RESEARCH PAPER

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Synthesis of Some 1,2,4-Triazole Derivatives as Potential Antitumor Agents

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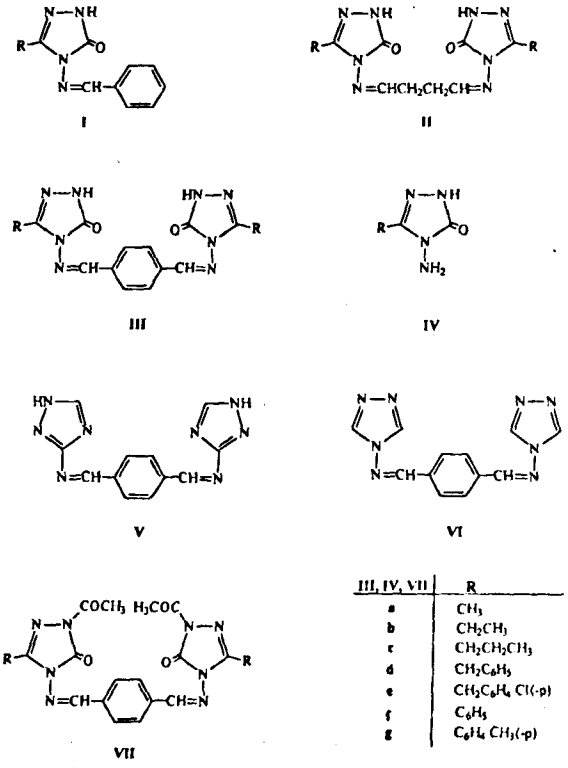
Thirteen new derivatives of 1,2,4-triazole were synthesized and characterised by elemental analysis, ^1H NMR, ^{13}C NMR and IR spectra. Three of these compounds were screened for their antitumor activities using cell lines derived from human solid tumors.

Various 1,2,4-triazole derivatives have been found to be associated with diverse pharmacological activities. Antibacterial, antifungal and tuberculostatic properties of some 4,5-dihydro-1H-1,2,4-trazol-5-ones have recently been reported[1-8]. Moreover, two articles[9-10] have been devoted to the antitumor activities of some 3-alkyl-4-benzylidenamino-4,5-dihydro-1H-1,2,4-triazol-5-ones [I] and N,N'-bis(3-alkyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-1,4-butanediimines [II]. Positive *in vitro* testing results reported for some of compounds I and II against some of 60 cell lines derived from human solid tumors prompted us to synthesize N,N'-bis(3-alkyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-1,4-xylenediimines [III] as potentially biological active compounds by the reaction of 3-alkyl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones [IV] with terephtaldialdehyde. The treatments of 3-amino-1,2,4-triazole and 4-amino-4H-1,2,4-triazole with tereph taldialdehyde to give N,N'-bis (1,2,4-triazol-3-yl)-1,4-xylenediimine [V] and N,N'-bis(4H-1,2,4-triazol-4-yl)-1,4-xylenediimine [VI] as the corresponding compounds were also studied. Furthermore, the acetylation of compounds [III] was also investigated and N,N'-bis(1-acetyl-3-alkyl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-1,4-xylenediimines [VII] were obtained in the study Scheme 1.



SCHEME - 1

EXPERIMENTAL

Synthesis:

Melting points were determined on a Buchi oil-heated melting point apparatus and are uncorrected. Experimental data for new compounds III, V, VI and VII are given in Table 1. The ^1H NMR and ^{13}C NMR spectra (δ, ppm) were run on a Varian 200 A spectrometer using tetramethylsilane as the internal reference Tables 2 and 3. The IR spectra (υ, cm^{-1}) were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer in potassium bromide discs Table 4. The combustion analyses were performed on a Carlo Erba 1106 elemental analyzer. The necessary chemicals were

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TABLE 1 : EXPERIMENTAL DATA OF COMPOUNDS III, V, VI AND VII

Compound No.	Yield %	Mp. (°C)	Molecular Formula[a] (Molecular Weight)
IIIa	91	361-362	$C_{14}H_{14}N_8O_2$ (326.31)
IIIb	83	350-351	$C_{16}H_{18}N_8O_2$ (354.37)
IIIc	84	344-345	$C_{18}H_{22}N_8O_2$ (382.42)
IIId	85	343-344	$C_{26}H_{22}N_8O_2$ (478.52)
IIIe	90	347-348	$C_{26}H_{20}Cl_2N_8O_2$ (547.41)
IIIf	86	348-349	$C_{24}H_{18}N_8O_2$ (450.47)
IIIg	77	351-352	$C_{26}H_{22}N_8O_2$ (478.52)
V	93	350-351	$C_{12}H_{10}N_8$ (266.26)
VI	95	340-341	$C_{12}H_{10}N_8$ (266.26)
VIIc	82	194-195	$C_{22}H_{26}N_8O_4$ (466.50)
VIId	89	251-252	$C_{30}H_{26}N_8O_4$ (562.59)
VIIe	78	289-290	$C_{30}H_{24}Cl_2N_8O_4$ (631.48)
VIIg	85	290-291	$C_{30}H_{26}N_8O_4$ (562.59)

[a] Elemental analyses (C,H,N) are in accordance with the calculated values.

obtained from Fluka and Merck. The starting compounds IV were synthesized from the treatment of ester ethoxycarbonylhydrazones with hydrazine hydrate as described earlier[11].

