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ABSTRACT

This work presents a new synthesis of the antiepileptic drug *rufinamide* — 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide) in chemical form — and some analogue compounds, through a one-pot reaction employing a solventless, metal-free catalysis and without any reducing reagent. The great novelty presented is the synthesis of 4-trichloroacetyl-1-(2,6-difluorobenzyl/benzyl/4-methoxybenzyl)-5-methyl(phenyl)-1*H*-1,2,3-triazoles as new precursors from a regioselective 1,3-dipolar cycloaddition reaction between 1,1,1-trichloro-4-alkoxyalk-3-en-2-ones and some benzyl azides , which are converted into *rufinamide* and the analogues by an addition-elimination reaction with an aqueous solution of NH_4OH in good yields (42 – 52 %).

1. Introduction

1,2,3-Triazoles are an important class of five-membered nitrogen heterocycles,[1] and they have found wide applications in organic synthesis, as well as in medicine, agriculture, and industry.[2] Among the heterocyclic compounds that have a triazolic core, we highlight 1-(2,6-difluorbenzyl)-1*H*-1,2,3-triazol-4-yl carboxamide (*rufinamide*), which is a drug that has anticonvulsant activity, especially when used in combination with other antiepileptic medications for the treatment of several forms of the childhood epilepsy known as Lennox-Gastaut syndrome.[3] Epilepsy is a neurological disorder that is characterized by recurrent seizures. Approximately 50 million people worldwide suffer from one of the more than 40 different forms of epilepsy.[4]

There are many methods described in the literature[3-11] for the synthesis of *rufinamide*, but all of them are based on the 1,3-dipolar cycloaddition synthesis between 2,6-difluorbenzyl azide, a dipole, and different dipolarophile precursors.[4] However, most methodologies have been patented and the reactions have been carried out from precursors with low selectivity or by procedures using metals as catalysts and/or reducing reagents. Also, these methodologies are customarily performed in more than one step, and in each step it is necessary to isolate the intermediates and the use of any solvent. Until now, the main methodologies described are the following:

In 1988, Meier et al.[5] reported the synthesis of *rufinamide* using 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid as the precursor, which is obtained through the 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide with propiolic acid at 80°C, using toluene as the solvent. The formation of a regioisomeric mixture of 1,4 and 1,5 disubstituted triazoles is a limiting factor of this procedure.

In 2012, Attolino et al.[6] reported three methods for the synthesis of *rufinamide*. The first of these occurs in two reaction steps, starting with 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid. This precursor is obtained regioselectively through the 1,3-dipolar cycloaddition reaction between 2,6-difluorobenzyl azide and propiolic acid, in a H_2O and *t*-BuOH reaction medium, using Cu(I) as the catalyst. The triazole obtained is reacted with thionyl chloride, followed by the addition of concentrated aqueous ammonia to give *rufinamide*. A second method described in this patent employs the reaction of propiolamide with 2,6-difluorobenzyl azide in methanol, in the presence of $CuSO_4$ and ascorbic acid, and ending with an aqueous solution of ammonia 33%. The third method uses the carboxylate of (2,6-difluorobenzyl)-1*H*-1,2,3-triazol-1-yl methyl, which is obtained by the reaction of methyl propiolate with 2,6-difluorobenzyl azide in the presence of ascorbic acid and $CuSO_4$ pentahydrate. The ester obtained is dissolved in methanol and treated with an aqueous ammonia solution for 3 h, thereby yielding *rufinamide*.

In 2010, Kankan et al.[7] performed the synthesis of *rufinamide* in two reaction steps without isolating intermediates. The methodology begins from the reaction of methyl propiolate with 2,6-difluorobenzyl azide, using water as the solvent. Finally, treatment with ammonia leads to *rufinamide*. That same year, Mudd et al.[4] described a new methodology for the synthesis of *rufinamide* via two methods. One of them started with 3-methoxy

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acrylonitrile and the other with methyl methoxyacrylate. Both methods use 2,6-difluorobenzyl azide as the second reaction component. The first method uses 3-methoxy acrylonitrile in a reaction with 2,6-difluorobenzyl azide to obtain a cyano-substituted triazole. In the second reaction step, this triazole is converted to *rufinamide* by hydrolysis. A disadvantage of this method is also the formation of regioisomers. The second proposed method uses a vinyl ester (methyl methoxyacrylate) in a regioselective 1,3-dipolar cycloaddition reaction with the 2,6-difluorobenzyl azide in order to obtain the corresponding triazole. As the best synthetic alternative, Mudde et al.[4] performed the cycloaddition reaction without solvent, but with heating at 135°C for 28 h. Subsequently, the ester function was converted to carboxamide via an ammonolysis reaction, using methanolic ammonia (7M solution) at room temperature for 18 h.

