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Synthesis, scope, ^{1}H and ^{13}C spectral assignments of isomeric dibenzofuran carboxaldehydes

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Abstract Two isomeric dibenzofuran carboxaldehydes, namely 2-methoxydibenzo[*b,d*]furan-1-carbaldehyde (**4**) and 2-methoxydibenzo[*b,d*]furan-3-carbaldehyde (**5**), were synthesized. Formylation of 2-methoxydibenzo[*b,d*]furan (**3**) with α,α-dichloromethyl methyl ether and tin(IV) chloride gave a mixture of aldehydes **4** and **5** in 95 % yield and in a 35:65 ratio. Their ^{1}H and ^{13}C NMR spectral signals were not sufficiently resolved in $CDCl_3$ solution to achieve their complete assignment, but this was possible in DMSO-d_6 with the help of 2D-NMR techniques: NOESY for ^{1}H–^{1}H interactions and HSQC and HMQC experiments for ^{1}H–^{13}C correlations. These aldehydes were used in the synthesis of novel *β*-phenylethylamines and NBOMe derivatives, which are undergoing biological evaluation.

Keywords NMR · ^{1}H · ^{13}C · 2-Methoxydibenzo[*b,d*]furan aldehyde regioisomers · *β*-Phenylethylamines and NBOMe derivatives

Introduction

Polycyclic heterocycles with oxygen in a central position constitute an important class of fused heterocycles found in numerous natural products that have also shown interesting biological properties. In particular, dibenzo[*b,d*]furan derivatives have attracted the interest of natural product and medicinal chemists over the past few decades because of their characteristic occurrence in lichens and fungi and as

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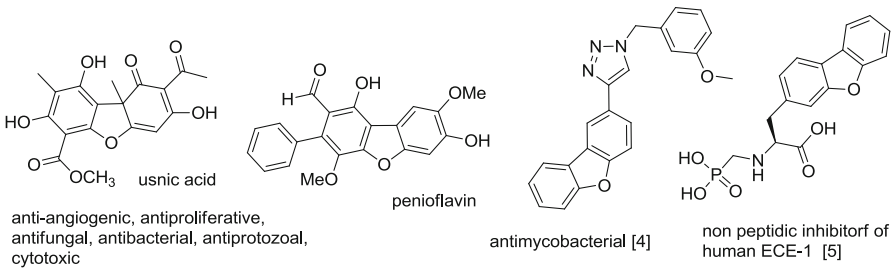


Fig. 1 Some dibenzofuran derivatives reported in the literature (natural and synthetic)

phytoalexins [1]. Dibenzofuran natural products, as well as many synthetic compounds (Fig. 1) containing this nucleus exhibit a broad variety of promising biological activities such as antibacterial (including antibiotic-resistant and antimycobacterial), antifungal, antiproliferative and potentially anticancer, and anti-inflammatory activities [2–8]. This interesting range of properties and the possible pharmaceutical applications have stimulated continued effort to obtain new derivatives incorporating a dibenzofuran unit for their pharmacological evaluation.

Experimental

Chemicals

The reagents required for this study were purchased from Merck S. A., Santiago, Chile. Commercial solvents used for the reactions were dried as per standard literature protocols. Silica gel having a pore size of 60 Å (70–230 mesh, 63–200 μm) used for column chromatography was purchased from Sigma-Aldrich Chile. 2-Hydroxydibenzo[*b,d*]furan (**2**) was prepared in two steps, according to a literature procedure [9].

Instrumentation

NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 at 300 K on a Bruker Avance III HD 400 (9.4 T, 400.13 MHz for ^{1}H, and 100.62 MHz for ^{13}C) spectrometer with a 5-mm inverse detection Smart Probe equipped with a z-gradient coil. Chemical shifts (δ in parts per million) are referenced to the solvent residual signals (^{1}H and ^{13}C at 7.26 and 77.16 ppm, respectively, in $CDCl_3$, and 2.50 and 39.52 ppm, respectively, for ^{13}C in DSO–d_6) [11]. Coupling constants (J in Hertz) are accurate to ±0.3 Hz for ^{1}H NMR. Typical parameters for ^{1}H NMR spectra were recorded with a spectral width of 4700 Hz and a pulse width of 10 μs at an attenuation level of 16.600 W. For ^{13}C NMR spectra, typical values were a spectral width of 21,000 Hz, a pulse width of 10 μs, an attenuation level of 69.000 W, and a relaxation delay of 2 s. Waltz16 was used for broad band proton decoupling; the FIDs were weighted exponentially (lb = 2 Hz) before Fourier transformation. Two-

