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ANTITUMOR ACTIVITY OF CHEMICAL MODIFIED NATURAL COMPOUNDS

MARILDA MEIRELLES DE OLIVEIRA

Seção de Farmacologia, Instituto Biológico 04014 São Paulo, SP, Brasil

Search of new activy substances starting from chemotherapeutic agents, continously appears in international literature. Perhaps this search has been done more frequently in the field of antitumor chemotherapy on account of the unsuccess in saving advanced stage patients. The new point in this matter during the last decade was computer aid in planning more rational drugs. In near future "the accessibility of supercomputers and emergence of computer net systems, will open new avenues to rational drug design" (Portoghese, P. S., J. Med. Chem. *1989,* 32, *1). Unknown pharmacological active compounds synthetized by plants can be found even without this eletronic devices, as tradicional medicine has pointed out in many contries, and give rise to a new drug. These compounds used as found in nature or after chemical modifications have produced successful experimental medicaments as FAA, "flavone acetic acid" with good results as inibitors of slow growing animal tumors currently in preclinical evaluation for human treatment. In this lecture some international contributions in the field of chemical modified compounds as antineoplasic drugs will be examined, particularly those done by Brazilian researches.*

Key words: antitumor activity – natural products

Malcoln Sainsburg said ten years ago, during a meeting of the British Association Chemistry, that nearly 50,000 synthetic substances were tested for anticancer activity each year and the success rate was low. The same point of view was expressed about twenty years ago by S. Morris Kupchan, an outstanding contributor to the field of antineoplastic drugs extracted from plants. He wrote: "there exists a need for new prototypes, as templates, for synthetic organic chemists to use in the design of potentially superior chemotherapeutic agents".

We think that hemisynthesis starting from natural compounds with already known activity against cancer is a shorter way to new successful drugs. Eventually it can lead to better performance such as: improved activity, diminished deleterious secondary effects and extended activity against other tumors.

Monoclonal antibodies conjugates or new devices, as the recently published monoclonal antibodies-enzyme conjugates (Senter et al., 1989), planned to guide toxins to the tumor cells or to overcome insufficient drug delivery are clever approaches to destroy cancer, where natural substances or the hemisynthetic agents can collaborate.

We will further mention from the world literature some chemically modified natural agents used against cancer.

Flavone acetic acid (FAA) (Fig. 1) is one of those, recently submited to phase I clinical test. This first experimental study was stopped because of adverse reactions showed by pacients (Kerr et al., 1987). A second trial is now being tested in Europe justified by the unprecedent good activity of the drug against solid human tumors implanted in nude mice.

FAA is active against adenocarcinoma of colon, ductal pancreatic adenocarcinoma, mammary adenocarcinoma and Glascow osteasarcoma.

The compound inhibits DNA and RNA synthesis, produces hemorrhagic areas in tumor resembling tumor necrosis factor. It is a modifier of biological response inducing natural killer cell activity.

Cell colonies formation assay using agar showed that FAA is selective for solid tumors when compared to ascitic tumors as P388 and L1210. Moreover, it has the unusual property of not being myeolodepressive as the majority of anticancer drugs (Rewcatle et al., 1989).

