Facile Synthesis of Fluorinated Purines and Thiapurines

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Abstract: The reaction of 2-(dialkylamino)-1,3-thiazol-4-amines and 1,2-dimethyl-1*H*-imidazol-5-amine with aryl isocyanates, α-chloroalkyl isocyanates, *N*-(alkoxycarbonyl)imidoyl chlorides and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine leads to thiapurines and purines containing trifluoromethyl groups in the 2- and 6-positions of the pyrimidine ring.

Key words: imidazole, thiazole, pyrimidine, isocyanate, annulation

When biomolecules are modified with fluorine-containing functional groups, new physiologically active compounds are often the result.[1] In particular, fluoro analogues of nucleosides have remarkable antitumor,[2] antiviral[3] and antineoplastic[4] in vivo activities. Simpler (polyfluoroalkyl)purines[5–7] and their derivatives exhibit pronounced antiviral[5e,f,7a] and phosphodiesterase inhibitory effects,[5c,8] while high antitumor activities have been discovered for 2-(trifluoromethyl)adenosine.[9]

Biological activities of 6-(fluoroalkyl)purines and their derivatives have not been studied in detail, primarily due to the lack of easy preparative procedures.[10] The recently discovered high cytostatic activity of some 6-(trifluoromethyl)purine ribosides[11a] and the studies on adenosine A3 receptor antagonists[11b] indicate that the trifluoromethyl group facilitates hydration at the 6-position of the purine ring, which might mimic the transition state for hydrolytic deamination of adenosine.[11c] On the other hand, 6-(trifluoromethyl)purine-substituted RNAs are valuable mimetics for structural studies of RNA and binding studies of RNA-modifying enzymes,[11d] such as RNA-editing adenosine deaminases.

Thiazolo[4,5-*d*]pyrimidines, which are thia analogues of the purine ring system, have been widely utilised as starting materials for the synthesis of thiaadenosine analogues.[12] Various derivatives of 3-β-D-ribofuranosyl[1,3]thiazolo[4,5-*d*]pyrimidine are clinically used as immunomodulators,[13] inhibitors of HCV replication,[14] and antiviral[15] and antitumor agents.[16]

Reactions of 1,3-*CCN*-bis-nucleophiles such as anilines and amino-substituted heterocycles with various 1,3-*CNC*-bis-electrophiles (functionalised isocyanates[17] and isothiocyanates,[18] N-acylated imidoyl chlorides,[19] imidates[20] and imines[21]) have been recently employed in the synthesis of annulated pyrimidines.

Retrosynthetic analysis revealed that purines and their thia analogues could be obtained by the reaction of 1,3-*CNC*-bis-electrophiles with 4(5)-aminoimidazoles and 4(5)-aminothiazoles, respectively. Herein we report a new method for the assembly of fluorine-containing purines and thiazolo[4,5-*d*]pyrimidines (7-thiapurines) using the reaction of 5-amino-1*H*-imidazoles[22] and 4-amino-1,3-thiazoles[23] with fluorine-containing 1,3-*CNC*-bis-electrophiles.

It has been shown previously that the deprotonation of salts **1**·HCl with bases gives bi-1,3-thiazoles **2** (Scheme 1).[23] In order to carry out acylation reactions, amines **1** were generated in the presence of isocyanates. The outcome of these acylations appeared to depend on the reaction conditions.

In the presence of an excess of an aryl isocyanate in boiling pyridine, thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **4** were obtained in 70–80% yield. The use of triethylamine as a base and dichloromethane or dioxane as a solvent at ambient temperatures afforded *N*-thiazolylureas **5** that could not be transformed into pyrimidinediones **4** upon treatment with an excess of aryl isocyanate in refluxing pyridine (Scheme 1). Apparently, the first step of the pyrimidine ring closure involves the C-acylation of amines **1** to give intermediates **3**. Subsequent N-acylation and elimination of aniline results in compounds **4**. The aniline formed reacts with the isocyanate to yield the *N*,*N*′-diarylurea. In contrast to the 1,3-thiazol-4-amines **1**, 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) reacts with phenyl and methyl isocyanate in pyridine or dichloromethane to give the corresponding ureas **7** (Scheme 1).

It should be noted that previous studies revealed that only cyclohepta[*b*]pyrrol-2-amine reacted with aryl isocyanates to give fused pyrimidinone derivatives in 10–30% yield.[24] Our approach with 70–80% isolated yield is therefore very attractive for the synthesis of xanthine-like compounds.[25]

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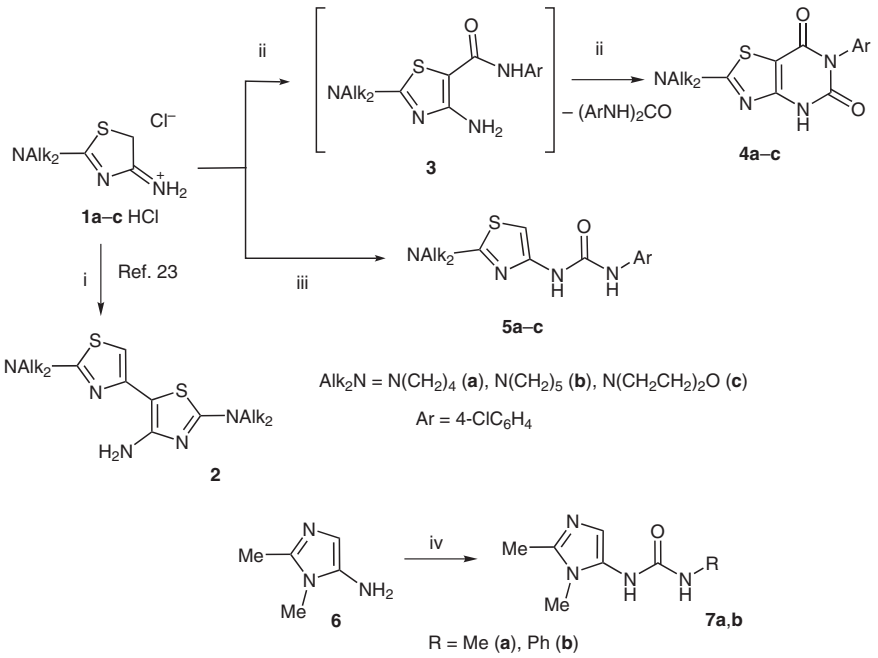
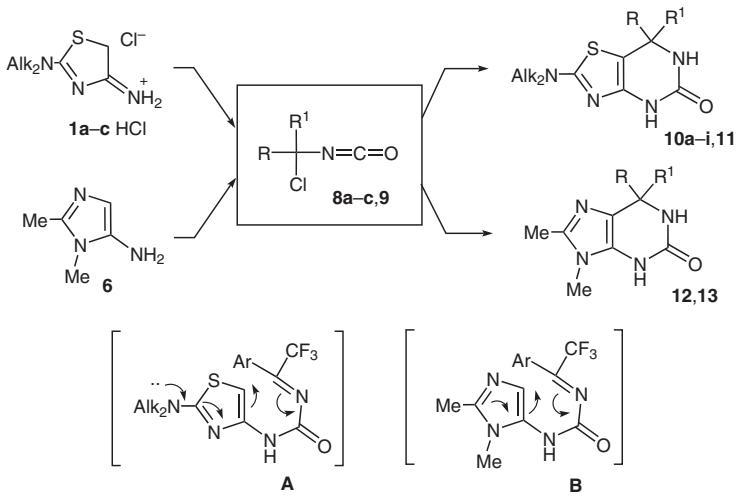


Scheme 1 *Reagents and conditions*: (i) treatment of base without external electrophile; (ii) ArNCO (3 equiv), py, reflux, 30 min; (iii) ArNCO (1 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to r.t.; (iv) ArNCO (1 equiv), Et_3N, CH_2Cl_2, r.t., 24 h.

Reaction of 2-(dialkylamino)-1,3-thiazol-4-amines, generated from their hydrochloride salts, and 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) with α-aryl-α-chloro-β,β,β-trifluoroethyl isocyanates **8** gave 2-(dialkylamino)-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-ones **10** and the 6-(trifluoromethyl)-1,3,6,9-tetrahydro-2*H*-purin-2-one **12**, respectively (Scheme 2, Table 1). ^{19}F NMR and GC/MS studies of the reaction mixtures showed that, at ambient temperatures, compounds **10** and **12** are formed quantitatively in 60 minutes. We suggest that the reaction proceeds through intermediates type **A** and **B**.

Slow crystallisation of compound **10f** from dichloromethane–chloroform afforded stable diffraction-quality crystals. Single-crystal X-ray analysis unambiguously revealed the thiapurine structure of molecule **10f** (Figure 1a). In the crystalline state the carbonyl and NH groups of molecule **10f** form four hydrogen bonds to its neighbours (Figure 1b,c). Two hydrogen-bonded molecules **A** and **B** are coplanar whereas molecule **C** is perpendicular to **A** and **B**. In this way, a complicated hydrogen bonding of molecules **10f** is formed in the crystal. The intermolecular distances indicate that fluorine atoms F2 and F3 are involved in rather strong C–H···F interactions.



