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Synthesis of original thiazoloindolo[3,2-*c*]quinoline and novel 8-*N*-substituted-11*H*-indolo[3,2-*c*]quinoline derivatives from benzotriazoles. Part I

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Abstract—Synthesis of novel thiazoloindolo[3,2-*c*]quinoline and 8-substituted-11*H*-indolo[3,2-*c*]quinolines was performed via Graebe–Ullmann thermal cyclization from appropriated *N*-arylated benzotriazoles. 7*H*-4,7-Diaza-benzo[*de*]anthracene, a by-product reaction structurally closed to pyridoacridine skeleton was also identified.

1. Introduction

The thiazole ring in various natural and synthetic products has generated interest of many groups on account of its useful biological properties.[1] Thus, in our laboratory we launched a research program dealing with the preparation and pharmacological evaluation of some original thiazolo derivatives.[2] We recently reported the regiocontrolled synthesis of substituted thiazoloheterocycles (**I** and **II**) mainly related to marine or terrestrial alkaloids (e.g., dercitine, kuanoniamine and ellipticine), which exhibit interesting antitumor activity (Fig. 1).[3] Numerous indoloquinoline alkaloids have been identified from extracts of West African plant *Cryptolepis sanguinolenta*. Isocryptolepine **III** (also referred to as cryptosanguinolentine) with a indolo[3,2-*c*]quinoline (or a benzo-γ-carboline) structure is very rare in nature (Fig. 1).[4] Owing to their growing use in compounds of therapeutic importance (antibacterial, antiplasmodial, anticancer drugs),[5] the synthesis of indoloquinoline derivatives has been actively pursued in the past decade.

We focussed our studies on the synthesis of biologically active compounds in which the thiazole ring might be fused onto indolo[3,2-*c*]quinoline skeleton. Synthetic strategies have been developed for benzo-γ-carboline based on palladium-catalyzed reactions (Heck, Buchwald/Hartwig),[6] Fischer indole cyclization[7] and thermal ring transformation[8] (Graebe–Ullmann). For the synthesis of thiazoloindoloquinoline **IV**, we firstly turned our attention to the Graebe–Ullmann reaction from 4-quinolinylthiazolobenzotriazole **VII** as outlined in Scheme 1. To the best of our knowledge, the chemical behaviour of 4-quinolinyl-functionalized benzotriazole has been rarely reported; a literature survey revealed cyclization of nude benzotriazole or 5,6-dimethylbenzotriazole coupled with quinoline.[5b]

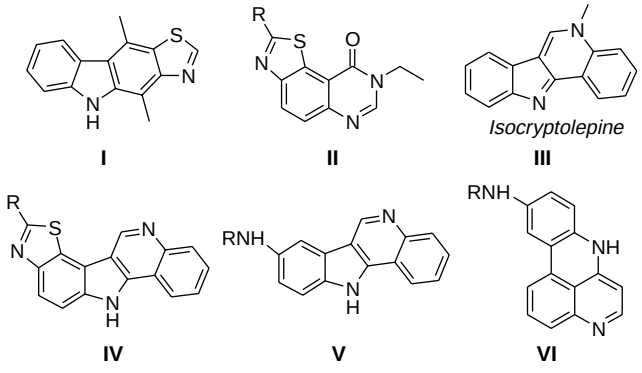

Figure 1. Structures of various potential biological heterocycles and expected skeletons studied in this paper.

Keywords: Indoloquinoline; Benzotriazoles; Fused ring systems; Graebe–Ullmann; Microwaves.
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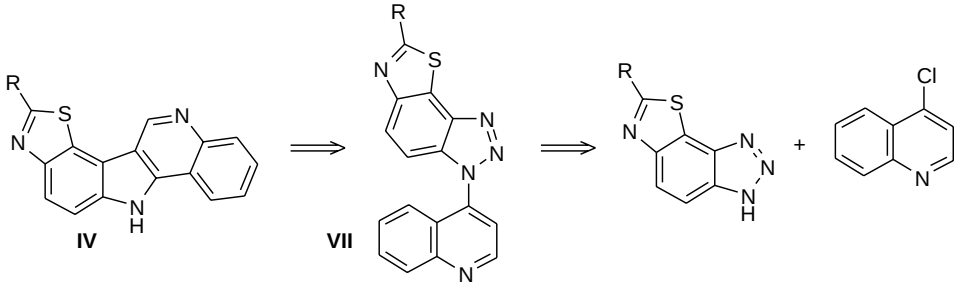
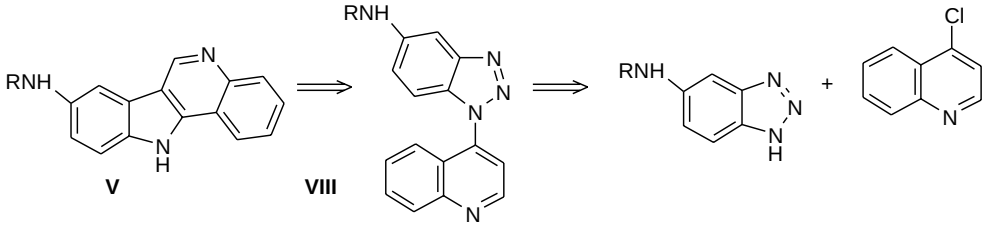


Scheme 1. Retrosynthetic pathway thiazoloindoloquinoline **IV**.



Scheme 2. Retrosynthetic pathway to 8-functionalized indolo[3,2-*c*]quinoline **V**.

After several attempts to obtain 8-functionalized indolo[3,2-*c*]quinoline **V**, we decided to study the thermal cyclization of (4-quinolinyl)-5-*N*-substituted-benzotriazole **VIII** precursor (Scheme 2). The thermal cyclization of this latest provided original 8-*N*-substituted-indolo[3,2-*c*]quinoline together with unexpected 10-*N*-substituted-7*H*-4,7-diazabenzo[*de*]anthracene skeleton **VI** (Fig. 1).

