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Expanding the chemical space of 3(5)-functionalized 1,2,4-triazoles

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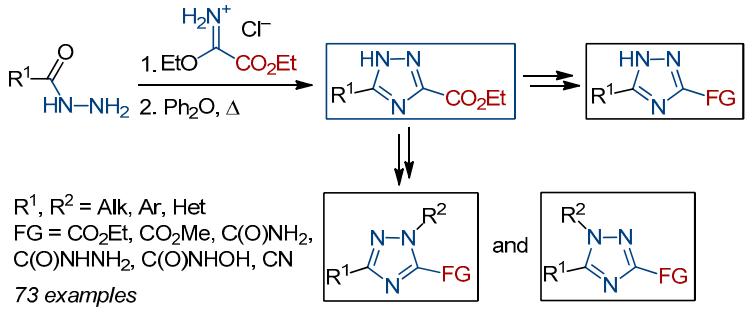


An efficient approach to the gram-scale synthesis of 3(5)-substituted, 1,3- and 1,5-disubstituted 1,2,4-triazole-derived building blocks is described. The key synthetic precursors – 1,2,4-triazole-3(5)-carboxylates (20 examples, 35–89% yield) were prepared from readily available acyl hydrazides and ethyl 2-ethoxy-2-iminoacetate hydrochloride. Further transformations were performed following the convergent synthetic strategy and allowed the preparation of 1,3- and 1,5-disubstituted 1,2,4-triazole-derived esters (16 examples, 25–75% yield), 3(5)-substituted, 1,3- and 1,5-disubstituted carboxylate salts (18 examples, 78–93% yield), amides (5 examples, 82–93% yield), nitriles (5 examples, 30–85% yield), hydrazides (6 examples, 84–89% yield), and hydroxamic acids (3 examples, 73–78% yield). Considering wide applications of the 1,2,4-triazole motif in medicinal chemistry, these compounds are valuable building blocks for lead-oriented synthesis; they have also great potential for coordination chemistry.

Keywords: acyl hydrazides, 1,2,4-triazoles, alkylation, cyclization, functional groups, regioisomers.

1,2,4-Triazole motif has been embedded into more than 30 approved and marketed medicines as well as more than 100 investigational and experimental drugs.[1] Among them, ribavirin (Fig. 1) – an antiviral medication used to treat respiratory syncytial virus infection, hepatitis C, and many other viral diseases.[2–4] Being one of the safest and most effective remedies needed in a health system, ribavirin has been included into the World Health Organization's List of Essential Medicines.[5] Moreover, recent studies confirmed the successful application of ribavirin as a cure of COVID-19.[6–8] Voriconazole is another example of choice used to treat serious fungal infections.[9–13]

On the other hand, 1,2,4-triazoles (especially bearing additional functional groups) are very promising ligands for coordination chemistry with multiple coordination modes possible.[14,15] In this view, they were used to obtain coordination polymers,[16] blue-emitting organic light-emitting diodes,[17] chemodynamic therapy agents against cancer cells,[18] spin crossover nanoparticles,[19] and other (potentially) useful materials.

Taking into account importance of the 1,2,4-triazole scaffold in drug discovery[20–29] and materials science, as well as in line with our ongoing efforts toward the synthesis of 1,2,4-triazole-derived building blocks,[30–32] we have aimed at the expanding the chemical space of 5-functionalized 1,2,4-triazoles with a special focus on (but not limiting by) low molecular weight compounds bearing

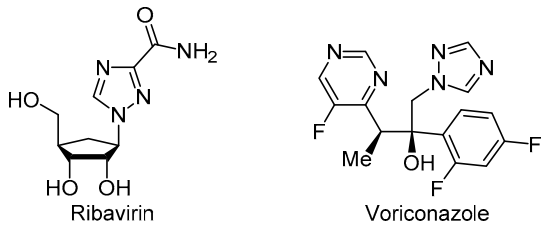
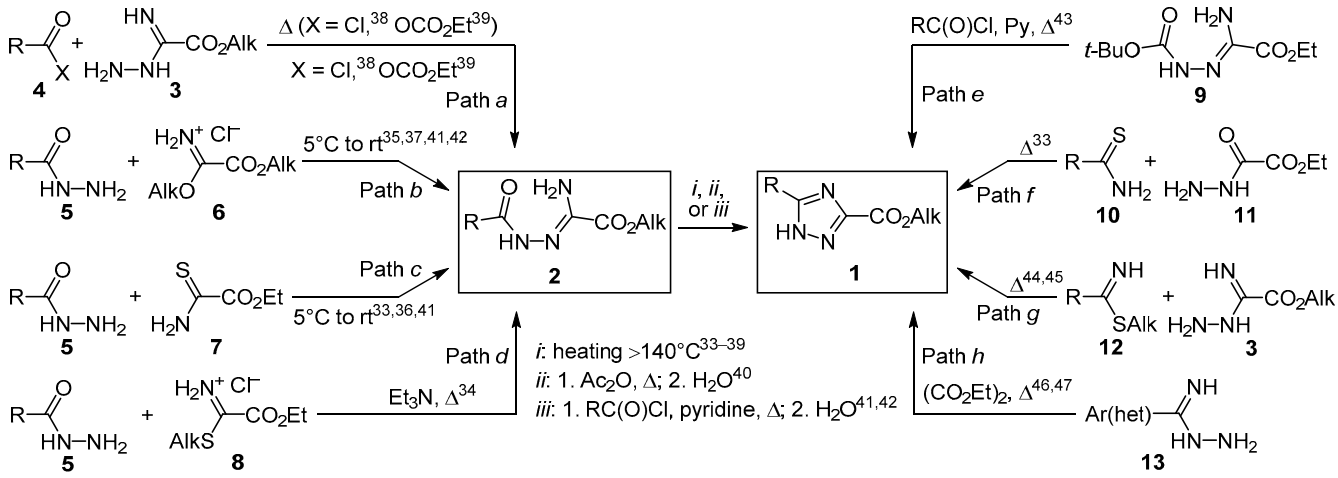


Figure 1. The chemical structures of ribavirin and voriconazole.

Scheme 1. The literature methods for the synthesis of 1,2,4-triazole-3(5)-carboxylates **1**



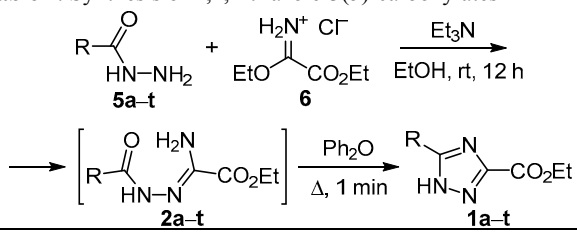
aliphatic substituents. Alkyl 1,2,4-triazole-5-carboxylates **1** were selected as the key intermediates to obtain the corresponding building blocks (i.e. carboxylates, nitriles, hydrazides, and hydroxamic acids).

Among the methods developed to date for the synthesis of alkyl 1,2,4-triazole-3(5)-carboxylates **1**, the cyclization of β-acylamidrazones **2** is the most common one. Primarily, it proceeds *via* thermal activation (Scheme 1, *i*)[33–39] or under either anhydride- (*ii*)[40] or acyl chloride-promoted (*iii*)[41,42]conditions. In its turn, the main synthetic precursor **2** can be obtained in several ways such as acylation with chlorides **4** of alkyl 2-hydrazinyl-2-iminoacetates **3** (Scheme 1, path *a*)[38,39] and condensation of acyl hydrazides **5** with alkyl 2-alkoxy-2-iminoacetates **6** (path *b*),[35,37,41,42] ethyl 2-amino-2-thioxoacetate (**7**) (path *c*),[33,36,41] or alkyl 2-(alkylthio)-2-iminoacetates **8** (path *d*).[34] Apart from that, 3-substituted alkyl 1,2,4-triazole-5-carboxylates **1** could be synthesized by reaction of acid chlorides with ethyl β-*N*-Boc-oxalamidrazone **9** (path *e*),[43] thermal induced condensation of thioamides **10** with ethyl 2-hydrazinyl-2-oxoacetate (**11**) (path *f*),[33] alkyl imidothioates **12** with alkyl 2-hydrazinyl-2-iminoacetates **3** (path *g*),[44,45] as well as diethyl oxalate with carboximidhydrazides **13** (path *h*).[46,47]

We commenced our study from the synthesis of a range of 3(5)-substituted ethyl 1,2,4-triazole-3(5)-carboxylates **1** following a previously described method.[48] In particular, the reaction of readily available hydrazides **5** with ethyl 2-ethoxy-2-iminoacetate hydrochloride (**6**)[35,49] under base-mediated conditions afforded the corresponding ethyl 2-(2-acylhydrazono)-2-aminoacetates **2**. Further thermal induced intramolecular condensation of acetates **2** in Ph_2O media gave the desired ethyl triazolecarboxylates **1a**–**t** (20 examples) in 35–89% overall yield (Table 1).

