Short communication

Sonochemistry in organocatalytic enamine-azide [3+2] cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides

Daiane M. Xavier, Bruna S. Goldani, Natália Seus, Raquel G. Jacob, Thiago Barcellos, Márcio W. Paixão, Rafael Luque, Diego Alves

PII: S1350-4177(16)30149-3
DOI: http://dx.doi.org/10.1016/j.ultsonch.2016.05.007
Reference: ULTSON 3216

To appear in: *Ultrasonics Sonochemistry*

Received Date: 8 February 2016
Revised Date: 4 May 2016
Accepted Date: 5 May 2016

Please cite this article as: D.M. Xavier, B.S. Goldani, N. Seus, R.G. Jacob, T. Barcellos, M.W. Paixão, R. Luque, D. Alves, Sonochemistry in organocatalytic enamine-azide [3+2] cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides, *Ultrasonics Sonochemistry* (2016), doi: http://dx.doi.org/10.1016/j.ultsonch.2016.05.007

Sonochemistry in organocatalytic enamine-azide [3+2] cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides.

Daiane M. Xavier[a], Bruna S. Goldani[a], Natália Seus[a], Raquel G. Jacob[a], Thiago Barcellos[b], Márcio W. Paixão[c], Rafael Luque[d] and Diego Alves[a,*]

[a] *Laboratório de Síntese Orgânica Limpa - LASOL - Universidade Federal de Pelotas - UFPel - P.O. Box 354, 96010-900, Pelotas - RS, Brazil.*

[b] *Laboratory of Biotechnology of Natural and Synthetic Products, Universidade de Caxias do Sul, Caxias do Sul - RS, Brazil.*

[c] *Laboratório de Síntese de Produtos Naturais, Universidade Federal de São Carlos, São Carlos - SP, Brazil.*

[d] *Departamento de Quimica Organica, Universidad de Cordoba, Campus de Rabanales, Cordoba, Spain.*

* corresponding author. Tel: +55 (53) 3275-7533.

E-mail adresses: daianedamotta@yahoo.com.br (D.M. Xavier), goldanibruna@gmail.com (B.S. Goldani), natyseus@gmail.com (N. Seus), raquel.jacob@ufpel.edu.br (R.G. Jacob), tbsilva6@ucs.br (T.B. Silva), mwpaixao@ufscar.br (M.W. Paixão), q62alsor@uco.es (R. Luque) and diego.alves@ufpel.edu.br (D. Alves).

Abstract: We described herein the use of sonochemistry in the organocatalytic enamine-azide [3+2] cycloadditions of *β*-oxo-amides with a range of substituted aryl azides. These sonochemical promoted reactions were found to be amenable to a range of β-oxo amides or aryl azides, providing and efficient access to new *N*-aryl-1,2,3-triazoyl carboxamides in good to excellent yields and short times of reaction.

Keywords: sonochemistry; cycloadditions; organocatalysis; 1,2,3-triazoles; carboxamides.

1. Introduction

Heterocycles represent one of the most general structural units found in several natural and synthetic bioactive compounds [1,2]. Particularly, 1,2,3-triazoles comprise an interesting class of nitrogen-based heterocycles widely used in the discovery and modulation of drug candidates and in new materials [3]. Therefore, several methodologies have been already reported for the preparation of these scaffolds, especially via thermal 1,3-dipolar cycloaddition of azides with alkynes [4] as well as copper or ruthenium catalyzed reactions [5-11]. In view of the restricted applications of metal-based methodologies in chemical biology [12-18], recent studies have been directed towards the development of metal-free methodologies for the synthesis of 1,2,3-triazole [19-20]. In this regard, organocatalytic approaches employing carbonyl compounds have been reported to promote the synthesis of highly functionalized 1,2,3-triazoles [21-23]. In these organocatalyzed [3+2] cycloadditions reactions, the generated enamines or enolates might act as the dipolarophile partner in the 1,3-dipolar cycloadditions with organic azides [21].

In the context of functionalized nitrogen compounds, *β*-oxo-amides and their derivatives exhibit attractive structural features as versatile organic intermediates. A large number of molecules containing these units display biological activities [24-26] and can be found in natural products [27-29] (Figure 1).

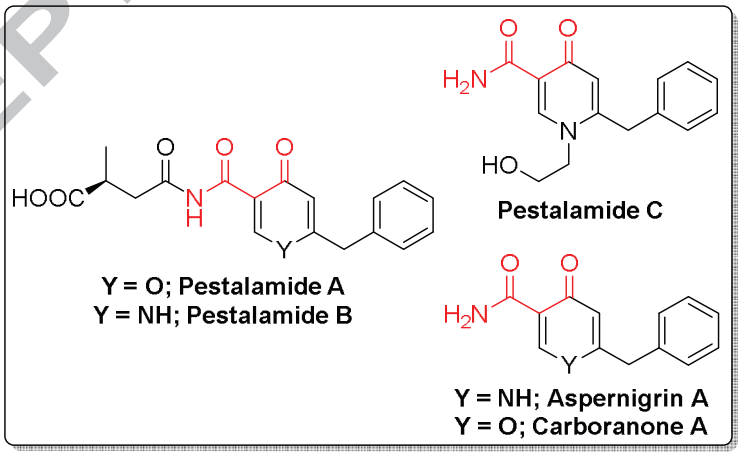


Figure 1. Natural products containing β-oxo amides.

Consequently, intensive research efforts based on the use of *β*-oxo-amides have been reported for the synthesis of a plethora of heterocycles [30-36]

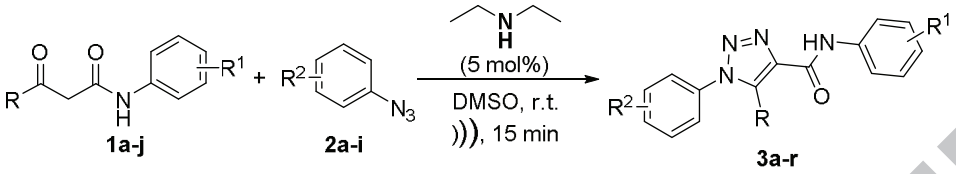
including 1,2,3-triazoyl-carboxamides [37-40]. As example, 1,2,3-triazole-4-carboxamide derivatives strongly inhibited the replication of various H3N2 and H1N1 influenza A virus strains [38]. Recently, our research group described in two independent works the synthesis of a range of 1,2,3-triazoyl-carboxamides by the organocatalytic enamine-azide cycloaddition of *β*-oxo-amides with 4-azido-7-chloroquinoline [39] or azidophenyl arylselenides [40]. Cycloaddition products were obtained in good to excellent yields and tolerated a series of substituted *β*-oxo-amides. Based on these premises, it is evident that the design of efficient methods using suitable, environmentally sound, cheap and high functionalized substrates and reaction conditions for the preparation of functionalized 1,2,3-triazoles still remains a challenge in modern Organic Synthesis.

In this sense, ultrasonic irradiation has gained popularity in the past decades as a versatile tool in a large variety of industrial and academic applications.[41-46]. The use of sonication as a tool in promoting organic synthesis (sonochemistry) is well documented [45-46]. This non-conventional energy source has been proved to be able to accelerate reactions or even to switch product profiles and selectivities through the formation of new reactive intermediates and compounds not usually observed under classical thermal conditions [45]. In addition, chemistries under ultrasound irradiation can be considered environmentally benign processes, being less energy intensive and generating reduced quantities of side products [41-46].

Despite the large interest in the synthesis of 1,2,3-triazoles, there are only a few contributions describing the use of sonochemistry for the preparation of such heterocycles [47-55]. As example, Chen and co-workers described the use of sonochemistry in the synthesis of chrysin derivatives linked with 1,2,3-triazoles by 1,3-dipolar cycloadditions. In this study, the reaction rate was significantly accelerated under ultrasound-assisted irradiation and the corresponding products were obtained in high yields [55].

To the best of our knowledge, the use of sonochemistry to synthesize highly functionalized 1,2,3-triazoles via organocatalytic enamine-azide cycloaddition with organic azides has not been explored to date. In addition, the substrate scope for the organocatalytic synthesis of 1,2,3-triazoyl-4-carboxamides is restricted to azidophenyl arylselenides and 4-azido-7-chloroquinoline. Therefore, our continued interest in the synthesis of functionalized 1,2,3-triazoles, led to report herein the use of sonochemistry in the organocatalyzed synthesis of novel *N*-aryl-1,2,3-

triazoyl carboxamides by reactions of *β*-oxo-amides with a range of substituted aryl azides (Scheme 1).



Scheme 1. Synthesis of novel *N*-aryl-1,2,3-triazoyl carboxamides using ultrasonic irradiation.

2. Experimental

2.1. General procedure for the synthesis of *N*-aryl-1,2,3-triazoyl carboxamides 3a-r under ultrasound irradiation

β-Oxo amides **1a-j** (0.3 mmol), aryl azides **2a-i** (0.3 mmol), Et_2NH (5 mol %) and DMSO (0.6 mL) were added to a glass tube. The ultrasound probe was placed in a glass vial containing the reaction mixture. The amplitude of the ultrasound waves was fixed in 40%. Then, the homogeneous reaction mixture was sonicated for 15 min. The crude product obtained was subsequently purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate (5:1) as eluent to afford the desired products **3a-r**.

5-methyl-*N*,1-diphenyl-1*H*-1,2,3-triazole-4-carboxamide [37] **(3a):** Yield: 0.079 g (95%); White solid; mp 134-135 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.61 (s, 1H), 7.03 (d, J = 8.1 Hz, 2H), 6.87-6.77 (m, 5H), 6.51 (t, J = 7.6 Hz, 2H), 6.26 (t, J = 7.6 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 159.37, 138.48, 138.18, 137.49, 135.18, 129.94, 129.60, 128.44, 125.33, 123.59, 120.33, 9.34. MS *m/z* (relative intensity): 279 (9), 278 (M^+, 52), 180 (5), 158 (47), 145 (7), 130 (39), 118 (29), 104 (16), 77 (100), 65 (12), 51 (26), 43 (6). HRMS calcd. for $C_{16}H_{15}N_4O$: $[M + H]^+$ 279.1246. Found: 279.1243.

5-methyl-1-phenyl-*N*-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide [37] **(3b):** Yield: 0.080 g (92%); White solid; mp 133-134 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.88 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.24-7.21 (m, 5H), 6.72 (d, J = 8.4 Hz, 2H), 2.88 (s,3H), 2.15 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 159.12, 138.19, 137.23, 135.89, 135.15, 132.48, 129.81, 129.50, 128.75, 125.23, 120.24, 20.27, 9.23. MS *m/z* (relative intensity): 292 (M^+, 72), 221 (10), 158 (33), 147 (16), 130

(42), 119 (56), 118 (38), 104 (20), 93 (11), 77 (100), 51 (22). HRMS calcd. for $C_{17}H_{17}N_4O$: $[M + H]^+$ 293.1402. Found: 293.1391.

***N*-(4-methoxyphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide** [37] **(3c):** Yield: 0.087 g (94%); Beige solid; mp 148-150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.95 (s, 1H), 7.61-7.55 (m, 5H), 7.47-7.45 (m, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.08, 156.65, 138.75, 137.13, 135.75, 130.98, 129.96, 129.63, 125.29, 121.64, 114.38, 55.51, 9.67. MS *m/z* (relative intensity): 308 (M^+, 75), 237 (14), 158 (18), 147 (29), 130 (46), 119 (97), 118 (38), 108 (13), 104 (33), 95 (16), 81 (20), 77 (100), 69 (31), 57 (18), 51 (22), 41 (16). HRMS calcd. for $C_{17}H_{17}N_4O_2$: $[M + H]^+$ 309.1352. Found: 309.1347.

5-methyl-1-phenyl-*N*-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide [37] **(3d):** Yield: 0.081 g (93%); Yellow solid; mp 99-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.02 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.60-7.53 (m, 3H), 7.48-7.46 (m, 2H), 7.27-7.22 (m, 2H), 7.09 (t, J = 7.4 Hz, 1H), 2.66 (s, 3H), 2.41(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.11, 138.71, 137.17, 135.51, 135.48, 130.39, 129.91, 129.57, 128.44, 126.63, 125.13, 124.70, 121.99, 17.60, 9.68. MS *m/z* (relative intensity): 292 (M^+, 17), 277 (17), 264 (80), 235 (7), 158 (35), 144 (17), 130 (43), 118 (44), 104 (19), 103 (11), 93 (15), 77 (100), 65 (7), 51 (22). HRMS calcd. for $C_{17}H_{17}N_4O$: $[M + H]^+$ 293.1402. Found: 293.1398.

***N*-(2-methoxyphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide** [37] **(3e):** Yield: 0.087 g (94%); White solid; mp 173-174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.18 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.29-7.23 (m, 5H), 6.73-6.72 (m, 2H), 6.62-6.57 (m, 1H), 3.55 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 158.26, 148.28, 137.71, 137.22, 134.98, 129.78, 129.40, 126.74, 125.09, 123.89, 120.34, 119.29, 110.87, 55.84, 8.99. MS *m/z* (relative intensity): 308 (M^+, 12), 277 (100), 158 (22), 130 (28), 118 (23), 104 (11), 77 (61), 65 (8), 51 (14). HRMS calcd. for $C_{17}H_{17}N_4O_2$: $[M + H]^+$ 309.1352. Found: 309.1344.

***N*-(2-chlorophenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide** [37] **(3f):** Yield: 0.080 g (86%); Yellow solid; mp 117-118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.67 (s, 1H), 8.53 (dd, J = 8.2 and 1.5 Hz, 1H), 7.60-7.55 (m, 3H), 7.49-

7.44 (m, 2H), 7.42 (dd, *J* = 8.2 and 1.5 Hz, 1H), 7.31 (dt, *J* = 7.8 and 1.4 Hz, 1H), 7.07 (dt, *J* = 7.8 and 1.4 Hz, 1H), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.20, 138.47, 137.46, 135.44, 134.54, 129.99, 129.62, 129.15, 127.51, 125.16, 124.55, 123.31, 121.28, 9.74. MS *m/z* (relative intensity): 312 (M^+, 4), 277 (100), 158 (33), 130 (37), 118 (22), 104 (10), 77 (76), 65 (5), 51 (19). HRMS calcd. for $C_{16}H_{14}ClN_4O$: $[M + H]^+$ 313.0853. Found: 313.0851.

***N*-(4-chlorophenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide** [37] **(3g):** Yield: 0.079 g (84%); White solid; mp 165-166 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.09 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.58-7.56 (m, 3H), 7.47-7.45 (m, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.11, 138.31, 137.42, 136.28, 135.43, 130.01, 129.61, 129.15, 128.95, 125.17, 120.97, 9.68. MS *m/z* (relative intensity): 314 (17), 312 (M^+, 49), 192 (5), 158 (45), 147 (15), 130 (49),119 (56), 104 (19), 93 (19), 77 (100), 51 (25). HRMS calcd. for $C_{16}H_{14}ClN_4O$: $[M + H]^+$ 313.0853. Found: 313.0850.

***N*-(4-fluorophenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (3h):** Yield: 0.074 g (83%); White solid; mp 161-162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.05 (s, 1H), 7.69-7.65 (m, 3H), 7.59-7.57 (m, 3H), 7.48-7.46 (m, 2H), 7.06 (t, *J* = 8.9 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.42 (d, *J* = 244 Hz), 159.17, 138.45, 137.39, 135.53, 133.72 (d, *J* = 2.7 Hz), 130.08, 129.68, 125.26, 121.59 (d, *J* = 7.8 Hz), 115.60 (d, *J* = 22.4 Hz), 9.74. MS *m/z* (relative intensity): 296 (M^+, 61), 158 (44), 147 (16), 130 (50), 119 (44), 118 (36), 104 (18), 93 (17), 83 (11), 77 (100), 51 (25). HRMS calcd. for $C_{16}H_{14}FN_4O$: $[M + H]^+$ 297.1152. Found: 297.1147.

5-methyl-*N*-(4-nitrophenyl)-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (3i): Yield: 0.077 g (80%); Orange solid; mp 231-232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.25 (dt, *J* = 9.2 and 2.8 Hz, 2H), 8.04 (dt, *J* = 9.2 and 2.8 Hz, 2H), 7.63-7.61 (m, 3H), 7.53-7.50 (m, 2H), 2.68 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.21, 143.62, 143.26, 137.79, 130.81, 129.80, 129.35, 124.94, 124.47, 120.45, 118.98, 9.17. MS *m/z* (relative intensity): 323 (M^+, 41), 158 (70), 147 (5), 130 (55), 118 (38), 104 (14), 93 (28), 77 (100), 67 (7), 51 (23), 43 (7). HRMS calcd. for $C_{16}H_{14}N_5O_3$: $[M + H]^+$ 324.1097. Found: 324.1091.

***N*,1,5-triphenyl-1*H*-1,2,3-triazole-4-carboxamide** [37] **(3j):** Yield: 0.083 g (81%); Beige solid; mp 143-145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.21 (s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.60-7.54 (m, 2H), 7.48-7.24 (m, 9H), 7.12-7.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 158.09, 139.51, 138.72, 136.08, 135.89, 130.40, 129.25, 128.92, 128.85, 128.80, 128.51, 128.25, 125.21, 124.28, 119.92. MS *m/z* (relative intensity): 340 (M^+, 3), 239 (18), 220 (7), 178 (6), 120 (45), 105 (72), 93 (100), 77 (67), 69 (21), 57 (14), 51 (78), 43 (17). HRMS calcd. for $C_{21}H_{17}N_4O$: $[M + H]^+$ 341.1402. Found: 341.1395.

5-methyl-*N*-phenyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide [37] **(3k):** Yield: 0.079 g (90%); Yellow solid; mp 204-205 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.08 (s, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.38-7.32 (m, 6H), 7.13 (t, J = 7.4 Hz, 1H), 2.64 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.26, 140.33, 138.50, 137.74, 137.33, 133.06, 130.18, 129.00, 125.06, 124.24, 119.83, 21.17, 9.70. MS *m/z* (relative intensity): 292 (M^+, 69), 235 (10), 221 (13), 194 (10), 172 (89), 158 (9), 144 (65), 133 (16), 118 (19), 107 (33), 93 (12), 91 (100), 77 (28), 65 (66), 51 (10), 44 (25). HRMS calcd. for $C_{17}H_{17}N_4O$: $[M + H]^+$ 293.1402. Found: 293.1397.

1-(4-methoxyphenyl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide [37] **(3l):** Yield: 0.085 g (92%); Brown solid; mp 179-181 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.08 (s, 1H), 7.71(d, J = 8.8 Hz, 2H), 7.39-7.37 (m, 4H), 7.14 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 160.75, 159.29, 138.40, 137.71, 137.50, 129.04, 128.32, 126.68, 124.27, 119.82, 114.81, 55.66, 9.71. MS *m/z* (relative intensity): 308 (M^+, 48), 265 (6), 237 (11), 210 (10), 188 (90), 173 (16), 160 (70), 146 (35), 134 (18), 123 (17), 117 (20), 107 (23), 104 (9), 92 (59), 77 (100), 64 (34), 51 (15). HRMS calcd. for $C_{17}H_{17}N_4O_2$: $[M + H]^+$ 309.1352. Found: 309.1359.

