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NOVEL SYNTHETIC INVESTIGATION IN THE FIELD OF INDOLO[2,3-B]QUINOXALINE RING CONTAINING TETRACYCLIC AND PENTACYCLIC HETEROCYCLES

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Abstract. A series of seven new indolo[2,3-b]quinoxaline ring containing compounds were efficiently synthesized in three different pathways. In the first case, the relevant pentacyclic systems **(3,4)** were received by the condensation reaction between 7-acetyl-1,5,6,7-tetrahydropyrrolo[3,2-f]indole-2,3-dione and o-phenylenediamine in glacial acetic acid. In the second case, tetracyclic indolo[2,3-b]quinoxaline derivatives (**7, 8a-d**) were synthesised by a one-pot approach using Pd-catalyzed Sonogashira-hagihara C-C cross-coupling reaction between various terminal acetylenes and 9-iodo-6H-indolo[2,3-b]quinoxaline in presence of various Pd catalysts. The third pathway is based on the Cu-catalyzed modified Ullmann protocol. The appropriate indolo-quinoxaline derivative (9) was successfully synthesized by arylamination, using benzylamine (as a nucleophile) and 6-benzyl-9-iodo-6H-indolo[2,3-b]quinoxaline as an aryl halide. The reaction was performed in DMF in the presence of CuI.

Keywords: *Indolo[2.3-b]quinoxaline, condensation, isatin, nitrogen heterocycles, Sonogashira C-C coupling, Ullmann C-N coupling.*

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1. Introduction

The synthesis of new physiologically active compounds is considered one of the most poignant issues of the contemporary chemical industry. In present therapy, the use of nitrogen-containing heterocycles is essential, because of their beneficial properties. One of the most interesting derivatives of Indole –4',6-diamidino-2-phenylindole (DAPI) is used as a marker in the fluorescent microscope (Tanious *et al*., 1992). Quinoxaline and its derivatives are characterised as the antimicrobial, mycostatic, anti-bacterial, anti-tumor and anti-inflammatory agents (Gupta & Verma, 2014; Sastry *et al*., 1990; El-Hawash *et al*., 1999). Within the last decades, intensive research has been done on the indolo-quinoxaline systems due to their multiple benefits. These condensed, tetracyclic systems are considered a significant group of nitrogen-containing heterocyclices, because of their dual nature. They combine on the one hand, a cycle of electron-rich indole core,

