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MICROWAVE-ASSISTED SYNTHESIS OF 3-METHYL-1-PHENYL-CHROMENO[4,3-*c*]PYRAZOL-4(1*H*)-ONES UNDER SOLVENT-FREE CONDITIONS

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Abstract – A novel microwave-assisted method for the synthesis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones by the cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-ones with CuO/SBA-15 under solvent-free conditions is described. The reaction gave the corresponding chromenopyrazole products in good to excellent yields and in short reaction times.

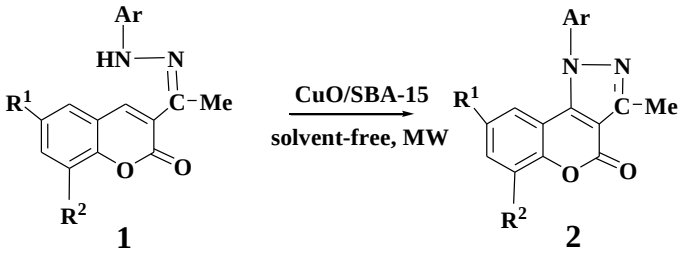
Pyrazoles are heterocyclic compounds with a five membered ring containing three carbons and two nitrogens. Such heterocyclic systems are widely distributed in nature. Pyrazoles have a wide range of applications as agro and pharma chemicals due to their biological activities such as antibacterial, antidepressant, antiamoebic, anti-inflammatory and antinociceptive activities.[1-4]

Coumarin derivatives have been widely reported to possess various biological activities, such as antimicrobial activity[5] and antifungal activity.[6] Chromenopyrazoles are heterocyclic compounds containing a rigid six-six-five tricyclic ring system. They have found application as ligands for the central benzodiazepine receptor (BZR). For example, 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones are commonly used to synthesize immunomodulatory drugs which can interact with the benzodiazepine central receptor.[7]

One of the early synthetic methods for chromeno-pyrazoles which has been reported utilizes the cyclization of 1-(phenylhydrazono)chromen-2-ones 4-substituted with –OH and –Cl in xylene with *p*-toluenesulfonic acid as catalyst.[8] Recently, a new method was reported for the preparation of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones using the oxidative cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-ones with copper acetate as catalyst.[9] However this method

suffers from drawbacks such as difficult separation and recycling of the homogeneous catalyst, low efficiency, solvent use, etc. In order to overcome these shortcomings, we decided to explore a catalyst-supported system, using CuO as the catalyst under solvent-free microwave-assisted conditions. SBA-15 was chosen as the carrier because of its relatively large specific surface area and uniform pore diameter distribution.[4,10-12] The supported catalyst CuO/SBA-15 has been used in many chemical reaction and has been found to have high activity and selectivity.[13,14] With the development of green chemistry, microwave synthesis and solventless synthesis have been attracting more and more attention in organic chemistry.[15-17]

In this paper, we report on the development of a novel microwave-assisted method for the synthesis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones (**2**) by the cyclization of 3-[1-(phenylhydrazono)-ethyl]chromen-2-ones (**1**) with supported Cu(II) (CuO/SBA-15) as the catalyst under solvent-free conditions (Scheme 1).



Scheme 1. Synthetic route of the compounds **2**

Under solvent-free conditions, two controlled trials were done to determine the influence of the catalyst and microwave. In one, an oil bath was used and compound **1a** was heated for 3 hours at 120 °C with CuO/SBA-15 as the catalyst (Table 1, entry 1, Conv: 85%). The other was run without the use of the catalyst and compound **1a** was heated for half an hour under microwave irradiation of 567 W (Table 1, entry 2, Conv: 46%). we were pleased to find that in the presence of catalyst CuO/SBA-15 the conversion of the compound **1a** was 97% when the reaction was done for half an hour under microwave irradiation of 567 W (Table 1, entry 5). These results show that the influence of the catalyst and microwave are significant.

