



The reaction of anthranilonitrile and triethylorthoformate revisited: formation of dimeric and trimeric species

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ARTICLE INFO

Article history:

Received 20 July 2010

Received in revised form 31 August 2010

Accepted 3 September 2010

Available online 15 September 2010

Keywords:

Nitrogen heterocycles

2-Aminobenzonitrile

Cascade reaction

Diazachrysenes

Triazachrysenes

ABSTRACT

The reaction of anthranilonitrile and triethylorthoformate was performed under different experimental conditions, leading to substituted quinazolines, triazachrysenes or quinazolinyl-aminophenyl quinazolines. A mechanistic proposal is presented to rationalize the formation of these compounds. The fluorescence properties of the highly conjugated triazachrysene structures were studied and the fluorescence quantum yield for compounds **5** and **13** was comparable to that of pyrene.

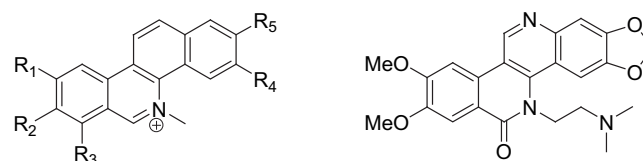
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1. Introduction

The reaction of amines with orthoesters is a convenient and widely used synthetic approach to prepare imidates.¹ The formation of a formimide function from the reaction of anthranilonitrile with triethylorthoformate was previously reported² and the product was generated by refluxing the amine in a large excess of orthoester. To our knowledge, no evidence was provided for the formation of other products in this reaction. The synthesis of imidates is usually followed by their combination with nucleophiles, in particular with amines to generate amidines, important units in biologically active compounds.^{1,3} Nevertheless, the formation of a symmetrical amidine from the reaction of 2-cyanophenylformimide with anthranilonitrile has not been reported. The same applies to the formation of substituted triazachrysenes from this synthetic approach.

Azachrysenes are tetracyclic aromatic compounds containing nitrogen in one of the ring positions.⁴ A number of natural products with the benzophenanthridine core unit (Fig. 1) present a broad spectrum of biological activity.⁵ These compounds have been important in particular for the drug industries, especially as anticancer,⁶ muscle relaxants,⁷ antimicrobial⁸ and anti-inflammatory agents.⁹ Their unique structure makes them valuable intermediates in the synthesis of azasteroids.¹⁰ Substituted diaza- and triazachrysenes are less known and their synthesis and biological

properties are mainly reported in patented work.¹¹ Compounds with this core structure (e.g., ARC-111, Fig. 1) proved to be potent topoisomerase-targeting agents with exceptional cytotoxic activity and have been studied as anticancer agents.¹²



fagarone ($R_1 R_2 R_4 = \text{OMe}$, $R_3 = \text{H}$, $R_5 = \text{OH}$)
nitidine ($R_1 R_2 = \text{OMe}$, $R_3 = \text{H}$, $R_4 R_5 = \text{OCH}_2\text{O}$)
chelerythrine ($R_1 = \text{H}$, $R_2 R_3 = \text{OMe}$, $R_4 R_5 = \text{OCH}_2\text{O}$)
sanguinarine ($R_1 = \text{H}$, $R_2 R_3 = \text{OCH}_2\text{O}$, $R_4 R_5 = \text{OCH}_2\text{O}$)

Fig. 1. Biologically active compounds with the azachrysene and diazachrysene core unit.

As part of our research work on the synthesis of novel atypical antipsychotic drugs,¹³ anthranilonitrile **1a** was reacted with triethylorthoformate to prepare imide **2a** to be used as a precursor of a variety of substituted amidines.

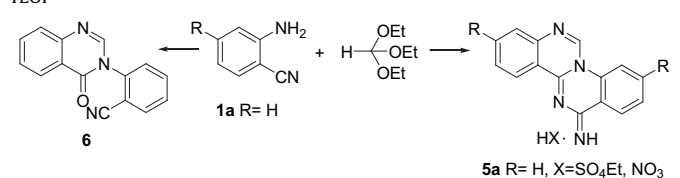
2. Results and discussion

The reaction of anthranilonitrile **1a** with triethylorthoformate (TEOF) was initially carried out in ethanol (1 mL/mmol **1a**) and using 3 mol equiv of the orthoester. The reaction was performed

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with nitric acid catalysis (16 $\mu\text{L}/\text{mmol}$ **1a**) and warmed in a water bath at 40 °C for 3 h. The tetracyclic compound **5a** precipitated from solution as the nitrate salt and was isolated as a yellow solid by simple filtration (Table 1, entry 1). The use of sulfuric acid (Table 1, entry 2) led to the formation of the same product, isolated in 47% yield after 3.5 h at 40 °C. In this case, the sulfate counterion was alkylated, probably due to the presence of an excess of orthoester and the product was isolated as the ethyl sulfate salt. The ethyl sulfate anion is a stable counterion used for commercially available ionic liquids and the NMR data registered for our compounds agrees with the values reported in the literature for a number of imidazolinium ethyl sulfate salts.¹⁴

Table 1
Effect of the acid and of the solvent on the annulation of anthranilonitrile (**1a**) with TEOF



Entry	Reactions conditions ^a	Product (yield)
1	Ethanol (1 mL/mmol 1a), HNO ₃ (16 $\mu\text{L}/\text{mmol}$ 1a), 40 °C, 3 h	5a , X=NO ₃ (76%)
2	Ethanol (1 mL/mmol 1a), H ₂ SO ₄ (13 $\mu\text{L}/\text{mmol}$ 1a), 40 °C, 3.5 h	5a , X=SO ₄ Et (47%)
3	Ethanol (1 mL/mmol 1a), CH ₃ COOH (12 $\mu\text{L}/\text{mmol}$ 1a), 40 °C, 11 days	Complex mixture ^b
4	CH ₃ CN (1 mL/mmol 1a), HNO ₃ (16 $\mu\text{L}/\text{mmol}$ 1a), 40 °C, 2.5 h	5a , X=NO ₃ (47%)
5	Petroleum ether (1 mL/0.4 mmol 1a), HNO ₃ (16 $\mu\text{L}/\text{mmol}$ 1a), 40 °C, 3.5 h	5a , X=NO ₃ (41%)
6	H ₂ O (1 mL/mmol 1a), HNO ₃ (230 $\mu\text{L}/\text{mmol}$ 1a), rt, 1.5 days	6 (33%)

^a Anthranilonitrile **1a** and TEOF were combined in a 1:3 molar ratio.

^b By TLC.

In the presence of acetic acid, the 2-aminobenzonitrile was only completely consumed after 11 days at 40 °C, leading to a complex product mixture (Table 1, entry 3).

The structure of compound **5** was assigned mainly on the basis of NMR spectroscopy. A broad singlet at δ 10.26 ppm, integrating for two protons, was assigned to the protonated imino substituent. Besides the aromatic protons, a singlet at δ 10.06 ppm integrating for one proton confirms that only 1 equiv of the orthoester was incorporated in the product. This high chemical shift value was considered a consequence of the anisotropic effect of the adjacent aromatic ring in the fused heteroaromatic structure. Correlation techniques (HMBC and HMQC) confirmed the position of the neighbouring carbon atoms, and supported the proposed structure.

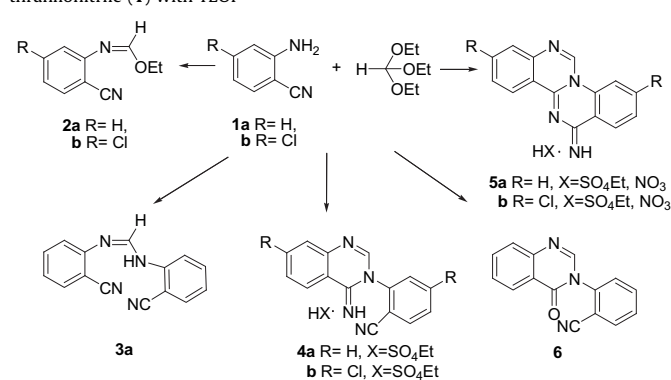
Nitric acid was selected as the most appropriate catalyst for this reaction and other solvents were used, keeping a constant temperature of 40 °C. Acetonitrile and petroleum ether (boiling range 40–60) resulted in the formation of the same product **5a** in a lower isolated yield (Table 1, entries 4 and 5). In water, the reaction evolves to the benzopyrimidinone **6** suggesting that imine hydrolysis from a possible intermediate prevents the formation of the expected triazachrysene structure (Table 1, entry 6).

Substituted benzopyrimidinones were previously prepared from the reaction of a range of substituted anthranilic acids with triethylorthoformate, in the presence of concentrated sulfuric acid and upon reflux in DMF.¹⁵ The synthesis of benzopyrimidinone **6** was reported from the reaction of **1a** with anhydrous formic acid¹⁶ or with *N*-formylanthranilonitrile in the presence of thionyl chloride.¹⁷ The structure of the product was confirmed by X-ray analysis¹⁷ and the reported IR spectrum agrees with the data obtained for compound **6**

that shows the cyano and carbonyl stretching vibrations at 2235 and 1687 cm^{-1} , respectively. In the ¹H NMR spectrum, the C–H signal is a singlet at δ 8.45 ppm, confirming that the aromatic substituent in the pyrimidone ring is now flexible and the ring current no longer affects this chemical shift. Correlation studies fully confirm the position of the neighbouring carbon atoms.