In this paper, we describe the chemical transformation of substituted benzotriazolylquinoline upon thermal cyclization and the synthesis of novel substituted polyheterocyclic compounds, which have never been described until now. Reactions were performed under microwave irradiation.[9]

2. Results and discussion

2.1. Synthesis of 3*H*-thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]-triazole-7-carbonitrile precursor

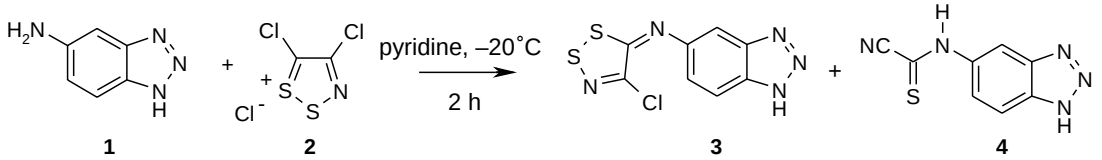
Studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) and its derivatives, it was previously shown that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles, which are stable crystalline solids, cyclized by vigorous heating to give sulphur, hydrogen chloride and 2-cyanobenzothiazoles.[10] Synthesis of rare thiazolobenzotriazole ring was then performed in two steps from the starting commercially available 5-aminobenzotriazole. Using a standard method applied to the preparation of *N*-arylimino-1,2,3-dithiazoles,[2,3] the starting amine was condensed with 4,5-dichloro-1,2,3-dithiazolium chloride in dichloromethane at room temperature, followed by addition of pyridine, to give the desired imino-1,2,3-dithiazolobenzotriazole **3** in moderate yield with cyanothioformamide **4** compound as major product. At low temperature (−20 °C), the reaction mainly yielded the attempted imine **3** (75%) (Scheme 3).

The thermolysis of the benzotriazole derivative **3** in a refluxed mixture of toluene and *N*-methylpyrrolidinone under microwave irradiation, gave the angular compound **5** in reasonable yield (68%) beside trace of decyanated counterpart **6**. No trace of linear isomer was detected. A mild procedure, which consists to heat an *ortho* bromoimine **7** in the presence of cuprous iodide in pyridine at reflux, was applied and afforded regioselectively this angular isomer **5** in good yield (73%) (Scheme 4).[2c]

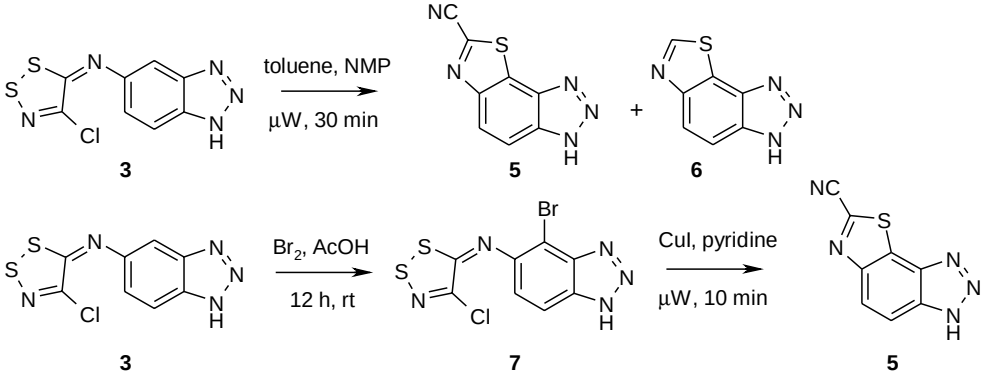
2.2. Synthesis of quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]-benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile

The preparation of quinolinylbenzotriazole by condensation of 4-chloroquinoline **8** and the corresponding benzotriazole **5** under neat conditions at high temperature led to carbonaceous mixtures. We found that microwave irradiation (160 °C, in sealed vial) of an equimolar mixture of 4-chloroquinoline and thiazolobenzotriazole in solution with a minimum of toluene afforded two condensed compounds **9** and **10** in moderate yields (33 and 44%) (Scheme 5).

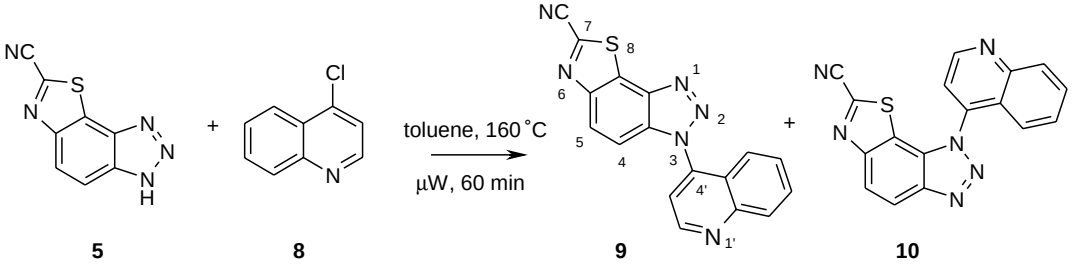
The presence of regioisomers is due to the tautomeric nature of the triazole function.[11] In literature, the alkylation of different 1,2,3-triazoles did not allow for any selective



Scheme 3. Synthesis of (1*H*-benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine **3**.



Scheme 4. Cyclization of (1*H*-benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine **3**.



