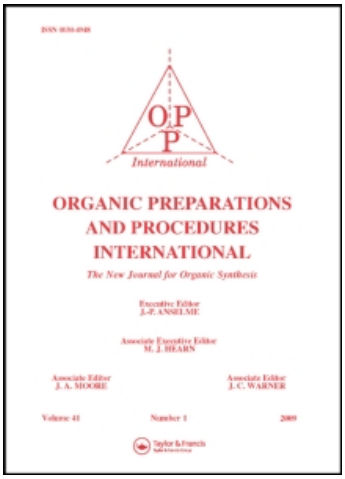

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SYNTHESIS OF AMINOTOLUENESULFONAMIDE DERIVATIVES USING CONVENTIONAL HEATING OR MICROWAVE-ASSISTED METHODS

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SYNTHESIS OF AMINOTOLUENESULFONAMIDE DERIVATIVES USING CONVENTIONAL HEATING OR MICROWAVE-ASSISTED METHODS

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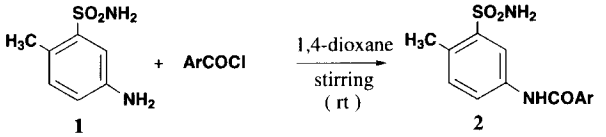
It is well known that compounds bearing the sulfonamido moiety show important diuretic and antihypertensive properties.[1] Our interest in preparing diuretic drugs prompted us to investigate several methods to synthesize amides **2** and Schiff's bases **3** derived from 5-amino-2-toluenesulfonamide (**1**). The formation of these derivatives occurred upon reaction of the amino group with acyl chlorides and aromatic aldehydes respectively. Two different procedures, conventional heating and microwave-assisted methods, were investigated for the synthesis of **3**, in order to compare their efficacy.

Five amide derivatives (**2a-2e**) were prepared following the conventional method by mixing, at room temperature, an equimolar amount of sulfonamide **1** and the appropriate acyl chloride. Even without any acid trap (such as tertiary amines or alkaline bases as recommended in the Schotten-Baumann reaction), satisfactory yields of amides **2** were obtained with reaction times never exceeding one hour (Table 1). These compounds were characterized by elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass spectra).



1 **2**

a) Ar = *p*-$NO_2C_6H_4$; b) Ar = *p*-ClC_6H_4; c) Ar = 2-furyl
d) Ar = 5-Br-2-furyl; e) Ar = 5-NO_2-2-furyl

TABLE 1. Yields, mps and Elemental Analyses of **2a-e**

Compd	Yield[a] (%)	Mp (°C)	Time (min)	Analysis (Found) C	H	N	S
2a	85	283-285[b]	30	50.15 (50.40)	3.91 (4.12)	12.52 (12.27)	9.56 (9.68)
2b	85	269-271[b]	60	51.77 (51.82)	4.01 (4.27)	8.62 (8.50)	9.86 (9.60)
2c	80	266-268[c]	60	51.42 (51.60)	4.32 (4.62)	9.99 (10.19)	11.44 (11.59)
2d	75	259-261[b]	30	40.17 (39.89)	3.07 (3.23)	7.81 (8.01)	8.92 (9.07)
2e	70	259-262[c]	30	44.31 (44.19)	3.41 (3.60)	12.92 (13.10)	9.86 (9.42)

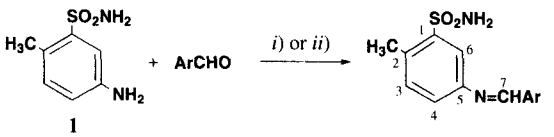
a) After recrystallization from suitable solvents. b) From EtOH. c) From acetone.

Schiff's bases **3a-3f** were obtained by mixing an equimolar amount of sulfonamide **1** and the appropriate aromatic aldehyde in refluxing ethanol (conventional method (i)). The alternative solvent-free microwave-assisted method (ii) using dried DMF (0.4 mL), as energy transfer medium, was also tested. In order to determine the role of DMF, reactions under microwave irradiation without any DMF were also carried out. Yields were lower than those obtained under microwave-DMF method (Table 2). Finally, the synthesis of imines **3** was attempted by a change of the heating method using a thermally regulated oil bath under the same reaction time and temperature as for the microwave-assisted experiment. All experiments under microwave irradiation were carried out in a domestic oven at output power of 175 W. Experiments performed at higher output power or longer exposure times were unsuccessful (no higher yields were observed and decomposition products were detected by tlc and gc analysis of reaction mixtures). Several reports have described the use of DMF in microwave-assisted reactions[2,3] as a useful energy transfer medium which allows that the heat-up of substances with low microwave susceptibility.