5-methyl-*N*-phenyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide [37] **(3m):** Yield: 0.063 g (72%); Pale brown solid; mp 117-118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.10 (s, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.42-7.39 (m, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.3 Hz, 1H), 7.14 (t, J = 7.3 Hz, 1H), 2.48 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.21, 138.19, 138.09, 137.68, 135.42, 134.33, 131.40, 130.72, 128.97, 127.09, 127.01, 124.22, 119.79, 17.08, 9.06. MS *m/z* (relative intensity): 292 (M^+, 88), 221 (15), 194 (9), 172 (76), 159

(10), 144 (85), 132 (41), 118 (46), 107 (30), 93 (16), 91 (100), 77 (37), 65 (83), 51 (14), 43 (16). HRMS calcd. for $C_{17}H_{17}N_4O$: $[M + H]^+$ 293.1402. Found: 293.1406.

1-(2-fluorophenyl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide (3n): Yield: 0.074 g (83%); Yellow solid; mp 88-89 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.66 (s, 1H), 7.05 (d, J = 7.7 Hz, 2H), 6.93-6.87 (m, 2H), 6.76 (t, J = 9.7 Hz, 1H), 6.66 (t, J = 7.7 Hz, 1H), 6.51 (t, J = 7.7 Hz, 2H), 6.27 (t, J = 7.7 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 159.13, 155.75 (d, J = 252 Hz), 138.89, 138.43, 137.95, 132.94 (d, J = 7.9 Hz), 128.93, 128.44, 125.53 (d, J = 3.8 Hz), 123.65, 122.58 (d, J = 12.4 Hz), 120.39, 116.92 (d, J = 19.1 Hz), 8.65. MS *m/z* (relative intensity): 296 (M^+, 100), 239 (12), 225 (13), 198 (16), 176 (76), 165 (19), 158 (23), 148 (86), 136 (96), 129 (18), 122 (57), 111 (39), 102 (14), 95 (99), 77 (38), 65 (28), 43 (51). HRMS calcd. for $C_{16}H_{14}FN_4O$: $[M + H]^+$ 297.1152. Found: 297.1147.

1-(4-fluorophenyl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide (3o): Yield: 0.080 g (90%); White solid; mp 178-179 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.64 (s, 1H), 7.07 (d, J = 8.1 Hz, 2H), 6.94-6.91 (m, 2H), 6.68 (t, J = 8.7 Hz, 2H), 6.54 (t, J = 7.7 Hz, 2H), 6.29 (t, J = 7.7 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 162.40 (d, J = 248 Hz), 159.32, 138.47, 138.11, 137.76, 131.54 (d, J = 3.0 Hz), 128.42, 127.82 (d, J = 9.1 Hz), 123.58, 120.34, 116.53 (d, J = 23.2 Hz), 9.24. MS *m/z* (relative intensity): 296 (M^+, 76), 239 (9), 225 (9), 198 (9), 176 (66), 148 (67), 136 (45), 122 (23), 111 (26), 95 (100), 77 (25), 65 (18), 43 (16). HRMS calcd. for HRMS calcd. for $C_{16}H_{14}FN_4O$: $[M + H]^+$ 297.1152. Found: 297.1148.

1-(4-chlorophenyl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide [37] **(3p):** Yield: 0.081 g (87%); Beige solid; mp 195-196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.05 (s, 1H), 7.71-7.69 (m, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.39-7.35 (m, 2H), 7.16-7.12 (m, 1H), 2.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 158.99, 138.71, 137.57, 137.33, 136.23, 133.94, 129.93, 129.03, 126.43, 124.36, 119.82, 9.75. MS *m/z* (relative intensity): 312 (M^+, 82), 241 (8), 221 (10), 192 (86), 164 (68), 158 (19), 152 (44), 146 (9), 138 (21), 127 (35), 111 (100), 102 (14), 93 (42), 77 (41), 65 (27), 51 (19), 43 (11). HRMS calcd. for $C_{16}H_{14}ClN_4O$: $[M + H]^+$ 313.0853. Found: 313.0850.

5-methyl-1-(2-nitrophenyl)-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide (3q): Yield: 0.085 g (88%); Orange solid; mp 189-190 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 9.96 (s, 1H), 8.14-8.13 (m, 1H), 8.09 (ddd, J = 8.3, 2.3 and 1.0 Hz, 1H), 7.77 (ddd, J = 8.3, 2.2 and 1.0 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.49-7.47 (m, 2H), 6.97-6.93 (m, 2H), 6.71 (t, J = 7.4 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 159.13, 148.29, 138.42, 138.38, 138.12, 135.99, 131.55, 131.14, 128.33, 124.50, 123.56, 120.34, 120.30, 9.16. MS *m/z* (relative intensity): 323 (M^+, 31), 203 (13), 192 (9), 164 (25), 157 (20), 149 (17), 137 (10), 129 (18), 123(10), 117 (16), 95 (23), 81 (51), 77 (19), 71 (28), 69 (100), 57 (55), 43 (36). HRMS calcd. for $C_{16}H_{14}N_5O_3$: $[M + H]^+$ 324.1097. Found: 324.1090.

5-Methyl-*N*-phenyl-1-(2-(phenylselanyl)phenyl)-1*H*-1,2,3-triazole-4-carboxamide [40] **(3r):** Yield: 0.119 g (91%); orange oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.12 (s, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.41-7.25 (m, 9H), 7.13 (t, J = 7.4 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 159.07, 138.43, 138.01, 137.66, 135.09, 134.92, 133.10, 132.85, 131.20, 129.58, 128.94, 128.72, 127.78, 127.71, 127.69, 124.17, 119.73, 9.26. MS (relative intensity) m/z: 435 (M^+, 12), 434 (47), 431 (23), 328 (14), 314 (37), 312 (20), 249 (100), 234 (26), 232 (28), 207 (37), 206 (33), 157 (25), 152 (50), 129 (19), 77 (64), 51 (20). HRMS calcd for $C_{22}H_{19}N_4OSe$ $[M + H]^+$: 435.0724. Found: 435.0744.

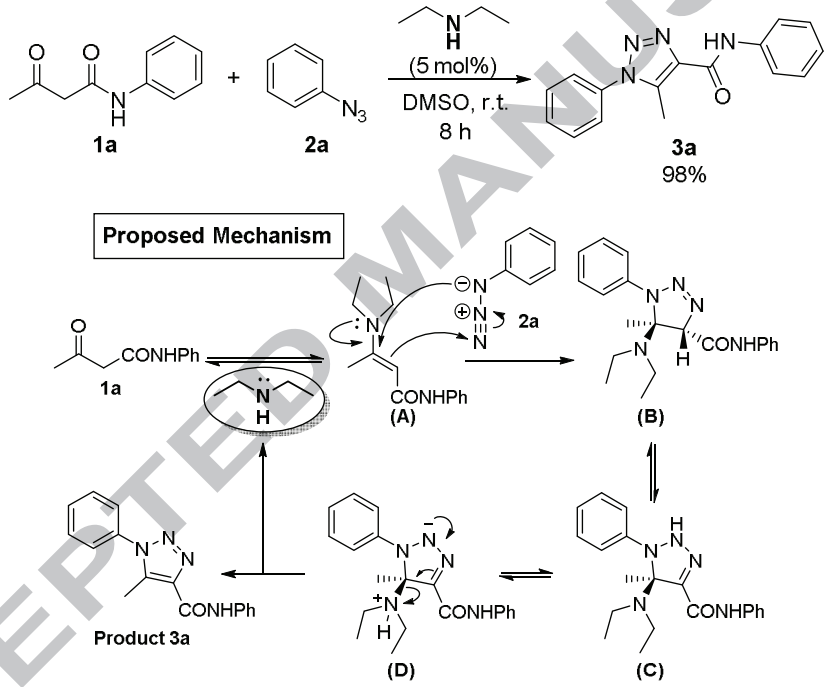
2.2. General procedure for the synthesis of *N*-aryl-1,2,3-triazoyl carboxamides under conventional conditions

β-Oxo amides **1** (0.3 mmol), aryl azides **2** (0.3 mmol), Et_2NH (5 mol %) and DMSO (0.6 mL) were added to a glass tube. The homogeneous reaction mixture was stirred in an open vial for 8 h. The crude product obtained was subsequently purified according to above procedure.

3. Results and Discussion

Preliminary experiments to optimize the reaction conditions using ultrasound irradiation were performed using *β*-oxo-amide **1a** and phenyl azide **2a** as model reaction substrates (Table 1). Firstly, based on our previous report on the reaction under conventional conditions [40], a homogeneous mixture of substrates **1a** (0.3 mmol) and **2a** in DMSO (0.6 mL) was stirred at room

temperature in the presence of 5 mol% of Et_2NH as organocatalyst, providing an excellent yield (98%) of the desired product **3a** after 8 h (Scheme 2). Regarding the mechanism of this reaction, it is thought that the enamine intermediate **(A)** is formed first, after the condensation of Et_2NH with the compound **1a**. A subsequent 1,3-dipolar cycloaddition between the electron-rich olefin **(A)** and the phenyl azide **2a** would give rise to triazoline intermediate **(B)**, which can undergo a plausible 1,3-hydride shift to generate triazoline intermediate **(C)**. Finally, the zwitterionic form of **(C)**, represented as intermediate **(D)**, could undergo an elimination reaction to regenerate Et_2NH to continue the catalytic cycle and produce the desired product **3a** (Scheme 2).



Scheme 2. Synthesis of 1,2,3-triazoyl carboxamide **3a** under conventional conditions.

Identical reaction conditions were applied for the reaction under ultrasonic irradiation (40% of frequency) at different reaction times (Table 1, entries 1-5). When a mixture of **1a** and **2a** was sonicated in the presence of Et_2NH (5 mol%) and DMSO (0.6 mL) as solvent during 5 min, the desired product **3a** was obtained in 69% yield (Table 1, entry 1). The yield of product **3a** was observed to increase with an increase in the reaction time from 10 to 20 min (Table 1, entries 2-4). Furthermore, the desired product **3a** was obtained in 95% yield after sonication for 15 or 20 min. When the reaction of substrates **1a** and **2a** was sonicated for 25 min,

a decrease in product **3a** yield was observed (Table 1, entry 5). A significant decrease in reaction yields were also observed (Table 1, entries 6-7) for reactions carried out in 15 min and decreased organocatalyst loadings (from 5 to 1 mol%). The corresponding product **3a** was not obtained in the absence of organocatalyst (Table 1, entry 8).

Insert Table 1 here

From Table 1, optimum reaction conditions to obtain 5-methyl-*N*,1-diphenyl-1*H*-1,2,3-triazole-4-carboxamide **3a** were clearly present in entry 4, in which a homogeneous mixture of *N*-phenylbutanamide **1a** (0.3 mmol), phenyl azide **2a** (0.3 mmol) and Et_2NH (5 mol%) in DMSO (0.6 mL) was sonicated at room temperature for 15 minutes.

The scope of the proposed methodology was then extended under optimised conditions to a range of β-oxo amides **1** and aryl azides **2** (Table 2). Phenyl azide **2a** reacted efficiently with electron-neutral and different electron-deficient β-oxo amides to give the corresponding *N*-aryl-1,2,3-triazoyl carboxamides **3a-j** in good to excellent yields. Reactions of phenyl azide **2a** with β-oxo amides containing electron-donating groups (EDG) **1b-e** and electron-withdrawing (EWG) substituents **1f-i** at the carboxamide moiety yielded the corresponding products **3b-i** in 80-94% yields (Table 2, entry 2-9). Generally speaking, the reactions were found to be slightly sensitive to electronic effects in the aromatic ring of β-oxo amides. For example, β-oxo amides containing EDG's at the aromatic ring provided higher yields as compared to those bearing EWG's (Table 2, entries 2-5 *vs.* 6-9). The reaction performed with β-oxo amide **1g** containing a phenyl group gave also access to the corresponding triazole **3j** in 81% yield (Table 2, entry 10).

The reactivity of *N*-phenylbutanamide **1a** with different functionalized aryl azides **2b-i** was subsequently investigated (under otherwise identical reaction conditions). In general, the reactions were found to be insensitive to the electronic conditions in the aryl ring of azides. Aryl azides containing either an EDG or an EWG on the aromatic ring delivered the expected *N*-aryl-1,2,3-triazoyl carboxamides **3k-q** in good to excellent isolated yields (Table 2, entries 11-17). However, an interesting steric effect could be observed when the reaction was performed with *o*-tolyl azide **2d** and 1-azido-2-fluorobenzene **2e**, furnishing the

corresponding products **3m** and **3n** in 72% and 83% yield, respectively (Table 2, entries 13 and14). Finally, extending the scope of this methodology, the reaction of **1a** with azidophenyl arylselenide **2i** was performed. In this case, the desired product **3r** was obtained in 91% yield (Table 2, entry 18).

Insert Table 2 here

With the aim to compare the effect of sonication in these reactions, we performed these organocatalytic cycloadditions of *β*-oxo-amides and aryl azides under conventional conditions for 8 h (Table 2, yields in brackets). The obtained results show that the use of ultrasound irradiation is better than conventional condition, furnishing the corresponding products in comparable yields but in very short reaction time.

3. Conclusion

In summary, we described the use of ultrasound irradiation as an alternative energy source in the organocatalytic enamine-azide [3+2] cycloadditions reactions. Using diethylamine as organocatalyst, phenyl azide reacted efficiently with electron-neutral and different electron-deficient β-oxo amides to give the corresponding products in good to excellent yields. Under the same reaction conditions, *N*-phenylbutanamide reacted smoothly with different functionalized aryl azides delivered the expected products in high yields. The accelerating effect in these ultrasound promoted reactions should largely be ascribed to mechanical effects (i.e. enhanced mass transfer). In addition, these organocatalytic reactions were performed under conventional conditions and the obtained results show that the use of ultrasound irradiation furnished the corresponding products in comparable yields but in very short reaction time, especially suitable for Green or Click Chemistry concepts.

Acknowledgements

We thank the CNPq (Grants 306430/2013-4, 400150/2014-0 and 447595/2014-8), CAPES, FAPERGS, FAPESP (15/17141-1 and 14/50249-8) and FINEP for the financial support. Rafael Luque graftefully acknowledges support from Ciencia sem Fronteiras Program (Grant 303415/2014-2) as Visiting Scientist to Universidade Federal de Pelotas, RS.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ultsonch.xxxxx.

References

[1] T. Eicher, S. Hauptmann, In: The Chemistry of Heterocycles, Wiley-VCH, Weinheim, 2003, pp. 1.

[2] A. R. Katrizky, A. F. Pozharskii, In: Handbook of Heterocyclic Chemistry, 2nd ed., Pergamon, Amsterdam, 2000, pp. 1.

[3] For a recent set of reviews in this area, see the themed issue: Applications of click chemistry. *Chem. Soc. Rev.,* **2010**, *39*, 1221-1407.

[4] R. Huisgen, 1.3-Dipolare cycloadditionen rückschau und ausblick, Angew. Chem. (75) 1963, 604-637.

[5] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, A stepwise Huisgen cycloaddition process: copper (I)-catalyzed regioselective "ligation" of azides and terminal alkynes, Angew. Chem. 41 (2002), 2596-2599.

[6] C. W. Tornøe, C. Christensen, M. Meldal, Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper (I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides, J. Org. Chem. 67 (2002), 3057-3064.

[7] A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless, H. C. Kolb, In situ selection of lead compounds by click chemistry: target-guided optimization of acetylcholinesterase inhibitors, J. Am. Chem. Soc. 127 (2005), 6686-6692.

[8] L. V. Lee, M. L. Mitchell, S. Huang, V. V. Fokin, K. B. Sharpless, C. Wong, A potent and highly selective inhibitor of human α-1,3-fucosyltransferase via click chemistry, J. Am. Chem. Soc. 125 (2003), 9588-9589.

[9] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, Ruthenium-catalyzed cycloaddition of alkynes and organic azides, J. Am. Chem. Soc. 127 (2005), 15998-15999.

[10] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, Ruthenium-catalyzed azide-alkyne cycloaddition: scope and mechanism, J. Am. Chem. Soc. 130 (2008), 8923-8930.

[11] J. A. Johnson, J. M. Baskin, C. R. Bertozzi, J. T. Koberstein, N. J. Turro, Copper-free click chemistry for the *in situ* crosslinking of photodegradable star polymers, Chem. Commun. 26 (2008), 3064-3066.

[12] J. M. Baskin, C. R. Bertozzi, Bioorthogonal click chemistry: covalent labeling in living systems, QSAR Comb. Sci. 26 (2007), 1211-1219.

[13] K. Jomova, M. Valko, Advances in metal-induced oxidative stress and human disease, Toxicology 283 (2011), 65-87.

[14] J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond, T. Carell, Click chemistry as a reliable method for the high-density postsynthetic functionalization of alkyne-modified DNA, Org. Lett. 8 (2006), 3639-3642.

[15] E. Lallana, E. Fernandez-Megia, R. Riguera, Surpassing the use of copper in the click functionalization of polymeric nanostructures: a strain-promoted approach, J. Am. Chem. Soc. 2009, *131*, 5748-5750.

[16] A. J. Link, M. K. S. Vink, D. A. Tirrell, Presentation and detection of azide functionality in bacterial cell surface proteins, J. Am. Chem. Soc. 126 (2004), 10598-10602.

[17 L. M. Gaetke, C. K. Chow, Copper toxicity, oxidative stress, and antioxidant nutrients, Toxicology 189 (2003), 147-163.

[18] D. C. Kennedy, C. S. McKay, M. C. B. Legault, D. C. Danielson, J. A. Blake, A. F. Pegoraro, A. Stolow, Z. Mester, J. P. Pezacki, Cellular consequences of copper complexes used to catalyze bioorthogonal click reactions, J. Am. Chem. Soc. 133 (2011), 17993-18001.

[19] M. F. Debets, S. S. Van Berkel, J. Dommerholt, A. J. Dirks, F. P. J. T. Rutjes, F. L. Van Delft, Bioconjugation with strained alkenes and alkynes, Acc. Chem. Res. 44 (2011), 805-815.

[20] J. M. Baskin, C. R. Bertozzi, Copper-free click chemistry: bioorthogonal reagents for tagging azides, Aldrichim. Acta 43 (2010), 15-23

[21] C. G. S. Lima, A. Ali, S. S. Van Berkel, B. Westermann, M. W. Paixão, Emerging approaches for the synthesis of triazoles: beyond metal-catalyzed and strain-promoted azide–alkyne cycloaddition, Chem. Commun. 51 (2015), 10784-10796.

[22] S. S. V. Ramasastry, Enamine/enolate-mediated organocatalytic azide-carbonyl [3+2] cycloaddition reactions for the synthesis of densely functionalized 1,2,3-triazoles**,** Angew. Chem., Int. Ed. 53 (2014), 14310-14312.

[23] J. John, J. Thomas, W. Dehaen, Organocatalytic routes toward substituted 1,2,3-triazoles, Chem. Commun. 51 (2015), 10797-10806.

[24] Y.-H. Chen, Y.-H. Zhang, H.-J. Zhang, D.-Z. Liu, M. Gu, J.-Y. Li, F. Wu, X.-Z. Zhu, J. Li, F.-J. Nan, Design, synthesis, and biological evaluation of isoquinoline-1,3,4-trione derivatives as potent caspase-3 inhibitors, J. Med. Chem. 49 (2006), 1613-1623.

