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Convergent procedure for the synthesis of trifluoromethyl-containing *N*-(pyridinyl-triazolyl)pyrimidin-2-amines

Helio G. Bonacorso *, Guilherme P. Bortolotto, Jussara Navarini, Liliane M.F. Porte, Carson W. Wiethan, Nilo Zanatta, Marcos A.P. Martins, Alex F.C. Flores

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil

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ABSTRACT

This study describes a simple and efficient procedure to synthesize a novel series of fourteen 4-substituted *N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines, where the 4-substituents are H, CH_3, C_6H_5, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$ and 2-Furyl; from the cyclocondensation reaction of *N*-[5-(pyridinyl)-1*H*-1,2,4-triazol-3-yl]guanidines with 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones. The reactions were carried out in ethanol under reflux for 18 h and led to 40–68% yields. *N*-(Pyridyl-triazolyl)guanidine precursors were further obtained from reactions of cyanoguanidine with nicotinic or isonicotinic acid hydrazides and the halogenated enones from trifluoroacetylation of enolethers or acetals.

1. Introduction

Fluorine-containing compounds have attracted much interest because of their unique chemical, physical and biological activities [1,2]. Also, it is well documented that the influence of the trifluoromethyl substituent on physiological activity is due mainly to the increased lipophilicity of the molecules, causing greater cell permeability [3]. In particular, fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activities with potential for applications in the fields of medicine and agriculture [4,5].

Among many useful reactions, the introduction of a trifluoromethyl group in organic molecules has received great attention in the literature [6a,6b], where methyl fluorosulphonyl difluoroacetate (MFSDA), as convenient-to-handle liquid reagent, has allowed the obtainment of a variety of CF_3-containing compounds from aryl, heteroaryl, vinyl, benzyl and allyl halides in good yields and under mild conditions [6c]. However, one of the best methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This building block relies on the trifluoroacetylation of enolethers or acetals to give, in one-step and good yields, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones which have proven to be useful starting materials for the regioselective synthesis of numerous heterocyclic compounds [6d].

Among the many well-known heterocycles, the literature has highlighted single pyridines [7], 1,2,4-triazoles [8–10], pyrimidines [11–16] and, less commonly, their linked and fused derivatives [13].On the other hand, when pyridines, triazoles and pyrimidines are linked by single bonds at the specific ring positions of bi- or tri-heterocyclic containing new molecules, interesting physiological proprieties are observed. For example, we can highlight the *N*-(1,2,4-triazolyl)pyrimidinamines. Recently, in order to expeditiously test his hypothesis, Ahmad et al. [17] designed an approach that introduced a variety of heterocycles bonded to a poly-substituted pyrimidin-2-amino skeleton. This effort, coupled with extensive in vitro and in vivo safety characterization, resulted in the identification of 7-(4-(4-fluorophenyl)-6-isopropyl-2-(methyl(1-methyl-1*H*-1,2,4-triazol-5-yl)amino)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoic acid (BMS-644950) as a novel, potent and efficacious HMGR inhibitor (treatment of hypercholesterolemia) with a potentially superior safety profile that was advanced into clinical development. However, it is not an easily synthetic process to achieve *N*-(1,2,4-triazol-3-yl)pyrimidin-2-amino compounds that contain substitution on the triazole and pyrimidine rings.The triazolylpyridine systems, which also deserve much attention, are not found free in nature, but its derivatives have many biological proprieties, mostly as insecticides and antibacterial agents [18] and, more recently, as carriers of anti-proliferative activity [19] against

* Corresponding author. Fax: +55 55 3220 8031.
E-mail address: heliogb@base.ufsm.br (H.G. Bonacorso).

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several tumor cell lines. For example, the synthesis of a 1,2,4-triazolylpyridine system, which causes cell cycle arrest in A431 cancer cell with EC_{50} values in the single digit nanomolar range, from the reaction of dimethoxyaniline with ethyl-2-chloronicotinate needed four-steps to promotes the 1,2,4-triazole ring closure [19].

Considering the importance of trifluoromethylated heterocycles, pyridines, 1,2,4-triazoles, pyridimidines, and the new and little studied triazolylpyridine and triazolylpyrimidinamine systems, the aim of this study is to report the results of cyclocondensation reactions of 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**1a–g**) with *N*-[3-(pyridinyl)-1*H*-1,2,4-triazol-5-yl]guanidines (**4**,**5**) to obtain new 4-alkyl(aryl/heteroaryl)-*N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines (**6**,**7**), as three-component aromatic heterocycles (Scheme 3). The method is convenient for the synthesis of a series of ligands in which the substituents at positions 3 and 5 of the triazole ring, as well as alkyl, aryl and heteroaryl substituents attached to the position 4 of the trifluoromethylpyrimidine can also be varied.

A review of the literature showed that the methodologies that have been used until now [17,18,20], though efficient for the synthesis of triazolylpyridines and triazolylpyrimidinamines, require drastic conditions and a long reaction time, and also involve many reactions steps with low yields. Therefore, we have sought to develop a simple method, to obtain new 4-alkyl(aryl/heteroaryl)-*N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines in a reaction with few steps where the trifluoromethyl group was introduced into an electrophilic precursor before the cyclocondensation reaction, through a conventional and efficient procedure.

