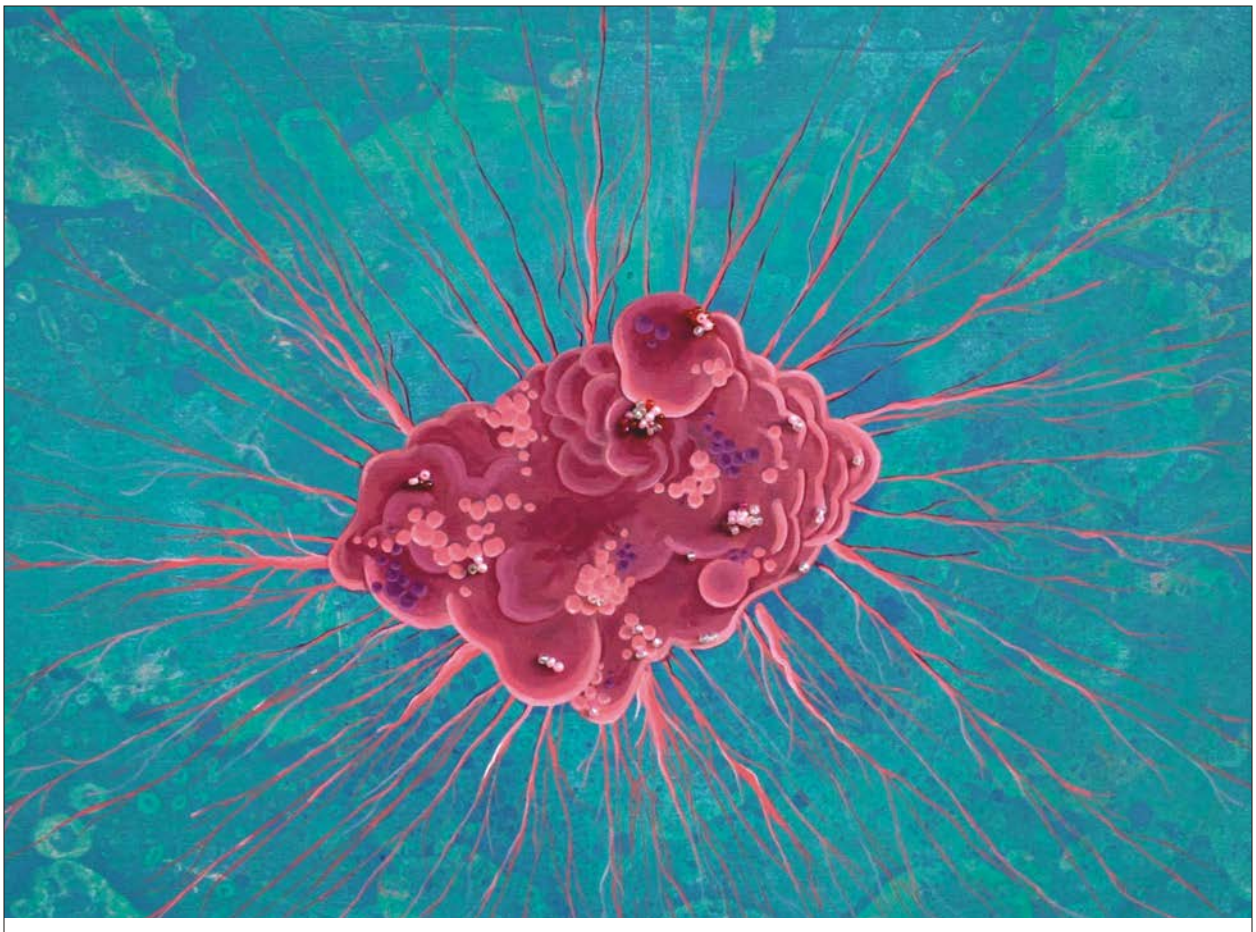

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Role of Some Newly Synthesized *Tetrahydronaphthalenthiazol* Derivatives as Anticancer Compounds

