APPLICATION OF 2-SUBSTITUTED ETHYL ISOTHIOCYANATES AND 2-AMINOTHIOLS IN THE SYNTHESIS OF THE ANALOGS OF INDOLE PHYTOALEXIN CAMALEXIN

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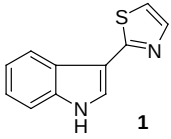
Dedicated to Professor Milan Kratochvíl on the occasion of his 75th birthday.

Treatment of (indol-1-yl)magnesium bromide or iodide with 2-bromoethyl isothiocyanate afforded 1-(4,5-dihydrothiazol-2-yl)indole (**6**). Analogous reaction with 2,2-dimethoxyethyl isothiocyanate led to corresponding 1-thiocarbamoylindole derivative (**7**), which was cyclized to 1-(5-methoxy-4,5-dihydrothiazol-2-yl)indole (**8**) by treatment with boron trifluoride etherate. New analogs of camalexin, namely 4′,5′-dihydrocamalexin (**12**) and benzocamalexin (**14**) were prepared by cyclocondensation reaction of 1-(*tert*-butoxycarbonyl)indole-3-carbaldehyde with cysteamine and 2-aminobenzenethiol. Antifungal activity of the prepared compounds was studied, using the fungi *Alternaria brassicae* and *Alternaria brassicicola*.

Key words: Indoles; Phytoalexins; Dihydrocamalexin; Benzocamalexin; Antifungal activity.

Many plants after their exposure to microbial pathogens produce antimicrobial compounds known as phytoalexins. An interesting example of this proup of secondary metabolites is camalexin (**1**), a phytoalexin produced by *Camelina sativa*[1] and *Arabidopsis thaliana*[2]. Camalexin [3-(thiazol-2-yl)indole] was prepared by alkylation of (indol-1-yl)magnesium iodide with 2-bromothiazole[3] or by reductive coupling of 2-formamidophenyl thiazol-2-yl ketone by low-valent titanium[4]. Analogs of camalexin with modified (reduced or substituted) thiazole or with benzothiazole ring have

not been described yet. On the other hand, the isomeric compounds possessing benzothiazole moiety in 1 or 2 position of indole nucleus (**2**, **3**) were prepared by photocyclization of substituted (indol-1-yl)thioureas[5], or by the reaction of 1-methylindole-2-carboxylate with 2-aminobenzenethiol in the presence of trimethylaluminum in toluene[6]. Thiazole and benzothiazole derivatives of indole have been found to exhibit antimicrobial[3] and cytotoxic[6] activity.



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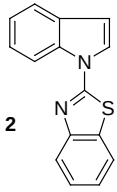

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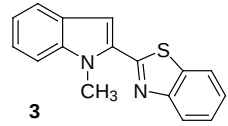

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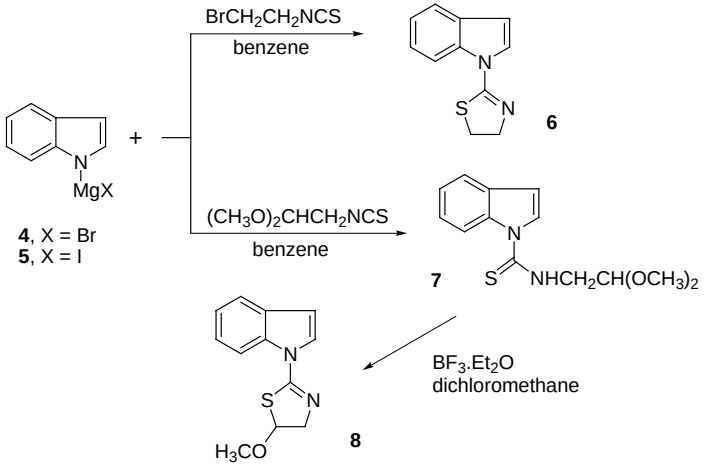
In this paper, we have studied the possibilities of the synthesis of camalexin analogs by using the enhanced reactivity of the position 3 in (indol-1-yl)magnesium halides against electrophilic reagents, and by cyclocondensation reactions of indole-3-carbaldehyde. It is known, that the alkylation[3,7] and acylation[8] of indole Grignard reagents proceed with the formation of 3-substituted indoles. Moreover, heating of indole with phenyl isothiocyanate at 80–90 °C without solvent results in the formation of 3-substituted indole thioamide[9]. Based on this information, we have studied the reaction of indole with 2-bromoethyl and 2,2-dimethoxyethyl isothiocyanate with the aim to obtain intermediates suitable for the synthesis of camalexin analogs. By heating of indole with the above isothiocyanates at various temperatures (40–100 °C) during 4–12 h without solvent, only unidentified decomposition products have been formed. To increase the reactivity of its position 3, indole was transformed to the corresponding *N*-magnesium bromide (**4**), or iodide (**5**) and then treated with substituted ethyl isothiocyanates. In these cases, the nucleophilic addition to NCS group proceeded exlusively *via* indole nitrogen with the formation of 1-substituted indole derivatives. 2-Bromoethyl isothiocyanate afforded with Grignard reagents **4** and **5** directly the 1-(thiazol-2-yl)indole (**6**), a positional isomer of dihydrocamalexin, whereas the reaction of 2,2-dimethoxyethyl isothiocyanate resulted in the formation of stable 1-[*N*-(2,2-dimethoxyethyl)thiocarbamoyl]indole (**7**, Scheme 1).