The use of Ph_2O as the solvent at the cyclization step has several advantages such as: a) completeness of the cyclization reaction; b) prevention of the side reactions; c) decreasing reaction time up to 1 min (the original methods require up to 4 h) and simplification of the work-up procedure; d) reusability of the solvent. In particular, unlike solvent-free procedures (performed by melting at 160–215°C)[33–35,37] and those with refluxing diglyme (bp 162°C)[36] or xylenes (bp 139°C)[38,39] as the media, the use of Ph_2O (bp 259°C) allows achieving better yields (by an average of 10%). The work-up procedure included simple filtration of warm (40°C) reaction mixture followed by washing the precipitate with hexane and subsequent recrystallization of thus obtained

Table 1. Synthesis of 1,2,4-triazole-3(5)-carboxylates **1**



Entry	Starting material	Product*	R	Yield, %
1	**5a**	**1a**[33,35,36,48]	H	89
2	**5b**	**1b**[33,34,37,41,44,48]	Me	79
3	**5c**	**1c**[41,42]	Et	76
4	**5d**	**1d**[41]	*n*-Pr	74
5	**5e**	**1e**[41]	*t*-Bu	78
6	**5f**	**1f**	$MeOCH_2$	85
7	**5g**	**1g**[50]	$NCCH_2$	63
8	**5h**	**1h**[41]	Cyclopropyl	60
9	**5i**	**1i**[33,37,41,48]	Ph	86
10	**5j**	**1j**	Bn	81
11	**5k**	**1k**	$PhOCH_2$	83
12	**5l**	**1l**	3-MeC_6H_4	76
13	**5m**	**1m**	4-MeC_6H_4	81
14	**5n**	**1n**	2-$MeOC_6H_4$	35
15	**5o**	**1o**	3-CNC_6H_4	71
16	**5p**	**1p**	3-BrC_6H_4	83
17	**5q**	**1q**[46]	4-ClC_6H_4	85
18	**5r**	**1r**[43,47,48]	Pyridin-2-yl	82
19	**5s**	**1s**[43,48]	Pyridin-3-yl	68
20	**5t**	**1t**[43,48]	Pyridin-4-yl	77

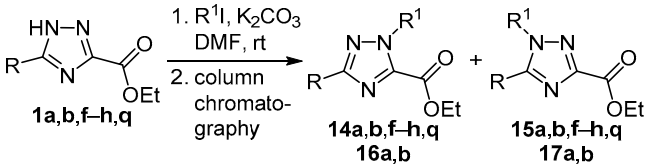
* If the references are provided, the product was described previously in the cited papers.

target product. The scope of the given method should be readily adaptable to the substrates of type **2** with a variety of other substituents. Finally, following the green chemistry principles, Ph_2O can be recovered *via* ordinary evaporation of the filtrate on a rotary evaporator and reused.

With compounds **1** in hands, we proceeded to evaluation of their chemical properties, concurrently expanding the library of 3(5)-functionalized 1,2,4-triazoles. The alkylation study was conducted first. As expected for the 1,2,4-triazole core, nearly equimolar mixtures of products **14** and **15** were obtained after reaction of compound **1** with MeI and K_2CO_3 in DMF media (Table 2, entries 1–6). The reaction was more selective with triazole **1q** (R = 4-ClC_6H_4) leading to product **14q** predominantly (ratio **14q**:**15q** = *ca.* 3:1), which can be addressed to a steric factor of the aryl substituent. Further chromatographic separation of these mixtures allowed the isolation of pure regioisomers **14** and **15**. Their structures were established by NOE, ^1H–^{13}C, and ^1H–^{15}N HMBC experiments (Fig. 2). An additional criterion was ^1H NMR shifts of the N–CH_3 protons that were by *ca.* 0.1–0.2 ppm higher for isomers **14** as compared to isomers **15**.

Considering the ratio of products **14** and **15** in the reaction mixture and their isolated yields, we also studied the alkylation reaction of triazole **1b** with higher alkyl halides (i.e. EtI and *i*-PrI, Table 2, entries 7 and 8). It turned out that with EtI, nearly 1:1 mixture of regioisomers **16a** and **17a** was obtained, whereas in the case of sterically demanding *i*-PrI, product **16b** was formed preferably (ratio **16b**:**17b** = *ca.* 3:1). This result demonstrates importance of the electronic effect of the CO_2Et moiety for the regioselectivity of the alkylation reaction with alkyl halides of lowered reactivity.

Table 2. Alkylation of 1,2,4-triazole-3(5)-carboxylates **1**



Entry	Starting material	R	R^1	Products (yield, %)	Ratio*
1	**1a**	H	Me	**14a** (35), **15a** (43)	45:55
2	**1b**	Me	Me	**14b** (40), **15b** (48)	44:56
3	**1f**	$MeOCH_2$	Me	**14f** (41), **15f** (44)	1:1
4	**1g**	$NCCH_2$	Me	**14g** (42), **15g** (39)	1:1
5	**1h**	Cyclopropyl	Me	**14h** (38), **15h** (41)	1:1
6	**1q**	4-ClC_6H_4	Me	**14q** (60), **15q** (15)	3:1
7	**1b**	Me	Et	**16a** (42), **17a** (48)	1:1
8	**1b**	Me	*i*-Pr	**16b** (68), **17b** (20)	3:1

* Product ratio (**14**:**15** or **16**:**17**) in the crude mixture according to ^1H NMR spectra.

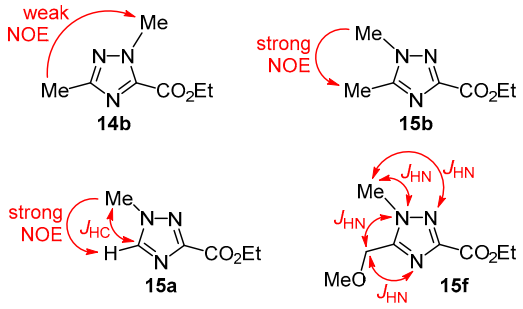
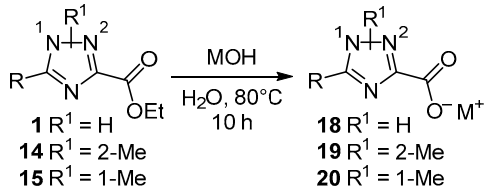


Figure 2. Important correlations observed for compounds **14b** and **15a**,**b**,**f**.

Saponification of esters **1**, **14**, and **15** proceeded smoothly with aqueous alkali at 80°C, but further isolation of the corresponding carboxylic acids was complicated by the partial decarboxylation. Therefore, the corresponding hydrolysis products were isolated as stable sodium or lithium salts **18**, **19**, and **20** in 80–93% yield (Table 3).

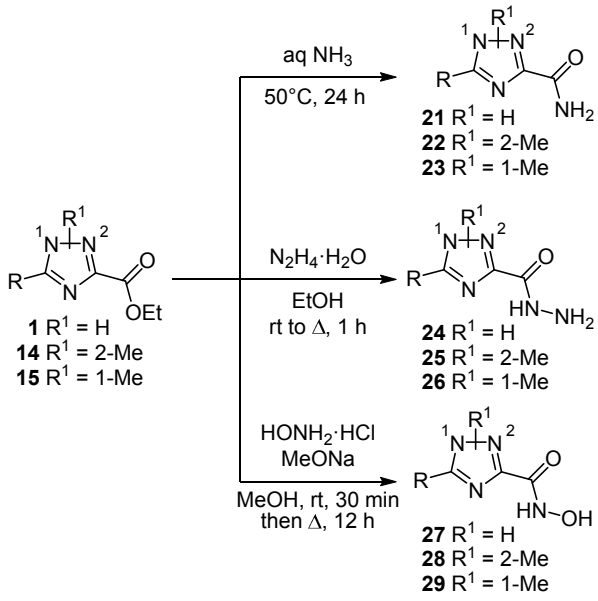
Esters **1**, **14**, and **15** also readily reacted with aqueous ammonia at 50°C (Table 4). In this way, the synthesis of *N*-1(2)-unsubstituted amides **21** as well as *N*-methylated amides **22** and **23** was achieved in 82–95% yield (Table 4, entries 1–5).

Table 3. Hydrolysis of esters **1**, **14**, and **15**



Entry	Starting material	Product	R	M	Yield, %
1	**1b**	**18b**	Me	Li	91
2	**1c**	**18c**	Et	Na	87
3	**1e**	**18e**	*t*-Bu	Na	90
4	**1f**	**18f**	$MeOCH_2$	Na	91
5	**1h**	**18h**	Cyclopropyl	Na	85
6	**1i**	**18i**	Ph	Na	92
7	**1j**	**18j**	Bn	Na	93
8	**1k**	**18k**	$PhOCH_2$	Na	90
9	**1n**	**18n**	2-$MeOC_6H_4$	Na	85
10	**1r**	**18r**	Pyridin-2-yl	Na	87
11	**14a**	**19a**	H	Na	87
12	**14b**	**19b**	Me	Li	88
13	**14f**	**19f**	$MeOCH_2$	Na	80
14	**14h**	**19h**	Cyclopropyl	Na	87
15	**15a**	**20a**	H	Na	90
16	**15b**	**20b**	Me	Li	91
17	**15f**	**20f**	$MeOCH_2$	Na	87
18	**15h**	**20h**	Cyclopropyl	Na	85

Table 4. Reaction of esters **1**, **14**, and **15** with N-nucleophiles

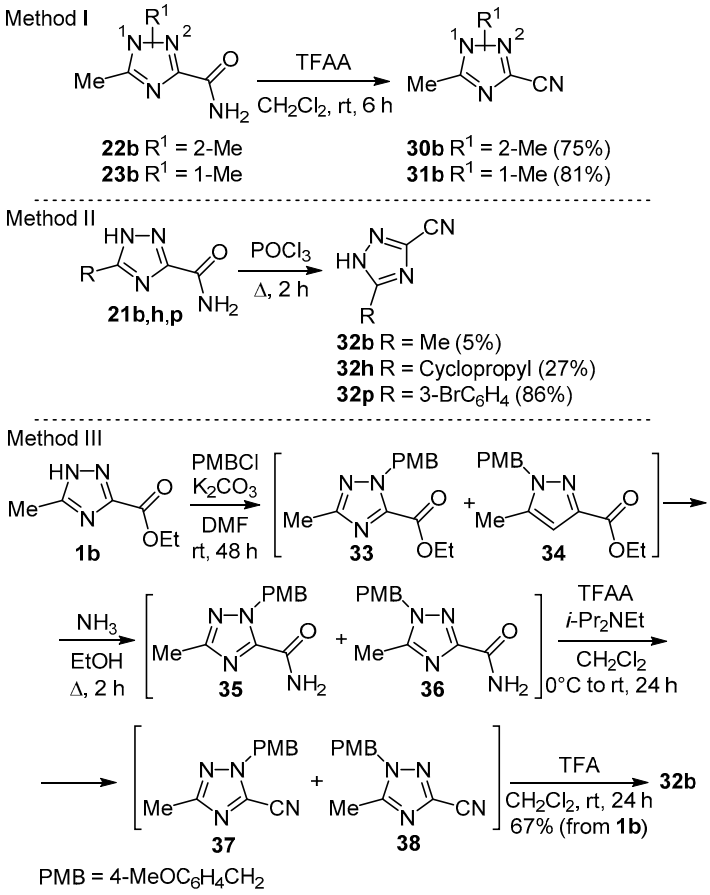


Entry	Starting material	Product	R	Yield, %
1	**1b**	**21b**[45]	Me	85
2	**1h**	**21h**	Cyclopropyl	82
3	**1p**	**21p**	3-BrC_6H_4	93
4	**14b**	**22b**	Me	90
5	**15b**	**23b**	Me	95
6	**1a**	**24a**	H	87
7	**1b**	**24b**	Me	85
8	**14a**	**25a**	H	89
9	**14b**	**25b**	Me	84
10	**15a**	**26a**	H	88
11	**15b**	**26b**	Me	85
12	**1b**	**27b**	Me	73
13	**14b**	**28b**	Me	78
14	**15b**	**29b**	Me	74

The reaction of compounds **1**, **14**, and **15** with hydrazine hydrate and hydroxylamine was also carried out in a straightforward manner in refluxing alcohol media (Table 4, entries 6–14). The corresponding hydrazides **24**–**26** and hydroxamic acids **27**–**29** were isolated in good yields (84–89% and 73–78%, respectively).

