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Studies on the interactions of 5-*R*-3-(2-pyridyl)-1,2,4-triazines with arynes: inverse demand aza-Diels–Alder reaction *versus* aryne-mediated domino process†

Dmitry S. Kopchuk,[a,b] Igor L. Nikonov,[a] Albert F. Khasanov,[a] Kousik Giri,[c] Sougata Santra, *[a] Igor S. Kovalev,[a] Emiliya V. Nosova,[a,b] Sravya Gundala,[a] Padmavathi Venkatapuram,[d] Grigory V. Zyryanov,[a,b] Adinath Majee [e] and Oleg N. Chupakhin [a,b]

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The interactions between substituted 5-*R*-3-(pyridyl-2)-1,2,4-triazines with *in situ* generated substituted aryne intermediates have been studied. The reaction afforded either inverse demand (ID) aza-Diels–Alder products or 1,2,4-triazine ring rearrangement (domino) products as major ones depending on the nature of both the substituents at the C5 position of the 1,2,4-triazine core or in the aryne moiety. The structures of the key products were confirmed based on X-ray data. Based on the density functional theoretical (DFT) studies of the Diels–Alder transition state geometries, the influence of the nature of arynes on the direction of the 1,2,4-triazine transformation has been proposed.

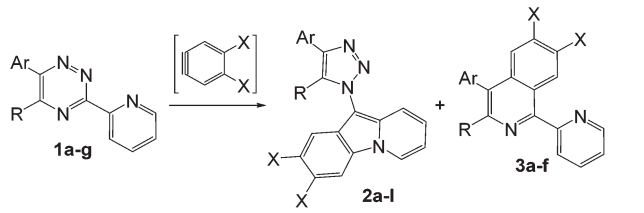
Introduction

The *in situ* generated aryne intermediates have been attracting attention in synthetic organic chemistry, including total synthesis[1] and chemistry of materials[2] since their discovery more than a century ago.[3] Now, the aryne-based methodology is well recognized as a convenient, one-pot synthetic approach to a great number of compounds with various applications, and most of them could not be obtained by using traditional synthetic methods.[4] However, the fundamental mechanistic path of the aryne-mediated transformations (such as the control and understanding of the selectivity in the nucleophilic substitution in the aryne core or aryne involving cycloaddition reactions) remains an important area of research.[5] Moreover, the discussions on the mechanistic aspects of the interactions of arynes or hetarynes with aza-heterocycles are very rare.[6] To the best of our knowledge, no studies have been put forth to predict/analyze the possible reaction pathway in the interactions between aza-heterocyclic substrates and arynes based on the first or last structures. It is worth mentioning that some reports were published previously on the interactions of 1,2,4,5-tetrazines and 1,2,4-triazines with certain aryne dienophiles to afford the corresponding isoquinolines *via* an inverse demand (ID) aza-Diels–Alder reaction[7] as well as some other interactions between arynes and 1,2,4-triazin-1-oxides.[8] Recently, we reported the interactions of arynes with 6-aryl-3-(2-pyridyl)-1,2,4-triazines **1**, bearing a hydrogen atom or aromatic substituents at the C5 position[9–11] as well as a cyano-substituent at the C5-position.[12] It has been found that in most cases these reactions led to domino products, namely, 1*H*-(1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **2**, while the expected 1-(2-pyridyl)isoquinolines **3** were isolated only as by-products in low yields (Table 1). However, the isoquinolines were obtained as major products when 5-cyano-3-(2-pyridyl)-1,2,4-triazines were used as starting compounds,[12] where pyrido[1,2-*a*]indoles were isolated as by-products. It is worth mentioning that these products are of wide interest due to their broad spectrum of biological activities, in particular cytostatic,[13] antiviral,[14] *etc.*

[a]*Department of Organic and Biomolecular Chemistry, Chemical Engineering Institute, Ural Federal University, 19 Mira Str., Yekaterinburg, K-2 620002, Russian Federation. E-mail: sougatasantra85@gmail.com, ssantra@urfu.ru*
[b]*I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Str., Yekaterinburg, 620219, Russian Federation*
[c]*Centre for Computational Sciences, School of Basic and Applied Sciences, Central University of Punjab, City Campus, Mansa Road, Bathinda-151001, India*
[d]*Department of Chemistry, Sri Venkateswara University, Tirupati-517502, Andhra Pradesh, India*
[e]*Department of Chemistry, Visva-Bharati (A Central University), Santiniketan-731235, India*

†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds (PDF), crystallographic data for compounds **2d**, **2j** and **3c** (CIF), DFT calculations and all computed structures (as .cif file), Cartesian coordinates (angstroms) and total energies (hartree) of the geometry-optimized structures of all computed compounds (PDF). CCDC 1562139, 1562142 and 1562138. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob00847g

Table 1 Our previous studies



Triazine	Ar	R	X	Product 2	Product 3
1a	Ph	Ph	H	**2a**[4]	—
			F	**2g**[5]	—
			OMe	**2j**[6]	**3d**[6]
1b	Ph	H	H	**2b**[4]	—
			OMe	**2k**[6]	**3e**[6]
1c	Biphenyl-2,2′-diyl		H	**2c**[4]	—
			F	**2i**[5]	—
			OMe	**2l**[6]	**3f**[6]
1d	Ph	CN	H	**2d**[7]	**3a**[7]
			OMe	—	**3g**[6]
1e	Tol	CN	H	**2e**[7]	**3b**[7]
1f	4-BrC_6H_4	CN	H	**2f**[7]	**3c**[7]
1g	4-FC_6H_4	H	F	**2h**[5]	—

(Fig. 1) as well as their unique fluorescence properties.[15] Isoquinolines[16] and their metal coordinated complexes[17] also possess biological activities, and the isoquinoline moiety is widely presented in alkaloids.[18]

In this work, we wish to disclose our studies on the interactions of 1,2,4-triazines with arynes, particularly to analyze the influence of the nature of the substituent in the C5-position of 6-aryl-3-(2-pyridyl)-1,2,4-triazines as well as that of the nature of aryne intermediates on the reaction pathway and on the types of products formed.

Results and discussion

Based on the literature, a commonly accepted mechanism for the ID aza-Diels–Alder reaction and the previously reported[9–11] aryne-mediated rearrangement of 1,2,4-triazines (domino reaction) are presented in Scheme 1.

Thus, as we can suggest, for both the pathways the formal 1,4-diaddition product (**I1**) is a key intermediate for the reaction between the aryne dienophile and 1,2,4-triazine diene (Scheme 1). Depending on the electronic factors of both the 1,2,4-triazine and the aryne, the subsequent transformation

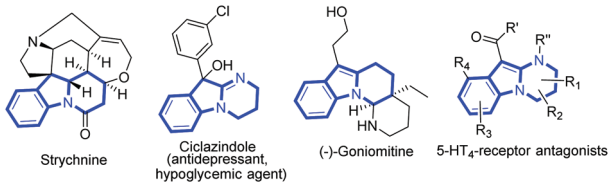


Fig. 1 Some biologically-active pyrido[1,2-*a*]indoles.

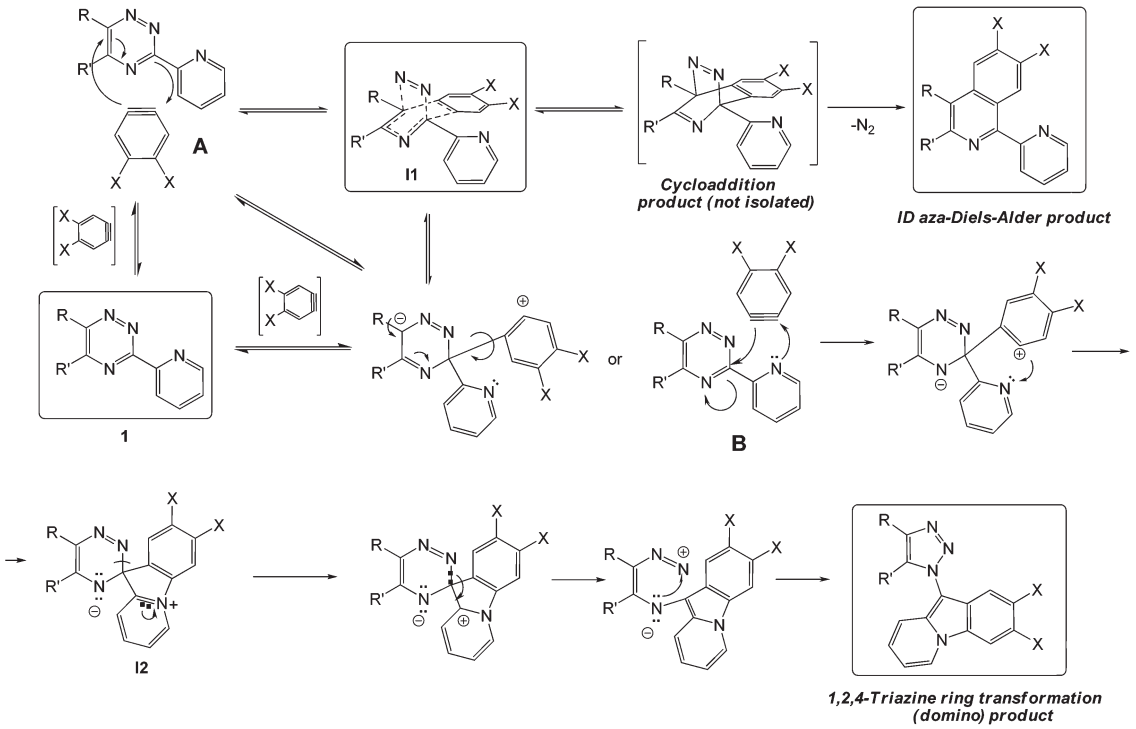
would afford either the classical ID aza-Diels–Alder product along with the elimination of an N_2 molecule and/or the 1,2,4-triazine ring rearrangement (domino) products, namely pyrido[1,2-*a*]indoles (*via* the intermediate **I2**).

1,2,4-Triazines and their *N*-oxides could be easily functionalized by means of the nucleophilic substitution of leaving groups (S_N^{ipso}) or by the nucleophilic substitution of hydrogen (S_N^H). For highly π-deficient systems, such as 1,2,4-triazines,[19] the S_N^H-based processes look more attractive especially based on the principles of atom economy[20] and green chemistry.[21]

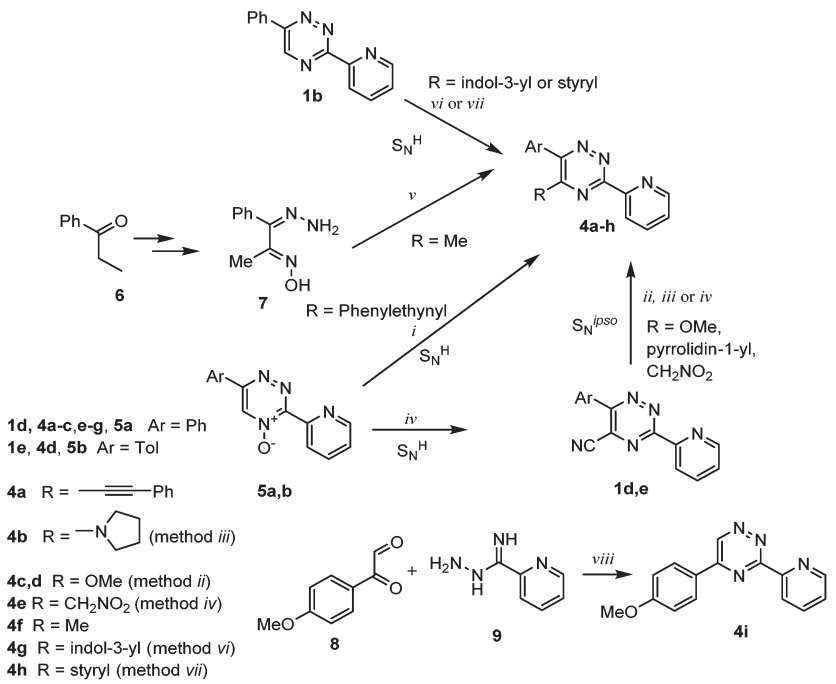
Thus, as a first step, using the previously reported S_N^H- or S_N^{ipso}-based procedures we prepared several 5-substituted 1,2,4-triazines **1** and **4** as starting materials. Thus, 5-phenylethynyl substituted 1,2,4-triazine **4a**[22] as well as 5-cyano-1,2,4-triazines **1d–e**[16] were prepared starting from 1,2,4-triazine-4-oxides **5a–b**[23] (Scheme 2). According to the previously reported methods, the *ipso*-substitution of the cyano group by the residues of methanol,[24] nitromethane[25] and pyrrolidine in triazines **1d–e** (*via* a solvent-free procedure[26]) afforded compounds **4b–d**. 5-(Indolyl-3)-substituted 1,2,4-triazine **4g** was obtained by an optimized procedure[27] as a result of oxidative nucleophilic substitution of the hydrogen by the indole moiety in the presence of trifluoroacetic acid. Styryl-substituted 1,2,4-triazine **4h** was synthesized according to the reported procedure[28] starting from 1,2,4-triazine **1b**.