Scheme 2 *Reagents and conditions*: isocyanate **8** (1 equiv), Et_3N (2 equiv), CH_2Cl_2, r.t., 5 h.

Table 1 Yields of Fused Dihydropyrimidinones **10–13**

Product	Alk_2N	R	R^1	Yield[a] (%)
10a	$N(CH_2)_4$	CF_3	Ph	81
10b	$N(CH_2)_4$	CF_3	4-MeC_6H_4	79
10c	$N(CH_2)_4$	CF_3	4-$MeOC_6H_4$	82
10d	$N(CH_2)_5$	CF_3	Ph	85
10e	$N(CH_2)_5$	CF_3	4-MeC_6H_4	87
10f	$N(CH_2)_5$	CF_3	4-$MeOC_6H_4$	87
10g	$N(CH_2CH_2)_2O$	CF_3	Ph	63
10h	$N(CH_2CH_2)_2O$	CF_3	4-MeC_6H_4	68
10i	$N(CH_2CH_2)_2O$	CF_3	4-$MeOC_6H_4$	62
11	$N(CH_2CH_2)_2O$	Ph	Ph	81
12	–	CF_3	4-MeC_6H_4	87
13	–	Ph	Ph	68

[a] Yields refer to pure isolated products.

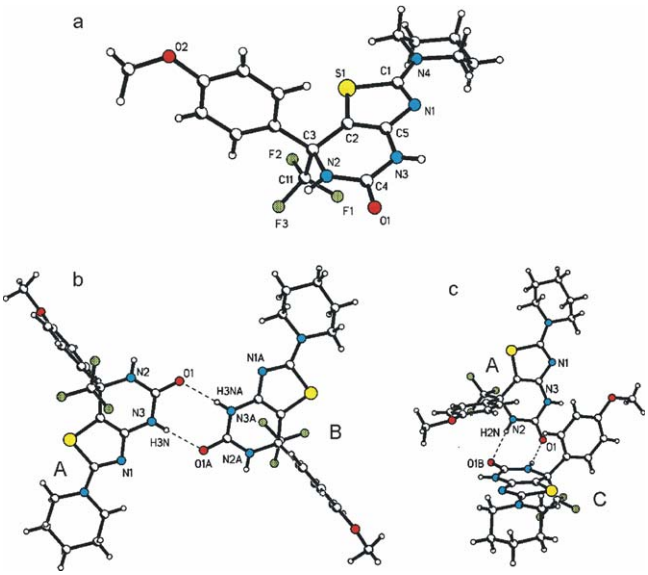


Figure 1 Molecular structure of compound **10f** (a) and its packing in the crystal state (b,c)

The structures of compounds **10** and **12** were also established by ^1H, ^{13}C and ^{19}F NMR spectroscopy. The most convincing evidence for the formation of the 7-trifluoromethyl-isomer is the chemical shift of C-7 (δ_C ~65 ppm) with a $^2J_{CF}$ coupling constant of ~30 Hz. For the 5-trifluoromethyl isomer, the signal of C-5 would be expected to be situated at δ_C 79 ppm.[26]

In order to establish the scope and limitations of the method, other electron-rich amino-substituted heterocycles were reacted with acyl isocyanates. It was found that the reactions of 5-amino-1*H*-pyrazole, 5-aminoisoxazole, 2-amino-5-methoxyfuran and 2-amino-5-methoxythiophene resulted in complex mixtures of unidentified products. The use of less reactive urethanes resulted in trifluoromethyl-containing hetarylamines.[27] Therefore, it seems likely that the heterocyclisations of 1,3-thiazole-2,4-diamines **1** and 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) occur owing to the optimal nucleophilicities of their carbon and nitrogen atoms.

The reaction of 1,3-*CNC*-bis-electrophiles such as PhC(H)(Cl)–N=C=O, $Me_2C(Br)$–N=C=O, $Me_2C(Br)$–N=C=S and PhC(Me)(Cl)–N=C=O with compounds **1** and **6** led to complex mixtures of many compounds most probably due to the instability of the heterocumulenes in basic media. According to this explanation, the stable α-chloro-α,α-diphenylmethyl isocyanate **9** reacted smoothly with a 1,3-thiazole-2,4-diamine salt and 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) to give thiapurine **11** and purine **13** (Scheme 2, Table 1). The structures of **11** and **13** were established by ^{13}C NMR spectroscopy, using compounds **10** and **12** as references.

The reaction of 2-(dialkylamino)-1,3-thiazol-4-amines **1** with α,α-dichloro-β,β,β-trifluoroethyl isocyanate [$F_3CC(Cl)_2N$=C=O] in dichloromethane in the presence of triethylamine gave 5-(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **16** in low yield (15%) after complicated chromatographic purification.

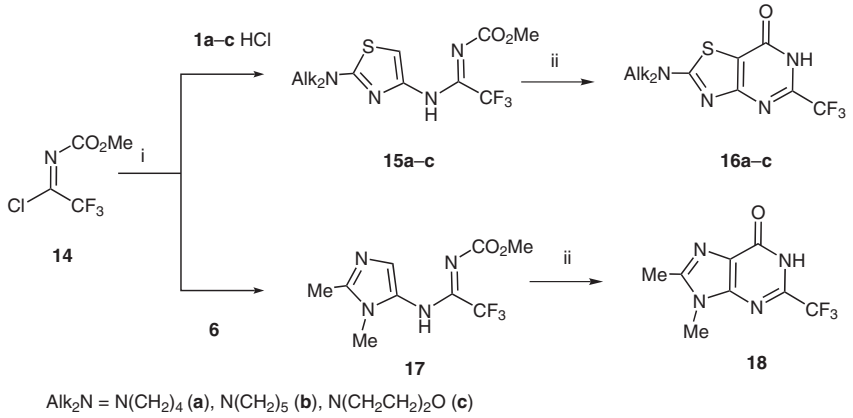
The reaction of compounds **1** and **6** with the less reactive and more selective methyl 1-chloro-2,2,2-trifluoroethylidenecarbamate (**14**)[19] afforded amidines **15** and **17**, respectively (Scheme 3). These intermediates underwent a 6-*exo*-*trig* cyclisation (toluene, reflux) to give the 5-(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **16** and 2-(trifluoromethyl)-1,9-dihydro-6*H*-purin-6-one **18** in 83–91% yield. The structures and composition of compounds **16** were corroborated through ^1H, ^{13}C and ^{19}F NMR spectroscopy, and elemental analysis.

The reaction of 1,3-thiazole-2,4-diamines **1** with 2,2,2-trifluoroacetyl isothiocyanate led to trifluoroacetylation of the 4-amino group, as was proved by NMR spectroscopy and alternative synthesis of the products by acylation with trifluoroacetic anhydride. 2,2,2-Trifluoroacetyl isocyanate reacts with compounds **1** to give inseparable, multicomponent mixtures.

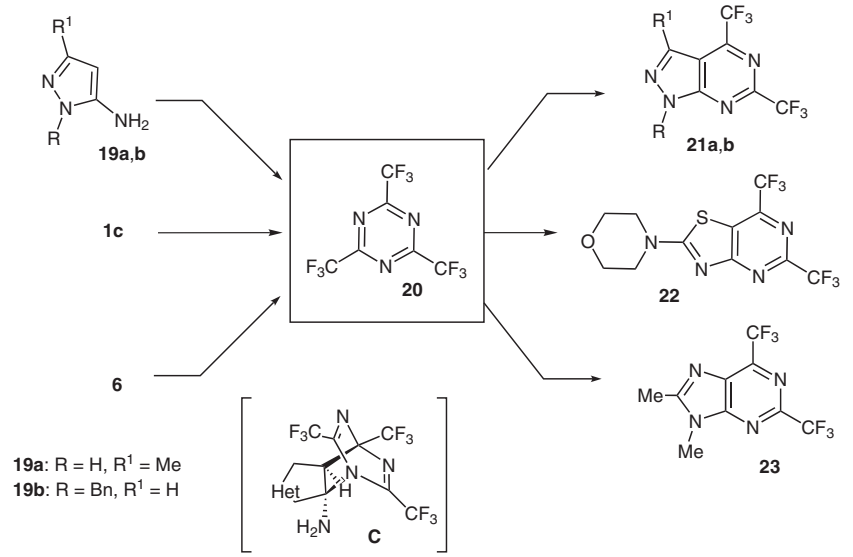
A recent publication[28a] on the synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidines from 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate through inverse-electron-demand Diels–Alder reactions with various 1,3,5-triazine derivatives prompted us to also apply this approach to the hydrochlorides of amines **1** and **6**.

The reaction of 1*H*-pyrazol-5-amines **19** with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**20**) afforded the 4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines **21** (through intermediate type **C**) in 90–95% yield (Scheme 4).

