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Reactions of ethyl cyanoformate with cycloimmonium salts: a direct pathway to fused or substituted azaheterocycles

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ABSTRACT

Aromatic cycloimmonium salts underwent different reaction pathways when treated with ethyl cyanoformate in triethyl amine medium, including selective γ-cyano substitutions (in case of phenanthrolinium and quinolinium salts) and 3+2 dipolar cycloadditions (for phthalazinium and isoquinolinium salts). When using phthalazinium salts, besides the 3+2 cycloaddition products (imidazo[2,1-*a*]phthalazines), we obtained 8,8*a*,16,16*a*-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazines as secondary products via a 3+3 cycloaddition dimerization. The structures of the synthesized compounds have been proved by spectral data, and X-ray diffraction for three of the new derivatives.

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1. Introduction

Methyl cyanoformate, known as Mander's reagent, is commonly used to perform the regioselective methoxycarbonylation of lithium enolates.[1] Ethyl and methyl cyanoformates are also known for formation of α-ketoesters from arylboronic acids in rhodium-catalysed reactions[2] and for use as selective cyanoethoxycarbonylation reagents,[3] cyanation reagents[4,5] or dipolarophiles in different cyclization reaction.[6–9]

Imidazole is a therapeutically active moiety exploited in recent years for the synthesis of diverse derivatives with various biological activities.[10] The fusion of two or more heterocycle rings results in different classes of compound, and fused heterocycles containing an imidazole ring are showing a broad range of properties including biological activity[11–13] optical[14] or electron-transport properties.[15]

Inspired by a recent report of using ethyl cyanoformate as a dipolarophile in the 3+2 cycloaddition of pyridinium ylides, with formation of a new fused imidazo[1,2-*a*]pyridine system,[7] and as a continuation of our work in the field of 3+2 cycloaddition reactions,[16,17] we decided to use ethyl cyanoformate in similar reactions of 1,10-, 1,7- and 4,7-phenanthrolinium ylides in order to obtain new imidazophenanthroline systems. Surprisingly, instead the expected cycloadducts, we prepared new γ-cyano-substituted phenanthrolines. This interesting behaviour prompted us to extend the study of the reactions of ethyl cyanoformate with different cycloimmonium salts (phthalazinium, quinolinium and isoquinolinium) in basic medium, and the results are presented herein.

2. Results and discussion

In our first attempt to synthesize a new imidazophenanthroline skeleton, we used 1,10-phenanthrolin-1-ium halides[18] **1** in basic medium (trimethylamine in dichloromethane) for the generation of the corresponding ylides in order to react with ethyl cyanoformate in 3+2 cycloaddition reaction. Instead the expected cycloadducts **2**, we obtained 4-cyano substituted 1,10-phenanthrolines **3** (Scheme 1). Interestingly, in case of the reaction of salt **1c**, the final product **3c** contained a methyl ester group instead the initial amide group, this replacement probably occurring during the column chromatography when we used $CHCl_3$/MeOH as eluent.

The structures of the compounds **3a**–**c** were established on the basis of spectral analyses (NMR, IR) and X-ray diffraction for compound **3a** (Fig. 1). Thus, the crystal structure of **3a** indicates that this compound has the following crystallographic characteristics: monoclinic, space group $P2_1/c$ (no. 14), a=4.973 Å, b=40.94 Å, c=8.604 Å, β=96.11°, V=1742.1 Å^3, Z=4. The analysis of data reveals that in the crystals of compound **3a** a series of C–H···O and C–H···N hydrogen bonds exists but no π–π interactions.

Regarding the mechanism, we suppose that ethyl cyanoformate reacts with triethylamine (TEA) used in excess and generates the

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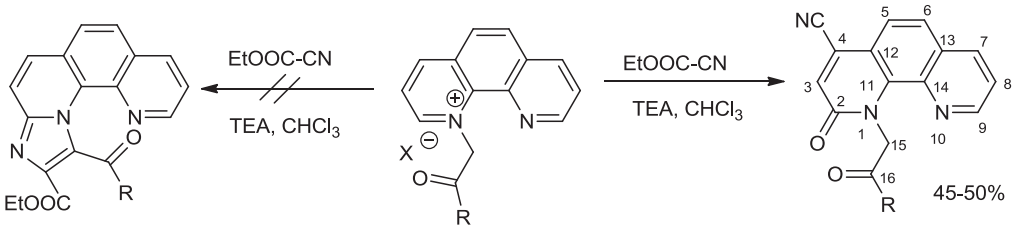


2a. R= -$C_6H_4OMe(p)$
2b. R= -$C_6H_4Cl(p)$
2c. R= -$CONH_2$

1a. R= -$C_6H_4OMe(p)$, X= Br
1b. R= -$C_6H_4Cl(p)$, X= Br
1c. R= -$CONH_2$, X= I

3a. R= -$C_6H_4OMe(p)$
3b. R= -$C_6H_4Cl(p)$
3c. R= -COOMe

Scheme 1. Synthesis of 4-cyano-substituted 2-oxo-1,2-dihydro-1,10-phenanthrolines **3**.

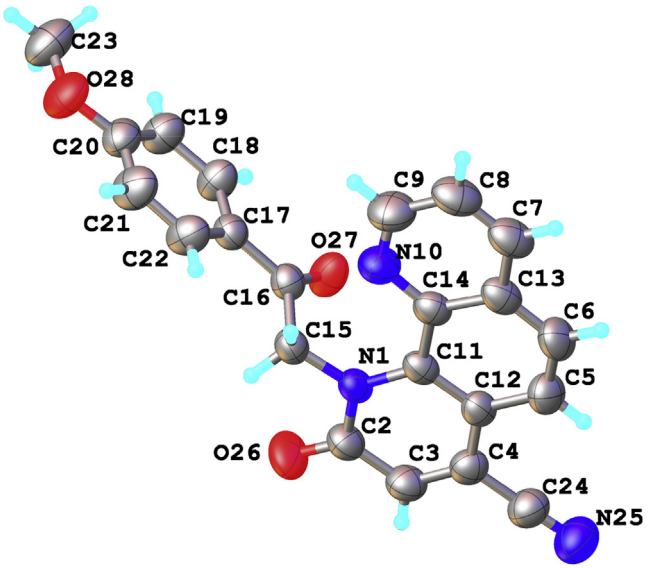
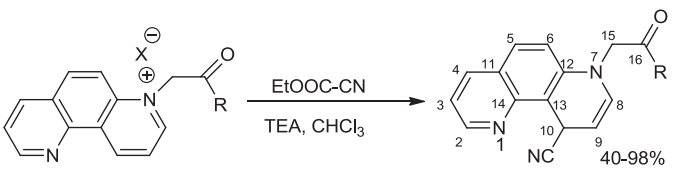


Fig. 1. X-ray crystal structure of compound **3a** with thermal ellipsoids at 50% probability level.

cyanide ion (CN^-). This ion acts as a nucleophile in reaction with the in situ generated phenanthrolinium ylides, leading selectively only to γ-cyano substituted 1,4-dihydro-1,10-phenanthrolines that are stabilised by α-oxidation in air during the work up, to lead to the final compounds **3**. As for the regioselectivity, the γ-substitution takes place in accordance with the existing theory stipulating that 'soft' nucleophiles (including cyanide ion) with high polarizability attack selectively at the 'softest' γ position of the heterocycle.[19–21]

We continued our study using 1,7-phenanthrolin-7-ium salts[22] **4** as substrates for the reaction with ethyl cyanoformate under similar conditions, and we obtained γ-substituted-7,10-dihydro-1,7-phenanthrolines **5**. In this case, derivatives **5** have not undergone the α-oxidation that was observed with the 1,10-phenathrolin-1-ium salts (Scheme 2).



4a. R= -NH_2, X= I
4b. R= -$C_6H_4Me(p)$, X= Br
4c. R= -$C_6H_4Cl(p)$, X= Br

5a. R= -NH_2
5b. R= -$C_6H_4Me(p)$
5c. R= -$C_6H_4Cl(p)$

Scheme 2. Synthesis of 10-cyano-substituted 1,7-phenanthrolines **5**.

