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Short communication

Synthesis and biological activity of new derivatives of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid

Bożena Modzelewska-Banachiewicz [a,*,b], Jacek Banachiewicz [b], Anna Chodkowska [c], Ewa Jagiełło-Wójtowicz [c], Liliana Mazur [d]

[a] Department of Organic Chemistry, Medical University, Jagiellońska 13, 85-067 Bydgoszcz, Poland
[b] Department of Organic Chemistry, The Feliks Skubiszewski Medical University, Staszica 6, 20-081 Lublin, Poland
[c] Department of Toxicology, the Feliks Skubiszewski Medical University, Chodźki 8, 20-093 Lublin, Poland
[d] Department of Chemistry, Maria Curie-Skłodowska University, 20-031 Lublin, Poland

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Abstract

New 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid derivatives (8–14) were synthesized by condensation of N^3-substituted amidrazones (1–7) with maleic anhydride. Molecular structure of obtained compounds was confirmed by an elemental analysis, IR and ^{1}H NMR spectra, and the X-ray crystallography for compound 11. The influence of the compound 9 on the central nervous system (CNS) of mice in some behavioural test was examined. The investigated compound showed anticonvulsive activity and potent antinociceptive action.

Keywords: CNS activity; 3,4-Diaryl-1,2,4-triazoles; Propenoic acid derivatives

1. Introduction

1,2,4-Triazole derivatives are known in the scientific literature for their wide pharmacological activity. Two main types of their activity are antiviral, antibacterial and antifungal activities, and central nervous system (CNS) activity. First type of activity is exhibited by e.g. Fluotrimazol, Ribavirine, Furazonal while the second type of activity is presented by e.g. Estazolam [1,2], Alprazolam [3] and Rizatriptane [4].

In this paper, we present synthesis and biological activity assessment for 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid derivatives **(8–14)** (Table 1). They were synthesized from N^3-substituted amidrazones [5] in condensation reaction with maleic acid anhydride.

Some behavioural tests (chimney test, pentobarbital-induced sleep, body temperature, "writhing syndrome" test, pentetrazole-induced seizures) were also performed to check the influence of the compound **9** on the CNS of mice.

2. Chemical part

Condensation of N^3-substituted amidrazones **(1–7)** [6] with maleic acid anhydride was carried out in ambient temperature. Substrates were solved in anhydrous ethyl ether prior to mixing them together in molar ratio 1:1 (Scheme 1).

Basing on the results of the elemental analysis and the spectral analysis (IR, H NMR) as well as the X-ray crystallography, it was revealed that reaction leads to formation of cyclic 5-membered ring system by instantaneous reaction on N_2 nitrogen atom of the hydrazino moiety and N_3 nitrogen atom of the amido moiety of amidrazone. Respective derivatives of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid **(8–14)** were obtained.

In the IR spectra of cyclic compounds, characteristic absorption bands of carbonyl group were present in the range 1700–1708 cm^{-1}.

In the ^{1}H NMR spectra, signals of the vinyl type hydrogens are observed at the 6.2–6.5 ppm. The carboxylic group hydrogens were observed as broad singlets in the range 13.5–13.8 ppm. Only for compound **12**, containing two pyridyl rings, the carbonyl group hydrogen signal was moved downfield to 15.5 ppm.

* Corresponding author.
E-mail address: modzel@panaceum.am.lublin.pl (B. Modzelewska-Banachiewicz).

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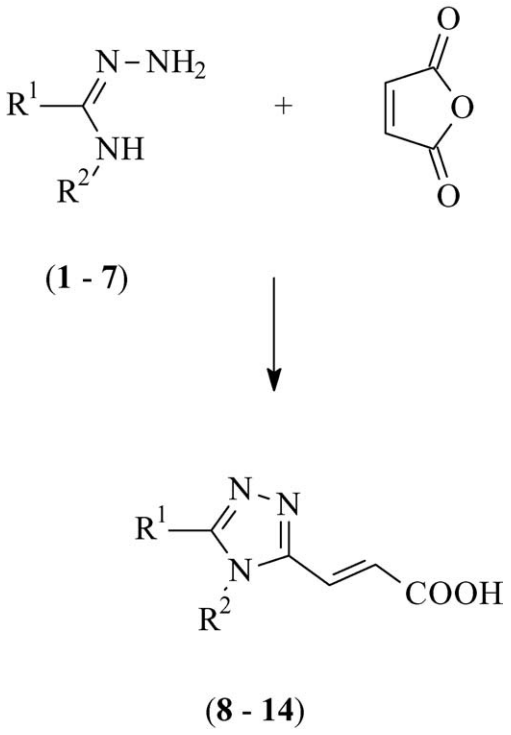
Table 1
Physicochemical properties of compounds **8–14**

