Review Article: A Brief Review on Exceedingly Rare *N, N'*-Bisindole

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ABSTRACT

The scope of the present review article is associated with diverse synthetic protocols and significance of *N,N'*-linked bisindole core. The chemistry involved in making of this type of extremely rare heterocycle always of high significance for the chemists in the field of synthetic chemistry as well as in natural products. The interest becomes need when the motif exists in some bioactive natural products. A detailed discussion has been confined to the literature published till September 2022. To our knowledge, this is the first review article on *N,N'*-bisindole motif.

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1. Introduction

The name *indole* is portmanteau of the words *indigo* and *oleum* since indole was first isolated by treatment of the indigo dye with oleum. The word indole is coined from the word India, a blue dye imported from India known as Indigo. Indigo can be converted to isatin, and then to oxindole [1]. Indole derivatives represent one of the most important heterocyclic rings which provide privileged scaffolds in drug discovery and medicinal chemistry. The substituted indole nucleus [2-4] is an important structural component of vast number of biologically active natural products such as heteroauxin [5-8], tryptophan [9-15], hypaphorine [16, 17], bufotenin [18], and gramine [19, 20], etc. Indole derivatives are also found widely in plants, animals, and marine organisms [21]. Moreover, the structure and activity of bisindole alkaloids have been reported and the investigation of isolated bisindole alkaloids are increasing day by day [22-27]. Bisindole natural products [28-32] consists of two monomeric indole alkaloid scaffolds as their necessitate ingredients and

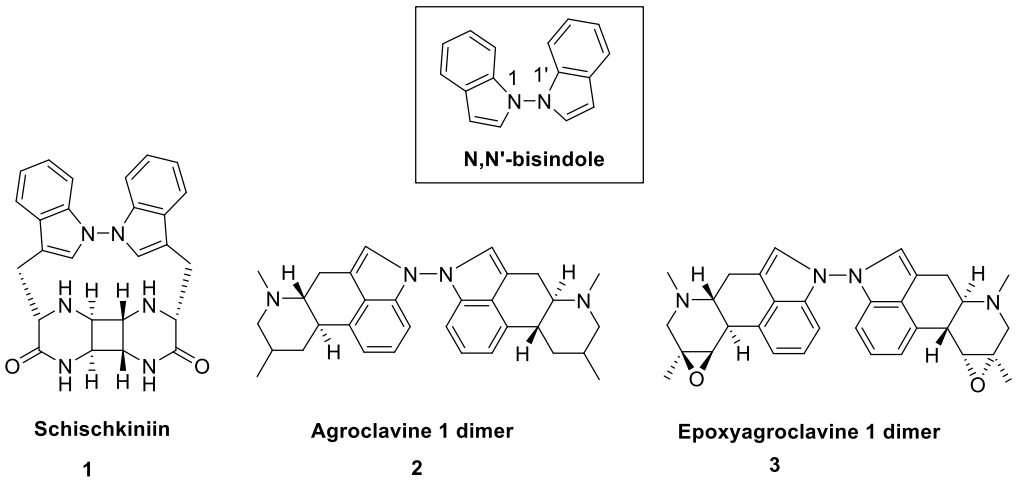


Figure 1. *N, N'*-bisindole nucleus containing natural products

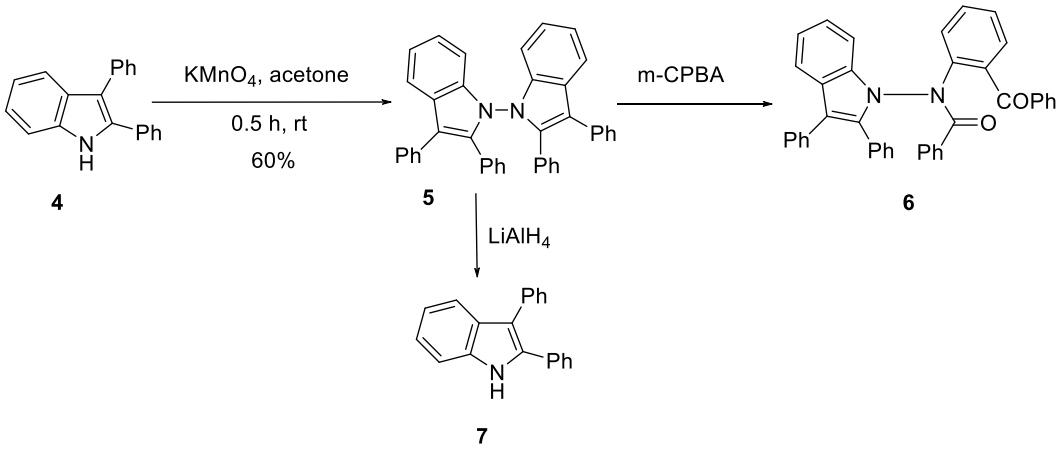
are more effective with regard to their respective monomeric units. In addition, establishing new protocols towards the bisindoles synthesis are more challengeable than the synthesis of monomeric indole alkaloids [33-35]. Among bisindoles, the *N, N'*-bisindoles are extremely rare and still there is a need to be explored in this area as very few synthetic methodologies have been reported. As the isolated alkaloids containing rare *N, N'*-bisindoles motif (**2, 3**) are increasing (**Figure 1**) [36, 37], we have decided to review the literature reports on the synthesis of *N, N'*-bisindoles. The review cited the references till September 2022.

2. Synthesis and Bioactivity

Although the *N, N'*-bisindole moiety was observed in a hypothetical intermediate during the oxidation of 3-indoleacetic acid over 60 years ago [38], synthesis for making this heterocyclic motif is not widely explored. In 2005, an anti-cancer bisindole natural product Schischkiniin (**1**) was isolated from seeds of the thistle *Centaurea schischkinii* by Sarker and co-workers [36]. This natural product possesses an extremely rare *N, N'*-linked bisindole motif embedded within a 14-membered macrocycle proposed to arise from dehydration of two Trp-Glydiketo piperazines followed by [2+2]-cycloaddition [39]. Schischkiniin (**1**) is assessed in DPPH assay for free radical scavenging properties, the general toxicity by brine shrimp lethality and cytotoxicity in MTT cytotoxicity assays using CaCo-2 colon cancer cell lines. It exhibited promising *in vitro* anticancer activity (IC_{50}=76 mM).

