College of Science, Department of Chemistry,[1] University of Al al-Bayt, Al-Mafraq, Jordan and Fakultät für Chemie[2], Universität Konstanz, Germany

Synthesis and antitumor activity of some new phthalimide analogues

Y. A. AL-SOUD[1] and N. A. AL-MASOUDI[2]

The reactive intermediate 1-(chloroalkyl)-1-aza-2-azoniaallene salts **3**, which were parepared by treatment of the α,α′-dichloroazo derivatives **2** with $SbCl_5$, underwent cycloaddition with the *N*-cyanoalkyl phthalimide compounds **4** and afforded the 1,2,4-triazolium salts **5**. These salts rearranged spontaneously to the protonated 1,2,4-triazoles **6**, followed by hydrolysis in situ to the 1,2,4-triazolo-alkyl-phthalimide compounds **7.** The newly synthesized compounds were then evaluated for their antitumor activity in three cell lines.

1. Introduction

Tumor necrosis factor alpha (TNF-α) is an important cytokine secreted by activated monocytes/macrophages and possesses favorable biological activities including direct tumor toxicity [1, 2], stimulation of the host immune system [2], and B-cell growth stimulation [3]. The unfavourable effects of TNF-α include induction of endotoxic shock that causes hemorragic necrosis of transplanted solid tumors[1], tissue inflammation [4], tumor-promoting action as well as stimulation of tumor metastasis, angiogenesis [5, 6] and stimulation of HIV replication [7].

Thalidomide [*N*-(α)-phthalimidoglutarimide] was introduced as a sedative drug but was removed from the market because of its teratogenicity [8, 9]. Recently, thalidomide proved its activity as potential inhibitor of TNF-α production [7, 10] and this immunosuppressive property led to its use in the treatment of graft-versus-host disease (GVHD), leprosy, AIDS, Behcet's disease, lupus erythematosus, malaria, and other related diseases [7, 11–15]. Recently, a new pharmacologically interesting compound within the series of phthalimides, NAN-190, is reported as a well recognized antagonist of postynaptic receptors 5-HT_{1A} [16]. On the basis of these findings, many laboratories are engaged in synthesis of various phthalimide derivatives and analogues such as *N*-substituted phthalimide with *n*-butyl, *ter*-butyl, hexyl and admantyl groups [17], and *N*-substituted phthalimides (2-substituted-1*H*-isoindole-1,3-diones) [8, 18–21]. We synthesized a series of new 1,2,4-triazolo-alkyl-phthalimides as potential antitumor agents *via* the cycloaddition of the *N*-alkylcyano derivatives of phthalimide with different reactive cumulenes.

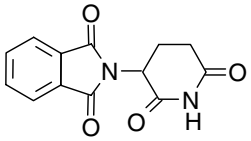
2. Investigations, results and discussion

2.1. Chemistry

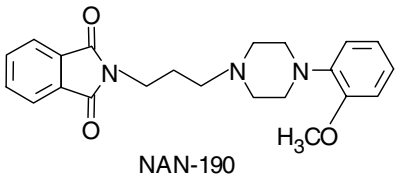
The 1-(chloroalkyl)-1-aza-2-azoniaallene cations **3** have recently been used in the preparation of 4,5-dihydropyrazonium salts [23] by reaction with various electron-rich alkenes in the presence of $SbCl_5$. These cations have been used in the synthesis of different 1,2,4-triazoles of C-nucleosides [24, 25], acyclic C-nucleosides and homo-C-analogues [26], C-nucleosides carrying acyclic sugar residues [27], and thymine derivatives [26] as compounds with potential biological activity. Jochims et al. [23] explained the formation of 1-aza-2-azoniallene hexachloroantimonates, as reactive intermediates in such a cycloaddition reaction, from the cations **3**. The cyanoalkyl phthalimide derivatives have been selected in this study as precursors of the target molecules. Thus, chlorination of **1** gave the dichlorides **2**. Treatment of **2** with $SbCl_5$ at −60 °C afforded the intermediates **3** which were reacted in situ, via cycloaddition, with *N*-(cyanomethyl)phthalimide **4a** [28, 29], *N*-(2-cyanoethyl)phthalimide **4b** and *N*-(3-cyanopropyl)phthalimide **4c** [30], respectively. These reactions were carried out for 1 h at −60 °C, 1 h at 0 °C and finally at RT for 10 min, to give the *N*-alkylphthalimido-1,2,4-triazolium hexachloroantimonates **5**, which were used in the next step without purification. The following step in these reactions is the migration of the alkyl groups at C-5 to N-1 via [1,2-shift], at the same time the ($CClR^1R^2$) group at N-2 is eliminated to give finally the protonated triazoles **6**. The migration might have occured during or after the cycloaddtion of **5** and **6**. In situ, hydrolysis of **6** with aqueous $NaHCO_3$ gave the phthalimido-triazole derivatives **7** as a crystalline precipitate in 70–84% yield (Scheme 1). The synthesis of the phthalimide derivatives was confirmed by homo- and heteronuclear NMR spectroscopic methods and MS.