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Abstract: Three newly synthesized tetrahydronaphthalenthiazol derivatives I, II and III were examined to elucidate their antitumor activity against Ehrlich's ascites carcinoma cells (EATCs) bearing mice through monitoring the tumor volume and life span of the mice. All the three compounds showed high antitumor potential in simultaneous treatment than the groups in which treatment was started 10 days post tumor inoculation especially compound III which showed highest activity on reduction tumor volume (from 6.00±0.46 to 2.10±0.18 CC) at 20 μg kg^{-1} b.w. in comparison to group treated with cisplatin which was used as a standard treatment drug and revealed reduction of tumor volume (from 6.00±0.46 to 0.50±0.04 CC) and also showed the most highest survival rate (34.50±2.70 days) with the increase of life span 67% at the same concentration compared to 74 and 0% in cisplatin and control groups, respectively. It is obviously from the present study that the tetrahydronaphthalenthiazol can possess antitumor activity and ameliorate and prolong the life span of mice bearing EATCs.

Key words: Tetrahydronaphthalenthiazol, antitumor activity, Ehrlich's ascites carcinoma cells, life span, tumor volume

INTRODUCTION

Numerous compounds with biological activity have been investigated, however many of them are not suitable for therapeutic use due to their toxic, carcinogenic and mutagenic properties. The use of chemotherapeutic drugs in cancer therapy involves the risk of life threatening host toxicity. The search therefore continues to develop the drugs which selectively act on tumor cells (Tsuchiya *et al*., 2000).

Belladonine (1, 2, 3, 4-tetrahydro-1-naphthalene dicarboxylic tropine ester) is the first tetralin natural product which was discovered in 1983 in the leaves of atropa *belladonna* L. and Allied solanacaeae. Tetralin compounds are considered to be one of the most important drugs with biological activity. Many researches have focused attention on the wide biological and pharmacological activity of tetralin derivatives. The antitumor activity of some terahydronaphthalen derivatives have been studied and showed various anticancer activities (Ohmo *et al*., 2002; Appelbe *et al*., 2003).

Different studies showed that tetralin nucleus posseses potent anti-HIV, antipoliovirus and antibacterial activities (Ferrante *et al*., 1995; Hara *et al*., 1997). Also several tetralins have been developed and tested for their analgesic and anti-inflammatory activities. Murphy *et al*. (1998) and others have been proposed to be quantitative of the estrogen receptors in the individual cells, thereby providing a clinically useful prognostic technique in the control of breast cancer (Fevieg *et al*., 1987).

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Moreover, heterocyclic rings such as diazole, thiatholidine, pyrimidines, imidazole and benzimidazole like tetralin have been known by their wide pharmacological and therapeutical effects as anti-inflammatory inhibitors (Sondhi *et al*., 2002). In addition, they have a great biological interest, especially as antiviral, antitumor and antimicrobial agents (Sayed *et al*., 2006) and highly efficiency as insecticide (Ruter *et al*., 2005).

Depending upon the above mentioned reasons and in order to obtain compounds with superior chemotherapeutic index in terms of increased bioavailability, higher cytotoxicity and lower side effects, we therefore designed and synthesized new kinds of tetrahydronaphthalenthiazol derivatives, to evaluate their cytotoxicity and antitumor activities *in vivo* against ascitic tumor and solid Ehrlich's tumor-bearing mice.

MATERIALS AND METHODS

This study was started on January 2005 at biochemistry department and therapeutic chemistry department, National Research Center, Cairo, Egypt.

Animals

Male Swiss albino mice (body weight 20±2 g) were purchased from animal breeding center of National Research Center, Egypt. They were kept for a week under environmentally controlled conditions (constant temperature 25-27°C, with 12 h light/dark cycle) for one week prior to starting the experiments. The mice were kept as 10 animals per cage and they were provided with tap water and commercial diets.

Chemicals

Dimethylsulphoxide (DMSO) was purchased from Merck (Darmstadt, Germany) and cisplatin [*cis*-dichlorodiammineplatinum (II)] was obtained from Sigma-Aldrich chemical Co. (St. Louis, MO, USA). All other chemicals and reagents used were of highly analytical grade.