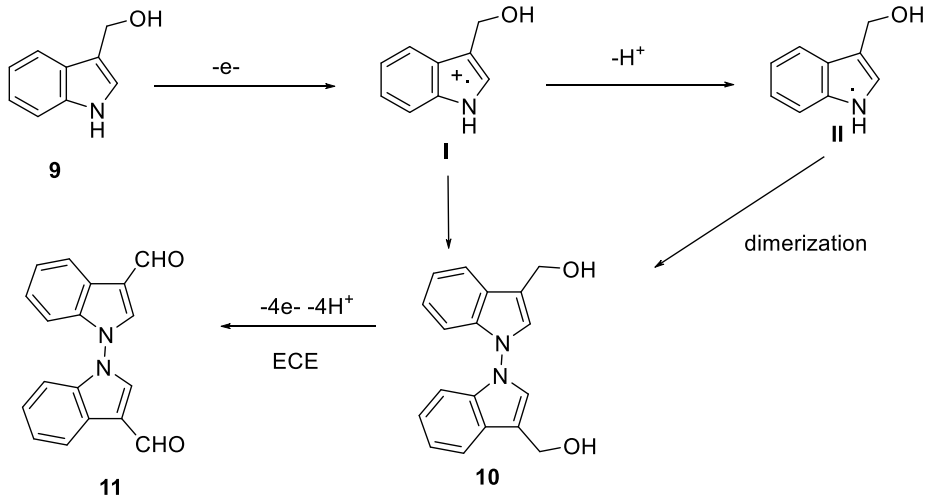
3. Miscellaneous Method of *N, N'*-Bisindole Synthesis

Koelsch [40] reported the formation of a compound, $C_{40}H_{28}N_2O+C_6H_6$ (from benzene-ethanol), m.p. 199-200 °C in 1944 by reacting 2, 3-diphenylindole (**4**) and potassium permanganate. However, no structure was assigned to that novel compound (**Scheme 1**). Almost a quarter century later Dave [41] characterized the product's structure as a *N, N'*-dimer based on the analytical data, spectroscopic, and chemical evidence. The spectroscopic data of the compound (molecular ion *m/e* 536) included the diphenylindole chromophore (UV), only aromatic hydrogen atoms (NMR) and no NH group (IR). These spectral data suggested the probable linking of two diphenylindole molecules **5** by the nitrogen atoms. This was definitely the case revealed by reductive cleavage of nitrogen-nitrogen single bond by lithium aluminum hydride to afford only 2, 3-diphenylindole (**7**) as a product. The dimeric indole structure **5** was further supported by the reaction with *m*-chloroperbenzoic acid (*m*-CPBA) which gave the *N*-benzoyl-*o*-aminobenzophenone derivative **6**.

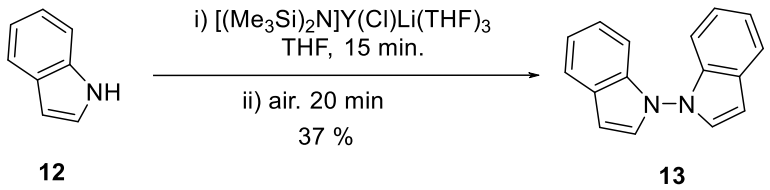


Scheme 1. Characterization of structure of *N*, *N*′-dimer

Goyal *et al.* [42] have developed the synthesis of 3-carbaldehydebisindole (**11**) (**Scheme 2**) from the electrochemical oxidation of indole-3-methanol in persulfate-medium and phosphate buffers. In this oxidation, pyrolytic graphite electrode (PGE) was used and the electrode reaction underwent the ECE (Electron transfer - Chemical reaction- Electron transfer) mechanism. The following mechanism can be proposed for the oxidation of indole-3-methanol (**9**) using PGE on the basis of voltammetric behavior, spectral behavior, coulometry and product characterization. In the first step, a radical cation moiety (**I**) was formed from the oxidation of indole-3-methanol by losing 1e (single electron) step as depicted in **Scheme 2**. However, one electron was removed from the pyrrole -NH of indole which was already reported in oxidation of indole [43]. The cation radical (**I**) further deprotonated to give neutral free radical **II** as well as dimerized by losing two protons to afford a dimer **10**. The participation of the free indolyl radical in this step was not completely ruled out in view of the pKa of the indolyl radical cation which is ~5.0 as reported in the literature [44]. Consequently, N–N linked dimer **10** was formed from the dimerization of radical cation. Then, the methanol group was oxidized *via* the ECE mechanism in a 2e, $2H^+$ process to provide the aldehydic dimer **11**, which has been characterized by its mass and NMR spectra.



Scheme 2. Electrochemical synthesis of 3-carbaldehyde bisindole



Scheme 3. Synthesis of *N, N*'-bisindole through oxidation

Zang *et al.* [45] have established a novel N-N coupling reaction by treatment of the easily available rare-earth-metal (RE) amides $[(Me_3Si)_2N]_3RE(\mu\text{-}Cl)Li(THF)_3$ with aromatic primary or secondary amines via oxidation of rare-earth-metal-nitrogen bonds produced. In this reaction, the symmetrical or unsymmetrical azo compounds and hydrazine derivatives were afforded under the mild conditions in good to high yields within a very short time. Using the yttrium amides $[(Me_3Si)_2N]_3Y(\mu\text{-}Cl)Li(THF)_3$ complex *N,N*'-bisindole was synthesized via oxidation of yttrium-nitrogen bonds in good yield (**Scheme 3)**.

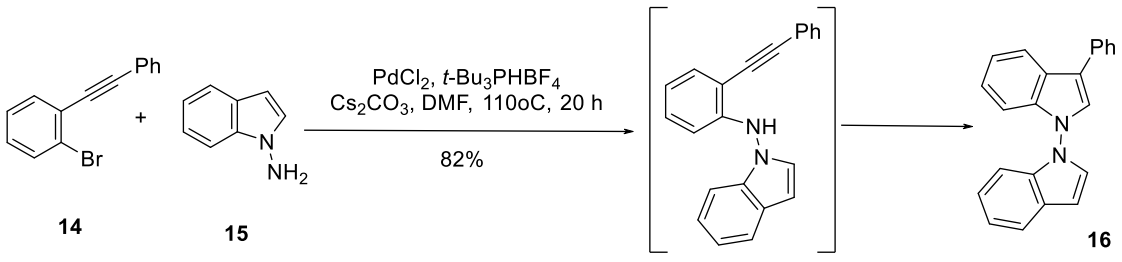
The amino radical obtained from the oxidation of rare-earth-metal-nitrogen (RE-N) bonds is responsible for the N-N coupling reaction. This experiment is supported on the basis of isolation of the amido complex, characterized by using NMR and ESR probes of the intermediates.

