Synthesis and DFT analysis of non-covalent interactions in crystal structures of 6-R-2-alkoxy-, 2,3-di-, and 2,2,3-tri-tert-butylpyrrolo[1,2-b][1,2,4]triazines

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Abstract
Novel 7-amino-3-tert-butyl-2-OR1-6-R2-pyrrolo[1,2-b][1,2,4]triazine-8-carbonitriles (R1 = CH2CO2Et, CH2Boc, Me, n-Bu; R2 = CO2Et, CO2n-Bu, CO2t-Bu, C6H4CO2i-Pr) have been synthesized and investigated by X-ray diffraction. Nucleophilic replacement of an alkoxy group with t-BuLi afforded sterically hindered tert-butyl 7-amino-2,3-di-tert-butyl- and 2,2,3-tri-tert-butyl-8-cyanopyrrolo[1,2-b][1,2,4]triazine-6-carboxylates. The lengths and bond angles as well as packing modes of molecules in crystals have been considered. The non-covalent interactions such as the changes in the H-bonding and close contacts were analyzed by DFT and the Hirshfeld surfaces and compared for different substituents.

Keywords
Crystal structure · X-ray diffraction · 1,2,4-triazine · pyrrolo[1,2-b][1,2,4]triazine · DFT calculation · Hirshfeld surface analysis

Introduction

Six-membered heterocycles containing one or two nitrogen atoms are ubiquitous in plants as alkaloids with a broad range of biological activities [1, 2]. Triazines are rarely found in nature (e.g., fervenulin, toxoflavin [3, 4], and fluvilids [5]); nevertheless, they also exhibit antibacterial, antifungal, and anticancer properties [6], which make them an important target for research and various applications. Azolotriazines are particularly interesting in terms of their diverse chemical transformations and the bioisosteric nature [7]. The quantitative and qualitative structural analysis of known azolo[1,2,4]triazines, along with molecular modeling, has been successfully used to identify the most privileged scaffolds for further drug design [8–10]. These developments resulted in the production of the 4-aminopyrrolo[2,1-f][1,2,4]triazine remdesivir, which is active against a number of viruses including Ebola virus and coronaviruses [11]. The interactions between an inhibitor and its molecular target are considered primarily non-covalent in nature and shape dependent. Therefore, the changes in the H-bonding and hydrophobic nature of the substituents can greatly affect the biological potency of the compounds [12–14]. It seems clear that investigation of such structural relationships, including novel hydrophilic and hydrophobic cases, can further shed light on mechanism of influence of different substituent configurations on the binding affinity.

Recently, we have investigated 2-alkoxy- and alklythio-pyrrolo[1,2,4]triazines with a moderate antimicrobial activity [15] synthesized by recyclization of pyrazolo[5,1-c][1,2,4]triazines and (1,2,4-triazin-3(2H)-ylidene)acetonitriles [16, 17]. In continuation of our studies, in the present work, we discuss the X-ray structures of novel 7-amino-3-tert-butyl-2-alkoxy-, 2,3-di-tert-butyl-, and 2,2,3-tri-tert-butylpyrrolo[1,2-b][1,2,4]triazine-8-carbonitriles, as well as the non-covalent interactions and packing modes in the single crystals.

Experimental

General experimental remarks

Melting points were determined on a STUART Melting point SMP30 apparatus. IR spectra were recorded in KBr...
pellets using Agilent Cary 660 FTIR infrared spectrophotometer. NMR spectra were recorded on Bruker AM-300, DRX-500, or AV-600 spectrometers operating at working frequencies of 300, 600 (1H), 75, 126, or 151 MHz (13C). Chemical shifts were related to that of the CHCl₃ (1H), or CDCl₃ (13C). High-resolution mass spectra were recorded on a Bruker MicroTOF II instrument in positive ion mode (capillary voltage 4500 V) using electrospray ionization (ESI) and methanol or acetonitrile as a solvent. Elemental analysis was performed on a PerkinElmer Series II 2400 Elemental Analyzer. All reagents were obtained from commercial sources and used without additional purification. All operations, except for chromatography, were carried out in argon atmosphere. Starting compound 1 was synthesized as described in literature [18].

**General procedure for the synthesis of compounds 2a,b and 3 (Scheme 1)**

Compound 1 (0.35 g, 1.61 mmol) was dissolved in 20 ml of dry DMF. To the resulting solution, powdered KOH (0.5 g, 8.91 mmol) was added in one portion. After stirring at r.t. for 15 min, the corresponding alkyl bromoacetate (5 mmol, for the synthesis of 2a,b) or isopropyl (p-bromomethyl)benzoate (2 mmol of BrCH₂CO₂i-Pr for 3) was added, and the reaction mixture was stirred at r.t. for 24 h (for the synthesis of 2a,b) or at 50 °C for 3 h (for the synthesis of 3). Next, an additional portion of alkyl bromoacetate (5 mmol) was added, and the stirring was continued at r.t. for 24 h. The reaction mixture was decanted and quenched with cooled H₂O (200 ml) with vigorous stirring, followed by extraction with dichloromethane (3 × 50 ml). The combined organic phases were washed with H₂O (3 × 100 ml), dried with crystalline K₂CO₃, and filtered. The solvents were removed in vacuo, and the residue was purified by flash column chromatography (eluted with EtOAc:heptane = 1:10–1:3) to give compounds 2a,b and 3. Spectral data for compound 2b, bright yellow powder, yield 0.63 g (1.41 mmol, 88%), mp. 185–186 °C, coincided with those described in literature [15].

