UDC 547.789+547.853.4+547.792

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REACTIVITY OF PHTHALIC ANHYDRIDE AND ITS STRUCTURAL ANALOGUES TOWARD 3-(2-AMINOPHENYL)-6-R-1,2,4-TRIAZIN-5(2H)-ONES

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This study explores the reactivity of phthalic anhydride and its structural analogues toward 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones. It was found that short-term refluxing of these starting compounds leads to the formation of the corresponding N-substituted cyclic imides. In contrast, prolonged refluxing of partially or fully hydrogenated phthalic anhydride with 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones results in the formation of substituted isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazolines via further cyclization. The structures of the synthesized compounds were confirmed by a combination of physicochemical methods, including HPLC-MS, NMR spectroscopy, and X-ray diffraction. The structural characteristics and crystallographic data of the products are discussed in detail. A plausible mechanism for the formation of the isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline system is also proposed and rationalized.

Keywords: phthalic anhydride, 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones, isoindole, isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazolines, X-ray diffraction.

DOI: 10.32434/0321-4095-2025-160-3-107-118

Introduction

Phthalic anhydride, along with its cage and saturated derivatives, represents an important class of reagents in organic chemistry, widely employed in the synthesis of diesters, polyesters, imides, optically active polyamides, symmetrical organic selenocyanates, diselenide dyes, epoxies, polyimides, and other valuable compounds [1–4]. The significant potential of cyclic anhydrides, including cage and saturated analogs of phthalic anhydride, has been demonstrated in the synthesis of chiral hemiamides, lactones, amido acids, and, more recently, keto acids and thioesters [5]. In addition, these compounds continue to play a crucial role as electrophilic synthons in both mono- and multicomponent reactions with nucleophiles, enabling the construction of novel heterocyclic structures with practically valuable properties. For instance, benzimidazole derivatives, synthesized through reactions between 1,4-NCCN-binucleophiles and these anhydrides, are among the most extensively studied compounds due to the high availability of o-phenylenediamines and their derivatives [6], as well as their broad applications in industry and medicine [7]. However, the acylation products of 1,5-NCCCN-binucleophiles with phthalic anhydride and its analogs remain unexplored [6]. In continuation of our research on the formation of novel heterocyclic systems within the class of condensed triazines, we aimed to investigate the reactivity of 2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazino-3-yl)anilines toward

phthalic anhydride and its structural analogs.

Experimental

Melting points were measured in open capillary tubes using a «Mettler Toledo MP 50» apparatus (Columbus, USA). Elemental analyses (C, H, N) were conducted on an ELEMENTAR vario EL cube analyzer (Langenselbold, Germany), with the results for elements or functional groups deviating by no more than ±0.3% with respect to the theoretical values. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 500 spectrometer (Varian Inc., Palo Alto, CA, USA), using TMS as an internal standard in a DMSO-d_6 solution. LC-MS data were acquired using a HPLC-MS system comprising the HPLC «Agilent 1100 Series» (Agilent, Palo Alto, CA, USA) equipped with a diode-matrix detector and mass-selective detector, «Agilent LC/MSD SL» (Agilent, Palo Alto, USA), with atmospheric pressure chemical ionization (APCI).

The starting substances of formulas **1.1−1.5** were prepared according to the previously described method and physicochemical constants that correspond to the literature data [8]. Synthetic studies were carried out according to general approaches using reagents from «Merck» (Darmstadt, Germany), «Sigma-Aldrich» (Missouri, USA) and «Enamine» (Kyiv, Ukraine).

General method for the synthesis of 2-[2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl]-1H-isoindole-1,3(2H)-diones (2)

0.78 g (0.005 M) of phthalic anhydride was added to a suspension of 0.005 M of the corresponding substituted 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one (**1**) in 15 mL of glacial acetic acid, the mixture was refluxed for 1 hour with water removal using a Dean-Stark apparatus. The reaction was monitored by thin layer chromatography. After completing the reaction, the mixture was cooled, and the solvent was removed in vacuo. The residue was crystallized from propanol-2.

2-(2-(5-oxo-6-phenyl-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-dione (2.1)

Yield: 94.1%, mp 292−294^{0}C; ^{1}H NMR, δ=14.48 (s, 1H, NH), 8.04 (d, 2H, *J*=7.2 Hz, H-2', 6' [6-Ph]), 7.99−7.88 (m, 5H, H-4, 5, 6, 7, isoindole; H-3 [2-Ph]), 7.84 (t, 1H, *J*=7.6 Hz, H-5 [2-Ph]), 7.78−7.62 (m, 2H, H-4, 6 [2-Ph]), 7.55−7.40 (m, 3H, H-3', 4', 5' [6-Ph]); ^{13}C NMR, δ=166.49 (CO), 158.43 (5-C), 147.65 (6-C), 135.43, 133.15, 132.75, 131.98, 130.75, 130.68, 130.46, 129.23, 128.75, 128.38, 124.32; LC-MS, *m/z*=395 [M+1]; Calculated for $C_{23}H_{14}N_4O_3$: C 70.05; H 3.58; N 14.21; Found: C 69.98; H 3.55; N 14.18.

2-(2-(5-oxo-6-(4-ethylphenyl-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-dione (2.2)

Yield 83.6%; mp 272−274^{0}C; ^{1}H NMR, δ=14.35 (s, 1H, NH), 8.05 (d, 2H, *J*=7.2 Hz, H-2', 6' [6-Ar]), 7.98−7.85 (m, 5H, H-4, 5, 6, 7 isoindole; H-3 [2-Ph]), 7.80 (t, 1H, *J*=7.2 Hz, H-5 [2-Ph]), 7.70 (t, 1H, *J*=7.3 Hz, H-4 [2-Ph]), 7.62 (d, 1H, *J*=7.7 Hz, H-6 [2-Ph]), 7.25 (d, 2H, *J*=7.8 Hz, H-3', 5' [6-Ar]), 2.68 (q, 2H, *J*=7.3 Hz, 4'-CH_2CH_3), 1.25 (t, 3H, *J*=7.4 Hz, 4'-CH_2CH_3); ^{13}C NMR: δ=167.08, 146.50, 135.11, 132.44, 131.83, 130.60, 130.32, 129.08, 128.95, 127.71, 123.96, 96.08, 40.49, 40.28, 40.07, 39.86, 39.65, 28.70, 15.83; Calculated for $C_{25}H_{18}N_4O_3$: C 71.08; H 4.29; N 13.26; Found: C 71.10; H 4.29; N 13.29.

2-(2-(6-(4-isopropylphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-dione (2.3)

Yield: 92.1%, mp 258−260^{0}C; ^{1}H NMR, δ=14.43 (s, 1H, NH), 7.99 (d, 2H, *J*=7.9 Hz, H-2', 6' [6-Ar]), 7.97−7.87 (m, 5H, H-4, 5, 6, 7 isoindole; H-3 [2-Ph]), 7.84 (t, 1H, *J*=7.4 Hz, H-5 [2-Ph]), 7.78−7.64 (m, 2H, H-4, 6 [2-Ph]), 7.33 (d, 2H, *J*=8.1 Hz, H-3', 5' [6-Ar]), 3.00−2.85 (m, 1H, −$CH(CH_3)_2$, 1.22 (d, 6H, *J*=6.9, −$CH(CH_3)_2$; ^{13}C NMR, δ=167.3 (CO), 161.9 (5-C), 158.6 (6-C), 151.3, 148.7, 135.4, 132.7, 131.9, 130.7, 129.5, 128.9, 126.8, 124.1, 40.3, 34.0, 24.1; LC-MS, *m/z*=437 [M+1]; Calculated for $C_{26}H_{20}N_4O_3$: C 71.55; H 4.62; N 12.84; Found: C 71.50; H 4.59; N 12.81.

