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One-pot synthesis of meridianins and meridianin analogues via indolization of nitrosoarenes

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ABSTRACT

Meridianins, marine alkaloids known as kinase inhibitors with an indole skeleton, and meridianin analogues were produced regioselectively and in moderate to good yields by thermal annulation of nitrosoarenes with 2-amino-4-ethynylpyrimidine and 2-chloro-4-ethynylpyrimidine, respectively, through a novel and atom-economical indolization process.

1. Introduction

C-Nitroso compounds, extremely versatile reagents, are extensively used in organic synthesis. They can be easily prepared following different procedures.[1–7] General and typical methods applied in medium and large scale preparation are carried out by oxidation of the corresponding anilines with Oxone®,[1] Na_2WO_4–H_2O_2,[2] molybdenum complexes–H_2O_2,[3] and in situ preparation using selenium derivatives.[4] A large scale and long known synthesis of nitrosobenzene involves the reduction of nitrobenzene to phenylhydroxylamine by Zn–NH_4Cl and the subsequent oxidation of the latter by $Na_2Cr_2O_7$.[5] Other methods developed involve the use of alkyl nitrites[6] and the conjugate addition of Grignard reagents to nitroarenes.[7] Nitrosoarenes and nitrosoacyl compounds are very useful synthetic intermediates for different purposes. Prominent nitrosoarene reactions are the oxaza-Cope rearrangement,[8] nitroso-ene reaction,[1a,9] α-aminoxylation,[10] including regioselective *N*- and *O*-variants[11a] and an organocatalytic version,[10a–c,11b] condensation to azo-derivatives[1c] and cycloaddition reactions, among which the hetero-Diels–Alder is the most important and valuable.[12] All these reactions allow rapid access to useful synthetic building blocks, scaffolds and core structures of natural products. Metal-catalyzed nitroso-ene reactions have been developed by in situ generation of nitrosoarenes via oxidation of arylhydroxylamines[13] or reduction of nitroarenes,[14] two different procedures used for the catalytic allylic amination of alkenes.[15] Although many reactions of nitroso compounds with alkenes, carbonyl derivatives, and dienes are known and well studied, the evaluation of the reactivity of nitrosoarenes with alkynes has been scarcely explored.[16] The first pioneering reports on this last topic are due to Alessandri[17] whose research was entirely devoted to the study of the reactions between nitrosoarenes and internal alkynes and terminal olefins affording nitrones via addition to the triple bond.

Our interest in the chemistry of nitroso compounds started with the disclosure of a novel synthetic approach to 3-substituted indoles, afforded regioselectively by reductive annulations of nitroarenes with alkynes under a CO atmosphere.[18] Subsequently, Ragaini and co-workers reported a similar palladium-catalyzed reaction with a more efficient Pd catalytic system[19a] and with Pd–Ru mixed catalyst.[19b] Carbonylative reduction of nitroarenes has long been studied and many heterocyclic molecules have been produced this way.[20] Some of us reported even the allylic amination of alkenes by reductive carbonylation of nitroarenes catalyzed by Ru[14a] and Fe[14b] complexes. Examining the reactions of nitrosoarenes with alkynes under the above catalytic conditions, we also reported an uncatalyzed version providing direct access to the indole ring[21] (Scheme 1).

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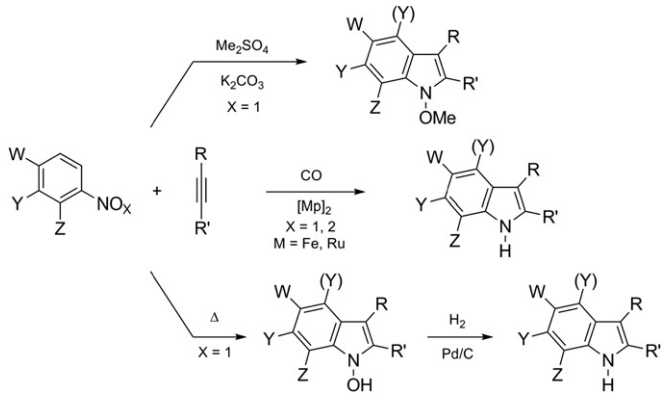


Scheme 1. Synthesis of the indole skeleton by cycloaddition of nitro- and nitrosoarenes with alkynes.

In contrast to the reactions with nitroaromatics the major products of this annulation process were *N*-hydroxyindoles, produced regioselectively, under mild conditions, with functional group tolerance and with an excellent atom economy (Scheme 1). The efficiency of the ArNO–alkyne cycloaddition can be improved significantly by alkylative trapping of the labile *N*-hydroxyindoles with K_2CO_3–Me_2SO_4,[22] providing access to a variety of *N*-methoxy indoles from substituted nitrosoarenes and arylacetylenes. The reactions with methyl propiolate afforded a one-step preparation of phytoalexin analogues from Wasabi. Very recently other *O*-protected 1-hydroxyindoles and *N*-protected indoles have been produced using this reaction.[23] Previously, we always carried out these reactions with the nitrosoaromatics as the limiting reagents in contrast to Alessandri's procedures. Terminal conjugated alkynes are privileged substrates, providing high yields and 3-position regioselectivity; non-conjugated and internal alkynes give lower yields and modest regioselectivities. Experimental and computational studies of the reaction mechanism show that the most plausible pathway for the nitrosoarene–alkyne cycloaddition is the formation of the C–N bond as a rate determining step followed by rapid C–C bond formation with a singlet diradical intermediate as the focal point of the mechanism.[24] More recently, some of us reported a related indole synthesis through the in situ formation and trapping of nitrosoarenes by oxidation of arylhydroxylamines by iron(II)–phthalocyanine complexes.[25]

Our final goal is the use of the novel nitrosoarene–alkyne indolization for the preparation of biologically active indole derivatives. The indole ring system is probably one of the most ubiquitous heterocycles in nature that occurs in many biologically active molecules.[26] The synthesis and functionalization of indoles are a major area of interest for synthetic organic chemists, and numerous methods and procedures for the preparation of indoles have been developed so far.[27] Similarly *N*-hydroxyindoles and their derivatives have received considerable attention in recent years, especially through the admirable work of different research groups.[28] Searching the literature we found an interesting class of indole based natural products, the meridianins A–G (Fig. 1).[29] Meridianins are marine indole alkaloids first isolated from the tunicate *Aplidium meridianum* (Ascidiae, Polyclinidae family) in the vicinity of the South Georgia Islands, South Atlantic.[30] Meridianins and their analogues have been deeply studied as potent inhibitors of several protein kinases.[31] These enzymes are extensively known as biological regulators in many different vital processes of the cells: signal transduction, cellular proliferation and motility, regulation of cell cycle and DNA damage response and repair. The meridianins have been recently screened as agents for cancer therapy.[32]

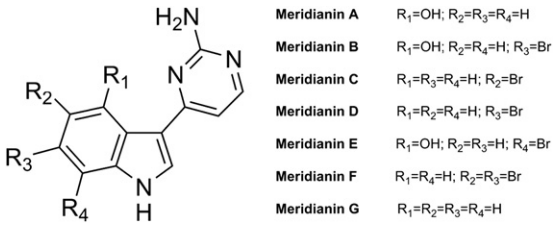


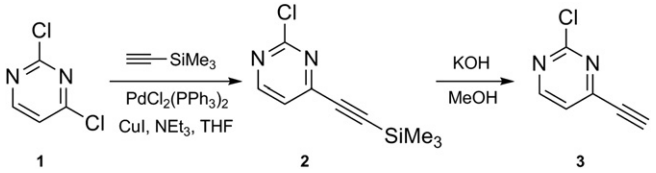
Figure 1. Natural Meridianins isolated from *Aplidium meridianum*.

