Hittite Journal of Science and Engineering, 2022, 9 (3) 235–239
ISSN NUMBER: 2148–4171
DOI: 10.17350/HJSE19030000276

# Synthesis of New Methoxy Actived Mono and Bis-indole Compounds

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***Article History:***
*Received: 2022/08/11*
*Accepted: 2022/09/23*
*Online: 2022/09/28*

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**ABSTRACT**

An indole hydrazone has successfully been synthesized employing Schiff base reaction conditions starting from 4,6-dimethoxy-2,3-diphenylindole-7-carbaldehyde with hydrazine hydrate. The reaction of this compound with acetone yielded indole based imine compound. The structure of targeted compound was identified by mass and $^1$H spectroscopy along with single crystal X-ray diffraction technique. Also, bromination of bis-indole with *N*-bromo succinimide was produced corresponding bromo bis-indol derivative.

**Keywords:**
Indole; *bis*-indole; Hydrazone; Bromination.

## INTRODUCTION

The synthesis of heterocyclic compounds containing nitrogen atoms has an important place in organic and medicinal chemistry. Especially, the wide range of biologically active molecules and alkaloids has led to great effort for the synthesis of these heterocyclic systems. Indole, which has an extremely important place in the family of heterocyclic compounds containing nitrogen; formed by the fusion of benzene and pyrrole rings and continues to play a key role in the development of new heterocyclic structures due to both its chemical and biological properties [1].

The availability of indole derivatives in natural products and their applications in pharmaceutical chemistry have been investigated for many years. The most important reason for this is that many indole derivatives have a wide range of biological activities [2, 3]. L-tryptophan, which is an amino acid, has an important place in human nutrition [2, 4], reserpine, which is used in the treatment of hypertension and mental diseases and has recently been accepted as a pandemic in the world with its infectious feature, has been studied to show that it is effective against the SARS-CoV-2 virus [2,5] and brassinin, which is produced by plants as a preservative against microorganisms and has been shown to have an anti-cancer effect [6-7], can be cited as examples of indole derivatives found in nature.

Indole derivatives can be isolated from natural products or produced synthetically and used as active pharmaceutical ingredients. Indomethacin used as a pain and fever reducer [8], sumatriptan used in the treatment of migraine pain [9] and pindolol, which has high blood pressure and heart rhythm regulating properties [10] can be given as examples of drugs containing the active ingredient indole which have taken their places on the shelves.

The imine structure -N=CH-, commonly known as Schiff bases, is usually synthesized by removing water as a result of a condensation reaction between activated carbonyl groups such as aldehydes or ketones and primary amine [11-13]. Schiff bases and their derivatives are an important class of compounds in organic chemistry, medical and supramolecular chemistry [11-14]. Schiff base ligands can bind to metal ions through the presence of a free donor pair on the nitrogen atom to form metal complexes with potential biological activities [15-16].

The hydrazone structures formed as a result of the Schiff base reaction containing different biological activities are well known as a result of studies carried out in recent years. Hydrazone compounds can easily form multiple hydrogen bonds with microorganism proteins, especially to increase the binding strength of the receptor. Therefore, they have been investigated in detail to find new antimicrobial agents [17]. For example; methisazone, which acts as an important thiosemicarbazone,

is a clinical drug used in the treatment of infections [18-19].

The more complex indole derivatives such as bis-indoles are chemical structures consisting of two indole compounds bonded together, usually with a heterocyclic molecule [20]. Bis-indole derivatives, like normal indole compounds, have important biological activity, and due to these interesting biological properties, they are very useful target products in drug design studies as an important structural class [21-23]. For instance; nortopsentin derivatives containing imidazole coupling product from bis-indole derivatives are effective against fungi, whereas topsentin compounds obtained from a keto-imidazole coupling product is known to have biological properties such as anti-tumor and anti-inflammatory [24-26].