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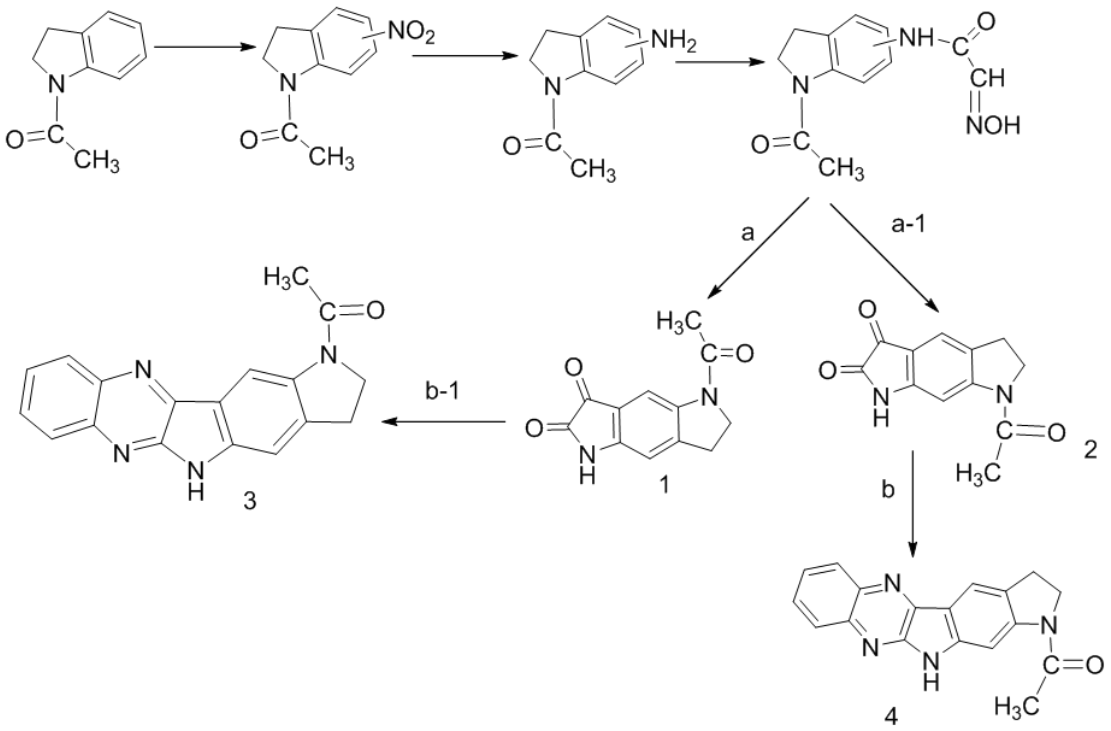
on the second hand, a fragment of electro-deficient quinoxaline that creates great interest among researchers. Discussion of indole-quinoxaline derivatives is an object of interest in terms of its pharmacological activity, which is basically conditioned by the capacity of intercalation with DNA (Gu *et al*., 2017; Peczynska-Czoch *et al*., 1994; Aragon *et al*., 2007). They are known to have anti-virus, anti-fungal and cytotoxic activities (Moorthy *et al*., 2010; 2013; Wilhelmsson *et al*., 2008). Indolo-quinoxaline derivatives and carbazole alkaloid ellipticine structurally look alike (Goodwin *et al*., 1959; Miller & Dugar, 1989). Ellipticine itself is a natural anti-tumor therapeutic (Paoletti *et al*., 1979; Kohn *et al*., 1975 15. Wilhelmsson *et al.,* 2010). One of the most active derivatives of indolo-quinoxaline systems is 2,2 Dimethyl (2-Dimethylaminoethyl)-6H-Indolo[2,3-b]quinoxaline, called B-220, which has shown remarkable activity against herpes virus (Harmenberg *et al*., 1988; Przyjana *et al*., 2004). Apart from the field of Medicine, Indolo-quinoxalines are used in Materials Science. These donor-acceptor systems are characterized by high thermostability. That is the reason why they are used in optoelectrical devices, excitonic solar cells and sensitizers (Su *et al*., 2013; Tyagi *et al*., 2011; Fan *et al*., 2011). According to the above-mentioned features, a great deal of research has been done on Indolo-quinoxalines up to now. In literature, plentiful data are accessible on the effect of substituent in 6-position (indole-N-H) (Wamberg *et al*., 2006). Comparatively, other active centers of the tetracyclic systems have insufficiently been researched. Furthermore, much less information is accessible regarding the reactivity of Indolo[2,3-b]quinoxaline systems in the metal-catalyzed reaction. Therefore, here we report the synthetic pathways of a series of new compounds with indoloquinoxaline skeleton by using Sonogashira C-C and modified Ullmann C-N bond formation protocols. Cross-coupling of halo(hetero)arenes with terminal alkynes is an effective method for the formation of a new carbon-carbon bond. Pd-complex and Copper-cocatalyst successfully promoted all of those reactions with appropriate coupling partners to achieve the corresponding products. We have isolated several indoloquinoxaline derivatives with alkyne bridges. Additionally, we have carried out Sandmeyer's classical reaction to synthesize the key products, isatines.

2. Results and discussions

2.1. Synthesis of pentacyclic systems (3,4)

The synthesis of desired five ring-containing compounds with indolo[2,3-b]quinoxaline moiety is outlined in Scheme 1.