Four different synthetic approaches to natural meridianins and analogues have been published to date.[33–36] Most of them start from a preformed indole ring, except a Fischer procedure reported by Palermo and Hernandez Franco for isomeridianin synthesis.[33] The more frequently used and general method shows the construction of the pyrimidine ring on 3-acyl-indole derivatives or 3-indolyl acetate with DMF–DMA followed by reactions with guanidine.[34] Afterwards, Jiang and co-workers introduced a different synthetic approach by using a Suzuki–Miyaura-type reaction starting from 3-indolylboronic acid with 2-amino-4-chloropyrimidine.[35] More recently Müller and co-workers reported an innovative strategy based on the carbonylative Sonogashira-type alkynylation for the synthesis of 3-acyl-indoles by using *N*-protected-3-iodoindoles and subsequent reaction with guanidine[36] as used by other groups.

2. Results and discussion

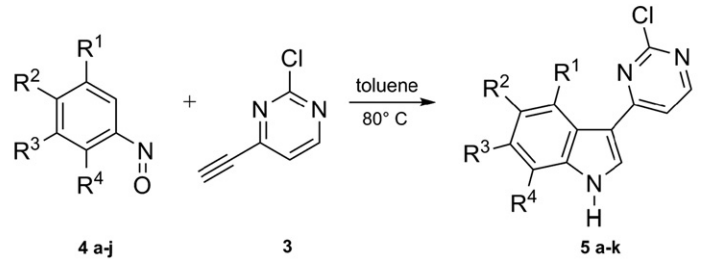
Stimulated by the intention to apply our convergent indole synthetic approach to the preparation of biologically active compounds we began by preparing ethynylpyrimidines that could undergo cycloaddition with nitrosoaromatics to produce pyrimidine substituted indoles. A useful synthetic approach to the substituted ethynylpyrimidines was introduced by Mani and Deng [37] and we could repeat and modify successfully some reactions reported there.

The synthesis of meridianin G started from 2-chloro-4-ethynylpyrimidine **3**, produced by Sonogashira coupling of 2,4-dichloro pyrimidine **1** with ethynyltrimethylsilane catalyzed by $PdCl_2(PPh_3)_2$ and CuI, followed by deprotection of the $SiMe_3$ group with KOH in methanol (Scheme 2). The Sonogashira reaction can be carried out even on a large scale (~40 g of compound **1**) and the alkynylation occurs in an intriguing regiospecific fashion. Alkyne **3** reacted reasonably efficiently with several nitrosoarenes **4a**–**j** (1:1 in toluene at 80 °C) affording substituted 3-(2-chloropyrimidinyl)-indoles **5a**–**k** in moderate to good yields (Scheme 3 and Table 1). A scale-up procedure for one reaction starting from 2 g of **4b** and 1.8 g of **3** was carried out affording the product **5b** in 74% yield.



Scheme 2. Synthesis of 2-chloro-4-ethynylpyrimidine.

An exploratory procedure for substitution of the chloro by an amino group was achieved in a sealed tube reaction with aqueous ammonia carried out on compound **6a** in 54% yield (Scheme 4). This reaction provided an easy and fast procedure to prepare meridianin G and potentially other related alkaloids. In contrast to previous total syntheses of meridianins we provided an easy access to the target molecules via an indolization reaction, not starting from a preformed indole. Its improvement in efficiency is clearly evident in comparison with some syntheses of meridianins previously realized.



a: $R^1=R^2=R^3=R^4=H$; **b**: $R^2=NO_2$, $R^1=R^3=R^4=H$;
c: $R^2=Br$, $R^1=R^3=R^4=H$; **d**: $R^2=CN$, $R^1=R^3=R^4=H$;
e: $R^4=NO_2$, $R^1=R^2=R^3=H$; **f**: $R^4=CF_3$, $R^1=R^2=R^3=H$;
g: $R^2=COOH$, $R^1=R^3=R^4=H$; **h**: $R^4=CH_3$, $R^1=R^2=R^3=H$;
i: $R^1=Br$, $R^2=R^3=R^4=H$; **j**: $R^2=OCH_3$, $R^1=R^3=R^4=H$

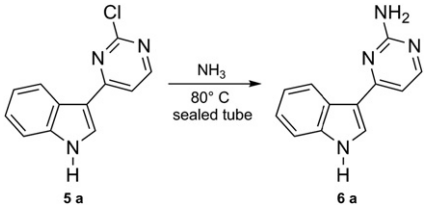
a: $R^1=R^2=R^3=R^4=H$; **b**: $R^2=NO_2$, $R^1=R^3=R^4=H$;
c: $R^2=Br$, $R^1=R^3=R^4=H$; **d**: $R^2=CN$, $R^1=R^3=R^4=H$;
e: $R^4=NO_2$, $R^1=R^2=R^3=H$; **f**: $R^4=CF_3$, $R^1=R^2=R^3=H$;
g: $R^2=COOH$, $R^1=R^3=R^4=H$; **h**: $R^4=CH_3$, $R^1=R^2=R^3=H$;
i: $R^1=Br$, $R^2=R^3=R^4=H$; **j**: $R^3=Br$, $R^1=R^2=R^4=H$;
k: $R^2=OCH_3$, $R^1=R^3=R^4=H$

Scheme 3. Synthesis of 3-(2-chloropyrimidin-4-yl)indoles.

Table 1
Results for the reactions between nitrosoarenes and 2-chloro-4-ethynylpyrimidine[a,b]

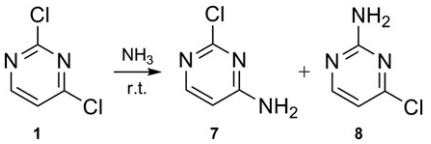
Entry	Compound	R^1	R^2	R^3	R^4	Yield (%)
1	**5a**	H	H	H	H	67
2	**5b**	H	NO_2	H	H	71 (74)[c]
3	**5c**	H	Br	H	H	54
4	**5d**	H	CN	H	H	49
5	**5e**	H	H	H	NO_2	38
6	**5f**	H	H	H	CF_3	30
7	**5g**	H	COOH	H	H	54
8	**5h**	H	H	H	CH_3	55
9	**5i**	Br	H	H	H	19[d]
10	**5j**	H	H	Br	H	20[d]
11	**5k**	H	OCH_3	H	H	23[e]

[a] All reactions were carried out for 5–12 h using ArNO and 2-chloro-4-ethynylpyrimidine in a 1:1 molar ratio monitoring the disappearance of the nitrosoarene by TLC.
[b] Some products were collected by filtration and no further purification was necessary.
[c] For this reaction a scale-up procedure was carried out starting from 2 g of **4b** and 1.8 g of **3** achieving the product **5b** in slightly better yield and in same reaction times.
[d] Detected by cycloaddition between 3-bromonitrosobenzene and 2-chloro-4-ethynylpyrimidine.
[e] The conversion of 4-methoxynitrosobenzene was 64%; yield calculated on converted nitroso compound.



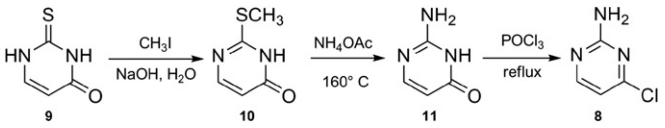
Scheme 4. Synthesis of meridianin G.

