Catalyzed and uncatalyzed procedures for the syntheses of isomeric covalent multi-indolyl hetero non-metallides: an account

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Abstract
Two or more indole molecules tailored to a single non-metal central atom, through any of their C2–7 positions are not only structurally engaging but also constitute a class of important pharmacophores. Although the body of such multi-indolyl non-metallide molecules are largely shared to the anticancer agent bis(indolyl)methane, other heteroatomic analogs also possess similar medicinal properties. This concise review will discuss various catalytic and uncatalytic synthetic strategies adopted for the synthesis of the non-ionic (non-metallic) versions of these important molecules till date.

Introduction
Indole can be considered as a “prodigy” in the family of nitrogen-based heterocycles, because of its diverse presence in bioactive molecules [1-8], coupled with the distinct nucleophilic chemistry revolving its aromatic benzo-fused pyrrole system as encountered throughout the bibliography [9-15]. It is therefore obvious that a non-metal hydride will become exceptionally crucial when its hydrogen atoms are replaced by this special heterocycle, forming a multi-indolyl hetero non-metal-lide. In contemporary period, the said molecules have earned extensive importance in pharmacology to prevent cancer of a number of human organs, certified by the recent flooding of scientific literature related to bis(indolyl)methanes, which shows the usefulness of this class of molecules for prevention of this terminal disease [16-23]. Related molecules consisting of heteroatoms at the central tethering position have also appeared in the spotlight of anticancer research recently. In line with this high importance associated with the molecules of current topic, i.e., more than one indole molecule flanked by a central atom, conglomeration of the available synthetic methods will have a high scientific value. This review will give a concise account of the same, although preparations of ionic bis(indolyl) metal salts will not be considered [24-33].

Review
The pyrrole C2 and C3 linkages
By virtue of the two available sites in its pyrrole substructure, two indoles can be attached to a central atom via their C-2 or C-3 positions in a symmetric way. The non-symmetric variety
may connect them with C-2 of one with the C-3 of another, via the central atom. Below described are such synthetic strategies which are classified depending on the central tethering atom, largely with boron, carbon, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and tellurium. This review will skip the reports on the corresponding carbon-centered analogs.

**Boranes**

First discovered in 1894 [34], 2,2'-bisarylborinates are used for treating prostate cancers utilizing their property of inhibiting the transient receptor potential channels such as TRPM-7 [35]. In 2015, Murakami synthesized the novel indole C-2 borinic acid derivative 3 by reacting N-methylindole (1) with trisopropyl borate (2) in a strongly basic medium (Scheme 1). The product formation proceeds through the indole C-2 deprotonation mechanism [36].

The reason behind the C-2 attachment of the boron atom rather than at the C-3 position of the indole ring was explained by McGough et al. [37]. They performed a base-free catalytic I₂-assisted indole C–H functionalization (electrophilic borylation) using the N-protected indole 1 and NHC·borane 4a that gave a mixture of the mono and bis isomers (5 and 6, respectively) in fair to excellent yields (Scheme 2a). Increasing the amount of iodine led to less unreacted starting material 1, and increased formation of the bisindole product 6. An almost quantitative conversion of 1 was observed with a high excess of the indole reactant.

**Scheme 1:** Synthesis of 2,2'-bis(indole)borinic ester 3.

![Scheme 1](image1)

**Scheme 2:** Synthesis of 2,2'-bisindole NHC·boranes by an S₈Ar mechanism.

![Scheme 2](image2)
It is seen that in the presence of a base the C-2 deprotonation becomes very fast in 9 (for regaining aromaticity) so the boron at the initial C-3-borylated intermediate 8 cannot migrate fast enough, leading to a C-3 borylation product 10a (unlike Pd) [38-40]. Here the absence of the base resulted in a slow or no C-2 deprotonation of 9, which in turn forces the boron to migrate to C-2 from C-3 (8, Scheme 2b) to result in the C-2 borylation (10b).

**Amines**

Bis(indolyl)amines have recently become important as organic electroluminescent materials [41]. Hongtao and co-workers reported the synthesis of tetrakisindole species 13 through the coupling of aniline (12) and indole-2-boronic acid pinacol ester 11 using the Buchwald–Hartwig method (Scheme 3a) [42]. In a similar fashion, Han reported the syntheses of the symmetric and unsymmetric triaryl-substituted amines 15, 18, and 20 [43]. Taking aniline as the pivotal moiety, it was coupled with isomeric bromoindoles 14 and 16 for the synthesis of the targeted products (Scheme 3b).