In an another important invention, Kushmaro *et al*. [46] reported bisindole**13** or a combination of **13** for the use in inhibiting biofilm [47-50] formation by bacteria on a surface or disrupting existing biofilm in medical and environmental settings.

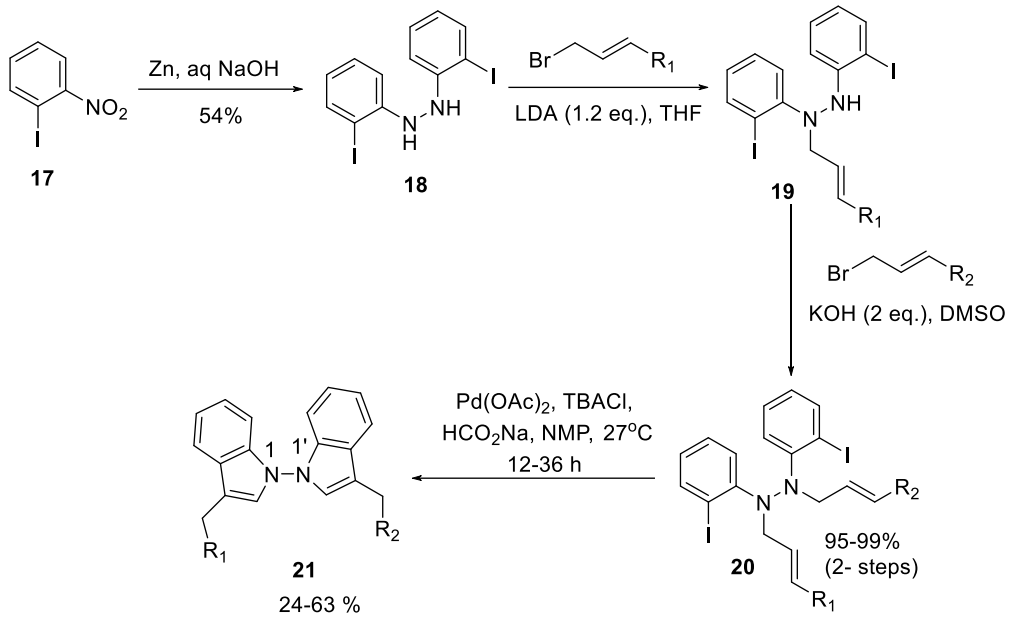
An efficient palladium catalyzed one-pot domino reaction was reported by Halland *et al*. [51] with 2-bromo phenyl acetylene and indol-1-amine gave N-indole substituted 2-phenylindoles in excellent yield (82%) (**Scheme 4**).

Initially, *N*'-aryl-*N,N*'-indole was formed through palladium catalyzed coupling between 2-bromo phenyl acetylene (**14**) and indol-1-amine (**15**), in this reaction which further underwent in situ *"5-endo-dig"* cyclization to obtain the desired 1-indol-1-yl-3-phenyl-indole (**16**). One of the synthetic precursor 1-aminoindoles of this palladium catalyzed domino synthesis was obtained from the reaction of readily available 2-halophenylacetylenes and *N, N*'-disubstituted hydrazines in good to excellent yields in just a few hours under mild reaction conditions with high functional group tolerance.

Recently, the first general synthetic approach to *N, N*'-bisindoles was reported by Wang *et al.* [52] using double Mori-Ban cyclization. Bisindolization of several diallylated hydrazobenzenes were affected by using simultaneous Mori–Ban reactions twice with minimal cleavage of the N–N bond (**Scheme 5**) under ambient temperature. The iodohydrozobenzene **18** was prepared from 2-iodonitrobenzene **17** by reduction with zinc metal. A series of diallylatedhydrazobenzenes **20** were afforded from two-steps allylation of



Scheme 4. Palladium catalyzed one-pot domino reaction to synthesize substituted *N, N*'-bisindole



Scheme 5. Synthetic approach to *N, N*'-bisindoles

18 with various allyl bromides *via* monoallylated **19** that was later subjected to intramolecular, base-free, reductive Heck reaction condition produced bisindolization **21** in 24-63% yields. The methodology was used to access different 3,3'-dialkyl-*N,N*'-bisindoles (**Figure 2**, **21a-e**), 3,3'-dibenzyl-*N,N*'-bisindoles (**21f**), and along with an unsymmetrical *N,N*'-bisindole (**21e**) in moderate to good yields which can be beneficial in future for synthesizing similar scaffolds.

Owing to its promising methodology, several attempts were made to the formal synthesis of Schischkiniin (**1**) [39], but the efforts went unsuccessful on final photochemical [2+2] cyclization step (**Scheme 6**).