Spectral data and X-ray diffraction of compound **5b** confirmed the proposed structure **5**. Interestingly, in the ^1H NMR of compounds **5**, the hydrogen atoms at C-15 showed two strongly coupled doublets induced by the asymmetry of carbon 10. The X-ray structure of compound **5b** (Fig. 2) indicates the following main crystal data: orthorhombic, space group $P2_12_12_1$ (no. 19), a=4.788 Å, b=14.184 Å, c=26.17 Å, V=1777 $Å^3$, Z=4. The crystallographic data shows that in the crystals of this compound a series of C–H···O and C–H···N hydrogen bonds exists but no π–π interactions are present.

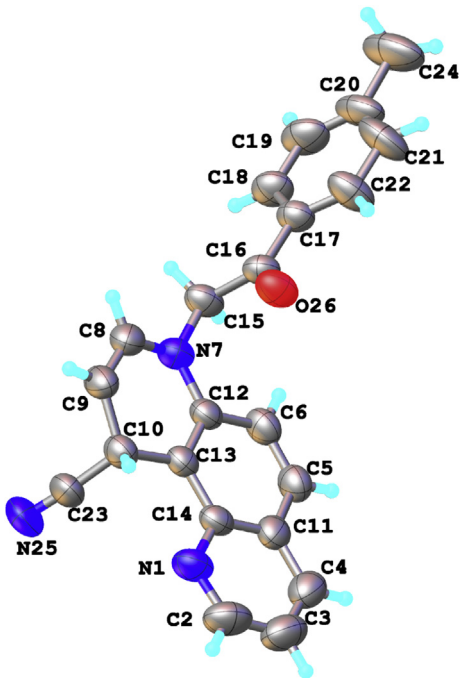


Fig. 2. X-ray crystal structure of compound **5b** with thermal ellipsoids at 50% probability level.

With 4,7-phenanthrolin-4-ium salts[23] **6** treated under similar conditions (Scheme 3), we isolated both γ-cyano-substituted 1,4-dihydro-4,7-phenanthrolines **7**, and 3-oxo-3,4-dihydro-4,7-phenanthrolines **8** (Scheme 3).

We then decided to extend the study to reactions of other cycloimmonium salts under similar conditions. Thus, quinolinium salts[24] **9** underwent similar γ-cyanation and α-oxidation yielding compounds **10a**–**c** and other byproducts (**11**, **12** and **13**) suggesting an instability of the in situ ylides generated from the salts **9** under the reaction conditions (Scheme 4).

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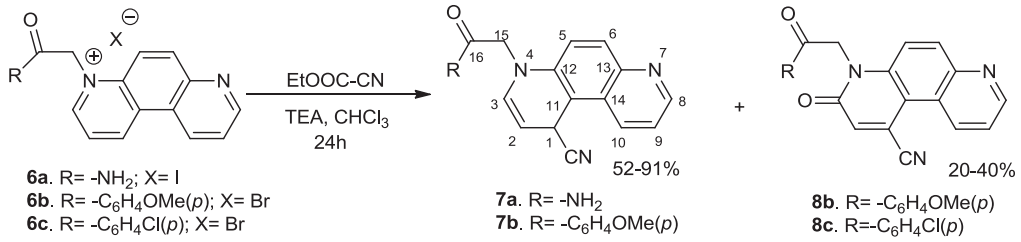
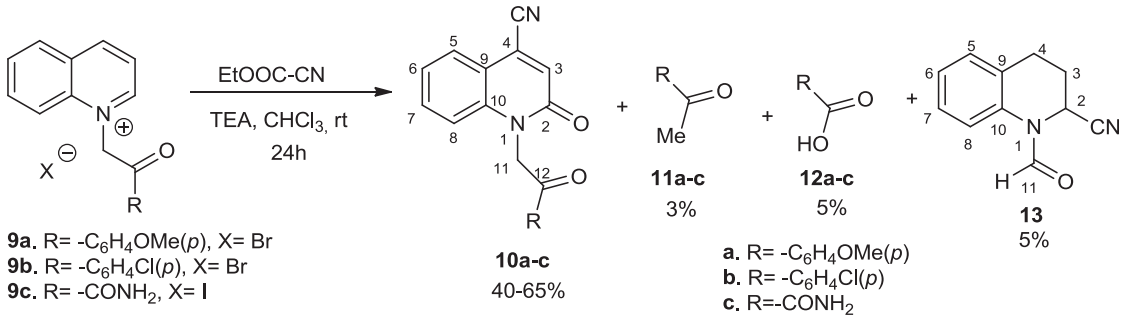


Scheme 3. Synthesis of 1-cyano-substituted 4,7-phenanthrolines **7** and **8**.

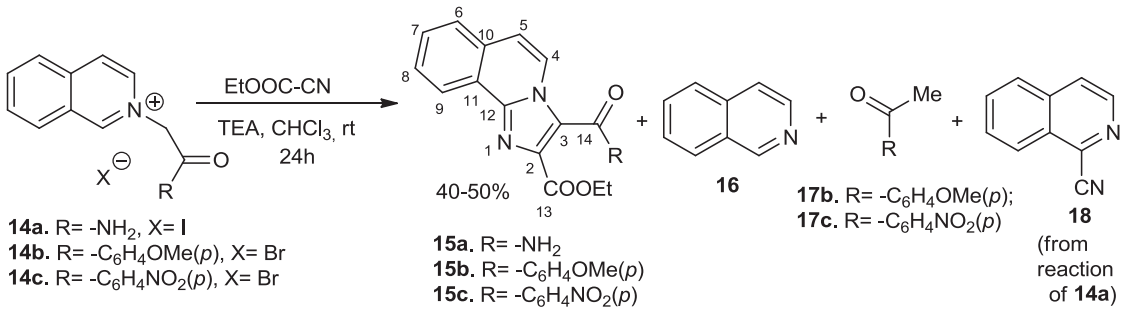


Scheme 4. Synthesis of 4-cyano substituted quinolines **10**.

Interestingly, isoquinolinium salts[25,26] **14** having no available γ-position for cyanation yielded 3+2 cycloadducts **15a**–**c** with imidazo[2,1-*a*]isoquinoline structure together with few decomposition coproducts (**16**, **17**, **18**) (Scheme 5).

dimerization via the [3+3] cycloaddition of the corresponding ylides.[28]

Luckily, we were able to grow a monocrystal of compound **21b** and to investigate the dimeric structure using X-ray diffraction.

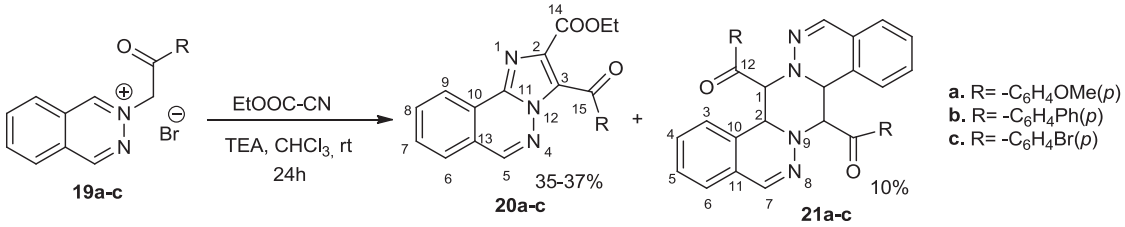


Scheme 5. Synthesis of imidazoisoquinolines **15**.

Finally, we investigated phthalazinium bromides[27] **19a**–**c**, also without an unsubstituted position γ to nitrogen, in similar reaction. As expected, we obtained the imidazo[2,1-*a*]phthalazines **20** as product of 3+2 cycloaddition. As secondary products in the same reaction we isolated compounds **21** with 8,8*a*,16,16*a*-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazine structure (Scheme 6) by

Thus, the X-ray structure of compound **21b** (Fig. 3) indicates the following main crystal data: triclinic, space group P-1 (no. 2), a=10.182 Å, b=13.366 Å, c=13.726 Å, α=67.18°, β=74.71°, γ=82.89°, V=1660 Å^3, Z=2.

The crystallographic data shows that in the crystals of this compound a series of π−π interactions are present as can be seen in Fig. 4.



Scheme 6. Synthesis of imidazophthalazines **20** and 8,8*a*,16,16*a*-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazines **21**.