**Ethyl 7-amino-3-tert-butyl-8-cyano-2-(2-ethoxy-2-oxoethoxy)pyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (2a)** Bright yellow crystals, yield 0.51 g (1.31 mmol, 81%), mp. 160–162 °C (decomp.). IR (KBr) ν = 3419, 3332, 3273, 3228, 3213 (NH), 2979, 2939, 2909, 2873 (CH), 2218 (CN), 1748, 1661, 1623 (2C=O), 1597, 1552, 1522, 1489, 1447, 1405, 1368, 1346, 1314, 1257, 1197, 1158, 1132, 1053, 1028, 947, 927, 878, 856, 766, 757, 731, 680, 664, 622, 540, 512, 477, 429 cm⁻¹. ¹H NMR: (300 MHz, CDCl₃) δ 1.33 (t, J = 7.2 Hz, 3H, C(6)–CO₂ CH₂ CH₃), 1.41 (t, J = 7.1 Hz, 3H, CH₂ CO₂ CH₂ CH₃), 1.49 (s, 9H, But), 4.29 (q, J = 7.1 Hz, 2H, C(6)–CO₂ CH₂ CH₃), 4.39 (q, J = 7.0 Hz, 2H, CH₂ CO₂ CH₂ CH₃), 5.10 (s, 2H, CH₂ CO₂ Et), 5.61 (br. s, 2H, NH₂). ¹³C{¹H} NMR: (APT, 75 MHz, CDCl₃) δ 14.15, 14.47 (2CO₂ CH₂ CH₃), 27.83 (C(CH₃)₃), 37.44 (C(CH₃)₂), 60.05, 61.77, 63.04 (C₆–CO₂ CH₂ CH₃), 113.17 (CN), 69.50, 100.16, 138.55, 147.95, 148.21, 153.50 (C₂, C₃, C₆, C₇, C₈, C₈a), 161.09, 167.10 (2CO₂ Et). HRMS m/z (Irel. %) calculated: 390.1772 [M+H]+, found: 390.1764 [M+H]+ (100). Anal. calcd. for C₁₈H₂₃N₅O₅ (%): C, 55.52, H, 5.95, N, 17.98. Found (%): C, 55.48, H, 5.91, N, 17.96.

**Isopropyl 4-(7-amino-2-(2-tert-butoxy-2-oxoethoxy)-3-tert-butyl-8-cyano)pyrrolo[1,2-b][1,2,4]triazin-6-yl)benzoate (3)** Orange crystals, yield 0.60 g (1.18 mmol, 73%), mp. 181–184 °C. IR (KBr) ν = 3441, 3364, 3249 (NH), 2978, 2928, 2873, 1748, 1661, 1623 (2C=O), 1597, 1552, 1522, 1489, 1447, 1405, 1368, 1346, 1314, 1257, 1197, 1158, 1132, 1053, 1028, 947, 927, 878, 856, 766, 757, 731, 680, 664, 622, 540, 512, 477, 429 cm⁻¹. ¹H NMR: (300 MHz, CDCl₃) δ 1.40 (t, J = 7.1 Hz, 3H, CH₂ CO₂ CH₂ CH₃), 1.49 (s, 9H, But), 4.29 (q, J = 7.1 Hz, 2H, C(6)–CO₂ CH₂ CH₃), 4.39 (q, J = 7.0 Hz, 2H, CH₂ CO₂ CH₂ CH₃), 5.10 (s, 2H, CH₂ CO₂ Et), 5.60 (br. s, 2H, NH₂). ¹³C{¹H} NMR: (APT, 75 MHz, CDCl₃) δ 14.15, 14.47 (2CO₂ CH₂ CH₃), 27.83 (C(CH₃)₃), 37.44 (C(CH₃)₂), 60.05, 61.77, 63.04 (C₆–CO₂ CH₂ CH₃), 113.17 (CN), 69.50, 100.16, 138.55, 147.95, 148.21, 153.50 (C₂, C₃, C₆, C₇, C₈, C₈a), 161.09, 167.10 (2CO₂ Et). HRMS m/z (Irel. %) calculated: 466.1972 [M+H]+, found: 466.1964 [M+H]+ (100). Anal. calcd. for C₁₉H₂₅N₆O₅ (%): C, 57.49, H, 6.88, N, 18.39. Found (%): C, 57.54, H, 6.91, N, 18.36.

![Scheme 1](image-url)
General procedure for the synthesis of compounds 2c–e (Scheme 2)

Compound 2a or 2b (0.51 mmol) was dissolved in 10 ml of dry MeOH (for the synthesis of 2d), 5 ml of dry ethylene glycol (for 2e), or 5 ml of n-butanol (for 2c,f). Next, powdered K₂CO₃ (0.1 g, 0.72 mmol) was added in one portion, and the reaction mixture was heated under reflux for 40 min (for 2d), 5 h (for 2c,f), or at 100 °C for 1 h (for 2e). After cooling to r.t., EtOAc (30 ml) was added with stirring. The resulting mixture was filtered, the solvents were removed in vacuo, and the residue was purified by flash column chromatography (eluted with EtOAc:heptane = 1:30–1:5) to give compounds 2c–f. Spectral and X-ray data for compound 2c, pale yellow crystals (CCDC 2,017,998), yield 0.17 g (0.44 mmol, 86%), mp. 159–160 °C, coincided with those described in literature [16].