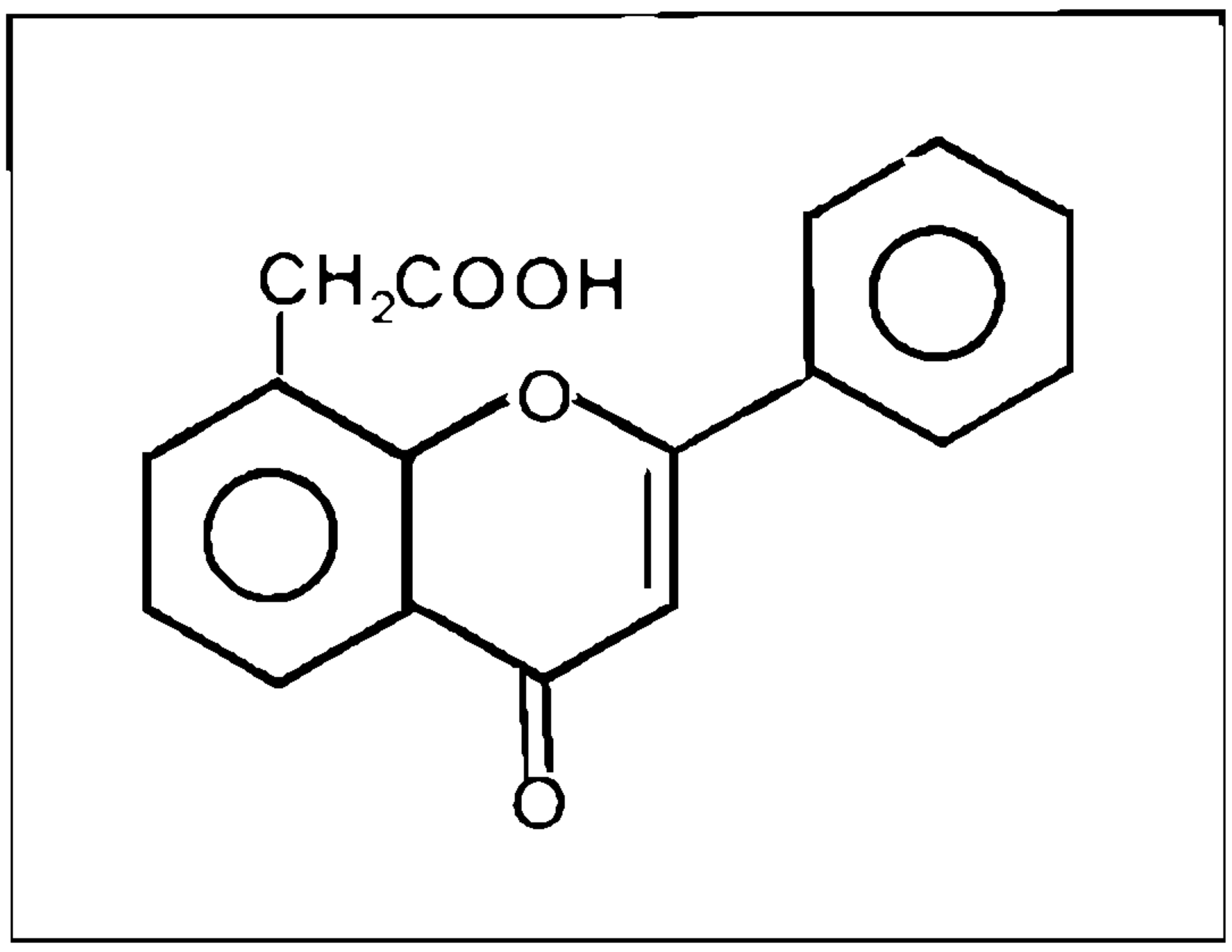


Fig. 1: flavone acetic acid.

The same class of compounds in a new design was studied by New Zealand investigators (Rewcatle et al., 1989). They synthetized xanthenones derivatives, (Fig. 2) during their search for successful agents against solid tumors.