The colorless crystals of 2-(2-(6-(4-isopropylphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-dione (2.3) ($C_{26}H_{20}N_4O_3$) are monoclinic. At 273 K, *a*=14.5732(12), *b*=12.5584(11), *c*=12.1438(8) Å, *β*=95.118(7)^0, V=2213.6(3) Å^3, M_r=436.46, Z=4, space group $P2_1/c$, d_{calc}=1.310 g/cm^3, μ(MoK_α)=0.088 mm^{-1}, F(000)=912. Intensities of 15798 reflections (3892 independent, R_{int}=0.0365) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK_a radiation, CCD detector, φ- and ω-scaning, $2\Theta_{max}$=50^0). The structure was solved by direct method using OLEX2 [9] package with SHELXT [10] and SHELXL modules [11]. Positions of the hydrogen atoms were located from electron density difference maps and refined using «riding» model with U_{iso}=nU_{eq} (n=1.5 for methyl groups and n=1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 3892 reflections was converged to wR_2=0.1701 (R_1=0.0540 for 2765 reflections with F>4σ(F), S=1.023). The final atomic coordinates, and crystallographic data for molecule **2.2** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and

are available on request quoting the deposition numbers CCDC 2424007).

2-(2-(6-(4-ethoxyphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-dione (2.4)

Yield: 93.1%, mp 247–249^{0}C; ^{1}H NMR, δ=14.19 (s, 1H, NH), 8.14 (d, 2H, *J*=8.1 Hz, H-2', 6' [6-Ar]), 7.97–7.81 (m, 5H, H-4, 5, 6, 7 isoindole; H-3 [2-Ph]), 7.77 (t, 1H, *J*=6.8, H-5 [2-Ph]), 7.66 (t, 1H, *J*=7.2, H-4 [2-Ph]), 7.56 (d, 1H, *J*=7.5 Hz, H-6 [2-Ph]), 6.86 (d, 2H, *J*=8.2 Hz, H-3', 5' [6-Ar]), 4.06 (q, 2H, *J*=6.6, –OCH_2CH_3), 1.39 (t, 3H, *J*=6.8, –OCH_2CH_3); ^{13}C NMR, δ=167.23 (CO), 167.32 (5-C), 160.95 (6-C), 149.98, 142.56, 134.92, 131.88, 130.53, 129.43, 123.91, 113.95, 63.69, 14.98; LC-MS, *m/z*=439 [M+1]; Calculated for $C_{25}H_{18}N_4O_4$: C 68.49; H 4.14; N 12.78; Found: C 68.52; H 4.13; N 12.76.

General method for the synthesis of 2-(2-(5-oxo-6-R-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a- tetrahydro-1H-4,7-methanoisoindole-1,3-diones (3.1–3.4)

0.60 g (0.0035 M) of carbic anhydride (*cis-endo*-5-norborane-2,3-dicarboxylic acid anhydride) was added to a suspension of 0.0035 M of substituted 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one (**1**) in 15 mL of glacial acetic acid, and the formed mixture was refluxed for 1 hour with water removal using a Dean-Stark apparatus. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. The formed residue was crystallized from propanol-2 and dried.

2-(2-(5-oxo-6-phenyl-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (3.1)

Yield: 73.4%, mp 253–255^{0}C; ^{1}H NMR, δ=14.23 (s, 1H, NH), 8.37–8.16 (m, 2H, H-2', 6' [6-Ph]), 7.84 (d, 1H, *J*=6.4 Hz, H-3 [2-Ph]), 7.75–7.53 (m, 2H, H-4, 5 [2-Ph]), 7.50–7.36 (m, 3H, H-3', 4', 5' [6-Ph]), 7.21 (d, 1H, *J*=7.2, H-6 [2-Ph]), 6.25 (s, 2H, H-5, 6 isoindole), 3.46 (s, 2H, H-3a, 7a isoindole), 3.38 (s, 2H, H-4, 7 isoindole), 1.69 (t, 2H, H-8 isoindole); LC-MS, m/z=411 [M+1]; Calculated for $C_{24}H_{18}N_4O_3$: C 70.23; H 4.42; N 13.65; Found: C 70.25; H 4.47; N 13.67.

2-(2-(6-(4-ethylphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (3.2)

Yield: 66.2%, mp 246–248^{0}C; ^{1}H NMR, δ=14.12 (s, 1H, NH), 8.25 (d, 2H, *J*=7.8 Hz, H-2', 6' [6-Ar]), 7.80 (d, 1H, *J*=6.8 Hz, H-3 [2-Ph]), 7.72–7.51 (m, 2H, H-4, 5 [2-Ph]), 7.18 (d, 1H, *J*=7.3 Hz, H-6 [2-Ph]), 6.92 (d, 2H, *J*=8.1 Hz, H-3', 5' [6-Ar]), 6.23 (s, 2H, H-5, 6 isoindole), 4.09 (q, 2H, *J*=6.7 Hz , 4'-OCH_2CH_3), 3.43 (s, 2H, H-3a, 7a isoindole), 3.35 (s, 2H, H-4, 7 isoindole), 1.66 (t, 2H, H-8 isoindole), 1.42 (t, 3H, *J*=6.7 Hz, 4'-OCH_2CH_3); ^{13}C NMR, δ=175.88 (CO), 173.20 (5-C), 168.23 (3-C), 160.93 (6-C), 148.81, 143.12, 134.86 (5'-C, 6'-C), 130.60, 114.01, 63.41, 45.94, 45.13 (8'-C), 40.51, 40.30, 40.10, 39.89, 39.68, 15.02; LC-MS, m/z=455 [M+1]; Calculated for $C_{26}H_{22}N_4O_4$: C 71.22; H 5.06; N 12.78; Found: C 71.25; H 5.09; N 12.75.

2-(2-(6-(4-isopropylphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (3.3)

Yield: 73.8%, mp 262–264^{0}C; ^{1}H NMR, δ=14.29 (s, 1H, NH), 8.10 (d, 2H, *J*=7.1 Hz, H-2', 6' [6-Ar]), 7.86 (d, 1H, *J*=6.5 Hz, H-3 [2-Ph]), 7.76–7.54 (m, 2H, H-4, 5 [2-Ph]), 7.38 (d, 2H, *J*=8.0 Hz, H-3', 5' [6-Ar]), 7.23 (d, 1H, *J*=7.6 Hz, H-6 [2-Ph]), 6.26 (s, 2H, H-5, 6 isoindole), 3.45 (s, 2H, H-3a, 7a isoindole), 3.32 (s, 2H, H-4, 7 isoindole), 3.02–2.89 (m, 1H, 4'-$CH(CH_3)_2$), 1.58 (t, 2H, *J*=8.6 Hz, H-8 isoindole), 1.25 (d, 6H, *J*=6.9 Hz, 4'-$CH(CH_3)_2$; LC-MS, m/z=453 [M+1]; Calculated for $C_{27}H_{24}N_4O_3$: C 71.67; H 5.35; N 12.38; Found: C 71.65; H 5.34; N 12.36.