Ethyl 7-amino-3-tert-butyl-8-cyano-2-methoxypyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (2d) Colorless crystals, yield

Reagents and conditions:

i: MeOH, K₂CO₃, Δ 40 min;

ii: Ethylene glycol, K₂CO₃, 100°C, 1 h;

iii: n-BuOH, K₂CO₃, Δ 5 h.
Ethyl 7-amino-3-tert-butyl-8-cyano-2-(2-hydroxyethoxy) pyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (2e) Colorless crystals, yield 0.14 g (0.40 mmol, 78%), mp. 95–110 °C (decomp.). IR (KBr) ν = 3421, 3334 (NH2), 2970, 2957, 2931 (CH), 2213, 1688, 1653 (C=O), 1523, 1597, 1548, 1522, 1482, 1463, 1410, 1382, 1369, 1348, 1311, 1261, 1202, 1158, 1131, 1097, 1049, 1026, 998, 905, 887, 824, 765, 724, 679, 632, 534, 517, 426 cm⁻¹.

1H NMR: (300 MHz, CDCl3) δ 1.42 (t, J = 7.0 Hz, 3H, OCH2CH3), 1.47 (s, 9H, But), 1.89 (br. s, 1H, OH). 13C{1H} NMR: (APT, 75 MHz, CDCl3), the signal of one of the quaternary carbons was not observed due to the broadening δ 13.88 (OCH2CH3), 27.26 (C(CH3)3), 59.05, 59.13 (OCH2CH2OH), 68.55 (OCH2CH3), 113.16 (CN), 98.96, 138.10, 147.45, 147.82, 154.13, 160.34 (C2), C(3), C(6), C(7), C(8), C(9) and CO2Et). HRMS m/z (Irel. %) calculated: 346.1668 [M+H]+, found: 346.1657 [M+H]+ (100). Anal. calc. for C16H19N3O4 (%): C, 55.76, H, 6.05, N, 22.07. Found (%): C, 56.81, H, 6.05, N, 22.03.

Butyl 7-amino-2-butoxy-3-tert-butyl-8-cyano-pyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (2f) Colorless crystals, yield 0.16 g (0.41 mmol, 80%), mp. 156–158 °C. IR (KBr) ν = 3421, 3329 (NH2), 2994, 2957, 2932, 2870 (CH), 1665 (C=O), 1622, 1552, 1519, 1481, 1418, 1366, 1350, 1315, 1261, 1203, 1167, 1137, 1119, 1057, 1024, 1012, 973, 941, 901, 861, 845, 817, 781, 766, 752, 720, 682, 632, 566, 538, 507, 429 cm⁻¹. 1H NMR: (300 MHz, CDCl3) δ 0.97 (t, J = 7.1 Hz, 3H, O(CH2)2CH3), 1.02 (t, J = 7.1 Hz, 3H, O(CH2)3CH2), 1.45 (s, 9H, But), 1.47–1.57 (m, 4H, 2 O(CH2)2CH2CH3), 1.72–1.91 (m, 4H, 2 OCH2CH2CH2CH3), 4.34 (t, J = 7.1 Hz, 2H, OCH2), 4.54 (t, J = 7.1 Hz, 2H, OCH2), 5.59 (br. s, 2H, NH2). 13C{1H} NMR: (APT, 151 MHz, CDCl3, the signals of the two quaternary carbons were not observed due to the broadening) δ 13.23 (2 OCH2CH3), two signals overlapped), 18.85, 18.94 (2 OCH2CH2CH2), 27.34 (C(CH3)3), 29.97, 30.38 (2 OCH2CH2CH2CH3), 36.90 (C.CH3), 63.47, 67.36 (2 OCH2CH2CH2CH3), 113.17 (CN), 99.25, 139.04, 147.67, 154.30, 160.78 (C2), C(3), C(6), C(7), C(8), C(8a) and CO2Bu). HRMS m/z (Irel. %) calculated: 394.2213 [M+Na]+, found: 394.2206 [M+Na]+ (100). Anal. calc. for C25H29N4O5 (%): C, 61.99, H, 7.54, N, 18.07. Found (%): C, 61.96, H, 7.51, N, 18.06.