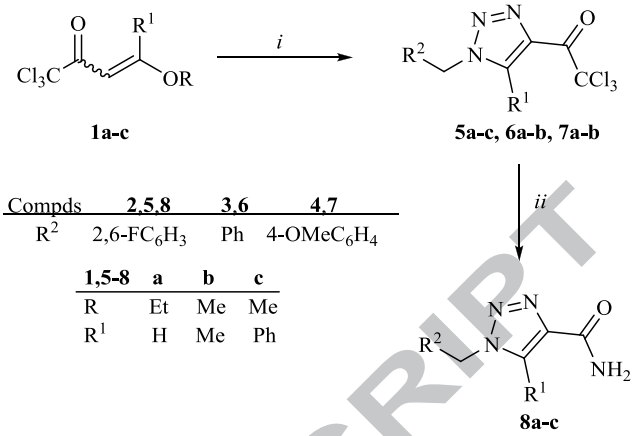
Finally, in 2013, Siyan et al.[8] described a process starting from 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid. This precursor is obtained from the reaction between 2,6-difluorobenzyl azide and the propiolic acid, in a mixture of alcohol and water of approximately 1:1 (v/v), at a temperature of 70°C–80°C for 16–18 h, resulting in an 80% yield. The 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylic acid is then esterified by treatment with alcohol in the presence of acid catalysis. The ester formed is treated with ammonia in order to obtain *rufinamide*, which is purified by recrystallization in DMF/H_2O.

So, in this Letter, we wish to report a regioselective reaction for the synthesis of *rufinamide* and analogues. According to the methodology patented by our group,[12] the procedure can be carried out at room temperature without needing to use solvents, metal catalysts, and/or reducing agents and the products isolated by a simple filtration process. The synthesis starts from new triazole core precursors **5-7**, which are obtained from 1,1,1-trichloro-4-alkoxyalk-3-en-2-ones[13] **1** and azides **2-4**, and which can be easily converted into triazole carboxamides **8**.

2. Results and discussion

Initially, for the synthesis of the 1*H*-1,2,3-triazole precursors **5**, we employed the enones **1** as dipolarofiles and the azides **2-4** as 1,3-dipoles, because from them it is possible to obtain triazoles containing the tricloroacetyl group as the substituent, which may provide a good leaving group (-CCl_3) in haloformic derivatization reactions.[15] These enones were synthetized from the acylation reaction of the respective enolethers or acetal with trichloroacetyl chloride, in accordance with the methodology already described in the literature.[13,14] The azides **2**, **3** and **4**, were used as dipoles and they were prepared using the methodology described by Kopach et al.,[16] which consists of the nucleophilic substitution reaction between benzyl chlorides and sodium azide in DMSO/H_2O at 40°C for 1 h.

The synthesis of 4-trichloroacetyl-1-(2,6-difluoro/4-methoxybenzyl)-5-alkyl(aryl)-1*H*-1,2,3-triazoles was achieved by a procedure based on the methodology described by Bonacorso et al.[17] The mixture of enones **1a-c** and substituted benzyl azides **2-4** was stirred and heated at different temperatures in the range of 130°C–150°C, without solvent and for between 2 and 4 days, depending on the substituent present in the 4-alkyl(aryl)-4-alkoxy-1,1,1-trichloro-3-alken-2-ones **1** and in the benzyl azides **2-4** (Scheme 1 and Table 1).



