DOI: 10.1002/ejoc.201001590

Unusual Expansion of the 1,2,4,5-Tetrazine Ring in [1,2,4]Triazolo[4,3-*b*]-[1,2,4,5]tetrazines Leading to [1,2,4,6]Tetrazepine Systems

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Keywords: Nitrogen heterocycles / Ring expansion / C–H activation / Nucleophilic substitution

Expansion of the tetrazine ring has first been found to occur when [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines were allowed to react with CH-active compounds in acetonitrile in the presence of triethylamine to give the unexpected series of 8,9-dihydro-7*H*-[1,2,4]-triazolo[4,3-*b*][1,2,4,6]tetrazepine derivatives.

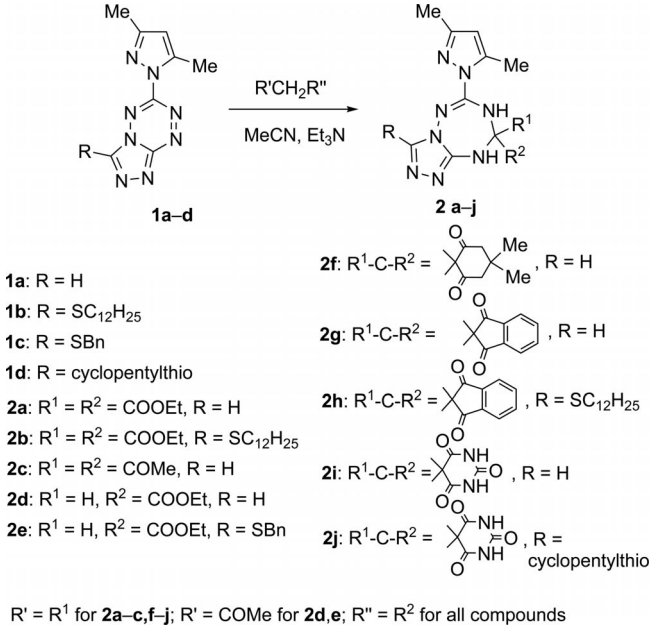
Introduction

It is well known that 1,2,4,5-tetrazines bearing leaving groups in the 3- and 6-positions are able to undergo nucleophilic substitution reactions by N, O, and S nucleophiles to give the corresponding mono- or disubstitution products.[1–7] Also, some carbon modifications of 1,2,4,5-tetrazines due to displacement reactions with anhydro bases of quinaldinium salts[8] and heterocyclic carbenes[9] or by cross-coupling reactions with arylboronic acids[10] and acetylenes[11] have been reported. There are also examples where instead of nucleophilic substitution reactions at C-3 or C-6, azaphilic addition[12,13] or [4+2]cycloaddition reactions[8,14] have been observed to give rise to the corresponding 1,4-dihydrotetrazines or pyridazine derivatives, respectively.

The reactions of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with nucleophilic reagents have so far been scarcely investigated. It has been reported that the 3,5-dimethylpyrazolyl substituents in [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines can easily be displaced with aliphatic amines or alcohols.[15] However, the reaction of 1,2,4-triazolo[4,3-*b*][1,2,4,5]tetrazines with C nucleophiles has never been studied.

Results and Discussion

In the course of this study it has been established that treatment of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines **1** with CH-active compounds in acetonitrile at room temperature in the presence of triethylamine results in the expansion of the tetrazine ring to yield previously unknown 8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines **2**, including spirocyclic derivatives **2f**–**j** (Scheme 1).



Scheme 1. Synthesis of 8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine derivatives.

Compounds **2** were obtained in 40–90% yield as colorless or light-yellow crystalline products. It has been shown that a substituent in the triazole ring of starting materials **1a**–**d** has no significant effect on the reaction rates and yields of the ring-expansion products. The formation of **2** can be rationalized through the addition of C nucleophile at the electron-deficient nitrogen atom in the 8-position of the triazolotetrazine system followed by ring opening and recyclization into the seven-membered ring (Scheme 2).

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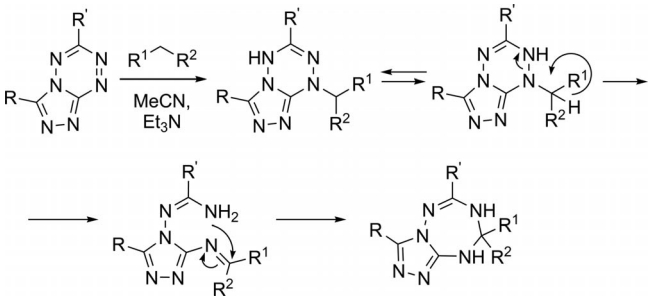
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001590.



Scheme 2. The mechanism suggested for the formation of 8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines.

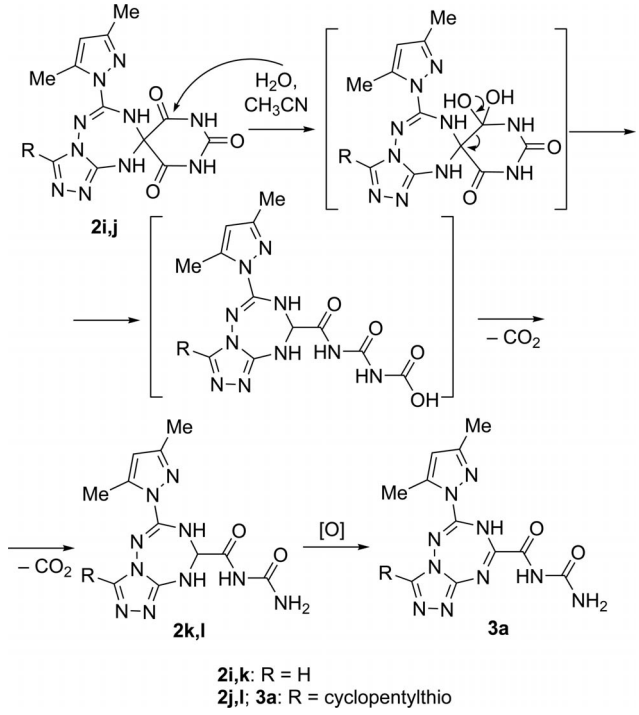
Although nucleophilic attack at a nitrogen atom is not typical for the vast majority of heterocyclic compounds, there are some examples in tetrazine chemistry where the extremely electron-deficient tetrazine ring undergoes azaphilic additions with methyllithium, Grignard reagents, or organozinc compounds to give 1-alkyl- or 1-aryl-substituted 1,4-dihydrotetrazines.[12,13] These literature data can be considered as an argument in favor of the first step of the suggested mechanism. Moreover, according to quantum chemical calculations the LUMO distribution in triazolotetrazines has the maximal coefficient for the N-8 nitrogen,[16] thus indicating that this nitrogen atom appears to be the most plausible site for nucleophilic attack.

It has been established that **2** containing the fragments of 1,3-dicarbonyl compounds are able to eliminate one of the carbonyl groups upon treatment with water. Thus, compounds **2i**,**j** derived from the addition of barbituric acid were transformed into triazolotetrazepines **2k**,**l** upon recrystallization from acetonitrile (Scheme 3). The formation of **2k**,**l** can be explained by hydrolytic cleavage of the barbituric acid fragment with subsequent decarboxylation. Indeed, yields of **2k**,**l** increase from 40 to 80% on transfer from acetonitrile to a mixture of water/acetonitrile as the solvent for recrystallization.

A similar elimination of the R^1 group was observed for the addition of ethyl acetoacetate to triazolotetrazines **1a** and **1c** (Scheme 1). These reactions gave rise to **2d**,**e**, which instead of an acetyl group bear a hydrogen atom at the sp^3 carbon atom in the seven-membered ring. The ^1H NMR spectra of **2d**,**e**,**k**,**l** exhibit characteristic spin–spin coupling constants between this hydrogen atom and the protons of one (for **2d**,**k**,**l**) or two (for **2e**) NH groups.

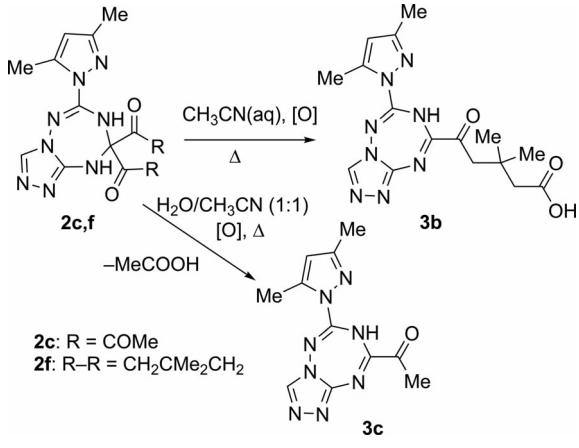
Also, it has been established that compounds **2** that bear a hydrogen atom in the 8-position (i.e., **2l**) can be easily oxidized by the oxygen present in air to afford the corresponding 7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines **3** (Scheme 3). Unlike colorless **2**, compounds **3** are intense yellow solids due to the system of conjugated bonds in their structure.