Alternatively, we directly prepared 2-amino-4-ethynylpyrimidine through formation of 2-amino-4-chloropyrimidine, easily available using two different reported procedures.[38] 2,4-Dichloropyrimidine **1** reacted with ammonia giving a mixture of the two regioisomers, 2-amino-4-chloropyrimidine **8** and 2-chloro-4-aminopyrimidine **7** in a molar ratio 4:6 (Scheme 5).[38a] Unfortunately, this technique gave us the desired isomer as the minor product.



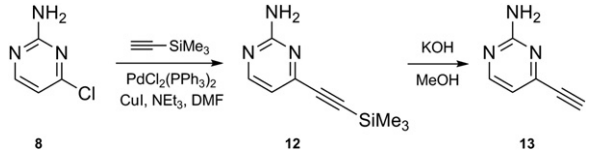
Scheme 5. Synthesis of 2-amino-4-chloropyrimidine and of 2-chloro-4-aminopyrimidine.

Another approach, more suitable to a large scale preparation of compound **8** required a multi-step synthetic strategy (Scheme 6). Starting from thiouracil **9**, 2-methylthio-3*H*-pyrimidine-4-one **10** was easily produced by methylation with CH_3I,[39] a reaction that occurs very quickly with precipitation of the product in quantitative yield.



Scheme 6. Alternative synthesis of 2-amino-4-chloropyrimidine.

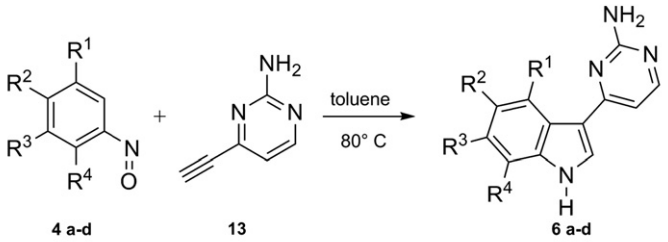
Compound **10** was converted to isocytosine **11**, a commercially available but quite expensive regioisomer of the natural nucleoside cytosine by reaction in a melted mixture with ammonium acetate at 160 °C.[40] The final procedure required reaction between compound **11** and $POCl_3$ at reflux for 3 h[38b] and, after work-up, 2-amino-4-chloropyrimidine was isolated in good yield and in sufficient amount to continue the preparation of 2-amino-4-ethynylpyrimidine **13**. Compound **8** reacted promptly under Sonogashira conditions giving 2-amino-4-[trimethysilylethynyl]pyrimidine **12** in 71% yield following a procedure reported for similar compounds (Scheme 7).[41] The intermediate **12** was readily converted to the terminal alkyne **13**, our starting material for the indolization reaction, by cleavage with KOH (0.01 equiv, 90% yield).



Scheme 7. Synthesis of 2-amino-4-ethynylpyrimidine.

The final cyclization was successfully conducted on compound **13** using nitrosoarenes **4a**–**d** under the standard conditions to provide a wide range of meridianin analogues **6a**–**e** substituted on the benzene ring of the indole fragment (Scheme 8 and Table 2).

By this synthetic approach two natural meridianins, C and G, were produced. Both nitrosoarenes with electron-withdrawing groups and nitrosoaromatics with electron-donating substituents reacted with alkynes. As already observed studying the reaction mechanism[24] nitrosoarenes with EWG gave faster reaction times and complete conversions. Nitroso compounds with EDG react



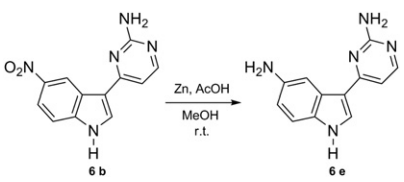
Scheme 8. Synthesis of 3-(2-aminopyrimidin-4-yl)indoles and of meridianins C and G.

Table 2
Results for the reactions between nitrosoarenes and 2-amino-4-ethynylprimidine[a,b]

Entry	Compound	R^1	R^2	R^3	R^4	Yield (%)
1	**6a**	H	H	H	H	41
2	**6b**	H	NO_2	H	H	62
3	**6c**	H	Br	H	H	28
4	**6d**	H	CN	H	H	48
5	**6a**	H	H	H	H	54[c]
6	**6e**	H	NH_2	H	H	quant.[d]

[a] All reactions were carried out for 5–12 h using ArNO and 2-amino-4-ethynylpyrimidine in a molar ratio 1:1 monitoring by TLC the disappearance of the nitrosoarene.
[b] Some products were collected by filtration and no further purification was necessary.
[c] Detected by reaction between the product of entry 1 in Table 1 (compound **5a**) with NH_3 in sealed tube (Scheme 4).
[d] Afforded by reduction of compound **6b** (Scheme 9).

slowly and sometimes without complete consumption (entry 11, Table 1). Working with *meta*-substituted nitrosarenes two different regioisomers were isolated (entries 9 and 10, Table 1). Substituent groups on the benzene ring of the indole structure could be the starting points for future further functionalizations. This study will be further focused after analyzing the biological and potential pharmacological activities of the molecules currently produced. By studying the binding modes of typical CDK (cyclin dependent kinases) inhibitors like meriolins and variolins (analogues of meridianins and related derivatives with azaindole skeleton) and CDK2 ATP binding site, some authors[31a,c,32a] focused on the formation of hydrogen bonds between nitrogen and oxygen atoms from these alkaloid structures (from pyridine and/or pyrimidine ring and amino or hydroxyl groups) and aminoacids in the active site of the enzyme. The presence of additional amino groups could generate an enhancement of this kind of interaction. The production of compound **6e** with a further amino group in position 5 of the indole ring was achieved in quantitative yields by reduction of **6b** with Zn–acetic acid in MeOH (Scheme 9). This product, like other compounds afforded in this research, is good candidate to be evaluated for biological activity.



Scheme 9. Synthesis of compound **6e**.

Unlike our previous studies in this area, we carried out all the reactions between nitrosoarenes and ethynylpyrimidines working at a 1:1 molar ratio. The use of a large excess of alkyne, typical of our previous contributions, did not improve the yields nor the selectivities of the final products. Another attractive feature of the process used by us here is the isolation of some of the major reaction products **5a**–**k** and **6a**–**e** by precipitation/filtration. Meridianin analogues are particularly insoluble in toluene even at 80 °C, so the isolation of all the 3-pyrimidinylindoles was quite easy and highly reproducible. In some cases no further purification was necessary. As reported in our previous papers on the annulation reactions of nitrosoarenes with alkynes, *N*-hydroxyindoles were typically the major products detected; sometimes indoles were obtained as minor products. In this report, as confirmed by all the analytical data recorded for compounds **5a**–**k** and **6a**–**e**, only N–H, i.e., reduced products were isolated. By analysis of the reaction solutions we could detect the presence of azoxyarenes, typical reduction products of ArNO. A plausible explanation for this difference could be the presence of side internal redox processes in which a relevant role is due to the electronic properties of the reagents and particularly the electronic properties of fragment from the alkynes. This mechanistic issue is under investigation and a further study will be part of our future efforts.

3. Conclusions

Whatever the mechanism is, the nitrosoarenes' cycloaddition with alkynyl-pyrimidines provides a new and efficient preparation of meridianins and meridianin analogues. Two natural meridianins (C and G) were thus produced. Key features of the indolization-based methodology are its convergency, regioselectivity and atom economy. We are directing future efforts in the use of nitrosoaromatics in the syntheses of natural compounds showing important biological and pharmacological properties.