2-(2-(6-(4-ethoxyphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (3.4)

Yield: 76.2%, mp 246–248^{0}C; ^{1}H NMR, δ=14.12 (s, 1H, NH), 8.25 (d, 2H, *J*=7.8 Hz, H-2', 6' [6-Ar]), 7.80 (d, 1H, *J*=6.8 Hz, H-3 [2-Ph]), 7.72–7.51 (m, 2H, H-4, 5 [2-Ph]), 7.18 (d, 1H, *J*=7.3 Hz, H-6 [2-Ph]), 6.92 (d, 2H, *J*=8.1 Hz, H-3', 5' [6-Ar]), 6.23 (s, 2H, H-5, 6 isoindole), 4.09 (q, 2H, *J*=6.7 Hz, 4'-OCH_2CH_3), 3.43 (s, 2H, H-3a, 7a isoindole), 3.35 (s, 2H, H-4, 7 isoindole), 1.66 t, 2H, H-8 isoindole), 1.42 (t, 3H, *J*=6.7 Hz, 4'-OCH_2CH_3); ^{13}C NMR, δ=175.88 (CO), 173.20 (5-C), 168.23 (3-C), 160.93 (6-C), 148.81, 143.12, 134.86 (5'-C, 6'-C), 130.60, 114.01, 63.41, 45.94, 45.13 (8'-C), 40.51, 40.30, 40.10, 39.89, 39.68, 15.02; LC-MS, m/z=455 [M+1]; Calculated for $C_{26}H_{22}N_4O_4$: C 68.71; H 4.88; N 12.33; Found: C 68.72; H 4.87; N 12.27.

The colorless crystals of 2-(2-(6-(4-ethoxyphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (3.4) ($C_{26}H_{22}N_4O_4$) are monoclinic. At 273 K, *a*=18.4274(14), *b*=6.5506(4), *c*=18.8137(12) Å, *β*=97.455(7)^0, V=2251.8(3) Å^3, M_r=454.47, Z=4, space group $P2_1/n$, d_{calc}=1.341 g/cm^3, μ(MoK_α)=0.093 mm^{-1}, F(000)=952. Intensities of 13020 reflections

(3957 independent, R_{int}=0.0386) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK_a radiation, CCD detector, φ- and ω-scaning, $2\Theta_{max}=50^0$). The structure was solved by direct method using OLEX2 [9] package with SHELXT [10] and SHELXL modules [11]. Positions of the hydrogen atoms were located from electron density difference maps and refined using «riding» model with $U_{iso}=nU_{eq}$ (n=1.5 for methyl group and n=1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 3957 reflections was converged to wR_2=0.1321 (R_1=0.0482 for 2664 reflections with $F>4\sigma(F)$, S=1.029). The final atomic coordinates, and crystallographic data for molecule 3.4 have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2424006).

General method for the synthesis of 2-(2-(5-oxo-6-R-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-diones (4)

0.005 M of cis-1,2,3,6-tetrahydrophthalic acid anhydride was added to a suspension of 0.005 M of substituted 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-one (**1**) in 15 mL of acetic acid and formed mixture was refluxed for 1 hour. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. The residue was crystallized from propanol-2.

2-(2-(5-oxo-6-phenyl-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4.1)

Yield: 77.1%, mp 216−218^{0}C; ^{1}H NMR, δ=14.32/14.23 (s, 1H, NH), 8.30−8.09 (m, 4H, H-3, 6 [2-Ph], H-2,6 [6-Ar]), 7.96−7.61 (m, 2H, H-4, 5 [2-Ph]), 7.56−7.28 (m, 3H, H-3,4,5 [6-Ar]), 6.00−5.82 (m, 2H, H-5,6 isoindole), 3.41−3.08 (m, 2H, isoindole H-3a,7a), 2.61−2.53 (m, 2H, isoindole H-4,7), 2.42−2.18 (m, 2H, isoindole H-4,7); LC-MS, *m/z*=399 [M+1]; Calculated for $C_{23}H_{18}N_4O_3$: C 69.34; H 4.55; N 14.06; Found: C 69.36; H 4.59; N 14.10.

2-(2-(6-(4-ethylphenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (4.2)

Yield: 65.7%, mp 226−228^{0}C; ^{1}H NMR, δ=14.26/14.15 (s, 1H, NH), 8.13 (d, *J*=8.0 Hz, 2H, H-2,6 [6-Ar]), 7.91 (d, *J*=7.9 Hz, 1H, H-3 [2-Ph]), 7.78−7.58 (m, 2H, H-4, 5 [2-Ph]), 7.33 (d, 1H, H-6 [2-Ph]), 7.26 (d, *J*=7.9 Hz, 2H, H-3,5 [6-Ar]), 6.06−5.73 (m, 2H, isoindole H-5,6), 3.37−3.05 (m, 2H, isoindole H-3a,7a), 2.79−2.63 (m, 2H, CH_2CH_3), 2.59−2.53 (m, 2H, isoindole H-4,7), 2.42−2.15 (m, 2H, isoindole H-4',7'), 1.29 (t, *J*=7.0 Hz, 3H, CH_2CH_3); LC-MS, m/z=427 [M+1]; Calculated for $C_{25}H_{22}N_4O_3$: C 70.41; H 5.20; N 13.14; Found: C 70.43; H 5.25; N 13.18.

General method for the synthesis of 2-R-11,14b-dihydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(14H)-diones (5)

Method A

0.005 M of *cis*-1,2,3,6-tetrahydrophthalic acid anhydride was added to a suspension of 0.005 M of the corresponding substituted 6-R-3-(2-aminophenyl)-1,2,4-triazin-5-one (**1**) in 30 mL of acetic acid and refluxed for 10 hours with removal of water using a Dean-Stark apparatus. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. 20 mL of propanol-2 was added to the residue and formed mixture was stirred. The resulting precipitate was filtered off, washed with water and dried. For analysis, the compounds were crystallized from a dioxane-water mixture.

Method B

A solution of 0.005 M of the corresponding 2-(2-(5-oxo-6-R-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3a,4,7,7*a*-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**4**) in 30 mL of acetic acid was refluxed for 10 hours with water removal using a Dean-Stark apparatus. The reaction is monitored chromatographically. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. 20 mL of propanol-2 was added to the residue and formed mixture was stirred. The resulting precipitate was filtered off, washed with water and dried. For analysis, the compounds could be crystallized from a dioxane-water mixture.

2-phenyl-11,14b-dihydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(14H)-dione (5.1)

Yield: 75.8%, mp 232−234^{0}C; ^{1}H NMR, δ=8.30 (d, *J*=7.8 Hz, 1H, H-5), 8.11 (d, *J*=7.7 Hz, 2H, H -2,6 [2-Ph]), 8.00 (d, *J*=8.1 Hz, 1H, H-8), 7.72 (t, *J*=8.2 Hz, 1H, H-7), 7.55−7.44 (m, 3H, H-3,4,5 [2-Ar]), 7.39 (t, *J*=7.6 Hz, 1H, H-6), 6.55 (s, 1H, 14b), 5.93−5.76 (m, 2H, H-12, 13), 3.97−3.72 (m, 1H, H-11), 3.47−3.26 (m, 1H, H-11'), 3.15−2.81 (m, 2H, H-14); LC-MS, *m/z*=381 [M+1]; Calculated for $C_{23}H_{16}N_4O_2$: C 72.62; H 4.24; N 14.73; Found: C 72.64; H 4.27; N 14.70.

2-(4-ethylphenyl)-11,14b-dihydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10 (14H)-dione (5.2)

Yield: 77.3%, mp 249−252^{0}C; ^{1}H NMR, δ=8.29 (d, *J*=7.8 Hz, 1H, H-5), 8.05 (d, *J*=7.8 Hz, 2H, H-2,6 [2-Ar]), 7.99 (d, *J*=8.0 Hz, 1H, H-8), 7.72 (t, *J*=7.5 Hz, 1H, H-7), 7.38 (t, *J*=7.6 Hz, 1H, H-6), 7.30 (d, *J*=7.8 Hz, 2H, H-3,5 [2-Ar]), 6.54 (s, 1H, 14b), 5.99−5.80 (m, 2H, H-12, 13), 3.97−3.71 (m, 1H, H-11), 3.49−3.26 (m, 1H, H-11'), 3.11−2.84 (m, 2H, H-14), 2.72 (q, *J*=7.3 Hz, 2H, CH_2CH_3), 1.30 (t, *J*=7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR, δ=166.95, 160.62, 152.86, 147.38, 146.72, 146.59, 135.55, 134.59, 133.63, 129.84, 128.72, 127.87, 127.50, 125.19, 123.53, 122.72, 120.05, 118.49, 74.85, 28.16, 27.92, 22.08, 15.40; LC-MS, *m/z*=409 [M+1]; Calculated for $C_{25}H_{20}N_4O_2$: C 73.51; H 4.94; N 13.72; Found: C 73.56; H 4.97; N 13.70.