Finally, the conversion of amides **21**, **22**, and **23** into the corresponding nitriles required some optimization studies. While *N*-methylated amides **22b** and **23b** were successively transformed into the corresponding nitriles **30b** and **31b** under TFAA-promoted conditions[51–55] at 0–5°C (Scheme 2, method I), this method appeared to be inapplicable for *N*-1-unsubstituted triazole-derived amides **21** and did not afford the desired product. Another procedure, $POCl_3$-mediated dehydration,[56–60] worked well only for *N*-unsubstituted substrate **21p** possessing aromatic substituent at the C-3 position; the corresponding nitrile **32p** was obtained in

Scheme 2. Synthesis of 1,2,4-triazole-derived carbonitriles **30b**, **31b**, and **32b**,**h**,**p**



86% yield (Scheme 2, method II). However, this method was inefficient for amides with C-3-aliphatic substituent. Specifically, when amides **21b**,**h** were subjected to these reaction conditions, they were converted into the corresponding nitriles **32b**,**h** in 5 and 27% isolated yields, respectively.

Eventually, this was circumvented by one more alternative synthetic approach. In this way, *N*-unsubstituted ester **1b** was treated with 4-methoxybenzyl chloride and K_2CO_3 in DMF media in order to install the PMB protecting group at the heterocyclic core and prevent side reactions at the dehydration step (Scheme 2, method III). The resulting crude mixture of *N*-protected regioisomers **33** and **34** was refluxed in ethanolic ammonia that gave a mixture of amides **35** and **36**. Subsequent TFAA-mediated dehydratation provided a mixture of PMB-protected nitriles **37** and **38**. Ultimately, TFA-promoted cleavage of PMB protecting group afforded the target *N*-unsubstituted nitrile **32b** in 67% overall yield.

In summary, an efficient approach to the gram-scale preparation of 3(5)-functionalized 1,2,4-triazoles is described. Particularly, a set of 3(5)-substituted, 1,3- and 1,5-disubstituted 1,2,4-triazole-derived esters, carboxylate salts, amides, nitriles, hydrazides, and hydroxamic acids (73 examples, 60 novel compounds) were prepared through the convergent synthetic strategy starting from readily available acyl hydrazides and ethyl 2-ethoxy-2-iminoacetate hydro-

chloride. Besides, the use of diphenyl ether as the solvent improved the outcome of the cyclization reaction of the key intermediate – ethyl 2-(2-acylhydrazono)-2-aminoacetates that eventually afforded 3(5)-substituted ethyl 1,2,4-triazole-3(5)-carboxylates in higher yields (by an average of 10%). Owing to low molecular weight and high hydrophilicity, the described compounds can be considered as building blocks for lead-oriented synthesis. They also represent an interest as ligands for coordination chemistry.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Agilent ProPulse 600 (600 and 151 MHz, respectively), Bruker 170 Avance 500 (500 and 126 MHz, respectively), or Varian Unity Plus 400 (400 and 101 MHz, respectively) spectrometers, using DMSO-d_6, $CDCl_3$, D_2O or TFA-*d* as solvents. TMS was used as internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)) and an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). High-resolution mass spectra were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Elemental analysis was performed on a CHNOS elementary Vario MICRO cube analyzer. All melting points were measured on a MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Compounds **14**–**17** were separated by column chromatography on silica gel (particle size 40–63 μm) using hexanes–*t*-BuOMe, 7:3 as eluent, MeCN, or CH_2Cl_2–EtOAc, gradient 0–100% as eluent.

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of moisture. All the starting materials were obtained from Enamine Ltd. and UORSY. The solvents were purified according to the standard procedures.[61]

Synthesis of ethyl 1,2,4-triazole-3-carboxylates 1a–t (General method). Acyl hydrazide **5a**–**t** (25.0 mmol) was added to a solution of ethyl 2-ethoxy-2-iminoacetate hydrochloride (**6**) (4.50 g, 25.0 mmol) and Et_3N (4.20 ml, 3.07 g, 30.3 mmol) in anhydrous EtOH (50 ml), and obtained solution was stirred at room temperature for 12 h. The formed ethyl 2-(2-acylhydrazono)-2-aminoacetate intermediate **2a**–**t** was filtered, washed with EtOH (3×20 ml), and dispersed (except for acetate **2a**) in Ph_2O (50 ml). The resulting mixture was brought to boil and refluxed for 1 min. After the temperature of the reaction mixture had dropped to 40°C, it was filtered. Thus obtained crude product was washed with hexane (3×50 ml) and recrystallized from PhMe to give the title compound **1b**–**t**. Compound **1a** was prepared by solvent-free melting of acetate **2a** at 150°C for 2 min.

Ethyl 1*H*-1,2,4-triazole-3-carboxylate (1a) was synthesized from compound **5a** (1.5 g). Yield 3.14 g (89%), white powder, mp 176–177°C (mp 169–171°C (absolute EtOH)[35]). Physical and spectral data were in accordance with the previously reported.[33,35,36,48]

Ethyl 5-methyl-1*H*-1,2,4-triazole-3-carboxylate (1b) was synthesized from compound **5b** (1.85 g). Yield 3.06 g (79%), colorless crystals, mp 187–189°C (mp 186°C[41]). Physical and spectral data were in accordance with the previously reported.[33,34,37,41,44,48]

Ethyl 5-ethyl-1*H*-1,2,4-triazole-3-carboxylate (1c) was synthesized from compound **5c** (2.2 g). Yield 3.21 g (76%), white powder, mp 107–108°C (mp 103–105°C[41]). Physical and spectral data were in accordance with the previously reported.[41,42]

Ethyl 5-propyl-1*H*-1,2,4-triazole-3-carboxylate (1d) was synthesized from compound **5d** (2.55 g). Yield 3.39 g (74%), white powder, mp 125–127°C (mp 128–130°C[41]). Physical and spectral data were in accordance with the previously reported.[41]

Ethyl 5-(*tert*-butyl)-1*H*-1,2,4-triazole-3-carboxylate (1e) was synthesized from compound **5e** (2.9 g). Yield 3.84 g (78%), white powder, mp 193–195°C (mp 184–186°C[41]). Physical and spectral data were in accordance with the previously reported.[41]

Ethyl 5-(methoxymethyl)-1*H*-1,2,4-triazole-3-carboxylate (1f) was synthesized from compound **5f** (2.6 g). Yield 3.94 g (85%), colorless crystals, mp 84–86°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.71 (1H, br. s, NH); 4.56 (2H, s, OCH_2); 4.31 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.33 (3H, s, OCH_3); 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 160.0; 155.3; 154.5; 65.5; 61.4; 58.6; 14.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 184 $[M–H]^-$ (100). Found, *m*/*z*: 186.0873 $[M+H]^+$. $C_7H_{12}N_3O_3$. Calculated, *m*/*z*: 186.0879.

Ethyl 5-(cyanomethyl)-1*H*-1,2,4-triazole-3-carboxylate (1g) was synthesized from compound **5g** (2.48 g). Yield 2.84 g (63%), yellow powder, mp 111–112°C (mp 111–112°C[50]). Physical and spectral data were in accordance with the previously reported.[50]

Ethyl 5-cyclopropyl-1*H*-1,2,4-triazole-3-carboxylate (1h) was synthesized from compound **5h** (2.5 g). Yield 2.72 g (60%), yellow powder, mp 130–131°C (mp 110–112°C[41]). Physical and spectral data were in accordance with the previously reported.[41]

Ethyl 5-phenyl-1*H*-1,2,4-triazole-3-carboxylate (1i) was synthesized from compound **5i** (3.40 g). Yield 4.67 g (86%), white powder, mp 164–165°C (mp 161–163°C[41]). Physical and spectral data were in accordance with the previously reported.[33,37,41,48]

Ethyl 5-benzyl-1*H*-1,2,4-triazole-3-carboxylate (1j) was synthesized from compound **5j** (3.75 g). Yield 4.68 g (81%), white powder, mp 150–152°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.44 (1H, br. s, NH); 7.37–7.19 (5H, m, H Ph); 4.29 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.13 (2H, s, $C\underline{H}_2Ph$); 1.28 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 160.4; 157.2; 154.7; 136.9 (2C); 129.1 (3C); 127.3 (2C); 61.2; 32.3; 14.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 230 $[M–H]^-$ (100). Found, %: C 62.38; H 5.99; N 17.79. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.33; H 5.67; N 18.17.

Ethyl 5-(phenoxymethyl)-1*H*-1,2,4-triazole-3-carboxylate (1k) was synthesized from compound **5k** (4.15 g). Yield 5.13 g (83%), white powder, mp 122–124°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.88 (1H, br. s, NH); 7.30 (2H, t, *J* = 7.7, H-3,5 Ph); 7.03 (2H,

d, *J* = 7.7, H-2,6 Ph); 6.96 (1H, t, *J* = 7.7, H-4 Ph); 5.23 (2H, s, CH_2OPh); 4.32 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 1.29 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, TFA-*d*), δ, ppm: 155.7; 155.5; 154.9; 146.7; 129.1; 122.9; 113.7; 65.4; 59.4; 11.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 246 $[M–H]^-$ (100). Found, *m*/*z*: 248.1022 $[M+H]^+$. $C_{12}H_{14}N_3O_3$. Calculated, *m*/*z*: 248.1035.