Tetrahydronaphthalenthiazol Compounds Preparation

2-amino-4-[5,6,7,8-tetrahydro-2-naphthyl]-thiazole is the main key compound in the present study which was prepared in a good yield according to the reported method of Nabih *et al*. (1985), it was subjected to several condensation with different reagents to give the compounds I, II and III. Briefly, it was reacted with potassium cyanate to give an intermediate that cyclized to give thiazolidinone derivative (compound I) and it was subjected to react with benzensulfonyl chloride in alcoholic NaOH (5%) to give compound II and finally it was refluxed with malonitrile in acetic acid for 6 h to give compound III.

The chemical structure of prepared tetrahydronaphthalenthiazol compounds was shown in the Fig. 1. Compound I is (2-amino-3-[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl]-1,3-thiazolidin-4-one), compound II is N[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiol-2-yl] benzensulphonamide, 4 methyl-N-[4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-thiazol-2-yl] benzensulphonamide, N-allyl-4(5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-tetrahydronaphthalen-2-yl)-1,3-thiol-2amine and compound III is 7-Imino-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-7H- thiolo[3,2-a]pyrimidin-5-yl amine.

Cell Line

Ehrlich's ascites carcinoma cells (EATCs) were obtained from National Cancer Institute, Cairo University, Egypt. The cells were maintained by intraperitoneal (i.p.) inoculation of 1×10^6 viable cells in mice.

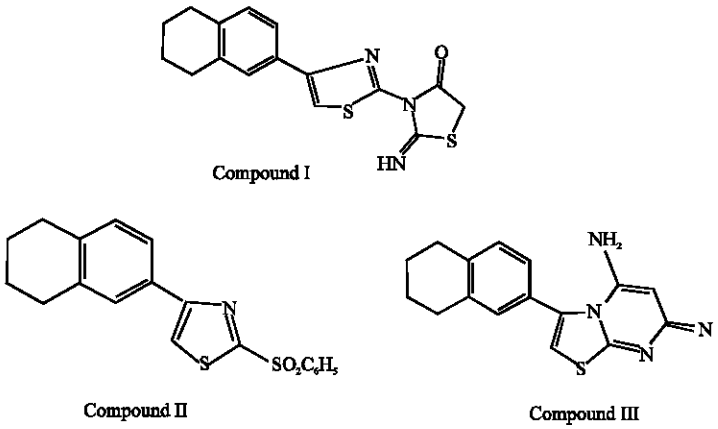

Fig. 1: The chemical structure of tetrahydronaphthalenthiazol compounds I, II and III

Assay of Acute Toxicity

The acute toxicity of the three prepared compounds was determined *in vivo* according to Prieur *et al*. (1973) and Ghosh (1984). Briefly, adult Swiss albino mice were divided into subgroups (10 mice each) administrated i.p. for five consecutive days with gradually doses of prepared compounds I, II and III. Control animals received the vehicle alone (DMSO). Mortality of the animals was observed up to one week post treatment. LD_{50} (the median lethal doses) of each compound was determined as (the dose resulted in 50% mortality of the animals).

Antitumor Activity

Antitumor activity of the prepared compounds I, II and III was determined as described by Joy *et al*. (2000) using ascites tumor and solid tumor models. The doses of each compound used were selected based on a preliminary study carried out above.

Ascites Tumor Model

Eighty animals were divided into eight groups of (10 mice each). All the animals were injected i.p. with 1×10^6 viable EATCs in PBS. After 24 h of tumor inoculation, tetrahydronaphthalenthiazol compounds I, II and III were administered i.p. at different concentrations of 100 and 200 μg kg^{-1} b.w. of compound I; 15 and 30 μg kg^{-1} b.w. of compound II, 10 and 20 μg kg^{-1} b.w. of compound III and continued for 5 consecutive days. The group administered with vehicle alone (DMSO) was maintained as control. Cisplatin (2 mg kg^{-1} b.w., i.p., for 10 days) was used as the standard reference drug. The mortality rate was noted in each group and the percent increase in life span (ILS) was calculated according to the methods of Ahluwalia *et al*. (1984) and Joy *et al*. (2000).