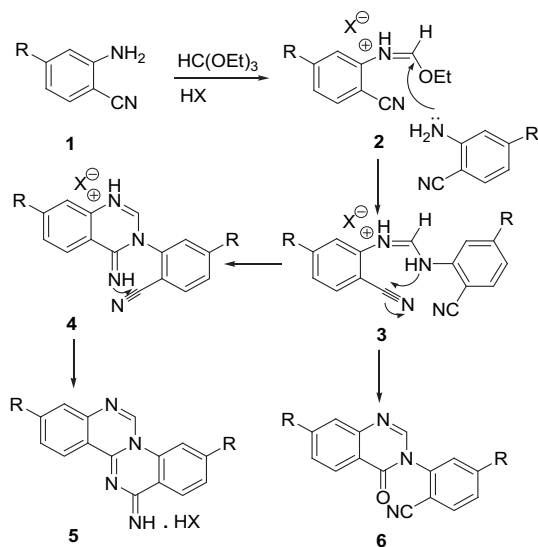
Anthranilonitrile and TEOF were combined with different solvents and acid catalysts. Table 2 summarizes the experimental conditions selected to prepare the intermediate structures involved in the synthetic pathway, as is represented in Scheme 1.

Table 2
Optimized experimental conditions for the acid-promoted reaction of anthranilonitrile (**1**) with TEOF



Entry	Reactions conditions	Product (yield)
1	1a +TEOF (1 mL/1.8 mmol 1a), reflux 45 min	2a (Quant)
2	1b +TEOF (1 mL/mmol 1b), reflux 45 min	2b (79%)
3	1b +TEOF (1:1), petroleum ether (1 mL/0.3 mmol 1b), CH ₃ COOH (23 $\mu\text{L}/\text{mmol}$ 1b), reflux 1 day	2b (88%)
4	1a +TEOF (1:1), petroleum ether (1 mL/0.6 mmol 1a), TFA (3 $\mu\text{L}/\text{mmol}$ 1a), rt, 18 h	3a (82%)
5	1a +TEOF (1:3), petroleum ether (1 mL/0.7 mmol 1a), TFA (3 $\mu\text{L}/\text{mmol}$ 1a), rt, 4.5 h	3a (45%)
6	1a +TEOF (1:3), CH ₃ CN (1 mL/1.7 mmol 1a), H ₂ SO ₄ (15 $\mu\text{L}/\text{mmol}$ 1a), rt, 1 h	4a , X=SO ₄ Et (83%)
7	1b +TEOF (1:3), CH ₃ CN (1 mL/0.3 mmol 1b), H ₂ SO ₄ (26 $\mu\text{L}/\text{mmol}$ 1b), rt, 2 h	4b , X=SO ₄ Et (80%)
8	1a +TEOF (1:3), H ₂ SO ₄ (7 $\mu\text{L}/\text{mmol}$ 1a), rt, 18 h	5a , X=SO ₄ Et (83%)
9	1b +TEOF (1:3), EtOH (1 mL/0.8 mmol 1b), HNO ₃ (19 $\mu\text{L}/\text{mmol}$ 1b), 40 °C, 3 days	5b , X=NO ₃ (79%)
10	1b +TEOF (1:1.2), CH ₃ CN (1 mL/0.3 mmol 1b), H ₂ SO ₄ (20 $\mu\text{L}/\text{mmol}$ 1b), rt, 2.5 days	5b , X=SO ₄ Et (71%)
11	1a +TEOF (1:3), H ₂ O (1 mL/0.7 mmol 1a), H ₂ SO ₄ (1 mL/3.5 mmol 1a), rt, 19 h	6 (26%)

Imide **2** could only be isolated when TEOF was used as solvent and the mixture was refluxed for 45 min (Table 2, entry 1). The product was quantitatively isolated as an oily material. This synthetic approach was previously reported in the literature² and, as far as we know, is the only procedure that allows the isolation of imide **2**. When a suspension of **1a** and TEOF (1:1 molar ratio) in petroleum ether and trifluoroacetic acid was stirred at room temperature, compound **3a** precipitated from solution as a yellow solid and was isolated in 82% yield after 18 h (Table 2, entry 4). Increasing the amount of TEOF (1:3 molar ratio) and decreasing the reaction time to 4.5 h resulted in a decrease in the isolated yield of **3a** to 45% (Table 2, entry 5). The structure of this compound could only be assigned on the basis of elemental analysis and IR spectroscopy as in solution it rapidly evolves to the bicyclic structure **4a**. The IR spectrum clearly shows the stretching vibration of the N–H bond (3353 cm^{-1}) and of the two cyano groups (2232 and 2219 cm^{-1}).



Scheme 1. Proposed mechanism for the reaction of 2-aminobenzonitrile **1** with TEOF leading to compounds **5** and **6**.

Compound **4a** was isolated in 83% yield from an acetonitrile solution of **1a** and TEOF in the presence of sulfuric acid. The reaction was complete after 1 h at room temperature (Table 2, entry 6).

The isolated yield of compound **5a** was improved (83%) when the amine and the orthoester were combined in the presence of sulfuric acid, and the mixture was stirred at room temperature for 18 h (Table 2, entry 8).

This reaction sequence was studied for the 4-chloro-2-aminobenzonitrile **1b** resulting in the isolation of **2b**, in the absence of solvent or in the presence of petroleum ether and acetic acid (Table 2, entries 2 and 3) and of **4b** from sulfuric acid and acetonitrile (Table 2, entry 7). The triazachryzene **5b** was also prepared either from ethanol and nitric acid (Table 2, entry 9) or from acetonitrile and sulfuric acid (Table 2, entry 10). The formation of the dimeric species **5** results from a cascade reaction, initiated by the acid catalyzed nucleophilic attack of a second molecule of anthranilonitrile to imidate **2** (Scheme 1). Two consecutive intramolecular cyclization processes led to the final structure **5**, always isolated as a salt.

The formation of compound **6** may result from hydrolysis of the imine function in compound **4**, as was previously reported.¹⁶

Compound **7a** was isolated when a 1:1 mixture of anthranilonitrile **1a** and TEOF was stirred at room temperature for 5 days, in the presence of acetic acid (Table 3, entry 1).

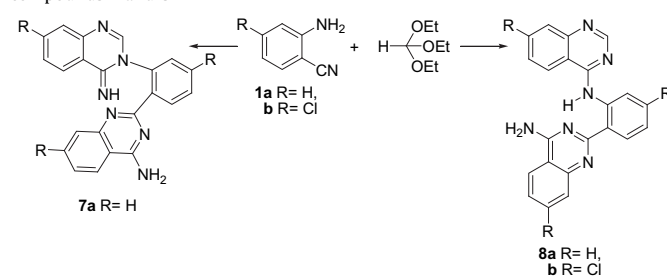
The use of petroleum ether as solvent led to the formation of compound **8a** either after 5 days at room temperature (Table 3, entry 2) or upon reflux for 30 min (Table 3, entry 3).

Compound **8a** was generated by Dimroth rearrangement of **7a**, as was confirmed by ¹H NMR spectroscopy. In DMSO-*d*₆ solution and in the presence of TFA (5 μL), **7a** (4 mg in 650 μL) gradually evolved to **8a**. After 10 days at room temperature, only traces of **7a** were detected in solution.

The reaction of 2-amino-4-chlorobenzonitrile (**1b**) with TEOF was carried out in ethanol with acetic acid catalysis, under reflux conditions (Table 3, entry 6). A clean but slow evolution to compound **8b** was confirmed by ¹H NMR on the reaction mixture, recorded at regular intervals. The solid suspension, filtered after 3 days, was identified as the pure product **8b** (4%). Only the reagents were present in the mother liquor and ¹H NMR confirmed the absence of the dimeric species **5b**. The pure starting material **1b** was also isolated in 80% yield. A similar experiment, where **1b** and TEOF were refluxed in petroleum ether, using acetic acid catalysis, led to the formation of imidate **2b** in 88% yield (Table 2, entry 3). The higher boiling point of ethanol combined with a prolonged reflux period was

Table 3

Optimized experimental conditions for the acid-promoted synthesis of trimeric compounds **7** and **8**



Entry	Reactions conditions	Product (yield)
1	1a +TEOF (1:1), CH ₃ COOH (13 μL/mmol 1a), rt, 5 days	7a (75%)
2	1a +TEOF (1:1), petroleum ether (1 mL/0.6 mmol 1a), CH ₃ COOH (13 μL/mmol 1a), rt, 5 days	8a (90%)
3	1a +TEOF (1:1), petroleum ether (1 mL/0.2 mmol 1a), CH ₃ COOH (13 μL/mmol 1a), reflux, 30 min	8a (52%)
4	1a +TEOF (1:1), ethanol (1 mL/mmol 1a), CH ₃ COOH (13 μL/mmol 1a), 40 °C, 11 days	7a + 8a , 1:2.4 (14%)
5	1a +TEOF (1:1), acetonitrile (1 mL/mmol 1a), CH ₃ COOH (13 μL/mmol 1a), 40 °C, 11 days	7a + 8a , 1:1 (11%)
6	1b +TEOF (1:2), EtOH (1 mL/0.2 mmol 1b), CH ₃ COOH (13 μL/mmol 1b), reflux, 3 days	8b (4%)