TABLE 2. Comparison of Yields by Three Methods[a]

Compd	EtOH-reflux (Yield)[b]	(Time)[c]	Microwave-DMF (Yield)[b]	(Time)[c]	Microwave-NoDMF (Yield)[b]	(Time)[c]	Oil bath-DMF (Yield)[b]	(Time)[c]
3a	80	180	98	1	40	1	5	1
3b	75	240	90	2	22	2	6	2
3c	70	300	72	2	20	3	5	3
3d	75	240	96	2	40	2	10	2
3e	75	120	96	2	20	2	5	2
3f	87	180	92	1	30	1	10	1

a) Yields were determined by gc analysis of the reaction mixtures. b) (%). c) min.



a) Ar = *p*-$NO_2C_6H_4$; b) Ar = *o*-ClC_6H_4; c) Ar = 2-furyl
d) Ar = 5-(*p*-$NO_2C_6H_4$)-2-furyl; e) Ar = 5-NO_2-2-furyl; f) Ar = 5-NO_2-2-thienyl

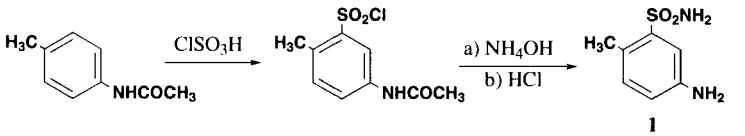
Since montmorillonite K10 is known to exhibit acidic catalytic effect on the reactivity of carbonyl compounds,[4,5] the preparation of the imines was also performed using K10 under microwave irradiation. However, low yields were obtained compared to those carried out with DMF.

TABLE 3. Mps and Elemental Analyses of **3a-f**

Compd	Mp (°C)[a]	Analysis (Found)			
		C	H	N	S
3a	225-227	52.66 (52.40)	3.91 (4.12)	12.52 (12.27)	9.56 (9.68)
3b	188-191	54.54 (54.22)	4.25 (4.53)	9.09 (9.34)	10.38 (10.04)
3c	104-105	54.53 (54.32)	4.58 (4.83)	10.60 (10.30)	12.13 (11.80)
3d	217-219	57.42 (57.12)	3.80 (3.95)	10.57 (10.77)	8.07 (8.22)
3e	224-226	46.40 (46.19)	3.58 (3.88)	13.59 (13.29)	10.37 (10.49)
3f	235-237	44.31 (44.12)	3.38 (3.70)	12.90 (12.64)	19.69 (19.45)

a) From EtOH.

Starting material **1** had been previously prepared[6] by reduction of the corresponding nitro derivative. In this work, compound **1** was synthesized *via* chlorosulfonation of N-acetyl-*p*-toluidine, under acidic conditions which leads the introduction of chlorosulfonyl moiety at the position *meta* to acetamido group, subsequent treatment with ammonia and hydrolysis of the acetyl group afforded **1**.



1

Unfortunately, no significant diuretic activity was observed with any of the compounds studied.

EXPERIMENTAL SECTION

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. Reactions were carried out in a Sanyo domestic microwave oven equipped with turnable plate, which allows the selection of output power up to 800 watts. TLC analyses were run on 60 F^{254} silicagel chromatoplates from Merck using a mixture of benzene and ethanol (8:2) as eluent. GC analyses were performed on a Shimadzu apparatus equipped with flame ionization detector and OV-101 column (1mx3mm) on chromosorb W-HP. The temperature was programmed in the range 80-100° at 6°/min (injector temperature 300°). All solvents were hplc grade from BDH. 5-Nitrofurfural was obtained by microwave-assisted deprotection of its geminal diacetate[5] and physical constants were in agreement with published data. All acyl chlorides and aldehydes came from commercial sources. N-Acetyl-*p*-toluidine and 5-nitrofurfural dimethylacetal came from Fluka. IR spectra were recorded on a Philips Analytical PU9600 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recordered on a Bruker AC-250 at 250 and 62.5 MHz respectively and in a Varian-Unity 500 at 500 and 125 MHz, using DMSO-d^6 as solvent. The mass spectra were performed on a DELSI/NERMAG Spectral 30 spectrometer. The

elementary analyses were performed on a Carlo Erba 1106 instrument. The presence of * in NMR data of compounds **2b**, **3b**, and **3e** means that assignments may be interchanged.