We have found that compound **7** can be cyclized to **8** (5′-methoxy derivative of **6**) by treatment with boron trifluoride etherate in dry dichloromethane at room temperature. The structure of compounds **6**–**8** as

1-substituted indole derivatives was confirmed by the absence of the absorption band of ν(N–H) at 3 400–3 500 cm^{-1} in the IR spectra which should be present with 3-substituted isomers. Also the signals corresponding to δ(NH) of compounds **6**–**8** in ^1H NMR spectra are missing, whereas the signals to 3 protons at 6.65–6.69 ppm are present.

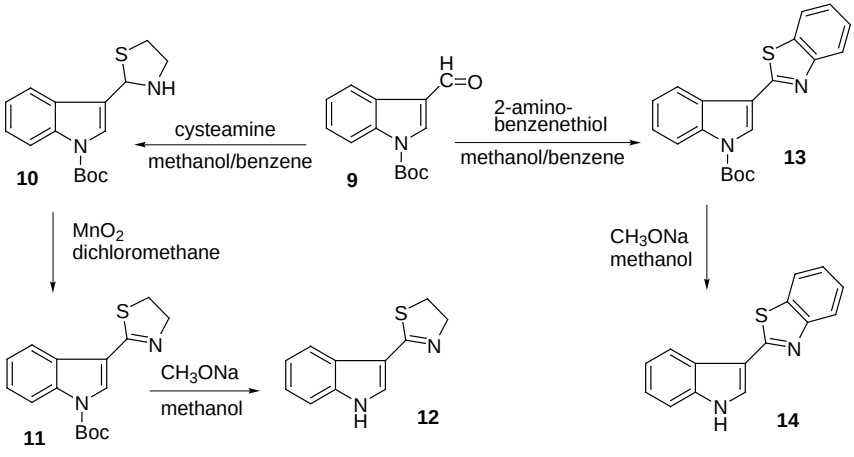


SCHEME 1

Since the reaction between (indol-1-yl)magnesium halides and substituted ethyl isothiocyanates afforded only positional isomers of dihydrocamalexin, our attention was next turned to cyclocondensation reactions of indole-3-carbaldehyde with 2-aminothiols. It should be noted that the reaction of aldehydes and ketones with 2-aminothiols is a useful method for the synthesis of thiazolidine and benzothiazole derivatives[10]. Unexpectedly, the reaction of indole-3-carbaldehyde with 2-aminothiols resulted in the formation of intractable mixture of decomposition products. Therefore, we have used protected 1-(*tert*-butoxycarbonyl)indole-3-carbaldehyde, which by the reaction with cysteamine hydrochloride in the presence of triethylamine afforded 1-(*tert*-butoxycarbonyl)- 3-(thiazolidine-2-yl)indole (**10**) in 89% yield (Scheme 2).

