in the same room as the operant chambers.

The rats were initially trained to respond on both of two levers under a variable interval 15-s (VI-15s) schedule of reinformcement. After lever responding was established, each daily session was preceded by an intraperitoneal (ip) injection of either (±)-DOM hydrochloride (1.0 mg/kg) or 0.9% saline (1.0 mL/kg). A pressession injection interval (psii) of 15 min was employed; during the period following administration of DOM or saline, the animals were kept in their individual home cages. Training sessions were of 15-min duration. Responding on one of the levers was reinforced after administration of DOM, whereas responding on the opposite lever was reinforced after administration of saline. Saline and DOM were administered on a double-alternation schedule. On every fifth day, discrimination learning was assessed during an initial 2.5-min extinction session, followed by a 12.5-min training session. After 26 training sessions, discrimination performance was stable under each treatment condition, i.e. the animals made greater than 80% of their responses on the DOM-appropriate lever when administered the training dose of the training drug, and less than 20% of their responses on the same lever after administration of saline.

Maintenance of the DOM/saline discrimination was insured in all six animals by continuation of the training sessions throughout the stimulus generalization studies. During the generalization studies, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under extinction conditions and were then returned to their home cages. An odd number of training sessions (not less than three) separated any two testing sessions. During these test sessions, doses of the challenge drugs were administered in a random sequence, using a 15-min psii. Stimulus generalization was said to occur when percent DOM-appropriate responding exceeded 80%. Animals making less than five total responses during the entire 2.5-min extinction session were reported as being disrupted. Where stimulus generalization occurred, ED_{50} values (i.e. doses at which the animals would be expected to make approximately 50% of their responses on the DOM-appropriate lever) were determined by the method of Finney.[20]

Note Added in Proof: Results of a preliminary study using [^{3}H]DOB as a radioligand for 5-HT_2 sites have just been published as a rapid communication (*Eur. J. Pharmacol.* **1985**, *117*, 145).

Acknowledgment. This work was supported, in part, by PHS Grant DA-01642. We also express our appreciation to Amy Hauck, Betsy Mack, and Mary Tocarz for their assistance with the discrimination studies and to Dr. J. Leysen for her evaluation of racemic DOB and DOI.

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Synthesis, Structure, and Antitumor Activity of *N*-Salicyloyl-*N'*-(2-furylthiocarbonyl)hydrazine and Its Copper(II) Complex

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N-Salicyloyl-*N'*-(2-furylthiocarbonyl)hydrazine (H_2sfth) and its Cu(II) complex [Cu(sfth)] were prepared and characterized by physicochemical studies. The IR and ESR spectral studies imply dibasic tetradentate behavior of the ligand bonding through "thiolo" sulfur, enolic oxygen, and hydrazinic nitrogens in a polymeric structure. The electronic spectrum of the complex indicates a square-planar geometry around Cu(II). Maximum antitumor activity was observed when 25 mg/kg dose levels of H_2sfth and Cu(sfth) were injected intraperitoneally in mice bearing either solid fibrosarcoma or ascites Dalton's lymphoma. However, H_2sfth appeared to possess better antitumor activity as demonstrated by higher T/C (percent) values than those observed for Cu(sfth). The appearance of lymphocytes, leukocytes, and macrophages within the tumor mass 2–6 days after treatment are indicative of involvement of the host's immune system.

Brockman et al. discovered the antitumor activity of 2-formylpyridine thiosemicarbazone against L1210, L82T, and L4946 leukemia in mice.[1] Furthermore, a number of derivatives of thiosemicarbazones have been shown to possess strong antineoplastic activity against a number of transplanted, spontaneous murine tumors[2] and in human tumor.[3] Role of metal chelation in the mechanism of action of these compounds has been discussed by French and his co-workers.[4-6] It has been established that copper ion chelation plays a definite role in the antineoplastic activity of 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone).[7] In fact, copper(II) complexes of substituted thiosemicarbazones and copper(II) and iron(II) complexes of 5-substituted 2-formylpyridine and 1-formylisoquinoline thiosemicarbazones[8-10] have been found to be cytotoxic to the tumor cells in vivo and in vitro. These complexes are strong inhibitors of the enzyme ribonucleotide reductase, an obligatory enzyme in the pathway of synthesis of precursors of DNA.[10-12]

