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(Hetero)Arene Ring-Fused [1,2,4]Triazines

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Abstract: Synthetic access to a five (hetero)arene ring-fused 3-phenyl[1,2,4]triazines is described. The resulting compounds were characterized via ^{1}H and ^{13}C NMR, IR, UV–vis spectroscopy and HRMS. The structure of 3-phenyl[1,2,4]triazino[5,6-*c*]quinoline was unambiguously confirmed by single crystal XRD.

Keywords: [1,2,4]triazines; ring-fused arene; heterocycles

1. Introduction

[1,2,4]Triazine and its derivatives represent an important class of nitrogen heterocycles that exhibit many biological activities, e.g., antitumor [1,2], antibacterial [3,4], anti-inflammatory [5] and antiviral activities [3,6] (Figure 1). Moreover, [1,2,4]triazines are also often used in materials chemistry for a wide range of organic optoelectronic applications, such as strong electron acceptor units for n-type semiconductors [7,8] or dye-sensitized solar cells [9].

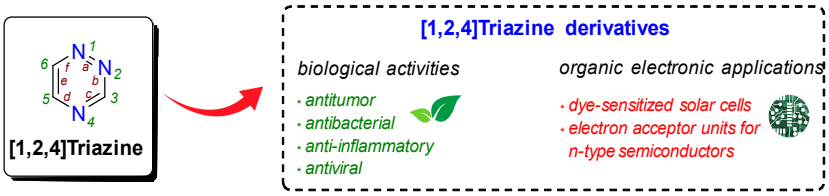

Figure 1. Chemical structure of [1,2,4]triazine and properties of its derivatives.

In spite of the broad application of [1,2,4]triazine derivatives, there are surprisingly few investigations of their (hetero)arene ring-fused derivatives [10–14], and existing reports are mostly outdated. There has been no systematic investigation of the synthetic access and study of their electronic properties. Thus, analytical data, XRD structures and UV–vis spectroscopic data are often limited.

In this work we present synthetic access to a group of five [1,2,4]triazines **1a**–**1e** with a fused (hetero)arene ring system at the *e* edge (Figure 2) and study the effect of ring fusion on their properties.

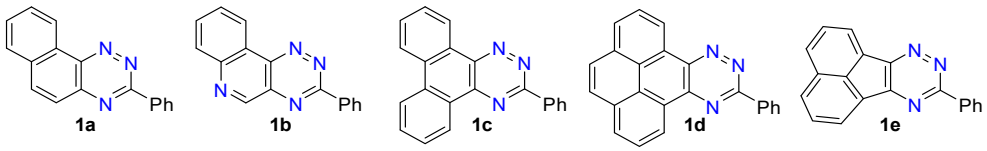

Figure 2. Structure of π-extended [1,2,4]triazines **1a**–**1e**.

2. Results and Discussion

Analysis of the literature data indicates that there are several synthetic methods suitable for the construction of ring-fused [1,2,4]triazines, including reductive cyclization

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of nitrophenylhydrazides [11,14–16], reductive deoxygenation of triazine *N*-oxides [12], photochemical oxidation of dihydro[1,2,4]triazines [10], reaction of *N*-aminobezamidine hydrochlorides with aryl ortho-quinone [17,18], one-pot three-step reaction of *N*-tosyl hydrazones and aziridines [19] and reaction of cyclic triazole with hydrazones [20].

In this work, two methods were used to synthesize a series of (hetero)arene ring-fused [1,2,4]triazines **1** (Figure 3). Method A involved reductive cyclization of nitroarylhydrazides **2** [15,16] obtained from ortho-nitro hydroxyarenes **3** through aromatic nucleophilic substitution with benzhydrazide [21,22]. In Method B, appropriate ortho-quinones **4** reacted with benzamidrazone [23] to yield desired triazines **1**.