Compound	R^1	R^2	Formula (m.w.)	M.p. (°C)	Yield (%)	IR (cm^{-1})	^1H NMR (ppm, TMS)
8	C_6H_5	C_6H_5	$C_{17}H_{13}N_3O_2$	234–6	72	3058 arom.; 1704 C=O	13.9 (s, 1H, COOH), 7.3–7.6 (m, 10H, ar), 6.3
			(291.2)			1618 C=N	(d, 1H, C1=), 6.2 (d, 1H, C2=)
9	2-C_5H_4N	C_6H_5	$C_{16}H_{12}N_4O_2$	224–6	70	3054 arom.; 1704 C=O	13.6 (s, 1H, COOH), 7.3–8.3 (m, 9H, ar), 6.4
			(292.1)			1616 C=N	(d, 1H, C1=), 6.3 (d, 1H, C2=)
10	2-C_5H_4N	4-$CH_3C_6H_4$	$C_{17}H_{14}N_4O_2$	184–6	70	3061 arom.; 1708 C=O	13.9 (s, 1H, COOH), 7.2–8.3 (m, 8H, ar), 6.4
			(316.1)			1640 C=N	(d, 1H, C1=), 6.3 (d, 1H, C2=), 2.3 (s, 3H, CH_3)
11	2-C_5H_4N	4-$NO_2C_6H_4$	$C_{16}H_{11}N_5O_4$	204–6	50	3060 arom.; 1700 C=O	13.7 (s, 1H, COOH), 6.9–7.9 (m, 8H, ar), 6.6
			(337.2)			1640 C=N	(d, 1H, C1=), 6.4 (d, 1H, C2=)
12	2-C_5H_4N	2-C_5H_4N	$C_{15}H_{13}N_5O_2$	155–7	50	3060 arom.; 1702 C=O	15.5 (s, 1H, COOH), 6.9–7.9 (m, 10H, ar), 6.5
			(295.1)			1612 C=N	(d, 1H, C1=), 6.3 (d, 1H, C2=)
13	4-C_5H_4N	C_6H_5	$C_{16}H_{12}N_4O_2$	210–2	60	3042 arom.; 1705 C=O	13.8 (s, 1H, COOH), 6.9–7.9 (m, 9H, ar), 6.4
			(292.1)			1618 C=N	(d, 1H, C1=), 6.2 (d, 1H, C2=)
14	4-C_5H_4N	4-$CH_3C_6H_4$	$C_{17}H_{14}N_4O_2$	182–4	70	3068 arom.; 1700 C=O	13.5 (s, 1H, COOH), 7.1–8.1 (m, 8H, ar), 6.4
			(316.1)			1612 C=N	(d, 1H, C1=), 6.2 (d, 1H, C2=), 2.4 (s, 3H, CH_3)



Scheme 1.

The molecular structure of the cyclization products of 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid derivatives **(8–14)** was confirmed by the X-ray crystal analysis of **11**. Numbering scheme and general view of the molecule **11** are shown in Fig. 1. Characteristic feature is formation of strong linear intramolecular O1–H1...N1 hydrogen bond (with the O...N distance of 2.64 Å and the angle O–H...N of 172°) which closes planar seven-membered ring. As a result, the acrylic part is nearly coplanar with the triazole and 2-pyridine systems. Bond distances observed in the 1,2,4-triazole ring are typical for this heterocyclic system.

3. Pharmacological investigations

The effect of the investigated compound **9** in behavioural studies was carried out on male Albino Swiss mice.

4. Results and discussion

4.1. Pharmacological tests

The behavioral study showed that the compound **9** in doses of 50 and 100 mg/kg i.p. exerts a week depressive action on CNS of mice. This compound in the above doses did not influence performance of mice in the chimney test. Compound **9** in a dose of 100 mg/kg i.p. did not change the body temperature of normothermic mice during 120 min observation.