The Diels–Alder reaction[28] of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**20**) with the 2-(dialkylamino)-1,3-thiazol-4-amine **1c** or 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) (AcOH, r.t.) gave the condensed thiapurine **22** and purine



Scheme 3 *Reagents and conditions*: (i) Et_3N (1–2 equiv), CH_2Cl_2, r.t., 4 h; (ii) toluene, reflux, 2–3 h.



Scheme 4 *Reagents and conditions:* CH_2Cl_2–AcOH (10:1), r.t., 36–48 h.

23, respectively. According to the expected structures, the ^{13}C NMR spectra of these compounds contain two quartets for CF_3 groups at 119 and 120 ppm ($^1J_{CF}$ ~275 Hz), whereas the signals of the C-5 and C-7 atoms of compound **22** emerge at 154 and 146 ppm, respectively ($^2J_{CF}$ ~38 Hz).

In conclusion, the reactions of 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) and 2-(dialkylamino)-1,3-thiazol-4-amines **1**, generated in situ, with aryl isocyanates, α-chloroalkyl isocyanates, *N*-(alkoxycarbonyl)imidoyl chlorides and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine were systematically studied. An easy method for annulation of the pyrimidine ring to 1,2-dimethyl-1*H*-imidazol-5-amine and the 2-(dialkylamino)-1,3-thiazol-4-amines was elaborated and sets of novel [1,3]thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones, 6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-ones, [1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones and 2-(dialkylamino)-5,7-bis(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidines were generated. Simple synthetic and purification procedures and high yields of the target compounds enable the synthesis of functionally diverse thiazolo[4,5-*d*]pyrimidines and purines, which are interesting objects for medicinal chemistry and drug discovery.

All solvents were purified and dried by standard methods. NMR spectra were recorded on Jeol JNM-LA 400, Varian VXR-300 or Varian Mercury-400 spectrometers. ^1H and ^{13}C NMR spectra (300 and 100 MHz, respectively) were recorded using TMS as an internal standard, and ^{19}F NMR spectra (282.2 MHz) with $CFCl_3$ as an internal standard. IR spectra were recorded on a Perkin–Elmer FT-IR 1600 spectrometer for samples in KBr discs. Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. Elemental analyses were carried out at the Microanalytical Laboratory of the University of Konstanz, Germany. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60 F254 plates were used for TLC. Commercially unavailable starting 2-(dialkylamino)-1,3-thiazol-4-amine salts **1**,[23a] α-chloro-β,β,β-trifluoroethyl isocyanates **8**[29] and ethanimidoyl chloride **14**[30] were obtained according to literature procedures.

X-ray Crystallography of 10f

$C_{18}H_{19}F_3N_4O_2S$, M = 412.43, monoclinic, space group *C2/c*, a = 27.523(7) Å, b = 10.080(2) Å, c = 14.043(2) Å, β = 95.19(2)°,

V = 3880.0(14) Å^3, Z = 8, D_c = 1.412 g·cm^{-3}, μ = 0.216 mm^{-1}, F(000) = 1712, colourless block with size 0.37 × 0.35 × 0.18 mm. All crystallographic measurements were performed at r.t. on a CAD4 Enraf–Nonius diffractometer operating in the ω-2θ-scan mode (scanning rate ratio ω/2θ = 1.2). Intensity data were collected within the range 3.2 ≤ θ ≤ 60.98° using Cu–$K_α$ radiation (λ = 1.54178 Å). Intensities of 3694 reflections (2945 unique reflections, R_{int} = 0.0385) were measured. Data were corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using SHELXS-97 and SHELXL-97 programs. Hydrogen atoms were calculated isotropically excluding hydrogen atoms of piperidine which were placed at the calculated positions as 'riding' models with U_{iso} = 1.2 U_{iso} of the supporting carbon atoms. The azimuthal absorption correction by PSI-scan (T_{min} 0.7342, T_{maxc} 0.9583) was applied. In the refinement 2945 reflections were used. Convergence was obtained at R_1 = 0.0559 and $wR_2(F^2)$ = 0.1454, GOF = 1.043 [2188 reflections with I 2σ(I), 290 parameters; observed/variable ratio 7.54], the largest and minimal peaks in the final difference map 0.43 and –0.23 eÅ^3, weighting scheme ω = 1/[σ^2(Fo^2) + (0.0938)P^2 + 1.5059P], where P = (Fo^2 + 2Fc^2)/3.

Crystallographic data (excluding structure factors) for the structure **10f** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 253573 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

Compounds 4a–c; General Procedure

To a mixture of salt **1** (1 mmol) and 4-chlorophenyl isocyanate (459 mg, 3 mmol), pyridine (8 mL) was added and the resulting soln was heated under reflux for 30 min. The solvent was evaporated under reduced pressure, and the residue was triturated with H_2O, dried (Na_2SO_4) and subjected to column chromatography over silica gel ($CHCl_3$–MeOH, 9:1). The product was recrystallised (MeOH) to afford **4**.

6-(4-Chlorophenyl)-2-pyrrolidin-1-yl[1,3]thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4a)

Yield: 274 mg (79%); colourless solid; mp >350 °C (MeOH); R_f = 0.60 ($CHCl_3$–MeOH, 9:1).

^{1}H NMR (DMSO-d_6): δ = 1.97 (br m, 4 H, CH_2), 3.25 (br m, 4 H, NCH_2), 7.29 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.50 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 12.20 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.6, 50.4, 119.8, 128.8, 131.4, 132.6, 134.7, 151.2, 156.1, 157.2, 172.7.

MS: *m*/*z* (%) = 350 (10) [M$^+$ + 2], 348 (32) [M$^+$], 97 (100), 71 (10), 55 (61).

Anal. Calcd for $C_{15}H_{13}ClN_4O_2S$: C, 51.65; H, 3.76; N, 16.06. Found: C, 51.67; H, 3.75; N, 16.03.

6-(4-Chlorophenyl)-2-piperidin-1-yl[1,3]thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4b)

Yield: 267 mg (74%); colourless solid; mp 198 °C (MeOH); R_f = 0.65 ($CHCl_3$–MeOH, 9:1).

IR: 3243, 3179, 3115, 3057, 2948, 2847, 1634, 1617, 1591, 1557, 1540, 1515, 1484, 1417, 1365, 1318, 1243, 1155, 1087, 1001, 888, 827, 776, 721 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.65 (br m, 6 H, CH_2), 3.60 (br m, 4 H, NCH_2), 7.30 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.48 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 12.24 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.3, 24.8, 49.3, 119.8, 128.8, 131.3, 132.6, 134.9, 151.1, 156.1, 157.8, 172.6.

MS: *m*/*z* (%) = 364 (19) [M$^+$ + 2], 363 (12) [M$^+$ + 1], 362 (64) [M$^+$], 236 (22), 111 (100), 69 (22), 55 (34), 41 (18).

Anal. Calcd for $C_{16}H_{15}ClN_4O_2S$: C, 52.96; H, 4.17; N, 15.44. Found: C, 52.96; H, 4.19; N, 15.41.

6-(4-Chlorophenyl)-2-morpholin-4-yl[1,3]thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (4c)

Yield: 259 mg (71%); colourless solid; mp >350 °C (MeOH); R_f = 0.45 ($CHCl_3$–MeOH, 9:1).

^{1}H NMR (DMSO-d_6): δ = 3.38 (br m, 4 H, NCH_2), 3.63 (br m, 4 H, OCH_2), 7.29 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.50 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 12.20 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 48.3, 65.8, 119.7, 128.8, 131.4, 132.6, 134.7, 151.1, 155.9, 157.1, 172.5.

MS: *m*/*z* (%) = 366 (12) [M$^+$ + 2], 365 (8) [M$^+$ + 1], 364 (41) [M$^+$], 238 (8), 113 (100), 69 (32), 55 (16), 42 (15).

Anal. Calcd for $C_{15}H_{13}ClN_4O_3S$: C, 49.39; H, 3.59; N, 15.36. Found: C, 49.41; H, 3.57; N, 15.35.

Compounds 5a–c; General Procedure

A soln of Et_3N (0.276 mL, 2 mmol) in CH_2Cl_2 (10 mL) was added to a stirred mixture of salt **1** (1 mmol) and 4-chlorophenyl isocyanate (153 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C for 10 min. The mixture was stirred at 0 °C for 3 h and then left overnight at r.t. Then, the reaction mixture was washed with H_2O (2 × 10 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallised (*i*-PrOH).

***N*-(4-Chlorophenyl)-*N*′-(2-pyrrolidin-1-yl-1,3-thiazol-4-yl)urea (5a)**

Yield: 229 mg (75%); colourless solid; mp 201 °C (*i*-PrOH).

IR: 3258, 3173, 3111, 3084, 2989, 2957, 2947, 2937, 2848, 1689, 1615, 1581, 1551, 1520, 1492, 1442, 1427, 1407, 1322, 1241, 1092, 1007, 880, 843, 810, 771, 728 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.96 (br m, 4 H, CH_2), 3.24 (br m, 4 H, NCH_2), 6.43 (s, 1 H, CH), 7.23 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.38 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.60 (s, 1 H, NH), 9.18 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.1, 49.7, 83.3, 119.6, 125.2, 128.1, 138.7, 144.1, 151.0, 168.9.