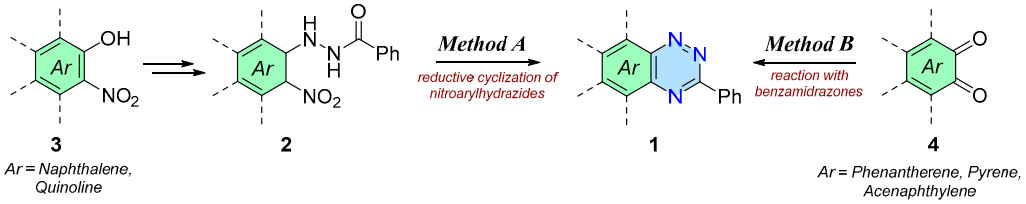
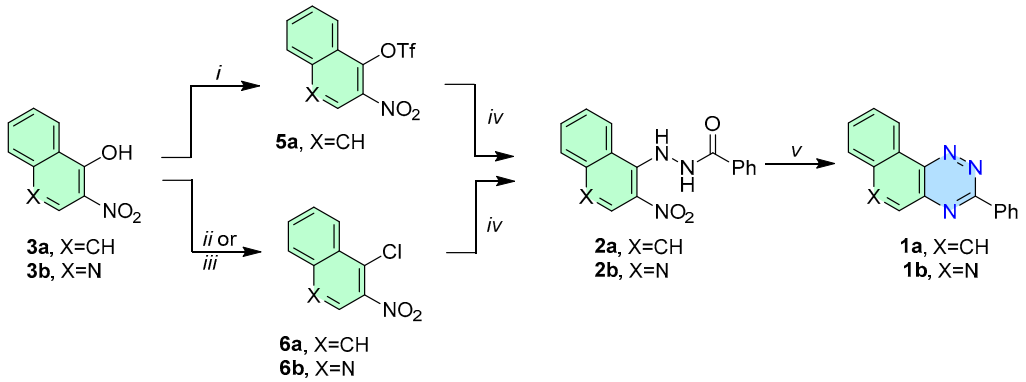


Figure 3. Two synthetic strategies towards [1,2,4]triazines **1** applied herein.

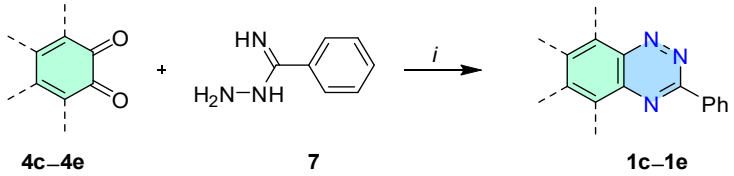
The requisite 3-phenyl[1,2,4]triazines **1a** and **1b** were synthesized by the cyclization reaction of hydrazides **2** under reductive conditions, as shown in Scheme 1. Triazines **1a** and **1b** were obtained in 80–84% and 50–55% yields, respectively. Appropriate hydrazides **2** were prepared in an aromatic nucleophilic substitution of triflate **5a** [24] or chlorides **6a**–**6b** [25] with benzhydrazide in DMSO. The use of triflate **5a** gave hydrazide **2a** in a 90% yield, and the utilization of chloride **6a** allowed to obtain hydrazide **2a** in a 69% yield. In the case of the reaction of 4-chloro-3-nitroquinoline (**6b**) with benzhydrazide, the desired hydrazide **2b** was formed in a 93% yield. Triflate **5a** was synthesized by the reaction of **3a** with triflic anhydride [26] in the presence of Et_3N in CH_2Cl_2 in a 91% yield. Chlorides **6a** and **6b** were obtained from appropriate ortho-nitrohydroxyarenes **3** according to the literature procedures [27–29] in 72% and 75% yields, respectively.



Scheme 1. Synthesis of triazines **1a**–**b**. Reagents and conditions: (*i*) triflic anhydride, Et_3N, DCM, 0 °C, 3 h, 91% yield; (*ii*) for obtaining **6a**; (*a*) $(NH_4)_2CO_3$, NH_{3aq}, 120 °C, overnight, 82% yield; (*b*) $NaNO_2$, H_2SO_4 aq, CuCl, HCl, 88% yield (**6a**); (*iii*) for obtaining **6b**; $POCl_3$, PCl_5, 110 °C, overnight, 75% yield (**6b**); (*iv*) benzhydrazide, DMSO, 65 °C, overnight; **2a**: 90% yield (from **5a**), 69% yield (from **6a**); **2b**: 93% yield (from **6b**); (*v*) (*a*) Sn, AcOH, 50 °C for 1 h and then 30 min at 65 °C, (*b*) $NaIO_4$, DCM/MeOH (1:1), rt, 30 min, 80–84% yield (**1a**), 50–55% yield (**1b**).