dimensional ^{1}H–^{13}C gs-HSQC and ^{1}H–^{13}C gs-HMQC experiments were carried out using standard Bruker software (https://www.bruker.com/products/mr/nmr/nmrsoftware/software/topspin/overview.html) and in non-phase-sensitive mode. Gradient selection was achieved through a 5 % sine truncated-shaped pulse gradient of 1 ms. Selected parameters for gs-HSQC and gs-HMQC experiments were a spectral width of 3649 Hz for ^{1}H and 18115 Hz for ^{13}C, 1024 × 128 data set, two scans each for gs-HSQC, and HMQC. The FIDs were processed using zero filling in the F1 domain, and a sine-bell window function in both dimensions was applied before the Fourier transformation. In the gs-HMQC experiment, GARP modulation of ^{13}C was used for decoupling. The ^{1}H–^{1}H NOESY experiments were recorded with a spectral width of 4.85 kHz in both F2 and F1 domains; 512 × 128 data points were acquired with four scans per increment and relaxation delays of 2.0 s. Data processing was performed on a 1024 × 1024 data matrix.

Preparation of 2-methoxydibenzo[*b,d*]furan (3)

To a solution of compound **2** (1.84 g, 0.01 mol) in dry THF, NaH (0.28 g, 0.012 mol) was added at 0 °C. After stirring the reaction mixture for 10 min, ICH_3 (1.70 g, 0.012 mol) was added and stirring was continued at RT for 1 h. After completion of the reaction (monitored by TLC), the mixture was carefully quenched with water and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. Chromatographic purification of the crude reaction mixture (on silica gel using 90:10, hexane:CH_2Cl_2 as eluent) gave **3** in quantitative yield as a yellow liquid which upon standing at −10 °C turned into a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, $J = 7.0$ Hz, 1H), 7.55 (d, $J = 8.3$ Hz, 1H), 7.49–7.41 (multiple peaks, 3H), 7.33 (td, $J = 7.3$ and 0.7 Hz, 1H), 7.05 (dd, $J = 9.0$ and 2.6 Hz, 1H), 3.92 (s, 3H).

The ^{1}H NMR data of compound **3** were in agreement with the literature [10].

Preparation of aldehydes 4 and 5

2-Methoxy[*b,d*]dibenzofuran (**3**) (1 g, 0.005 mol) was dissolved in CH_2Cl_2 (35 mL) and $SnCl_4$ (1.50 g, 0.006 mol) was added slowly with continuous stirring at RT. After 10 min, $CHCl_2OCH_3$ (0.69 g, 0.006 mol) was added slowly and the resulting mixture was stirred at RT for another hour. Then the reaction mixture was quenched with 1 N HCl (15 mL) and the organic phase was treated successively with water, $NaHCO_3$ solution and finally saturated brine. After drying the organic layer with anhydrous sodium sulfate, it was concentrated in a rotary evaporator. Silica gel column chromatography (hexane:CH_2Cl_2 from 80:20 to 30:70) afforded the pure aldehydes **4** and **5** in 95 % combined yield in a 35:65 ratio.

2-Methoxydibenzo[*b,d*]furan-1-carbaldehyde (4)

Light yellow solid; m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.05 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.56–7.51 (m, 2H), 7.39–7.34

(m, 1H), 7.10 (d, $J = 9.0$ Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 159.7, 157.8, 150.8, 128.8, 127.1, 123.5, 123.4, 122.5, 119.7, 117.9, 111.0, 110.7, 56.7.