5-Amino-2-toluenesulfonamide (1).- Chlorosulfonic acid (20 mL), at 15°, was slowly added to dry N-acetyl-*p*-toluidine (7 g, 50 mmol). The temperature of reaction mixture was kept below 45°. After dissolution of the acetyl-*p*-toluidine, the reaction mixture was heated on a steam bath for 45 min and then was carefully poured into a mixture of ice/water (200 mL). The original syrup slowly solidified. The solid N-acetylamino-2-toluenesulfonyl chloride (70%) was collected, dried and used immediately . Then, a conc. solution of ammonium hydroxide (25 mL) was added to the sulfonyl chloride (10.7 g). The mixture was cooled down in an ice-bath and a 20% sulfuric acid solution was slowly added. The mixture was kept at 0-5° for 5 min. The corresponding sulfonamide was collected, washed with ice water and dried to yield (67%) a crystalline crude white solid, mp. 220°, lit.[12] mp. 222°. Then, 15 mL of a 18% hydrochloric acid was added to 5.6 g of N-acetyltoluenesulfonamide and the mixture was gently refluxed during 20 min. The resulting solution was diluted with an equal volume of water and sodium carbonate was added up until pH 8. After cooling, the precipitate was collected and washed with ice water and hot petroleum ether. Compound **1** was obtained in 75% yield, mp.165-167°, lit.[11] mp. 164°. ^{1}H NMR (250 MHz): δ 7.27 (s, 2H, SO_2NH_2), 7.10 (d, $J_{6,4}$ = 2.0 Hz, 1H, H-6), 6.97 (d, $J_{3,4}$ = 8.1 Hz, 1H, H-3), 6.63 (dd, 1H, H-4), 5.28 (s, 2H, NH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (62.5 MHz): δ 146.7 (C-5), 142.1 (C-1), 132.7 (C-3), 121.6 (C-2), 116.9 (C-4), 112.6 (C-6), 18.9 (CH_3).

Synthesis of Amides 2.- An equimolar mixture (5 mmol) of 5-amino-2-toluenesulfonamide (**1**) and the appropriate acyl chloride was stirred in a 100 mL round-bottom flask with 1,4-dioxane (25 mL), at room temperature, until precipitation was complete. The precipitate was collected and washed with coldethanol. Compounds were recrystallized from suitable solvent in each case.

5-(*p*-Nitrobenzoylamino)-2-toluenesulfonamide (2a).- IR(KBr): 3355, 3254 (NH_2), 3114 (NH), 1666 (CO), 1533, 1348 (NO_2), 1330, 1166(SO_2) cm^{-1}; ^{1}H NMR (500 MHz): δ 10.75 (s, 1H, NH exchanged with D_2O), 8.37 (d, $J_{o,m}$ = 9.0 Hz, 2H, H-*m*), 8.36 (d, $J_{6,4}$ = 2.1 Hz, 1H, H-6), 8.19 (d, 2H, H-*o*), 7.91 (dd, $J_{3,4}$ = 8.2 Hz, 1H, H-4), 7.37 (s, 2H, NH_2 exchanged with D_2O), 7.36 (d, 1H, H-3), 2.56 (s, 3H, CH_3); ^{13}C NMR: δ 163.9 (C-7), 149.2 (C-*p*), 142.2 (C-1), 140.1 (C-*ipso*), 136.6 (C-5), 132.5 (C-3), 131.2 (C-2), 129.2 (C-*o*), 123.5 (C-*m*), 123.3 (C-4), 119.3 (C-6), 19.3 (CH_3); ms (m/z): 335 m$^+$, 254, 151.