2. Results and discussion

Recently, we reported the synthesis of a series of 4-(trihalomethyl)dipyrimidin-2-ylamines from the cyclocondensation reaction of 4-(trichloromethyl)-2-guanidinopyrimidine with 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro(chloro)alk-3-en-2-ones [21]. The reactions were carried out in acetonitrile under reflux for 16 h, leading to the dipyrimidin-2-ylamines in 65–90% yields. However, the 4-(trichloromethyl)-2-guanidinopyrimidine precursor was prepared from 4-(trichloromethyl)pyrimidin-2(1*H*)-one by treatment with $POCl_3$ followed by nucleophilic substitution of the 2-chloropyrimidine derivative by guanidine hydrochloride in the presence of potassium *tert*-butoxide, according to reference [22].

In the present study we employ *N*-[5-(pyridinyl)-1*H*-1,2,4-triazol-3-yl]guanidines (**4**,**5**) as new precursors, which have been easily synthesized by a two-step procedure to prepare now the interesting tricyclic amino systems (**6**,**7**) by a convergent methodology.

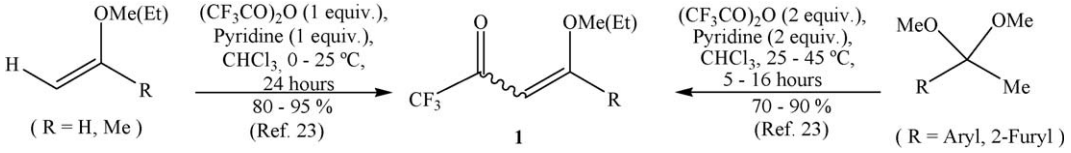
Thus, 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**1a–g**) are readily available as 1,3-dielectrophile synthetic blocks and were prepared from trifluoroacetylation reactions of commercially available enol ethers (for **1a–b**) or generated *in situ* from the respective aryl- (for **1c–f**) or heteroaryl- (for **1g**) methyl ketone acetals with trifluoroacetic anhydride, respectively, in the presence of pyridine (Scheme 1), as described in the literature [23].

In parallel, *N*-[5-(pyridinyl)-1*H*-1,2,4-triazol-3-yl]guanidines (**4**,**5**) were obtained by an intramolecular cyclization of *N*-(iso)nicotinamidobiguanides (**2**,**3**) by heating at 80 °C in a 2.5 M sodium hydroxide solution for 6 h (Scheme 2). Previously, commercially available hydrazides derived from nicotinic or isonicotinic acids and cyanoguanidine reacted to each other, under reflux for 8 h in an acidic (HCl) ethanol solution (37%) as solvent, furnishing biguanides **2** and **3** in good yields (≥80%) [24].

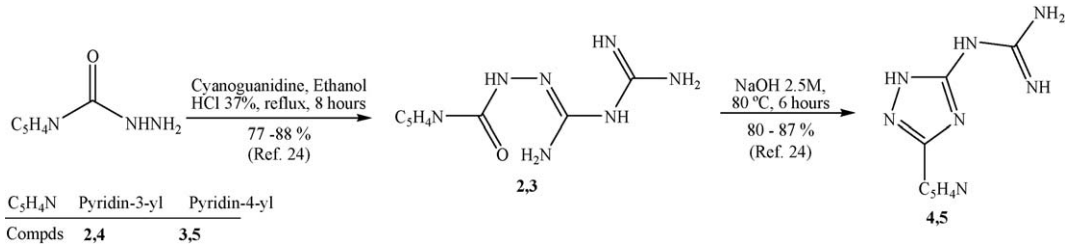
Converging, we found that alkyl-, aryl- and heteroaryl-substituted trifluoromethylated ketones **1a–g**, when treated directly with *N*-[5-(pyridinyl)-1*H*-1,2,4-triazol-3-yl]guanidines (**4**,**5**) at a molar ratio of 1:1, in anhydrous ethanol as solvent and under reflux for 18 h, produced fourteen new 2,4,6-trisubstituted-pyrimidines, as 4-alkyl(aryl/heteroaryl)-*N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluomethyl)pyrimidin-2-amines (**6**,**7**) (Scheme 3), which were easily isolated as stable white powders with melting points in the range of 274–328 °C, in an analytically pure form (elemental analysis) and in moderate yields (40–68%). It should be also mentioned that due to the weakly solubility of compounds **6** and **7** in various solvents, it was possible to perform NMR structural analysis only in DMSO-d_6.

The structures of 4-alkyl(aryl/heteroaryl)-*N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines (**6a–g**, **7a–g**) were deduced from NMR experiments and by comparison with NMR data of other pyrimidines [25] and pyridines [26] formerly synthesized in our laboratory and of 1,2,4-triazoles from literature data [27].