[25] S. Chatterjee, D. Dunn, M. Tao, G. Wells, Z.-Q. Gu, R. Bihovsky, M. A. Ator, R. Siman, J. P. Mallamo, P_2-achiral, P'-extended α-ketoamide inhibitors of calpain I, Bioorg. Med. Chem. Lett. 9 (1999), 2371-2374.

[26] C. E. Augelli-Szafran, C. J. Blankley, B. D. Roth, B. K. Trivedi, R. F. Bousley, A. D. Essenburg, K. L. Hamelehle, B. R. Krause, R. L. Stanfield, Inhibitors of acyl-CoA:cholesterol acyltransferase. 5. Identification and structure-activity relationships of novel beta-ketoamides as hypocholesterolemic agents, J. Med. Chem. 36 (1993), 2943-2949.

[27] G. Ding, L. Jiang, L. Guo, X. Chen, H. Zhang, Y. Che, Pestalazines and pestalamides, bioactive metabolites from the plant pathogenic fungus *Pestalotiopsis theae,* J. Nat. Prod. 71 (2008)*,* 1861-1865.

[28] Y. Ye, H. Zhu, Y. Song, J. Liu, R. Tan, Structural Revision of Aspernigrin A, reisolated from *Cladosporiumherbarum* IFB-E002, J. Nat. Prod. 68 *(*2005), 1106-1108.

[29] Y. Zhang, T. Zhu, Y. Fang, H. Liu, Q. Gu, W. Zhu, Carbonarones A and B, new bioactive γ-pyrone and α-pyridone derivatives from the marine-derived fungus *Aspergillus carbonarius*, J. Antibiot. 60 (2007), 153-157.

[30] Z. Zhang, S. Fang, Q. Liu, G. Zhang, Approach to polysubstituted 4-pyridones from N-aryl acetoacetamides via a N to C 1,3-acyl migration mediated by sodium persulfate, J. Org. Chem. 77 (2012), 7665-7670.

[31] Y. Ouyag, J. Huang, W. Pan, Y. Liang, Y. Yang, D. Dong, [4+2] Annulation – convenient synthesis of substituted dihydropyranones in aqueous media, Eur. J. Org. Chem. 2009 (2009), 2003-2009.

[32] M. N. S. Saudi, M. M. A. El-Semary, R. Y. Elbayaa, M. I. Jaeda, M. M. Eissa, E. I. Amer, N. M. Baddour, Synthesis and biological evaluation of a novel class as antileishmanial agent, Med. Chem. Res. 21 (2012), 257-267.

[33] H. -L. Wang, Z. Li, G. -W. Wang, S. -D. Yang, Silver catalyzed intramolecular cyclization for synthesis of 3-alkylideneoxindoles *via* C–H functionalization, Chem. Commun. 47 (2011), 11336-11338.

[34] D. Xiang, X. Xin, X. Liu, R. Zhang, J. Yang, D. Dong, Regioselective synthesis of 3-arylamino- and 5-arylaminoisoxazoles from enaminones, Org. Lett. 14 (2012), 644-647.

[35] G. Tenti, M. T. Ramos, J. C. Menendez, One-pot access to a library of structurally diverse nicotinamide derivatives via a three-component formal aza [3 + 3] cycloaddition, ACS Comb. Sci. 14 (2012), 551-557.

[36] L. Xia, Y. R. Lee, Efficient one-step synthesis of pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives by organocatalytic cascade reactions of isatins and β-ketoamides, Org. Biomol. Chem. 11 (2013), 5254-5263.

[37] Z. Wang, X. Bi, P. Liao, R. Zhang, Y. Liang, D. Dong, Intramolecular hydrogen bonding-assisted cyclocondensation of α-diazoketones with various amines: a strategy for highly efficient Wolff 1,2,3-triazole synthesis, Chem. Commun. 48 (2012), 7076-7078.

[38] H. Cheng, J. Wan, M. -I. Lin, Y. Liu, X. Lu, J. Liu, Y. Xu, J. Chen, Z. Tu, Y. -S. E. Cheng, K. Ding, Design, Synthesis, and in vitro biological evaluation of 1*h*-1,2,3-triazole-4-carboxamide derivatives as new anti-influenza A agents targeting virus nucleoprotein, J. Med. Chem. 55 (2012), 2144-2153.

[39] E. A. Wilhelm, N. C. Machado, A. B. Pedroso, B. S. Goldani, N. Seus, S. Moura, L. Savegnago, R. G. Jacob, D. Alves, Organocatalytic synthesis and evaluation of 7-chloroquinoline-1,2,3-triazoyl carboxamides as potential antinociceptive, anti-inflammatory and anticonvulsant agent, RSC Adv. 4 (2014), 41437- 41445.

[40] N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, Organocatalytic synthesis of (arylselanyl)phenyl-1*h*-1,2,3-triazole-4-carboxamides by cycloaddition between azidophenyl arylselenides and β-oxo-amides, Eur. J. Org. Chem. 2014 (2014), 1059-1065.

[41] Z. Li, J. Hong, X. Zhou, An efficient and clean CuI-catalyzed chalcogenylation of aromatic azaheterocycles with dichalcogenides, Tetrahedron 67 (2011) 3690-3697.

[42] M.M. Mojtahedi, M. S. Abaee, Ultrasound Applications in Synthetic Organic Chemistry, In: D. Chen, S.K. Sharma, A. Mudhoo (Eds.), Handbook on Applications of Ultrasound Sonochemistry for Sustainability, CRC Press, New York, 2012, pp 281-322.

[43] G. Cravotto, P. Cintas, Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications, Chem. Soc. Rev. 35 (2006) 180-196.

[44] T.J. Mason, Sonochemistry and the environment – Providing a “green” link between chemistry, physics and engineering, Ultrason. Sonochem. 14 (2007) 476-483.

[45] M. Nüchter, B. Ondruschka, A. Jungnickel, U. Müller, Organic processes initiated by non-classical energy sources, J. Phys. Org. Chem. 13 (2000) 579-586.

[46] T.J. Mason, Ultrasound in synthetic organic chemistry, Chem. Soc. Rev. 26 (1997) 443-451.

[47] G. Cravotto, V. V. Fokin, D. Garella, A. Binello, L. Boffa, A. Barge, Ultrasound-promoted copper-catalyzed azide-alkyne cycloaddition, J. Comb. Chem. 12 (2010), 13–15.

[48] M. F. Mady, G. E. A. Awad, K. B. Jørgensen, Ultrasound-assisted synthesis of novel 1,2,3-triazoles coupled diaryl sulfone moieties by the CuAAC reaction, and biological evaluation of them as antioxidant and antimicrobial agents, Eur. J. Med. Chem. 84 (2014) 433-443.

[49] H. Marzag, S. Alaoui, H. Amdouni, A. R. Martin, K. Bougrin, R. Benhida, Efficient and selective azidation of per-*O*-acetylated sugars using ultrasound activation: application to the one-pot synthesis of 1,2,3-triazole glycosides, New J. Chem. 39 (2015), 5437-5444.

[50] S. B. Nallapati, B. Y. Sreenivas, R. Bankala, K. V. L. Parsa, S. Sripelly, K. Mukkanti, M. Pal, 1,2,3-Triazoles derived from olanzapine: their synthesis *via* an ultrasound assisted CuAAC method and evaluation as inhibitors of PDE4B, RSC Adv. 5 (2015), 94623-94628.

[51] H. Naeimi, S. Dadashzadeh, M. Moradian, Facile and efficient sonochemical synthesis of 1,4-disubstituted 1,2,3-triazole derivatives catalyzed by CuI under mild conditions, Res. Chem. Intermed. 41 (2015), 2687–2695.

[52] H. A. Stefani, H. A. Canduzini, F. Manarin, Modular synthesis of mono, di, and tri-1,4-disubstituted-1,2,3-triazoles through copper-mediated alkyne–azide cycloaddition, Tetrahedron Lett. 52 (2011), 6086–6090.

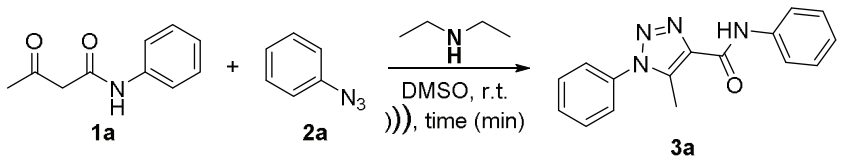
[53] H. A. Stefani, N. C. S. Silva, F. Manarin, D. S. Lüdtke, J. Zukerman-Schpector, L. S. Madureira, E. R. T. Tiekink, Synthesis of 1,2,3-triazolylpyranosides through click chemistry reaction, Tetrahedron Lett. 53 (2012), 1742–1747.

[54] H. A. Stefani, A. S. Vieira, M. F. Z. J. Amaral, L. Cooper, Synthesis of 5-alkynyl-2,2,6-trimethyl-1,3-dioxin-4-ones and 1,4-disubstituted-1,2,3-triazoles, Tetrahedron Lett. 52 (2011), 4256–4261.

[55] Y. Jiang, X. Chen, L. Qua, J. Wang, J. Yuan, S. Chen, X. Li, C. Qu, Ultrasonic-assisted synthesis of chrysin derivatives linked with 1,2,3-triazoles by 1,3-dipolar cycloaddition reaction, Ultrason. Sonochem. 18 (2011), 527–533.

Tables

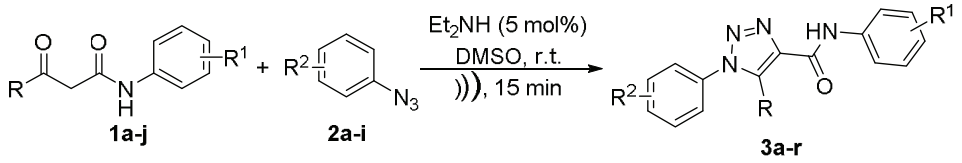
Table 1. Optimization studies for preparation of 1,2,3-triazoyl carboxamide **3a**.[a]



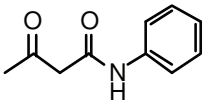
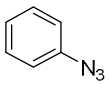
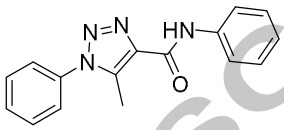
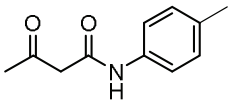
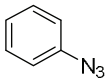
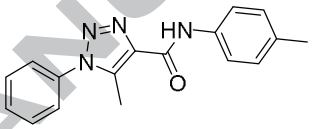
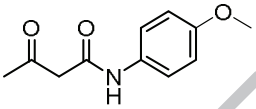
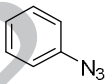
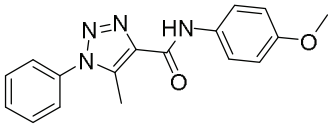
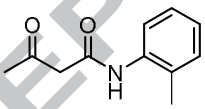
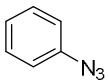
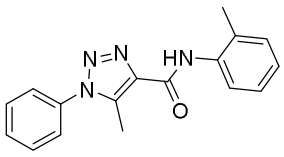
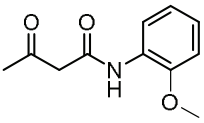
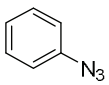
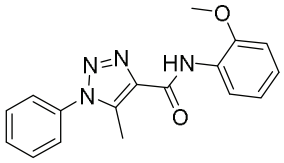
Entry	Et_2NH (mol%)	Time (min)	Yield of **3a** (%)[b]
1	5	5	69
2	5	10	82
3	5	15	95
4	5	20	95
5	5	25	82
6	3	15	40
7	1	15	17
8	-	15	nd

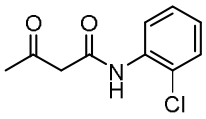
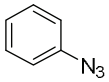
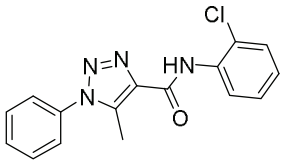
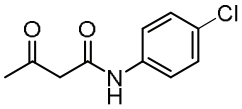
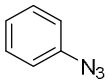
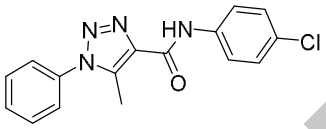
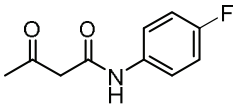
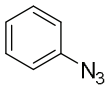
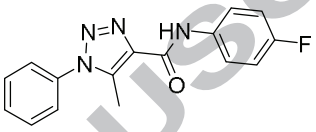
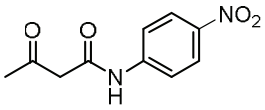
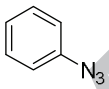
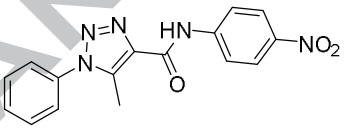
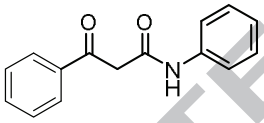
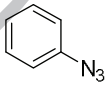
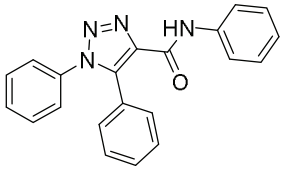
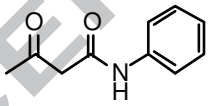
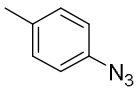
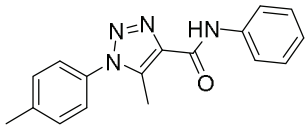
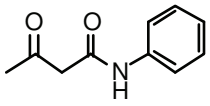
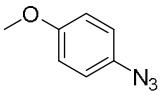
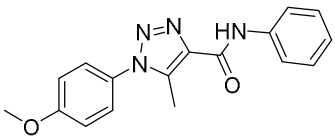
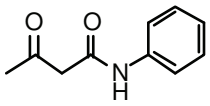
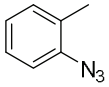
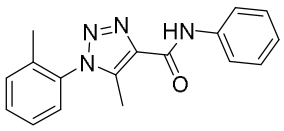
[a] Reactions were performed with β-keto amide **1a** (0.3 mmol) and phenyl azides **2a** (0.3 mmol) in DMSO (0.6 mL) as solvent under ultrasound irradiation (40% of the amplitude) at room temperature. [b] Yields are given for isolated products.

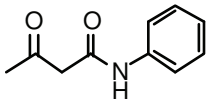
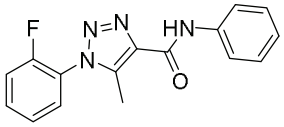
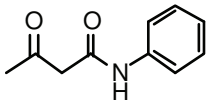
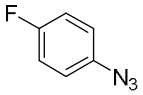
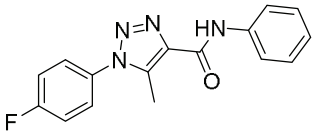
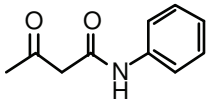
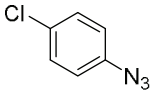
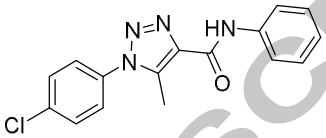
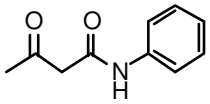
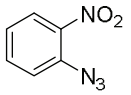
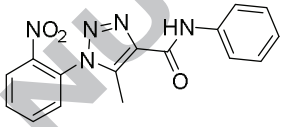
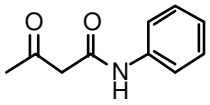
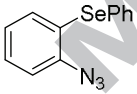
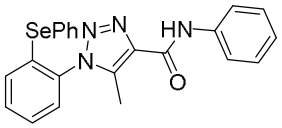
Table 2. Variability in the synthesis of *N*-aryl-1,2,3-triazoyl carboxamides.[a]



1a-j **2a-i** **3a-r**

Entry	*β*-Oxo-amides **1a-j**	Aryl azide **2a-i**	Product	Yield (%)[b,c]
1	 **1a**	 **2a**	 **3a**	95 (98)
2	 **1b**	 **2a**	 **3b**	92 (90)
3	 **1c**	 **2a**	 **3c**	94 (91)
4	 **1d**	 **2a**	 **3d**	93
5	 **1e**	 **2a**	 **3e**	94 (88)

6	 **1f**	 **2a**	 **3f**	86 (80)
7	 **1g**	 **2a**	 **3g**	84
8	 **1h**	 **2a**	 **3h**	83 (76)
9	 **1i**	 **2a**	 **3i**	80
10	 **1j**	 **2a**	 **3j**	81
11	 **1a**	 **2b**	 **3k**	90
12	 **1a**	 **2c**	 **3l**	92 (70)
13	 **1a**	 **2d**	 **3m**	72

14	 **1a**	 **2e**	 **3n**	83
15	 **1a**	 **2f**	 **3o**	90
16	 **1a**	 **2g**	 **3p**	87 (89)
17	 **1a**	 **2h**	 **3q**	88
18	 **1a**	 **2i**	 **3r**	91

[a] Reactions were performed with β-keto amides **1a-j** (0.3 mmol) and aryl azides **2a-i** (0.3 mmol), using Et_2NH (5 mol%) as catalyst in DMSO (0.6 mL) as solvent under ultrasound irradiation (40% of amplitude) at room temperature for 15 min. [b] Yields are given for isolated products. [c] Yields in brackets were obtained in reactions performed under conventional conditions for 8 h.

Sonochemistry in organocatalytic enamine-azide [3+2] cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides.

Daiane M. Xavier[a], Bruna S. Goldani[a], Natália Seus[a], Raquel G. Jacob[a], Thiago Barcellos[b], Márcio W. Paixão[c], Rafael Luque[d] and Diego Alves[a,*]

[a] *Laboratório de Síntese Orgânica Limpa - LASOL - Universidade Federal de Pelotas - UFPel - P.O. Box 354, 96010-900, Pelotas - RS, Brazil.*

[b] *Laboratory of Biotechnology of Natural and Synthetic Products, Universidade de Caxias do Sul, Caxias do Sul - RS, Brazil.*

[c] *Laboratório de Síntese de Produtos Naturais, Universidade Federal de São Carlos, São Carlos - SP, Brazil.*

[d] *Departamento de Quimica Organica, Universidad de Cordoba, Campus de Rabanales, Cordoba, Spain.*

* corresponding author. Tel: +55 (53) 3275-7533. e-mail: diego.alves@ufpel. edu.br

Contents

General Information: The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizant agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Baker silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. A Cole Parmer-ultrasonic processor Model CPX 130, with a maxim power of 130 W, operating at amplitude of 40% and a frequency of 20 kHz was used. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker DPX 400 spectrometer. Spectra were recorded in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublets), t (triplet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of DMSO-d_6 or $CDCl_3$. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416.

