4-Thiazolylmethoxyureas as Potential Anticancer Agents

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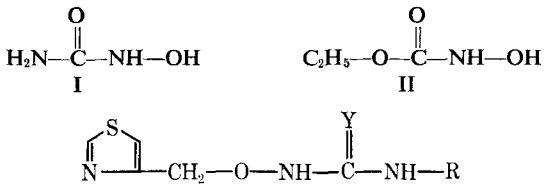
Abstract □ Preparation of a series of substituted 4-thiazolylmethoxyureas and 4-thiazolylmethoxythioureas is described. These compounds, which are structurally related to the antitumor agent hydroxyurea, were essentially inactive when screened against the L-1210 lymphoid leukemia test system. One compound, 4-thiazolylmethoxyurea, showed moderate anti-inflammatory activity in the carrageenin-induced rat paw edema test.

Keyphrases □ Anticancer agents, potential—synthesis □ 4-Thiazolylmethoxyureas—synthesis □ Pharmacological screening—4-thiazolylmethoxyureas □ IR spectrophotometry—identity

Recent studies have demonstrated the antineoplastic activity of hydroxyurea (I) (1, 2) and hydroxyurethan (II) (3). Hydroxyurea has been shown to inhibit several mouse tumors and has been used clinically in the treatment of cancer (4–6).

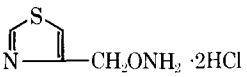
The aim of the present work is the synthesis of some 4-thiazolylmethoxyurea derivatives (III) for evaluation as possible antineoplastic agents. These 4-thiazolylmethoxyureas are structurally related to hydroxyurea, and also are related to 4-thiazolylmethoxyamine (IV) which is a potent histidine decarboxylase inhibitor (7). Histamine biosynthesis and histidine decarboxylase activity have been reported to increase in tumor tissue (8–11).



I

II

III

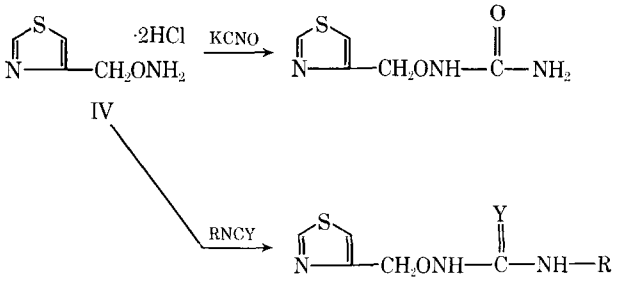


IV

Y = O; R = H, phenyl, 1-naphthyl, cyclohexyl
Y = S; R = phenyl

The five 4-thiazolylmethoxyureas synthesized are listed and their analytical data and melting points given in Table I and have the formula shown above (III). These ureas were prepared as shown in Scheme I.

The synthesis of the starting 4-thiazolylmethoxyamine dihydrochloride (IV) is described in another publication (7). The desired 4-thiazolylmethoxyurea was prepared by the reaction of potassium cyanate and 4-thiazolylmethoxyamine dihydrochloride by the method used by Bauer and Dalalian for the synthesis of aryloxyureas (12). By a modification of this method, the reaction of IV with phenyl isocyanate, with 1-naphthyl isocyanate, and with cyclohexyl isocyanate gave, respectively, 1-phenyl-3-(4-thiazolylmethoxy)urea, 1-(1-naphthyl)-3-(4-thiazolylmethoxy)urea, and 1-cyclohexyl-3-(4-thiazolylmethoxy)urea. The use of the alkyl isocyanates, methyl, ethyl, and *n*-butyl isocyanate, with IV by the above method gave no desired compounds.



Y = O; R = phenyl, 1-naphthyl, cyclohexyl
Y = S; R = phenyl

Scheme I

The reaction of phenyl isothiocyanate and IV yielded the expected 1-phenyl-3-(4-thiazolylmethoxy)thiourea. This thiourea showed apparent decomposition upon standing at room temperature for 2 months. The synthesis of 4-thiazolylmethoxythiourea by the method used in the preparation of 4-thiazolylmethoxyurea was attempted. However, the isolation and purification of the desired 4-thiazolylmethoxythiourea could not be accomplished, because the compound was very unstable, apparently decomposing in 1–2 hr.

BIOLOGICAL RESULTS

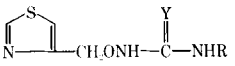
Anticancer Screening—Four of the compounds, namely 4-thiazolylmethoxyurea (Compound No. 1, Table I) (NSC 116197), 1-phenyl-3-(4-thiazolylmethoxy)urea (No. 2) (NSC 116723), 1-cyclohexyl-3-(4-thiazolylmethoxy)urea (No. 4) (NSC 119183), and 1-phenyl-3-(4-thiazolylmethoxy)thiourea (No. 5) (NSC 119182), were submitted to the Cancer Chemotherapy National Service Center, National Cancer Institute, for screening against the L-1210 lymphoid leukemia test system (13). None of the compounds possessed any significant antitumor activity. The cyclohexyl derivative (No. 4) was considerably more toxic than the other alkoxyureas, being lethal to 5/6 mice at a dose of 75 mg./kg., injected intraperitoneally. The other three compounds tested showed no lethality at 400 mg./kg.

Antimalarial Screening—Two compounds (Nos. 1 and 3) were tested for antimalarial activity against *Plasmodium berghei* in mice under the auspices of Walter Reed Army Institute of Research and were found to be inactive.