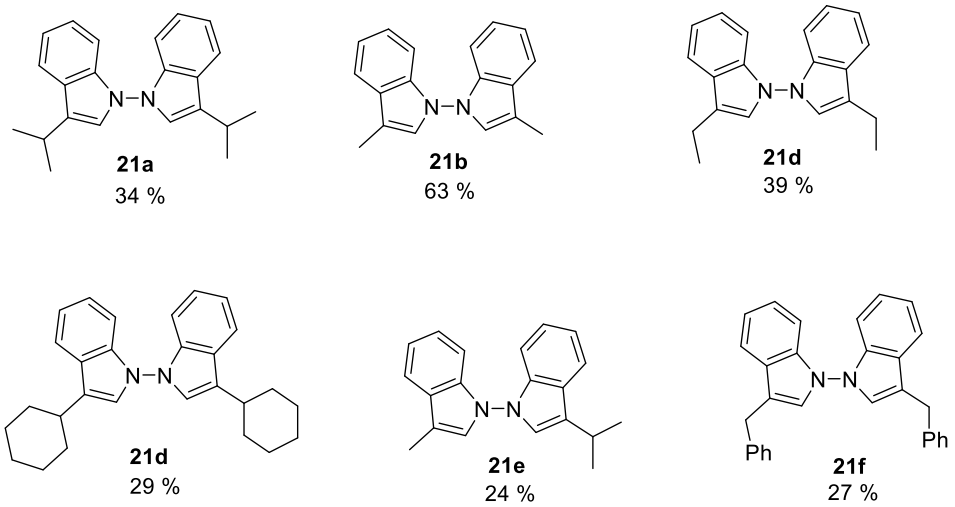
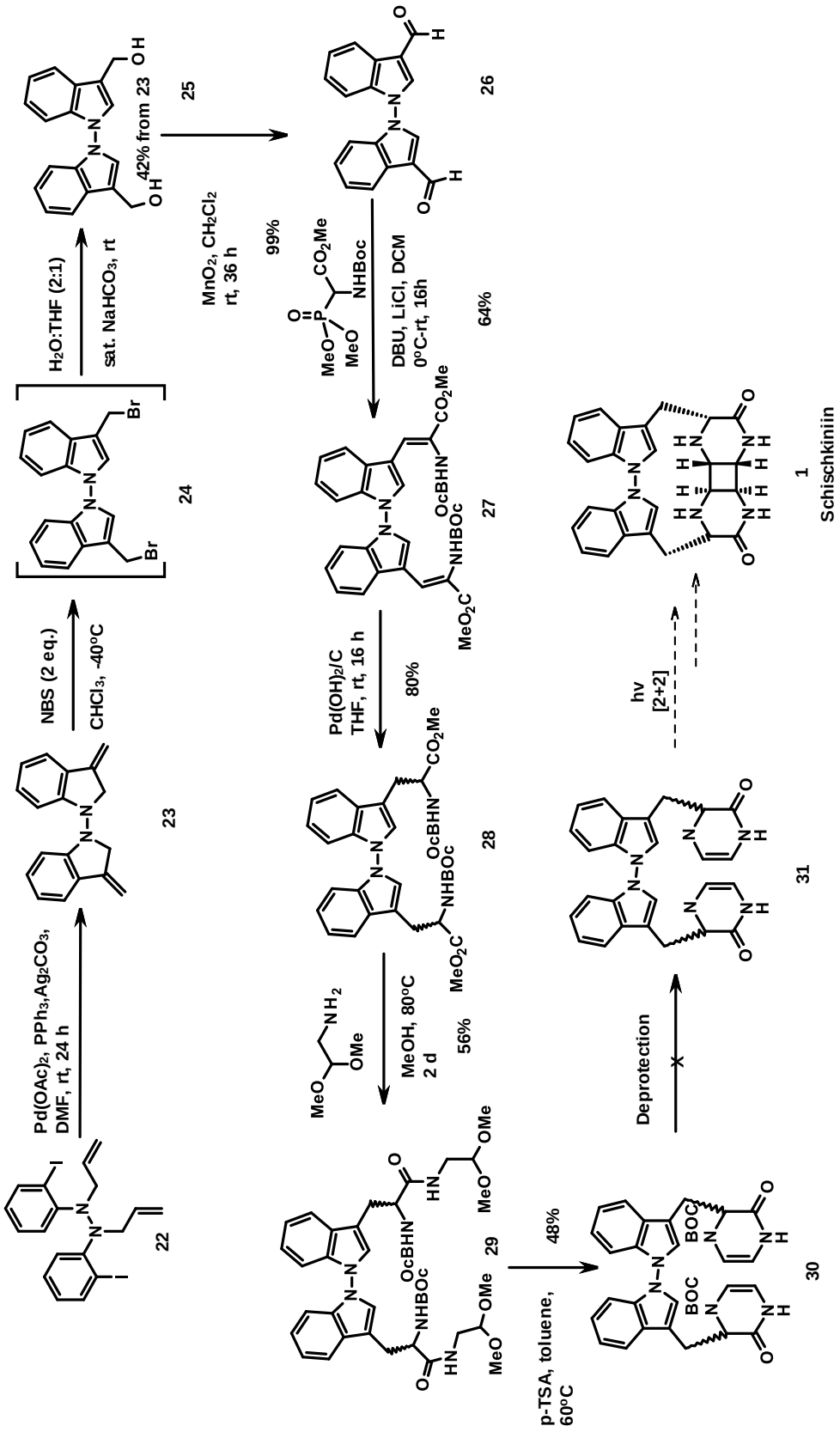


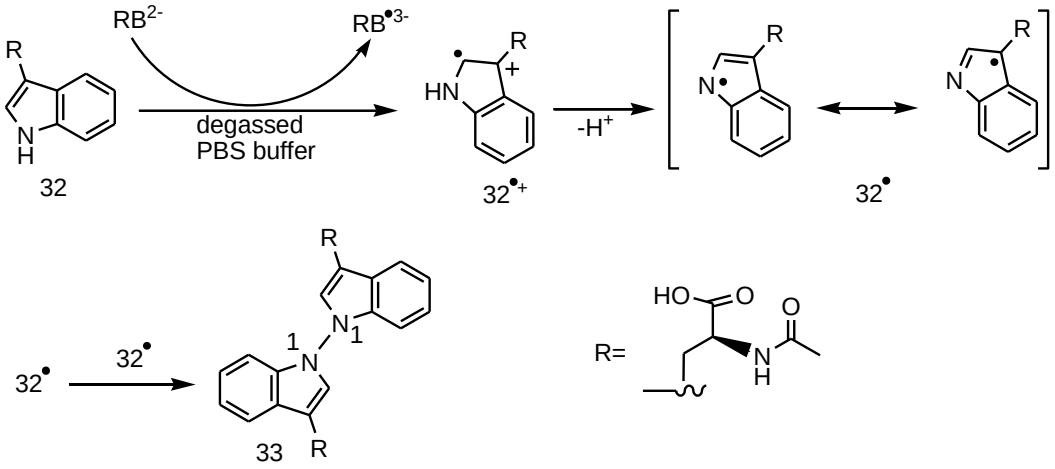
Figure 2. *N, N*'-Bisindole derivatives synthesized by double Mori-Ban cyclization



Scheme 6. Synthetic Scheme of Schischkiniin (**1**)