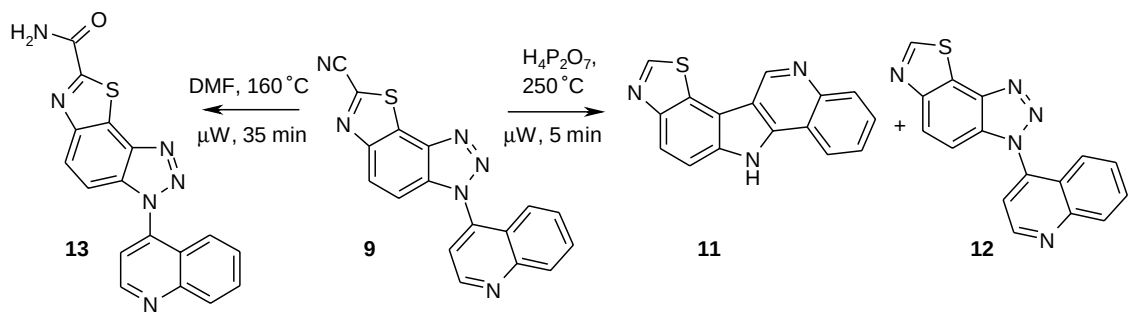
Scheme 5. Condensation of thiazolobenzotriazole with 4-chloroquinoline.

anticipation of N-alkylation of the thiazolo condensed-1,2,3-triazole. In order to establish unambiguously the structure of the different regioisomers, we envisaged an X-ray diffraction study. Unfortunately, all attempts to obtain suitable crystals failed. Because of the steric hindrance, we assumed that the isomer **9** generated arylation in position 3 of the thiazolobenzotriazole ring was the major compound. It must be noted that 2D ^{1}H–^{13}C correlation experiments and ^{1}H NMR NOESY experiments on the derivative **9** were also non-conclusive.

2.3. Thermolysis of quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]-benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile

Classic Graebe–Ullmann conditions for the elimination of nitrogen from 1-aryl-1*H*-benzo-1,2,3-triazoles involve heating the triazole derivative beyond its melting point. Inspired by Alvarez-Builla's procedure, we firstly used pyrophosphoric acid as solvent.[5b,8d] Microwave irradiation of the *N*-arylated benzotriazole **9** in a quartz glassware with pyrophosphoric acid and toluene at 250 °C for 5 min afforded a complex mixture from which thiazolo-indolo[3,2-*c*]quinoline **11** and decyanated *N*-arylbenzo-triazole **12** were isolated in, respectively, 17 and 23% yields (Scheme 6). A long exposition at high temperature was unfruitful and led to the degradation of the material and a longer reaction time at a lowest temperature (180 °C) yielded mainly to compound **12**. After several attempts with various acids, the reaction was carried out in DMF at reflux. The reaction afforded 75% of carboxamide **13**. Exposing the same benzotriazole **9** to microwave irradiation, neat in glass vial with a screw cap lid, or with few drops of acid or polar solvent (DMF, NMP, etc.) were also unsuccessful.

To the best of our knowledge, the synthesis of indolo-[3,2-*c*]quinoline fused onto 7,8-thiazole (or 8*H*-1-thia-3,6,11-triaza-cyclopenta[*d*]-benzo[*a*]fluorene) has never been reported until now.

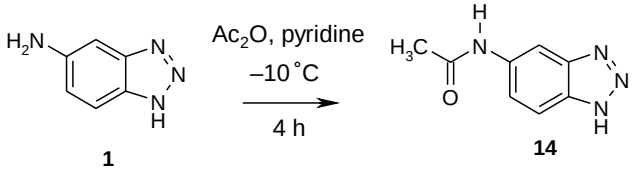


Scheme 6. Thermal cyclization of 3-*N*-aryl-thiazolobenzotriazole.

2.4. Synthesis of *N*-(quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide

The following part of our study was focused on the synthesis of original *N*-8-substituted-indolo[3,2-*c*]quinoline. According to the results obtained above, we decided to study the chemical transformation of *N*-(quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide (Scheme 2).

n-Acetylation of 5-aminobenzotriazole **1** was performed with 1 equiv of acetic anhydride in pyridine at low temperature (−10 °C) to overcome additional acetylation on triazole nitrogen and yielded 75% of acetamide **14** (Scheme 7).[12]



Scheme 7. Protection of 5-aminobenzotriazole **1**.

Using the same procedure described in Section 2.2, the acetamide **14** was subjected to the action of 4-chloroquinoline **8** under microwave irradiation. Whatever the solvent used (toluene, DMF or NMP), reaction yielded mixtures of three monoalkylated derivatives (**15**: 43%, **16**: 30% and **17**: 10%) (Scheme 8). The structures of compounds **15**–**17** were confirmed by their analytical and spectroscopic data. The isomer **17** obtained in 10% yield, was easily identified on the basis of mass spectral evidence. In agreement with the known behaviour of 2-substituted 1,2,3-triazoles to electron impact, its mass spectrum did not exhibit peaks issued from molecular ions through the initial extrusion N_2.

To unambiguously identify the regioisomers formed by arylation in position 1 and 3 on the triazole, 2D ^{1}H–^{13}C NMR (HMBC and HMQC) correlation experiments were performed on compounds **15** and **16**, but the detected ^{1}H–^{13}C correlations were not helpful for a structural determination. Unequivocal differenciation of substitution of quinoline at position N-1 or N-3 was determined by performing by ^{1}H NMR COSY, NOESY experiments on the derivative **15**, the NOE experiments showing strong effect between 7-H of triazole and 3′-H of quinoline and weaker effects between 7-H of triazole and 5′-H of quinoline (Fig. 2).

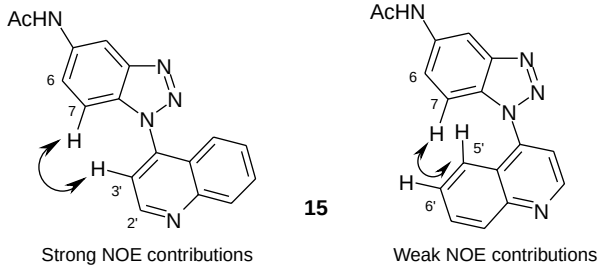


Figure 2. NOE contributions.