Ethyl 5-(3-methylphenyl)-1*H*-1,2,4-triazole-3-carboxylate (1l) was synthesized from compound **5l** (3.75 g). Yield 4.39 g (76%), yellowish powder, mp 137–139°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.05 (1H, br. s, NH); 7.87 (1H, s, H-2 Ph); 7.82 (1H, d, *J* = 7.7, H-6 Ph); 7.41 (1H, t, *J* = 7.7, H-5 Ph); 7.30 (1H, d, *J* = 7.7, H-4 Ph); 4.36 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 2.37 (3H, s, CH_3); 1.32 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, TFA-*d*), δ, ppm: 155.3; 154.6; 145.1; 141.0; 136.2; 129.5; 127.4; 124.3; 116.5; 65.6; 18.7; 11.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 230 $[M–H]^-$ (100). Found, *m*/*z*: 232.1088 $[M+H]^+$. $C_{12}H_{14}N_3O_2$. Calculated, *m*/*z*: 232.1086.

Ethyl 5-(4-methylphenyl)-1*H*-1,2,4-triazole-3-carboxylate (1m) was synthesized from compound **5m** (3.75 g). Yield 4.68 g (81%), white powder, mp 208–210°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.99 (1H, br. s, NH); 7.91 (2H, d, *J* = 7.8, H-2,6 Ph); 7.33 (2H, d, *J* = 7.8, H-3,5 Ph); 4.34 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 2.34 (3H, s, CH_3); 1.31 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, TFA-*d*), δ, ppm: 155.4; 154.5; 148.3; 145.0; 130.3; 127.1; 113.5; 65.6; 19.5; 11.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 230 $[M–H]^-$ (100). Found, *m*/*z*: 232.1073 $[M+H]^+$. $C_{12}H_{14}N_3O_2$. Calculated, *m*/*z*: 232.1086.

Ethyl 5-(2-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylate (1n) was synthesized from compound **5n** (4.15 g). Yield 2.16 g (35%), white powder, mp 159–161°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.22 (1H, s, NH); 8.06 (1H, d, *J* = 7.7, H-6 Ph); 7.50 (1H, t, *J* = 7.7, H-4 Ph); 7.21 (1H, d, *J* = 7.7, H-3 Ph); 7.10 (1H, t, *J* = 7.7, H-5 Ph); 4.34 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.95 (3H, s, OCH_3); 1.31 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 160.4; 157.1; 154.0; 153.1; 132.6; 129.7; 121.3; 115.3; 112.3; 61.4; 56.1; 14.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 246 $[M–H]^-$ (100). Found, *m*/*z*: 248.1025 $[M+H]^+$. $C_{12}H_{14}N_3O_3$. Calculated, *m*/*z*: 248.1035.

Ethyl 5-(3-cyanophenyl)-1*H*-1,2,4-triazole-3-carboxylate (1o) was synthesized from compound **5o** (4.03 g). Yield 4.3 g (71%), yellow powder, mp 207–209°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.32 (1H, br. s, NH); 8.34 (1H, s, H-2 Ph); 8.30 (1H, d, *J* = 7.8, H-6 Ph); 7.93 (1H, d, *J* = 7.8, H-4 Ph); 7.72 (1H, t, *J* = 7.8, H-5 Ph); 4.37 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 1.33 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 158.8; 157.5; 157.2; 134.0; 131.1; 130.9 (2C); 129.9; 118.6; 112.7; 62.0; 14.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 241 $[M–H]^-$ (100). Found, %: C 59.58; H 4.26; N 23.05. $C_{12}H_{10}N_4O_2$. Calculated, %: C 59.50; H 4.16; N 23.13.

Ethyl 5-(3-bromophenyl)-1*H*-1,2,4-triazole-3-carboxylate (1p) was synthesized from compound **5p** (5.38 g). Yield 6.14 g (83%), white powder, mp 164–166°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.24 (1H, br. s, NH); 8.18 (1H, s, H-2 Ph); 8.02 (1H, d, *J* = 7.9, H-6 Ph); 7.69 (1H, d, *J* = 7.9, H-4 Ph); 7.49 (1H, t, *J* = 7.9, H-5 Ph); 4.36 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 1.32 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, TFA-*d*), δ, ppm: 155.2; 153.6; 145.8; 137.8; 130.7; 130.1; 125.6; 123.7; 119.4; 65.7; 11.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 294 $[M(^{79}Br)–H]^-$ (100), 296 $[M(^{81}Br)–H]^-$ (100). Found, *m*/*z*: 296.0024 $[M+H]^+$. $C_{11}H_{11}BrN_3O_2$. Calculated, *m*/*z*: 296.0034.

Ethyl 5-(4-chlorophenyl)-1*H*-1,2,4-triazole-3-carboxylate (1q) was synthesized from compound **5q** (4.27 g). Yield 5.35 g (85%), yellow powder, mp 221–223°C (mp 220–223°C (*i*-PrOH)[46]). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.23 (1H, br. s, NH); 8.04 (2H, d, *J* = 8.2, H-2,6 Ph); 7.61 (2H, d, *J* = 8.2, H-3,5 Ph); 4.37 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 1.34 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 160.0; 158.8; 155.4; 135.5; 134.3; 129.7 (2C); 128.5 (2C); 61.8, 14.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 250 $[M–H]^-$ (100), 252 $[M–H]^-$ (32). Found, *m*/*z*: 252.0528 $[M+H]^+$. $C_{11}H_{11}ClN_3O_2$. Calculated, *m*/*z*: 252.0540.

Ethyl 5-(pyridin-2-yl)-1*H*-1,2,4-triazole-3-carboxylate (1r) was synthesized from compound **5r** (3.43 g). Yield 4.47 g (82%), yellow powder, mp 163–164°C (mp 164–166°C[43]). Physical and spectral data were in accordance with the previously reported.[43,47,48]

Ethyl 5-(pyridin-3-yl)-1*H*-1,2,4-triazole-3-carboxylate (1s) was synthesized from compound **5s** (3.43 g). Yield 3.71 g (68%), yellow powder, mp 180–182°C (mp 161–163°C[43]). Physical and spectral data were in accordance with the previously reported.[43,48]

Ethyl 5-(pyridin-4-yl)-1*H*-1,2,4-triazole-3-carboxylate (1t) was synthesized from compound **5t** (3.43 g). Yield 4.2 g (77%), yellow powder, mp 164–166°C (mp 163–165°C[43]). Physical and spectral data were in accordance with the previously reported.[43,48]

Synthesis of ethyl 1-alkyl-1*H*-1,2,4-triazole-3-carboxylates 14a,b,f–h,q, 16a,b and ethyl 1-alkyl-1*H*-1,2,4-triazole-5-carboxylates 15a,b,f–h,q, 17a,b (General method). Ethyl 1,2,4-triazolecarboxylate **1a**,**b**,**f–h**,**q** (10.0 mmol) was added to a dispersion of K_2CO_3 (2.08 g, 15.0 mmol) in DMF (20 ml), and the resulting mixture was stirred at room temperature for 15 min. After, MeI (1.78 g, 12.5 mmol), EtI (1.95 g, 12.5 mmol), or *i*-PrI (2.13 g, 12.5 mmol) was added and the obtained mixture was stirred at the same temperature (until TLC analyses indicated that the starting material was consumed (normally 14 h)). Reaction mixture was filtered, the filtrate was evaporated at reduced pressure, diluted with CH_2Cl_2 (50 ml), washed with H_2O (2×10 ml), and evaporated. Thus obtained crude mixture of compounds **14**–**17** was subjected to column chromatography affording the title compounds **14a**,**b**,**f–h**,**q**, **15a**,**b**,**f–h**,**q**, **16a**,**b**, and **17a**,**b**.

Ethyl 1-methyl-1*H*-1,2,4-triazole-5-carboxylate (14a) was synthesized from compound **1a** (1.41 g). Yield 543 mg (35%), white powder, mp 37–39°C, R_f 0.71 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.10 (1H, s, CH); 4.37 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.12 (3H, s, NCH_3); 1.33 (3H, t, *J* = 7.1,

$CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 158.0; 150.7; 144.8; 62.3; 38.7; 14.3. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 83 $[M–C_2H_4–CO_2]^+$ (100), 155 $[M]^+$ (12). Found, %: C 46.13; H 5.46; N 27.39. $C_6H_9N_3O_2$. Calculated, %: C 46.45; H 5.85; N 27.08.

Ethyl 1,3-dimethyl-1*H*-1,2,4-triazole-5-carboxylate (14b) was synthesized from compound **1b** (1.55 g). Yield 676 mg (40%), colorless crystals, mp 92–93°C, R_f 0.63 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.34 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.04 (3H, s, NCH_3); 2.27 (3H, s, CH_3); 1.32 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 159.2; 158.0; 144.7; 62.2; 38.3; 14.3; 13.7. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 170 $[M+H]^+$ (100). Found, %: C 49.48; H 6.33; N 24.48. $C_7H_{11}N_3O_2$. Calculated, %: C 49.70; H 6.55; N 24.84.

Ethyl 3-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (14f) was synthesized from compound **1f** (1.85 g). Yield 816 mg (41%), colorless crystals, mp 34–35°C, R_f 0.59 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.40 (2H, s, CH_2O); 4.36 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 4.10 (3H, s, OCH_3); 3.28 (3H, s, NCH_3); 1.33 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 159.6; 157.9; 145.2; 66.8; 62.3; 58.2; 38.7; 14.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 200 $[M+H]^+$ (100), 168 $[M–CH_3O]^+$ (65). Found, *m*/*z*: 200.1026 $[M+H]^+$. $C_8H_{14}N_3O_3$. Calculated, *m*/*z*: 200.1035.

