...
which structure can be found back in paullones with anticancer activity [45]. The conformationally restricted structures 54 were tested against various cancer cell lines, however, the antiproliferation activity was not improved compared to previous analogs [46].

A three-component reaction was developed using various 1,3-cyclohexadiones 8, 3-nitrochromenes 55, and ammonium acetate which yielded functionalized 3,4,10,11-tetrahydroindolo[1,2-α]quinoxaline structures 56 in a cascade reaction forming the pyrrole and fused quinoxaline moiety in multiple steps, including two equivalents of cyclohexanedione in the final product (Scheme 8) [47,48]. A tentative reaction mechanism was proposed, although the exact mechanism is not known so far. Most likely, an oxidation step with HNO₃ or oxygen is required. These complex polyheterocycles were obtained in 58–72% yield.

Chen et al. developed a Rh(III)-catalyzed double C-H activation of α-C-H bond of N-aryl azoles such as N-phenyl pyrroles without heteroatom directing assistance, followed by an annulation reaction with alkynes 58 to give pyrrolo-[α]fused quinolines (Scheme 9) [49]. A broad scope of N-(hetero)aryl and N-vinyl imidazoles provided the fused quinolines in good to excellent yields (43–99%). N-Aryl pyrroles gave lower, albeit acceptable yields (21–62%). When N-phenyl-4,5,6,7-tetrahydroindol-4-one 57 was used, 59 was obtained in 49% yield.

Tetrahydroindololo fused isoquinoline derivatives, having an additional tetrahydroindolone side group, were synthesized using a one-pot two-step reaction of 1-bromo-2-(2,2-
of the human protein kinase CK2 and the breast cancer resistance protein ABCG
saturated indeno[1,2-b]indoles and ninhydrin selective synthesis of membered rings are not reported. However, Hemmerling and Reiss disclosed a regiose-
4.1.
4.1. Synthesis of [2,3]-Fused Polyheterocyclic Structures
4.1. Five-Membered Rings
Post-functionalizations of pyrrolocyclohexanones forming [2,3]-annulated five-
membrated rings are not reported. However, Hemmerling and Reiss disclosed a regio-
selective synthesis of vic-dihydroxy-indenoindoles 67 from 3-aminocyclohex-2-enones 65
and ninhydrin 66 (Scheme 12) [52]. Deoxygenation of 67 with N,N,N',N'-tetramethylsulfu-
rous diamide 68 provides an efficient and facile procedure for the synthesis of partially
saturated indeno[1,2-b]indoles 69 derivatives which are a novel class of potent inhibitors
of the human protein kinase CK2 and the breast cancer resistance protein ABCG2 [53–56].
Scheme 13. Synthesis and aromatization of isocoumarin fused pyrrolocyclohexanones 70.

4.2. Six-Membered Rings

4.2.1. Rearrangement

As an alternative to the deoxygenation of 67, discussed in previous section, Pramanik et al. disclosed the acid-catalyzed rearrangement of 67 to isocoumarin fused pyrrolocyclohexanones 70 in good yields (78–90%) (Scheme 13) [57]. A mechanism is proposed where one alcohol forms a hydroxy epoxide intermediate with the adjacent ketone. Loss of water from the ortho-position of the nitrogen leads to the formation of a cationic intermediate followed by ring expansion through breaking the epoxy C-C bond to finally obtain 70. Furthermore, dehydrogenation of 70 (R² = H) with 10% Pd/C produced 4-hydroxyindole fused isocoumarins 71 in good yields (73–82%). These 4-hydroxyindole fused isocoumarins have interesting spectral properties, such as high quantum yields of fluorescence and ability to act as fluorescence “turn-off” sensor for Cu²⁺- and Fe³⁺-ions [57].

Scheme 13. Synthesis and aromatization of isocoumarin fused pyrrolocyclohexanones 70.

4.2.2. Electrophilic Aromatic Substitutions

Mannich reaction with 2,3-unsubstituted 4,5,6,7-tetrahydroindol-4-one 72, formaldehyde and aminoacetal affords acetal protected Mannich bases 73 which upon acidic hydrolysis ring-close to the corresponding hydroxy compounds 74 (Scheme 14). Finally, hydrogenolysis of 74 with Pd/C afforded various β-caroline derivatives 75 [11].

Dielectrophiles can react twice with pyroles in a one-pot reaction in a similar fashion. Chunchatprasert and Shannon disclosed the double substitution of 2,3-unsubstituted pyrrolocyclohexanones 72 with pyrrole 76 (Scheme 14) [58]. N-H pyrrolocyclohexanone 72 was unreactive under the given conditions. However, with the N-benzyl derivative, 77 was obtained in 16% yield together with regioisomer 78 (3%). Moreover, 10-pyrrolomethyl derivative 79 was obtained in 6% yield and acyl monosubstituted product 80 in 10% yield. The product 80 can be seen as a precursor to 77.
Pramanik et al. developed a multicomponent condensation reaction of enamines 22, arylglyoxals 81 and malononitrile forming cyclohexanone-fused 2-(3-pyrrrolyl)-2-cyanoacetamides 82 in high yields (70–79%) (Scheme 15) [59]. These 3-substituted 2-arylpyrrolo-cyclohexanones 82 are converted into highly substituted benzo[α]carbazoles 83 through a cyclization and Pd-catalyzed aromatization. Without Pd-catalyzed aromatization, 84 was isolated, which is evidence that the cyclization is indeed thermal.