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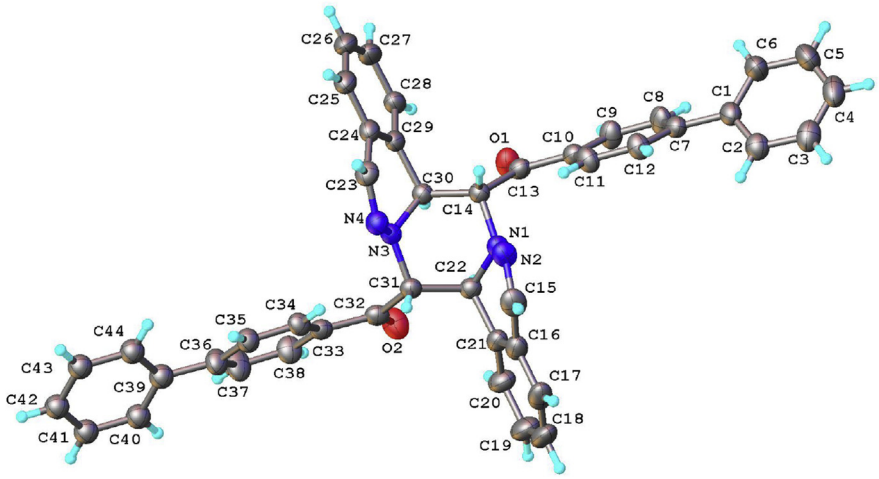


Fig. 3. X-ray crystal structure of compound **21b** with thermal ellipsoids at 50% probability level.

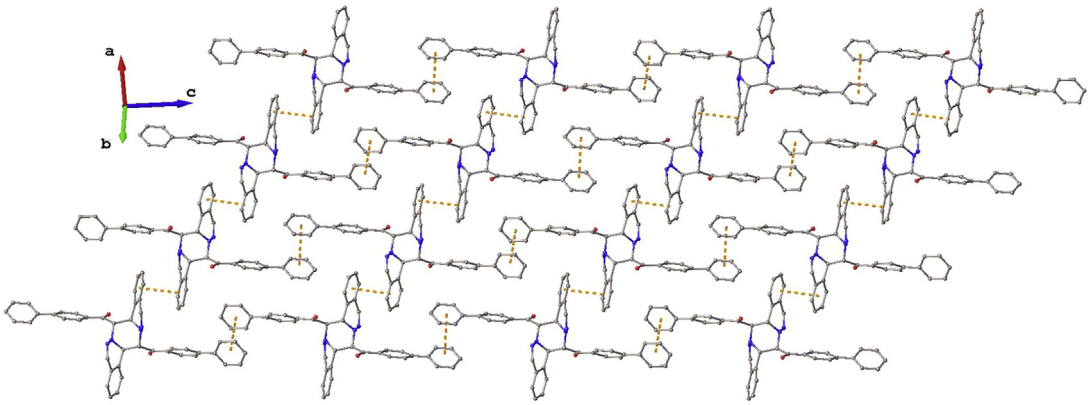
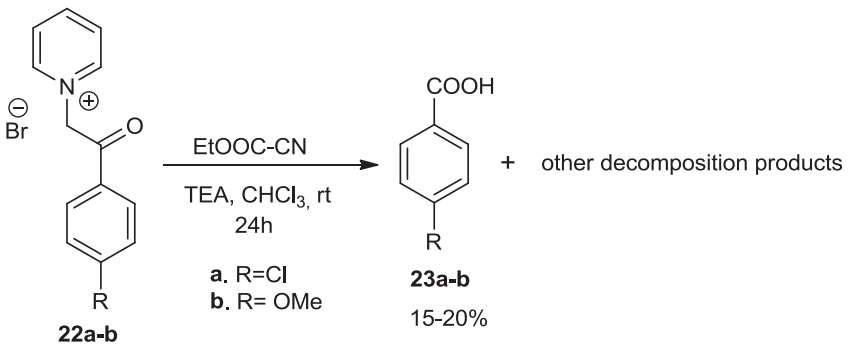


Fig. 4. π–π Interactions in the crystal of compound **21b**.

We also performed similar reactions using two pyridinium salts with unsubstituted pyridine ring **22**, but unfortunately we were able only to isolate and characterize from the reaction mixture the corresponding *para*-substituted benzoic acid **23** (Scheme 7).

of the cycloimmonium ylide and the possible initial formation of the 1,4-dihydropyridine derivative.

In order to explain the different behaviour of reactivity of ethyl cyanoformate in respect with the cycloimmonium ylides, having in



Scheme 7. Reaction of pyridinium salts **22** with ethyl cyanoformate in basic conditions.

Interestingly, Sandeep and collab,[7] synthesized imidazo[1,2-*a*] pyridines by similar reactions using 3- and 4-acetylpyridinium salts. All these observations emphasize the importance of the substituent with electron withdrawing ability on the stabilization

view the above results, we may conclude that the structure of the ylide is determinant for the reaction pathway. Thus, when the γ-position of the ylide is free (canonical structure **c**), a nucleophilic attack of the cyanide ion take place and the substitution product is

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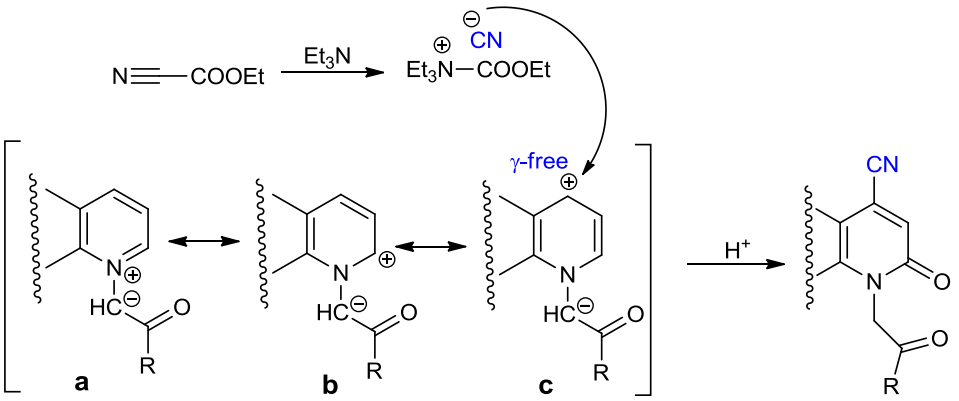
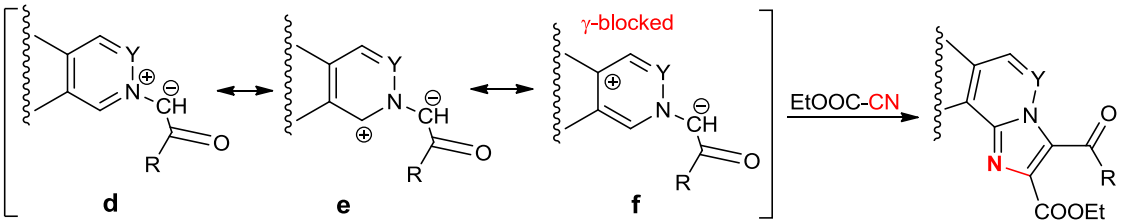
obtained (this is the case of phenanthroline and quinoline derivatives) (Scheme 8).



Scheme 8. The proposed mechanism for the synthesis of γ-cyano substituted azaheterocycles.

When the γ-position of the ylide is not free, the ylide reacts as 1,3-dipole (canonical structure **e**) in a 3+2 dipolar cycloaddition to ethyl cyanoformate, leading to the corresponding fused imidazoazaheterocycles. This is the case of isoquinoline and phthalazine derivatives (Scheme 9).



Scheme 9. The proposed mechanism for the synthesis of the new fused imidazoheterocycles derivatives.

3. Conclusion

Reactions of cycloimmonium salts with ethyl cyanoformate in basic conditions undergo two different pathways depending of the availability of the γ-position of the heterocycle for a nucleophilic cyanation. Thus, for 1,10-phenanthrolin-1-ium salts, 1,7-phenanthrolin-7-ium salts, 4,7-phenanthrolin-4-ium salts and quinolinium salts, ethyl cyanoformate acts as a source of cyanide ion, leading selectively to the corresponding γ-cyano substituted compounds. In case of isoquinolinium and phthalazinium ylides having bridged γ-position, ethyl cyanoformate acts as dipolarophile in 3+2 dipolar cycloaddition, leading to new two classes of compound with imidazo[2,1-*a*]isoquinoline and imidazo[2,1-*a*]phtalazine skeleton, respectively. From the reaction mixtures of phthalazinium ylides with ethyl cyanoformate we isolated as by-products 8,8*a*,16,16*a*-tetrahydropyrazino[2,1-*a*:5,4-*a*′]diphthalazine dimers.

