Acta Poloniae Pharmaceutica – Drug Research, Vol. 57 No. 2 pp. 119–122, 2000

ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

A STUDY ON SOME 4,5–DIHYDRO–1*H*–1,2,4–TRIAZOL–5–ONE DERIVATIVES

BAHİTTİN KAHVECİ and AYKUT A. İKİZLER*

Department of Chemistry, Karadeniz Technical University, 61080 – Trabzon, Turkey

Abstract: Fourteen new potentially biologically active 4,5–dihydro–1*H*–1,2,4–triazol–5–one derivatives were synthesized and characterized by elemental analysis, 1H NMR, IR and UV spectra. Three of these compounds were screened for their antitumor activities.

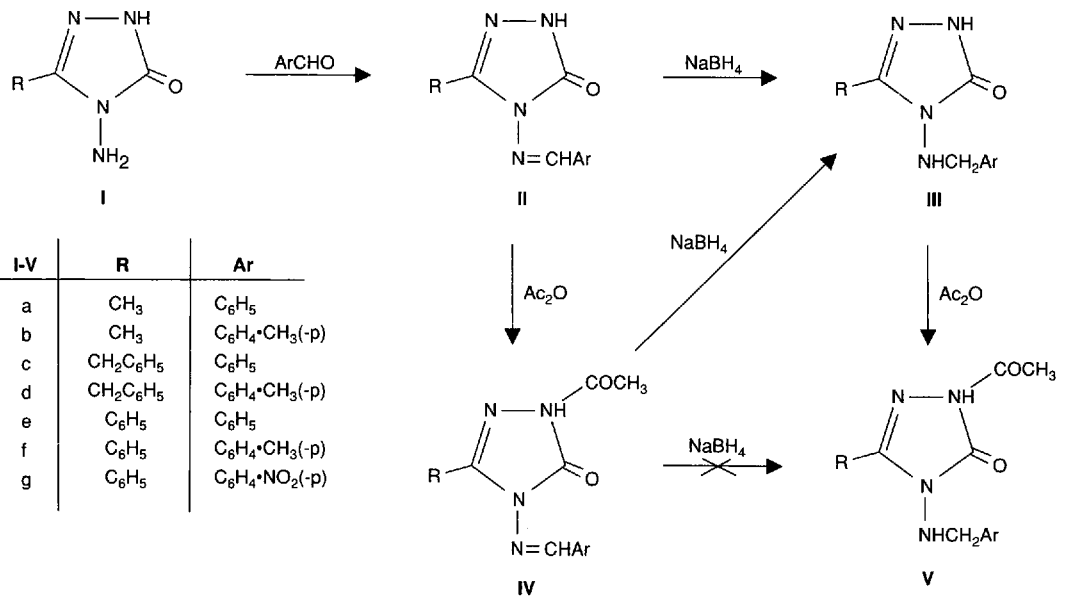
Keywords: 4,5–Dihydro–1*H*–1,2,4–triazol–5–ones, synthesis, antitumor activity.

Several methods have recently been developed for the synthesis of 3–alkyl–4–amino–4,5–dihydro–1*H*–1,2,4–triazol–5–ones **I** (1–6). Furthermore, the reaction of compounds **I** with aldehydes leading to the formation of 3–alkyl–4–arylidenamino–4,5–dihydro–1,2,4–triazol–5–ones **II** has also been reported (1–3, 6–8). In the present study, six new 3–alkyl–4–(alkyl–amino)–4,5–dihydro–1*H*–1,2,4–triazol–5–ones of the type **III** were obtained by the reduction of compounds **II** with $NaBH_4$ as a reducing agent. Moreover, seven new 1–acetyl–3–alkyl–4–(arylideneamino)–4,5–dihydro–1*H*–1,2,4–triazol –5–ones **IV** were synthesized by the reaction of compounds **II** with acetic anhydride. Instead of the expected compounds **V**, the treatment of compounds **IV** with $NaBH_4$ resulted in the formation of compounds **III**. However, compound **Vf** could be synthesized by acetylation of **IIIf** with acetic anhydride. In addition, compounds **IIIe**, **IIIf**, and **IVg** were tested for their in vitro antitumor activities (Scheme 1).