Platinum, iron, copper, palladium, and zinc complexes of 2-formylpyridine thiosemicarbazone have been proved to be significant antitumor agents against Ehrlich ascites carcinoma and L1210 leukemia in mice.[13-15] Bis(2-

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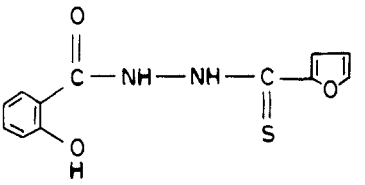

Figure 1. Structure of *N*-salicyloyl-*N'*-(2-furylthiocarbonyl)-hydrazine.

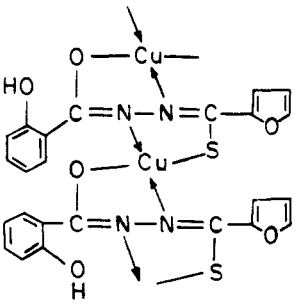

Figure 2. Structure of [*N*-salicyloyl-*N'*-(2-furylthiocarbonyl)-hydrazidato]copper(II).

formylpyridine thiosemicarbazonato)copper(II) inhibited the cellular DNA synthesis and DNA isolated from mitochondria, but RNA synthesis was less affected.[14] Copper(II) and cadmium(II) complexes of substituted bis(thiosemicarbazones) inhibited the incorporation of [^{3}H]thymidine into the DNA and respiration of tumor cells.[16,17] Antitumor activity has been reported for some metal chelates of the derivative of dithiocarbazic acid possessing the cytostatic activity in the 9KB test of human epidermoid carcinoma of the nasopharynx[18] and *S*-methyl dithiocarbazate[19] against P388 lymphoid leukemia in mice.

There is very little information available on the synthesis and structural studies on metal chelates of thiohydrazides and their derivatives.[20-22] Although thiohydrazides are structurally similar to thiosemicarbazides, not much data is available on the antineoplastic activity of transition-metal complexes of thiohydrazides. Therefore, it was of interest to study the antitumor activity of transition-metal complexes of thiohydrazides. *N*-Salicyloyl-*N'*-(2-furylthiocarbonyl)hydrazine (H_2sfth, Figure 1) and its 3d metal complexes have therefore been synthesized and characterized by analytical and physicochemical methods. The present paper also reports the antitumor activity of H_2sfth and its Cu(II) complex (Figure 2) against murine tumors.

Biological Results and Discussion

Characterizaton of the Complex. The molar conductance value of 20 Ω^{-1} cm^2 mol^{-1} for the complex in DMF demonstrate its nonionic nature. Because of the insolubility of the complex in water, ethanol, benzene, etc., it has not been possible to determine the molecular weight. The electronic spectrum of Cu(sfth) shows a broad band at 14080 cm^{-1} that was assigned to the envelope of $^2B_{1g} \rightarrow$

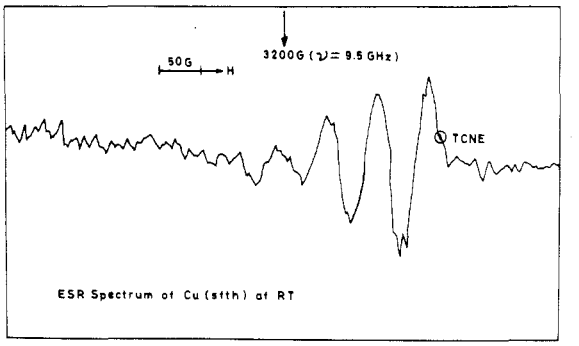

Figure 3. ESR spectrum of Cu(sfth) at room temperature.