The colorless crystals of 2-(4-ethylphenyl)-11,14b-dihydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(14H)-dione (5.2) ($C_{25}H_{20}N_4O_2$) are triclinic. At 273 K, *a*=8.599(2), *b*=10.698(3), *c*=11.933(3) Å, α=75.78(2)^0, *β*=74.94(2)^0, *γ*=72.13(2)^0, V=992.3(4) Å^3, M_r=408.45, Z=2, space group $P\bar{1}$, d_{calc}=1.367 g/cm^3, μ(MoK_α)=0.089 mm^{-1}, F(000)=428. Intensities of 6755 reflections (3497 independent, R_{int}=0.0340) were measured on the Bruker APEX II diffractometer (graphite monochromated MoK_a radiation, CCD detector, φ- and ω-scaning, $2\Theta_{max}$=50^0). The structure was solved by direct method using OLEX2 [9] package with SHELXT [10] and SHELXL modules [11]. Positions of the hydrogen atoms were located from electron density difference maps and refined using «riding» model with U_{iso}=nU_{eq} (n=1.5 for methyl group and n=1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 3497 reflections was converged to wR_2=0.2454 (R_1=0.0703 for 1868 reflections with F>4σ(F), S=1.028). The final atomic coordinates, and crystallographic data for molecule **5.2** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2424005).

General method for the synthesis of 2-(2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)hexahydro-1H-isoindole-1,3(2H)-diones (6)

0.005 M of cis-hexahydrophthalic acid anhydride was added to a suspension of 0.005 M of corresponding 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-one (**1**) in 15 mL of acetic acid and formed mixture was refluxed for 1 h. The reaction was monitored using thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. 20 mL of propanol was added to the residue and resulting precipitate was filtered off, washed with water and dried. For additional purification, the obtained compound was crystallized from propanol-2.

2-(2-(6-phenyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)hexahydro-1H-isoindole-1,3(2H)-dione (6.1)

Yield: 81.7%, mp 209−210^{0}C; ^{1}H NMR, δ=14.32 (s, 1H, NH), 8.38−8.06 (m, 2H, H-2,6 [6-Ph]), 7.88−7.56 (m, 3H, H-3, 5, 6 [2-Ph]), 7.56−7.29 (m, 4H. H-4 [2-Ph], H-3,4,5 [6-Ph]), 3.11−2.97 (m, 2H, *isoindole* 3a, 7a), 2.17−1.20 (m, 8H, *isoindole* 4,4',5,5',6,6',7,7'); LC-MS, m/z=401 [M+1]; Calculated for $C_{23}H_{20}N_4O_3$: C 68.99; H 5.03; N 13.99; Found: C 69.03; H 5.07; N 14.03.

2-(2-(6-(4-fluorophenyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)hexahydro-1H-isoindole-1,3(2H)-dione (6.2)

Yield: 83.7%, mp 241−244^{0}C; ^{1}H NMR, δ=14.48 (s, 1H, NH), 8.33−8.04 (m, 2H, H-2,6 [6-Ar]), 7.82 (d, *J*=7.3 Hz, 1H, H-3 [2-Ph]), 7.80−7.72 (m, 1H, H-5 [2-Ph]), 7.66 (d, *J*=7.3 Hz, 1H, H-4 [2-Ph]), 7.48 (d, *J*=7.2 Hz, 1H, H-6 [2-Ph]), 7.33 (t, *J*=8.2 Hz, 2H, H-3,5 [6-Ar]), 3.15−2.86 (m, 2H, *isoindole* 3a, 7a), 2.08−1.01 (m, 8H, *isoindole* 4,4',5,5',6,6',7,7'); ^{1}H-^{13}C HSQC, δ=8.21/130.58, 7.82/129.56, 7.76/131.93, 7.66/128.64, 7.48/19.56, 3.06/39.08, 1.89/21.48, 1.66/21.48, 1.30/21.48; ^{1}H-^{13}C HMBC, δ=8.20/115.14, 8.20/130.76, 8.20/145.90, 8.20/163.89, 7.32/115.14, 7.32/115.14, 7.82/130.6, 7.65/130.76, 7.32/163.89, 7.13/163.89, 3.06/179.61, 3.06/21.47, 3.06/39.47, 1.30/39.65, 1.92/21.47; LC-MS, *m/z*=419 [M+1]; Calculated for $C_{23}H_{19}FN_4O_3$: C 66.02; H 4.58; F 4.54; N 13.39; Found: C 66.06; H 4.57; N 13.43.

General method for the synthesis of 2-R_1-11,13,14,14b-tetrahydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(12H)-diones (7)

Method A

0.005 M of cis-hexahydrophthalic acid anhydride was added to a suspension of 0.005 mol of the substituted 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one (**1**) in 30 mL of acetic acid and refluxed for up to 50 h, with removal of water using Dean-Stark apparatus. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. 20 mL of propanol-2 was added and mixture was stirred. The resulting precipitate was filtered off, washed with water and dried.

Method B

A solution of 0.005 M of 2-(2-(5-oxo-6-phenyl-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)hexahydro-1*H*-isoindole-1,3(2H)-dione (**6.1**) in 30 mL of acetic acid was refluxed for up to 50 h, with removal of the water using Dean-Stark apparatus. The reaction was monitored thin layer chromatography. After completion of the reaction, the mixture was cooled, and the solvent was removed in vacuo. 20 mL of propanol-2 was added and mixture was stirred. The resulting precipitate was filtered off, washed with water and dried. For analysis, the compounds are crystallized from a dioxane-water mixture.

2-phenyl-11,13,14,14b-tetrahydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(12H)-dione (7.1)

Yield: 70.8%, mp 196–197^{0}C; ^{1}H NMR, δ=8.29 (d, *J*=7.6 Hz, 1H, H-5), 8.13 (d, *J*=7.8 Hz, 2H, H-2,6 [2-Ph]), 7.98 (d, *J*=8.1 Hz, 1H, H-8), 7.71 (t, *J*=7.7 Hz, 1H, H-7), 7.54–7.42 (m, 3H, H-3,4,5 [2-Ph]), 7.38 (t, *J*=7.4 Hz, 1H, H-6), 6.49 (s, 1H, H-14b), 3.18–3.01 (m, 1H, H-11), 2.73–2.59 (m, 1H, H-11'), 2.40–2.16 (m, 2H, H-14, 14'), 2.11–1.87 (m, 2H, H-12, 13), 1.79–1.58 (m, 2H, H-12', 13'); LC-MS, *m/z*=383 [M+1]; Calculated for $C_{23}H_{18}N_4O_2$: C 72.24; H 4.74; N 14.65; Found: C 72.26; H 4.77; N 14.72.