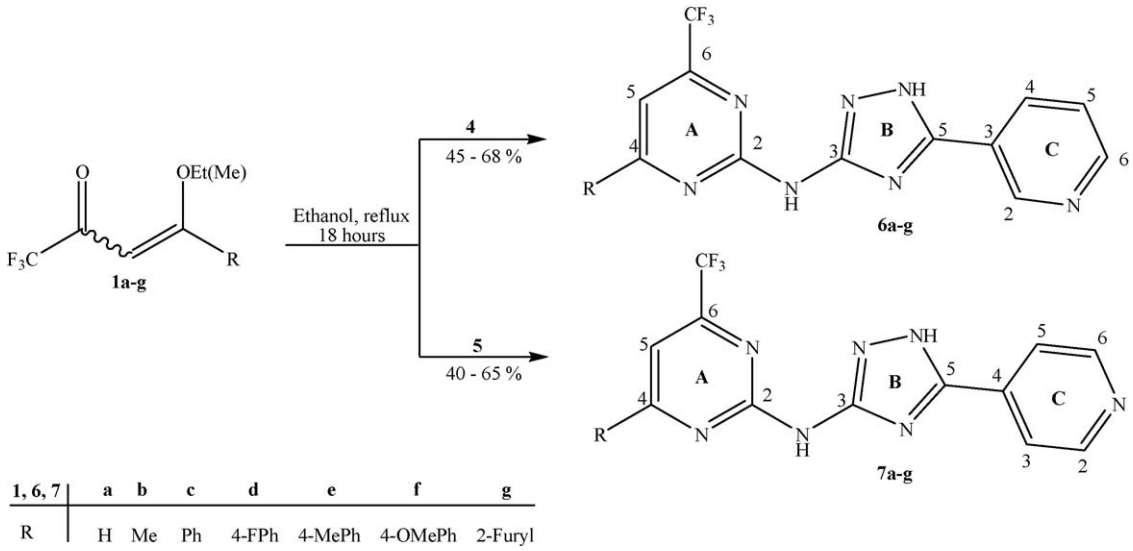
The trifluoromethylated heterocycles **6** and **7** present the typical ^{1}H chemicals shifts of pyrimidine ring (A) proton H-5 in the range of δ 7.36–8.01 ppm. The NH of the triazole ring (B) showed ^{1}H chemical shifts in the narrow range of δ 13.17–13.62 ppm. The proton of the pyrimidin-2-amino group showed ^{1}H chemical shifts



Scheme 1. Synthesis of 4-alkoxy-1,1,1-trifluoroalk-3-en-2-ones (**1a–g**).



Scheme 2. Synthesis of *N*-[5-(pyridinyl)-1*H*-1,2,4-triazol-3-yl]guanidines (**4**,**5**).



Scheme 3. Convergent synthesis of 4-alkyl(aryl/heteroaryl)-*N*-(5-pyridinyl-1*H*-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines (**6a–g**, **7a-g**).

also in a narrow range of δ 11.33–11.79 ppm. The 3-pyridinyl and the 4-pyridinyl rings (C) showed characteristic ^{1}H NMR chemical shifts according to the literature [26].

The typical ^{13}C NMR chemical shifts for the trifluoromethylated heterocycles **6** and **7** presented the pyrimidine ring carbons in the range of δ 158.3–172.9 ppm (C-2), mainly due to the electronic effect of the substituents at position 4 of the pyrimidine ring and at δ 154.3–156.2 ppm (C-6, ^2J = 35 Hz), δ 119.7–120.5 ppm (CF_3, ^1J = 275 Hz), δ 147.8–150.3 ppm (C-4) and δ 102.6–109.1 ppm (C-5). The 1,2,4-triazolyl moiety showed signals in the range of δ 153.7–158.9 ppm for C-3′ and at δ 153.7–156.5 ppm for C-5′. The 3-pyridinyl and the 4-pyridinyl rings again showed characteristic ^{13}C NMR chemical shifts according to the literature [26].

Although, the compounds **1**–**5** exhibited signals for all carbons of the molecules, surprisingly, due to the weakly solubility in DMSO-d_6, we did not observe a signal relative to quaternary C-4 (pyrimidine ring A) for compounds **6c**, **6e**, **6g** and **7d** nor for quaternary C-5 (triazole ring B) for **6c–f**, **7c–d** and **7f**. This phenomenon has been observed previously for other similar trifluoromethylated pyrimidines [28].

3. Conclusion

In conclusion, we consider this multi-step convergent reaction reported here to be a useful, simple, and convenient method, which employs commercially available reagents and mild conventional conditions to obtain novel interesting alkyl-, aryl- and heteroaryl-substituted trifluoromethylated pyrimidines bearing at position 2 a *N*-moiety, *viz*. a pyridinyl-triazolyl system derived from nicotinic and isonicotinic acids.

4. Experimental

4.1. Synthesis

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. Cyanoguanidine, nicotinic acid hydrazide, isonicotinic acid hydrazide were obtained commercially from Aldrich (ACS grade). All melting points were determined on a Reichert Thermovar or Electrothermal Mel-Temp 3.0 apparatus. The ^{1}H and ^{13}C spectra were recorded at 298 K on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.63 MHz) with digital resolution of ±0.01 ppm, in DMSO-d_6 and using TMS as internal reference. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier. Elemental analyses were performed on a PerkinElmer 2400 CHN elemental analyzer (São Paulo University-São Paulo, Brazil).

4.2. Preparation of 4-substituted N-(5-pyridinyl-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amines (6,7)

4.2.1. General procedure

A stirred solution of *N*-(5-pyridinyl-1,2,4-triazol-3-yl)guanidines (**4**,**5**) (0.5 g, 2.5 mmol) and 4-alkoxy-4-alkyl(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (**1**) (2.5 mmol) in ethanol (12 mL) was heated under reflux for 18 h. After cooling, the products were filtered, washed with cold ethanol and dried under reduced pressure.