EXPERIMENTAL

Synthesis

Melting points were determined on a Büci oil heated melting point apparatus and are uncorrected. Experimental data for new compounds **III**, **IV** and **V** are given in Table 1. ^{1}H NMR spectra (δ, ppm) were run on a Varian 200A or a Varian 60A



I-V	R	Ar
a	CH_3	C_6H_5
b	CH_3	C_6H_4•CH_3(-p)
c	$CH_2C_6H_5$	C_6H_5
d	$CH_2C_6H_5$	C_6H_4•CH_3(-p)
e	C_6H_5	C_6H_5
f	C_6H_5	C_6H_4•CH_3(-p)
g	C_6H_5	C_6H_4•NO_2(-p)

Scheme 1.

Table 1. Experimental data for new compounds

Compound	Yield (%)	M.p. (°C) Crystallized from	Formula (M.W.)	Calculated/Found %C	%H	%N
IIIa	58[a]	172–173	$C_{10}H_{12}N_4O$	58.81	5.92	27.44
	53[b]	water	(204.2)	58.83	6.17	27.90
IIIb	55[a]	176–177	$C_{11}H_{14}N_4O$	60.53	6.47	25.67
	51[b]	water	(218.3)	60.56	6.86	25.98
IIIc	41[a]	179–180	$C_{16}H_{16}N_4O$	68.55	5.75	19.99
	40[b]	ethyl acetate	(280.3)	68.30	5.88	19.77
IIId	54[a]	167–168	$C_{17}H_{18}N_4O$	69.37	6.16	19.04
	51[b]	ethyl acetate	(294.4)	68.94	6.42	18.67
IIIe	50[a]	186–187	$C_{15}H_{14}N_4O$	67.65	5.30	21.04
	48[b]	ethyl acetate	(266.3)	67.26	5.43	20.97
IIIf	54[a]	158–160	$C_{16}H_{16}N_4O$	68.55	5.75	19.99
	49[b]	ethyle acetate	(280.3)	68.64	5.67	19.88
IVa	88	148–149	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94
		ethanol	(244.3)	58.90	5.05	22.90
IVb	91	147–148	$C_{13}H_{14}N_4O_2$	60.45	5.46	21.70
		ethanol	(258.3)	60.52	5.60	22.10
IVc	91	175–176	$C_{18}H_{16}N_4O_2$	67.48	5.03	17.49
		ethanol	(320.3)	67.14	5.43	17.71
IVd	93	156–157	$C_{19}H_{18}N_4O_2$	68.24	5.42	16.76
		ethanol	(334.4)	68.49	5.66	16.85
IVe	92	126–127	$C_{17}H_{14}N_4O_2$	66.65	4.61	18.29
		ethanol	(306.3)	66.72	4.87	18.54
IVf	94	149–150	$C_{18}H_{16}N_4O_2$	67.48	5.03	17.49
		ethanol	(320.3)	67.84	5.41	17.84
IVg	89	200–201	$C_{17}H_{13}N_5O_3$	60.89	3.91	20.89
		ethanol	(335.3)	60.58	4.02	21.12
Vf	48	137–138	$C_{18}H_{18}N_4O_2$	67.06	5.63	17.38
		ethanol/water (1:3)	(322.4)	67.35	5.85	17.07

[a] Starting from the corresponding compound **II**.
[b] Starting from the corresponding compound **IV**

spectrometer using tetramethylsilane as the internal reference (Table 2). IR spectra (ν, cm^{-1}) were recorded on a Perkin–Elmer 1600 FTIR or a Perkin–Elmer 377 spectrophotometer in KBr discs (Table 3). The UV absorption measurements were carried out in 1.10^{-5}–1.10^{-4} ethanolic solutions and the spectra were measured between 200 and 400 nm with a Shimadzu–1201 spectrophotometer using 10 mm quartz cells (Table 3). Combustion analyses were performed on a Carlo Erba 1106 elemental analyzer. The necessary chemicals were obtained from Fluka and Merck. The starting compounds **I** and **II** were prepared by the methods reported earlier (2, 6, 7).