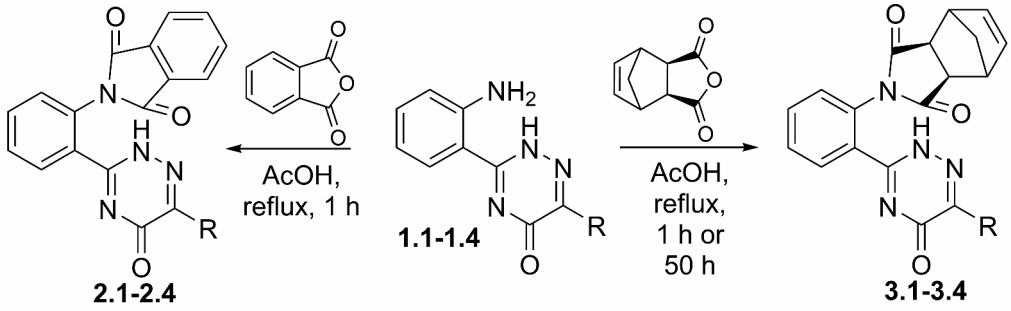
2-(4-ethylphenyl)-11,13,14,14b-tetrahydro-3H-isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline-3,10(12H)-dione (7.2)

Yield: 63.4%, mp 218–220^{0}C; ^{1}H NMR, δ=8.27 (d, *J*=6.9, 1H, H-5), 8.06 (d, *J*=7.4, 2H, H-2,6 [2-Ar]), 7.97 (d, *J*=7.6, 1H, H-8), 7.70 (t, *J*=7.7, 1H, H-7), 7.36 (t, *J*=7.2, 1H, H-6), 7.28 (d, *J*=7.6, 2H, H-3,5 [2-Ar]), 6.46 (s, 1H, H-14b), 3.19–3.03 (m, 1H, H-11), 2.78–2.60 (m, 3H, H-11', CH_2CH_3), 2.41–2.27 (m, 2H, H-14, 14'), 2.09–1.83 (m, 2H, H-12, 13), 1.81–1.63 (m, 2H, H-12', 13'), 1.29 (t, *J*=7.3, 3H, CH_2CH_3); LC-MS, *m/z*=411 [M+1]; Calculated for $C_{25}H_{22}N_4O_2$: C 73.15; H 5.40; N 13.65; Found: C 73.16; H 5.49; N 13.73.

Results and discussion

The reaction of phthalic anhydride with 2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazino-3-yl)anilines (**1**) predictably resulted in the formation of *N*-substituted isoindoles (**2**, Scheme 1) with yields ranging from 83.6% to 93.1%. This process occurs via acylation followed by cyclization of the initially formed monoamide of phthalic acid. The reaction pathway is dictated by the planar and rigid structure of the anhydride. A similar reaction pathway is observed when compounds **1** react with caged cis-5-norbornene-endo-2,3-dicarboxylic anhydride (carbic anhydride), yielding *N*-substituted 4,7-methanoisoindole-1,3(2H)-diones (**3**) with yields ranging from 66.2% to 76.2% (Scheme 1). Notably, extending the reaction time for both of the above-mentioned reactions up to 50 hours does not lead to further intramolecular cyclization products.

At the same time, the interaction of saturated analogs of phthalic anhydride with compounds **1** led to unexpected results. Refluxing of compounds **1** with *cis*-1,2,3,6-tetrahydrophthalic anhydride in acetic acid for 6 hours resulted in the formation of a product mixture (Scheme 2). According to HPLC-MS data, one of the products was identified as the corresponding *N*-substituted tetrahydro-1H-isoindole-1,3(2H)-dione. The other component of the product mixture has a molecular weight 18 u less than *N*-substituted and is likely its dehydration product. The reaction conditions were modified to isolate the components of the mixture as individual compounds. It was shown that shortening of the reaction period to 1 hour resulted in the formation of compounds **4.1** and **4.2**, while extending the reaction time to 10 hours with the removal of water from the reaction mixture allowed the isolation of compounds **5**. Additionally, compounds **5** were obtained by refluxing of compounds **4** in acetic acid



1.1, **2.1**, **3.1** R = Ph; **1.2**, **2.2**, **3.2** R = 4-EtC_6H_4; **1.3**, **2.3**, **3.3** R = 4-i-Pr-C_6H_4; **1.4**, **2.4**, **3.4** R = 4-EtOC_6H_4

Scheme 1. Reactivity of 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones (**1.1–1.4**) towards phthalic and carbic anhydride

for 10 hours with continuous water removal.

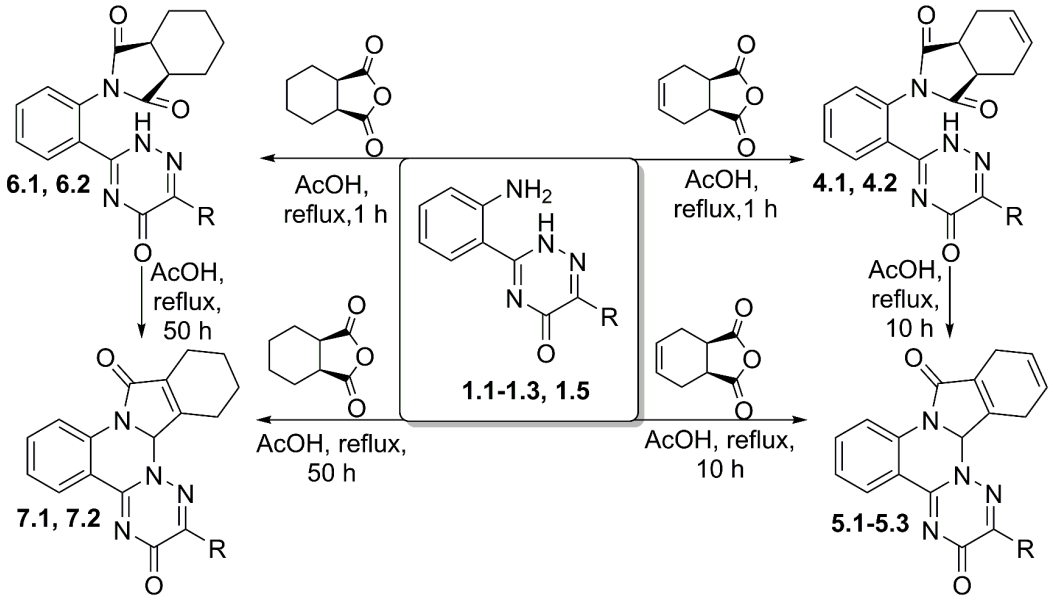
Similar results were observed in case of reaction between anilines **1** and hexahydrophthalic anhydride. It was found that refluxing of compounds **1** with equimolar quantity of abovementioned anhydride in acetic acid for 1 h led to the formation of *N*-substituted hexahydroisoindoles **6** (Scheme 2). Extension of the reaction time to 10 h led to the formation of a mixture of compounds **6** and the product of its further dehydration **7** as minor component (15%.) Compounds **7** were obtained by refluxing of anilines **1** and hexahydrophthalic anhydride in acetic acid for up to 50 h with removal of water from the reaction mixture.

The formation of *N*-substituted isoindoles (**2**, **3**, **4** and **6**) and isoindolo[2,1-*a*][1,2,4]triazino [2,3-*c*]quinazolines (**5** and **7**) was supported by the data HPLC-MS spectra, which show a high-intensity peak of the ion [M+1], that by *m/z* value corresponded to the proposed structures.

In the ^{1}H NMR spectra of compounds **2**, **3**, **4** and **6**, the signal of deshielded proton of the NH group of the triazine cycle at the 14.48–13.93 ppm was observed. The significant paramagnetic shift of this signal was associated with the hydrogen bond between the NH group of the triazine cycle and the oxygen of the isoindole cycle. Additionally, for some compounds (**4**), the proton of the NH group of the triazine cycle was doubled due to the tautomeric transformations in the molecule.