4.2.1.1. N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (6a). White solid, yield 63%, mp 290–292 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.55 (s, H-1B), 11.79 (s, NH), 9.18 (s, H-4A), 8.94 (s, H-2C), 8.64 (s, H-6C), 8.31 (d, J = 8 Hz, H-4C), 7.49–7.53 (m, H-5C and H-5A).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.3 (C-2A), 158.2 (C-3B), 155.9 (C-5B), 154.8 (C-6A, ^2J = 35 Hz), 150.1 (C-4A), 149.4 (C-2C), 146.3 (C-6C), 132.5 (C-4C), 123.3 (C-5C), 119.9 (CF_3, ^1J = 275 Hz), 108.8 (C-5A).

GC–MS (EI, 70 eV): m/z (%) = 307 (M^+, 100), 238 (5), 148 (48), 79 (14).

Anal. Calcd. for $C_{12}H_8F_3N_7$ (307.23): C, 46.91; H, 2.62; N, 31.91%. Found: C, 46.89; H, 2.61; N, 31.91%.

4.2.1.2. 4-Methyl-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl) pyrimidin-2-amine (6b). White solid, yield 68%, mp 276–277 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.22 (s, H-1B), 11.46 (s, NH), 9.17 (s, H-2C), 8.61 (d, J = 4 Hz, H-6C), 8.29 (d, J = 8 Hz, H-4C), 7.50 (H-5C), 7.36 (s, H-5A), 2.64 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.9 (C-2A), 158.1 (C-3B), 156.2 (C-5B), 154.7 (C-6A, ^2J = 35 Hz), 150.3 (C-4A), 149.7 (C-2C), 146.6 (C-6C), 132.8 (C-4C), 127.1 (C-3C), 123.8 (C-5C), 120.5 (CF_3, ^1J = 275 Hz), 109.1 (C-5A), 23.8 (Me).

GC–MS (EI, 70 eV): *m*/*z* (%) = 321 (M^+, 95), 302 (10), 252 (5), 162 (67), 78 (10).

Anal. Calcd. for $C_{13}H_{10}F_3N_7$ (321.26): C, 48.60; H, 3.14; N, 30.52%. Found: C, 48.72; H, 3.12; N, 30.57%.

*4.2.1.3. 4-Phenyl-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**6c**). White solid, yield 57%, mp 308–310 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.26 (s, H-1B), 11.37 (s, NH), 9.19 (s, H-2C), 8.63 (d, *J* = 4 Hz, H-6C), 8.29–8.31 (m, 2H, Ph and H-4C), 7.95 (s, H-5A), 7.58–7.60 (m, 3H, Ph), 7.51 (t, *J* = 5 Hz, H-5C).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (C-2A), 158.9 (C-3B), 155.7 (C-6A, ^2J = 35 Hz), 149.4 (C-2C), 146.3 (C-6C), 134.7 (Ph), 132.4 (C-4C), 131.5 (Ph), 128.4 (Ph), 127.3 (C-3C), 123.3 (C-5C), 120.1 (CF_3, ^1J = 275 Hz), 104.7 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 383 (M^+, 90), 364 (5), 224 (81), 77 (62).

Anal. Calcd. for $C_{18}H_{12}F_3N_7$ (383.33): C, 56.40; H, 3.16; N, 25.58%. Found: C, 56.41; H, 3.15; N, 25.59%.

*4.2.1.4. 4-(4-Fluorophenyl)-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**6d**). White solid, yield 48%, mp 308–310 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.22 (s, H-1B), 11.41 (s, NH), 9.18 (s, H-2C), 8.62 (s, H-6C), 8.36–8.40 (m, 2H, Ph), 8.30 (d, *J* = 8 Hz, H-4C), 7.96 (s, H-5A), 7.56 (s, H-5C), 7.38–7.42 (m, 2H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (C-2A), 164.5 (Ph, ^1J = 250 Hz), 158.9 (C-3B), 156.0 (C-6A, ^2J = 35 Hz), 150.0 (C-2C), 149.3 (C-4A), 146.3 (C-6C), 134.3 (C-4C), 131.3 (Ph), 130.2 (Ph, ^3J = 9 Hz), 127.2 (C-3C), 124.4 (C-5C), 120.2 (CF_3, ^1J = 275 Hz), 115.6 (Ph, ^2J = 22 Hz), 105.2 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 333 (100), 247 (5), 77 (67).

Anal. Calcd. for $C_{18}H_{11}F_4N_7$ (401.32): C, 53.87; H, 2.76; N, 24.43%. Found: C, 53.61; H, 2.71; N, 24.35%.

*4.2.1.5. 4-(4-Methylphenyl)-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**6e**). White solid, yield 52%, mp 325–328 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.34 (s, H-1B), 11.56 (s, NH), 9.19 (s, H-2C), 8.64 (s, H-6C), 8.32 (d, *J* = 8 Hz, H-4C), 8.24 (s, 2H, Ph), 8.00 (s, H-5A), 7.54 (s, H-5C), 7.41 (s, 2H, Ph), 2.42 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.3 (C-2A), 158.3 (C-3B), 155.7 (C-6A, ^2J = 35 Hz), 149.5 (C-2C), 146.4 (C-6C), 142.7 (Ph), 132.4 (C-4C), 131.8 (Ph), 128.4 (Ph), 127.5 (C-3C), 123.3 (C-5C), 120.1 (CF_3, ^1J = 275 Hz), 105.6 (C-5A), 24.9 (Me).