This reaction was investigated for various reaction parameters such as time, microwave power and catalyst loading. The effect of time on the conversion of the reactant was monitored from 10 to 30 min (Table 1, entries 3-5). The conversion of compound **1a** reached 97% when the time was 30 min. When the microwave power was increased from 406 to 567 W (Table 1, entries 5, 6), the conversion of compound **1a** increased from 10% to 97%. When the microwave power was increased from 567 to 700 W (Table 1,

entries 5, 7), the yield of product **2a** decreased from 92% to 86%. When the molar ratio of the catalyst and the reactant **1a** was varied from 0.35 to 1.4 $\times 10^{-2}$ (Table 1, entries 7-9), the conversion of compound **1a** increased from 52% to 100%, and the time required for completing the reaction decreased from 30 to 20 minutes. This fully indicates that microwave power and catalyst amount are the key parameters affecting the reaction rate. We also found that when the molar ratio of the catalyst and the reactant **1a** increased from 0.7 to 1.4 $\times 10^{-2}$ (Table 1, entries 5, 9), there was little decrease in the selectivity of the product **2a**. In comprehensive consideration of the reaction rate and product selectivity, 0.7×10^{-2} molar ratio of the catalyst and the reactant **1a** was optimum formulation.

Various chromenopyrazoles were efficiently synthesized with this green method. It was observed that the coumarin hydrazones were easily converted into the expected products in excellent yields (Table 2). We found that compounds containing electron withdrawing groups in the coumarin ring showed lower yields (Table 2, entries 6, 8). Similarly, compounds containing electron withdrawing groups in the *N*-benzene ring also showed lower yields (Table 2, entries 13, 14). These results show that electron withdrawing groups are unfavorable for the cyclization of 3-[1-(phenylhydrazono)ethyl]chromen-2-ones.

Table 1. Effect of microwave power, time and catalyst loading on the formation of compound **2a** under microwave conditions

Entry	Catalyst loading /%mol	Microwave time/min	Microwave power/w	Conversion/%[a]	Yield/%[b]
1[a]	0.7	_	_	85	76
2	0	30	567	46	40
3	0.7	10	567	18	15
4	0.7	20	567	66	61
5	0.7	30	567	97	92
6	0.7	30	406	10	7.3
7	0.7	30	700	100	86
8	0.35	30	567	52	48
9	1.4	20	567	100	93

Reaction conditions: At the temperature 120 °C in oil bath for 3 h.
[a] Determined by HPLC analysis of crude reaction mixture.
[b] Isolated yields.

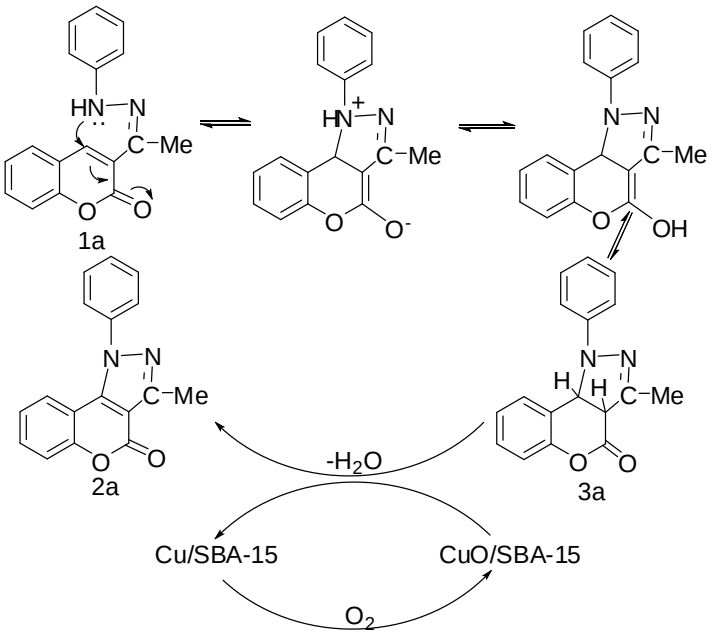
A proposed mechanism for the synthesis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones is shown in Scheme 2, which includes the Michael addition of an amino group to the enone, and then oxidation to give the product.

