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Synthesis of Δ^2 (1,2,3)-Triazolines *via* 1,3-dipolar cycloaddition between organic azides and 1-morpholinocyclopentene derivatives

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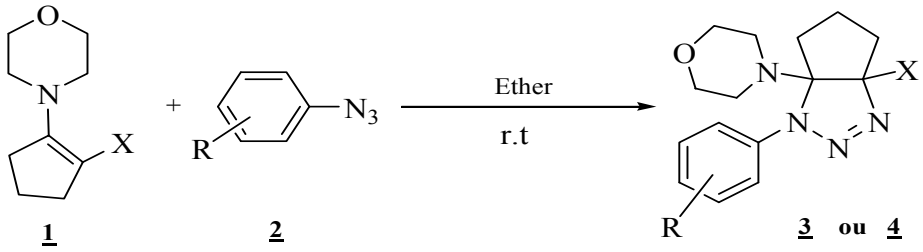
Abstract- The synthesis of some bicyclic Δ^2-1,2,3-triazolines performed by 1,3-dipolar cycloaddition reaction between cyclopentenic enamines and arylazides, at room temperature in ether, led to the expected triazolines with yields which vary according to the structure of the arylazide and enamine. The structure of the obtained triazolines was determined by the usual spectroscopic methods: (IR, ^{1}H NMR, ^{13}C NMR).

Key words: 1,3-dipolar cycloaddition, 1-morpholinocyclopentene, Organic azides, Triazolines Secondary amine, Heterocycles, Biological activities

1-INTRODUCTION

Heterocycles are a class of compounds commonly found in various natural and pharmaceutical products. They play an important role in the field of plastics, agricultural products, dyes industries, cosmetics ... and pharmaceuticals. They have various biological and therapeutic properties [1]. The nuclei triazolines and triazoles, five membered heterocycles containing tree nitrogens, are known for their multiple and diverse biological activities: antibacterial, fungic, anti-inflammatory, antiallergic and ... inhibitor of HIV [2]. Associated with other structures, they find their use in the pharmaceutical industry. As examples, we cite fluconazole as an antifungal, the Tazobactam and cefatrizine as antibiotics [3] and Ribavirin as antiviral [4]. The reaction of 1,3-dipolar cycloaddition in organic synthesis is one of the most widely methods used for the construction of five-membered heterocyclic. Thus, the addition of 1,3-dipole such as azides, nitrile oxides, diazo compounds or nitrones on multiple bonds: alkenes, alkynes, …. leads to the formation of triazolines, isoxazole, pyrazoline, and ... isoxazolines [5].

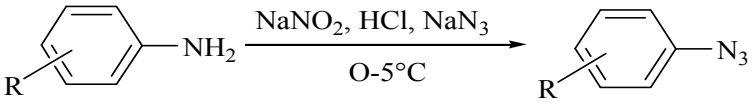
The synthesis method we adopted consists in reacting enamines of cyclopentanone or 2-carboxylate cyclopentanone **1** with arylazides **2** lead to variously substituted bicyclic triazolines. The reaction is carried out in ether at room temperature.



1 **2** **3** ou **4**

X = H, CO_2CH_3 R = H, *p*-NO_2, *p*-OMe, 2-Cl 4-NO_2, *m*-CF_3, *p*-F

The arylazides used were prepared according to the method of Noelting and Michel [6] and improved by Ranu [7]. This path consists in preparing beforehand the diazonium salt from the substituted aniline on which the sodium azid reacts.

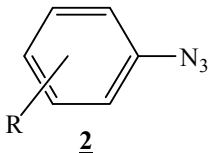


2

R = H, *p*-NO_2, *p*-OMe, 2-Cl 4-NO_2, *m*-CF_3, *p*-F

The physical characteristics of arylazides **2** are summarized in Table 1.