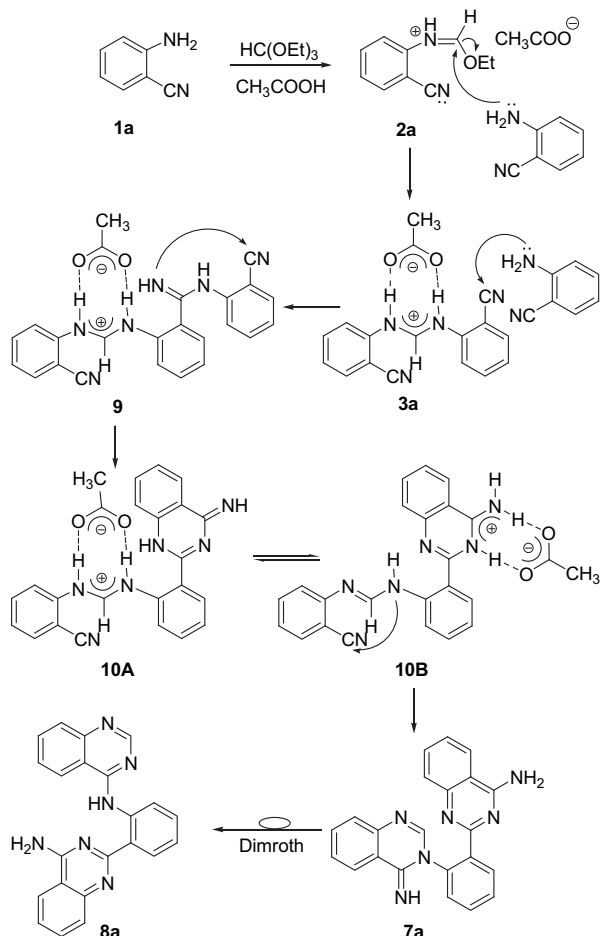
expected to extend the reaction sequence to generate the trimeric species **8b**. The low isolated yield of this compound and the recovery of 2-amino-4-chlorobenzonitrile suggest that it is difficult to generate the imidate function under these experimental conditions.

The formation of a trimeric species can be associated with the use of acetic acid as catalyst and not with the use of petroleum ether as solvent. The reaction of anthranilonitrile **1a** and TEOF was performed in petroleum ether using nitric acid, sulfuric acid and trifluoroacetic acid. With nitric acid, the dimer **5a** was isolated in 41% yield after 3.5 h at 40 °C (Table 1, entry 5). With trifluoroacetic acid, compound **3** precipitated from solution and was isolated after 18 h at room temperature (Table 2, entry 4). With sulfuric acid, a complex mixture was detected by TLC after 1 day at 40 °C.

The reaction of anthranilonitrile **1a** and TEOF in the presence of acetic acid was also performed in ethanol and in acetonitrile. In both cases, the homogeneous reaction mixture was stirred at 40 °C leading to a solid suspension after 6 days. The solid was filtered after 11 days at 40 °C, when the starting material was no longer detected in solution. ¹H NMR showed that the product was a mixture of compounds **7a** and **8a** in a 1:2.4 molar ratio (14% from ethanol, Table 3, entry 4) and in a 1:1 molar ratio (11% from acetonitrile, Table 3, entry 5). The mother liquor contains a complex mixture in both cases.

The formation of compound **7a**, promoted by acetic acid, can be rationalized if intramolecular cyclization in compound **3a** is prevented through a tight ionic interaction between the amidinium and acetate ions (Scheme 2). The cyano group is now available for nucleophilic attack by another molecule of anthranilonitrile leading to **9**. Intramolecular cyclization between the imino nitrogen and the cyano group leads to intermediate **10A**, where a new, more basic aminopyrimidine unit is formed.

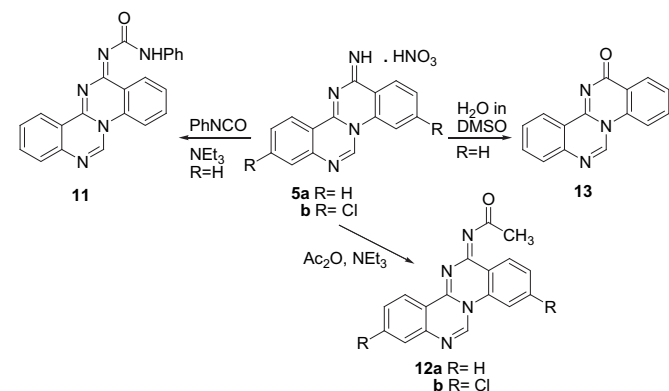
The acetate ion will now be preferentially stabilized through an ionic interaction with this amidine moiety (intermediate **10B**) enabling intramolecular cyclization to generate **7a**. A non-polar solvent would favour the formation of a tight ion pair, ultimately responsible for the major pathway. This could also explain the excellent yield of the trimeric product obtained in petroleum ether. The formation of **8a** is the result of Dimroth rearrangement of **7a**, catalyzed by acid, after prolonged stirring at room temperature or upon reflux.



Scheme 2. Postulated mechanism for the reaction of 2-aminobenzonitrile **1** with TEOF leading to compounds **7** and **8**.

Compound **5a** was reacted with phenylisocyanate and triethylamine, at room temperature (Table 4, entry 1). The acylated product **11** was isolated in 88% yield after 2 h. The reaction with acetic anhydride was also performed at room temperature and in the

Table 4
Optimized experimental conditions for the reaction of dimer **5** with water, acetic anhydride and phenylisocyanate



Entry	Reactions conditions	Product (yield)
1	5a +PhNCO (1:1.2), NEt ₃ (265 μL/mmol 5a), rt, 2 h	11 (88%)
2	5a +Ac ₂ O (1:8), NEt ₃ (60 μL/mmol 5a), rt, 3 h	12a (82%)
3	5a +Ac ₂ O (1:8), NEt ₃ (115 μL/mmol 5a), CH ₃ CN (1 mL/0.13 mmol 5a), reflux, 3 h	12a (88%)
4	5b +Ac ₂ O (1:8), NEt ₃ (400 μL/mmol 5b), rt, 18 h	12b (73%)
5	5a , DMSO (600 μL/mmol 5a), heating to dryness	13 (93%)

presence of triethylamine. Products **12a** and **12b** were isolated in 82% yield (after 3 h) and 73% yield (after 18 h), respectively (Table 4, entries 2–4).

Heating compound **5a** in a small volume of DMSO for 10–15 min (until most of the solvent is eliminated) resulted in its evolution to compound **13**. This product probably arises from hydrolysis through moisture retained by the solvent, under the high temperature conditions required for the reaction. Reducing the heating time prevented complete evolution of the starting material **5a** (identified in the reaction mixture by ¹H NMR) and performing the reaction under reflux conditions for longer time periods (up to 3 h) led mainly to decomposition products.

2.1. UV absorption and fluorescence measurements

The planar and highly conjugated structure of these dimeric compounds suggested that they might be useful fluorophores and the fluorescent properties of the nitrate salt of **5a** and of compounds **11**, **12a** and **13** were studied. The values recorded were compared with those for pyrene, a well known and widely used fluorescent probe.¹⁸ The absorption and fluorescence spectra were recorded in a polar and a non-polar solvent (ethanol and chlorobenzene) and the data are summarized in Table 5.

The nitrate salt of **5a** was insoluble in chlorobenzene and the only data available was recorded in ethanol.

Table 5

Absorption maxima (λ_{abs}), molar extinction coefficients (ϵ), excitation wavelength ($\lambda_{\text{excitation}}$) and fluorescence quantum yield (ϕ_f) for compounds **5a**, **11**, **12a** and **13** in chlorobenzene (1.0×10^{-6} M) and in ethanol (1.0×10^{-6} M)

Comp	Solvent	Absorption λ_{abs} [nm] (ϵ) [$10^4 \text{ M}^{-1} \text{ cm}^{-1}$]	Fluoresc. ^a ϕ_f^b
5a HNO ₃	EtOH	323 (1.01), 337 (1.27), 353 (1.14)	337 0.24
	C ₆ H ₅ Cl	— ^c	— ^c
11	EtOH	320 (1.16), 340 (1.01), 360 (0.95)	320 0.02
	C ₆ H ₅ Cl	313 (0.94), 326 (0.97), 352 (0.75), 370 (0.60), 390 (0.24)	326 0.03
12a	EtOH	320 (0.95), 346 (0.89), 360 (0.81), 378 (0.38)	320 0.03
	C ₆ H ₅ Cl	313 (0.57), 324 (0.58), 355 (0.40), 370 (0.30), 390 (0.11)	324 0.12
13	EtOH	320 (0.95), 335 (0.98), 354 (0.77), 373 (0.50)	335 0.25
	C ₆ H ₅ Cl	325 (0.88), 340 (1.00), 358 (0.83), 377 (0.53)	340 0.49
Pyr.	EtOH	334 (4.63) ^d	334 0.32 ^d
	C ₆ H ₅ Cl	305 (0.81), 318 (1.53), 333 (2.00)	338 0.39

^a The measurements were performed under degassed conditions by bubbling of Ar.