Cleavage of the diketonic fragment followed by aromatization of triazolotetrazepines is also observed for **2c**,**f** derived from the addition of dimedone (**2f**) and acetylacetone (**2c**; Scheme 4). When heated in acetonitrile, compound **2f** is converted slowly (for 10 h) into triazolotetrazepine **3b**,



Scheme 3. Transformations of 8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines bearing a barbituric acid fragment.

having the 3,3-dimethyl-5-oxopentanic acid fragment. Compound **2c** is more stable than spiro derivative **2f**, and it is not transformed into **3c** upon heating at reflux in acetonitrile. On the other hand, triazolotetrazepine **3c** was obtained from **2c** upon continuous heating at reflux for 5 h in aqueous acetonitrile (Scheme 4).



Scheme 4. Transformations of 8-acyl-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines.

The structural data for compounds **2a**,**d**–**f** and **3b**, belonging to the novel family of [1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepines, was obtained by X-ray crystallography (Figures 1 and 2). The differences in the crystal structures of **2a**,**d**–**f** are not significant, as all these compounds show similar organization. Indeed, the measured bond lengths and angles proved to have expected values, whereas the crystal packings for these compounds are determined mainly by

contribution of the intermolecular hydrogen bonds between the NH of the dihydrotetrazepine ring and the nitrogen atom of the triazole moiety. It is quite natural that the conformations of the dihydrotetrazepine rings and the molecular packings vary from compound to compound, as they are subject to the effects of the substituents in the azabicyclic system.

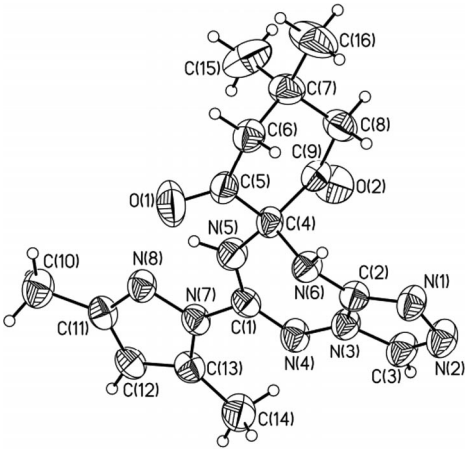


Figure 1. The X-ray structure of 8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine **2f**.

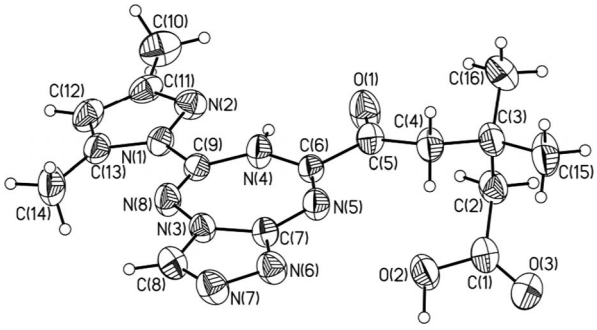
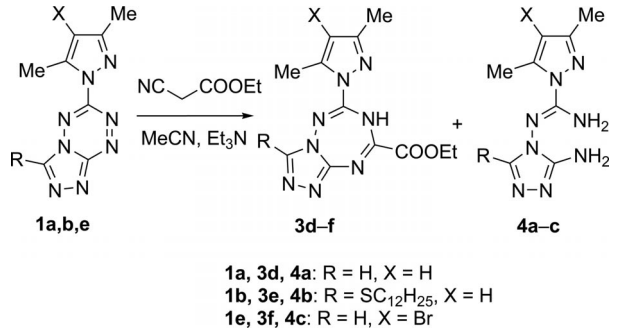


Figure 2. The X-ray structure of 7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]-tetrazepine **3b**.

The tetrazepine ring in compound **3b** is planar, and the maximum deviation of the atoms from the plane of the azaaromatic ring is 0.03 Å. Dispersions of bond lengths in the tetrazepine ring, varying from 1.39 to 1.26 Å, are normal for the azaaromatic compounds. The conformation of **3b** is determined by two types of hydrogen bonds: the intramolecular three-centered hydrogen bonds N4–H4···O1 and N4–H4···N2 and the intermolecular hydrogen bond O2–H2···N6[$-x$, $-y + 1$, $-z + 1$].

The nitrile group in CH-active compounds affects their reactivity. Indeed, reactions of triazolotetrazines **1** with ethyl cyanoacetate result in the formation of both ring-expansion (i.e., **3**) and ring-cleavage products (i.e., **4**; Scheme 5). Dihydrotriazolotetrazepines with cyano- and ethoxycarbonyl fragments in the 8-position have never been obtained. For triazolotetrazines **1a**,**b** the ratio of **3** and **4** proved to be 1:1, whereas yields of these products were only 25–30%. Compound **1e** was transformed into ring-expansion product **3f** in 50% yield, whereas compound **4c** was isolated in only 20% yield.



Scheme 5. The reaction of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with ethyl cyanoacetate.

Evidence for the formation of diamino compounds **4a**–**c** was obtained by X-ray crystallographic analysis, as exemplified by the structure of **4c** (Figure 3).

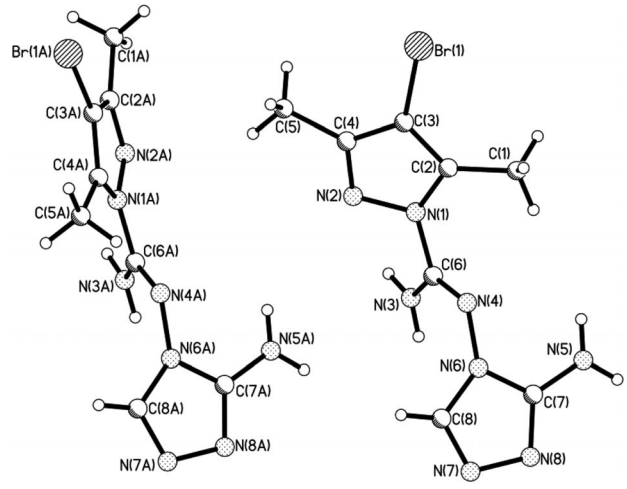


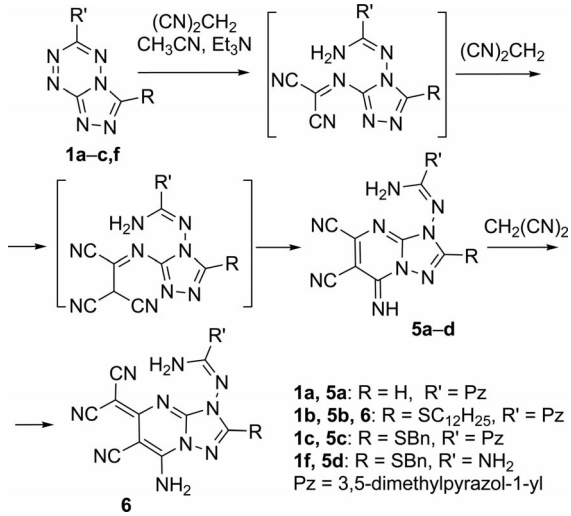
Figure 3. Two independent units in the cell of compound **4c**.

The interaction of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with malononitrile proceeds unexpectedly, resulting in the formation of triazolo[1,5-*a*]pyrimidines **5** instead of triazolo[1,2,4,6]tetrazepine derivatives (Scheme 6). A plausible mechanism for the transformation of **1** into **5** suggests displacement of the cyano group in the reaction intermediate by a second molecule of malononitrile, followed by condensation into the pyrimidine ring (Scheme 6).

All attempts to detect the formation of tetrazepines similar to **2** in these reactions failed, even though the reaction temperatures and concentrations of reagents were varied. Also, it is worth noting that in the reaction of **1b** with malononitrile, besides the formation of triazolopyrimidine **5b**, nucleophilic displacement of the cyano group in **5b** by malononitrile takes place, affording compound **6** (Scheme 6).

Evidence for the structures **5** and **6** is provided by X-ray crystallography (Figures 4 and 5).

Also, it has been found unexpectedly that triethylamine itself is capable of reacting with triazolotetrazines **1**, although it requires a higher temperature and other different



Scheme 6. Interaction of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with malononitrile.

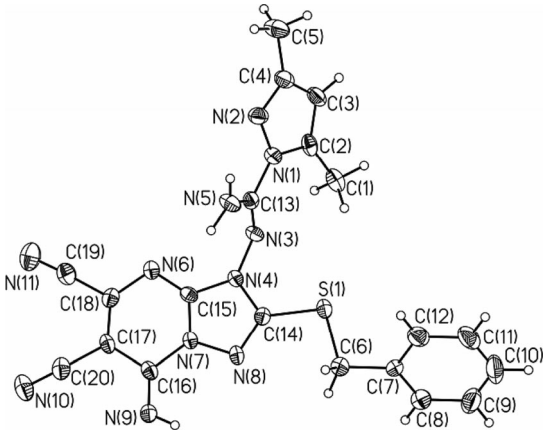


Figure 4. The X-ray structure of [1,2,4]triazolo[1,5-*a*]pyrimidine **5c**.

