RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

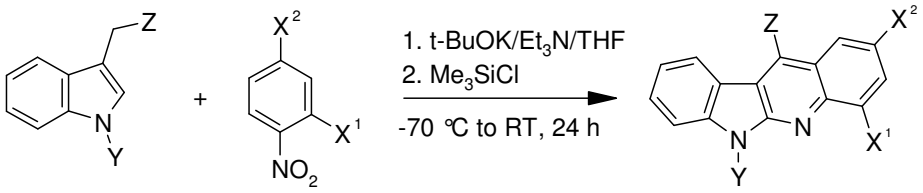
Simple access to 11-substituted norcryptotackieine derivatives

Michał Nowacki and Krzysztof Wojciechowski

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

e-mail: kwojciechowski@icho.edu.pl

Graphical Abstract



Z = CN, CO_2Et, SO_2Ph
Y = CO_2Bu-t, $SiMe_2Bu$-t
X^1 = H, Cl; X^2 = F, Cl, Br

11-62%

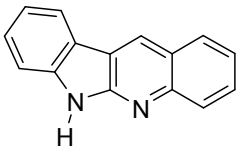
Simple synthesis 11-substituted norcryptotackieine derivatives

Michał Nowacki and Krzysztof Wojciechowski*
Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
e-mail: kwojciechowski@icho.edu.pl

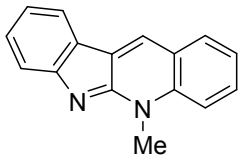
Abstract: 11-Substituted (CN, CO_2Et, SO_2Ph) indolo[2,3-b]quinolines were obtained in reactions of N-protected ($SiMe_2t$-Bu, CO_2t-Bu) indol-3-yl-acetonitrile, -acetate, and -methylsulfone with nitrobenzene derivatives in presence of base and trialkylchlorosilanes.

Introduction

Norcryptotackieine (quinindoline, 6*H*-indolo[2,3-*b*]quinoline, **1**) and neocryptolepine (cryptotackieine **2**) are natural alkaloids isolated from *Cryptolepis sanguinolenta*, the plant used in traditional West African medicine for treatment of malaria[1, 2]. The planar structure of these alkaloids is a good starting platform for DNA-binding agents of potential anticancer activity.[3]



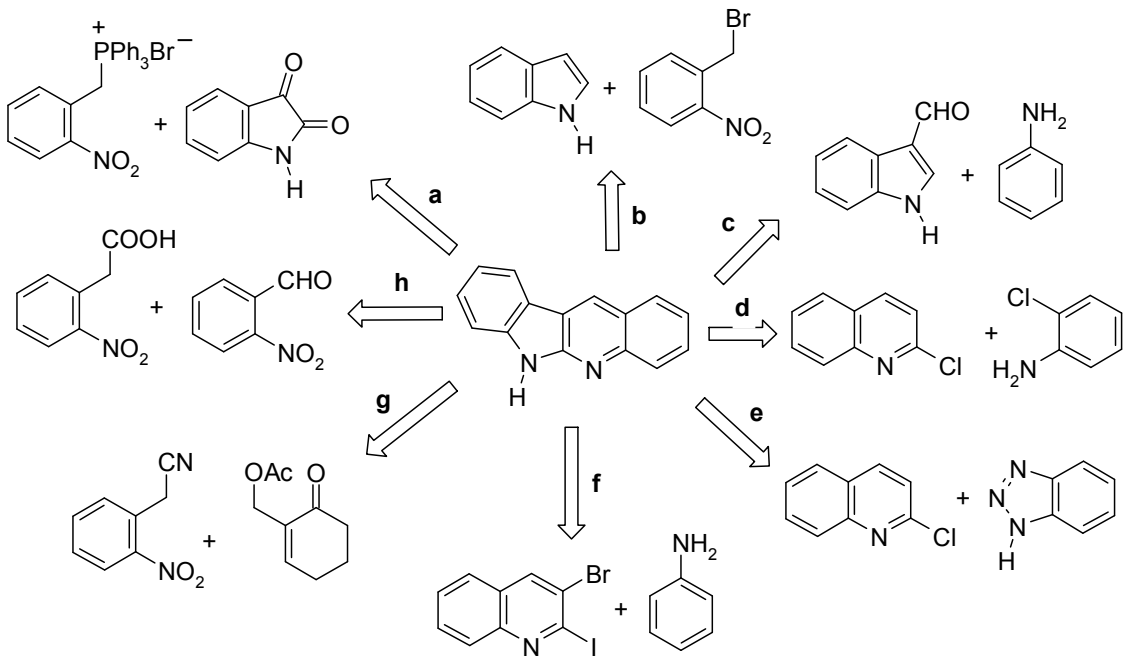
1
norcryptotackieine
(quindoline)



2
neocryptolepine
(cryptotackieine)

The chemistry of 5H- and 6H-indolo[*2,3-b*]quinolines has been recently reviewed[4]. Several methods of construction of this heterocyclic system have been developed, some of them were known[5] before isolation of norcryptotackieine from natural sources. Selected starting materials that in a few steps can be transformed into indolo[2,3-b]quinoline framework are presented in the Scheme 1. These methods include reactions of 2-nitrobenzyltriphenylphosphonium bromide with isatin (**a**), indole with 2-nitrobenzylbromide (**b**)[6], indole-3-carbaldehyde with aniline (**c**)[7], 2-chloroquinoline with 2-chloroaniline (**d**)[8] or benzotriazole (**e**)[9], 2-iodo-3-bromoquinoline with aniline (**f**)[10], 2-nitrophenylacetic acid with

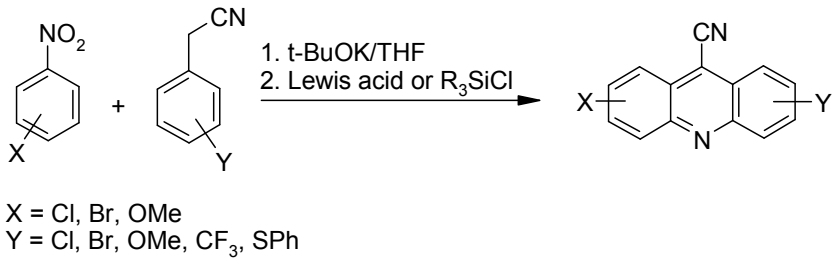
2-nitrobenzaldehyde (**g**)[11], and 2-nitrobenzyl cyanide with 2-acetoxymethyl-2-cyclohexenone (**h**)[12].