^b The fluorescence quantum yield values are relative to that of anthracene ($\phi_f=0.27$ in ethanol).¹⁹

^c The compound was insoluble in chlorobenzene.

^d Ref. 18.

All compounds show a very similar absorption envelope, although compounds **5a** and **13** present a more structured pattern, resembling that of pyrene. For compound **13**, the three well resolved absorption bands in the 300–350 nm region show a red shift of approximately 20 nm relative to those of pyrene, probably as a result of the increase in π -electron density due to the presence of nitrogen atoms in the aromatic core structure. In the UV spectrum of compound **13**, an extra absorption band is visible at 377 nm (chlorobenzene) or at 373 nm (ethanol). In general, the electronic absorption and fluorescence emission features of these compounds show only marginal dependence on the solvent polarity.

The fluorescence quantum yield, an important parameter in accessing the ability of these compounds to act as fluorescent probes, varies from 0.02 to 0.49, with higher values recorded in deoxygenated chlorobenzene rather than in ethanol. The low values (below 0.12) measured for compounds **11** and **12a** (Table 5) indicate

a significant involvement of non-radiative relaxation pathways that may be associated with the conjugation of the π -electrons with the exocyclic carbonyl double bond. Compounds **5a** and **13** show high fluorescence quantum yields ($\phi_f=0.24$ – 0.49) comparable with the values reported for pyrene ($\phi_f=0.32$)¹⁸ or determined under identical conditions to those used in the characterization on the new structures ($\phi_f=0.39$).

The normalized fluorescence and absorption spectra of compounds **5a** and **13** (Fig. 2) provide evidence for the structured absorption spectra of these compounds and the absence of significant shifts in the fluorescence spectrum of **13** when the solvent is changed from chlorobenzene to ethanol. The diagram also evidences a loss of vibrational structure and a blue shift in the emission spectrum of the nitrate salt **5a** compared with that of compound **13** (22 nm).

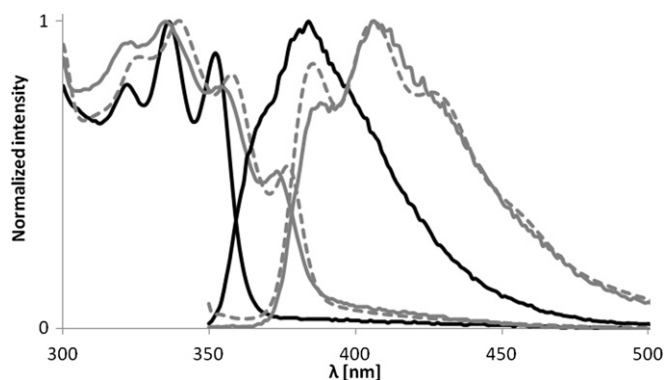


Fig. 2. Absorption and fluorescence spectra of **5a** (—) in ethanol and **13** in ethanol (—) and chlorobenzene (-----) at an excitation wavelength of 340 nm.

3. Conclusion

Anthranilonitrile and triethylorthoformate, two commercially available reagents, were used as precursors of highly conjugated triazachrysene structures. These novel compounds were prepared under mild experimental conditions and were isolated in a high purity form by simple filtration. The appropriate selection of solvent, acid, reaction time and temperature, resulted in the formation of different derivatives, including trimeric species. A mechanistic proposal was presented to support these results. Compounds **5** were functionalized through the exocyclic imine nitrogen, upon reaction with acetic anhydride and phenylisocyanate.

4. Experimental section

4.1. General methods

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded on a Varian Unity Plus (^1H : 300 MHz, ^{13}C : 75 MHz), or Bruker Avance II+ 400 (^1H : 400 MHz, ^{13}C : 100 MHz) including the ^1H – ^{13}C correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The coupling constants, J , are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument. Petroleum ether with a boiling range 40–60 was used in all the experiments.

4.2. Spectroscopic measurements

Fluorescence quantum yields (ϕ_f) of pyrene and compounds **5a**, **11**, **12a** and **13** were determined using anthracene as a standard with a known ϕ_f of 0.27 in ethanol.¹⁹ The fluorescence quantum yields were calculated according to the following equation:

$$\phi_{f(\text{spl})} = \phi_{f(\text{std})} \times [A_{\text{std}}/A_{\text{spl}}] \times [I_{\text{spl}}/I_{\text{std}}] \times [n_{\text{spl}}/n_{\text{std}}]^2$$

In this equation, $\phi_{f(\text{spl})}$ and $\phi_{f(\text{std})}$ are quantum yields of a sample and of the standard, respectively. A_{spl} , I_{spl} and n_{spl} are the optical density, the integrated emission intensity at the excitation wavelength and the value of the refractive index of the sample, respectively. A_{std} , I_{std} and n_{std} are those for the standard. Sample solutions (3.0×10^{-6} M in ethanol and in chlorobenzene) were degassed with argon before the measurements.

4.3. Procedure for the synthesis of ethyl (2-cyanophenyl)imidoformate (**2a**)

The colourless solution of the 2-aminobenzonitrile (0.21 g, 1.78 mmol) in triethylorthoformate (1 mL) was refluxed for 45 min., leading to a yellow solution. The solvent was concentrated in the rotary evaporator and the resulting yellow oil was identified as ethyl (2-cyanophenyl)imidoformate **2a**: ^1H NMR (300 MHz, DMSO- d_6) δ 8.09 (s, 1H, CH), 7.74 (dd, 1H, H -3, J_1 1.5 Hz and J_2 7.8 Hz), 7.61 (td, 1H, H -5, J_1 1.5 Hz and J_2 7.8 Hz), 7.26 (td, 1H, H -4, J_1 0.9 Hz and J_2 7.8 Hz), 7.21 (d, 1H, H -6, J 8.1 Hz), 4.30 (q, 2H, CH_2 , J 6.9 Hz), 1.33 (t, 3H, CH_3 , J 6.9 Hz); ^{13}C NMR (75 MHz, DMSO- d_6) δ 158.13 (CH), 150.70 (C1), 134.16 (C5), 133.02 (C3), 124.64 (C4), 120.98 (C6), 117.41 (CN), 106.30 (C2), 62.76 (CH_2), 13.90 (CH_3); IR (Nujol mull) 2226, 1640, 1594, 1571, 1485, 1447, 1391, 1372, 1305, 1293, 1271, 1257, 1203, 1161, 1101, 1038, 1011 cm^{-1} .

4.4. Procedure for the synthesis of ethyl (5-chloro-2-cyanophenyl)imidoformate (**2b**)

Method A: Triethylorthoformate (0.20 g, 1.36 mmol, 226 μL , 1 equiv) and acetic acid (23 μL) were added to a yellow suspension of 2-amino-4-chlorobenzonitrile (0.21 g, 1.36 mmol) in petroleum ether (5 mL) and the mixture was refluxed. After 1 day, a yellow solid was filtered and washed with petroleum ether and identified as ethyl (5-chloro-2-cyanophenyl)imidoformate **2b** (0.23 g, 1.09 mmol, 88%).

Method B: The yellow suspension of the 2-aminobenzonitrile (0.16 g, 1.04 mmol) in triethylorthoformate (1 mL) was refluxed for 45 min, leading to a yellow solution. After 2 h at room temperature a yellow solid precipitate was filtered and washed with n -hexane and identified as ethyl (5-chloro-2-cyanophenyl)imidoformate **2b** (0.17 g, 0.82 mmol, 79%); mp 71–73 $^\circ\text{C}$; ^1H NMR (300 MHz, DMSO- d_6) δ 8.16 (s, 1H, CH), 7.79 (d, 1H, H -3, J 8.1 Hz), 7.41 (d, 1H, H -6, J 1.8 Hz), 7.33 (dd, 1H, H -4, J_1 1.8 Hz and J_2 8.1 Hz), 4.30 (q, 2H, CH_2 , J 6.9 Hz), 1.33 (t, 3H, CH_3 , J 6.9 Hz); ^{13}C NMR (75 MHz, DMSO- d_6) δ 159.26 (CH), 152.07 (C1), 138.63 (C5), 134.02 (C3), 124.66 (C4), 121.02 (C6), 116.66 (CN), 105.45 (C2), 63.08 (CH_2), 13.85 (CH_3); IR (Nujol mull) 2228, 1640, 1589, 1577, 1561, 1463, 1404, 1377, 1287, 1273, 1263, 1200, 1177, 1135, 1111, 1082, 1009 cm^{-1} . Anal. Calcd for $\text{C}_{10}\text{H}_9\text{N}_2\text{OCl}$: C, 57.56; H, 4.36; N, 13.43. Found: C, 57.67; H, 4.49; N, 13.71.