Effect of Tetrahydronaphthalenthiazol Compounds I, II and III When Administered Simultaneously with Tumor Inoculation

Viable EATCs (1×10^6) in 0.1 mL PBS were transplanted subcutaneously into the right groin of mice. Tetrahydronapthalenthiazol compounds I, II and III were administered i.p. at different concentration doses as previously mentioned 24 h post tumor implantation and extended for 5 consecutive days. The control group was treated with vehicle (DMSO) and the standard reference group was treated with cisplatin (2 mg kg^{-1} b.w., i.p., 10 days). The tumor development in animals of each group was determined by measuring the diameter of tumor growth in two perpendicular planes on every fifth day. The tumor volume was calculated as described by Ma *et al*. (1991), Mary *et al*. (1994).

Antitumor and Chemotherapeutic Effect of Tetrahydronaphthalenthiazol Compounds When Administered after Tumor Development

Viable EATCs (1×10^6) in 0.1 mL PBS were transplanted subcutaneously into the right groin of mice. Solid tumor development in mice was induced after 10 days; animal groups were i.p. subjected to tetrahydronaphthalenthiazol administration at different doses as mentioned before for 5 consecutive days. The group treated with vehicle (DMSO) was maintained as control and the standard reference group was treated with cisplatin (2 mg kg^{-1} b.w., 10 days). Tumor diameter was measured on every fifth day and volume was calculated (Ajith and Janardhanan, 2003).

Statistical Analysis

Values are recorded as mean±SE. The data were analyzed by Student's t-test; differences below the 0.5 level ($p<0.05$) was considered as statistically significant.

RESULTS

***In vivo* Assay of Acute Toxicity**

The compounds 1, II and III showed marked acute activity. The concentrations required by tetrahydronaphthalenthiazol compounds I, II and III for 50% mortality of the animals was found to be 870, 145 and 104 μg kg^{-1} b.w., respectively.

Antitumor Activity

As shown in Table 1, in the ascites tumor model the administration of compound I at a dose of 100 μg and 200 μg kg^{-1} b.w. showed no activity. Whereas, compound II showed increase of life span of animals 22 and 36%, respectively ($p<0.05$). However, compound III showed 43.50 and 67% life span increase at 10 and 20 μg kg^{-1} b.w. The standard reference drug (cisplatin 2 mg kg^{-1} b.w.) exhibited 74% ($p<0.05$) increase life span of the animals. All the animals in the EATCs injected with the vehicle alone group were died after 21 days.

Intraperitoneal administration of the compound I, II and III simultaneously into animal groups showed significant antitumor activities against solid tumor and reduce the tumor volume in a dose dependent mannar (Fig. 2A). Among the three compounds, compound III showed marked antitumor activity especially at 20 μg kg^{-1} b.w. than the groups treated with compound I and II. The tumor volume of the control groups on the 30th day of tumor inoculation was found to be 6.00 CC. The tumor volume reduced to 5.11 and 4.30 CC when treated with 100 and 200 μg kg^{-1} b.w. of compound I. Increase reduction to 3.9 and 3.50 CC upon treatment with 15 and 30 μg kg^{-1} b.w. of compound II. Whereas tumor volume recorded a marked reduction of 2.70 and 2.10 CC when treated with 10 and 20 μg kg^{-1} b.w. of compound III.

The prepared compounds were also highly effective against the development of solid tumor. The treatment with compound I, II and III for 5 consecutive days after tumor development showed dose-dependent reduction in the volume tumor (Fig. 2B). The tumor volume of the control group animals on 30th day post tumor inoculation was found to be 6.60 CC. The tumor volume reduced to 6.11 and 5.66 CC when treated with 100 and 200 μg kg^{-1} b.w. of compound I, continue to be reduced to 4.86 and 4.12 CC upon treatment with 15 and 30 μg kg^{-1} b. w. of compound II. Whereas compound III reduced tumor volume to 3.72 and 3.35 CC upon treatment with the doses of 10 and 20 μg kg^{-1} b.w.