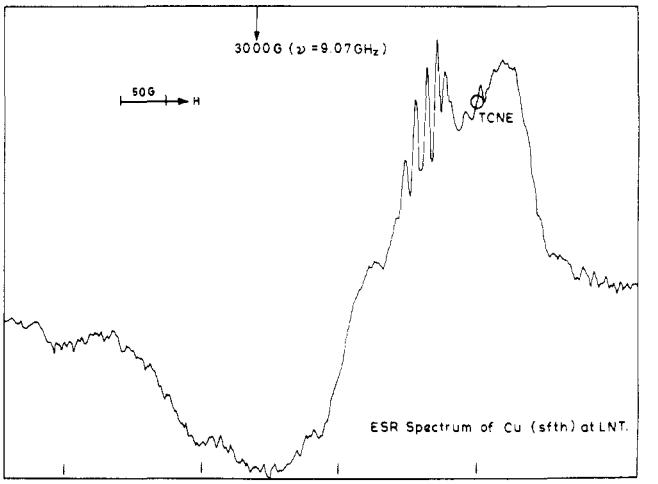

Figure 4. ESR spectrum of Cu(sfth) at 77 K.

$^2A_{1g}$, $^2B_{2g}$, ^2E_g transitions, suggesting a square-planar geometry for the complex.[23] The IR spectrum of the ligand displays bands at 3340, 1640, and 910 cm^{-1}, which may be assigned to ν(NH), ν(C=O), and ν(C=S), respectively. Disappearance of the above bands in the spectrum of Cu(sfth) and appearance of new bands at 1530 and 725 cm^{-1} due to ν(NCO) and ν(C–S), respectively, imply removal of both the NH protons via enolization and thioenolization and bonding of the resulting "thiolo" sulfur and "enolic" oxygen with Cu(II).[24] Positive shift of 40 cm^{-1} in ν(N–N) is suggestive of the involvement of both the hydrazinic nitrogens in coordination in a polymeric structure.[25] Appearance of broad band due to ν(OH) in the spectrum of the ligand at 3140 and 3420 cm^{-1} in the complex indicates that the OH group remains intact on complexation, but its appearance at a higher frequency suggests the presence of intramolecular hydrogen bonding in the free ligand,[26] which is broken on complex formation.

Cu(sfth) shows an isotropic ESR spectrum at room temperature and is nearly axially symmetric at 77 K, typical of a Cu(II) chelate; the values of the various ESR magnetic parameters calculated from the analysis of the spectra are as follows:

$$g_{iso} = 2.077,\ g_{\parallel} = 2.144,\ g_{\perp} = 2.043$$

$$A_{iso}(Cu) = 58.75\ G,\ A_{\parallel}(Cu) = 150\ G,\ A_{\perp}(Cu) = 70\ G$$

$$A_{iso}(^{14}N) = 7.5,\ A_{\parallel}(^{14}N) = 6.2\ G,\ A_{\perp}(^{14}N) = 10.83\ G$$

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Table I. Screening Data for H_2sfth and Cu(sfth) in the MFS_8 Fibrosarcoma (Solid) and Dalton's Lymphoma (Ascites) Test System in Tumor-Bearing Mice

		no. of mice injected (T/C)		av body wt change,[b] %		mean life span of nonsurvivors in days (T/C)[c]		no. of mice surviving > 6 months[d]		T/C, %	
	dosage[a]	I[g]	II	I	II	I	II	I	II	I	II
fibrosarcoma[e]	untreated			22.75	21.72						
	5/ip	8/6	8/8	15.1	15.47	41/27	34/26	4 (50)	2 (25)	152	131
	5/sc	7/7	6/6	11.62	19.39	36/26	30/27			139	111
	10/ip	6/6	8/8	11.27	18.27	38/26	35/27	3 (50)		146	130
	10/sc	8/7	8/7	12.31	5.86	37/27	41/28			137	146
	25/ip	10/10	7/7	7.88	12.04	40/28	33/25	5 (50)	3 (38)	143	132
	25/sc	8/9	8/6	9.96	5.51	41/26	39/29	6 (75)	6 (75)	158	135
	50/ip	8/8	10/6	2.65	8.51	45/27	37/28	6 (75)	4 (40)	167	132
Dalton's lymphoma[f]	2/ip	5/5	5/5			27/21	24/23			128	104
	10/ip	5/5	5/5			33/21	30/23			157	130
	25/ip	5/5	5/5			41/21	38/23			195	165