2.5. Thermolysis of *N*-1-quinolin-4-yl-benzotriazole 15

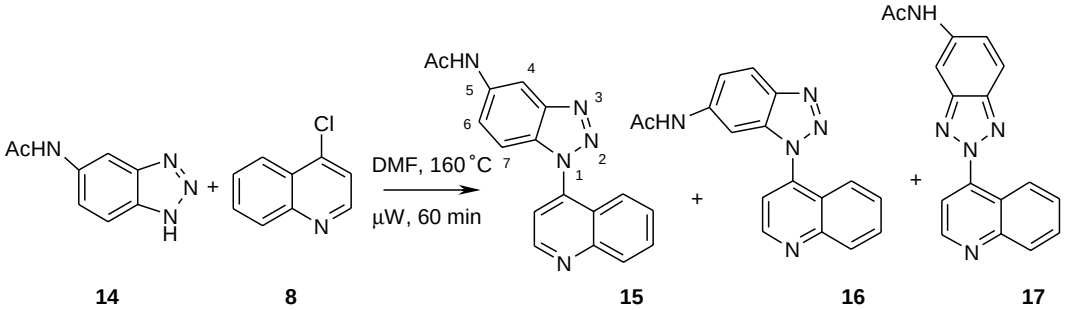
Expecting a similar chemical behaviour to that observed for benzotriazole **9**, the cyclization of *N*-protected benzotriazole **15** was also studied under microwave irradiation. Various attempts under neat conditions or in boiling neutral media (toluene or triglyme) afforded small amounts of 8-*N*-acetamidoindolo[3,2-*c*]quinoline **18** (6%) from complicated mixture. Thermolysis (in boiling pyrophosphoric acid at 250 °C) led to the complete degradation of the reactant within less than 5 min. Performed at 200 °C during 3 min, the same reaction in boiling acid appeared more efficient and yielded, respectively, 27% of deprotected 8-amino-11*H*-indolo[3,2-*c*]quinoline **19**, 8% of *N*-acetamidotetracycle **18** besides traces of non-cyclized amines **21** and **22**. Most unexpected was the isolation of a different fused ring system **20** in moderate yield 35% (Scheme 9).[5e,8f]

Furthermore, the ^{1}H NMR spectrum was different from the normal indolo[3,2-*c*]quinoline pattern showing a *H*-C6 characteristic singulet. The theoretical signal of the quinoline H-2 ($\delta=8.53$ ppm, d, $J=5.2$ Hz) and its coupling with the H-3 ($\delta=6.83$ ppm, d, $J=5.2$ Hz) still appeared. All the spectroscopic data fitted well for a fused quinolinoquinoline structure.

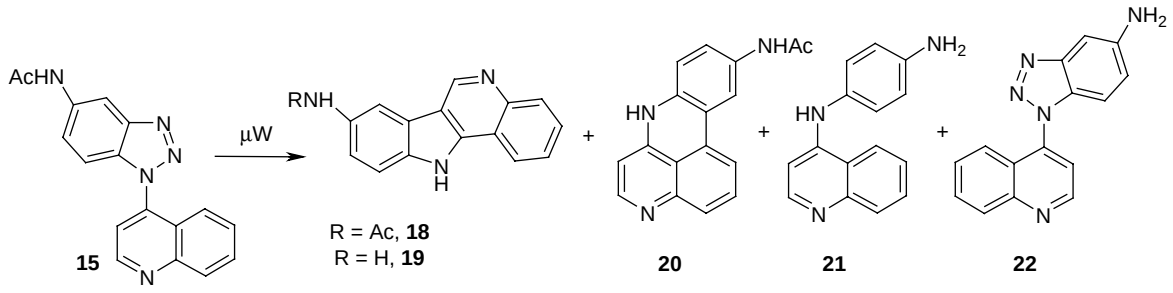
The *N*-(7*H*-4,7-diaza-benzo[*de*]anthracen-10-yl)-acetamide **20**, which is structurally closed to pyrodoacridine skeleton present in marine alkaloid can be considered as an interesting intermediate for the preparation of novel rings.[1d,e,13]

3. Conclusion

In conclusion, we showed that 4-(substituted-benzotriazolyl)quinoline might be a convenient precursor for the synthesis of the original fused ring like



Scheme 8. Condensation of acetamidobenzotriazole **14** with 4-chloroquinoline.



Scheme 9. Thermal cyclization of *N*-1-aryl-acetamidobenzotriazole.

thiazoloindolo[3,2-*c*]quinoline and quinolinoquinoline rings system, following a microwave-assisted Graebe–Ullmann cyclization.

The chemical and biological interest of thiazoloindolo[3,2-*c*]quinoline **11**, 8-amino-11*H*-indolo[3,2-*c*]quinoline derivatives **18**, **19** and quinolinoquinoline **20** mainly obtained in these experiments are under investigation. This latest new ring system was identified as a suitable starting precursor for conversion to dercitin analogs.[13]

4. Experimental

4.1. General remarks

All solvents and reagents were reagent grade and were used without purification. Melting points were determined using a Köfler melting point apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Centre Commun d'Analyses, Université de la Rochelle) and on a Brucker Avance 500 and 300 MHz (HMBC, HMQC and NOE experiments) in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO); chemical shifts (δ) are reported in part per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Coupling constants *J* are given in Hz. The mass spectra (HRMS) were recorded on a Varian MAT 311 spectrometer in the CRMPO, Université de Rennes. Column chromatography was performed by using Merck silica gel (70–230 mesh) at medium pressure. Light petroleum ether refers to the fraction boiling point 40–60 °C. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 aluminium backed plates.

After purification by chromatography on silica gel, compounds **3**, **4**, **5**, **7**, **9**, **10**, **12**, **15**, **16**, **17** were recrystallized in ethanol and compound **13** in DMF.

Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM Discover™ or Synthewave®402 Prolabo). The instrument consists of a continuous focused microwave power output from 0–300 W. Reactions were performed in a glass vessel (CEM) and in quartz reactor vessel (Prolabo) prolonged by a condenser; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar, tubes of 10 mL, sealed with a septum) if necessary. The temperature content of a vessel is monitored using a calibrated infrared sensor mounted under the vessel.[14] All the experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature was selected together with a power. The target temperature was reached with a ramp of 2 min and the chosen microwave power stayed constant to hold the mixture at this temperature. The reaction time does not include the ramp period.

4.2. Synthesis of iminodithiazoles

Under an inert atmosphere of argon, 4,5-dichloro-1,2,3-dithiazolium chloride **2** (1.71 g, 74.5 mmol) was added to a stirred solution of commercially available 5-aminobenzotriazole **1** (1.00 g, 74.5 mmol) in dichloromethane (30 mL) at −20 °C. After 45 min, pyridine (1.32 mL, 163.9 mmol) was added and the mixture stirred for 2 h. The obtained precipitate was filtered and purified by chromatography on silica gel with dichloromethane–methanol (99/1) as eluent to give the expected iminodithiazole **3** with cyanothioformamide **4**.

4.2.1. (1*H*-Benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine 3. Yield: 75%. Mp=195–197 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=15.70 (br s, 1H, NH), 8.04 (d, *J*=8.8 Hz, 1H, 7-H), 7.65 (s, 1H, 4-H), 7.26 (dd, *J*=8.8, 2.2 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=159.91, 148.90, 146.44, 138.32, 137.92, 119.39, 117.10, 102.19. IR=3099, 2768, 1694, 1574, 1200, 1199, 861 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_4N_5Cl_2$): calcd 268.9597; found 268.9599.

4.2.2. *N*-(1*H*-Benzotriazol-5-yl)-2-nitrilo-thioacetamide 4. Yield: 5%. Mp=130–132 °C (ethanol). ^{1}H NMR (DMSO-d_6+D_2O, 400 MHz) δ=8.79 (s, 1H, ArH), 8.02 (d, *J*=8.4 Hz, 1H, ArH), 7.67 (d, *J*=8.4 Hz, 1H, ArH). IR=3254, 2224, 1701, 1609, 1409, 1203, 995, 620 cm^{-1}. HRMS (EI) $[M-HCN]^{+}$ ($C_7H_3N_4S$): calcd 176.0156; found 176.0152.

4.3. Bromination

Under an inert atmosphere of argon, to a solution of imine **3** (0.36 g, 13.35 mmol) in dichloromethane (5 mL) was added dropwise bromine (0.08 mL, 14.68 mmol) in solution in acetic acid (3 mL). After 12 h under stirring at room temperature, the residue was treated with a saturated

solution of sodium thiosulfate Na_2SO_3 (15 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and the filtrate was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (95/5) as eluent to give the bromo derivative **7**.

4.3.1. 4-Bromo-5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidenamino)benzotriazole 7. Yield: 87%. Mp=200–202 °C (ethanol). ^{1}H NMR (DMSO-d_6+D_2O, 400 MHz) δ=7.99 (d, J=8.8 Hz, 1H, 7-H), 7.26 (d, J=8.8 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=163.55, 148.11, 146.06, 140.12, 137.07, 126.67, 118.51, 116.64. IR=3238, 2792, 1596, 1201, 1147, 857 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_3N_5^{35}Cl^{79}BrS_2$): calcd 346.8702; found 346.8703.

4.4. Cyclization

Method A. Under an inert atmosphere of argon, a solution of iminodithiazole **3** (1.0 g, 3.72 mmol) in *N*-methylpyrrolidin-2-one/toluene (5 mL, v/v) was irradiated during 30 min. The irradiation in CEM oven was programmed to maintain a constant temperature (180 °C) with a maximal power output of 150 W. After cooling, the toluene was removed under reduced pressure. The mixture was diluted with ethyl acetate (20 mL) and washed with water (3× 15 mL). The organic layer was dried ($MgSO_4$) and the filtrate was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (90/10) as eluent to give the thiazolo derivative **5** (68%).

Method B. Under an inert atmosphere of argon, a suspension of bromo imine **7** (0.3 g, 8.6 mmol), copper iodide (0.17 g, 8.6 mmol) in pyridine (5 mL) was irradiated during 10 min. The irradiation was programmed to obtain a constant temperature (110 °C) with a maximal power output of 80 W. After cooling, the mixture was treated with a saturated solution of Na_2SO_3 (20 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (90/10) as eluent to give the thiazolo derivative **5** (85%).

4.4.1. 3*H*-Thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile 5. Yield: 85% (obtained from method A). Mp=228–230 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=16.50 (br s, 1H, NH), 8.26 (d, J=8.8 Hz, 1H, 4-H), 8.15 (d, 1H, J=8.8 Hz, 5-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=170.31, 152.2, 150.20, 135.09, 124.1, 122.79, 114.65, 113.25. IR=3111, 2830, 2239, 1712, 1694, 1407, 1197, 804 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_3N_5S$): calcd 201.0109; found 201.0108.

4.4.2. 3*H*-Thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]triazole 6. Yield: trace (method A). Mp=>260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ=16.23 (br s, 1H, NH), 9.47 (s, 1H, 7-H), 8.14 (d, J=8.8 Hz, 1H, 4-H or 5-H), 7.98 (d, 1H, J=8.8 Hz, 5-H or 4-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=155.21, 155.12, 152.17, 136.50, 122.37, 120.77, 113.08. IR=3436, 3073, 2925, 1412, 1315, 1189, 876 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_7H_4N_4S$): calcd 176.0156; found 176.0152.