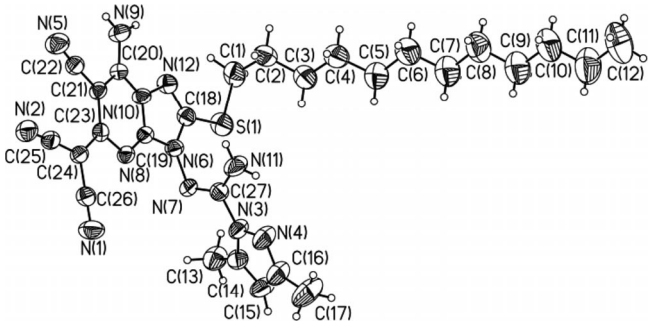
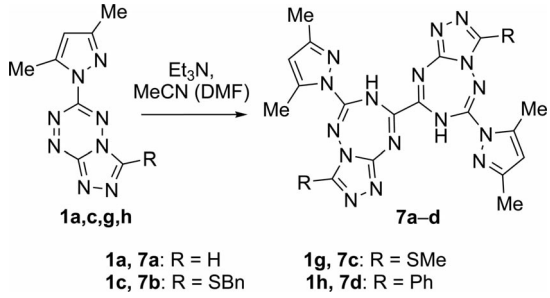


Figure 5. The X-ray structure of [1,2,4]triazolo[1,5-*a*]pyrimidine **6**.

reaction conditions. Indeed, heating compounds **1** with triethylamine in acetonitrile at reflux affords derivatives of 7*H*,7′*H*-8,8′-bis[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine **7** in 20–30% yield (Scheme 7). A similar yield of **7a** was reached in DMSO, and the yield improved to 40% when the reaction was carrying out in DMF.



Scheme 7. Synthesis of 7*H*,7′*H*-8,8′-bis[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine derivatives.

Compounds **7** possess rather high melting points (above 350 °C) and a low solubility in many organic solvents, which makes it difficult to register high-resolution NMR spectra. Therefore, the structure of **7a** was established by X-ray crystallography (Figure 6).

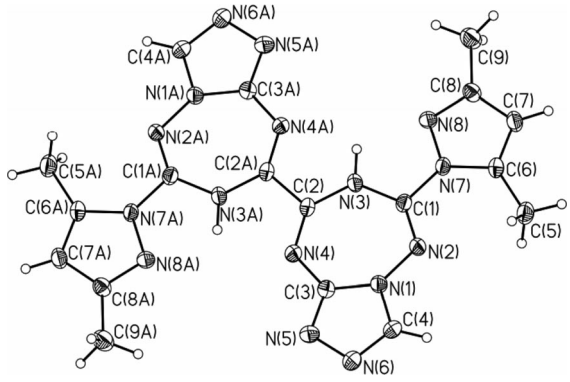


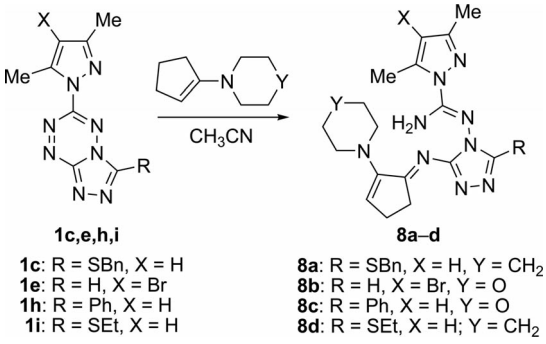
Figure 6. The X-ray structure of 7*H*,7′*H*-8,8′-bis[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine **7a**.

Bonds lengths and the general geometry of the tetrazepine ring in 7**a** are in a good agreement with those for **3b**. The conformation of the molecule was determined by the intramolecular hydrogen bond N3–H3···N8 and is stabilized by strong π–π interactions; the distance between centroids C1N2N1C4N6 and C1N2N1C4N6 [1 – *x*, –*y*, 1 – *z*] is 3.235 Å.

The formation of compounds **7** can possibly be explained by interaction of triazolotetrazines **1** with diethylaminoethene, which is formed under the reaction conditions due to oxidation of triethylamine. This assumption is substantiated by the fact that this enamine is capable of reacting with 1,2,4,5-tetrazines to give [4+2] cycloaddition products.[17]

In order to prove or reject the opportunity of triazolotetrazines **1** reacting with enamines, we studied the reactions of **1** with 1-piperidinocyclopentene and 1-morpholinocyclopentene. These enamines are known to react with noncondensed 1,2,4,5-tetrazines to give pyridazines[18] or tricyclic adducts.[19] The structure of triazolo[4,3-*b*][1,2,4,5]-tetrazines does not contain a fixed *cis*-diene system that is necessary for realization of the [4+2] cycloaddition process. Therefore, we expected that enamines might act as C nucleophiles to give ring-expansion products like compounds

2. However, the experiments showed that the reaction of **1** with enamines stops after opening of the tetrazine ring, affording products **8** without further cyclization (Scheme 8).



Scheme 8. Interaction of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines with enamines.

The structure of compounds **8** was confirmed by X-ray analysis (Figure 7), thus providing an additional argument in favor of the suggested mechanism, which involves the addition of C nucleophiles at the 8-position of the triazolotetrazine system. The LC–MS analysis data showed that compounds **8** easily undergo hydrolysis into their diamino derivatives **4**.

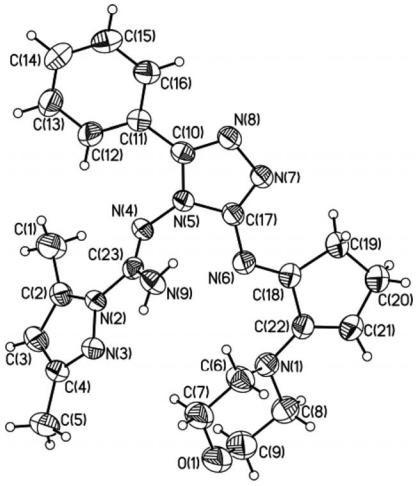


Figure 7. The X-ray structure of compound **8c**.

According to the X-ray data, all analyzed compounds with the open tetrazine ring (i.e., **4c**, **5c**, **6**, **8c**) have some general features, despite the variety of substituents. All structures are characterized with high values for angles between the planes of the amidine moiety and the triazole ring. In all compounds the molecular packing is determined by a strong system of intermolecular hydrogen bonds between the NH_2 groups and the nitrogen atoms of the azole system (for **4c**, **8c**), the imino group (for **5c**), or the cyano groups (for **6**).

Conclusions

Transformations of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines by action of C nucleophiles have been studied. It has been established that these reactions are initiated by nucleophilic attack at the ring nitrogen atom, which appears to be a rare phenomenon in heterocyclic chemistry. The ring opening of the tetrazine ring followed by recyclization provide new opportunities for construction of [1,2,4]triazolo[1,5-*a*]pyrimidines and [1,2,4]triazolo[4,3-*b*][1,2,4,6]-tetrazepines, as representatives of a new heterocyclic system.

Experimental Section

General: All reagents were commercially available and used without further purification. Melting points were determined with a Stuart melting-point apparatus. NMR spectra were recorded with a Bruker Avance DRX-400 spectrometer using Me_4Si as an internal standard. Mass spectromeric data were obtained with a Bruker microTOF-Q II LC-mass spectrometer and a Shimadzu LCMS-2010 instrument operating in electrospray ionization mode. Elemental analyses were carried out with an automated Perkin–Elmer PE-2400 microanalyzer.

Synthesis of 1a-i: Compounds **1a**–**c**,**e**,**g**–**i** have been described earlier.[15,20] Compounds **1d**,**f** were synthesized following the reported procedures.[15]

3-(Cyclopentylthio)-6-(3,5-dimethylpyrazol-1-yl)[1,2,4]triazolo-[4,3-*b*][1,2,4,5]tetrazine (1d): Yield: 72%. M.p. 119 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.63–1.77 (m, 6 H, 3 CH_2), 2.17 (m, 2 H, CH_2), 2.29 (s, 3 H, pyrazole-CH_3), 2.59 (s, 3 H, pyrazole-CH_3), 4.17 (m, 1 H, SCH), 6.38 (s, 1 H, pyrazole 4-H) ppm. $C_{13}H_{16}N_8S$ (316.38): calcd. C 49.35, H 5.10, N 35.42; found C 49.47, H 5.22, N 35.32.

3-Amino-6-(benzylthio)[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine (1f): Yield: 73%. M.p. 188–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.63 (s, 2 H, SCH_2Ph), 5.60 (br. s. 2 H, NH_2), 7.26–7.40 (m, 5 H, Ph) ppm. $C_{10}H_9N_7S$ (259.29): calcd. C 46.32, H 3.50, N 37.81; found C 46.59, H 3.33, N 38.06.