General Method for the Synthesis of Compounds III:

A mixture of the corresponding amino compound IV (0.01 mole) tereph taldialdehyde (0.005 mole) was heated in an oil bath at 185-190° for 1.5 h and then allowed to cool. The solid product was recrystallized several times from dimethyl sulfoxide to afford the desired compound.

Synthesis of Compounds V and VI:

3-Amino-1,2,4-triazol (0.01 mole) or 4-amino-4H-1,2,4-triazol (0.01) mole) was heated with tereph taldialdehyde (0.005 mole) in an oil bath at 165-170° for 1.5 h and then allowed to cool. The solid product was recrystallized several times from dimethylsulfoxide to give V or VI.

General Method for the Synthesis of Compounds VII:

The corresponding compound III (0.01 mole) was treated with 25 ml of acetic anhydride and the mixture was refluxed for 0.5 h. After the addition of 75 ml of

TABLE 2 : ^{1}H-NMR DATA (δ/PPM) FOR COMPOUNDS III, V, VI AND VII[a]

Compd No.	$2CH_3$	$2COCH_3$	$2CH_2$	$2CH_2$	$2CH_2Ph$	2CH	2NH	$-C_6H_4-$	Ar-H
IIIa	2.30 (s)	-	-	-	-	9.75 (s)	11.87 (s)	7.95 (s)	-
IIIb	1.25 (t)	-	2.35 (q)	-	-	9.80 (s)	11.90 (s)	7.95 (s)	-
IIIc	1.00 (t)	-	1.60-1.80 (m)	2.70 (t)	-	9.80 (s)	11.90 (s)	7.95 (s)	-
IIId	-	-	-	-	4.10 (s)	9.75 (s)	12.05 (s)	7.90 (s)	7.20-7.40 (m, 10H)
IIIe	-	-	-	-	4.10 (s)	9.75 (s)	12.05 (s)	7.90 (s)	7.20-7.45 (m, 10H)
IIIf	-	-	-	-	-	9.77 (s)	12.40 (s)	b	b
IIIg	2.40 (s)	-	-	-	-	9.77 (s)	12.00 (s)	7.95 (s)	7.40 (d, 4H) 7.80 (d, 4H)
V	-	-	-	-	-	9.35(s)[c]	14.15 (s)	8.20 (s)	-
VI	-	-	-	-	-	9.22 (s)[d]	-	8.03 (s)	-
VIIc	1.00 (t)	1.95 (s)	1.65-1.82 (m)	2.75 (t)	-	9.70 (s)	-	8.02 (s)	-
VIId	-	1.90 (s)	-	-	4.05 (s)	9.85 (s)	-	7.95 (s)	7.20-7.50 (m, 10H)
VIIe	-	1.95 (s)	-	-	4.13 (s)	9.85 (s)	-	8.00 (s)	7.20-7.45 (m, 10H)
VIIg	2.40 (s)	2.00 (s)	-	-	-	9.75 (s)	-	8.05 (s)	7.45 (d, 4H) 7.85 (d, 4H)

[a]The spectra for III, V and VI were recorded in DMSO-d_6 and for VII in DMSO-d_6/TFA (4:1).
[b]7.45-7.65 (m, 6H), 7.80-8.05 (m, 8H); [c]8.45 (s, 2H, 2CH); [d]9.18 (s, 2H, 2CH).

TABLE 3 : ^{13}C-NMR DATA (δ/PPM IN DMSO-d_6) FOR COMPOUNDS III, V, VI AND VII

Compd. No.	Triazole C-3 (2C)	Triazole C-5 (2C)	N-CH (2C)	Alifatic carbons	Aromatic Carbons
IIIa	143.9	151.8	150.7	10.6 (2C)	135.6 (2C), 127.6 (4C)
IIIb	147.5	151.8	150.8	18.0 (2C), 9.6 (2C)	135.6 (2C), 127.6 (4C)
IIIc	146.5	151.9	150.8	26.2 (2C), 18.5 (2C), 13.1 (2C)	135.6 (2C), 127.6 (4C)
IIId	145.8	151.7	150.7	30.6 (2C)	135.6 (2C), 135.3 (2C) 128.4 (4C), 128.0 (4C) 127.7 (4C), 126.3 (2C)
IIIe	145.5	151.8	150.7	30.0 (2C)	135.6 (2C), 134.3 (2C) 131.0 (2C), 130.3 (4C) 127.9 (4C), 127.7 (4C)
IIIf	143.8	154.2	150.4	-	135.2 (2C), 129.3 (2C) 127.7 (6C), 127.6 (4C) 127.2 (4C)
IIIg	139.5	154.5	150.9	-	135.6 (2C), 129.3 (2C) 128.8 (4C), 128.0 (4C) 127.6 (4C), 123.3 (2C)
V	126.3	145.8	155.8	-	135.8 (2C), 128.1 (4C)
VI	a	a	156.6	-	134.9 (2C), 128.6 (4C)

[a]138.6 (4C, triazole ring carbons).