SELECTED SPECTRA

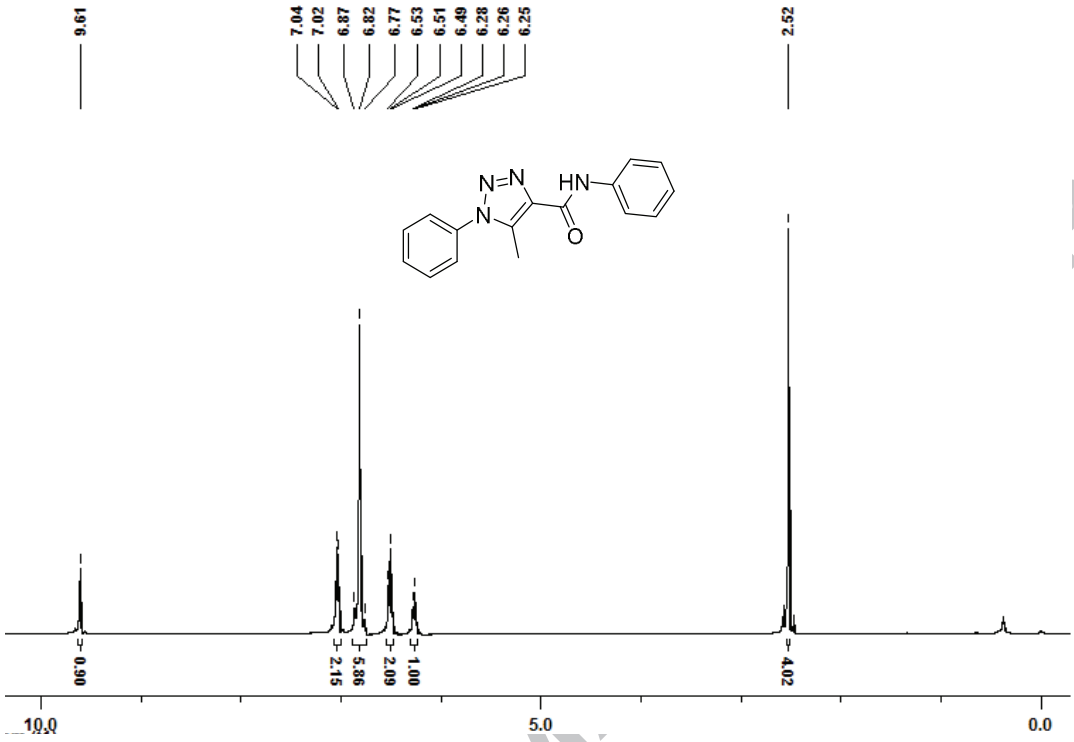


Figure 1. ^{1}H NMR (400 MHz) spectrum for compound **3a** in DMSO-d_6.

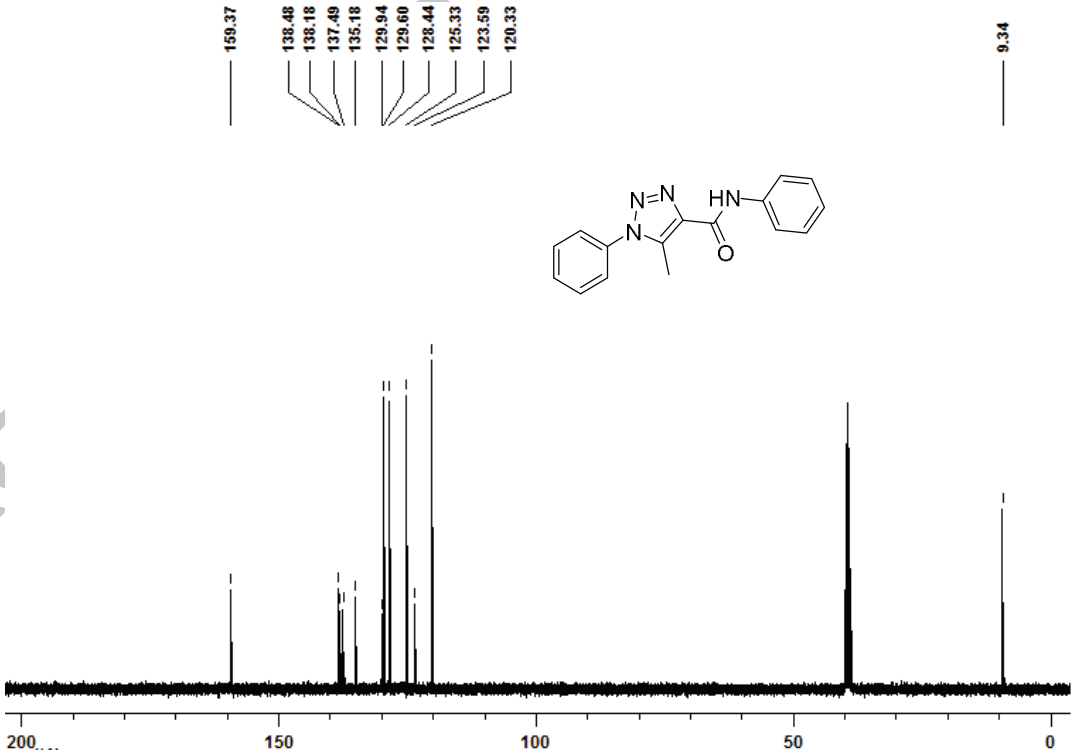


Figure 2. ^{13}C NMR (100 MHz) spectrum for compound **3a** in DMSO-d_6.

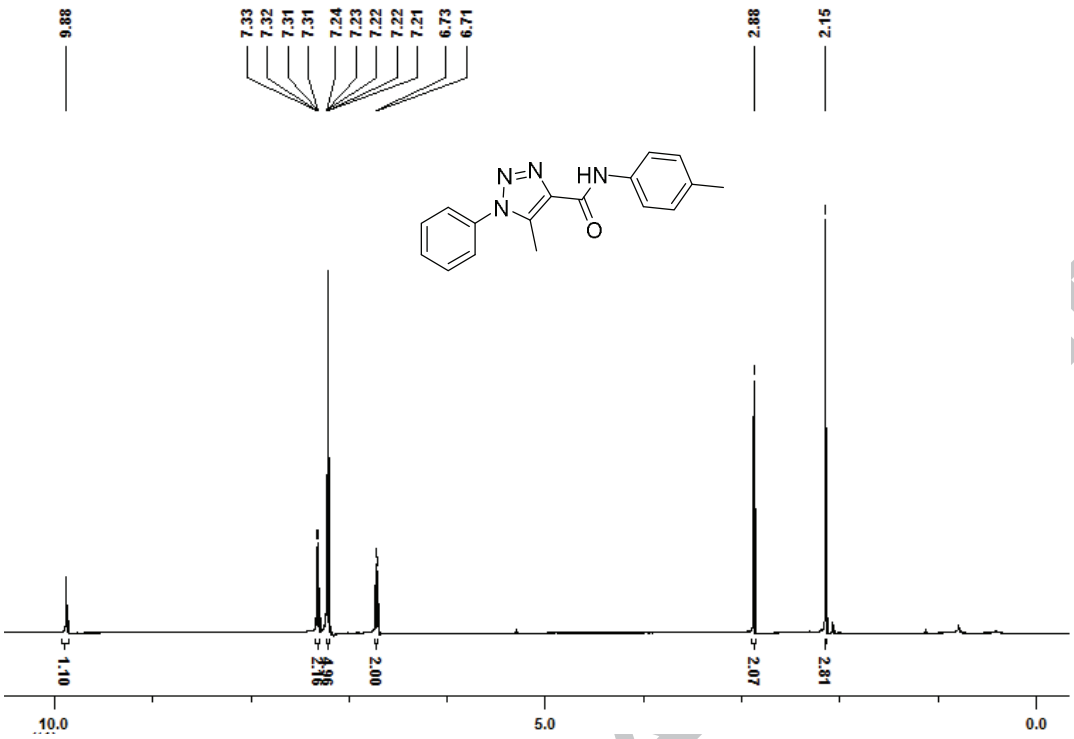


Figure 3. ^{1}H NMR (400 MHz) spectrum for compound **3b** in DMSO-d_6.

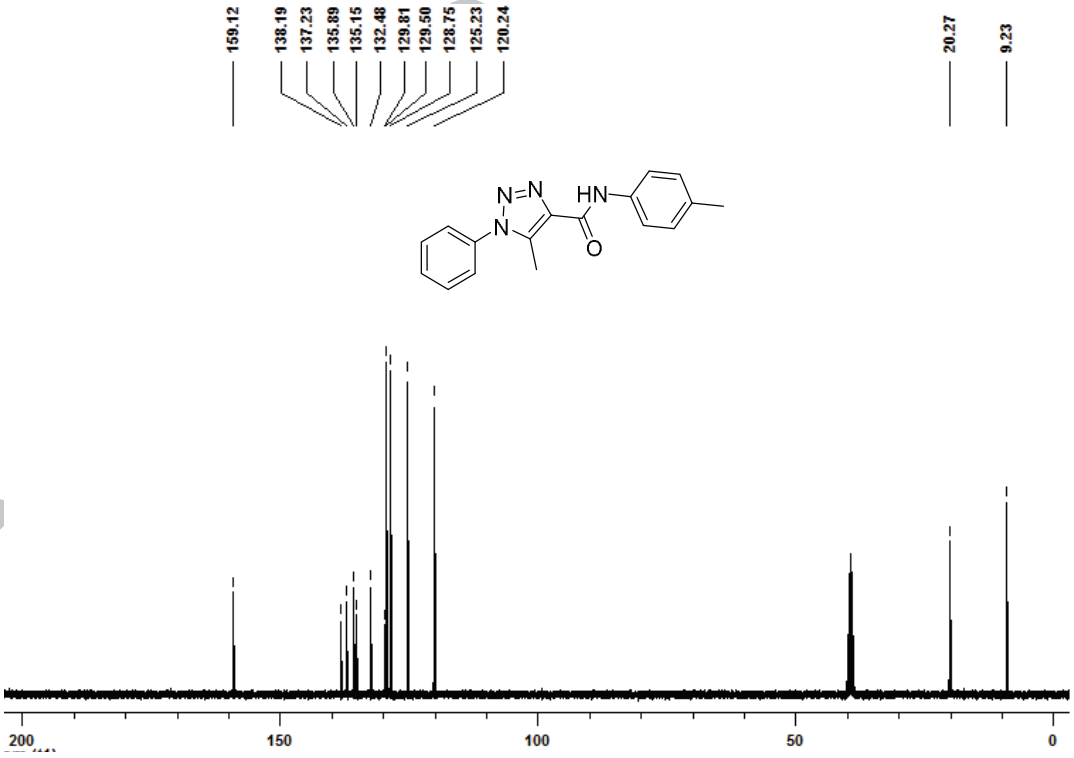


Figure 4. ^{13}C NMR (100 MHz) spectrum for compound **3b** in DMSO-d_6.

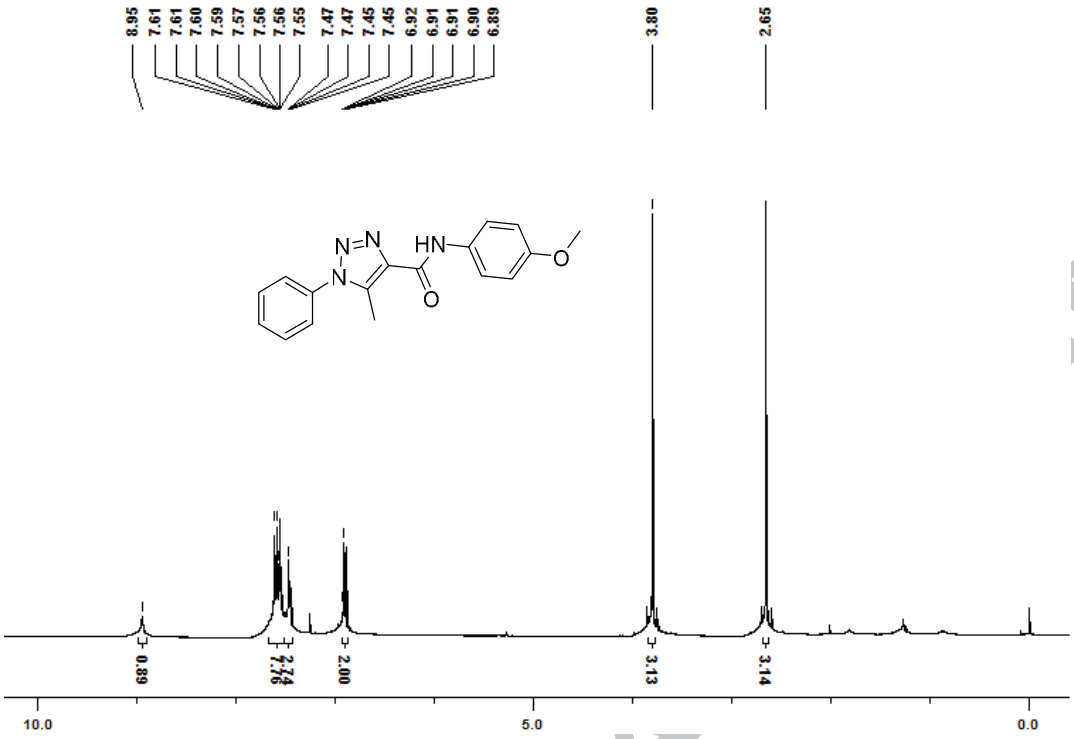


Figure 5. ^{1}H NMR (400 MHz) spectrum for compound **3c** in $CDCl_3$.

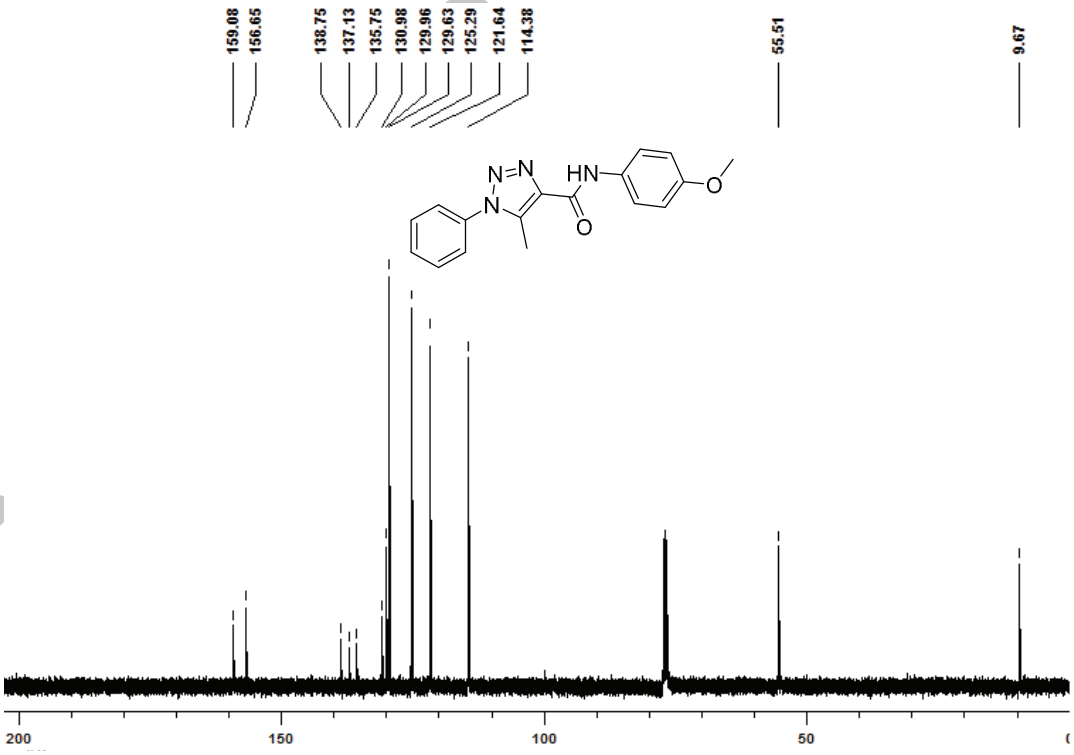


Figure 6. ^{13}C NMR (100 MHz) spectrum for compound **3c** in $CDCl_3$.

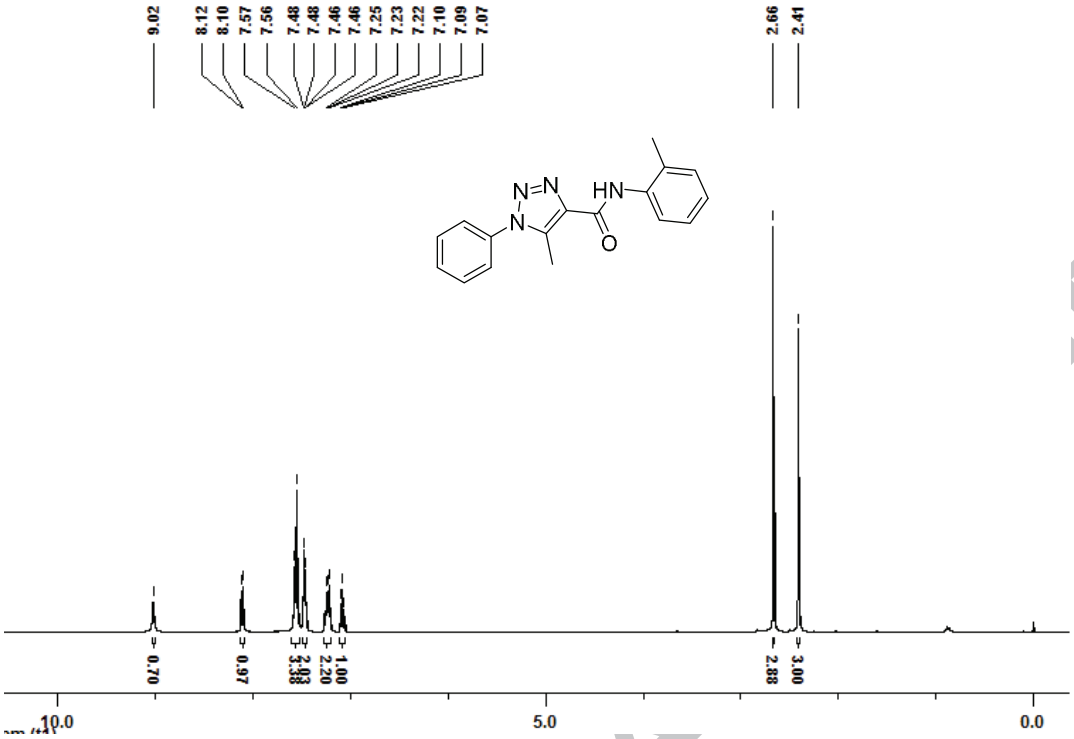


Figure 7. ^{1}H NMR (400 MHz) spectrum for compound **3d** in DMSO-d_6.