Scheme 15. Thermal cyclization and Pd-catalyzed aromatization of 82.

4.2.3. C-H Activation

As was mentioned in Section 3.1.2, C-H activation on pyrroles is an attractive functionalization strategy. However, to overcome regioselectivity issues, a DG such as pyrimidine (pym) onto the N-pyrrole could direct the electrophilic metal-complex to formal C2-H activation. This strategy is used for the benzannulation of N-pyrimidine 4,5,6,7-tetrahydroindol-4-one 47 toward indolocyclohexanones. Wang et al. disclosed the Cp*Rh(III)-catalyzed benzannulation of pyrrolocyclohexanone 47 with enaldiazo compound 85 (Scheme 16A) [60]. A plausible mechanism was proposed wherein a rhodium carbenoid complex is formed from the enaldiazo compound 85, followed by α-insertion and protonation which results in the alkenated intermediates. Bronsted acid-catalyzed double bond isomerization, followed by Friedel-Crafts cyclization and subsequent dehydration provides the benzo-fused product. The corresponding indole product 86 was obtained in 88% yield.

While this benzannulation is convenient, the availability of these enaldiazo compounds 85 is limited. Therefore, research has been done utilizing easily accessible, however, less reactive 1,3-dienes 87 as synthons for the benzannulation of N-heterocycles. Wang et al. described a Rh(III)-catalyzed formal oxidative [4+2] cycloaddition of nitrogen heterocycles, including 47, with 1,3-dienes 87 (Scheme 16B) [61]. Mechanistically, the π-
allyl metal species, which is generated via C-H activation and diene insertion, is trapped by the nucleophilic β-position of the N-heterocycles. Lastly, Cu(II)-catalyzed oxidation of the intermediate delivers the aromatized products. Due to the electron withdrawing effect of the ketone moiety in 47 which limits the nucleophilicity of the β-position, 88 was obtained in only 41% yield.

The disrupted aromaticity and weak N-O bond causes anthranils (2,1-benzisoxazoles) like 89 to be unstable, though interesting building blocks in organic chemistry. Kim et al. developed a regioselective Cp*Rh(III)-catalyzed direct amination of 47 with 89 followed by an intramolecular cyclization to afford 90 in 82% yield (Scheme 16C) [62]. Mechanistically, a cationic Rh(III) complex can be generated with the pyrrole via a formal C-H activation process. Coordination of the anthranil and migratory insertion provides the amino species which upon protonation delivers the C-2-aminated pyrrole which can further cyclize with the formed ketone to 90.

![Scheme 16](image)

**Scheme 16.** C-H activation of 47 toward [2,3]-benzo-fused and quinoline-fused 4,5,6,7-tetrahydroindol-4-one.

Similar to the intermolecular aromatic substitution of Rh-carbenoid complexes with C2-H activated pyroles, Khlebnikov et al. disclosed the intramolecular aromatic substitution of 3-phenyl-2-(diazoacetyl)-tetrahydroindolone 92 which was formed from 2-diazoacetylazirines 91 and 1,3-cyclohexadiene 8 (Scheme 17) [63]. Interestingly, use of the Co(III) catalyst did not affect the diazoacetyl functionality. Next, a Cu(OTf)2 catalyzed intramolecular aromatic substitution of the 3-aryl group onto the copper carbenoid delivered interesting benzo-fused 1H-indol-7-ol 93 in 70% yield.

![Scheme 17](image)

**Scheme 17.** Metal-catalyzed intramolecular aromatic substitution onto an α-diazoacarbonyl moiety.
5. Synthesis of [3,4]-Fused Polyheterocyclic Structures

5.1. Five-Membered Rings

Only one example that uses the pyrrolocyclohexanone structure for the synthesis of [3,4]-annulated five-membered rings can be found in literature. This is most likely due to the considerable ring strain of these structures. Baudoin et al. reported the intramolecular Pd-catalyzed alkane C-H arylation from aryl chlorides [64]. One example of the extensive scope uses 94 which is synthesized starting from 4,5,6,7-tetrahydroindol-4-one 1 via tosylation (83% yield) and double chlorination with CuCl$_2$ (83% yield), followed by a Horner-Wadsworth-Emmons reaction (quantitative) and aromatization with loss of one chloride (85%) (Scheme 18). Double methylation of 94 delivered 95. Intramolecular Pd-catalyzed methyl C-H arylation of 95 afforded the expected cyclobutarene 96 surprisingly together with 97 as an inseparable mixture with a ratio of 2:5, respectively. The unintended isomer 97 presumably arises from a palladium migration, however, the exact mechanism is not elucidated. The same procedure was used for the synthesis of indane 99 starting from 98 with only one diastereomer being observed as a result of steric hindrance.

![Scheme 18. Intramolecular Pd-catalyzed alkane C-H arylation from aryl chlorides.](image)

5.2. Six-Membered Rings

5.2.1. Condensation Reactions

Due to the antitumoral and antibiotic activity of Chuangxinmycin 104, synthesis of analogs of this natural product have gained research interest. Murase et al. reported the synthesis of 4-alkylsulfanylindole 101 starting from 1 by converting the ketone to thioke- tone 100, followed by alkylation with methyl bromoacetate and DDQ-mediated dehydrogenation [65]. The sulfide 101 is an interesting building block for the [3,4]-fused indole core. Kozikowski et al. acetylated 101 at the 3-position, followed by intramolecular Knoevenagel condensation of 102 to obtain dehydrochuangxinmycin methyl ester 103 [66]. Reduction of the double bond with hydrogen gas and a sulfided Pd/C catalyst, followed by hydrolysis of the ester afforded Chuangxinmycin 104 (Scheme 19).
1,4-Dicarbonyls can condense with hydrazine to give access to six-membered rings. Thus, treatment of 4-oxo-4,5,6,7-tetrahydroindole-3-carboxamide 105 with hydrazine formed tricyclic pyrrolo fused cinnolinone 106 in 65% yield (Scheme 20) [67]. Similar compounds have been tested against several tumor cell lines, however, only low tumor growth cell inhibitory activities were observed [68].