General method for the synthesis of compounds III:

The corresponding compound **II** or **IV** (0.01 mole) was dissolved in 40 ml of dry diglyme with slowly heating. A solution of $NaBH_4$ (0.03 mole) in 30 ml of diglyme was added and the mixture was refluxed for 8 hours and then allowed to cool. A sufficient amount of water was added to the solution and the mixture was allowed to stand overnight at 0–5°C. The precipitate formed was filtered and washed with cold water. After drying in vacuo, the product was recrystallized from an appropriate solvent to give pure compound **III**.

Table 2. ^{1}H NMR data of new compounds (δ/ppm in DMSO-d_6)[a]

Compd.	CH_3	CH_2	CH	NNH	NH	Ar-H
IIIa	1.82(s)	4.10(d)	–	5.28(t)	10.60(s)	7.25–7.40(m,5H)
IIIb	1.70(s,3H)	4.10(d)	–	6.20(t)	11.10(s)	7.00–7.25(m,4H)
	2.30(s,3H)					
IIIc	–	3.48(s,2H)	–	6.36(t)	11.28(s)	6.80–7.40(m,10H)
		4.00(d,2H)				
IIId	2.38(s)	3.40(s,2H)	–	6.24(t)	11.20(s)	6.80–7.30(m,9H)
		3.90(d,2H)				
IIIe	–	4.15(d)	–	6.44(t)	11.38(s)	7.10–7.80(m,10H)
IIIf	2.36(s)	4.20(d)	–	6.48(t)	11.40(s)	6.80–800(m,9H)
IVa	2.26(s,3H)	–	9.52(s)	–	–	7.50–7.70(m,5H)
	2.40(s,3H)					
IVb	2.04(s,3H)	–	9.40(s)	–	–	7.20–7.60(m,4H)
	2.15(s,3H)					
	2.40(s,3H)					
IVc	2.44(s)	4.00(s)	9.40(s)	–	–	7.00–7.60(m,10H)
IVd	2.32(s,3H)	4.05(s)	9.40(s)	–	–	7.00–7.70(m,9H)
	2.44(s,3H)					
IVe	2.54(s)	–	9.50(s)	–	–	7.20–7.80(m,10H)
IVf	2.20(s,3H)	–	9.40(s)	–	–	7.05–7.90(m,9H)
	2.44(s,3H)					
IVg	2.50(s)	–	9.60(s)	–	–	7.20–8.40(m,9H)
Vf	2.20(s,3H)	4.00(d)	–	6.48(t)	–	7.10–8.00(m,9H)
	2.48(s,3H)					

a) $CDCl_3$for compound **IIIa.**

Table 3. IR data (KBr/cm^{-1}) and UV data of new compounds

Compd.	ν_{NH}	$\nu_{C=O}$	$\nu_{C=N}$	ν subst. benzonoid ring	λ_{max}, nm(εx10^{-3}) (in ethanol)
IIIa	3240, 3100	1690	1600	745, 690	207 (9.6)
IIIb	3208, 3045	1695	1595	805	211 (7.7)
IIIc	3260, 3090	1700	1580	710, 690	207 (13.3), 258 (0.4)
IIId	3280, 3090	1700	1590	820, 690, 650	210 (17.3), 261 (0.8)
IIIe	3250, 3060	1715	1545	755, 700, 680, 660	211 (22.1), 256 (13.8)
IIIf	3290, 3100	1710	1560	810, 740, 680	211 (17.3), 257 (9.8)
IVa	–	1705	1630, 1560	740, 690	252 (13.0)
IVb	–	1700	1620, 1550	825	257 (27.7)
IVc	–	1730	1615, 1565	760, 725, 705, 695	273 (23.0)
IVd	–	1730	1620, 1550	830, 750, 710	249 (27.7)
IVe	–	1715	1605, 1550	755, 725, 690, 670	246 (27.1)
IVf	–	1715	1605, 1555	820, 730, 690	264 (27.1)
IVg	–	1720	1560, 1520	825, 730, 688	–
Vf	3300	1718	1590	820, 740, 693	266 (6.7), 374 (4.3)

General method for the synthesis of compounds IV:

The corresponding compound **II** (0.01 mole) was treated with 10 ml of acetic anhydride and the mixture was refluxed for 30 minutes. After addition of 40 ml of absolute ethanol to the cooled solution, the mixture was refluxed for one hour. Evaporation of the resulting solution at 30–35°C and several recrystallizations of the residue from an appropriate solvent afforded pure comound **IV**.