MS: *m*/*z* (%) = 322 (7) [M$^+$], 178 (100), 155 (29), 153 (69), 127 (17), 126 (22), 125 (21), 98 (21), 91 (25), 71 (26), 57 (59), 46 (28).

Anal. Calcd for $C_{14}H_{15}ClN_4OS$: C, 52.09; H, 4.68; N, 17.36. Found: C, 52.07; H, 4.68; N, 17.35.

***N*-(4-Chlorophenyl)-*N*′-(2-piperidin-1-yl-1,3-thiazol-4-yl)urea (5b)**

Yield: 253 mg (78%); colourless solid; mp 194–195 °C (*i*-PrOH).

IR: 3250, 3189, 3110, 3084, 2951, 2943, 2852, 1691, 1610, 1583, 1551, 1530, 1492, 1442, 1403, 1378, 1322, 1248, 1091, 1008, 889, 829, 814, 776, 729 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.81 (br m, 6 H, CH_2), 3.58 (br m, 4 H, NCH_2), 6.40 (s, 1 H, CH), 7.23 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.38 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.74 (s, 1 H, NH), 9.24 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.3, 24.7, 48.5, 83.8, 119.4, 125.0, 128.7, 138.3, 144.7, 151.4, 168.7.

MS: *m*/*z* (%) = 336 (5) [M$^+$], 237 (13), 169 (100), 159 (32), 157 (81), 125 (23), 122 (12), 121 (29), 99 (33), 91 (27), 71 (31), 56 (35), 46 (38).

Anal. Calcd for $C_{15}H_{17}ClN_4OS$: C, 53.49; H, 5.09; N, 16.63. Found: C, 53.49; H, 5.08; N, 16.65.

***N*-(4-Chlorophenyl)-*N*′-(2-morpholin-4-yl-1,3-thiazol-4-yl)urea (5c)**
Yield: 254 mg (75%); colourless solid; mp 183 °C (*i*-PrOH).

^{1}H NMR (DMSO-d_6): δ = 3.38 (br m, 4 H, NCH_2), 3.63 (br m, 4 H, OCH_2), 6.51 (s, 1 H, CH), 7.24 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.39 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.58 (s, 1 H, NH), 9.14 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 48.0, 64.9, 83.7, 119.1, 125.3, 128.0, 138.1, 144.8, 151.0, 168.8.

MS: *m*/*z* (%) = 338 (8) [M$^+$], 213 (20), 185 (100), 155 (31), 154 (14), 153 (86), 129 (19), 128 (25), 127 (90), 125 (31), 113 (34), 91 (26), 74 (30), 70 (33), 45 (30).

Anal. Calcd for $C_{14}H_{15}ClN_4O_2S$: C, 49.63; H, 4.46; N, 16.54. Found: C, 49.61; H, 4.44; N, 16.53.

Compounds 7; General Procedure
To a mixture of 1,2-dimethyl-1*H*-imidazol-5-amine (**6**; 222 mg, 2 mmol) in CH_2Cl_2 (30 mL), isocyanate (2 mmol) was added. Then, in a few minutes, Et_3N (1 drop) was added. The mixture was stirred at r.t. for 24 h. Then, the CH_2Cl_2 was evaporated from the reaction mixture and the residue was recrystallised from the appropriate solvent.

***N*-(1,2-Dimethyl-1*H*-imidazol-5-yl)-*N*′-methylurea (7a)**
Yield: 178 mg (53%); colourless solid; mp 187–190 °C (precipitated from the reaction mixture).

^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3 H, 2-CH_3), 2.56 (d, $^3J_{HH}$ = 4.4 Hz, 3 H, NCH_3), 3.22 (s, 3 H, 1-CH_3), 6.07 (q, $^3J_{HH}$ = 4.4 Hz, 1 H, NH), 6.45 (s, 1 H, CH), 7.95 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 13.4, 26.4, 28.7, 120.3, 127.3, 141.5, 157.0.

MS: *m*/*z* (%) = 168 (48) [M$^+$], 112 (17), 111 (100), 110 (78), 70 (49), 58 (31), 57 (18), 56 (80), 55 (17), 54 (14), 43 (60), 42 (48).

Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 50.00; H, 7.19; N, 33.30.

***N*-(1,2-Dimethyl-1*H*-imidazol-5-yl)-*N*′-phenylurea (7b)**
Yield: 336 mg (73%); colourless solid; mp 185–187 °C (*i*-PrOH).

^{1}H NMR (DMSO-d_6): δ = 2.57 (s, 3 H, 2-CH_3), 3.73 (s, 3 H, 1-CH_3), 6.41 (s, 1 H, CH), 7.19 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.54 (br m, 3 H, CH), 8.40 (s, 1 H, NH), 9.21 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): 12.3, 29.0, 121.4, 124.3, 126.9, 128.6, 131.8, 138.9, 141.0, 161.7.

MS: *m*/*z* (%) = 230 (32) [M$^+$], 138 (15), 137 (11), 120 (33), 119 (25), 112 (23), 111 (100), 110 (67), 77 (18), 46 (37).

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 54.94; H, 5.38; N, 21.36. Found: C, 54.95; H, 5.39; N, 21.34.

Compounds 10; General Procedure
A mixture of a salt **1** (1 mmol) and an isocyanate **8** (1 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 10–20 min and then a soln of Et_3N (0.276 mL, 2 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at r.t. for 5 h. Then, the reaction mixture was washed with H_2O (2 × 10 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to column chromatography over silica gel (EtOAc) to afford **10**.

7-Phenyl-2-pyrrolidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10a)
Yield: 298 mg (81%); colourless solid; mp 140 °C; R_f = 0.9 (EtOAc).

IR: 3455 (br), 3220, 3059, 2942, 2856, 1689, 1618, 1546, 1488, 1450, 1326, 1276, 1172, 908, 719 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.99 (br m, 4 H, CH_2), 3.35 (br m, 4 H, NCH_2), 7.39 (m, 3 H, CH), 7.56 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.21 (s, 1 H, NH), 9.88 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.7, 49.4, 64.8 ($^2J_{CF}$ = 28.8 Hz), 85.1, 125.9 ($^1J_{CF}$ = 288 Hz), 128.3, 129.9, 133.3, 138.1, 141.2, 153.1, 171.1.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 368 (5) [M$^+$], 300 (16), 299 (100), 77 (16), 55 (22), 32 (27), 31 (36).

Anal. Calcd for $C_{16}H_{15}F_3N_4OS$: C, 52.17; H, 4.10; N, 15.21. Found: C, 52.18; H, 4.13; N, 15.21.

7-(4-Methylphenyl)-2-pyrrolidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10b)
Yield: 302 mg (79%); colourless solid; mp 134–135 °C; R_f = 0.9 (EtOAc).

IR: 3440 (br), 3398 (br), 3220, 3106, 2971, 2954, 2925, 2875, 1691, 1614, 1560, 1481, 1457, 1319, 1166, 921, 813, 727 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.91 (br s, 4 H, CH_2), 2.34 (s, 3 H, CH_3), 3.32 (br s, 4 H, NCH_2), 7.17 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.42 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.08 (s, 1 H, NH), 9.79 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.1, 25.1, 48.9, 64.7 ($^2J_{CF}$ = 28.8 Hz), 85.1, 125.8 ($^1J_{CF}$ = 288 Hz), 126.7, 129.7, 136.1, 138.4, 146.2, 153.1, 171.1.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 382 (8) [M$^+$], 314 (18), 313 (100), 55 (10).

Anal. Calcd for $C_{17}H_{17}F_3N_4OS$: C, 53.40; H, 4.48; N, 14.65. Found: C, 53.42; H, 4.47; N, 14.67.

7-(4-Methoxyphenyl)-2-pyrrolidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10c)
Yield: 327 mg (82%); colourless solid; mp 139 °C; R_f = 0.85 (EtOAc).

IR: 3433 (br), 3370 (br), 3225, 3101, 2969, 2956, 2928, 2870, 1694, 1610, 1563, 1515, 1459, 1318, 1261, 1168, 1032, 921, 830, 697 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.98 (br s, 4 H, CH_2), 3.30 (br s, 4 H, NCH_2), 3.77 (s, 3 H, OCH_3), 7.00 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.46 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.24 (s, 1 H, NH), 9.91 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.3, 48.9, 55.7, 64.5 ($^2J_{CF}$ = 28.8 Hz), 85.2, 114.4, 128.1 ($^1J_{CF}$ = 288 Hz), 128.7, 130.9, 146.1, 152.8, 159.6, 170.9.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 398 (7) [M$^+$], 330 (19), 299 (100).

Anal. Calcd for $C_{17}H_{17}F_3N_4O_2S$: C, 51.25; H, 4.30; N, 14.06. Found: C, 51.23; H, 4.31; N, 14.04.