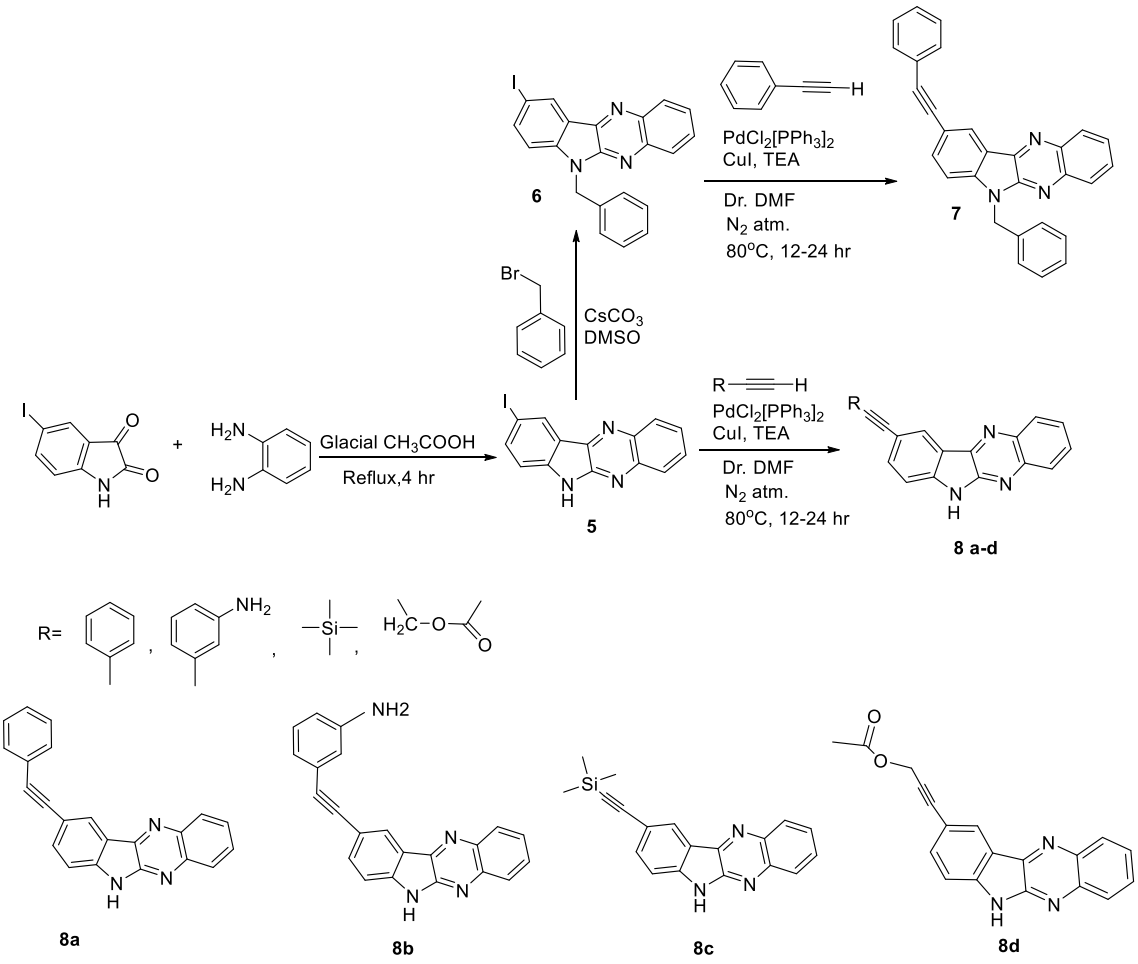
The required key compounds 5-acetyl-1,5,6,7-tetrahydropyrrolo[2,3-f]indole-2,3-dione (1) and 7-acetyl-1,5,6,7-tetrahydropyrrolo[3,2-f]indole-2,3-dione (2) were prepared in 69% and 54% yield by a multi-step transformation of N-acetylindoline via Sandmeyer classical reaction. The condensation reactions between these compounds and o-phenylendiamine were carried out in glacial acetic acid (reaction b, b-1). As a result of the reactions, we received a mixture of four components in both cases. We could manage to divide the mixture through the chromatographic column, Adsorbent – Silica Gel, Eluent – Hexane/acetone – 2:1. Primary component of these mixtures was inear isomers-1-(3,5-dihydropyrrolo[2',3':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (3) and 1-(3,11-dihydropyrrolo[3',2':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (4).