Simultaneous i.p., administration of the three tested compounds into the animal groups (Fig. 2A) showed more antitumor activity than that obtained when the animal groups were subjected to treatment 10 days post inoculation (Fig. 2B).

Table 1: Effect of treatment with tetrahydronaphthalenthiazol compounds I, II and III on the survival of ascites tumor harboring mice inoculated with EATCs

Groups	Survival time (days)	% increase in life span of animals
Control	20.70±0.90	0
Cisplatin (2 mg kg^{-1} b.w.)	36.00±4.20[a]	74
Compound I		
100 μg kg^{-1} b.w.	NA	-
200 μg kg^{-1} b.w.	NA	-
Compound II		
15 μg kg^{-1} b.w.	25.20±1.40[a]	22
30 μg kg^{-1} b.w.	28.20±1.80[a]	36
Compound III		
10 μg kg^{-1} b.w.	29.70±2.50[a]	43.5
20 μg kg^{-1} b.w.	34.50±2.70[a]	67

Values are mean±SE.; n = 10 mice; NA = No activity, [a]$p<0.05$ significant with respect to control

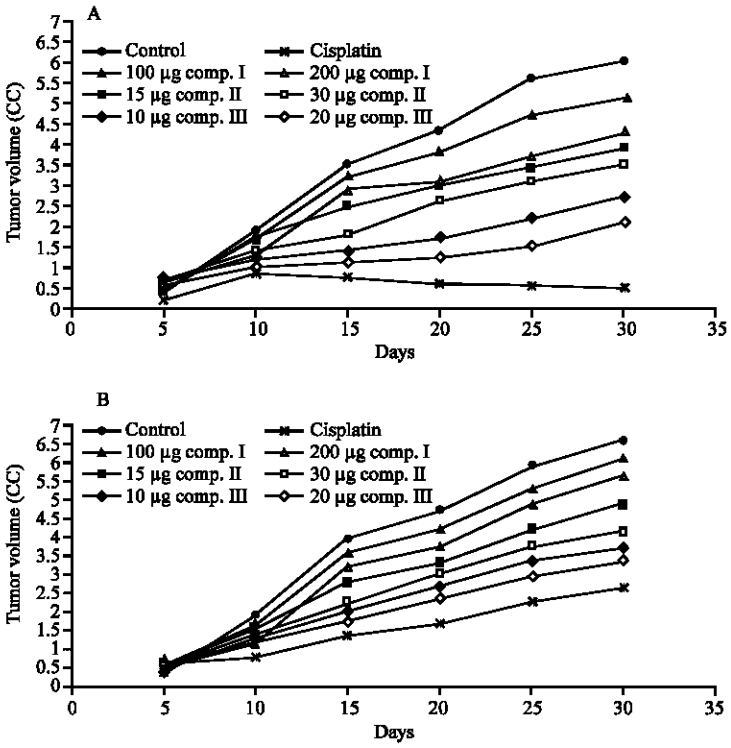

Fig. 2: Effect of tetrahydronaphthalenthiazol compounds I, II and III administration (A) On solid tumor development (simultaneous treatment). (B) On solid tumor development (after 10 days treatment)

DISCUSSION

There is a need for chemotherapeutic agents for treatment of neoplastic diseases that are safe for therapeutic use and that exhibit selective toxicity with respect to the pathological condition. Furthermore, there is a need for chemotherapeutic agents with modified or improved profiles of activity. The search therefore continues to develop the drugs which selectively act on tumor cells. The search for new antitumor agents has been extensively studied.