7-Phenyl-2-piperidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10d)
Yield: 325 mg (85%); colourless solid; mp 147–148 °C; R_f = 0.75 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 1.65 (br s, 6 H, CH_2), 3.27 (br s, 4 H, NCH_2), 7.38 (m, 3 H, CH), 7.52 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.24 (s, 1 H, NH), 9.98 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.8, 25.1, 48.9, 64.7 ($^2J_{CF}$ = 28.8 Hz), 85.1, 125.9 ($^1J_{CF}$ = 288 Hz), 128.0, 129.8, 133.1, 138.3, 141.0, 153.1, 171.2.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 382 (100) [M$^+$], 314 (25), 313 (100).

Anal. Calcd for $C_{17}H_{17}F_3N_4OS$: C, 53.40; H, 4.48; N, 14.65. Found: C, 53.41; H, 4.49; N, 14.61.

7-(4-Methylphenyl)-2-piperidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10e)
Yield: 345 mg (87%); colourless solid; mp 141–142 °C; R_f = 0.75 (EtOAc).

IR: 3341 (br), 3210, 3100, 2982, 2957, 2923, 2857, 1695, 1615, 1549, 1487, 1447, 1387, 1328, 1260, 1169, 1020, 921, 813, 731 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.67 (br s, 6 H, CH_2), 2.30 (s, 3 H, CH_3), 3.24 (br s, 4 H, NCH_2), 7.25 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.45 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.20 (s, 1 H, NH), 9.95 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.0, 25.6, 50.3, 64.7 ($^2J_{CF}$ = 28.8 Hz), 85.1, 125.1, 125.8 ($^1J_{CF}$ = 288 Hz), 126.9, 129.7, 136.1, 138.4, 146.2, 153.1, 171.1.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 396 (7) [M^+], 328 (31), 327 (100).

Anal. Calcd for $C_{18}H_{19}F_3N_4OS$: C, 54.54; H, 4.83; N, 14.13. Found: C, 54.55; H, 4.83; N, 14.10.

7-(4-Methoxyphenyl)-2-piperidin-1-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10f)
Yield: 358 mg (87%); colourless solid; mp 139–140 °C; R_f = 0.7 (EtOAc).

IR: 3421 (br), 3220, 3108, 2939, 2856, 1691, 1612, 1550, 1515, 1448, 1259, 1170, 829 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.61 (br s, 6 H, CH_2), 3.23 (br s, 4 H, NCH_2), 3.71 (s, 3 H, OCH_3), 6.93 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.43 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.16 (s, 1 H, NH), 9.95 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.0, 25.6, 50.3, 55.8, 64.5 ($^2J_{CF}$ = 28.8 Hz), 85.2, 114.5, 124.4 ($^1J_{CF}$ = 288 Hz), 128.1, 130.9, 146.1, 152.8, 159.6, 170.9.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 412 (10) [M^+], 344 (20), 343 (100).

Anal. Calcd for $C_{18}H_{19}F_3N_4O_2S$: C, 52.42; H, 4.64; N, 13.58. Found: C, 52.43; H, 4.64; N, 13.56.

2-Morpholin-4-yl-7-phenyl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10g)
Yield: 242 mg (63%); colourless solid; mp 162 °C; R_f = 0.55 (EtOAc).

^1H NMR (DMSO-d_6): δ = 3.32 (br s, 4 H, NCH_2), 3.65 (br s, 4 H, OCH_2), 7.39 (m, 3 H, CH), 7.56 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.25 (s, 1 H, NH), 9.93 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 47.8, 64.6 ($^2J_{CF}$ = 28.8 Hz), 65.7, 85.0, 125.1 ($^1J_{CF}$ = 288 Hz), 127.9, 129.5, 133.2, 138.3, 141.1, 153.1, 171.7.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 384 (5) [M^+], 316 (20), 315 (100), 118 (15).

Anal. Calcd for $C_{16}H_{15}F_3N_4O_2S$: C, 50.00; H, 3.93; N, 14.58. Found: C, 49.98; H, 3.92; N, 14.59.

7-(4-Methylphenyl)-2-morpholin-4-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10h)
Yield: 271 mg (68%); colourless solid; mp 164 °C; R_f = 0.55 (EtOAc).

IR: 3421 (br), 3237 (br), 3121 (sh), 2996, 2923, 2854, 1685, 1614, 1540, 1448, 1166, 1116, 925, 890, 813 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.31 (s, 3 H, CH_3), 3.31 (br s, 4 H, NCH_2), 3.68 (br s, 4 H, OCH_2), 7.26 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.42 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.31 (s, 1 H, NH), 9.90 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.0, 47.7, 55.8, 64.6 ($^2J_{CF}$ = 28.8 Hz), 65.8, 86.1, 125.7 ($^1J_{CF}$ = 288 Hz), 126.6, 129.7, 136.1, 138.4, 146.1, 159.7, 171.4.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 398 (5) [M^+], 330 (20), 329 (100), 118 (19).

Anal. Calcd for $C_{17}H_{17}F_3N_4O_2S$: C, 51.25; H, 4.30; N, 14.06. Found: C, 51.23; H, 4.30; N, 14.06.

7-(4-Methoxyphenyl)-2-morpholin-4-yl-7-(trifluoromethyl)-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (10i)
Yield: 257 mg (62%); colourless solid; mp 168 °C; R_f = 0.50 (EtOAc).

^1H NMR (DMSO-d_6): δ = 3.32 (br s, 4 H, NCH_2), 3.67 (br s, 4 H, OCH_2), 3.77 (s, 3 H, OCH_3), 6.92 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.43 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.15 (s, 1 H, NH), 9.92 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 47.8, 55.7, 64.6 ($^2J_{CF}$ = 28.8 Hz), 65.7, 86.2, 114.1, 125.7 ($^1J_{CF}$ = 288 Hz), 128.2, 130.8, 146.1, 152.8, 159.7, 171.4.

^{19}F NMR (DMSO-d_6): δ = –76.5.

MS: *m*/*z* (%) = 414 (5) [M^+], 346 (21), 345 (100), 118 (18).

Anal. Calcd for $C_{17}H_{17}F_3N_4O_3S$: C, 49.27; H, 4.13; N, 13.52. Found: C, 49.30; H, 4.12; N, 13.53.

2-Morpholin-4-yl-7,7-diphenyl-6,7-dihydro[1,3]thiazolo[4,5-*d*]pyrimidin-5(4*H*)-one (11)
A mixture of salt **1c** (437 mg, 2 mmol) and isocyanate **9** (487 mg, 2 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 10 min and then a soln of Et_3N (0.55 mL, 4 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at r.t. for 24 h. Then, the reaction mixture was washed with H_2O (2 × 20 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallised (EtOH).

Yield: 635 mg (81%); colourless solid; mp 295–297 °C (EtOH).

^1H NMR (DMSO-d_6): δ = 3.30 (br m, 4 H, NCH_2), 3.65 (br m, 4 H, OCH_2), 7.31 (br m, 10 H, CH), 7.67 (s, 1 H, NH), 9.44 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 47.1, 64.3, 65.1, 84.7, 129.4, 130.3, 133.9, 139.1, 143.7, 152.5, 170.5.

MS: *m*/*z* (%) = 393 (20) [M^+ + 1], 392 (20) [M^+], 317 (29), 316 (61), 315 (100), 43 (33).

Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28; Found: C, 64.30; H, 5.12; N, 14.27.

8,9-Dimethyl-6-(4-methylphenyl)-6-(trifluoromethyl)-1,3,6,9-tetrahydro-2*H*-purin-2-one (12)
A mixture of 1,2-dimethyl-1*H*-imidazol-5-amine (**6**; 222 mg, 2 mmol) and isocyanate **8b** (531 mg, 2 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 10 min and then a soln of Et_3N (0.27 mL, 2 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at r.t. for 36 h. Then, the reaction mixture was washed with H_2O (2 × 20 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography over silica gel.

Yield: 563 mg (87%); colourless solid; mp >350 °C; R_f = 0.75 ($CHCl_3$–MeOH, 9:1).

^1H NMR (DMSO-d_6): δ = 2.25 (s, 3 H, CH_3), 2.29 (s, 3 H, 8-CH_3), 3.41 (s, 3 H, 9-CH_3), 7.23 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 7.79 (d, $^3J_{HH}$ = 8.2 Hz, 2 H, CH), 8.25 (s, 1 H, NH), 9.98 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 12.8, 20.7, 29.3, 63.27 ($^2J_{CF}$ = 28.8 Hz), 108.4, 124.9 ($^1J_{CF}$ = 288 Hz), 127.1, 128.4, 129.5, 135.0, 137.3, 139.9, 152.1.

^{19}F NMR (DMSO-d_6): δ = –76.

MS: *m*/*z* (%) = 324 (53) [M$^+$], 256 (66), 255 (100), 212 (35), 162 (27), 127 (30), 56 (49).

Anal. Calcd for $C_{15}H_{15}F_3N_4O$: C, 55.55; H, 4.66; N, 17.28. Found: C, 55.53; H, 4.67; N, 17.29.