[a] Only single injection of the following doses was given. [b] Average weight change from day of drug treatment to 21 days. [c] In calculating average survival time, mice surviving 6 months or more were not included. [d] Number in parentheses indicates the percent of mice surviving 6 months or more. [e] Treatment was initiated on day three after transplantation. [f] Treatment was initiated on day two after tumor transplantation. [g] I = H_2sfth, II = Cu(sfth).

The room-temperature spectrum shows ligand hyperfine splittings although not very prominent but consistent with the interaction of the unpaired spin of Cu(II) with the ^{14}N nucleus (Figure 3). The presence of five distinct hyperfine lines in one perpendicular signal of Cu(II) in the ESR spectrum at 77 K further supports the coordination of both the hydrazinic nitrogens with the metal ion in a polymeric structure (Figure 4).[27] The trend $g_{\parallel} > g_{\perp} > 2.0023$, observed for the complex, indicates that the unpaired electron is most likely in the $d_{x^2-y^2}$ orbital of Cu(II).[23]

Antitumor Activity against Fibrosarcoma and Dalton's Lymphoma. The experiments carried out under the conditions described for the determination of antitumor activity of H_2sfth and Cu(sfth) are summarized in Table I. Inhibition of tumor growth was observed for both the compounds administered either ip or sc at four doses (5, 10, 25, and 50 mg/kg of body weight). In general, antineoplastic activity of H_2sfth and Cu(sfth) was observed at the 5 mg/kg dose but the highest percentage of tumor-free survivors with the increased T/C value were reported at the 25 and 50 mg/kg dose levels (Table I). The treatment with H_2sfth at all doses caused considerable increase in the number (percent) of tumor-free survivors as compared to Cu(sfth). Mice bearing solid tumor showed better results when compounds were injected ip as compared to sc. Comparatively, more pronounced effects were observed when H_2sfth or Cu(sfth) was injected at a dose level of 25 mg/kg in mice bearing ascites Dalton's lymphoma; however, no tumor-free survivors were obtained.

Both H_2sfth and Cu(sfth) caused the inhibition of tumor growth, but treatment with Cu(sfth) at any dose appeared to be less well tolerated as judged by the loss of body weight up to 6 days after 2 days of injection; later the weight increased and some of the animals died with the tumor load. Nevertheless, treatment with either H_2sfth or Cu(sfth) at the higher dose (50 mg/kg) did cause loss of body weight, indicating possible toxicity. There was minor body weight loss at 5, 10, and 25 mg of H_2sfth/kg of body weight treatment. With Cu(sfth) the loss in body weight for doses of 5, 10, and 25 mg/kg of body weight was comparatively more than observed in H_2sfth-treated mice. In the control, the animals gained weight and died as a consequence of tumors. The significance of loss of body weight up to 6 days may imply the toxicity of compound, but finally the animals showed an increase in body weight.