tert-Butyl 7-amino-2,3-di-tert-butyl-8-cyano-pyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (4b) BuLi solution (1.7 M in n-pentane, 1.5 ml, 2.55 mmol) was added dropwise over 5 min to a cooled (−110 °C) solution of compound 2b (0.5 mmol) in 30 ml of dry THF, with vigorous stirring. After the addition was complete, the reaction mixture was further stirred at −100 for 20 min. Next, the cooling bath was removed, and 3 ml of a saturated KH2PO4/H2O solution was added dropwise over 1 min. The resulting mixture was stirred for 30 min (the inner temperature reached 0 °C), quenched with H2O (30 ml), EtOAc (30 ml), and heptane (20 ml). The organic phase was separated, washed with H2O (1×50 ml), dried with anhydrous MgSO4, and filtered. The solvents were removed in vacuo, and the residue was purified by column chromatography (eluted with EtOAc:heptane = 1:1–1:2) to give compound 4a, bright yellow crystals (CCDC 2,055,900), yield 20 mg (0.06 mmol, 13%), mp. 140–150 °C (dec.), spectral and X-ray data coincided with those described in literature [19]). and compound 4b as yellow crystals, yield 0.14 g (0.38 mmol, 75%), mp. 181–183 °C. IR (KBr) ν = 3431, 3321 (NH2), 3051, 3031, 3006, 2982, 2965, 2930 (CH), 2227 (CN), 1661 (C=O), 1615, 1550, 1473, 1451, 1391, 1381, 1322, 1253, 1200, 1217, 1148, 1098, 1068, 1009, 924, 848, 825, 787, 767, 707, 692, 678, 621, 603, 515, 479, 430 cm⁻¹. 1H NMR: (300 MHz, CDCl3) δ 1.56, 1.59, 1.64 (3 s, 9H + 9H + 9H, 3 Bu), 5.75 (br. s, 2H, NH2). 13C NMR: (APT, 75 MHz, CDCl3) δ 28.88, 31.70, 32.13 (3 C(CH3)3), 40.31, 41.58 ((C2), (C3)−(C(CH3))3), 69.46 (C8), 81.90 (O−(C(CH3))3), 113.75 (CN), 101.69, 136.28, 149.48, 154.99, 160.81, 160.87 (C2), C(3), C(6), C(7), C(8a) and CO2Bu). HRMS m/z (Irel. %) calculated: 394.2213 [M+Na]+, found: 394.2206 [M+Na]+ (100). Anal. calc. for C25H29N4O5 (%): C, 64.66, H, 7.87, N, 18.85. Found (%): C, 64.60, H, 7.92, N, 18.89.
was added dropwise over 5 min to a cooled (−110 ± −105 °C) solution of compound 4b (0.5 mmol) in 30 ml of dry THF, with vigorous stirring. After the addition was complete, the reaction mixture was further stirred at −85 ± −80 °C for 30 min. Next, the cooling bath was removed, and 3 ml of a saturated KH₂PO₄/H₂O solution was added dropwise over 1 min. The resulting mixture was stirred for 30 min (the inner temperature reached 0 °C), and the product was isolated by chromatography, analogously as described above (for 4a, b).

Compound 5, colorless crystals, yield 0.18 g (0.42 mmol, 84%), m.p. 140–150 °C (decomp.). IR (KBr) ν = 3477, 3360, 3343 (NH), 3031, 2967, 2928 (CH), 2206 (CN), 1646 (C = O), 1624, 1607, 1539, 1507, 1475, 1457, 1420, 1396, 1358, 1305, 1262, 1221, 1185, 1145, 1088, 1059, 1030, 985, 943, 920, 883, 850, 819, 785, 760, 680, 663, 635, 598, 517, 490, 461, 425 cm⁻¹. ¹H NMR: (⁵¹H/²H, ¹³C) HMBC, 600 MHz, CDCl₃ δ 1.23 (s, 18H, C(2)(But)₂), 1.56 (s, 9H, C(3)(Bu)), 1.58 (s, 9H, OBut), 5.10 (br. s, 1H, N(1)–H), 5.22 (br. s, 2H, NH₂). ¹³C NMR: (75 MHz APT/151 MHz ¹H–¹³C) HMBC, CDCl₃ δ 29.22 (OC(CH₃)₃), 29.36 (C(2)(CH₃)₂), 34.45 (C(3)(CH₃)₂), 43.34 (C(3)(CH₂)₃), 43.78 (C(1)(CH₂)₃), 59.98 (C(8)), 71.88 (C(2)), 79.91 (O–C(CH₃)₃), 114.66 (CN), 98.24, 145.52 (C(6), C(7)). HRMS m/z (Irel. %) calculated: 452.2996 [M + Na]+, found: 452.2986 [M + Na]+ (100). Anal. calcd. for C₂₄H₃₉N₅O₂ (%): C, 67.10, H, 9.15, N, 16.30. Found (%): C, 67.16, H, 9.13, N, 16.28.

For X-ray single crystal studies, all compounds were recrystallized by slow solvent evaporation at r.t. from nearly saturated solutions in ethyl acetate/heptane mixture (2:1 v/v).

X-ray data collection and refinement

X-ray diffraction data were collected at 100 K (compounds 2a, e, f, 3, 4b, 5) or 250 K (compound 2d) on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless φ-, and ω-scan technique), using Mo Kα-radiation (0.71073 Å). The intensity data were integrated by the SAINT program [20] and were corrected for absorption and decay using SADABS [21]. The structures were solved by direct methods using SHELXTL [22] and refined on F² using SHELXL-2018 [23]. All non-hydrogen atoms were refined with individual anisotropic displacement parameters. Locations of H-atoms of amino (H6A and H6B for 2a, f and 3, H6A, H6B, H6C, and H6D for 2d, H4A, H4B, H9A, and H9B for 2e, H2A and H2B for 4b, H1, H4A, and H4B for 5) and hydroxy (H2 and H6 for 2e) groups were found from the electron density-difference map; these atoms were refined with individual isotropic displacement parameters. Positions of atoms H6A and H6B in 3 were restrained at the distance of 0.85(3)Å from N6. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. A rotating group model was applied for methyl groups in 5.

The SHELXTL program suite [20] was used for molecular graphics. Displacement ellipsoids are set to the 50% probability level on all figures below (see Electronic Supplementary Material (ESM) for more details on X-ray data collection and refinement).

Crystal data, data collection, and structure refinement details for 2a, d–f and 3, 4b, 5 are summarized in Table 1 and Table 2. Crystal data for compounds 2c (CCDC 2,017,998) and 4a (CCDC 2,055,900) have been previously described in literature [16, 19]. Bond distances and angles, as well as additional ORTEP drawings, are presented in ESM for this paper. The structures 2a, f and 3, 4b, 5 have been deposited at the Cambridge Crystallographic Data Center with the reference CCDC numbers 202443, 2,024,440, 2,077,346, 2,077,350–2,077,352, and 2,098,491; they also contain the supplementary crystallographic data. These data can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/data_request/cif.

