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FACILE AND EFFICIENT MICROWAVE-ASSISTED SYNTHESIS OF BICYCLIC Δ^2 (1,2,3)-TRIAZOLINES VIA 1,3-DIPOLAR CYCLOADDITION BETWEEN ORGANIC AZIDES AND 1-MORPHOLINOCYCLOPENTENE

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Abstract
The reaction between organic azides and 1-morpholinocyclopentene has been developed for direct and efficient access to bicyclic (1,2,3)-triazolines through 1,3-dipolar cycloaddition reaction under microwave irradiations. The bicyclic (1,2,3)-triazolines were isolated in very high yields and purities without the need of any purification step and in very short times.

Keywords: triazolines; 1,3-dipolar cycloaddition; microwave-assisted; organic azide; heterocycles; enamines.

Introduction

The eternally increasing demand for new effective drugs and the necessity for new discovery have resulted in a continuous search for simple, efficient, selective and rapid synthetic strategies that should allow gathering a large number of potentially biologically and pharmacologically active compounds in a very short time.[i] In this context the 1,3-dipolar cycloaddition reactions (1,3-DC) have emerged as a highly versatile and powerful tool to fulfill these criteria by allowing the construction of heterocyclic rings.[ii] Among the heterocyclic compounds, (1,2,3)-triazolines and (1,2,3)-triazoles are the most common derivatives synthesisables by 1,3-dipolar cycloaddition reactions.[iii] These pentagonal heterocycles possessing three nitrogen atoms represent a class of compounds with proven wide range of biological activity [iv] including, anticonvulsant [v], antiischemic [vi], antitubercular [vii], anti-inflammatory [viii], antifungal [ix], antiviral [x], antiallergic [xi], antidiabetic [xii] and antibacterial [xiii]. Associated with other structures, they find their use in the pharmaceutical industry. As examples, we cite Tazobactam (**I)** and cefatrizine (**II)** as an antibiotics [xiv] and rufinamide **(III)**, an anticonvulsant [xv] agent (Figure 1).

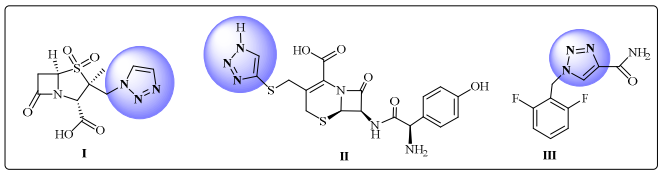
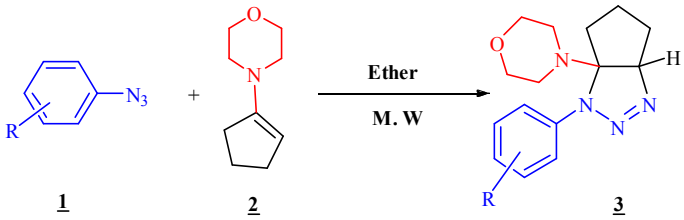


Figure1. Drugs bearing (1,2,3)-Triazole.

However, the classical conditions used for the 1,3-dipolar cycloaddition are becoming increasingly constraining in relation to several disadvantages such as: the use of expensive catalysts, high temperatures, longer time reactions and the generated low yields of final products. For these reasons, (1,3-DC) assisted by microwave irradiations [xvi,xvii] is an interesting solution to counteract these problems. Since the innovative work of *Gedye et al* [xviii], a significant number of publications on the synthesis of heterocyclic compounds using microwave technology have appeared due to the remarkable rate enhancements and dramatic reductions of reaction times. [xix]

While a rising number of articles have advocated the use of microwave technology in the synthesis of (1,2,3)-triazole, only few works have been realized for the synthesis of (1,2,3)-triazolines using this technology, one can mention the work of *Palacios et al* [xx] who prepared triazolines by addition of phosphorylated azides to functionalized enamines. Unfortunately, these triazolines were degraded into triazoles by elimination of a pyrrolidine molecule. Within this field of research [xxi], we focus on the preparation of bicyclic Δ^2 (1,2,3)-triazolines by microwave activation as the main objective, using the 1,3- dipolar cycloaddition reaction. Thus we developed an efficient, practical and high yielding method for the microwave-assisted synthesis of bicyclic (1,2,3)-triazolines **3** via 1,3-dipolar reaction between substituted easily accessible aryl azides **1** and 1-morholino-cyclopentene **2** (Scheme 1).