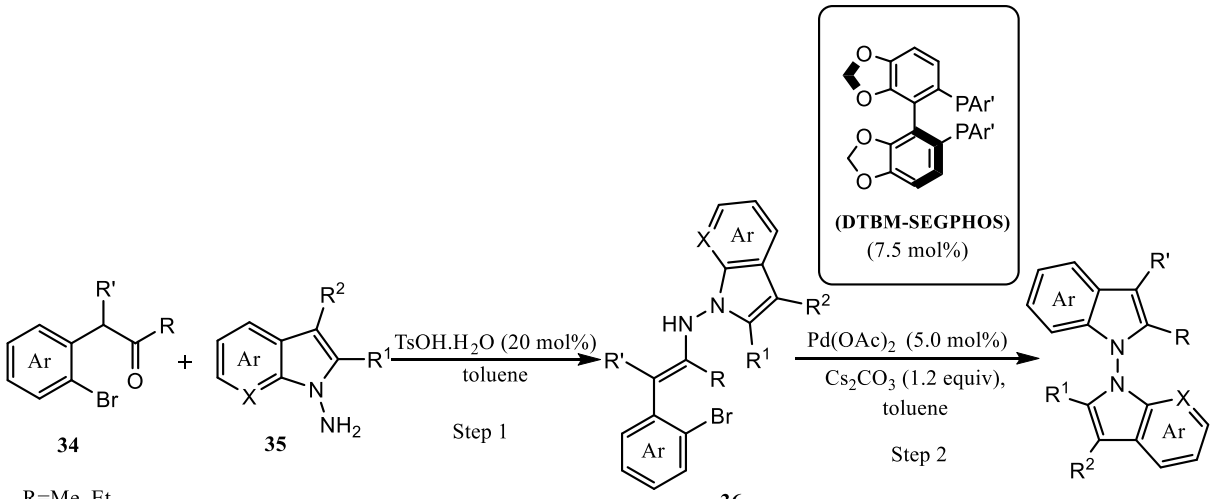
The *N, N*'-bisindole **23** was constructed from diallylated hydrazobenzene (**22**) using two simultaneous Sakamoto's modified Mori-Ban indolization reaction condition which gave access to the non-isomerized product in preference to the 3-substituted indole. Bromination of the *N, N*'-bisindoline with NBS produced the desired dibromide compound **24**. Because of the associated instability of **24**, the compound was subjected for hydrolysis as such without isolation to yield a stable 3, 3′-dimethanol-*N, N*'-bisindole (**25**). The straightforward oxidation of **25** gave the desired dicarbaldehyde **26** followed by a double Horner-Wadsworth-Emmons (HWE) reaction using methyl 2-dimethoxyphosphorylpropanoate in the DBU presence and an excess of lithium chloride, produced the *N,N*'-bisdehydrotryptophan (**27**) in good yield. The palladium catalyzed hydrogenationin a non-stereoselective manner delivered *N, N*'-bistryptophan (**28**) in excellent yield as an inseparable 1:1 mixture of diastereomers. The amidation of bistryptophan compound was achieved using excess of amino acetaldehyde to give the desired bisamide **29** in 56% yields. After the successful synthesis of **29**, several attempts were made to synthesize the bis cyclized intermediate **30** using various acids (HCl, H_2SO_4,TFA, and acetic acid) did not yield the desired product **30**, rather it led to the extensive degradation of starting material **29**. However, *para*-toluenesulfonicacid (*p*-TSA) did affect the cyclization of **29**, affording bis-dihydropyrazinone (**30)** that had surprisingly retained the Boc groups. As such, a separate set of conditions was sought to cleave the Boc groups to the desired bis-dihydropyrazinone. Unfortunately, treatment of **30** with various acids gave none of the desired product **31** but led to extensive degradation. Similar attempts were made to cleave the Boc protecting group under thermal conditions failed to deliver **31**. Finally, the focus was turned to conduct the [2+2]-cycloaddition on compound **30**, which followed the deprotection of Boc, expected to give **1**. However, the attempted photocycloaddition of **30** failed due to the restriction of free rotation about the N-N bond due to the inherent Boc groups, hence preventing the two alkenes aligning into the close proximity required for the [2,2]-cycloaddition to occur. Although the methodology was esthetically planned to construct the *N,N*'-bisindole core during final photochemical [2+2] cyclization step did not yield any success due to unforeseen complications in the molecular orientations of the molecule which resisted the molecule cyclization.

Recently, Ludvikova *et al*. [53] reported photosensitized cross-linking of N-acetyl derivatives of Tryptophan **32** using rose bengal in phosphate buffer saline (**Scheme 7**). Dimeric and higher oligomeric products [54, 55] were formed by cross-linking the amino acid **32** under anoxic conditions in the presence of rose bengal sacrificial oxidant. Here, they react predominantly with singlet oxygen fabricated by rose bengal in aerated solutions. In this investigation, a comprehensive view was obtained for the first steps of rose bengal photosensitized cross-linking of this amino acid. The postulated mechanisms for the observed photosensitized cross-linking reactions of **32** was that the rose bengal singlet excited state upon irradiation efficiently intersystem crosses (Φisc≈ 1 in water) to give the triplet excited state $^3RB^{2-}$. One electron is accepted by this species from the amino acid derivative to furnish a rose bengal anion radical ($RB^{\bullet 3-}$) and the cation radical of **32** (**32**$^{\bullet+}$), and also $RB^{\bullet 3-}$is directly detected by nanosecond transient spectroscopy. The cation radical was subsequently deprotonated to give the neutral radical **32**$^{\bullet}$ (**Scheme 7**). The results achieved in this work illustrated that N1−N1 dimer is very likely among the observed products, whereas C2−C2 product is obtained in trace amount. Consequently, the recombination of **32**$^{\bullet}$ appears to be a plausible major reaction pathway towards the formation of bisindole derivative **33**. These reported results can be helpful for future applications of rose bengal and related dyes, such as photochemical tissue bonding or visible light photocatalysis.