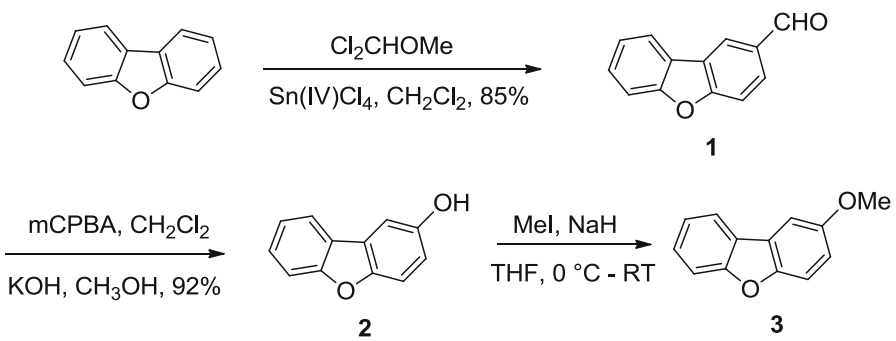
2-Methoxydibenzo[*b,d*]furan-3-carbaldehyde (5)

White solid; m.p. 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.00 (s, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.58–7.46 (m, 2H), 7.38 (s, 1H), 7.36 (dd, $J = 7.5$ and 6.8 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 158.3, 158.1, 150.2, 130.6, 129.0, 124.0, 123.4, 122.9, 121.3, 112.1, 110.6, 102.5, 56.2.

Results and discussion

In this context, we wished to synthesize methoxy substituted dibenzofuran aldehydes as precursors for new potentially bioactive compounds, starting from the relatively inexpensive dibenzo[*b,d*]furan. Although there are literature reports of ring closure reactions to obtain dibenzofuran analogues [12–14], and functionalized, but not annulated furan derivatives are the subject of modern synthetic approaches [15]; a few start from dibenzo[*b,d*]furan. With this in mind, we chose 2-methoxydibenzo[*b,d*]furan (**3**) [10] as the key intermediate and prepared it via the known 2-hydroxydibenzo[*b,d*]furan (**2**) [9] according to Scheme 1. Methylation of the previously described **2** using sodium hydride and methyl iodide gave the required starting material **3** in quantitative yield as a yellow liquid. The ^{1}H NMR spectrum of compound **3**, 2-methoxydibenzo[*b,d*]furan, agreed with the published data [10].

2-Methoxydibenzo[*b,d*]furan-3-carbaldehyde (**5**) had been described many years ago as the sole isolated product of the Vilsmeier formylation of **3**, and its structure was then decided convincingly on the basis of further reactions to afford a known compound [16]. More recently, both **4** and **5** were mentioned as intermediates for a variant of the Peachmann synthesis leading in these cases to benzofuran annulated coumarins at the 5,6 and 6,7 positions [17]. In that paper 2-methoxydibenzo[*b,d*]-furan was formylated (no details given) using α,α-dichloromethyl methyl ether and



Scheme 1 Synthesis of 2-methoxydibenzo[*b,d*]furan (**3**)

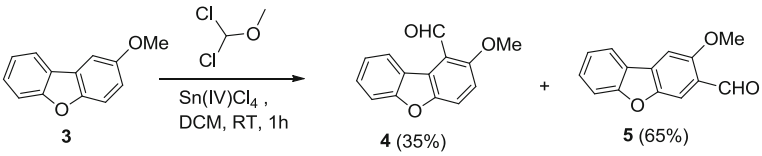
titanium(IV) chloride [18], and the products used without any characterization at all in the successive synthetic reactions [17]. In our hands, the formylation proceeded in excellent yield (95 %) with α,α-dichloromethyl methyl ether and tin(IV) chloride giving 2-methoxydibenzo[*b,d*]furan-1-carbaldehyde (**4**) and 2-methoxydibenzo[*b,d*]furan-3-carbaldehyde (**5**) in 95 % combined yield and in a 35:65 ratio, which could be separated by chromatography on silica gel (Scheme 2). As these two compounds were required for further synthetic steps, we decided to characterize them completely by ^{1}H and ^{13}C NMR and with mass-spectrometry.