4. Experimental section

4.1. Chemistry

All the reagents and solvents employed were used without further purification. Melting points were recorded on an A. Krüss Optronic Melting Point Meter KSPI and are uncorrected. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on a Bruker Avance 400 DRX (400 MHz), or a DRX-500 Bruker (500 MHz). The following abbreviations were used to designate chemical shift multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. All chemical shifts are quoted on the δ-scale in ppm. Coupling constants are given in Hz. Mass spectra were recorded on a HRMS Thermo Scientific Q Exactive spectrometer using DART in the positive mode; *m*/*z* values are reported in Daltons. IR spectra were recorded on a FTIR Shimadzu or Jasco 660 *plus* FTIR spectrophotometer. The microanalyses were in satisfactory agreement with the calculated values: C, ±0.15; H, ±0.10; N, ±0.30. Thin layer chromatography (TLC) was carried out on Merck silica gel 60F_{254} plates. Column chromatography was carried out on silica gel (Roth 60, 0.04–0.063 mm). Visualization of the plates was achieved using a UV lamp (λ_{max}=254 or 365 nm). All commercially available products were used without further purification unless otherwise specified.

4.2. X-ray crystallography

Crystallographic measurements for **3a**, **5b** and **21b** were carried out on a SuperNova, Dual, Cu at zero, Eos diffractometer. Single crystals of compound **3a**, **5b** and **21b** were obtained by crystallization from chloroform/methanol (1/1, v/v). A suitable crystal was selected and used for the determination of structure using single crystal X-ray diffraction method. The crystal was kept at 294 K during data collection. The unit cell determination and data integration were carried out using the CrysAlisPro package of Oxford Diffraction. Using Olex2,[29] the structure was solved with the ShelXS[29] or ShelXT[30] structure solution program using Direct Methods and refined with the ShelXL[31] refinement package using Least Squares minimization.

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The main crystallographic data together with refinement details are summarized in Tables S1–S22 (ESI). CCDC 1453425 (**3a**), 1454004 (**5b**) and 1471832 (**21b**) contain the full crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.3. Experimental procedure for synthesis of compounds 1, 4, 6, 9, 14, and 19

1,10-Phenanthrolin-1-ium halides **1** were synthesized using the procedure reported in Ref. 18, 1,7-phenanthrolin-7-ium salts **4** using the procedure reported in Ref. 22, 4,7-phenanthrolin-4-ium salts **6** as in Ref. 23, quinolinium salts **9** as in Ref. 24, isoquinolinium salts **14** as in Refs. 25,26 and phthalazinium bromides **19** as in Ref. 27.

4.4. General procedure for synthesis of compounds 3, 5, 7, 8, 10, 15, 20 and 21

The corresponding cycloimmonium salt (1 mmol, 1 equiv) and ethyl cyanoformate (1.1 mmol, 1.1 equiv) were added to 5 mL of dichloromethane and the obtained suspension was stirred under N_2 atmosphere at room temperature (rt). Triethylamine (TEA) (3 mmol, 3 equiv) was added drop-wise over 30 min (magnetic stirring) and the resulting mixture was then stirred for 24 h at room temperature or reflux. Methanol (5 mL) was added and the resulting mixture was kept for 24 h without stirring. In most of the reaction a precipitate formed and it was collected by filtration to give a powder which was washed with few mL methanol. The product was crystallized from an appropriate solvent. For every reaction mixture, parallel, we carried out column chromatography of the reaction mixture in order to identify eventual coproducts.

*4.4.1. 1-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-oxo-1,2-dihydro-1,10-phenanthroline-4-carbonitrile (**3a**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (98/2, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 50% yield; mp=251–253 °C. R_f (CH_2Cl_2) 0.55. IR (KBr), ν(cm^{-1}): 2168, 1655, 1595, 1236. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 3.93 (1H, s, OMe), 6.62 (2H, s, H-15), 7.03 (2H, d, J=8.5 Hz, H-3′), 7.42 (1H, s, H-3), 7.44 (1H, dd, J=8.0, 4.5 Hz, H-8), 7.72 (1H, d, J=8.5 Hz, H-5), 8.04 (3H, m, H-2′, H-6), 8.21 (1H, d, J=8.0 Hz, H-7), 8.38 (1H, s, H-9). ^{13}C NMR (DMSO-d_6 125 MHz, δ(ppm)): 53.6 (C-15), 55.7 (OMe), 114.2 (C-3′), 114.8 (CN), 117.4 (C-12), 123.1 (C-8), 123.5 (C-5), 124.0 (C-2′), 124.3 (C-4), 128.7 (C-1′), 129.2 (C-3), 130.2 (C-6), 130.9 (C-13), 137.7 (C-7, C-14, C-11), 147.34 (C-9), 161.0 (C-2), 163.5 (C-4′), 191.3 (C-16). Anal. Calcd for $C_{22}H_{15}N_3O_3$: C 71.54; H 4.09; N 11.38. Found: C 71.79; H 4.02; N 11.45.

*4.4.2. 1-(2-(4-Chlorophenyl)-2-oxoethyl)-2-oxo-1,2-dihydro-1,10-phenanthroline-4-carbonitrile (**3b**).* Obtained by general procedure at room temperature or reflux. Purified crystallization from $CHCl_3$/MeOH 1/1, v/v. Yellow solid, 45% yield; mp=260–262 °C. R_f (1% MeOH/CH_2Cl_2) 0.72. IR (KBr), ν(cm^{-1}): 3064, 2248, 1694, 1662, 1461, 1407, 994, 840. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 6.62 (2H, s, H-15), 7.43 (1H, s, H-3), 7.44 (1H, dd, J=8.5, 4.0 Hz, H-8), 7.56 (2H, d, J=8.5 Hz, H-3′), 7.73 (1H, d, J=8.5 Hz, H-5), 8.06 (3H, m, H-2′, H-6), 8.20 (1H, dd, J=8.5, 1.5 Hz, H-7), 8.28 (1H, d, J=2.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 53.6 (C-15), 114.9 (CN), 117.4 (C-12), 123.1 (C-8), 123.8 (C-4), 124.1 (C-6), 124.2 (C-5), 128.9 (C-3), 129.3 (C-3′), 129.6 (C-2′), 130.9 (C-13), 134.2 (C-1′), 137.1 (C-7), 137.3 (C-11), 138.4 (C-14), 139.7 (C-4′), 147.5 (C-9), 161.2 (C-2), 191.0 (C-16). Anal. Calcd for $C_{21}H_{12}ClN_3O_2$: C 67.48; H 3.24; N 11.24. Found: C 67.45; H 3.19; N 11.32.

*4.4.3. Methyl 2-(4-cyano-2-oxo-1,10-phenanthrolin-1(2H)-yl) acetate (**3c**).* Obtained by general procedure at reflux. Purified by column chromatography (DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH 1/1, v/v. Yellow solid, 45% yield; mp=189–193 °C. R_f (1% MeOH/CH_2Cl_2) 0.72. IR (KBr), ν(cm^{-1}): 3026, 2924, 2236, 1748, 1667, 1612, 1543, 1462, 1219. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 3.78 (1H, s, OMe), 5.95 (2H, s, H-15), 7.37 (1H, s, H-3), 7.58 (1H, dd, J=8.5, 4.0 Hz, H-8), 7.74 (1H, d, J=9.0 Hz, H-5), 8.02 (1H, d, J=8.5 Hz, H-6), 8.25 (1H, dd, J=8.5, 1.5 Hz, H-7), 8.28 (1H, dd, J=4.0, 1.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 50.3 (C-15), 52.5 (OMe), 114.8 (CN), 117.2 (C-13), 123.2 (C-8), 123.8 (C-4), 123.9 (C-6), 124.3 (C-5), 129.0 (C-3), 131.0 (C-12), 137.8 (C-11), 136.9 (C-7), 139.1 (C-14), 147.9 (C-9), 161.2 (C-2), 169.5 (C-16). Anal. Calcd for $C_{17}H_{11}N_3O_4$: C 63.55; H 3.45; N 13.08. Found: C 63.45; H 3.40; N 13.15.

