ELSEVIER

Il Farmaco 53 (1998) 395–398

IL FARMACO

Synthesis of some new biologically active thiadiazolotriazinones [1]

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Received 8 September 1997; accepted 24 April 1998

Abstract

4-Amino-6-arylmethyl-3-mercapto-1,2,4-triazin-5(4*H*)-ones **1** are condensed with aromatic carboxylic acids, aryloxyacetic acids and anilinoacetic acids **2** to yield 7-substituted-3-arylmethyl-4*H*-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-4-ones **3**. Phosphorus oxychloride is used as cyclizing agent. Some of the newly synthesized compounds are screened for their antibacterial activities.

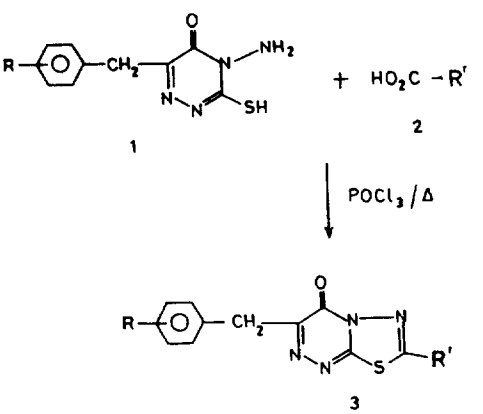
Keywords: Thiadiazolotriazinones; Antibacterial activity

1. Introduction

Several thiadiazoles find important application in the field of medicine, agriculture and industry [1,2]. Triazinones are also used as effective herbicides and fungicides [3]. Synthesis of azauracils and their thio and thioalkyl derivatives having antidiuretic and neurodepressant activities was reported by Timer and Draber [4]. In view of possible pharmacological activity of these new purine analogues, a series of 1,3,4-thiadiazolo[2,3-c]-*as*-triazines were synthesized following the procedure reported in literature [5]. Further, the presence of substituents like aryloxymethyl and anilinomethyl, etc. is known to enhance the biological activities of the molecules [6]. Prompted by these findings and in continuation of our studies on condensed heterocycles [7–13], three 4-amino-6-arylmethyl-3-mercapto-1,2,4-triazin-5(4*H*)-ones were prepared and condensed with aromatic carboxylic acids, aryloxyacetic acids and anilinoacetic acids to yield new thiadiazolotriazinones. Some of the newly synthesized thiadiazolotriazinones were screened for their antibacterial activities. The results of such studies are discussed in this paper.

2. Chemistry

For the present work, three arylmethyl (R = benzyl,4-chlorobenzyl and 3,4-methylenedioxybenzyl)-substituted-4-amino-3-mercapto-*as*-triazin-5(4*H*)-ones were prepared by condensing azalactones with thiocarbohydrazide [14]. The triazinones **1** were condensed with aromatic carboxylic acids, aryloxyacetic acids and anilinoacetic acids **2** in the presence of phosphorus oxychloride to afford 7-substituted-3-arylmethyl-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-4-ones **3** in rather good yields (Scheme 1). Formation of these thiadiazolotriazinones were confirmed by elemental analysis and



R=H
4-Cl
3,4,-o-CH_2-o-

R' = phenyl
4-nitrophenyl
4-chloro-3-methylphenoxymethyl
4-fluoro-3-chloroanilinomethyl
2-hydroxyphenyl
2, 3-dichlorophenoxymethyl
4-chlorophenoxymethyl
4-bromoanilinomethyl
4-chloroanilinomethyl

Scheme 1. Condensation of triazinones **1** with aromatic carboxylic acids, aryloxyacetic acids and anilinoacetic acids.

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[1] Presented at the 84th Session of the Indian Science Congress Association, New Delhi, India, 3–7 Jan. 1997.

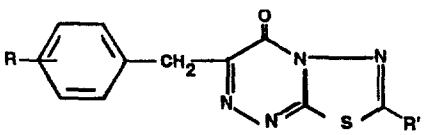
0014-827X/98/$ - see front matter
PII S0014-827X(98)00036-6

spectral studies. The characterization data of these compounds **3** are given in Table 1.

All the newly synthesized compounds gave satisfactory analyses for their nitrogen content. The IR spectrum of compound **3c** showed no absorption bands due to the $-NH_2$ group, thus confirming the bicyclic ring formation. The C=O stretching frequency was seen at 1690 cm^{-1}. The shift in the carbonyl stretching frequency could also be attributed to the formation of the N-bridged heterocyclic ring. In addition to this, the absorption bands characteristic of the SH group of the parent triazinones **1** were absent in the IR spectra of the cyclized products **3**.