Compound **9** at doses 50 and 100 mg/kg i.p. prolonged the sleep induced by pentobarbital by 112.6% ($P < 0.001$) and 140% ($P < 0.001$), respectively (Table 2). Moreover, compound **9** (50 and 100 mg/kg i.p.) produced a significant anticonvulsant activity in the pentetrazole-induced seizures (Table 3). It significantly decreased the incidence of tonic seizures and the lethality at both doses. The investigated compound in doses of 50 and 100 mg/kg i.p. showed potent antinociceptive properties (Table 4). These doses produced a

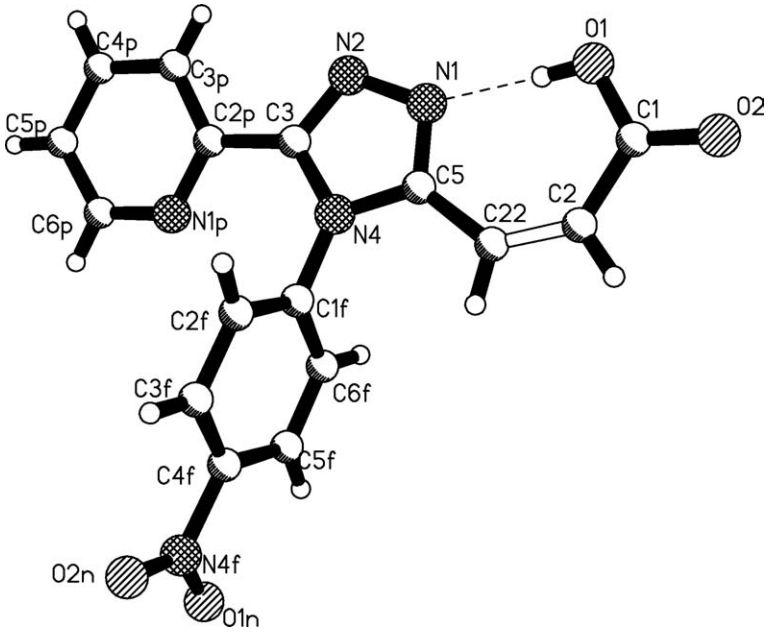


Fig. 1. Molecular structure and atom numbering scheme for **11**.

Table 2
The influence of the compound **9** on pentobarbital-induced sleep ($N = 10$)

Compound	Treatment (mg/kg) i.p.	Sleeping time	
		Min ± SEM	(%)
Control	–	19.4 ± 5.5	100.0 ± 28.4
9	25.0	16.0 ± 7.7	82.5 ± 39.7
	50.0	41.3 ± 12.2 *	212.6 ± 62.9 *
	100.0	46.6 ± 18.2 *	240.0 ± 93.8 *

* $P < 0.001$ vs. the control group.

Table 3
The influence of the investigated compound on pentetrazole-induced convulsions in mice ($N = 10$)

Compound	Treatment (mg/kg) i.p.	Tonic seizure (%)	Lethality (%)
Control	–	80	80
9	25.0	80	70
	50.0	40 *	40 *
	100.0	20 *	20 *

* $P < 0.05$ vs. the control group.

Table 4
Antinociceptive activity of **9** in the "writhing syndrome" test in mice ($N = 10$)

Compound	Treatment (mg/kg) i.p.	Mean writhing number	Inhibition (%)
Control	–	15.6 ± 2.5	0
9	25.0	11.5 ± 2.1	24.0
	50.0	7.9 ± 1.3 *	55.0 *
	100.0	4.0 ± 1.1 *	70.0 *

% of inhibition obtained by comparison with control groups.
* $P < 0.001$ vs. the control group.

decrease (by 55% and 70%, respectively) in a number of animals exhibiting pain reactivity in the "writhing syndrome" test.

In conclusion, we have demonstrated that investigated compound has antinociceptive and anticonvulsive properties, which deserve further investigations of the action in rodents.

5. Experimental protocols

5.1. Chemical analysis

Melting points were measured on Boetius apparatus and are given uncorrected. ^{1}H NMR spectra were recorded on Tesla BS 567A (100 MHz) apparatus in D_6-DMSO with

TMS as an external standard. IR spectra were recorded on Specord IR-75 spectrometer. Results of elemental analysis for C, H, N by method of microanalysis performed in Department of Organic Chemistry, Medical University Lublin were in acceptable accordance with calculated values (±0.7% for C, 0.75% for N and 0.9% for H).

The purity of the obtained compounds was examined by TLC method. Chromatography was performed on 10 × 10 cm TLC plates precoated with silica gel RP-18 F_{254} and silica gel Si 60 F_{254} (E. Merck, Darmstadt, Germany). Mobile phase for normal system was prepared from mixtures of acetone, toluene and acetic acid (8:2:1) and for reversed phase system from methanol. Water and formic acid (5:5:0.5). Compounds were dissolved in methanol (5 mg ml^{-1}) and 10 μl samples of these solutions were spotted on the plates. After development in horizontal Teflon DS chambers (Chromdes, Lublin, Poland) and drying, the spots were visualized under UV light at $\lambda = 254$ nm.