GC–MS (EI, 70 eV): *m*/*z* (%) = 397 (M^+, 100), 238 (43), 77 (5).

Anal. Calcd. for $C_{19}H_{14}F_3N_7$ (397.36): C, 57.43; H, 3.55; N, 24.67%. Found: C, 57.40; H, 3.47; N, 24.63%.

*4.2.1.6. 4-(4-Methoxyphenyl)-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**6f**). White solid, yield 55%, mp 311–313 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.17 (s, H-1B), 11.33 (s, NH), 9.18 (s, H-2C), 8.62 (d, *J* = 4 Hz, H-6C), 8.32 (s, H-4C), 8.28 (d, *J* = 8 Hz, 2H, Ph), 7.89 (s, H-5A), 7.51 (s, H-5C), 7.12 (d, *J* = 8 Hz, 2H, Ph), 3.87 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.9 (C-2A), 162.4 (Ph), 158.8 (C-3B), 155.5 (C-6A, ^2J = 35 Hz), 150.1 (C-4A), 149.7 (C-2C), 146.9 (C-6C), 133.0 (C-4C), 130.0 (Ph), 127.6 (C-3C), 127.0 (Ph), 124.7 (C-5C), 120.1 (CF_3, ^1J = 275 Hz), 114.1 (Ph), 104.3 (C-5A), 55.2 (OMe).

GC–MS (EI, 70 eV): *m*/*z* (%) = 413 (M^+, 100), 254 (52), 77 (10).

Anal. Calcd. for $C_{19}H_{14}F_3N_7O$ (413.36): C, 55.21; H, 3.41; N, 23.72%. Found: C, 55.17; H, 3.41; N, 23.68%.

*4.2.1.7. 4-(2-Furyl)-N-(5-(pyridin-3-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl) pyrimidin-2-amine (**6g**). White solid, yield 45%, mp 281–283 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.17 (s, H-1B), 11.75 (s, NH), 9.18 (s, H-2C), 8.63 (s, H-6C), 8.31 (d, *J* = 8 Hz, H-4C), 8.12 (s, 1H, furyl), 7.87 (s, H-5A), 7.72 (s, 1H, furyl), 7.53 (s, H-5C), 6.84 (s, 1H, furyl).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.3 (C-2A), 157.5 (C-3B), 156.0 (C-5B), 155.2 (C-6A, ^2J = 35 Hz), 149.1 (C-2C), 146.8 (furyl), 146.1 (C-6C), 132.2 (C-4C), 123.1 (C-5C), 119.7 (CF_3, ^1J = 275 Hz), 115.5 (furyl), 112.5 (furyl), 102.6 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 373 (M^+, 100), 214 (76), 77 (29).

Anal. Calcd. for $C_{16}H_{10}F_3N_7O$ (373.29): C, 51.48; H, 2.70; N, 26.27%. Found: C, 50.93; H, 2.69; N, 26.30%.

*4.2.1.8. N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7a**). White solid, yield 56%, mp 296–297 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.62 (s, H-1B), 11.77 (s, NH), 8.93 (d, *J* = 4 Hz, H-4A), 8.68 (d, *J* = 5 Hz, H-2C and H-6C), 7.90 (d, *J* = 5 Hz, H-3C and H-5C), 7.48 (d, *J* = 4 Hz, H-5A).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.5 (C-2A), 158.3 (C-3B), 156.5 (C-5B), 155.0 (C-6A, ^2J = 35 Hz), 150.2 (C-4A), 150.0 (C-2C and C-6C), 138.1 (C-4C), 120.0 (CF_3, ^1J = 275 Hz), 119.6 (C-3C and C-5C), 109.1 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 307 (M^+, 100), 288 (5), 238 (5), 148 (62), 79 (10).

Anal. Calcd. for $C_{12}H_8F_3N_7$ (307.23): C, 46.91; H, 2.62; N, 31.91%. Found: C, 46.82; H, 2.70; N, 31.93%.

*4.2.1.9. 4-Methyl-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7b**). White solid, yield 65%, mp 305–306 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.33 (s, H-1B), 11.47 (s, NH), 8.67 (d, *J* = 5 Hz, H-2C and H-6C), 7.89 (d, *J* = 5 Hz, H-3C and H-6C), 7.36 (s, H-5A), 2.64 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.2 (C-2A), 157.7 (C-3B), 156.0 (C-5B), 154.3 (C-6A, ^2J = 35 Hz), 150.0 (C-4A), 149.6 (C-2C and C-6C), 137.9 (C-4C), 119.9 (CF_3, ^1J = 275 Hz), 119.2 (C-3C and C-5C), 108.7 (C-5A), 23.2 (Me).

GC–MS (EI, 70 eV): *m*/*z* (%) = 321 (M^+, 100), 302 (5), 251 (2), 162 (81), 78 (6).

Anal. Calcd. for $C_{13}H_{10}F_3N_7$ (321.26): C, 48.60; H, 3.14; N, 30.52%. Found: C, 48.57; H, 3.09; N, 30.48%.