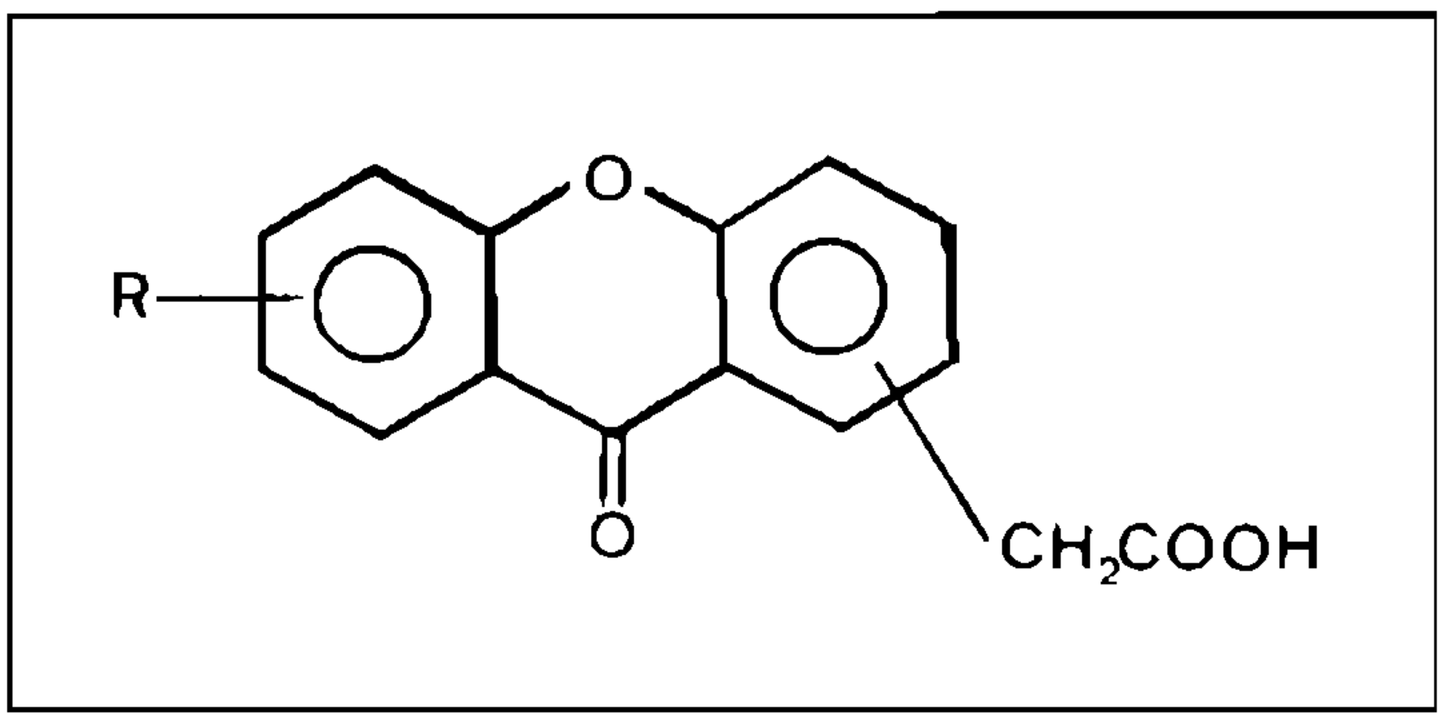


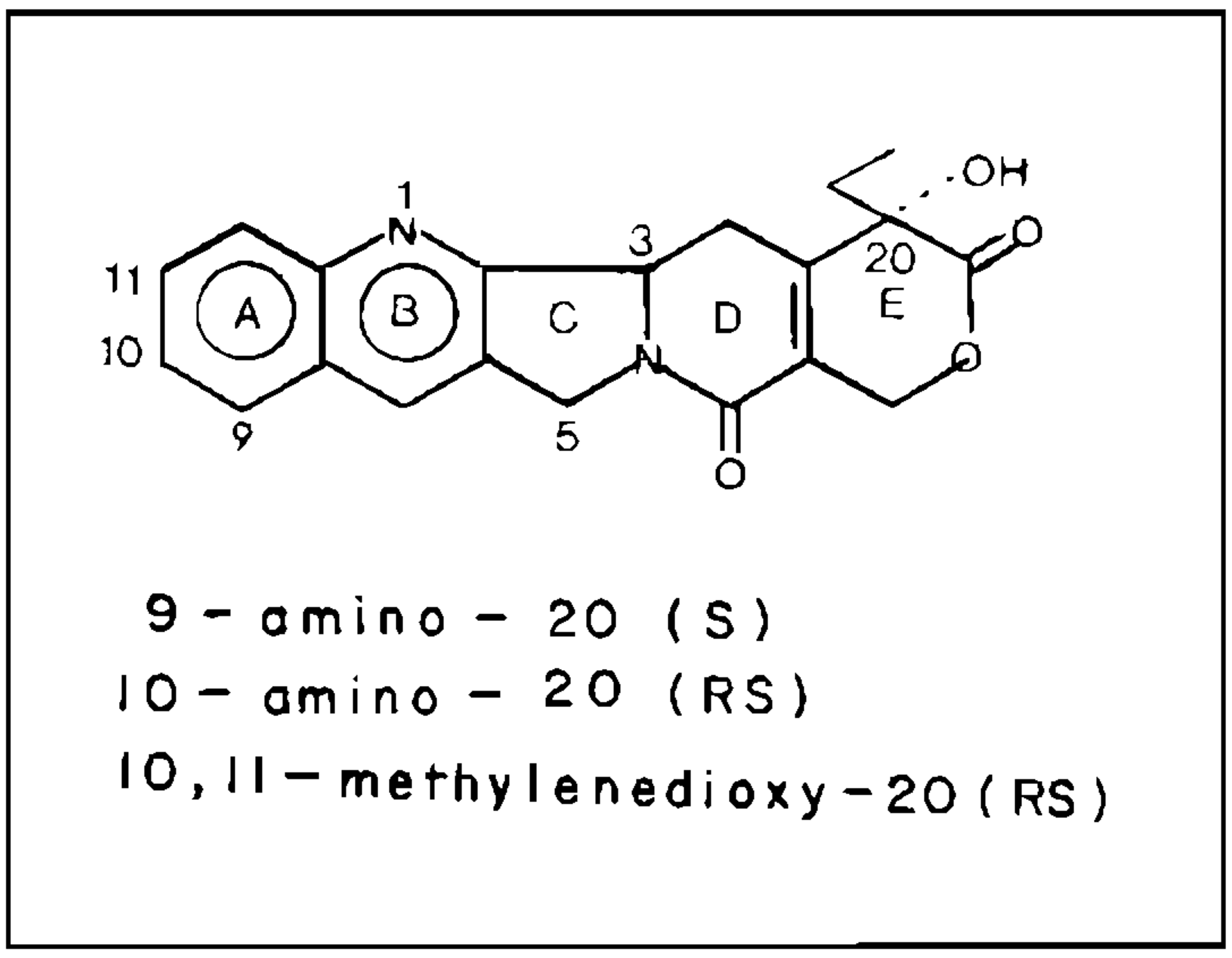
Fig. 2: xanthenones derivatives.

Xanthenones, the parent compound, are secondary metabolites of plants. Several of these substances, about sixty, were isolated from Guttiferae, Gentianaceae, Moraceae and Plygalaceae families by Gottlieb and his collaborators (Gottlieb, 1970).

The new Zealand team produced forty eight new compounds. Several radicals were introduced in ring A and or in ring C: such as Cl, Me, NO2 and OH in ring A and CH2COOH in ring C. Overall activity decreased from Cl group to hydroxi group and is improved with CH2COOH in position 4.

Another aspect we would like to emphasize is the early experimental dropping of some promissing active drugs.

Fortunately this has not been done with camptothecin (Fig. 3) isolated by wall 1966, from a Chinese plant.