**Ethers**

Hongtao and co-workers also studied the electroluminescence properties of the 3,3’-bis(indolyl) ether derivatives 23, 26, and 28. The materials were prepared by the Pd(0)-mediated coupling of lithium N-arylindole-3-alkoxide 21 with 3-bromo-N-arylindole 22, followed by a further C-2 bromination (24) and subsequent Suzuki reaction with boronic acids 27 or 25 (Scheme 4) [42]. A similar class of molecules have found broad applications in organic electroluminescent devices [44].

**Silanes**

Heteroaryl compounds containing silicon, an earth abundant and non-toxic element, are important in organic electronics or photonics and in the field of drug discovery and nuclear medicine [45-50]. The first property could be attributed to the facile orbital interactions of the σ* orbital of silicon and the π* orbital of the butadiene unit, which overall lowers the energy of the LUMO [51,52]. Known previously with expensive transition-metal
Grubbs demonstrated the first KOr-Bu-catalyzed C2–H silylation of N-methylindole (1) with observed H₂ evolution [54]. Here the di(indol-2-yl)silane (31) was found as a minor product though (Scheme 5a). The reaction has a high turnover number of 92 and it was halted in the presence of radical scavengers. However, the mechanism was unidentified,
although it was proved to not going via a Minisci-type silyl radical addition [55], as the reaction with pyridine did not afford any product.

Bell studied the properties of such molecules which are similar to those used in OLED devices (organic light emitting diodes) in 2017. The molecule 34 was synthesized by base-mediated reaction of bisindole derivative 32 with Ph₂SiCl₂ (33, Scheme 5b) [56]. The dissociation of the indole C-2–Si bond upon UV light excitation generates a hole transport layer (HTL) in these materials, facilitating the optical activity [57].

In 1996, Frenzel reported the synthesis of bis(indol-3-yl)silane 38 that involved n-BuLi as the base [58]. The strategy was later adopted by Ohshita in 2004 (40a, Scheme 6) [59].

Between 2016 and 2018, some acid-catalyzed syntheses of bis(indol-3-yl)silanes appeared [60-63]. Chen and co-workers demonstrated a Brønsted acid-catalyzed Friedel–Crafts process, where hydroxilsilanes 41 were treated with an excess amount of indoles (Scheme 7a and Scheme 7b) [60]. Brookhart’s acid [H(OEt₂)₂][BArF₄] − (42) was used to generate ether-stabilized silicon cations of type 46 and norbornene was added as a proton scavenger [64]. Following this procedure, Yonekura synthesized the similar compound 40, using a catalytic Lewis acid Zn(NTf₂)₂ and stoichiometric Lewis base γ-picoline combination in n-butyronitrile as solvent (Scheme 7c) [61]. This electron-donating solvent and toluene in the former reaction acted as stabilizers to the electron-deficient silicon species in the similar mechanisms. First, the Brønsted or Lewis acid coordinates with silane 51 leading to a solvent-stabilized electron-deficient silane complex 57, where N-protected indole attacks in a Friedel–Crafts fashion to give the 3-silylindoles 60 along with molecular hydrogen (Scheme 7b and Scheme 7d). A repetition of the processes leads to the bis(indol-3-yl)silanes 40.

Han described a Lewis acid-promoted C3-silylation of N-protected substituted indoles by a disproportionation mechanism of the latter. He used both Bi(C₆F₅)₃ and Al(C₆F₅)₃ in the reactions (Scheme 8a and Scheme 8c) which followed a similar mechanism (Scheme 8b) [62,63]. The reduced form of indole, i.e., indoline 50 coordinates with the Lewis acid to form a complex which activates PhSiH₃ (frustrated Lewis pair) for silylation (69, Scheme 8b).

Phosphines

The base-mediated syntheses of bis(indol-2-yl)phosphines 76 and 78 were demonstrated by Yu. A suitable halophosphine 75 was reacted with C₂-deprotonated C₃-tethered (77) or untethered (74) N-protected indoles for that purpose (Scheme 9a) [65]. Later, Wassenaar reported a similar strategy with trichlorophosphine as the electrophile for attaching three indole moieties to a single P-atom (80, Scheme 9b) [66]. A similar protocol was adopted by van de Watering in their recent syntheses [67,68].