Scheme 1. Selected starting materials used for synthesis of 6*H*-indolo[*2,3-b*]quinolines

In the course of our studies on reactions of nucleophilic substitution of hydrogen in nitroarenes we developed numerous transformations enabling direct synthesis of heterocycles, particularly indoles and quinolines, in reactions of carbanions with nitroarenes[13-16]. The methods applicable to synthesis of quinolines consist of transformation of σ^H-adducts formed from nitroarenes and allyl carbanions generated from allyl sulfones[17] or aminocrotonates[18]. It was found that carbanions of arylylacetonitriles react with nitroarenes in the presence of Lewis acids or silylating agents to form 9-cyanoacridine derivatives (Scheme 2)[19]. Two variants of this methodology were developed. In the first one, all reagents: phenylacetonitrile, nitroarene, a relatively weak base such as DBU and a silylating agent (e. g. trimethylchlorosilane) or a Lewis acid (e.g. $MgCl_2$) are mixed at once and stirred to complete the reaction. In the second protocol the mixture of carbanion precursor, nitroarene and a base (e.g. triethylamine) is treated at low temperature with a strong base such as t-BuOK. The formed carbanion adds to nitroarene to form σ^H-adduct that is then treated with a silylating

agent and in the presence of the initially added base (triethylamine) creates pyridine ring yielding finally acridine.



Scheme 2. Synthesis of acridines in the reaction of nitroarenes and phenylacetonitriles.

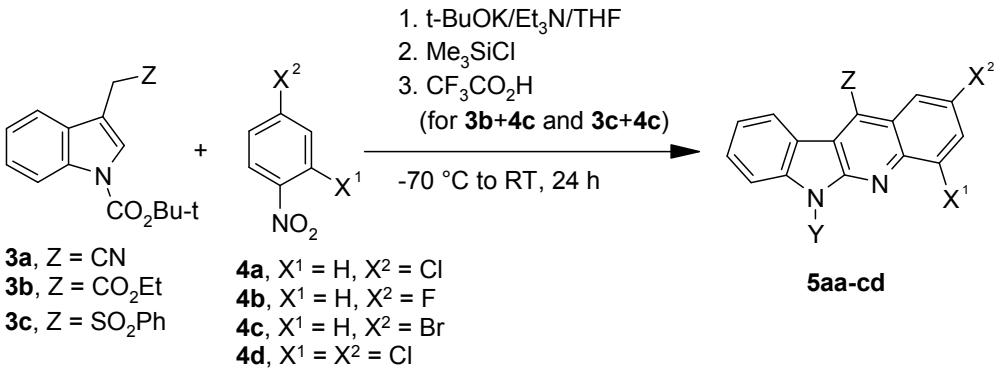
It is worth mentioning that arylacetonitriles and nitroarenes in the presence of base in protic media transform into 3-aryl-2,1-benzisoxazoles (anthranils)[20]. We studied the effect of the reaction conditions on the competition between formation of acridines and anthranils from arylacetonitriles and nitroarenes[21]. The reactions of nitroarenes with benzyl sulfone carbanions mediated by Lewis acid ($MgCl_2$)[22] or silylating agent[21] led to 3-aryl-2,1-benzisoxazoles, instead of 9-(arenesulfonyl)acridines.

Results and discussion

In this paper we present application of reactions of indol-3-ylmethyl carbanions with nitrobenzene derivatives to synthesis of 11-substituted 6*H*-indolo[2,3-b]quinolines. As starting materials we have chosen indole derivatives **3** bearing at position 3 cyanomethyl, ethoxycarbonylmethyl, and benzenesulfonylmethyl groups. Since indole is a relatively strong N-H acid these derivatives were protected with t-butoxycarbonyl group.

In our approach, potassium tert-butoxide was added to tetrahydrofuran solution containing *N*-(tert-butoxycarbonyl)indol-3-ylacetonitrile (**3a**, Z = CN) , 4-chloronitrobenzene (**4a**) and triethylamine cooled to -70 ºC. The generated *in-situ* carbanion reacts with the nitroarene to form σ-adduct, which was then treated with trimethylchlorosilane. The reaction mixture was then allowed to reach room temperature and stirred for 24 h giving after work-up indoloquinoline **5aa** in 57% yield. Similarly reacted other nitrobenzene derivatives: 4-fluoronitrobenzene (**4b**), 4-bromonitrobenzene (**4c**) and 2,4-dichloronitrobenzene (**4d**). No formation of indoloquinoline was observed in reaction of nitrobenzene with indol-3-ylacetonitrile (**3a**, Z = CN). The carbanion precursor was consumed but complex mixture of products was formed arising probably from the σ^H-adduct formed at the *para*-position to the

nitro group. Attempts to use of N-BOC protected ethyl indol-3-ylacetate (**3b**, Z = CO_2Et) as carbanion precursor were partly successful. Its reaction with 4-bromonitrobenzene (**4c**) led to complex mixture of products from which after treatment of the reaction mixture with trifluoroacetic acid N-BOC deprotected indoloquinoline **5bc** was isolated in 25% yield. In the reaction of the ester **3b** with 2,4-dichloronitrobenzene (**4d**) the expected indoloquinoline **5bd** was isolated in 11% yield.