A geometry optimization was calculated using GAUSSIAN 09 software [24] with the B3LYP/6-31G(d) basis set at the level of DFT theory. Hirshfeld surface analysis was calculated using CrystalExplorer 21.5 [25] and comprised 2D (two-dimensional) fingerprint plots and dnorm surface plots [26]. The electrostatic potentials were mapped on the Hirshfeld surfaces using the B3LYP/6-31G(d) basis set using TONTO computational package integrated into CrystalExplorer software [27]. The crystallographic information files (CIF) of the compounds 2a, 2e, 3, 4a, 4b, and 5 were used as input for the analysis.

Results and discussion

Synthesis

The starting pyrrolotriazines 2a, b were synthesized by N,O-bis-alkylation and Thorpe-Ziegler 5-exo-dig type cyclizations [17] of 2-(6-tert-butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3(2H)-ylidene)malononitrile 1 [18] with bromoacetic esters in the presence of potassium hydroxide (Scheme 1). Compound 3 was synthesized analogously, by treatment of 1 with isopropyl (p-bromomethyl)benzoyl; this reagent also has the ability to stabilize the negative charge at the methylene moiety due to the π-conjugation [16, 28] with the carbonyl group in p-position. It is worth mentioning that an application of less hindered ethyl (p-bromomethyl)benzoyl or
p-nitrobenzyl bromide led to resinification, presumably, due to the ease of competing condensations with formed amino groups.

Nucleophilic heteroaromatic substitution [15, 29] of the C2-OCH2CO2Et group in 2a with methanol or ethylene glycol proceeded on heating in the presence of a catalytic amount of potassium carbonate, to give compounds 2d and 2e, respectively (Scheme 2). The process probably involves coordination of a metal cation [30], as no reaction was observed when K2CO3 was replaced with triethylamine. In the case of n-BuOH, a transesterification [31] of the C6-carboxyethyl group to give the corresponding n-butyl ester became the main competing process, which led to isolation of butyl 7-amino-2-butoxy-3-tert-butyl-8-cyanopyrrolo[1,2-b] [1,2,4]triazine-6-carboxylate 2f in good yield (Scheme 2). tert-Butyl carboxylate 2b was significantly more stable towards transesterification and reacted with n-BuOH/K2CO3 under analogous conditions to afford the expected compound 2c (Scheme 2) [16]. Heterocycle 2b also reacted with t-BuLi at low temperature (THF, −100 °C) to selectively give the aromatic 2,3-di-tert-butyl pyrrolotriazine 4b, along with a small amount of by-product 4a as a result of hydride transfer reduction [32, 33] (Scheme 3). XRD data for 2c and 4a were previously described in literature [16, 19]. On treatment with excess t-BuLi, 4b afforded the sterically hindered non-conjugated tert-butyl 7-amino-2,2,3-tri-tert-butyl-8-cyano-1,2-dihydropyrrolo[1,2-b]
[1,2,4]triazine-6-carboxylate 5. An application of n-BuLi or Grignard reagents gave no reaction or resinification at elevated temperatures. It is worth mentioning that the mechanism of t-BuLi addition (to give 4b and 5) may differ from simple nucleophilic heteroaromatic substitution, as it may involve single electron transfer and further recombination of radicals [33].

Crystals were successfully grown for the novel compounds 2a,d–f and 3, 4b, 5 and X-ray diffraction analyses were carried out.

**Crystal structure discussion**

**Molecular structure description**

The series of synthesized 7-amino-3-tert-butyl-8-cyano-2-alkoxy[1,2-b][1,2,4]triazine-6-(p-phenylene)carboxylates 2a,c–f and 3 crystallize from ethyl acetate/heptane (2:1) mixture in triclinic (P I for 2a,d and 3) or monoclinic (Cc for 2e, P21/c for 2f, and P21/n for 2c) crystal systems without inclusion of solvent molecules into the crystal lattice. Compounds 4a,b, and 5 were crystallized also in monoclinic crystal system (the P21/n space groups for 4a and 5, and P21/c for 4b, respectively). Results of X-ray diffraction studies for novel compounds 2a,d–f, 3 (Figs. 1, 2, and 3) and 4b, 5 (Fig. 4) are presented in Tables 3, 4, 5, and 6.

The isolated 2-alkoxy substituted compounds 2a,c–f, 3 (Figs. 1, 2, and 3) possess aromatic pyrrolotriazine system fully conjugated with the exocyclic amino, cyano, and ester groups; the notable exception is 6-arylsubstituted compound 3 (Fig. 1, ESM Fig. S31), which features non-coplanar hetaryl and disordered phenyl moieties (C7–C6–C20–C25A, θ = −31.8(3)°, C7–C6–C20–C25B, θ = 28.0(3)°). The C8–C8a bond in 3 is 0.017–0.023 Å shorter than in 2a,c–f,