Table 1. Yields and melting points of arylazides **2**



2

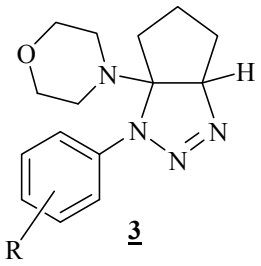
Entry	R	Yield %	m.p(°C)
2a	H	85	liq
2b	*p*-NO_2	83	69-71
2c	2-Cl, 4-NO_2	82	70-72
2d	*p*-OMe	93	<25
2e	*m*-CF_3	88	liq
2f	*p*-F	81	liq

2-RESULTS AND DISCUSSION

Addition of enamines of cyclopentanone or 2-methyl carboxylate cyclopentanone **1** and arylazides **2**, in ether at room temperature, in a single step leading to triazolines **3**, **4** with yields which vary according to the structure of arylazides and cyclopentenic enamines [8].
The reaction times and yields of bicyclic triazolines obtained by 1,3-dipolar cycloaddition are summarized in table 2 for the heterocycles **3** and table 3 for heterocycles **4**.

Table 2. Reaction time and yields bicyclic triazolines 3

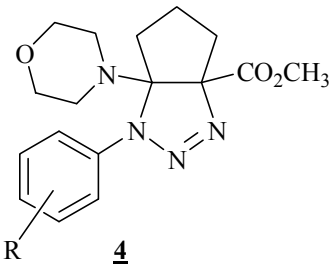
Entry	R	Time	Yield %	m.p(°C)
3a	H	5d	98-100	82
3b	*p*-NO_2	24h	192-194	86
3c	2-Cl, 4NO_2	24h	114-116	73
3d	*p*-OMe	5d	Liq.	88
3e	*m*-CF_3	7d	86-88	88
3f	*p*-F	5d	80-82	90



3

Table 3. Reaction time and yields triazolines bicyclic **4**

Entry	R	Time	Yield %	m.p(°C)
4a	H	6d	108-110	19
4b[(i)]	*p*-NO_2	24h	190-192	45
4c[(i)]	2-Cl, 4NO_2	24h	116-118	36
4d	*p*-OMe	3d	Liq.	14
4e[(ii)]	*m*-CF_3	5d	84-86	51
4f[(ii)]	*p*-F	7d	94-96	53



4

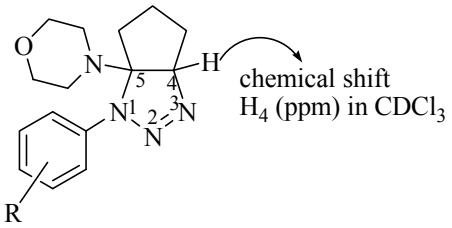
(i) The reactions carried out with p-chloro-and nitrophenylazide, provided unexpected triazolines **3b** and **3c**. (ii) The spectra of the reaction products with fluorinated azides are not usable.

It was noted that the reaction of 1,3-dipolar cycloaddition carried out in ether led to bicyclic triazolines **3** expected with yields varying between 73 and 90% at a time ranging from 24 hours to 7 days. Monofluorinated azide leads to better yield.

The structures of various bicyclic triazolines **3**, **4** were determined by NMR spectroscopy. The chemical shift of the proton in position 4 of pentagonal heterocycle is shown in Table 4.

Table 4. Chemical shift of H4 and coupling constants of the triazolines **3**

Entry	R	δ of H4 (ppm) (dd)	*J (Hz)*
3a	H	4,77	3,66; 5,10
3b	*p*-NO_2	4,95	3,78; 5,01
3c	2-Cl,4-NO_2	4,84	3,77; 5,47
3d	*p*-OMe	4,74	3,10; 5,20
3e	*m*-CF_3	4,82	3,51; 5,52
3f	*p*-F	4,78	3,40;5,47



3 - CONCLUSION

The application of 1,3-dipolar cycloaddition reaction involving enamines of cyclopentanone or 2-carboxylate cyclopentanone and arylazides in ether at room temperature, allowed us to prepare five-membered heterocycles in mild conditions.

4- MATERIALS AND METHODS

Cyclopentanone was distilled before use. Melting points were determined using a Banc Kofler and were not corrected.