Antitumor potential of these compounds can be compared with the antitumor activity of *cis*-dichlorodiammineplatinum(II) (cis-Platin), which has also been shown to be effective in the regression of some transplantable animal tumors such as sarcoma-180,[28] leukemia L1210,[29] and fibrosarcoma.[30] Sarcoma-180 in Swiss white mice regressed completely after a single ip injection of 8.0 mg of cis-Platin/kg of body weight without any apparent irreversible damage to the host.[28]

Light microscopic study reveals that untreated fibrosarcoma show compact cellular organization with cells having a spherical to oval shaped large nucleus with a single prominant nucleoli. Only few leukocytes/lymphocytes with a large number of mitotic figures can be seen in the untreated mass of tumor. Following the 25 and 50 mg of H_2sfth and Cu(sfth)/kg of body weight injection, the cellular compactness is lost, the cytoplasm appears to be distorted, the nucleus becomes more translucent with chromatin dispersed in the form of small granules, and finally the cytoplasmic boundaries are disrupted. Only few isolated mitotic figures can be seen immediately after the treatment. One can observe the infiltration of a large number of leukocytes, lymphocytes, and macrophages within the regressing tumor mass after 2–6 days of the treatment. Similar observations have been made after cis-Platin treatment, where it has been reported that the mitotic activity was immediately inhibited after platinum treatment and also increased infiltration of lymphocytes and macrophages in the regressing tumor mass was observed.[28,30]

The results reported in this study show that H_2sfth and Cu(sfth) are strong antitumor compounds effective against transplantable tumors in mice. These compounds possibly act in a number of ways to regress the tumor in mice after a single injection. Initially, it seems reasonable to assume that H_2sfth and Cu(sfth) inhibit the mitotic activity of the tumor cells, because no mitotic figure was observed in treated tumor. This inhibition could be because of the inhibition of DNA duplication.[14] Appearance of lymphocytes and macrophages in the tumor mass after the H_2sfth and Cu(sfth) treatment also suggest that the host's immune system is enhanced. Highly damaged tumor masses with the 50 mg/kg of body weight of H_2sfth and Cu(sfth)

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treatment indicate that high doses are cytotoxic. The dose of 25 mg was more effective as antitumor compound with less pronounced damage to the cells. Further, the results of antitumor activity of these compounds are qualitatively parallel with the previously reported bis(thiosemicarbazones) and their Cu(II) complexes in showing that the free ligand is better tolerated than the copper complex. However, it has been established that the active species is the Cu(II) complex which is formed in vivo from the free ligand and endogenous copper.[7]

Experimental Section

Preparation of H_2sfth. Salicylic acid hydrazide[31] and carboxymethyl 2-furandithiocarboxylate[32] were prepared by the literature methods. Equimolar amounts of salicylic acid hydrazide and carboxymethyl 2-furandithiocarboxylate were dissolved separately in 2 and 1 equiv of aqueous 2 N NaOH, respectively, the solutions were mixed, and the solution was left for ~2 h at room temperature. The desired product was precipitated by adding dilute acetic acid dropwise to the above reaction mixture. The product thus obtained was suction filtered, washed with H_2O, dried, and recrystallized from hot ethanol (mp 208 °C). Anal. ($C_{12}H_{10}O_3N_2S$) C, H, S, N: calcd, 54.95; found, 54.45; calcd, 3.81; found, 3.61; calcd, 10.69; found, 10.49; calcd, 12.21; found, 12.61, respectively.

Preparation of Cu(sfth). The complex was prepared by digesting the solutions of copper(II) acetate monohydrate (0.99 g in 30 mL of 50% methanol) and the ligand (1.31 g in 60 mL of methanol + 1 g of sodium acetate) in a boiling water bath for ~15 min. On cooling, the dark green complex thus obtained was suction filtered, washed successively with a water–methanol mixture and hot ethanol, and dried in vacuo. The complex was analyzed for its metal, nitrogen, and sulfur content following the standard procedures as reported earlier.[33] Anal. Cu($C_{12}H_8O_3N_2S$) Cu, S, N: calcd, 19.58; found 19.09; calcd, 9.88; found, 10.03; calcd, 8.63; found, 8.82, respectively.

Physical Measurements. Electrical conductance, magnetic susceptibility, and infrared and electronic spectra of the complex was recorded as described earlier.[25] The X-band esr spectrum of the complex was obtained in chloroform on a Varian E-11 spectrometer using TCNE as a $\langle g \rangle$ marker.