General Procedure for the Synthesis of 8,9-Dihydro-7*H*-[1,2,4]-triazolo[4,3-*b*][1,2,4,6]tetrazepine Derivatives 2a–j: To a stirred mixture of **1** (1 mmol) and the CH-active compound (1.2 mmol) in CH_3CN (5 mL) was added TEA (1 mmol). The reaction mixture was stirred at room temperature. Upon completion of the reaction, as monitored by TLC, a white or pale-yellow precipitate was filtered off and washed with CH_3CN.

Diethyl 6-(3,5-Dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine-8,8(9*H*)-dicarboxylate (2a): Compound **2a** was prepared from **1a** and diethyl malonate (reaction time 5 min). Yield: 207 mg (55%). M.p. 183–184 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.16 (t, J = 7.1 Hz, 6 H, 2 OCH_2CH_3), 2.19 (s, 3 H, pyrazole-CH_3), 2.49 (s, 3 H, pyrazole-CH_3), 4.24 (m, 4 H, 2 OCH_2CH_3), 6.20 (s, 1 H, pyrazole 4-H), 8.28 (s, 1 H, 3-H), 8.57 (s, 1 H, NH), 8.76 (br. s, 1 H, NH) ppm. MS (ESI): m/z (%) = 377.2 (100) [M + 1]$^+$. $C_{15}H_{20}N_8O_4$ (376.37): calcd. C 47.87, H 5.36, N 29.77; found C 47.83, H 5.37, N 29.79.

Diethyl 6-(3,5-Dimethylpyrazol-1-yl)-3-(dodecylthio)-7*H*-[1,2,4]-triazolo[4,3-*b*][1,2,4,6]tetrazepine-8,8(9*H*)-dicarboxylate (2b): Compound **2b** was prepared from **1b** and diethyl malonate (reaction time 5 min). Yield: 473 mg (82%). M.p. 105–106 °C. ^{1}H NMR

(400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 [t, J = 7.0 Hz, 3 H, (CH$_2$)$_{11}$CH_3], 1.15 (t, J = 7.1 Hz, 6 H, 2 OCH$_2$CH_3), 1.23 [m, 16 H, (CH$_2$)$_8$], 1.36 (m, 2 H, CH$_2$), 1.65 (m, 2 H, CH$_2$), 2.20 (s, 3 H, pyrazole-CH$_3$), 2.56 (s, 3 H, pyrazole-CH$_3$), 3.06 (t, J = 7.3 Hz, 2 H, SCH$_2$), 4.24 (m, 4 H, 2 OCH_2CH$_3$), 6.22 (s, 1 H, pyrazole 4-H), 8.61 (s, 1 H, NH), 8.70 (br. s, 1 H, NH) ppm. MS (ESI): m/z (%) = 577.3 (100) [M + 1]$^+$. $C_{27}H_{44}N_8O_4S$ (576.75): calcd. C 56.23, H 7.69, N 19.43; found C 56.23, H 7.64, N 19.66.

6-(3,5-Dimethylpyrazol-1-yl)-8,8-diacetyl-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine (2c): Compound **2c** was prepared from **1a** and 2,4-pentanedione (reaction time 10 min). Yield: 221 mg (70%). M.p. 178–181 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.21 (s, 3 H, pyrazole-CH$_3$), 2.33 (s, 6 H, 2 Ac), 2.45 (s, 3 H, pyrazole-CH$_3$), 6.17 (s, 1 H, pyrazole 4-H), 8.24 (s, 1 H, 3-H), 8.86 (s, 1 H, NH), 9.00 (br. s, 1 H, NH) ppm. MS (ESI): m/z (%) = 317.2 (100) [M + 1]$^+$. $C_{13}H_{16}N_8O_2$ (316.32): calcd. C 49.36, H 5.10, N 35.42; found C 49.37, H 5.08, N 35.31.

Ethyl 6-(3,5-Dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo-[4,3-*b*][1,2,4,6]tetrazepine-8-carboxylate (2d): Compound **2d** was prepared from **1a** and ethyl acetoacetate (reaction time 24 h). Yield: 180 mg (59%). M.p. 206–207 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.08 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3), 2.19 (s, 3 H, pyrazole-CH$_3$), 2.46 (s, 3 H, pyrazole-CH$_3$), 4.08 (m, 2 H, OCH_2CH$_3$), 5.15 (d, J = 6.5 Hz, 1 H, 8-H), 6.14 (s, 1 H, pyrazole 4-H), 8.21 (s, 1 H, 3-H), 8.32 (s, 1 H, NH), 8.83 (d, J = 6.5 Hz, 1 H, NH) ppm. MS (ESI): m/z (%) = 305.2 (100) [M + 1]$^+$. $C_{12}H_{16}N_8O_2$ (304.31): calcd. C 47.36, H 5.30, N 36.82; found C 47.30, H 5.60, N 36.87.

Ethyl 3-(Benzylthio)-6-(3,5-dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-carboxylate (2e): Compound **2e** was prepared from **1c** and ethyl acetoacetate (reaction time 24 h). Yield: 257 mg (55%). M.p. 164–166 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.07 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3), 2.07 (s, 3 H, CH$_3$CN), 2.19 (s, 3 H, pyrazole-CH$_3$), 2.52 (s, 3 H, pyrazole-CH$_3$), 4.09 (m, 2 H, OCH_2CH$_3$), 4.32 (s, 2 H, CH_2Ph), 5.17 (dd, J = 6.5, 5.5 Hz, 1 H, 8-H), 6.16 (s, 1 H, pyrazole 4-H), 7.21–7.42 (m, 5 H, Ph), 8.39 (d, J = 5.5 Hz, 1 H, NH), 8.88 (d, J = 6.5 Hz, 1 H, NH) ppm. MS (ESI): m/z (%) = 427.1 (100) [M + H]$^+$. $C_{19}H_{22}N_8O_2S{\cdot}CH_3CN$ (467.55): calcd. C 53.95, H 5.39, N 26.96; found C 53.88, H 5.21, N 26.71.

6-(3,5-Dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine-8-spiro-2′-(5′,5′-dimethylcyclohexane-1′,3′-dione) (2f): Compound **2f** was prepared from **1a** and dimedone (reaction time 2 h). Yield: 200 mg (56%). M.p. 202–204 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 (s, 3 H, CH$_3$), 1.15 (s, 3 H, CH$_3$), 2.21 (s, 3 H, pyrazole-CH$_3$), 2.51 (s, 3 H, pyrazole-CH$_3$), 2.69 (d, J = 13.5 Hz, 2 H, 2 H$_A$), 3.23 (d, J = 13.5 Hz, 2 H, 2 H$_B$), 6.19 (s, 1 H, pyrazole 4-H), 8.33 (s, 1 H, 3-H), 8.42 (br. s, 1 H, NH), 8.51 (s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 13.36, 14.16, 26.54, 28.91, 30.77, 49.39, 80.36, 110.10, 141.78, 142.14, 143.46, 148.23, 149.38, 198.92 ppm. MS (ESI): m/z (%) = 357.2 (100) [M + 1]$^+$. $C_{16}H_{20}N_8O_2$ (356.38): calcd. C 53.92, H 5.66, N 31.44; found C 54.01, H 5.32, N 31.49.

6-(3,5-Dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine-8-spiro-2′-indene-1′,3′-dione(2g): Compound **2g** was prepared from **1a** and indanedione (reaction time 2 h). Yield: 138 mg (38%). M.p. 229–230 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.14 (s, 3 H, pyrazole-CH$_3$), 2.48 (s, 3 H, pyrazole-CH$_3$), 6.12 (s, 1 H, pyrazole 4-H), 8.06 (m, 4 H, Ar), 8.44 (s, 1 H, 3-H), 8.75 (br. s, 1 H, NH), 8.92 (s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 13.24, 13.69, 68.36, 109.17, 124.17, 137.05, 139.42, 141.12, 141.62, 142.80, 148.75, 149.97, 192.57 ppm. MS (ESI): m/z (%) = 363.1 (100) [M + 1]$^+$. $C_{17}H_{14}N_8O_2$ (362.35): calcd. C 56.35, H 3.89, N 30.92; found C 56.27, H 3.67, N 30.89.

6-(3,5-Dimethylpyrazol-1-yl)-3-dodecylthio-8,9-dihydro-7*H*-[1,2,4]-triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-spiro-2′-indene-1′,3′-dione (2h): Compound **2h** was prepared from **1b** and indanedione (reaction time 2 h). Yield: 259 mg (46%). M.p. 186–187 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 [t, J = 7.0 Hz, 3 H, (CH$_2$)$_{11}$CH_3], 1.24 [m, 16 H, (CH$_2$)$_8$], 1.39 (m, 2 H, CH$_2$), 1.69 (m, 2 H, CH$_2$), 2.15 (s, 3 H, pyrazole-CH$_3$), 2.58 (s, 3 H, pyrazole-CH$_3$), 3.10 (t, J = 7.3 Hz, 2 H, SCH$_2$), 6.15 (s, 1 H, pyrazole 4-H), 8.02–8.11 (m, 4 H, Ar), 8.72 (br. s, 1 H, NH), 8.91 (s, 1 H, NH) ppm. MS (ESI): m/z (%) = 563.3 (100) [M + 1]$^+$. $C_{29}H_{38}N_8O_2S$ (562.73): calcd. C 61.90, H 6.81, N 19.91; found C 61.51, H 6.53, N 19.86.