Scheme 7. Pathway of complex photosensitized cross-linking of **32** by Rose Bengal

Very recently, Zhang *et al.* [56] have developed a protocol for the enantioselective synthesis of N-N bisindole atropisomers **37** (**Scheme 8**). In the first step, enamine is formed from their corresponding α-arylketones **34** and 1-amine indole **35** in presence of $TsOH.H_2O$ (20 mol%) and toluene. The enamine **36** was further reacted with Chiral biphosphines (DTBM-SEGPHOS) using $Pd(OAc)_2$ (5.0 mol%) and Cs_2CO_3 (1.2 equiv) in toluene (2.0 mL) to afford the corresponding enantioselective N-N bisindole atropisomers **37**. A broad range of axially chiral bisindoles were conveniently accessed via the de novo construction of one indole ring in high yields and with excellent enantioselectivities. Moreover, structurally diverse indole-pyrrole, indole-carbazole, and non-biaryl-indole atropisomers possessing a chiral N-N axis were reported. The utility of the current protocol was highlighted by successful gram-scale experiments and further product



Scheme 8. Enantioselective synthesis of N-N bisindole atropisomers

conversion into synthetically useful molecules containing N-N atropisomeric skeletons. Furthermore, mechanistic investigations through DFT calculations revealed the details of the reaction pathways, and the enantioselectivity was shown to be determined by the steric repulsion in the rearrangement transition states.

In summary, the synthetic sequence demonstrates that *N, N*'-bisindoles are capable of participating in diverse synthetic transformations exhibiting the sustenance to various reagents and keen participants in lengthy synthetic sequences. This brief review emphasizes the importance of bisindole scaffolds in the field of organic synthesis and medicinal chemistry, and also provides a new challenges and opportunities to explore their chemistry.

4. Conclusion

In this review, we have tried to be inclusive and attempts were made to summarize the recent developments in *N*, *N*'-bisindole chemistry, its biological and other industrial applications. We hope that the synthetic methodologies outlined here for the *N*, *N*'-bisindole synthesis will be useful to the chemists and will stimulate new thinking in the field of bisindole. A detailed discussion has been confined to the literature published till September 2022. To our knowledge, this is the first review article on *N,N*'-bisindole motif.

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References

[1] A. Bayer, Ueber die reduction aromatischer verbindungen mittelst zinkstaub, *European Journal of Organic Chemistry*, **1866**, *140*, 295-296. [Crossref], [Google Scholar], [Publisher]

[2] P. Fernandes, P. Patil, R. Shete, An outline to preparation of biological active benzimidazoles using microwave approach. *Journal of Chemical Reviews*, **2022**, *4*, 25-39. [Crossref], [Google Scholar], [Publisher]

[3] S. Sajjadifar, H. Hamidi, K. Pal, Revisiting of boron sulfonic acid applications in organic synthesis: Mini-review, *Journal of Chemical Reviews*, **2019**, *1*, 35-46. [Crossref], [Google Scholar], [Publisher]

[4] a) M. Asif, A Review on pyridazinone ring containing various cardioactive agents, *Journal of Chemical Reviews*, **2019**, *1*, 66-77. [Crossref], [Google Scholar], [Publisher] b) M.M. Heravi, H. Hamidi, N. Karimi, A. Amouchi, Caro's acid-silica gel catalyzed regioselective ring opening of epoxides with indoles and imidazoles under solvent-free conditions, *Advanced Journal of Chemistry, Section A*, **2018**, *1*, 1-6. [Crossref], [Google Scholar], [Publisher]

[5] C. Georgi, A. Beguin, Heteroauxin production by efficient and inefficient strains of *Rhizobia*, *Nature*, **1939**, *143*, 25. [Crossref], [Google Scholar], [Publisher]

[6] W.F. Loehwing, L.C. Bauguess, Plant growth effects of heteroauxin applied to soil and plants, *Science*, **1936**, *84*, 46-47. [Crossref], [Google Scholar], [Publisher]

[7] M. Bein, R. Signer, W.H. Schopper, Einfluß von penicillin auf die wurzelkultur*(Zea mays)* nachweis von β-indolylessigsäure (Heteroauxin) im handelspenicillin, *Experientia*, **1947**, *3*, 291-292. [Crossref], [Google Scholar], [Publisher]

[8] A.T. Novikova, L.D. Irtuganova, Heteroauxin production by soil microorganisms, *Mikrobiologiia*, **1966**, *35*, 707-711. [Google Scholar], [Publisher]

[9] a) F.G. Hopkins, S.W. Cole, A contribution to the chemistry of proteids, *The Journal of physiology,* **1903**, *29*, 451–466. [Crossref], [Google Scholar], [Publisher] b) G. Sharma, S.B. Sharma, Synthetic impatienol analogues as potential cyclooxygenase-2 inhibitors: a preliminary study, *Journal of Applied Organometallic Chemistry*, **2021**, *1*, 66-75. [Crossref], [Google Scholar], [Publisher]

[10] D.M. Richard, M.A. Dawes, C.W. Mathias, A. Acheson, N. Hill-Kapturczak, D.M. Dougherty, L-Tryptophan: Basic metabolic functions, behavioral research and therapeutic indications, *International Journal of Tryptophan Research*, **2009**, *2*, 45–60. [Crossref], [Google Scholar], [Publisher]

[11] W. Marsh, Tryptophan, *xPharm: The Comprehensive Pharmacology Reference*, **2007**, *2007*, 1-5. [Crossref], [Publisher]

[12] T. Farkas, D. L. Dunner, R. R. Fieve, L-tryptophan in depression, *Biological Psychiatry*, **1976**, *11*, 295–302. [Google Scholar], [Publisher]

[13] J. Mendels, J.L. Stinnett, D. Burns, A. Frazer, Amine precursors and depression, *Archives of General Psychiatry*, **1975**, *32*, 22–30. [Crossref], [Google Scholar], [Publisher]

[14] K. Shaw, J. Turner, C. Del Mar, Are tryptophan and 5-hydroxytryptophan effective treatments for depression? A meta-analysis, *Australian & New Zealand Journal of Psychiatry*, **2002**, *36*, 488–491. [Crossref], [Google Scholar], [Publisher]

[15] A.J. Cooper, Tryptophan antidepressant 'physiological sedative': fact or fancy, *Psychopharmacology*, **1979**, *61*, 97–102. [Crossref], [Google Scholar], [Publisher]