In terms of chemical reactions, the most active position of indole compounds against electrophilic aromatic substitution reactions is C3. When this position is closed with a group, the C2 position becomes more active and the reactions proceed through this position. In activated indoles containing methoxy groups at C4 and C6 positions, the normally inactive C7 position becomes active and thus the C7 position becomes available for further chemical reactions [27]. In addition, indole gives its electrons on the nitrogen atom to the π electron system, making the structure aromatic, while giving it a weakly basic feature. In this case, the N-H bond becomes weakly acidic and allows nucleophilic substitution reactions to take place on the nitrogen atom [26]. As a result of these functional properties, many reactions of indole and its derivatives such as acylation, formylation, and nitration have been carried out [28-30].

One of these reactions is the bromination. It is well established that indoles containing bromine molecule form new C-C bonds especially via Suzuki and Stille coupling reactions to give novel bis-indoles [31]. In this study, by providing bromination of bis(4,6-dimethoxy-2,3-diphenyl)methane **8**, bis(5-bromo-4,6-dimethoxy-2,3-diphenyl)methane **9** was obtained. Also, synthesis of indole ylidine hydrazone compound, which has a high biological activity potential, was discussed.

The 'Vilsmeier-Haack reaction' method was first found by Vilsmeier and Haack in 1927 and brought to the literature under their own name. This method has been used for formylation of the aromatic compounds for many years. It allows direct formylation of the aromatic structures and has some advantages such as being an easy method to implement, its reagents are easily available, the reactions do not take long and it generally has good yields. $POCl_3$ and DMF are used as reagents. The chloro iminium cation obtained by the reaction of these reagents in cold environment acts as an electrophile and its reaction with aromatic structures results in formylation of the aromatic structure [32-33]. Given the advantages of method, we decided to apply it in the synthesis of the indole-7-carbaldehyde **5** which was then used for the synthesis of indole ylidine hydrazone **7**.

## MATERIAL AND METHODS

All reagents used in the reactions were purchased from Sigma-Aldrich, Acros Organic, Matrix Scientific and Merck companies and used in the reactions without any purification. $^1$H-NMR and $^{13}$C-NMR data were obtained in $CDCl_3$ and DMSO-*d6* solvents using a Varian 500 MHz spectroscopy. Perkin Elmer Spectrum 100 FT-IR device was used to record IR measurements in the range of 650-4000 $cm^{-1}$. X-ray data was obtained with Bruker APEX II QUAZAR three-circle diffractometer. The reaction was followed by thin layer chromatography consisting of silica gel coated on an aluminum layer of Merck GF254. Thin layer chromatography was followed by a UV lamp with wavelengths 254 nm and 365 nm.

### Synthesis of (E)-4,6-dimethoxy-2,3-diphenyl-7-((propan-2- ylidenehydrazono)methyl)-1H-indole (7)

Indole hydrazine **6** (158 mg, 0,43 mmol) was stirred in acetone (15mL) for 3 h. The solvent was evaporated and the residue quenched with water. The solid was filtered off and washed with water and dried on air. The recrystallisation of indole **7** from acetone yielded the indole hydrazone **7** as yellow crystals (140 mg, 80%). $^1$H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3H, Me), 2.16 (s, 3H, Me), 3.76 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.47 (s, 1H, H5), 7.23-7.32 (m, 10H, aryl H), 8.94 (s, 1H, NH). The sample was not soluble enough for $^{13}$C NMR measurement. $[M]^+$: requires 411.194; found 411.162.

### Synthesis of Bis(5-bromo-4,6-dimethoxy-2,3-diphenyl-1H-indol-7-yl)methane (9)

To a solution of bis-indole (104 mg, 0,155 mmol) in chloroform (15mL), NBS (60,7 mg, 0,34 mmol) was added and the reaction mixture was heated at reflux for 5 h. The half of the solvent was then removed under reduced pressure. The water was added and the mixture was extracted with DCM. The combined organic filtrate was washed with brine, dried over anhydrous sodium sulfate and the solvent evaporated in *vacuo*. The solid was dried and purified by flash chromatography using dichloromethane as eluent to give bis-indole **9** as yellow solid. (65 mg, 51%). IR (KBr): υmax 2934, 1534, 1460, 1444, 1407, 1335, 1119, 1090, 971 $cm^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$) δ 3.40 (d, 6H, OMe), 3.87 (d, 6H, OMe), 4.95 (d, 2H, $CH_2$), 7.04-7.87 (m, 20H, aryl H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 176.48,