3-Phenyl[1,2,4]triazines **1c**–**1e** were obtained according to the literature procedure [30] from appropriate ortho-quinones **4c**–**4e** and benzamidrazone **7** (Scheme 2). Benzamidrazone was prepared from benzonitrile and hydrazine hydrate [10]. Thus, the 3-phenylphenanthro[9,10-*e*][1,2,4]triazine (**1c**) was obtained in a 86% yield, and 3-phenylpyreno[9,10-*e*][1,2,4]triazine (**1d**) and 9-phenyl-3a,10b-dihydroacenaphtho[1,2-*e*][1,2,4]triazine (**1e**) were obtained in 73% and 43% yields, respectively. Attempted synthesis of triazines **1c**–**1e** via

an alternative procedure [17] involving three-component condensation of ortho-quinones, acid hydrazide and ammonium acetate in the presence of sodium bisulphate adsorbed on silica as a catalyst did not provide the expected products.



Scheme 2. Synthesis of triazines **1c–e**. Reagents and conditions: (*i*) MeOH, rt, 30 min, 86% yield (**1c**), 73% yield (**1d**), 43% yield (**1e**).

Among the final [1,2,4]triazines obtained, **1a–1c** and **1e** are known in the literature, while triazine **1d** is a new compound. The yields of the obtained products were much higher than those previously reported in the literature [10,12,17,20,23], with the exception of **1e**, which was obtained with a slightly lower yield than in the patent report [18]. All compounds obtained were fully characterized using ^{1}H and ^{13}C NMR, IR, UV–vis spectroscopy and HRMS techniques.

The molecular structure of **1b** was confirmed with the single-crystal X-ray diffraction analysis of an orange needle-shaped monoclinic crystal characterized by a $P2_1/n$ space group. The asymmetric unit contained one molecule of **1b** adopting a nearly planar conformation. The phenyl ring was twisted relative to the core plane by 3.3°. The dimensions of triazine fragment were similar to those found in 11-methyl-3-phenyl-11*H*-[1,2,4]-triazino[6,5-*a*]carbazole [31]. Results are shown in Figure 4, and full data are provided in the Supplementary Materials.

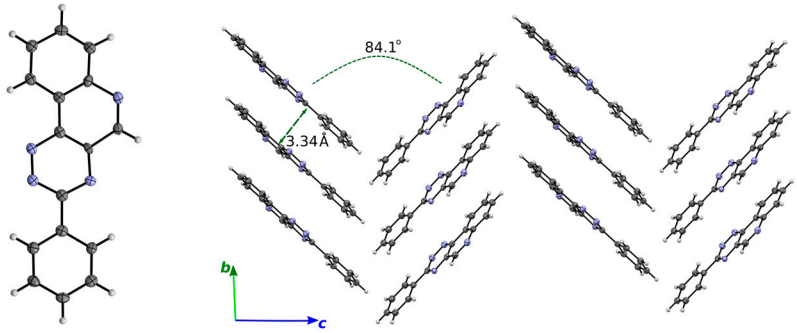


Figure 4. Left: molecular structure of **1b**. Atomic displacement parameters are drawn at 50% probability level. Right: partial crystal packing of **1b**. Only the main component of disordered structure is shown for clarity.

The nearly planar conformation of the [1,2,4]triazine phenyl ring at the C3 position made the ortho-protons sensitive to changes in the electronic structure of the triazine caused by ring fusion. This, in turn, facilitated recording the alteration in electronic properties using the ^{1}H NMR technique. The analysis of ^{1}H NMR spectra of **1** revealed that the values of chemical shifts of ortho-protons of the C3 phenyl group (indicated in red) increased upon ring expansion from naphthalene, through phenanthrene to the pyrene ring appended to 3-phenyl-1,2,4-triazine (Figure 5). The fusion of quinoline or acenaphthylene with [1,2,4]triazine has little effect on values of chemical shifts of ortho-protons.