[16] M. Ozawa, K. Honda, I. Nakai, A. Kishida, A. Ohsaki, Hypaphorine, an indole alkaloid from *Erythrina velutina*, induced sleep on normal mice, *Bioorganic & Medicinal Chemistry Letters*, **2008**, *18*, 3992-3994. [Crossref], [Google Scholar], [Publisher]

[17] B.O. Keller, B.T.F. Wu, S.S.J. Li, V. Monga, S.M. Innis, Hypaphorine is present in human milk in association with consumption of legumes, *Journal of Agricultural and Food Chemistry*, **2013**, *61*, 7654–7660. [Crossref], [Google Scholar], [Publisher]

[18] R.W. Fuller, H.D. Snoddy, K.W. Perry, Tissue distribution, metabolism and effects of bufotenine administered to rats, *Neuropharmacology*, **1995**, *34*, 799-804. [Crossref], [Google Scholar], [Publisher]

[19] L.J. Corcuera, Biochemical basis for the resistance of barley to aphids, *Phytochemistry*, **1993**, *33*, 741–747. [Crossref], [Google Scholar], [Publisher]

[20] Y. Sun, Z. Zang, L. Zhong, M. Wu, Q. Su, X. Gao, W. Zan, D. Lin, Y. Zhao, Z. Zhang, Identification of adiponectin receptor agonist utilizing a fluorescence polarization based high throughput assay, *Plosone*, **2013**, *8*, e63354. [Crossref], [Google Scholar], [Publisher]

[21] a) S. Samala, K.R. Arigela, R. Kant, B. Kundu, Diversity-oriented synthesis of ketoindoloquinoxalines and indolotriazoloquinoxalines from 1-(2-nitroaryl)-2-alkynylindoles, *The Journal of Organic Chemistry*, **2014**, *79*, 2491-2500. [Crossref], [Google Scholar], [Publisher] b) Z. Saeid, F. Mohammadkhani Orouji, Necessities of sustainable development in the coastal areas of Iran, *Journal of Engineering in Industrial Research*, **2022**, *3*, 34-44. [Crossref], [Publisher]

[22] G.A. Cordell, J. E. Saxton, Bisindole alkaloids, *The Alkaloids: Chemistry and Physiology*, *20*, **1981**, 1-295. [Crossref], [Google Scholar], [Publisher]

[23] G.A. Cordell, The bisindole alkaloids, *The Chemistry of Heterocyclic Compounds: Indoles, Part Four, The Monoterpenoid Indole Alkaloids*, *25*, **1983**, 539-728. [Crossref], [Google Scholar], [Publisher]

[24] T-S. Kam, Y-M. Choo, Bisindole alkaloids, *The Alkaloids: Chemistry and Biology*, *63*, **2006**, 181-337. [Crossref], [Google Scholar], [Publisher]

[25] V. Askam, R. H. L. Deeks, Derivatives of indole in an attempted cyclisation of *o*-nitrophenylsuccinic acid, *Journal of the Chemical Society C: Organic*, **1968**, 1243-1245. [Crossref], [Google Scholar], [Publisher]

[26] A. Mauger, M. Jarret, C. Kouklovsky, E. Poupon, L. Evanno, G. Vincent, The chemistry of mavacurane alkaloids: a rich source of bis-indole alkaloids, *Natural Product Reports*, **2021**, *38*, 1852-1886. [Crossref], [Google Scholar], [Publisher]

[27] A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, L. Landi, C. Prata, M. V. Berridge, C. Grasso, H.-H. Fiebig, G. Kelter, A. M. Burger, M. W. Kunkel, Antitumor activity of bis-indole derivatives, *Journal of Medicinal Chemistry*,

2008, *51*, 4563–4570. [Crossref], [Google Scholar], [Publisher]

[28] D.J. Newman, G.M. Cragg, Natural products as sources of new drugs over the 30 years from 1981 to 2010, *Journal of Natural Products*, **2012**, *75*, 311–335. [Crossref], [Google Scholar], [Publisher]

discovery, *Phytotherapy Research,* **2001**, *15*, 183–205. [Crossref], [Google Scholar], [Publisher]

[31] L.F. Tietze, H.P. Bell, S. Chandrasekhar, Natural product hybrids as new leads for drug discovery, *Angewandte Chemie International Edition,* **2003**, *42*, 3996–4028. [Crossref], [Google Scholar], [Publisher]

[32] B. B. Mishra, V.K. Tiwari, Natural products: an evolving role in future drug discovery, *European journal of medicinal chemistry,* **2011**, *46*, 4769–4807. [Crossref], [Google Scholar], [Publisher]

[33] X.-Z. Zhong, G.-C. Wang, Y. Wang, X.-Q. Zhang, W.-C. Ye, Monomeric indole alkaloids from the aerial parts of Catharanthus roseus, *Acta Pharmaceutica Sinica*, **2010**, *45*, 471-474. [Google Scholar], [Publisher]

[34] C.-H. Wang, G.-C. Wang, Y. Wang, X. -Q. Zhang, X. -J. Huang, W.-C. Ye, Three new monomeric indole alkaloids from the roots of *Catharanthus roseus, Journal of Asian Natural Products Research*, **2012**, *14*, 249-255. [Crossref], [Google Scholar], [Publisher]

[35] R. L. Garnick, P. W. L. Quesne, Biomimetic transformations among monomeric macroline-related indole alkaloids, *Journal of the American Chemical Society*, **1978**, *100*, 4213–4219. [Crossref], [Google Scholar], [Publisher]

[36] M. Shoeb, S. Celik, M. Jaspars, Y. Kumarasamy, S.M. MacManus, L. Nahar, P. K Thoo-Lin, S.D. Sarker, Isolation, structure elucidation and bioactivity of schischkiniin, a unique indole alkaloid from the seeds of Centaurea schischkinii, *Tetrahedron*, **2005**, *61*, 9001-9006. [Crossref], [Google Scholar], [Publisher]

[37] N.F. Zelenkova, N.G. Vinokurova, M.U. Arinbasarov, Analysis of secondary metabolites of microscopic fungi of the genus *Penicillium* by chromatographic techniques, *Applied Biochemistry and Microbiology*, **2003**,

[29] M.S. Butler, Natural products to drugs: natural product-derived compounds in clinical trials, *Natural Product Reports*, **2008**, *25*, 475–516. [Crossref], [Google Scholar], [Publisher]