Scheme (1). Preparation of pentacyclic systems with 6H-indolo[2,3-b]quinoxaline moiety. Reagents and conditions: (1,2) 0.5 mmol isonitrosoacetindolines, 5ml H2SO4, 700C. (3,4) 2.5 mmol isatines, 2.5 mmol o-diaminobenzene, 10 ml glac. Acetyc acid

2.2. The synthesis of 9-substituted Indolo-quinoxalines via Sonogashira-Hagihara cross-coupling protocol

The synthesis of target four ring containing compounds with indolo[2,3-b]quinoxaline moiety is outlined in (Scheme 2). Acetylene systems containing indolo-quinoxaline moiety imply a double-stage reaction. Specifically, the first stage implies building the moiety of quinoxaline with o-phenylenediamine through the cycle condensation method. Through this method, we received a key compound. (5) The second type serves as a reaction among Aril halogenide and terminal acetylene based on the Sonogashira reaction. We selected palladium complexes with triphenylphosphine: $PdCl_2[PPh_3]_4$ and $Pd[PPh_3]_4$ and Cul as a co-catalyst. We used tertiary amine-triethylamine and selected dry DMF as a solvent to create a weak base area. Because of the air sensitivity of the reaction, we conducted a synthesis in the inert area (under a nitrogen atmosphere). We used the following compounds as terminal alkynes: Phenylacetylene, trimethylsilylacetylene, 3-amino-Phenylacetylene and propargyl acetate. We conducted a reaction at 70-80^{0}C during 12-24 hours in the conditions of permanent stirring. In the four cases, we received a targeted result. In one of the cases, we protected Indole N-H of 9-iodo-6H-Indolo[2,3-b]quinoxaline with the benzyl group and reacted with phenylacetylene to receive the desired compound (7) with a yield of 28,8 %.



Scheme 2. Preparation of 9-substituted 6H-indolo[2,3-b]quinoxalines 3, 4a-d,via Sonogashira Miaura C-C cross coup¬ling reactions. Reagents and conditions. Method a) 9-Iodo-6H-indolo[2,3-b]quinoxaline 5 (0.2 mmol), terminal alkyne (0.6 mmol, 3 equiv), PdCl2(PPh3)2 (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh3 (5 mg, 10 mol%), then anhyd Et3N (4 mL) and anhyd DMF (2 mL). Method b) 9-Iodo-6H-indolo[2,3- b]quinoxaline 5 (2.5 mmol), terminal alkyne (2.75 mmol), Pd(PPh3)4 (0.5mmol, 20 mol%), pyrrolidine (2 equiv) and anhydrous DMF (5 ml)

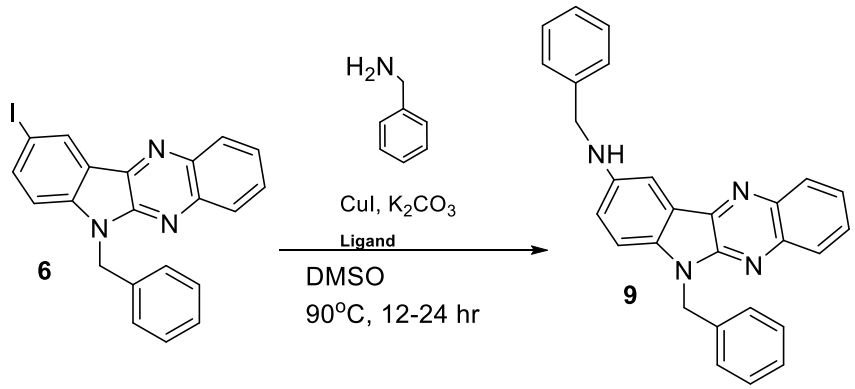
The most common problem, while conducting Sonogashira cross-coupling reaction, is the homocoupling reaction between alkynes. In our case, we exhibited another limitation related to Copper co-catalyst. We found it hard to maintain an inert atmosphere during the reaction. The decomposition of copper iodide led to the formation of Copper (I) oxide inside the reaction mixture as a by-product. As a result, we had a comparatively low yield of the key product and a trace of the starting substances. To avoid this problem we attempted to optimize the conditions of the reaction to increase the yield of the targeted products. Specifically, we performed a copper-free Sonogashira reaction. The results are summarised in Table 1. We have applied pyrrolidine as a base and $Pd[PPh_3]_4$ as a catalyst. In these conditions, we could not receive the 8^{th}c and 8^{th}d compounds. In the event of the other four, the yield increased. The maximum yield was 69.8 %- Compound **8b**.