| Compound | 3 | 4b | 5 |
|----------|---|----|---|
| Formula  | C27H33N5O5 | C20H29N5O2 | C24H39N5O2 |
| MR       | 507.58 | 371.48 | 429.60 |
| Crystal system | Triclinic | Monoclinic | Monoclinic |
| Space group | P I | P21/c | P21/n |
| Unit cell dimensions | a (Å) 6.5352(2) b (Å) 11.5286(4) c (Å) 18.2987(7) β (°) 94.5953(10) | 9.2224(2) 12.0168(3) 18.8805(4) 97.7864(6) 14.7166(6) | 13.5941(6) 12.2011(5) 14.7166(6) |
| Volume, Å³ | 1325.39(8) | 2073.12(8) | 2378.42(17) |
| Z | 2 | 4 | 4 |
| Calcd. density (g/cm³) | 1.272 | 1.190 | 1.200 |
| µ (mm⁻¹) | 0.089 | 0.079 | 0.078 |
| F(000) | 540 | 800 | 936 |
| Crystal size (mm) | 0.19 × 0.03 × 0.02 | 0.48 × 0.43 × 0.24 | 0.47 × 0.38 × 0.25 |
| Θ range (°) | 2.255 to 34.986 | 2.760 to 35.008 | 2.192 to 33.176 |
| Completeness to Θmax | 0.997 | 0.998 | 0.985 |
| Index ranges | | | |
| Reflections | Measured | 64,206 | 68,972 | 60,463 |
| Independent [Rint] | 11,655 [0.0960] | 9131 [0.0337] | 8943 [0.0807] |
| Observed [I > 2σ(I)] | 5283 | 7517 | 6136 |
| Parameters, restraints | 483, 702 | 0 | 304, 0 |
| R1, wR2 [I > 2σ(I)] | 0.0732 | 0.0453 | 0.0592 |
| R1, wR2 (all data) | 0.1572 | 0.1180 | 0.1335 |
| GooF on F² | 1.008 | 1.023 | 1.033 |
| Δρmax, Δρmin (e Å⁻³) | 0.345, −0.389 | 0.469, −0.296 | 0.523, −0.287 |
| CCDC number | 2024440 | 2077346 | 2098491 |
Reagents and conditions:

\(i\): \(t\)-BuLi, THF, \(-100^\circ\text{C}, 20\) min;

\(ii\): \(t\)-BuLi, THF, \(-80^\circ\text{C}, 30\) min.

Scheme 3  Synthesis of compounds 2b, 4a,b, and 5

Fig. 1  Molecular structures of 2a and 3. H-atoms of alkyl and aryl groups are omitted; displacement ellipsoids are shown at the 50% probability level.
which also demonstrated the somewhat different π-electron density distribution in the system. Other heterocyclic bond differences within the series are subtle and typically lied within 0.01 Å.

On switching from oxygen in the C2 ring position of 2a,c–f and 3 to tert-butyl group in compound 4b (Fig. 4), a marked increase in the lengths of all the 1,2,4-triazine bonds non-shared with the pyrrole N1–C2, C2–C3 and C3–N4 by 0.02–0.04 Å was observed, together with a slight decrease of the shared bonds N1–C8a, N4–N5 by ~0.02 Å, which was apparently the result of the steric repulsion between the bulky t-Bu substituents in the nearby positions. On the other hand, compound 4a non-substituted in C2 position showed C2–C3 bond lengths considerably shortened (by 0.03–0.05 Å) when compared with its closest analogs 2c and 4b. Triazine ring strain was substantiated by the practically

Fig. 2 Molecular structures of 2d and 2f. H-atoms of alkyl groups are omitted; displacement ellipsoids are shown at the 50% probability level

Fig. 3 Packing of compound 2e in a single crystal. H-atoms of alkyl groups are omitted; displacement ellipsoids are shown at the 50% probability level
planar conformation of the bicycle 4b in the single crystal: N1–C2–C3–N4 and Me3C–C2–C3–CMe3, θ = −3.0(1)° and 3.7(1)°, respectively. Six-membered ring in compound 5, despite also being nearly planar (with the deviations of about 3–8°), is non-aromatic, as evidenced from the alternating single and double bond lengths: N1–C2, C3–N4 = 1.4979(16) and 1.2882(16) Å, respectively for 5, and within 1.30–1.33 Å for other analyzed compounds 2a,c–f, 3, and 4a,b.

The C6–CO2 Alk distance arises with increase in the size of the Alk substituent: from 1.427–1.439 (Alk = Et, in 2a,e,d), 1.437 Å (Alk = n-Bu, in 2f) to 1.448–1.457 Å (Alk = t-Bu, in 2c and 4a,b). The C2–O in 3 is notably longer

Table 3  Selected bond distances in 2a,e-f and 3 (Å)