5-Methyl-1,2,4-triazine **4e** was easily prepared starting from the commercially available propiophenone **6** *via* the formation of acetophenone hydrazone **7** by using the previously described procedure,[29] and followed by the reaction of **7** with pyridine-2-carbaldehyde in boiling acetic acid. 6*H*-1,2,4-Triazine **4i** was obtained by the reaction between the corresponding arylglyoxal **8** and amidrazone **9** according to the previously reported method.[30]

In the course of our work, we also analyzed the possible methods for the *in situ* generation of various[31] arynes from the viewpoint of their convenient use in the following interactions with 1,2,4-triazines. Among the common methods for the aryne generation only two were found to be the most suitable based on the synthetic availability of the reagents: one is *via* the dehydrohalogenation reactions of monohalogenaryls in the presence of strong bases (*e.g.* *t*-BuOK, $NaNH_2$, *etc.*), and another one is *via* the diazotization reaction of anthranilic acid derivatives. At first, we tested the monohalogenaryl-based method, and only a few isoquinolines were isolated in low yields as a result of the reactions with substituted 1,2,4-triazines in an autoclave.[32] Unfortunately, further detailed analysis of the reaction mixture composition revealed the presence of a significant amount of 1,2,4-triazine ring decomposition products, most probably, in the presence of a strong base.[33] Therefore, this method was found to be inappropriate for the aryne generation by the reactions with 1,2,4-triazines, and in our further experiments we used an anthranilic acid-based methodology. Anthranilic acid is the cheapest commercially available precursor for the *in situ* generation of simplest aryne, namely 1,2-dehydrobenzene (benzyne). In addition, 4,5-difluoro- and 4,5-dimethoxy-1,2-dehydrobenzenes (Fig. 2) were



Scheme 1 A commonly accepted ID aza-Diels–Alder reaction mechanism affording isoquinolines, and the benzyne-mediated rearrangement of 1,2,4-triazines (domino reaction) affording pyrido[1,2-*a*]indoles.



Scheme 2 Synthetic approaches towards 5-substituted 1,2,4-triazines. Reagents and conditions: (i) phenylacetylene, *n*-BuLi, THF, –78 °C, 20 min, then AcCl; (ii) sodium, methanol, 65 °C, 2 min, then 20 °C, 1 h; (iii) pyrrolidine, neat, 150 °C, 3 h, 1 h; (iv) acetone cyanohydrin, Et_3N, DCM, reflux, 30 min; (v) pyridine-2-carbaldehyde, ethanol, 20 °C, 10 h, then AcOH, 118 °C, 5 min; (vi) indole, CF_3COOH, 1,2-dichloroethane, 20 °C, 12 h, then Na_2CO_3, 20 °C, 10 min, then DDQ, DCM, 20 °C, 30 min; (vii) BuLi, phenylacetylene, THF/toluene (1 : 9), –78 °C, 5 min, then 20 °C, overnight, then methanol, 20 °C; (viii) ethanol, reflux, 10 h.

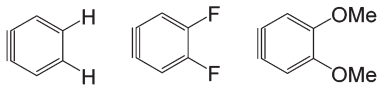


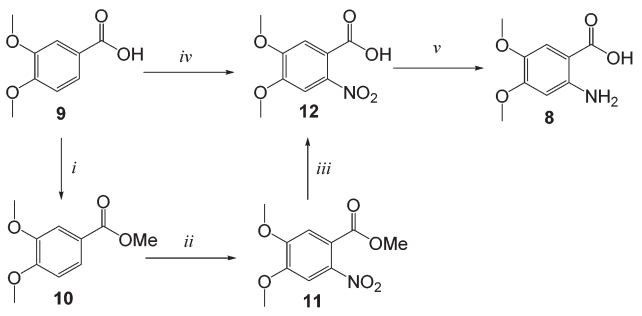
Fig. 2 Structures of used aryne intermediates.

tested, and their precursors were synthesized by means of optimized methods.

Thus, a synthetic precursor of 4,5-difluoro-1,2-dehydrobenzene, 2-amino-4,5-difluorobenzoic acid, was synthesized according to the optimized conditions by our procedure *via* the oxidation of the previously described 5,6-difluoro-1*H*-indole-2,3-dione[34] **2** with hydrogen peroxide in an alkaline medium.

The synthetic precursor of 4,5-dimethoxy-1,2-dehydrobenzene, 2-amino-4,5-dimethoxybenzoic acid **8**, was obtained from the commercially available veratric acid **9**. For this acid and its methyl ester **10**, the previously reported methods[35] were used for the chemoselective introduction of the nitro group into the C2-position of the benzene ring. Thus, the nitration of the ester **10** proceeded very smoothly, and subsequent hydrolysis of compound **11** afforded 2-nitroveratric acid **12** (Scheme 3). In both the steps, the yields of the products were very high, and the procedures were easily realizable. In the final step, the reduction of **12** (by hydrogen gas over 10% palladium on activated carbon) afforded the desired 2-amino-4,5-dimethoxybenzoic acid **8** in 97% yield. It is worth mentioning that we also tried to carry out the direct nitration of veratric acid according to a reported procedure;[36] however, the reaction afforded the desired product **12** in very low yield. The modification of the original procedure allowed us to obtain the desired product in up to 73% yield.

Next, the reactions of arynes with 6-aryl-5-*R*-1,2,4-triazines were studied. Similar to 6-aryl-5-*R*-3-(pyridyl-2)-1,2,4-triazines **1a–c** and **1g** (R = H or R = Ar), the introduction of electron-donor substituents at the C5-position of the 1,2,4-triazine moiety did not alter the reaction pathway for all three arynes. Thus, by the reactions with all three arynes, 5-methoxy- and 5-pyrrolidino-1,2,4-triazines **4b,d** afforded the corresponding 1,2,4-triazine ring rearrangement products (domino) as the only products, namely pyrido[1,2-*a*]indoles **15** (Table 2). 6*H*-1,2,4-Triazine **4i** also reacted with benzyne to afford 1,2,4-triazine rearrangement product **15g**. The introduction of electron-rich substituents, such as indole, at the C5-postion of the 1,2,4-triazine moiety (**4g**) also did not alter the reaction pathway, although the yield of the product **15e** was much lower, and extensive tarring of the reaction mixture was observed.



Scheme 3 Synthesis of 3,4-dimethoxyanthranilic acid. Reagents and conditions: (i) methanol, H_2SO_4, 65 °C, 10 h; (ii) HNO_3 (40%), 20 °C, 24 h; (iii) NaOH, ethanol, 1 h, 78 °C, then HCl, 20 °C; (iv) HNO_3 (conc.), 20 °C, 12 h; (v) H_2, Pd/C, methanol, 20 °C, 6 h.

The introduction of electron-withdrawing substituents, such as phenylethynyl-, phenylvinyl- or cyano group, at the C5-position altered the direction of the main transformation of the 1,2,4-triazine ring (Table 2). The previously reported[12] 1-(2-pyridyl)-3-cyanoisoquinolines **3** were isolated as major products in the reaction of 5-cyano-1,2,4-triazines **1d,e** with 1,2-dehydrobenzene, and pyrido[1,2-*a*]indoles **2** were isolated only as minor products. Moreover, in the reaction with less electrophilic aryne, 4,5-dimethoxy-1,2-dehydrobenzene, the rearrangement products **2** were not detected at all in the reaction mixture, and the yield of isoquinoline **3g** was found to be noticeably lower compared to that observed for unsubstituted aryne.[12] We found that a similar reaction of 5-phenylethynyl- and 5-styryl-3-(pyridyl-2)-1,2,4-triazines **4a,h** with benzyne afforded pyrido[1,2-*a*]indoles **15a,f** as major products along with isoquinolines **16a,b** as minor ones (in 12% and 3% yields, respectively).

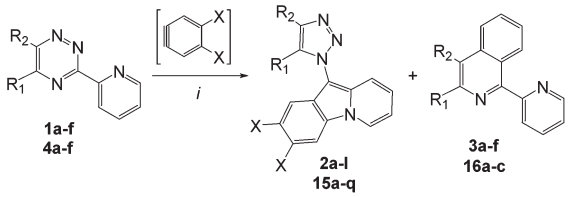
Thus, in this reaction the amount of the classical ID aza-Diels–Alder products, namely isoquinolines, is changed in accordance with an acceptor strength of the substituent at the C5-position of the 1,2,4-triazine moiety, and the enhancement of acceptor strength lying in the row "styryl group–phenylethynyl group–cyano group" led to an increase in the amount of isoquinolines in the composition of the products, thus facilitating the course of the classical ID aza-Diels–Alder reaction.

It is worth mentioning that 1,2,4-triazine **4e** substituted with the nitromethane moiety at the C5-position was also tested in the reaction with 1,2-dihydrobenzene. However, the reaction led to the formation of a complex, an inseparable mixture of products, and neither the ID aza-Diels–Alder reaction product nor the 1,2,4-triazine transformation product was detected. This is probably due to the existence of compound **4e** in two tautomeric forms (Scheme 4). According to ^{1}H NMR spectroscopy, the form **B** is preferable, which was confirmed based on the presence of a one-proton singlet in the 6.59 ppm region.

In order to study the influence of electron-withdrawing substituents at the C6-position of the triazine moiety, 6-(4-nitrophenyl)-1,2,4-triazine **1h** was reacted with 1,2-dehydrobenzene; the reaction afforded only the rearrangement product, namely pyrido[1,2-*a*]indole **15h**, and no classical ID aza-Diels–Alder reaction product (isoquinoline) was detected.

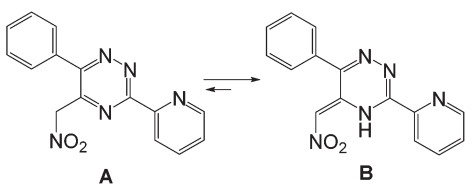
Unlike the interactions of 1,2-dehydrobenzene and 4,5-dimethoxy-1,2-dehydrobenzene (in reactions with 1,2,4-triazines **4a,c**), the interaction of 4,5-difluoro-1,2-dehydrobenzene with all 5-*R*-3-(pyridyl-2)-1,2,4-triazines substituted with both the electron-withdrawing or electron-donating groups afforded pyrido[1,2-*a*]indoles as the only products, and no corres-

Table 2 Interactions between arynes and 5-R-3-(pyridyl-2)-1,2,4-triazines



X	Triazine	R_2	R_1	Pyridoindole (yield[a])	Isoquinoline (yield[a])
H	**1a**	Ph	Ph	**2a** (49%)	—
	1b	Ph	H	**2b** (49%)	—
	1c	Biphenyl-2,2′-diyl		**2c** (60%)	—
	1d	Ph	CN	**2d** (4%)	**3a** (36%)
	1e	Tol	CN	**2e** (3%)	**3b** (31%)
	1f	4-BrC_6H_4	CN	**2f**[b]	**3c** (39%)
	4a	Ph	Ph-ethynyl	**15a** (28%)	**16a** (12%)
	4b	Ph	Pyrrolidine-1-yl	**15b** (35%)	—
	4c	Ph	OMe	**15c** (40%)	—
	4e	Ph	CH_2NO_2	Complex mixture of products	
	4f	Ph	Me	**15d** (49%)	—
	4g	Ph	Indol-3-yl	**15e** (18%)	—
	4h	Ph	Styryl	**15f** (31%)	**16b** (3%)
	4i	H	4-$MeOC_6H_4$	**15g** (25%)	—
	1h	4-$NO_2C_6H_4$	H	**15h** (40%)	—
F	**1a**	Ph	Ph	**2g** (37%)	—
	1b	Biphenyl-2,2′-diyl		**2h** (45%)	—
	1g	4-FC_6H_4	H	**2i** (35%)	—
	1d	Ph	CN	**15i** (37%)	—
	1e	Tol	CN	**15j** (45%)	—
	4a	Ph	Ph-ethynyl	**15k** (41%)	—
	4b	Ph	Pyrrolidine-1-yl	**15l** (40%)	—
	4d	Tol	OMe	**15m** (49%)	—
	4f	Ph	Me	Complex mixture of products	
	4h	Ph	Styryl	**15n** (42%)	—
OMe	**1a**	Ph	Ph	**2j** (26%)	**3d** (7%)
	1b	Ph	H	**2k** (25%)	—
	1c	Biphenyl-2,2′-diyl		**2l** (44%)	**3e**[b]
	1d	Ph	CN	—	**3f** (10%)
	1e	Tol	CN	—	**16c** (14%)
	4a	Ph	Ph-ethynyl	Tarring	
	4b	Ph	Pyrrolidine-1-yl	**15o** (25%)	—
	4c	Ph	OMe	Tarring	
	4f	Ph	Me	**15p** (28%)	—
	4h	Ph	Styryl	**15q** (30%)	—

Reagents and conditions: (i) Anthranilic acid, iso-amyl nitrite, toluene/1,4-dioxane (4 : 1), reflux, 1.5 h. [a] Isolated yields. [b] Detected by mass spectrometry.