Scheme 20. Formation of a tricyclic pyrrolo fused cinnolinone.

Pyrrolo fused pyrylium salts are useful synthetic precursors of the corresponding pyrrolo fused pyridines via ring opening and recyclization with ammonium or hydrazine acetate [69]. Pyrylium salts are accessible by dehydration of 1,5-dicarbonyls with an acylating mixture of 70% perchloric acid and acetic anhydride (Scheme 21). These 1,5-dicarbonyls, e.g., 109 are obtained by condensing various β-enaminones such as 107 with dibenzoylethylene 108. The pyrylium salts were obtained in 91–98% yield with the exception of tetrahydroindole derivative 109 with only 25% yield of 110 due to considerable ring strain. Furthermore, in the same report various pyrylium salts were converted to the corresponding pyridines, pyridinium salts or pyridinones. However, no conversion of 109 to any corresponding N-containing six-membered ring was reported. Probably, this conversion did not succeed because of the ring strain of this system.

Scheme 21. Synthesis of pyrrole fused pyrylium salt 109.

5.2.2. C-H Activation

The tetrahydrobenzo[cd]indole 115 has an interesting skeleton which can be found in a variety of natural products, e.g., in ergoline alkaloids. Formal intramolecular C-H bond
insertion by diazoketones has become an attractive strategy toward this constrained skeleton. Thus, Matsumoto and Watanabe disclosed the synthesis of 4-(4-indolyl)-3-oxobutanonic acid derivatives 113 (Scheme 22) [70]. Introduction of a 5-halogen substituent onto the tetrahydroindolone, utilizing CuX₂ such as in compound 111 ensures mild aromatization later on in the synthesis. Condensation of ketone 111 with double anionic ethyl acetoacetate followed by LiBr mediated aromatization yields 112. Furthermore, the ketoesters 112 were converted to the diazo compounds 113 with 4-acetamidobenzensulfonyl azide (p-ABSA) which can undergo a metal-catalyzed formal intramolecular C-H bond insertion. Matsumoto, Watanabe and Kobayashi reported the use of Pd(OAc)₂ as the catalyst for the synthesis of structure 114 [71]. However, while using Rh₂(OAc)₄ as well as Cu(acac)₂, as well as Cu(acac)₃, the C-H insertion occurred on the 5-position to obtain a [4,5]-annulated five-membered structure 117. It is worth mentioning that N-substituted indoles did not form tetrahydrobenzo[cd]indole 114. However, under rhodium catalyzed conditions, N-substituents were compatible and 117 was formed in good yields. Hansen et al. further investigated the introduction of the diazo functionality at an earlier stage in the synthesis, however, they concluded that the diazo is best introduced at the end [72]. Additionally, Rosenberg reported that 114 was isolated in equilibrium with its tautomer 115 which could undergo a proton transfer to form the thermodynamically preferred naphthalene derivative 116 (Scheme 22).

\[\begin{align*}
\text{Scheme 22. Formal C-H insertion of metal carbenoids in the C3-H or C5-H bond.}
\end{align*}\]

### 5.3. Seven-Membered Rings

**Arcyriacyanin A** 124 is a green-blue pigment found in the mycetozoa *Arcyria obvelata* with potential anticancer activity. It was synthesized by Murase et al. by nucleophilic addition of lithiated 1-methoxyindole 119 on the ketone functionality of N-tosyl 4,5,6,7-tetrahydroindol-4-one 118 to give 120, which was treated with DDQ to obtain the unsymmetrical 2,4'-biindole 121 (Scheme 23) [73]. Deprotection of both the indoles was accomplished by reaction with magnesium in methanol. Finally, 122 can be transformed by formation of the bismagnesium salt followed by double substitution onto N-tert-butyldimethylsilyl (TBS) dibromomaleimide 123 which is deprotected under the reaction conditions. Arcyriacyanin A 123 was evaluated as cell growth inhibitor against a panel of human cell lines, however, the EC₅₀ value was rather high [73].

\[\begin{align*}
\text{Scheme 23. Synthesis of Arcyriacyanin A 124.}
\end{align*}\]
Scheme 23. Total synthesis of arcyriacyanin A 124.

6. Synthesis of [4,5]-Fused Polyheterocyclic Structures
6.1. Five-Membered Rings
6.1.1. Hantsch Thiazole Synthesis

Condensation of α-bromoketones with thiourea remains one of the most reliable routes to aminothiazoles. Remers et al. condensed N-protected benzenesulfonyl and benzoyl 5-bromo-4-oxo-4,5,6,7-tetrahydroindoles 125 with substituted thioureas 126 (Scheme 24) [67,74]. Surprisingly, in ethanol with an excess of triethylamine, exclusively the imine is formed without substitution of the bromine. However, when the reaction is executed in methanol, all tetrahydroindoles are converted to the corresponding thiazole 127. The benzenesulfonyl-group as well as the benzoyl-group can be deprotected with NaOH in methanol. DDQ mediated dehydrogenation of unprotected 128 furnished the fully aromatic derivatives 129 in low yield. DDQ mediated aromatization of benzoyl-protected derivatives 127 was unsuccessful. However, phenyltrimethylammonium tribromide has proven to be very effective for dehydrogenation of N-H 128 and N-benzoyl 127. Interestingly, 128 with R² and R³ being a methyl or NR³ being a piperazine moiety, showed anti-inflammatory activity while only low activities were found for in vitro antibacterial and antifungal screenings [67].