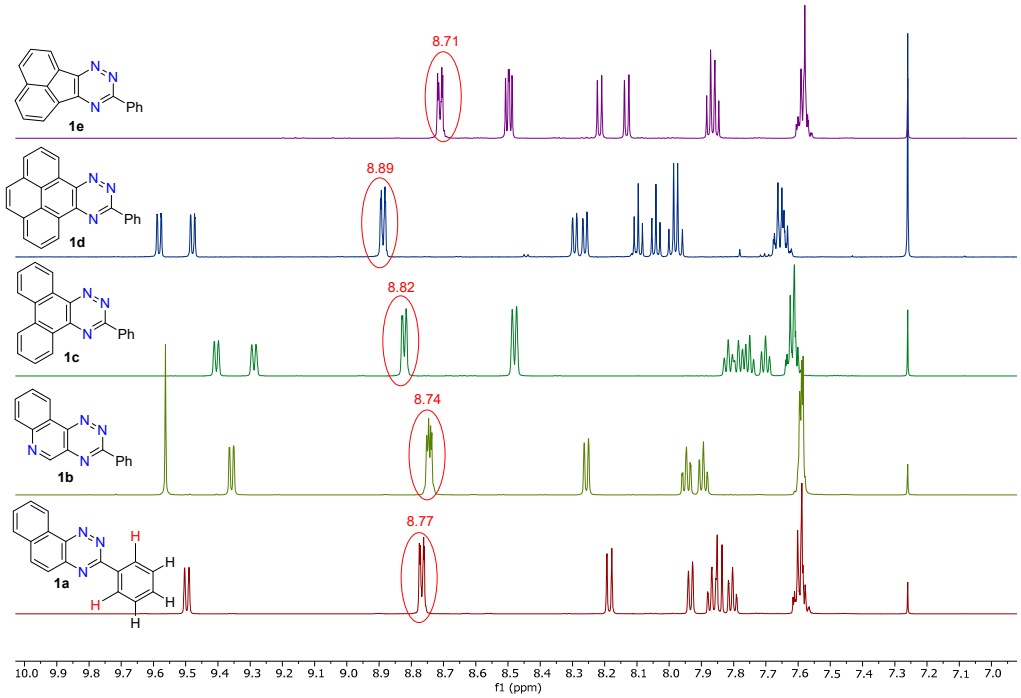


Figure 5. ^{1}H NMR spectra of triazines **1a**–**1e** with indications, in red, of changes in chemical shifts of ortho-protons of the C3 phenyl group.

To assess the effect of the fusion of (hetero)arene rings on electronic properties, triazines **1** were analyzed using UV–vis spectroscopy, and the results are shown in Figure 6. Data analysis revealed that triazines **1** in CH_2Cl_2 solutions exhibit typical strong absorption in the UV region and lower intensity absorption bands in the visible range up to 500 nm, related to n–π* transitions. Analysis of a series of triazines **1a**–**1e** indicated that the size of the rings had some, albeit modest, effects on the electronic absorption energy of the molecules, and that ring expansion caused hypsochromic shift of the lowest energy absorption maxima.

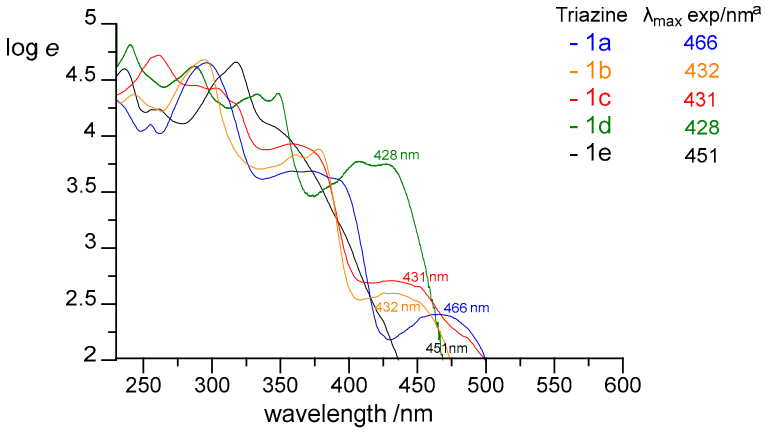


Figure 6. Electronic absorption spectra of triazines **1a**–**1e** recorded in CH_2Cl_2. [a] Lowest energy absorption bands.