Attempted oxidation of **10** to dihydrocamalexin with cerium ammonium nitrate[11] (CAN), pyridinium chlorochromate[12] (PCC) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[13] (DDQ) resulted in the formation of aldehyde **9** and other unidentified decomposition products. Oxidation of **10** with activated manganese(IV) oxide in anhydrous dichloromethane under nitrogen atmosphere resulted in the formation of desired 1-(*tert*-butoxycarbonyl)-3-(4,5-dihydrothiazol-2-yl)indole (**11**). The protecting group was

readily removed by treatment of **11** with sodium methoxide under formation of 4′,5′-dihydrocamalexin (**12**). All attempts to obtain camalexin by oxidation of protected or deprotected dihydrocamalexin failed. Cyclocondensation reaction of aldehyde **9** with 2-aminobenzenethiol in methanol–benzene (2 : 1) afforded 1-(*tert*-butoxycarbonyl)-3-(benzothiazol-2-yl)-indole (**13**), the first known indole, possessing benzothiazole moiety in position 3. Deprotection with sodium methoxide resulted in the formation of benzocamalexin (**14**) in 72% yield. The structures of compounds **10**–**14** have been confirmed by IR, ^{1}H NMR, ^{13}C NMR spectra and mass spectrometry. Compounds **10**, **11** and **13** exhibit in their IR spectra the absorption bands of ν(C=O) at 1 725–1 733 cm^{-1}, which are not present in the spectra of products **12** and **14** obtained after removal of protecting group. Instead, absorption bands of ν(N–H) at 3 470 and 3 475 cm^{-1} are present in the IR spectra of **12** and **14**. ^{1}H NMR spectrum of compound **10** shows the signals of CH and NH protons at 5.78 and 8.36 ppm, which are missing in the spectra of products **11**–**14**, thus evidencing the presence of C=N double bond.



SCHEME 2

Antifungal activity of compounds **6** and **8** was determined by using the fungi *Alternaria brassicae* and *Alternaria brassicicola* at concentrations ranging from 1 to 100 μg ml^{-1}, and at incubation periods 2, 10 and 20 h. Unfortunately the other synthesized compounds, in particular **13** and **14**, were not sufficiently soluble for these antifungal test. The minimum inhibition concentration (MIC) for complete inhibition of germination of *Alternaria brassicae* was 20 μg ml^{-1} for camalexin and 40 μg ml^{-1} for compound **8**,

whereas MIC for compound **6** was higher than 100 μg ml^{-1} (Table I). Analogously, the MIC value for *Alternaria brassiciccola* was 20 μg ml^{-1} for camalexin, whereas for compounds **6** and **8**, the MIC values are higher than 100 μg ml^{-1} (Table II). For *Alternaria brassicae* and *Alternaria brassicicola*, the germination inhibition rates decreased with increasing inhibition time (Tables III and IV).

EXPERIMENTAL

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. The infrared absorption spectra were recorded on an IR-75 (Zeiss, Jena) in chloroform; the

TABLE I
Multigroup comparison of germination inhibition rates (%) of *Alternaria brassicae* spores at different concentrations of compounds **6** and **8**

Compound	Concentration[a], μg ml^{-1}								
	2	4	6	10	20	40	60	80	100
Camalexin	35.40	50.10	66.4	74.40	99.70	99.90	100.00	100.00	100.00
6	17.11	17.11	24.78	27.67	32.67	48.56	55.44	64.89	83.00
8	17.00	19.50	22.70	31.10	48.50	98.80	99.90	99.90	100.00

[a] Means of all germination inhibition rates (%) after 2, 10, and 20 h.

TABLE II
Multigroup comparison of germination inhibition rates (%) of *Alternaria brassicicola* spores at different concentrations of compounds **6** and **8**

Compound	Concentration[a], μg ml^{-1}									
	1	2	4	6	10	20	40	60	80	100
Camalexin	23.60	34.40	43.90	63.90	76.10	99.40	99.20	99.90	99.60	99.30
6	7.40	8.20	10.90	18.40	24.00	38.00	38.20	44.90	55.90	61.80
8	10.30	10.30	12.10	13.80	17.70	26.50	43.60	52.10	55.60	60.90

[a] Means of all germination inhibition rates (%) after 2, 10, and 20 h.

wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a Tesla BS 487A (80 MHz) spectrometer in hexadeuterioacetone (compounds **6**–**8**), deuteriochloroform (compounds **10**–**14**) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured on BS 567 (25.15 MHz) in deuteriochloroform (compounds **6** and **14**). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The EI mass spectra of compounds **13** and **14** were recorded on a JMS 100D spectrometer (Jeol) at ionization energy 70 eV. The reaction course was monitored by thin-layer chromatography (TLC) on Silufol plates (Kavalier, Czech Republic).