![Scheme 24. Aminothiazole fused indole synthesis.](image)

6.1.2. Paal-Knorr Type Syntheses from 1,4-Diketones

Synthesis of [4,5]-fused five-membered heterocycles can be realized using the Paal-Knorr condensation of 1,4-dicarbonyls with nucleophiles. Alkylation of N-substituted 4,5,6,7-tetrahydroindol-4-one 130 with chloroacetone did not afford the desired 1,4-diketone building blocks 132. Therefore, Martínez and Oloarte reported the alkylation of 130 with allyl bromide using lithium diisopropylamide (LDA) to obtain 131 followed by a Wacker-Tsuji oxidation (Scheme 25) [75]. Furthermore, 132 was condensed with Lawesson’s reagent in a benzene-dimethoxylethane (DME) mixture or methylene hydrochloride, and aromatization occurred under the reaction circumstances to obtain thieno-133 and pyrrolo-indoles 134, respectively. Interestingly, the aromatization step occurred without additional oxidant. Later on, Chacón-García and Martinez reported the cytotoxic properties of these pyrrolo-134 and thieno-indoles 133, most likely due to DNA intercalation [76]. Various anilines as well as dianilines were used to build a small library of potential DNA intercalators 133 and 134, and double DNA intercalators 135, respectively.
6.1.3. [3+2] Paal-Knorr Type Syntheses from 1,3-Dicarbonyls

Similar as in the Paal-Knorr pyrrole and thiophene synthesis, five-membered heterocycles can be synthesized from 1,3-dicarbonyls and 1,2-dinucleophiles such as hydrazine and hydroxylamine to obtain pyrazoles and isoxazoles, respectively. Inspired by work of Remers and coworkers [74], Nikolaropoulos et al. reported the formylation of ethoxymethyl (EOM) protected 4,5,6,7-tetrahydroindol-4-one 136a with ethyl formate in the presence of sodium hydride to obtain enol tautomer 137a (Scheme 26) [77]. Condensation with methylhydrazine or phenyl hydrazine afforded the corresponding pyrazole 138a (R1 = EOM) regioselectively in 72% and 46% yield, respectively. Similarly, condensation of 137a with hydroxylamine hydrochloride provided the isoxazole fused dihydroindole 141a in 75% yield. Subsequently, the derivatives 138a and 141a were dehydrogenated on treatment with DDQ in dioxane to the corresponding fused tricyclic indole derivatives 139a (R2 = Me, Ph) and 142a, respectively. However, extensive attempts to cleave the EOM group of 139a and 142a with HCl did not yield the N-deprotected derivatives 140 or 143, respectively. When a 2-(trimethylsilyl)ethoxymethyl (SEM) group is used instead of EOM, deprotection of the pyrazole fused tricyclic indole derivatives 139b afforded the N-unprotected products 140 in 26% (R2 = Me) and 37% (R2 = Ph) yield, respectively. However, deprotection of the isoxazole-fused tricyclic indole 142b led to decomposition. Evaluation of the inhibitory activity of these fused tricyclic indoles against soluble guanylate cyclase (sGC) demonstrated in vitro activity with 142a being the most potent derivative [77].

Scheme 25. Paal-Knorr syntheses toward thieno- and pyrrolo-indoles as potential DNA intercalators.

Scheme 26. Synthetic pathway toward tricyclic indoles from 1,3-dicarbonyls.

In a study concerning the cytostatic activity in cancer cell lines of novel conformationally rigid pyrazoles, Kasioti et al. synthesized two pyrazole-fused tetrahydroindol-4-
ones [78]. Therefore, benzyl-protected tetrahydroindol-4-one 144 in the presence of lithium hexamethyldisilazane (LiHMDS) base under anhydrous conditions provided the corresponding enolate, which was subsequently condensed with 3-chlorobenzothiophene-2-carbonyl chloride or p-anisoyl chloride to afford the 1,3-diketone derivatives (Scheme 27). The one-pot condensation of the latter with hydrazine and its methoxyphenyl counterpart afforded the desired pyrazole derivatives 145 and 146 in 49% and 60% yield, respectively. Demethylation of 146 delivered diphenolic compound 147 in 85% yield. Evaluation of the cytostatic activity revealed that 147 had the most potent inhibitory activity against the growth of the panel of tested cancer cell lines [78].