The formation of the cyclized products **3** was further supported by recording the proton magnetic resonance (PMR) spectra of some selected compounds. The PMR spectrum of thiadiazolotriazinone **3c** showed a sharp singlet at $\delta = 4.11$ pmm, integrating for two protons, characteristic of the benzyl group. The phenyl protons resonated at $\delta = 7.2$, while the

Table 1
7-Substituted-3-arylmethyl-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-4-ones **3**



Comp.	R	R′	M.p. (°C)	Yield (%)	Molecular formula
3a	H	phenyl	142	73	$C_{17}H_{12}N_4OS$
3b	H	2-hydroxyphenyl	>300	74	$C_{17}H_{12}N_4O_2S$
3c [a]	H	4-nitrophenyl	220	74	$C_{17}H_{11}N_5O_3S$
3d [b]	H	4-chlorophenoxymethyl	216	95	$C_{18}H_{13}ClN_4O_2S$
3e	H	2,3-dichlorophenoxymethyl	154	86	$C_{18}H_{12}Cl_2N_4O_2S$
3f	H	4-chloro-3-methylphenoxymethyl	156	96	$C_{19}H_{15}ClN_4O_2S$
3g	H	4-bromoanilinomethyl	84	56	$C_{18}H_{14}BrN_5OS$
3h [c]	H	4-chloroanilinomethyl	104	62	$C_{18}H_{14}ClN_5OS$
3i	H	4-fluoro-3-chloro-anilinomethyl	92	65	$C_{18}H_{13}ClFN_5OS$
3j [d]	4-chloro	phenyl	238	73	$C_{17}H_{11}ClN_4OS$
3k	4-chloro	2-hydroxyphenyl	294	71	$C_{17}H_{11}ClN_4O_2S$
3l	4-chloro	4-nitrophenyl	186	71	$C_{17}H_{10}ClN_5O_3S$
3m	3,4-methylene dioxy	phenyl	75	69	$C_{10}H_{12}N_4O_3S$
3n	3,4-methylene dioxy	2-hydroxyphenyl	280	68	$C_{18}H_{12}N_4O_4S$
3o	3,4-methylene dioxy	4-nitrophenyl	152	67	$C_{18}H_{11}N_5O_5S$

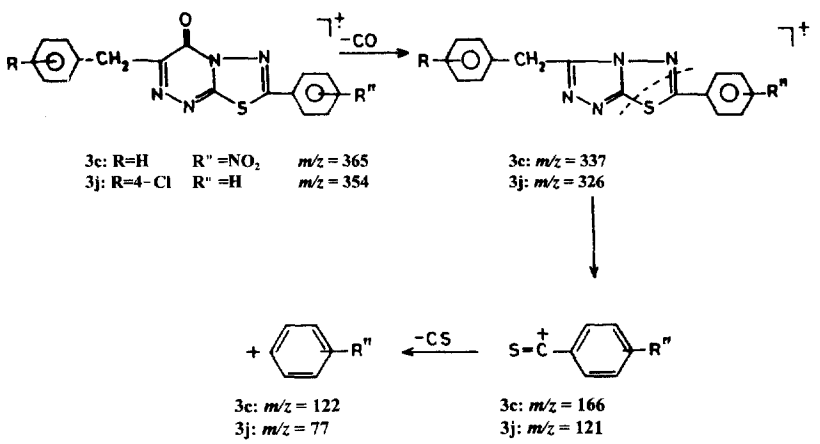
All compounds were analysed satisfactorily for their N content.

[a] IR: 1690 cm^{-1} ($\gamma_{C=O}$); PMR (DMSO-d_6): δ 4.1 (s, 2H, benzyl), 7.2 (m, 5H, aromatic protons), 8.1 (d, 2H, $J = 10$ Hz, aromatic protons), 8.2 (d, 2H, $J = 10$ Hz, aromatic protons); MS: m/z 365 (M^+), 166 ($NO_2C_6H_4$–CS^+), 122 (NO_2–$C_6H_4^+$).

[b] PMR (DMSO-d_6): δ 5.5 (s, 2H, aryloxymethyl protons), 4.1 (s, 2H, benzyl protons), 7.2 (m, 5H, aryl protons), 8.1 (d, 2H, $J = 9$ Hz, aromatic protons), 8.2 (d, 2H, $J = 9$ Hz, aromatic protons).

[c] PMR (DMSO-d_6): δ 5.4 (s, 2H, anilinomethyl protons), 3.8 (s, 1H, NH proton), 4.1 (s, 2H, benzyl protons), 7.2 (m, 5H, aromatic protons), 8.1 (d, 2H, $J = 9$ Hz, aromatic protons), 8.2 (d, 2H, $J = 9$ Hz, aromatic protons); MS: m/z 292 (M-91, loss of benzyl radical).

[d] MS: m/z 354 (M^+), 121 (C_6H_5–CS^+), 77 ($C_6H_5^+$).



Scheme 2. Mass spectral fragmentation pattern of thiadiazolotriazinones.

aromatic protons of the *p*-nitrophenyl residue resonated as doublets at $\delta = 8.2$ ($J = 10$ Hz) and $\delta = 8.4$ ($J = 10$ Hz).