Indole-3-carbaldehyde, cysteamine and 2-aminobenzenethiol (Aldrich) and activated manganese(IV) oxide (Fluka) were used as commercial chemicals. Starting (indol-1-yl)magnesium bromide (**4**) and (indol-1-yl)magnesium iodide[3] (**5**), 1-(*tert*-butoxycarbonyl)indole-3-carbaldehyde[14]

TABLE III
Multigroup comparison of germination inhibition rates (%) of *Alternaria brassicae* spores at different incubation periods

Compound	Incubation periods[a], h		
	2	10	20
Camalexin	93.50	81.20	67.50
6	64.90	35.70	23.10
8	69.00	56.50	53.60

[a] Means of all germination inhibition rates (%) at 2, 4, 6, 10, 20, 40, 60, 80, and 100 μg ml^{-1}.

TABLE IV
Multigroup comparison of germination inhibition rates (%) of *Alternaria brassicicola* spores at different incubation periods

Compound	Incubation periods[a], h		
	2	10	20
Camalexin	91.40	73.60	56.80
6	63.70	21.60	0.00
8	58.00	21.98	3.90

[a] Means of all germination inhibition rates (%) at 2, 4, 6, 10, 20, 40, 60, 80, and 100 μg ml^{-1}.

(**9**), 2,2-dimethoxyethyl isothiocyanate and 2-bromoethyl isothiocyanate[15] were prepared according to the literature procedures. Antifungal activity was determined according to previously reported procedure[16].

1-(4,5-Dihydrothiazol-2-yl)indole (**6**)

To a solution of (indol-1-yl)magnesium bromide (**4**) or iodide (**5**, 20 mmol) in dry benzene (50 ml), a solution of 2-bromoethyl isothiocyanate (830 mg, 5 mmol) in dry benzene (20 ml) was added dropwise. After stirring for 1 h at room temperature, the reaction mixture was acidified with a solution of acetic acid (13 ml) in water (30 ml). Benzene layer was extracted with chloroform (3 × 15 ml). Collected organic layers were washed with 4% sodium hydrogencarbonate solution (25 ml), dried with anhydrous sodium sulfate and solvent evaporated. The crude product was chromatographed on silica gel (acetone–cyclohexane 5 : 1). Yield from **4**: 630 mg (63%), from **5**: 400 mg (40%), m.p. 54–55.5 °C (acetone–cyclohexane). For $C_{11}H_{10}N_2S$ (202.3) calculated: 65.31% C, 4.98% H, 13.84% N; found: 65.38% C, 5.00% H, 13.93% N. IR: 3 000, 2 860, 1 615, 1 335, 1 010, 890. ^{1}H NMR: 3.58 t, 2 H, *J* = 8.8 (CH_2); 4.37 t, 2 H, *J* = 7.7 (CH_2); 6.69 d, 1 H, *J* = 3.5 (H-3); 7.25 m, 2 H (H-5, H-6); 7.49 d, 1 H, *J* = 3.5 (H-2); 7.62 m, 1 H (H-4) and 8.47 m, 1 H (H-7). ^{13}C NMR: 35.05 (CH_2), 62.45 (CH_2), 107.54 (C-3), 116.09 (C-5), 121.62 (C-6), 123.29 (C-2), 124.56 (C-4), 128.41 (C-7), 131.24 (C-9), 136.77 (C-8), 156.33 (C-2′).