Compound **7l** was selected for NMR spectroscopic studies where the proton spin systems were elucidated from DQF-COSY [31] spectra, chemical shifts are listed in the experimental section. Proton bearing carbons were detected by HMQC [32] NMR. The gradient selected HMBC [33] spectrum showed $^2J_{C,H}$ correlation of C-3 (δ_C 160.0) and CH_2-3′ (δ_H 2.51), as well as $^3J_{C,H}$ correlation with CH_2-2′ (δ_H 1.95). There are three correlations of C-5 (156.7): $^2J_{C,H}$ with CH_2-6 (δ_H 2.69), $^3J_{C,H}$ correlations with CH_2-7 (δ_H 1.47) and CH_2-10 (δ_H 3.99). CH_2-1′ is inferred via its $^3J_{C,H}$ correlation (δ_H 3.62) with the carbonyl groups C-2 and C-9 at δ_C 168.2.

Additionaly, the phthalimide residues are usually considered interesting protecting groups in the synthesis of tri-

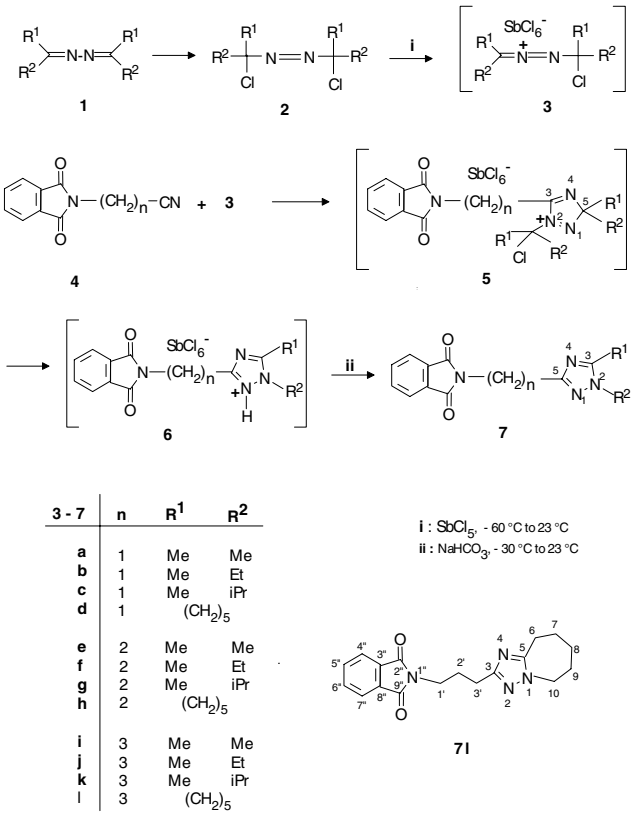


Thalidomide



NAN-190

Scheme 1



3 - 7	n	R^1	R^2
a	1	Me	Me
b	1	Me	Et
c	1	Me	iPr
d	1	$(CH_2)_5$	
e	2	Me	Me
f	2	Me	Et
g	2	Me	iPr
h	2	$(CH_2)_5$	
i	3	Me	Me
j	3	Me	Et
k	3	Me	iPr
l	3	$(CH_2)_5$	

azolamines. Therefore, it is worth to study the acid hydrolysis of the phthalimide derivatives in order to prepare the aminoalkyl 1,2,4-triazoles which are potential biologically active compounds. Hydrolysis of **7b** and **7h** with 30% HBr afforded the amino hydrobromide salts **8** and **9** in 74% and 65% yield, respectively (Scheme 2). The structures of these products were confirmed by homo- and heteronuclear NMR spectroscopic methods and mass spectra. The antitumor activity of these compounds is currently under investigation.