6-(3,5-Dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine-8-spiro-5′-pyrimidine-2′,4′,6′(1′*H*,3′*H*,5′*H*)-trione (2i): Compound **2i** was prepared from **1a** and barbituric acid (reaction time 2 h). Yield: 405 mg (91%). M.p. 211–212 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.96 [t, J = 7.2 Hz, 9 H, (CH_3CH$_2$)$_3$N], 2.18 (s, 3 H, pyrazole-CH$_3$), 2.52 [q, J = 7.2 Hz, 6 H, (CH$_3$CH_2)$_3$N], 2.51 (s, 3 H, pyrazole-CH$_3$), 6.15 (s, 1 H, pyrazole 4-H), 8.33 (s, 1 H, 3-H), 9.22 (br. s, 2 H, 2 NH), 10.5 (br. s, 2 H, 2 NH) ppm. MS (ESI): m/z (%) = 345.1 (100) [M + 1]$^+$. $C_{12}H_{12}N_{10}O_3{\cdot}Et_3N$ (445.48): calcd. C 48.53, H 6.11, N 34.59; found C 48.64, H 6.15, N 34.92.

3-Cyclopentylthio-6-(3,5-dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-spiro-5′-pyrimidine-2′,4′,6′(1′*H*,3′*H*,5′*H*)-trione (2j): Compound **2j** was prepared from **1d** and barbituric acid (reaction time 2 h). Yield: 406 mg (72%). M.p. 198 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.03 [t, J = 7.1 Hz, 9 H, (CH_3CH$_2$)$_3$N], 1.57 (m, 4 H, 2 CH$_2$), 1.70 (m, 2 H, CH$_2$), 2.07 (m, 2 H, CH$_2$), 2.19 (s, 3 H, pyrazole-CH$_3$), 2.61 (s, 3 H, pyrazole-CH$_3$), 2.70 [q, J = 7.1 Hz, 6 H, (CH$_3$CH_2)$_3$N], 3.79 (m, 1 H, SCH), 6.19 (s, 1 H, pyrazole 4-H), 8.75 (br. s, 1 H, NH), 9.26 (br. s, 1 H, NH), 11.0 (br. s, 2 H, 2 NH) ppm. MS (ESI): m/z (%) = 445.2 (100) [M + 1]$^+$. $C_{17}H_{20}N_{10}O_3S{\cdot}Et_3N{\cdot}H_2O$ (563.68): calcd. C 49.01, H 6.62, N 27.33; found C 49.22, H 6.37, N 27.49.

General Procedure for the Synthesis of [1,2,4]Triazolo[4,3-*b*]-[1,2,4,6]tetrazepine Derivatives 2k,l and 3a–c: Compound **2** (0,5 mmol) in acetonitrile or aqueous acetonitrile (3 mL) was heated at reflux for 10 min to 10 h. After cooling to room temperature the precipitate formed was filtered off and air dried.

1-{6-(3,5-Dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo-[4,3-*b*][1,2,4,6]tetrazepine-8-carbonyl}urea (2k): Compound **2k** was prepared from **2i** in aqueous acetonitrile (water/CH$_3$CN, 1:10; reaction time 10 min). Yield: 133 mg (79%). M.p. 199–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.19 (s, 3 H, pyrazole-CH$_3$), 2.46 (s, 3 H, pyrazole-CH$_3$), 5.21 (br. s, 1 H, 8-H), 6.14 (s, 1 H, pyrazole 4-H), 7.36 (br. s, 2 H, NH$_2$), 7.98 (s, 1 H, CON*H*CO), 8.22 (s, 1 H, 3-H), 8.69 (d, J = 6.1 Hz, 1 H, NH), 10.36 (br. s, 1 H, NH) ppm. MS (ESI): m/z (%) = 319.3 (100) [M + 1]$^+$. $C_{11}H_{14}N_{10}O_2{\cdot}H_2O$ (336.31): calcd. C 39.28, H 4.80, N 41.65; found C 39.66, H 4.60, N 41.68.

1-{3-Cyclopentylthio-6-(3,5-dimethylpyrazol-1-yl)-8,9-dihydro-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-carbonyl}urea (2l): Compound **2l** was prepared from **2j** in aqueous acetonitrile (water/CH$_3$CN, 1:10; reaction time 10 min). Yield: 171 mg (80%). M.p. 181–183 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.57 (m, 4 H, 2 CH$_2$), 1.69 (m, 2 H, CH$_2$), 2.07 (m, 2 H, CH$_2$), 2.19 (s, 3

H, pyrazole-CH_3), 2.55 (s, 3 H, pyrazole-CH_3), 3.78 (m, 1 H, CH), 5.22 (br. s, 1 H, 8-H), 6.16 (s, 1 H, pyrazole 4-H), 7.36 (br. s, 2 H, NH_2), 8.01 (s, 1 H, CON*H*CO), 8.73 (d, *J* = 6.1 Hz, 1 H, NH), 10.37 (br. s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 419.1 (100) [M + 1]$^+$. $C_{16}H_{22}N_{10}O_2S{\cdot}0.5H_2O$ (427.48): calcd. C 44.95, H 5.42, N 32.77; found C 44.88, H 5.48, N 32.59.

1-{3-Cyclopentylthio-6-(3,5-dimethylpyrazol-1-yl)-7*H*-[1,2,4]-triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-carbonyl}urea (3a): Compound **3a** was prepared from **2j** in acetonitrile (reaction time 5 h). Yield: 73 mg (35%). M.p. 232 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.61 (m, 4 H, 2 CH_2), 1.71 (m, 2 H, CH_2), 2.18 (m, 2 H, CH_2), 2.20 (s, 3 H, pyrazole-CH_3), 2.49 (s, 3 H, pyrazole-CH_3), 3.91 (m, 1 H, SCH), 6.30 (s, 1 H, pyrazole 4-H), 7.39 (s, 2 H, NH_2), 9.81 (s, 1 H, NH), 10.24 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 417.2 (100) [M + 1]$^+$. $C_{16}H_{20}N_{10}O_2S$ (416.46): calcd. C 46.14, H 4.84, N 33.63; found C 46.28, H 4.80, N 33.61.

5-{6-(3,5-Dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]-tetrazepin-8-yl}-3,3-dimethyl-5-oxopentanoic Acid (3b): Compound **3b** was prepared from **2f** in acetonitrile (reaction time 10 h). Yield: 91 mg (49%). M.p. 218–220 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.10 (s, 6 H, 2 CH_3), 2.22 (s, 3 H, pyrazole-CH_3), 2.34 (s, 2 H, CH_2), 2.49 (s, 3 H, pyrazole-CH_3), 3.10 (s, 2 H, CH_2), 6.29 (s, 1 H, pyrazole 4-H), 8.41 (s, 1 H, 3-H), 10.03 (s, 1 H, NH), 12.10 (s, 1 H, COOH) ppm. MS (ESI): *m*/*z* (%) = 373.2 (100) [M + 1]$^+$. $C_{16}H_{20}N_8O_3$ (372.38): calcd. C 51.61, H 5.41, N 30.09; found C 51.47, H 5.52, N 29.94.

8-Acetyl-6-(3,5-dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepine (3c): Compound **3c** was prepared from **2c** in aqueous acetonitrile (water/CH_3CN,1:10; reaction time 5 h). Yield: 88 mg (65%). M.p. 220 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 25 °C): δ = 2.21 (s, 3 H, pyrazole-CH_3), 2.47 (s, 3 H, Ac), 2.49 (s, 3 H, pyrazole-CH_3), 6.29 (s, 1 H, pyrazole 4-H), 8.42 (s, 1 H, 3-H), 9.97 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 273.1 (20) [M + 1]$^+$. $C_{11}H_{12}N_8O$ (272.27): calcd. C 48.53, H 4.44, N 41.16; found C 48.55, H 4.39, N 41.04.

General Procedure for the Synthesis of 7*H*-[1,2,4]Triazolo-[4,3-*b*][1,2,4,6]tetrazepine Derivatives 3d–f and *N*′-(3-Amino-4*H*-1,2,4-triazol-4-yl)-3,5-dimethylpyrazole-1-carboxamidine Derivatives 4a–c: To a stirred mixture of **1** (1 mmol) and ethyl cyanoacetate (1.2 mmol) in CH_3CN (5 mL) was added TEA (1 mmol). The reaction mixture was stirred at room temperature for 20 min.