4.5. Procedure for the synthesis of N,N' -bis(2-cyanophenyl)imidoformamide (**3a**)

Method A: Triethylorthoformate (0.27 g, 1.84 mmol, 1 equiv, 310 μL) and TFA (6 μL) were added to a solution of the 2-aminobenzonitrile **1a** (0.22 g, 1.84 mmol) in petroleum ether (3 mL), and the reaction mixture was stirred at room temperature for 18 h. The white precipitate was filtered and washed with diethyl ether. The

product was identified as *N,N'*-bis(2-cyanophenyl)imidoformamide **3a** (0.19 g, 0.75 mmol, 82%).

Method B: Triethylorthoformate (0.98 g, 6.60 mmol, 3 equiv, 1100 μ L) and TFA (6 μ L) were added to a solution of the 2-aminobenzonitrile **1a** (0.26 g, 2.20 mmol) in petroleum ether (3 mL), and the reaction mixture was stirred at room temperature for 4.5 h. The white precipitate was filtered and washed with diethyl ether. The product was identified as *N,N'*-bis(2-cyanophenyl)imidoformamide **3a** (0.12 g, 0.49 mmol, 45%); mp 222–224 °C; ^1H and ^{13}C NMR it is very unstable in solution; IR (Nujol mull) 3353, 2232, 2219, 1688, 1667, 1630, 1590, 1571, 1538, 1484, 1454, 1414, 1377, 1323, 1285, 1256, 1231, 1201, 1177, 1155, 1125, 1097, 1041 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_4 \cdot 1/3\text{CF}_3\text{COOH}$: C, 66.20; H, 3.64; N, 19.72. Found: C, 65.90; H, 3.53; N, 19.74.

4.6. Procedure for the synthesis of the ethyl sulfate salt of 3-(2-cyanophenyl)-quinazolin-4(3H)-imine (**4a**)

Acetonitrile (3 mL) and sulfuric acid (78 μ L) were added to a yellow suspension of 2-aminobenzonitrile (0.60 g, 5.08 mmol) in triethylorthoformate (2.23 g, 15.03 mmol, 2500 μ L, 3 equiv). The reaction mixture was stirred at room temperature and followed by TLC. After 1 h the white precipitate was filtered and washed with diethyl ether. The product was identified as the ethyl sulfate salt of 3-(2-cyanophenyl)quinazolin-4(3H)-imine **4a** (0.75 g, 2.10 mmol, 83%); mp 241–243 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.68 (br s, 1H, NH), 8.69 (d, 1H, H-5, J 1.2 Hz), 8.31 (dd, 1H, H-3', J_1 1.2 Hz and J_2 8.0 Hz), 8.21 (td, 1H, H-7, J_1 1.2 Hz and J_2 7.2 Hz), 8.13 (td, 1H, H-5', J_1 1.2 Hz and J_2 7.2 Hz), 8.06 (dd, 1H, H-6', J_1 1.2 Hz and J_2 8.0 Hz), 8.04 (dd, 1H, H-8, J_1 1.2 Hz and J_2 8.4 Hz), 7.99–7.93 (m, 2H, H-6+H-4'), 3.72 (q, 2H, CH_2 , J 7.2 Hz), 1.11 (t, 3H, CH_3 , J 7.2 Hz); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 155.91 (C4), 145.56 (C8a), 144.33 (CH), 137.90 (C7), 136.80 (C1'), 136.17 (C5'), 135.07 (C3'), 132.53 (C4'), 129.96 (C6), 129.92 (C6'), 128.77 (C8), 125.66 (C5), 114.89 (CN), 113.82 (C4a), 111.33 (C2'), 61.12 (CH_2), 15.11 (CH_3); IR (Nujol mull) 3203, 3043, 2227, 1690, 1629, 1602, 1583, 1491, 1482, 1465, 1376, 1298, 1268, 1204, 1193, 1107, 1062, 1020, 1010 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_4 \cdot \text{HSO}_4\text{C}_2\text{H}_5$: C, 54.85; H, 4.30; N, 15.05; S, 8.60. Found: C, 54.95; H, 4.33; N, 15.00; S, 8.90.

4.7. Procedure for the synthesis of the ethyl sulfate salt of 7-chloro-3-(5-chloro-2-cyanophenyl)quinazolin-4(3H)-imine (**4b**)

Acetonitrile (5 mL) and sulfuric acid (26 μ L) were added to a yellow suspension of 2-amino-4-chlorobenzonitrile (0.20 g, 1.31 mmol) in triethylorthoformate (0.58 g, 3.93 mmol, 650 μ L, 3 equiv). The reaction mixture was stirred at room temperature and followed by TLC. After 2 h the yellow precipitate was filtered and washed with diethyl ether. The product was identified as the ethyl sulfate salt of 7-chloro-3-(5-chloro-2-cyanophenyl)quinazolin-4(3H)-imine **4b** (0.22 g, 0.52 mmol, 80%); mp 261–263 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.72 (br s, 1H, NH), 8.76 (s, 1H, CH), 8.70 (d, 1H, H-5, J 8.8 Hz), 8.36 (d, 1H, H-3', J 8.4 Hz), 8.25 (d, 1H, H-6', J 2.0 Hz), 8.17 (d, 1H, H-8, J 2.0 Hz), 8.11 (dd, 1H, H-4', J_1 2.0 Hz and J_2 8.4 Hz), 8.06 (dd, 1H, H-6, J_1 2.0 Hz and J_2 8.8 Hz), 3.71 (q, 2H, CH_2 , J 7.2 Hz), 1.09 (t, 3H, CH_3 , J 7.2 Hz); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 155.56 (C4), 146.50 (C8a), 145.32 (CH), 142.79 (C7), 140.17 (C5'), 137.70 (C1'), 136.42 (C3'), 132.83 (C4'), 130.50 (C6'), 130.41 (C6), 128.01 (C8), 127.71 (C5), 114.23 (CN), 112.88 (C4a), 110.48 (C2'), 61.13 (CH_2), 15.10 (CH_3); IR (Nujol mull) 3207, 3032, 2236, 1698, 1631, 1610, 1586, 1566, 1524, 1463, 1443, 1377, 1322, 1293, 1265, 1243, 1215, 1153, 1139, 1123, 1087, 1062, 1015 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_8\text{N}_4\text{Cl}_2 \cdot \text{HSO}_4\text{C}_2\text{H}_5$: C, 46.26; H, 3.17; N, 12.70; S, 7.27. Found: C, 46.22; H, 3.28; N, 12.74; S, 6.89.

4.8. Procedure for the synthesis of the ethyl sulfate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine (**5a**)

Method A: Triethylorthoformate (0.91 g, 6.12 mmol, 3 equiv, 1020 μ L) and sulfuric acid (26 μ L) were added to a suspension of the 2-aminobenzonitrile (0.24 g, 2.04 mmol) in ethanol (2 mL) and the reaction mixture was stirred at 40 °C for 3.5 h. The pale yellow precipitate was filtered and washed with diethyl ether. The product was identified as the ethyl sulfate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine **5a** (0.18 g, 0.48 mmol, 47%).

Method B: Sulfuric acid (13 μ L) was added to a solution of 2-aminobenzonitrile (0.21 g, 1.75 mmol) and triethylorthoformate (0.78 g, 5.25 mmol, 3 equiv, 875 μ L) and the reaction mixture was stirred at room temperature for 18 h. The white precipitate was filtered and washed with diethyl ether. The product was identified as the ethyl sulfate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine **5a** (0.27 g, 0.73 mmol, 83%); mp 244–247 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.24 (br s, 2H, NH₂), 10.04 (s, 1H, CH), 8.97 (d, 1H, H-4, J 8.7 Hz), 8.80 (d, 1H, H-11, J 7.8 Hz), 8.63 (d, 1H, H-1, J 8.1 Hz), 8.27 (t, 1H, H-3, J 8.4 Hz), 8.16 (td, 1H, H-9, J_1 1.2 Hz and J_2 7.2 Hz), 8.06 (d, 1H, H-8, J 7.5 Hz), 8.00 (t, 1H, H-2, J 7.5 Hz), 7.94 (t, 1H, H-10, J 7.8 Hz), 3.74 (q, 2H, CH_2 , J 7.2 Hz), 1.09 (t, 3H, CH_3 , J 7.2 Hz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 161.11 (C13), 150.60 (C11b), 144.67 (C7a), 138.90 (CH), 136.79 (C3), 136.70 (C3), 135.81 (C4a), 129.97 (C10), 129.88 (C2), 127.95 (C8), 126.51 (C11), 125.93 (C1), 119.57 (C11a), 117.23 (C4), 113.04 (C13a), 61.23 (CH_2), 15.49 (CH_3); IR (Nujol mull) 3375, 3297, 1676, 1624, 1598, 1573, 1532, 1501, 1467, 1412, 1378, 1357, 1340, 1317, 1253, 1245, 1216, 1198, 1164, 1146, 1121, 1073, 1062, 1051, 1040, 1020 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{10}\text{N}_4 \cdot \text{HSO}_4\text{C}_2\text{H}_5 \cdot \text{H}_2\text{O}$: C, 52.29; H, 4.66; N, 14.35; S, 8.21. Found: C, 52.47; H, 4.60; N, 14.48; S, 8.07.