To confirm their structures, monocrystals of chromenopyrazole **2d** suitable for X-ray crystal diffraction measurements were obtained by slow evaporation in acetic acid. X-Ray data for crystals of **2d** were collected by graphite monochromatized Mo K_α radiation at 293K. Crystal data and experimental details for compound **2d** are summarized in Table 3. The crystal structure and molecular packing of compound **2d** are shown in Figure 1 and Figure 2, respectively. It can be seen that the benzopyran ring and the pyrazole ring are essentially coplanar. The other benzene ring is at an approximately 90° angle to the plane. Molecules of compound **2d** are packed through weak interaction to form layered stacks.

Table 2. Preparation of products **2** by using various compounds **1** under microwave conditions

Entry	Ar	R^1	R^2	Product **2**	Microwave time/min	Yield/%[a]
1	Ph	H	H	**2a**	30	80
2	Ph	Cl	H	**2b**	40	81
3	Ph	Br	H	**2c**	40	72
4	Ph	H	MeO	**2d**	45	76
5	Ph	H	EtO	**2e**	45	86
6	Ph	Cl	Cl	**2f**	30	50
7	Ph	Br	Br	**2g**	40	60
8	Ph	NO_2	H	**2h**	45	41
9	4-FC_6H_4	H	H	**2i**	30	58
10	4-ClC_6H_4	H	H	**2j**	30	68
11	4-BrC_6H_4	H	H	**2k**	25	70
12	4-MeC_6H_4	H	H	**2l**	40	64
13	3-$NO_2C_6H_4$	H	H	**2m**	40	55
14	3,5-$(Cl)_2C_6H_3$	H	H	**2n**	45	50
15	2,4-$Me_2C_6H_3$	H	H	**2o**	30	78
16	4-$MeOC_6H_4$	H	H	**2p**	20	81

Reaction conditions: Compounds **1** (0.72 mmol), CuO/SBA-15 (0.7 mol%), microwave power (567 W).
[a] Isolated yields.