1-[*N*-(2,2-Dimethoxyethyl)thiocarbamoyl]indole (**7**)

To a solution of (indol-1-yl)magnesium iodide (**5**, 4 mmol) in dry benzene (20 ml), a solution of 2,2-dimethoxyethyl isothiocyanate (290 mg, 2 mmol) in dry benzene (15 ml) was added dropwise. After stirring for 70 min at room temperature the mixture was poured into a solution of acetic acid (5 ml) in water (15 ml). The organic layer was separated and the aqueous layer extracted with benzene (3 × 10 ml). The combined extracts were washed with a 4% solution of sodium hydrogencarbonate (20 ml), dried with anhydrous sodium sulfate, the solvent was evaporated and the residue chromatographed on silica gel (benzene–acetone 25 : 1). Yield 370 mg (70%), m.p. 63.5–66.5 °C (cyclohexane–acetone). For $C_{13}H_{16}N_2O_2S$ (264.3) calculated: 59.07% C, 6.10% H, 10.59% N; found: 59.09% C, 6.13% H, 10.62% N. IR: 3 400, 2 940, 2 840, 1 600, 1 245, 1 070, 890. ^{1}H NMR: 3.45 s, 6 H $[(OCH_3)]_2$; 4.00 d, 2 H, *J* = 5.3 (CH_2); 4.89 t, 1 H, *J* = 5.5 (CH); 6.65 d, 1 H, *J* = 3.5 (H-3); 7.22 m, 2 H (H-5, H-6); 7.90 d, 1 H, *J* = 3.7 (H-2); 7.61 m, 1 H (H-4) and 8.12 m, 1 H (H-7); 8.80 s, 1 H (NH).

1-(5-Methoxy-4,5-dihydrothiazol-2-yl)indole (**8**)

To a solution of derivative **7** (150 mg, 0.56 mmol) in dichloromethane (5 ml), boron trifluoride etherate (0.1 ml, 0.84 mmol) was added at 0 °C and the mixture was stirred for 30 min at room temperature. The resulting solution was washed with a 4% solution of sodium hydrogencarbonate (6 ml), layers separated and water layer extracted with dichloromethane. The combined extracts were dried wih anhydrous sodium sulfate, solvent was evaporated and the residue crystallized from dichloromethane. Yield 100 mg (77%), m.p. 35–36.5 °C. For $C_{12}H_{12}N_2OS$ (232.3) calculated: 62.04% C, 5.20% H, 12.06% N; found: 62.09% C, 5.29% H, 12.15% N. IR: 3 005, 2 940, 2 830, 1 620, 1 335, 1 085, 885. ^{1}H NMR: 3.33 s, 3 H (OCH_3); 4.41 d, 2 H, *J* = 3.4 (CH_2); 5.78 t, 1 H, *J* = 3.7 (CH); 6.68 d, 1 H, *J* = 4.7

(H-3); 7.24 m, 2 H (H-5, H-6); 7.50 d, 1 H, *J* = 3.7 (H-2); 7.65 m, 1 H (H-4) and 8.52 m, 1 H (H-7).

1-(*tert*-Butoxycarbonyl)-3-(thiazolidin-2-yl)indole (**10**)

To a solution of cysteamine hydrochloride (284 mg, 2.5 mmol) in a mixture of methanol–benzene (1 : 2, 3 ml) was added with stirring 1-(*tert*-butoxycarbonyl)indole- 3-carbaldehyde (**9**, 254 mg, 1 mmol) and triethylamine (304 mg, 0.42 ml, 3 mmol). The mixture was stirred for 30 min at room temperature an then concentrated to 1/3 of its original volume. The residue was chromatographed on silica gel (cyclohexane–acetone 2 : 1). Yield 271 mg (89%) oil. For $C_{16}H_{20}N_2O_2S$ (304.4) calculated: 63.31% C, 6.62% H, 9.21% N; found: 63.59% C, 6.81% H, 9.84% N. IR: 3 323, 2 985, 2 930, 1 727, 1 607, 1 367, 1 155. ^{1}H NMR: 1.66 s, 9 H (*t*-Bu); 3.88 m, 4 H $[(CH_2)]_2$; 5.78 d, 1 H (CH); 7.20–8.18 m, 5 H (H-arom.); 8.36 s, 1 H (NH).