Table 1. The optimization of synthetic methods of Sonogashira reaction

No	Compounds	Yield % Sonogashira reaction with $PdCl_2[PPh_3]_2$,CuI, TEA DMF, PPh_3	Yield % copper-free sonogashira reaction with $Pd[PPh_3]_4$, Pyrrolidine, DMF
1	7	28,8	30.6
2	8a	27.5	48
3	8b	46,6	69,8
4	8c	63.05	No conversion
5	8d	66.9	No conversion

2.3. Synthesis of compound 9 via modified Ullmann C-N coupling reaction

The third pathway of synthesis implies studying the reaction capacity of 6-benzyl-9-Iodo-6H-Indolo[2,3-b]quinoxaline in the modified Ullmann reaction (Scheme 3). We used CuI as a catalyst for the reaction. We have chosen benzylamine as the primary amine, DMSO as a solvent and amino acid N-metylglicine as a ligand, which worked as a promotor of the reaction. We selected 90^0C as an optimal temperature. The reaction was in progress for 24 hours. We obtained N,6-dibenzyl-6H-indole[2,3-b]quinoxalin-9-amine with yield 71.6%.



Scheme 3. Preparation of 9-substituted 6H-indolo[2,3-b]quinoxalines 5 via modified Ullmann C-N coupling reaction. Reagents and conditions: CuI (0.5 mmol), N-methylglycine(1 mmol), aryl iodide (5 mmol), benzylamine (7.5 mmol), K_2CO_3 (10mmol), DMSO (3 mL), 90 ^{0}C

2.4. The spectroscopic data of the new compounds

The 1H NMR spectra of pentacyclic condensed product 1-(3,5-dihydropyrrolo[2',3':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (3) recorded in DMSO-d6 solvent, showed the linear structure of corresponding compound. Indole N-H group broadened singlet signal appeared in the region 11.89 ppm. Two singlets signals were assigned to indole benzene fragments at 7.22 and 8.900 ppm respectively. The rest of the signals were observed in the following way: characteristic signals of quinoxaline protons in the form of doublets and multiplets appeared with the chemical shift between 87,42-8,34 ppm. The protons singlet signal of the Acetyl group at 2,21 ppm area was observable. Two triplets in 4,15 and 3,27 ppm existing on the spectrum are assigned to dihydropyrrole ring.

The second isomer of pentacyclic systems- 1-(3,11-dihydropyrrolo[3',2':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (4) showed the

similar data of 1H NMR. In this case, Indole N-H group broadened singlet signal appeared in the region 11.88 ppm while the singlet signal of acetyl group protons was observed at 2,23 ppm respectively.

The 1H NMR spectra of other new compounds 7, 8a-8d, 9 demonstrated the following signals: For compound 7 the multiple chemical shifts of phenyl ring assigned at the region of 7.26-8.38 ppm, while two singlet signals of benzene CH_2 at 5.79 ppm was observed. For 8a-d compounds, indole N-H singlet signals appeared with chemical shifts between 12,04-12.28 ppm regions. Compound 9 showed the typical signals of two aryl groups between 7,20-745 ppm regions

3. Experimental

1 H and 13C NMR spectra were recorded with a Bruker AV400 [400 MHz (1 H) and 100 MHz (13C)] or a Bruker AV500 [500 MHz (1 H) and 125 MHz (13C)] spectrometer as well as a Bruker Avance III 400 MHz using tetramethylsilane (TMS) as internal standard and Dimethylsulfoxide (DMSO-d_6) as a solvent. Proton chemical shifts (δ) are relatived to TMS at δ 0.00 ppm (^{1}H) and to DMSO-d6 at 39.50 ppm (^{13}C) as internal standard and are expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in Hertz. MS spectra were obtained by using Agilent Technologies 6539 Accurate –Mass Q-TOF LC/MS spectrometer. The high-resolution mass spectral analysis (HRMS) data was measured on a Finnigan MAT 95, CI (gas–reagent–methane). Melting points of crystalline compounds were determined on a digital melting point visual device DMP-800 and were uncorrected. All chemicals were of reagent grade and used as commercially purchased without further purification. Solvents were purified and dried following standard procedures. All reactions were monitored by thin-layer chromatography (TLC) on silica gel Al-foils using ultraviolet light or iodine spray (if applicable) and as eluent was used PE:ETAC, in different ratios. Column chromatography was performed on silica gel (60-120 mesh) using hexane and ethyl acetate as an eluent.