8,9-Dimethyl-6,6-diphenyl-1,3,6,9-tetrahydro-2*H*-purin-2-one (13)

A mixture of 1,2-dimethyl-1*H*-imidazol-5-amine (**6**; 222 mg, 2 mmol) and isocyanate **9** (487 mg, 2 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t. for 10 min and then a soln of Et_3N (0.27 mL, 2 mmol) in CH_2Cl_2 (20 mL) was slowly added. The mixture was stirred at r.t. for 72 h. Then, the reaction mixture was washed with H_2O (2 × 20 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallised (EtOH).

Yield: 432 mg (68%); colourless solid; mp 310–313 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 2.22 (s, 3 H, CH_3), 3.43 (s, 3 H, CH_3), 7.36 (br m, 10 H, CH), 7.87 (s, 1 H, NH), 9.67 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 12.9, 29.4, 64.2, 115.4, 126.3, 127.2, 127.3, 127.4, 139.7, 146.8, 152.7.

MS: *m*/*z* (%) = 319 (24) [M$^+$ + 1], 318 (58) [M$^+$], 274 (36), 242 (60), 241 (100), 197 (25), 56 (46), 44 (25).

Anal. Calcd for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60; Found: C, 71.69; H, 5.70; N, 17.59.

Compounds 15a–c, 17; General Procedure

A mixture of a salt **1** or 1,2-dimethyl-1*H*-imidazol-5-amine (**6**) (2 mmol) and the ethanimidoyl chloride **14** (0.378 mg, 2 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 10 min and then a soln of Et_3N (0.557 mL, 4 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was stirred at r.t. for 4 h and was left overnight. Then, the reaction mixture was washed with H_2O (2 × 10 mL) and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography over silica gel (EtOAc) to afford **15** or **17**. In the case of the imidazolamine **6**, Et_3N (0.23 mL, 2 mmol) in CH_2Cl_2 (15 mL) was added.

Methyl 2,2,2-Trifluoro-1-[(2-pyrrolidin-1-yl-1,3-thiazol-4-yl)amino]ethylidenecarbamate (15a)

Yield: 370 mg (55%); colourless solid; mp 143–144 °C; R_f = 0.75 (EtOAc).

IR: 3200 (br), 3080 (br), 2954, 2833, 1687, 1671, 1598, 1541, 1488, 1381, 1374, 1341, 1270, 1197, 1167, 1123, 997, 805, 771 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.00 (br m, 4 H, CH_2), 3.58 (br m, 4 H, NCH_2), 3.70 (s, 3 H, OCH_3), 6.97 (s, 1 H, CH), 11.51 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.8, 49.4, 53.6, 107.1, 118.5 ($^1J_{CF}$ = 276 Hz), 136.3 ($^2J_{CF}$ = 36.7 Hz), 151.6, 164.9, 170.1.

^{19}F NMR (DMSO-d_6): δ = –68.7.

MS: *m*/*z* (%) = 323 (9) [M$^+$ + 1], 322 (68) [M$^+$], 321 (10) [M$^+$ – 1], 290 (45), 262 (21), 169 (26), 114 (37), 98 (45), 72 (26), 71 (29), 70 (70), 69 (59), 59 (39), 55 (100), 51 (15), 45 (89), 43 (25), 42 (28).

Anal. Calcd for $C_{11}H_{13}F_3N_4O_2S$: C, 40.99; H, 4.07; N, 17.38. Found: C, 40.97; H, 4.07; N, 17.35.

Methyl 2,2,2-Trifluoro-1-[(2-piperidin-1-yl-1,3-thiazol-4-yl)amino]ethylidenecarbamate (15b)

Yield: 350 mg (52%); colourless solid; mp 148 °C; R_f = 0.65 (EtOAc).

IR: 3215 (br), 3075 (br), 2962, 2855, 1685, 1672, 1592, 1540, 1499, 1480, 1381, 1350, 1270, 1235, 1200, 1160, 1120, 1003, 803, 771 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.65 (br m, 6 H, CH_2), 3.44 (br m, 4 H, NCH_2), 3.68 (s, 3 H, OCH_3), 6.93 (s, 1 H, CH), 11.72 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.8, 25.1, 48.9, 53.3, 107.1, 118.5 ($^1J_{CF}$ = 276 Hz), 136.2 ($^2J_{CF}$ = 36.7 Hz), 151.5, 164.8, 169.7.

^{19}F NMR (DMSO-d_6): δ = –68.7.

MS: *m*/*z* (%) = 337 (11) [M$^+$ + 1], 336 (100) [M$^+$], 301 (21), 291 (47), 244 (43), 167 (31), 114 (15), 111 (22), 97 (15), 72 (19), 70 (34), 69 (32), 59 (39), 55 (32), 51 (15), 45 (41), 43 (11), 42 (38).

Anal. Calcd for $C_{12}H_{15}F_3N_4O_2S$: C, 42.85; H, 4.50; N, 16.66. Found: C, 42.82; H, 4.51; N, 16.67.

Methyl 2,2,2-Trifluoro-1-[(2-morpholin-4-yl-1,3-thiazol-4-yl)amino]ethylidenecarbamate (15c)

Yield: 332 mg (49%); colourless solid; mp 139–140 °C; R_f = 0.40 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.41 (br m, 4 H, NCH_2), 3.67 (br m, 4 H, OCH_2), 3.71 (s, 3 H, OCH_3), 7.01 (br m, 1 H, CH), 11.24 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 47.8, 53.1, 65.7, 107.1, 118.4 ($^1J_{CF}$ = 276 Hz), 136.2 ($^2J_{CF}$ = 36.7 Hz), 151.5, 164.8, 169.7.

^{19}F NMR (DMSO-d_6): δ = –68.7.

MS: *m*/*z* (%) = 339 (14) [M$^+$ + 1], 338 (100) [M$^+$], 307 (13), 306 (58), 249 (29), 208 (11), 130 (16), 113 (23), 110 (13), 87 (30), 86 (38), 72 (22), 69 (49), 59 (57), 57 (19), 55 (17), 45 (58), 42 (48).

Anal. Calcd for $C_{11}H_{13}F_3N_4O_3S$: C, 39.05; H, 3.87; N, 16.56. Found: C, 39.06; H, 3.85; N, 16.55.

Methyl 1-[(1,2-Dimethyl-1*H*-imidazol-5-yl)amino]-2,2,2-trifluoroethylidenecarbamate (17)

Yield: 190 mg (36%); colourless solid; mp 197–199 °C; R_f = 0.55 ($CHCl_3$–MeOH, 9:1).

^{1}H NMR (DMSO-d_6): δ = 2.57 (s, 3 H, 2-CH_3), 3.68 (s, 3 H, OCH_3), 3.73 (s, 3 H, 1-CH_3), 6.59 (br s, 1 H, CH), 11.10 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.1, 29.3, 53.9, 103.9, 119.1 ($^1J_{CF}$ = 276 Hz), 141.2 ($^2J_{CF}$ = 36.7 Hz), 153.7, 168.8, 171.1.

^{19}F NMR (DMSO-d_6): δ = –69.3.

MS: *m*/*z* (%) = 265 (10) [M$^+$ + 1], 264 (100) [M$^+$], 233 (21), 205 (39), 171 (11), 112 (18).

Anal. Calcd for $C_9H_{11}F_3N_4O_2$: C, 40.91; H, 4.20; N, 21.21. Found: C, 40.93; H, 4.19; N, 21.20.

Compounds 16a–c, 18; General Procedure

An amidine **15** (1 mmol) was dissolved in toluene (20 mL) and heated under reflux for 2–3 h, then left at r.t. overnight. The precipitate formed was collected by filtration, washed with toluene (1 mL) and with hexane (2 × 3 mL), and dried under reduced pressure to afford **16**. Compound **18** was prepared in a similar way from amidine **17**.

2-Pyrrolidin-1-yl-5-(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16a)

Yield: 240 mg (83%); colourless solid; mp 257–258 °C.

^{1}H NMR (DMSO-d_6): δ = 2.05 (br m, 4 H, CH_2), 3.51 (br m, 4 H, NCH_2), 13.38 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.6, 50.3, 107.5, 119.7 ($^1J_{CF}$ = 275 Hz), 151.3 ($^2J_{CF}$ = 35 Hz), 162.2, 169.3, 170.5.

^{19}F NMR (DMSO-d_6): δ = –69.

MS: *m*/*z* (%) = 291 (11) [M$^+$ + 1], 290 (100) [M$^+$], 267 (41), 242 (38), 232 (29), 221 (17), 73 (12), 71 (11), 70 (17), 57 (21), 42 (31).

Anal. Calcd for $C_{10}H_9F_3N_4OS$: C, 41.38; H, 3.13; N, 19.30. Found: C, 41.40; H, 3.14; N, 19.32.

2-Piperidin-1-yl-5-(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16b)
Yield: 264 mg (87%); colourless solid; mp 288–289 °C.