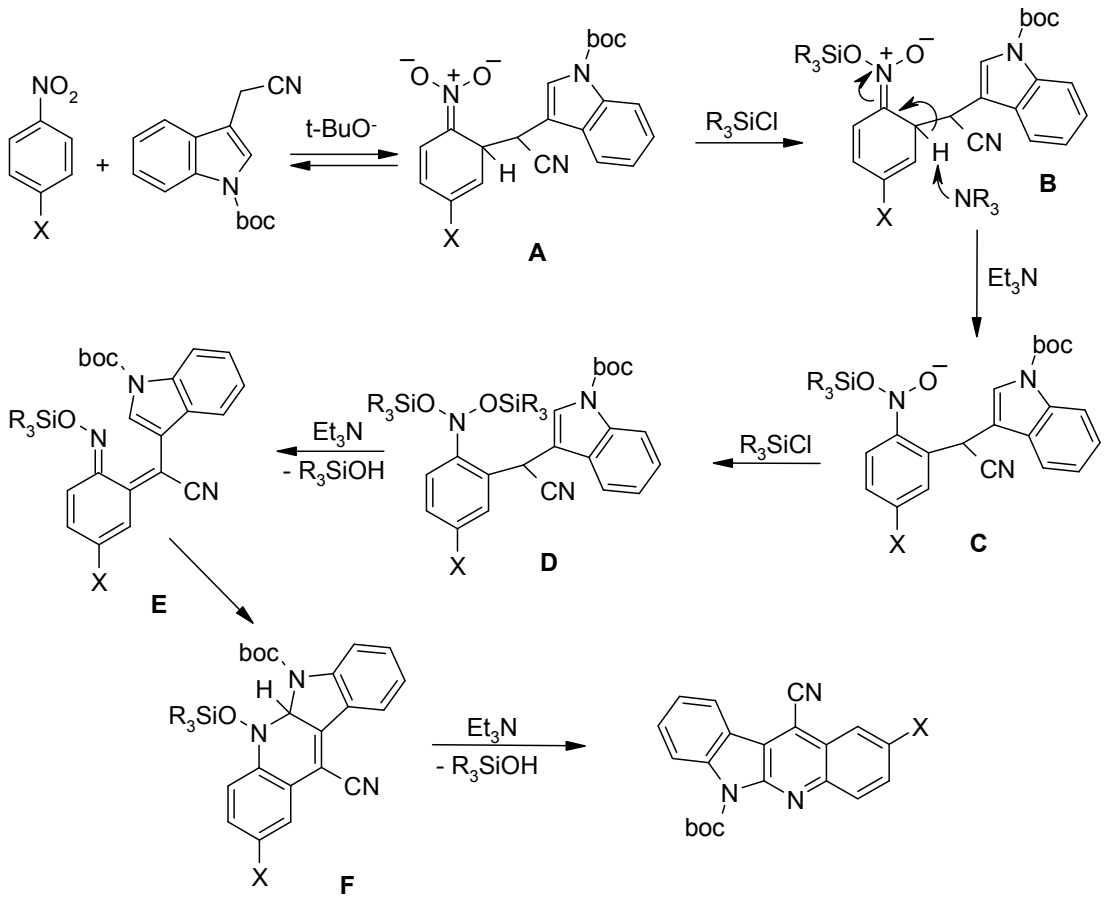
	Z	Y	X^1	X^2	Yield (%)
5aa	CN	t-$BuCO_2$	H	Cl	57
5ab	CN	t-$BuCO_2$	H	F	49
5ac	CN	t-$BuCO_2$	H	Br	58
5ad	CN	t-$BuCO_2$	Cl	Cl	45
5bc	CO_2Et	H	H	Br	25[a]
5bd	CO_2Et	t-$BuCO_2$	Cl	Cl	11
5ca	SO_2Ph	t-$BuCO_2$	H	Cl	40
5cc	SO_2Ph	H	H	Br	62[a]
5cd	SO_2Ph	t-$BuCO_2$	Cl	Cl	56

[a] Yield of N-BOC deprotected product obtained after treatment of the reaction mixture with trifluoroacetic acid.

Scheme 3. Synthesis of indolo[2,3-b]quinoline derivatives.

The plausible way of formation of indoloquinolines from σ^H-adduct **A** generated from N-protected indol-3-ylacetonitrile and nitroarenes is shown in Scheme 4. In the first step the σ^H-adduct **A** undergoes silylation and the formed silyl nitronate **B** is deprotonated to form intermediate **C**, that can be considered a product of replacement of hydrogen at the *ortho*-

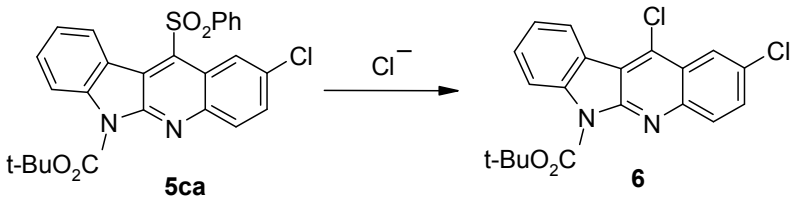
position to the nitro group in the original nitroarene by the carbanion moiety. Further deprotonation of **C** followed by silylation leads to bis-silylated intermediate **D**, which in turn eliminates silanol to form azaxylylene **E**. The electrocyclization of azaxylylene **E** leads to 5,5a-dihydroindoloquinoline framework **F** from which after elimination of another molecule of silanol the final product is formed. Similar electrocyclizations of aza-*ortho*-xylylenes leading to condensed heterocycles are known processes [23, 24]. The crucial point of the proposed mechanism is formation of bis-silylated intermediate **D**. There are some literature precedences of this type bis-silylated dihydroxylamines formed via double deprotonation/silylation of nitroalkenes. The most fitting example is N,N-bis-(tert-butyldimethylsilyloxy)aniline obtained in reaction of 1-nitro-1,3-cyclohexadiene with tert-butyldimethylsilyl triflate [25].



Scheme 4. The proposed way of formation in reactions of indol-3-ylacetonitrile with nitroarenes mediated by trilakylchlorosilanes.

The reaction of N-BOC protected indol-3-yl sulfone (**3c**, Z = SO_2Ph) with 4-chloronitrobenzene led after 24 hr to 11-(benzenesulfonyl)indolo[2,3-b]quinoline (**5ca**) in

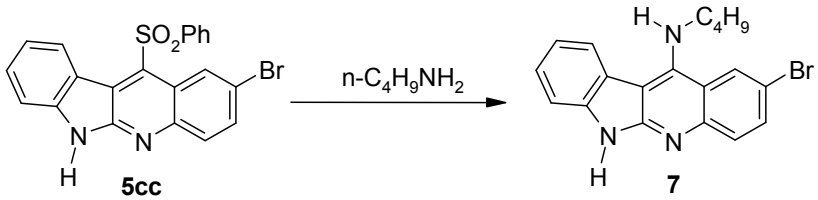
40% yield. However, when the reaction time was extended another product has appeared. After six days transformation of the initially formed benzenesulfonyl derivative **5ca** was completed and 11-chloro derivative **6** was isolated. Formation of this product is a result of substitution of benzenesulfonyl group with chloride anions present in the reaction mixture (Scheme 5). Such replacement of arenesulfonyl group with various nucleophiles was earlier observed in 4-(arenesulfonyl)quinolines.[26, 27]



Scheme 5. Formation of 11-chloroindolo[2,3-b]quinoline.

The N-BOC protecting group can be easily removed from the formed products by treatment with trifluoroacetic acid. This approach was used for the product formed from the sulfone **3c** and 4-bromonitrobenzene (**4c**) giving the product **5cc**.