2.2. *Antitumor activity*

The ten synthesized compounds **7a**–**i** and **7l** were evaluated in the NCI *in vitro* diseases-oriented human cells screening panel assay [34]. 3-Cell lines of three tumor subpanels out of 60 cell lines have been choosen for this assay: NC1-H460 (lung), MCF7 (breast) and SF-268 (CNS) cancers. Compounds were tested in a concentration of 10^{-4} M. The percent growth inhibition (GIPRCNT) values have been summarized in the Table. The requirement

Scheme 2

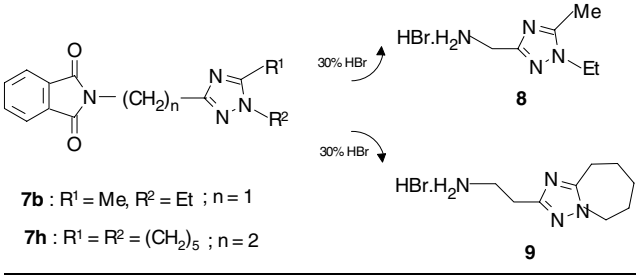


Table: Growth inhibition

Compd.	Growth %		
	(Lung)-H460	(Breast) MCF7	(CNS) SF-268
7a	120	95	102
7b	107	95	78
7c	130	87	103
7d	133	86	39
7e	137	96	82
7f	138	100	83
7g	123	107	94
7h	133	97	86
7i	132	97	107
7l	116	91	93

for cell-line screening set by NCI is that the GIPRCNT is 30% or less, in at least one of the cell lines. Except **7d**, which showed a GIPRCNT of 39% in the SF-268 (CNS) cells the tested compounds did not approach this value. Structure activity correlation of the obtained results revealed that the short alkyl group as well as the cyclic substituent of triazole can play an important role in increasing antitumor activity. Therefore, this value of percent growth inhibition reached by compound **7d** (39%) encouraged us to further modify these molecules.

3. Experimental

3.1. *General method* [35]

3.2. *Preparation of 1,3-dioxo-1,3-dihydro-isoindol-2-yl-alkyl derivatives of 1,5-dialkyl-1H-1,2,4-triazoles*

A solution of $SbCl_5$ (4.0 mmol) in dry CH_2Cl_2 (4 ml) was added dropwise to a stirred, cooled (−60 °C) solution of the phthalimide cyanide **4** (3.0 mmol) and the 1-(chloroalkyl)azo compound **3** (4.0 mmol) in dry CH_2Cl_2 (30 ml). The reaction mixture was stirred under anhydrous condition at −60 °C for 1 h, then at 0 °C for 1 h and finally at RT for 10 min. Pentane (60 ml) was then added and the precipitate was filtered off and then dissolved in CH_3CN (50 ml). After cooling the acetonitrile solution containing the product to 0 °C, an aq. solution of $NaHCO_3$ (3.36 g, 40 mmol in 40 ml H_2O) was added and the mixture was stirred at room temperature for 2 h. The mixture was evaporated and the aqueous phase was extracted with $CHCl_3$ (3 × 30 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The residue was recrystallised from an appropriate solvent to yield the pure triazolo-phthalimide derivatives.

3.2.1. *1,5-Dimethyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-methyl)-1H-1,2,4-triazole* (**7a**)

From **3a** (0.73 g, 4.0 mmol). Yield: 0.63 g, 82%, m.p.: 129–131 °C. δ_H ($CDCl_3$): 7.90–7.64 (m, 4H, Ar); 4.90 (s, 2H, (CH_2)-1′); 3.72 (s, 3H, N−Me); 2.41 (s, 3H, C_5-Me). δ_C ($CDCl_3$): 168.2 (C-2″); 167.8 (C-9″); 157.3 (C-5); 153.0 (C-3); 134.2, 133.7, 123.8, 123.5 (Ar); 132.4 (C-3, C-8″); 35.3 (C-1′); 35.2 (N−Me); 11.8 (C_5-Me). MS: *m/z* (FAB) 257 [M + H^+]. $C_{13}H_{12}N_4O_2$ (256.2)

3.2.2. *1-Ethyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-methyl)-1 H-1,2,4-triazol* (**7b**)