Scheme 4 Possible tautomeric equilibrium of compound **4e**.

ponding ID aza-Diels–Alder products (isoquinolines) were detected. Likewise for 1,2-dehydrobenzene, the reaction of 1,2,4-triazines with 1,2-dehydro-4,5-dimethoxybenzene afforded the 1,2,4-triazine ring transformation products along with ID aza-Diels–Alder products as minor ones. Table 2 summarizes all the data for the interaction between arynes and 5-*R*-3-(pyridyl-2)-1,2,4-triazines obtained herein as well as some previously reported examples.

The structures of all new products were confirmed based on the data of ^1H and ^{13}C NMR spectroscopy, elemental analysis and in some cases IR spectroscopy. In all cases, there is a clear correlation with the data for analogous compounds with other substituents reported earlier. In some cases, one can note the presence of characteristic signals of the corresponding substituents in the structure of the products. In particular, for the phenylethynyl substituents in the ^{13}C NMR spectrum, the characteristic signals of sp-hybridized carbon atoms were observed in the region of 76.2–102.7 ppm.

In some cases, the X-ray data were used as a key method for establishing the structure of products. Thus, in order to

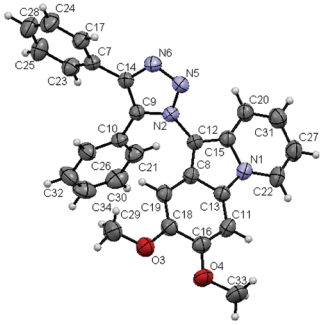


Fig. 3 Crystal Structure of pyrido[1,2-*a*]indole **2j** (CCDC # 1562139†).

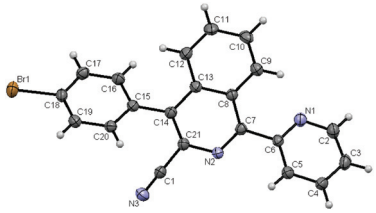


Fig. 5 Crystal structure of isoquinoline **3c** (CCDC # 1562138†).

confirm the structure of the 1,2,4-triazine transformation product obtained by the reaction of 4,5-dimethoxy-1,2-dehydrobenzene,[11] such as compound **2j**, the X-ray diffraction experiment was performed (Fig. 3). According to the collected XRD data, the compound is crystallized in the centrosymmetric space-group. The molecule is non-planar, and the 1,2,3-triazol ring is turned towards the pyrido[1,2-*a*]indole moiety at an angle of 57°. All bond distances and angles in the molecule are within the standard values. In particular, the single and double bonds in the pyridine ring of pyrido[1,2-*a*]indole (1.41 and 1.35 Å, respectively) are well distinguished (approximately 0.05 Å). The non-hydrogen atoms of the methoxy-substituents are located in the plane of the pyrido[1,2-*a*]indole moiety. In the crystal, the molecules form a one-dimensional structure, and the close contacts are not detected with neighboring molecular chains (see Fig. S1 in the ESI†).

According to the XRD data of another transformation product **2d**, its molecule is non-planar (Fig. 4). The phenyl substituent is placed approximately in the plane of the 1,2,3-triazole ring (with some deviation of the C-atom at the *para*-position of the phenyl ring from the plane less than 0.2 Å). The 1,2,3-triazole ring is turned towards the pyrido[1,2-*a*]indole tricyclic system at an angle of 52°. In the crystal, the molecules form the centrosymmetric dimers with the formation of shortened π–π C···C contacts between tricyclic moieties. In particular, the observed contacts between pyrido[1,2-*a*]indole tricyclic systems with symmetry transformation $[-1 - x, -y, 1 - z]$ are the C(1)···C(14) contact is equal to 3.266 Å and the contact C(13)···C(13) is less efficient and equal to 3.309 Å (see Fig. S2 and S3 in the ESI†). The N-atom of the CN-group in the dimer forms a weak intermolecular H-bond of the N···HC type with the carbon atom of C(20) of the pyrido[1,2-*a*]indole tricyclic system, in order to stabilize the conformation of the molecule. The 4-Ph-5-CN-1,2,3-triazole moiety also forms some shortened intermolecular π–π C···C contacts (see Fig. S2 and S3 in the ESI†); however, the interatomic distances for these contacts are greater than for discussed above.

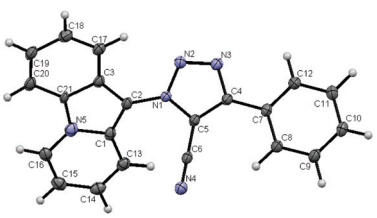


Fig. 4 Crystal structure of pyrido[1,2-*a*]indole **2d** (CCDC # 1562142†).

In accordance with XRD data, the molecule of isoquinoline **3c** is non-planar (Fig. 5). The 4-bromophenyl substituent is turned towards the heterocyclic moiety at an angle of 56°, and the pyridine ring is turned towards the isoquinoline moiety at an angle of −47° with anticlinal placing of the N-atoms of the heterocyclic rings. In the crystal, the molecules of **3c** form stacks with intermolecular distances of 3.4–3.9 Å (see Fig. S4 in the ESI†).

As we previously mentioned,[11] in the ^{1}H NMR spectra of some products of the reactions between 1,2,4-triazines and 1,2-dehydro-4,5-dimethoxy-benzene (dimethoxyaryne), namely **2j–2l**, at room temperature, the signals of the aromatic protons of the C5-aryl substituent as well as the signals of the protons of one of the methoxy groups of the pyrido[1,2-*a*]indole moiety are observed as broadened singlets (Fig. 6). We assumed that the rotation of the dimethoxy-substituted pyrido[1,2-*a*]indole moiety is somehow hampered with respect to the diaryl-substituted 1,2,3-triazole moiety due to one methoxy group pointed towards the aromatic substituent of the 1,2,3-triazole moiety. To confirm this case, we measured the ^{1}H NMR spectra of the most representative compound **2j** at a temperature of −56 °C (217 K) (Fig. 6). As it can be seen that the lowering of the temperature significantly reduces the speed of the rotation around the C–N bond between the pyrido[1,2-*a*]indole and 1,2,3-triazole moieties, and only one set of sharp peaks could be observed.

Additionally, in $CDCl_3$ in the ^{1}H NMR spectra of pyrido[1,2-*a*]indoles **15f**, **15n** and **15q** with a stylbene residue, we did not observe the characteristic signals of this moiety as two characteristic doublets were observed at around 7.00 ppm instead of only one two-proton singlet at around 7.00 ppm. However, in CD_3CN a typical resonance peak of the styrene moiety was observed, and the *trans*-configuration was confirmed based on the coupling constant data (J = 15.5 Hz).

DFT-supported evaluation of the Diels–Alder *vs.* domino reactivity of the arynes in reactions with 1,2,4-triazines

In Diels–Alder reactions, two new bonds are simultaneously formed between the diene and dienophile in a $[\pi^4s + \pi^2s]$

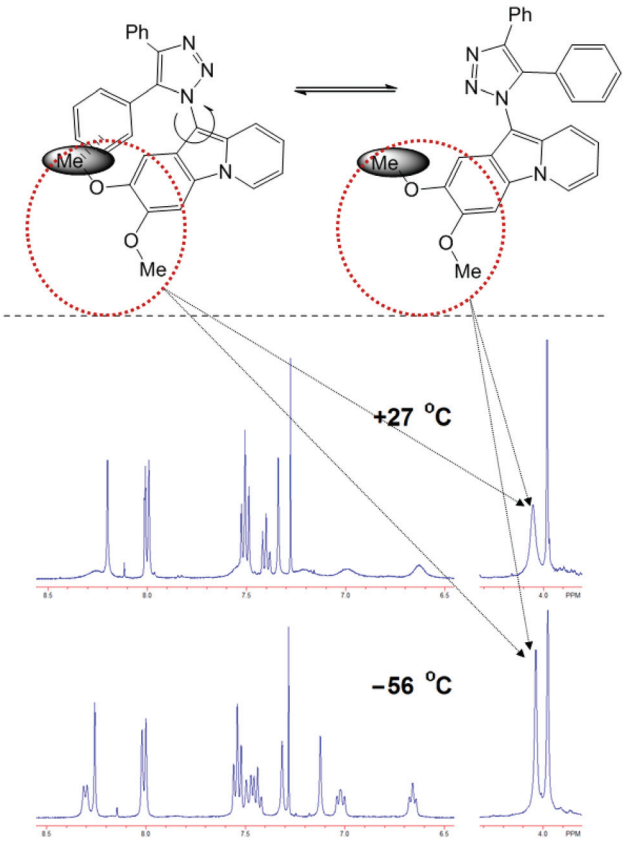
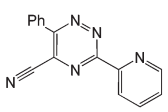
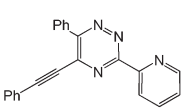
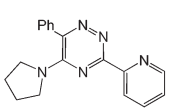


Fig. 6 ^{1}H NMR spectra of compound **2j** in $CDCl_3$ at different temperatures.

fashion. The reaction kinetics is governed by the energy differences between the HOMO and LUMO; the smaller the energy differences between the Frontier Molecular Orbitals (FMO), the faster the reaction.[37] Here the present reported ID aza-Diels–Alder reactions were governed by the $HOMO_{dienophile}$–$LUMO_{diene}$ gap.[38] In order to analyze the above experimental results, particularly to estimate the influence of the substituents in both the aryne intermediates and 1,2,4-triazines, the theoretical calculations of the HOMO and LUMO energies and the HOMO–LUMO gap for arynes (dienophiles) and 1,2,4-triazines (dienes) were carried out (Table 3). The obtained results of the density functional theoretical (DFT) calculations suggest that compared to the HOMO of benzyne (−9.69 eV)[39] the introduction of both the fluorine atom and methoxy-group strongly increases the HOMO level of aryne dienophile compared to that of 1,2-dehydrobenzene (benzyne), which decreases the $HOMO_{aryne}$–$LUMO_{1,2,4\text{-triazine}}$ gap. Thus, based on the lowest values for the HOMO–LUMO gap, the ID aza-Diels–Alder reaction between 1,2,4-triazines **1d**,**4a**,**4b** and 4,5-difluoro-1,2-dehydrobenzene looks the most favorable (Table 3). However, in our experiments with all 1,2,4-triazines, even those substituted with the cyano-group at the C5-position of the 1,2,4-triazine moiety we observed either the formation of 1,2,4-triazine ring rearrangement products (domino products), such as pyrido[1,2-*a*]indoles with no ID aza-Diels–Alder products or observed no reaction at all (Table 2). Some of our additional findings, namely DFT calculations of localization of HOMO lobes in benzyne and 4,5-difluoro-1,2-dehydro-benzene, have demonstrated the predominant localization of the HOMO lobes at the "triple bond" carbons, while in 4,5-difluoro-1,2-dehydro-benzene the HOMO lobes are mainly localized at the "HC-CF-CF-CH" moiety of the aryne molecule (Fig. S9, ESI†). This suggests that the cycloaddition process with LUMOs of 1,2,4-triazine would be more favorable in the case of benzyne. On the other hand, the nucleophilic addition to arynes occurs at the reaction site with the highest contribution of the LUMO.[40] Here, opposite to the HOMOs, the predominant localization of the LUMO lobes at the "triple bond" 4,5-difluoro-1,2-dehydro-benzene carbons (Fig. S10, ESI†) leads to the conclusion that a nucleophilic attack (by the lone pair of the pyridine atom of 1,2,4-triazine, Scheme 1) is considerably more favorable than in the case of benzyne at these particular positions. In fact, based on DFT calculations (Table 3), the LUMO energy of 4,5-difluoro-1,2-dehydro-benzene is 0.87 eV (20.06 kcal mol^{-1}), which is lower than those of benzyne and 4,5-dimethoxy-1,2-dehydro-benzene and this makes the formation of addition products at the "triple bond" of 4,5-difluoro-1,2-dehydro-benzene to be the most favorable.