This methodology avoids the use of harsh reactions conditions and allows an easy isolation of the desired products with high purities and yields after a very short time.



1 **2** **3**

R = H, (*o*, *m*, *p*)-NO_2 , (*o*, *m*, *p*)-Br, (*o*, *m*, *p*)-F, 2-Cl, 4-NO_2, *m*-CF_3, 2-F, 4-Cl

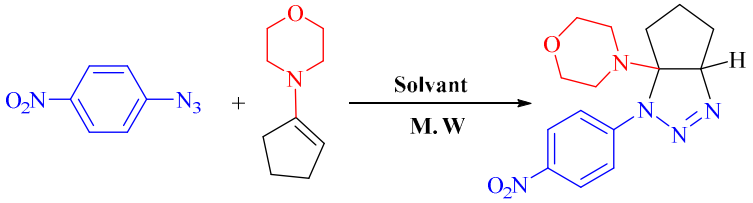
Scheme1. General route for the Synthesis of 1,2,3-triazolines **3**

The structures of various bicyclic (1,2,3)- triazolines **3** were determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectroscopy and analysis, which gave good agreement with the proposed structures.

Results and Discussion

As illustrated in Table 1, some preliminary experiments were realized in order to find the right conditions of this cycloaddition. We started our study by reacting the organic azides **1b** with 1-morpholinocyclopentene **2** in the presence of different polar and apolar solvents. The reactions were microwave-heated for 10 min.

Table 1. Optimization of the reaction conditions[a]



1b **2** **3b**

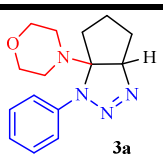
Entry	Solvent	Yield (%)[b]
1	**Et_2O[b]**	**94%**
2	MeOH[b]	41%
3	DMF[*b]	74%
4	Toluene[*b]	64%
5	THF[*b]	44%
6	CH_2Cl_2[*b]	73%
7	$CHCl_3$[*b]	52%
8	H_2O[*b]	55%

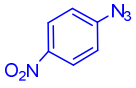
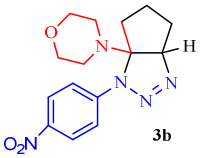
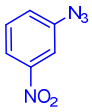
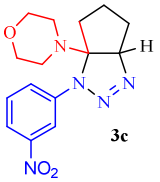
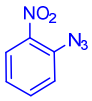
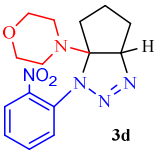
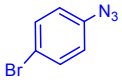
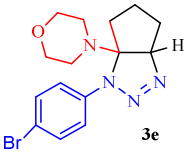
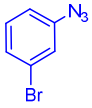
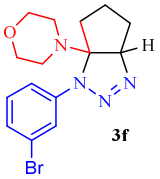
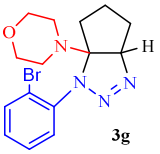
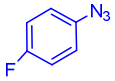
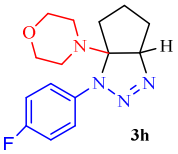
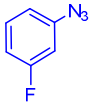
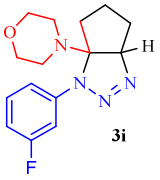
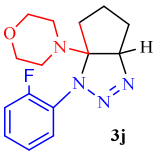
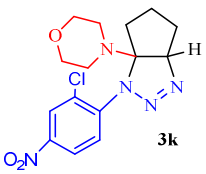
[a]Reaction conditions: paranitrophenylazide **1b** (0,6 mmol, 1 equiv.), 1-morpholinocyclopentene **2** (0,6 mmol, 1 equiv.), and Et_2O (8 mL). [b] Isolated yield after simple filtration ,[*b] Isolated yield after simple filtration followed by recrystallization in MeOH.