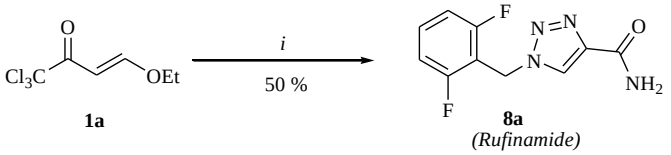
Compds	2,5,8	3,6	4,7
R^2	2,6-FC_6H_3	Ph	4-$OMeC_6H_4$

1,5-8	a	b	c
R	Et	Me	Me
R^1	H	Me	Ph

Scheme 1. Synthesis of Rufinamide and analogs. Reagents and conditions: *i* = $R^2CH_2N_3$ (**2-4**), neat, 130 - 150 °C, 2 - 4 days, 40 - 70 %; *ii* = MeOH, NH_4OH, Et_3N, 0.4 - 24h, 50 - 60 %.

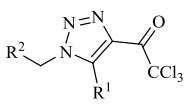
After synthesis of the substituted trichloroacetyl triazoles **5-7**, and to illustrate this method, the triazoles **5a-c** derived from the reactions of 2,6-difluorobenzyl azide **2** with the enones **1a-c**, were subjected to reaction with an aqueous solution of NH_4OH 33% for the production of *rufinamide* (**8a**) and structural analogues **8b-c**. The reactions were successful and the products **8a-c** were obtained at yields of 42%, 44%, and 40%, respectively.

In the search for a better methodology for synthesis of *rufinamide*, a direct conversion of the trichloro acetyl group, which is present in the triazole precursor **5a**, into carboxamide, which is present in **8a**, was performed. Therefore, by reacting 4-trichloroacetyl-1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole (**5a**), which had been previously synthesized and isolated, with ammonium hydroxide, at 25°C for 18 h, using methanol as the solvent, *rufinamide* (**8a**) was successfully obtained — see Scheme 2. Aiming to further reduce the number of reaction steps, we tested a domino reaction process. Thus, the synthesis of *rufinamide* occurred directly, without isolation of the trichloroacetyl-substituted 1*H*-1,2,3-triazole **5a**. This occurred when the reaction between the ketone **1a** and the azide **2** proceeded initially without solvent and at 130°C for 48 h. After this initial step, and under magnetic stirring, the addition of an aqueous solution of ammonium hydroxide 33%, to the initial reaction medium, using methanol as the solvent, at 25°C for 30 min, permitted the isolation of *rufinamide* (**8a**) by simple filtration at normal pressure, and at a 50% yield. This protocol proved to be the most efficient, economical, and fastest for obtaining *rufinamide* (Scheme 2).



Scheme 2. Synthesis of Rufinamide. Reagents and conditions: *i* = 1) 2,6-Difluorobenzyl azide, neat, 130 °C, 48 h; 2) MeOH, NH_4OH, 25 °C, 30 min.

Table 1. Reactions conditions,[a] yields and melting points for isolated trichloroacetyl triazoles **5**–**7** and carboxamides **8**.



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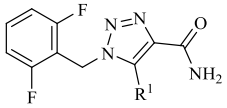

8a-c

Enone + Azide	R^1	R^2	Reaction time (days)	Reaction temp. (°C)	Product	Molecular formula	M.p. (°C)	Yield (%)
1a+2	H	2,6-FC_6H_3	2.0	130	**5a**	$C_{11}H_6Cl_3F_2N_3O$	139 – 140	70
1b+2	CH_3	2,6-FC_6H_3	3.0	130	**5b**	$C_{12}H_8Cl_3F_2N_3O$	109 – 110	60
1c+2	C_6H_5	2,6-FC_6H_3	4.0	150	**5c**	$C_{17}H_{10}Cl_3F_2N_3O$	113 – 115	60
1a+3	H	C_6H_5	2.0	130	**6a**	$C_{11}H_8Cl_3N_3O$	85 – 86	48
1b+3	CH_3	C_6H_5	3.0	130	**6b**	$C_{12}H_{10}Cl_3N_3O$	100 – 102	40
1a+4	H	4-$OMeC_6H_4$	2.0	130	**7a**	$C_{12}H_{10}Cl_3N_3O_2$	92 – 93	45
1b+4	CH_3	4-$OMeC_6H_4$	2.5	130	**7b**	$C_{13}H_{12}Cl_3N_3O_2$	oil	41
1a+2	H	2,6-FC_6H_3	2.0	130	**8a**	$C_{10}H_8F_2N_4O$	240 – 241	42-50
1b+2	CH_3	2,6-FC_6H_3	3.0	130	**8b**	$C_{11}H_{10}F_2N_4O$	212 – 213	42
1c+2	C_6H_5	2,6-FC_6H_3	5.0	150	**8c**	$C_{16}H_{12}F_2N_4O$	172 – 174	52

[a] Solventless.