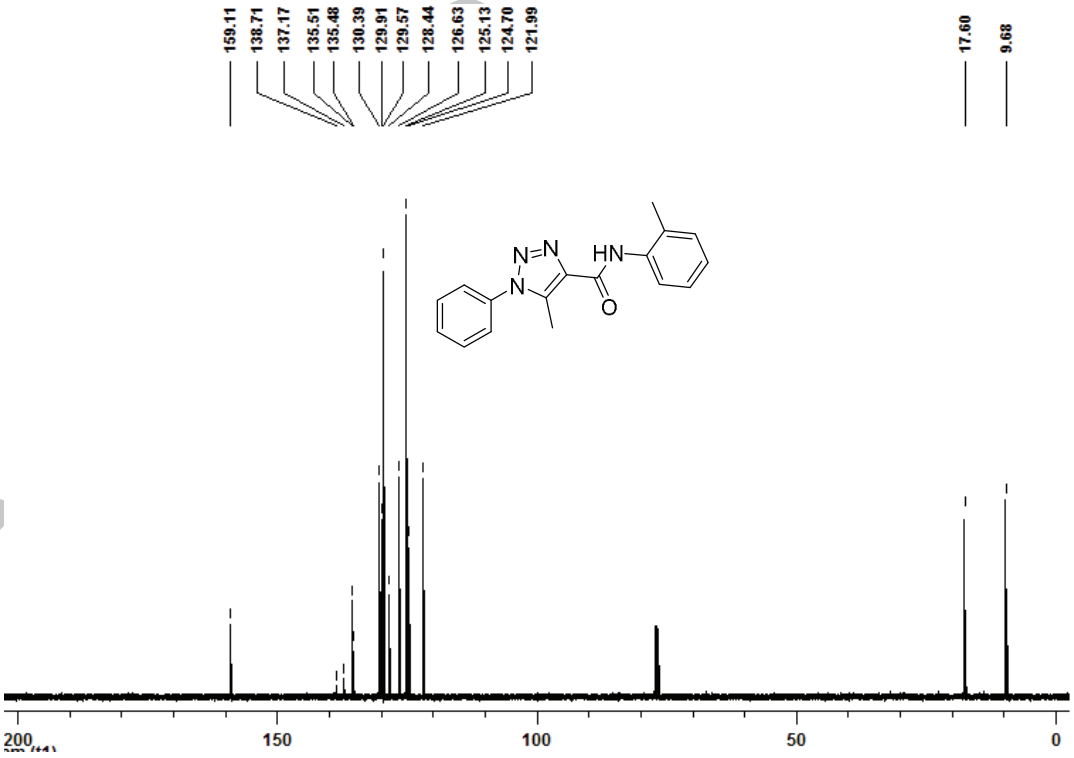


Figure 8. ^{13}C NMR (100 MHz) spectrum for compound **3d** in DMSO-d_6.

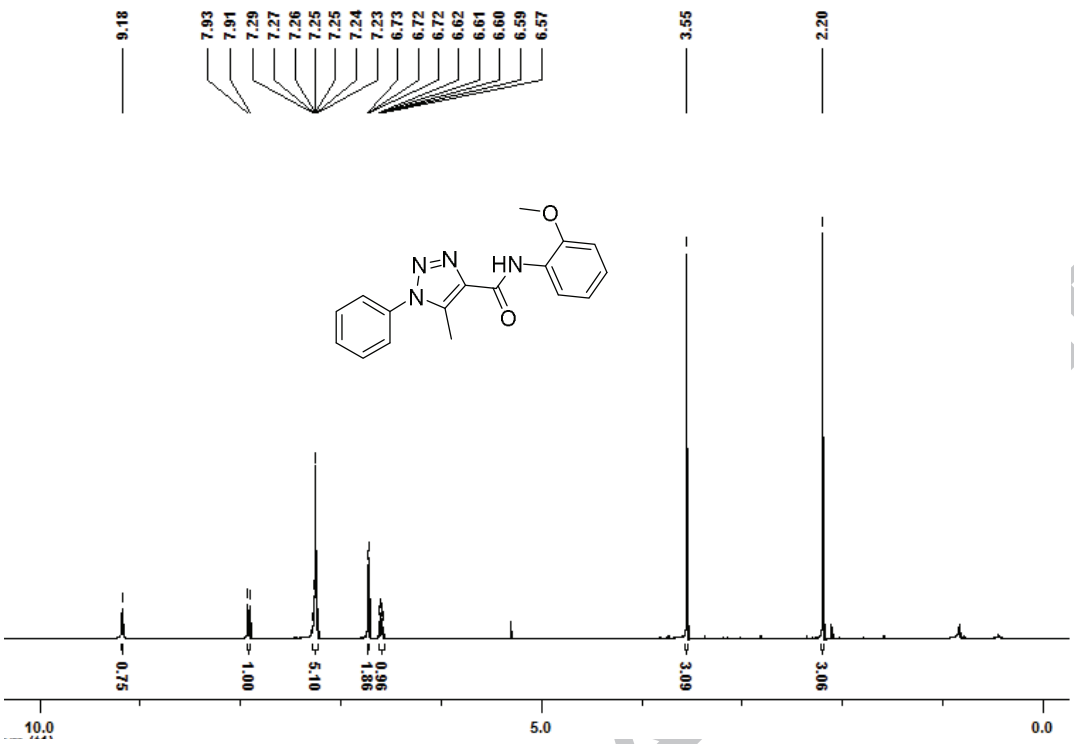


Figure 9. ^{1}H NMR (400 MHz) spectrum for compound **3e** in DMSO-d_6.

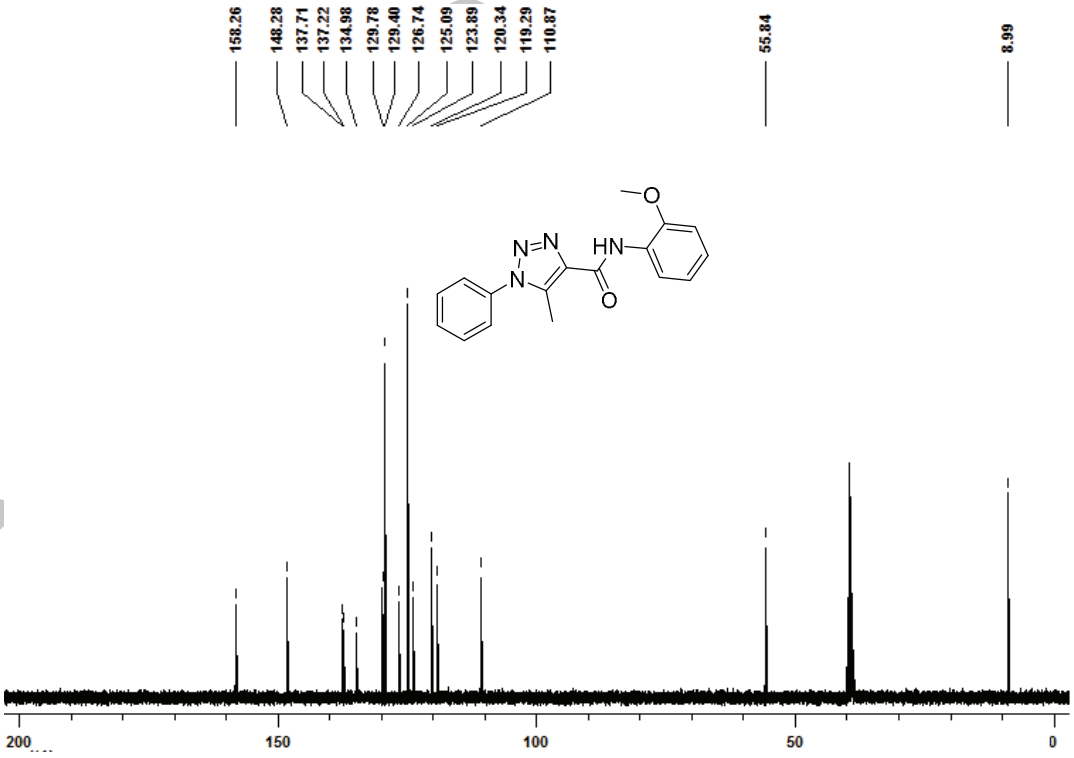


Figure 10. ^{13}C NMR (100 MHz) spectrum for compound **3e** in DMSO-d_6.

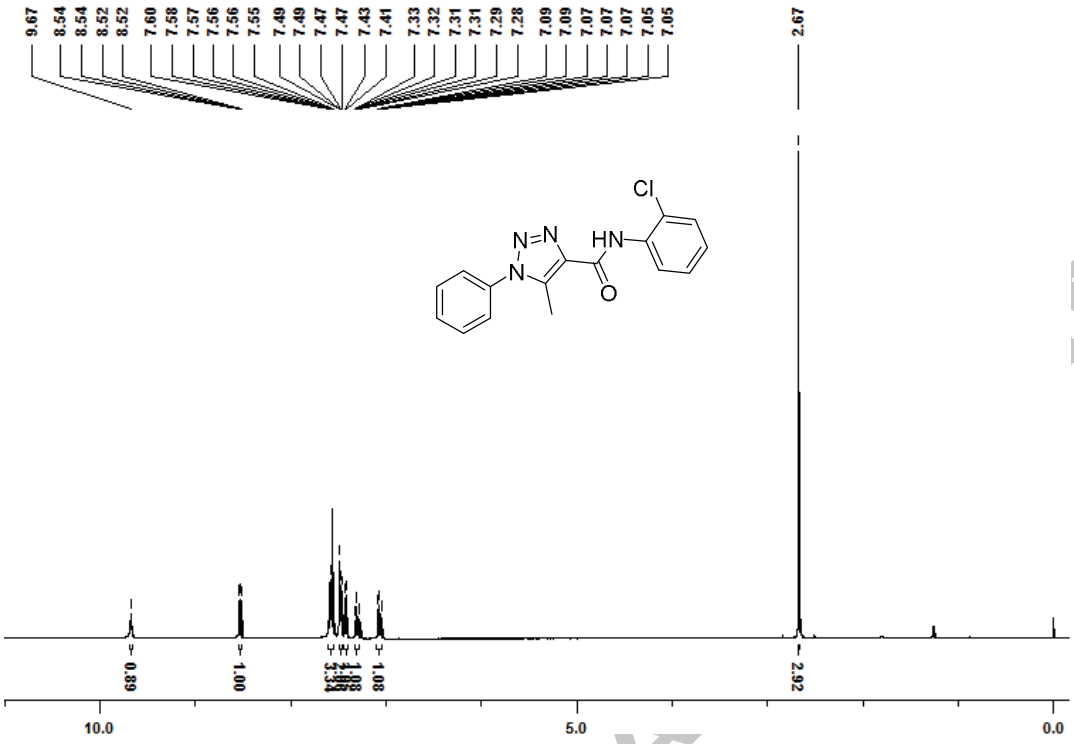


Figure 11. ^{1}H NMR (400 MHz) spectrum for compound **3f** in $CDCl_3$.

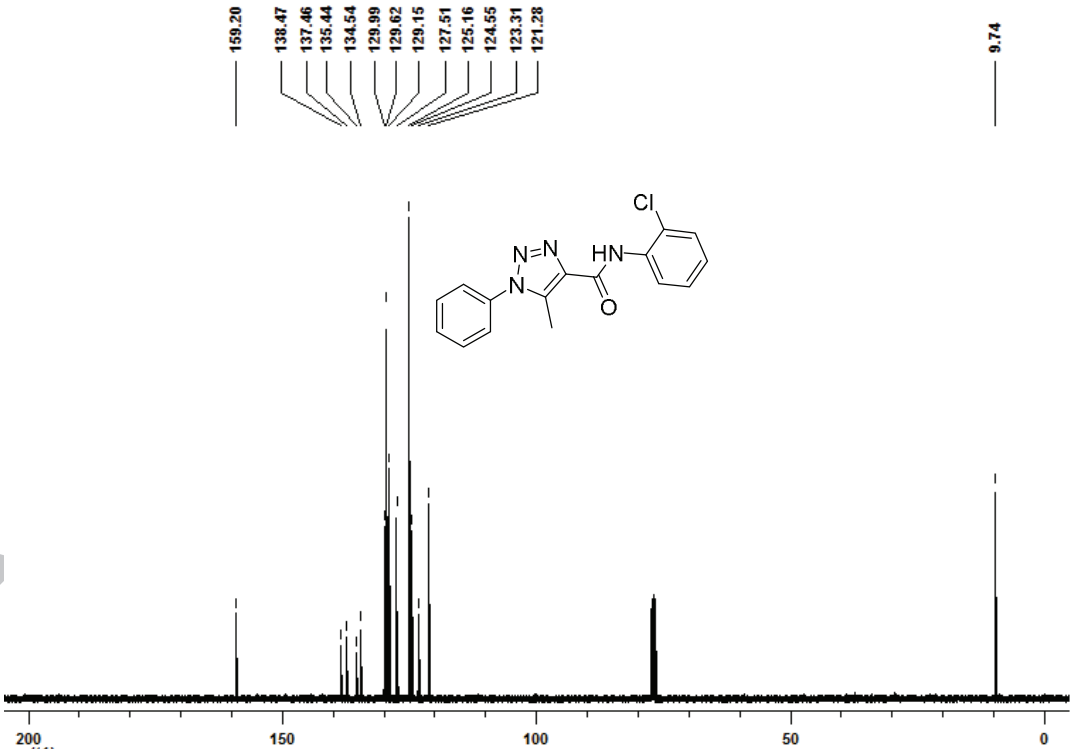


Figure 12. ^{13}C NMR (100 MHz) spectrum for compound **3f** in $CDCl_3$.

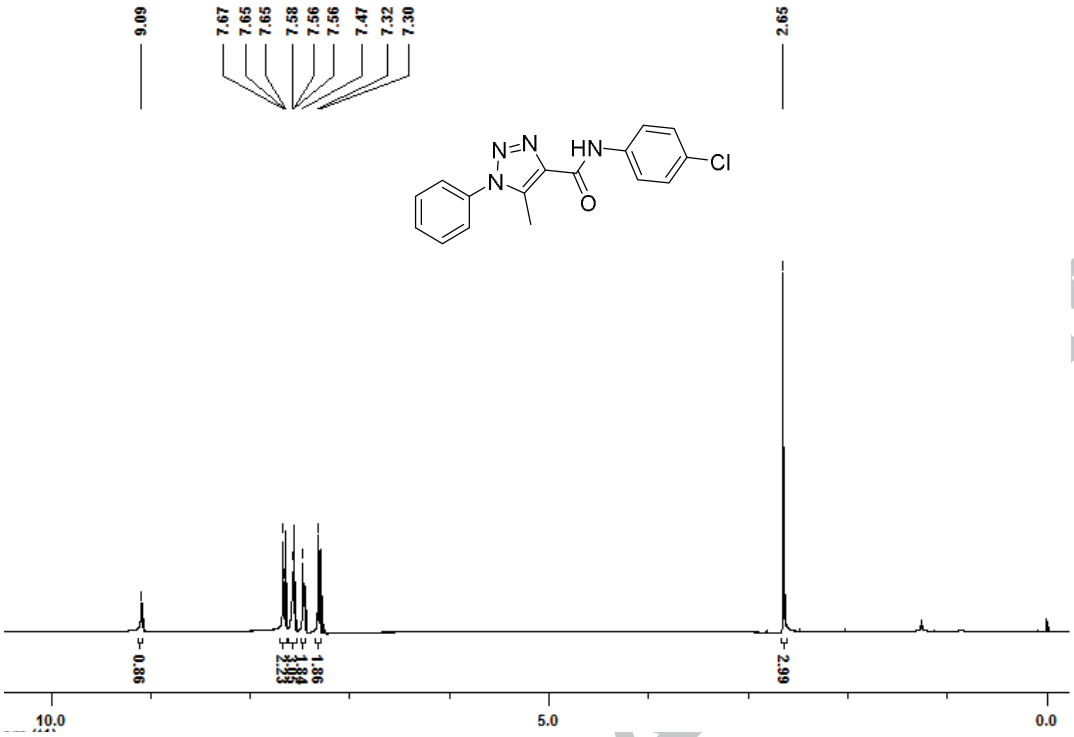


Figure 13. ^{1}H NMR (400 MHz) spectrum for compound **3g** in $CDCl_3$.

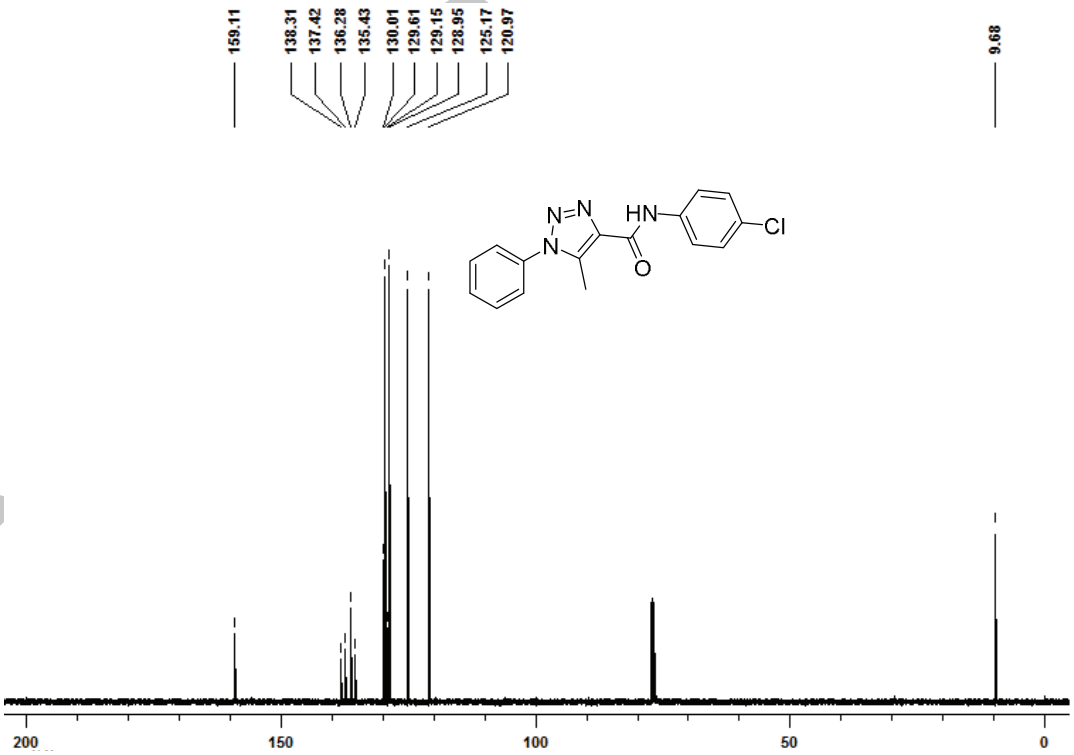


Figure 14. ^{13}C NMR (100 MHz) spectrum for compound **3g** in $CDCl_3$.

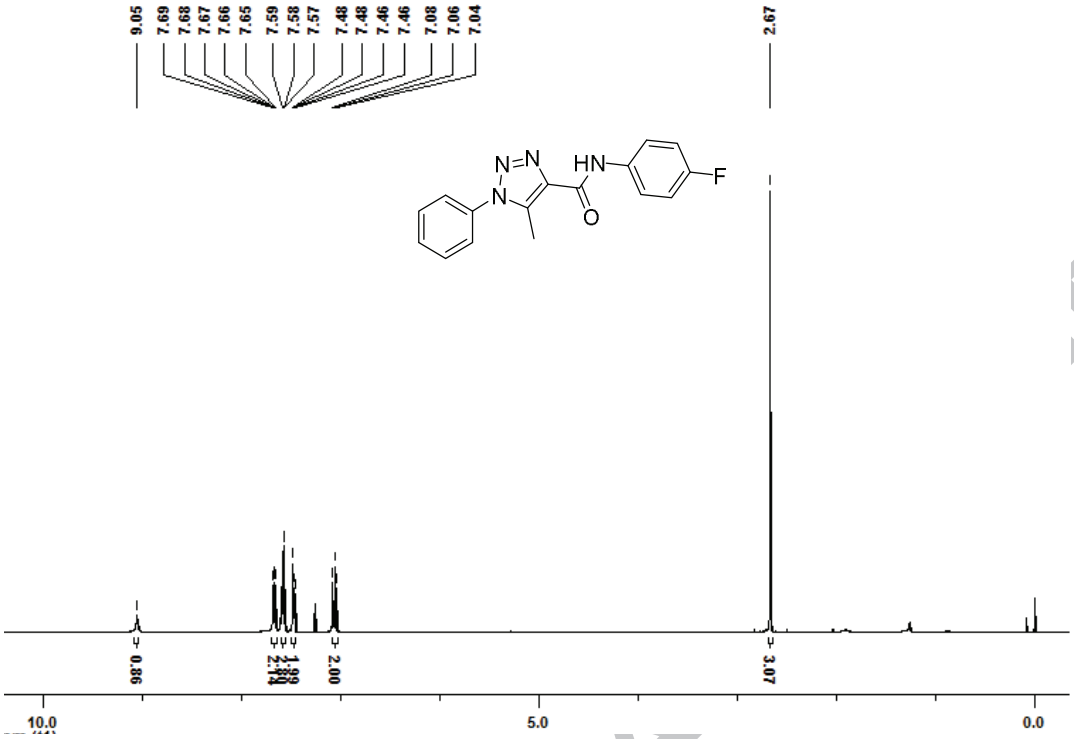


Figure 15. ^{1}H NMR (400 MHz) spectrum for compound **3h** in $CDCl_3$.