**Scheme 27.** One-pot procedure toward pyrazole-fused dihydroindoles.

### 6.1.4. [3,3]-Sigmatropic Rearrangements

The ketone functionality in 4-oxytetrahydroindole 148 can be converted to arylhydrazones that can be subjected to [3,3]-sigmatropic rearrangements leading to the Fischer indole synthesis. Condensing phenylhydrazine hydrochloride with 148 in acetic acid and subsequent rearrangement gave the pyrrolo[3,2-a]carbazoles 149 in yields of 21–55% (Scheme 28) [79]. Surprisingly, aromatization occurred without additional oxidant. Furthermore, the reaction did not occur when two methyl groups were placed on the 6-position of the tetrahydroindolone 148, most likely due to steric hindrance. In subsequent work, these pyrrolocarbazoles 149 were investigated for their selective kinase inhibitory activity in solid cancer treatment (Scheme 28) [80]. However, Fischer indole synthesis with unsubstituted tetrahydroindolone 1 resulted in poor yields and purification difficulties. When benzenesulfonyl-protected 4,5,6,7-tetrahydroindol-4-one 148 (R¹ = SO₂Ph, R² = R³ = H) was used, the corresponding pyrrolo[3,2-a]carbazole 149 was isolated in 24% yield. Smooth deprotection and formylation afforded 150 as a potential kinase inhibitor. However, the inhibitory activity of the isomeric pyrrolo[2,3-a]carbazole 154 which was prepared similarly starting from 4,5,6,7-tetrahydroindol-7-one 151 was superior to 150. Changing the solvent for the Fischer indole synthesis from acetic acid to a choline chloride–zinc chloride ionic liquid with subsequent one-pot DDQ oxidation increased the yield of 152 from 17% to 78% [80].
Instead of indole formation, a related thermal [3,3] sigmatropic rearrangement of O-alkenoates gives rise to a pyrrole-fused pyrrolocyclohexanone structure (Scheme 29) [81]. O-Alkenoates of 4,5,6,7-tetrahydroindol-4-one were synthesized by condensing hydroxyl amine with 155 followed by addition onto dimethyl acetylenedicarboxylate (DMAD) to obtain 156. Thermal rearrangement at 120–140°C afforded the corresponding pyrrole-fused tetrahydroindoles 157 in low yields (exact yield was not reported). Interestingly, oxidation to the benzodipyrrrole did not occur at these elevated temperatures. Thermal rearrangement of O-vinylketoximes of 156 failed due to a retro-Michael addition.

6.1.5. 1,3-Dipolar Cycloaddition

Recently, our group and Hao’s group independently introduced bis(difluoroboron) pyrrole acylhydrazones (BOPAHY) [82,83]. This novel fluorophore shows intriguing photophysical properties, including high fluorescent quantum yields in solution and in solid state and tunable absorption/emission properties. Very recently, our group reported the synthesis and spectroscopic properties of novel 1,2,3-triazole BOPAHY dyes and their corresponding triazolium salts (Scheme 30) [84]. Thus, we started from N-tosyl-4,5,6,7-tetrahydroindol-4-one 118 and performed our in-house developed general metal-free triazolization reaction [85–89]. This route toward 1,2,3-triazoles starts from enolizable ketones, primary amines and 4-nitrophenyl azide as diazo-transfer agent. The reaction of N-tosyl-4,5,6,7-tetrahydroindol-4-one 118 with hexylamine or 2-methoxyethyl amine afforded the corresponding 1,2,3-triazole 158 in 82% and 83%, respectively. It is worth mentioning that without tosyl protection the triazolization reaction did not occur. Deprotection of the tosyl group with NaOH resulted in the free NH-pyrrole 159 which could be α-formylated with a Vilsmeier reaction. These pyrrole-2-carbaldehydes 160 were then used in the synthesis of BOPAHY dyes 161 by condensation with acyl hydrazides and subsequent complexation with BF₃·OEt₂ in a one-pot procedure. Furthermore, oxidation of 160 with DDQ delivered the tricyclic 1,2,3-triazolo fused indole 161. The obtained 1,2,3-triazole BOPAHYs were methylated with to obtain 1,2,3-triazolium BOPAHY salts 162 with limited water solubility.

![Scheme 28. Fischer indole synthesis.](image)

![Scheme 29. [3+3] sigmatropic rearrangement of O-alkenoates.](image)
6.2. Six-Membered Rings

6.2.1. [4+2]-Cycloadditions

4,5-Fused six-membered rings on the indole nucleus are interesting as this may lead to potentially pharmacologically active compounds. Therefore, the 4,5,6,7-tetrahydroindol-4-one is particularly suitable for the synthesis of these tricyclic heterocycles. Reaction of 4,5,6,7-tetrahydroindol-4-ones 163 with ethyl formate and sodium methoxide or potassium tert-butoxide regioselectively a-formylated the ketone functionality to 164 in 70–88% yield (Scheme 31) [90]. Enaminoketones 165 were prepared from 164 and secondary amines in 51–98% yield. These enaminoketones 165 are the starting products for multiple tricyclic heterocycles. [4+2]-Cycloaddition of 165 with dichloroketene (generated in situ from reaction of dichloroacetyl chloride and triethylamine) only resulted in the expected [4+2]-cycloaddition product 166 with R-N-R being a piperidino group. However, the other examples all afforded compound 167. [4+2]-Cycloaddition of 165 with sulfinyl (generated in situ from elimination reaction of mesyl chloride with triethylamine) occurred readily in the case of R being aliphatic to give 1,2-oxathioino 2,2-dioxide fused 6,7-dihydrohydroindole structure 168 [91]. Complete aromatization of 168 was tried with DDQ. When R-N-R was a dimethylamino group, elimination of the amino group and aromatization occurred to obtain the least substituted 1,2-oxathioino[6,5-α]indole 169 in low yield. However, with R-N-R being morpholine, aromatization occurred without loss of the amino group to obtain 170.

Scheme 30. Synthesis of 1,2,3-triazole-linked BOPAHY dyes and their triazolium salts.

