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Synthesis, Characterization and Antimicrobial Properties of Some 1,3,4-Thiadiazolines

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Abstract: Through The literature, there is little information about the antibacterial activity of 1,3,4-thiadiazoles. In order to verify if drugs based on this family of compounds could constitute an alternative to the antibiotics usually used in the antimicrobial fight, the aim of this work was to synthesize, to confirm the structures and then to test some 1,3,4-thiadiazolines for their antimicrobial activity against microbes. Twelve 1,3,4- thiadiazolines were synthesized with yields going from 27 to 95%. The products purity was confirmed by mass spectrometry coupled with high-performance liquid chromatography (LC/MS) and there were characterized using spectrometry IR, NMR ^{1}H and ^{13}C (nuclear magnetic resonance). The synthesized compounds were tested on strains of *Escherichia coli* ATCC 25922 and *Salmonella typhimurium* R 30951401 according to the macro-dilution method in liquid environment for a comparison of their antibacterial activity. Thiadiazoline 1 has been shown to be more active than other products. The most antibacterial thiadiazolines are those having para-electro attractor groups and also alkyl groups at R2. It could be a good drug candidate against these microbes.

Keywords: 1,3,4-Thiadiazolines, Spectrometric Confirmation, Antimicrobial Properties

1. Introduction

Antimicrobial resistance is considered a serious threat to health worldwide [1, 2]. It is estimated that it is already causing 700,000 deaths each year and, in the absence of effective action, it is expected that it will cause 10 million deaths a year by 2050. However, humanity has a limited number of effective antibiotics. It is then necessary to broaden the spectrum of antimicrobials and to develop new antibacterial molecules. Thiosemicarbazones have many biological activities such as: antiviral, antifunga l [5, 6], antimalarial, antitumor [7-8]. Thiosemicarbazones are also known for their antibacterial properties [9-10]. In addition, thiosemicarbazones are important intermediates in drugs synthesis, formation of metal complexes and heterocycles such as thiadiazolines preparation.

The 1,3,4-thiadiazoles and 1,3,4-thiadiazolines which are cyclic derivatives of the thiosemicarbazones exhibit various biological activities such as antituberculosis anti-inflammatory [11], anticonvulsant antihypertensive anticancer and hypoglycemic activities [12]. Therefore, 1, 3, 4-Thiadiazole and related compounds are of great interest in chemistry owing to their bioactivity of certain plant growth regulating effects [13]. The thiosemicarbazones and 1,3,4-thiadiazolines thus presented have about the same biological properties however there is little information about the antibacterial activity of 1,3,4-thiadiazolines.

The aim of this work is to synthesize, to confirm the structures by spectrometric methods and then to test the antimicrobial activity of some 1,3,4-thiadiazolines on

microbes. Its interest lies in the fact that it will make it possible to see if drugs based on 1,3,4-thiadiazolines could constitute an alternative to the antibiotics usually used in the antimicrobial fight.

2. Material and Methods

2.1. Chemistry

We used thin layer chromatography (TLC) to estimate the purity of the compounds, to follow the evolution of the reaction and then to achieve their purification on silica gel column. The solvent used is the mixture of dichloromethane/ethylacetate (2/1) or dichloromethane/methanol (9/1). Compounds purity was confirmed by LC/MS. The melting points were taken on the fusionometer *eletrothermal 1A 9000.* The spectrometric data were recorded with the following instruments: IR, Perkin Elmer FT-IR 286; ^{1}H NMR and ^{13}C NMR, Bruker 400; LC/MS in mode APCI on column C18. The 1,3,4-thiadiazolines are synthesized as follows:

1) Synthesis of the thiosemicarbazones. A mixture of ketone (20 mmol dissolved in 100 mL of ethanol) and thiosemicarbazide (20 mmol dissolved in 20 ml of 1 N hydrochloric acid) is stirred until the thiosemicarbazone precipitates. The precipitate is filtered, dried and then recrystallized in ethanol (96°C) to give thiosemicarbazone crystals (Figure 1).