Reactions of 1a,e with Ethyl Cyanoacetate: Compounds **4a**,**c** were obtained as white solid precipitates, which were filtered off and air dried. Filtrates were evaporated and yellow residues were recrystallized from EtOAc or MeCN to give **3d** and **3f**, respectively.

Reaction of 1b with Ethyl Cyanoacetate: The yellow precipitate of **3e** was filtered off and air dried. The filtrate was stayed for 8 h, and a white precipitate of **4b** was filtered off.

Ethyl 6-(3,5-Dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4,6]tetrazepin-8-carboxylate (3d): Yield: 91 mg (30%). M.p. 207–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.43 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.26 (s, 3 H, pyrazole-CH_3), 2.52 (s, 3 H, pyrazole-CH_3), 4.44 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.07 (s, 1 H, pyrazole 4-H), 7.83 (s, 1 H, 3-H), 10.46 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 303.1 (100) [M + 1]$^+$. $C_{12}H_{14}N_8O_2$ (302.29): calcd. C 47.68, H 4.67, N 37.07; found C 47.78, H 4.91, N 36.73.

Ethyl 6-(3,5-Dimethylpyrazol-1-yl)-3-dodecylthio-7*H*-[1,2,4]triazolo-[4,3-*b*][1,2,4,6]tetrazepin-8-carboxylate (3e): Yield: 126 mg (25%). M.p. 131–132 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 [t, *J* = 7.2 Hz, 3 H, $(CH_2)_{11}CH_3$], 1.24 [m, 16 H, $(CH_2)_8$], 1.31 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 1.36 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 2.18 (s, 3 H, pyrazole-CH_3), 2.46 (s, 3 H, pyrazole-CH_3), 3.11 (m, 2 H, SCH_2), 4.31 (m, 2 H, OCH_2CH_3), 6.26 (s, 1 H, pyrazole 4-H), 10.06 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 503.3 (100) [M + 1]$^+$. $C_{24}H_{38}N_8O_2S$ (502.68): calcd. C 57.34, H 7.62, N 22.29; found C 56.99, H 7.62, N 22.09.

Ethyl 6-(4-Bromo-3,5-dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepin-8-carboxylate (3f): Yield: 191 mg (50%). M.p. 218–220 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 1.33 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.23 (s, 3 H, pyrazole-CH_3), 2.51 (s, 3 H, pyrazole-CH_3), 4.34 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 8.43 (s, 1 H, 3-H), 9.96 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 381.0 (100) [M]$^+$. $C_{12}H_{13}BrN_8O_2$ (381.19): calcd. C 37.81, H 3.44, N 29.40; found C 37.74, H 3.48, N 29.53.

***N*′-(3-Amino-4*H*-1,2,4-triazol-4-yl)-3,5-dimethylpyrazol-1-carboxamidine (4a):** Yield: 66 mg (30%). M.p. 230–231 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.18 (s, 3 H, pyrazole-CH_3), 2.52 (s, 3 H, pyrazole-CH_3), 5.55 (s, 2 H, NH_2), 6.14 (s, 1 H, pyrazole 4-H), 7.30 (s, 2 H, NH_2), 7.87 (s, 1 H, triazole 5-H) ppm. MS (ESI): *m*/*z* (%) = 221.1 (100) [M + 1]$^+$. $C_8H_{12}N_8$ (220.23): calcd. C 43.63, H 5.49, N 50.88; found C 43.66, H 5.82, N 50.71.

***N*′-(3-Amino-5-dodecylthio-4*H*-1,2,4-triazol-4-yl)-3,5-dimethylpyrazol-1-carboxamidine (4b):** Yield: 105 mg (25%). M.p. 137–139 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 0.85 [t, *J* = 7.1 Hz, 3 H, $(CH_2)_{11}CH_3$], 1.22 [m, 16 H, $(CH_2)_8$], 1.28 (m, 2 H, CH_2), 1.55 (m, 2 H, CH_2), 2.18 (s, 3 H, pyrazole-CH_3), 2.54 (s, 3 H, pyrazole-CH_3), 2.84 (t, *J* = 7.1 Hz, 2 H, SCH_2), 5.65 (s, 2 H, NH_2), 6.14 (s, 1 H, pyrazole 4-H), 7.36 (s, 2 H, NH_2) ppm. MS (ESI): *m*/*z* (%) = 421.3 (100) [M + 1]$^+$. $C_{20}H_{36}N_8S$ (420.62): calcd. C 57.11, H 8.63, N 26.64; found C 57.14, H 8.75, N 26.42.

***N*′-(3-Amino-4*H*-1,2,4-triazol-4-yl)-4-bromo-3,5-dimethylpyrazol-1-carboxamidine (4c):** Yield: 60 mg (20%). M.p. 236–237 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.22 (s, 3 H, pyrazole-CH_3), 2.54 (s, 3 H, pyrazole-CH_3), 5.60 (s, 2 H, NH_2), 7.51 (s, 2 H, NH_2), 7.89 (s, 1 H, triazole 5-H) ppm. MS (ESI): *m*/*z* (%) = 299.0 (100) [M]$^+$. $C_8H_{11}BrN_8$ (299.13): calcd. C 32.12, H 3.71, N 37.46; found C 32.26, H 3.48, N 37.07.

General Procedure for the Synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidine Derivatives 5a–d and 6: To a stirred mixture of **1** (1 mmol) and malononitrile (2 mmol) in CH_3CN (5 mL) was added TEA (1 mmol). The reaction mixture was stirred at room temperature. Upon completion of the reaction, which was monitored by TLC, a white precipitate was filtered off and recrystallized from CH_3CN.

***N*′-{5,6-Dicyano-7-imino[1,2,4]triazolo[1,5-*a*]pyrimidin-3(7*H*)-yl}-3,5-dimethylpyrazol-1-carboxamidine (5a):** Compound **5a** was prepared from **1a** (reaction time 20 min). Yield: 135 mg (42%). M.p. >350 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.22 (s, 3 H, pyrazole-CH_3), 2.54 (s, 3 H, pyrazole-CH_3), 6.24 (s, 1 H, pyrazole 4-H), 7.98 (br. s, 2 H, NH_2), 8.16 (s, 1 H, triazole CH), 9.24 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 322.1 (100) [M + 1]$^+$. $C_{13}H_{11}N_{11}$ (321.30): calcd. C 48.60, H 3.45, N 47.95; found C 48.70, H 3.29, N 47.88.

***N*′-{5,6-Dicyano-2-(dodecylthio)-7-imino-[1,2,4]triazolo[1,5-*a*]-pyrimidin-3(7*H*)-yl}-3,5-dimethylpyrazol-1-carboxamidine (5b):** Compound **5b** was prepared from **1b** (reaction time 30 min) and purified by column chromatography (MeCN/benzene, 1:1; R_f = 0.8). Yield: 167 mg (32%). M.p. 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 [t, *J* = 7.1 Hz, 3 H, $(CH_2)_{11}CH_3$], 1.25 [m, 16 H, $(CH_2)_8$], 1.47 (m, 2 H, CH_2), 1.85 (m, 2 H, CH_2), 2.25 (s, 3 H, pyrazole-CH_3), 2.62 (s, 3 H, pyrazole-CH_3), 3.46 (t, *J* = 6.8 Hz, 2 H, SCH_2), 6.05 (s, 1 H, pyrazole 4-H), 7.63 (br. s, 3 H, NH,

NH_2) ppm. MS (ESI): *m*/*z* (%) = 522.3 (100) $[M + 1]^+$. $C_{25}H_{35}N_{11}S$ (521.68): calcd. C 57.56, H 6.76, N 29.53; found C 57.76, H 6.72, N 29.57.

***N*′-{2-(Benzylthio)-5,6-dicyano-7-imino-[1,2,4]triazolo[1,5-*a*]-pyrimidin-3(7*H*)-yl}-3,5-dimethylpyrazol-1-carboxamidine (5c):** Compound **5c** was prepared from **1c** (reaction time 30 min). Yield: 151 mg (34%). M.p. 197–200 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.21 (s, 3 H, pyrazole-CH_3), 2.52 (s, 3 H, pyrazole-CH_3), 4.58 (s, 2 H, SCH_2), 6.24 (s, 1 H, pyrazole 4-H), 7.26–7.37 (m, 3 H, Ph), 7.56 (m, 2 H, Ph), 8.05 (s, 1 H, NH), 7.96–8.21 (br. s, 2 H, NH_2) ppm. MS (ESI): *m*/*z* (%) = 444.2 (100) $[M + 1]^+$. $C_{20}H_{17}N_{11}S$ (443.49): calcd. C 54.16, H 3.86, N 34.74; found C 54.18, H 3.96, N 34.60.