*4.2.1.10. 4-Phenyl-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7c**). White solid, yield 58%, mp 274–275 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.54 (s, H-1B), 11.58 (s, NH), 8.71 (d, *J* = 5 Hz; H-2C and H-6C), 8.34 (d, *J* = 8 Hz; 2H, Ph), 8.00 (s, H-5A), 7.93 (d, *J* = 5 Hz, H-3C and H-5C), 7.60–7.63 (m, 3H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2 (C-2A), 158.7 (C-3B), 155.6 (C-6A, ^2J = 35 Hz), 149.7 (C-2C and C-6C), 149.4 (C-4A), 137.6 (C-4C), 134.5 (Ph), 131.6 (Ph), 128.4 (Ph), 127.3 (Ph), 120.0 (CF_3, ^1J = 275 Hz), 119.2 (C-3C and C-5C), 104.8 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 383 (M^+, 88), 224 (100), 78 (56).

Anal. Calcd. for $C_{18}H_{12}F_3N_7$ (383.33): C, 56.40; H, 3.16; N, 25.58%. Found: C, 56.42; H, 3.10; N, 25.63%.

*4.2.1.11. 4-(4-Fluorophenyl)-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7d**). White solid, yield 40%, mp 280–282 °C.* ^{1}H NMR (400 MHz,DMSO-d_6): δ = 13.54 (s, H-1B), 11.64 (s, NH), 8.70 (d, *J* = 5 Hz, H-2C and H-6C), 8.39–8.46 (m, 2H, Ph), 8.01 (s, H-5A), 7.93 (d, *J* = 5 Hz, H-3C and H-5C), 7.40–7.49 (m, 2H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4 (C-2A), 164.4 (Ph, ^1J = 250 Hz), 158.9 (C-3B), 156.0 (C-6A, ^2J = 35 Hz), 150.0 (C-2C and C-6C), 138.2 (C-4C), 131.3 (Ph), 130.2 (Ph, ^3J = 9 Hz), 120.1 (CF_3, ^1J = 275 Hz), 119.5 (C-3C and C-5C), 115.6 (Ph, ^2J = 22 Hz), 105.0 (C-5A).

GC–MS (EI, 70 eV): *m*/*z* (%) = 401 (M^+, 100), 382 (5), 242 (62), 78 (10).

Anal. Calcd. for $C_{18}H_{11}F_4N_7$ (401.32): C, 53.87; H, 2.76; N, 24.43%. Found: C, 53.85; H, 2.69; N, 24.10%.

*4.2.1.12. 4-(4-Methylphenyl)-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7e**). White solid, yield 59%, mp 312–314 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.48 (s, H-1B), 11.57 (s, NH), 8.70 (d, J = 5 Hz, H-2C and H-6C), 8.24 (d, J = 8 Hz, 2H, Ph), 8.00 (s, H-5A), 7.92 (d, J = 5 Hz, H-3C and H-5C), 7.40 (d, J = 8 Hz, 2H, Ph), 2.41 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6 + TFA): δ = 162.9 (C-6A, ^2J = 40 Hz), 158.4 (C-2A), 154.7 (C-3B), 153.7 (C-5B), 151.5 (C-4C), 147.8 (C-4), 146.3 (C-2C and C-6C), 134.5 (Ph), 131.6 (Ph), 128.2 (Ph), 119.0 (CF_3, ^1J = 285 Hz), 112.4 (C-5A), 23.8 (Me).

GC–MS (EI, 70 eV): m/z (%) = 397 (M^+, 100), 238 (86), 77 (14).

Anal. Calcd. for $C_{19}H_{14}F_3N_7$ (397.36): C, 57.43; H, 3.55; N, 24.67%. Found: C, 57.51; H, 3.61; N, 24.69%.

*4.2.1.13. 4-(4-Methoxyphenyl)-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl)pyrimidin-2-amine (**7f**). White solid, yield 51%, mp 289–290 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.48 (s, H-1B), 11.50 (s, NH), 8.71 (d, J = 5 Hz, H-2C and H-6C), 8.33 (d, J = 8 Hz; 2H, Ph), 7.97 (s, H-5A), 7.93 (d, J = 5 Hz, H-3C and H-5C), 7.14 (d, J = 8 Hz, 2H, Ph), 3.87 (s, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8 (C-2A), 162.4 (Ph), 158.8 (C-3B), 155.5 (C-6A, ^2J = 35 Hz), 150.1 (C-2C and C-6C), 149.7 (C-4A), 137.9 (C-4C), 129.5 (Ph), 127.0 (Ph), 120.4 (CF_3, ^1J = 275 Hz), 119.5 (C-3C and C-5C), 114.1 (Ph), 104.3 (C-5A), 55.2 (OMe).

GC–MS (EI, 70 eV): m/z (%) = 413 (M^+, 100), 344 (6), 254 (65), 77 (15).

Anal. Calcd. for $C_{19}H_{14}F_3N_7O$ (413.36): C, 55.21; H, 3.41; N, 23.72%. Found: C, 54.81; H, 3.45; N, 23.71%.