2) Synthesis of 1,3,4-thiadiazolines. Thiosemicarbazone (0.25 mmol) was dissolved in 0.5 mL of pyridine and 0.5 ml of acetic anhydride and the mixture was heated at 110°C during 3 h with magnetic stirring to give the 1, 3, 4-thiadiazoline derivative which is filtered and purified by flash chromatography (Figure 1).

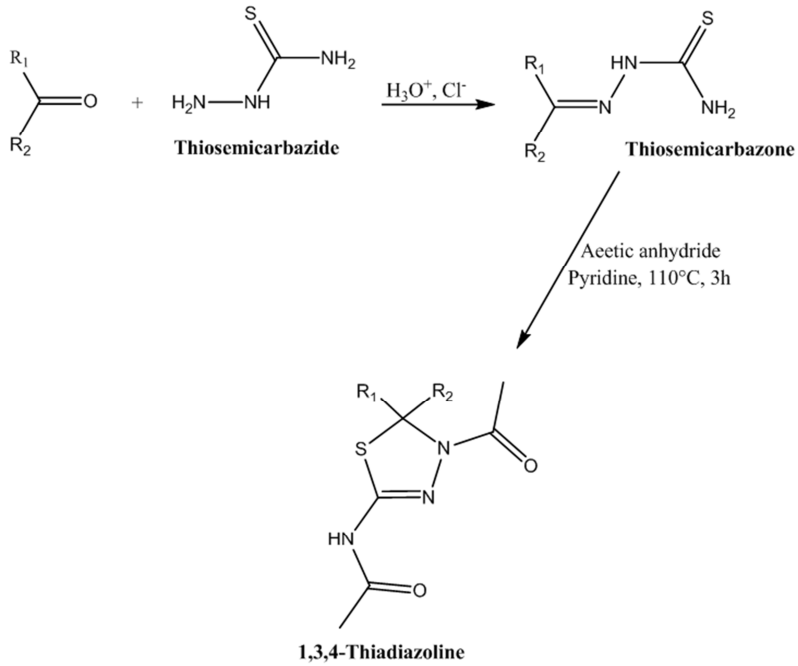


Figure 1. *Synthesis of 1,3,4-thiadiazolines (1-12).*

2.2. Antimicrobial Test

The synthesized compounds were tested on strains of *Escherichia coli* ATCC 25922 and *Salmonella typhimurium* R 30951401. The method used is that of dilution in a liquid medium. The solutions of 1,3,4-thiadiazolines were carried out at an initial concentration of 20 mg/ ml in acetone. The bacterial suspensions were carried out at a colony for 5 ml in LB medium (Luria Bertani) for *Escherichia coli* and *Salmonella typhimurium*.

Three series of eight wells initially containing 100 µl of distilled water were made. 100µl of solution of 1,3,4-thiadiazolines were added to the first well; and a 2-to-2 dilution from one row to another until the eighth set of wells. The microbial suspensions were then added and the wells incubated in an oven at 37°C.

After 18 hours of incubation, 40 µl of a 0.2 mg/ ml solution of p-iodonitrotetrazolium violet (p-INT) are added to each well and the whole is incubated for one hour.

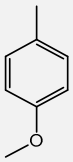
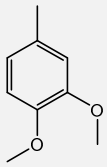
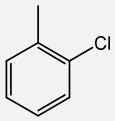
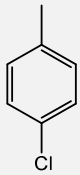
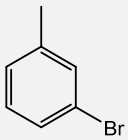
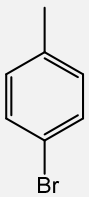
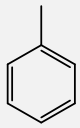
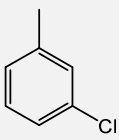
Iodonitrotetrazolium is a reagent for the detection of enzymatic activity. In the medium, it is reduced by mitochondrial enzymes and stains red; thus marking the presence of life and enzymatic activity in the environment. Wells stained red are those in which the concentration of synthetic products is insufficient to inhibit bacterial growth. The MIC corresponds to the concentration of the undyed well in which there is the lowest amount of 1,3,4-thiadiazolines. The reading is done in comparison with the control wells. It should also be noted that a series of positive controls has been performed with equivalent concentrations of gentamycin.