The signals of the isoindole fragment protons (compound **2**) in the spectrum were observed as multiplets at the 7.99–7.81 ppm. Whereas, the hydrogenated 4,7-methanoisoindole cycle (compound **3**) was characterized by signals of the equivalent protons H-5 and H-6 at the 6.26–6.22 ppm, H-8 protons due to appear as a triplet in the high field at the 1.69–1.58 ppm and the protons H-3a, 7a and H-4, 7 are singlet signals at the 3.46–3.41 ppm and 3.38–3.32 ppm, respectively. At the same time, the tetrahydroisoindole fragment (compound **4**) was characterized by the signals of isoindole cycle protons at the sp^2-hybridized in the form of a multiplet at the 6.06–5.73 ppm protons of positions 3a and 7a in the form of a multiplet at the 3.41–3.05 ppm and protons of positions 4 and 7 in the form of a series of two two-proton multiplets at the 2.61–2.53 ppm and 2.42–2.15 ppm. Whereas, the signals of the hexahydroisoindole fragment protons in the ^{1}H NMR spectrum of compounds **6** were observed as two-proton multiplets (H3a, H7a) at the 3.15–2.86 ppm and an eight-proton multiplet at the 2.17–1.20 ppm. The proton signals in the aromatic part of the spectrum also fully correspond to the proposed structure [15].

In the ^{1}H NMR spectra of the isoindolo [2,1-a]triazinoquinazolines (compounds **5** and **7**), signals of exchangeable protons were not observed. The same signal of the proton at position 14b at the 6.55–6.46 ppm was registered. Additionally, a series of the multiplet signals that corresponded to the



1.1, 4.1, 5.1, 6.1, 7.1 R = Ph; **1.2**, **4.2, 5.2, 7.2** R = 4-EtC_6H_4; **1.3**, **5.3** R = 4-i-Pr-C_6H_4; **1.5**, **6.2** R = 4-FC_6H_4

Scheme 2. Reactivity of 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-ones (**1.1-1.3**, **1.5**) towards phthalic and carbic anhydride

dihydro- or tetrahydroisoindole cycle was observed in the spectra of compounds **5** and **7**. Abovementioned fragments were associated with the signals at the 5.93–5.76 ppm (H-12, 13), 3.97–3.72 ppm (H-11), 3.47–3.26 ppm (H-11), and 3.15–2. 81 ppm (H-14) for compounds **5** and at the 3.18–3.01 ppm (H-11), 2.73–2.59 ppm (m, 1H, H-11), 2.40–2.16 ppm (H-14, 14), 2.11–1.87 ppm (H-12, 13) and 1.79–1.58 ppm (H-12, 13) for compounds **7**. The expected doubling of the signals of methylene protons of the hydrogenated isoindole cycle positions is caused by the appearance of asymmetric center at the position 14b. Among the features of the ^{1}H NMR spectra of compounds **5** and **7** should be mentioned a significant paramagnetic shift of the signals that corresponded to the proton of position 8 due to the formation of a hydrogen bond with the oxygen atom at position 10. Additionally, in the spectra of compounds **5** and **7** were observed signals of the aromatic protons of the heterocyclic fragment and substituents of position **2** [12].

In the ^{13}C NMR spectra of compounds **2**, **3** and **6**, signals were registered associated with deshielded sp^2-hybridized carbon atoms of positions 1 and 3 of the isoindole fragment and position 5 of the triazine cycle at 175.8–166.4, 169.2–158.3 and 166.3–159.8 ppm, respectively. The structure of compounds **3** was additionally confirmed by the signals of carbon atoms of the partially hydrogenated 4.7-methanoisoindole cycle, which appeared at the 134.89–134.35 ppm (5 and 6), 51.87–45.43 ppm (8), 45.95–40.10 ppm (3a and 7a), and 39.89–39.13 ppm (4 and 7). ^{13}C NMR spectrum of compound **6.2** shoed the signals of carbon atoms of position 14b at the 74.85 ppm, position 10 at the 166.95 ppm, and position 3 at the 160.62 ppm.

The obtained spectral data (^{1}H and ^{13}C NMR spectra) enabled the identification of compounds **2**, **3**, **4**, and **6**. However, the spectral analysis did not allow for the unambiguous structural determination of compounds **5** and **7** due to the potential formation of two isomeric tetracyclic systems: isoindolo[2,1-*a*][1,2,4]triazino[2,3-*c*]quinazoline and isoindolo[2,1-*a*][1,2,4]triazino[4,3-*c*]quinazoline. Therefore, to confirm their structural features, an X-ray diffraction study was conducted on compounds **2.3**, **3.4**, and **5.2** (Figs. 1, 2, and 3).

It was found that the vicinal arrangement of substituents in the benzene ring C9...C14 of compound **2.3** (Fig. 1) leads to a significant steric repulsion in the molecule, as indicated by shortened intramolecular contacts H13...N3 2.64 Å (van der Waals radii sum [13] is 2.68 Å, H13...H3N 2.15 Å (2.28 Å), H3N...C13 2.55 Å (2.84 Å), H23...C16 2.81 Å (2.84 Å), O1...C15 2.87 Å (3.14 Å), C1...C15 3.01 Å (3.40 Å), C1...N2 2.91 Å (3.24 Å), and N1...N2 2.88 Å (3.08 Å). These results in a number of deformations of the molecular fragments aimed at reducing steric repulsion. In particular, the triazinone ring adopts a twist-boat conformation (the puckering parameters are as follows: S=0.20, Θ=73.8^0, and Ψ=17.7^0). The deviations of the N4 and C17 atoms from the mean-square plane of the remaining atoms of the cycle are 0.18 Å and 0.26 Å, respectively. It should be noted that these atoms are deflected to the side opposite to the isoindoldione substituent. It should also be noted the noticeable torsion of the endocyclic double bond N4=C17 (the torsion angle N3–N4–C17–C16 is −6.1(3)^0). Another direction of reducing the steric repulsion in the molecule is the rotation of the cycles relative to each other. Thus, if the conjugation between the π-systems of the triazine and phenyl cycles is largely preserved (the torsion angles C13–C14–C15–N3 −40.5(3)^0, and N4–C17–C18–C19 36.9(3)^0), then in the case of the isoindoldione bicycle, not only is the conjugation significantly disrupted (the torsion angle C8–N1–C9–C10 is −60.9(3)^0), but also the C9 atom deviates from the isoindoldione plane by −0.18 Å. The isopropyl substituent is disordered over two positions A and B due to rotation around the C21–C24 bond with equal probability of occupancy and is turned in such a way that the torsion angle C22–C21–C24–H24 is −129^0 in conformer A and 170^0 in conformer B. In this case, shortened intramolecular contacts H22...C25a 2.49 Å (2.84 Å) in conformer Å and H20...H24b 2.19 Å (2.28 Å) in conformer B arise. In the crystal of compound **2.3**, the molecules form infinite chains in the crystallographic direction [0 0 1] due to the intermolecular hydrogen bond N3–H...O3' (x, 1.5–y, 0.5+z) H...O 1.89 Å N–H...O 149^0. The formation of a strong enough hydrogen bond leads to the elongation of the O3–C16 bond up to 1.238(2) Å compared to its average value of 1.210 Å [14]. The molecules in the chain are arranged in such a way that the existence of a stacking interaction between the triazine cycle and the isoindoldione fragment of neighboring molecules can be assumed (the distance between the mean square plane of the cyclic fragments is 3.5 Å).