[30] G.A. Cordell, M.L. Quinn-Beattie, N.R. Farnsworth, The potential of alkaloids in drug

39, 44-54. [Crossref], [Google Scholar], [Publisher]

[38] W.H. Houff, O.N. Hinsvark, L.E. Weller, S.H. Wittwer, H. M. Sell, The Nature of an oxidation product of 3-indoleacetic acid, *Journal of the American Chemical Society*, **1954**, *76*, 5654-5656. [Crossref], [Google Scholar], [Publisher]

[39] C. Wang, J. Sperry, Towards a biomimetic synthesis of schischkiniin: assembling the bis-dihydropyrazinone cycloaddition precursor, *Tetrahedron*, **2014**, *70*, 3430-3439. [Crossref], [Google Scholar], [Publisher]

[40] C.F. Koelsch, The bromination of 1-acetyl-2, 3-diphenylindole, *Journal of the American Chemical Society,* **1944**, *66*, 1983-1984. [Crossref], [Google Scholar], [Publisher]

[41] V. Dave, Reaction of 2,3-diphenylindole with permanganate rearrangements of *N*, *N*′-dimers, *Canadian Journal of Chemistry*, **1972**, *50*, 3397-3401. [Crossref], [Google Scholar], [Publisher]

[42] R.N. Goyal, A. Kumar, P. Gupta, Oxidation chemistry of indole-3-methanol, *Journal of the Chemical Society, Perkin Transactions 2*, **2001**, 618-623. [Crossref], [Google Scholar], [Publisher]

[43] R.N. Goyal, N. Kumar, N. K. Singhal, Oxidation chemistry and biochemistry of indole and effect of its oxidation product in albino mice, *Bioelectrochemistry and Bioenergetics*, **1998**, *45*, 47-53. [Crossref], [Google Scholar], [Publisher]

[44] L. Nadjo, J.M. Saveant, Electro dimerization: VIII. Role of proton transfer reactions in the mechanism of electrohydrodimerization formal kinetics for voltammetric studies (linear sweep, rotating disc, polarography), *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry*, **1973**, *44*, 327-366. [Crossref], [Google Scholar], [Publisher]

[45] L. Zhang, J. Xia, Q. Li, X. Li, S. Wang, Fast synthesis of hydrazine and azo derivatives by oxidation of rare-earth-metal–nitrogen bonds, *Organometallics*, **2011**, *30*, 375-378. [Crossref], [Google Scholar], [Publisher]
[46] A. Kushmaro, R. S. Marks, K. Golberg, Indole derivatives for biofilm disruption and inhibition, US Patent 2021/0338637A1. [Crossref], [Publisher]
[47] a) R.M. Donlan, Biofilm formation: A clinically relevant microbiological process, *Clinical Infectious Diseases*, **2001**, *33*, 1387–1392. [Crossref], [Google Scholar], [Publisher] b) Nugrahani, N. A., & Pudji Rahayu, A. R. Solution for root canal treatment failure: Comparison of antibiofilm between aloe vera extracts and chitosan shrimp shells of the formation biofilm enterococcus faecalis, *Journal of Medicinal and Chemical Sciences*, **2022**, *5*, 393-399. [Crossref], [Google Scholar], [Publisher] c) M. Hassani, M. Zeeb, A. Monzavi, Z. Khodadadi, M.R. Kalaee, Response surface modeling and optimization of microbial fuel cells with surface-modified graphite anode electrode by ZSM-5 nanocatalyst functionalized, *Chemical Methodologies*, **2022**, *6*, 253-268. [Crossref], [Google Scholar], [Publisher]
[48] M.H. Muhammad, A. L. Idris, X. Fan, Y. Guo, Y. Yu, X. Jin, J. Qiu, X. Guan, T. Huang, Beyond risk: Bacterial biofilms and their regulating approaches, *Frontiers in Microbiology*, **2020**, *11*, 1-20. [Crossref], [Google Scholar], [Publisher]
[49] S. Galie, C. García-Gutierrez, E. M. Miguelez, C. J. Villar, F. Lombo, Biofilms in the food industry: Health aspects and control methods, *Frontiers in Microbiology*, **2018**, *9*, 1-18. [Crossref], [Google Scholar], [Publisher]
[50] M. Abdallah, C. Benoliel, D. Drider, P. Dhulster, , N.E. Chihib, Biofilm formation and persistence on abiotic surfaces in the context of food and medical environments, *Archives of Microbiology*, **2014**, *196*, 453–472. [Crossref], [Google Scholar], [Publisher]
[51] N. Halland, M. Nazare, J. Alonso, O. Rkyek, A. Lindenschmidt, A general and mild domino approach to substituted 1-aminoindoles, *Chemical Communications*, **2011**, *47*, 1042-1044. [Crossref], [Google Scholar], [Publisher]
[52] C. Wang, J. Sperry, Schischkiniin support studies: synthetic access to 1,1′-bisindoles, *Chemical Communications*, **2013**, *49*, 4349-4351. [Crossref], [Google Scholar], [Publisher]
[53] L. Ludvikova, P. Stacko, J. Sperry, P. Klan, Photosensitized Cross-Linking of Tryptophan and Tyrosine Derivatives by Rose Bengal in Aqueous Solutions, *The Journal of Organic Chemistry*, **2018**, *83*, 10835-10844. [Crossref], [Google Scholar], [Publisher]
[54] K.M. Chan, D.D. Huang, Y.J. Li, M.N. Chan, J.H. Seinfeld, C.K. Chan, Oligomeric products and formation mechanisms from acid-catalyzed reactions of methyl vinyl ketone on acidic sulfate particles, *Journal of Atmospheric Chemistry*, **2013**, *70*, 1–18. [Crossref], [Google Scholar], [Publisher]
[55] S.A. Snyder, A.M. ElSohly, F. Kontes, Synthetic approaches to oligomeric natural products, *Natural Product Reports*, **2011**, *28*, 897-924. [Crossref], [Google Scholar], [Publisher]
[56] P. Zhang, Q. Xu, X.M. Wang, J. Feng, C.J. Lu, Y. Li, R.R. Liu, Enantioselective synthesis of N-N bisindole atropisomers, *Angewandte Chemie International Edition,* **2022**, *134*, e202212101. [Crossref], [Google Scholar], [Publisher]