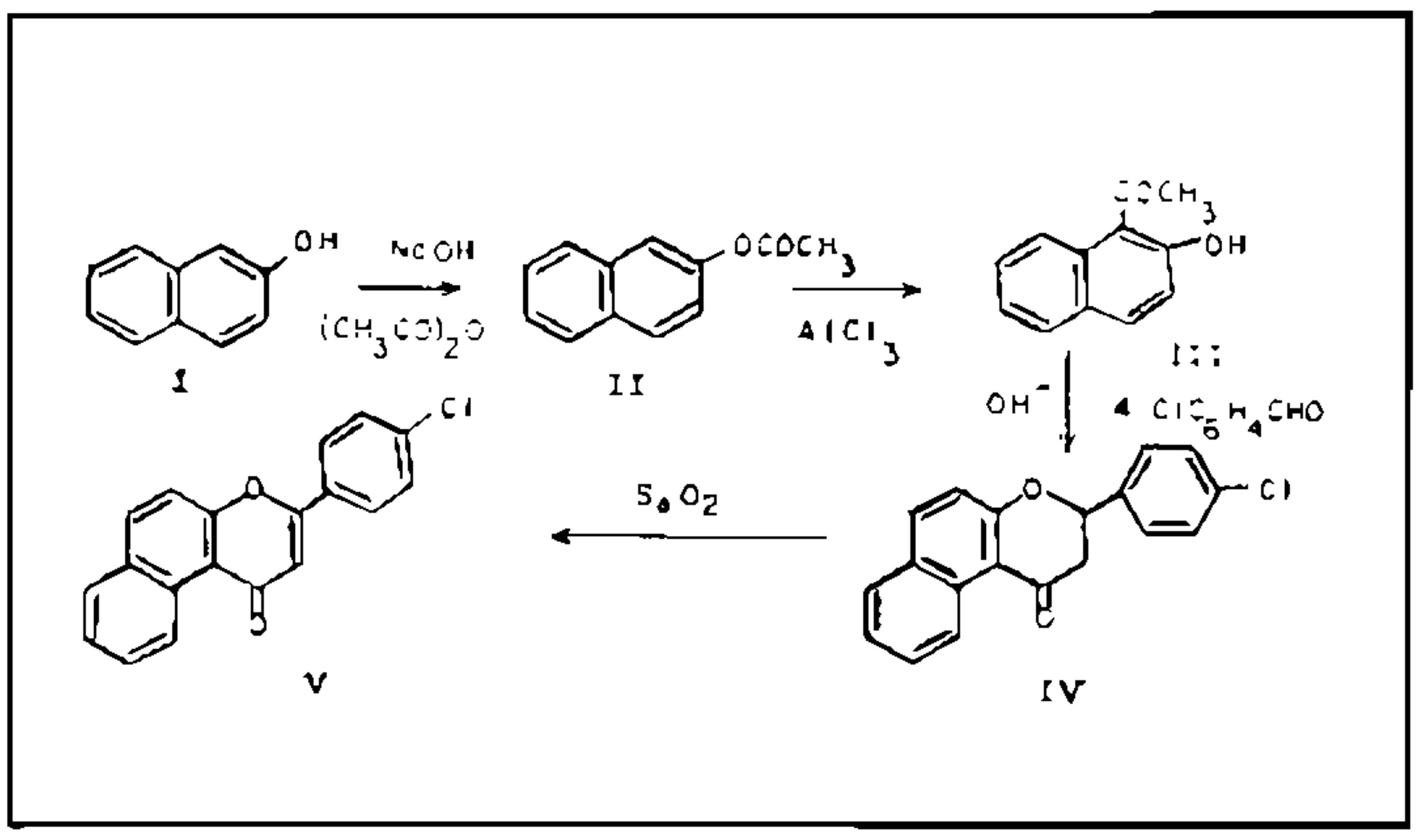


9 − amino − 20 (S)
10 − amino − 20 (RS)
10, 11 − methylenedioxy − 20 (RS)

Fig. 3: camptothecin.

Camptotheca acumulata, Nyssaceae family, which continued to give rise to new active agents (Wani et al., 1987) as those recently prepared by Wani et al. They succeded in preparing several active compounds selected by two biological models: extension of necrosis area in colon 38 tumor implanted in mice and increase in life span of mice inoculated with P388 leukemia. Three particularly active compounds were obtained (Wani et al., 1987) as shown in Fig. 3, they prolonged survival and cured some of the treated animals.

Searching for what has been done in Brazil in the field of chemically modified agents, we would like to mention the work of Mello & Rocha Pitta (1982/83) who synthetised a flavonol analogue (Scheme 1) as a potencial activator of the benzo(a)pyrene hydroxilase.



Scheme 1: synthesis of flavonone derivative.

We also worked with flavanol condensed tannins with good results, by using intraperitoneal administration in animals bearing subcutaneous tumors (De-Oliveira et al., 1972, 1985). Dimeric compounds produced no harmful effects in rats, but oligomeric (Fig. 4), although more active, produced adherence when injected in the peritoneum. We should perhaps, overcome this inconvience through reduction of free hydroxi groups.