IR: 3040, 2916, 2867, 2688, 1669, 1559, 1417, 1329, 1212, 1153, 779 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.63 (br m, 6 H, CH_2), 3.48 (br m, 4 H, NCH_2), 13.57 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.8, 25.1, 50.4, 107.7, 119.7 ($^1J_{CF}$ = 275 Hz), 151.2 ($^2J_{CF}$ = 35 Hz), 162.2, 169.3, 170.3.

^{19}F NMR (DMSO-d_6): δ = –69.

MS: *m*/*z* (%) = 305 (13) [M^+ + 1], 304 (100) [M^+], 303 (11), 289 (10), 275 (46), 261 (11), 249 (28), 248 (31), 236 (37), 221 (18), 71 (12), 70 (14), 69 (21), 55 (27), 41 (37).

Anal. Calcd for $C_{11}H_{11}F_3N_4OS$: C, 43.42; H, 3.64; N, 18.41. Found: C, 43.43; H, 3.65; N, 18.40.

2-Morpholin-4-yl-5-(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidin-7(6*H*)-one (16c)
Yield: 279 mg (91%); colourless solid; mp 297–298 °C.

^1H NMR (DMSO-d_6): δ = 3.52 (br m, 4 H, NCH_2), 3.68 (br m, 4 H, OCH_2), 12.92 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 47.7, 65.7, 107.8, 119.7 ($^1J_{CF}$ = 275 Hz), 151.2 ($^2J_{CF}$ = 35 Hz), 162.2, 169.3, 170.2.

^{19}F NMR (DMSO-d_6): δ = –69.

MS: *m*/*z* (%) = 307 (11) [M^+ + 1], 306 (100) [M^+], 287 (32), 267 (43), 241 (21), 222 (15), 71 (18), 69 (34), 55 (19), 42 (21).

Anal. Calcd for $C_{10}H_9F_3N_4O_2S$: C, 39.22; H, 2.96; N, 18.29. Found: C, 39.22; H, 2.92; N, 18.30.

8,9-Dimethyl-2-(trifluoromethyl)-1,9-dihydro-6*H*-purin-6-one (18)
Yield: 204 mg (88%); colourless solid; mp 278–281 °C.

^1H NMR (DMSO-d_6): δ = 2.57 (s, 3 H, 8-CH_3), 3.73 (s, 3 H, 9-CH_3), 11.10 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.9, 29.3, 111.9, 122.3 ($^1J_{CF}$ = 275 Hz), 143.4 ($^2J_{CF}$ = 35 Hz), 154.3, 169.1, 171.8.

^{19}F NMR (DMSO-d_6): δ = –69.

MS: *m*/*z* (%) = 233 (43) [M^+ + 1], 232 (100) [M^+], 203 (22), 163 (87), 154 (17).

Anal. Calcd for $C_8H_7F_3N_4O$: C, 41.39; H, 3.04; N, 24.13. Found: C, 41.42; H, 3.04; N, 24.11.

Compounds 21–23; General Procedure
A mixture of the initial amino-substituted heterocycle **19a**, **19b**, **1c**, or **6** (2 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**20**) (570 mg, 2 mmol) in CH_2Cl_2–AcOH (10:1, 30 mL) was stirred at r.t. for 36–48 h, until the initial amino-substituted heterocycle vanished (by GC/MS analysis). Then, the reaction mixture was concentrated and the residue was purified by column chromatography over silica gel. In the case of salt **1c**, NaOAc (1.1 equiv) was added.

3-Methyl-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (21a)
Yield: 540 mg (95%); colourless solid; mp 106–108 °C; R_f = 0.7 (EtOAc–hexane, 1:4).

^1H NMR ($CDCl_3$): δ = 2.77 (s, 3 H, CH_3), 12.75 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.6 ($^5J_{CF}$ = 4 Hz), 110.1, 119.9 ($^1J_{CF}$ = 275 Hz), 120.7 ($^1J_{CF}$ = 275 Hz), 143.8, 151.3 ($^2J_{CF}$ = 35 Hz), 152.8 ($^2J_{CF}$ = 35 Hz), 156.0.

^{19}F NMR (DMSO-d_6): δ = –69.9, –66.1.

MS: *m*/*z* (%) = 270 (100) [M^+], 269 (69), 251 (27), 250 (27), 69 (32).

Anal. Calcd for $C_8H_4F_6N_4$: C, 35.57; H, 1.49; N, 20.74. Found: C, 35.55; H, 1.50; N, 20.75.

1-Benzyl-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (21b)
Yield: 623 mg (90%); colourless solid; mp 93–95 °C; R_f = 0.8 (EtOAc–hexane, 1:4).

^1H NMR (DMSO-d_6): δ = 5.65 (s, 2 H, CH_2), 7.18–7.30 (br m, 5 H, C_6H_5), 8.27 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 51.8, 110.7, 119.1 ($^1J_{CF}$ = 275 Hz), 120.3 ($^1J_{CF}$ = 275 Hz), 128.5, 128.6, 128.9, 132.5, 134.7, 150.4 ($^2J_{CF}$ = 38 Hz), 153.1 ($^2J_{CF}$ = 38 Hz), 153.6.

^{19}F NMR (DMSO-d_6): δ = –71.3, –69.7.

MS: *m*/*z* (%) = 347 (24) [M^+ + 1], 346 (100) [M^+], 327 (40), 326 (26), 91 (92).

Anal. Calcd for $C_{14}H_8F_6N_4$: C, 48.57; H, 2.33; N, 16.18. Found: C, 48.52; H, 2.35; N, 16.19.

2-Morpholin-4-yl-5,7-bis(trifluoromethyl)[1,3]thiazolo[4,5-*d*]pyrimidine (22)
Yield: 508 mg (71%); colourless solid; mp 99–101 °C; R_f = 0.85 (EtOAc).

^1H NMR ($CDCl_3$): δ = 3.61 (br s, 4 H, NCH_2), 4.00 (br s, 4 H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 49.4, 65.9, 119.2 ($^1J_{CF}$ = 275 Hz), 120.1 ($^1J_{CF}$ = 275 Hz), 146.4 ($^2J_{CF}$ = 38 Hz), 154.5 ($^2J_{CF}$ = 38 Hz), 172.5, 174.3.

^{19}F NMR (DMSO-d_6): δ = –72.1, –70.2.

MS: *m*/*z* (%) = 358 (45) [M^+], 339 (20), 327 (22), 314 (21), 301 (100), 281 (20), 273 (52).

Anal. Calcd for $C_{11}H_8F_6N_4OS$: C, 36.88; H, 2.25; N, 15.64. Found: C, 36.86; H, 2.25; N, 15.65.

8,9-Dimethyl-2,6-bis(trifluoromethyl)-9*H*-purine (23)
Yield: 540 mg (95%); colourless solid; mp 77–79 °C; R_f = 0.75 (CH_2Cl_2–MeOH, 10:1).

^1H NMR ($CDCl_3$): δ = 2.79 (s, 3 H, 8-CH_3), 3.88 (s, 3 H, 9-CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.8, 29.6, 119.3 ($^1J_{CF}$ = 275 Hz), 120.5 ($^1J_{CF}$ = 275 Hz), 131.0, 131.5, 143.1 ($^2J_{CF}$ = 38 Hz), 148.8 ($^2J_{CF}$ = 38 Hz), 155.9, 160.8.

^{19}F NMR ($CDCl_3$): δ = –70.6, –67.9.

MS: *m*/*z* (%) = 284 (100) [M^+], 269 (18), 265 (20), 216 (26), 121 (23).

Anal. Calcd for $C_9H_6F_6N_4$: C, 38.04; H, 2.13; N, 19.72. Found: C, 38.03; H, 2.12; N, 19.74.