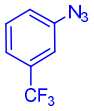
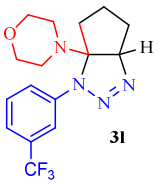
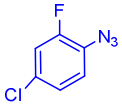
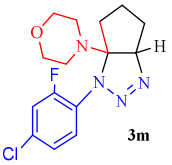
Among all the solvents used, the reaction in diethyl ether gave the best result inducing the (1,2,3)-triazoline in a very good yield and purity (Table 1, entry 1), whereas the reaction in THF and methanol led to the desired product at low yield (Table 1, entries 2 and 5). Under microwave heating of an apolar solvent such as toluene, the triazoline **3b** was obtained in moderate yield (64%) after 10 min reaction time (entry 4). When the reaction was carried out in H_2O, CH_2Cl_2, $CHCl_3$ and DMF, the product was obtained in yields of 55, 73, 52 and 74% respectively. It should be noted that with the exception of diethyl ether and methanol, it was necessary to purify the final product by recrystallization.

These preliminary results showed clearly that the diethyl ether is the best solvent to reach our synthetic aim. Next, we started to evaluate the scope of the reaction between various aryl azides **1** (1eq) and 1-morholinocyclopentene **2** (1eq) in diethyl ether in microwave for 10min.The results of this investigation for the synthesis of bicyclic triazolines **3** are summarized in table 2.

Table 2. Triazolines **3** prepared from 1-morpholinocyclopentene[a]

Entry	Azide	Product	Yield (%)[b]
1		 **3a**	87

2		 **3b**	94
3		 **3c**	81
4		 **3d**	62
5		 **3e**	88
6		 **3f**	73
7		 **3g**	65
8		 **3h**	85
9		 **3i**	76
10		 **3j**	68
11		 **3k**	71

12		 **3l**	92
13		 **3m**	65

[a]Reaction conditions : organic azide **1** (0,6 mmol, 1 equiv.), 1-morpholinocyclopentene **2** (0,6 mmol, 1 equiv.), and Et_2O (8 mL). [b]Isolated yield after simple filtration.

This reaction of 1,3-dipolar cycloaddition was performed in diethyl ether under microwave irradiation with 1-morpholinocyclopentene **2** in the presence of various organic azides **1** to give access to the corresponding (1,2,3)-triazolines **3**. In most cases, the final products were obtained with a high purity without the need of any purification steps. Analysis of Table 1 shows that all the heterocycles were obtained with rather good yields varying from 62 to 94% in a very short reaction time.

Initially, the (1,2,3)-triazolines **3b**, **3e**, **3h**, **3l** derived from reacting respectively *p*-NO_2 phenylazide, *p*-Br phenylazide, *p*-F phenylazide and *m*-CF_3 phenylazide and 1-morpholinocyclopentene were isolated with the highest yields as 94, 88, 85 and 92% (Table 2, entries 2, 5, 8 and 12).

Neutral group, like phenyl azide (Table 2, entry 1) and aryl azides bearing electron-withdrawing groups like halogen atom in the *meta* position (Table 2, entries 6, 9) and *ortho* position (Table 2, entries 7, 10), allowed the generation of the desired compounds in moderate to good yields. These results show clearly that a lower yield was noted when the halogen group was present at the 3rd or 2nd position (Table 2, entries 6, 9, 7 and 10) instead of the 4th position (Table 2, entries 5 and 8).

Similar observations were recorded with the nitro group. Whereas an excellent result was obtained under these conditions from *p*-nitro phenylazide (Table 2, entries 2), moderate to good yields of the expected triazolines **3c** and **3d** were observed using *m*-NO_2 phenylazide or *o*-NO_2 phenylazide with 81% and 62% respectively (Table 2, entries 3 and 4).

Using aromatic azides containing both halogen and nitro groups as a substitutes, allowed the reaction to be performed under microwave irradiations in diethyl ether in a satisfying yields of the corresponding compounds **3m**, **3k** with 65, 71% (Table 2, entries 11, 13).