From **3b** (0.88 g, 4.0 mmol). Yield: 0.68 g, 84%, m.p.: 128–131 °C. δ_H ($CDCl_3$): 7.90–7.68 (m, 4H, Ar); 4.90 (s, 2H, (CH_2)-1′); 4.0 (q, 2H, J 7.1 Hz, CH_2CH_3); 2.36 (s, 3H, C_5-Me); 1.39 (t, 3H, J 7.1 Hz, CH_2CH_3). δ_C ($CDCl_3$): 167.8 (C-2″, C-9″); 167.4 (C-3); 152.1 (C-5); 134.2, 132,3, 123.5 (Ar); 132.8 (C-3″); 132.3 (C-8″); 43.3 (CH_2CH_3); 35.4 (C-1′); 14.9 (CH_2CH_3); 11.8 (C_5-Me). MS: *m/z* (FAB) 293 [M + Na^+]. $C_{14}H_{14}N_4O_2$ (270.3)

3.2.3. *1-Isopropyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-methyl)-1 H-1,2,4-triazol* (**7c**)

From **3c** (0.96 g, 4.0 mmol). Yield: 0.79 g, 79%, m.p.: 82–86 °C. δ_H ($CDCl_3$): 7.91–7.69 (m, 4H, Ar); 4.92 (s, 2H, (CH_2)-1′); 4.37 (m, 1H, $CH(CH_3)_2$); 2.38 (s, 3H, C_5-Me); 1.42 (2s, 3H each, $CH(CH_3)_2$]. δ_C ($CDCl_3$): 168.4 (C-9″); 167.8 (C-3″); 157.2 (C-5); 151.3 (C-3); 134.2, 133.9, 123.5, 123.4 (Ar); 132.9 (C-3″); 132.4 (C-8″); 50.1 ($CH(CH_3)_2$); 35.6 (C-1′); ($CH(CH_3)_2$); 11.9 (C_5-Me). MS: *m/z* (FAB) 285 [M + H^+]. $C_{15}H_{16}N_4O_2$ (284.3)

3.2.4. 6,7,8,9-Tetrahydro-2-[1,3-dioxo-1,3-dihydro-isoindol-2-yl-methyl)-5 H-1,2,4-triazolo-[1,5-a]azepine (**7d**)

From **3d** (1.05 g, 4.0 mmol). Yield: 0.65 g, 73%, m.p.: 120–124 °C. δ_H ($CDCl_3$): 7.90 (m, 4 H, Ar); 4.92 (s, 2 H, (CH_2)-1′); 4.15 (m, 2 H, (CH_2)-10); 2.81 (m, 2 H, (CH_2)-6); 2.90 (m, 2 H, (CH_2)-8); 1.87 (m, 2 H, (CH_2)-9); 1.67 (m, 2 H, (CH_2)-7). δ_C ($CDCl_3$): 168.1 (C-2″); 167.8 (C-9″); 158.1 (C-3); 156.3 (C-5); 134.1, 133.7, 123.4, 123.3 (Ar); 132.7 (C-3″); 132.2 (C-8″); 51.1 (C-10); 35.2 (C-1′); 30.2 (C-8); 27.3 (C-9); 24.7 (C-6); 24.3 (C-7). MS: *m/z* (FAB) 297 [M + H^+].
$C_{16}H_{16}N_4O_2$ (296.3)

3.2.5. 1,5-Dimethyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-ethyl)-1 H-1,2,4-triazole (**7e**)

From **3a** (0.73 g, 4.0 mmol). Yield: 0.58 g, 81%, m.p.: 132–136 °C. δ_H ($CDCl_3$): 7.81–7.61 (m, 4 H, Ar); 4.00 (m, 2 H, (CH_2)-1′); 3.64 (s, 3 H, N–Me); 2.96 (m, 2 H, (CH_2)-2′); 2.35 (s, 3 H, C_5-Me). δ_C ($CDCl_3$): 168.1 (C-2″, C-9″); 159.3 (C-3); 152.3 (C-5); 133.8, 123.2 (Ar); 132.2 (C-3″, C-8″); 36.7 (C-1′); 35.0 (N–Me); 27.1 (C-2′); 11.7 (C_5-Me). MS: *m/z* (FAB) 271 (M + H^+].
$C_{14}H_{14}N_4O_2$ (270.3)

3.2.6. 1-Ethyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-ethyl)-1 H-1,2,4-triazol (**7f**)