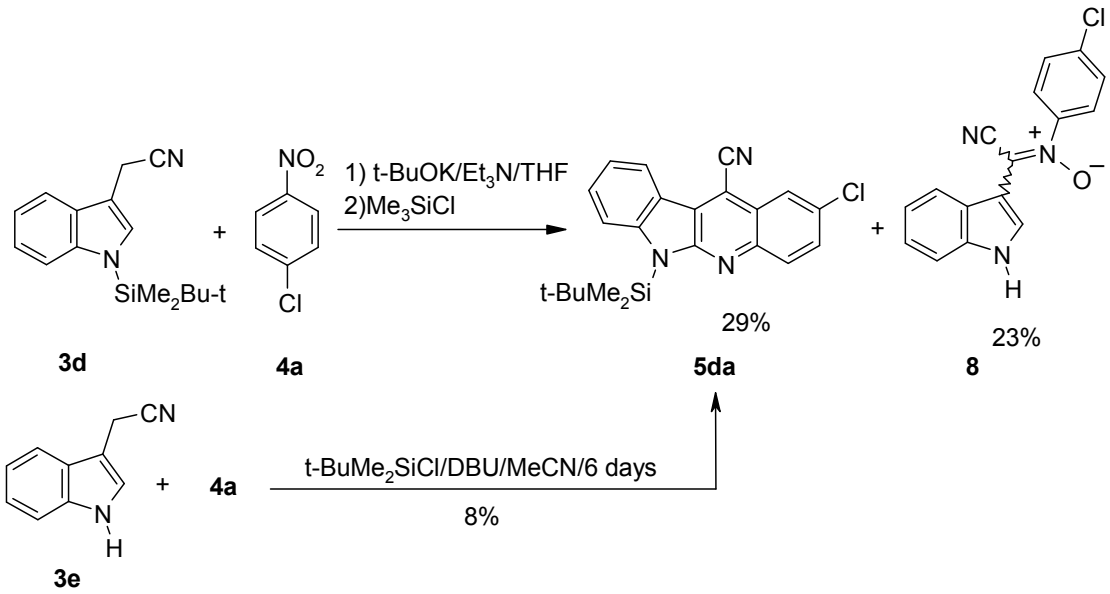
We found that the benzenesulfonyl group in the 11-benzenesulfonyl indoloquinolines can be easily replaced by an alkylamino group as was exemplified by the reaction of the indoloquinoline **5cc** with n-butylamine leading to 11-alkylamino derivative **7**. The 11-(alkylamino)indolo[2,3-b]quinolines focused recently an interest as potential antimalarials[28].



Scheme 6. Replacement of benzenesulfonyl group in **5cc** with n-butylamine.

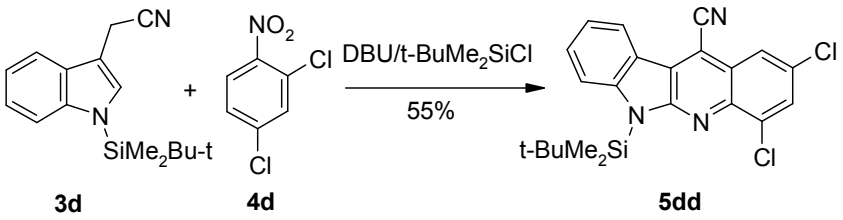
We attempted to use N-trialkylsilyl protected indole derivatives in these reactions, but our efforts were only partly successful. Attempts to obtain N-(trimethylsilyl)indol-3-ylacetonitrile from indol-3-ylaceyonitrile under standard conditions using trimethylchlorosilane and amine (Et_3N or DBU) failed. This indole derivative proved unstable and during isolation decomposed to the starting indol-3-ylacetonitrile. We found that more stable was N-(tert-butyldimethylsilyl)indol-3-ylacetonitrile **3d** obtained from indol-3-ylacetonitrile and tert-butyldimethylchlorosilane. The anion of **3d** generated with potassium tert-butoxide reacted

with 4-chloronitrobenzene (**4a**) and the formed σ^H-adduct upon treatment with trimethylchlorosilane gave the expected 6-silylated derivative **5da** in moderate yield 29% (Scheme 7). An additional product was isolated in this reaction. On the basis of the high resolution mass spectrum for this product molecular formula $C_{16}H_{10}N_3OCl$ was established, for which we proposed structure of nitrone **8**, formed probably from direct attack of the carbanion of the indol-3-ylacetonitrile on the nitro group of the 4-chloronitrobenzene.



Scheme 7. Reaction of N-silylated indol-3-yl acetonitrile with 4-chloronitrobenzene

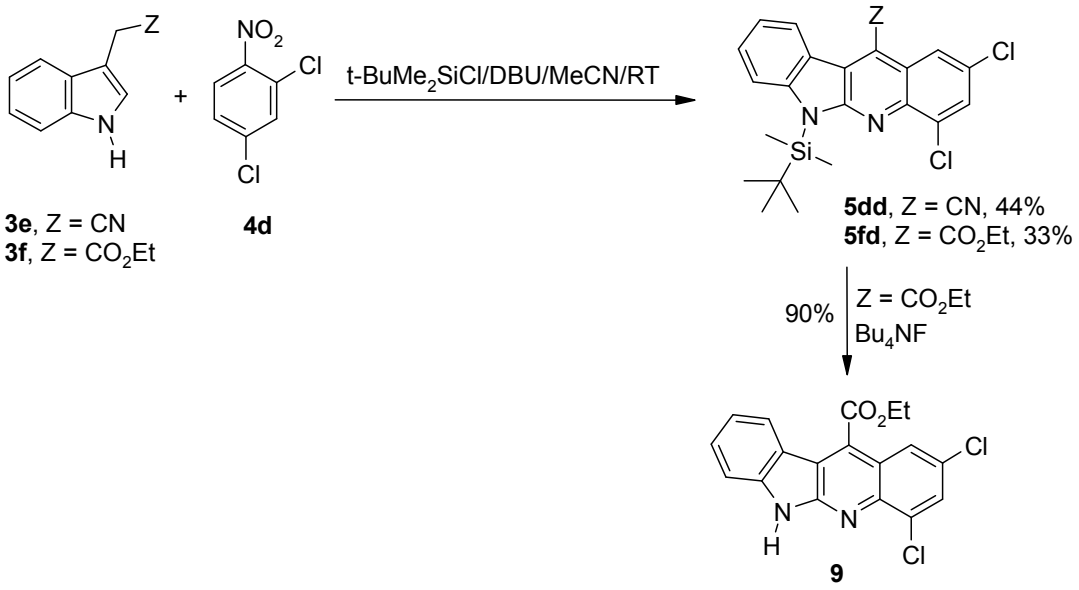
When we used DBU, a weaker base, the reaction of the silylated indol-3-ylacetonitrile **3d** with 2,4-dichloronitrobenzene (**4d**) in the presence of additional tert-butyldimethylchlorosilane gave the expected 6-silylated tetracyclic derivative **5dd** in 55% yield (Scheme 8).



Scheme 8. Reaction of N-silylated indol-3-yl acetonitrile with 4-chloronitrobenzene in the presence of weak base.