Scheme 31. [4+2] cycloaddition to afford 4,5-fused six-membered rings.
6.2.2. Multistep Condensation Reactions

Dall’Acqua et al. reported the synthesis of 5,6-dihydropyrrolo[2,3-\(h\)]quinolinones 174 as possible DNA intercalators with photo-binding ability and with lower toxicity compared to psoralens used in photo treatment of several skin diseases by intercalation and [2+2] photocycloaddition with DNA strands (Scheme 32) [92]. \(\beta\)-Aminoenones 172 discussed in the previous section are useful building blocks for this synthesis by conjugate addition of various cyanomethylene (RCH=CN) compounds followed by elimination of Et3N. Next, cyclization to a non-isolable 2H-pyran-2-imine intermediate followed by a Dimroth-type rearrangement affords 5,6-dihydropyrrolo[2,3-\(h\)]quinolinones 173 [93]. In order to obtain flat molecules which could intercalate in double stranded DNA, similar to the natural product angelicin, aromatization of 173 was attempted, however, it did not succeed due to solubility issues [94]. Furthermore, oxidation of the \(\beta\)-aminoenones 172 did only afford traces of the oxidized hydrolyzed product 179 which could be obtained directly from 171 in good yields. Attempts to synthesize the oxidized \(\beta\)-aminoenones 177 from 176 was unsuccessful. Therefore, an alternative synthetic pathway was followed for the synthesis of pyrrolo[2,3-\(h\)]quinolinone 174 analogs where the pyrrole ring is formed with a Fischer indole synthesis starting from hydrazone 175. Surprisingly, 174 did not inhibit proliferation of tumor cell lines in phototherapy while the 5,6-dihydropyrrolo[2,3-\(h\)]quinolinones 173 bearing a phenylsulfonyl group exhibited high photoactivities [94]. Regarding the mechanism of action, 173 did not intercalate with DNA upon irradiation which is of great relevance in decreasing long-term toxic effects such as mutagenesis. It seems that lysosomes and/or mitochondria could be targeted by 173 induced photodamage to lipids and proteins with the involvement of free radicals.

\begin{center}
\textbf{Scheme 32.} Synthesis of 5,6-dihydropyrrolo[2,3-\(h\)]quinolinones 168 and attempted aromatization.
\end{center}

In 2005, Dall’Acqua et al. reported the synthesis of thiopyrano[2,3-\(c\)]indol-2-ones 187, resembling angelicin analogs with potential photochemotherapeutic activities [95]. Due to the interesting results, further research on this work was done and an extended report was published in 2008 (Scheme 33) [96]. Chloroformylation of various 4,5,6,7-tetrahydroindol-4-ones 178 with the Vilsmeier–Haack reagent provided unstable aldehyde 179. Low yields were obtained with N-unsubstituted tetrahydroindol-4-ones due to solubility issues. When the pyrrole moiety was not fully substituted, regioselectivity and overformylation issues occurred due to pyrrole formylation. Nucleophilic substitution of the chlorine atom with ethanethiol afforded thioethers 180. Oxidation of these thioethers with DDQ afforded the corresponding stable aromatic aldehydes 181 in good yields. Wittig–Horner reaction onto aldehydes 180 and 181 afforded 182 and 184, respectively, in good yields. Hydrolysis of the ester provided carboxylic acids 183 and 185. Polyphosphoric acid (PPA) catalyzed cyclization succeeded only in low yield (30–40%) for the dihydrothiopyranoindoles 186 except with R\(^2\) bearing an ester or acid functionality. In the case of the aromatized acids 185, only two examples afforded the corresponding thiopyranoidoines.
Direct oxidation of 186 was not successful. All derivatives of 186 and 187 possessed photo-antiproliferative activity with the most active being the fully aromatic compound 187 with R1 = Me [95]. In contrast with the series 173 and 174, the dihydro derivatives 186 were less active. However, analogous to 173, these compounds were not able to intercalate and form covalent adducts with DNA upon UV irradiation, although they were able to photo oxidize DNA bases, in particular pyrimidine bases. Again the involvement of free radicals, in particular the hydroxyl radical, was proven [96]. It was again postulated that mitochondria and liposomes are targeted, inducing apoptosis.

The chloroformylated product 188 can condense with 1,3-dinucleophiles. Batra et al. reported the copper-mediated coupling of 188 with acetamidine hydrochloride to obtain pyrroloquinazolines 189 in good yields (75–76%) (Scheme 34) [97]. No oxidation attempts of 189 have been reported.