2-{2-(Benzylthio)-5,6-dicyano-7-imino[1,2,4]triazolo[1,5-*a*]pyrimidin-3(7*H*)-yl}guanidine (5d): Compound **5d** was prepared from **1f** (reaction time 24 h). Yield: 120 mg (33%). M.p. >350 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 4.51 (s, 2 H, SCH_2), 6.03 (s, 2 H, NH_2), 6.18 (s, 2 H, NH_2), 7.26–7.38 (m, 3 H, Ph), 7.54 (m, 2 H, Ph), 7.88 (s, 1 H, NH) ppm. MS (ESI): *m*/*z* (%) = 365.1 (100) $[M + 1]^+$. $C_{15}H_{12}N_{10}S$ (364.39): calcd. C 49.44, H 3.32, N 38.44; found C 49.15, H 3.06, N 37.99.

***N*′-{7-Amino-6-cyano-5-(dicyanomethylene)-2-(dodecylthio)[1,2,4]-triazolo[1,5-*a*]pyrimidin-3(5*H*)-yl}-3,5-dimethylpyrazole-1-carboxamidine (6):** Compound **6** was prepared from **1b** (reaction time 30 min) and purified by column chromatography (MeCN/benzene, 1:1; R_f = 0.2). Yield: 151 mg (27%). M.p. 232–235 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85 [t, *J* = 7.0 Hz, 3 H, $(CH_2)_{11}CH_3$], 1.23 [m, 16 H, $(CH_2)_8$], 1.39 (m, 2 H, CH_2), 1.75 (m, 2 H, CH_2), 2.22 (s, 3 H, pyrazole-CH_3), 2.54 (s, 3 H, pyrazole-CH_3), 3.26 (t, *J* = 7.2 Hz, 2 H, SCH_2), 6.22 (s, 1 H, pyrazole 4-H), 8.04 (br. s, 2 H, NH_2), 8.94 (s, 2 H, NH_2) ppm. MS (ESI): *m*/*z* (%) = 561.3 (100) $[M + 1]^+$. $C_{27}H_{36}N_{12}S$ (560.72): calcd. C 57.83, H 6.47, N 29.98; found C 57.71, H 6.35, N 29.59.

General Procedure for the Synthesis of 7*H*,7′*H*-8,8′-Bis[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine Derivatives 7a–d: Compound **1** (1 mmol) and TEA (1 mmol) in acetonitrile (5 mL) were heated at reflux for 1 h. After cooling to room temperature a dark-yellow precipitate was filtered off, washed with CH_3CN, and air dried.

6,6′-Bis(3,5-Dimethylpyrazol-1-yl)-7*H*,7′*H*-8,8′-bis[1,2,4]triazolo-[4,3-*b*][1,2,4,6]tetrazepine (7a): Compound **7a** was prepared from **1a**. Yield: 76 mg (33%) [92 mg (40%) in DMF]. M.p. >350 °C. MS (ESI): *m*/*z* (%) = 459.2 (100) $[M + 1]^+$. $C_{18}H_{18}N_{16}$ (458.44): calcd. C 47.16, H 3.96, N 48.88; found C 47.08, H 3.98, N 48.76.

6,6′-Bis(3,5-Dimethylpyrazol-1-yl)-3,3′-bis(benzylthio)-7*H*,7′*H*-8,8′-bis[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine (7b): Compound **7b** was prepared from **1c**. Yield: 88 mg (25%). M.p. 302–303 °C. MS (ESI): *m*/*z* (%) = 703.3 (100) $[M + 1]^+$. $C_{32}H_{30}N_{16}S_2$ (702.82): calcd. C 54.69, H 4.30, N 31.89; found C 54.70, H 4.29, N 31.60.

6,6′-Bis(3,5-Dimethylpyrazol-1-yl)-3,3′-bis(methylthio)-7*H*,7′*H*-8,8′-bis[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine (7c): Compound **7c** was prepared from **1g**. Yield: 105 mg (38%). M.p. >350 °C. MS (ESI): *m*/*z* (%) = 551.2 (100) $[M + 1]^+$. $C_{20}H_{22}N_{16}S_2$ (550.63): calcd. C 43.63, H 4.03, N 40.70; found C 43.61, H 4.08, N 41.03.

6,6′-Bis(3,5-dimethylpyrazol-1-yl)-3,3′-diphenyl-7*H*,7′*H*-8,8′-bis-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine (7d): Compound **7d** was prepared from **1h**. Yield: 67 mg (22%). M.p. 358–360 °C. MS (ESI): *m*/*z* (%) = 611.26 (100) $[M + 1]^+$. $C_{30}H_{26}N_{16}$ (610.63): calcd. C 59.01, H 4.29, N 36.70; found C 58.73, H 4.11, N 36.39.

General Procedure for the Synthesis of *N*′-(4*H*-1,2,4-triazol-4-yl)-3,5-dimethylpyrazol-1-carboxamidine Derivatives 8a–d: To a stirred solution of **1** (1 mmol) in CH_3CN (5 mL) was added the corresponding enamine (1.1 mmol). The reaction mixture was stirred at room temperature for 20–30 min. Upon completion of the reaction, as monitored by TLC, a white or pale-yellow precipitate was filtered off, washed with CH_3CN, and air dried.

***N*′-[3-(Benzylthio)-5-(2-piperidinocyclopent-2-enylideneamino)-4*H*-1,2,4-triazol-4-yl]-3,5-dimethylpyrazol-1-carboxamidine (8a):** Compound **8a** was prepared from **1c** and 1-piperidinocyclopentene. Yield: 323 mg (66%). M.p. 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.47 (m, 6 H, 3 CH_2), 2.22 (s, 3 H, pyrazole-CH_3), 2.52 (m, 2 H, CH_2), 2.62 (s, 3 H, pyrazole-CH_3), 3.06 (m, 6 H, 3 CH_2), 4.42 (s, 2 H, SCH_2), 5.97 (s, 1 H, pyrazole 4-H), 6.14 (t, *J* = 3.0 Hz, 1 H, C=CH), 6.76 (s, 2 H, NH_2), 7.19–7.30 (m, 3 H, Ph), 7.38 (m, 2 H, Ph) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 13.51, 15.52, 24.46, 25.41, 27.03, 33.64, 35.82, 50.61, 110.53, 127.42, 128.51, 129.05, 129.18, 131.13, 136.84, 143.38, 148.19, 150.18, 152.94, 154.83, 155.13, 180.67 ppm. MS (ESI): *m*/*z* (%) = 490.1 (100) $[M + 1]^+$. $C_{25}H_{31}N_9S$ (489.64): calcd. C 61.32, H 6.38, N 25.75; found C 60.99, H 6.22, N 25.66.

***N*′-[3-(2-Morpholinocyclopent-2-enylideneamino)-4*H*-1,2,4-triazol-4-yl]-4-bromo-3,5-dimethylpyrazol-1-carboxamidine (8b):** Compound **8b** was prepared from **1e** and 1-morpholinocyclopentene. Yield: 399 mg (89%). M.p. 180 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.22 (s, 3 H, pyrazole-CH_3), 2.53 (s, 3 H, pyrazole-CH_3), 2.55 (m, 2 H, CH_2), 3.04 (m, 6 H, 3 CH_2), 3.44 (m, 4 H, 2 CH_2), 6.20 (t, *J* = 3.0 Hz, 1 H, C=CH), 7.61 (s, 2 H, NH_2), 8.41 (s, 1 H, triazole 5-H) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 12.23, 13.44, 26.24, 33.16, 49.01, 65.71, 98.52, 129.90, 139.83, 140.51, 147.98, 151.11, 152.62, 155.28, 178.58 ppm. MS (ESI): *m*/*z* (%) = 448.1 (100) $[M + 1]^+$. $C_{17}H_{22}BrN_9O$ (448.32): calcd. C 45.54, H 4.95, N 28.12; found C 45.81, H 4.76, N 28.07.

***N*′-[3-(2-Morpholinocyclopent-2-enylideneamino)-5-phenyl-4*H*-1,2,4-triazol-4-yl]-3,5-dimethylpyrazole-1-carboxamidine (8c):** Compound **8c** was prepared from **1h** and 1-morpholinocyclopentene. Yield: 370 mg (76%). M.p. 174–176 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 2.07 (s, 3 H, CH_3CN), 2.20 (s, 3 H, pyrazole-CH_3), 2.48 (s, 3 H, pyrazole-CH_3), 2.54 (m, 2 H, CH_2), 3.08 (m, 6 H, 3 CH_2), 3.39 (m, 4 H, 2 CH_2), 6.18 (s, 1 H, pyrazole 4-H), 6.20 (t, *J* = 3.0 Hz, 1 H, C=CH), 7.41–7.51 (m, 3 H, Ph), 7.61 (s, 2 H, NH_2), 7.88 (m, 2 H, Ph) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 13.32, 14.55, 26.36, 33.40, 49.01, 65.70, 109.90, 126.63, 127.80, 128.37, 128.53, 129.23, 129.73, 142.37, 148.75, 149.49, 151.23, 153.85, 155.86, 178.20 ppm. MS (ESI): *m*/*z* (%) = 446.2. (100) $[M + 1]^+$. $C_{23}H_{27}N_9O{\cdot}CH_3CN$ (486.57): calcd. C 61.71, H 6.21, N 28.79; found C 61.52, H 6.14, N 28.50.