151.32, 135.45, 131.07, 131.05, 130.13, 129.02, 128.65, 128.61, 128.29, 128.23, 128.21, 128.10, 128.05, 126.74, 111.63 (Aryl C), 60.94 ($OCH_3$), 60.52 ($OCH_3$), 29.70 ($CH_2$). $[M-2H]^+$: requires 826,104; found 824.184.

## RESULTS AND DISCUSSION

Bischer indole synthesis is used for the synthesis of 2,3-disubstituted indole. According to this method, a hot melt solution **2** of 3,5-dimethoxy aniline **1** and benzoin were prepared. The reaction brought to room temperature and aniline in catalytic ratio and acetic acid as solvent were added to the melt. As a result of heating the mixture under reflux, the targeted 2,3-diphenyl-4,6-dimethoxy indole **3** was synthesized and purified by washing with methanol (figure 1) [34].

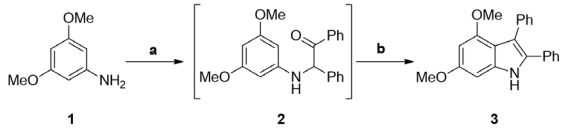


**Figure 1.** Reaction and Conditions: a) benzoin, 130 °C; b) Aniline, AcOH, reflux

In accordance with the Vilsmeier and Haack method, the 2,3-diphenyl indole **3** gives an electrophilic aromatic substitution reaction with the chloro iminium cation from the C7 position and compound **4** is obtained as an intermediate product. Indole-7-carbaldehyde **5** was synthesized from compound **4** which was allowed to react directly with water and sodium hydroxide without being isolated (Figure 2) [33].

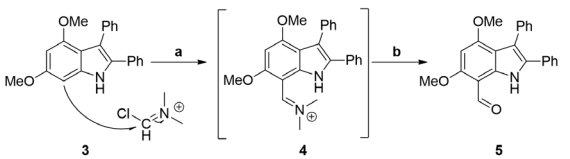


**Figure 2.** Reaction and Conditions: a) POCl3, DMF; b) NaOH, KOH

In the next step, indole-7-carbaldehyde **5** was allowed to react with an excess of hydrazine hydrate in a solvent mixture containing THF and methanol and indole **6** was successfully synthesized. The reaction was primarily carried out in methanol alone; however, the indole **5** did not fully dissolve in this solvent and thus make difficult the reaction to proceed. It was observed that the reaction of carbaldehyde **5** in THF continued very slowly. Therefore, the experiment was repeated by in a mixture of THF and methanol and it was determined that the starting material was exhausted after 24 hours. After the reaction, it was also determined that the indole-7-hydrazonomethyl **6** is highly reactive and has rapid degradation potential and therefore it was used for the next reaction shortly after its synthesis [35]. In the last step, compound **6** was spun in acetone at room temperature and the targeted indole **7** was successfully synthesized (figure 3).

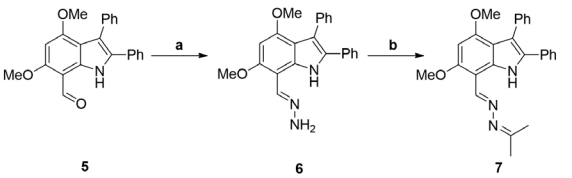


**Figure 3.** Reaction and conditions: a) hydrazine hydrate, THF/MeOH; b) Acetone, room temperature

It was determined as a result of X-ray crystal analysis that indole ylidine hydrazone **7** was synthesized. Crystallization was carried out in acetone (figure 4).