4. Experimental section

4.1. General

All reactions for the synthesis of indole compounds, except the procedure for **6a** (method A) and **6e**, were carried out under nitrogen. All substituted anilines, 2,4-dichloropyrimidine, nitrosobenzene, 2-nitrosotoluene and 2-thiouracil were commercially available and were purchased from Sigma–Aldrich Chemical Co. and used directly. Distilled solvents were used for all the reactions. NMR spectra were obtained using the Bruker Avance 400 MHz spectrometer. Mass spectra were obtained by VG 7070 EQ mass spectrometer with CI (chemical ionization). GC–MS analyses were run on Shimadzu GC-MS-QP5000. IR spectra were obtained using the Nicolet Magna-IR Spectrometer 550. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2400.

*4.1.1. 4-Nitro-nitrosobenzene (**4b**).* To an aqueous solution of Oxone (32.1 g in 300 mL, 52.2 mmol), 4-nitroaniline (7.2 g, 52.1 mmol)

was added at 0 °C and the suspension was vigorously stirred at rt for 48 h, then filtered. The product was collected as a yellow solid. After double recrystallization from methanol, 4-nitro-nitrosobenzene was isolated (5.61 g, 71% yield) as yellow plates, mp 126–127 °C (lit.[42a] 128–130 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.52 (d, J=8.9 Hz, 2H), 8.06 ppm (d, J=8.9 Hz, 2H).

*4.1.2. 4-Bromo-nitrosobenzene (**4c**).* To a solution of 4-bromoaniline (3.44 g, 20 mmol) in a 1:1 mixture of CH_2Cl_2 (50 mL) and *n*-pentane (50 mL), sodium tungstate dihydrate (0.66 g, 2.0 mmol), phosphoric acid (1 mL of a 85% solution), hydrogen peroxide (20 mL of a 30% solution) and tetrabutylammonium bromide (0.2 g, 0.6 mmol) were added. After 2.5 h at 35–40 °C, TLC (CH_2Cl_2–petroleum ether=80:20) showed complete consumption of the aniline. The reaction mixture was then washed with 0.01 M HCl (50 mL) and water (50 mL), the organic layers dried over Na_2SO_4, filtered and rotary evaporated. After recrystallization from hexane, 2.42 g of the desired product was isolated in 65% yield as a yellow solid, mp 99–101 °C (lit.[42b] 98–100 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.00 (d, J=8.7 Hz, 2H), 7.89 ppm (d, J=8.7 Hz, 2H).

*4.1.3. 4-Cyano-nitrosobenzene (**4d**).* To a solution of 4-aminobenzonitrile (2.36 g, 20.0 mmol) in a 1:1 mixture of CH_2Cl_2 (50 mL) and *n*-pentane (50 mL), sodium tungstate dihydrate (0.66 g, 2.0 mmol), phosphoric acid (1 mL of a 85% solution), hydrogen peroxide (20 mL of a 30% solution) and tetrabutylammonium bromide (0.2 g, 0.6 mmol) were added. After 2.5 h at 35–40 °C, TLC (CH_2Cl_2–petroleum ether=80:20) showed complete consumption of the aniline. The reaction mixture was then washed with 0.01 M HCl (50 mL) and water (50 mL), the organic layers were dried over Na_2SO_4, filtered and rotary evaporated. After recrystallization from hexane, 1.63 g of the desired product was isolated in 62% yield as a yellow solid, mp 133–135 °C (lit.[42c] 136–137 °C). ^{1}H NMR and ^{13}C NMR as reported in literature.[42d]

*4.1.4. 2-Nitro-nitrosobenzene (**4e**).* To a solution of 2-nitroaniline (1.4 g, 10.1 mmol) in ethanol (20 mL), sodium tungstate dihydrate (1.0 g, 3.0 mmol), H_3PO_4 (1 mL of a 85% solution) and hydrogen peroxide (10 mL of a 30% solution) were added. The mixture was stirred at 60–65 °C until precipitation of a solid was observed. At reaction completed (TLC: CH_2Cl_2–AcOEt=80:20), the solid was filtered and washed with water to give 1.07 g (70% yield) of 2-nitro-nitrosobenzene as a yellow solid, mp 135–137 °C (lit.[42e] 126–127 °C). ^{1}H NMR and ^{13}C NMR as reported in literature.[42f]

*4.1.5. 2-(Trifluoromethyl)-nitrosobenzene (**4f**).* To an aqueous solution of Oxone (7.38 g in 150 mL, 12.0 mmol), 2-(trifluoromethyl)aniline (1.61 g, 10.0 mmol) was added at 0 °C and the suspension vigorously stirred at rt for 24 h, then filtered. The product was collected (1.12 g, 64% yield) as green-brown needles, mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.07 (d, J=7.7 Hz, 1H), 7.83 (t, J=7.7 Hz, 1H), 7.60 (t, J=7.7 Hz, 1H), 6.26 ppm (d, J=7.7 Hz, 1H). IR (KBr, ν): 1610, 1467, 1321, 1281, 1172, 1137, 1114, 771 cm^{-1}.

*4.1.6. 4-Nitrosobenzoic acid (**4g**).* To a solution of 4-aminobenzoic acid (1.0 g, 9.3 mmol) in CH_2Cl_2 (12 mL), an aqueous solution of Oxone (8.97 g in 45 mL, 14.6 mmol) was added and the suspension vigorously stirred at rt for 1 h (TLC: CH_2Cl_2–MeOH=9:1). The product, which precipitated was isolated by filtration, washed with H_2O and dried to give 1.1 g of 4-nitrosobenzoic acid in quant. yield as bright yellow powder, mp 227–230 °C (dec) (lit.[42g] 250 °C, dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 13.5 (br, 1H), 8.27 (d, J=8.8 Hz, 2H), 8.08 ppm (d, J=8.8 Hz, 2H).

*4.1.7. 3-Bromo-nitrosobenzene (**4i**).* To a solution of 3-bromoaniline (3.44 g, 5.81 mmol) in a 1:1 mixture of CH_2Cl_2 (15 mL) and *n*-pentane (15 mL), sodium tungstate dihydrate (192 mg, 0.58 mmol), phosphoric acid (291 μL of a 85% solution), hydrogen peroxide (5.8 mL of a 30% solution) and tetrabutylammonium bromide (58 mg, 0.17 mmol) were added. After 2.5 h at 35–40 °C, TLC (Hexane–AcOEt=80:20) showed complete consumption of the aniline. The reaction mixture was then washed with 0.01 M HCl (20 mL) and water (20 mL), the organic layers dried over Na_2SO_4, filtered and rotary evaporated to provide 1.06 g of the desired product in 97% yield as a brown solid (green in solution), mp 77 °C (lit.[42h] 77–78 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.11 (d, J=7.9 Hz, 1H), 8.54 (dt, J^3=7.9 Hz, J^4=1.7 Hz, 1H), 7.77 (t, J=1.7 Hz, 1H), 7.57 ppm (t, J=7.9 Hz, 1H).

*4.1.8. 4-Methoxynitrosobenzene (**4j**).* Under nitrogen, to a solution of $NOBF_4$ (3.25 g, 27.78 mmol) in acetonitrile (40 mL), anisole (1 mL, 9.26 mmol) was added and the mixture was stirred at rt. After 30 min, water was added and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and rotary evaporated. After separation on silica gel (Hexane–CH_2Cl_2=70:30), 4-methoxynitrosobenzene (884 mg, 70% yield) was isolated as a green-light blue oil (lit.[42b] mp 20–21 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C, TMS) δ: 7.93 (d, J=7.0 Hz, 2H), 7.05 (d, J=7.0 Hz, 2H), 3.97 ppm (s, 3H). GC–MS (EI): *m*/*z* 137.