1-(3,5-dihydropyrrolo[2',3':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (3)

A two-necked round bottom flask equipped with a reflux condenser and magnetic stirrer 5-acetyl-1,5,6,7-tetrahydropyrrolo[2,3-f]indole-2,3-dione **1** (0,582g, 2,5 mmol) and benzene-1,2-diamine (0,273g, 2,5 mmol) dissolved in glacial acetic acid (10 mL). The reaction mixture was thoroughly stirred at the reflux temperature for 1-2 h. The monitoring of the reaction was carried out by the TLC method. After that, the reaction mixture was poured into 300 ml cold water. Then 200 ml 5% sodium bicarbonate was added and after 24 h the crude product was filtered off, washed with water and dried to afford (2) as a light yellow solid. m.p 345-346 ^{0}C, Yeld 49% **^{1}H NMR** (DMSO-d_6): 11.89 (1H, s, NH), 8.90 (1H, s, 12H), 8.34 (1H, d, 10H J=8 Hz), 7.85 (1H, d, 7H J=8 Hz), 7.48 (1H, m, 9H), 7.42 (1H, m, 8H), 7.22 (1H, s, 4H), 4.15 (2H, t, 2CH_2 J=8 Hz), 3.27 (2H, t, CH_2 J=8 Hz), 2.21 (3H, s, CH_3). **^{13}C NMR** (DMSO-d_6) δ=168.6, 147.7, 143.5, 139.8, 138.9, 138.3, 133.3, 130.4, 124.6, 123.2, 114.4, 111.7, 110.7, 109.5, 47.8, 27.3, 23.7.

1-(3,11-dihydropyrrolo[3',2':5,6]indolo[2,3-b]quinoxalin-1(2H)-yl)ethan-1-one (4)

A two-necked round bottom flask equipped with a reflux condenser and magnetic stirrer 7-acetyl-1,5,6,7-tetrahydropyrrolo[3,2-f]indole-2,3-dione **2** (582 mg, 2,5 mmol) and benzene-1,2-diamine (273 mg, 2,5 mmol) dissolved in glacial acetic acid (10 mL). The reaction mixture was thoroughly stirred at the reflux temperature for 1-2 h. The monitoring of the reaction was carried out by the TLC method. After that, the reaction mixture was poured into 300 ml cold water. Then 200 ml 5% sodium bicarbonate was added and after 24 h the crude product was filtered off, washed with water and dried to afford (4) as a yellow-orange solid. m.p. 364-365^{0}C, Yeld 54% **^{1}H NMR** (DMSO-d_6): 11.58 (1H, s, NH), 8.31 (1H, s, 11H), 8,19 (1H, d, 1H J= 4 Hz), 8.11 (1H, s, 7H), 8.03 (1H, d, 4H J=8 Hz), 7.74 (1H, t, 2H J=8 Hz), 7,68 (1H, t, 3H J=8 Hz), 4.25 (2H, t, 9CH_2 J=8 Hz), 3.33 (2H, t, 10CH_2 J=8 Hz), 2.29 (3H, s, CH_3). **^{13}C NMR** (DMSO-d_6) δ=169.65, 146.93, 146.37, 145.31, 140.21, 140.12, 139.40, 129.19(2C), 128.22, 127.85, 126.03, 118.41, 114.67, 99.96, 49.90, 27.29, 24.42. **HR-MS** calcd. for $C_{18}H_{14}O_1N_4$, $[M]^+$ 302.1168 found 302.1168.

General synthesis of (7, 8 a-d) with method A

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline **5** (69 mg, 0.2 mmol), appropriate terminal alkyne (0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh3 (5 mg, 10 mol%), then Et3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1).

General synthesis of (7, 8 a-d) with method B

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline **5** (862.5mg, 2.5 mmol), appropriate terminal alkyne (2.75 mmol), $Pd(PPh_3)_4$ (223 mg, 0.5mmol, 20 mol%), pyrrolidine (0,355 mL, 2 equiv) and anhydrous DMF (5 mL). Then the reaction mixture was stirred at 70-80°C for 24 h. The reaction mixture was cooled to room temperature, poured into cold water and extracted with EtOAc (2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1).