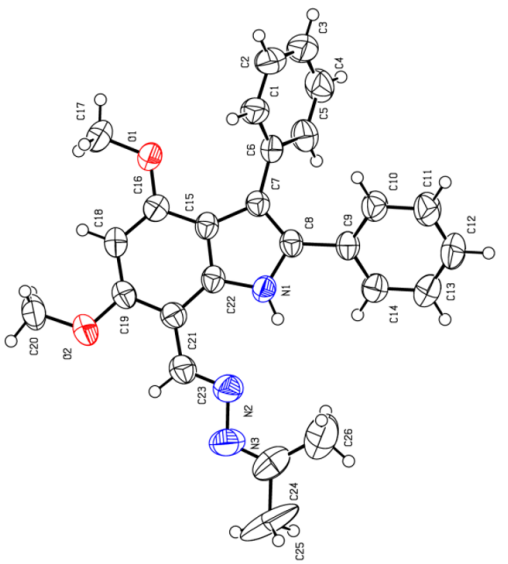


**Figure 4.** X-ray crystal structure of indole 7

The synthesis of another targeted indole **9** was started with the synthesis of the bis-indole **8**. The indole **3** was vigorously stirred in THF at room temperature in the presence of formaldehyde and acid. As a result of the reaction, the desired product solidified in solution and was subjected to direct filtration. Compound **8** was obtained in high yield without any purification [36-37]. In the last step of the synthesis chain, the bis-indole **8** was heated with NBS in chloroform. The target product **9** was obtained as a result of purification of the crude product obtained at the end of the reaction by column chromatography (Figure 5).

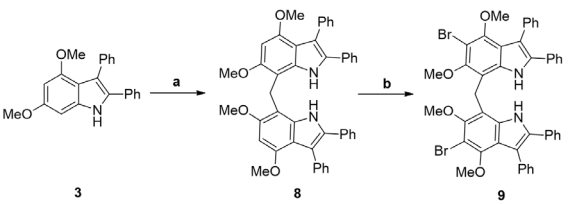


**Figure 5.** Reaction and conditions: a) $CH_2O$, HCl, THF; b) NBS, $CHCl_3$

The synthesis of the indole **9** compound was determined with the evidence of the peak visible at 824 m/z on the mass spectrometer. It was also understood that the bromine

atoms on the molecule were in the form of the 79 isotope. In addition, the $^1$H NMR spectroscopy of the indole **9** proved success of bromination *via* disappearance of the H5 peak at 6.25 ppm.

## CONCLUSION

Indole hydrazone obtained as a result of the Schiff base reaction with hydrazine hydrate starting from indole-7-carbaldehyde **5**. The reaction of indole hydrazone with acetone on Schiff base conditions produced indole-2-ylidine hydrazone. Moreover; the bis(5-bromo-4,6-dimethoxy-2,3-diphenyl) methane **9** was also obtained from the corresponding bis-indole **8** *via* bromination with NBS.


## ACKNOWLEDGEMENT

I would like to thank Tugce Nur USLU for her support to this study.


## CONFLICT OF INTEREST

The author deny any conflict of interest.