*4.1.9. 2-Chloro-4-((trimethylsilyl)ethynyl)pyrimidine (**2**).* To a solution of $PdCl_2(PPh_3)_2$ (94 mg, 0.13 mmol) and PPh_3 (7.0 g, 0.27 mmol) in a mixed solvent of THF (20 mL) and Et_3N (30 mL), 2,4-dichloropyrimidine (4.0 g, 26.85 mmol) was added under inert atmosphere. After bubbling N_2 into the solution for 15 min, CuI (51 mg, 0.27 mmol) and trimethylsilylacetylene (4.2 mL, 29.55 mmol) were added sequentially. The reaction mixture was heated at reflux for 4 h and cooled to rt. The white precipitate ($Et_3N\cdot HCl$) was filtered off and washed with EtOAc. The filtrate solution was concentrated to afford a brown oil. After separation on silica gel (Hexane–AcOEt=80:20), 3.97 g of 2-chloro-4-((trimethylsilyl)ethynyl)pyrimidine was isolated in 70% yield as an orange solid, mp 51–52 °C (lit.[37] 51–54 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.58 (d, J=5.0 Hz, 1H), 7.31 (d, J=5.0 Hz, 1H), 0.28 ppm (s, 9H). GC–MS (EI): *m*/*z* 211, 209, 197, 195, 183.

*4.1.10. 2-Chloro-4-ethynylpyrimidine (**3**).* A solution of 2-chloro-4-((trimethylsilyl)ethynyl)pyrimidine (3.02 g, 14.34 mmol) in methanol (25 mL) was treated with a solution of KOH (4 mg, 0.005 equiv) in 2.5 mL of MeOH. After 30 min, additional KOH (4 mg) in 2.5 mL of methanol was added and the mixture was stirred at rt until TLC (Hexane–AcOEt=80:20) showed total consumption of the reactant. Then the mixture was rotary evaporated to afford a dark orange solid. After separation on silica gel (Hexane–AcOEt=80:20), 2-chloro-4-ethynylpyrimidine (1.96 g, 97% yield) was isolated as a white-grey solid, mp 139–141 °C (lit.[43] 132–134 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.64 (d, J=5.0 Hz, 1H), 7.38 (d, J=5.0 Hz, 1H), 3.48 ppm (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 161.8, 159.9, 152.2, 122.3, 83.9, 79.6 ppm. GC–MS (EI): *m*/*z* 138, 110, 103, 87, 76, 50.

*4.1.11. 4-Amino-2-chloropyrimidine (**7**).* A suspension of 2,4-dichloropyrimidine (7.45 g, 50.0 mmol) in ammonium hydroxide (28%, 150 mL) was stirred at rt for 5 h. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column, eluted with 0–10% EtOH in $CHCl_3$, to give 4-amino-2-chloropyrimidine (3.8 g, 59%, crystallized from MeOH) as a white solid, mp 223 °C (dec) (lit.[44] 219–220 °C, dec). ^{1}H NMR and ^{13}C NMR as previously reported.[38a]

*4.1.12. 2-Amino-4-chloropyrimidine (**8**). Method A*: 2-amino-3*H*-pyrimidine-4-one (**11**) (10 g, 80 mmol) and $POCl_3$ (15 mL, 160 mmol)

were heated at reflux for 1.5 h. The reaction mixture was poured onto ice and then basified to pH 9 by the addition of solid Na_2CO_3. The solution was extracted with EtOAc (2×400 mL) and CH_2Cl_2 (300 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, and evaporated to give an off-white solid, which was purified by flash chromatography (SiO_2, EtOAc 40 to 100 in pentane) to give 2-amino-4-chloropyrimidine as a white solid (5.9 g, 52%). *Method B*: a suspension of 2,4-dichloropyrimidine (7.45 g, 50.0 mmol) in ammonium hydroxide (28%, 150 mL) was stirred at rt for 5 h. The solvent was removed in vacuo, and the residue was purified by a silica gel column, eluted with 0–10% EtOH in $CHCl_3$, to give 2-amino-4-chloropyrimidine (2.4 g, 37%, crystallized from MeOH) as a white solid, mp 169 °C (dec) (lit.[44] 168–169 °C, dec). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.16 (d, J=5.2 Hz, 1H), 7.06 (br, 2H), 6.64 ppm (d, J=5.2 Hz, 1H).

*4.1.13. 2-Methylthio-3H-pyrimidine-4-one (**10**).* A mixture of 2-thiouracil (12.8 g) and finely powdered sodium hydroxide (4.3 g) was suspended in water (35 mL) and heated to 60–70 °C until the solids were dissolved. Ethanol (70 mL) was then added, the solution cooled to about 30 °C and methyl iodide (6.3 mL) was added. The solution was reheated to 50–60 °C for 20 min, and then cooled to rt. A white solid precipitated from the solution and was collected by filtration. The washings were acidified with acetic acid, and the excess solvent was removed in vacuo until precipitation of a white solid was observed. After filtration, the combined precipitates were thoroughly washed with water and recrystallized from ethanol to give 2-methylthio-3*H*-pyrimidine-4-one in quantitative yield as a white solid, mp 200–201 °C (lit.[45] 203–204 °C). ^{1}H NMR and ^{13}C NMR as reported.[46]

*4.1.14. 2-Amino-3H-pyrimidine-4-one (isocytosine) (**11**).* 2-Methylthio-3*H*-pyrimidine-4-one (1.0 g, 6.4 mmol) was heated for 1 h with ammonium acetate (6.5 g) at 160 °C. Water (7 mL) was added and the mixture was chilled and filtered to give 0.9 g of product. This was dissolved in 8 mL of water, warmed and brought to pH 8 with sodium carbonate, then chilled and filtered to give 0.40 g of isocytosine as a white solid mp 278–279 °C (lit.[47] 277–279 °C).

*4.1.15. 2-Amino-4-((trimethylsilyl)ethynyl)pyrimidine (**12**).* Dimethylformamide (10 mL), trimethylsilylacetylene (2.2 mmol) and Et_3N (0.3 mL) were added through septum to a nitrogen purged flask containing 2-amino-4-chloropyrimidine (2 mmol), CuI (20 mg) and $PdCl_2(PPh_3)_2$ (100 mg, 0.07 mmol). The mixture was stirred at rt overnight. The solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (EtOAc–Hexane). Product was collected in 71% yield as a white solid, mp 117 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.26 (d, J=4.7 Hz, 1H), 6.70 (d, J=4.7 Hz, 1H), 5.38 (br, 2H), 0.26 ppm (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ: 163.1, 158.7, 151.1, 114.0, 101.9, 98.8, −0.3 ppm. IR (KBr, ν): 3481, 3312, 3162, 2959, 2183, 1627, 1570, 1545, 1463, 1248, 848 cm^{-1}. GC–MS (EI): m/z 191, 190, 175, 159, 148, 133, 107, 106, 98, 87, 66. Elemental analyses for $C_9H_{13}N_3Si$: calcd (%) C 56.51, H 6.85, N 21.96; found (%) C 56.35, H 6.92, N 21.61.

*4.1.16. 2-Amino-4-ethynylpyrimidine (**13**).* A solution of 2-amino-4-((trimethylsilyl)ethynyl)pyrimidine (2.0 g) in methanol (20 mL) was treated with KOH (3.0 mg, 0.005 equiv) in MeOH (2 mL). After 30 min, additional KOH (3.0 mg) in MeOH (2 mL) was added and the mixture was stirred at rt until TLC (toluene–AcOEt=50:50) showed total consumption of the reactant. The solution was rotary evaporated to afford 2-amino-4-ethynylpyrimidine (1.12 g, 90% yield) as a dark-brown solid, mp 145–146 °C, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 8.29 (d, J=4.6 Hz, 1H), 6.75 (d, J=4.6 Hz, 1H), 5.16 (br, 2H) 3.48 ppm (s, 1H). IR (KBr, ν): 3321, 3264, 3165, 2111, 1651, 1558, 1467, 1340, 1209 cm^{-1}. GC–MS (EI): m/z 119, 118, 91, 64, 57. Elemental analyses for $C_6H_5N_3$: calcd (%) C 60.50, H 4.23, N 35.27; found (%) C 60.36, H 3.99, N 35.41.