TABLE 4 : IR DATA (KBr/cm^{-1}) FOR COMPOUNDS III, V, VI AND VII.

Compound No.	νNH	νC=O	νC=N	Monosubstituted benzenoid ring	1,4-Disubstituted benzenoid ring
IIIa	3182	1700	1608,1592	-	800
IIIb	3177	1700	1607,1589	-	808
IIIc	3255	1705	1605,1586	-	803
IIId	3168	1706	1604,1583	725,702	812
IIIe	3182	1706	1604,1586	-	814, 797
IIIf	3157	1696	1582,1558	726, 687	802
IIIg	3161	1698	1580,1558	-	814
V	3142	-	1609,1560,1528	-	835
VI	-	-	1608,1516	-	833
VIIc	-	1789,1698	1610,1592	-	784
VIId	-	1785,1692	1614,1594	731,704	776
VIIe	-	1770,1700	1612,1592	-	802,775
VIIg	-	1738,1721	1615,1589	-	781

TABLE 5 : ANTITUMORAL TESTING RESULTS OF COMPOUNDS IIId AND IIIe[A]

Compound No.	Subpanel	Cell Line	GI50	TGI
IIId	Leukemia	CCRF-CEM	2.38E-05[b]	5.07E-05
		HL-60 (TB)	4.05E-05	> 1.00E-04
		K-562	2.02E-05	5.05E-05
		MOLT-4	1.94E-05	4.70E-05
	Non-Small Cell Lung Cancer	HOP-62	5.76E-05	> 1.00E-04
	CNS Cancer	SF-295	7.73E-05	> 1.00E-04
		U251	5.73E-05	> 1.00E-04
	Renal Cancer	RXF 393	3.53E-05	> 1.00E-04
		TK-10	5.40E-05	> 1.00E-04
	Breast Cancer	MDA-MB-231/ATCC	3.88E-05	> 1.00E-04
IIIe	Non-Small Cell	HOP-62	1.70E-05	5.75E-05
	Lung Cancer	HOP-92	2.83E-05	> 1.00E-04
		NCI-H226	9.65E-05	> 1.00E-04
	CNS Cancer	SF-268	3.79E-05	> 1.00E-04
		SNB-19	5.07E-05	> 1.00E-04

Compound No.	Subpanel	Cell Line	GI50	TGI
		U251	2.66E-05	9.79E-05
	Melanoma	SK-MEL-2	3.85E-05	> 1.00E-04
	Ovarian Cancer	OVCAR-3	8.16E-05	> 1.00E-04
		OVCAR-4	7.63E-05	> 1.00E-04
		OVCAR-8	5.39E-05	> 1.00E-04
	Renal Cancer	786-0	1.33E-05	5.31E-05
		ACHN	3.00E-05	> 1.00E-04
		CAKI-1	3.33E-05	> 1.00E-04
		RXF 393	2.97E-05	> 1.00E-04
		SN12C	5.73E-05	> 1.00E-04
		TK-10	8.56E-07	> 1.00E-04
	Breast Cancer	NCI/ADR-RES	9.02E-05	> 1.00E-04
		MDA-MB-231/ATCC	1.72E-05	7.05E-05
		HS 578T	3.58E-05	> 1.00E-04

[a]GI50: Molar concentration for 50% growth inhibition. TGI: Molar concentration for total growth inhibition. [b]The expression 2.38E-05 is shorthand for 2.38 x 10^{-5} (Molar).

absolute ethanol to the cooled solution, the mixture was refluxed for one more hour. After cooling, the precipitate formed was recrystallized several times from dimethyl sulfoxide to afford pure compound VII.

Antitumoral Screening:

Three compounds (IIIb, IIId and IIIe) were selected for *in vitro* anticancer screening by the National Cancer Institute, Bethesda, Maryland U.S.A. These compounds were tested against a panel of approximately 60 cell lines derived from human solid tumors (lung, colon, melanoma, renal, ovarian, CNS, prostate, breast and leukemia).

RESULTS AND DISCUSSION

It this study, 13 new potentially biological active compounds were synthesized in good yields. The higher melting points and lower solubility in common solvents seem to be characteristic of III, V and VI. Compound IIIb was evaluated as inactive. But, compounds IIId and IIIe showed weak cytostatic activity against some of the 60 cell lines as given in Table 5. However, compounds IIId and IIIe did not show higher cytostatic activity as compared to compounds I and II described in our earlier studies[9,10]. The activity shown by compounds I was not increased by the two imine functions of III and the inserting of 4,4'-phenylene group to the structure.

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