Conclusion

In conclusion, we have shown that microwave assisted 1,3-cycloaddition reaction involving cyclic enamines and organic azides in diethyl ether is an efficient way for the direct access to (1,2,3)-triazolines cores. The reaction proceeded in short time under mild and catalyst-free conditions and allowed the isolation of the desired products with high chemical purities without any supplementary purification step. Further investigations for extension of the reactions to substituted cyclopentanes are currently underway in our research group. Also a biological study of the synthesized products shows a very good biological activity of these heterocycles and the results will be published in an appropriate journal.

Experimental

All the reagents and solvents were purchased from commercial sources. All the reactions were followed by thin layer chromatography carried out on Merck silica gel 60 F254 plates

with fluorescent indicator. The plates were visualized with UV light (254 nm). Preparative chromatographic purifications were performed using a silica gel column (Kieselegel 60). Melting points were determined by a Kofler hot-stage apparatus and are uncorrected. The structures were verified spectroscopically by ^{1}H and ^{13}C-NMR, ESI-MS and elemental analysis. Spectra of the final products were recorded on a Brüker Avance-300 spectrometer for NMR (300 MHz and 75 MHz for ^{1}H and ^{13}C respectively) in $CDCl_3$, an "API III Plus triple quadrupôle" instrument for mass spectroscopy and a "Thermo Finnigan EA 1112" instrument for elemental analysis. Chemical shifts are given as δ with respect to Me_4Si.

Microwave equipment

The synthetic steps performed by microwave irradiation were carried out using a microwave oven "Microwave Synthesis Reactor (300) Discover", especially designed for organic synthesis. Microwave reactions were performed in an Open Vessel (atmospheric pressure). The irradiation time and power were monitored with the microwave oven software.

General procedure for the synthesis of cyclic enamine and organic azides:

The starting reagents were prepared according to the literature procedures for enamine **2** [xxii] and organic azide **1**.[xxiii]

General procedure for the synthesis of bicyclic (1,2,3)-triazolines 3a-k :

The organic azide **1** (0,6 mmol, 1 equiv.) and enamine **2** (0,6 mmol, 1 equiv.) are mixed in equimolar amounts and placed in ether (8 mL) under stirring in a Microwave Reactor and monitored by a TLC. The irradiation power (850 w) was monitored with the microwave oven software.

After ten minutes, the triazolines **3(a-k)** were obtained with yields which vary according to the structure of arylazides. The chemical shift values of different triazolines are in good agreement with the proposed structure.

The products **3a-k** together with their physical constants are listed below.

4-(3-phenyl-3,3a,4,5,6,6a-hexahydrocyclopent[d](1,2,3)triazol-3a-yl)morpholine (3a).

Brown solid. mp 98-100°C; Yield 87%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.22-1.37 (m, 1H), 1.59-1.67 (m, 1H), 1.89-1.96 (m, 1H), 2.02-2.14 (m, 2H), 2.21-2.30 (m,1H), 2.44 (t, *J*=4.03 Hz 4H), 3.67 (t, *J*=4.49 Hz 4H), 4.81 (dd, *J*=3.48 Hz ; *J*=5.41 Hz 1H), 7.07 (t, *J*=7.34 Hz 1H), 7.33 (t, *J*=7.70 Hz 2H), 7.64 (d, *J*=7.79 Hz 2H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.29, 32.41, 33.47, 46.49, 66.91, 78.13, 91.10, 116.75, 123.19, 129.02, 139.49. Anal. Calcd for $C_{15}H_{20}N_4O$ (%): C 66.14, H 7.48, N 19.05. Found C 65.79, H 7.38, N 18.36. MS (ESI) m/z (%) : 273.171 $(M+H)^+$.

4-(3-(4-nitrophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3b).