6-benzyl-9-(phenylethynyl)-6H-indolo[2,3-b]quinoxaline (7)

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline **5** (69 mg, 0.2 mmol), phenylacetylene (0.066 mL, 0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1). light yellow solid m.p. 186-187 °C Yeld 28.8 % **^{1}H**

NMR (DMSO-d_6): 8.56 (d, 1H, 6H, J=1.2 Hz), 8.33 (dd, 1H, 8H J=8 Hz), 8.17 (dd, 1H, 7H, J=8 Hz), 7.75-7.93 (m, 4H 1-4H), 7.42-7.63 (m, 5H, H-Ar), 7.26-7.38 (m, 5H, Ph-H), 5,79 (s, 2H, CH_2). **^{13}C NMR** (DMSO-d_6) δ= 145.96, 144.12, 140.62, 139.56, 139.37, 137.09, 134.77, 131.81, 130.06, 129.74,129.45, 128.93 , 128.11 (2C) 127.62, 127.16, 125.60, 122.99, 119.62, 115.51, 111.85, 89.97, 89.23, 44.81. **LC-MS** calcd. for $C_{29}H_{19}N_3H$, $[M+1]^+$ 410.1657 found 410.1717.

9-(phenylethynyl)-6H-indolo[2,3-b]quinoxaline (8a)

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 6-benzyl-9-iodo-6H-indolo[2,3-b]quinoxaline **6** (87 mg, 0.2mmol), phenylacetylene (0,066 mL, 0.6 mmol, 3 equiv), $PdCl_2(PPh3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1). Yellow solid m.p. 186-187 °C Yeld 28.8 % **^{1}H NMR** (DMSO-d_6): 12.04 (s, 1H, NH), 8.51 (d, 1H, 10 H J=0.94 Hz), 8.29 (dd, 1H, 8 H J=0.94 Hz), 8.11 (d, 1H, 7H J=0.94 Hz), 7.63-7.89 (m, 4H, 1-4 H). **^{13}C NMR** (DMSO-d_6) δ=146.81, 144.30, 140.99, 139.75, 139.49, 134.61, 131.75, 129.67, 129.46, 129.10(2C), 128.87, 128.07 (2C), 126.69. 125. 52, 123,35, 120.04, 115.16, 112.99, 90.29, 88.98. **LC-MS** calcd. for $C_{22}H_{13}N_3H$, $[M+1]^+$ 320.1187, found 320.2827.

3-((6H-indolo[2,3-b]quinoxalin-9-yl)ethynyl)aniline (8b)

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer was introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline 5 (69 mg, 0.2 mmol), 3-ethynylaniline (0,068 mL, 0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1). Yellow solid m.p. 302-303 °C Yeld 46.6 % **^{1}H NMR** (DMSO-d_6): 12,28 (s, 1H NH), 8,44 (s, 1H, 10H), 8.27 (dd, 1H, H-Ar j=4 Hz), 8.10 (d, 1H, 7H j=4 Hz) 7.83 (m, 2H, 3,4H), 7.75 (dd, 1H, 2H J=4 Hz), 7,61 (d, 1H, 7H J=4 Hz), 7.07 (t, 1H, H-Ar J=8 Hz), 6,67 (d, 1H, H-Ar J=8 Hz), 6,78 (s, 1H, H-Ar J=8 Hz), 6.73 (d, 1H, H-Ar J=8 Hz), 5.25 (s, 2H NH_2). **^{13}C NMR** (DMSO-d_6) δ= 148.81, 146.09, 143.50, 140.28, 139.13, 138.73, 134.24, 129.19(3C), 127.59, 126.31, 124.87, 122.74, 119.26, 118.83, 116.08, 114.71, 114.42, 112.51, 89.32, 88.26.