Scheme 2. Proposed reaction mechanism for the catalytic cyclization

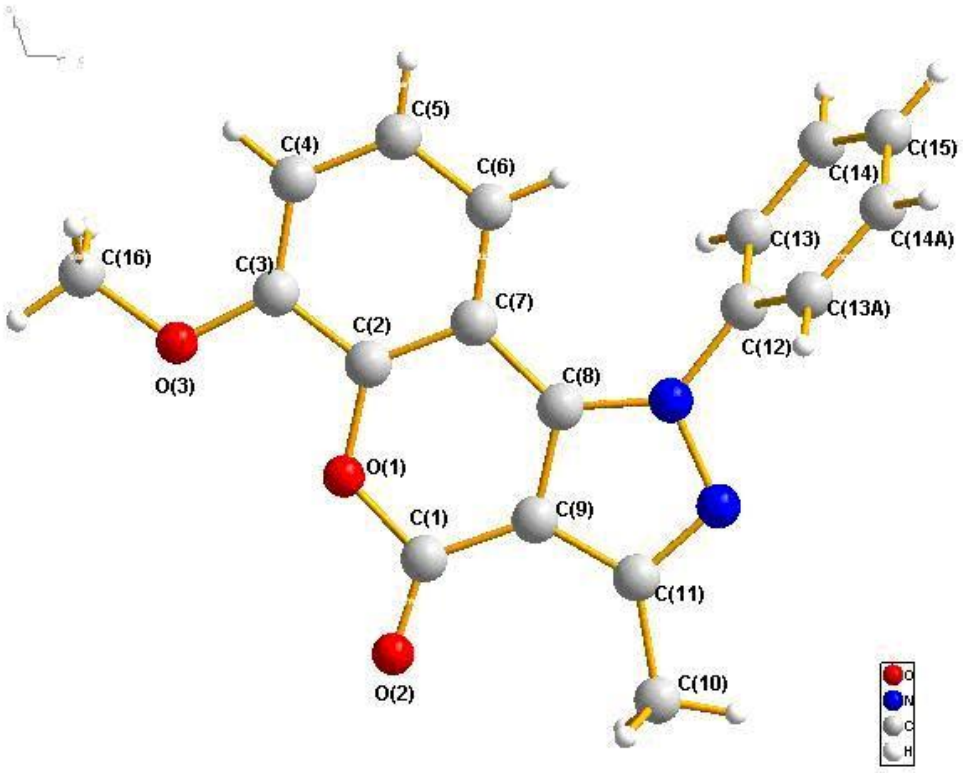


Figure 1. X-Ray crystal structure of chromenopyrazole **2d**

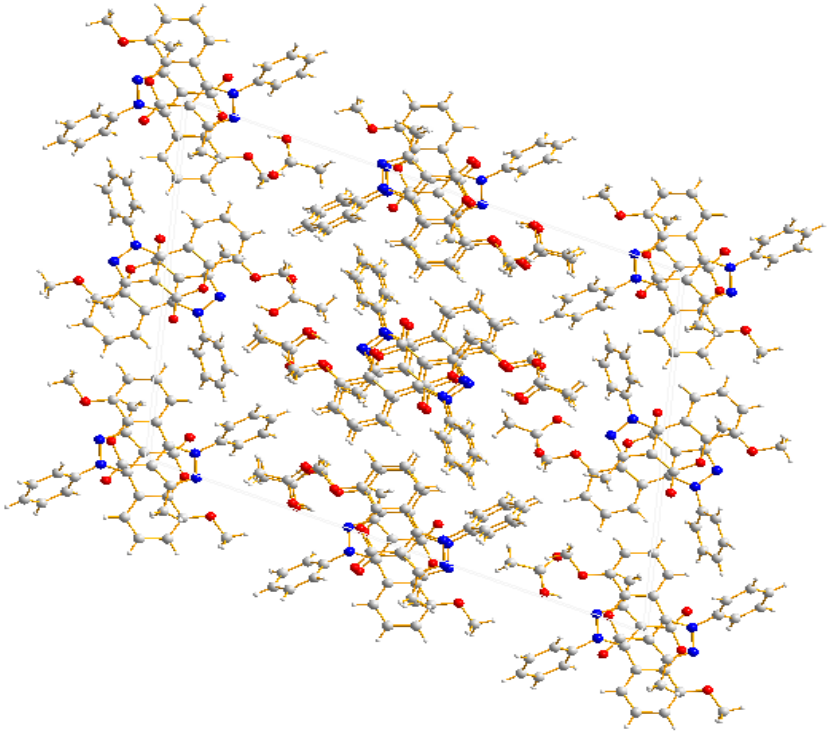


Figure 2. A view of the molecular packing of compound **2d**

Table 3. Crystal data and experimental details for compound **2d**.

Empirical formula	$C_{18}H_{14}N_2O_3$
Formula weight	306.32
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 1 21/c 1 (14)
Unit cell dimensions	*a*=20.3573(13) Å, *alpha* = 90 deg. *b*=7.1099(5) Å, *beta* = 107.251(7) deg. *c*= 25.7968(16) Å, *gamma* = 90 deg.
Volume	3565.8(4) $Å^3$
Z, Calculated density	1, 0.171 Mg/m^3
Absorption coefficient	0.012 mm^{-1}
F(000)	192
Crystal size	0.24×0.22×0.20 mm
Theta range for data collection	2.98 to 26.37 deg.
Limiting indices	-17≦h≦25, -8≦k≦8, -32≦l≦32
Reflections collected/unique	19572 / 7269 [*R*(int) = 0.0507]
Completeness to theta =26.00	99.8%
Absorption correction	None
Data/restraints/parameters	7269 / 0 / 495
Goodness-of-fit on *F*^2	1.079
Final R indices [I>2sigma(I)]	*R*1 = 0.0817, w*R*2 = 0.1853
R indices (all data)	*R*1 = 0.1460, w*R*2 = 0.2141
Largest diff. peak and hole	0.312 and -0.293 e. $Å^{-3}$

Table 4. Experiment on the recycling of the CuO/SBA-15 catalyst.