*4.1.17. 3-(2-Chloropyrimidin-4-yl)-1H-indole (**5a**).* Nitrosobenzene (107 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (138 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 5 h. After 2 h the product precipitated from the solution and after the complete conversion of the nitrosoarene the solid was collected by filtration to give 3-(2-chloropyrimidin-4-yl)-1*H*-indole (153 mg, 67% yield) as a light-brown solid, mp 157–158 °C (sub.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.05 (s, 1H), 8.68 (s, 1H), 8.51 (d, J=5.5 Hz, 1H), 8.44 (dt, J^3=7.8 Hz, J^4=0.6 Hz, 1H), 7.87 (d, J=5.5 Hz, 1H), 7.50 (dt, J^3=7.8 Hz, J^4=0.6 Hz, 1H), 7.31 (td, J^3=7.2 Hz, J^4=1.2 Hz, 1H), 7.23 ppm (td, J^3=7.2 Hz, J^4=1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 164.5, 160.2, 158.5, 134.3, 129.6, 123.1, 121.9, 121.8, 121.6, 114.4, 109.4, 106.4 ppm. MS (CI): m/z 230 [M+1], 232. IR (KBr, ν): 2923, 2854, 1577, 1381, 1340, 802 cm^{-1}. Elemental analyses for $C_{12}H_8ClN_3$: calcd (%) C 62.76, H 3.51, N 18.30; found (%) C 62.38, H 3.40, N 18.56.

*4.1.18. 3-(2-Chloropyrimidin-4-yl)-5-nitro-1H-indole (**5b**).* 4-Nitronitrosobenzene (152 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (138 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 6 h. After 2 h the product precipitated from the solution and, after the complete conversion of the nitrosoarene, the solid was collected by filtration to give 3-(2-chloropyrimidin-4-yl)-5-nitro-1*H*-indole (195 mg, 71% yield) as a light-brown solid, mp 203 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.57 (s, 1H), 9.42 (d, J=2.3 Hz, 1H), 8.99 (s, 1H), 8.64 (d, J=5.4 Hz, 1H), 8.18 (dd, J^3=9.0 Hz, J^4=2.3 Hz, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.72 ppm (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 163.4, 160.2, 159.3, 142.7, 136.7, 133.0, 120.6, 118.9, 118.3, 114.9, 110.2, 108.8 ppm. MS (CI): m/z 277, 275 [M+1], 247, 245. IR (KBr, ν): 2925, 2856, 1632, 1582, 1513, 1540, 1384, 1331, 1304, 1188, 1083, 1002, 812, 749, 737, 673 cm^{-1}. Elemental analyses for $C_{12}H_7ClN_4O_2$: calcd (%) C 52.48, H 2.57, N 20.40; found (%) C 52.72, H 2.63, N 20.36.

*4.1.19. 5-Bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (**5c**).* 4-Bromonitrosobenzene (186 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 6 h. After 2 h the product precipitated from the solution and, after the complete conversion of the nitrosoarene, the solid was collected by filtration to give 5-bromo-3-(2-chloropyrimidin-4-yl)-1*H*-indole (166 mg, 54% yield) as a brown solid, mp 260–261 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.26 (s, 1H), 8.58 (d, J=2.0 Hz, 1H), 8.56 (d, J=1.9 Hz, 1H), 8.54 (d, J=5.4 Hz, 1H), 7.92 (d, J=5.4 Hz, 1H), 7.49 (d, J=8.6 Hz, 1H), 7.36 ppm (dd, J^3=8.6 Hz, J^4=1.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 164.5, 158.8, 146.2, 136.0, 132.3, 126.6, 125.3, 123.8, 114.6, 114.4, 114.1, 111.4 ppm. MS (CI): m/z 309 [M+1], 311. IR (KBr, ν): 2958, 2924, 1570, 1383, 1343, 796 cm^{-1}. Elemental analyses for $C_{12}H_7BrClN_3$: calcd (%) C 46.71, H 2.29, N 13.62; found (%) C 46.84, H 2.17, N 13.82.

*4.1.20. 3-(2-Chloropyrimidin-4-yl)-1H-indole-5-carbonitrile (**5d**).* 4-Cyanonitrosobenzene (132 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 6 h. After 2 h the product precipitated from the solution and, after the complete conversion of the nitrosoarene, the solid was collected by filtration to give 3-(2-chloropyrimidin-4-yl)-1*H*-indole-5-carbonitrile (125 mg, 49% yield) as a brown solid, mp 146–147 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.46 (s, 1H),

8.92 (s, 1H), 8.85 (s, 1H), 8.62 (d, J=5.4 Hz, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.72–7.69 ppm (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 165.0, 163.6, 159.2, 134.6, 132.0, 127.1, 125.7, 121.1, 120.2, 114.0, 111.0, 107.3, 104.0 ppm. MS (CI): m/z 255 [M+1]. IR (KBr, ν): 2924, 2224, 1615, 1592, 1532, 1371, 809 cm^{-1}. Elemental analyses for $C_{13}H_7ClN_4$: calcd (%) C 61.31, H 2.77, N 22.00; found (%) C 60.99, H 2.53, N 22.13.

*4.1.21. 3-(2-Chloropyrimidin-4-yl)-7-nitro-1H-indole (**5e**).* 2-Nitronitrosobenzene (152 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 6 h. After the complete conversion of the nitrosoarene, the reaction mixture was cooled to rt and the solvent was removed in vacuo to give a black solid. Separation of the crude material on silica gel (Hexane–EtOAc=30:70) afforded 3-(2-chloropyrimidin-4-yl)-7-nitro-1H-indole (104 mg, 38% yield) as an orange solid, mp 205 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ: 10.41 (br, 1H), 8.98 (d, J=8.0 Hz, 1H), 8.50 (d, J=5.4 Hz, 1H), 8.29 (d, J=8.0 Hz, 1H), 8.18 (d, J=2.8 Hz, 1H), 7.55 (d, J=5.4 Hz, 1H), 7.45–7.43 ppm (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 165.1, 160.3, 158.6, 137.3, 129.0, 125.4, 122.7, 121.6, 121.4, 114.6, 112.4, 111.8 ppm. MS (CI): m/z 277, 275 [M+1], 247, 245. IR (KBr, ν): 2964, 1637, 1583, 1383, 1262, 801 cm^{-1}. Elemental analyses for $C_{12}H_7ClN_4O_2$: calcd (%) C 52.48, H 2.57, N 20.40; found (%) C 52.56, H 2.48, N 20.33.