Sulfides

The C₂ tethering of indoles with sulfur can be achieved in neutral medium by treatment with various SL₂ (L is a leaving group) moieties [69,70]. This is a common method for the synthesis of bis(indol-2-yl)sulfides which are the precursors of potent bioactive molecules [71-73].

The simple synthetic strategies for the molecular units 82 were first reported by Barbier in 1989. The condensation of tryptamine monoacetate (81a) or indole oxime (81b) with sulfur dichloride in a Friedel–Crafts fashion (Scheme 10a) gave 82.
Scheme 7: Acid-catalyzed syntheses of bis(indol-3-yl)silanes and mechanisms.
Scheme 8: B(C₆F₅)₃ and Al(C₆F₅)₃-catalyzed syntheses of bis(indol-3-yl)silanes reported by Han.

with moderate to good product yields, respectively [69,70]. A similar work by Janosik involved strongly basic conditions at low temperature with bis(phenylsulfonyl)sulfide (83) as the sulfur donor (Scheme 10b) [73,74].

Disulfides are also important reagents for accessing bis(indolyl)sulfides. To synthesize the unsymmetrical bis(indolyl)sulfide 88, Janosik reacted the indole disulfide 87 with free indole and obtained the product 88 in 81% yield, where the sulfur linkages were 2,3'- with respect to the two indole nuclei (Scheme 11a) [73-76]. Hall and Dockendorf prepared the corresponding 2,2'-sulfur-substituted compounds 90 by reacting tryptophan amines 89 and 90 with S₂Cl₂ under neutral and acidic conditions, respectively (Scheme 11b and Scheme 11c) [77,78].

Kamal took a different approach using a CuO nanoparticle-supported graphene-oxide (denoted as CuO@GO, 0.38 mol %) catalyzed S-arylation (C–S coupling) of 2-iodoindole (92) to synthesize diindol-2-ylsulfide (84) in 75% yield (Scheme 12) [79]. Here 1.5 equivalents of thiourea acted as the sulfur source.

Bis(indol-3-yl)sulfides are also present as structural motifs in important organic compounds having semiconductor properties [80]. The syntheses of these compounds were studied by Janosik in 2006. The N-silyl-protected 3-bromoindole 93 was
Scheme 9: Base-mediated syntheses of bis and tris(indol-2-yl)phosphines.

a) Yu, 2005 [65]

\[
\text{Scheme 10: Synthesis of bis(indol-2-yl)sulfides using SL}_2\text{-type reagents.}
\]

b) Wassenaar, 2010 [66]

\[
\text{Scheme 10: Synthesis of bis(indol-2-yl)sulfides using SL}_2\text{-type reagents.}
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subjected to strong basic medium (t-BuLi) at low temperature and then quenched with either bis(phenylsulfonyl)sulfide (83) or indole disulfide 94 (Scheme 13) to afford the products 95 or 96, respectively [76].

Manishankar and co-workers dealt with a facile Fischer indole process to convert thiodiketones 97 to bis(indol-3-yl)sulfides 98 by refluxing them with phenylhydrazine hydrochloride salt in ethanol [81]. Interestingly, changing the solvent to THF switched the product to thioketone 99 (Scheme 14). Refluxing the thioketones 99 again with phenylhydrazine in ethanol resulted in the desired bis(indol-3-yl)sulfides 98. On the other hand, the treatment of thioketones 99 with phenylhydrazine afforded the corresponding hydrazones 100 only, thus stating the requirement of acid for this Fischer indole synthesis.

Elemental sulfur has also been utilized in preparing bis(indol-3-yl)sulfides under transition-metal compound catalyzed spontaneous oxidation of the central chalcogen atom. Such reactions were carried out by Shibahara (2014) and Yang (2016) [82,83]. Both reactions used aerial oxygen as the oxidizing agent for sulfur (Scheme 15). Shibahara utilized 20 mol % copper(I) thioephene-2-carboxylate (CuTC) as the catalyst, where heating N-methylindole (1) with elemental sulfur in DMSO as solvent at 90 °C under aerial oxygen led to the desired product 101 in 49% yield [82]. Other copper catalysts such as CuCl or CuBr gave low yields, even when used with 2,2'-bipyridyl as the ligand. First, oxidation of copper(I) takes place, which interacts with elemental sulfur to "activate" it. A nucleophilic attack from N-methylindole (1) to the sulfur species 102 takes place to generate copper sulfide complex 103. An oxidative homocoupling gives the bis(indol-3-yl)sulfide 101. Simultaneously, an oxidative homocoupling of the copper sulfide complex can take place to afford disulfide 104, that reacts with N-methylindole again under oxidative conditions, catalyzed by CuTC to give the desired product 101 (Scheme 15a).
Scheme 13: Synthesis of bis(indol-3-yl)sulfides using N-silylated 3-bromoindole 93.