Structural elucidation of the synthesized aldehydes **4** and **5** was achieved by routine ^{1}H and ^{13}C techniques. Nevertheless, for a definitive assignment of all signals, two-dimensional NMR techniques were used as follows: (1) 2D-HSQC spectra to determine the ^{1}H–^{13}C correlations for carbons bonded to hydrogen; (2) 2D-HMQC spectra to assign the signals of quaternary carbons via two-bond and three-bond ^{1}H–^{13}C interactions and (3) 2D-NOESY experiments to determine the spatial interaction of protons.

The ^{1}H NMR spectrum of **4** in $CDCl_3$ showed the formyl and methoxyl singlets at δ 10.80 and 3.99 ppm, two sharp doublets centered at 7.43 and 7.10 ppm that could be tentatively assigned to H-4 and H-3, and a broader doublet at 9.05 ppm, presumably assignable to H-9, but the remaining signals were confusing multiplets, around 7.62 and 7.36 ppm, that could not be assigned directly. The ^{13}C NMR spectrum and 2D experiments failed to clarify this situation. Similarly, in the case of aldehyde **5** the spectra in $CDCl_3$ were unsatisfactory for complete assignment of the signals, largely because of the near overlap of some multiplets.

Recording the spectra of **4** and **5** in DMSO-d_6 this difficulty was overcome, and the complete assignments for these compounds are shown in Tables 1 and 2. HSQC experiments done on aldehydes **4** and **5** related the ^{13}C NMR signals to their attached ^{1}H nuclei. The results obtained from the 2D-HSQC experiments are shown in Tables 1 and 2.

Using 2D-Heteronuclear Multiple Quantum Coherence (HMQC) NMR experiments, the observed correlations for the aldehydes are represented in Fig. 2. For compound **4**, a distinct correlation between hydrogen (δ_H) and their corresponding carbon (δ_C) was found. For example, the $-OCH_3$ (δ 4.00) is in correlation with the ^{13}C signal at 159.6 ppm which is assigned to C-2. Similarly the CHO proton (δ 10.68) is in correlation with the 121.9 ppm signal which is assigned to C-11. Also, correlations between H-3 (δ 7.43) and C-1 (δ 122.6), C-13 (δ 150.0); H-4 (δ 8.04) and C-2 (δ 159.6), C-11(δ 121.9); H-3 (δ 7.43) and C-1 (δ 122.6), C-13 (δ 150.0); H-6 (δ 7.70) and C-10 (δ 118.8); H-7 (δ 7.61) and C-12 (δ 157.0); H-8 (δ 7.41) and C-10 (δ 118.8); H-9 (δ 8.89) and C-11 (δ 121.9), C-12 (δ 157.0) were observed. In order to decide the still dubious



Scheme 2 Formylation of 2-methoxydibenzo[*b,d*]furan (**3**)

Table 1 ^{1}H NMR assignments of compounds **4** and **5** recorded in DMSO-d_6 at 300 K

S. no	Aldehyde	^{1}H	Multiplicity	δ (ppm)	J (Hz)
1	**4**	H-3	*d(unclear)*	7.43	–
2		H-4	*d*	8.04	9.0
3		H-6	*d*	7.70	8.3
4		H-7	*t*	7.61	8.0 and 7.3
5		H-8	*t(unclear)*	7.41	–
6		H-9	*d*	8.89	8.0
7		H-14 (−OC$\underline{H}_3$)	*s*	4.00	
8		H-15 (−C$\underline{H}$O)	*s*	10.68	
9	**5**	H-1	*s*	7.98	
10		H-4	*s*	7.87	
11		H-6	*d*	7.69	8.3
12		H-7	*t*	7.60	7.8 and 7.5
13		H-8	*t*	7.43	7.5 and 7.3
14		H-9	*d*	8.23	7.8
15		H-14 (−OC$\underline{H}_3$)	*s*	4.03	
16		H-15 (−C$\underline{H}$O)	*s*	10.42	

Table 2 ^{13}C NMR assignments of compounds **4** and **5** recorded in DMSO-d_6 at 300 K