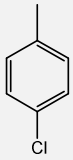
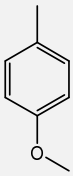
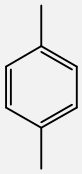
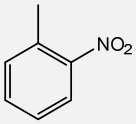
3. Results and Discussions

3.1. Chemistry

Twelve 1, 3, 4- thiadiazolines were synthesized with yields going from 27 to 95%. The physical and spectrometric data of the 12 compounds are reported in Table 1. Thin layer chromatography (TLC) shows that 1,3,4-thiadiazolines have Rf up 0.37 to 0.77.

Table 1. *Chemical structure, yield, and melting point of synthesized 1,3,4-thiadiazolines (1-12).*

Compounds	R1	R2	Yield (%)	Rf	M. P (°C)
1		-CH_3	32	0.60	188-189
2		-CH_3	49	0.33	156-157
3		-CH_3	27	0.58	130-132
4		-CH_3	58	0.61	214-216
5		-CH_3	95	0.60	238-239
6		-CH_3	79	0.67	211-213
7		-H	87	0.40	221-222
8		-H	81	0.61	195-196

Compounds	R1	R2	Yield (%)	Rf	M. P (°C)
9		-H	77	0.77	228-230
10		$-CH_2-CH_3$	66	0.60	209-210
11		-H	70	0.56	210-211
12		-H	94	0.37	245-246

The spectrometric data of this table are in conformity with the structures suggested for the products.

Thus the IR spectra of 1,3,4-thiadiazolines show bands in the range of 3146-3232 cm^{-1} due to the stretching vibration of NH.

The NH group is also demonstrated in ^{1}H NMR through its hydrogen which has chemical shifts of between 9.10 and 11.90 ppm for the twelve 1,3,4-thiadiazolines synthesized.

In ^{13}C NMR spectra, ring closure in 1,3,4-thiadiazolines may be observed by (1) the disappearance of the signal between 177 and 179 corresponding to the thiocarbonyl group, (2) the appearance of a signal between 63 and 81 ppm assigned to C-2 and (3) the signals of the carbonyl and methyl moieties of the acetyl groups incorporated to the molecule.

In mass spectrometry, the $[MH]^{+}$ peaks obtained in APCI mode correspond to molecular weights expected for all products. In LC mode, all 1,3,4-thiadiazolines have a single peak confirming their purity.

The details concerning the spectral data are listed in the appendix. The synthesized compounds were tested for their antibacterial activity on *Escherichia coli* ATCC 25922 and *Salmonella typhimurium* R 30951401.

3.2. Microbiology

The antimicrobial test results of the twelve 1,3,4-thiadiazolines synthesized are shown in Table 2 below. Following the analysis of this result, we find that 1,3,4-thiadiazolines are more active on *Salmonella typhimurium* than on *Escherichia coli*. 1, 3, 4-thiadiazoline 1 is the most active of all with a MIC of 0.625 mg/ mL on *Salmonella typhimurium*. 1,3,4-thiadiazolines 11, 6 and 5 are the least active on *Salmonella typhimurium*. The *para*-methoxy group on 1, 3, 4-thiadiazoline 1 seems to play an important role in inhibiting the growth of *Salmonella typhimurium* because its replacement with a chlorine or bromine atom in compounds 4 and 6 is reflected by a gradual loss of activity. It also finds a decrease in activity when an additional methoxy group is added in the *meta* position at compound 2 level.

Table 2. *Minimal inhibitory concentration (MIC) of synthesized compounds.*

Compounds	MIC (mg/mL)	
	Escherichia coli	***Salmonella typhimurium***
1	> 10	0.625
2	> 10	10
3	> 10	10
4	5	2.5
5	> 10	> 10
6	> 10	> 10
7	10	2.5
8	> 10	10
9	> 10	10
10	1.25	5
11	> 10	> 10
12	5	5

The presence of the methyl group in R2 of the thiadiazolines is also important for the inhibition of the growth of *Salmonella typhimurium* because, its replacement by a hydrogen atom in the compound 4 leads to the compound 9 thus causing an increase in the MIC which goes from 5 mg/ mL to more than 10 mg/ mL. There is also a decrease in inhibitory activity when in thiadiazoline 1 which

has a MIC of 0.625 mg/ ml is replaced by methyl in R2 by an ethyl group; a MIC of 5 mg/ mL is increased with thiadiazoline 10.