9-((trimethylsilyl)ethynyl)-6H-indolo[2,3-b]quinoxaline (8c)

In an oven-dried (130^{0}C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline **5** (69 mg, 0.2 mmol), trimethyllsylylacetylene (0.085ml 0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$,

filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (PE: EtOAc 1:1). Orange solid m.p. 319-320°C Yeld 63.05 %**^{1}H NMR** (DMSO-d_6): 12.11 (1H, s, NH), 8.19 (1H, d, 10H J=8 Hz), 7.91 (1H, dd, 4H J=8 Hz), 7.66 (1H, ddd, 2H J=8C Hz), 7.59 (1H, dd, 8H J=8 Hz), 7.58 (1H, td, 3H J=8 Hz), 7.40 (1H, d, 7H J=8 Hz), 0.10 (9H, s, CH_3). **^{13}C NMR** (Benzene-d_6) δ=142.39, 140.35, 134.01, 130.01, 129.32, 126.22, 120.49, 111.25, 105.77, 93.07, 44.90, 30.06, 22.09. **LC-MS** calcd. for $C_{19}H_{17}N_3SiH$, $[M+1]^+$ 316.1270 found 316.2879.

3-**(6H-indolo[2,3-b]quinoxalin-9-yl)prop-2-yn-1-yl-acetate (8d)**

In an oven-dried (130^0C- 3 h) Schlenk tube with screw cap and magnetic stirrer were introduced under nitrogen 9-Iodo-6H-indolo[2,3-b]quinoxaline **5** (0.069 g, 0.2 mmol), propargyl acetate (0.06 mL, 0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature Abel Maharramov and poured into cold water and extracted with EtOAc(2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. Yellow solid, m.p. 234-235°C Yeld 66.9 % **^{1}H NMR** (DMSO-d_6): 12.28 (1H, s, NH), 8.37 (1H, d, 10H J=8 Hz), 8. 27 (1H, dd, 1H J=8 Hz), 8.09 (1H, dd, 4H J=8 Hz), 7.84 (1H, ddd, 2H J=8 Hz), 7.78 (1H, m, 7H), 7.77 (1H, m, 3H), 7.60 (1H, dd, 8H J=8 Hz), 4.99 (2H, s, CH_2), 2.12 (3H, s, CH_3). **^{13}C NMR** (DMSO-d_6) δ= 170.35, 146.57, 144.34, 140.78, 139.51, 139.22, 134.96, 129.65 (2C), 128.08, 126.87, 125.75, 119.67, 113.94, 113.04, 86.49, 83.62, 52.90, 21.03. **LC-MS** calcd. for $C_{19}H_{13}N_3O_2H$, $[M+1]^+$ 316.1086 found 316.2715

N,6-dibenzyl-6H-indolo[2,3-b]quinoxalin-9-amine (9)

A two-necked round bottom flask equipped with 6-benzyl-9-iodo-6H-indolo[2,3-b]quinoxaline **6** (1.7 g, 5 mmol) and benzylamine (0.82 mL,7.5 mmol) were dissolved in DMSO (3 mL). Then CuI (0.096 g, 0.5 mmol) and L-proline (0.11g 1 mmol) were added. The reaction mixture was stirred at 90 ^{0}C for 24 h. After that, the reaction mixture was cooled to room temperature and extracted with ethyl acetate 3 times. All the organic layers were combined and dried over $MgSO_4$ and evaporated to afford the crude product, which was further purified by flash chromatography. Yellow solid, m.p. 176-177 °C Yeld 71.6% **^{1}H NMR** (DMSO-d_6): 8.22 (1H, dd, 4H J=4 Hz), 8.06 (1H, dd, 1H J=8 Hz), 7.77 (1H, ddd, 3H J=8 Hz), 7.67 (1H, ddd, 2H J=8 Hz), 7.20-7.45 (12H, m, Ph-H, 7H, 10H), 7.13 (1H, dd, 8H J=4 Hz), 6.41 (1H,t, NH J=4 Hz) 5.63 (2H, s, N-CH_2), 4.41 (2H, d, NH-CH_2 J=4 Hz). **^{13}C NMR** (DMSO-d_6) δ= 145.06, 144.23, 140.10, 139.83, 139.63, 138.36, 137.22, 136.15, 129.00, 128.60 (3C), 128.34(3C), 127.11(4C), 127.08 (2C), 126.64, 125.61, 119.22, 111.34, 102.79, 47.02. **LC-MS** calcd. for $C_{28}H_{22}N_4H$, $[M+1]^+$ 415.1925 found 415.1978.

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