4.5. Synthesis of quinolinylbenzotriazoles

Under an inert atmosphere of argon, a solution of an equimolar mixture of commercial 4-chloroquinoline (0.12 g, 0.73 mmol) and thiazolobenzotriazole **5** (0.14 g, 0.73 mmol) in toluene (2 mL) was heated at 160 °C in a sealed tube for 1 h. After cooling, the toluene was removed in vacuo. The mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel, with light petroleum ether–ethyl acetate (80/20) as eluent to provide 2 regioisomers **9** and **10** in, respectively, 44 and 33% yield.

4.5.1. 3-Quinolin-4-yl-1*H*-thiazolo[4′,5′:3′,4]benzo[1,2-*d*]-[1,2,3]triazole-7-carbonitrile 9. Yield: 44%. Mp=238–240 °C (ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ=9.23 (d, J=4.4 Hz, 1H, 2′-$H_{quinolin.}$), 8.38 (d, J=9.2 Hz, 1H, ArH), 8.33 (d, J=9.2 Hz, 1H, 5-H or 4-H), 7.92 (ddd, J=2.0, 6.8, 9.2 Hz, 1H, ArH), 7.69 (d, J=4.4 Hz, 1H, 3′-$H_{quinolin.}$), 7.68 (ddd, J=2.0, 6.8, 9.2 Hz, 1H, ArH), 7.66 (d, J=9.2 Hz, 1H, ArH), 7.62 (d, J=9.2 Hz, 1H, 4-H or 5-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=151.00, 150.42 (2′-C), 150.12, 139.75, 136.24, 135.79, 133.81, 131.12 (7′-C), 130.45, 128.77, 126.71, 125.69, 122.91, 122.55, 117.72 (3′-C), 112.63, 111.09. IR=2921, 2339, 1435, 1260, 805, 760 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_8N_6S$): calcd 328.0531; found 328.0530.

4.5.2. 1-Quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]benzo[1,2-*d*]-[1,2,3]triazole-7-carbonitrile 10. Yield: 33%. Mp=252–254 °C (ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ=9.16 (d, J=4.9 Hz, 1H, 2′-$H_{quinolin.}$), 8.84 (d, J=8.0 Hz, 1H, 4-H or 5-H), 8.31 (d, J=8.0 Hz, 1H, 5-H or 4-H), 8.26 (d, J=9.3 Hz, 1H, ArH), 8.20 (d, J=9.3 Hz, 1H, ArH), 8.12 (d, J=4.9 Hz, 1H, 3′-$H_{quinolin.}$), 7.91 (t, J=7.2 Hz, 1H, ArH), 7.77 (t, J=7.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=153.09, 150.24, 150.16, 144.73, 143.09, 139.61, 139.65, 130.55, 130.24, 128.69, 125.12, 124.54, 124.03, 120.72, 119.03, 116.17, 112.70. IR=3069, 2919, 2230, 1715, 1562, 1501, 1432, 1395, 995, 831, 774 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_8N_6S$): calcd 328.0531; found 328.0530.

4.6. Cyclization of quinolinylbenzotriazole

In a quartz reactor, a solution of the corresponding benzotriazolylquinoline **9** (0.08 g, 0.26 mmol) and $H_4P_2O_7$ (1 mL) in toluene (1 mL) placed was heated at 250 °C until the evolution of nitrogen ceased after 5 min. The reaction mixture was then triturated with water and basified with a saturated solution of $NaHCO_3$ (8 mL). The resulting precipitate was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane as eluent, to give the thiazoloindolo-[3,2-*c*]quinoline **11** and the compound **12**.

4.6.1. 8*H*-1-Thia-3,10,12-triaza-benzo[*a*]cyclopenta[*d*]-fluorene 11. Yield: 17%. Mp=>260 °C. ^{1}H NMR (CD_3OD+D_2O, 400 MHz) δ=9.47 (s, 1H, 11-$H_{quinolin.}$), 9.30 (s, 1H, 2-$H_{thiazol.}$), 8.50 (dd, J=6.8, 1.2 Hz, 1H, ArH),

8.24–8.18 (m, 2H, ArH), 7.92 (d, $J=8.8$ Hz, 1H, 4-H or 5-H), 7.82 (t, $J=7.2$ Hz, 1H, ArH), 7.75 (t, $J=7.2$ Hz, 1H, ArH). IR=2920, 1787, 1713, 1288, 611 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{16}H_9N_3S$): calcd 275.0517; found 275.0513.

4.6.2. *N*-(3-Quinolin-4-yl)-1*H*-thiazolo[5′,4′:3,4]benzo-[1,2-*d*][1,2,3]triazole 12. Yield: 23%. Mp=228–230 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.17$ (s, 1H, 7-H), 9.14 (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.91 (d, $J=8.8$ Hz, 1H, ArH), 8.29 (d, $J=8.8$ Hz, 1H, ArH), 8.14 (d, $J=9.2$ Hz, 1H, ArH), 8.12 (d, $J=4.4$ Hz, 1H, 3′-$H_{quinolin.}$), 8.08 (d, $J=9.2$ Hz, 1H, ArH), 7.87 (t, $J=7.2$ Hz, 1H, ArH), 7.75 (t, $J=7.2$ Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta=154.40$, 154.25, 148.20, 144.54, 141.09, 131.56, 129.23, 128.19, 125.80, 125.10, 121.36, 120.88, 116.87, 115.62. IR=3487, 1920, 1727, 1631, 1305, 1230, 991, 829, 760 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{16}H_9N_5S$): calcd 303.0568; found 303.0566.

4.6.3. *N*-(3-Quinolin-4-yl)-1*H*-thiazolo[5′,4′:3,4]benzo-[1,2-*d*][1,2,3]triazole-7-carboxamide 13. Yield: 75% (from DMF). Mp=>260 °C. ^1H NMR (CD_3OD+D_2O, 400 MHz) $\delta=9.15$ (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.89 (dd, $J=8.8$, 0.8 Hz, 1H, ArH), 8.29 (t, $J=8.4$ Hz, 1H, ArH), 8.19 (t, $J=8.4$ Hz, 1H, ArH), 8.14 (s, 1H, ArH), 7.88 (dd, $J=8.4$, 0.8 Hz, 1H, ArH), 7.71 (d, $J=8.4$ Hz, 1H, ArH), 7.53 (d, $J=8.4$ Hz, 1H, ArH). IR=3313, 2904, 1712, 1663, 1505, 1400, 1118, 805, 758 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{10}N_6OS$): calcd 346.0636; found 346.0639.