The 1,3,4-thiadiazolines synthesized are not very active on *Escherichia coli*. However, the best MIC is 1.25 mg/ mL for compound 10. The trend observed for the structure-activity relationship of thiadiazolines in *Salmonella typhimurium* appears to be the same with *Escherichia coli* with a few exceptions. Indeed, in the case of compound 10, the presence of the ethyl group in R2 instead of the methyl group is rather beneficial for the inhibition of the growth of *Escherichia coli*.

4. Conclusion

From this work which consisted in highlighting the antibacterial activity of certain 1,3,4-thiadiazolines on *Salmonella typhimurium* and *Escherichia coli*, it appears that the antibacterial potency of thiadiadiazolines varies according to the microbial strains. The synthesized compounds seem more active against *Salmonella typhimurium* than *Escherichia coli*. Among the twelve tested compounds, N-(4-acetyl-5-ethyl-5-(4-methoxyphenyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)acetamide (10) was the most active against *Escherichia coli* with MIC < 1.5 mg/mL and N-(4-acetyl-5-(4-methoxyphenyl)-5-methyl-4, 5-dihydro-1,3,4-thiadiazol-2-yl)acetamide (1), the most active against *Salmonella typhimurium* with MIC < 0.7 mg/mL. The most antibacterial thiadiazolines are those that have para-electroattractor groups and also alkyl groups at R2. They could be good drug candidates against these microbes.

Appendix

Spectral data of 1,3,4-thiadiazolines (1-12)

N-(4-acetyl-5-(4-methoxyphenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (1):

LC/MS: $[MH]^+$calculated: 308, 1063 $[MH]^+$ found: 308, 1059.

IR m (KBr cm^{-1}): 3171 (NH); 1691, 1643 and 1614 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1, 88 (3H, s, CH_3); 2, 19 (3H, s, CH_3 amide); 2, 27 (3H, s, CH_3 amide); 3, 34 (3H, s, O-CH_3); 6, 75-7, 27 (4H, several signals, ArH); 9, 13 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm): 22, 87 (CH_3); 23, 89 and 26, 86 (2. CH_3 amides); 55, 29 (O-CH_3) 80, 03 (C2 of the ring); 124, 99-142, 82 (Aromatic C); 143, 48 (C=N); 168, 84 and 169, 27 (C=O amides).

N-(4-acetyl-5-(3, 4-dimethoxyphenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (2):

LC/MS: $[MH]^+$ calculated: 338, 1169 $[MH]^+$found: 338, 1165.

IR m (KBr cm^{-1}): 3169 (NH); 1698, 1646 and 1601 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1, 80 (3H, s, CH_3); 2, 23 (3H, s, CH_3 amide); 2, 25 (3H, s, CH_3 amide); 3, 78 (3H, s, O-CH_3); 3, 79 (3H, s, O-CH_3); 6, 68-6, 91 (3H, several signals, ArH); 9, 94 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm): 22, 64 (CH_3); 23, 86 et 26, 68 (2. CH_3 amides); 55, 91 (O-CH_3); 56, 91 (O-CH_3) 79, 72 (C2 of the ring); 109, 14-135, 17 and 148, 83; 148, 90 (Aromatic C); 144, 22 (C=N); 169, 33 and 169, 34 (C=O amides).

N-(4-acetyl-5-(2-chlorophenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (3)

LC/MS: $[MH]^+$ calculated: 312, 0568; $[MH]^+$ found: 312, 0565.