1-(*tert*-Butoxycarbonyl)-3-(4,5-dihydrothiazol-2-yl)indole (**11**)

To a solution of compound **10** (304 mg, 1 mmol) in anhydrous dichloromethane (15 ml), manganese(IV) oxide (435 mg, 5 mmol) was added and reaction mixture was stirred for 48 h at room temperature under nitrogen atmosphere. The mixture was filtered, filtrate concentrated to 1/3 of its original volume and chromatographed on aluminium oxide, eluent cyclohexane–acetone (2 : 1). Yield 78 mg (26%), m.p. 150–152 °C (ethanol). For $C_{16}H_{18}N_2O_2S$ (302.4) calculated: 63.55% C, 5.99% H, 9.26% N; found: 63.58% C, 6.00% H, 9.29% N. IR: 2 980, 2 930, 2 850, 1 725, 1 637, 1 365, 1 150. ^{1}H NMR: 1.67 s, 9 H (*t*-Bu); 3.15 t, 2 H, *J* = 6.5 (CH_2); 3.92 t, 2 H, *J* = 6.5 (CH_2); 7.20–8.50 m, 5 H (H-arom.).

3-(4,5-Dihydrothiazol-2-yl)indole (4′,5′-Dihydrocamalexin) (**12**)

To a suspension of compound **11** (100 mg, 0.3 mmol) in methanol (10 ml), sodium (100 mg, 4.35 mmol) was added and the mixture was stirred for 2 h at room temperature. During this time the starting compound has completely dissolved. After pouring into water (50 ml) the product was extracted wih dichloromethane (3 × 10 ml), the extract dried with anhydrous sodium sulfate, solvent evaporated and the obtained residue crystallized from ethanol. Yield 20 mg (33%), m.p. 85–87 °C. For $C_{11}H_{10}N_2S$ (202.3) calculated: 65.32% C, 4.98% H, 13.84% N; found: 65.44% C, 5.01% H, 13.96% N. IR: 3 470, 2 990, 2 925, 1 635, 1 225. ^{1}H NMR: 3.10 t, 2 H, *J* = 6.9 (CH_2); 4.02 t, 2 H, *J* = 6.9 (CH_2); 7.52–8.51 m, 5 H (H-arom.); 9.00 s, 1 H (NH).

1-(*tert*-Butoxycarbonyl)-3-(benzothiazol-2-yl)indole (**13**)

To a solution of 2-aminobenzenethiol (125 mg, 1 mmol) in a mixture methanol–benzene (1 : 2, 3 ml), aldehyde **9** (245 mg, 1 mmol) was added and the mixture was stirred at room temperature for 25 h. After evaporation of solvent the obtained crude product was crystallized from ethanol. Yield 170 mg (48%), m.p. 168–170 °C. For $C_{20}H_{18}N_2O_2S$ (350.4) calculated: 68.55% C, 5.18% H, 7.99% N; found: 68.50% C, 5.14% H, 7.91% N. IR: 2 990, 1 733, 1 620, 1 370, 1 155. ^{1}H NMR: 1.73 s, 9 H (*t*-Bu); 7.10–7.85 m, 5 H (indole); 8.10–8.75 m, 4 H (C_6H_4). MS, *m*/*z* (%): 350 (M^+, 2), 295 (3), 251 (14), 142 (3), 56 (64), 41 (100).

3-(Benzothiazol-2-yl)indole (Benzocamalexin) (**14**)

To a suspension of **13** (275 mg, 0.78 mmol) in methanol (40 ml), sodium (420 mg, 18.3 mmol) was added and reaction mixture was stirred at room temperature for 24 h. After pouring into water (250 ml) the product was extracted with dichloromethane (3 × 50 ml), dried with anhydrous sodium sulfate, solvent evaporated, and the obtained crude product crystallized from ethanol. Yield 150 mg (72%), m.p. 124–127 °C. For $C_{15}H_{10}N_2S$ (250.3) calculated: 71.97% C, 4.03% H, 11.19% N; found: 71.89% C, 4.01% H, 11.08% N. IR: 3 475, 2 930, 2 860, 1 610, 1 415. ^{1}H NMR: 7.13–7.57 m, 7 H (C_6H_4 + H-5, H-6, H-7); 7.66 d, 1 H, J = 7.5 (H-2); 8.05 m, 1 H (H-4); 8.86 m, 1 H (NH). ^{13}C NMR: 112.76, 117.58, 122.54, 123.00, 124.36, 125.25, 126.14, 126.68, 127.94, 132.95, 134.43, 138.72, 151.27, 155.80, 161.11. MS, *m*/*z* (%): 250 (M^+, 100), 248 (10), 130 (16), 124 (6), 108 (3), 69 (2).

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