*4.4.4. 2-(10-Cyano-1,7-phenanthrolin-7(10H)-yl)acetamide (**5a**).* Obtained by general procedure at reflux. Purified by crystallization from $CHCl_3$/MeOH 1/1, v/v. Brown solid, 98% yield; mp=202–205 °C. R_f (1% MeOH/CH_2Cl_2) 0.72. IR (KBr), ν(cm^{-1}): 3387, 3202, 2234, 1670, 1610, 827. ^{1}H NMR (DMSO-d_6, 500 MHz, δ(ppm)): 4.30 (1H, d, J=17.5 Hz, H-15a), 4.40 (1H, d, J=17.5 Hz, H-15b), 4.89 (1H, dd, J=7.5, 5.0 Hz, H-9), 5.75 (1H, d, J=5.0 Hz, H-10), 6.55 (1H, d, J=8.0 Hz, H-8), 7.15 (1H, d, J=9.5 Hz, H-6), 7.25 (1H, s, NH), 7.43 (1H, dd, J=8.0 4.5 Hz, H-3), 7.60 (1H, s, NH), 7.91 (1H, dd, J=9.0 Hz, H-5), 8.27 (1H, d, J=8.0 Hz, H-4), 8.91 (1H, d, J=3.5 Hz, H-2). ^{13}C NMR (DMSO-d_6, 125 MHz, δ(ppm)): 25.5 (C-10), 52.1 (C-15), 92.2 (C-9), 106.7 (CN), 115.0 (C-6), 119.2 (C-3), 120.9 (C-13), 123.2 (C-11), 128.8 (C-5), 135.4 (C-8), 135.8 (C-4), 140.4 (C-12), 145.6 (C-14), 150.6 (C-2), 170.0 (C-16). Anal. Calcd for $C_{15}H_{12}N_4O$: C 68.17; H 4.58; N 21.20. Found: C 68.45; H 4.48; N 21.32.

*4.4.5. 7-(2-(p-Tolyl)ethyl)-7,10-dihydro-1,7-phenanthroline-10-carbonitrile (**5b**).* Obtained by general procedure, at room temperature or reflux. Purified by crystallization from $CHCl_3$/MeOH 1/1, v/v. Brown solid, 40% yield; mp=197–200 °C. R_f (1% MeOH/CH_2Cl_2) 0.76. IR (KBr), ν(cm^{-1}): 2227, 1681, 1604, 1226, 1177, 796. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 2.46 (1H, s, Me), 4.89 (1H, d, J=18.5 Hz, H-15a), 5.06 (1H, dd, J=7.5, 5.5 Hz, H-9), 5.27 (1H, d, J=18.5 Hz, H-15b), 6.00 (1H, s, H-10), 6.29 (1H, d, J=8.0 Hz, H-8), 6.84 (1H, d, J=9.0 Hz, H-6), 7.35 (2H, d, J=8.0 Hz, H-3′), 7.38 (1H, dd, J=8.0, 3.0 Hz, H-3), 7.65 (1H, d, J=9.0 Hz, H-5), 7.93 (2H, d, J=8 Hz, H-2′), 8.07 (1H, d, J=8.0 Hz, H-4), 8.95 (1H, d, J=3.0 Hz, H-2). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 22.0 (Me), 26.0 (C-10), 56.4 (C-15), 94.8 (C-9), 106.5 (CN), 114.8 (C-6), 119.3 (C-3), 120.7 (C-13), 124.2 (C-11), 128.2 (C-2′), 129.1 (C-5), 130.0 (C-3′), 132.0 (C-1′), 134.7 (C-8, C-4), 140.9 (C-12), 145.7 (C-4′, C-14), 150.2 (C-2), 193.3 (C-16). Anal. Calcd for $C_{22}H_{17}N_3O$: C 77.86; H 5.05; N 12.38. Found: C 77.90; H 5.00; N 12.41.

*4.4.6. 7-(2-(4-Chlorophenyl)-2-oxoethyl)-7,10-dihydro-1,7-phenanthroline-10-carbonitrile (**5c**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 55% yield; mp=191–193 °C. R_f (1% MeOH/CH_2Cl_2) 0.72. IR (KBr), ν(cm^{-1}): 2230, 1688, 1222, 1089, 824. ^{1}H NMR (DMSO-d_6, 500 MHz, δ(ppm)): 4.94 (1H, dd, J=8.0, 4.5 Hz, H-9), 5.42 (1H, d, J=19.5 Hz, H-15a), 5.59 (1H, d, J=19 Hz, H-15b), 5.80 (1H, d, J=4.5 Hz, H-10), 6.56 (1H, d, J=7.5 Hz, H-8), 7.20 (1H, d, J=9.5 Hz, H-6), 7.43 (1H, dd, J=7.5, 4.0 Hz, H-3), 7.69 (2H, d, J=8.0 Hz, H-19), 7.82 (1H, dd, J=9.0 Hz, H-5), 8.08 (2H, d, J=8 Hz, H-18), 8.26 (1H, d, J=8.5 Hz, H-4), 8.92 (1H, d, J=2.5 Hz, H-2). ^{13}C NMR (DMSO-d_6, 125 MHz, δ(ppm)): 25.3 (C-10),

55.9 (C-15), 92.8 (C-9), 106.7 (CN), 115.6 (C-6), 119.2 (C-3), 120.9 (C-13), 123.3 (C-11), 128.7 (C-5), 129.0 (C-3′), 130.0 (C-2′), 133.4 (C-1′), 135.0 (C-8), 135.8 (C-4), 138.8 (C-4′), 140.5 (C-12), 145.6 (C-14), 150.5 (C-2), 194.2 (C-16). Anal. Calcd for $C_{21}H_{14}ClN_3O$: C 70.10; H 3.92; N 11.68. Found: C 70.08; H 3.88; N 11.72.

*4.4.7. 2-(1-Cyano-4,7-phenanthrolin-4(1H)-yl)acetamide (**7a**).* Obtained by general procedure at reflux. Purified by crystallization from $CHCl_3$/MeOH 1/1, v/v. Yellow solid, 91% yield; mp=244–245 °C. R_f (1% MeOH/CH_2Cl_2) 0.76. IR (KBr), ν(cm^{-1}): 3341, 3168, 3055, 2193, 1675, 1673, 1503, 795. ^{1}H NMR (DMSO-d_6, 500 MHz, δ(ppm)): 4.30 (1H, d, J=17.5 Hz, H-15a), 4.41 (1H, d, J=17.5 Hz, H-15b), 4.82 (1H, dd, J=7.5, 4.5 Hz, H-2), 5.80 (1H, d, J=4.5 Hz, H-1), 6.57 (1H, d, J=8.0 Hz, H-3), 7.26 (1H, s, NH), 7.30 (1H, d, J=9.5 Hz, H-5), 7.60 (2H, m, H-9, NH), 8.33 (1H, d, J=8.5 Hz, H-6), 8.33 (1H, d, J=7.5 Hz, H-10), 8.78 (1H, d, J=4.0 Hz, H-8). ^{13}C NMR (DMSO-d_6, 125 MHz, δ(ppm)): 25.9 (C-1), 52.2 (C-15), 90.4 (C-2), 104.7 (CN), 118.0 (C-5), 120.1 (C-11), 122.2 (C-9), 126.3 (C-14), 129.8 (C-10), 130.3 (C-6), 135.7 (C-3), 137.7 (C-12), 144.2 (C-8), 147.6 (C-13), 170.0 (C-16). Anal. Calcd for $C_{15}H_{12}N_4O$: C 68.17; H 4.58; N 21.20. Found: C 68.19; H 4.51; N 21.24.

*4.4.8. 4-(2-(4-Methoxyphenyl)-2-oxoethyl)-1,4-dihydro-4,7-phenanthroline-1-carbonitrile (**7c**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 52% yield; mp=157–160 °C. R_f (CH_2Cl_2) 0.71. IR (KBr), ν(cm^{-1}): 2167, 1674, 1601, 1237, 1176, 829. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 3.91(3H, s, OMe), 4.85 (1H, d, J=17.5 Hz, H-15a), 4.96 (1H, dd, J=7.5, 5.0 Hz, H-2), 5.27 (1H, d, J=17.5 Hz, H-15b), 5.51 (1H, d, J=5.0 Hz, H-1), 6.32 (1H, d, J=7.5 Hz, H-3), 7.03 (3H, ad, J=9.5 Hz, H-3′, H-5), 7.50 (1H, dd, J=8.5, 4.5 Hz, H-9), 7.96 (1H, d, J=9.0 Hz, H-6), 8.01 (2H, d, J=9.0 Hz, H-2′), 8.19 (1H, d, J=9.0 Hz, H-10), 8.82 (1H, dd, J=4.0, 1.0 Hz, H-8). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 26.9 (C-1), 55.8 (OMe), 56.2 (C-15), 92.0 (C-2), 105.3 (CN), 114.5 (C-3′), 117.4 (C-5), 119.5 (C-11), 122.5 (C-9), 127.0 (C-14), 127.5 (C-1′), 129.6 (C-10), 131.6 (C-6), 130.5 (C-2′), 135.1 (C-3), 137.7 (C-12), 145.1 (C-13), 148.1 (C-8), 164.6 (C-4′)192.1 (C-16). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C 74.35; H 4.82; N 11.82. Found: C 74.38; H 4.80; N 11.88.