4.9. Procedure for the synthesis of the nitrate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine (**5a**)

Method A: Triethylorthoformate (0.89 g, 6.0 mmol, 3 equiv, 1000 μ L) and nitric acid (31 μ L) were added to a solution of the 2-aminobenzonitrile (0.24 g, 2.0 mmol) in petroleum ether (5 mL) and the reaction mixture was stirred at 40 °C for 3.5 h. The yellow precipitate was filtered and washed with diethyl ether. The product was identified as the nitrate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine **5a** (0.13 g, 0.41 mmol, 41%).

Method B: Triethylorthoformate (2.29 g, 15.48 mmol, 3 equiv, 2500 μ L) and nitric acid (96 μ L) were added to a solution of the 2-aminobenzonitrile (0.61 g, 5.16 mmol) in ethanol (5 mL), and the reaction mixture was stirred at 40 °C for 3 h. The yellow precipitate was filtered and washed with diethyl ether. The product was identified as the nitrate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine **5a** (0.61 g, 1.97 mmol, 76%).

Method C: Triethylorthoformate (0.93 g, 6.27 mmol, 3 equiv, 1045 μ L) and nitric acid (31 μ L) were added to a solution of the 2-aminobenzonitrile (0.25 g, 2.09 mmol) in acetonitrile (2 mL) and the reaction mixture was stirred at 40 °C for 3 days. The yellow precipitate was filtered and washed with diethyl ether. The product was identified as the nitrate salt of 13H-quinazolino[3,4-a]quinazolin-13-imine **5a** (0.15 g, 0.49 mmol, 47%); mp 262–264 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.26 (br s, 2H, NH₂), 10.05 (s, 1H, CH), 8.97 (d, 1H, H-4, J 8.4 Hz), 8.81 (dd, 1H, H-11, J_1 1.2 Hz and J_2 8.0 Hz), 8.63 (dd, 1H, H-1, J_1 1.2 Hz and J_2 8.0 Hz), 8.27 (td, 1H, H-3, J_1 1.2 Hz and J_2 7.2 Hz), 8.16 (td, 1H, H-9, J_1 1.2 Hz and J_2 7.2 Hz), 8.07 (d, 1H, H-8, J 8.4 Hz), 8.01 (t, 1H, H-2, J 7.6 Hz), 7.94 (td, 1H, H-10, J_1 1.2 Hz and J_2 7.2 Hz); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 161.08 (C13), 150.59 (C11b), 144.65 (C7a), 138.89 (CH), 136.74 (C3), 136.66 (C9), 135.80 (C4a), 129.94 (C10), 129.85 (C2), 127.93 (C8), 126.48 (C11), 125.90 (C1), 119.56 (C11a), 117.20 (C4), 113.03 (C13a); IR (Nujol mull) 3278, 3051, 1675, 1623, 1598, 1569, 1535, 1500, 1469, 1412, 1378, 1339, 1310, 1254, 1173, 1141, 1120, 1076, 1037, 1029 cm^{-1} . Anal. Calcd for

C₁₅H₁₀N₄·HNO₃: C, 58.24; H, 3.59; N, 22.65. Found: C, 58.28; H, 3.47; N, 22.62.

4.10. Procedure for the synthesis of the nitrate salt of 3,9-dichloro-13H-quinazolino[3,4-a]quinazolin-13-imine (5b)

Triethylorthoformate (0.69 g, 4.68 mmol, 3 equiv, 780 µL) and nitric acid (30 µL) were added to a suspension of the 2-amino-4-chlorobenzonitrile (0.24 g, 1.56 mmol) in ethanol (5 mL) and the reaction mixture was stirred at 40 °C for 3 days. The yellow precipitate was filtered and washed with diethyl ether. The product was identified as the nitrate salt of 3,9-dichloro-13H-quinazolino[3,4-a]quinazolin-13-imine **5b** (0.23 g, 0.61 mmol, 79%): mp 215–217 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.41 (br s, 2H, NH₂), 10.02 (s, 1H, CH), 9.17 (d, 1H, *H*-4, *J* 1.5 Hz), 8.74 (d, 1H, *H*-1, *J* 9.0 Hz), 8.63 (d, 1H, *H*-11, *J* 9.0 Hz), 8.23 (d, 1H, *H*-8, *J* 2.1 Hz), 8.16 (dd, 1H, *H*-2, *J*₁ 1.5 Hz and *J*₂ 8.7 Hz), 8.03 (dd, 1H, *H*-10, *J*₁ 2.1 Hz and *J*₂ 8.7 Hz); IR (Nujol mull) 3434, 3064, 1677, 1624, 1592, 1528, 1492, 1465, 1378, 1319, 1312, 1244, 1177, 1162, 1110, 1075, 1052, 1039 cm⁻¹. Anal. Calcd for C₁₅H₈N₄·HNO₃·H₂O: C, 45.47; H, 2.80; N, 17.68. Found: C, 45.59; H, 2.90; N, 17.46.

4.11. Procedure for the synthesis of the ethyl sulfate salt of 3,9-dichloro-13H-quinazolino[3,4-a]quinazolin-13-imine (5b)

Triethylorthoformate (0.23 g, 1.58 mmol, 1.2 equiv, 265 µL) and sulfuric acid (26 µL) were added to a solution of the 2-amino-4-chlorobenzonitrile (0.20 g, 1.32 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature and followed by TLC. The yellow precipitate was filtered and washed with diethyl ether after 2.5 days. The product was identified as the ethyl sulfate salt of 3,9-dichloro-13H-quinazolino[3,4-a]quinazolin-13-imine **5b** (0.20 g, 0.47 mmol, 71%): mp 269–271 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.46 (br s, 2H, NH₂), 10.01 (s, 1H, CH), 9.16 (d, 1H, *H*-4, *J* 1.8 Hz), 8.64 (d, 1H, *H*-1, *J* 8.7 Hz), 8.73 (d, 1H, *H*-11, *J* 9.0 Hz), 8.20 (d, 1H, *H*-8, *J* 2.1 Hz), 8.13 (dd, 1H, *H*-2, *J*₁ 1.5 Hz and *J*₂ 9.0 Hz), 8.01 (dd, 1H, *H*-10, *J*₁ 2.1 Hz and *J*₂ 9.0 Hz), 3.71 (q, 2H, CH₂, *J* 6.9 Hz), 1.08 (t, 3H, CH₃, *J* 6.9 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 160.60 (C13), 150.49 (C11b), 145.45 (C7a), 142.03 (C3), 141.60 (C9), 140.28 (CH), 136.65 (C4a), 130.52 (C10), 130.36 (C2), 128.40 (C11), 127.90 (C1), 127.23 (C8), 118.83 (C13a), 118.34 (C11a), 117.44 (C4), 61.16 (CH₂), 15.11 (CH₃); IR (Nujol mull) 3265, 3067, 1679, 1622, 1610, 1591, 1563, 1525, 1492, 1467, 1439, 1377, 1348, 1328, 1297, 1265, 1245, 1217, 1195, 1159, 1143, 1108, 1071, 1054, 1040, 1016 cm⁻¹. Anal. Calcd for C₁₅H₈N₄Cl₂·0.5H₂SO₄·0.5HSO₄C₂H₅: C, 44.96; H, 2.81; N, 13.11; S, 7.49. Found: C, 45.14; H, 2.94; N, 13.10; S, 7.42.

4.12. Procedure for the synthesis of 2-(4-oxoquinazolin-3(4H)-yl)benzonitrile (6)

Method A: To a white suspension of the 2-aminobenzonitrile (0.41 g, 3.47 mmol) in water (5 mL) were added triethylorthoformate (1.54 g, 10.41 mmol, 3 equiv, 1750 µL) and sulfuric acid (1 mL) and the reaction mixture was stirred at room temperature for 19 h. The yellow precipitate was filtered and washed with ethanol. The product was identified as 2-(4-oxoquinazolin-3(4H)-yl)benzonitrile **6** (0.11 g, 0.44 mmol, 26%).

Method B: Triethylorthoformate (0.96 g, 6.48 mmol, 3 equiv, 1080 µL) and nitric acid (0.5 mL) were added to a suspension of the 2-aminobenzonitrile (0.26 g, 2.16 mmol) in water (2 mL) and the reaction mixture was stirred at 25 °C for 1.5 days. The white precipitate was filtered and washed with ethanol. The product was identified as 2-(4-oxoquinazolin-3(4H)-yl)benzonitrile **6** (0.09 g, 0.36 mmol, 33%): mp 200–203 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (s, 1H, CH), 8.24 (d, 1H, *H*-5, *J* 8.4 Hz), 8.10 (d, 1H, *H*-6', *J* 7.6 Hz), 7.96 (t, 1H, *H*-4', *J* 1.2 Hz), 7.94 (t, 1H, *H*-7, *J* 1.2 Hz), 7.85 (d,

1H, *H*-5', *J* 8.0 Hz), 7.80 (d, 1H, *H*-8, *J* 8.4 Hz), 7.76 (t, 1H, *H*-3', *J* 7.6 Hz), 7.65 (t, 1H, *H*-6, *J* 7.6 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.62 (CO), 147.61 (C8a), 146.41 (CH), 139.54 (C2'), 135.25 (C7), 134.74 (C4'), 133.54 (C6'), 130.16 (C3'), 129.66 (C5'), 127.91 (C6), 127.57 (C8), 126.52 (C5), 121.43 (C4a), 115.79 (CN), 111.75 (C1'); IR (Nujol mull) 2235, 1687, 1609, 1597, 1561, 1494, 1465, 1456, 1396, 1377, 1320, 1307, 1291, 1277, 1252, 1187, 1121, 1024 cm⁻¹. Anal. Calcd for C₁₅H₉N₃O: C, 72.86; H, 3.68; N, 17.00. Found: C, 72.79; H, 3.60; N, 17.16.