The infrared spectra were recorded on a FTIR spectrometer Alpha Diamond ATR (Bruker Optics). Sample liquids are examined in KBr film, while solids are recorded on a spectrometer Infrared Fourier Transform Infrared (FTIR) Thermo-Nicolet IR200 controlled by the EZ OMNIC 7.2a software. The absorption frequencies are expressed in cm-1 to their maximum intensity and the intensities are denoted as follows: FF very strong, strong F, mean m and f low.

The thin-layer chromatography (TLC) was performed on silica plates Merck 230-400 mesh silica. The elution solvents are mixtures of ethyl acetate and petroleum ether, and revealed in most cases by a Ultra-violet lamp.

The nuclear magnetic resonance (1H, 13C, DEPT) were recorded with a Bruker AC-300 (300 MHz) or AC-400 aircraft. The internal standard is chloroform (7.26 ppm) and the proton resonance (77.0 ppm) for the resonance of carbon.

Chemical shifts are given in δ scale and expressed in parts per million (ppm) and refer to the residual solvent peak. All spectra were carried out in deuterated chloroform.

The functions of signals for carbon spectra were recorded by DEPT (Distortion Less Enhancement by Polarization Transfer), which differentiates the CH and CH3 CH2, allows the assignment of signals.

Abbreviations s, d, dd, t, td, m and adopted respectively mean singlet, doublet, doublet of doublet, triplet, triplet dedoubled and multiplet.

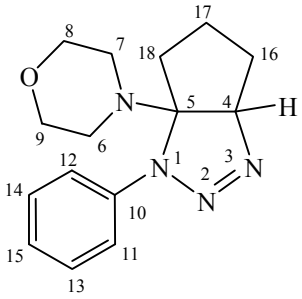
Coupling constants (J) are expressed in Hertz (Hz). * Indicates an international agreement possible.

General procedure for the synthesis of triazolines

Cyclic enamines **1** and organic azides RN_3 **2** are mixed into equimolar quantity in ether with stirring. The reaction mixture was kept at room temperature and monitored by TLC.

The chemical shift values of different triazolines are in good agreement with the proposed structure.

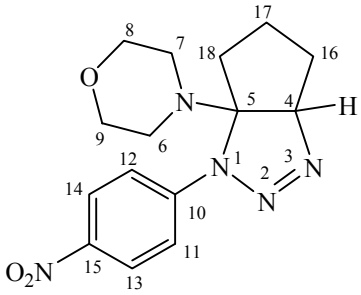
- ***4-(3-phényl-3,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine* 3a**



3a

Appearance : brown solid
yield : 82% in ether
m.p : 98-100°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,22-1,23 (m, 1H16b), 1,55-1,65 (m, 1H16a), 1,88-1,98 (m, 1H18b), 2,01-2,14 (m, 2H17), 2,17-2,29 (m,1H18a), 2,41 (t, *J*= 4,39 4H6,7), 3,64 (t, *J*= 4,39 4H8,9), 4,77 (dd, *J*= 3,66;*J*=5,10 1H4), 7,04 (t, *J*= 7,03 1H15), 7,30 (t, *J*= 7,60 2H13,14), 7,61 (d, *J*= 8,4 2H11,12).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,26; C16: 32,29 ; C18: 33,44; C6,7: 46,41; C8,9: 66,87; C4: 78,00; C5: 91,07 ; C11,12: 116,66; C15: 123,17 ; C13,14: 129,00 ; C10: 139,38.