Ethyl 3-(cyanomethyl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (14g) was synthesized from compound **1g** (1.80 g). Yield 815 mg (42%), yellow powder, mp 80–81°C, R_f 0.68 (MeCN). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.37 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.22 (2H, s, CH_2CN); 4.10 (3H, s, NCH_3); 1.33 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 157.5; 154.0; 145.6; 117.3; 62.5; 38.8; 17.5; 14.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 195 $[M+H]^+$ (100). Found, %: C 49.29; H 5.50; N 28.97. $C_8H_{10}N_4O_2$. Calculated, %: C 49.48; H 5.19; N 28.85.

Ethyl 3-cyclopropyl-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (14h) was synthesized from compound **1h** (1.81 g). Yield 741 mg (38%), colorless liquid, R_f 0.81 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.33 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.02 (3H, s, NCH_3); 2.04–1.94 (1H, m, CH cyclopropyl); 1.31 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 0.97–0.88 (2H, m, CH_2 cyclopropyl); 0.83–0.75 (2H, m, CH_2 cyclopropyl). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 164.3; 157.9; 144.6; 62.2; 38.4; 14.4; 8.9; 8.1 (2C). Mass spectrum (CI), *m*/*z* (I_{rel}, %): 196 $[M+H]^+$ (100). Found, *m*/*z*: 196.1078 $[M+H]^+$. $C_9H_{14}N_3O_2$. Calculated, *m*/*z*: 196.1086.

Ethyl 3-(4-chlorophenyl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (14q) was synthesized from compound **1q** (2.52 g). Yield 1.6 g (60%), colorless crystals, mp 129–131°C, R_f 0.65 (CH_2Cl_2–EtOAc, gradient 0–100%). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.00 (2H, d, *J* = 8.4, H-2,6 Ph); 7.54 (2H, d, *J* = 8.4, H-3,5 Ph); 4.40 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.17 (3H, s, NCH_3); 1.36 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 159.1; 157.8; 145.8; 134.7; 129.4 (2C); 129.3; 128.0 (2C); 62.5; 39.1; 14.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 266 $[M+H]^+$ (100), 268 $[M+H]^+$ (32). Found, *m*/*z*: 266.0683 $[M+H]^+$. $C_{12}H_{13}ClN_3O_2$. Calculated, *m*/*z*: 266.0696.

Ethyl 1-methyl-1*H*-1,2,4-triazole-3-carboxylate (15a) was synthesized from compound **1a** (1.41 g). Yield 667 mg (43%), colorless crystals, mp 114–115°C, R_f 0.16 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.63 (1H, s, CH); 4.31 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.95 (3H, s, NCH_3); 1.29 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 159.9; 154.3; 146.7; 61.4; 37.0; 14.5. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 110 $[M–C_2H_5O]^+$ (100), 83 $[M–C_2H_4–CO_2]^+$ (53). Found, *m*/*z*: 156.0764 $[M+H]^+$. $C_6H_{10}N_3O_2$. Calculated, *m*/*z*: 156.0773.

Ethyl 1,5-dimethyl-1*H*-1,2,4-triazole-3-carboxylate (15b) was synthesized from compound **1b** (1.55 g). Yield 810 mg (48%), beige crystals, mp 93–94°C, R_f 0.14 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 4.28 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.84 (3H, s, NCH_3); 2.42 (3H, s, CH_3); 1.28 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 160.1; 154.5; 152.4; 61.2; 36.1; 14.5; 11.8. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 169 $[M]^+$ (10), 124 $[M–C_2H_5O]^+$ (100). Found, %: C 49.96; H 6.24; N 24.97. $C_7H_{11}N_3O_2$. Calculated, %: C 49.70; H 6.55; N 24.84.

Ethyl 5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (15f) was synthesized from compound **1f** (1.85 g). Yield 876 mg (44%), colorless crystals, mp 46–48°C, R_f 0.24 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.62 (2H, s, CH_2O); 4.30 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.92 (3H, s, NCH_3); 3.30 (3H, s, OCH_3); 1.29 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 159.8; 154.0; 152.7; 64.3; 61.4; 58.5; 36.6; 14.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 200 $[M+H]^+$ (100), 154 $[M+H–C_2H_5OH]^+$ (42). Found, *m*/*z*: 200.1027 $[M+H]^+$. $C_8H_{14}N_3O_3$. Calculated, *m*/*z*: 200.1035.

Ethyl 5-(cyanomethyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (15g) was synthesized from compound **1g** (1.80 g). Yield 757 mg (39%), yellow crystals, mp 111–113°C, R_f 0.14 (MeCN). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.49 (2H, s, CH_2CN); 4.32 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.88 (3H, s, NCH_3); 1.30 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 159.6; 152.8; 149.0; 115.9; 61.5; 36.5; 16.3; 14.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 195 $[M+H]^+$ (100). Found, %: C 49.48; H 5.35; N 29.11. $C_8H_{10}N_4O_2$. Calculated, %: C 49.48; H 5.19; N 28.85.

Ethyl 5-cyclopropyl-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (15h) was synthesized from compound **1h** (1.81 g). Yield 800 mg (41%), colorless oil, R_f 0.4 (hexanes–*t*-BuOMe, 7:3). ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.27 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 3.94 (3H, s, NCH_3); 2.18 (1H, tt, *J* = 8.5, *J* = 4.8, CH cyclopropyl); 1.27 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 1.12–1.03 (2H, m, CH_2 cyclopropyl); 0.96–0.89 (2H, m, CH_2 cyclopropyl). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 160.1; 159.4; 152.3; 61.2; 35.8; 14.6; 8.8 (2C); 6.2. Mass

spectrum (CI), *m*/*z* (I_{rel}, %): 196 $[M+H]^+$ (100). Found, *m*/*z*: 196.1077 $[M+H]^+$. $C_9H_{14}N_3O_2$. Calculated, *m*/*z*: 196.1086.

Ethyl 5-(4-chlorophenyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (15q) was synthesized from compound **1q** (2.52 g). Yield 400 mg (15%), white powder, mp 115–117°C, R_f 0.18 (CH_2Cl_2–EtOAc, gradient 0–100%). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.84 (2H, d, *J* = 8.4, H-2,6 Ph); 7.65 (2H, d, *J* = 8.4, H-3,5 Ph); 4.34 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.04 (3H, s, NCH_3); 1.31 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 159.9; 154.8; 152.9; 135.9; 131.0 (2C); 129.4 (2C); 126.2; 61.5; 38.2; 14.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 266 $[M+H]^+$ (100), 268 $[M+H]^+$ (32). Found, *m*/*z*: 266.0687 $[M+H]^+$. $C_{12}H_{13}ClN_3O_2$. Calculated, *m*/*z*: 266.0696.

Ethyl 1-ethyl-3-methyl-1*H*-1,2,4-triazole-5-carboxylate (16a) was synthesized from compound **1b** (1.55 g). Yield 770 mg (42%), colorless crystals, mp 47–48°C, R_f 0.57 (hexanes–*t*-BuOMe, 7:3). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.44 (2H, q, *J* = 7.2, $OC\underline{H}_2CH_3$); 4.33 (2H, q, *J* = 7.2, $NC\underline{H}_2CH_3$); 2.26 (3H, s, CH_3); 1.33 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$); 1.30 (3H, t, *J* = 7.2, $NCH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 159.0; 157.5; 143.6; 61.8; 45.5; 15.1; 13.9; 13.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 184 $[M+H]^+$ (100). Found, *m*/*z*: 184.1079 $[M+H]^+$. $C_8H_{14}N_3O_2$. Calculated, *m*/*z*: 184.1086.

Ethyl 1-isopropyl-3-methyl-1*H*-1,2,4-triazole-5-carboxylate (16b) was synthesized from compound **1b** (1.55 g). Yield 1.34 g (68%), colorless oil, R_f 0.61 (hexanes–*t*-BuOMe, 7:3). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 5.30 (1H, hept, *J* = 6.8, $C\underline{H}(CH_3)_2$); 4.33 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 2.27 (3H, s, CH_3); 1.38 (6H, d, *J* = 6.8, $CH(C\underline{H}_3)_2$); 1.30 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 158.9; 157.7; 143.3; 61.8; 51.6; 22.3; 13.9; 13.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 198 $[M+H]^+$ (100). Found, *m*/*z*: 198.1235 $[M+H]^+$. $C_9H_{16}N_3O_2$. Calculated, *m*/*z*: 198.1242.

Ethyl 1-ethyl-5-methyl-1*H*-1,2,4-triazole-3-carboxylate (17a) was synthesized from compound **1b** (1.55 g). Yield 878 mg (48%), colorless crystals, mp 34–36°C, R_f 0.38 (hexanes–*t*-BuOMe, 7:3). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.26 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.16 (2H, q, *J* = 7.3, $NC\underline{H}_2CH_3$); 2.42 (3H, s, CH_3); 1.32 (3H, t, *J* = 7.3, $NCH_2C\underline{H}_3$); 1.26 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 159.6; 153.3; 152.2; 60.7; 43.4; 14.5; 14.1; 11.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 184 $[M+H]^+$ (100). Found, *m*/*z*: 184.1080 $[M+H]^+$. $C_8H_{14}N_3O_2$. Calculated, *m*/*z*: 184.1086.

Ethyl 1-isopropyl-5-methyl-1*H*-1,2,4-triazole-3-carboxylate (17b) was synthesized from compound **1b** (1.55 g). Yield 394 mg (20%), colorless oil, R_f 0.61 (hexanes–*t*-BuOMe, 7:3). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 4.65 (1H, hept, *J* = 6.6, $C\underline{H}(CH_3)_2$); 4.28 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 2.45 (3H, s, CH_3); 1.38 (6H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 1.28 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 160.2; 153.2; 152.7; 61.2; 50.5; 22.5; 14.6; 11.9. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 198 $[M+H]^+$ (100). Found, *m*/*z*: 198.1238 $[M+H]^+$. $C_9H_{16}N_3O_2$. Calculated, *m*/*z*: 198.1242.