3. Materials and Methods

3.1. General Information

Commercially available reagents and solvents were used as obtained. NMR spectra were obtained at 600 MHz (^{1}H), 151 MHz (^{13}C) in $CDCl_3$ and referenced to the solvent (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C) or in DMSO-d_6 and referenced to the solvent (δ = 2.50 ppm for ^{1}H and δ = 39.52 ppm for ^{13}C). A Nexus FT-IR Thermo Nilolet IR

spectrometer was used to record IR spectra (KBr tablets). A Jasco V770 spectrophotometer (Jasco, Oklahoma City, OK, USA) was used to detect UV spectra in CH_2Cl_2. Uncorrected melting points were established using a Stuart SMP30 Advanced Digital Melting Point Apparatus. High-resolution mass spectrometry (HRMS) measurements were carried out utilizing a Bruker SYNAPT G2-Si High-Definition Mass Spectrometer equipped with an ESI or APCI source and a quantitative time-of-flight (QuanTof) mass analyzer. An inert atmosphere (Ar gas) was used for reactions, while reaction workups were conducted in air. Oil baths were used to provide heat for processes that required high temperatures. Volatiles were evaporated under reduced pressure. The progress of reaction mixtures and column eluents were monitored by TLC using aluminum-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F254 or, where stated, Merck Al_2O_3 F254 neutral). For chromatographic separation, silica gel 60 (70−230 μm) was used in column chromatography.

3.2. General Procedure for the Synthesis of Triazines **1a**–**1b**—*Method A*

To the solution of compound **2** (1.73 mmol) in warm acetic acid (10 mL), tin powder (4.0 eq, 812 mg, 6.92 mmol) was added in one portion and the mixture was stirred at room temperature for 1 h and then for 30 min at 65 °C. After cooling, it was poured into water (100 mL), filtered through Cellite®, which was well washed with AcOEt, and the resulting yellow-orange filtrate was extracted with AcOEt (3×). Water (100 mL) was added to the combined extracts, and while stirring, solid $NaHCO_3$ was added in portions until complete neutralization of AcOH. The organic layer was separated, dried (Na_2SO_4), and the solvent was removed, leaving a brown-red solid. The residue was dissolved in a CH_2Cl_2/MeOH mixture (1:1, 10 mL) and solid $NaIO_4$ (1.4 eq, 2.4 mmol, 510.0 mg) was added in one portion. The mixture was stirred for 30 min, filtered, the solid was washed with CH_2Cl_2, and the filtrate was evaporated. The resulting residue was passed through a SiO_2 plug (20% CH_2Cl_2/pet. ether), the solvent was evaporated, and product **1** was recrystallized (EtOH).

3-Phenylnaphtho[2,1-e][1,2,4]triazine (**1a**). 360–378 mg (80–84% yield) as a yellow solid: mp 135–140 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.50 (d, J = 8.1 Hz, 1H), 8.77 (dt, J_1 = 8.4 Hz, J_2 = 2.3 Hz, 2H), 8.19 (d, J = 9.1 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.89–7.83 (m, 2H), 7.83–7.78 (m, 1H), 7.65–7.51 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.4, 144.9, 143.1, 138.3, 135.7, 132.8, 131.5, 130.2, 129.4, 129.4, 129.0, 128.6, 125.8, 124.0; IR (KBr) ν 1599, 1518, 1434, 1384, 1276, 1219, 1160, 1048, 927, 849, 738, 689, 544 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ε) 295 (4.65), 358 (3.68), 373 (3.69), 388 (3.62 sh), 466 (2.41) nm; HRMS (ESI) [M + H]$^+$ *m/z* calcd for $C_{17}H_{12}N_3$: 258.1031; found: 258.1029. Anal. Calcd for $C_{17}H_{11}N_3$: C, 79.36; H, 4.31; N, 16.33. Found: C, 79.15; H, 4.27; N, 16.44.