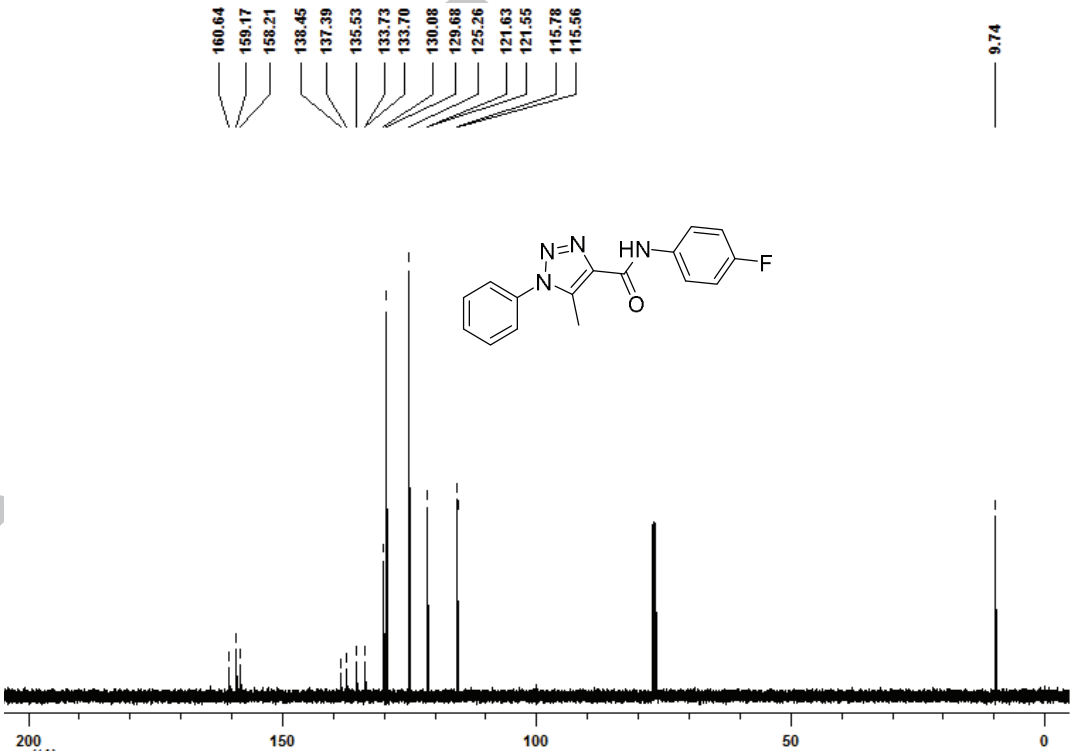


Figure 16. ^{13}C NMR (100 MHz) spectrum for compound **3h** in $CDCl_3$.

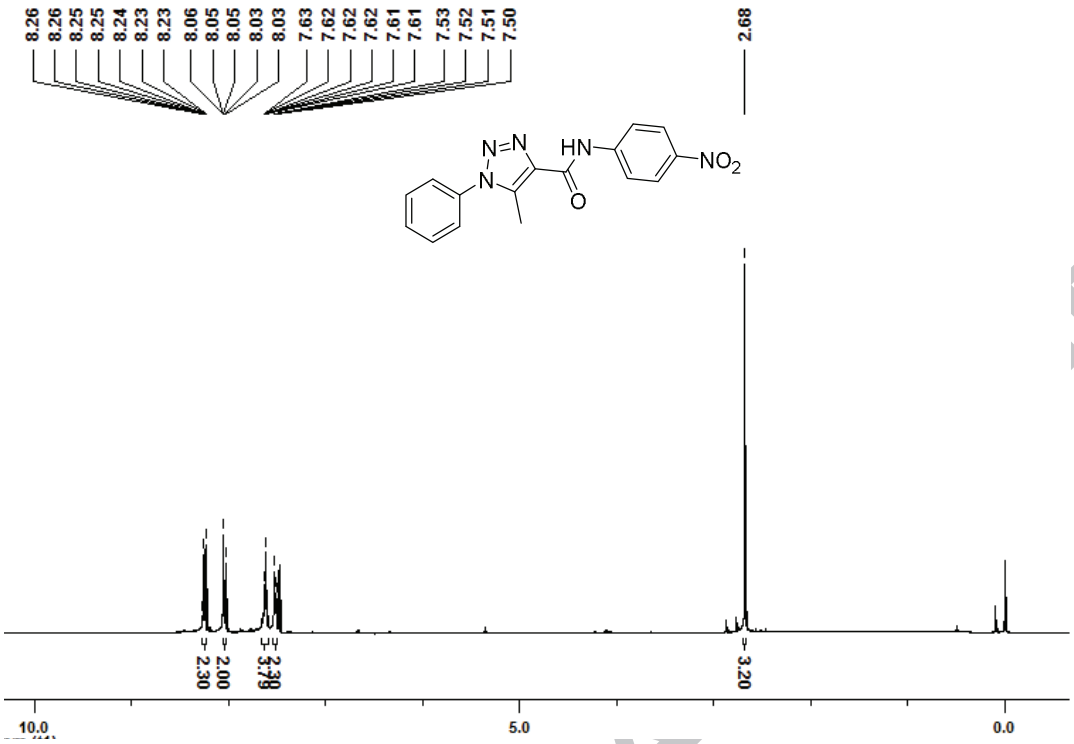


Figure 17. ^{1}H NMR (400 MHz) spectrum for compound **3i** in $CDCl_3$.

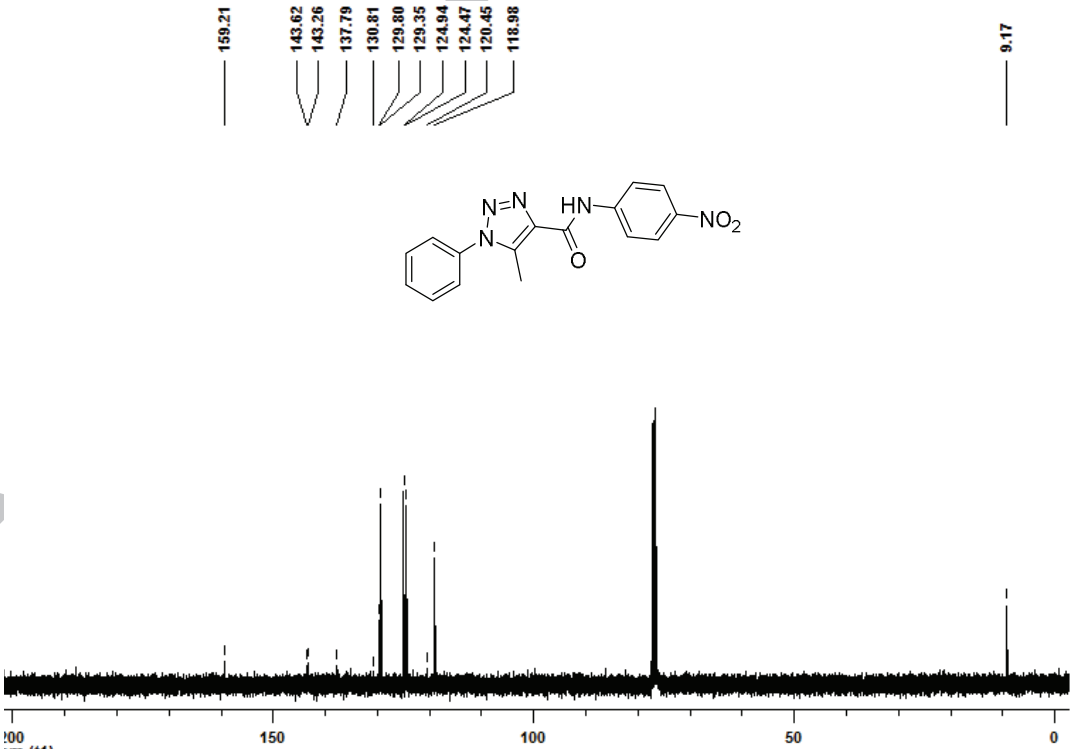


Figure 18. ^{13}C NMR (100 MHz) spectrum for compound **3i** in $CDCl_3$.

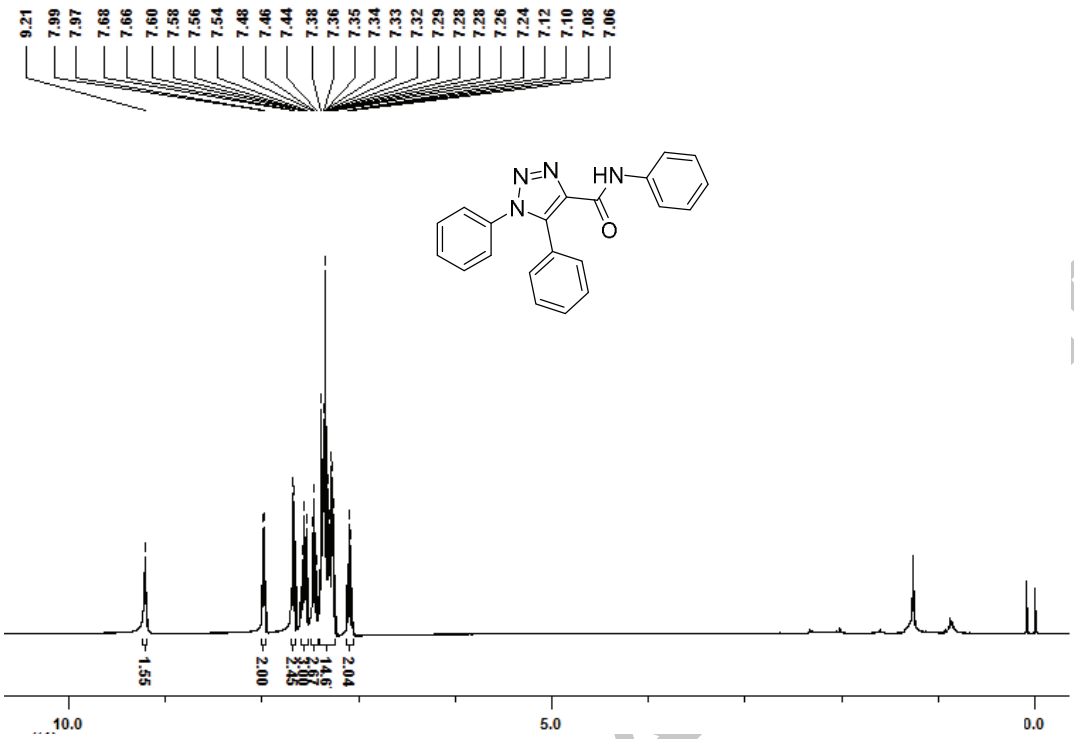


Figure 19. ^{1}H NMR (400 MHz) spectrum for compound **3j** in $CDCl_3$.

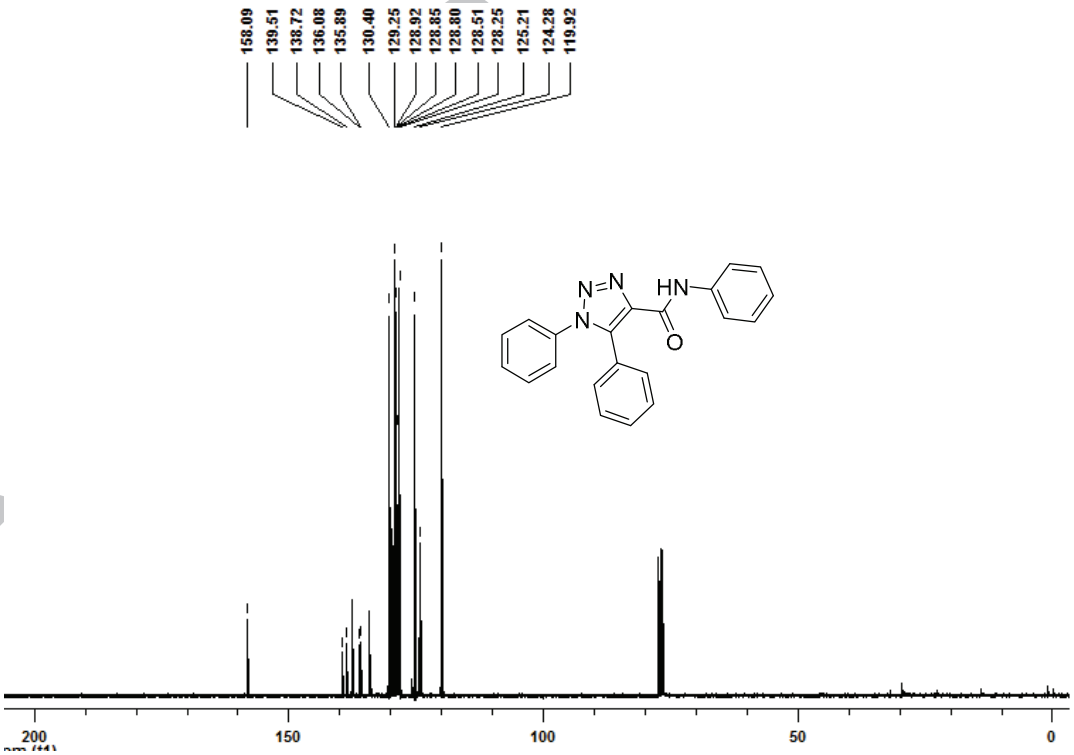


Figure 20. ^{13}C NMR (100 MHz) spectrum for compound **3j** in $CDCl_3$.

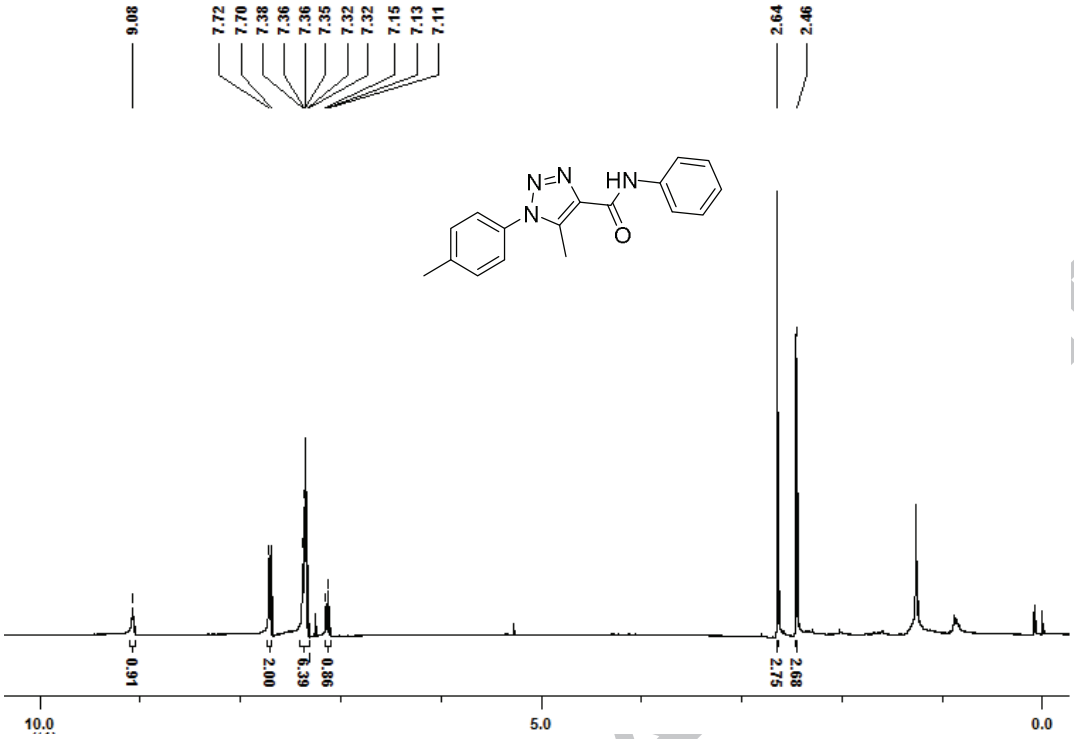


Figure 21. ^{1}H NMR (400 MHz) spectrum for compound **3k** in $CDCl_3$.

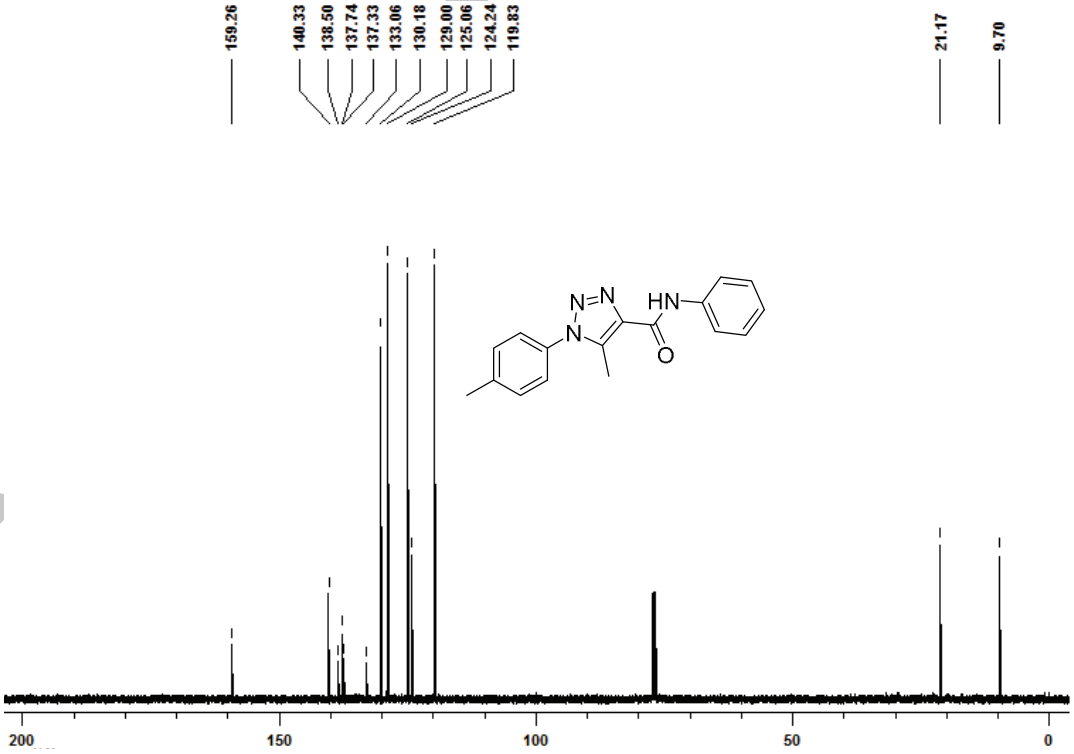


Figure 22. ^{13}C NMR (100 MHz) spectrum for compound **3k** in $CDCl_3$.