The indolo[3,2-c]quinolinone and pyridazinoquinoline structures are found in naturally occurring alkaloids and are extensively studied in medicinal chemistry. Due to the biological relevance of the indole, quinoline and pyridazine nucleus, Dandia et al. combined these moieties to obtain a pentacyclic heterocyclic ring system 192 (Scheme 35) [98]. Therefore, the tetrahydroindolone-fused quinolinone structure 186 was prepared via a Fischer indole cyclization of (2-oxo-1,2-dihydroquinolin-4-yl)hydrazine 185 and 1,3-cyclohexadione 8 under microwave irradiation with a small amount of DMF as energy transfer and dehydrating agent. One-pot reaction of key intermediate 186 with glyoxalic acid monohydrate with a few drops of DMF under microwave conditions followed by addition of hydrazine hydrate afforded 187 after 3–5 min in 85–88% yield without the need for further purification.
Furanoflavonoids such as karanjin are naturally occurring compounds which possess various kinds of biological activities. Maurya et al. explored the potential of the furanoflavonoid nucleus as antifungal and antibacterial agents and synthesized pyrrole and thiopehe analogs of furanoflavonoids [99]. For the pyrrole analogs, 1-methyl 4,5,6,7-tetrahydroindol-4-one 193 was acylated with dimethyl carbonate (DMC) or ethyl acetate (EtOAc) with NaH as a base, which resulted in methyl 5-carboxylate 194 and 5-acetyl tetrahydroindolone 198, respectively (Scheme 36). Thereafter, DDQ mediated dehydrogenation of 194 and 198 afforded indoles 195 and 199. Nucleophilic acyl substitution of the dimesyl anion on ester 195 afforded β-ketosulfoxide 196, which upon treatment with substituted benzaldehydes and piperidine in toluene produced pyrroloflavon analogs 197 in 70–74% yield. Chalcone 200 was achieved in good yields via a Claisen–Schmidt condensation of 199 with benzaldehydes in the presence of barium hydroxide. Flavanol 201 was achieved applying an Algar-Flynn-Oyamada reaction of the corresponding chalcone 200 (R = H) in 59% yield together with two minor products 202 and 203. When R = OMe, a complex reaction mixture was obtained. Screening 195, 197, 198, 200 and 201 together with the thiophene analogs against various bacteria and fungi demonstrated higher inhibition activities of thiophene analogs compared to the pyrrole analogs [99]. Nevertheless, chalcone 200 (R = H) and flavone 197 (R = H) showed minimum inhibitory concentrations (MIC) against fungi comparable with natural furanoflavonoid karanjin.

Scheme 36. Synthesis of pyrroloflavanoids as Karajin derivatives.

In search of analogs of the well-established antipsychotics Molindone and Piquinone, N-benzenesulfonyl-protected 4,5,6,7-tetrahydroindol-4-one 204 was alkylated with a-bromoesters 205 with lithium diisopropylamide (LDA) as a base (Scheme 37) [100]. One-pot benzenesulfonyl deprotection and ester hydrolysis of 206 afforded potential antipsychotics 207 with only one diastereomer (if R = Me) isolated. Cyclization with hydrazine hydrate yielded the pyridazin-3-(2H)-one fused dihyroindoles 208.
In 2014, Jørgensen et al. disclosed the asymmetric synthesis of optically active six-membered carbocycles, fused with a variety of ring systems [101]. This method uses an asymmetric γ-alkylation of enals onto olefins bearing a phosphonate substituent followed by an intramolecular Horner-Wadsworth-Emmons (HWE) reaction. Thus, enal 211 was prepared from the corresponding Boc-protected 4,5,6,7-tetrahydroindol-4-one 209 via a HWE reaction with diethyl cyanomethylphosphonate 210 and sodium hydride followed by DIBAL-H reduction of the nitrile to the aldehyde (yield was not reported) (Scheme 38). The asymmetric γ-alkylation of enal 211 with electrophile 212 was catalyzed with a trimethylsilyl (TMS) protected diphenylprolinol 213 via its dienamine intermediate with the bulky substituent of 213 shielding one side of the nucleophilic center. Next, through addition of Cs2CO3, an intramolecular HWE reaction occurred in a one-pot fashion affording the optically active six-membered carbocycle 214 in 72% yield with a remarkable enantiomeric excess of 93%.

Scheme 38. Asymmetric synthesis of six-membered carbocycles.

7. Synthesis of Spiro Compounds

The synthesis of spiro compounds is of great importance in view of their medicinal applications. In 2007, Miller et al. reported an enantioselective formal [3+2]-cycloaddition of allenolate esters with enones which was catalyzed with Boc-protected diphenylphosphine amino ester 217 (Scheme 39) [102]. Mechanistically, it is thought that the Lewis basic phosphine forms a zwitterionic dipole with the allenic ester which can undergo a [3+2]-cycloaddition onto enones. The effect of various N-substituents on the catalyst on the reaction output suggested that it is required that the N-H forms a hydrogen bond in the transition state. Furthermore, the approach of the dipolarophile is at the opposite site compared to the bulky diphenyl phosphate. Thus, enone 215 was prepared from 4,5,6,7-tetrahydroindol-4-one 1 via acetyl protection and subsequent Mannich/elimination reaction with paraformaldehyde and N-methylanilinium trifluoroacetate. However, the yield was only 5% over two steps. Next, reaction of 215 with benzyl allenic ester 216 with catalytic amount of 217 afforded 283 in 51% yield and an enantiomeric excess of 71%.
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8. Miscellaneous

Rearrangements

Many examples can be found in literature where pyrrole-fused azepinones are formed through Beckmann or Schmidt rearrangements. In this review, we focus on Beckmann or Schmidt rearrangements with the formation of polyheterocyclic structures. In 1978, Bardakos and Milburn reported the formation of tetrazole 210 through the Schmidt reaction of 219 with an excess of hydrazoic acid in chloroform in 34% yield (Scheme 40) [103]. Interestingly, only one regioisomer was observed. An intramolecular Schmidt reaction was attempted with 222, however, it did not afford the envisioned product 223 (Scheme 40) [104]. The Beckmann ring expansion with hydroxylamine and POCl₃ followed by intramolecular substitution of the chloride did afford tricyclic compound 223 in 47–67% yield. Recently, azides 222 have shown to be potential inhibitors of the SARS-CoV-2 main protease [105]. Biological activities of these tricyclic pyrrole-fused azepinones 223 are yet unknown.