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References

(1) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.
(2) (a) Montgomery, J. A. *Cancer Res.* **1982**, *42*, 3911. (b) Temmink, O. H.; Prins, H.-J.; van Gelderop, E.; Peters, G. J. *Br. J. Cancer* **2007**, *96*, 61.
(3) (a) Montgomery, J. A. *Med. Res. Rev.* **1982**, *2*, 271. (b) Kaufmann, H. E. *Ann. N. Y. Acad. Sci.* **1965**, *130*, 168.
(4) (a) Kaufman, H. E.; Heidelberger, C. *Science* **1964**, *145*, 585. (b) Duschinsky, R.; Pleven, E.; Heidelberger, C. *J. Am. Chem. Soc.* **1957**, *79*, 494. (c) Heidelberger, C. *Prog. Nucleic Acid Res.* **1965**, *4*, 1.
(5) (a) Kelley, J. L.; Linn, J. A.; Selway, J. W. T. *J. Med. Chem.* **1989**, *32*, 218. (b) Kelley, J. L.; Linn, J. A.; Selway, J. W. T. *J. Med. Chem.* **1989**, *32*, 1757. (c) Bourguignon, J.-J.; Desaubry, L.; Raboisson, P.; Wermuth, C.-G.; Lugnier, C. *J. Med. Chem.* **1997**, *40*, 1768. (d) Meyer, R. B.; Shuman, D. A.; Robins, R. K. *J. Am. Chem. Soc.* **1974**, *96*, 4962. (e) Isobe, Y.; Ogita, H.; Tobe, M.; Takahisa, H.; Matsui, H.; Tomisawa, H. JP 11180982, **1999**. (f) Silhar, P.; Pohl, R.; Votruba, I.; Hocek, M. *Org. Biomol. Chem.* **2005**, *3*, 3001.
(6) (a) Albert, A. *J. Chem. Soc. B* **1966**, 438. (b) Fenn, M. D.; Lister, J. H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 485. (c) Chea, M. Y.; Swenn, K.; Kanugula, S.; Dolan, M. E.; Pegg, A. E.; Moschel, R. C. *J. Med. Chem.* **1995**, *38*, 359.
(7) (a) Obe, T.; Sueoka, H.; Terasawa, M. JP 62010085, **1987**. (b) Pfleiderer, W. M.; Shanshal, M. *Justus Liebigs Ann. Chem.* **1969**, *726*, 201. (c) Srinivas, K.; Rao, P. S.; Narsaiah, B.; Rao, J. M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40*, 191.
(8) (a) Sakaguchi, O.; Takeshita, M.; Izumi, T. JP 2004217582, **2004**. (b) Lerner, A.; Tiwari, S. WO 2006062817, **2006**. (c) Germeyer, S.; Meade, M. C. J.; Meissner, H.; Morschhaeuser, G.; Pairet, M.; Pestel, S.; Pieper, M. P.; Pohl, G.; Reichl, R.; Speck, G. WO 2005013967, **2005**. (d) Warner, J. M. WO 2004067006, **2004**.
(9) (a) Ealick, S. E.; Parker, W. B.; Seerist, J. A.; Sorscher, E. J. WO 2003035012, **2003**. (b) Matulic-Adamic, J.; Takahashi, K.; Chou, T. C.; Gadler, H.; Price, R. W.; Watanabe, K. A.; Reddy, A. R. V.; Kalman, T. I. *J. Med. Chem.* **1988**, *31*, 1642.
(10) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755.
(11) (a) Hocková, D.; Hocek, M.; Dvořáková, H.; Votruba, I. *Tetrahedron* **1999**, *55*, 11109. (b) Koch, M.; Den, H.; Jacobus, A.; Koomen, J.; Wanner, G.-J.; Martinus, J.; Roelof, F. W. WO 2006027365, **2006**. (c) Erion, M. D. M.; Reddy, R. *J. Am. Chem. Soc.* **1998**, *120*, 3295. (d) Véliz, E. A.; Stephens, O. M.; Beal, P. A. *Org. Lett.* **2001**, *3*, 2969.
(12) Nagahara, K.; Anderson, J. D.; Kini, G. D.; Dalley, N. K.; Larson, S. B.; Smee, D. F.; Jin, A.; Sharma, B. S.; Jolley, W. B.; Robins, R. K.; Cottam, H. B. *J. Med. Chem.* **1990**, *33*, 407.
(13) Berger, C. J. US 2001047021, **2001**.
(14) (a) Berger, C. J.; Dabek, R. A. WO 2002009716, **2002**. (b) Gorenstein, D. G.; Luxon, B. A.; Barrett, A.; Holbrook, M.; Bassett, S.; Somasunderam, A. WO 2005037053, **2005**.
(15) Blatt, L. M.; Andrews, S. W.; Condroski, K. R.; Doherty, G. A.; Jiang, Y.; Josey, J. A.; Kennedy, A. L.; Madduru, M. R.; Stengel, P. J.; Wenglowsky, S. M.; Woodard, B. T.; Woodard, L. US 2005267018, **2005**.
(16) Webber, S.; Haley, G. J.; Lennox, J. R.; Xiang, A. X.; Rueden, E. J. WO 2006066080, **2006**.
(17) (a) Bandurco, V. T.; Schwender, C. F.; Bell, S. C.; Combs, D. W.; Kanojia, R. M.; Levine, S. D.; Mulvey, D. M.; Appollina, M. A.; Reed, M. S.; Malloy, E. A.; Falotico, R.; Moore, J. B.; Tobia, A. J. *J. Med. Chem.* **1987**, *30*, 1421. (b) Marsh, A.; Silvestri, M.; Lehn, J.-M. *Chem. Commun.* **1996**, 1527. (c) Gehring, H.; Daltrozzo, E. *Helv. Chim. Acta* **1998**, *81*, 236. (d) Hirota, K.; Huang, J.; Sajiki, H.; Maki, Y. *Heterocycles* **1986**, *24*, 2293. (e) Vovk, M. V.; Dorokhov, V. I.; Bol'but, A. V. *Russ. J. Org. Chem. (Engl. Transl.)* **1997**, *33*, 1666.
(18) (a) Uher, M.; Ilavsky, D.; Foltin, J.; Skvareninova, K. *Collect. Czech. Chem. Commun.* **1981**, *46*, 3128. (b) Kavwamura, S.; Sanemishitsu, Y. *J. Org. Chem.* **1993**, *58*, 414. (c) El-Bahaie, S.; Assy, M. G.; Kadry, A. *Collect. Czech. Chem. Commun.* **1990**, *55*, 1049. (d) Iwakawa, T.; Sato, T.; Murabayashi, A. *Heterocycles* **1994**, *38*, 1015. (e) Elghandour, A. H. H.; Ramiz, M. M. M.; Elnagdi, M. H. *Synthesis* **1989**, 775. (f) Chakrabarti, S.; Srivastava, M. C.; Ila, H.; Junjappa, H. *Synlett* **2003**, 2369. (g) Hahnemann, C.; Hartman, H. *Helv. Chim. Acta* **2003**, *86*, 1949.
(19) (a) Vovk, M. V.; Bol'but, A. V.; Boiko, V. I.; Pirozhenko, V. V.; Chernega, A. N. *Mendeleev Commun.* **2001**, 198. (b) Vovk, M. V.; Bol'but, A. V.; Dorokhov, V. I.; Pyrozhenko, V. V. *Synth. Commun.* **2002**, *32*, 3749. (c) Vovk, M. V.; Bolbut, A. V.; Dorokhov, V. I. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2004**, *40*, 496. (d) Vovk, M. V.; Bol'but, A. V.; Boiko, V. I.; Pirozhenko, V. V.; Chernega, A. N.; Tolmachev, A. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2004**, *40*, 370.
(20) (a) Parrot-Lopez, H.; Delacotte, J.-M.; Renault, J.; Cros, S. *J. Heterocycl. Chem.* **1986**, *23*, 1039. (b) Al-Shaar, A. H. M.; Chambers, R. K.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2789.
(21) (a) Chkanikov, N. D.; Vershinin, V. L.; Galakov, M. V.; Kolomiets, A. F.; Fokin, A. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1989**, *38*, 113. (b) Sokolov, V. B.; Aksinenko, A. Y.; Martynov, I. V. *Russ. Chem. Bull.* **2001**, *50*, 1113.
(22) (a) Lythgoe, D. J.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1994**, *61*, 1. (b) Groziak, M. P.; Ding, H. *Acta Chim. Slov.* **2000**, *47*, 1. (c) Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2779.
(23) (a) Flaig, R.; Hartmann, H. *Monatsh. Chem.* **1997**, *128*, 1051. (b) Flaig, R.; Hartmann, H. *J. Heterocycl. Chem.* **1997**, *34*, 1291.
(24) Abe, N.; Matsuda, H.; Sugihara, Y.; Kakehi, A. *J. Heterocycl. Chem.* **1996**, *33*, 1323.
(25) Carson, D. A.; Cottam, H. B.; Deng, L. WO 00/69861, **2000**; *Chem. Abstr.* **2000**, *133*, 362771.
(26) (a) Vovk, M. V.; Lebed, P. S.; Chernega, A. N.; Pirozhenko, V. V.; Boiko, V. I.; Tsymbal, I. F. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2004**, *40*, 47. (b) Vovk, M. V.; Lebed', P. S.; Sukach, V. A.; Kornilov, M. Y. *Russ. J. Org. Chem. (Engl. Transl.)* **2003**, *39*, 1781.
(27) Vovk, M. V.; Bol'but, A. V.; Volochnyuk, D. M.; Pinchuk, A. M. *Russ. J. Org. Chem. (Engl. Transl.)* **2004**, *40*, 63.
(28) For related inverse-electron-demand Diels–Alder reactions, see: (a) Dang, Q.; Brown, B. S.; Erion, M. D. *J. Org. Chem.* **1996**, *61*, 5204. (b) Dang, Q.; Gomez-Galeno, J. E. *J. Org. Chem.* **2002**, *67*, 8703. (c) Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc.* **1999**, *121*, 5833.
(29) Fetyukhin, V. N.; Koretskii, A. S.; Gorbatenko, V. I.; Samarai, L. I. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 244.
(30) Samarai, L. I.; Boiko, V. I.; Gertsyuk, M. N. *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *26*, 640.