Then, we attempted one-pot reaction of N-H unprotected indolyl-3-acetonitrile (**3e**) with nitrobenzenes. Thus when we mixed this indole derivative with 4-chloronitrobenzene with

tert-butyldimethylchlorosilane and DBU in acetonitrile we observed by TLC slow formation of a product. After six-day stirring we isolated 6-silylated-2-chloro-11-cyanoindoloquinoline **5da** in 8% yield (Scheme 7). Similarly, reactions of the nitrile **3e** and ester **3f** with more electrophilic 2,4-dichloronitrobenzene (**4d**) after three-weeks stirring at room temperature gave the expected products **5dd** in 44% and **5fd** in 33% yields, respectively (Scheme 9). Deprotection of 6-N-silylated derivatives can be executed by a simple treatment with tetrabutylammonium fluoride as exemplified by reaction of N-silylated derivative **5fd** leading to indoloquinoline ester **9**.



Scheme 9. Reaction of in situ generated N-silylated indol-3-ylmethyl derivatives with 2,4-dichloronitrobenzene.

Conclusion

We developed simple synthesis of indolo[2,3-b]quinoline derivatives in reaction of nitroarenes with indol-3-ylmethyl carbanions generated from easily accessible starting materials. The elaborated method does not employ transition metals at any stage thus might be applicable in synthesis of pharmaceutically important intermediates.

Experimental

Mp are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 or Varian vnmr s500 (both 500 MHz for ^{1}H and 125 MHz for ^{13}C spectra) instruments at 298 K.

Chemical shifts δ are expressed in parts per million (ppm) referred to TMS, coupling constants in hertz (Hz). Electron impact mass spectra (EI, 70 eV) were obtained on AutoSpec Premier spectrometer. Electrospray mass spectra (ESI) were obtained on 4000 Q-TRAP and SYNAPT G2-S HDMS. Elemental analyses were performed on Elementar Vario EL III instrument. Silica gel (Merck 60, 230-400 mesh) was used for column chromatography (CC). Toluene or hexane/ethyl acetate mixtures were used for elution. TLC analyses were performed on Merck Kieselgel 60 F_{254} Alufolien with hexane/ethyl acetate mixtures. All reagents and solvents were of reagent grade or purified according to standard methods before use. All reactions were run under argon atmosphere.

Reactions of N-BOC protected indol-3-ylmethyl derivatives with nitroarenes. General Procedure.

To a stirred solution of indole derivative **3** (1 mmol), nitroarene **4** (1 mmol) and triethylamine (5 mmol) in THF (10 mL) cooled to -70 ºC a solution of potassium tert-butoxide (0.14 g, 1.2 mmol) in THF (5 mL) was added maintaining the temperature below -65 ºC. After 10 min to the reaction mixture trimethylchlorosilane (0.55 g, 5 mmol) was added dropwise maintaining the temperature below -65 ºC. After addition the reaction mixture was stirred at this temperature for 3 h and then allowed to reach room temperature and stirred for 24 h. The reaction mixture was then quenched with aqueous saturated NH_4Cl (20 mL). The precipitated product was separated, washed in water, dissolved in ethyl acetate and dried with Na_2SO_4. After evaporation of the solvent the product was subjected to column chromatography on silicagel with toluene as eluent.

In the reactions of **3b** with **4c** and **3c** with **4c** the crude product was dissolved in methylene chloride (10 mL) and stirred with trifluoroacetic acid (2 mL) at room temperature for 24 h. The product was isolated by standard procedure.

The following compounds were obtained:

***t*-Butyl 2-chloro-11-cyano-6H-indolo[2,3-b]quinoline-6-carboxylate (5aa).** Yellow solid, yield 57%: mp >300°C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 9H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 8.29 (s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), δ 8.64 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.31, 85.27, 107.13, 114.86, 116.39, 119.73, 121.91, 122.96, 123.50, 124.08, 124.29, 131.12, 131.40, 131.65, 133.52, 140.85, 144.29, 149.20, 150.82. HRMS (ESI) calcd for $C_{21}H_{16}N_3O_2Na^{35}Cl^+$: 400.0829; found: 400.0826.

***t*-Butyl 11-cyano-2-fluoro-6H-indolo[2,3-b]quinoline-6-carboxylate (5ab).** Yellow solid, yield 44%: mp >300 °C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 9H), 7.52 (br s, 1H), 7.62 (br s, 1H), 7.71 (br s, 1H), 7.94 (br s, 1H), 8.28 (br s, 1H), 8.38 (br s, 1H), 8.65 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.33, 85.18, 107.50, 108.40 (d, J_{CF} = 25 Hz), 114.99, 116.38, 119.70, 120.48 (d, J_{CF} = 26 Hz), 121.86, 122.94, 124.24, 131.60, 132.41, 140.80, 142.91, 149.27, 150.38, 161.10 (d, J_{CF} = 250 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -110.81. HRMS (ESI) calcd for $C_{21}H_{16}N_3O_2NaF^+$: 384.1124; found: 384.1128.

***t*-Butyl 2-bromo-11-cyano-6H-indolo[2,3-b]quinoline-6-carboxylate (5ac)**. Yellow solid, yield 58%: mp >320°C (AcOEt – hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 9H), 7.51 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.71 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.89 (dd, *J* = 8.9, 1.9 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 1.9 Hz, 1H), 8.64 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.32, 85.27, 107.02, 114.88, 116.40, 119.73, 121.55, 121.87, 122.98, 124.30, 124.53, 126.79, 131.49, 131.67, 133.68, 140.89, 144.53, 149.20, 150.86. HRMS (ESI) calcd for $C_{21}H_{16}N_3O_2Na^{79}Br^+$: 444.0324; found: 444.0305.

***t*-Butyl 2,4-dichloro-11-cyano-6H-indolo[2,3-b]quinoline-6-carboxylate (5ad).** Yellow solid**,** yield 45%: mp >300°C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.83 (s, 9H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.74 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.91 (s, 1H), 8.22 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 7.8 Hz, H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.41, 85.38, 107.57, 114.62, 116.53, 119.22, 122.58, 122.61, 123.06, 124.43, 124.83, 130.89, 132.20, 132.61, 135.13, 140.69, 141.51, 149.57, 150.48. HRMS (ESI) calcd for $C_{21}H_{15}N_3O_2Cl_2Na$: 434.0439; found: 434.0435

Ethyl 2-bromo-6H-indolo[2,3-b]quinoline-11-carboxylate (**5bc**). Column chromatography (AcOEt : hexane, then AcOEt). Yellow solid, yield 25%: mp. 286.5 – 288 °C (AcOEt). IR (KBr) 3138, 3078, 2983, 1722, 1612, 1577, 1487, 1462, 1440, 1405, 1366, 1345, 1299, 1255, 1214 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.47 (t, *J* = 7.1Hz, 3H), 3.32 (s, 9H), 4.76 (q, *J* = 7.1Hz, 2H), 7.32 (t, *J* = 7.4Hz, 1H), 7.57 (d, *J* = 8.0Hz, 1H), 7.64 (t, *J* = 7.6Hz, 1H), 7.91 (dd, *J* = 9.0, 1.9Hz, 1H), 8.03 (t, *J* = 7.8 Hz, 2H), 8.27 (d, *J* = 1.8, 1H), 12.15 (s, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz ; DMSO-d_6) δ 13.97, 62.57, 111.47, 114.55, 116.41, 117.98, 120.29, 120.38, 123.28, 126.67, 129.45, 129.67, 129.71, 132.00, 142.35, 144.57, 152.57, 166.25 (one missing). HRMS (ESI) calcd for $C_{18}H_{14}N_2O_2Br^+$: 369.0239; found: 369.0240.