Scheme 14: Fischer indole synthesis of bis(indol-3-yl)sulfides using thio diketones.

On the other hand, Yang synthesized bis(indol-3-yl)sulfides 105 through the reaction of indole with elemental sulfur, catalyzed by iron(II) sulfate in the presence of stoichiometric amounts of KI in air [83]. The I\(^-\) from KI formed ferrous iodide, which reacts with indole to form the bis-indolide 107, followed by reaction with N,N-dimethylmethanethioamide to get the S atom inserted (108). A reductive elimination then generated the bis(indol-3-yl)sulfides 105 along with Fe\(^0\), which was re-oxidized by aerial oxygen to re-participate in the reaction (Scheme 15b).

There are several uses of sulfoxides as a thiol-free sulfur source for introducing sulfur at the indole C3 position [84-86]. In 2013, Hamashima reported a synthesis of di(indol-3-yl)sulfide (105a) by reacting indole with DMSO in the presence of trifluoroacetic anhydride (TFAA) in total 6 steps (Scheme 16a) [84]. Already used by Hartke in 1988, this reagent combination (109) is a source for MeS\(^+\), so its use does not lead to any formation of disulfides [87]. First, 109 is attacked by indole and a demethylation of sulfur occurs leading to 3-(methylthio)indole (111). As the sulfur in 111 is methyl-protected, no dimerization occurs. Oxidation of sulfur by oxone followed by repetition of the previous steps afford the diindol-3-ylsulfonium salt 114, which in the presence of a base gives product 105a.

Li et al. used 2-(fluorosulfonyl)difluoroacetic acid (115) as the “S” source to synthesize bis(indol-3-yl)sulfides 116 from...
N-protected indoles 1 or 61 [85]. The products 116 were formed within a few seconds in the presence of a moderate base at high temperature (Scheme 16b), tolerating groups having both electron-donating and withdrawing nature on 1. Here the base assisted the condensation of 2-(fluorosulfonyl)difluoroacetic acid (115) with 1 followed by decarboxylation to give difluorocarbene and sulfinate 119, that combine to produce sulfanol 121, which in the presence of acid and reaction with another molecule of indole affords 105.

In 2018, Procter used a similar strategy to that reported by Hamashima for the synthesis of similar molecules 125 with good to moderate yields using electron-donating groups at the indole ring. The yields decreased with indoles having electron-withdrawing groups (Scheme 16c) [86]. Here diallyl sulfoxide (123) was used with TFCA to obtain diallyl intermediate 127. The latter undergoes a [3,3]-sigmatropic reaction to afford allyl (2-allylindol-3-yl)sulfide 128, which is oxidized by m-CPBA to sulfine 124. Repetition of the steps along with indole addition

**Scheme 15**: Oxidative synthesis of bis(indol-3-yl)sulfides using indoles and elemental sulfur.
Scheme 16: Synthesis of bis(indol-3-yl)sulfides using sulfoxides as sulfur source.
led to the desired products. Here the absence of a β-hydrogen in the diallylsulfoxide (123) did not allow any Pummerer rearrangement [88,89].

Selenides
In 1997, Showalter synthesized bis(indol-2-yl)selenanes (or selenides) 130 having potential tyrosine kinase inhibitor activities [90,91]. The synthesis was achieved by reacting diselenium dichloride with (R)-tryptophan amide 129 (Scheme 17a) [92]. Bis(indol-2-yl)selane 130 was found as a byproduct having very low such bioactivity. The polyselenanes formed were separated by treating them with NaBH₄, which did not affect the monoselane 130.

On the other hand, selenopyrans structurally resemble indolocarbazoles, which possess AhR affinity [93]. Janosik presented a synthesis of such selenopyrans 132 via the bis(indol-2-yl)selenanes 131 [73]. Treating these compounds with orthoformate esters in the presence of the Brønsted acid MeSO₃H led to the target selenopyrans (Scheme 17b). The methylated analogs of 132 displayed high efficiency for activating AhR.