Synthesis of compound Vf:

Compound **IIIf** (0.01 mole) was dissolved in 200 ml of xylene with gently heating. After addition of acetic anhydride (0.011 mole) to the solution, the mixture was refluxed for 3 hours and then was allowed to stand overnight at 0–5°C. The precipitate formed was filtered and dried in vacuo. Several recrystallization of this product from (1:3) ethano–water gave pure compound **III**.

Pharmacology

The antitumor screening experiments were performed by the Developmental Therapeutics Program of the National Cancer Institute, Bethesda, Maryland, U.S.A. Compound **IVg** was tested for its in vitro antitumor activity against a panel of approximately 60 cell lines derived from human solid tumors (lung, colon, melanoma, renal, ovarian, CNS, prostate, leukemia and breast). Compounds **IIIe** and **IIIf** were only screened for the 3 cell lines (lung: NCI–H460; breast: MCF7 and CNS: SF–268). Compounds **IIIe** and **IIIf** were evaluated as inactive. But compound **IVg** showed weak cytostatic activity against some of the 60 cell lines (lung: EKVX, HOR–92, NCI–H322 M and NCI–H522; CNC: SF–268; ovarian: OVCAR–4 and SKOV–3; breast: MDA–MB–231/ATCC).

RESULTS AND DISCUSSION

Ample research has been devoted to the synthesis and pharmacological investigation of certain 1,2,4–triazole and 4,5–dihydro–1*H*–1,2,4–triazol–5–one derivatives (6, 9). Thus, compounds of type **II** have been described as a new class of antitumor agent (Scheme 1) (6). In this connection, 14 new potentially biologically active compounds were synthesized in the present study starting from compounds **II**. The 1–acetyl derivatives of **II** (compounds **IV**) were prepared in good yields by using acetic anhydride as an acylating agent. In *in vivo* biological studies, compounds **IV** are predicted to be more soluble than compounds **II**. The treatment of compounds **IV** with $NaBH_4$ led to the formation of compounds **III** via the rupture of the acetyl group. However, the reduction of compounds **II** with $NaBH_4$ can be considered a general and convenient method for the synthesis of type **III** 4–alkylamino compounds.

The higher antitumoral activity of compound **IIg** has recently been reported (6). But, an important decrease in this activity was observed in the case of the corresponding acetyl derivative of type **IV** (compound **IVg**). The weak cytostatic activities of compounds **IIa**, **IIc**, **IId** and **II** have also been reported (6). In contrast, the reduction compounds **IIIe** and **IIIf** showes no cytostatic activity.

REFERENCES

1. Kröger C.F., Hummel L., Mutcher M., Beyer H.: Chem. Ber. 98, 3025 (1965).
2. İkizler A.A., Ün R.: Chim. Acta Turc. 7, 269 (1979).
3. Milcent R., Redeuilh C.: J. Heterocycl. Chem. 16, 403 (1979).
4. İkizler A.A., İkizler A., Yüksek H., Bahçeci Ş., Sancak K.: Tr. J. Chem. 18, 51 (1994).
5. İkizler A., Demirbaş N., Demirbaş A., İkizler A.A.: Polish J. Chem. 70, 1114 (1996).
6. İkizler A.A., İkizler A., Serdar M., Yıldırım N.: Acta Polon. Pharm. – Drug Research 54, 363 (1997).
7. İkizler A.A., İkizler A., Yıldırım N.: Monatsh. Chem. 122, 557 (1991).
8. İkizler A.A., Uçar F., Yüksek H., Aytin A., Yaşa İ., Gezer T.: Acta Polon. Pharm. – Drug Research 54, 135 (1997).
9. İkizler A.A., Demirbaş A., Johansson C.B., Çelik C., Serdar M., Yüksek H.: Acta Polon. Pharm. – Drug Research 55, 117 (1998).

Received: 20.10.1999