***t*-Butyl 2,4-dichloro-11-ethoxycarbonyl-6H-indolo[2,3-b]quinoline-6-carboxylate (5bd).** Column chromatography (PhMe/hexane 1:1, then PhMe). Pale yellow solid, yield 11%: mp. 142-144 °C (hexane : AcOEt). IR (KBr) 3092, 3054, 3002, 2976, 2958, 2931, 2904, 1937, 1733 (C=O), 1721 (C=O), 1602, 1573, 1542, 1482, 1464, 1393, 1370, 1351, 1326, 1303, 1272, 1244, 1220, 1201 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$) δ 1.55 (t, *J* = 7.2Hz, 3H), 1.83 (s, 9H), 4.75 (q, *J* = 7.1Hz, 2H), 7.41 (t, *J* = 7.6Hz, 1H), 7.64 (t, *J* = 7.7Hz, 1H), 7.89 (d, *J* = 2.0Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 7.8, 1H), 8.51 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz; $CDCl_3$) δ 14.26, 28.45, 62.88, 84.87, 116.38, 117.14, 120.02, 122.76, 122.86, 122.91, 123.76, 130.08, 130.45, 130.69, 130.90, 134.61, 140.93, 141.18, 150.03, 151.08, 166.37. HRMS (ESI) calcd for $C_{23}H_{20}N_2O_4Cl_2$: 458.0800; found: 458.0810.

***t*-Butyl 11-(benzenesulfonyl)-2-chloro-6H-indolo[2,3-b]quinoline-6-carboxylate (5ca)**. Yellow solid, yield 40%: mp 230 °C (AcOEt : hexane). ^1H NMR (500 MHz, DMSO-d_6) δ 1.75 (s, 9H), 7.40 – 7.45 (m, 1H), 7.56-7.62 (m, 2H), 7.70 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.74 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.93 (dd, *J* =9.0, 2.1 Hz, 1H), 7.94-7.99 (m, 2H), 8.19 (d, *J* = 9.0 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.90 (d, *J* = 8.3 Hz, 1H), 9.09 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.26, 84.67, 114.80, 118.72, 119.30, 121.42, 123.20, 123.41, 125.52, 128.62, 129.92, 130.42, 131.19, 131.49, 131.51, 134.41, 141.00, 141.02, 144.42, 148.57, 150.66. HRMS (ESI) m/z calcd for $C_{26}H_{22}N_2O_4S^{35}Cl^+$:493.0989; found: 493.0990.

11-(Benzenesulfonyl)-2-bromo-6H-indolo[2,3-b]quinoline (5cc). Yellow solid, yield 62%: mp 239 – 240 °C (decomp) (MeOH). IR (KBr) 3137, 3085, 3002, 2918, 2850, 2773, 1613, 1583, 1571, 1503, 1481, 1458, 1445, 1431, 1416, 1384, 1371, 1346, 1328, 1309, 1294, 1262, 1242, 1223, 1163 cm^{-1} ^1H NMR (500 MHz, DMSO-d_6) δ 7.31 (td, *J* = 7.6, 0.8 Hz, 1H), 7.58 – 7.64 (m, 3H), 7.66 – 7.73 (m, 2H), 7.95 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 8.08 (d, *J* = 9.0 Hz, 1H), 9.01 (d, *J* = 8.3 Hz, 1H), 9.30 (d, *J* = 1.9 Hz, 1H), 12.55 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 111.36, 117.16, 117.42, 117.67, 120.03, 120.32, 125.53, 126.24, 128.80, 129.93, 130.07, 130.93, 132.04, 134.01, 134.23, 141.28, 143.83, 144.83, 152.72. MS (EI): m/z(%) 440 (7), 438 (100), 437 (24), 436 (95), 313 (15), 311 (16), 298 (5), 297 (12), 296 (10), 295 (14), 294 (21), 293 (72), 292 (15), 285 (9), 283 (10), 216 (43), 215 (14), 189 (11), 188 (15), 179,5 (5), 178,5 (5), 146,5 (5), 77 (9). HRMS (EI) m/z calcd for $C_{21}H_{14}N_2O_2S^{79}Br^+$:436.9959; found: 436.9960.

***t*-Butyl 11-(benzenesulfonyl)-7,9-dichloro-6H-indolo[2,3-b]quinoline-6-carboxylate (5cd)**. Yellow solid, yield 56%: mp > 300°C (boiled with AcOEt : hexane). IR (KBr) 3489, 3378, 3306, 3086, 3002, 2987, 2932, 1950, 1909, 1870, 1795, 1756, 1738, 1729, 1631, 1592, 1550, 1541, 1481, 1457, 1443, 1428, 1397, 1371, 1353, 1307, 1248, 1204 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 9H), 7.40 – 7.46 (m, 3H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.85 – 7.90 (m, 3H), 8.47 (d, *J* = 8.5 Hz, 1H), 9.15 – 9.19 (m, *J* =9.0, 2.1 Hz, 2H. ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.35, 85.38, 115.15, 119.15, 120.29, 122.75, 123.12, 123.76, 126.08, 129.43, 129.49, 130.31, 131.68, 131.71, 133.89, 134.48, 136.32, 141.39, 141.77, 141.94, 149.60, 151.00. HRMS (ESI) m/z calcd for $C_{26}H_{20}N_2O_4NaS^{35}Cl_2^+$:549.0419; found: 549.0414.