The PMR spectrum of the product **3d** showed a sharp singlet at $\delta = 5.5$, integrating for two protons, which is characteristic of $-OCH_2$ protons or the aryloxymethyl group. The phenyl protons resonated at $\delta = 7.2$, while the aromatic protons of the chlorophenyl ring resonated as doublets at $\delta = 8.1$ ($J = 9$ Hz) and $\delta = 8.2$ ($J = 9$ Hz). The PMR spectrum of product **3h** showed a singlet at $\delta = 5.4$, integrating for two protons. A singlet at $\delta = 3.8$, corresponding to an NH proton confirmed the formation of the cyclized product with an anilinomethyl substituent in it. A singlet at $\delta = 4.1$, integrating for two protons, was observed for the benzylic moiety. The phenyl protons resonated at $\delta = 7.2$, while the chlorophenyl protons appeared as doublets in the region $\delta = 8.1$ ($J = 9$ Hz) and $\delta = 8.2$ ($J = 9$ Hz). The disappearance of the signal due to –SH protons, at $\delta = 13.8$, of the parent triazinones in the products **3c,d,h** confirmed the involvement of –SH protons in the condensation reaction.

The mass spectra of the products (**3c,j**) showed molecular ion peaks at $m/z = 365$ and 354, which were consistent with the molecular formulae $C_{17}H_{11}N_5O_3S$ and $C_{17}H_{11}ClN_4OS$, respectively. In both cases the molecular ion peaks were fairly intense, suggesting the stability of the thiadiazolotriazinone ring system. Molecular ions underwent fragmentations with the loss of carbon monoxide and produced ions at $m/z = 337$ and 326, respectively. These ions underwent further fragmentation to produce ions at $m/z = 166$ and 121, respectively (Scheme 2). The peaks at $m/z = 122$ and 77 are attributable to the respective aryl cations. The mass spectrum of the compound **3h** did not show a molecular ion peak at $m/z = 383$. However, it showed an intense peak at $m/z = 292$, confirming the loss of the benzyl radical from the molecular ion.

3. Experimental

3.1. Chemistry

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in nujol mull were recorded on a Perkin-Elmer infrared spectrophotometer. PMR spectra were recorded in DMSO-d_6 on a JEOL GHX 400–400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a VG Micromass mass spectrometer operating at 70 eV. Purity of the compounds was checked by thin-layer chromatography (TLC) on silica gel plates using a benzene/methanol (9:1) solvent system and iodine as the visualizing agent. Arylmethyl aminomercaptotriazinones **1** were prepared according to the method reported by us earlier [14].

3.1.1. 7-(Substituted)-3-arylmethyl-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-4-ones (3a-o)

A mixture of triazinone **1** (10 mmol), substituted carboxylic acid **2** (10 mmol) and phosphorus oxychloride (10 ml) was refluxed for about 5 h over a water bath. Excess phosphorus oxychloride was removed under reduced pressure. The reaction mixture was cooled and poured onto crushed ice (200 g). The resulting solid product was filtered, washed with aqueous (2%) sodium bicarbonate solution, followed by water. It was dried and recrystallized from aqueous dioxane. The characterization data of **3a–o** prepared according to this method are given in Table 1.

Table 2
Antibacterial activities of thiadiazolotriazinones (minimum inhibitary concentration (μg/ml))

Comp.	*S. areus*	*E. coli*	*P. aeruginosa*	*Bacillus*
3a	6	6	6	6
3b	12.5	6	12.5	12.5
3c	12.5	6	6	12.5
3d	12.5	6	12.5	12.5
3e	12.5	12.5	2.5	12.5
3f	12.5	12.5	12.5	12.5
3g	12.5	12.5	6	6
3h	12.5	12.5	6	6
3i	12.5	12.5	6	6
3j	12.5	12.5	6	6
3k	12.5	12.5	6	6
3l	12.5	12.5	6	6
3m	12.5	12.5	6	6
3n	12.5	12.5	6	6
3o	12.5	12.5	12.5	6
Furacin	12.5	6	12.5	12.5

3.2. Antibacterial activity

Some of the newly synthesized compounds were screened for their in vitro antibacterial activity against *genus Bacillus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Staphylococcus aureus* according to the serial dilution technique [15]. Furacin was used as a standard drug. The results of the screening studies are given in Table 2.

4. Results and discussion

Among all the compounds tested, thiadiazolotriazinone **3a** (R = H, Ar = phenyl) showed a high degree of antibacterial activity against all the bacteria tested. Hence compound **3a** stands to be a promising antibacterial agent.

Acknowledgements

The authors thank the Head RSIC, Punjab University, Chandigarh, and Head RSIC, IIT, Madras, for providing elemental analyses, mass and NMR spectra of the compounds reported herein. The authors are also grateful to Smt Shalini Shenoy, Department of Microbiology, KMC, Mangalore, for providing the antibacterial activity data reported in this paper.

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