The structures of all the compounds of **5a-c**, **6a-b**, **7a-b** and **8a-c** were confirmed by ^1H and ^{13}C {^1H} NMR and high resolution mass spectrometry (HRMS) data analysis.[20-26,29-31] The conversion of the trichloroacetyl group into the carboxamide function can also be confirmed by melting points and ^1H and ^{13}C NMR.[20,29] Differences in melting point, solubility, and ^1H and ^{13}C NMR data, can easily be observed to distinguish the precursor **5a** and the product **8a**. A difference of 100°C in the melting point, the high solubilities of **5a** in $CHCl_3$ and in DMSO, while the product **8a** is soluble only in DMSO, the appearance of two broad singlets related to the hydrogens of the NH_2 group of the amide function for the ^1H NMR spectrum of **8a**, and the difference between chemical shifts related to the carbonyl carbon in the ^{13}C NMR spectra for **5a** (161.7 ppm) and **8a** (173.9 ppm), are striking differences between the two compounds, which may also be considered for **5b-c** and **8b-c**.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^1H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^1H at 200.13 MHz and ^{13}C at 50.32 MHz) or Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.61 MHz), 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in $CDCl_3$ or DMSO-d_6, using TMS as internal reference. All melting points were determined using coverslips on an Microquímica MQAPF - 302 apparatus and are uncorrected. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo, Brazil). High resolution mass spectra were recorded on a Waters SYNAPT G2-Si Source mass spectrometer on ESI positive mode

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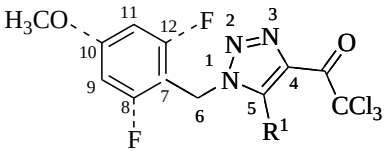
19. *Synthesis of 4-trichoroacetyl-1-(benzyl/2,6-difluoro/4-methoxybenzyl)-5-methyl(phenyl)-1H-1,2,3-triazoles* (**5a-c**, **6a-b**, **7a-b**). *General procedure*: A stirred mixture of **1a-c** and benzyl azides (**2-4**) were heated under solvent free conditions according to the reaction temperatures and times specified in Table 1. The resulting products **5a-c**, **6a-b** and **7a-b** were purified following the next procedures. Compounds **5a-b, 6a-b** and **7a-b** were obtained as solids and recrystallized in hexane/ethyl acetate 10:5 v/v. The compound **5c** was purified by chromatography on column using silica gel flash like SilicaFlash^R

G60 (70 - 230 mesh) and using hexane/ethyl acetate 10:2 v/v, as the eluent.



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20. *Data of 4-trichloroacetyl-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole* (**5a**): Yield 70%, mp. 139 – 140 ºC. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 8.37 (s, 1H, H-5), 7.43 (tt, *J* = 8.4 Hz e *J* = 6.9 Hz, 1H, H-10), 7.06-6.98 (m, 2H; H-9, H-11), 5.73 (s, 2H, H-6). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 173.9 (CO), 161.3 (dd, $^{1}J_{C\text{-}F}$ = 251.8 Hz, $^{3}J_{C\text{-}F}$ = 6.7 Hz, C-8, C-12), 139.9 (C-4), 132.0 (t, $^{3}J_{C\text{-}F}$ = 10.3 Hz, C-10), 130.2 (C-5), 112.0 (dd, $^{2}J_{C\text{-}F}$ = 19.1 Hz, $^{4}J_{C\text{-}F}$ = 5.7 Hz, C-9, C-11), 109.7 (t, $^{2}J_{C\text{-}F}$ = 18.8 Hz, C-7), 94.4 (CCl_3), 41.8 (t, $^{3}J_{C\text{-}F}$ = 4.0 Hz, C-6). Anal. Calc. for $C_{11}H_6Cl_3F_2N_3O$ (338.95): C, 38.80, H, 1.78, N, 12.34%. Found: C, 39.03, H, 1.79, N, 12.37%.