### References


1. Saglam MF, Bingul M, Şenkuytu E, Boga M, Zorlu Y, Kandemir H, Sengul IF. Synthesis, Characterization, UV-Vis Absorption and Cholinesterase Inhibition Properties of Bis-Indolyl Imine Ligand Systems. Journal of Molecular Structure 1215 (2020) 128-308.
2. Joshi KC, Chand P. Biologically Active Indole Derivatives. Pharmazie 37(1) (1982) 1-12.
3. Bingul M, Saglam MF, Kandemir H, Boga M, Sengul IF. Synthesis of Indole-2-Carbohydrazides and 2-(Indol-2-yl)-1,3,4-Oxadiazoles as Antioxidants and Their Acetylcholinesterase Inhibition Properties. Monatshefte für Chemie - Chemical Monthly 150 (2019) 1553-1560.
4. Berger M, Gray JA, Roth BL. The Expanded Biology of Serotonin. Annual Review of Medicine 60(1) (2009) 355-366.
5. Duarte RRR, Copertino Jr DC, Iñiguez LP, Marston JL, Nixon DF, Powell TR. Repurposing FDA-Approved Drugs for COVID-19 Using a Data-Driven Approach. ChemRxiv. Preprint. https://chemrxiv.org/engage/chemrxiv/article-details/60c74a1f469df4a040f43cb6 (2020) Erişim tarihi : 09.09.2021, https://doi.org/10.26434/chemrxiv.12148764.v1
6. Mehta RG, Liu J, Constantinou A, Thomas CF, Hawthorne M, You M, Gerhüser C, Pezzuto JM, Moon RC, Moriarty RM. Cancer Chemopreventive Activity of Brassinin, a Phytoalexin from Cabbage. Carcinogenesis 16(2) (1995) 399-404.
7. Pedras MSC, Montaut S, Suchy M. Phytoalexins from the Crucifer Rutabaga: Structures, Syntheses, Biosyntheses, and Antifungal Activity. The Journal of Organic Chemistry 69(13) (2004) 4471-4476.
8. Lal S, Snape TJ. 2-Arylindoles: A Privileged Molecular Scaffold with Potent, Broadranging Pharmacological Activity. Current Medicinal Chemistry 19(28) (2012) 4828-4837.
9. Sravanthi TV, Manju SL. Indoles - a Promising Scaffold for Drug Development. European Journal of Pharmaceutical Sciences 91 (2016) 1-10.
10. Feniuk W, Humphrey PPA. The Development of a Highly Selective 5-HT1 Receptor Agonist, Sumatriptan, for the Treatment of Migraine. Drug Development Research 26 (1992) 235.
11. Sinha D, Tiwari AK, Singh S, Shukla G, Mishra P, Chandra H, Mishra AK. Synthesis, Characterization and Biological Activity of Schiff Base Analogues of Indole-3-Carboxaldehyde, European Journal of Medicinal Chemistry 43 (2008) 160-165.
12. Karthikeyan MS, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS. Synthesis and Biological Activity of Schiff and Mannich Bases Bearing 2,4-Dichloro-5-Fluorophenyl Moiety. Bioorganic Medicinal Chemistry 14 (2006) 7482-7489.
13. Bingul M, Şenkuytu E, Saglam MF, Boga M, Kandemir H, Sengul IF. Synthesis, Photophysical and Antioxidant Properties of Carbazole-Based Bis-Thiosemicarbazones. Research on Chemical Intermediates 45 (2019) 4487-4499.
14. Abu-Hussen AAA. Synthesis and Spectroscopic Studies on Ternary Bis-Schiff-Base Complexes Having Oxygen and/or Nitrogen Donors. Journal of Coordination Chemistry 59 (2006) 157-176.
15. Campbell MJM. Transition Metal Complexes of Thiosemicarbazide and Thiosemicarbazones. Coordination Chemistry Reviews 15 (1975) 279-319.
16. Gupta KC, Sutar AK. Catalytic Activities of Schiff Base Transition Metal Complexes. Coordination Chemistry Reviews 252 (2008) 1420-1450.
17. Özbek N, Katırcıoğlu H, Karacan N, Baykal T. Synthesis, Characterization and Antimicrobial Activity of New Aliphatic Sulfonamide. Bioorganic & Medicinal Chemistry 15(23) (2007) 5105-5109.
18. Avais M, Rashid G, Ijaz M, Khan MA, Nasir A, Jahanzaib MS, Khan JA, Hameed S, Reichel MP. Evaluation of Furazolidone, Sulfadimidine and Amprolium to Treat Coccidiosis in Beetal Goats Under Field Conditions. Pakistan Journal of Pharmaceutical Sciences 29(2) (2016) 485-487.
19. Main RJ. The Nitrofurans a New Type of Antibacterial Agent. Journal of the American Pharmacists Association 36(10) (1947) 317-320.
20. Gibbs TJK, Tomkinson NCO. Aminocatalytic Preparation of Bisindolylalkanes. Organic and Biomolecular Chemistry 3 (2005) 4043-4045.
21. Oh KB, Mar W, Kim S, Kim JY, Lee TH, Kim JG, Shin D, Sim CJ, Shin J. Antimicrobial Activity and Cytotoxicity of Bis(indole) Alkaloids from the Sponge Spongosorites sp. Biological and Pharmaceutical Bulletin 29 (2006) 570-573.
22. Bergman J, Janosik T, Wahlström N. Indolocarhazoles. Advances in Heterocyclic Chemistry 80 (2001) 1-71.
23. Knölker HJ, Reddy KR. Isolation and Synthesis of Biologically Active Carbazole Alkaloids. Chemical Reviews 102 (2002) 4303-4427.
24. Sánchez C, Méndez C, Salas JA. Indolocarbazole Natural Products: Occurrence, Biosynthesis, and Biological Activity. Natural Product Reports 23 (2006) 1007-1045.
25. Sakemi S, Sun HH. Nortopsentins A, B, and C. Cytotoxic and Antifungal Imidazolediylbis[indoles] from the Sponge Spongosorites Ruetzleri. The Journal of Organic Chemistry 56 (1991) 4304-4307.
26. Alvarez-Builla, J, Vaquero JJ, Barluenga, J. Five-Membered Heterocycles: Indole and Related Systems. Modern Heterocyclic Chemistry 1 (2011) 377-513.
27. Beyer RL, Kandemir H, Bhadbhadea M, Sengul IF, Leu C-W, Wenholz D, Kumar N, Black DStC. Synthesis of Dipyrrolo[2,3-a:1′,2′,3′-fg]Acridin-12(1H)-Ones. Tetrahedron Letters 59 (2018)