*4.2.1.14. 4-(2-Furyl)-N-(5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl)-6-(trifluoromethyl) pyrimidin-2-amine (**7g**). White solid, yield 47%, mp 305–307 °C.* ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.29 (s, H-1B), 11.76 (s, NH), 8.70 (d, J = 5 Hz; H-2C and H-6C), 8.12 (s, 1H, furyl), 7.92 (d, J = 5 Hz, H-3C and H-5C), 7.87 (s, H-5A), 7.71 (s, 1H, furyl), 6.84 (s, 1H, furyl).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6 (C-2A), 157.9 (C-5B), 156.4 (C-5B), 155.6 (C-6, ^2J = 35 Hz), 150.0 (C-2C and C-6C), 149.5 (C-4A), 147.4 (furyl), 138.0 (C-4C), 120.1 (CF_3, ^1J = 275 Hz), 119.5 (C-3C and C-5C), 116.1 (furyl), 113.0 (furyl), 103.1 (C-5A).

GC–MS (EI, 70 eV): m/z (%) = 373 (M^+, 75), 354 (6), 214 (100), 78 (31).

Anal. Calcd. for $C_{16}H_{10}F_3N_7O$ (373.29): C, 51.48; H, 2.70; N, 26.27%. Found: C, 51.62; H, 2.68; N, 26.29%.