5-(*p*-Chlorobenzoylamino)-2-toluenesulfonamide (2b).- IR (KBr): 3333, 3182 (NH_2), 3066 (NH), 1649 (CO), 1316, 1149 (SO_2) cm^{-1}; ^{1}H NMR (250 MHz): δ 10.50 (s, 1H, NH exchanged with D_2O), 8.36 (d, $J_{6,4}$ = 2.4 Hz, 1H, H-6), 8.00 (d, J*o,m* = 9.0 Hz, 2H, H-*o*), 7.90 (dd, $J_{4,3}$ = 8.8 Hz, 1H, H-4), 7.61 (d, 1H, H-*m*), 7.36 (s, NH_2 exchanged with D_2O), 7.33 (d, 1H, H-3), 2.50 (s, 3H, CH_3); ^{13}C NMR: δ 164.4 (C-7), 142.0 (C-1), 136.8 (C-*ipso*)*, 136.5 (C-5)*, 133.1 (C-*p*), 132.3 (C-3), 130.8 (C-2), 129.5 (C-*o*), 128.4 (C-*m*), 123.2 (C-4), 119.2 (C-6), 19.2 (CH_3); ms (m/z): 324/326 m$^+$, 243/245, 139/141, 105.

5-(2'-Furoylamino)-2-toluenesulfonamide (2c).- IR (KBr): 3280, 3200 (NH_2), 3080 (NH), 1320, 1160 (SO_2) cm^{-1}; ^1H NMR (250 MHz): δ 10.40 (s, 1H, NH exchanged with D_2O), 8.29 (d, $J_{6,4}$ = 2.0, 1H, H-6), 7.89 (d, $J_{10,11}$=1.7 Hz, 1H, H-11), 7.82 (dd, $J_{4,3}$ = 8.0 Hz, 1H, H-4), 7.36 (s, NH_2 exchanged with D_2O), 7.31 (d, $J_{9,10}$ = 3.5, 1H, H-9), 7.26 (d, 1H, H-3), 6.67 (dd, 1H, H-10), 2.50 (s, 3H, CH_3); ^{13}C NMR: δ 156.2 (C-7), 147.2 (C-8), 145.2 (C-11), 142.1 (C-1), 136.5 (C-5), 132.3 (C-3), 130.7 (C-2), 123.2 (C-4), 119.1 (C-6), 114.6 (C-9), 112.1 (C-10), 19.3 (CH_3); ms (m/z): 280 m^+, 199, 95, 39.

5-(5'-Bromo-2'-furoylamino)-2-toluenesulfonamide (2d).- IR (KBr): 3350, 3260 (NH_2), 3166 (NH), 1660 (CO), 1330, 1165 (SO_2) cm^{-1}; ^1H NMR (250 MHz): δ 10.40 (s, 1H, NH exchanged with D_2O), 8.29 (d, $J_{6,4}$ = 2.0 Hz, 1H, H-6), 7.86 (dd, $J_{4,3}$ = 8.4 Hz, 1H, H-4), 7.38 (d, $J_{9,10}$ = 3.5 Hz, 1H, H-9), 7.36 (s, NH_2 exchanged with D_2O), 7.33 (d, 1H, H-3), 6.86 (d, 1H, H-10), 2.50 (s, 3H, CH_3); ^{13}C NMR: δ 155.2 (C-7), 149.0 (C-8), 142.1 (C-1), 136.3 (C-5), 132.5 (C-3), 130.9 (C-2), 125.6 (C-11), 123.3 (C-4), 119.2 (C-6), 117.3 (C-10), 114.3 (C-9), 19.2 (CH_3); ms (m/z): 358/360 m^+, 277/279, 174/176, 105, 77.

5-(5'-Nitro-2'-furoylamino)-2-toluenesulfonamide (2e).- IR (KBr): 3399, 3299 (NH_2), 3116 (NH), 1666 (CO), 1333, 1166 (SO_2) cm^{-1}; ^1H NMR (250 MHz): δ 10.82 (s, 1H, NH exchanged with D_2O), 8.29 (d, $J_{6,4}$ = 2.3, 1H, H-6), 7.90 (dd, $J_{4,3}$ = 8.2 Hz, 1H, H-4), 7.80 (d, $J^{10,9}$ = 3.9 Hz, 1H, H-10), 7.65 (d, 1H, H-9), 7.39 (s, NH_2 exchanged with D_2O), 7.37 (d, 1H, H-3), 2.57 (s, 3H, CH_3); ^{13}C NMR: δ 154.8 (C-7), 151.9 (C-11), 147.7 (C-8), 142.3 (C-1), 135.9 (C-5), 132.8 (C-3), 131.8 (C-2), 123.7 (C-4), 119.6 (C-6), 116.8 (C-9), 113.5 (C-10), 19.4 (CH_3); ms (m/z): 325 m^+, 244, 140, 96, 58, 43.