*4.1.22. 3-(2-Chloropyrimidin-4-yl)-7-(trifluoromethyl)-1H-indole (**5f**).* 2-(Trifluoromethyl)-nitrosobenzene (175 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 6 h. After the complete conversion of the nitrosoarene, the reaction mixture was cooled to rt and the solvent was removed in vacuo to give a dark solid. Separation of the crude material on silica gel (Hexane–EtOAc=30:70) afforded 3-(2-chloropyrimidin-4-yl)-7-(trifluoromethyl)-1H-indole (89 mg, 30% yield) as an orange solid, mp 194 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.23 (s, 1H), 8.84 (d, J=7.8 Hz, 1H), 8.83 (s, 1H), 8.60 (d, J=5.4 Hz, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.40 ppm (t, J=7.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 163.8, 160.2, 159.1, 131.9, 129.2, 126.6, 125.0, 123.6, 122.3, 121.6, 120.9, 115.2, 107.5 ppm. MS (CI): m/z 300, 298 [M+1]. IR (KBr, ν): 2924, 2856, 1633, 1584, 1382, 1293, 801 cm^{-1}. Elemental analyses for $C_{13}H_7ClF_3N_3$: calcd (%) C 52.46, H 2.37, N 14.12; found (%) C 52.42, H 2.45, N 14.16.

*4.1.23. 3-(2-Chloropyrimidin-4-yl)-1H-indole-5-carboxylic acid (**5g**).* 4-Nitrosobenzoic acid (151 mg, 1.0 mmol) was suspended in dioxane (10 mL) and heated until the solid was completely dissolved, then 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) was added and the mixture was heated at reflux for 7.5 h. After the complete conversion of the nitrosoarene, the reaction mixture was cooled to rt and the solvent removed in vacuo to give an orange solid. Separation of the crude material on silica gel (CH_2Cl_2–MeOH) afforded 3-(2-chloropyrimidin-4-yl)-1H-indole-5-carboxylic acid (147 mg, 54% yield) as an orange solid, mp 253–255 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.96 (br, 1H), 12.25 (s, 1H), 9.15 (dd, J^4=1.6 Hz, J^5=0.8 Hz, 1H), 8.81 (s, 1H), 8.57 (dd, J^3=5.4 Hz, J^4=0.8 Hz, 1H), 7.91 (d, J=5.4 Hz, 1H), 7.89 (dd, J^3=8.6 Hz, J^4=1.6 Hz, 1H), 7.58 ppm (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 167.9, 164.1, 160.3, 158.9, 136.3, 131.2, 124.7, 124.4, 124.2, 121.1, 114.8, 109.2, 107.8 ppm. MS (CI): m/z 276, 274 [M+1]. IR (KBr, ν): 3448, 2855, 1686, 1578, 1460, 1422, 1384, 1290, 1082, 744 cm^{-1}. Elemental analyses for $C_{13}H_8ClN_3O_2$: calcd (%) C 57.05, H 2.95, N 15.35; found (%) C 56.94, H 3.10, N 15.22.

*4.1.24. 3-(2-chloropyrimidin-4-yl)-7-methyl-1H-indole (**5h**).* 2-Nitrosotoluene (121 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (12 mL) and the reaction mixture was heated at 80 °C for 7 h. After the complete conversion of the nitrosoarene, the reaction mixture was cooled to rt, and the solvent was removed in vacuo to give a dark solid. Separation of the crude material by chromatography on silica gel (CH_2Cl_2–MeOH=98:2) afforded 3-(2-chloropyrimidin-4-yl)-7-methyl-1H-indole (135 mg, 55% yield) as a dark-brown solid, mp 193–195 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.08 (s, 1H), 8.50 (d, J=5.5 Hz, 1H), 8.49 (d, J=3.1 Hz, 1H), 8.24 (d, J=8.0 Hz, 1H), 7.92 (d, J=5.5 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.02 (d, J=8.0 Hz, 1H), 2.48 ppm (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 165.1, 160.3, 158.5, 136.8, 130.9, 124.7, 123.3, 121.6, 121.5, 119.2, 114.6, 112.3, 16.7 ppm. MS (CI): m/z 246, 244 [M+1]. IR (KBr, ν): 2925, 1574, 1341, 1133, 787 cm^{-1}. Elemental analyses for $C_{13}H_{10}ClN_3$: calcd (%) C 64.07, H 4.14, N 17.24; found (%) C 64.23, H 4.08, N 17.15.

*4.1.25. 4-Bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (**5i**) and 6-bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (**5j**).* 3-Bromo-nitrosobenzene (186 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (10 mL) and the solution was heated at 80 °C for 7 h. After 2 h, precipitation of a solid byproduct was observed. After the complete conversion of the nitrosoarene, the solid was removed by filtration, and the washings rotary evaporated to afford a dark-brown solid. Separation of the crude material on silica gel (Hexane–AcOEt=40:60) afforded 4-bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (60 mg, 19% yield) as a brown solid and 6-bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (62 mg, 20% yield) as a brown solid.

*4.1.26. 4-Bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (**5i**).* ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.39 (s, 1H), 8.93 (d, J=5.1 Hz, 1H), 7.99 (d, J=5.1 Hz, 1H), 7.11–7.08 (m, 2H), 7.06 (dd, J^3=6.9 Hz, J^4=2.0 Hz, 1H), 5.68 ppm (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): 168.8, 161.4, 159.8, 153.9, 133.6, 129.6, 128.3, 119.1, 118.2, 116.0, 96.2, 85.3 ppm. MS (CI): m/z 308 [M+1], 310, 312. IR (KBr, ν): 2960, 2924, 1567, 1383, 1342, 795 cm^{-1}. Elemental analyses for $C_{12}H_7BrClN_3$: calcd (%) C 46.71, H 2.29, N 13.62; found (%) C 46.85, H 2.21, N 13.72. Brown solid, mp 208–209 °C (dec).

*4.1.27. 6-Bromo-3-(2-chloropyrimidin-4-yl)-1H-indole (**5j**).* ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.18 (s, 1H), 8.55 (d, J=5.5 Hz, 1H), 8.53 (d, J=3.0 Hz, 1H), 8.35 (d, J=8.6 Hz, 1H), 7.91 (d, J=5.5 Hz, 1H), 7.69 (d, J=1.6 Hz, 1H), 7.37 ppm (dd, J^3=8.6 Hz, J^4=1.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): 164.6, 160.3, 158.9, 138.1, 131.9, 124.3, 124.0, 123.3, 115.4, 115.0, 114.7, 112.0 ppm. MS (CI): m/z 308 [M+1], 310, 312. IR (KBr, ν): 2957, 2924, 2854, 1573, 1383, 1344, 798 cm^{-1}. Elemental analyses for $C_{12}H_7BrClN_3$: calcd (%) C 46.71, H 2.29, N 13.62; found (%) C 46.88, H 2.17, N 13.66. Brown solid, mp 197–199 °C (dec).

*4.1.28. 3-(2-Chloropyrimidin-4-yl)-5-methoxy-1H-indole (**5k**).* 4-Methoxynitrosobenzene (137 mg, 1.0 mmol) was added to a solution of 2-chloro-4-ethynylpyrimidine (139 mg, 1.0 mmol) in toluene (12 mL) and the solution was heated at 80 °C for 48 h. The reaction mixture was cooled to rt and the solvent was removed in vacuo to give a dark red-brown solid. After separation of the crude material on silica gel (CH_2Cl_2–MeOH=98:2) unreacted nitrosoarene (64% conversion) and 3-(2-chloropyrimidin-4-yl)-5-methoxy-1H-indole (39 mg, 23% yield) as a red-brown solid were collected. Red-brown solid, mp 222–223 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 11.96 (s, 1H), 8.49 (d, J=5.5 Hz, 1H), 8.43 (d, J=2.7 Hz, 1H), 7.93 (d, J=2.5 Hz, 1H), 7.86 (d, J=5.5 Hz, 1H), 7.39 (d, J=8.8 Hz, 1H), 6.88 (dd, J^3=8.8 Hz, J^4=2.5 Hz, 1H), 3.81 ppm (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 164.8, 160.0, 158.2, 154.8, 132.0, 131.1, 125.4, 114.1, 112.8, 112.0, 111.3, 103.7, 55.0 ppm. MS (CI): m/z

260[M+1], 262. IR (KBr, ν): 2921, 1575, 1472, 1384, 1216, 1161, 774 cm^{-1}. Elemental analyses for $C_{13}H_{10}ClN_3O$: calcd (%) C 60.13, H 3.88, N 16.18; found (%) C 60.36, H 3.91, N 16.24.