Yellow solid. mp 192-194°C; Yield 94%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.27-1.39 (m, 1H), 1.68-1.72 (m, 1H), 1.92-2.00 (m, 1H), 2.11-2.21 (m, 2H), 2.30-2.32 (m, 1H), 2.33-2.40 (m, 2H), 2.44-2.51 (m, 2H), 3.66-3.69 (m, 4H), 4.95 (dd, *J*=3.76 Hz ; *J*=5.13 Hz 1H), 7.78 (d, *J*=9.35 Hz 2H), 8.22 (d, *J*=9.26 Hz 2H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.75, 32.74, 33.55, 46.78, 67.14, 79.73, 91.03, 115.49, 199.32, 125.79, 144.80. Anal. Calcd for $C_{15}H_{19}N_5O_3$ (%) : C 57.18, H 5.96, N 21.95. Found C 57.12, H 5.97, N 21.74. MS (ESI) m/z (%) : 318.1561 $(M+H)^+$.

4-(3-(3-nitrophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3c).

Yellow crystals. mp 120-122°C; Yield 81%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.25-1.40 (m, 1H), 1.63-1.72 (m, 1H), 1.93-2.00 (m, 1H), 2.06-2.17 (m, 2H), 2.24-2.34 (m, 1H), 2.40-2.52 (m, 4H), 3.71 (t, *J*=4.68 Hz 4H), 4.87 (dd, *J*=3.48 Hz ; *J*=5,41 Hz 1H), 7.49 (t, *J*=8.25 Hz 1H), 7.90 (dd, *J*=2.29 Hz; *J*=5.04 Hz 1H), 8.00 (dd, *J*=2.29 Hz ; *J*=5.04 Hz 1H), 8.54 (t, *J*=2.20 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.26, 32.21, 33.38, 46.38, 66.83,

78.32, 90.93, 103.41, 103.77, 109.69, 111.94, 130.32, 140.71.

4-(3-(2-nitrophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3d). Yellow solid . mp 148-150°C; Yield 62%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm: 1.61-1.67 (m, 1H), 1.68-1.73 (m, 1H), 1.90-1.97 (m, 1H), 1.99-2.18 (m, 2H), 2.27-2.34 (m, 1H), 2.38-2.50 (m, 4H), 3.72 (t, *J*=4.58 Hz 4H), 4.84 (dd, *J*=3,74 Hz ; *J*=4,12 Hz 1H), 7.19 (td, *J*=1.32 Hz ; *J*=7.06 Hz 1H), 7.52 (td, *J*=1.32 Hz ; *J*=7.06 Hz 1H), 7.65 (d, *J*=8.25 Hz 1H), 8.04 (d, *J*=8,25 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.40, 32.19, 33.18, 46.20, 66.70, 78.32, 91.97, 119. 97, 123.88, 125.22, 132.40.

4-(3-(4-bromophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3e) Light brown crystals. mp 106-108°C; Yield 88%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.23-1.36 (m, 1H), 1.58-1.70 (m, 1H), 1.87-1.96 (m, 1H), 2.01-2.10 (m, 2H), 2.19-2.29 (m, 1H), 2.34-2.48 (m, 4H), 3.66 (t, *J*=4.68 Hz 4H), 4.82 (dd, *J*= 3.58 Hz ; *J*=5.32 Hz 1H), 7.42 (d, *J*=8.99 Hz 2H), 7.55 (d, *J*=8.99 Hz 2H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.26, 32.24, 33.37, 46.43, 66.84, 78.27, 90.91, 115.83, 117.99, 132.01, 138.44. Anal. Calcd for $C_{15}H_{19}N_4OBr$ (%) : C 62.20, H 6.65, N 18.97. Found C 62.26, H 6.64, N 18.93. MS (ESI) m/z (%) : 318.1561 $(M+H)^+$. MS (ESI) m/z (%) : 318.1561 $(M+H)^+$.

4-(3-(3-bromophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3f). Brown solid. mp 112-114°C; Yield 73%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.61-1.72 (m, 1H), 1.90-1.96 (m, 1H), 1.99-2.07 (m, 1H), 2.08-2.22 (m, 2H), 2.24-2.32 (m, 1H), 2.35-2.50 (m, 4H), 3.69 (t, *J*=4.52 Hz 4H), 4.84 (dd, *J*=3.39 Hz ; *J*=5.65 Hz 1H), 7.18 (d, *J*=8.10 Hz 1H), 7.20 (d, *J*=8.10 Hz 1H) , 7.60 (t, *J*=6.59 Hz 1H), 7.86 (s, 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 22.71, 31.66, 32.79, 45.84, 66.29, 77.84, 90.38, 114.20, 118.65, 122.27, 125.28, 129.85, 140.00.