4.7. Acetylation

Under an inert atmosphere of argon, acetic anhydride (1.06 mL, 11.82 mmol) was added to a solution of 5-aminobenzotriazole **1** (1.50 g, 11.82 mmol) in pyridine (7 mL) at −10 °C. After 4 h, the resulting precipitate was filtered and purified by chromatography on silica gel with dichloromethane as eluent, to give acetamide **14**.

4.7.1. *N*-(1*H*-Benzotriazol-5-yl)-acetamide 14. Yield: 75%. Mp=>260 °C. ^1H NMR (DMSO-d_6, 400 MHz) $\delta=$ 15.39 (s, 1H, NH), 10.14 (s, 1H, NH), 8.23 (s, 1H, 4-H), 7.83 (d, $J=8.8$ Hz, 1H, 6-H or 7-H), 7.34 (d, $J=8.8$ Hz, 1H, 7-H or 6-H), 2.55 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) $\delta=169.54$, 149.40, 137.12, 123.98, 118.73, 109.93, 30.52, 23.69. IR=3087, 1738, 1682, 1568, 1413, 1257, 1204, 1007, 810 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_8N_4O$): calcd 176.0698; found 176.0694.

4.8. Synthesis of acetamidoquinolinylbenzotriazoles

Under an inert atmosphere of argon, a solution of 4-chloroquinoline **8** (0.93 g, 5.6 mmol) and acetamidobenzotriazole **14** (1.0 g, 5.6 mmol) in DMF (2 mL) was heated at 160 °C for 1 h. After cooling, the DMF was removed under reduced pressure. The mixture was diluted with ethyl acetate (15 mL) and washed with water (2×15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (30/70) as eluent to provide the regioisomers **15**, **16**, **17** in 43, 30 and 10% yields, respectively.

4.8.1. *N*-(1-Quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide 15. Yield: 43% (0.72 g). Mp=>260 °C (ethanol). ^1H NMR (DMSO-d_6, 400 MHz) $\delta=10.37$ (s, 1H, NH), 9.21 (d, $J=4.5$ Hz, 1H, 2′-$H_{quinolin.}$), 8.65 (d, $J=0.9$ Hz, 1H, 4-H), 8.27 (d, 1H, $J=8.4$ Hz, 8′-H), 7.95 (d, $J=4.5$ Hz, 1H, 3′-$H_{quinolin.}$), 7.94 (td, $J=1.5$, 6.7 Hz, 7′-H), 7.79 (dd, $J=$ 1.0, 8.7 Hz, 1H, 5′-H), 7.72 (td, $J=1.0$, 6.7 Hz, 6′-H partially mixed with 6-H), 7.70 (d, 1H, 6-H), 7.63 (d, $J=$ 8.9 Hz, 1H, 7-H), 2.14 (s, 3H, $COCH_3$). ^{13}C NMR (CD_3OD, 100 MHz) $\delta=168.68$, 151.04, 149.19, 145.61, 139.46, 136.64, 130.68, 129.91, 129.51, 128.29, 123.00, 122.60, 122.33, 117.53, 110.91, 107.32, 23.96. IR=3487, 1666, 1378, 1305, 1041, 809, 757 cm^{-1}. MS (*m*/*z*) 303, 275 ($M^{+\cdot}-N_2$). HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1120.

4.8.2. *N*-(3-Quinolin-4-yl-3*H*-benzotriazol-5-yl)-acetamide 16. Yield: 30% (0.49 g). Mp=>260 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.15$ (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.30 (d, 1H, $J=8.8$ Hz, ArH), 8.20 (s, 1H, ArH), 8.13 (d, 1H, $J=8.8$ Hz, ArH), 7.89–7.81 (m, 2H, ArH), 7.64–7.60 (m, 2H, $J=4.4$ Hz, 3′-$H_{quinolin.}$, ArH), 7.51 (br s, 1H, NH), 7.21 (dd, 1H, $J=2.0$, 8.8 Hz, ArH), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta=168.54$, 150.42, 150.05, 142.71, 140.44, 138.51, 134.76, 130.73, 130.09, 128.18, 123.31, 123.09, 120.86, 118.19, 117.06, 99.94, 24.80. IR= 3243, 3069, 1696, 1555, 1496, 1261, 813 cm^{-1}. MS (*m*/*z*) 303, 275 ($M^{+\cdot}-N_2$). HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1112.

4.8.3. *N*-(2-Quinolin-4-yl-3*H*-benzotriazol-5-yl)-acetamide 17. Yield: 10% (0.17 g). Mp=226–228 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.11$ (d, $J=4.8$ Hz, 1H, 2′-$H_{quinolin.}$), 8.88 (d, 1H, $J=8.4$ Hz, ArH), 8.48 (s, 1H, ArH), 8.26 (d, 1H, $J=8.8$ Hz, ArH), 8.07 (d, 1H, $J=4.8$ Hz, 3′-$H_{quinolin.}$), 7.97 (d, 1H, $J=8.8$ Hz, ArH), 7.85 (t, 1H, $J=$ 7.8 Hz, ArH), 7.72 (t, 1H, $J=7.8$ Hz, ArH), 7.39 (dd, 1H, $J=2.0$, 8.8 Hz, ArH), 7.37 (s, 1H, NH), 2.29 (s, 3H). IR= 3423, 2953, 1693, 1498, 1261, 668, 612 cm^{-1}. MS (*m*/*z*) 303. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1122.