The transition structures for the Diels–Alder/domino reactions between the most representative 1,2,4-triazine **1d**, and benzyne and 4,5-difluoro-1,2-dehydro-benzene are shown in

Table 3 The HOMO–LUMO calculations for 1,2,4-triazines **1a**, **4a**, **4b** and arynes

	1d 	**4a** 	**4b** 	Benzyne[39]	4,5-Dimethoxy-1,2-dehydro-benzene	4,5-Difluoro-1,2-dehydro-benzene
E_{LUMO}, eV	0.64	0.95	1.58	1.42	1.38	0.87
E_{HOMO}, eV	−8.95	−8.35	−8.18	−9.69	−9.25	−10.09
ΔE, eV, ($E_{HOMOdienophile} - E_{LUMOdiene}$)						
Benzyne	9.05	8.74	8.11	—		
4,5-Dimethoxy-1,2-dehydro-benzene	8.61	8.30	7.67			
4,5-Difluoro-1,2-dehydro-benzene	9.45	9.14	8.51			

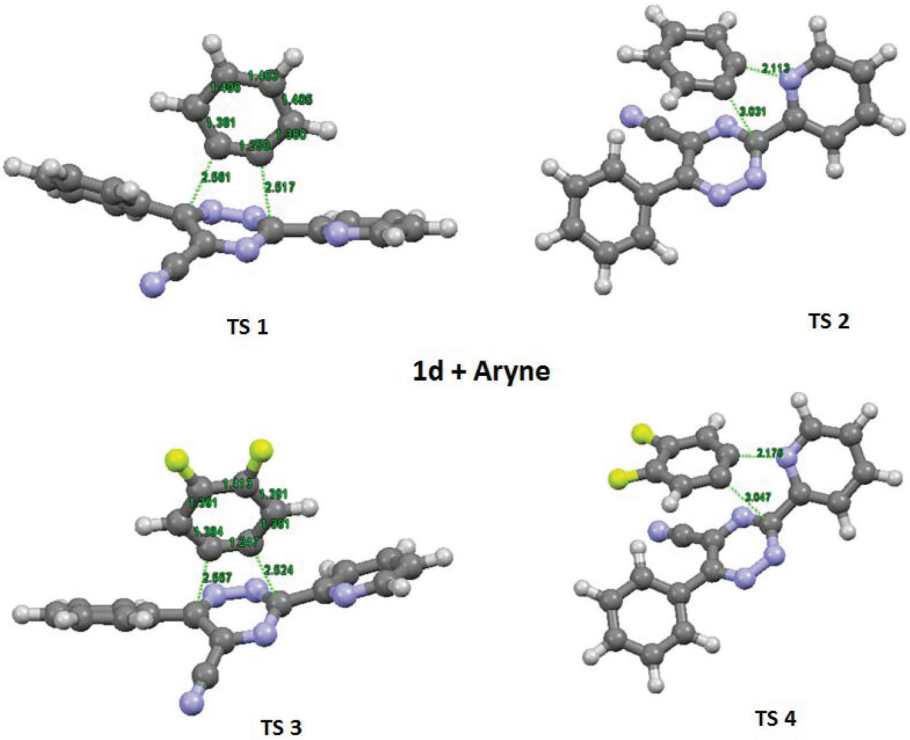


Fig. 7 M06-2X/6-31G(d) – optimized transition state structures for the reaction of 1,2,4-triazine (**1a**) with benzyne (**TS1–2**) and difluoro-benzene (**TS3–4**).

Fig. 7 (please also see the ESI, Fig. S5, S8, S11 and S12†). Herein the activation enthalpy ($\Delta H^{\ddagger}$), activation free energy ($\Delta G^{\ddagger}$), and reaction free energy (ΔG_{rxn}) for each combination were calculated. Based on the calculated $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$ and ΔG_{rxn} values, the interaction between **1d** and benzyne affording the ID Diels–Alder product (**TS1**) requires 2.768 kcal mol^{-1} less energy than the energy required for the domino product (**TS2**). In the case of 4,5-difluoro-1,2-dehydro-benzene, both interactions will proceed with very close activation free energies, namely 8.550 kcal mol^{-1} (**TS3**) and 9.004 kcal mol^{-1} (**TS4**) and these are also very close to the value calculated for **TS3** (8.826 kcal mol^{-1}) in the case of benzyne. In other words, based on the literature,[41] the formation of products *via* **TS1** and **TS3–TS4** would proceed with very similar reaction rates. To prove this, the second order rate constants were computed by using the Eyring transition state theory at 298 K (Table 4) and, except **TS2**, the remaining are lying in the range of 1.5–3.3 × 10^{6} M^{-1} s^{-1}.

Table 4 The activation enthalpy ($\Delta H^{\ddagger}$), activation free energy ($\Delta G^{\ddagger}$) and reaction free energy (ΔG_{rxn}) for the interaction of **1d** and arynes

Transition state	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔG_{rxn}	k_2 (M^{-1} s^{-1})
1,2-Dehydro-benzene				
TS1	−3.887	8.826	−141.039	2.10 × 10^{6}
TS2	−2.040	11.594	−81.913	1.97 × 10^{4}
4,5-Difluoro-1,2-dehydro-benzene				
TS3	−4.300	8.550	−144.821	3.36 × 10^{6}
TS4	−4.715	9.004	−83.901	1.56 × 10^{6}

Next, the interaction/distortion analysis[41,42] was performed on all possible transition states (**TS1–TS4**). Fig. 8 shows the graphs obtained for the interactions between 1,2,4-triazine **1a** and benzyne or 4,5-difluoro-1,2-dehydro-benzene. It can be clearly seen that distortion energies for the interactions between **1d** and arynes affording domino products are always larger than that for ID Diels–Alder products and this is assuming the late transition states (**TS2**, **TS4**).[41] In these interactions, the contribution of the distortion energy of diene **1d** is almost the same, while the distortion energy of the benzyne is 1.5 times higher than the distortion energy of 4,5-difluoro-1,2-dehydro-benzene. Additionally, for the interaction with the last one, both aryne and **1d** are almost equally contributed to the total ΔE_{dist} value, while in the case of benzyne the contribution of benzyne (pre)distortion is much larger. In the ID Diels–Alder process, the diene **1d** has the largest contribution in the ΔE_{dist} value and this is almost the same for both benzyne and 4,5-difluoro-1,2-dehydro-benzene, and the contribution of two last ones is very small. By summarizing all the above, it was assumed that 4,5-difluoro-1,2-dehydro-benzene is predistorted much better for the domino reaction. Finally, the interaction between **1d** and 4,5-difluoro-1,2-dehydro-benzene proceeds with the most negative interaction energy affording the domino product, and this is also assuming the lowest activation energy.[41] Thus, according to the DFT studies, in the interaction between 4,5-difluoro-1,2-dehydro-benzene and

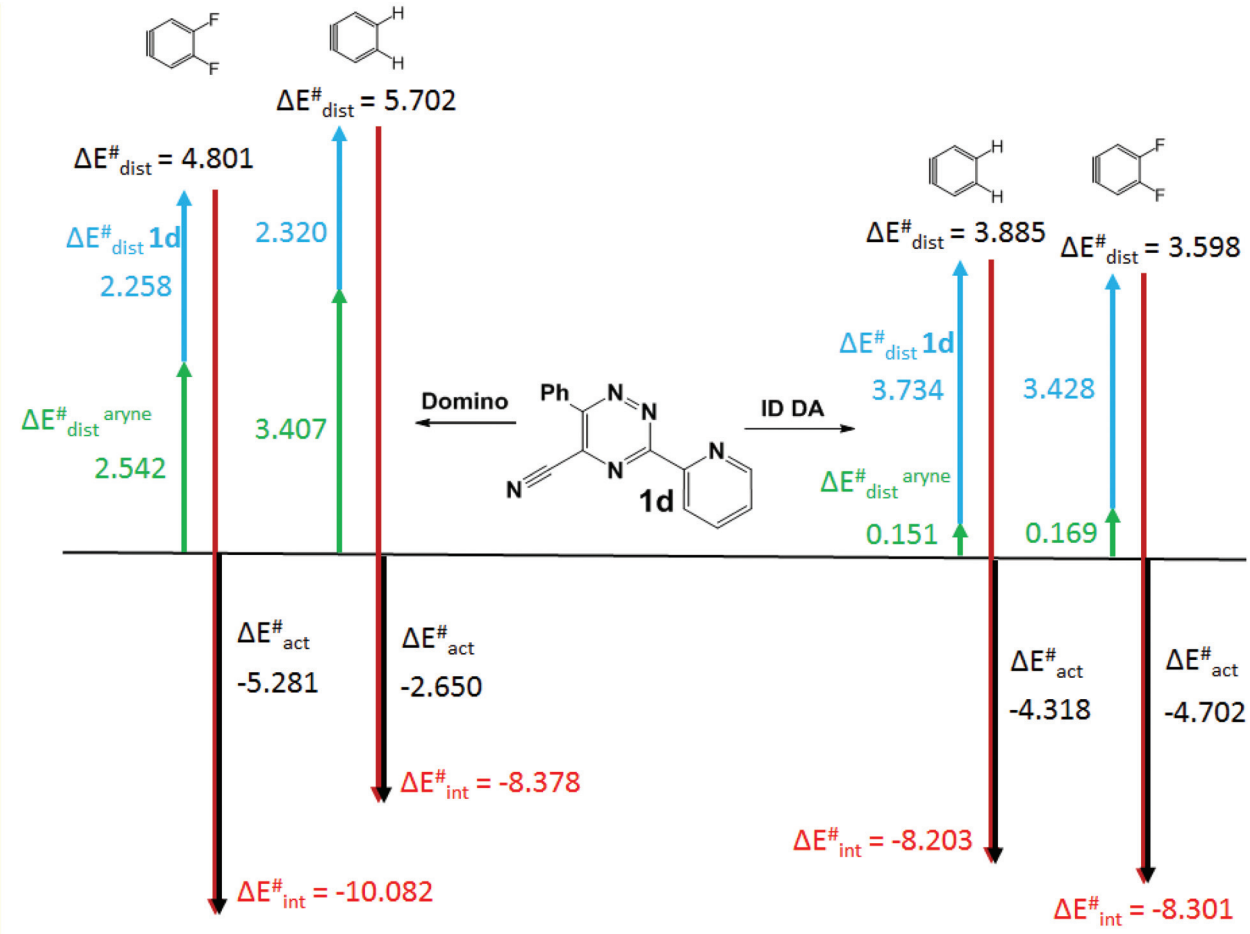


Fig. 8 Graph of distortion, interaction, and activation energies for the transition states of reactions between the most representative 1,2,4-triazine **1d** and benzyne or 4,5-difluoro-1,2-dehydro-benzene (green: distortion energy of aryne, blue: distortion energy of **1d**, red: interaction energy, black: activation energy, in kcal mol^{-1}).

1,2,4-triazine **1d**, the domino reaction is the only process due to both the electronic and steric effects.

Conclusions

Thus, in this article the main features of the interactions of 3-(2-pyridyl)-1,2,4-triazines with aryne intermediates, such as 1,2-dehydrobenzene and its 4,5-difluoro- and 4,5-dimethoxy substituted derivatives, have been studied. It was found that 3-(2-pyridyl)-1,2,4-triazines, which are 5-unsubstituted or substituted with electron-donating substituents at the C5 position, such as aryl and methoxy groups, and pyrrolidyl residue, react with all three arynes to afford the 1,2,4-triazine ring rearrangement (domino) products, namely pyrido[1,2-*a*]indoles, as major products. In the case of less electrophilic 4,5-dimethoxy-1,2-dehydrobenzene along with the triazine ring rearrangement products, the formation of the classical ID aza-Diels–Alder reaction products took place; however, the yields were not exceeding 7%. Upon the introduction of the electron-withdrawing substituents at the C5-position of 3-(2-pyridyl)-1,2,4-triazine, the formation of the expected isoquinoline derivatives takes place to a major extent, and the greater the acceptor character of the introduced residue, the higher the yield of the isoquinolines formed. This is confirmed by comparing the yields of isoquinolines formed in the series of 5-phenylethynyl-, 5-styryl- and 5-cyano-1,2,4-triazines. 4,5-Difluoro-1,2-dehydrobenzene is the only exception to this pattern, and in all cases the only products were exclusively pyrido[1,2-*a*]indoles as domino products. Based on the DFT calculations and the interaction/distortion analysis, it was suggested that the presence of two fluorine atoms in this aryne contributes to its high electrophilicity and/or high "predistortion" for the domino reactions. The structures of the three key products were confirmed based on the X-ray data.