*4.4.9. 4-(2-(4-Methoxyphenyl)-2-oxoethyl)-3-oxo-3,4-dihydro-4,7-phenanthroline-1-carbonitrile (**8b**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 20% yield; mp=284–285 °C. R_f (1% MeOH/CH_2Cl_2) 0.51. IR (KBr), ν(cm^{-1}): 3028, 2814, 2224, 1688, 1661, 1601, 1505, 1238, 1182, 837. ^{1}H NMR (DMSO-d_6, 500 MHz, δ(ppm)): 3.90 (3H, s, OMe), 6.12 (2H, s, H-15), 7.16 (2H, d, J=9.0 Hz, H-3′), 7.69 (1H, s, H-2), 7.85 (1H, dd, J=8.5, 4.0 Hz, H-9), 7.97 (1H, d, J=9.5 Hz, H-5), 8.15 (2H, d, J=8.5 Hz, H-2′), 8.26 (1H, d, J=10.0 Hz, H-6), 9.00 (1H, dd, J=4.5, 1.0 Hz, H-8), 9.68 (1H, d, J=8.5 Hz, H-10). ^{13}C NMR (DMSO-d_6, 125 MHz, δ(ppm)): 50.1 (C-15), 55.8 (OMe), 109.7 (C-11), 114.2 (C-3′), 117.9 (C-1), 119.5 (CN), 120.0 (C-5), 123.0 (C-9), 123.7 (C-14), 127.3 (C-1′), 130.5 (C-10), 130.6 (C-2), 130.8 (C-2′), 134.6 (C-6), 140.5 (C-12), 144.0 (C-13), 150.0 (C-8), 158.8 (C-3), 164.0 (C-4′), 190.7 (C-16). Anal. Calcd for $C_{22}H_{15}N_3O3$: C 71.54; H 4.09; N 11.38. Found: C 71.52; H 4.01; N 11.42.

*4.4.10. 4-(2-(4-Chlorophenyl)-2-oxoethyl)-3-oxo-3,4-dihydro-4,7-phenanthroline-1-carbonitrile (**8c**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 40% yield; mp=282–283 °C. R_f (1% MeOH/CH_2Cl_2) 0.51. IR (KBr), ν(cm^{-1}): 3016, 2918, 2309, 1691, 1649, 1504, 1231, 1096, 818. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 5.97 (2H, s, H-15), 7.41 (1H, d, J=9.5 Hz, H-5), 7.44 (1H, s, H-2), 7.57 (2H, d, J=8.5 Hz, H-3′), 7.67 (1H, dd, J=8.5, 4.0 Hz, H-9), 8.05 (2H, d, J=8.5 Hz, H-2′), 8.29 (1H, d, J=9.5 Hz, H-6), 9.00 (1H, d, J=3.5 Hz, H-8), 9.82 (1H, d, J=9.0 Hz, H-10). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 49.9 (C-15), 110.9 (C-11), 117.9 (C-1), 118.3 (C-5), 120.6 (CN), 123.4 (C-9), 124.8 (C-14), 129.7 (C-2′), 129.8 (C-3′), 131.0 (C-10), 131.1 (C-2), 132.7 (C-1′), 135.9 (C-6), 140.4 (C-12), 141.5 (C-4′), 144.8 (C-13), 150.3 (C-8), 159.3 (C-3), 190.1 (C-16). Anal. Calcd for $C_{21}H_{12}ClN_3O_2$: C 67.48; H 3.24; N 11.24. Found: C 67.51; H 3.20; N 11.29.

*4.4.11. 1-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-oxo-1,2-dihydroquinoline-4-carbonitrile (**10a**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 40% yield; mp=195–197 °C. R_f (1% MeOH/CH_2Cl_2) 0.58. IR (KBr), ν(cm^{-1}): 2924, 2309, 1680, 1659, 1601, 1265, 1240, 1175. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 3.92 (3H, s, OMe), 5.77 (2H, s, H-11), 7.02 (2H, d, J=8.5 Hz, H-3′), 7.05 (1H, d, J=8.5 Hz, H-5), 7.20 (1H, s, H-3), 7.37 (1H, t, J=7.5 Hz, H-7), 7.59 (1H, dt, J=7.5, 1.0 Hz, H-6), 7.98 (1H, dd, J=8.0, 1.0 Hz, H-8), 8.06 (2H, d, J=8.5 Hz, H-2′). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 48.8 (C-11), 55.8 (OMe), 114.4 (C-3′), 114.7 (CN), 115.0 (C-5), 117.5 (C-9), 123.7 (C-7, C-4), 127.2 (C-8), 127.7 (C-1′), 128.5 (C-3), 130.7 (C-2′), 132.8 (C-6), 139.9 (C-10), 160.0 (C-2), 164.6 (C-4′), 189.7 (C-12). Anal. Calcd for $C_{19}H_{14}N_2O_3$: C 71.69; H 4.43; N 8.80. Found: C 71.65; H 4.40; N 8.88.

*4.4.12. 1-(2-(4-Chlorophenyl)-2-oxoethyl)-2-oxo-1,2-dihydroquinoline-4-carbonitrile (**10b**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Pale yellow solid, 40% yield; mp=145–146 °C. R_f (1% MeOH/CH_2Cl_2) 0.61. IR (KBr), ν(cm^{-1}): 2922, 2308, 1692, 1651, 1589, 1230, 1094, 991, 752. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 5.76 (2H, s, H-11), 7.03 (1H, d, J=8.5 Hz, H-5), 7.20 (1H, s, H-3), 7.39 (1H, t, J=7.5 Hz, H-7), 7.54 (2H, d, J=8.5 Hz, H-3′), 7.60 (1H, t, J=7.5 Hz, H-6), 7.99 (1H, d, J=8.0 Hz, H-8), 8.02 (2H, d, J=8.0 Hz, H-2′). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 49.1 (C-11), 114.5 (CN), 114.8 (C-5), 117.6 (C-9), 123.8 (C-7, C-4), 127.3 (C-8), 128.4 (C-3), 129.6 (C-2′), 129.7 (C-3′), 132.9 (C-6, C-1′), 139.7 (C-10), 141.2 (C-4′), 159.9 (C-2), 190.4 (C-12). Anal. Calcd for $C_{18}H_{11}ClN_2O_2$: C 66.99; H 3.44; N 8.68. Found: C 67.01; H 3.40; N 8.78.

*4.4.13. 2-(4-Cyano-2-oxoquinolin-1(2H)-yl)acetamide (**10c**).* Obtained by general procedure at reflux. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 65% yield; mp=249–251 °C. R_f (1% MeOH/CH_2Cl_2) 0.60. IR (KBr), ν(cm^{-1}): 3393, 3192, 2918, 2849, 2236, 1678, 1657, 1593, 1422, 1292, 891. ^{1}H NMR (DMSO-d_6, 500 MHz, δ(ppm)): 4.90 (2H, s, H-11), 7.33 (1H, s, NH), 7.42–7.48 (2H, m, H-5, H-7), 7.48 (1H, s, H-3), 7.70 (1H, s, NH), 7.75 (1H, t, J=8.5 Hz, H-6), 7.85 (1H, d, J=8.0 Hz, H-8). ^{13}C NMR (DMSO-d_6, 125 MHz, δ(ppm)): 44.9 (C-11), 114.6 (CN), 115.6 (C-5), 116.5 (C-4), 122.0 (C-9), 123.4 (C-7), 125.8 (C-8), 129.1 (C-3), 132.6 (C-6), 139.7 (C-10), 159.2 (C-2), 168.1 (C-12). Anal. Calcd for $C_{12}H_9ClN_3O_2$: C 63.43; H 3.99; N 18.49. Found: C 63.40; H 3.96; N 18.52.