4483-4486.
28. Black DStC, Bowyer MC, Kumar N, Mitchell PSR. Calix[3] indoles, New Macrocyclic Tris(indolylmethylene) Compounds with 2,7-Linkages. Journal of the Chemical Society, Chemical Communications (1993) 819-821.
29. Black DStC, Keller PA, Kumar N. Palladium-Catalysed Intramolecular Cyclisation of 7-Halo-N-Allyl-Indoles. Tetrahedron 48 (1992) 7601-7608.
30. Wahyuningsih TD, Kumar N, Nugent SJ, Black DStC. Effective Synthesis of Some Indole Nitriles from the Related Carbaldoximes. Tetrahedron 61 (2005) 10501-10506.
31. Deodhar M, Black DStC, Chan DS-H, Kumar N. Synthesis of Some New Biheterocycles by a One-Pot Suzuki-Miyaura Coupling Reaction. Chem Inform 80 (2010) 1267-1274.
32. Vilsmeier A, Haack A. Über die Einwirkung von Halogenphosphor auf Alkyl Formanilide. Eine Neue Methode zur Darstellung Sekundärer und Tertiärerp-Alkylamino-Benzaldehyde. Berichte der Deutschen Chemischen Gesellschaft, 60 (1927) 119-122.
33. Sengul IF, Bingul M, Kandemir H, Kumar N, Black DStC. Synthesis, Reactivity And Biological Properties Of Methoxy Activated Indoles, in: Attanasi OA, Gabriele B, Merino P, Spinelli D (Eds.). Targets In Heterocyclic Systems. Società Chimica Italiana, Urbino, pp. 162-212, 2021.
34. Black D StC, Kumar N, Wong L C H, Investigation of the Bischler Indole Synthesis from 3,5-Dimethoxyaniline. Australian Journal of Chemistry 39 (1986) 15-20.
35. Kandemir H, İzgi, S, Cınar, I, Cebeci, F, Dirican, E, Saglam, MF, Sengul IF. Methoxy-activated indole-7-carbohydrazides; synthesis, antioxidant, and anticancer properties. Journal of Heterocyclic Chemistry Erişim tarihi : 19 August 2022, https:// doi.org/10.1002/jhet.4562
36. Black D StC, Bowyer MC, Catalano MM, Ivory AJ, Keller PA, Kumar N, Nugent SJ. Substitution, Oxidation and Addition Reactions at C-7 of Activated Indoles. Tetrahedron 50 (1994) 10497-10508.
37. Purwono B, Kumar N, Black DStC. Mannich Reactions of Activated 4,6-Dimethoxyindoles. Arkivoc 4 (2022) 58-69.