Cycle	1	2	3	4
Yield/% [a]	90	93	83	86

Reaction conditions: Compound **1a** (0.72 mmol), CuO/SBA-15 (0.7 mol%), microwave power (567 W), microwave time (35 min).
[a] Isolated yield of product.

The reusability of the CuO/SBA-15 catalyst was studied under microwave conditions. After the completion of the reaction for the first run, the reaction mixture was thoroughly washed with methylene chloride until the products were completely removed from the catalyst. Then the catalyst was washed with ethyl alcohol, filtered and dried in an oven at 120 °C for 4 h. The dried catalyst was used for the next runs and the same procedure was adopted for all the recyclability studies. The conversion of compound **1a** for the various runs are listed in Table 4. The result shows that the catalytic activity of the CuO/SBA-15 could be kept at a constant high level.

In conclusion, a novel green, and atom economical method was developed for the synthesis of 3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-ones (**2**) by the cyclization of 3-[1-(phenylhydrazono)-ethyl]chromen-2-ones (**1**) in the presence of CuO/SBA-15 under solvent-free and microwave irradiation conditions. Compared with existing methods, the current protocol gives the targeted products in higher yields and in shorter reaction times owing to the use of microwave. Moreover, making use of the recoverable Cu catalyst under solvent-free conditions rendered this protocol advantageous, although solvents are necessary for the isolation of the products as well as catalyst recovery in the work-up step.

EXPERIMENTAL

All solvents and reagents were purchased from commercial sources and were used without additional purification. Melting points were determined with a X-5 digital microscopic melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (400MHz) instrument in $CDCl_3$ with TMS as the internal standard. HRMS measurements were performed on a Waters Q-Tof MicroTM instrument. HPLC analysis was performed on an Agilent 1200 HPLC (Chromatographic Column: XDB-C18 column with MeOH–H_2O as eluent) equipped with an Agilent 1200 UV detector. ICP were measured on an inductively coupled plasmas atomic emission spectrometer from the American Thermo Electron company.

CCDC-929647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data-request/cif.

The preparation of the catalyst CuO/SBA-15

0.48 g (2.4 mmol) of $Cu(MeCOO)_2 \cdot H_2O$ was dissolved in 75 mL of 1.6 mol/L HCl, and 2 g of p123 (EO20PO70EO20, Aldrich) was added to the above solution with stirring. The mixture was stirred until the p123 dissolved. Then, 5 mL of TEOS as the silica source was added dropwise to the aqueous solution with vigorous stirring. After the mixture was stirred for 24 h at 40 °C and aged for 24 h at 100 °C, the solid obtained was filtered off, dried at 120 °C for 8 h, and calcined at 550 °C for 4 h. The sample thus obtained is denoted as CuO/SBA-15 (0.16% by ICP).

Typical procedure for the preparation of compounds 2a-p.

3-[1-(Phenylhydrazono)ethyl]chromen-2-ones **1** (0.72 mmol), CuO/SBA-15 (0.7 mol%) and 4 g silica as media were thoroughly grinded in a mortar. The silica supported mixture was heated with a microwave at 567 W. The sample was monitored by HPLC. After completion of the reaction, the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The solvent was removed by reduced pressure distillation. The crude product was recrystallized from EtOH to give compounds **2**.