From **3b** (0.88 g, 4.0 mmol). Yield: 0.66 g, 78%, m.p.: 124–128 °C. δ_H ($CDCl_3$): 7.86–7.68 (m, 4 H, Ar); 4.10 (m, 4 H, N–CH_2CH_3, (CH_2)-1′); 3.21 (m, 2 H, (CH_2)-2′); 2.39 (s, 3 H, C_5-Me); 1.32 (t, 3 H, J 7.1 Hz, N–CH_2CH_3). δ_C ($CDCl_3$): 168.1 (C-9″, C-3″); 159.6 (C-5); 151.5 (C-3); 134.2, 133.8, 123.5, 123.1 (Ar); 132.4 (C-8″, C-3″); 43.1 (N–CH_2CH_3); 36.9 (C-1′); 27.0 (C-2′); 14.9 (N–CH_2CH_3); 11.7 (C_5-Me). MS: *m/z* (FAB) 285 [M + H^+].
$C_{15}H_{16}N_4O_2$ (284.3)

3.2.7. 1-Isopropyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-ethyl)-1 H-1,2,4-triazol (**7g**)

From **3c** (0.96 g, 4.0 mmol). Yield: 0.67 g, 75%, m.p.: 109–113 °C. δ_H ($CDCl_3$): 7.85–7.63 (m, 4 H, Ar); 4.30 (m, 1 H, $CH(CH_3)_2$); 3.97 (m, 2 H, (CH_2)-1′); 3.00 (m, 2 H, (CH_2)-2′); 2.36 (s, 3 H, C_5-Me); 1.40, 1.38 (2s, 3 H each, $CH(CH_3)_2$]. δ_C ($CDCl_3$): 168.1 (C-9″); 167.4 (C-3″); 158.8 (C-5); 150.5 (C-3); 134.4, 133.7, 123.6, 123.0 (Ar); 132.1 (C-3″); 131.9 (C-8″); 49.7 ($CH(CH_3)_2$); 36.7 (C-1′); 27.0 (C-2′); 22.0 ($CH(CH_3)_2$]; 11.5 (C_5-Me). MS: *m/z* (FAB) 299 [M + H^+].
$C_{16}H_{18}N_4O_2$ (298.3)

3.2.8. 6,7,8,9-Tetrahydro-2-[1,3-dioxo-1,3-dihydro-isoindol-2-yl-ethyl)-5 H-1,2,4-triazolo-[1,5-a]azepine (**7h**)

From **3d** (1.05 g, 4.0 mmol). Yield: 0.72 g, 78%, m.p.: 102–106 °C. δ_H (DMSO-d_6): 7.92–7.55 (m, 4 H, Ar); 4.11 (m, 2 H, (CH_2)-10); 4.02 (m, 1 H, H-1′); 2.98 (m, 1 H, H-2′); 2.82 [m, 2 H, (CH_2)-6); 1.86 (m, 2 H, (CH_2)-8); 1.77 (m, 2 H, (CH_2)-9); 1.69 (m, 2 H, (CH_2)-7). δ_C ($CDCl_3$): 168.0 (C-2″, C-9″); 158 (C-3); 157.4 (C-5); 133.8, 123.1 (C-4″, C-5″, C-6″, C-7″ (Ar)); 132.2 (C-3″, C-8″); 50.9 (C-10); 36.8 (C-1′); 30.3 (C-8); 27.4 (C-9); 27.2 (C-6); 27.0 (C-2′); 24.9 (C-7]. MS: *m/z* (FAB) 333 [M + Na^+].
$C_{17}H_{18}N_4O_2$ (310.3)

3.2.9. 1,5-Dimethyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-propyl)-1 H-1,2,4-triazole (**7i**)

From **3a** (0.73 g, 4.0 mmol). Yield: 0.68 g, 80%, m.p.: 79–81 °C. δ_H ($CDCl_3$): 7.85–7.65 (m, 4 H, Ar); 3.75 (m, 2 H, CH_2)-1′); 3.61 (s, 3 H, C_5-Me); 2.60 (m, 2 H, (CH_2)-3′); 2.12 (m, 2 H, (CH_2)-2′); 2.35 (s, 3 H, C_5-Me). δ_C ($CDCl_3$): 168.3 (C-2″); 168.2 (C-9″); 161.1 (C-3); 152.1 (C-5); 134.1, 133.1, 123.4, 123.1 (Ar); 132.0 (C-3″); 131.8 (C-8″); 37.6 (C-1′); 34.8 (N–Me); 27.0 (C-2′); 25.7 (C-3′); 11.6 (C_5-Me). MS: *m/z* (FAB) 285 [M + H^+].
$C_{15}H_{16}N_4O_2$ (284.3)