| Bond       | 2a      | 2e      | 2d      | 3        | 2f      | 2c      |
|------------|---------|---------|---------|----------|---------|---------|
| N1–C2      | 1.3101(9)| 1.309(3)| 1.311(4)| 1.298(2) | 1.311(2)| 1.3108(17)|
| N1–C8a     | 1.3484(9)| 1.346(3)| 1.350(3)| 1.342(2) | 1.347(2)| 1.3479(17)|
| C2–C3      | 1.4478(10)| 1.450(3)| 1.427(5)| 1.444(2) | 1.449(2)| 1.4498(19)|
| C3–N4      | 1.3110(9)| 1.310(3)| 1.314(4)| 1.315(2) | 1.311(2)| 1.3112(17)|
| N4–N5      | 1.3414(8)| 1.344(2)| 1.353(3)| 1.3475(19)| 1.3444(18)| 1.3449(15)|
| N5–C6      | 1.3991(9)| 1.404(3)| 1.403(3)| 1.392(2) | 1.405(2)| 1.4039(17)|
| N5–C8a     | 1.3783(9)| 1.377(3)| 1.364(4)| 1.3885(19)| 1.373(2)| 1.3803(17)|
| C6–C7      | 1.4041(10)| 1.401(3)| 1.386(4)| 1.406(2) | 1.397(2)| 1.3953(19)|
| C7–C8      | 1.4275(10)| 1.431(3)| 1.427(4)| 1.425(2) | 1.425(2)| 1.4289(19)|
| C8–C8a     | 1.3987(9)| 1.397(3)| 1.394(4)| 1.377(2) | 1.399(2)| 1.4002(19)|
| C8–CN      | 1.4126(10)| 1.414(3)| 1.405(4)| 1.416(2) | 1.412(2)| 1.417(2)  |
| C7–NH2     | 1.3527(9)| 1.347(3)| 1.349(3)| 1.359(2) | 1.360(2)| 1.3565(18)|
| C2–O       | 1.3371(8)| 1.338(2)| 1.340(3)| 1.356(2) | 1.334(2)| 1.3360(16)|
| C6–CO, CAr | 1.4384(10)| 1.439(3)| 1.427(4)| 1.458(2) | 1.437(2)| 1.4479(19)|
Table 4  Selected experimental and calculated (B3LYP/6-31G(d), gas phase) bond distances in 4a,b and 5 (Å)

| Bond | 4a (X-ray)       | 4b (DFT)       | 4b (X-ray)      | 5 (DFT)       | 5 (X-ray)       |
|------|------------------|----------------|-----------------|---------------|-----------------|
| N1–C2 | 1.320(3), 1.328(3) | 1.3442         | 1.3255(9)       | 1.4878        | 1.4979(16)      |
| N1–C3a | 1.346(3), 1.335(3) | 1.3336         | 1.3289(10)      | 1.3430        | 1.3365(16)      |
| C2–C3 | 1.416(3), 1.415(3) | 1.4673         | 1.4658(10)      | 1.6027        | 1.5847(16)      |
| C3–N4 | 1.325(3), 1.328(3) | 1.3480         | 1.3288(9)       | 1.2923        | 1.2882(16)      |
| N4–N5 | 1.342(3)          | 1.3395         | 1.3313(8)       | 1.3521        | 1.3574(14)      |
| N5–C6 | 1.391(3), 1.390(3) | 1.3992         | 1.3931(9)       | 1.4317        | 1.4240(16)      |
| N5–C8a | 1.388(3), 1.396(3) | 1.4052         | 1.3733(10)      | 1.3509        | 1.3460(15)      |
| C6–C7 | 1.406(3), 1.411(3) | 1.4265         | 1.4120(10)      | 1.4007        | 1.3859(17)      |
| C7–C8 | 1.421(3), 1.419(3) | 1.4292         | 1.4168(11)      | 1.4409        | 1.4343(17)      |
| C8–C8a | 1.397(3)          | 1.4050         | 1.4009(10)      | 1.4014        | 1.4076(17)      |
| C8–CN | 1.414(3)          | 1.4065         | 1.4110(11)      | 1.4074        | 1.4094(17)      |
| C7–NH₂     | 1.345(3)          | 1.3506         | 1.3500(10)      | 1.3541        | 1.3626(17)      |
| C2–O, C3-Bu | 1.5596         | 1.5510(11)     | 1.6230, 1.6358  | 1.6080(18), 1.6168(17) | 1.4372(17) |

Table 5  Intermolecular hydrogen-bond parameters (Å, °) in 2a, 2e, and 3

| Compound | D—H···A | D—H (Å) | H···A (Å) | D···A (Å) | D—H···A (°) |
|----------|---------|---------|-----------|-----------|-------------|
| 2a       | N(6)—H(6A)···O(4) | 0.863(13) | 2.225(14) | 3.0379(9) | 156.8(12) |
| 2e       | O(6)—H(6)···O(2)  | 1.00(5)   | 1.82(5)   | 2.785(3)  | 162(5)      |
| 3        | N(6)—H(6A)···O(4) | 0.862(14) | 2.294(15) | 3.1648(10) | 169.3(13) |

Symmetry codes: (i) −x + 1, −y + 2, −z; (ii) −x + 2, −y + 1, −z; (iii) x, −y + 1, z − 1/2; (iv) x + 1/2, y − 1/2, z + 1; (v) x + 1/2, −y + 3/2, z + 3/2; (vi) x − 1/2, −y + 3/2, z − 3/2; (vii) x + 1/2, −y + 1/2, z + 3/2; (viii) x − 1/2, −y + 1/2, z − 3/2; (ix) x − y, −y + 1, −z + 1; (x) −x, −y, −z + 1

Table 6  Intermolecular hydrogen-bond parameters (Å, °) in 2d, 2f, 2c, 4a, 4b, and 5

| Compound | D—H···A | D—H (Å) | H···A (Å) | D···A (Å) | D—H···A (°) |
|----------|---------|---------|-----------|-----------|-------------|
| 2d       | N(6)—H(6A)···N(27) | 0.89(3)   | 2.22(3)   | 3.098(4)  | 169(3)      |
| 4a       | N(10A)—H(3)···N(11B) | 0.88(3)   | 2.39(2)   | 3.048(3)  | 132(2)      |
| 4b       | N(2)—H(2B)···N(3) | 0.87(2)   | 2.31(2)   | 3.1717(18) | 153.6(17) |
| 5        | N(1)—H(1)···N(5)  | 0.845(17) | 2.294(17) | 3.1190(15) | 165.3(16) |