3-Phenyl-[1,2,4]triazino[5,6-c]quinoline (**1b**). 227–248 mg (50–55% yield) as orange needles: mp 204–205 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.56 (s, 1H), 9.36 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 8.74 (dd, J_1 = 6.7 Hz, J_2 =3.0 Hz, 2H), 8.26 (d, J = 8.1 Hz, 1H), 7.97–7.93 (m, 1H), 7.92–7.87 (m, 1H), 7.63–7.53 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 162.7, 154.8, 145.8, 144.6, 134.8, 134.6, 132.2, 132.0, 130.3, 129.9, 129.2, 128.7, 123.2, 121.7; IR (KBr) ν 1607, 1509, 1419, 1376, 1271, 1120, 1004, 931, 853, 766, 688, 563 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ε) 296 (4.72), 360 (3.83), 378 (3.88), 432 (2.60) nm; HRMS (ESI) [M + H]$^+$ *m/z* calcd for $C_{16}H_{11}N_4$: 259.0984; found: 259.0988. Anal. Calcd for $C_{16}H_{10}N_4$: C, 74.40; H, 3.90; N, 21.69. Found: C, 74.53; H, 3.92; N, 21.80.

3.3. General Procedure for Synthesis of Triazines **1c**–**1e**—*Method B*

Into the ice-cooled solution of stirred benzonitrile (100 mmol, 10.3 g) in dry MeOH (5.0 mL), dry gaseous HCl was bubbled until the substrate was finished. The mixture was refrigerated overnight and then poured into Et_2O (100 mL). Colorless crystals were collected and washed with Et_2O (2 × 30 mL). Saturated aqueous $NaHCO_3$ was added to the solution of obtained crystals in DCM (20 mL) until neutralization. The organic layer was separated and the aqueous phase was extracted with DCM (50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness.

To an ice-cooled stirred solution of the product from the previous step (3.1 g, 22.8 mmol) in *i*PrOH (30 mL) hydrazine hydrate (1.0 mL, 21.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h under gradual warming up to room temperature, and then at room temperature overnight. After the evaporation of volatiles, the residue was treated with Et_2O (50 mL) and cooled in ice. Crystals of benzamidrazone **7** formed, were filtered off, dried in vacuo, and immediately used in the next step.

A suspension of an appropriate ortho-quinone **4** (1 mmol) in dry methanol (5 mL) was added to a solution of benzamidrazone **7** (1.5 mmol) in dry methanol under an argon atmosphere and stirred at room temperature. After 30 min, the precipitate was filtered off, washed with methanol, and recrystallized (EtOH) to give the pure product **1**.

3-Phenylphenanthro[9,10-e][1,2,4]triazine (**1c**). 266 mg (86% yield) as a yellow powder: mp 175–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.41 (d, *J* = 7.8 Hz, 1H), 9.29 (d, *J* = 7.9 Hz, 1H), 8.87–8.79 (m, 2H), 8.48 (d, *J* = 8.0 Hz, 2H), 7.85–7.73 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.66–7.57 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.3, 144.8, 143.0, 135.8, 133.9, 132.4, 131.5, 131.0, 130.7, 129.0, 128.7, 128.5, 128.2, 128.1, 127.7, 126.6, 124.9, 123.1, 123.1; IR (KBr) ν 1607, 1508, 1448, 1408, 1369, 1279, 1167, 1080, 960, 870, 758, 690, 541, 431 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ε) 261 (4.72), 289 (4.45), 303 (4.43), 316 (4.30 sh), 431 (2.70) nm; HRMS (ESI) [M + H]$^+$ *m*/*z* calcd for $C_{21}H_{14}N_3$: 308.1188; found: 308.1191. Anal. Calcd for $C_{21}H_{13}N_3$: C, 82.06; H, 4.26; N, 13.67. Found: C, 82.16; H, 4.26; N, 13.49.

3-Phenylpyreno[9,10-e][1,2,4]triazine (**1d**). 242 mg (73% yield) as a yellow solid: mp 246–247 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.58 (dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 9.48 (dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 8.89 (dt, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 2H), 8.28 (dd, J_1 = 19.3 Hz, J_2 = 7.6 Hz, 2H), 8.10 (t, *J* = 7.7 Hz, 1H), 8.04 (t, *J* = 7.6 Hz, 1H), 7.98 (q, *J* = 8.9 Hz, 2H), 7.70–7.58 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.6, 145.7, 144.0, 135.8, 131.6, 131.4, 131.3, 131.1, 129.4, 129.1, 128.6, 127.7, 127.5, 127.3, 127.3, 127.2, 126.9, 126.8, 125.2, 124.6, 122.6; IR (KBr) ν 3049, 1625, 1492, 1444, 1364, 1294, 1228, 1175, 1053, 928, 831, 769, 697 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ε) 240 (4.81), 287 (4.62), 333 (4.37), 348 (4.38), 407 (3.77), 428 (3.75) nm; HRMS (ESI) [M + H]$^+$ *m*/*z* calcd for $C_{23}H_{14}N_3$: 332.1188; found: 332.1186. Anal. Calcd for $C_{23}H_{13}N_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.82; H, 4.27; N, 12.85.