3.2.10. 1-Ethyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-propyl)-1H-1,2,4-triazol (**7j**)

From **3b** (0.88 g, 4.0 mmol). Yield: 0.75 g, 84%, m.p.: 56–60 °C. δ_H ($CDCl_3$): 7.90–7.68 (m, 4 H, Ar); 3.98 (q, 2 H, J 7.0 Hz, N-CH_2CH_3); 3.80 (m, 1 H, (CH_2)-1′); 2.74 (m, 2 H, (CH_2)-3′); 2.40 (s, 3 H, C_5-Me); 2.13 (m, 2 H, (CH_2)-2′); 1.40 (t, 3 H, J 7.0 Hz, N–CH_2CH_3). δ_C ($CDCl_3$): 168.4 (C-9″); 168.3 (C-2″); 161.6 (C-3); 151.3 (C-5); 133.8, 123.5, 123.1 (Ar); 132.2 (C-3″, C-8″); 43.1 (N–CH_2CH_3); 37.7 (C-1′); 27.0 (C-2′); 25.8 (C-3′); 15.0 (N–CH_2CH_3); 11.6 (C_5-Me).
$C_{16}H_{18}N_4O_2$ (298.3). MS: *m/z* (FAB) 299 [M + H^+]

3.2.11. 1-Isopropyl-5-methyl-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl-propyl)-1 H-1,2,4-triazol (**7k**)

From **3c** (0.96 g, 4.0 mmol). Yield: 0.66 g, 71%, oil. δ_H ($CDCl_3$): 7.89–7.68 (m, 4 H, Ar); 4.35 (m, 1 H, $CH(CH_3)_2$]; 3.80 (m, 2 H, (CH_2)-1′); 2.75 (m, 2 H, (CH_2)-3′); 2.13 (m, 2 H, (CH_2)-2′); 2.40 (s, 3 H, C_5-Me); 1.41, 1.39 [2s, 3 H each, $CH(CH_3)_2$). δ_C ($CDCl_3$): 168.3 (C-9″); 168.2 (C-3″); 160.9 (C-5); 150.3 (C-3); 134.2, 133.9, 123.3, 123.1 (Ar); 49.3 ($CH(CH_3)_2$); 37.6 (C-1′); 27.1 (C-2′); 25.7 (C-3′); 22.1 ($CH(CH_3)_2$); 11.6 (C_5-Me). MS: *m/z* (FAB) 335 [M + Na^+].
$C_{17}H_{20}N_4O_2$ (312.4)

3.2.12. 6,7,8,9-Tetrahydro-2-[1,3-dioxo-1,3-dihydro-isoindol-2-yl-propyl)-5 H-1,2,4-triazolo-[1,5-a]-azepine (**7l**)

From **3d** (1.05 g, 4.0 mmol). Yield: 0.68 g, 70%, m.p.: 84–87 °C. δ_H (600 MHz, HMQC, DMSO-d_6): 7.80 (s, 4 H, Ar); 3.99 (m, 2 H, (CH_2)-10); 3.62 (mt, 2 H, (CH_2)-1′); 2.69 (m, 2 H, (CH_2)-6); 2.51 (m, 2 H, (CH_2)-3′); 1.95 (m, 2 H, (CH_2)-2′); 1.72 (m, 2 H, (CH_2)-8); 1.56 (m, 2 H, (CH_2)-9); 1.47 (m, 2 H, (CH_2)-7). δ_C (150 MHz, HMQC, DMSO-d_6): 168.2 (C-2″, C-9″); 160.0 (C-3); 156.7 (C-5); 134.2, 122.9 (C-4″, C-5″, C-6″, C-7″ (Ar)]; 131.6 (C-3″, C-8″); 49.8 (C-10); 37.4 (C-1′); 29.4 (C-8); 27.9 (C-9); 26.2 (C-6); 26.1 (C-2′); 25.1 (C-3′); 24.5 (C-7). MS: *m/z* (FAB) 347 [M + Na^+].
$C_{18}H_{20}N_4O_2$ (324.4)

3.3. General procedure for the hydrolysis of the phthalimide derivatives 7b *and* 7h

A solution of the appropriate phthalimide (1.85 mmol) was heated in 30% HBr solution (10 ml) under reflux for 5 h. After cooling, the mixture was evaporated and the residue was co-evaporated with toluene. The product was recrystallized from EtOH/EtOAc.