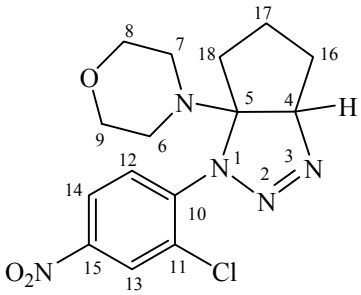
- ***4-(3-(4-nitrophényl)-3, 3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine (3b)***



3b

appearance: yellow solid
yield: 86% in ether
m.p : 192-194°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,26-1,41(m, 1H16b), 1,66-1,72 (m, 1H16a), 1,91-2,00 (m, 1H18b), 2,11-2,17 (m, 2H17), 2,30-2,32(m,1H18a),2,34-2,39(m,2H6),2,44-2,49(m,2H7), 3,67-3,69 (m,4H8,9), 4,95 (dd, *J*= 3,78;*J*=5,01 1H4), 7,78 (d, *J*= 9,25 2H11,12), 8,23 (d, *J*= 9,25 2H13,14).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,75; C16: 32,74 ; C18:33,55; C6,7: 46,78; C8,9: 67,14; C4: 79,73; C5: 91,03 ; C11,12: 115,49; C15: 199,32 ; C13,14: 125,79 ; C10: 144,80.

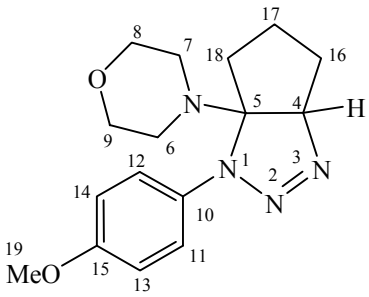
- ***4-(3-(2-chloro,4-nitrophényl)-3,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine (3c)***



3c

appearance : Light yellow solid
yield : 73% in ether
m.p : 114-116°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,46-1,56 (m, 1H16b), 1,65-1,72 (m, 1H16a), 1,75-1,82 (m, 1H18b), 1,98-2,10 (m, 2H17), 2,20-2,28 (m,1H18a), 2,48 (t, *J*= 4,72 4H6,7), 3,74 (t, *J*= 4,72 4H8,9), 4,84 (dd, *J*= 3,77;*J*=5,47 1H4), 8,06 (d large, *J*= 9,06 1H12), 8,14 (dd, *J*= 2,64;*J*=6,42 1H14), 8,34 (d, *J*=2,45 1H13).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 24,24; C16: 32,62 ; C18: 33,28; C6,7: 46,82; C8,9: 67,13; C4: 78,41; C5: 93,38 ; C12: 122,78; C14: 123,09 ; C13: 127,57 ; C11: 129,22; C15: 142,44; C10: 144,85.

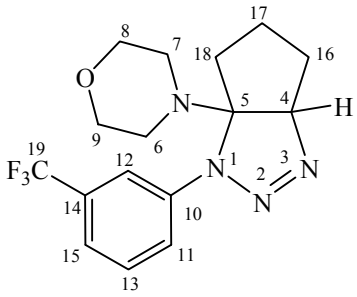
- ***4-(3-(4methoxyphényl)-3,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine(3d***



3d

appearance: brown oil
yield : 88% in ether
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,19-1,39 (m, 1H16b), 1,58-1,69 (m, 1H16a), 1,94-1,98 (m, 1H18b), 2,03-2,10 (m, 2H17), 2,13-2,18 (m,1H18a),2,45-2,47(m,4H6,7),3,67(t,*J*=4,44H8,9), 3,79 (s,3H19), 4,77 (dd, *J*= 3,10;*J*=5,20 1H4), 6,88 (d, *J*= 9,15 2H11,12), 7,52 (d, *J*= 9,15 2H13,14).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,73; C16: 32,45 ; C18: 33,29; C6,7: 46,32; C19: 54,85; C8,9: 66,74; C4: 77,83; C5: 91,25 ; C11,12: 114,16; C13,14: 119,11 ; C10: 132,91; C15: 156,26.