6-(*t*-Butyldimethylsilyl)-2-chloro-6H-indolo[2,3-b]quinoline-11-carbonitrile (5da). Yellow solid, yield 8%: mp 201-202 °C (CH_2Cl_2 – MeCN). IR (KBr) 3060, 2980, 2962, 2947, 2928, 2883, 2855, 2644, 2223, 1925, 1895, 1767, 1729, 1670, 1650, 1620, 1604, 1593, 1561, 1491, 1477, 1470, 1458, 1403, 1390, 1342, 1306, 1295, 1271, 1257, 1245, 1222, 1209, 1154, 1131, 1118, 1085, 1050, 1022, 1006 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 6H), 1.06 (s, 9H), 7.40 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.62 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.67 – 7.73 (m, 2H), 8.06 (d, *J* = 9.0 Hz, 1H), 8.31 (d, *J* = 2.5 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -1.62, 20.08, 26.73, 105.89, 114.19, 115.52, 121.24, 122.16, 122.88, 123.44, 123.56, 130.15, 130.25, 130.41, 131.41, 143.77, 147.70, 157.46 (one carbon signal missing). MS (EI): m/z (%) = 393 (10), 392 (8), 391 (26), 338 (8), 337 (32), 336 (59), 335 (81), 334 (10), 322 (5), 320 (15), 306 (6), 304 (15), 284 (5). HRMS (EI) m/z calcd for $C_{22}H_{22}N_3SiCl$:391.1272; found: 391.1281.

6-(*t*-Butyldimethylsilyl)-2,4-dichloro-6H-indolo[2,3-b]quinoline-11-carbonitrile (5dd). Yellow solid, yield 44%: mp226-228°C (CH_2Cl_2 – MeCN). IR (KBr); 2950, 2926, 2896, 2882, 2856, 2350, 2224, 1952, 1909, 1866, 1825, 1780, 1732, 1718, 1706, 1619, 1594, 1556, 1481, 1467, 1456, 1393, 1365, 1338, 1305, 1295, 1282, 1255, 1238, 1210, 1187, 1157, 1120, 1102, 1066, 1042, 1023, 1003 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 (s, 6H), 1.05 (s, 9H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.64 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 8.23 (d, *J* = 2.2 Hz, 1H), 8.66 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -1.91, 20.41, 26.70, 106.45, 114.35, 115.23, 120.88, 121.55, 122.47, 122.86, 123.59, 123.79, 129.91, 130.91, 134.23, 140.34, 148.05, 148.05, 157.41. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_3SiCl_2^+$:426.0960; found: 426.0955.

Ethyl 6-(*t*-butyldimethylsilyl)-6H-indolo[2,3-b]quinoline-11-carboxylate (5fd).
Yellow solid, yield 33%: mp 129-130 °C (hexane : AcOEt). IR (KBr); 3051, 2952, 2926, 2854, 1916, 1878, 1729, 1622, 1596, 1562, 1478, 1459, 1391, 1373, 1341, 1311, 1287, 1267, 1254, 1243, 1200, 1154, 1116, 1097, 1067, 1029, 1007, 949 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (s, 6H), δ 1.07 (s, 9H), δ 1.55 (t, *J* = 7.2 Hz, 3H), δ 4.75 (q, *J* = 7.2 Hz, 2H), 7.28 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H). . ^{13}C NMR ($CDCl_3$) δ -1.77, 14.31, 20.44, 26.79, 62.57 114.15, 117.38, 120.79, 121.42, 121.50, 122.67, 123.58, 128.60, 129.11, 129.21, 129.73, 133.72, 140.81, 147.38, 158.04, 167.02. HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_2SiCl_2^+$:473.1219; found: 473.1213.

***t*-Butyl 2,11-dichloro-6H-indolo[2,3-b]quinoline-6-carboxylate (6).** Yellow solid, yield 37%: mp 170-171 °C (hexane – AcOEt). ^1H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 9H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 8.13 (t, *J* = 8.8 Hz, 1H), 8.32 (m, *J* = 2H), 8.59 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.36, 84.76, 115.92, 117.38, 121.33, 122.56, 123.64 123.88, 124.43, 129.63, 130.50, 131.02, 131.78, 134.24, 139.75, 144.96 149.48, 151.41. HRMS (ESI) m/z calcd for $C_{20}H_{16}N_2O_2Na^{35}Cl_2^+$:409.0487; found: 409.0484.

2-Bromo-N-(n-butyl)-6H-indolo[2,3-b]quinolin-11-amine (7).
Indoloquinoline **5cc** (50 mg, 0.11 mmol) was dissolved in n-butylamine (1 mL) and stirred at room temperature for 2.5 hr. The reaction mixture was pored into saturated aqueous NH_4Cl (10 mL) extacted with ethyl acetate (3 x 10 mL), washed with brine (20 mL) and dried with Na_2SO_4. After evaporation of solvent the product was washed with hot methanol. Yield 100%: Pale yellow solid, mp 250-252°C (boiled with MeOH). IR (KBr) 3445, 3219, 3136, 3076, 3051, 3007, 2955, 2926, 2866, 1920, 1892, 1611, 1571, 1508, 1489, 1442, 1403, 1383, 1306, 1290, 1244 cm^{-1} ^1H NMR (DMSO-d_6) δ 0.78 (t, *J* = 7.4 Hz, 3H), 1.26 (hex, *J* = 7.4 Hz, 2H), 1.66 (quint, *J* = 7.3 Hz, 2H), 3.67 (m, 2H), 6.55 (m, 1H), 7.24 (td, *J* = 6.9, 2.2 Hz, 1H), 7.40 – 7.45 (m, 2H), 7.70 - 7.78 (m, 2H), 8.02 (d, *J* = 7.9 Hz, 1H), 8.74 (d, *J* = 1.5 Hz, 1H), 11.60 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.57, 19.38, 32.88, 47.71, 103.06, 110.24, 113.27, 118.90, 119.37, 120.40, 122.87, 125.10, 125.75, 128.88, 131.35, 139.69, 145.48, 148.08, 154.43. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_3{}^{79}Br^+$: 368.0762; found: 368.0760.

1-(*t*-Butyldimethylsilyl)indol-3-ylacetonitrile (3d).

Solution of indol-3-ylacetonitrile (0.94 g, 6 mmol) in dry THF (5 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil; 0.40 g, 9.9 mmol) in dry THF (10 mL) keeping temp. 0 – 5 °C. After being stirred for 30 min, a solution of *tert*-butyldimethylsilyl chloride (1.13 g, 7.5 mmol) in dry THF (2.0 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C, quenched with water (25 mL), extracted with Et_2O (5 x 15 mL). The organic extracts were washed with water (25 mL) and brine (50 mL), dried over Na_2SO_4 and evaporated. The crude product (in order to remove mineral oil) was dissolved in Et_2O and precipitated from hexane (with the use of rotary evaporator). The product was collected and washed with cold hexane; yield 1.507 g (93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.61 (s, 6H), 0.93 (s, 9H), 3.81 (s, 2H), 7.16 (s, 1H), 7.14 – 7.19 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -3.90, 14.43, 19.40, 26.24, 106.58, 114.28, 117.99, 118.10, 120.19, 125.77, 129.33, 129.29.