9-Phenylacenaphtho[1,2-e][1,2,4]triazine (**1e**). 121 mg (43% yield) as a yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74–8.68 (m, 2H), 8.53–8.47 (m, 2H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.86 (dt, *J* = 8.2, 7.2 Hz, 2H), 7.62–7.54 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.5, 157.7, 155.1, 136.0, 134.3, 132.3, 131.4, 130.2, 130.1, 130.0, 129.5, 129.1, 128.9, 128.8, 128.5, 125.2, 123.6; IR (KBr) ν 1617, 1565, 1528, 1479, 1382, 1353, 1207, 1159, 1110, 1028, 831, 775, 705; UV (CH_2Cl_2) λ_{max} (log ε) 318 (4.66), 347 (4.08 sh), 451 (1.47) nm; HRMS (ESI) [M + H]$^+$ *m*/*z* calcd for $C_{19}H_{12}N_3$: 282.1031; found: 282.1033. Anal. Calcd for $C_{19}H_{11}N_3$: C, 81.12; H, 3.94; N, 14.94. Found: C, 81.07; H, 3.89; N, 14.93.

3.4. General Procedure for the Synthesis of Hydrazides 2

N′-(2-Nitronaphthalen-1-yl)benzohydrazide (**2a**). A mixture of compound **5** or **6** (2.0 mmol) and benzhydrazide (1 eq, 2.0 mmol) in DMSO (8 mL) was stirred at 65 °C under an argon atmosphere overnight. The mixture was cooled and poured into water (50 mL). The resulting yellow solid was filtered, washed with water, and dried. The crude product was purified by silica column chromatography (50% DCM/pet. ether) and recrystallized (EtOH) to give 553 mg (90% yield) of **2a** from **5a**, and 424 mg (69% yield) of **2a** from **6a**. Yellow solid: mp 195–200 °C; ^{1}H NMR (600 MHz, DMSO–d_6) δ 11.03 (s, 1H), 9.32 (s, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 9.1 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 9.1 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 166.7, 142.8, 135.8, 134.7, 132.0, 131.9, 129.5, 128.5, 127.3, 126.5, 125.8, 125.0, 121.4, 120.6; IR (KBr) ν 3260, 1648, 1578, 1515, 1457, 1393, 1303, 1211, 1140, 1092, 1025, 903, 812, 761, 689 cm^{-1}; HRMS (ESI) [M − H]$^-$ *m*/*z* calcd for $C_{17}H_{12}N_3O_3$: 306.0879; found: 306.0884. Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.30; H, 4.42; N, 13.52.

N′-(3-Nitroquinolin-4-yl)benzohydrazide (**2b**). 573 mg (93% yield) of **2b** from **6b**. Yellow solid: mp 228–229 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.86 (s, 1H), 8.06–7.97 (m, 2H), 7.84 (d, J = 7.6 Hz, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 168.0, 166.2, 142.4, 138.4, 133.5, 133.1, 131.0, 130.5, 129.0, 128.9, 128.2, 127.9, 127.7, 126.1, 119.7; IR (KBr) ν 3100, 3007, 2944, 2796, 1987, 1687, 1595, 1526, 1348, 1265, 1077, 1023, 880, 840, 754, 690, 608, 532, 445 cm^{-1}; HRMS (ESI) $[M + H]^+$ m/z calcd for $C_{16}H_{13}N_4O_3$: 309.0988; found: 309.0991. Anal. Calcd for $(C_{16}H_{12}N_4O_3)_2H_2O$: C, 60.57; H, 4.13; N, 17.66. Found: C, 56.69; H, 3.88; N, 16.60.

Supplementary Materials: The following data are available online: additional synthetic details, ^{1}H-NMR, ^{13}C-NMR (Figures S1–S7), crystal data and refinement parameters for **1b** (Table S1, Figure S8), UV–Vis spectra (Figures S9–S13) and references [26–28,32–36].

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