Experimental section

General information

Unless otherwise indicated all common reagents and solvents were obtained from commercial suppliers and used without

further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as the internal reference for ^{1}H and ^{13}C NMR spectroscopy or $CFCl_3$ for ^{19}F NMR spectroscopy. The XRD analyses were accomplished by a standard procedure (MoK-irradiation, ω-scans with 1° step). Empirical absorption corrections were applied using Olex2,[43] the structures were solved with the Superflip[44] structure solution program using Charge Flipping and refined with the ShelXL[45] refinement package using Least Squares minimisation. The non-hydrogen atoms were refined in anisotropic approximation; the H-atoms were added in the calculated positions and were refined in isotropic approximation in the "rider" model.

Computational methods

The optimization of the geometrical structures and harmonic vibrational analysis has been performed using the Gaussian 09 suite of programs.[46] The DFT (M06-2X) method[47] has been used with the 6-311+G(d,p) basis set for all atoms as implemented in the Gaussian 09 program. The minima and transition states (TS) on the potential energy surface have been confirmed by the analysis of the harmonic vibrational frequencies. For thermochemistry analysis the frequency scale factor 0.97 is used to compensate for the harmonic approximation. The ultrafine integration grid and tight geometry optimizations were used to enhance the calculation accuracy. All calculations have been performed for the molecules in a singlet state. The frontier molecular orbitals (FMOs) and their energies were computed at the HF/6-311+G(d,p) level using the M06-2X/6-311+G(d,p) geometries. Distortion and interaction energies, as well as intrinsic reaction coordinates were carried out at the M06-2X/6-311+G(d,p) level. Please also see the ESI† for details.

Starting compounds. 1,2,4-Triazines **1a**,[30] **1b**, **1h**, **1g**,[28] **1c**,[48] **1d–f**,[22] **4a**,[23] **4h**,[29] 2-(4-methoxyphenyl)-2-oxoacetaldehyde **8**,[49] picolinimidohydrazide **9**,[48] and 2-amino-4,5-difluorobenzoic acid[10] were synthesized according to the previously reported methods.

4,5-Dimethoxy-2-nitrobenzoic acid (12).[35] Synthesis was fulfilled in accordance with the optimized method. In a typical experimental procedure, 4,5-dimethoxybenzoic acid **9** (3.00 g, 16.5 mmol) was dissolved in concentrated nitric acid (16.5 mL). The resulting mixture was stirred at room temperature for 12 h. The obtained precipitate was filtered off, washed with water and dried. The crude product was purified by recrystallization (toluene). Yield 2.36 g (73%). M.p. 198–200 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H, MeO), 3.92 (s, 3H, MeO), 7.21 (s, 1H, H-3), 7.46 (s, 1H, H-6), 13.26 (brs, 1H, COOH).

2-Amino-4,5-dimethoxybenzoic acid (8).[49] 4,5-Dimethoxy-2-nitrobenzoic acid **12** (2.36 g, 11.97 mmol) was dissolved in methanol (40 mL), Pd/C (10%, 0.24 g) was added and the resulting mixture was stirred at room temperature for 6 h under a hydrogen atmosphere (P = 10 atm.). The reaction mixture was filtered off from the catalyst and the solvent from the filtrate was removed under reduced pressure. The product was used for aryne generation without additional purification. Yield 2.29 g (97%). M.p. 198–200 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.63 (s, 3H, MeO), 3.72 (s, 3H, MeO), 6.22 (s, 1H, H-3), 7.22 (s, 1H, H-6).

6-Phenyl-5-(pyrrolidin-1-yl)-3-(2-pyridyl)-1,2,4-triazine (4b). The mixture of 5-cyano-6-phenyl-3-(2-pyridyl)-1,2,4-triazine **1d** (300 mg, 1.16 mmol) and pyrrolidine (0.095 mL, 1.16 mmol) was stirred at 150 °C for 3 h under an argon atmosphere. The product was used in the next step without additional purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87 (m, 2H, pyrrolidine), 3.43 (brs, pyrrolidine), 7.41 (m, 1H, H-5 (Py)), 7.43–7.51 (m, 3H, Ph), 7.62 (m, 2H, Ph), 7.86 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.56 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.85 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 49.7, 123.9, 124.6, 128.2, 128.6, 128.8, 136.6, 137.2, 146.6, 150.0, 152.4, 154.2, 159.1. Anal. calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09%; found: C, 71.21; H, 5.68; N, 23.02%.

General method for the synthesis of 5-methoxy-1,2,4-triazines (4c and 4d). Synthesis was fulfilled in accordance with the improved method presented for similar compounds.[24] The corresponding 5-cyano-1,2,4-triazine **1** (2 mmol) was added to a solution of sodium (50 mg) in methanol (10 mL). The resulting mixture was heated to reflux and then stored at room temperature for 1 h. Water (80 mL) was added and the precipitate obtained was filtered off. The analytical sample was obtained by recrystallization (methanol).

5-Metoxy-6-phenyl-3-(2-pyridyl)-1,2,4-triazine (4c). Yield 315 mg (60%). M.p. 214–216 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.25 (s, 3H, OMe), 7.52–7.59 (m, 4H, Ph, H-5 (Py)), 8.00 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.11 (m, 2H, Ph), 8.53 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.81 (dd, 1H, J = 4.8, 1.8 Hz, H-6 (Py)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.4, 123.8, 125.6, 128.4, 129.1, 130.3, 132.4, 137.3, 148.9, 150.0, 152.4, 160.4, 161.0. Anal. calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20%; found C, 68.01; H, 4.43; N, 20.98%.

5-Metoxy-3-(2-pyridyl)-6-tolyl-1,2,4-triazine (4d). Yield 360 mg (65%). M.p. 209–211 °C. ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, Me), 4.23 (s, 3H, OMe), 7.33 (m, 2H, Tol), 7.54 (m, 1H, H-5 (Py)), 7.95–8.03 (m, 3H, Tol, H-4 (Py)), 8.50 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.79 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)). Anal. calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13%; found: C, 68.89; H, 4.92; N, 20.01%.

(*Z*)-5-(Nitromethylene)-6-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1,2,4-triazine (4e). Potassium hydroxide (340 mg, 6.07 mmol) was suspended in DMSO (3 mL). Cyanotriazine (225 mg, 0.87 mmol) and nitromethane (0.13 mL, 1.74 mmol) were dissolved in THF (5 mL), the resulting solution was added dropwise to the suspension of KOH at room temperature, and then the resulting mixture was stirred at room temperature for 1 h. The resulting mixture was poured to ice/water. The precipitate obtained was filtered off, washed with water and dried. The product was used in the next step without additional purification. Yield 167 mg (0.57 mmol, 65%). M.p. 224–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.59 (s, 1H, $CHNO_2$), 7.43–7.54 (m, 4H, Ph, H-5 (Py)), 7.93 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.52 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.75 (dd, J = 4.8,

1.8 Hz, 1H, H-6 (Py)). Anal. calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88%; found: C, 61.18; H, 3.59; N, 23.62%.

5-Methyl-6-phenyl-3-(2-pyridyl)-1,2,4-triazine (4f). The hydrazone **7** (1 g, 5.64 mmol) was dissolved in ethanol (25 mL), pyridine-2-carbaldehyde (0.54 mL, 5.64 mmol) was added and the resulting mixture was kept at room temperature for 10 h. The solvent was removed under reduced pressure. Glacial acetic acid was added to the residue and the resulting mixture was heated to reflux 5 times. Then the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was triturated with ethanol, and the resulting precipitate was filtered off, washed with ethanol and dried. The analytical sample was obtained by recrystallization (ethanol). Yield 760 mg (54%). M.p. 195–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.71 (s, 3H, Me), 7.53–7.61 (m, 4H, Ph, H-5 (Py)), 7.77 (m, 2H, Ph), 8.00 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.51 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.81 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)). Anal. calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57%; found: C, 72.39; H, 4.67; N, 22.33%.

3-(6-Phenyl-3-(pyridin-2-yl)-1,2,4-triazin-5-yl)-1*H*-indole (4g). The starting triazine **1b** (500 mg, 2.14 mmol) was dissolved in 1,2-dichloroethane (50 mL). Trifluoroacetic acid (0.49 mL, 6.42 mmol) and indole (250 mg, 2.14 mmol) were added and the resulting mixture was stirred at room temperature for 24 h. Then the resulting mixture was washed with water solution of sodium carbonate, and the precipitate formed was filtered off and dried. Then the obtained σ-adduct (600 mg, 1.71 mmol, 80% yield) was dissolved in DCM (40 mL), DDQ (430 mg, 1.88 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. The product was separated by column chromatography (neutral Al_2O_3 and ethylacetate as eluents). Yield 412 mg (total yield 55%). M.p. > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.89 (brs, 1H, H-2 (indole)), 7.17–7.22 (m, 2H, indole), 7.41 (m, 1H, indole), 7.55–7.61 (m, 4H, Ph, H-5 (Py)), 7.70 (m, 2H, Ph), 8.04 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.57 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.71 (m, 1H, indole), 8.89 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)), 11.66 (brs, 1H, NH). Anal. calcd for $C_{22}H_{15}N_5$: C, 75.63; H, 4.33; N, 20.04%; found: C, 75.53; H, 4.50; N, 19.92%.

5-(4-Methoxyphenyl)-3-(pyridin-2-yl)-1,2,4-triazine (4h). Picolinimidohydrazide **9** (1 g, 7.34 mmol) and 2-(4-methoxyphenyl)-2-oxoacetaldehyde **8** (1.2 g, 7.34 mmol) were dissolved in ethanol (60 mL). The resulting mixture was stirred under reflux for 5 h and cooled to room temperature. Water (300 mL) was added and the resulting mixture was stirred at room temperature for 1 h. The precipitate formed was filtered off, washed with water and dried. The analytical sample was obtained by recrystallization (ethanol). Yield 1.57 g (81%). M. p. > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.91 (s, 3H, OMe), 7.12 (m, 2H, 4-methoxyphenyl), 7.56 (m, 1H, H-5 (Py)), 8.00 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.44 (m, 2H, 4-methoxyphenyl), 8.53 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.82 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)), 9.96 (s, 1H, H-5). Anal. calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20%; found: C, 68.01; H, 4.69; N, 20.98%.

General method for the interaction of 1,2,4-triazines with aryne intermediates

The corresponding 1,2,4-triazine **1** or **4** (1 mmol) was suspended in dry toluene (60 mL). Isoamyl nitrite (0.47 mL, 3.5 mmol) was added to this mixture. The resulting mixture was stirred under reflux while a solution of the corresponding anthranilic acid (3.5 mmol) in dry 1,4-dioxane (15 mL) was added by means of a dropping funnel for 30 min. The reaction mixture was heated under reflux for 1 h and then cooled to room temperature. Then the reaction mixture was washed with potassium hydroxide solution (3 M, 3 × 50 mL) and dried with anhydrous sodium sulfate. Solvents were removed under reduced pressure. The products of the reaction were separated by column chromatography (silica gel, the corresponding eluent).

10-(4,5-Diphenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2a). Eluent: ethyl acetate/toluene (1 : 1), R_f = 0.8. Yield 190 mg (49%). M.p. 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (m, 1H), 6.95 (m, 1H), 7.10–7.24 (m, 5H), 7.25–7.39 (m, 6H), 7.42 (m, 1H), 7.71 (m, 2H), 7.85 (m, 1H), 8.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.4, 109.1, 110.4, 115.9, 117.5, 120.8, 124.1, 124.2, 124.3, 124.6, 125.0, 127.4, 127.5, 127.6, 127.8, 127.9, 128.3, 128.6, 128.7 (2C), 128.9, 129.1, 129.4, 130.5, 131.2, 132.3, 135.9, 143.9. Anal. calcd for $C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50%; found: C, 80.62; H, 4.55; N, 14.57%.