S. no	Aldehyde **4**		Aldehyde **5**	
	^{13}C	δ (ppm)	^{13}C	δ (ppm)
1	C-1	122.6	C-1	109.5
2	C-2	159.6	C-2	158.0
3	C-3	122.5	C-3	130.2
4	C-4	118.8	C-4	104.4
5	C-6	111.3	C-6	111.8
6	C-7	129.0	C-7	129.4
7	C-8	112.3	C-8	123.2
8	C-9	126.1	C-9	122.3
9	C-10	118.8	C-10	122.9
10	C-11	121.9	C-11	123.3
11	C-12	157.0	C-12	157.3
12	C-13	150.0	C-13	149.2
13	C-14	57.0	C-14	56.5
14	C-15	190.1	C-15	188.7

assignments of H-3 (δ 7.43) and H-8 (δ 7.41), 2D- NOESY experiments were conducted finding a distinct correlation between the –OCH_3 (δ 4.00) and H-3 (δ 7.43); and between H-8 (δ 7.41) and H-9 (δ 8.89) (Fig. 3).

For aldehyde **5**, the structural assignments of the proton and carbon chemical shifts could also be made with the help of 2D-HMQC NMR. The correlations between

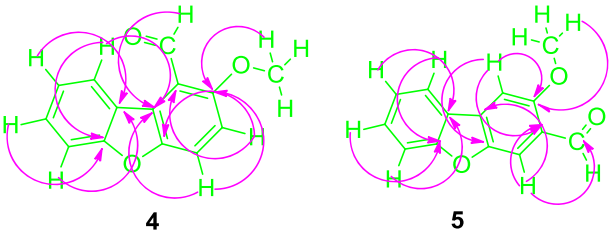


Fig. 2 Diagnostic correlations observed from the 2D-HMQC NMR experiments on compounds **4** and **5** in DMSO-d_6

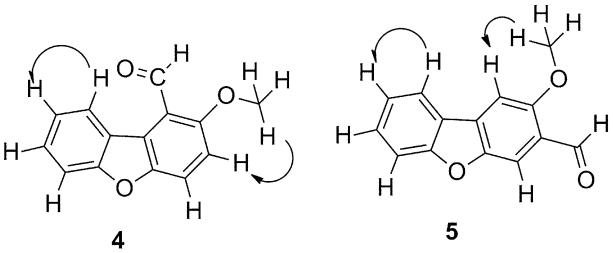


Fig. 3 Observed ^{1}H–^{1}H NOESY correlations for compounds **4** and **5**

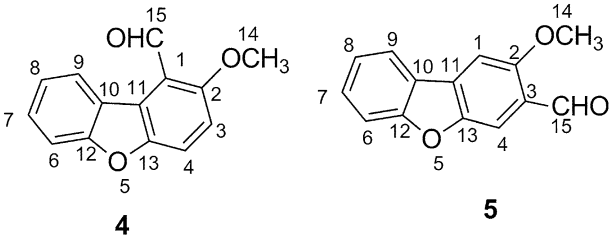
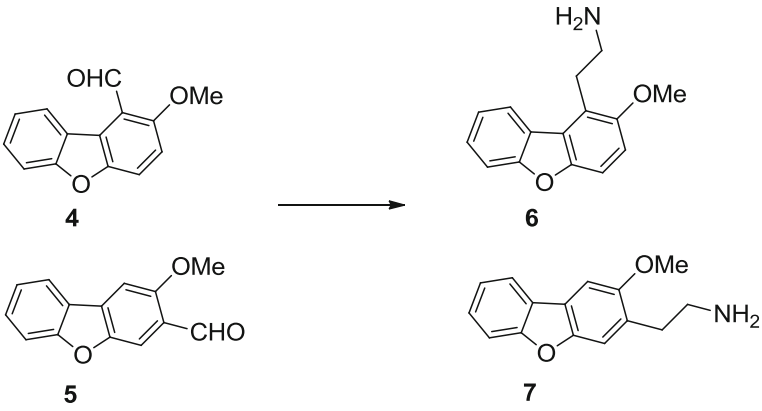