Nitrone (8)

Column chromatography (AcOEt : hexane 1:2, then 2:1). Yellow solid, yield 23 %: mp. 231-234°C (decomp.) (CH_2Cl_2 : MeCN). IR (KBr) 3175, 2919, 2857, 2221 (CN), 1722, 1615, 1584, 1615, 1584, 1517, 1487, 1475, 1435, 1402, 1371, 1325, 1276, 1242; cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.26-7.41 (m, 2H), 7.66 (d, J = 6.9 Hz, 2H), 7.74 (d, J = 6.6 Hz, 2H), 7.93 (d, J = 6.8 Hz, 2H), 8.23 (d, J = 6.8 Hz, 1H), 9.30 (s, 1H), 12.27 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 104.47, 112.80, 115.07, 117.90, 118.60, 121.21, 123.30, 123.40, 126.29, 129.41, 130.68, 135.17, 136.05, 145.53. HRMS (ESI) m/z calcd for $C_{16}H_{10}N_3O^{35}Cl^+$: 318.0410; found: 318.0407.

Desilylation of ethyl 6-(tert-butyldimethylsilyl)-6H-indolo[2,3-b]quinoline-11-carboxylate (5fd)

Indoloquinoline **5fd** (60 mg, 0.13 mmol) was dissolved in ethyl acetate (5 mL) and treated with added dropwise solution of tetrabutylammonium fluoride (48 mg, 0.15 mmol) in ethyl acetate (5 mL) at room temperature. After addition the reaction mixture was stirred for 40 min, quenched with saturated aqueous NH_4Cl (10 mL). Aqueous phase was extracted with ethyl acetate (3 x 10 mL). Combined organic solution was washed with diluted HCl (10 mL), brine (10 mL) and dried with Na_2SO_4. After evaporation of solvent crude product was triturated with boiling acetonitrile. **Ethyl 6H-indolo[2,3-b]quinoline-11-carboxylate (9)**

was obtained as yellow solid, yield 90%: mp. > 305°C. IR (KBr); 3332, 3054, 2984, 2962, 1730 (C=O), 1611, 1573, 1497, 1484, 1464, 1442, 1398, 1383, 1342, 1282, 1254, 1223, 1200 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 1.49 (t, J = 7.1 Hz, 3H), 4.76 (q, J = 7.1 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H) 8.01 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 8.08 (dd, J = 2.0 Hz, 1H), 12.27 (s, 1H). ^{13}C NMR (Bruker 125 MHz, DMSO-d_6) δ 13.49, 62.25, 111.22, 115.22, 117.51, 120.15, 120.28, 122.55, 123.04, 126.79, 128.48, 129.56, 129.83, 131.79, 140.30, 142.34, 152.46, 165.52. HRMS (ESI) calcd for $C_{18}H_{13}N_2O_2{}^{35}Cl_2^+$: 359.0354; found: 359.0344.

Acknowledgement: This work was financially supported by National Scientific Center grant No 2012/07/B/ST5/00813

References

1. C. Wright, *Phytochem. Rev.*, 2005, **4**, 55-61.
2. C. W. Wright, *J. Pharm. Pharmacol.*, 2007, **59**, 899-904.
3. L. Kaczmarek, W. Peczynska-Czoch, A. Opolski, J. Wietrzyk, E. Marcinkowska, J. Boratynski and J. Osiadacz, *Anticancer Research*, 1998, **18**, 3133-3138.
4. A. B. J. Bracca, D. A. Heredia, E. L. Larghi and T. S. Kaufman, *Eur. J. Org. Chem.*, 2014, **2014**, 7979-8003.
5. S. J. Holt and V. Petrow, *J. Chem. Soc.*, 1948, 922-924.
6. H. K. Kadam, P. T. Parvatkar and S. G. Tilve, *Synthesis*, 2012, **44**, 1339-1342.
7. P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *J. Org. Chem.*, 2009, **74**, 8369-8372.
8. T. Dhanabal, R. Sangeetha and P. S. Mohan, *Tetrahedron*, 2006, **62**, 6258-6263.
9. Ł. Kaczmarek, R. Balicki, P. Nantka-Namirski, W. Peczyńska-Czoch and M. Mordarski, *Arch. Pharm.*, 1988, **321**, 463-467.
10. B. Boganyi and J. Kaman, *Tetrahedron*, 2013, **69**, 9512-9519.
11. P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *Tetrahedron Lett.*, 2007, **48**, 7870-7872.
12. D. Basavaiah and D. Mallikarjuna Reddy, *Org. Biomol. Chem.*, 2012, **10**, 8774-8777.
13. M. Mąkosza and K. Wojciechowski, *Chem. Rev.*, 2004, **104**, 2631-2666.
14. M. Mąkosza and K. Wojciechowski, *Heterocycles*, 2014, **88**, 75-101.
15. M. Mąkosza and K. Wojciechowski, *Top. Heterocycl. Chem.*, 2014, **37**, 51-106.
16. M. Mąkosza and K. Wojciechowski, *Chem. Heterocycl. Comp.*, 2015, **51**, 210-222.
17. K. Anczkiewicz, M. Królikiewicz, Z. Wróbel and K. Wojciechowski, *Tetrahedron*, 2015, **71**, 3924-3931.
18. R. Bujok, A. Kwast, P. Cmoch and Z. Wróbel, *Tetrahedron*, 2010, **66**, 698-708.
19. M. Bobin, A. Kwast and Z. Wróbel, *Tetrahedron*, 2007, **63**, 11048-11054.
20. R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, 1960, **25**, 1884-1888.
21. M. Więcław, M. Bobin, A. Kwast, R. Bujok, Z. Wróbel and K. Wojciechowski, *Molecular Diversity*, 2015, **19**, 807-816.
22. Z. Wróbel, *Pol. J. Chem.* 1998, **72**, 2384-2388.
23. K. Wojciechowski, *Eur. J. Org. Chem.*, 2001, 3587-3605.
24. V. H. M. Elferink and H. J. T. Bos, *J. Chem. Soc. Chem. Commun.*, 1985, 882-883.

25. A. D. Dilman, I. M. Lyapkalo, P. A. Belyakov, S. L. Ioffe, Y. A. Strelenko and V. A. Tartakovsky, *Russ. Chem. Bull.*, 2000, **49**, 1649-1650.
26. Z. Wróbel, *Tetrahedron*, 1998, **54**, 2607-2618.
27. Z. Wróbel, *Eur. J. Org. Chem.*, 2000, 521-525.
28. I. El Sayed, P. Van der Veken, K. Steert, L. Dhooghe, S. Hostyn, G. Van Baelen, G. Lemiere, B. U. W. Maes, P. Cos, L. Maes, J. Joossens, A. Haemers, L. Pieters and K. Augustyns, *J. Med. Chem.*, 2009, **52**, 2979-2988.