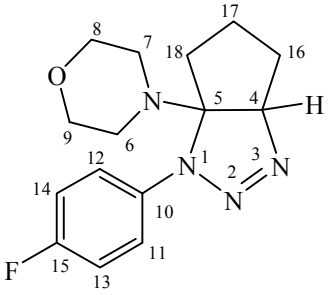
- ***4-(3-(3-(trifluoromethyl)phenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine (3e)***



3e

appearance: Light yellow solid
yield : 88% in ether
m.p: 86-88°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,28-1,36 (m, 1H16b), 1,62-1,71 (m, 1H16a), 1,91-1,98 (m, 1H18b), 2,02-2,14 (m, 2H17), 2,24-2,31 (m,1H18a),2,38-2,51 (m,4H6,7) ,3,67 (t, *J*= 4,70 4H8,9), 4,82 (dd, *J*= 3,51;*J*=5,52 1H4), 7,30 (d, *J*= 7,78 1H11), 7,43 (t, *J*= 8,03 1H13), 7,84 (d, *J*=8,28 1H15) ,7,97 (s, 1H12).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,26; C16: 32,16 ; C18: 33,33; C6,7: 46,38; C8,9: 66,84; C4:78,44; C5: 90,90 ; C12: 110,42; C11: 112,78 ; C13: 119,34 ; C19: 125,76; C15: 129,60; C14: 131,28; C10: 139,72 .

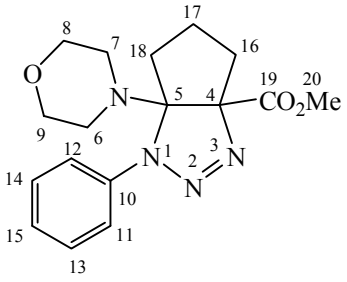
- ***4-(3-(4-fluorophenyl)-3,3a,4,5,6,6a--hexahydrocyclopenta[d][1,2,3]triazol-3a-yl)morpholine(3f)***



3f

appearance: Yellow solid caramel
yield: 90% in ether
m.p : 80-82°C
IR: 2960,80 (m) ; 1637,63(m) ; 1108,56(F) ; 1499,44(m) ; 880,31 (m) ; 535,77 (p) .
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,21-1,32 (m, 1H16b), 1,58-1,68 (m, 1H16a), 1,86-1,94 (m, 1H18b), 2,00-2,06 (m, 2H17),2,16-2,24 (m,1H18a),2,40-2,44 (m,4H6,7), 3,68 (t,*J*=4,9 4H8,9), 19 (s,3H19), 4,78 (dd, *J*= 3,40;*J*=5,47 1H4), 7.01 (dd, *J*= 4,70;*J*=4,90 2H11,12), 7.58 (dd, *J*= 4,70;*J*=4,90 2H13,14).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,60; C16: 32,66 ; C18: 33,81; C6,7: 46,83; C8,9: 67,25; C4:78,39; C5: 91,57 ; C11,12: 115,95; C13,14: 118,77 ; C10: 136,08; C15: 157,96.

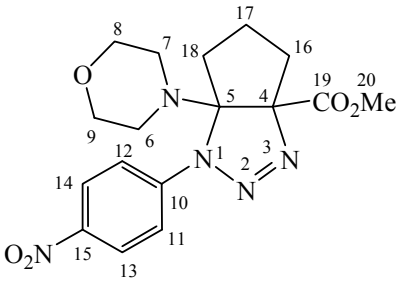
- ***Methyl6a-morpholino-1-phenyl-1,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-carboxylate(4a)***



4a

appearance: Solid chocolate brown
yield : 19% in ether
m.p : 108-110°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,60-1,68 (m, 1H16b), 1,85-1,91 (m,1H16a),2,03-2,07 (m,1H18b),2,16-2,20 (m,2H17) ,2,29-2,32 (m,1H18a),3,50 (t, *J*=4,52 4H6,7), 3,68 (t,*J*=4,52 4H8,9), 3,68 (s,3H20), 7,15 (d, *J*= 7,281H15), 7.35 (t, *J*= 7,52 2H13,14), 7,45 (d, *J*=8,78 2H11,12).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 22,26; C16: 31,39 ; C18: 33,55; C19: 52,95; C6,7: 46,84; C8,9: 67,77; C4:79,00; C5: 93,07 ; C11,12: 115,68; C15: 125,47 ; C13,14: 130,54 ; C10: 142,38; C20: 168,24.