Fig. 4 Atom numbering for aldehydes **4** and **5**

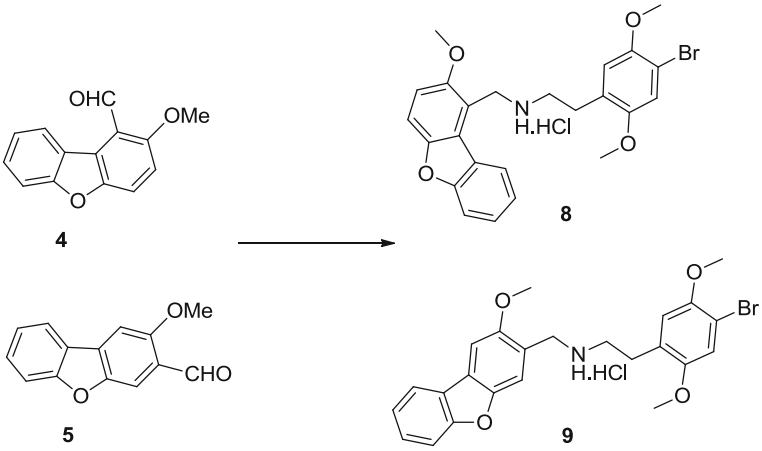
$-OCH_3$ (δ 4.03) and C-2 (δ 158.0); –CHO (δ10.42) and C-1 (δ 109.5); H-1 (δ 7.98) and C-2 (δ 158.0), C-3 (δ 130.2), C-13 (δ 149.2); H-4 (δ 7.87) and C-3 (δ 130.2), C-11 (δ 123.3), C-15 (δ 188.7); H-6 (δ 7.69) and C-10 (δ 122.9); H-7 (δ 7.60) and C-12 (δ 157.3); H-8 (δ 7.43) and C-10 (δ 122.9); H-9 (δ 8.23) and C-12 (δ 157.3), respectively, were observed for compound **5** (Fig. 1) in the HMQC experiment. Furthermore, a good correlation between $-OCH_3$ (δ 4.03) and H-1 (δ 7.98); H-8 (δ 7.43) and H-9 (δ 8.23) was found for compound **5** in the 2D-NOESY experiment (Fig. 3).

With the help of the above experimental observations, the complete NMR assignments for aldehydes **4** and **5** are presented in Tables 1 (^{1}H NMR) and 2 (^{13}C NMR) according to the numbering shown in Fig. 4.

In view of the potential importance of dibenzofuran derivatives in medicinal chemistry applications, the following dibenzofuran embedded β-phenethylamines [19–21] **6** and **7** were synthesized for the first time according to Scheme 3.



Scheme 3 Synthesis of dibenzofuran β-phenylethylamines **6** and **7**



Scheme 4 Synthesis of novel dibenzofuran NBOMe derivatives **8** and **9**

These dibenzofuran aldehydes were also utilized in synthesizing novel NBOMe analogues **8** and **9** (Scheme 4) by reaction with 2-(4-bromo-2,5-dimethoxyphenyl) ethaneamine, an important core unit in serotonin receptor ligands [22, 23].

Conclusions

In conclusion, an efficient protocol for the synthesis of the isomeric 2-methoxydibenzo[*b,d*]furan-1-carbaldehyde (**4**) and 2-methoxydibenzo[*b,d*]furan-3-carbaldehyde (**5**) is described for the first time. These aldehydes were synthesized in good combined yield (95 %) and in a 35:65 (**4**:**5**) ratio starting from 2-methoxydibenzo[*b,d*]furan (**3**) using α,α-dichloromethyl methyl ether and tin(IV) chloride. The structures of these aldehydes were assigned unambiguously by ^{1}H and ^{13}C

NMR spectrometry including 2D-NOESY, 2D-HSQC, and HMQC experiments. It may be noted that the spectra recorded in $CDCl_3$ could not be completely interpreted, but this could be done after re-recording them in DMSO-d_6. These findings should be very helpful in ongoing research where the 2-methoxydibenzofuran aldehydes are being used as precursors in the synthesis of derivatives for pharmacological studies. The structure confirmation and biological evaluations of newly synthesized derivatives **6–9** and some analogues are in progress.

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