Synthesis of Imine Derivatives 3. Conventional Method.- An equimolecular mixture (16 mmol) of 5-amino-2-toluenesulfonamide (**1**) and the appropriate aldehyde was placed into a 100 mL round-bottom flask equipped with a reflux condenser and containing absolute ethanol (25 mL). The mixture was refluxed for several hours (Table 2) and then poured into ice-water. The precipitate was collected and dried. The crude solid was recrystallized from ethanol.

Synthesis of Imine Derivatives 3. Microwave-DMF Method.- An equimolar mixture (20 mmol) of 5-amino-2-toluenesulfonamide (**1**) and the appropriate aldehyde with 0.4 mL of dry DMF was placed into a pyrex-glass open vessel and irradiated in a domestic microwave oven at output power of 175 W. Reaction products were precipitated from ice-water, collected and dried. In some cases, products did not require any further recrystallization.

The imine derivative **3e** was obtained from the starting aldehyde previously obtained by microwave-assisted deprotection[5] of 5-nitrofurfural dimethylacetal which was dispersed on montmorillonite K10 and irradiated at a power of 385 W. Then, the resulting aldehyde was quantitatively eluted from K10 with methylene chloride. This procedure was used to obtain the aldehyde for the further classical and microwave-assisted syntheses of the desired Schiff's base from 5-amino-2-toluenesulfonamide (**1**).

5-(*p*-Nitrobenzylideneamino)-2-toluenesulfonamide (3a).- ^1H NMR (250 MHz): δ 8.56 (s, 1H, H-7), 8.33 (d, $J_{o,m}$ = 9.1 Hz, 2H, H-*m*), 8.11 (d, 2H, H-*o*), 7.78 (d, $J_{6,4}$ = 2.0 Hz, 1H, H-6), 7.45 (dd, $J_{3,4}$ = 8.7, 1H, H-4), 7.42 (s, 2H, NH_2 exchanged with D_2O), 7.38 (d, 1H, H-3), 2.56 (s, 3H. CH_3); ^{13}C NMR (62.5 MHz): δ 159.6 (C-7), 149.0 (C-5), 143.0 (C-1), 141.2 (C-*p*), 134.4 (C-*ipso*), 133.2 (C-3), 130.6

(C-2), 129.7 (C-*o*), 124.0 (C-*m*), 123.7 (C-4), 120.6 (C-6), 19.3 (CH_3).

5-(*o*-Chlorobenzylideneamino)-2-toluenesulfonamide (3b).- ^{1}H NMR (250 MHz): δ 8.91 (s, 1H, H-7), 8.18 (dt, $J_{o,m}$ = 6.7, $J_{o,p}$ = 1.2 Hz, 1H, H-*o*), 7.76 (t, $J_{6,4} = J_{6,3}$ = 1.3 Hz, 1H, H-6), 7.60-7.57 (m, 3H, H-*m* and H-*p*), 7.45 (s, 2H, NH_2 exchanged with D_2O), 7.44 (d, 2H, H-3 and H-4), 2.60 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz) ; δ 157.0 (C-7), 148.7 (C-5), 143.0 (C-1), 135.1 (C-*ipso*), 133.9 (C-*o*), 133.2 (C-*o*')*, 133.1 (C-3)*, 132.4 (C-2), 130.0 (C-*m*), 128.4 (C-*m*'), 127.6 (C-*p*), 123.8 (C-4), 119.2 (C-6), 19.4 (CH_3).