In the molecule **3.4**, the planar pyrrolidine fragment of the substituent at atom C6 is noticeably turned relative to the aromatic cycle (the torsion angle C14–N1–C6–C1 is −59.9(3)^0) and is located in the exo position relative to the framework fragment (the torsion angle C11–C12–C13–C14 is −47.0(3)^0) (Fig. 2). The six-membered carbocycle of the

framework fragment adopts a boat conformation, the puckering parameters are as follows: S=1.13, Θ=89.7°, and Ψ=0.1°. The deviations of the atoms C9 and C12 from the mean-square plane of the remaining atoms of the cycle are −0.82 Å. Both five-membered rings of the framework are in the «envelope» conformation with a deviation of the C(15) atom by −0.82 Å. In the framework fragment, the elongation of the C8−C9 bonds by 1.567(3) Å and C12−C13 bonds by 1.558(3) Å was detected compared to the average value of 1.540 Å [14]. The triazine ring and the aromatic ring C1...C6 are noticeably rotated relative to each other (the torsion angle C6−C1−C16−N2 is −44.8(3)°). At the same time, the rotation of the triazine ring and the aromatic ring C19...C24 is smaller (the torsion angle C17−C18−C19−C20 is 16.1(3)°), which can be explained by the formation of intramolecular hydrogen bonds C20−H...O3 (H...O 2.25 Å, C−H...O 124°) and C24−H...N3 (H...N 2.42 Å, C−H...N 100°). The ethoxyl substituent is coplanar with the plane of the aromatic ring, despite the noticeable repulsion between the atoms of the ring and the substituent (shortened intramolecular contacts H23...C25 2.54 Å (sum of van der Waals radii: 2.84 Å, H23...H25a 2.26 Å (2.28 Å), H25a...C23 2.71 Å (2.84 Å), H25b...C23 2.83 Å (2.84 Å)) [13]. The ethyl group is in the *ap*-conformation with respect to the C22−O4 bond (the torsion angle C22−O4−C25−C26 is −175.5(2)°). In the crystal of compound **3.4**, the molecules form infinite chains (Fig. 2) in the crystallographic direction [0 1 0] due to the intermolecular hydrogen bond N4−H...O3' (x, y+1, z), H...O 1.83 Å N−H...O 157°. The formation of the hydrogen bond also leads to the elongation of the O3−C17 bond up to 1.232(2) Å compared to the average value of 1.210 Å. The crystal reveals also a C−H...p hydrogen bond C26−H26c...C3' (p) (1−x, 1−y, 1−z), H...p 2.79 Å, C−H...p 166°.

The five-membered and triazine rings in the molecule **5.2** are planar with an accuracy of 0.01 Å (Fig. 3). The pyrimidine ring adopts a sofa conformation (the puckering parameters are as follows: S=0.58, Θ=46.0°, and Ψ=11.0°). The deviations of the N3 and C8 atoms from the mean-square plane of the other atoms of the ring are 0.12 Å and 0.59 Å, respectively. The partially saturated carbocycle adopts a strongly flattened boat conformation (the puckering parameters are as follows: S=0.12, Θ=76.6°, and Ψ=14.6°). The deviations of the C21 and C24 atoms from the plane of the other atoms of the cycle are −0.09 Å and −0.06 Å, respectively. At the same time, in the polycyclic fragment of the molecule, shortened intramolecular contacts H24b...N4 2.60 Å and H3...N1 2.54 Å arise (the van der Waals radii sum is 2.68 Å [13]). The substituent at the C9 atom is slightly non-coplanar with the plane of the triazine ring (the torsion angle C10−C9−C11−C16 is −9.0(6)°), despite the presence of an intramolecular hydrogen bond C16−H...O1 (H...O 2.21 Å, C−H...O 126°) and an attractive interaction H12...N4 2.42 Å (2.68 Å). In the crystal, molecules of **5.2** form head-to-tail stacking dimers (Fig. 3), with a distance between π-systems of 3.43 Å

Therefore, the cyclization of *N*-substituted hydrogenated isoindoles **4** and **6** resulted in the formation of the isoindolo[2,1-*a*][1,2,4]triazino[2,3-*c*]quinazoline system. Abovementioned process is not possible for sterically hindered 2-(2-(5-oxo-6-R-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)-3*a*,4,7,7*a*-tetrahydro-1*H*-4,7-methanoisoindole-1,3-diones (**3**) and aromatic 2-[2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl]-1*H*-isoindole-1,3(2*H*)-diones (**2**). According to the proposed mechanism, in the first stage, *N*-substituted hydrogenated isoindoles **4** and **6** form a carbocation as result of protonation of one of the carbonyl fragments (Scheme 3). The next stages include nucleophilic attack of the nitrogen atom of

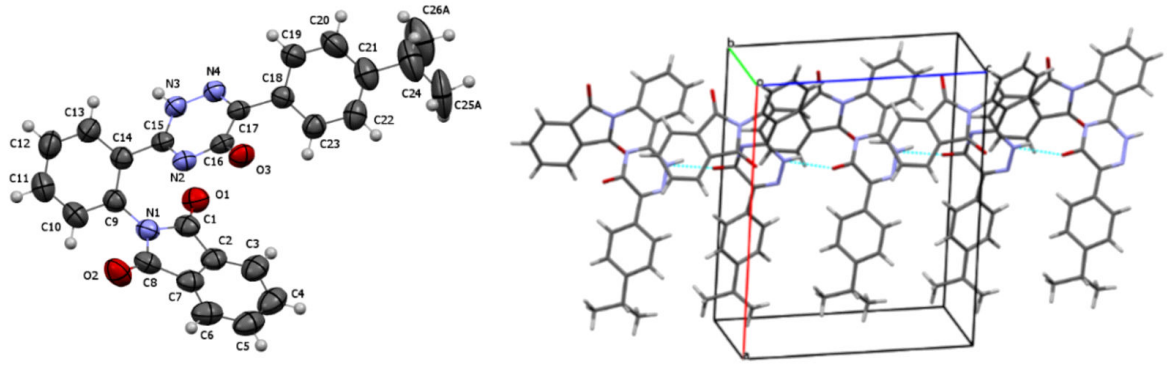


Fig. 1. Molecular structure and packing of molecules in the crystal of compound **2.3** in the crystallographic direction [0 1 0] according to X-ray diffraction data

the triazine cycle by the carbocation, elimination of molecule of the water, hydride shift and deprotonation followed by formation of double bond.

Conclusions

Refluxing 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2*H*)-one with equimolar amounts of phthalic anhydride or its structural analogues (carbic anhydride, tetrahydrophthalic anhydride, and hexahydrophthalic anhydride) in acetic acid for 1 hour led to the formation of the corresponding N-substituted isoindoles. Extending the reaction time in the case of tetrahydrophthalic or hexahydrophthalic anhydride resulted in further cyclization, leading to the formation of the isoindolo[2,1-*a*][1,2,4]triazino[2,3-*c*]quinazoline system. However, this process was not observed under the same conditions for N-substituted isoindoles obtained from phthalic and carbic anhydride. The structures of the synthesized compounds were confirmed using a combination of physicochemical methods, including X-ray diffraction analysis. Their molecular structures and crystallographic characteristics were thoroughly examined. The proposed mechanism for the formation of the isoindolo[2,1-*a*][1,2,4]triazino [2,3-*c*]quinazoline system involves the protonation of one of the carbonyl fragments, nucleophilic attack by the nitrogen atom of the triazine ring on the resulting carbocation, elimination of a water molecule, a hydride shift, and subsequent deprotonation, leading to double bond formation.