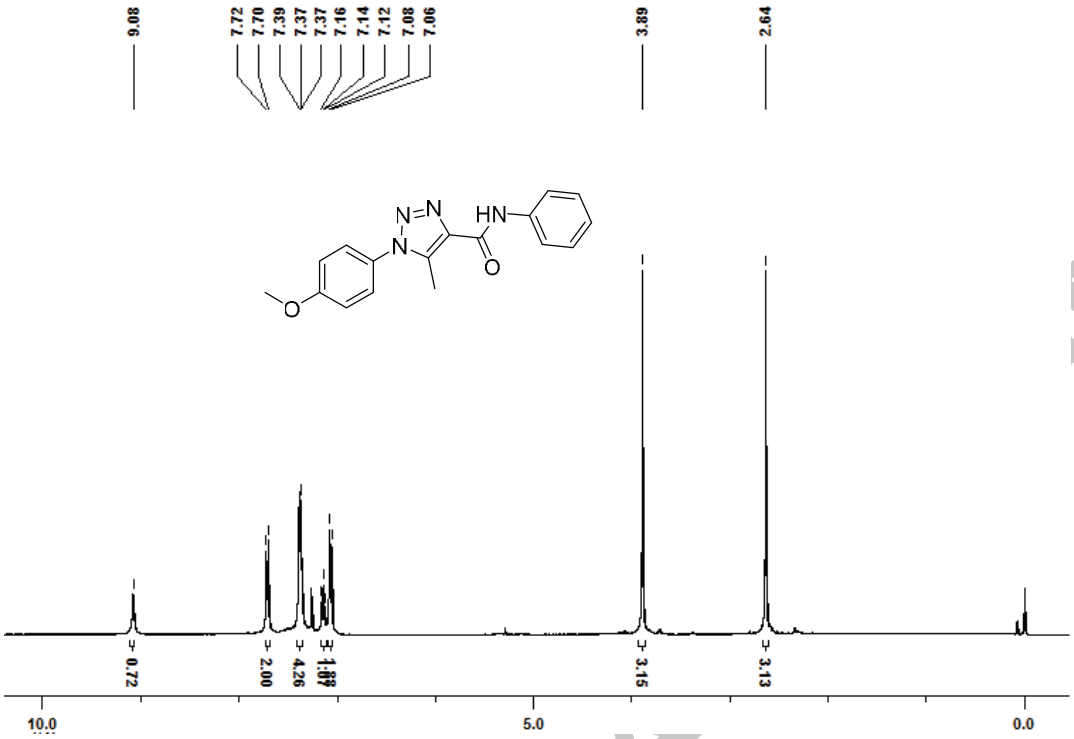


Figure 23. ^{1}H NMR (400 MHz) spectrum for compound **3l** in $CDCl_3$.

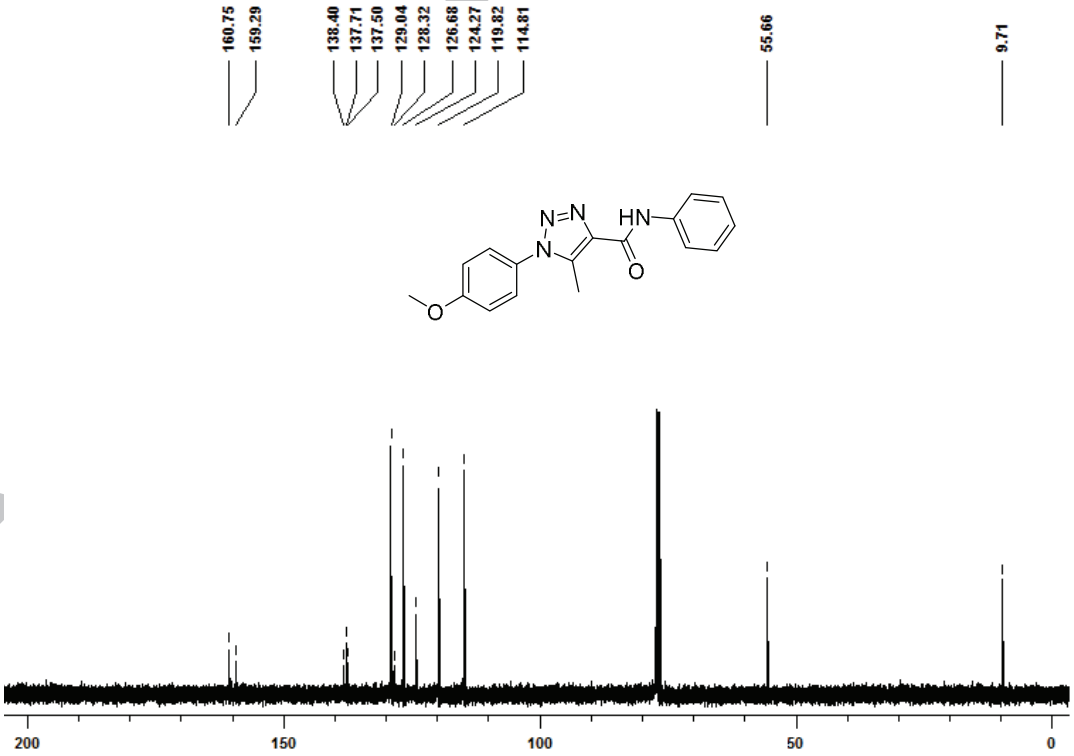


Figure 24. ^{13}C NMR (100 MHz) spectrum for compound **3l** in $CDCl_3$.

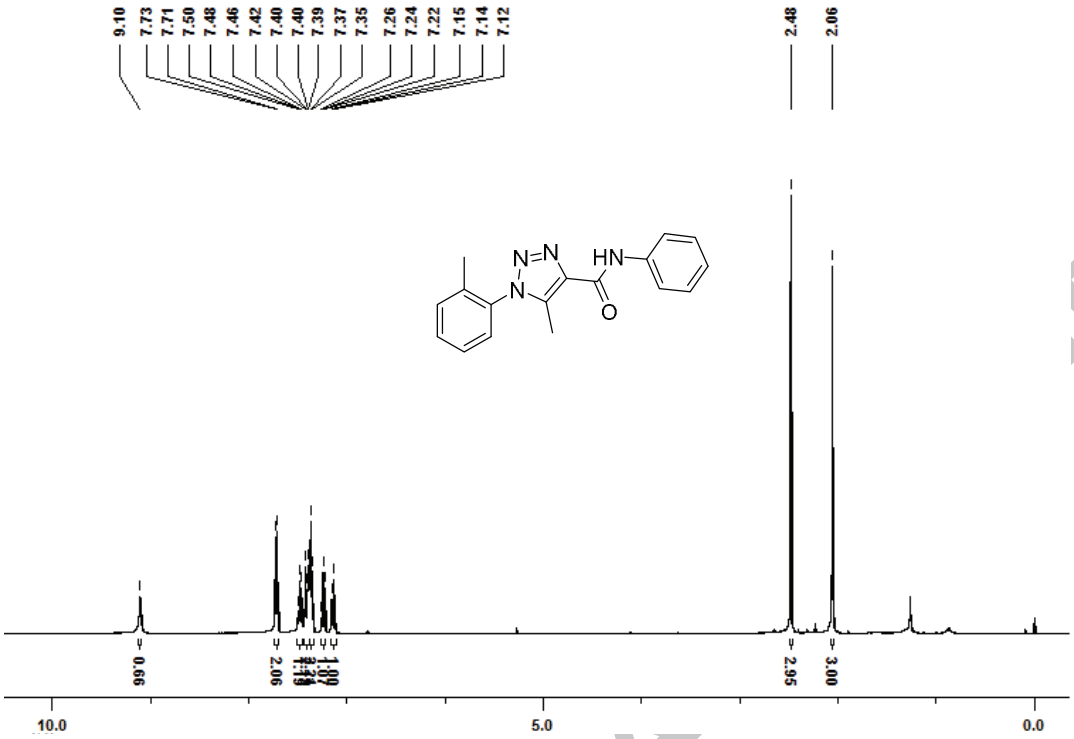


Figure 25. ^{1}H NMR (400 MHz) spectrum for compound **3m** in $CDCl_3$.

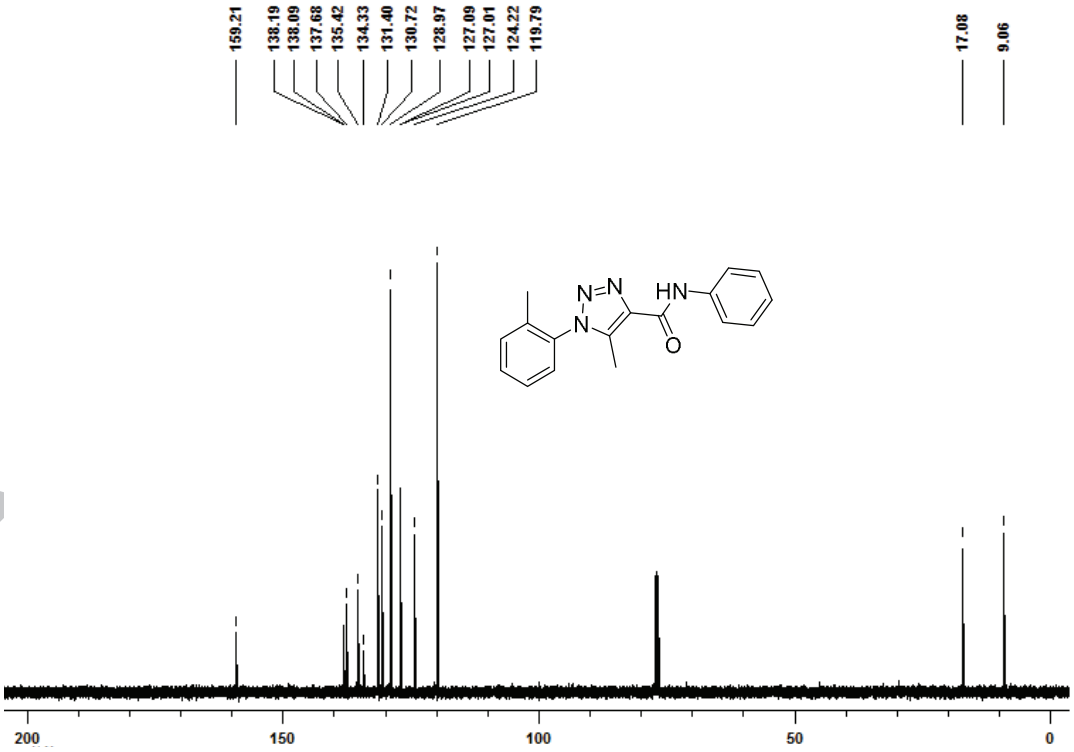


Figure 26. ^{13}C NMR (100 MHz) spectrum for compound **3m** in $CDCl_3$.

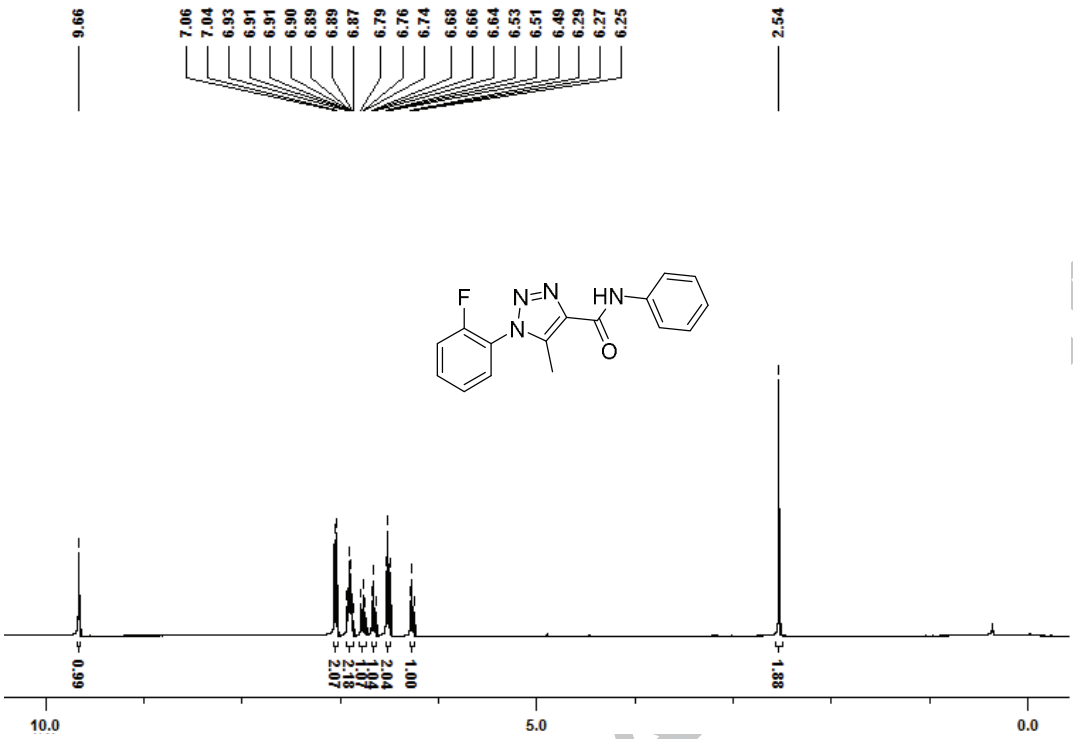


Figure 27. ^{1}H NMR (400 MHz) spectrum for compound **3n** in DMSO-d_6.

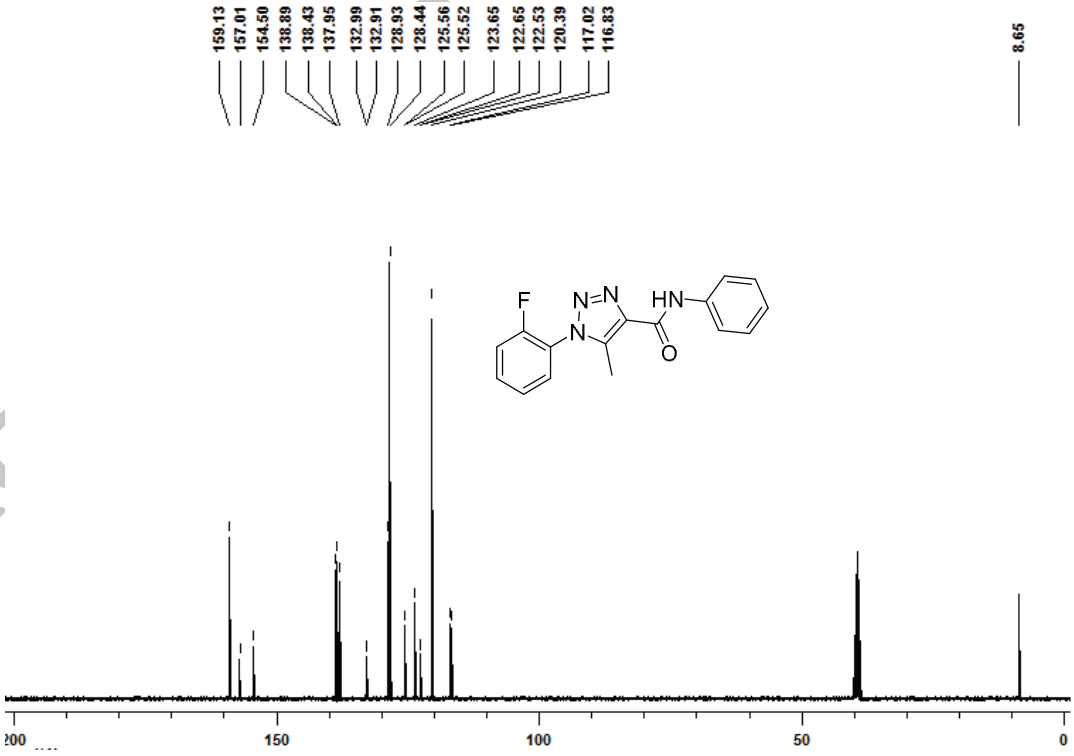


Figure 28. ^{13}C NMR (100 MHz) spectrum for compound **3n** in DMSO-d_6.

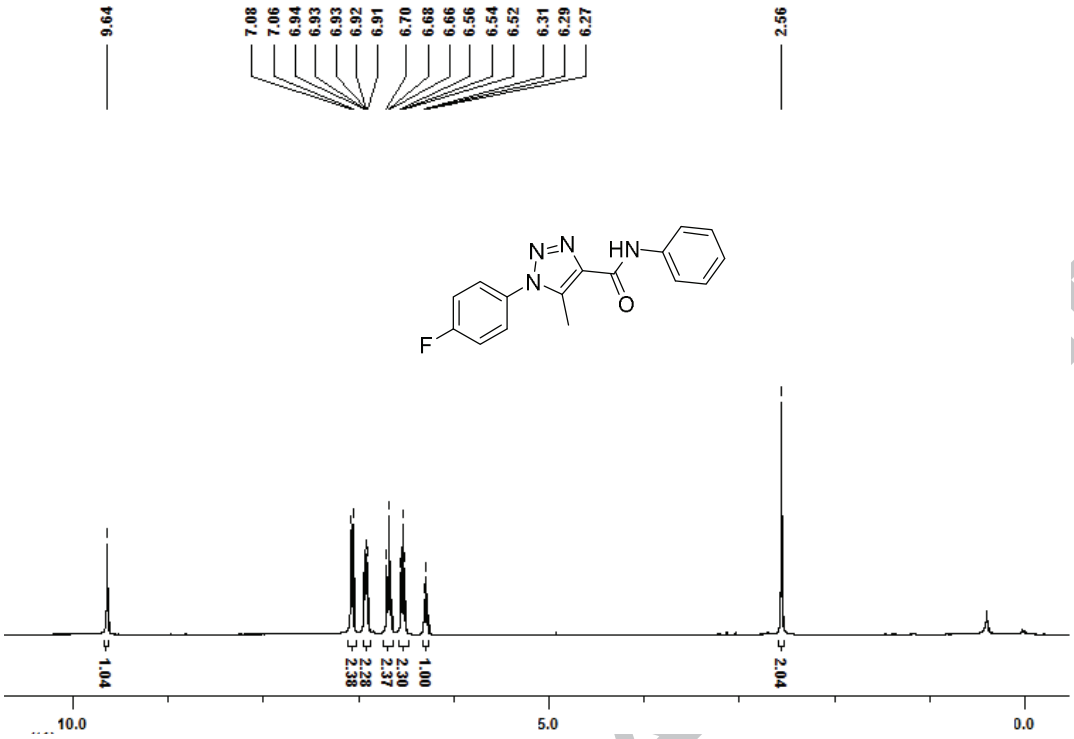


Figure 29. ^{1}H NMR (400 MHz) spectrum for compound **3o** in DMSO-d_6.