*4.4.14. 1-Formyl-1,2,3,4-tetrahydroquinoline-2-carbonitrile (**13**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Brown solid, ~5% yield; mp=189–190 °C. R_f(CH_2Cl_2) 0.62. IR (KBr), ν(cm^{-1}): 2928, 2245, 1680, 1649, 1586, 1495, 1259, 764. ^{1}H NMR

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($CDCl_3$, 500 MHz, δ(ppm)): 2.12–2.16 (1H, m, H-3a), 2.24–2.28 (1H, m, H-3b), 2.80–2.85 (1H, m, H-4a), 3.05–3.11 (1H, m, H-4b), 5.61 (2H, d, *J*=5.0 Hz, H-2), 8.72 (1H, s, H-11). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 24.2 (C-4), 26.1 (C-3), 39.8 (C-2), 117.0 (CN), 117.7 (C-8), 126.0 (C-7), 126.9 (C-9), 128.1 (C-6), 130.1 (C-5), 134.4 (C-10), 160.3 (C-11). MS ($DART^+$) (*m*/*z*): 187.09 ($M+H^+$). HRMS (DART+) calcd for $C_{11}H_{11}N_2O$ (MH^+) 187.0871. Found: 187.0874.

*4.4.15. Ethyl 3-carbamoylimidazo[2,1-a]isoquinoline-2-carboxylate (**15a**).* Obtained by general procedure, at reflux. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Beige solid, 50% yield; mp=250–253 °C. R_f (1% MeOH/CH_2Cl_2) 0.54. IR (KBr), ν(cm^{-1}): 3290, 3142, 2916, 2848, 1700, 1683, 1607, 1366, 1232. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 1.08 (3H, t, *J*=7.0 Hz, CH_2CH_3), 4.03 (2H, q, *J*=7.0 Hz, CH_2CH_3), 5.86 (1H, NH), 7.28 (1H, d, *J*=7.5 Hz, H-5), 7.69 (2H, m, H-7, H-8), 7.78 (1H, dd, *J*=8.5, 3.0 Hz, H-6), 8.79 (1H, dd, *J*=8.5, 3.0 Hz, H-9), 9.60 (1H, d, *J*=7.5 Hz, H-4), 10.02 (1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 13.9 (CH_2CH_3), 61.8 (CH_2CH_3), 116.0 (C-5), 122.9 (C-2), 123.1 (C-11), 124.7 (C-9), 125.3 (C-4), 127.0 (C-6), 128.7 (C-8), 130.3 (C-7), 130.6 (C-10), 134.6 (C-3), 144.2 (C-12), 161.6 (C-14), 166.1 (C-13). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C 63.60; H 4.63; N 14.83. Found: C 63.56; H 4.60; N 14.86.

*4.4.16. Ethyl 3-(4-methoxybenzoyl)imidazo[2,1-a]isoquinoline-2-carboxylate (**15b**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (97/3, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 40% yield; mp=137–140 °C. R_f (1% MeOH/CH_2Cl_2) 0.78. IR (KBr), ν(cm^{-1}): 2922, 1730, 1628, 1591, 1504, 1323, 1251, 1177, 1028. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 0.98 (3H, t, *J*=7.0 Hz, CH_2CH_3), 3.87 (3H, s, OMe), 4.04 (2H, q, *J*=7.0 Hz, CH_2CH_3), 6.94 (2H, d, *J*=8.5 Hz, H-3′), 7.24 (1H, d, *J*=7.5 Hz, H-5), 7.67–7.71 (2H, m, H-7, H-8), 7.75 (1H, dd, *J*=7.0, 2.0 Hz, H-6), 7.87 (2H, d, *J*=8.5 Hz, H-2′), 8.42 (1H, d, *J*=7.0 Hz, H-4), 8.60 (1H, dd, *J*=7.0, 1.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 13.8 (CH_2CH_3), 55.7 (OMe), 61.7 (CH_2CH_3), 114.0 (C-3′), 116.0 (C-5), 122.9 (C-4), 123.2 (C-11), 124.8 (C-9), 125.88 (C-2), 127.1 (C-6), 128.9 (C-8), 130.2 (C-7), 130.6 (C-10), 131.8 (C-2′), 132.0 (C-1′), 137.9 (C-3), 144.3 (C-12), 162.9 (C-13), 164.2 (C-4′), 185.6 (C-14). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C 70.58; H 4.85; N 7.48. Found: C 70.55; H 4.81; N 7.51.

*4.4.17. Ethyl 3-(4-nitrobenzoyl)imidazo[2,1-a]isoquinoline-2-carboxylate (**15c**).* Obtained by general procedure, at room temperature. Purified by crystallization from $CHCl_3$/MeOH, 1/1, v/v. Brown solid, 45% yield; mp=184–186 °C. R_f (CH_2Cl_2) 0.55. IR (KBr), ν(cm^{-1}): 3034, 1732, 1643, 1520, 1344, 1321, 1215, 1200, 938, 787. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 1.08 (3H, t, *J*=7.0 Hz, CH_2CH_3), 4.02 (2H, q, *J*=7.0 Hz, CH_2CH_3), 7.39 (1H, d, *J*=7.0 Hz, H-5), 7.75–7.77 (2H, m, H-7, H-8), 7.84 (1H, dd, *J*=7.0, 2.5 Hz, H-6), 8.01 (2H, d, *J*=8.5 Hz, H-2′), 8.34 (2H, d, *J*=8.5 Hz, H-3′), 8.64 (1H, d, *J*=7.5 Hz, H-4), 8.88 (1H, dd, *J*=7.0, 1.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 14.0 (CH_2CH_3), 62.2 (CH_2CH_3), 117.0 (C-5), 123.1 (C-4, C-11), 123.9 (C-3′), 124.6 (C-2), 125.1 (C-9), 127.2 (C-6), 129.3 (C-8), 130.0 (C-2′), 130.8 (C-7), 131.0 (C-10), 141.0 (C-3), 144.6 (C-1′), 145.4 (C-12), 150.3 (C-4′), 162.6 (C-13), 185.2 (C-14). Anal. Calcd for $C_{21}H_{15}N_3O_5$: C 64.78; H 3.88; N 10.79. Found: C 64.81; H 3.85; N 10.82.

*4.4.18. Ethyl 3-(4-methoxybenzoyl)imidazo[2,1-a]phthalazine-2-carboxylate (**20a**).* Obtained by general procedure, at room temperature or reflux. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 35% yield; mp=168–170 °C. R_f (CH_2Cl_2) 0.60. IR (KBr), ν(cm^{-1}): 2994, 1703, 1661, 1595, 1317, 1255, 1180. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 1.11 (3H, t, *J*=7.0 Hz, CH_2CH_3), 3.83 (3H, s, OMe), 4.27 (2H, q, *J*=7.0 Hz, CH_2CH_3), 6.95 (2H, d, *J*=8.5 Hz, H-3′), 7.84 (1H, t, *J*=7.5 Hz, H-7), 7.89 (2H, d, *J*=8.5 Hz, H-2′), 7.94 (1H, d, *J*=8.0 Hz, H-6), 8.00 (1H, t, *J*=7.5 Hz, H-8), 8.73 (1H, s, H-5), 8.96 (1H, d, *J*=8.0 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 14.0 (CH_2CH_3), 55.8 (OMe), 61.8 (CH_2CH_3), 114.3 (C-3′), 123.6 (C-13), 124.2 (C-9), 125.0 (C-10), 128.2 (C-6), 130.4 (C-2), 130.7 (C-1′), 131.0 (C-7), 131.6 (C-3), 132.4 (C-2′), 134.2 (C-8), 137.1 (C-11), 148.3 (C-5), 161.7 (C-14), 164.8 (C-4′), 184.9 (C-15). Anal. Calcd for $C_{21}H_{17}N_3O_4$: C 67.19; H 4.56; N 11.19. Found: C 67.15; H 4.49; N 11.21.