4-(3-(2-bromophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3g) Light brown crystals. mp 138-140°C; Yield 65%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.58-1.66 (m, 1H), 1.66-1.72 (m, 1H), 1.75-1.84 (m, 1H), 1.92-2.11 (m, 2H), 2.13-2.20 (m,1H), 2.42-2.59 (m, 4H), 3.73 (t, *J*=4.52 Hz 4H), 4.73 (dd, *J*=3.96 Hz ; *J*=5.27 Hz 1H), 7.11 (td, *J*=1.13 Hz ; *J*=7.72 Hz 1H), 7.33 (td, *J*=1.32 Hz ; *J*=7.53 Hz 1H), 7.65 (dd, *J*=1.13 Hz ; *J*=8.10 Hz 1H), 7.69 (dd, *J*=1.50 Hz ; *J*=8.10 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 24.10, 33.00, 33.10, 46.52, 66.91, 77.78, 92.61, 120.12, 127.12, 125.66, 134.69, 137.81.

4-(3-(4-fluorophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3h) Brown solid. mp 100-102°C; Yield 85%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.21-1.35 (m, 1H), 1.58-1.69 (m, 1H), 1.87-1.96 (m, 1H), 1.99-2.07 (m, 2H), 2.16-2.24 (m, 1H), 2.41-2.43 (m, 4H), 3.67 (t, *J*=4.68 Hz 4H), 4.79 (dd, *J*=3.48 Hz ; *J*=5.41Hz 1H), 7.02 (dd, *J*=4.40 Hz ; *J*=4.77Hz 2H), 7.58 (dd, *J*=4.40 Hz ; *J*=4.77 Hz 2H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.60, 32.66, 33.81, 46.83, 67.25, 78.39, 91.57, 115.95, 118.77, 136.08, 157.96. Anal. Calcd for $C_{15}H_{19}N_4OF$ (%) : C 51.77, H 5.29, N 15.74. Found C 51.50, H 5.30, N 15.76. MS (ESI) m/z (%) : 318.1561 $(M+H)^+$.

4-(3-(3-fluorophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3i). Brown crystals. mp 76-78°C; Yield 76%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.26-1.37 (m, 1H), 1.62-1.73 (m, 1H), 1.92-1.98 (m, 1H), 2.07-2.19 (m, 2H), 2.24-2.32 (m, 1H), 2.38-2.50 (m, 4H), 3.71 (t, *J*=4,68 Hz 4H), 4.89 (dd, *J*=3.48 Hz ; *J*=5.41 Hz 1H), 7.47 (t, *J*=8.25 Hz 1H), 7.87 (dd, *J*=1.19 Hz; *J*=6.96 Hz 1H), 7.98 (dd, *J*=1.19 Hz ; *J*=7.06 Hz 1H), 8.53 (t, *J*=2.01 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.23, 32.11, 33.18, 46.33, 66.73, 78.80, 90.80, 110.37, 117.19, 121.62, 129.85, 140.15, 148.82.

4-(3-(2-fluorophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl)morpholine (3j). Yellow solid. mp 122-124°C; Yield 68%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.46-1.59 (m, 1H), 1.68-1,75 (m, 1H), 2.00-2,0 (m, 1H), 2.05-2.10 (m, 2H), 2.16-2.20 (m, 1H), 2,41-2.48 (m, 2H), 2.60-2.67 (m, 2H), 3,62 (t, *J*=4,67 Hz 4H), 4,71 (dd, *J*= 3,31 Hz ; *J*=5,42 Hz 1H),

7,13 (dd, *J*=2,01 Hz; *J*=7,60 Hz 1H), 7.18 (dd, *J*=1.37 Hz ; *J*=7.80 Hz 1H), 7.22 (td, *J*=1.37 Hz ; *J*=7.52 Hz 1H), 7.57 (td, *J*=1.39 Hz ; *J*=7.58 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.76, 32.73, 34.45, 46.95, 67.06, 81.35, 92.54, 116.82, 117.10, 125.87, 127.49, 154.98, 158.30.