***N*′-[3-Ethylthio-5-(2-piperidinocyclopent-2-enylideneamino)-4*H*-1,2,4-triazol-4-yl]-3,5-dimethylpyrazol-1-carboxamidine (8d):** Compound **8d** was prepared from **1i** and 1-piperidinocyclopentene. Yield: 321 mg (75%). M.p. 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40 (t, *J* = 7.3 Hz, 3 H, SCH_2CH_3), 1.48 (m, 6 H, 3 CH_2), 2.23 (s, 3 H, pyrazole-CH_3), 2.52 (m, 2 H, CH_2), 2.66 (s, 3 H, pyrazole-CH_3), 3.07 (m, 6 H, 3 CH_2), 3.19 (q, *J* = 7.3 Hz, 2 H, SCH_2CH_3), 5.99 (s, 1 H, pyrazole 4-H), 6.12 (t, *J* = 3.0 Hz, 1 H, C=CH), 6.81 (s, 2 H, NH_2) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 13.51, 14.75, 15.47, 24.48, 25.42, 25.74, 27.03, 33.63, 50.60, 110.50, 130.97, 143.38, 148.46, 150.16, 152.94, 154.73, 155.10, 180.51 ppm. MS (ESI): *m*/*z* (%) = 428.1 (100) $[M + 1]^+$. $C_{20}H_{29}N_9S$ (427.57): calcd. C 56.18, H 6.84, N 29.48; found C 56.29, H 6.84, N 29.35.

X-ray Structure Data Collection and Refinement: Single crystals suitable for X-ray analysis were obtained by slow evaporation from

Table 1. X-ray crystallography data for 7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine derivatives **2a**, **2d**–**f**, **3b**, and **7a**.

	2a	**2d**	**2e**	**2f**	**3b**	**7a**
Crystal size [mm]	0.52 × 0.47 × 0.35	0.49 × 0.35 × 0.27	0.22 × 0.14 × 0.08	0.37 × 0.23 × 0.15	0.48 × 0.23 × 0.05	0.41 × 0.34 × 0.12
Crystal color	colorless	colorless	colorless	colorless	yellow	orange
Empirical formula	$C_{15}H_{20}N_8O_4$	$C_{12}H_{16}N_8O_2$	$C_{21}H_{25}N_9O_2S$	$C_{16}H_{20}N_8O_2$	$C_{19}H_{27}N_9O_4$	$C_{24}H_{32}N_{18}O_2$
Temperature [K]	295(2)	295(2)	295(2)	295(2)	295(2)	135(2)
Crystal system	triclinic	monoclinic	triclinic	monoclinic	triclinic	triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a [Å]	9.530(2)	11.0427(18)	8.7474(12)	7.0613(16)	7.1382(7)	8.2080(15)
b [Å]	10.4179(12)	14.5205(18)	11.3138(15)	13.2039(19)	11.0063(17)	9.7675(19)
c [Å]	10.5811(13)	9.9544(11)	12.8395(19)	18.885(2)	14.5308(19)	10.701(2)
α [°]	101.539(10)	90	111.530(13)	90	94.685(12)	65.970(19)
β [°]	113.864(15)	111.618(13)	101.637(12)	97.897(14)	99.666(10)	88.906(15)
γ [°]	102.047(14)	90	97.241(11)	90	93.060(10)	68.323(18)
Volume, *Z*	890.8(2), 2	1483.9(3), 4	1129.5(3), 2	1744.1(5), 4	1119.0(3), 2	719.4(2), 1
μ [mm^{-1}]	0.106	0.100	0.182	0.096	0.097	0.099
Reflections collected	8028	10299	5235	8205	6513	5544
Independent reflections (R_{int})	5147 (0.0233)	4419 (0.0319)	4491 (0.0359)	3539 (0.0431)	4451 (0.0314)	3440 (0.0329)
S	1.006	1.000	1.000	1.010	1.002	1.004
R_1 [$I > 2\sigma(I)$]	0.0467	0.0459	0.0439	0.0382	0.0422	0.0394
wR_2 [$I > 2\sigma(I)$]	0.0955	0.0892	0.0885	0.0579	0.0655	0.0607
R_1 (all data)	0.1020	0.1309	0.0858	0.1028	0.1196	0.0948
wR_2 (all data)	0.1037	0.0968	0.0924	0.0613	0.0723	0.0633
Larg. diff. peak, hole [e Å^{-3}]	0.352, –0.229	0.184, –0.257	0.373, –0.207	0.178, –0.135	0.200, –0.118	0.198, –0.206
Completeness [%] to *θ* (°)	97.7 (26.00)	97.6 (30.51)	97.4 (26.37)	99.4 (26.37)	97.6 (26.37)	96.8 (28.28)

Table 2. X-ray crystallography data for the tetrazine ring opening products **4c**, **5c**, **6**, and **8c**.

	4c	**5c**	**6**	**8c**
Crystal size [mm]	0.18 × 0.09 × 0.03	0.43 × 0.34 × 0.21	0.44 × 0.36 × 0.09	0.48 × 0.33 × 0.21
Crystal color	colorless	colorless	light brown	light brown
Empirical formula	$C_8H_{11}BrN_8$	$C_{22}H_{20}N_{12}S$	$C_{27}H_{38}N_{12}OS$	$C_{25}H_{30}N_{10}O$
Temperature [K]	295(2)	130(2)	295(2)	295(2)
Crystal system	triclinic	monoclinic	monoclinic	triclinic
Space group	$P\bar{1}$	$P2_1/c$	$C2/c$	$P\bar{1}$
a [Å]	7.2903(8)	15.8451(16)	46.648(9)	8.4222(8)
b [Å]	10.2961(12)	6.2850(6)	12.5144(5)	9.906(2)
c [Å]	15.881(4)	24.365(3)	10.788(2)	15.4653(15)
α [°]	99.696(14)	90	90	78.927(13)
β [°]	95.313(14)	94.563(9)	98.882(2)	86.020(8)
γ [°]	90.457(9)	90	90	82.042(12)
Volume, *Z*	1169.7(3), 4	2418.7(4), 4	6222.2(17), 8	1252.8(3), 2
μ [mm^{-1}]	3.507	0.171	0.146	0.085
Reflections collected	8435	8708	13588	10824
Independent reflections (R_{int})	4716 (0.0341)	4824(0.0368)	6318(0.0409)	5986 (0.0314)
S	1.012	0.998	1.003	1.000
R_1 [$I > 2\sigma(I)$]	0.0438	0.0418	0.0366	0.0418
wR_2 [$I > 2\sigma(I)$]	0.0832	0.0648	0.0518	0.0758
R_1 (all data)	0.1026	0.0972	0.0989	0.1178
wR_2 (all data)	0.0890	0.0682	0.0543	0.0794
Larg. diff. peak, hole [e Å^{-3}]	0.535, –0.573	0.273, –0.281	0.205, –0.228	0.192, –0.177
Completeness [%] to *θ* (°)	98.7 (26.37)	97.6 (26.37)	98.9 (26.38)	97.1 (26.00)

MeCN (for compounds **2a**, **2d**–**f**, **4c**, **5c**, **6**, **8c**) or from DMF (for compounds **3b**, **7a**). X-ray intensity data were collected with a Xcalibur CCD diffractometer using Mo-K_α (λ = 0.71069 Å) radiation. Crystal data and data collection parameters are summarized in Tables 1 and 2. The unit cell parameters were refined using all collected spots after the integration process. With exception of **4c**, the data were not corrected for absorption, but the data collection mode partially take into account the absorption phenomena (see the total number of collected reflections vs. the independent number of reflections in Tables 1 and 2). For **4c** the analytical absorption data correction was used.[21] The structures were solved by direct methods with SHELX97.[22] All structures were refined by full-matrix least-squares on F^2 using SHELX97.[22] All non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms of NH-group were localized by Fourier-difference synthesis, while other H atoms were calculated with AFIX. The H atoms were included in the refinement with an isotropic temperature factor.

CCDC-807605 (for **2a**), -807604 (for **2d**), -807606 (for **2e**), -807609 (for **2f**), -807610 (for **3b**), -807607 (for **4c**), -807602 (for **5c**), -807614 (for **6**), -807613 (for **7a**), and -807603 (for **8c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Detailed information concerning crystal structures of compounds **2a**, **2d**–**f**, **3b**, **4c**, **5c**, **6**, **7a**, and **8c** provided by X-ray analysis.

Acknowledgments

The work was financially supported by the Russian Academy of Sciences (grants 09-I-3-2004, 09-P-3-2001, 09-T-3-1016), the Russian Foundation for Basic Research (grant 11-03-00545-a), the State Contract (02.740.11.0260), and the State Program for Supporting of Leading Scientific Schools of Russian Federation (grant NSh-65261.2010.3)

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Received: November 25, 2010
Published Online: March 2, 2011