21. *Data of 4-trichloroacetyl-1-(2,6-difluorobenzyl)-5-methyl-1H-1,2,3-triazole* (**5b**): Yield 60 %, mp. 109 – 110 ºC. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 7.38 (tt, *J* = 8.3 Hz, *J* = 6.4 Hz, 1H, H-10), 6.99-6.95 (m, 2H, H-9, H-11), 5.57 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 175.5 (CO), 161.2 (dd, $^{1}J_{C\text{-}F}$ = 251.7 Hz, $^{3}J_{C\text{-}F}$ = 7.3 Hz, C-8, C-12), 142.6 (C-4), 136 (C-5), 131.5 (t, $^{3}J_{C\text{-}F}$ = 10.2 Hz, C-10), 111.7 (dd, $^{2}J_{C\text{-}F}$ = 19.0 Hz, $^{4}J_{C\text{-}F}$ = 5.8 Hz, C-9, C-11), 109.7 (t, $^{2}J_{C\text{-}F}$ = 18.3 Hz, C-7), 94.8 (CCl_3), 39.4 (t, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C-6), 9.3 (CH_3). Anal. Calc. for $C_{12}H_8Cl_3F_2N_3O$ (352.97): C, 40.65, H, 2.27, N, 11.85%. Found: C, 40.62, H, 2.35, N, 11.83%.

22. *Data of 4-trichloroacetyl-5-phenyl-1-(2,6-difluorobenzyl)-1H-1,2,3-triazole* (**5c**): Yield 60 %, mp. 113 – 115 ºC. ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 7.54-7.51 (m, 3H, Ph), 7.36-7.25 (m, 3H, H-10 and Ph), 6.84 (t, *J* = 7.9 Hz, H-9, H-11), 5.46 (s, 2H, H-6). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 174.4 (CO), 161.3 (dd, $^{1}J_{C\text{-}F}$ = 251.8 Hz, $^{3}J_{C\text{-}F}$ = 6.8 Hz, C-8, C-12), 144.7 (C-4), 136.3 (C-5), 131.3 (t, $^{3}J_{C\text{-}F}$ = 10.4 Hz, C-10), 130.5 (Ph), 129.2 (Ph), 128.8 (Ph), 125.1 (Ph), 111.4 (dd, $^{2}J_{C\text{-}F}$ = 19.1 Hz, $^{4}J_{C\text{-}F}$ = 5.7 Hz, C-9, C-11), 109.9 (t, $^{2}J_{C\text{-}F}$ = 18.3 Hz, C-7), 95.0 (CCl_3), 40.4 (t, $^{3}J_{C\text{-}F}$ = 3.7 Hz, C-6). HRMS (ESI): *m/z* calc. 415.9930 ($M+H^+$). Found 415.9930.

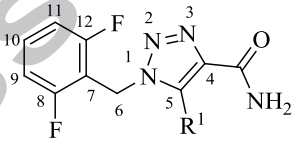
23. *Data of 1-benzyl-4-trichloroacetyl-1H-1,2,3-triazole* (**6a**): Yield 48 %, mp. 85 – 86 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.34 (s, 1H, H-5), 7.41-7.34 (m, 5H, H-8 to H-12), 5.74 (s, 1H, H-6). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 173.8 (CO), 137.9 (C-4), 134.8 (C-7), 132.2 (C-5), 128.6 (C-9, C-11), 128.2 (C-10), 127.9 (C-8, C-12), 94.2 (CCl_3), 53.1 (C-6). Anal. Calc. for $C_{11}H_8Cl_3N_3O$ (304.56) C, 43.38, H, 2.65, N, 13.80%. Found: C, 43.41, H, 2.67, N, 13.82%.

24. *Data of 1-benzyl-4-trichloroacetyl-5-methyl-1H-1,2,3-triazole* (**6b**): Yield 40 %, mp. 100 – 102 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.42-7.35 (m, 3H, H-9 to H-11), 7.30 (d, *J* = 6.7 Hz, 2H, H-8, H-12), 5.72 (s, 2H, H-6), 2.61 (s, 3H, CH_3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 174.9 (CO), 143.6 (C-5), 135.3 (C-4), 134.5 (C-7), 128.8 (C-9, C-11), 128.2 (C-10), 127.6 (C-8, C-12), 94.7 (CCl_3), 50.8 (C-6), 9.4 (CH_3). Anal. Calc. for $C_{12}H_{10}Cl_3N_3O$ (318.57) C, 45.24, H, 3.16, N, 13.19%. Found: C, 45.29, H, 3.19, N, 13.25%.