Syntesis of lithium or sodium 1,2,4-triazole carboxylates 18b,c,e,f,h–k,n,r, 19a,b,f,h, and 20a,b,f,h (General method). Ethyl 1,2,4-triazolecarboxylate **1b**,**c**,**e**,**f**,**h**–**k**,**n**,**r**, **14a**,**b**,**f**,**h**, or **15a**,**b**,**f**,**h** (5.00 mmol) was added to a solution of NaOH (200 mg, 5.00 mmol) or $LiOH·H_2O$ (210 mg, 5.00 mmol) in H_2O (10 ml), and the resulting mixture was stirred at 80°C for 10 h. Then solvent was evaporated under reduced pressure, the residue was dispersed in *i*-PrOH (10 ml), brought to reflux, cooled, filtered, and dried to constant weight at 120°C thus affording the title compounds **18b**,**c**,**e**,**f**,**h**–**k**,**n**,**r**, **19a**,**b**,**f**,**h**, and **20a**,**b**,**f**,**h**.

Lithium 5-methyl-1*H*-1,2,4-triazole-3-carboxylate (18b) was synthesized from compound **1b** (775 mg). Yield 678 mg (91%), white powder, mp 275–277°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.22 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 160.9; 156.1; 151.5; 13.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 128 $[M–Li+2H]^+$ (100). Found, *m*/*z*: 126.0306 $[M–Li]^-$. $C_4H_4N_3O_2$. Calculated, *m*/*z*: 126.0304.

Sodium 5-ethyl-1*H*-1,2,4-triazole-3-carboxylate (18c) was synthesized from compound **1c** (845 mg). Yield 710 mg (87%), white powder, mp 220–222°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.58 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 1.16 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 162.7; 161.8; 155.8; 21.2; 13.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 140 $[M–Na]^-$ (51), 96 $[M–Na–CO_2]^-$ (100). Found, *m*/*z*: 140.0466 $[M–Na]^-$. $C_5H_6N_3O_2$. Calculated, *m*/*z*: 140.0460.

Sodium 5-(*tert*-butyl)-1*H*-1,2,4-triazole-3-carboxylate (18e) was synthesized from compound **1e** (985 mg). Yield 860 mg (90%), white powder, mp 208–210°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.27 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 169.5; 161.7; 155.4; 32.6; 30.0. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 170 $[M–Na+2H]^+$ (100). Found, %: C 44.32; H 4.88; N 21.58. $C_7H_{10}N_3NaO_2$. Calculated, %: C 43.98; H 5.27; N 21.98.

Sodium 5-(methoxymethyl)-1*H*-1,2,4-triazole-3-carboxylate (18f) was synthesized from compound **1f** (925 mg). Yield 814 mg (91%), white powder, mp 180–182°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 4.35 (2H, s, CH_2O); 3.25 (3H, s, OCH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 160.9; 159.2; 155.8; 67.2; 57.9. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 158 $[M–Na+2H]^+$ (100), 126 $[M–Na–CH_3O+H]^+$ (58). Found, *m*/*z*: 156.0415 $[M–Na]^-$. $C_5H_6N_3O_3$. Calculated, *m*/*z*: 156.0409.

Sodium 5-cyclopropyl-1*H*-1,2,4-triazole-3-carboxylate (18h) was synthesized from compound **1h** (905 mg). Yield 744 mg (85%), white powder, mp 179–181°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.92 (1H, tt, *J* = 8.5, *J* = 5.1, CH cyclopropyl); 0.90–0.73 (4H, m, $2CH_2$ cyclopropyl). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 163.5; 161.7; 155.7; 9.1; 7.9 (2C). Mass spectrum (CI), *m*/*z* (I_{rel}, %): 154 $[M–Na+2H]^+$ (100), 136 $[M–Na+2H–H_2O]^+$ (42). Found, *m*/*z*: 152.0458 $[M–Na]^-$. $C_6H_6N_3O_2$. Calculated, *m*/*z*: 152.0460.

Sodium 5-phenyl-1*H*-1,2,4-triazole-3-carboxylate (18i) was synthesized from compound **1i** (1.09 g). Yield 970 mg (92%), white powder, mp >300°C. ^{1}H NMR spectrum

(400 MHz, D_2O), δ, ppm: 7.75–7.65 (2H, m, H-2,6 Ph); 7.38–7.26 (3H, m, H-3,4,5 Ph). ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 164.2; 158.7; 155.3; 130.3; 128.9; 127.7; 126.2. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 190 $[M–Na+2H]^+$ (100), 172 $[M–Na+2H–H_2O]^+$ (72). Found, *m*/*z*: 188.0456 $[M–Na]^–$. $C_9H_6N_3O_2$. Calculated, *m*/*z*: 188.0460.

Sodium 5-benzyl-1*H*-1,2,4-triazole-3-carboxylate (18j) was synthesized from compound **1j** (1.16 g). Yield 1.05 g (93%), white powder, mp 105–106°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 13.80 (1H, br. s, NH); 7.45–7.02 (5H, m, H Ph); 3.91 (2H, s, CH_2). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 172.2; 160.6 (2C); 139.3; 129.1; 128.6; 126.4; 34.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 204 $[M–Na+2H]^+$ (100). Found, %: C 53.66; H 3.63; N 18.56. $C_{10}H_8N_3NaO_2$. Calculated, %: C 53.34; H 3.58; N 18.66.

Sodium 5-(phenoxymethyl)-1*H*-1,2,4-triazole-3-carboxylate (18k) was synthesized from compound **1k** (1.24 g). Yield 1.08 g (90%), white powder, mp >300°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm (*J*, Hz): 7.15 (2H, t, *J* = 8.1, H-3,5 Ph); 6.93–6.79 (3H, m, H-2,4,6 Ph); 5.02 (2H, s, OCH_2). ^{13}C NMR spectrum (126 MHz, D_2O), δ, ppm: 164.9; 157.7; 157.0; 155.9; 129.4; 121.5; 114.7; 62.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 220 $[M–Na+2H]^+$ (100). Found, *m*/*z*: 218.0573 $[M–Na]^–$. $C_{10}H_8N_3O_3$. Calculated, *m*/*z*: 218.0566.

Sodium 5-(2-methoxyphenyl)-1*H*-1,2,4-triazole-3-carboxylate (18n) was synthesized from compound **1n** (1.24 g). Yield 1.02 g (85%), beige powder, mp >300°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.98 (1H, d, *J* = 7.7, H-6 Ph); 7.36 (1H, t, *J* = 7.7, H-4 Ph); 7.09 (1H, d, *J* = 7.7, H-3 Ph); 6.96 (1H, t, *J* = 7.7, H-5 Ph); 3.84 (3H, s, OCH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 162.0; 157.1; 156.8; 155.9; 130.1; 120.3; 119.3; 111.8; 55.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 220 $[M–Na+2H]^+$ (100), 202 $[M–Na+2H–H_2O]^+$ (14). Found, *m*/*z*: 218.0559 $[M–Na]^–$. $C_{10}H_8N_3O_3$. Calculated, *m*/*z*: 218.0566.

Sodium 5-(pyridin-2-yl)-1*H*-1,2,4-triazole-3-carboxylate (18r) was synthesized from compound **1r** (1.09 g). Yield 931 mg (87%), white powder, mp >300°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm (*J*, Hz): 8.39 (1H, d, *J* = 4.9, H-6 Py); 7.81–7.76 (1H, m, H-3 Py); 7.73 (1H, t, *J* = 7.7, H-4 Py); 7.33–7.23 (1H, m, H-5 Py). ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 164.5; 158.8; 155.8; 149.1; 146.9; 138.2; 124.9; 122.0. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 191 $[M+H]^+$ (100). Found, *m*/*z*: 189.0410 $[M–Na]^–$. $C_8H_5N_4O_2$. Calculated, *m*/*z*: 189.0413.

Sodium 1-methyl-1*H*-1,2,4-triazole-5-carboxylate (19a) was synthesized from compound **14a** (775 mg). Yield 648 mg (87%), white powder, mp 312–315°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm: 7.79 (1H, s, CH); 3.94 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 163.3; 150.5; 149.1; 37.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 126 $[M–Na]^–$ (100). Found, %: C 32.61; H 2.84; N 28.54. $C_4H_4N_3NaO_2$. Calculated, %: C 32.23; H 2.70; N 28.19.

Lithium 1,3-dimethyl-1*H*-1,2,4-triazole-5-carboxylate (19b) was synthesized from compound **14b** (845 mg). Yield 647 mg (88%), white powder, mp 336–338°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 4.00 (3H, s, NCH_3); 2.17 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 160.1; 156.8; 152.8; 37.0; 13.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 142 $[M–Li+2H]^+$ (100), 98 $[M–Li+2H–CO_2]^+$ (35). Found, %: C 40.71; H 3.95; N 28.73. $C_5H_6LiN_3O_2$. Calculated, %: C 40.84; H 4.11; N 28.57.

Sodium 3-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (19f) was synthesized from compound **14f** (995 mg). Yield 772 mg (80%), white powder, mp 238–241°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 4.30 (2H, s, CH_2O); 4.06 (3H, s, NCH_3); 3.25 (3H, s, OCH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 160.3; 157.7; 153.4; 67.1; 57.9; 37.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 172 $[M–Na+2H]^+$ (100). Found, *m*/*z*: 170.0565 $[M–Na]^–$. $C_6H_8N_3O_3$. Calculated, *m*/*z*: 170.0566.

Sodium 3-cyclopropyl-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (19h) was synthesized from compound **14h** (975 mg). Yield 822 mg (87%), white powder, mp 310–312°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 3.99 (3H, s, NCH_3); 1.87 (1H, tt, *J* = 8.1, *J* = 5.2, CH cyclopropyl); 0.90–0.71 (4H, m, $2CH_2$ cyclopropyl). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 162.2; 160.5; 152.8; 37.4; 9.1; 7.7 (2C). Mass spectrum (CI), *m*/*z* (I_{rel}, %): 166 $[M–Na]^–$ (100), 122 $[M–Na–CO_2]^–$ (20). Found, %: C 44.42; H 3.91; N 22.18. $C_7H_8N_3NaO_2$. Calculated, %: C 44.45; H 4.26; N 22.22.

Sodium 1-methyl-1*H*-1,2,4-triazole-3-carboxylate (20a) was synthesized from compound **15a** (775 mg). Yield 572 mg (90%), white powder, mp >300°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm: 8.08 (1H, s, H-5); 3.70 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, D_2O), δ, ppm: 166.3; 158.6; 145.4; 36.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 126 $[M–Na]^–$ (100). Found, %: C 32.28; H 2.30; N 28.52. $C_4H_4N_3NaO_2$. Calculated, %: C 32.23; H 2.70; N 28.19.