IR m (KBr cm^{-1}): 3160 (NH); 1698, 1644 et 1611 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1, 86 (3H, s, CH_3); 2, 26 (3H, s, CH_3 amide); 2, 36 (3H, s, CH_3 amide) 7, 19-7, 42 (4H, several signals, ArH); 9, 61 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm):28, 85 CH_3; 22, 96 et 23, 01 (2. CH_3 amides); 78, 35 (C2 of the ring); 126, 64-137, 27 (C Aromatic); 144, 37 (C=N); 168, 68 and 169, 78 (C=O amides).

N-(4-acetyl-5-(4-chlorophenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (4)

LC/MS: $[MH]^+$ calculated: 312, 0568; $[MH]^+$ found: 312, 0567.

IR m (KBr cm^{-1}): 3146 (NH); 1694, 1633 et 1617 (C=O amides)

^1H NMR d ($CDCl_3$ ppm): 1, 75 (3H, s, CH_3); 2, 22 (3H, s, CH_3 amide); 2, 24 (3H, s, CH_3 amide) 7, 19-7, 27 (4H, several signals, ArH); 10, 14 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm):22, 49 (CH_3); 23, 78 et 26, 62 (2. CH_3 amides); 78, 90 (C2 of the ring); 126, 68-141, 31 (C Aromatic); 144, 86 (C=N); 169, 40 and 169, 56 (C=O amides).

N-(4-acetyl-5-(3-bromophenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (5)

LC/MS: $[MH]^+$ calculated: 357, 0102; $[MH]^+$ found: 357, 097.

IR m (KBr cm^{-1}): 3218, 3146 ν (NH); 1694, 1614 (C=O amides).

^1H NMR d (DMSO-d_6 ppm): 2, 03 (3H, s, CH_3); 2, 20 (3H, s, CH_3 amide); 2, 27 (3H, s, CH_3 amide) 7, 32-7, 59 (4H, several signals, ArH); 11, 69 (1H, s, NH).

^{13}C NMR d (DMSO-d_6): 22, 40 (CH_3); 23, 58 et 26, 30 (2. CH_3 amides); 77, 86 (C2 of the ring); 121, 72-142, 30 (C Aromatic); 146, 84 (C=N); 167, 77 and 169, 45 (C=O amides).

N-(4-acetyl-5-(4-bromophenyl)-5-methyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (6)

LC/MS: $[MH]^+$ calculated: 358, 0048; $[MH]^+$ found: 358, 0042.

IR m (KBr cm^{-1}): 3217, 3148 (NH); 1695, 1614 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1, 75 (3H, s, CH_3); 2, 22 (3H, s, CH_3 amide); 2, 24 (3H, s, CH_3 amide); 7, 21-7, 37 (4H, several signals, ArH); 10, 32 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm): 22, 54 (CH_3); 23, 85 et 26, 59 (2. CH_3 amides); 78, 95 (C2 of the ring); 121, 93-141, 85 (C Aromatic); 144, 34 (C=N); 169, 39 and 169, 55 (C=O amides).

N-(4-acetyl-5-phenyl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)

acetamide (7):

LC/MS: $[MH]^+$calculated: 264,0801; $[MH]^+$found: 264,0796.

IR m (KBr cm^{-1}): 3216, 3165 (NH); 1713, 1702, 1634 (C=O amides).

^1H NMR d (DMSO-d_6 ppm): 2, 04 (3H, s, CH_3 amide); 2, 21 (3H, s, CH_3 amide); 6, 84 (1H, s, CH); 7, 24-7, 37 (5H, several signals, ArH); 11, 76 (1H, s, NH).

^{13}C NMR d (DMSO-d_6): 21, 85 and 22, 52 (2. CH_3 amides); 65, 79 (C2 of the ring); 125, 04-141, 37 (Aromatic C); 145, 97 (C=N); 167, 27 and 167, 39 (C=O amides).

N-(4-acetyl-5-(3-chlorophenyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (8)

LC/MS: $[MH]^+$ calculated: 298,0411; $[MH]^+$ found: 298,0410.

IR m (KBr cm^{-1}): 3208 (NH); 1663 et 1625 (C=O amides).

^1H NMR d (DMSO-d_6 ppm): 2, 04 (3H, s, CH_3 amide); 2, 22 (3H, s, CH_3 amide); 7, 21-7, 42 (5H, several signals, 4H ArH and 1H CH_2); 11, 80 (1H, s, NH).