4.13. Procedure for the synthesis of 2-[2-(4-iminoquinazolin-3(4H)-yl)phenyl]quinazolin-4-amine (7a)

Acetic acid (23 µL) was added to a solution of the 2-aminobenzonitrile (0.21 g, 1.74 mmol) in triethylorthoformate (0.26 g, 1.74 mmol, 1 equiv, 290 µL). The reaction mixture was stirred at room temperature and followed by TLC. After 5 days the yellow precipitate was filtered and washed with a mixture of diethyl ether and petroleum ether (1:1). The product was identified as 2-[2-(4-iminoquinazolin-3(4H)-yl)phenyl]quinazolin-4-amine **7a** (0.16 g, 0.44 mmol, 75%): mp 228–230 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (m, 1H, *H*-6'), 8.12 (d, 1H, *H*-5', *J* 7.6 Hz), 8.06 (d, 1H, *H*-5, *J* 7.6 Hz), 7.87 (s, 1H, CH), 7.68–7.66 (m, 2H, *H*-5'+*H*-4'), 7.60 (td, 1H, *H*-7, *J*₁ 1.2 Hz and *J*₂ 8.0 Hz), 7.55–7.51 (m, 2H, *H*-3'+*H*-7''), 7.49 (dd, 1H, *H*-8, *J*₁ 0.8 Hz and *J*₂ 8.0 Hz), 7.35 (td, 1H, *H*-6'', *J*₁ 1.2 Hz and *J*₂ 8.4 Hz), 7.31 (td, 1H, *H*-6, *J*₁ 1.2 Hz and *J*₂ 8.4 Hz), 6.99 (d, 1H, *H*-8'', *J* 8.0 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.80 (C4''), 159.17 (C2''), 154.28 (C4), 149.69 (C8a'), 148.12 (CH), 145.16 (C8a), 137.00 (C2'), 132.75 (C7''), 132.20 (C7), 131.45 (C6'), 130.73 (C4'), 130.35 (C3'), 129.26 (C5'), 127.20 (C8''), 126.68 (C8), 126.04 (C6), 125.52 (C6''), 125.02 (C5), 123.32 (C5''), 121.96 (C4a), 112.65 (C4a'); the signal for C1' is not visible in the spectrum; IR (Nujol mull) 3305, 3133, 1667, 1633, 1604, 1567, 1547, 1505, 1459, 1377, 1366, 1339, 1299, 1256, 1242, 1184, 1164, 1112 cm⁻¹. Anal. Calcd for C₂₂H₁₆N₆·0.2CH₃COOH: C, 71.49; H, 4.47; N, 22.34. Found: C, 71.77; H, 4.52; N, 22.24.

4.14. Procedure for the synthesis of 2-[2-(quinazolin-4-ylamino)phenyl]quinazolin-4-amine (8a)

Method A: Triethylorthoformate (0.26 g, 1.73 mmol, 1 equiv, 288 µL) and acetic acid (23 µL) were added to a solution of the 2-aminobenzonitrile (0.20 g, 1.73 mmol) in petroleum ether (10 mL). The reaction mixture was refluxed for 30 min. The resulting yellow precipitate was filtered and washed with ethanol. The product was identified as 2-[2-(quinazolin-4-ylamino)phenyl]quinazolin-4-amine **8a** (0.11 g, 0.30 mmol, 52%).

Method B: Triethylorthoformate (0.27 g, 1.83 mmol, 1 equiv, 305 µL) and acetic acid (23 µL) were added to a solution of the 2-aminobenzonitrile (0.22 g, 1.83 mmol) in petroleum ether (3 mL). The reaction mixture was stirred at room temperature and followed by TLC. After 5 days the yellow precipitate was filtered and washed with diethyl ether. The product was identified as 2-[2-(quinazolin-4-ylamino)phenyl]quinazolin-4-amine **8a** (0.20 g, 0.55 mmol, 90%): mp 251–253 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.96 (s, 1H, NH), 8.99 (d, 1H, *H*-3', *J* 7.6 Hz), 8.72 (s, 1H, CH), 8.62 (d, 1H, *H*-6', *J*₁ 1.2 Hz and *J*₂ 7.8 Hz), 8.53 (d, 1H, *H*-5, *J* 8.4 Hz), 8.31 (d, 1H, *H*-5'', *J* 8.0 Hz), 8.16 (br s, 2H, NH₂), 7.96–7.89 (m, 3H, *H*-6''+*H*-7+*H*-7''), 7.85 (d, 1H, *H*-8, *J* 7.2 Hz), 7.80 (td, 1H, *H*-6, *J*₁ 1.2 Hz and *J*₂ 8.4 Hz), 7.57 (dd, 1H, *H*-8'', *J*₁ 1.6 Hz and *J*₂ 8.0 Hz), 7.53 (dd, 1H, *H*-4', *J*₁ 1.6 Hz and *J*₂ 8.4 Hz), 7.21 (td, 1H, *H*-5', *J*₁ 1.2 Hz and *J*₂ 8.4 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.80 (C4''), 161.12 (C2''), 157.21 (C4), 154.54 (CH), 149.68 (C8a), 148.37 (C8a'), 139.78 (C2'), 133.91 (C7''), 133.15 (C7), 130.78 (C6'), 130.49 (C4'), 128.18 (C8), 126.88 (C6), 126.07 (C6''), 125.99 (C8''), 124.65 (C1'), 123.93 (C5''), 122.31 (C5), 122.06 (C5'), 121.39 (C3'), 116.12 (C4a), 112.81 (C4a'); IR (Nujol mull) 3314,

3407, 1656, 1632, 1601, 1575, 1542, 1499, 1463, 1436, 1412, 1376, 1356, 1330, 1320, 1286, 1277, 1242, 1159, 1112, 1075, 1029 cm⁻¹.

4.15. Procedure for the synthesis of 7-chloro-2-{4-chloro-2-[(7-chloroquinazolin-4-yl)amino]phenyl}quinazolin-4-amine (**8b**)

Triethylorthoformate (0.48 g, 3.26 mmol, 2 equiv, 550 μ L) and acetic acid (23 μ L) were added to a yellow suspension of 2-amino-4-chlorobenzonitrile (0.25 g, 1.63 mmol) in ethanol (7 mL). The reaction mixture was refluxed for 3 days. The resulting yellow solid was filtered and washed with diethyl ether to give the compound 7-chloro-2-{4-chloro-2-[(7-chloroquinazolin-4-yl)amino]phenyl}quinazolin-4-amine **8b** (0.01 g; 0.02 mmol; 4%): mp >300 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.95 (s, 1H, NH), 9.09 (d, 1H, H-3', *J* 2.0 Hz), 8.80 (s, 1H, CH), 8.60 (d, 1H, H-6', *J* 8.8 Hz), 8.46 (d, 1H, H-5', *J* 8.8 Hz), 8.33 (d, 1H, H-5'', *J* 8.8 Hz), 8.33 (br s, 2H, NH₂), 7.94 (d, 1H, H-8, *J* 2.0 Hz), 7.88 (d, 1H, H-8'', *J* 2.0 Hz), 7.69 (dd, 1H, H-6, *J*₁ 2.0 Hz and *J*₂ 8.8 Hz), 7.63 (dd, 1H, H-6'', *J*₁ 2.0 Hz and *J*₂ 8.8 Hz), 7.29 (dd, 1H, H-5', *J*₁ 2.0 Hz and *J*₂ 8.8 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.64 (C4''), 161.26 (C2''), 157.16 (C4), 155.65 (CH), 150.71 (C8a), 146.72 (C8a'), 140.85 (C2'), 138.51 (C7''), 137.8 (C7 or C4'), 137.2 (C7 or C4'), 132.42 (C6'), (C4'), 127.07 (C8), 127.07 (C6), 126.51 (C6''), 126.05 (C5''), 125.22 (C8''), 124.86 (C5), 122.94 (C1'), 122.26 (C5'), 120.66 (C3'), 111.56 (C4a'); IR (Nujol mull) 3434, 3321, 1637, 1604, 1567, 1536, 1491, 1461, 1401, 1377, 1341, 1317, 1261, 1238, 1162, 1083 cm⁻¹. Not enough sample was available for elemental analysis. Removal of the solvent from the mother liquor led to the isolation of 2-amino-4-chlorobenzonitrile (0.20 g; 1.31 mmol; 80%). The structure of this compound was confirmed by comparison of the ¹H NMR spectrum with that of a commercial sample.