Bis(indol-3-yl)selenanes possess antioxidant properties. Pioneered by Wilshire [94], their syntheses were studied by Abele [95], Naidu [96], Yang [83], Thurow [97], and Talukdar [98]. The work of Abele in 2004 involved refluxing SeO₂ with N-unprotected indole in benzene which resulted in low yields of the products 134 (Scheme 18a) [44]. Using different N-protected substituted indoles 135, Naidu observed improved yields of 136 when catalytic oxidant I₂ was added in 1,4-dioxane as solvent (Scheme 18b) [96]. Using aerial oxygen as the oxidant, Yang used Se⁰ in the presence of stoichiometric KI and catalytic amounts of Fe⁵⁺ for the synthesis of similar bis(indol-3-yl)selenanes (Scheme 18c) [83].

In 2018 Thurow reported a method using stoichiometric SeO₂ along with sub-stoichiometric PhSSPh (138) to obtain a mixture of the desired diindol-3-ylselenane (137a) along with mono- and di(phenylthio)-substituted indoles 139 and 140 (Scheme 18d) [97]. Catalytic iodine was used to oxidize PhSSPh (138) to PhSI (141), to which indole adds to give (phenylthio)indole 139 along with HI. HI reduces SeO₂ to Se. Se interacts with two molecules of indole in the presence of air to give the desired product 137a. In a parallel pathway the product decomposes to selenone 144, 3-(phenylthio)indole (139) and regenerates Se.

In a recent effort by Talukdar, the cheap and non-anhydrous solvent ethanol was used to prepare the desired bis(indol-3-yl)selenanes 136 in moderate yields [98]. Following the assumption (formation of triselenide 145) made by Wilshire [94] together with the detection of the oxidized products isatins in the reaction mixture, a disproportionation mechanism of SeO₂ can be drawn giving bis(indol-3-yl)triselenide 145 and Se⁶⁺ (Scheme 18e). The triselenide 145 converts into bis(indol-3-yl)selane 146 with liberation of Se⁰. Se⁶⁺ can generate Se⁵⁺ or

\[ \text{Scheme 17: Syntheses of bis(indol-2-yl)selenanes.} \]
Scheme 18: Syntheses of bis(indol-3-yl)selanes.
SeIV by either oxidizing indoles to isatins, or by a comproportionation reaction with Se0 to give 136.

**Tellurides**
Engman claimed a synthesis of the titular compounds 147 and 148 in the year 1994 by reacting the C2 anion 149 of the N-sulfonfyl-protected indole 1o with metallic Te in four steps including desulfonation (Scheme 19) [99]. The treatment with base followed by the addition of elemental tellurium to N-protected indole 1o generates lithium telluride 150. Telluride 150 is then oxidized to ditelluride 151 by treatment with ferrocyanide. A Cu powder-mediated reduction gives the N-protected bis(indolyltellane 147. The final desulfonated product 148 is a potent thiol peroxidase reducing agent [100].

**The benzenoid C4 and C7 linkages**
The syntheses of bisindolyl non-metallides connected through benzenoid rings of the indoles are less studied compared to the same through their pyrrole counterpart. The corresponding compounds are investigated for boron, nitrogen, oxygen, sulfur, and selenium as the central connecting atom.

**Boranes**
The indole alkaloid dragmacidin D is a marine secondary metabolite which was recently found active against Parkinson’s and Alzheimer’s diseases [101-103]. In 2002, Jiang, while studying its synthesis, found the tris(indolyl)borane 154 instead of the desired chiral indole alcohol 155 while reacting the N-silylated 4-bromoindole 152 with n-BuLi in a failed regioselective ring opening attempt of chiral oxirane 153 in the presence of BF3Et2O (Scheme 20) [104]. The synthetic route to the desired product was smoothly brought to its course by employing CuCN in the medium.

![Scheme 20: Synthesis of tris(indolyl)borane 154.](image-url)

**Scheme 19: Synthesis of bis(indol-2-yl)tellane 147.**
Amines

The enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase (TDO) are responsible for tryptophan metabolism in the human body. Thus, the inhibition of these enzymes may help in tumor immunotherapy [105-107]. Xu recently found indole-2-carboxylic acid derivatives as IDO1/TDO dual inhibitors. In their effort to synthesize the following bis(indol-4-yl)amine derivatives via a Buchwald amination led to the 4-amino-substituted compounds 158 or acids 159 after basic hydrolysis (Scheme 21) [108]. Compound 159c had the maximum potency against IDO1 and TDO with IC$_{50}$ values of 2.72 mM and 3.48 mM, respectively compared to 159a and 159b, which is 15 and 28.5 times higher than that of hit compound 160.