Preliminary Pharmacological Screening—Preliminary pharmacological results[1] are available for 4-thiazolylmethoxyurea (No. 1) and 1-phenyl-3-(4-thiazolylmethoxy)urea (No. 2). Compound No. 1 has no cardiovascular effect in the dog on i.v. injection. Tests performed in the rat (oral administration) showed that No. 1 has slight antipyretic and moderate anti-inflammatory (carrageenin-induced edema in the rat paw) effects, has a slight antidiuretic effect, and causes considerable anorexia. Tests in mice (i.p. injection) showed that the compound has no analgesic, antielectroshock,

[1] The authors thank Riker Laboratories, Northridge, CA 91324, for performing the pharmacological testing.

Table I—4-Thiazolylmethoxyureas



No.	Y	R	M.p., °C.	Formula	Anal., % Calcd.	Found
1	O	H	124–5	$C_5H_7N_3O_2S$	C, 34.67 H, 4.07 N, 24.26	C, 34.46 H, 4.46 N, 24.00
2	O	C_6H_5	100–1	$C_{11}H_{11}N_3O_2S$	C, 52.99 H, 4.45 N, 16.85 S, 12.86	C, 53.23 H, 4.54 N, 16.61 S, 12.51
3	O	1-Naphthyl	132–4	$C_{15}H_{13}N_3O_2S$	C, 60.18 H, 4.38 N, 14.04	C, 60.54 H, 4.46 N, 13.75
4	O	Cyclohexyl	76–7	$C_{11}H_{17}N_3O_2S$	C, 51.73 H, 6.71 N, 16.45	C, 52.12 H, 6.93 N, 16.39
5	S	C_6H_5	119–21	$C_{11}H_{11}N_3OS_2$	C, 49.78 H, 4.18 N, 15.83	C, 49.75 H, 4.21 N, 15.85

antiamphetamine, nor antireserpine activity and no effect on conditioned avoidance response. It decreases considerably the locomotor activity of the animal (i.p. or p.o.). At very high doses it causes hyperactivity. The LD_{50} of the compound in mice (i.p.) is greater than 800 mg./kg. (0/10 mice dead).

Compound No. 2 has no cardiovascular effects in the dog. In contrast to the results on No. 1, slight increases in the amount of urine and in the body temperature of the rat (p.o.) were seen. There was no effect on conditioned avoidance response. Anorexic activity was present. Tests in mice (i.p.) showed a slight antielectroshock, a slight analgesic, and no antiamphetamine nor antireserpine effect. The compound (i.p., mice) slightly increased locomotor activity, and at high doses caused ataxia. The LD_{50} of the compound is greater than 800 mg./kg., i.p. (3/10 mice dead).

EXPERIMENTAL

The syntheses of the compounds reported in Table I are described here. All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Elemental microanalyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. The IR spectra of all compounds were determined on a Perkin-Elmer Infracord apparatus in mineral oil mulls, and were in agreement with the assigned structures.

4-Thiazolylmethoxyurea (No. 1)—To 20.31 g. (0.1 mole) of 4-thiazolylmethoxyamine dihydrochloride (7) dissolved in 150 ml. H_2O was added 8.9 g. (10% excess) of potassium cyanate. The solution was stirred at 60° for 1 hr. and then left overnight at 60° to evaporate to dryness. Extraction of the residue with 50 ml. boiling acetone, followed by concentration of the solution and cooling gave 6.2 g. (33.8% yield), m.p. 124–125°. An analytical sample was obtained by three recrystallizations from acetone.

1-Phenyl-3-(4-thiazolylmethoxy)urea (No. 2)—To a solution of 0.6 g. (0.003 mole) of 4-thiazolylmethoxyamine dihydrochloride in 10 ml. of water was added 100 ml. of benzene. Sufficient anhydrous K_2CO_3 (approximately 30 g.) was added not only to form the free base but also to remove all water. The mixture was filtered through a folded filter paper and the water layer (if any) discarded. To the benzene layer containing the free 4-thiazolylmethoxyamine was added 0.325 ml. (0.003 mole) phenyl isocyanate; the mixture was stirred for 30 min. at room temperature and then let evaporate to dryness overnight at room temperature to yield 0.48 g. (63%), m.p. 100°.

1-(1-Naphthyl)-3-(4-thiazolylmethoxy)urea (No. 3)—The naphthyl compound was synthesized by the same procedure used for the phenyl derivative above. From 1.02 g. (0.005 mole) 4-thiazolylmethoxyamine dihydrochloride and 0.85 g. (0.72 ml., 0.005 mole) 1-naphthyl isocyanate was obtained a white, crystalline product, which after three recrystallizations from benzene weighed 0.7 g. (49%), m.p. 132°.

1-Cyclohexyl-3-(4-thiazolylmethoxy)urea (No. 4)—The cyclohexyl derivative was prepared similarly. From 1.34 g. (0.0066 mole) 4-thiazolylmethoxyamine dihydrochloride and 0.83 g. (0.0066 mole) cyclohexyl isocyanate were obtained 0.67 g. (39%) of product, m.p. 76°. An analytical sample was obtained by three recrystallizations from anhydrous ether.

1-Phenyl-3-(4-thiazolylmethoxy)thiourea (No. 5)—In a similar manner, 1.02 g. (0.005 mole) of 4-thiazolylmethoxyamine dihydrochloride and 1.08 g. (0.6 ml., 0.005 mole) phenyl isothiocyanate gave, after recrystallization from benzene, 0.6 g. (45%) of cream-colored solid, m.p. 119°.

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