In 2013, the group of Booker-Milburn disclosed the synthesis of complex tricyclic and tetracyclic (in the case of tetrahydroindol-4-one 224) aziridines from the photo-induced rearrangement of pyrroles [106]. Thus, N-butyl substituted pyrroles were irradiated with a 6 W low pressure mercury lamp (with most of the emission centered at 254 nm and a small amount of radiation at 312 nm) inducing intramolecular [2+2]-photocycloaddition forming a cyclobutane-fused dihydropyrrole. In cyclobutanes bearing an acyl group at C4 of the pyrrole, such as 225, further excitation leads to biradical bond cleavage and rearrangement to the corresponding aziridine 226 (Scheme 41). Furthermore, it was demonstrated that scale-up of these reactions could be achieved through flow chemistry. In their research concerning the synthetic possibilities of these complex aziridine rings, Knowles and Milburn reported the unusually facile thermal homodiencyl-[1,5]-hydrogen shift reaction of 226 [107]. The formed tetracyclic aziridines 226 were unstable and spontaneously underwent the following thermal [1,5]-hydrogen shift reaction at room temperature toward 227, which explains the moderate yield of 226 due to purification issues. The scope of the reaction was investigated and utilized for kinetic studies which suggest that the high reaction rate of some substrates is due to a combination of ring strain and a highly rigid conformation.

Scheme 39. Enantioselective synthesis of spiro compound 215.

Scheme 40. Beckmann rearrangements with the formation of polyheterocyclic structures.
9. Conclusions

The inherent reactivity of the pyrrole and ketone functionality make 4,5,6,7-tetrahydroindol-4-ones valuable building blocks for the synthesis of medicinally or spectroscopically interesting structures. In this review, a brief overview of the strategies toward 4,5,6,7-tetrahydroindol-4-ones is given. Afterward, we discussed the use of this multifunctional building block for the construction of polyheterocyclic structures which were categorized based on the size and attachment point of the newly formed (heterocyclic) ring. Medicinal or spectroscopic applications were briefly mentioned.

In general, most [1,2]-fused polyheterocyclic structures are originating from an intramolecular electrophilic aromatic substitution (or formal C-H activation) with an N-substituent bearing an electrophilic functionality. This strategy is mostly followed due to the inherent nucleophilicity of the C-2 position of the pyrrole and used for the synthesis of five-, six- and seven-membered (hetero)cycles. The electrophilic functionalities explored are halogens, carbonyls, allenes and alkynes. Other examples are the use of a Dieckmann condensation and a three-component reaction with an unidentified mechanism, however, most likely an oxidation step with air or HNO3 is involved.

When both the N-H of the pyrrole and the C-2 position are substituted, the C-3 position shows nucleophilicity. Therefore, synthesis of [2,3]-fused polyheterocycles from 4,5,6,7-tetrahydroindol-4-ones are mostly starting from an N-substituted pyrrole with the C-2 bearing an electrophilic functionality, which can be introduced on the C-2 position via an electrophilic aromatic substitution or also with formal C-H activation. We discussed the intramolecular electrophilic aromatic substitution on the C-3 as well as double electrophilic aromatic substitutions and C-H activations, first on the C-2 and subsequently on the C-3 position. In the literature, we found multiple examples of six-membered rings fused onto the [2,3]-position of 4,5,6,7-tetrahydroindol-4-ones. However, research onto the synthesis of other ring-sizes fused onto the [2,3]-position is limited by one example where a five-membered fused ring was obtained in one step starting from 3-aminocyclohex-2-enones and ninhydrin.

Due to the considerable ring strain of [3,4]-fused indoles, reports involving tetrahydroindolone are rare. Only one example is found of a five-membered ring [3,4]-fused to an indole, obtained in multiple steps from tetrahydroindolone, which was an unexpected outcome of the reaction. Six- and seven-membered rings are also reported, often in multi-step procedures. These [3,4]-fused six-membered rings are interesting structures resembling derivatives of ergoline alkaloids with potential medicinal applications.

The enolizable ketone functionality of 4,5,6,7-tetrahydroindol-4-ones is an excellent starting point to form [4,5]-fused indoles. This includes pyrroles, pyrazoles, 1,2,3-triazoles, isoxazoles, thiazoles, thiophenes and indoles for five-membered rings as well as (thio)pyranones, pyridinones, pyridazinones, pyrimidine and a carbocycle for the six-membered rings. Interestingly, dehydrogenation of the [4,5]-fused dihydroindole provides the fused indole. However, depending on the reaction conditions, aromatization can occur already during the attempted formation of the fused dihydroindole. Many of these fused indoles have been explored as potentially interesting biological compounds. Therefore, we are convinced that many new routes toward these [4,5]-fused indoles will be explored in the near future.
Interestingly, only one example of the synthesis of spiro compounds starting from tetrahydroindolones can be found. It can be stated that to further explore the chemical space in biologically relevant indolones, more research should be devoted to the exploration of these spiro compounds.

Lastly, a Beckmann and Schmidt rearrangement was discussed to expand the six-membered ring of tetrahydroindolones to obtain seven-membered rings fused to indoles. Another interesting report uses a light-promoted intramolecular [2+2]-cycloadDITION of N-allyl tetrahydroindolone to obtain an instable cyclobutane ring which could further rearrange to interesting tetracyclic aziridines.

Author Contributions: All authors contributed to the review. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by FWO, grant number G0F6619N.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Sample Availability: Not applicable.

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