4-(3-(2-chloro,4-nitrophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl) morpholine (3k).

Light yellow solid. mp 116-118°C; Yield 71%; ^{1}H NMR (300 MH_Z, $CDCl_3$) δ ppm : 1.46-1.56 (m, 1H), 1.65-1.72 (m, 1H), 1.75-1.82 (m, 1H), 1.98-2.10 (m, 2H), 2.20-2.28 (m, 1H), 2.48 (t, *J*=4.72 Hz 4H), 3.74 (t. *J*=4.72 Hz 4H), 4.84 (dd, *J*=3.77 Hz ; *J*=5.47 Hz 1H), 8.06 (d large, *J*=9.06 Hz 1H), 8.14 (dd, *J*=2.64 Hz ; *J*=6.42 Hz 1H), 8.34 (d, *J*=2.45 Hz 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 24.24, 32.62, 33.28, 46.82, 67.13, 78.41, 93.38, 122.78, 123.09, 127.57, 129.22, 142.44, 144.85.

4-(3-(3-(trifluoromethyl)phenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl) morpholine (3l).

Yellow brown solid. mp 76-78°C; Yield 92%; ^{1}H NMR (300 MH_Z, $CDCl_3$), δ ppm : 1.25-1.36 (m, 1H), 1.62-1.70 (m, 1H), 1.94-1.98 (m, 1H), 2.06-2.16 (m, 2H), 2.24-2.32 (m, 1H), 2.36-2.51 (m, 4H), 3.67 (t, *J*=4.50 Hz 4H), 4.87 (dd, *J*=3.58 Hz ; *J*=5.32 Hz 1H), 7.30 (d, *J*=7.70 Hz 1H), 7.43 (t, *J*=8.07 Hz 1H), 7.84 (d, *J*=8.25 Hz 1H), 7.97 (s, 1H) ; ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.26, 32.21, 33.32, 46.41, 66.85, 78.52, 90.91, 110.42, 112.75, 119.34, 125.77, 129.59, 131.74, 139.78. Anal. Calcd for $C_{16}H_{19}N_4OF_3$ (%) : C 56.81, H 5.74, N 15.09. Found C 56.49, H 5.90, N 14.89. MS (ESI) m/z (%): 318.1561 $(M+H)^+$.

4-(3-(2-fluoro,4-nitrophenyl)-3,3a,4,5,6,6a-hydrocyclopenta[d](1,2,3)triazol-3a-yl) morpholine (3m).

Light brown solid. mp 126-128°C; Yield 65%; ^{1}H NMR (300 MH_Z, $CDCl_3$), δ ppm : 1.39-1.53 (m, 1H), 1.66-1.76 (m, 1H), 1.96-2.02 (m, 1H), 2.03-2.08 (m, 2H), 2.10 -2.15 (m, 1H), 2.39-2.46 (m, 2H), 2.54-2.61 (m, 2H), 3.62 (t, *J*=4.68 Hz 4H), 4.72 (dd, *J*=3.48 Hz ; *J*=5.41 Hz 1H), 7.14 (td, *J*=2.56 Hz ; *J*=7.20 Hz 1H), 7.20 (d, *J*=2.29 Hz 1H), 7.53 (t, *J*=8.62 Hz 1H). ^{13}C NMR (75 MH_Z, $CDCl_3$) δ ppm : 23.67, 32.65, 34.18, 46.89, 66.89, 81.17, 92.51, 117.91, 124.80, 131.98, 125.91, 154.37, 157.75. Anal. Calcd for $C_{15}H_{18}N_4OFCl$ (%) : C 56.02, H 5.36, N 15.09. Found C 56.49, H 5.90, N 14.89. MS (ESI) m/z (%): 318.1561 $(M+H)^+$.

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