25. *Data of 4-trichloroacetyl-1-(4-methoxybenzyl)-1H-1,2,3-triazole* (**7a**): Yield 45 %, mp. 92 – 93 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.32 (s, 1H, H-5), 7.41 (d, *J* = 7.6 Hz, 2H, H-8, H-12), 6.97 (d, *J* = 7.5 Hz, 2H, H-9, H-11), 5.68 (s, 2H, H-6), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 174.5 (CO), 159.9 (C-10), 138.6 (C-4), 132.7 (C-5), 130.4 (C-8, C-12), 127.4 (C-7), 114.7 (C-9, C-11), 94.8 (CCl_3), 55.6 (OCH_3), 53.4 (C-6). Anal. Calc. for $C_{12}H_{10}Cl_3N_3O_2$ (334.59) C, 43.08, H, 3.01, N, 12.56%. Found: C, 43.09, H, 3.01, N, 12.59%.

26. *Data of 4-trichloroacetyl-1-(4-methoxybenzyl)-5-methyl-1H-1,2,3-triazole* (**7b**): Yield 41%, yellow oil. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.28 (d, *J* = 8.4 Hz, 2H, H-8, H-12), 6.95 (d, *J* = 8.5 Hz, 2H, H-9, H-11), 5.63 (s, 2H, H-6), 3.74 (s, 3H, OCH_3), 2.61 (s, 3H, CH_3). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 174.9 (CO), 159.1 (C-10), 143.3 (C-5), 135.3 (C-4), 129.3 (C-8, C-12), 126.4 (C-7), 114.2 (C-9, C-11), 94.7 (CCl_3), 55.1 (OCH_3), 50.4 (C-6), 9.4 (CH_3). Anal. Calc. for $C_{13}H_{12}Cl_3N_3O_2$ (348.61) C, 44.79, H, 3.47, N, 12.05 %. Found: C, 44.91, H, 3.58, N, 12.20%.

27. *Synthesis of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamides* (**8a-c**). *General procedure:* To a mixture of 4-trichloroacetyl-1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazoles (**5a-c**) (1 mmol) in methanol (3 ml) was added ammonium hydroxide aqueous solution 28 – 30 % NH_3 basis (1.5 ml) and Et_3N (0.5 ml) at 25 °C for 0.4 to 24 h. During this time, the product **8a** precipitated immediately, while the products **8b-c** precipitate during the reaction, as a white solids and were isolated by filtration, washed with cold methanol, and drying under reduced pressure, furnishing **8a-c** in high degree of purity.



8a-c

28. *Synthesis one-pot of Rufinamide* (**8a**). *General procedure:* 2,6-Difluorobenzyl azide (**2**) (1 mmol, 0.169g) and (*E*)-1,1,1-trichloro-4-ethoxybut-3-en-2-one (**1a**) (1 mmol, 0.215g) were heated, in absence of solvent to 130 °C for 48 h. Subsequently, methanol (3 ml) was added to reactional mixture, followed by the addition of ammonium hydroxide aqueous solution 28 – 30 % NH_3 basis (1,5 ml) at 25 °C for 30 min. During this time, the Rufinamide precipitated immediately as a white solid and was isolated by filtration, washed with cold methanol, and drying under reduced pressure, furnishing **8a** in high degree of purity.