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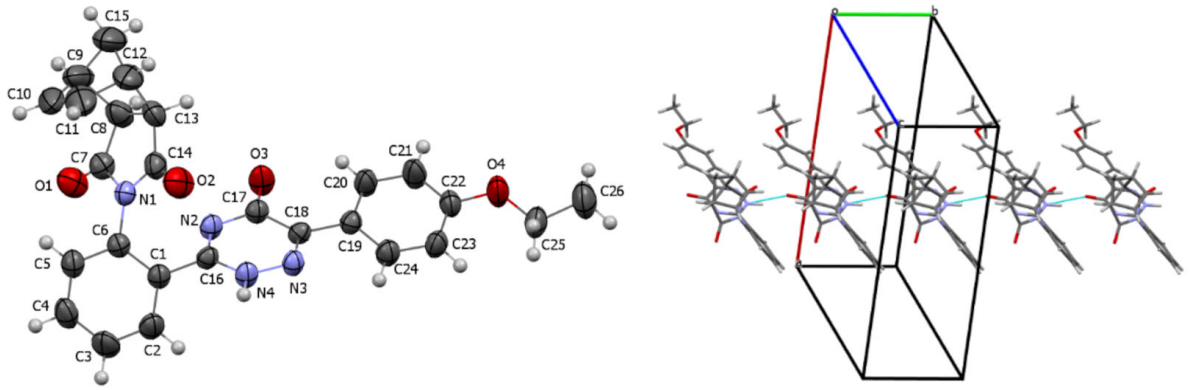


Fig. 2. Molecular structure and packing of molecules in the crystal of compound **3.4** in the crystallographic direction [0 1 0] according to X-ray diffraction data

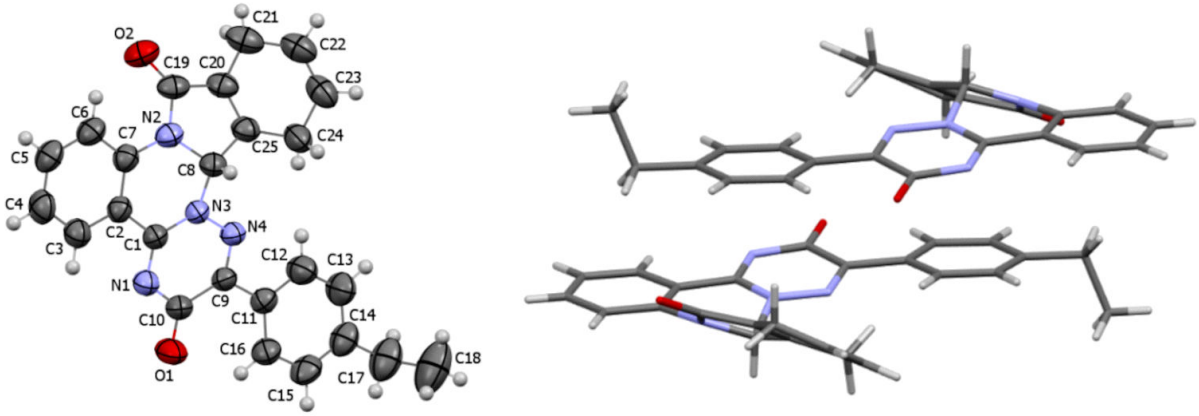
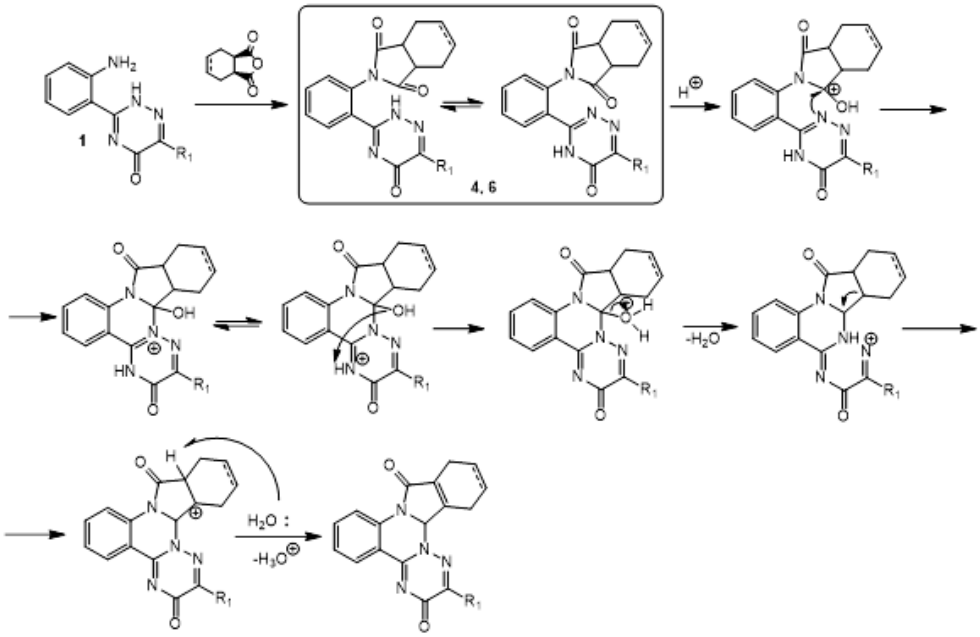


Fig. 3. Molecular structure and stacking dimer of molecules **5.2** in the crystal according to X-ray diffraction data



Scheme 3. Probable mechanism of cyclization of imides **4** and **6** with formation of substituted isoindolo[2,1-*a*][1,2,4]triazino[2,3-*c*]quinazolines

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Received 10.03.2025

РЕАКЦІЙНА ЗДАТНІСТЬ ФТАЛЕВОГО АНГІДРИДУ ТА ЙОГО СТРУКТУРНИХ АНАЛОГІВ ПО ВІДНОШЕННЮ ДО 3-(2-АМІНОФЕНІЛ)-6-R-1,2,4-ТРИАЗИН-5(2H)-ОНІВ

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Надана робота присвячена дослідженню реакційної здатності фталевого ангідриду та його структурних аналогів за відношенням до 3-(2-амінофеніл)-6-R-1,2,4-триазин-5(2*H*)-онів. Встановлено, що короткочасне кип'ятіння названих вихідних речовин приводить до утворення відповідних N-заміщених ізоіндолів. Тривале кип'ятіння частково або повністю гідрогенізованих фталевих ангідридів з 3-(2-амінофеніл)-6-R-1,2,4-тріазин-5(2*H*)-онами приводить до подальшої циклізації та формування відповідних

заміщених ізоіндоло[2,1-*a*][1,2,4]триазино[2,3-*c*]хіназолінів. Структуру одержаних сполук підтверджено комплексом фізико-хімічних методів, вклю- чаючи ВЕРХ-МС, ЯМР-спектроскопію та рентгеноструктурний аналіз. Обговорено структурні особливості одержаних сполук, а також дані рентгеноструктурного аналізу. Крім того, запропоновано та обгрунтовано механізм утворення ізоіндоло [2,1-a][1,2,4]триазино[2,3-c]хіназолінової системи.

Ключові слова: фталевий ангідрид, 3-(2-амінофеніл)-6-R-1,2,4-триазин-5(2H)-они, ізоіндол, ізоіндоло [2,1-a][1,2,4]триазино[2,3-c]хіназоліни, рентгеноструктурний аналіз.

REACTIVITY OF PHTHALIC ANHYDRIDE AND ITS STRUCTURAL ANALOGUES TOWARD 3-(2-AMINOPHENYL)-6-R-1,2,4-TRIAZIN-5(2H)-ONES

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This study explores the reactivity of phthalic anhydride and its structural analogues toward 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones. It was found that short-term refluxing of these starting compounds leads to the formation of the corresponding N-substituted cyclic imides. In contrast, prolonged refluxing of partially or fully hydrogenated phthalic anhydride with 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones results in the formation of substituted isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazolines via further cyclization. The structures of the synthesized compounds were confirmed by a combination of physicochemical methods, including HPLC-MS, NMR spectroscopy, and X-ray diffraction. The structural characteristics and crystallographic data of the products are discussed in detail. A plausible mechanism for the formation of the isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazoline system is also proposed and rationalized.

Keywords: phthalic anhydride; 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones; isoindole; isoindolo[2,1-a][1,2,4]triazino[2,3-c]quinazolines; X-ray diffraction.

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