*4.1.29. 3-(2-Aminopyrimidin-4-yl)-1H-indole [meridianin G] [debromomeridinanin D] (**6a**). Method A*: in a sealed tube, 3-(2-chloropyrimidin-4-yl)-1*H*-indole (**5a**) (229 mg, 1.0 mmol) in aqueous ammonia (10 mL) was heated at 80 °C for three days. The reaction mixture was cooled to rt and the solvent evaporated to dryness. The resulting brown oil was purified on silica gel (CH_2Cl_2–MeOH=92:8), affording 3-(2-aminopyrimidin-4-yl)-1*H*-indole (113 mg, 54% yield). *Method B*: nitrosobenzene (107 mg, 1.0 mmol) was added to a solution of 2-amino-4-ethynylpyrimidine (119 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 7 h. After the complete conversion of the nitrosoarene, the reaction was cooled to rt, and the solvent removed in vacuo to give a dark solid. Separation of the crude material on silica gel (CH_2Cl_2–MeOH=92:8) afforded 3-(2-aminopyrimidin-4-yl)-1*H*-indole (86 mg, 41% yield) as a dark-brown solid, mp 183 °C (lit.[29b] 183–185 °C). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 11.64 (br, 1H), 8.56 (d, J=7.9 Hz, 1H), 8.18 (d, J=2.9 Hz, 1H), 8.08 (d, J=5.3 Hz, 1H), 7.42 (d, J=7.9 Hz, 1H), 7.19–7.18 (m, 2H), 7.01 (d, J=5.3 Hz, 1H), 6.40 ppm (br, 2H). ^{13}C NMR as reported in literature.[32b] MS (CI): m/z 211 [M+1]. Elemental analyses for $C_{12}H_{10}N_4$: calcd (%) C 68.56, H 4.79, N 26.65; found (%) C 68.47, H 4.81, N 26.72.

*4.1.30. 3-(2-Aminopyrimidin-4-yl)-5-nitro-1H-indole (**6b**).* 4-Nitronitrosobenzene (152 mg, 1.0 mmol) was added to a solution of 2-amino-4-ethynylpyrimidine (119 mg, 1.0 mmol) in toluene (10 mL) and the reaction mixture was heated at 80 °C for 7 h. After 2 h the product precipitated from the solution and after the complete conversion of the nitrosoarene the solid was collected by filtration to afford 3-(2-aminopyrimidin-4-yl)-5-nitro-1*H*-indole (158 mg, 62% yield) that was isolated as a brown solid mp 212 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.38 (s, 1H), 9.40 (d, J=2.2 Hz, 1H), 8.42 (s, 1H), 8.10 (d, J=5.3 Hz, 1H), 7.94 (dd, J^3=9.0 Hz, J^4=2.2 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 6.95 (d, J=5.3 Hz, 1H), 6.47 ppm (br, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 163.5, 161.2, 157.4, 141.6, 136.3, 131.1, 120.4, 119.5, 116.8, 110.0, 109.6, 105.4 ppm. MS (CI): m/z 256 [M+1]. IR (KBr, ν): 3447, 2926, 2852, 1630, 1585, 1381, 1335, 809 cm^{-1}. Elemental analyses for $C_{12}H_9N_5O_2$: calcd (%) C 56.47, H 3.55, N 27.44; found (%) C 56.62, H 3.48, N 27.64.

*4.1.31. 3-(2-Aminopyrimidin-4-yl)-5-bromo-1H-indole [meridianin C] (**6c**).* 4-Bromo-nitrosobenzene (185 mg, 1.0 mmol) was added to a solution of 2-amino-4-ethynylpyrimidine (119 mg, 1.0 mmol) in toluene (10 mL) and the solution was heated at 80 °C for 7 h. After 30 min the product precipitated from the solution, and after the complete conversion of the nitrosoarene the solid was collected by filtration to afford 3-(2-aminopyrimidin-4-yl)-5-bromo-1*H*-indole (81 mg, 28% yield) that was isolated as a brown solid, mp 106 °C (lit.[34b] 103–106 °C). ^{1}H NMR and ^{13}C NMR as reported in literature.[34b] Elemental analyses for $C_{12}H_9BrN_4$: calcd (%) C 49.85, H 3.14, N 19.38; found (%) C 50.01, H 3.03, N 19.47.

*4.1.32. 3-(2-Aminopyrimidin-4-yl)-5-cyano-1H-indole (**6d**).* 4-Cyanonitrosobenzene (132 mg, 1.0 mmol) was added to a solution of 2-amino-4-ethynylpyrimidine (119 mg, 1.0 mmol) in toluene (10 mL) and the solution was heated at 80 °C for 7 h. After 30 min, the product precipitated from the solution and after the complete conversion of the nitrosoarene the solid was collected by filtration to give 3-(2-aminopyrimidin-4-yl)-5-cyano-1*H*-indole (113 mg, 48% yield) as a brown solid, mp 214 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 12.2 (br, 1H), 9.16 (dd, J^4=1.4 Hz, J^5=0.7 Hz, 1H), 8.60 (s, 1H), 8.13 (d, J=5.3 Hz, 1H), 7.61 (dd, J^3=8.5 Hz, J^5=0.7 Hz, 1H), 7.57 (dd, J^3=8.5 Hz, J^4=1.4 Hz, 1H), 7.04 (d, J=5.3 Hz, 1H), 6.64 ppm (br, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ: 163.5, 161.3, 157.3, 135.2, 129.8, 128.5, 125.1, 121.3, 120.5, 110.2, 109.4, 105.1, 102.9 ppm. MS (CI): m/z 236 [M+1]. IR (KBr, ν): 3406, 2905, 2840, 2223, 1572, 1462, 1215, 824 cm^{-1}. Elemental analyses for $C_{13}H_9N_5$: calcd (%) C 66.37, H 3.86, N 29.77; found (%) C 66.44, H 3.80, N 29.77.

*4.1.33. 5-Amino-3-(2-aminopyrimidin-4-yl)-1H-indole (**6e**).* To a suspension of 3-(2-aminopyrimidin-4-yl)-5-nitro-1*H*-indole (20 mg) in methanol (3 mL), zinc (52 mg) and acetic acid (7–8 drops) were added. After 2 h at rt, TLC (CH_2Cl_2–MeOH=92:8) displayed total consumption of the reactant. Zinc was removed by filtration and the washings rotary evaporated to afford 5-amino-3-(2-aminopyrimidin-4-yl)-1*H*-indole in quant. yield as a brown solid, mp 209 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ: 11.44 (s, 1H), 8.12 (s, 1H), 7.94 (d, J=5.9 Hz, 1H), 7.70 (d, J=2.0 Hz, 1H), 7.16 (d, J=8.6 Hz, 1H), 6.91 (d, J=5.9 Hz, 1H), 6.77 (br, 2H), 6.63 (dd, J^3=8.6 Hz, J^4=2.0 Hz, 1H), 6.38 ppm (s, 2H). IR (KBr, ν): 3427, 2910, 1569, 1389, 800 cm^{-1}. Elemental analyses for $C_{12}H_{11}N_5$: calcd (%) C 63.99, H 4.92, N 31.09; found (%) C 63.86, H 4.90, N 31.24.

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