In the present study three tetrahydronaphthalenthiazol derivatives were examined for their *in vivo* antitumor action. Tetrahydronaphthalenthiazol derivatives exhibit a relevant antitumor activity and showing potency near cisplatin cytotoxic activity specially compound III. The preliminary evaluation of *in vivo* antitumor activity of the three derivatives, in ascetic and solid Ehrlich tumor-bearing mice showed noticeable activity for compound II and III near that of cisplatin in increasing the life span of treated animals; furthermore, in case of solid tumor-bearing mice, the data suggest that the treatment with antitumor compounds resulted in a significant tumor mass reduction in comparison with cisplatin-treated animals (Fregona *et al*., 2003; Giovagnini *et al*., 2005; Ronconi *et al*., 2005).

On the other hand, in EATCs-tumor bearing mice, a regular rapid increase in ascitic tumor volume was observed. Ascitic fluid is the direct nutritional source for tumor cells and increase in ascitic fluid with tumor growth would be a means to meet the nutritional requirement of tumor cells (Prasad and Giri, 1994), this was completely noticed in the control groups in comparison to the groups treated by tetrahydronaphthalenthiazol derivatives. So it may be concluded that these new synthesized compounds by decreasing the nutritional fluid volume and arresting the tumor growth with increases the life span of EATCs-bearing mice.

The results of the present study showed the tumor volume in control group was 6.0±0.46 CC on the end of the thirty day. Moreover, it was 0.50±0.04 CC in the group treated by cisplatin 2 mg kg^{-1} b.w. Compound I showed slight tumor volume decrease to 5.11±0.60 CC at concentration 100 μg kg^{-1} b.w. reduced to 4.30±0.52 CC at concentration 200 μg kg^{-1} b.w. Compound II showed a slight moderate reduction in tumor volume to 3.90±0.43 CC at concentration of 15 μg kg^{-1} b.w. decreased to 3.50±0.32 CC with increasing concentration to 30 μg kg^{-1} b.w. comparing to cisplatin. For surprising compound III achieved the highest reduction in tumor volume 2.70±0.29 CC which was obviously decreased to 2.10±0.18 CC with increasing concentration from 10 to 20 μg kg^{-1} b.w. recorded high percentage of tumor volume reduction compared to the other two compounds. These results may be explained on the basis of inclusion of the thiazol ring in the composition of the three compounds, since thiazol ring has been known to posses a variety of biological activities as mentioned by Elslager *et al*. (1981). Moreover, it was reported that several urea derivaties are of promising biological active agents in the field of tumor treatment (Mounetou *et al*., 2001). Compound I was characterized by fusing thiazolidine ring which was recorded to have a very important role as anti-inflammation agent according to Sondhi *et al*. (2002), furthermore compound II combined with benzenesulphonamide the compound which known to be used for treating or preventing pathological states arising from abnormal or inappropriate cell proliferation including angiogenesis, either alone or in conjunction with other treatment (Shriram *et al*., 2006). While compound III structurally fused with pyrimidine ring, it is well known that pyrimidine and heterocyclic derivatives are of great biological interest, especially as an antiviral (Shigeta *et al*., 2002; Rashad and Ali, 2006), antitumor and antimicrobial agents (Al-Thebeity, 2001).

From the results obtained we can notice that the reduction of tumor volume was dose dependant and that our results are in complete agreement with the published data of Musa *et al*. (2004), Rajeshwar *et al*. (2005). Furthermore our results are in line with the main concept of cancer research that evaluation of any tested substance depends on extension of the survival time of cancer patients and that an increase in the life span of drug tested tumor-bearing mice ≥ 125% as compared to control is considered indicative of presumptive drug activity (Buc-Calderon *et al*., 1989; Rajeshwar *et al*., 2005).

Presently we have shown that the tetrahydronaphthalenthiazol derivatives possess significant antitumor activity so far fusing pyrimidine ring increased the anticancer activity as seen from the reduction of tumor size as well as increasing the survival of animals. This study is encouraging especially for compound III since it shown prolongation of time life span of the tumor bearing mice and marked amelioration in tumor volume, the matter which suggests that compound III has antitumor activity comparable to the activity of commonly used anticancer drug, cisplatin.

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