10-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2b). Eluent: ethyl acetate/toluene (1 : 1), R_f = 0.8. Yield 150 mg (49%). M.p. 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (m, 1H), 7.12 (m, 1H), 7.36–7.45 (m, 2H, Ph), 7.46–7.54 (m, 3H, Ph), 7.72 (m, 1H), 7.90 (m, 3H), 8.24 (s, 1H, H-5), 8.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 110.6, 116.7, 117.3, 121.0, 121.1, 123.1, 124.1, 124.6, 124.9, 125.9 (2C), 127.8, 128.2, 128.9, 130.5, 130.7, 146.3. Anal. calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05%; found: C, 77.31; H, 4.42; N, 17.87%.

1-(Pyrido[1,2-*a*]indol-10-yl)-1*H*-phenantro[9,10-*d*][1,2,3]triazole (2c). Eluent: ethyl acetate/toluene (1 : 1), R_f = 0.8. Yield 230 mg (60%). M.p. 233–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (m, 1H), 7.03 (m, 1H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H), 7.60 (m, 2H), 7.74 (m, 1H), 7.83 (m, 1H), 8.06 (m, 1H), 8.52 (m, 1H), 8.66–8.76 (m, 2H), 8.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.4, 109.5, 110.8, 116.2, 117.9, 120.7, 121.3, 122.9, 123.0, 123.5, 124.0, 124.4, 124.7, 125.1, 125.2, 125.3, 127.1, 127.2, 127.7, 128.2 (2C), 129.1, 130.2, 131.1, 132.8, 141.4. Anal. calcd for $C_{26}H_{16}N_4$: C, 81.23; H, 4.20; N, 14.57%; found: C, 81.02; H, 4.11; N, 14.34%.

10-(5-Cyano-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2d). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.8. Yield 0.013 g (4%). M.p. 196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 7.22 (ddd, J = 9.4, 6.5, 1.0 Hz, 1H), 7.45 (m, 1H), 7.48–7.61 (m, 5H), 7.75 (m, 1H), 8.00 (m, 1H), 8.22 (m, 2H), 8.50 (m, 1H). Anal. calcd for $C_{21}H_{13}N_5$: C, 75.21; H, 3.91; N, 20.88%; found: C, 74.98; H, 3.94; N, 20.73%. CCDC # 1562142† contains the supplementary crystallographic data for this compound.

10-(5-Cyano-4-tolyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2e). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.8. Yield 0.013 g (3%).

M.p. 196–198 °C. IR-spectra (neat, ν/cm^{-1}): 2232 (CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H, Me), 6.77 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H), 7.21 (m, 1H), 7.37 (m, 2H, Tol), 7.44 (m, 1H), 7.48–7.56 (m, 2H), 7.75 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 8.11 (m, 2H, Tol), 8.48 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 110.0, 110.3, 110.7, 115.9, 117.2, 117.4, 121.7, 123.7, 124.4, 125.1, 125.1, 125.9, 126.6, 128.1, 130.0, 131.9, 140.6, 146.3. Anal. calcd for $C_{22}H_{15}N_5$: C, 75.63; H, 4.33; N, 20.04%; found: C, 75.54; H, 4.23; N, 20.09%.

2,3-Difluoro-10-(4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2g). Eluent: ethyl acetate/DCM (3 : 1), R_f = 0.8. Yield 0.153 g (37%). M.p. 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (ddd, J = 7.5, 6.8, 1.3 Hz, 1H), 6.99 (ddd, J = 9.8, 6.5, 1.0 Hz, 1H), 7.13 (dd, J = 10.4, 7.6 Hz, 1H), 7.19 (m, 4H), 7.21–7.26 (m, 2H), 7.30–7.39 (m, 3H), 7.63–7.72 (m, 3H), 8.17 (dd, J = 8.2, 1.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −141.95 (d, J = 20.7 Hz, 1F), −138.97 (d, J = 20.7 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.0 (d, J = 21.3 Hz), 103.9 (d, J = 21.3 Hz), 109.9, 115.9, 120.7 (d, J = 8.5 Hz), 122.5 (d, J = 8.5 Hz), 123.9, 124.6, 127.4, 127.5, 128.0, 128.6, 128.9, 129.3, 129.3, 130.9, 133.4 (d, J = 3.2 Hz), 135.8, 144.1, 147.0 (dd, J = 220.8, 14.6 Hz), 149.4 (dd, J = 222.4, 15.4 Hz). Anal. calcd for $C_{26}H_{16}F_2N_4$: C, 73.93; H, 3.82; N, 13.26%; found: C, 73.78; H, 3.72; N, 12.99%.

1-(2,3-Difluoropyrido[1,2-*a*]indol-10-yl)-1*H*-phenantro[9,10-*d*][1,2,3]triazole (2h). Eluent: ethyl acetate/DCM (3 : 1), R_f = 0.8. Yield 0.19 g (45%). M.p. 196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (m, 1H), 7.06 (m, 1H), 7.12–7.28 (m, 3H), 7.52 (m, 1H), 7.63 (m, 1H), 7.75 (m, 1H), 7.80–7.90 (m, 2H), 8.38 (dt, J = 7.4, 1.0, 1.0 Hz, 1H), 8.70 (d, J = 8.2 Hz, 1H), 8.74 (d, J = 8.2 Hz, 1H), 8.96 (dd, J = 8.2, 1.0 Hz, 1H); ^{19}F NMR (375.5 MHz, $CDCl_3$): −δ 141.29 (d, J = 20.4 Hz, 1F), −138.18 (d, J = 20.4 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.5 (d, J = 22.8 Hz), 104.4 (d, J = 21.6 Hz), 105.2, 110.3, 116.3, 120.4, 121.0 (d, J = 8.5 Hz), 122.5, 122.9 (d, J = 8.5 Hz), 123.0, 123.4, 124.2, 125.2 (d, J = 3.7 Hz), 127.2, 127.3, 127.9, 128.3, 129.1, 130.1, 131.2, 134.0 (d, J = 3.0 Hz), 136.1, 141.5, 147.3 (dd, J = 221.0, 16.8 Hz), 149.1, 149.8 (dd, J = 223.0, 15.3 Hz). Anal. calcd for $C_{26}H_{14}F_2N_4$: C, 74.28; H, 3.36; N, 13.33%; found: C, 74.11; H, 3.18; N, 12.95%.

2,3-Difluoro-10-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2i). Eluent: ethyl acetate/DCM (3 : 1), R_f = 0.8. Yield 0.127 g (35%). M.p. 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (ddd, J = 6.9, 6.9, 1.0 Hz, 1H), 7.12 (ddd, J = 9.5, 6.6, 1.2 Hz, 1H), 7.18 (m, 2H, 4-FC_6H_5), 7.55–7.65 (m, 2H), 7.76 (dd, J = 9.8, 6.4 Hz, 1H), 7.94 (m, 2H, 4-FC_6H_5), 8.13 (s, 1H, H-4), 8.25 (m, 1H); ^{19}F NMR (375.5 MHz, $CDCl_3$): δ −141.25 (d, 1F, J 20.4 Hz), −138.46 (d, 1F, J = 20.4 Hz), −113.18 (s, 1F). Anal. calcd for $C_{20}H_{11}F_3N_4$: C, 65.94, H, 3.04, N, 15.38%; found: C, 65.82; H, 2.89; N, 15.13%.

2,3-Dimethoxy-10-(4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2j). Eluent: DCM/ethyl acetate (3 : 2), R_f = 0.6. Yield 0.116 g (26%). M.p. 201–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, OMe), 4.00 (brs, 3H, OMe), 6.58 (brs, 1H), 6.69 (brs, 1H), 6.79–6.92 (brs, 1H), 7.12–7.29 (m, 7H), 7.30–7.42 (m, 3H), 7.72 (m, 2H), 8.18 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 56.4, 93.1, 97.9, 101.4, 109.0, 116.0, 118.7, 121.7, 122.3, 123.2, 127.5, 127.9, 127.9, 128.5, 128.7, 129.1, 129.4, 131.1, 131.2, 135.5, 143.9, 146.6, 148.7. Anal. calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55%; found: C, 75.26; H, 4.89; N, 12.53%. CCDC # 1562139† contains the supplementary crystallographic data for this compound.

2,3-Dimethoxy-10-(4-phenyl-1*H*-1,2,3-triazole-1-yl)pyrido[1,2-*a*]indole (2k). Eluent: DCM/ethyl acetate (3 : 1), R_f = 0.8. Yield 0.093 g (25%). M.p. 189–191 °C. ^{1}H NMR ($CDCl_3$, +27 °C): δ 3.96 (s, 3H, OMe), 4.03 (brs, 3H, OMe), 6.61 (brs, 1H), 6.98 (brs, 1H), 7.19 (brs, 1H), 7.32 (s, 1H), 7.38 (m, 1H), 7.45–7.55 (m, 3H), 7.98 (m, 2H), 8.18 (s, 1H), 8.24 (brs, 1H); ^{1}H NMR ($CDCl_3$, −56 °C): δ 3.95 (s, 3H, OMe), 4.02 (s, 3H, OMe), 6.64 (t, J = 6.5, 6.5 Hz, 1H), 7.00 (td, J = 7.5, 7.5, 1.9 Hz, 1H), 7.10 (s, 1H), 7.29 (s, 1H), 7.38–7.56 (m, 4H), 7.99 (m, 2H), 8.24 (s, 1H), 8.28 (d, J = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 56.3, 56.4, 93.1, 97.8, 103.1, 109.1, 115.9, 117.3, 121.1, 121.7, 122.5, 123.3, 125.8, 128.3, 129.0, 129.1, 130.7, 146.9, 147.5, 149.0. Anal. calcd for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13%; found: C, 71.30; H, 4.81; N, 15.02%.

1-(2,3-Dimethoxypyrido[1,2-*a*]indol-10-yl)-1*H*-phenanthro[9,10-*d*][1,2,3]triazole (2l). Eluent: DCM/ethyl acetate (3 : 1), R_f = 0.8. Yield 0.195 g (44%) M.p. 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H, OMe), 4.00–4.15 (brs, 3H, OMe), 6.70 (brs, 1H), 6.75 (brs, 1H), 6.90–7.00 (brs, 1H), 7.12–7.20 (brs, 1H), 7.20–7.28 (m, 1H), 7.47 (s, 1H), 7.57–7.65 (m, 2H), 7.72–7.80 (td, J = 8.5, 7.5, 1.5 Hz, 1H), 7.80–7.87 (td, J = 7.5, 7.5, 1.0 Hz, 1H), 8.39 (brs, 1H), 8.68–8.71 (dd, J = 8.4, 1.0, 1H), 8.71–8.74 (dd, J = 8.4, 1.0 Hz, 1H), 8.93–9.00 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 56.5, 93.4, 97.9, 102.1, 109.4, 116.0, 119.2, 120.6, 122.1, 122.9, 122.9, 123.0, 123.4, 123.5, 124.0, 125.2, 127.1, 127.3, 127.8, 128.2, 129.1, 130.2, 131.1, 131.6, 141.3, 146.9, 149.2. Anal. calcd for $C_{28}H_{20}N_4O_2$: C, 75.66; H, 4.54; N, 12.60%; found: C, 75.56; H, 4.56; N, 12.50%.

3-Cyano-4-phenyl-1-(2-pyridyl)isoquinoline (3a). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.6. Yield 0.111 g (36%). M.p. 171–173 °C. IR-spectra (neat, ν/cm^{-1}): 2227 (CN). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53–7.60 (m, 3H, Ph), 7.62–7.69 (m, 3H, Ph, H-5 (py)), 7.74 (m, 1H, isoquin.), 7.82–7.87 (m, 2H, isoquin.), 8.06 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H, H-4 (py)), 8.12 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (py)), 8.80 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (py)), 8.92 (m, 1H, isoquin.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.6, 123.9, 125.4, 125.6, 126.5, 127.5, 128.6, 128.9, 129.4, 130.1, 130.2, 131.4, 133.8, 135.9, 137.3, 140.5, 148.7, 157.0. Anal. calcd for $C_{21}H_{13}N_3$: C, 82.07; H, 4.26; N, 13.67%; found: C, 82.07; H, 4.26; N, 13.62%.