^{13}C NMR d (DMSO-d_6): 21, 81 et 22, 52 (2. CH3 amides); 65, 08 (C2 du cycle); 123, 76-143, 74 (C Aromatic); 145, 94 (C=N); 167, 53 et 169, 50 (C=O amides).

N-(4-acetyl-5-(4-chlorophenyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl) acetamide (9):

LC/MS: $[MH]^+$calculated: 298,0412; $[MH]^+$found: 294,0407.

IR m (KBr cm^{-1}): 3216, 3163 (NH); 1698, 1637, 1612 (C=O amides).

^1H NMR d (DMSO-d_6 ppm): 2, 04 (3H, s, CH_3 amide); 2, 20 (3H, s, CH_3 amide); 6, 83 (1H, s, CH_2); 7, 28-7, 42 (4H, several signals, ArH); 11, 78 (1H, s, NH).

^{13}C NMR d (DMSO-d_6): 21, 83 and 22, 51 (2. CH_3 amides); 65, 15 (C2 of the ring); 127, 13-140, 28 (Aromatic C); 145, 88 (C=N); 167, 44 and 169, 44 (C=O amides).

N-(4-acetyl-5-ethyl-5-(4-methoxyphenyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)acetamide (10):

LC/MS: $[MH]^+$calculated: 322,1225; $[MH]^+$found: 322,1217.

IR m (KBr cm^{-1}): 3227, 3177 (NH); 1697, 1643 and 1610 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1,06 (3H, t, CH_3); 2,18 (2H, q, CH_2); 2,23 (3H, s, CH_3 amide); 2,26 (3H, s, CH_3 amide); 3,67 (3H, s, O-CH_3); 7,73-7,25 (4H, several signals, ArH); 9,84 (1H, s, NH).

^{13}C NMR d ($CDCl_3$): 9, 91 (CH_3-CH_2-); 22, 61 and 23, 80 (2. CH_3 amides); 29, 95 (CH_3-CH_2-); 55,29 (O-CH_3); 84,85 (C_2 of the ring); 113,82-135,89 and 159,07 (Aromatic C); 144,17 (C=N); 169,28 and 169,43 (C=O amides).

N-(4-acetyl-5-(p-tolyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)acetamide (11)

LC/MS: $[MH]^+$ calculated: 278,0958; $[MH]^+$ found: 278,0953.

IR m (KBr cm^{-1}): 3215, 3164 (NH); 1698 et 1636 (C=O amides).

^1H NMR d ($CDCl_3$ ppm): 1, 98 (3H, s, Ar- CH_3); 2, 20 (3H, s, CH_3 amide); 2, 23 (3H, s, CH_3 amide); 6, 71 (1H, s, CH_2); 7, 02-7, 10 (4H, several signals, ArH); 9, 42 (1H, s, NH).

^{13}C NMR d ($CDCl_3$ ppm):21, 16 (CH_3); 22, 14 et 23, 01 (2. CH_3 amides); 67, 51 (C2 of the ring); 125, 65-138, 63 (C Aromatic); 146,80 (C=N); 168,91 and 169,11 (C=O amides).

N-(4-acetyl-5-(2-nitrophenyl)-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)acetamide (12):

LC/MS: $[MH]^+$ calculated: 309,0652; $[MH]^+$found: 309,064

IR m (KBr cm^{-1}): 3232, 3192 (NH); 1682, 1664 and 1622 (C=O amides).

^1H NMR d (DMSO-d_6 ppm): 2, 04 (3H, s, CH_3 amide); 2, 26 (3H, s, CH_3 amide); 7, 06 (1H, s, CH_2); 7, 33-8, 18 (4H, several signals, ArH); 11, 86 (1H, s, NH).

^{13}C NMR d (DMSO-d_6): 21, 70 and 22, 41 (2. CH_3 amides); 63, 15 (C2 of the ring); 125, 52-145, 01 (Aromatic C); 146, 31 (C=N); 167, 77 et 169, 66 (C=O amides).

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