As discussed earlier, bis(indolyl)amines possess electroluminescent properties [41,109]. In 2009, Yagi and co-workers synthesized a large library of bis(indol-5-yl)amines 163 for studying their efficiency in organic electroluminescent devices, where 5-bromoindoles and 5-aminoindoles were taken as partners in a Buchwald coupling (Scheme 22a) [44]. On the other hand, in 2015, Organ’s group performed a phosphine-ligand free Buchwald amination of 5-chloroindole (164) with amine 165 to give the desired product 167, where the use of the Pd-PEPPSI-
IPent\textsuperscript{Cl} precatalyst 166 in presence of the strong base led to the formation of the over-aminated product 168 (Scheme 22b) \[110]\).

Alzheimer’s disease is caused by the β-amyloid-42 aggregation in brain tissue \[111,112]\). In 2017, Sreenivasachary synthesized a library of 6,5'- and 6,6'-bis(indolyl)amines and other similar 7-azaindole derivatives as potent anti-Alzheimer agents (171, 172) by a Buchwald coupling of the corresponding C3-substituted amines 170 and indole 5/6-bromides 169 (Scheme 23) \[113]\). Cyano, 4-piperidinyl and N-methylpiperidinyl substitutions at the indole and 7-azaindoles were necessary to improve the brain penetration ability of the products. Up to >80% inhibition of the amyloid-β peptide aggregates were achieved with these compounds, with the highest activity found for the 4-N-methylpiperidinyl derivative.

**Ethers**

The synthesis of the bis(indol-6-yl) ether 175 was performed by Chai in 2017. Their protocol used a Cu(OAc)\textsubscript{2}-mediated coupling of N-silylated 6-hydroxyindole 174 with the corresponding boronic acid 173 (Scheme 24) \[114]\). For further synthetic transformations of 175, N-protection with bromo esters 176 followed by hydrolysis towards acids 177a and 177b were performed. The products 177a and 177b are potent anti-HIV agents.
Although the synthesis of 7,7'-bis-indolyl ether was known prior to Chai’s report [114]. In 1989, Black found the 7,7'-dimerised product 179 of the indole derivative 178 as a hindered biphenyl analog via its prompt oxidation in the presence of quinones. The bis(indol-7-yI) ether 180 was found in 10% yield when chloranil was used as the oxidant (Scheme 25) [115]. The high electrophilicity of 178 at the C7 position resulted in this product formation. The reaction proceeds through the radical intermediate 181.

**Sulfides**
Reddy synthesized the di(indol-5-yI)sulfide (183) via a cascade strategy with 5-iodoindole (182) in the presence of thiourea and a recyclable CuO nanoparticle catalyst (Scheme 26) [116]. This heterogeneous catalysis strategy bypasses the use of unpleasant aryl thiols, which are generally coupled with other aryl halides in the presence of transition-metal catalysts for obtaining diaryl sulfides [117].

**Selenides**
Along with the oxygen insertion, Black et al. also performed the oxidative selenium insertion into the C-7 position of highly electrophilic 2-methylindole derivative 184. The dual role of selenium dioxide consists of activation of the C-7 position giving the dimerized 7,7'-bis(indolyl) products 185 with the 2-methyl group transformed to the aldehyde in the same step (Scheme 27) [118,119]. The less electronically activated N-acyl substrate gave a slightly better yield. Selenation occurs at C-3 instead of C-7 for the C-3 unsubstituted substrates.

**Conclusion**
This review summarizes the various (un)catalytic synthetic techniques of the symmetric and unsymmetric bis/tris(indolyl)-containing non-metallides consisting of multiple indole molecules covalently connected via C2, C3 (pyrrole ring) and C4–C7 (benzenoid ring) by different central atoms. Like the bis(indolyl)methanes (anticancer substances), these products are
important potential pharmaceutically active ingredients as well. As a result, they have gathered much attention in the current decade as suggested by the number of contemporary publications associated. The described schemes involve both simple and challenging strategies depending on the central tethering atom involved. As time progresses, research on the synthesis and application of this class of molecules will be more broadened.

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