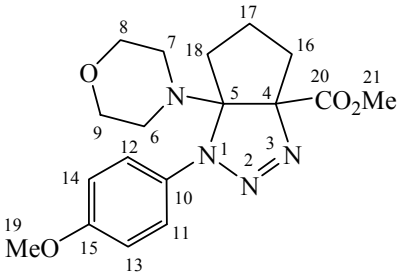
- ***Methyl6a-morpholino-1-(4-nitrophenyl)-1,3a,4,5,6,6a-hexahydrocyclopenta[d][1,2,3]triazol-3a-carboxylate (4b)***



4b

appearance: yellow solid
yield : 45% in ether
m.p : 190-192°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,14-1,40(m, 1H16b), 1,61-1,65(m,1H16a),1,81-1,94(m,1H18b),1,82-2,16(m,2H17) ,2,48-2,50(m,1H18a),2,53-2,60(m,2H6),2,63-2,74(m,2H7), ,3,45-3,58(m,4H8,9), 3,88(s,3H20), 7,61(d,*J*=9,51 2H11,12), 8,24 (d, *J*=9,51 2H13,14).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 23,24; C16: 31,65; C18: 33,27; C6,7: 46,74; C19: 54,64 C8,9: 68,83; C4:79,81; C5:95,48 ; C12:120,18; C14: 125,19 ; C13: 128,52 ; C11: 130,22; C15: 145,84; C10: 142,85; C20: 170,25.

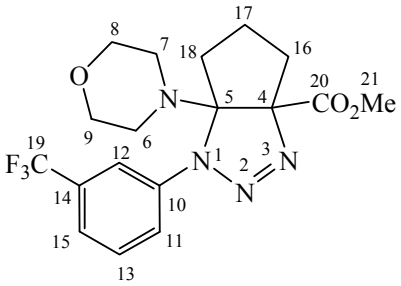
- ***Methyl1-(4-methoxyphenyl))-6a-mopholino-1,3a,4,5,6^a hexahydrocyclopenta[d] [1,2,3]triazole-3a-carboxylate (4c)***



4c

appearance: brown oil
yield: 14% in ether
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,62-1,66 (m, 1H16b), 1,82-1,87 (m,1H16a),2,08-2,12 (m,1H18b),2,37-2,41 (m,2H17),2,48-2,50(m,1H18a),3,47-3,50(m,4H6,7), 3,80(t,*J*=3,79 4H8,9),3,87 (s,3H19),3,80 (s,3H21), 6,87(d,*J*=9,27 2H11,12), 7,35(d, *J*=9,27 2H13,14).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 22,73; C16: 30,45 ; C18: 32,29; C6,7: 46,54; C21: 52,95; C19: 55,7; C8,9: 67,74; C4:77,87; C5: 92,25 ; C11,12: 114,25; C13,14: 118,15 ; C10: 134,91; C15: 152,26; C20: 169,54.

- ***Methyl6a-morpholino-1-(3-(trifluoromethyl)phenyl)-1,3a,4,5,6,6a-hexahydrocyclopenta[d] [1,2,3]triazol-carboxylate(4d)***



4d

appearance: Yellow solid honey
yield: 51% in ether
m.p : 84-86°C
^{1}H NMR (300 MH_Z, $CDCl_3$), δ: 1,27-1,35(m, 1H16b), 1,81-1,88(m,1H16a),2,05-2,10(m,1H18b),2,19-2,37(m,2H17) ,2,45-2,48(m,1H18a),2,50-2,71(m,4H6,7),3,44-3,49(m,4H8,9),3,86(s,3H21),7,36(d,*J*=7,781H11), 7,43(t,*J*=8,031H13), 7,69(d, *J*=8,28 1H15) ,7,75(s,1H12).
^{13}C NMR (300 MHZ, CDCl3) , δ ppm : C17: 22,78; C16: 32,28 ; C18:39,50; C6,7:48,57; C21:52,90; C8,9: 67,29; C4:92,96; C5:94,78 ; C12:106,95; C15:113,35 ; C11: 118,93; C19: 120,04; C13: 129,84 ;C14: 131,81; C10: 139,98; C20: 170,64

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