6-Ethoxy-3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (2e): yield 198 mg (86%); white powder; mp 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (t, *J* = 7.2 Hz, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.17-7.54 (m, 2H, CH_2), 6.64-6.66 (m, 1H, ArH), 6.92-6.96 (m, 1H, ArH), 6.99-7.02 (m, 1H, ArH), 6.99-7.02 (m, 1H, ArH), 7.53-7.55 (m, 2H, ArH), 7.59-7.61 (m, 3H, ArH); ^{13}C NMR (100MHz, $CDCl_3$): δ = 12.93, 14.75, 65.05, 106.38, 112.61, 113.88, 114.24, 123.69, 127.01, 129.79, 130.10, 139.49, 141.94, 147.52, 150.75, 157.49 ppm; HRMS (ESI^+): *m/z* calcd for $[C_{19}H_{17}N_2O_3]^+$: ($M + H^+$) 321.1239; found: 321.1238.

6,8-Dibromo-3-methyl-1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (2g): yield 188 mg (60%); yellow powder; mp 246-250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3H, CH_3), 7.12 (d, *J* = 2 Hz, 1H, ArH), 7.51-7.54 (m, 2H, ArH), 7.64-7.66 (m, 3H, ArH), 7.81 (d, *J* = 2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.83, 106.68, 112.67, 114.23, 116.33, 124.21, 126.70, 130.09, 130.68, 136.68, 138.63, 139.85, 149.04, 150.97, 156.02 ppm; HRMS (ESI^+): *m/z* calcd for $[C_{17}H_{11}Br_2N_2O_2]^+$: ($M + H^+$) 432.9187; found: 432.9191.

1-(4-Bromophenyl)-3-methylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (2k): yield 179 mg (70%); white powder; mp 225-227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3H, CH_3), 7.07-7.11(m, 1H, ArH), 7.15-7.17 (m, 1H, ArH), 7.43-7.49 (m, 4H, ArH), 7.74-7.77 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.86, 106.64, 111.59, 118.20, 122.26, 123.99, 124.17, 128.39, 131.29, 133.09, 138.35, 141.74, 151.16, 153.27, 157.77 ppm; HRMS (ESI^+): *m/z* calcd for $[C_{17}H_{12}BrN_2O_2]^+$: ($M + H^+$) 355.0082; found: 355.0083.

1-(2,4-Dichlorophenyl)-3-methylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (2n): yield 124 mg (50%); light yellow powder; mp 262-264 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 3H, CH_3), 7.15 (t, *J* = 7 Hz,

ArH), 7.23 (d, *J* = 8 Hz, 1H, ArH), 7.46 (d, *J* = 8 Hz, 1H, ArH), 7.50-7.54 (m, 3H, ArH), 7.61(s, 1H, ArH). ^{13}C NMR (100MHz, $CDCl_3$): δ = 12.83, 106.98, 111.27, 118.34, 122.16, 124.20, 125.52, 130.33, 131.58, 136.13, 140.88, 141.88, 151.57, 153.32, 157.53 ppm. HRMS (ESI^+): *m/z* calcd for $[C_{17}H_{11}Cl_2N_2O_2]^+$: ($M + H^+$) 345.0198; found: 345.0199.

1-(2,4-Dimethylphenyl)-3-methylchromeno[4,3-*c*]pyrazol-4(1*H*)-one (2o): yield 170 mg (78%); yellow powder; mp 176-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 6.83 (d, *J* = 8 Hz, 1H, ArH), 7.00-7.04 (m, 1H, ArH), 7.20-7.29 (m, 3H, ArH), 7.42-7.44 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.01, 17.19, 21.40, 105.66, 112.01, 117.93, 121.83, 124.19, 127.50, 28.12, 130.99, 132.15, 135.71, 135.80, 140.84, 142.16, 150.65, 153.24, 158.11 ppm. HRMS (ESI^+): *m/z* calcd for $[C_{19}H_{17}N_2O_2]^+$: ($M + H^+$) 305.1290; found: 305.1288.

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