4.16. Procedure for the synthesis of *N*-phenyl-*N'*-[13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]urea (**11**)

Triethylamine (40 μ L) was added to a yellow suspension of compound **5a** (0.05 g, 0.16 mmol) and phenyl isocyanate (0.02 g, 0.18 mmol, 1.2 equiv, 20 μ L). The reaction mixture was stirred at room temperature. After 2 h the white solid was filtered and washed with few drops of acetonitrile and water leading to the pure product. The product was identified as *N*-phenyl-*N'*-[13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]urea **11** (0.05 g, 0.14 mmol, 88%): mp 210–212 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.48 (s, 1H, CH), 9.45 (s, 1H, NH), 8.50 (d, 1H, H-4, *J* 8.7 Hz), 8.36 (d, 1H, H-11, *J* 7.8 Hz), 8.31 (d, 1H, H-1, *J* 7.5 Hz), 7.91–7.85 (m, 2H, H-9+H-3), 7.77 (d, 1H, H-8, *J* 8.1 Hz), 7.71–7.60 (m, 4H, H-10+H-2'+H-6'+H-2), 7.29 (t, 2H, H-3'+H-5', *J* 7.5 Hz), 6.98 (t, 1H, H-4', *J* 7.2 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 162.18 (CO), 151.57 (C13), 146.86 (C11b), 144.04 (C7a), 140.36 (C1'), 139.40 (CH), 135.24 (C4a), 134.69 (C9), 133.22 (C3), 128.58 (C10), 128.61 (C3' and C5'), 128.26 (C2), 127.26 (C8), 126.63 (C1), 125.81 (C11), 121.98 (C4'), 120.36 (C11a), 118.94 (C13a), 118.54 (C2' and C6'), 115.49 (C4); IR (Nujol mull) 3301, 1660, 1624, 1603, 1591, 1569, 1547, 1521, 1486, 1473, 1465, 1441, 1377, 1353, 1309, 1290, 1276, 1238, 1217, 1183, 1172, 1147, 1121, 1090, 1077, 1037, 1001 cm⁻¹. Anal. Calcd for C₂₂H₁₅N₅O: C, 72.31; H, 4.15; N, 19.17. Found: C, 72.17; H, 4.25; N, 19.03.

4.17. Procedure for the synthesis of *N*-[13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]acetamide (**12a**)

Method A: Triethylamine (40 μ L) was added to a suspension of compound **5a** (0.20 g, 0.65 mmol) in acetic anhydride (0.53 g, 5.20 mmol, 8 equiv, 490 μ L). The reaction mixture was stirred at room temperature and followed by TLC. After 3 h the white solid was filtered and washed with diethyl ether and a few drops of acetonitrile. The product was identified as *N*-[13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]acetamide **12a** (0.15 g, 0.53 mmol, 82%).

Method B: Triethylamine (48 μ L) was added to a suspension of compound **5a** (0.12 g, 0.40 mmol) in acetonitrile (3 mL) and acetic anhydride (0.33 g, 3.20 mmol, 8 equiv, 300 μ L). The reaction mixture was refluxed for 3 h. Yellow crystals were formed on cooling. The solid was filtered and washed with ethanol to give *N*-[13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]acetamide **12a** (0.10 g, 0.35 mmol, 88%): mp 224–227 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.46 (s, 1H, CH), 8.48 (d, 1H, H-4, *J* 1.2 Hz), 8.45 (d, 1H, H-11, *J* 1.5 Hz), 8.17 (dd, 1H, H-1, *J*₁ 1.5 Hz and *J*₂ 7.8 Hz), 7.93–7.82 (m, 1H, H-9+H-3), 7.77 (dd, 1H, H-8, *J*₁ 0.9 Hz and *J*₂ 7.2 Hz), 7.71–7.61 (m, 1H, H-10+H-2), 2.28 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 186.97 (CO), 148.74 (C13), 147.15 (C11b), 144.06 (C7a), 139.39 (CH), 135.32 (C4a), 134.76 (C9), 133.21 (C3), 128.70 (C10), 128.33 (C2), 127.30 (C8), 126.70 (C1), 125.99 (C11), 120.42 (C11a), 118.72 (C13a), 115.57 (C4), 26.25 (CH₃); IR (Nujol mull) 1674, 1631, 1608, 1591, 1567, 1538, 1477, 1465, 1415, 1377, 1350, 1311, 1293, 1280, 1241, 1223, 1179, 1145, 1118, 1086, 1036, 1018 cm⁻¹. Anal. Calcd for C₁₇H₁₂N₄O: C, 70.81; H, 4.20; N, 19.44. Found: C, 70.57; H, 4.31; N, 19.24.

4.18. Procedure for the synthesis of *N*-[3,9-dichloro-13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]acetamide (**12b**)

Triethylamine (40 μ L) was added to a suspension of compound **5b** (0.03 g, 0.09 mmol) in acetic anhydride (0.07 g, 0.72 mmol, 8 equiv, 68 μ L). The reaction mixture was stirred at room temperature and followed by TLC. After 18 h the pale yellow solid was filtered and washed with diethyl ether and a few drops of acetonitrile. The product was identified as *N*-[3,9-dichloro-13H-quinazolino[3,4-*a*]quinazolin-13-ylidene]acetamide **12b** (0.02 g, 0.06 mmol, 73%): mp 268–270 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.39 (s, 1H, CH), 8.59 (d, 1H, H-4, *J* 1.5 Hz), 8.40 (d, 1H, H-1, *J* 9.0 Hz), 8.15 (d, 1H, H-11, *J* 8.7 Hz), 7.82 (d, 1H, H-8, *J* 2.1 Hz), 7.71–7.65 (m, 2H, H-10+H-2), 2.40 (s, 3H, CH₃); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 169.96 (CO), 147.45 (C13), 146.63 (C11b), 144.78 (C7a), 140.46 (CH), 139.30 (C9), 137.92 (C3), 137.36 (C13a), 135.94 (C4a), 128.75 (C10), 128.37 (C2), 128.27 (C1), 127.68 (C11), 126.26 (C8), 119.03 (C11a), 115.56 (C4), 24.82 (CH₃); IR (Nujol mull) 1686, 1634, 1592, 1540, 1485, 1467, 1430, 1377, 1354, 1338, 1317, 1286, 1264, 1236, 1214, 1147, 1112, 1081, 1052, 1015 cm⁻¹. Anal. Calcd for C₁₇H₁₂N₄O.0.3H₂O: C, 56.30; H, 2.92; N, 15.45. Found: C, 56.33; H, 2.99; N, 15.44.

4.19. Procedure for the synthesis of 13H-quinazolino[3,4-*a*]quinazolin-13-one (**13**)

DMSO (90 μ L) was added to compound **5a** (0.04 g, 0.14 mmol) and the reaction mixture was heated to dryness in a hot plate (ca. 10 min). The solid was filtered after the addition of water, leading to the pure product that was identified as 13H-quinazolino[3,4-*a*]quinazolin-13-one **13** (0.03 g, 0.13 mmol, 93%): mp 181–183 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.28 (s, 1H, CH), 8.72 (dd, 1H, H-11, *J*₁ 1.2 Hz and *J*₂ 7.8 Hz), 8.32 (dd, 1H, H-1, *J*₁ 1.2 Hz and *J*₂ 8.1 Hz), 7.95 (td, 1H, H-3, *J*₁ 1.2 Hz and *J*₂ 6.9 Hz), 7.89 (td, 1H, H-9, *J*₁ 1.2 Hz and *J*₂ 6.9 Hz), 7.84 (dd, 1H, H-8, *J*₁ 1.2 Hz and *J*₂ 8.1 Hz), 7.82 (dd, 1H, H-4, *J*₁ 1.5 Hz and *J*₂ 8.1 Hz), 7.72 (td, 1H, H-10, *J*₁ 1.5 Hz and *J*₂ 6.9 Hz), 7.59 (td, 1H, H-2, *J*₁ 1.2 Hz and *J*₂ 8.1 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 157.75 (CO), 147.13 (C4a), 144.49 (C7a), 142.89 (C11b), 138.18 (CH), 135.97 (C3), 133.85 (C9), 128.90 (C10), 127.73 (C8), 127.37 (C4), 127.00 (C1), 126.50 (C2), 125.41 (C11), 121.24 (C13a), 118.74 (C11a); IR (Nujol mull) 1703, 1625, 1602, 1588, 1557, 1530, 1480, 1463, 1378, 1339, 1328, 1301, 1268, 1246, 1218, 1179, 1152, 1137, 1096, 1027 cm⁻¹. Anal. Calcd for C₁₅H₉N₃O.0.7H₂O: C, 69.32; H, 4.04; N, 16.17. Found: C, 69.31; H, 3.80; N, 16.04.

Acknowledgements

This work was supported by the University of Minho and by Fundação para a Ciência e a Tecnologia through project (PCDT/QUI/59356/2004) and a Ph.D. grant awarded to R.A. (SFRH/BD/38318/2007).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.013. These data include MOL files and InChIKeys of the most important compounds described in this article.

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