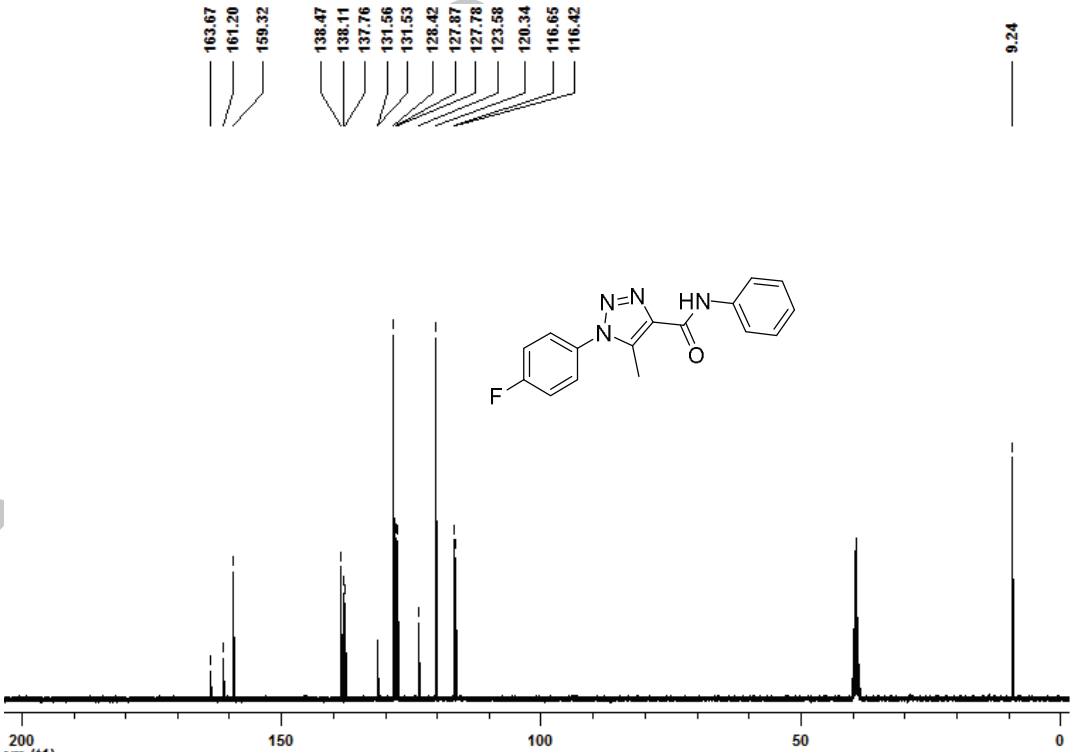


Figure 30. ^{13}C NMR (100 MHz) spectrum for compound **3o** in DMSO-d_6.

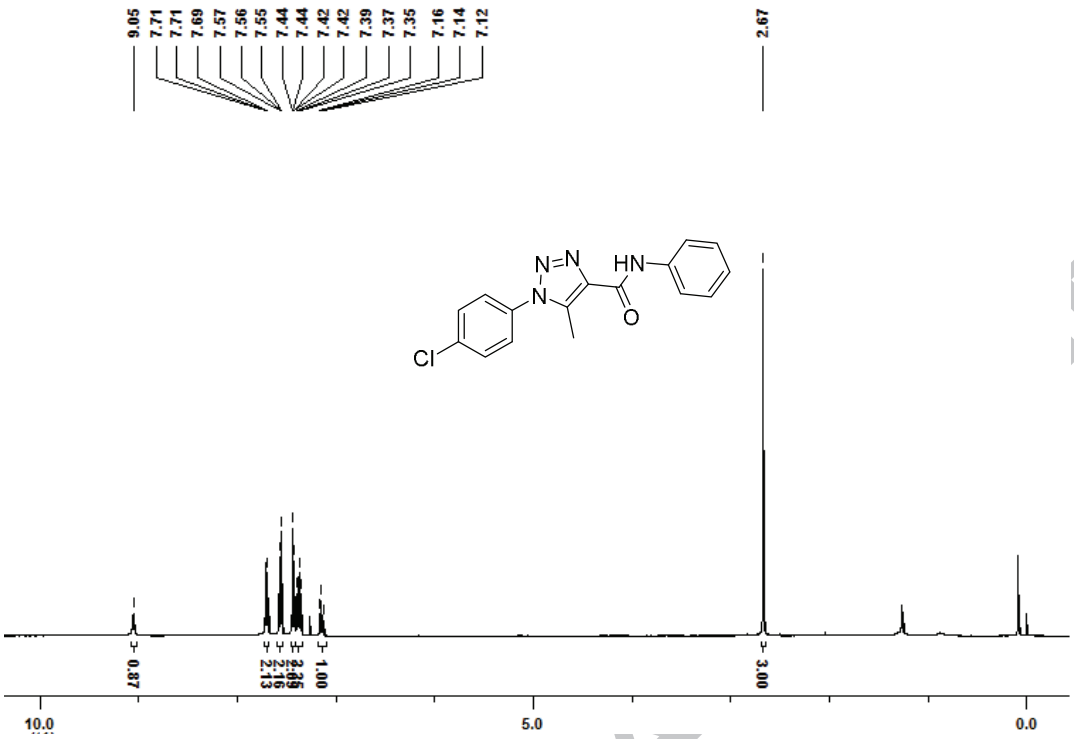


Figure 31. ^{1}H NMR (400 MHz) spectrum for compound **3p** in $CDCl_3$.

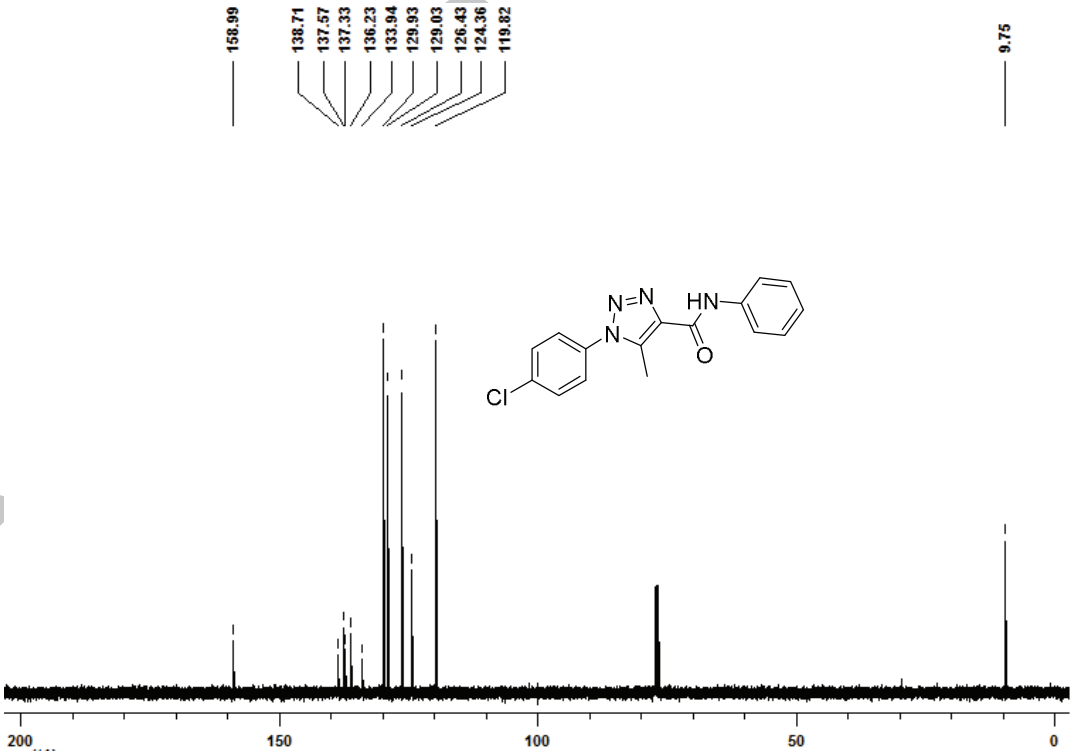


Figure 32. ^{13}C NMR (100 MHz) spectrum for compound **3p** in $CDCl_3$.

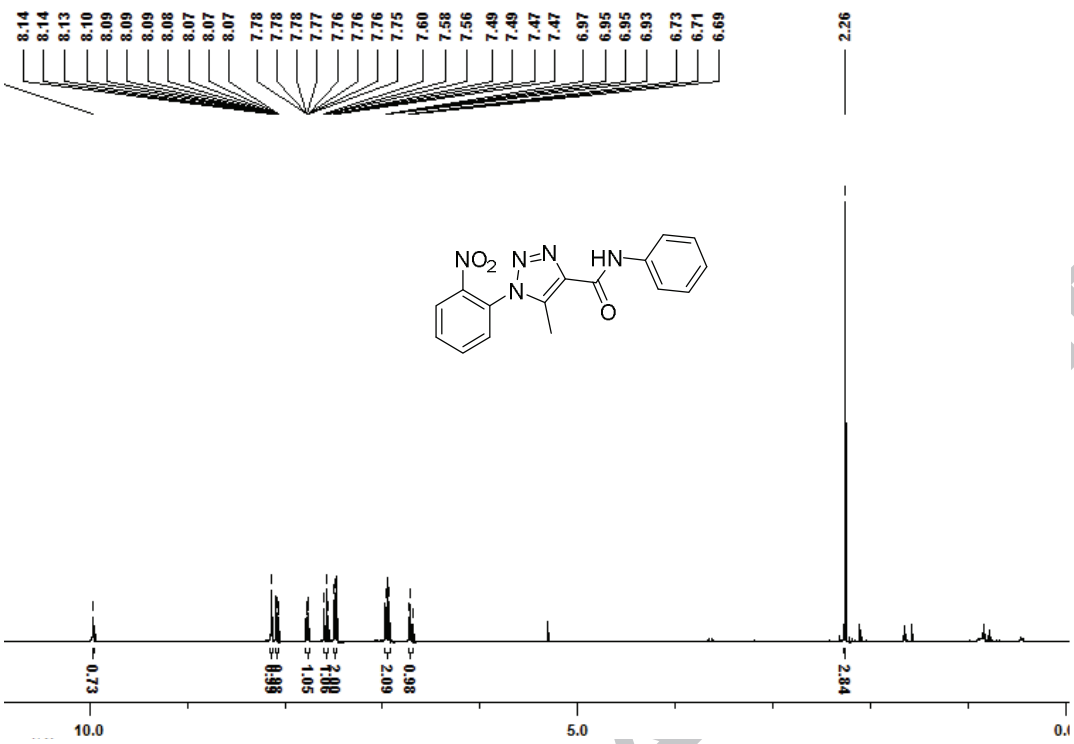


Figure 33. ^{1}H NMR (400 MHz) spectrum for compound **3q** in DMSO-d_6.

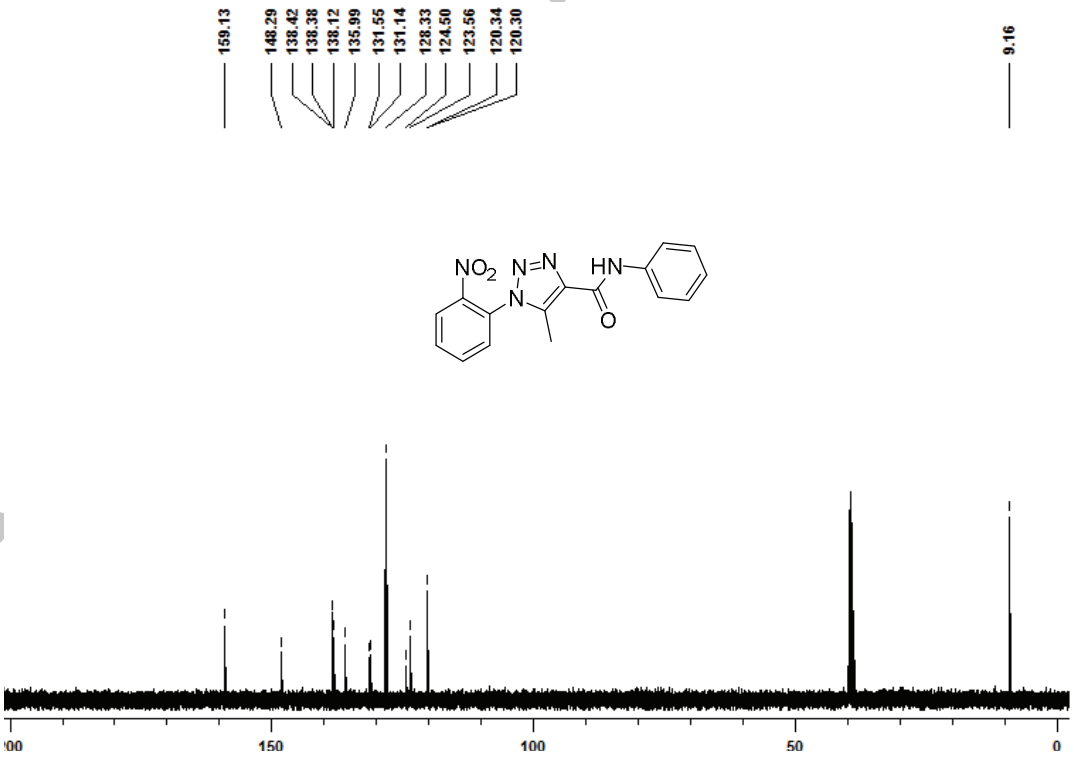


Figure 34. ^{13}C NMR (100 MHz) spectrum for compound **3q** in DMSO-d_6.

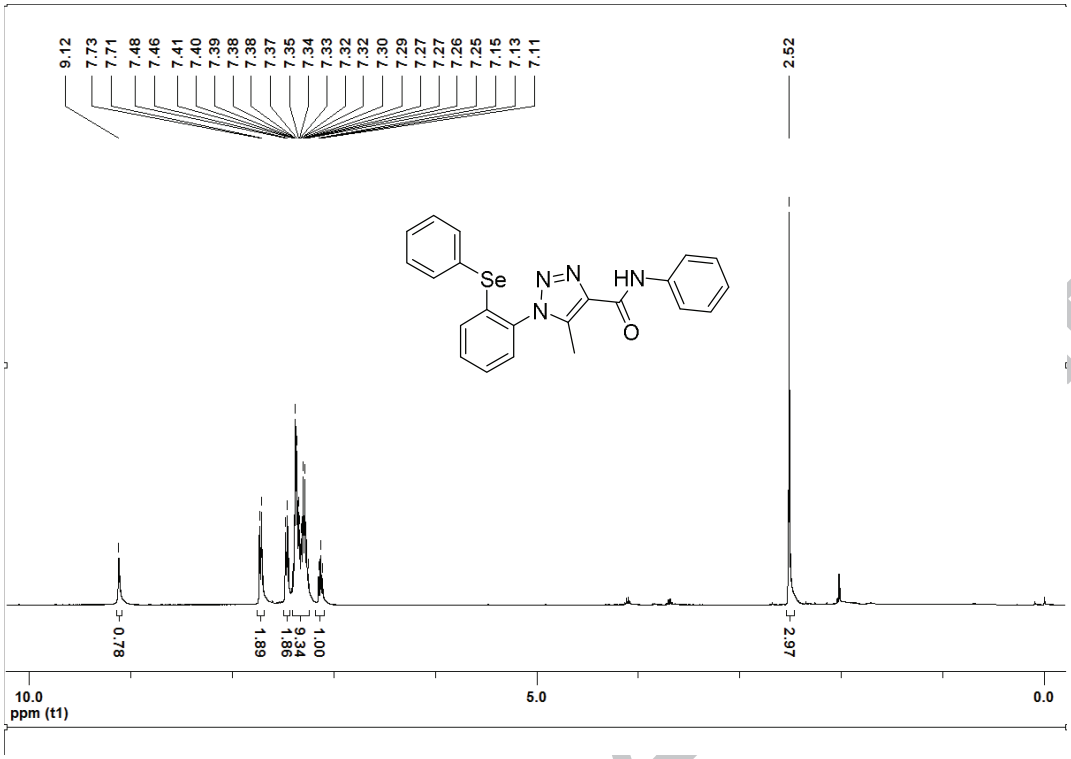


Figure 35. ^{1}H NMR (400 MHz) spectrum for compound **3r** in $CDCl_3$.

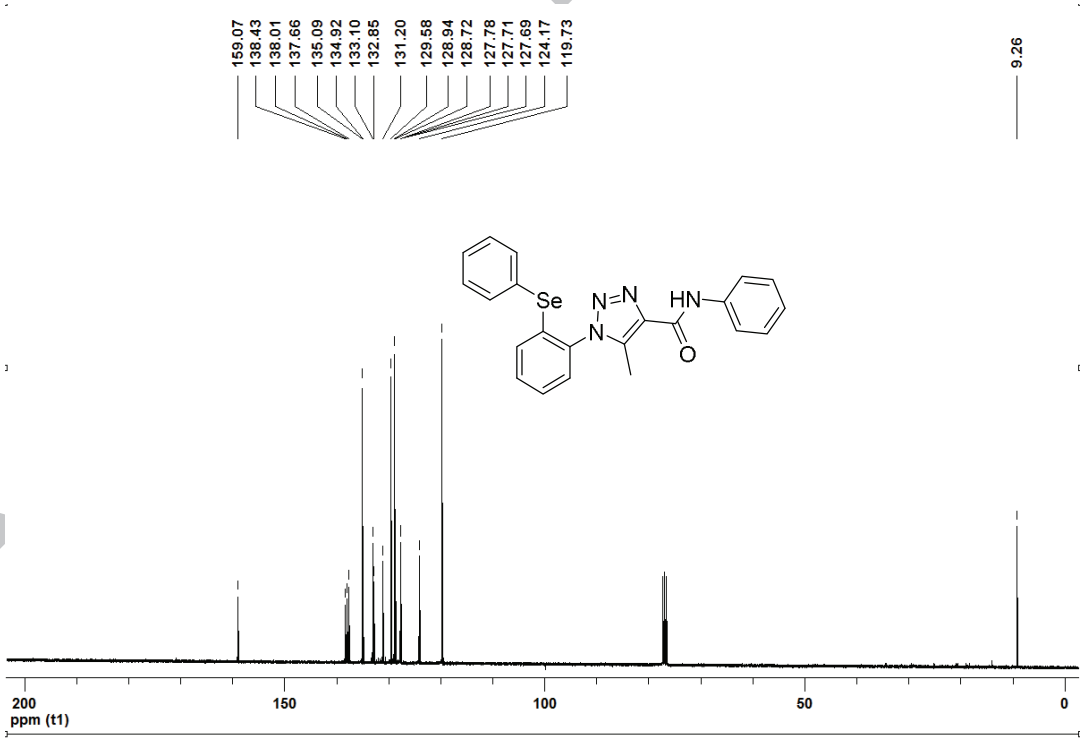


Figure 36. ^{13}C NMR (100 MHz) spectrum for compound **3r** in $CDCl_3$.

- Sonochemistry in the organocatalytic enamine-azide [3+2] cycloadditions.
- New functionalized triazoles in excellent yields and short times of reaction.
- Reactions were found to be amenable to a range of β-oxo amides or aryl azides.