3.3.1. 1-Ethyl-5-methyl-3-methylamino-1 H-1,2,4-triazole dihydrobromide (**8**)

From **7b** (0.50 g). Yield: 0.30 g, 74%; m.p.: 265–268 °C dec. δ_H (DMSO-d_6): 8.25 (br s, 2 H, NH_2); 4.12 (q, 2 H, J 7.0 Hz, CH_2CH_3); 4.02 (d (AB system), 2 H, J 6.0 Hz, (CH_2)-1′); 2.44 (s, 3 H, C_5-Me); 1.36 (t, 3 H, J 7.0 Hz, CH_2CH_3). δ_C (DMSO-d_6): 155.2 (C-3); 152.6 (C-5); 42.8 (CH_2CH_3); 36.0 (C-1′); 14.7 (CH_2CH_3); 11.2 (C_5-Me). MS: *m/z* (FAB) 244 [M + Na^+].
$C_6H_{13}BrN_4$ (221.1)

3.3.2. 6,7,8,9-Tetrahydro-2-(2-ethylamino)-1 H-1,2,4-triazolo-[1,5-a]-azepine hydrobromide (**9**)

From **7h** (0.57 g). Yield: 0.31 g, 65%, m.p.: 138–145 °C dec. δ_H (DMSO-d_6): 8.40 (bs, 2 H, NH_2); 3.18 (m, 2 H, (CH_2)-1′); 3.10 (m, 2 H, (CH_2)-2′); 2.45 (m, 2 H, (CH_2)-6); 1.88 (m, 2 H, (CH_2)-8); 1.79 (m, 2 H, (CH_2)-9); 1.72 (m, 2 H, (CH_2)-7). δ_C (DMSO-d_6): 155.4 (C-3); 150.6 (C-5); 52.2 (C-10); 36.1 (C-1′); 28.4 (C-8); 25.4 (C-9); 24.3, 23.4 (C-2′, C-6); 22.8 (C-7).
$C_9H_{17}BrN_4$ (261.1). MS: *m/z* (FAB) 284 (M + Na^+].

Acknowledgement: Y. Al-Soud would like to thank Professor Latsch, Fakultät für Chemie, Universität Göttingen for the hospitality and the lab. facilities. We thank greatfuly the NCI (U.S.A.) for the antitumor screening. Our appreciation also to Dr. A. Geyer, Fakultät für Chemie, Universität Konstanz for the NMR experiments.

References

1 Carswell, E. A.; Old, L. J.; Green, R. L.; Foire, N.; Williamson, B.: Proc. Natl. Acad. Sci. U.S.A. **72**, 3666 (1975)
2 Debs, R. J.; Fuchs, H. J.; Philip, R.; Brunette, E. N.; Duzgunes, N.; Shellito, J. E.; Liggitt, D.; Patton, J.: Cancer Res. **50**, 375 (1990)
3 Boussiotis, V. A.; Nadler, L. M.; Strominger, J. L.; Goldfeld, A. E.: Proc. Natl. Acad. Sci. U.S.A. **91**, 7007 (1994)
4 Manda, T.; Nishigaki, F.; Hemmi, H.; Ishida, N.: Cancer Res. **48**, 4250 (1988)
5 Komori, A.; Yatsunami, J.; Suganuma, M.; Okabe, M.; Abe, A.; Sakai, A.; Sasaki, K.; Fujiki, H.: Cancer Res. **53**, 1982 (1993).
6 D'Amato, R. J.;. Loughnan, M. S.; Flynn, E; Folkman, J.: Proc. Natl. Acad. Sci. U.S.A. **91**, 4082 (1994)
7 Makonkawkeyoon, S.; Limson-Pombre, R. N. R.; Moreira, A. L.; Schauf, V.; Kaplan, G.: Proc. Natl. Acad, Sci. U.S.A. **90**, 5974 (1993)
8 Shibata, Y.; Sasaki, K.; Hashimoto, Y.; Iwasaki, S.: Chem. Pharm. Bull. **44**, 156 (1996), and references cited therein
9 Kelsey, F. O.: Teratology **38**, 221 (1988)
10 Sampio, E. P.; Sarno, E. N.; Galilly, R.; Cohn, Z. A.; Kaplan, G.: J. Exp. Med. **173**, 699 (1991)
11 Hashimoto, Y.: Chemistry Today **283,** 38 (1994)
12 Randall, T.: J. Am. Med. Assoc. **263**, 1467 (1990)
13 Kaplan, G.: Immunobiology **191**, 564 (1994)
14 Feldmann, R.; Salomon, D.; Saurat, J. H.: Dermatology **189**, 425 (1994)