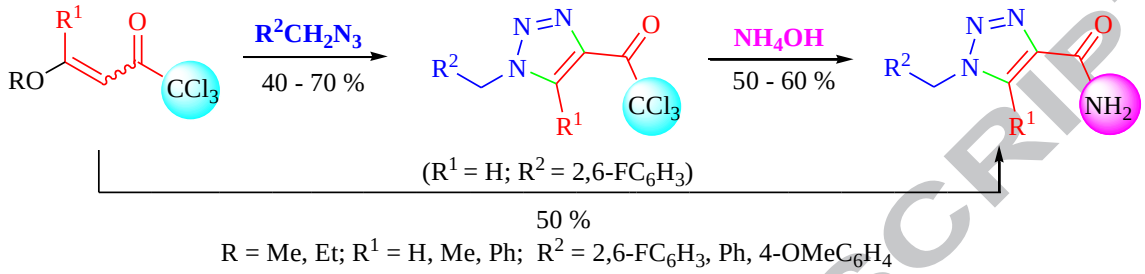
29. *Data of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (Rufinamide)* (**8a**): Yield 50 – 60 %, mp. 240 – 241 ºC. Lit. 240 – 241 ºC.[4] ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 8.53 (s, 1H, H-5), 7.74 (br s, 1H, NH), 7.52 (tt, *J* = 8.3 Hz, *J* = 6.8 Hz, 1H, H-10), 7.38 (br s, 1H, NH), 7.18 (t, *J* = 8.0 Hz, 2H, H-9, H-11), 5.72 (s, 2H, CH_2). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 161.2 (dd, $^{1}J_{C\text{-}F}$ = 249.4 Hz, $^{3}J_{C\text{-}F}$ = 7.3 Hz, C-8, C-12), 161.7 (CO), 143.3 (C-4), 132.3 (t, $^{3}J_{C\text{-}F}$ = 10.4 Hz, C-10), 127.2 (C-5), 112.4 (dd, $^{2}J_{C\text{-}F}$ = 18.7 Hz, $^{4}J_{C\text{-}F}$ = 5.4 Hz, C-9, C-11), 111.5 (t, $^{2}J_{C\text{-}F}$ = 19.0 Hz, C-7), 41.6 (t, $^{3}J_{C\text{-}F}$ = 3.6 Hz, C-6).

30. *Data of 1-(2,6-difluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide* (**8b**): Yield 42 %, mp. 212 – 213 ºC. Lit. 208 – 210 ºC.[32] ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.63 (br s, 1H, NH), 7.49 (tt, *J* = 8.1 Hz e *J* = 7.1 Hz, 1H, H-10), 7.31 (br s, 1H, NH), 7.15 (t, *J* = 8.0 Hz, 2H, H-9, H-11), 5.58 (s, 2H, CH_2), 2.54 (s, 3H, CH_3). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 163.2 (CO), δ 161.2 (dd, $^{1}J_{C\text{-}F}$ = 249.1 Hz, $^{3}J_{C\text{-}F}$ = 7.4 Hz, C-8, C-12), 138.2 (C-4), 136.7 (C-5), 132.1 (t, $^{3}J_{C\text{-}F}$ = 10.4 Hz, C-10), 112.3 (dd, $^{2}J_{C\text{-}F}$ = 18.7 Hz, $^{4}J_{C\text{-}F}$ = 5.9 Hz, C-9, C-11), 111.2 (t, $^{2}J_{C\text{-}F}$ = 18.8 Hz, C-7), 39.1 (C-6), 8.4 (CH_3).

31. *Data of 1-(2,6-difluorobenzyl)-5-phenyl-1H-1,2,3-triazole-4-carboxamide* (**8c**): Yield 52 %, mp. 172 – 174 ºC. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.72 (br s, 1H, NH), 7.49-7.37 (m, 5H, Ph), 7.34 (br s, 1H, NH), 7.02 (t, *J* = 8.1 Hz, 2H, H-9, H-11), 5.53 (s, 2H, CH_2). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 162.1 (CO), 161.1 (dd, $^{1}J_{C\text{-}F}$ = 249.4 Hz, $^{3}J_{C\text{-}F}$ = 7.3 Hz, C-8, C-12), 139.2 (C-5), 139 (C-4), 131.8 (t, $^{3}J_{C\text{-}F}$ = 10.5 Hz, C-10), 130.3 (Ph), 129.9 (Ph), 128.6 (Ph), 126.5 (Ph), 112.0 (dd, $^{2}J_{C\text{-}F}$ = 18.8 Hz, $^{4}J_{C\text{-}F}$ = 5.7 Hz, C-9, C-11), 111.3 (t, $^{2}J_{C\text{-}F}$ = 18.7 Hz, C-7), 40.6 (t, $^{3}J_{C\text{-}F}$ = 3.7 Hz, C-6). HRMS (ESI): *m/z* calc. 315.1052 ($M+H^+$). Found 315.1039.

32. Meier, R. EP Patent 0 199 262 A2, 1986.

Graphical Abstract Pictogram



R = Me, Et; R^1 = H, Me, Ph; R^2 = 2,6-FC_6H_3, Ph, 4-$OMeC_6H_4$