5.1.1. Synthesis (general procedure)

A 0.1 mol of the maleic acid anhydride in 20 ml of anhydrous ethyl ether was added to the solution of 0.1 mol of amidrazone **(1–7)** in 40 ml of anhydrous ethyl ether. Mixture was left in the room temperature for 48 h. Precipitation was collected and purified by crystallization from the water-:methanol (1:1) mixture. The yields and physical and spectral data of compounds **(8–14)** are given in Table 1.

5.1.2. X-ray crystallography

Crystal data for **11**: space group $P2_1/c$, $a = 15.446(3)$ Å, $b = 9.027(2)$ Å, $c = 12.687(3)$ Å, $\beta = 97.28(3)°$, $V = 1754.6(7)$ $Å^3$, $Z = 4$, $d_{calc} = 1.277$ g cm^{-3}, $\mu = 0.804$ mm^{-1}.

X-ray diffraction data were measured on a KM4 diffractometer using variable scan speed ($\omega - 2\theta$ scan mode) and graphite-monochromatized CuK_α radiation ($\lambda = 1.54178$ Å). Reflections were collected up to $\theta_{max} = 79.93°$; 3272 reflections were measured. Crystal structure was solved by direct methods using the SHELXS97 [6] program and refined by the full-matrix least squares on F^2 using the SHELXL97 [7]. Non-hydrogen atoms were refined with anisotropic displacement parameters. H-atom positions were located from the geometry, and isotropic factors of 1.2 U_{eq} of the bonded C/O-atoms were given, the 'riding' model was used in the refinement. Final discrepancy factors are $R_1 = 0.0324$, $wR_2 = 0.1517$ for $I > 2\sigma(I)$.

5.2. Pharmacology

5.2.1. Behavioural experiments

The study was conducted on Albino Swiss male mice weighing 20–23 g purchased from a licensed dealer, Górzkowska, Warsaw, Poland. The animals were housed in colony cages with free access to tap water and food (standard laboratory pellets, Bacutil, Motycz, Poland) and maintained under 12/12 h light–dark cycle (light on from 7 a.m. to 7 p.m.). Experimental and control groups consisting of 10 animals each were selected by means of a randomized schedule. The experiments were performed between 8 a.m. and 3 p.m. The investigated compound **9** was administered intraperitoneally (i.p.) in doses of 25, 50 and 100 mg/kg as suspensions in a 3% Tween 80 in the constant volume of 10 ml/kg. Control animals received the equivalent volume of solvent.

*5.2.2. The influence of compound **9** on the motor impairment in mice*

Chimney test. The effect of compound **9** on motor impairment was quantified with the chimney test [8]. Briefly, mice had to climb up backwards in a plastic tube (3 cm in inner diameter, 25 cm long). Mice unable to perform the task within 60 s were considered to display motor impairment. Motor impairment was quantified as the percentage of animals that failed to complete the test.

*5.2.3. The influence of the tested compound **9** on the body temperature*

The rectal body temperature in mice (measured with an Ellab thermometer) was recorded 15, 30, 45, 60, 90 and 120 min after the administration of compound **9** in a dose 100 mg/kg i.p.

*5.2.4. The influence of the investigated compound **9** on pentobarbital-induced sleep*

Pentobarbital, at a dose of 100 mg/kg i.p., was given 30 min after administration of the tested compound in doses of 50 and 100 mg/kg i.p. The period during which the animals lost righting reflex was regarded as a sleeping time.

*5.2.5. Pain reactivity in the "writhing syndrome test" in mice for compound **9***

Pain reactivity was measured in mice by the "writhing syndrome" test of Witkin et al. [9]. Thirty minutes after the administration of compound **9** in doses of 25, 50 and 100 mg/kg i.p., the animals were injected with 0.6% acetic acid i.p. and the number of writhing episodes was counted for 30 min.

*5.2.6. The influence of the investigated compound **9** on pentetrazole-induced convulsions*

Pentetrazole, at a dose of 100 mg/kg s.c., was injected 30 min after the administration of the compound **9** in doses of 25, 50 and 100 mg/kg i.p. This dose produced the tonic convulsions in 80% and mortality in 80% of non-pretreated mice. The observation (during 30 min) of individual animals to note occurrence of tonic convulsions as well as mortality of mice started immediately after the injection of pentetrazole.

5.2.7. Statistical analysis

Student's *t*-test (for analyzing the data from the Tables 2 and 4) or *Fisher's two-tailed exact probability test* (for analyzing the data from the Table 3) were used to determine

the significance of differences between mean values of the control and investigated groups. Differences were considered significant when $P < 0.05$.

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