3-Cyano-1-(2-pyridyl)-4-tolylisoquinoline (3b). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.6. Yield 0.119 g (31%). M.p. 213–215 °C. IR-spectra (neat, ν/cm^{-1}): 2224 (CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H, Me), 7.42 (m, 4H, Tol), 7.47 (m, 1H, H-5 (py)), 7.71–7.79 (m, 2H, isoquin.), 7.83 (m, 1H, isoquin.), 7.97 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H, H-4 (py)), 8.13 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (py)), 8.80–8.86 (m, 2H, isoquin., H-6 (py)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 117.8, 123.9, 125.4, 125.6, 126.6, 127.5, 128.5, 129.6, 130.0, 130.1, 130.7, 131.3, 136.0, 137.3, 139.4, 140.6, 148.6, 157.0, 158.0. Anal.

calcd for $C_{21}H_{12}BrN_3$: C, 82.22; H, 4.70; N, 13.07%; found: C, 82.05; H, 4.54; N, 12.93%.

4-(4-Bromophenyl)-3-cyano-1-(2-pyridyl)isoquinoline (3c). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.65. Yield 0.150 g (39%). M.p. 213–215 °C. IR-spectra (neat, ν/cm^{-1}): 2224 (CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 2H, 4-BrPh), 7.48 (m, 1H, H-5 (py)), 7.72–7.81 (m, 5H, 4-BrPh, isoquin.), 7.97 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H, H-4 (py)), 8.14 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (py)), 8.82 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (py)), 8.86 (m, 1H, isoquin.); ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.4, 124.0, 124.1, 125.3, 125.6, 126.1, 127.4, 128.8, 130.3, 131.6, 131.8, 132.3, 132.7, 135.6, 137.3, 139.2, 148.7, 156.8, 158.5. Anal. calcd for $C_{21}H_{12}BrN_3$: C, 65.30; H, 3.13; N, 10.88%; found: C, 65.11; H, 2.97; N, 10.56%. CCDC # 1562138† contains the supplementary crystallographic data for this compound. Crystallographic data are collected as shown in the ESI.†

6,7-Dimethoxy-1-(pyridin-2-yl)-3,4-diphenylisoquinoline (3d). Eluent: DCM/ethyl acetate (3 : 2), R_f = 0.4. Yield 0.029 mg (7%). M.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, OMe), 3.99 (s, 3H, OMe), 6.96 (s, 1H, H-8 (isoquin.)), 7.12–7.22 (m, 3H, Ph), 7.23–7.32 (m, 2H, Ph), 7.32–7.44 (m, 6H, Ph, H-5 (Py)), 7.88–7.95 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.21–8.25 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.30 (s, 1H, H-5 (isoquin.)), 8.80 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.4, 50.7, 99.0, 99.5, 100.7, 116.4, 117.8, 120.4, 121.6, 122.1, 122.3, 123.2, 125.0, 125.1, 125.9, 129.1, 131.9, 132.7, 135.8, 142.9, 143.4, 144.7, 147.2, 148.3, 153.9. Anal. calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69%; found: C, 80.29; H, 5.35; N, 6.61%.

6,7-Dimethoxy-1-(pyridin-2-yl)-4-phenylisoquinoline-3-carbonitrile (3f). Eluent: DCM/ethyl acetate (3 : 1), R_f = 0.3. Yield 0.037 g (10%). M.p. 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, OMe), 4.00 (s, 3H, OMe), 7.00 (s, 1H, H-8 (isoquin.)), 7.42–7.47 (ddd, J = 7.7, 4.8, 1.0 Hz, 1H, H-5 (Py)), 7.50–7.70 (m, 5H, Ph), 7.95–8.03 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.20–8.23 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.46 (s, 1H, H-5 (isoquin.)), 8.80 (dd, J = 4.8, 2.0 Hz, 1H, H-6 (Py)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.7, 50.9, 99.3, 101.6, 112.8, 118.6, 118.8, 119.1, 120.4, 123.7, 124.1, 124.8, 127.6, 129.0, 132.2, 133.6, 143.1, 146.9, 148.1, 149.7, 152.3. Anal. calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44%; found: C, 75.18; H, 4.57; N, 11.48%.

10-(4-Phenyl-5-phenylethynyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15a). Eluent: DCM/ethyl acetate (5 : 2), R_f = 0.7. Yield 115 mg (28%). M.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69 (td, J = 6.5, 6.5, 1.0 Hz, 1H), 7.08–7.16 (m, 3H), 7.20–7.33 (m, 3H), 7.38–7.57 (m, 5H), 7.61 (m, 1H), 7.89 (m, 1H), 7.99 (m, 1H), 8.37 (m, 2H), 8.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.7 (C-sp), 102.4 (C-sp), 109.4, 110.5, 117.0, 118.6, 119.1, 121.0, 121.6, 124.0, 124.2, 124.3, 124.7, 126.4, 128.0, 128.4, 128.6, 128.8, 129.3, 130.5, 131.3, 131.5, 147.3. Anal. calcd for $C_{28}H_{18}N_4$: C, 81.93; H, 4.42; N, 13.65%; found: C, 81.76; H, 4.23; N, 13.46%.

10-(4-Phenyl-5-(pyrrolidin-1-yl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15b). Eluent: DCM/ethyl acetate (5 : 1), R_f = 0.6. Yield 133 mg (35%). M.p. 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (m, 4H, pyrrolidine), 2.94 (m, 4H, pyrrolidine), 6.66 (td, J = 6.5, 6.5, 1.0 Hz, 1H), 7.07 (ddd, J = 9.3, 6.5, 1.0 Hz, 1H), 7.33–7.49 (m, 7H), 7.64 (m, 1H), 7.75 (m, 2H), 7.96 (m, 1H), 8.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (pyrrolidine), 44.4 (pyrrolidine), 99.9, 103.8, 105.2, 111.1, 112.5, 115.6, 119.0, 119.0, 119.3, 120.1, 122.1, 122.6, 122.9, 123.1, 127.1, 127.3, 129.0, 137.0. Anal. calcd for $C_{24}H_{21}N_5$: C, 75.97; H, 5.58; N, 18.46%; found: C, 75.79; H, 5.44; N, 18.31%.

10-(5-Metoxy-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15c). Eluent: DCM/ethyl acetate (15 : 1), R_f = 0.6. Yield 136 mg (40%). M.p. 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H, OMe), 6.68 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 7.11 (ddd, J = 9.3, 6.5, 1.0 Hz, 1H), 7.33–7.43 (m, 2H), 7.45–7.54 (m, 4H), 7.78 (m, 1H), 7.97 (m, 1H), 8.06 (m, 2H), 8.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.6, 109.4, 110.5, 116.5, 118.0, 121.1, 124.2, 124.3, 124.6, 124.9, 125.7, 127.7, 128.1, 128.8, 130.6, 131.2, 131.5, 149.4. Anal. calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46%; found: C, 73.91; H, 4.61; N, 16.29%.

10-(3-Methyl-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15d). Eluent: DCM/ethyl acetate (9 : 1), R_f = 0.8. Yield 159 mg (49%). M.p. 151–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 6.66 (m, 1H), 7.06 (m, 1H), 7.30 (m, 1H), 7.34–7.42 (m, 2H), 7.45 (m, 1H), 7.47–7.56 (m, 3H), 7.91 (2H), 7.97 (m, 1H), 8.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8, 100.9, 109.3, 110.7, 116.1, 117.4, 121.0, 124.3, 124.5, 124.8, 124.9, 126.9, 127.6, 128.0, 128.8, 131.9, 132.1, 132.5, 143.9. Anal. calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27%; found: C, 77.71; H, 5.06; N, 17.39%.

10-(5-(1*H*-indol-3-yl)-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15e). Eluent: DCM/ethyl acetate (5 : 1), R_f = 0.8. Yield 77 mg (18%). M.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (ddd, J = 6.5, 6.5, 1.2 Hz, 1H), 6.88–6.94 (m, 2H), 6.97 (d, J = 2.7 Hz, 1H, H-2 (indole)), 7.08–7.15 (m, 2H), 7.22 (m, 1H), 7.25–7.32 (m, 6H), 7.42 (m, 1H), 7.79 (m, 2H, Ph), 7.85 (m, 1H), 8.11 (brs, 1H, NH), 8.31 (m, 1H). Anal. calcd for $C_{28}H_{19}N_5$: C, 79.04; H, 4.50; N, 16.46%; found: C, 78.82; H, 4.35; N, 16.29%.

(*E*)-10-(4-Phenyl-4-styryl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15f). Yield 128 mg (31%). M.p. 139–141 °C. IR-spectra (neat, ν/cm^{-1}): 1198, 1262, 1338, 1474, 1628, 1725, 2919, 3058. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (td, J = 6.5, 6.5, 1.0 Hz, 1H), 6.88 (s, 2H, PhCHCH), 7.04–7.12 (m, 3H), 7.18 (m, 3H), 7.36–7.48 (m, 4H), 7.52 (m, 2H), 7.64 (m, 1H), 7.92 (m, 2H), 8.00 (m, 1H), 8.46 (m, 1H). ^{1}H NMR (400 MHz, CD_3CN): 6.71–6.80 (m, 2H), 6.95 (d, J = 16.8 Hz, 1H, CHCH), 7.09 (m, 2H), 7.14–7.22 (m, 4H), 7.33–7.50 (m, 4H), 7.55 (m, 3H), 7.91 (m, 2H), 8.19 (m, 1H), 8.70 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 100.9, 110.0, 112.6, 113.2, 115.6, 117.3, 121.3, 124.4, 125.0, 126.5, 126.5, 127.0, 128.2, 128.3, 128.7, 129.2, 129.2, 129.4, 131.8, 132.1, 133.3, 135.4, 136.0, 144.0. Anal. calcd for $C_{28}H_{20}N_4$: C, 81.53; H, 4.89; N, 13.58%; found: C, 81.33; H, 4.90; N, 13.61%.

10-(5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15g). Eluent: DCM/ethyl acetate (2 : 3), R_f = 0.8. Yield 85 mg (25%). M.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (s, 3H, OMe), 6.62 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 6.69 (m, 2H,

4-methoxyphenyl), 6.98 (m, 1H), 7.19 (m, 2H, 4-methoxyphenyl), 7.30–7.40 (m, 4H), 7.93 (m, 1H), 7.98 (s, 1H, H-4), 8.39 (m, 1H). Anal. calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46%; found: C, 73.78; H, 4.58; N, 16.21%.

10-(4-(4-Nitrophenyl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15h). Eluent: DCM/ethyl acetate (10 : 1), R_f = 0.8. Yield 142 mg (40%). M.p. > 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 7.16 (ddd, J = 9.6, 6.5, 1.2 Hz, 1H), 7.44 (m, 1H), 7.53 (m, 1H), 7.73 (m, 1H), 7.85 (m, 1H), 8.00 (m, 1H), 8.16 (m, 2H, nitrophenyl), 8.37 (m, 2H, nitrophenyl), 8.38 (s, 1H, H-5 (triazole)), 8.46 (m, 1H). Anal. calcd for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.69; N, 19.71%; found: C, 67.51; H, 3.56; N, 19.48%.

2,3-Difluoro-10-(5-cyano-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15i). Eluent: DCM, R_f = 0.7. Yield 137 mg (37%). M.p. 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 7.23 (ddd, J = 9.4, 6.5, 1.0 Hz, 1H), 7.45–7.61 (m, 6H), 7.71 (dd, J = 5.8, 3.2 Hz, 1H), 7.80 (dd, J = 9.6, 6.2 Hz, 1H), 8.21 (m, 2H), 8.32 (m, 1H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −142.83 (d, J = 21.9 Hz, 1F), −139.43 (d, J = 21.9 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.4 (d, J = 23.1 Hz), 100.2 (d, J = 4.2 Hz), 104.2 (d, J = 20.5 Hz), 109.2, 109.9, 110.7, 115.9, 119.6 (d, J = 7.7 Hz), 122.9 (d, J = 9.6 Hz), 124.2, 125.9, 126.7, 129.3, 130.5, 132.5, 132.9 (d, J = 3.0 Hz), 147.6 (dd, J = 245.6, 17.3 Hz), 149.8 (d, J = 247.0, 15.9 Hz), 151.9. Anal. calcd for $C_{21}H_{11}F_2N_5$: C, 67.92; H, 2.99; N, 18.86%; found: C, 67.90; H, 2.88; N, 18.71%.