Symmetry codes: (i) x + 1, y, z − 1; (ii) x − 1, y, z + 1; (iii) x, y, z − 1; (iv) x, y, z + 1; (v) −x + 1, y + 1/2, z + 3/2; (vi) −x + 1, y − 1/2, z − 3/2; (vii) −x + 1, −y − z − 1; (viii) x − 1, y, z; (ix) −x + 2, −y + 1, −z + 1; (x) −x, −y + 1, −z + 1; (xi) −x + 1, −y + 1, −z + 1
(by 0.016–0.022 Å) than the corresponding bond in other compounds; this may also be due to the bulky exocyclic substituent (CH₂Boc vs Me, n-Bu and CH₂CO₂Et). A sharp increase in the lengths of the C2–C₄Bu and C3–C₄Bu bonds on switching from 2a–c, f, 3, 4a (1.52–1.53 Å) to compounds 4b (1.55 Å) and 5 (up to 1.6168(17) Å) is no doubt due to the rising steric hindrance [34, 35]. According to the NMR (¹H and ¹³C at 600 and 151 MHz, respectively), t-Bu groups in the C₂ ring position, as well as the intermolecular N—H···O=C(OEt) bonds with the nearby molecule; the dimers form infinite nearly planar chains along the a axes were formed via H-bonding between the C₈-nitrile nitrogen and the second hydrogen atom of C₇–NH₂ (Fig. 1 and Table 5). The other bond differences were subtle and typically lied within 0.01 Å, and good correlations between the calculated and experimental values were obtained for N1–C₂–C₈A–N₅, θ = 2.7(2)° and 13.8° for the experimental and DFT optimized structures, respectively).

Hirshfeld surface analysis

Hirshfeld surface analysis (HSA) has proved to be a useful tool for enhancing exploration of the intermolecular interactions in crystals of a wide range of organic molecules [27] including heterocycles [36, 37]. To visualize the intermolecular contacts in the studied structures, HSA was performed as an additional method to X-ray diffraction analysis. In compounds 2a, 2e (hydrogen-bonded dimer),
Fig. 6 The $d_{\text{norm}}$ surfaces for 2a, 2e (hydrogen-bonded dimer), 3, 4a, 4b, and 5, H···N and H···O contacts (top) and their overall 2D fingerprint plots (bottom). Blue and red regions are weak and strong interactions, respectively. Isovalues range from $-0.39$ to $+1.75$ (2a), from $-0.48$ to $+1.58$ (2e), from $-0.25$ to $+1.41$ (3), from $-0.38$ to $+1.60$ (4a), from $-0.47$ to $+1.62$ (4b), and from $-0.38$ to $+1.61$ (5).
3, 4a, 4b, and 5, the main contribution to the energy of the non-valent interactions was made by the N⋯H bonds. For all the analyzed compounds, surface area also included the expected O⋯H reciprocal contacts (4.2% for 4b, 4.9% for 5, 6.1% for 4a, 11.1% for the dimer of 2e, 11.6% for 3, and 14.1% for 2a), which is consistent with the XRD data. These contacts are shown as colored sections on the graph of \( d_{\text{norm}} \) surfaces where \( d_{\text{norm}} = d_i + d_e \) and red \( (d_{\text{norm}} < \text{VdW radii}) \), blue \( (d_{\text{norm}} > \text{VdW radii}) \), white \( (d_{\text{norm}} = \text{VdW radii}) \) (Fig. 6). The intermolecular energies in crystal packing and the fingerprint plots with \( d_{\text{norm}} \) surfaces were calculated at B3LYP/6-31G(d) level of theory.

Analysis of the Hirshfeld surface for compound 3 also revealed notable H⋯H type of short contact between the isopropyl and phenyl groups which was not observed for other compounds. The calculated shortest interatomic distances \( H_{i,p}⋯H_{p} \) lied in range 1.625–1.787 Å and were in satisfactory agreement with the experimental X-ray diffraction analysis (1.6898–1.8790 Å). The reciprocal contacts between nearby molecules and the resulting fingerprint plots are shown on Fig. 6.

**Conclusions**

To summarize, a series of novel 7-amino-3-tert-butyl-8-cyanopyrrolo[1,2-b][1,2,4]triazine-6-(p-phenylene)carboxylates bearing different substituents in the C2 ring position (OCH\(_2\)CO\(_2\)Et, OCH\(_2\)Boc, OMe, OBu, OCH\(_2\)CH\(_2\)OH, H, t-Bu) have been synthesized by alkylation, 5-exo-dig cyclization, and nucleophilic substitution, and their structures were investigated by X-ray diffraction. The experimental results indicated the changes in the electron density distribution, as well as a marked increase in the bond lengths for the sterically hindered derivatives. The crystals of the studied compounds also showed diverse packing modes based on hydrogen bonding, which nature changed with the substitution pattern in heterocyclic nucleus and was successfully investigated by the DFT calculations and Hirshfeld surface analysis.

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**Author contribution** The authors of the current manuscript Denis S. Koltun and Sergey M. Ivanov contributed equally to this work. All authors read and approved the final manuscript.

**Data availability** The structures have been deposited at the Cambridge Crystallographic Data Center with the reference CCDC numbers 2024439, 2024440, 2077346, 2077350–2077352, and 2,098,491; they also contain the supplementary crystallographic data. These data can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk. The online version of this article contains electronic supplementary material (ESM) on crystal structures, IR, NMR, and HRMS data for all new compounds.

**Code availability** Not applicable.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

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