Lithium 1,5-dimethyl-1*H*-1,2,4-triazole-3-carboxylate (20b) was synthesized from compound **15b** (845 mg). Yield 670 mg (91%), white powder, mp 318–322°C. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.73 (3H, s, NCH_3); 2.33 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 163.2; 159.9; 152.1; 35.5; 11.7. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 142 $[M–Li+2H]^+$ (49), 124 $[M–Li+2H–H_2O]^+$ (100). Found, *m*/*z*: 140.0464 $[M–Li]^–$. $C_5H_6N_3O_2$. Calculated, *m*/*z*: 140.0460.

Sodium 5-(methoxymethyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (20f) was synthesized from compound **15f** (995 mg). Yield 840 mg (87%), white powder, mp 131–134°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm: 4.55 (2H, s, CH_2O); 3.79 (3H, s, NCH_3); 3.29 (3H, s, OCH_3). ^{13}C NMR spectrum (126 MHz, D_2O), δ, ppm: 165.7; 156.9; 152.4; 63.2; 57.7; 35.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 172 $[M–Na+2H]^+$ (100). Found, *m*/*z*: 170.0566 $[M–Na]^–$. $C_6H_8N_3O_3$. Calculated, *m*/*z*: 170.0566.

Sodium 5-cyclopropyl-1-methyl-1*H*-1,2,4-triazole-3-carboxylate (20h) was synthesized from compound **15h** (975 mg). Yield 803 mg (85%), white powder, mp 230–233°C. ^1H NMR spectrum (400 MHz, D_2O), δ, ppm: 3.77 (3H, s, NCH_3); 1.98–1.81 (1H, m, CH cyclopropyl); 1.05–0.92 (2H, m, CH_2 cyclopropyl); 0.90–0.75 (2H, m, CH_2 cyclopropyl). ^{13}C NMR spectrum (126 MHz, D_2O), δ, ppm:

166.0; 158.8; 156.3; 34.4; 6.9 (2C); 5.2. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 166 $[M–Na]^-$ (100), 122 $[M–Na–CO_2]^-$ (80). Found, *m*/*z*: 166.0614 $[M–Na]^-$. $C_7H_8N_3O_2$. Calculated, *m*/*z*: 166.0617.

Synthesis of 1,2,4-triazole carboxamides 21b,h,p, 22b, and 23b (General method). Ethyl 1,2,4-triazolecarboxylate **1b**,**h**, **14b**, or **15b** (5.00 mmol) was dissolved in 25% aqueous NH_3 (10 ml) while triazole **1p** was dissolved in a mixture EtOH – 25% aqueous NH_3, 1:1 (10 ml), and the resulting solution was stirred at 50°C for 24 h. The formed precipitate was filtered to give the title compounds **21p**, **22b**, or **23b**. Alternatively, the reaction mixture was evaporated at reduced pressure, and the residue was recrystallized from H_2O thus affording the title compounds **21b**,**h**.

5-Methyl-1*H*-1,2,4-triazole-3-carboxamide (21b) was synthesized from compound **1b** (775 mg). Yield 536 mg (85%), white powder, mp 223–225°C (mp 221–225°C (MeCN)[45]). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 14.09 (1H, br. s, NH); 7.81 (1H, br. s, NH_2); 7.56 (1H, br. s, NH_2); 2.35 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 160.8; 155.8; 154.4; 12.5. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 127 $[M+H]^+$ (100), 110 $[M+H–NH_3]^+$ (49). Found, %: C 38.24; H 4.89; N 44.11. $C_4H_6N_4O$. Calculated, %: C 38.09; H 4.80; N 44.42.

5-Cyclopropyl-1*H*-1,2,4-triazole-3-carboxamide (21h) was synthesized from compound **1h** (905 mg). Yield 623 mg (82%), white powder, mp 192–194°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.09 (1H, br. s, NH); 7.72 (1H, br. s, NH_2); 7.55 (1H, br. s, NH_2); 2.03 (1H, tt, *J* = 8.7, *J* = 4.9, CH cyclopropyl); 1.08–0.94 (2H, m, CH_2 cyclopropyl); 0.94–0.78 (2H, m, CH_2 cyclopropyl). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 160.7; 159.8; 157.9; 8.4 (2C); 7.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 153 $[M+H]^+$ (100), 136 $[M+H–NH_3]^+$ (64). Found, *m*/*z*: 153.0773 $[M+H]^+$. $C_6H_9N_4O$. Calculated, *m*/*z*: 153.0776.

5-(3-Bromophenyl)-1*H*-1,2,4-triazole-3-carboxamide (21p) was synthesized from compound **1p** (1.48 g). Yield 1.24 g (93%), white powder, mp 262–264°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.81 (1H, br. s, NH); 8.21 (1H, s, H-2 Ph); 8.11 (1H, s, NH_2); 8.03 (1H, d, *J* = 8.0, H-6 Ph); 7.86 (1H, s, NH_2); 7.65 (1H, d, *J* = 8.0, H-4 Ph); 7.47 (1H, t, *J* = 8.0, H-5 Ph). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 159.6; 153.3; 145.4; 132.7; 132.5; 131.7; 129.0; 125.3; 122.6. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 266 $[M(^{79}Br)+H]^+$ (100), 268 $[M(^{81}Br)+H]^+$ (100). Found, *m*/*z*: 268.9852 $[M+H]^+$. $C_9H_8BrN_4O$. Calculated, *m*/*z*: 266.9881.

1,3-Dimethyl-1*H*-1,2,4-triazole-5-carboxamide (22b) was synthesized from compound **14b** (845 mg). Yield 630 mg (90%), white powder, mp 217–219°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 8.06 (1H, s, NH); 7.82 (1H, s, NH); 4.02 (3H, s, NCH_3); 2.23 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 159.4; 158.2; 146.9; 37.8; 13.7. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 141 $[M+H]^+$ (100). Found, *m*/*z*: 141.0772 $[M+H]^+$. $C_5H_9N_4O$. Calculated, *m*/*z*: 141.0776.

1,5-Dimethyl-1*H*-1,2,4-triazole-3-carboxamide (23b) was synthesized from compound **15b** (845 mg). Yield 595 mg (85%), white powder, mp 187–189°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 7.64 (1H, s, NH); 7.42 (1H, s, NH); 3.79 (3H, s, NCH_3); 2.38 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 161.2; 155.3; 153.7; 35.8; 11.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 141 $[M+H]^+$ (100). Found, *m*/*z*: 141.0771 $[M+H]^+$. $C_5H_9N_4O$. Calculated, *m*/*z*: 141.0776.

Synthesis of 1,2,4-triazole carbohydrazides 24a,b, 25a,b, and 26a,b (General method). Ethyl 1,2,4-triazolecarboxylate **1a**,**b**, **14a**,**b, 15a**,**b** (5.00 mmol) was dissolved in EtOH (10 ml) followed by addition of $N_2H_4·H_2O$ (313 mg, 0.31 ml, 6.25 mmol), and the resulting solution was refluxed for 1 h. Then it was cooled, the precipitate formed was filtered and washed with EtOH (10 ml) thus affording the title compounds **24a**,**b**, **25a**,**b**, or **26a**,**b**.

1*H*-1,2,4-Triazole-3-carbohydrazide (24a) was synthesized from compound **1a** (705 mg). Yield 552 mg (87%), white powder, mp 282–284°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 13.91 (1H, br. s, NH); 9.84 (1H, br. s, N<u>H</u>NH_2); 8.43 (1H, s, CH); 4.54 (2H, br. s, NHN<u>H</u>$_2$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 165.0; 157.5; 146.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 128 $[M+H]^+$ (100). Found, %: C 28.55; H 3.87; N 55.46. $C_3H_5N_5O$. Calculated, %: C 28.35; H 3.97; N 55.10.

5-Methyl-1*H*-1,2,4-triazole-3-carbohydrazide (24b) was synthesized from compound **1b** (775 mg). Yield 600 mg (85%), white powder, mp 213–215°C (mp 211–213°C[62]). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 13.80 (1H, s, NH); 9.67 (1H, s, N<u>H</u>NH_2); 4.51 (2H, s, NHN<u>H</u>$_2$); 2.33 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 158.5; 154.9 (2C); 12.4. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 142 $[M+H]^+$ (100). Found, *m*/*z*: 142.0725 $[M+H]^+$. $C_4H_8N_5O$. Calculated, *m*/*z*: 142.0729.

1-Methyl-1*H*-1,2,4-triazole-5-carbohydrazide (25a) was synthesized from compound **14a** (775 mg). Yield 627 mg (89%), white powder, mp 160–162°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 10.09 (1H, br. s, N<u>H</u>NH_2); 8.01 (1H, s, H-5); 4.60 (2H, s, NHN<u>H</u>$_2$); 4.10 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 156.4; 150.1; 146.2; 37.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 142 $[M+H]^+$ (100). Found, *m*/*z*: 142.0723 $[M+H]^+$. $C_4H_8N_5O$. Calculated, *m*/*z*: 142.0651.

1,3-Dimethyl-1*H*-1,2,4-triazole-5-carbohydrazide (25b) was synthesized from compound **14b** (845 mg). Yield 651 mg (84%), white powder, mp 154–156°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 10.05 (1H, s, N<u>H</u>NH_2); 4.58 (2H, s, NHN<u>H</u>$_2$); 4.03 (3H, s, NCH_3); 2.24 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 158.4; 156.5; 146.4; 37.5; 13.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 156 $[M+H]^+$ (100). Found, *m*/*z*: 156.0879 $[M+H]^+$. $C_5H_{10}N_5O$. Calculated, *m*/*z*: 156.0885.