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References

[1] (a) T. Hiyama, Organofluorine Compounds, Springer, Berlin, 2000;
(b) M. Hudlicky, Chemistry of Organic Fluorine Compounds, 2nd ed., Ellis Harwood, Chichester, UK, 1976.
[2] (a) J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, NY, 1991;
(b) J. Prabhakaran, M.D. Underwood, R.V. Parsey, V. Arango, V.J. Majo, N.R. Simpson, R.V. Heertum, J.J. Mann, J.S.D. Kumar, Bioorg. Med. Chem. 15 (2007) 1802.
[3] (a) R. Filler, Y. Kobayashi, Biomedicinal Aspects of Fluorine Chemistry, Kodansha & Elsevier Biomedical, Tokyo, 1982;
(b) R. Filler, Y. Kobayashi, L.M. Yagupolskii, Organofluorine Compounds in Medical Chemistry and Biomedical Application, Elsevier, Amsterdam, 1993.
[4] R. Filler, R.E. Banks, Organofluorine and Their Industrial Applications, Ellis Horwood, Chichester, UK, 1979.
[5] (a) M. Frezza, D. Balestrino, L. Soulére, S. Reverchon, Y. Queneau, C. Forestier, A. Doutheau, Eur. J. Org. Chem. (2006) 4731;
(b) F. Leroux, O. Lefebvre, M. Schlosser, Eur. J. Org. Chem. (2006) 3147;
(c) J.T. Welch, Tetrahedron 43 (1987) 3123;
(d) S. Buscemi, A. Pace, A. Piccionello, G. Macaluso, N. Vivona, J. Org. Chem. 70 (2005) 3288.
[6] (a) G.K.S. Prakash, A.K. Yudin, Chem. Rev. 97 (1997) 757;
(b) M.A. McClinton, D.A. McClinton, Tetrahedron 48 (32) (1992) 6555;
(c) W.K.J. Hagmann, J. Med. Chem. 51 (2008) 4359;
(d) S.V. Druzhinin, E.S. Balenkova, V.G. Nenajdenko, Tetrahedron 63 (2007) 7753.
[7] P.Y. Park, M.J. Lee, J.N. Kim, Tetrahedron Lett. 46 (2005) 8799.
[8] C.T. King, P.D. Rogers, J.D. Claery, S.W. Chapman, Clin. Infect. Dis. 27 (1998) 1151.
[9] L. Jeu, F.J. Piacenti, A.G. Lyakhovetskiy, H.B. Fung, Clin. Ther. 25 (2003) 1321.
[10] P. Kale, L.B. Johnson, Drugs Today 41 (2005) 91.
[11] A.E.A. Porter, in: P.G. Sammes (Ed.), Comprehensive Organic Chemistry, vol. 4, Pergamon Press, 1979, pp. 85–141.
[12] S.H. Pine, Organic Chemistry, 3rd ed., McGraw-Hill International Editions, 1987, p. 849.
[13] A.R. Katritzky, C.W. Rees, E.F.V. Scriven, 1st ed., Comprehensive Heterocyclic Chemistry II, vols. 2–8, Pergamon Press, Oxford, 1996.
[14] R.M. Acheson, An Introduction to the Chemistry of Heterocyclic Compounds, 3rd ed., John Wiley & Sons, 1976, pp. 392–407.
[15] D.L. Ladd, J. Heterocycl. Chem. 19 (1982) 917.
[16] D.J. Brown, in: A. Weissberger (Ed.), The Chemistry of Heterocyclic Compounds, vol. 16, Wiley Interscience Publishers, New York, 1962, Chapter IX, 306.
[17] S. Ahmad, C.S. Madsen, P.D. Stein, E. Janovitz, C. Huang, K. Ngu, S. Bisaha, L.J. Kennedy, B.C. Chen, R. Zhao, D. Sitkoff, H. Monshizadegan, X. Yin, C.S. Ryan, R. Zhang, M. Giancarli, E. Bird, M. Chang, X. Chen, R. Setters, D. Search, S. Zhuang, V. Nguyen-Tran, C.A. Cuff, T. Harrity, C.J. Darienzo, T. Li, R.A. Reeves, M.A. Blanar, J.C. Barrich, R. Zahler, J.A. Robl, J. Med. Chem. 51 (2008) 2722.
[18] K.Y. Chang, S.H. Kwon, G. Nam, J.H. Seo, S.H. Kim, K.I. Choi, J.H. Kim, D.C. Ha, J. Antibiot. 54 (2001) 460.
[19] X. Ouyang, X. Chen, E.L. Piatnitski, A.S. Kiselyov, H.Y. He, Y. Mao, V. Pattaropong, Y. Yu, K.H. Kim, J. Kincaid, L. Smith, W.C. Wong, S.P. Lee, D.L. Milligan, A. Malikzay, J. Fleming, J. Gerlak, D. Deevi, J.F. Doody, H.H. Chiang, S.N. Patel, Y. Wang, R.L. Rolser, P. Kussie, M. Labelle, M.C. Tuma, Bioorg. Med. Chem. Lett. 15 (2005) 5154.
[20] C.W. Thornber, J.M. Farell, D.S. Clarke, Synthesis (1983) 222.
[21] N. Zanatta, E.C.S. Lopes, L. Fantinel, H.G. Bonacorso, M.A.P. Martins, J. Heterocycl. Chem. 39 (2002) 943.
[22] N. Zanatta, I.L. Pacholski, D. Faoro, H.G. Bonacorso, M.A.P. Martins, Synth. Commun. 31 (2001) 2855.
[23] (a) M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda, S. Matsuo, Chem. Lett. (1976) 499;
(b) F. Effenberger, K.H. Schonwalder, Chem. Ber. 117 (1984) 3270;
(c) Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi, T. Nishigaki, Synthesis (1986) 340;
(d) M. Hojo, R. Masuda, E. Okada, Tetrahedron Lett. (1986) 1013;
(e) F. Effenberger, R. Maier, K.H. Schonwalder, T. Ziegler, Chem. Ber. 115 (1982) 2766;
(f) M. Hojo, R. Masuda, S. Sakaguchi, M. Takagawa, Synthesis (1986) 1016;
(g) A. Colla, M.A.P. Martins, G. Clar, S. Krimmer, P. Fischer, Synthesis (1991) 483;
(h) M.A.P. Martins, G.M. Siqueira, A.F.C. Flores, G. Clar, N. Zanatta, Quim. Nova 17 (1994) 24;
(i) H.G. Bonacorso, S.R.T. Bittencourt, M.A.P. Martins, R.V. Lourega, N. Zanatta, A.F.C. Flores, J. Fluorine Chem. 99 (1999) 177;
(j) A.F.C. Flores, S. Brondani, N. Zanatta, A. Rosa, M.A.P. Martins, Tetrahedron Lett. 43 (2002) 8701.
[24] (a) P. Mamalis, J. Green, D. McHale, J. Chem. Soc. (1960) 229;
(b) W. Ogemann, D. Artini, L. Canavesi, G. Tosolini, Chem. Ber. 96 (1963) 2909;
(c) A.V. Dolzhenko, B.J. Tan, A.V. Dolzhenko, G.N.C. Chiu, W.K. Chui, J. Fluorine Chem. 129 (2008) 429.
[25] (a) H.G. Bonacorso, I.S. Lopes, A.D. Wastowski, N. Zanatta, M.A.P. Martins, J. Fluorine Chem. 120 (2003) 29;
(b) N. Zanatta, L. Fantinel, R.V. Lourega, H.G. Bonacorso, M.A.P. Martins, Synthesis (2008) 358;
(c) N. Zanatta, S.S. Amaral, J.M. dos Santos, D.L. de Mello, L. da S. Fernandes, H.G. Bonacorso, M.A.P. Martins, A.D. Andricopulo, D.M. Borchhardt, Bioorg. Med. Chem. 16 (2008) 10236;
(d) N. Zanatta, D. Faoro, L. da S. Fernandes, P.B. Brondani, D.C. Flores, A.F.C. Flores, H.G. Bonacorso, M.A.P. Martins, Eur. J. Org. Chem. (2008) 5835.
[26] (a) H.G. Bonacorso, G.R. Paim, C.Z. Guerra, R.C. Sehnem, C.A. Cechinel, L.M.F. Porte, M.A.P. Martins, N. Zanatta, J. Braz. Chem. Soc. 20 (2009) 509;
(b) H.G. Bonacorso, R.V. Lourega, E.D. Deon, N. Zanatta, M.A.P. Martins, Tetrahedron Lett. 48 (2007) 4835;
(c) H.G. Bonacorso, R.V. Lourega, F.J. Righ, E.D. Deon, N. Zanatta, M.A.P. Martins, J. Heterocycl. Chem. 45 (2008) 1679.
[27] (a) M. Kammoun, A. Chihi, B. Hajjem, M. Bellassoued, Synth. Commun. 38 (2008) 148;
(b) X.-W. Sun, P.-F. Xu, Z.-Y. Zhang, Magn. Reson. Chem. 36 (1998) 459;
(c) A.M. Orendt, J. Michl, J. Reiter, Magn. Reson. Chem. 27 (1989) 1.
[28] H.G. Bonacorso, D.B. Martins, M.A.P. Martins, N. Zanatta, A.F.C. Flores, Synthesis (2005) 809.