*4.4.19. Ethyl 3-([1,1′-biphenyl]-4-carbonyl)imidazo[2,1-a]phthalazine-2-carboxylate (**20b**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 37% yield; mp=180–182 °C. R_f (CH_2Cl_2) 0.60. IR (KBr), ν(cm^{-1}): 3030, 1722, 1657, 1603, 1526, 1219, 1184, 743. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 1.07 (3H, t, *J*=7.0 Hz, CH_2CH_3), 4.24 (2H, q, *J*=7.0 Hz, CH_2CH_3), 7.40 (1H, t, *J*=7.5 Hz, H-4″), 7.46 (2H, t, *J*=7.5 Hz, H-3″), 7.62 (2H, d, *J*=7.5 Hz, H-2″), 7.70 (2H, d, *J*=9.0 Hz, H-3′), 7.82 (1H, t, *J*=7.5 Hz, H-7), 7.94 (1H, d, *J*=7.5 Hz, H-6), 7.96–8.00 (3H, m, H-2′, H-8), 8.73 (1H, s, H-5), 8.84 (1H, d, *J*=8.0 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 13.9 (CH_2CH_3), 61.7 (CH_2CH_3), 123.5 (C-13), 123.7 (C-9), 124.5 (C-2″), 125.4 (C-10), 127.5 (C-3′), 128.2 (C-6), 128.6 (C-4″), 129.1 (C-3″), 130.3 (C-2), 130.4 (C-2′), 130.7 (C-7), 132.7 (C-3), 134.1 (C-8), 136.1 (C-1′), 137.4 (C-11), 139.7 (C-1″), 147.0 (C-4′), 148.2 (C-5), 162.1 (C-14), 186.3 (C-15). Anal. Calcd for $C_{26}H_{19}N_3O_3$: C 74.10; H 4.54; N 9.97. Found: C 74.06; H 4.46; N 10.01.

*4.4.20. Ethyl 3-(4-bromobenzoyl)imidazo[2,1-a]phthalazine-2-carboxylate (**20c**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 35% yield; mp=243–245 °C. R_f (1% MeOH/CH_2Cl_2) 0.62. IR (KBr), ν(cm^{-1}): 2986, 1735, 1660, 1583, 1525, 1212, 1175, 754. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 1.11 (3H, t, *J*=7.0 Hz, CH_2CH_3), 4.25 (2H, q, *J*=7.0 Hz, CH_2CH_3), 7.62 (2H, d, *J*=8.5 Hz, H-3′), 7.78 (2H, d, *J*=8.5 Hz, H-2′), 7.82 (1H, t, *J*=7.5 Hz, H-7), 7.94 (1H, d, *J*=8.0 Hz, H-6), 7.98 (1H, t, *J*=7.5 Hz, H-8), 8.72 (1H, s, H-5), 8.82 (1H, d, *J*=8.0 Hz, H-9). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 13.9 (CH_2CH_3), 61.8 (CH_2CH_3), 123.5 (C-13), 123.7 (C-9), 125.4 (C-10), 128.2 (C-6), 129.7 (C-4′), 130.2 (C-2), 130.8 (C-7), 131.2 (C-2′), 132.3 (C-3′), 133.1 (C-3), 134.1 (C-8), 136.2 (C-1′), 137.6 (C-11), 148.2 (C-5), 162.0 (C-14), 185.8 (C-15). Anal. Calcd for $C_{20}H_{14}BrN_3O_3$: C 56.62; H 3.33; N 9.90. Found: C 56.60; H 3.27; N 9.93.

*4.4.21. (8,8a,16,16a-Tetrahydropyrazino[2,1-a:5,4-a′]diphthalazine-8,16-diyl)bis((4-methoxyphenyl)methanone) (**21a**).* Obtained by general procedure, at room temperature or reflux. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Pale orange solid, 10% yield; mp=269–270 °C. R_f (CH_2Cl_2) 0.58. IR (KBr), ν(cm^{-1}): 2924, 2837, 1678, 1603, 1510, 1254, 1082, 1030, 829, 768. ^{1}H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 3.79 (3H, s, OMe), 5.39 (1H, d, *J*=9.5 Hz, H-2), 5.44 (1H, d, *J*=9.5 Hz, H-1), 6.83 (2H, d, *J*=8.5 Hz, H-3′), 7.09 (1H, d, *J*=8.0 Hz, H-3), 7.13–7.20 (3H, m, H-4, H-5, H-6), 7.64 (1H, s, H-7), 8.03 (2H, d, *J*=8.5 Hz, H-2′). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 48.3 (C-2), 55.6 (OMe), 66.1 (C-1), 113.7 (C-3′), 124.8 (C-10), 125.0 (C-6), 127.0 (C-3), 128.4 (C-5), 128.9 (C-1′), 130.7 (C-11), 131.1 (C-4), 132.0 (C-2′), 138.7 (C-7), 163.8 (C-4′), 193.2 (C-12). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C 73.37; H 5.07; N 10.07. Found: C 73.35; H 4.99; N 10.10. MS ($DART^+$) (*m*/*z*): 279 (100), 557 ($M+H^+$).

*4.4.22. 8,8a,16,16a-tetrahydropyrazino[2,1-a:5,4-a′]diphthalazine-8,16-diyl)bis([1,1′-biphenyl]-4-ylmethanone (**21b**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 10%

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yield; mp=269–271 °C. R_f (1% MeOH/CH_2Cl_2) 0.78. IR (KBr), ν(cm^{-1}): 3019, 2928, 1686, 1602, 1189, 1079, 760. ^1H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 5.36 (1H, d, J=9.5 Hz, H-2), 5.44 (1H, d, J=9.5 Hz, H-1), 7.06 (1H, d, J=6.5 Hz, H-3), 7.09 (1H, d, J=7.5 Hz, H-6), 7.13–7.15 (2H, m, H-4, H-5), 7.29 (1H, t, J=7.0 Hz, H-4″), 7.29 (2H, t, J=7.5 Hz, H-3″), 7.47 (2H, d, J=7.5 Hz, H-2″), 7.51 (2H, d, J=8.5 Hz, H-3′), 7.62 (1H, s, H-7), 8.07 (2H, d, J=8.0 Hz, H-2′). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 48.2 (C-2), 66.4 (C-1), 124.8 (C-10), 125.2 (C-6), 127.0 (C-3), 127.3 (C-3′), 127.4 (C-2″), 128.3 (C-4″), 128.5 (C-5), 129.0 (C-3″), 130.2 (C-2′), 130.8 (C-4), 131.0 (C-11), 134.5 (C-1′), 139.1 (C-7), 140.0 (C-1″), 146.2 (C-4′), 194.1 (C-12). Anal. Calcd for $C_{22}H_{16}N_2O$: C 81.46; H 4.97; N 8.64. Found: C 81.43; H 4.94; N 8.67. MS (DART$^+$) (m/z): 325 (100), 649 (M+H$^+$).

*4.4.23. 8,8a,16,16a-tetrahydropyrazino[2,1-a:5,4-a′]diphthalazine-8,16-diyl)bis((4-bromophenyl)methanone (**21c**).* Obtained by general procedure, at room temperature. Purified by column chromatography (dichloromethane (DCM)→DCM/MeOH (99/1, v/v)), then crystallized from $CHCl_3$/MeOH, 1/1, v/v. Yellow solid, 10% yield; mp=258–260 °C. R_f (1% MeOH/CH_2Cl_2) 0.56. IR (KBr), ν(cm^{-1}): 1681, 1585, 1211, 775. ^1H NMR ($CDCl_3$, 500 MHz, δ(ppm)): 5.31 (1H, d, J=10.0 Hz, H-2), 5.38 (1H, d, J=10.0 Hz, H-1), 7.09 (1H, dd, J=7.0, 1.5 Hz, H-3), 7.09 (1H, dd, J=6.5, 2.0 Hz, H-6), 7.20–7.24 (2H, m, H-4, H-5), 7.50 (2H, d, J=8.5 Hz, H-3′), 7.67 (1H, s, H-7), 7.92 (2H, d, J=8.5 Hz, H-2′). ^{13}C NMR ($CDCl_3$, 125 MHz, δ(ppm)): 48.0 (C-2), 66.3 (C-1), 124.6 (C-10), 125.3 (C-6), 127.0 (C-3), 128.7 (C-5), 128.9 (C-4′), 130.8 (C-11), 131.0 (C-4), 131.2 (C-2′), 131.9 (C-3′), 134.4 (C-1′), 139.4 (C-7), 193.6 (C-12). Anal. Calcd for $C_{16}H_{11}BrN_2O$: C 58.74; H 3.39; N 8.56. Found: C 58.71; H 3.35; N 8.60. MS (DART$^+$) (m/z): 327 (100), 653 (M+H$^+$).

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Supplementary data

Supplementary data (Tables S1–S22 (Crystallographic data and refinement details of compounds **3a**, **5b** and **21b**), (Figures S1–S14 (Copies of ^1H and ^{13}C NMR spectra of compounds **3a**, **5c**, **7b**, **10a**, **15c**, **20a** and **21a**))) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.05.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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