1-Methyl-1*H*-1,2,4-triazole-3-carbohydrazide (26a) was synthesized from compound **15a** (775 mg). Yield 620 mg (88%), white powder, mp 200–202°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 9.62 (1H, br. s, N<u>H</u>NH_2); 8.53 (1H, s, CH); 4.47 (2H, s, NHN<u>H</u>$_2$); 3.89 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 158.8; 156.6; 145.8; 36.7. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 142 $[M+H]^+$ (100). Found, *m*/*z*: 142.0721 $[M+H]^+$. $C_4H_8N_5O$. Calculated, *m*/*z*: 142.0729.

1,5-Dimethyl-1*H*-1,2,4-triazole-3-carbohydrazide (26b) was synthesized from compound **15b** (845 mg). Yield 660 mg (85%), white powder, mp 152–154°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 9.54 (1H, s, N<u>H</u>NH$_2$); 4.43 (2H, s, NHN<u>H$_2$</u>); 3.78 (3H, s, NCH$_3$); 2.38 (3H, s, CH$_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 158.5; 154.2; 153.1; 35.4; 11.3. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 156 $[M+H]^+$ (100). Found, *m*/*z*: 156.0880 $[M+H]^+$. $C_5H_{10}N_5O$. Calculated, *m*/*z*: 156.0885.

Synthesis of 1,2,4-triazole *N*-hydroxycarboxamides 27b, 28b, and 29b (General method). To a solution of MeONa (810 mg, 15.0 mmol) in anhydrous MeOH (50 ml), $H_2NOH{\cdot}HCl$ (1.04 g, 15.0 mmol) was added, and the obtained mixture was stirred at room temperature for 30 min. Then ethyl 1,2,4-triazole-3-carboxylate **1b**, **14b**, or **15b** (5.00 mmol) was added and the reaction mixture was refluxed for 12 h. After this time, solvent was evaporated at reduced pressure, obtained residue was diluted with H_2O (25 ml) and acidified with AcOH (pH 7–8), followed by filtration of formed product thus affording the title compounds **27b**, **28b**, or **29b**.

***N*-Hydroxy-5-methyl-1*H*-1,2,4-triazole-3-carboxamide (27b)** was synthesized from compound **1b** (775 mg). Yield 520 mg (73%), white powder, mp 174–175°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 2.26 (3H, s, CH$_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 157.6; 156.6; 154.5; 13.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 143 $[M+H]^+$ (100). Found, *m*/*z*: 143.0564 $[M+H]^+$. $C_4H_7N_4O_2$. Calculated, *m*/*z*: 143.0569.

***N*-Hydroxy-1,3-dimethyl-1*H*-1,2,4-triazole-5-carboxamide (28b)** was synthesized from compound **14b** (845 mg). Yield 605 mg (78%), white powder, mp 192–194°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 11.58 (1H, s, OH); 9.30 (1H, s, NH); 4.01 (3H, s, NCH$_3$); 2.24 (3H, s, CH$_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 158.4; 155.2; 145.7; 37.4; 13.7. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 155 $[M–H]^–$ (100). Found, *m*/*z*: 157.0720 $[M+H]^+$. $C_5H_9N_4O_2$. Calculated, *m*/*z*: 157.0725.

***N*-Hydroxy-1,5-dimethyl-1*H*-1,2,4-triazole-3-carboxamide (29b)** was synthesized from compound **15b** (845 mg). Yield 580 mg (74%), white powder, mp 182–183°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.11 (1H, br. s, OH); 9.12 (1H, br. s, NH); 3.79 (3H, s, NCH$_3$); 2.40 (3H, s, CH$_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 157.4; 154.2; 153.6; 35.8; 11.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 157 $[M+H]^+$ (100). Found, *m*/*z*: 157.0712 $[M+H]^+$. $C_5H_9N_4O_2$. Calculated, *m*/*z*: 157.0725.

Synthesis of 1,2,4-triazole carbonitriles 30b and 31b (General method I). TFAA (2.10 g, 10.0 mmol) was added to a stirred solution of 1,2,4-triazole carboxamide **22b**, **23b** (5.00 mmol) in CH_2Cl_2 (50 ml). Stirring was continued until TLC analyses indicated that the starting material was consumed (normally 6 h). Then reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with H_2O (3 × 10 ml), dried over Na_2SO_4, and evaporated at reduced pressure thus affording the title compounds **30b**, **31b**.

1,3-Dimethyl-1*H*-1,2,4-triazole-5-carbonitrile (30b) was synthesized from compound **22b** (700 mg). Yield 458 mg (75%), yellow crystals, mp 84–86°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.99 (3H, s, NCH$_3$); 2.32 (3H, s, CH$_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 161.3; 130.3; 109.8; 37.3; 13.7. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 122 $[M]^+$ (100). Found, *m*/*z*: 123.0670 $[M+H]^+$. $C_5H_7N_4$. Calculated, *m*/*z*: 123.0671.

1,5-Dimethyl-1*H*-1,2,4-triazole-3-carbonitrile (31b) was synthesized from compound **23b** (700 mg). Yield 494 mg (81%), yellow crystals, mp 74–76°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.88 (3H, s, NCH$_3$); 2.46 (3H, s, CH$_3$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 155.7; 136.2; 113.2; 36.6; 11.8. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 123 $[M+H]^+$ (100). Found, %: C 49.33; H 4.61; N 46.22. $C_5H_6N_4$. Calculated, %: C 49.17; H 4.95; N 45.88.

Synthesis of 1,2,4-triazole carbonitriles 32b,h,p (General method II). 1,2,4-Triazole carboxamide **21b**,**h**,**p** (5.00 mmol) was dispersed in $POCl_3$ (16.4 g, 10 ml, 107 mmol), gradually heated, and refluxed for 2 h. Then the reaction mixture was cooled and poured onto ice. After $POCl_3$ had been quenched, mixture was neutralized with aqueous 2 M NaOH (pH 6–7) and thus obtained mixture was either filtered affording compound **32p**, or extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated at reduced pressure to give compounds **32b**,**h**.

5-Methyl-1*H*-1,2,4-triazole-3-carbonitrile (32b) was synthesized from compound **21b** (630 mg). Yield 27 mg (5%), white solid, mp 132–133°C (mp 135–136°C (PhMe)[63]). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 14.76 (1H, br. s, NH); 2.41 (3H, s, CH$_3$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 155.8; 138.0; 113.5; 11.9. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 109 $[M+H]^+$ (100). Found, %: C 44.48; H 4.03; N 51.83. $C_4H_4N_4$. Calculated, %: C 44.44; H 3.73; N 51.83.

5-Cyclopropyl-1*H*-1,2,4-triazole-3-carbonitrile (32h) was synthesized from compound **21h** (760 mg). Yield 180 mg (27%), white powder, mp 113–115°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.80 (1H, br. s, NH); 2.12 (1H, tt, *J* = 8.6, *J* = 4.8, CH cyclopropyl); 1.15–1.05 (2H, m, CH$_2$ cyclopropyl); 0.99–0.90 (2H, m, CH$_2$ cyclopropyl). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 161.5; 137.8; 113.5; 9.2 (2C); 7.2. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 135 $[M+H]^+$ (100). Found, *m*/*z*: 135.0665 $[M+H]^+$. $C_6H_7N_4$. Calculated, *m*/*z*: 135.0671.

5-(3-Bromophenyl)-1*H*-1,2,4-triazole-3-carbonitrile (32p) was synthesized from compound **21p** (1.34 g). Yield 1.07 g (86%), beige powder, mp 212–214°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.72 (1H, br. s, NH); 8.18 (1H, s, H-2 Ph); 8.00 (1H, d, *J* = 7.9, H-6 Ph); 7.78 (1H, d, *J* = 7.9, H-4 Ph); 7.55 (1H, t, *J* = 7.9, H-5 Ph). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 155.4; 138.7; 134.5; 132.0; 129.5; 128.2; 126.1; 122.8; 113.1. Mass spectrum (CI), *m*/*z* (I_{rel}, %): 247 $[M(^{79}Br)–H]^–$ (100), 249 $[M(^{81}Br)–H]^–$ (100). Found, *m*/*z*: 248.9767 $[M+H]^+$. $C_9H_6BrN_4$. Calculated, *m*/*z*: 248.9776.

5-Methyl-1*H*-1,2,4-triazole-3-carbonitrile (32b) (Method III). K_2CO_3 (10.4 g, 75.0 mmol) and 4-methoxybenzyl chloride (7.60 g, 6.90 ml, 60.0 mmol) were added to a stirred solution of ethyl 5-methyl-4*H*-1,2,4-triazole-

3-carboxylate (**1b**) (7.76 g, 50.0 mmol) in anhydrous DMF (100 ml), and thus obtained mixture was stirred for 48 h. Reaction mixture was filtered, solvent was evaporated at reduced pressure, the residue was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined extracts were dried over Na_2SO_4 and evaporated at reduced pressure yielding 17.7 g of a mixture of esters **33** and **34** that was dissolved in EtOH (250 ml) and refluxed under an atmosphere of NH_3 for 2 h. Filtration of cooled reaction mixture afforded 13.2 g of a mixture of amides **35** and **36** that was dispersed in a solution of DIPEA (19.4 g, 150 mmol) in CH_2Cl_2 (250 ml) followed by addition of TFAA (13.7 g, 65.0 mmol) at 0–5°C. Thus obtained mixture was stirred at room temperature until TLC analyses indicated that the starting material was consumed (normally 24 h). Then it was washed with H_2O (3×50 ml), dried over Na_2SO_4, and evaporated at reduced pressure affording 10.1 g of a mixture of nitriles **37** and **38**. Thus obtained crude product was dissolved in CH_2Cl_2 (100 ml) followed by addition of TFA (23.0 g, 200 mmol), and the resulting mixture was stirred at room temperature until TLC analyses indicated that the starting material was consumed (typically 24 h). Reaction mixture was evaporated at reduced pressure, diluted with H_2O (50 ml), and washed with CH_2Cl_2 (3×10 ml). The aqueous layer was treated with $NaHCO_3$ (4.20 g, 50.0 mmol) and stirred at room temperature for 12 h. After, reaction mixture was evaporated at reduced pressure, diluted with MeCN (50 ml), brought to boil, and filtered. Finally, thus obtained filtrate was evaporated under reduced pressure affording 3.60 g (67%) of the title product **32b**. This product was identical to the sample of product **32b** synthesized as described above according to general method II.

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