5-(2'-Furfurylideneamino)-2-toluenesulfonamide (3c).- ^{1}H NMR (250 MHz): δ 8.48 (s, 1H, H-7), 7.96 (d, $J_{11,10}$ = 1.7 Hz, 1H, H-11), 7.71 (bs, 1H, H-6), 7.40 (s, NH_2 exchanged with D_2O), 7.39 (bs, 2H, H-4 and H-3), 7.21 (d, $J_{9,10}$ = 3.4 Hz, 1H, H-9), 6.73 (dd, 1H, H-10), 2.59 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz): δ 151.7 (C-8), 148.9 (C-7), 148.8 (C-5), 146.7 (C-11), 142.9 (C-1), 133.4 (C-2), 133.2 (C-3), 130.7 (C-3), 123.8 (C-4), 120.0 (C-6), 117.7 (C-10), 112.6 (C-9), 19.3 (CH_3).

5-[5'-(*p*-Nitrophenyl)-2'-furfurylideneamino]-2-toluenesulfonamide (3d).- ^{1}H NMR (250 MHz): δ 8.56 (s, H-7), 8.34 (d, $J_{m,o}$ = 9.1 Hz, 2H, H-*m*), 8.09 (d, 2H, H-*o*), 7.79 (d, $J_{6,4}$ = 1.9 Hz, 1H, H-6), 7.52 (d, $J_{10,9}$ = 3.6 Hz, 1H, H-10), 7.46 (dd, $J_{4,3}$ = 9.0 Hz, 1H, H-4), 7.43 (s, NH_2 exchanged with D_2O), 7.40 (d, 1H, H-3), 7.38 (d, 1H, H-9), 2.60 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz): δ 153.7 (C-8), 152.7 (C-11), 148.5 (C-7), 146.7 (C-5), 143.0 (C-1), 134.9 (C-2), 133.7 (C-*p*), 133.2 (C-3), 125.9 (C-*ipso*), 125.1 (C-*o*), 124.5 (C-*m*), 123.6 (C-4), 120.3 (C-6), 120.2 (C-9), 112.5 (C-10), 19.4 (CH_3).

5-(5'-Nitro-2'-furfurylideneamino)-2-toluenesulfonamide (3e).- ^{1}H NMR (500 MHz): δ 8.68 (s, H-7), 7.84 (d, $J_{6,4}$ = 2.0 Hz, 1H, H-6), 7.82 (d, $J_{10,9}$ = 3.4 Hz, H-10), 7.52 (dd, $J_{4,3}$ = 7.8 Hz, 1H, H-4), 7.46 (d, 1H, H-9), 7.46 (s, 2H, NH_2 exchanged with D_2O), 7.44 (d, 1H, H-3), 2.61 (s, 3H, CH_3); ^{13}C NMR (125 MHz): δ 152.5 (m, C-11)*, 152.4 (m, C-8)*, 148.5 (C-7), 147.4 (C-5), 143.1 (C-1), 135.0 (C-2), 133.3 (C-3), 123.8 (C-4), 120.6 (C-6), 118.4 (C-9), 114.0 (C-10), 19.4 (CH_3).

We would like to report here that compound **3e** was also prepared by addition of compound **1** (0.76 g, 4.1 mmole) to K10 supported 5-nitrofurfural (0.57 g, 4 mmole). The reaction mixture was submitted to microwave irradiation (3 min. and 245 W). Compound **3e** was extracted from the support with a minimal volume of DMF and precipitated with ice-water, collected and dried, yield 95%. Analytical data are identical to those obtained by the other methods.

5-(5'-Nitro-2'-thienylmethylideneamino)-2-toluenesulfonamide (3f).- ^{1}H NMR (250 MHz): δ 8.83 (s, 1H, H-7), 7.84 (d, $J_{6,4}$ = 2.3 Hz, 1H, H-6), 7.73 (dd, $J_{4,3}$ = 8.0 Hz, 1H, H-4), 7.46 (s, 2H, NH_2 exchanged with D_2O), 7.43 (d, 1H, H-3), 7.39 (d, $J_{10,9}$ = 3.0 Hz, 1H, H-10), 7.23 (d, 1H, H-9), 2.60 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz): δ 154.1 (C-11), 152.7 (C-8), 148.2 (C-7), 146.9 (C-5), 143.0 (C-1), 135.0 (C-2), 133.4 (C-3), 132.5 (C-9), 130.4 (C-10), 123.9 (C-4), 120.9 (C-6), 19.5 (CH_3).

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