15 Siadak, M; Sullivan, K. M.: Blood Rev. **8**, 154 (1994)
16 Raghupthi, R. K.; Rydelek-Fitzgerald, L.; Teitler, M.; Glennon, R. A.: J. Med. Chem. **34**, 2633 (1991)
17 Shibata, Y.; Shichita, M.; Sasaki, K.; Nishimura, K.; Hashimoto, Y.; Iwasaki, S.: Chem. Pharm. Bull. **43**, 177 (1995)
18 Parker, P. M.; Chao, N.; Nademanee, A.; O'Donnell, M. R.; Schmidt, G. M.; Snyder, D. S.; Stein, A. S.; Smith, A. P.; Molina, A.; Stepan, D. E.; Kashyap, A.; Planas, I.; Spielberger, R.; Somlo, G.; Margolin, K.; Zwingenberger, K.; Wilsman, K.; Negrin, R. S.; Gwynn, Long, G. D.; Niland, J. C.; Blume, K. G.; Forman, S. J.: Blood **86**, 3604 (1995)
19 Ochnisky, S.; Verroust, J.; Batuji-Garin, S.; Gherardi, R.; Revus, J.: Arch. Dermatol. **130**, 66 (1994)
20 Miyachi, H.; Azuma, A.; Ogasawara, A.; Uchimura, E.; Watanabe, N.; Kobayashi, Y.; Kato, F.; Kato, M.; Hashimotom, Y.: J. Med. Chem. **40**, 2858 (1997)
21 Miyachi, H.; Ogasawara, A.; Azuma, A.; Hashimoto, Y.: Bioorg. Med. Chem. **5**, 2095 (1997)
22 Shimazawa, R.; Takayama, H.; Hashimoto, Y.: J. Synthetic Org. Chem. (Japan) **57**, 92 (1999)
23 Al-Soud, Y.; Wirschun, W.; Hassan, N. A.; Maier, G.-M.; Jochims, J. C.: Synthesis, 721 (1998), and references cited therein
24 Al-Masoudi, N. A.; Hassan, N. A.; Al-Soud, Y. A.; Schmidt, P.; Gaafar, A.E-D.M.; Weng, M.; Marino, S.; Amer, A.; Jochims, J. C.: J. Chem. Soc. Perkin Trans. 1 947 (1998)
25 Al-Soud, Y. A.; Al-Masoudi, W. A.; El-Halawa, R. A.; Al-Masoudi, N. A.: Nucleosides Nucleotides **18**, 1985 (1999)
26 Al-Masoudi, N. A.; Al-Soud, Y. A.; Geyer, A.: Tetrahedron **55**, 751 (1999)
27 Al-Soud, Y. A.; Al-Masoudi, N. A.: Arch. Pharm. Med. Chem. **332**, 143 (1999)
28 Getz, J. J.; Prankerd, R. J.; Sloan, K. B.: J. Org. Chem. **85**, 4913 (1993)
29 Groutas, W. C.; Chong, L. S.; Venkataraman, R.; Epp, J. B.; Kuang, R.; Houser-Archield, N.; Hoidal, J. R.: Bioorg. & Med. Chem. **3**, 187 (1995)
30 Thiruvengadam, T. K.; Gould, S. J.; Aberhart, D. J.; Lin, H-J.: J. Am. Chem. Soc. **105**, 5470 (1993)
31 Piantini, U.; Sorensen, O. W.; Ernst, R.: J. Am. Chem. Soc. **104**, 6800 (1982)
32 Müller, L.: J. Am. Chem. Soc. **101**, 4481 (1979)
33 Willker. W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W.: Mag. Res. Chem. **31**, 287 (1993)
34 El-Subbagh, H. I.; Abadi, A. H.; Al-Khawad, I. E.; Al-Rashood, K. A.: Arch. Pharm. Pharm. Med. Chem. **332**, 19 (1999), and references cited therein
35 Al-Masoudi, N. A.; Al-Soud, Y. A.; Lagoja, I. M.: Carbohydr. Res. **318**, 67 (1999)

Received June 28, 2000
Accepted September 26, 2000

Prof. Dr. Najim A. Al-Masoudi
Fakultät für Chemie
Universität Konstanz
Postfach 5560
D-78434 Konstanz
Najim-Al-Masoudi@uni-konstanz.de