2,3-Difluoro-10-(5-cyano-4-tolyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15j). Eluent: DCM/ethyl acetate (7 : 5), R_f = 0.7. Yield 180 mg (45%). M.p. 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H, Me), 6.81 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 7.23 (ddd, J = 9.4, 6.5, 1.0 Hz, 1H), 7.37 (m, 2H, Tol), 7.49 (m, 2H), 7.79 (dd, 1H, 9.5, 6.3 Hz), 8.09 (m, 2H, Tol), 8.31 (m, 1H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −140.55 (d, J = 19.4 Hz, 1F), −137.42 (d, J = 19.4 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 99.3 (d, J = 20.9 Hz), 100.1 (d, J = 3.8 Hz), 104.1 (d, J = 21.2 Hz), 108.7, 110.0, 110.6, 115.8, 119.5 (d, J = 8.2 Hz), 122.7 (d, J = 9.5 Hz), 124.1, 124.7, 125.8, 126.5, 129.9, 132.8 (d, J = 3.0 Hz), 140.7, 147.5 (dd, J = 246.7, 16.3 Hz), 149.7 (dd, J = 247.6, 15.4 Hz), 152.0. Anal. calcd for $C_{22}H_{13}F_2N_5$: C, 68.57; H, 3.40; N, 18.17%; found: C, 68.43; H, 3.23; N, 17.99%.

2,3-Difluoro-10-(4-phenyl-5-phenylethynyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15k). Eluent: DCM/ethyl acetate (5 : 1), R_f = 0.7. Yield 183 mg (41%). M.p. 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (td, J = 6.9, 6.9, 1.0 Hz, 1H), 7.13 (ddd, J = 9.2, 6.3, 0.8 Hz, 1H), 7.19–7.23 (m, 2H), 7.27–7.37 (m, 3H), 7.44 (m, 1H), 7.54 (m, 2H), 7.58–7.67 (m, 2H), 7.78 (dd, J = 9.8, 6.5 Hz, 1H), 8.28 (m, 1H), 8.34 (m, 2H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −141.68 (d, J 20.7 Hz, 1F), −139.05 (d, J = 20.7 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.2 (C-sp), 99.1 (d, J = 22.6 Hz), 102.1 (d, J = 3.6 Hz), 102.7 (C-sp), 105.2 (d, J = 21.9 Hz), 110.1, 117.1, 119.0, 119.7 (d, J = 8.4 Hz), 121.3, 122.7 (d, J = 9.8 Hz), 123.9, 124.6, 126.4, 128.5, 128.8, 128.8, 129.6, 130.3, 131.3, 132.5 (d, J = 3.1 Hz), 147.3 (dd, J = 244.1, 16.3 Hz), 147.6, 149.3 (dd, J = 244.8, 14.3 Hz). Anal. calcd for $C_{28}H_{16}F_2N_4$: C, 75.33; H, 3.61; N, 12.55%; found: C, 75.19; H, 3.50; N, 12.39%.

2,3-Difluoro-10-(4-phenyl-5-(pyrrolidin-1-yl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15l). Eluent: DCM/ethyl acetate (10 : 3), R_f = 0.7. Yield 153 g (40%). M.p. 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (m, 4H, pyrrolidine), 2.93 (m, 4H, pyrrolidine), 6.69 (td, J = 6.5, 6.5, 1.0 Hz, 1H), 7.07 (ddd, J = 9.3, 6.5, 1.0 Hz, 1H), 7.34–7.42 (m, 3H), 7.43–7.50 (m, 2H), 7.67–7.78 (m, 3H), 8.25 (m, 1H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −142.02 (d, J = 20.7 Hz, 1F), −139.03 (d, J = 20.7 Hz, 1F). Anal. calcd for $C_{24}H_{19}F_2N_5$: C, 69.39; H, 4.61; N, 16.86%; found: C, 69.22; H, 4.51; N, 16.72%.

2,3-Difluoro-10-(5-methoxy-4-tolyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15m). Eluent: DCM/ethyl acetate (15 : 1), R_f = 0.7. Yield 0.19 g (49%). M.p. 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H, Me), 3.64 (s, 3H, OMe), 6.71 (td, J = 6.5, 6.5, 1.0 Hz, 1H), 7.10 (ddd, J = 9.3, 6.2, 0.8 Hz, 1H), 7.30 (m, 2H, Tol), 7.50–7.57 (m, 2H), 7.75 (dd, J = 9.7, 6.3 Hz, 1H), 7.91 (m, 2H, Tol), 8.26 (m, 1H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −141.69 (d, J = 20.6 Hz, 1F), −138.79 (d, J = 20.6 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 61.4, 99.1 (d, J = 22.8 Hz), 100.0, 104.7 (d, J = 20.2 Hz), 110.1, 116.7, 119.7 (d, J = 8.8 Hz), 122.7 (d, J = 10.3 Hz), 124.0, 124.7, 125.8, 127.4, 129.5, 131.4, 132.4 (d, J = 2.9 Hz), 137.7, 147.3 (dd, J = 245.2, 15.5 Hz), 148.8, 149.6 (dd, J = 245.2, 15.5 Hz). Anal. calcd for $C_{22}H_{16}F_2N_4O$: C, 67.69; H, 4.13; N, 14.35%; found: C, 67.50; H, 3.98; N, 14.15%.

(*E*)-2,3-Difluoro-10-(4-phenyl-4-styryl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15n). Yield 188 mg (42%). M.p. 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 6.84 (s, 2H, PhCHCH), 7.06–7.13 (m, 3H), 7.18–7.24 (m, 3H), 7.34–7.48 (m, 3H), 7.53 (m, 2H), 7.79 (dd, 9.8, 6.2 Hz, 1H), 7.90 (m, 2H), 8.29 (m, 1H); ^{1}H NMR (400 MHz, CD_3CN): 6.73 (d, J = 16.6 Hz, 1H, CHCH), 6.80 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 6.94 (d, J = 16.6 Hz, 1H, CHCH), 7.10–7.23 (m, 6H), 7.35 (m, 1H), 7.39–7.50 (m, 2H), 7.55 (m, 2H), 7.90 (m, 2H), 8.12 (dd, J = 9.8, 6.2 Hz, 1H), 8.56 (m, 1H); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −141.47 (d, J = 20.8 Hz, 1F), −138.37 (d, J = 20.8 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.2 (d, J = 23.2 Hz), 99.3, 101.7, 104.4 (d, J = 21.3 Hz), 110.1, 112.5, 116.4, 120.7 (d, J = 9.5 Hz), 122.8 (d, J = 9.5 Hz), 124.0, 124.9, 126.6, 128.3, 128.4, 128.7, 128.7, 128.8, 131.6, 132.8, 133.5, 135.1, 136.0, 144.7, 147.4 (dd, J = 245.6, 16.5 Hz), 149.6 (dd, J = 245.6, 14.8 Hz). Anal. calcd for $C_{28}H_{18}F_2N_4$: C, 74.99; H, 4.05; N, 12.49%; found: C, 74.88; H, 3.93; N, 12.40%.

2,3-Dimetoxy-10-(4-phenyl-5-(pyrrolidin-1-yl)-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15o). Eluent: DCM/ethyl acetate (10 : 3), R_f = 0.7. Yield 110 mg (25%). M.p. 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (m, 4H, pyrrolidine), 2.94 (m, 4H, pyrrolidine), 3.93 (s, 3H, OMe), 4.03 (s, 3H, OMe), 6.61 (m, 1H), 6.94 (m, 1H), 6.99 (s, 1H), 7.28–7.39 (m, 3H), 7.42–7.49 (m, 2H), 7.76 (m, 2H), 8.26 (m, 1H). Anal. calcd for $C_{26}H_{25}N_5O_2$: C, 71.05; H, 5.73; N, 15.93%; found: C, 70.80; H, 5.55; N, 15.68%.

2,3-Dimethoxy-10-(3-methyl-4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (15p). Eluent: DCM/ethyl acetate (9 : 1), R_f = 0.7. Yield 108 mg (28%). M.p. 140–142 °C. ^{1}H NMR

(400 MHz, $CDCl_3$): δ 2.40 (s, 3H, Me), 3.93 (s, 3H, OMe), 4.04 (s, 3H, OMe), 6.65 (td, J = 6.9, 6.9, 1.0 Hz, 1H), 6.89 (s, 1H), 6.98 (ddd, J = 9.2, 6.5, 0.8 Hz, 1H), 7.23 (m, 1H), 7.37 (s, 1H), 7.52 (m, 3H, Ph), 7.92 (m, 2H, Ph), 8.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8, 56.3, 56.5, 93.3, 97.6, 100.6, 109.2, 115.8, 119.0, 122.6, 123.4, 126.9, 127.6, 128.8, 131.2, 131.9, 132.0, 143.8, 146.8, 149.1, 160.5. Anal. calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57%; found: C, 71.98; H, 5.09; N, 14.76%.

(*E*)-2,3-Dimethoxy-10-(4-phenyl-4-styryl-1*H*-1,2,3-triazol-1-yl) pyrido[1,2-*a*]indole (15q). Yield 142 mg (30%). M. p. 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H, OMe), 4.05 (s, 3H, OMe), 6.65 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 6.90 (s, 2H, PhCHCH), 6.93–7.00 (m, 2H), 7.10 (m, 2H), 7.20 (m, 2H), 7.34 (m, 1H), 7.36–7.47 (m, 3H), 7.52 (m, 2H), 7.93 (m, 2H), 8.30 (m, 1H); ^{1}H NMR (400 MHz, CD_3CN): δ 3.74 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.71 (td, J = 6.6, 6.6, 1.0 Hz, 1H), 6.76 (d, J = 16.7 Hz, CHCH, 1H), 6.96 (m, 2H), 7.03 (m, 1H), 7.09–7.14 (m, 2H), 7.17–7.24 (m, 3H), 7.30 (m, 2H), 7.46 (m, 1H), 7.55 (m, 2H), 7.65 (s, 1H), 7.92 (m, 2H), 8.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.2, 56.5, 93.4, 98.2, 101.4, 109.3, 113.0, 116.2, 118.8, 122.0, 122.6, 123.3, 126.5, 128.2, 128.4, 128.6, 128.6, 128.8, 131.2, 131.8, 132.7, 134.6, 136.2, 144.4, 146.9, 149.2. Anal. calcd for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.86%; found: C, 76.09; H, 5.10; N, 11.90%.

4-Phenyl-5-phenylethynyl-1-(2-pyridyl)isoquinoline (16a). Eluent: DCM/ethyl acetate (5 : 2), R_f = 0.55. Yield 46 mg (12%). M.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.30 (m, 5H), 7.43 (m, 1H, H-5 (Py)), 7.50–7.65 (m, 6H), 7.70 (m, 1H, isoquinoline), 7.94 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H, H-4 (Py)), 8.09 (m, 1H, isoquinoline), 8.57 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.81 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 89.6 (C-sp), 92.4 (C-sp), 122.9, 123.5, 126.5, 125.8, 125.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 130.5, 130.8, 131.8, 143.6, 136.3, 136.7, 137.0, 137.2, 148.6, 157.6, 157.8. Anal. calcd for $C_{28}H_{18}N_2$: C, 87.93; H, 4.74; N, 7.32%; found: C, 87.77; H, 4.60; N, 7.06%.

(*E*)-4-Phenyl-1-(2-pyridyl)-3-styrylisoquinoline (16b). Yield 12 mg (3%). M.p. 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 15.6 Hz, CHCH, 1H), 7.19 (m, 1H), 7.22–7.30 (m, 2H), 7.37–7.46 (m, 5H), 7.48–7.60 (m, 6H), 7.93–8.00 (m, 2H, CHCH, H-4 (Py)), 8.21 (dd, J = 7.8, 0.8 Hz, 1H, H-3 (Py)), 8.67 (m, 1H, isoquinoline), 8.82 (dd, J = 4.8, 1.8 Hz, 1H, H-6 (Py)). Anal. calcd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29%; found: C, 87.32; H, 5.11; N, 7.22%.

6,7-Dimethoxy-1-(pyridin-2-yl)-4-tolylisoquinoline-3-carbonitrile (16c). Eluent: DCM/ethyl acetate (3 : 1), R_f = 0.55. Yield 0.053 g (14%). M.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, Me), 3.83 (s, 3H, OMe), 3.99 (s, 3H, OMe), 7.04 (s, 1H, H-5 (isoquin.)), 7.38–7.45 (brs, 5H, Ph, H-5 (Py)), 7.95–7.96 (ddd, J = 7.7, 7.7, 2.0 Hz, 1H, H-4 (Py)), 8.19–8.21 (dd, J = 7.7, 1.0 Hz, 1H, H-3 (Py)), 8.44 (s, 1H, H-8 (isoquin.)), 8.78–8.79 (s, J = 4.8 Hz, 1H, H-6 (Py)). Anal. calcd for $C_{24}H_{19}N_3O_2$: C, 75.59; H, 4.96; N, 11.00%; found: C, 75.57; H, 5.02; N, 11.02%.

Conflicts of interest

There are no conflicts to declare.

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