MFS_8 Solid Fibrosarcoma for Evaluation of Antitumor Effect. C_3H/He mice of either sex and weighing 25–30 g were used in this study. Mice maintained in the laboratory were given food and water supply freely. MFS_8 solid fibrosarcoma (chemically induced) of Swiss white origin was supplied by Tata Memorial Cancer Research Institute, Bombay, and was passaged at intervals of 15 days by subcutaneous (sc) inoculation of a single cell suspension of 4×10^6 cells of fibrosarcoma into Swiss white mice.

Dalton's Lymphoma Test System for Evaluation of Antitumor Effect. Dba mice (-Mti strain) of either sex and weighing 18–20 g were used in this study. Dalton's lymphoma (spontaneously induced) of Dba origin was also supplied by Tata Memorial Cancer Research Institute, Bombay, and was passaged at weekly intervals by intraperitoneal (ip) injection of 2×10^7 ascites tumor cells into Dba mice (minimum number of cells for the growth of tumor in the peritoneal cavity).

Test for Toxicity. Animals were injected with 4×10^6 cells of fibrosarcoma sc or 2×10^7 cells of Dalton's lymphoma ip. On day three of fibrosarcoma and day two of Dalton's lymphoma inoculation, the test compound in different doses was injected ip as a single injection. Five animals were used per dose level. Toxic dose was estimated on the basis of survivals on the fifth day of injection.

Dose Schedule. Five to ten animals were used for each set of experiments. H_2sfth or Cu(sfth) was injected only once ip or sc at appropriate dose levels in mice on day three (for fibrosarcoma) and day two (for Dalton's lymphoma) after tumor transplantation. Compound suspension was freshly prepared in saline (0.89%). Controls were injected with the same volume of sterile saline. To test the toxicity of compound, the day when test material was injected in different doses was taken as day zero. At alternate days up to 4 weeks tumor-bearing animals were weighed to determine the change in body weight. The acute toxicity of Cu(sfth) was determined after 48 h of compound injection in tumor-bearing mice. The following LD_{50} values were obtained: 45 mg/kg of body weight for Dalton's lymphoma in Dba and 75 mg/kg of body weight for fibrosarcoma in Swiss white mice. The difference in LD_{50} dose for Dba and Swiss white mice could be due to the strain difference.

Evaluation of Antitumor Activity. Therapeutic effectiveness of H_2sfth and Cu(sfth) against tumor-bearing mice was assessed from the mean survival time of the treated animals excluding tumor-free survivors divided by mean life span of untreated mice multiplied by 100, giving the T/C percentage. A T/C value of 115 indicates significant activity, whereas a value for T/C > 125 indicates that complex is worthy of testing in other tumor system.[34] Mice were considered "tumor-free" when they survived 6 months or more after drug treatment.

Histological Study. Fibrosarcoma tumor was transplanted sc and the day of tumor transplantation was taken as day zero; on day three after tumor transplantation, animals were given a single ip injection of Cu(sfth) in physiological saline at a dose of 25 and 50 mg/kg of body weight. Controls were given saline only. Animals from both control and treated batches were killed at 2-day intervals up to 6 days. Tumor tissue was fixed in Bouin's fluid (aqueous) for about 22 h, dehydrated, kept in cedar wood oil for 3 days and embedded in paraffin. Paraffin sections of 5 μm were cut, stained in Ehrlich's hemotoxylin/eosin stain, dehydrated, cleared in xylene, and mounted in DPX. Slides were studied under the light microscope.

Acknowledgment. We thank Prof. B. N. Bhattacharya, the Head, RSIC, I.I.T., Bombay, for recording the ESR spectra of the complex. We also thank DAE and CSIR for providing financial support in the form of SRF.

Registry No. H_2sfth, 99268-53-8; Cu(sfth), 99268-54-9; salicylic acid hydrazide, 936-02-7; carboxymethyl 2-furandithiocarboxylate, 38204-39-6.

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