4.9. Cyclization of acetamidoquinolinylbenzotriazole

Method A. In a sealed vial, a solution of the corresponding benzotriazolylquinoline **15** (0.10 g, 0.33 mmol) in DMF (2 mL) was heated at 250 °C during 60 min. The reaction mixture was then triturated with water (8 mL). The precipitate formed was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by recrystallization to afford the expected acetamido indolo[3,2-*c*]quinoline **18**.

4.9.1. *N*-(11*H*-Indolo[3,2-*c*]quinolin-8-yl)-acetamide 18. Yield: 6% (0.007 g). Mp=>260 °C. ^1H NMR (DMSO-d_6, 400 MHz) $\delta=12.71$ (s, 1H, NH), 10.04 (s, 1H, NH), 9.52 (s, 1H, 6-H), 8.57 (d, $J=1.0$ Hz, 1H, 7-H), 8.49 (d, 1H, $J=$ 8.0 Hz, 1-H), 8.11 (d, 1H, $J=8.0$ Hz, 4-H), 7.74 (t, 1H, $J=$ 6.8 Hz, 3-H), 7.68 (t, 1H, $J=6.8$ Hz, 2-H), 7.64 (d, 1H, $J=8.8$ Hz, 10-H), 7.56 (dd, 1H, $J=2.0$, 8.8 Hz, 9-H), 2.11 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) $\delta=24.39$, 110.89 (7-C), 112.30 (10-C), 114.74, 115.18, 119.26 (9-C),

122.51 (1-C), 123.48, 126.12 (2-C), 128.46 (3-C), 129.98 (4-C), 133.48, 135.63, 138.90, 140.66, 145.05 (6-C), 168.47. IR = 3485, 1669, 1128, 1016, 754, 514 cm^{-1}. HRMS (EI) $[M+H]^{+\cdot}$ ($C_{17}H_{14}N_3O$): calcd 276.1137; found 276.1136.

Method B. In a quartz reactor, a solution of the corresponding benzotriazolylquinoline **15** (0.18 g, 0.54 mmol) and $H_4P_2O_7$ (1 mL) in toluene (1 mL) placed was heated at 200 °C until the evolution of nitrogen ceased after 3 min. The reaction mixture was then triturated with water and basified with a saturated solution of $NaHCO_3$ (8 mL). The resulting precipitate was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–methanol (90/10) as eluent to provide 8-amino-11*H*-indolo[3,2-*c*]quinoline **19**, quinolinoquinoline **20** and amino by-products **21**.

4.9.2. 11*H*-Indolo[3,2-*c*]quinolin-8-ylamine 19. Yield: 27% (0.06 g). Mp = 180–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 12.28 (s, 1H, NH), 9.38 (s, 1H, 6-H), 8.44 (dd, J = 1.2, 8.0 Hz, 1H, 4-H or 1-H), 8.07 (d, J = 8.0 Hz, 1H, 1-H or 4-H), 7.68 (td, J = 1.2, 8.0 Hz, 1H, 2-H or 3-H), 7.63 (td, J = 1.2, 8.0 Hz, 1H, 3-H or 2-H), 7.41 (d, J = 8.5 Hz, 1H, 10-H), 7.38 (d, J = 2.1 Hz, 1H, 7-H), 6.86 (dd, J = 2.1, 8.5 Hz, 1H, 9-H), 5.06 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 103.40 (7-C), 112.53 (10-C), 114.45, 115.61 (9-C), 117.75, 122.40 (4-C), 123.23, 125.82 (2-C), 128.01 (3-C), 129.77 (1-C), 132.13, 140.00, 143.67, 144.98 (6-C), 145.47. IR = 3341, 1632, 1566, 1509, 1341, 1240, 1176, 755 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{15}H_{11}N_3$): calcd 233.0953; found 233.0952.

4.9.3. *N*-(7*H*-4,7-Diaza-benzo[*de*]anthracen-10-yl)-acetamide 20. Yield: 35% (0.054 g). Mp = > 260 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.53 (d, J = 5.2 Hz, 1H, 5-$H_{quinolin.}$), 8.07 (d, J = 8.8 Hz, 1H, 3-H or 1-H), 7.96 (d, J = 8.8 Hz, 1H, 1-H or 3-H), 7.71 (t, J = 7.6 Hz, 1H, 2-H), 7.61 (d, J = 2.0 Hz, 1H, 11-H), 7.56–7.50 (m, 2H, 9-H, 8-H), 6.83 (d, 1H, J = 5.2 Hz, 6-$H_{quinolin.}$), 2.60 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 171.24, 165.30, 150.85, 148.63, 148.25, 142.72, 135.96, 130.07, 128.48, 125.40, 121.12, 119.41, 119.21, 114.92, 111.03, 101.51, 29.70. IR = 3341, 1632, 1566, 1509, 1341, 1240, 1176, 755 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_3O$): calcd 275.1059; found 275.1062.

4.9.4. *N*-Quinolin-4-yl-benzene-1,4-diamine 21. Yield: 5% (0.006 g). Mp = 152–154 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.48 (d, J = 5.5 Hz, 1H, 2-$H_{quinolin.}$), 8.06 (d, J = 8.4 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 1H, ArH), 7.69 (td, J = 1.2, 6.4 Hz, 1H, ArH), 7.50 (td, J = 1.2, 6.4 Hz, 1H, ArH), 7.12 (dd, J = 2.4, 6.4 Hz, 2H, ArH), 6.76 (dd, J = 2.4, 6.4 Hz, 2H, ArH), 6.65 (d, J = 5.2 Hz, 1H, 3-$H_{quinolin.}$), 3.49 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 150.62, 149.40, 148.48, 144.62, 129.97, 129.74, 129.35, 126.50, 125.04, 119.39, 118.88, 116.05, 100.93. IR = 3421, 2314, 1709, 1260, 1124 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{15}H_{13}N_3$): calcd 235.1109; found 235.1094.

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