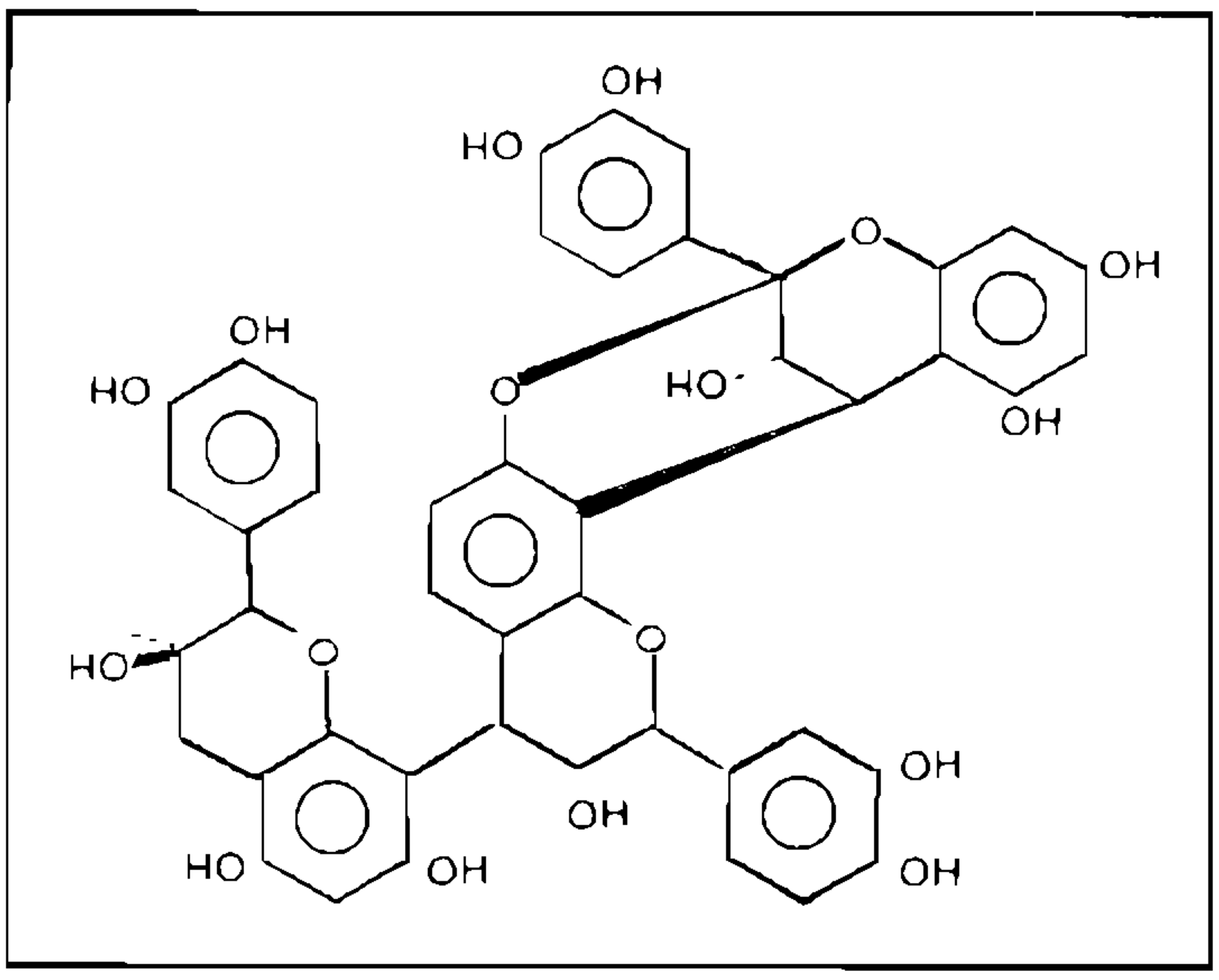


Fig. 4: a polimeric flavanol.

Other classes of natural compounds such as gossipol (Fig. 5) have been described as antineoplasic drugs. It is a chiralic substance found in cotton seeds. The rotation restriction is responsible for the existence of two isomers: (–) gossipol is antispermatogenic and anticancer agent; (+) gossipol produces leucocites DNA breakage. Studies carried out in São Carlos Federal University showed that fluorescent Schiff bases synthetised from this compound could be used as a probe for gossipol distribution.

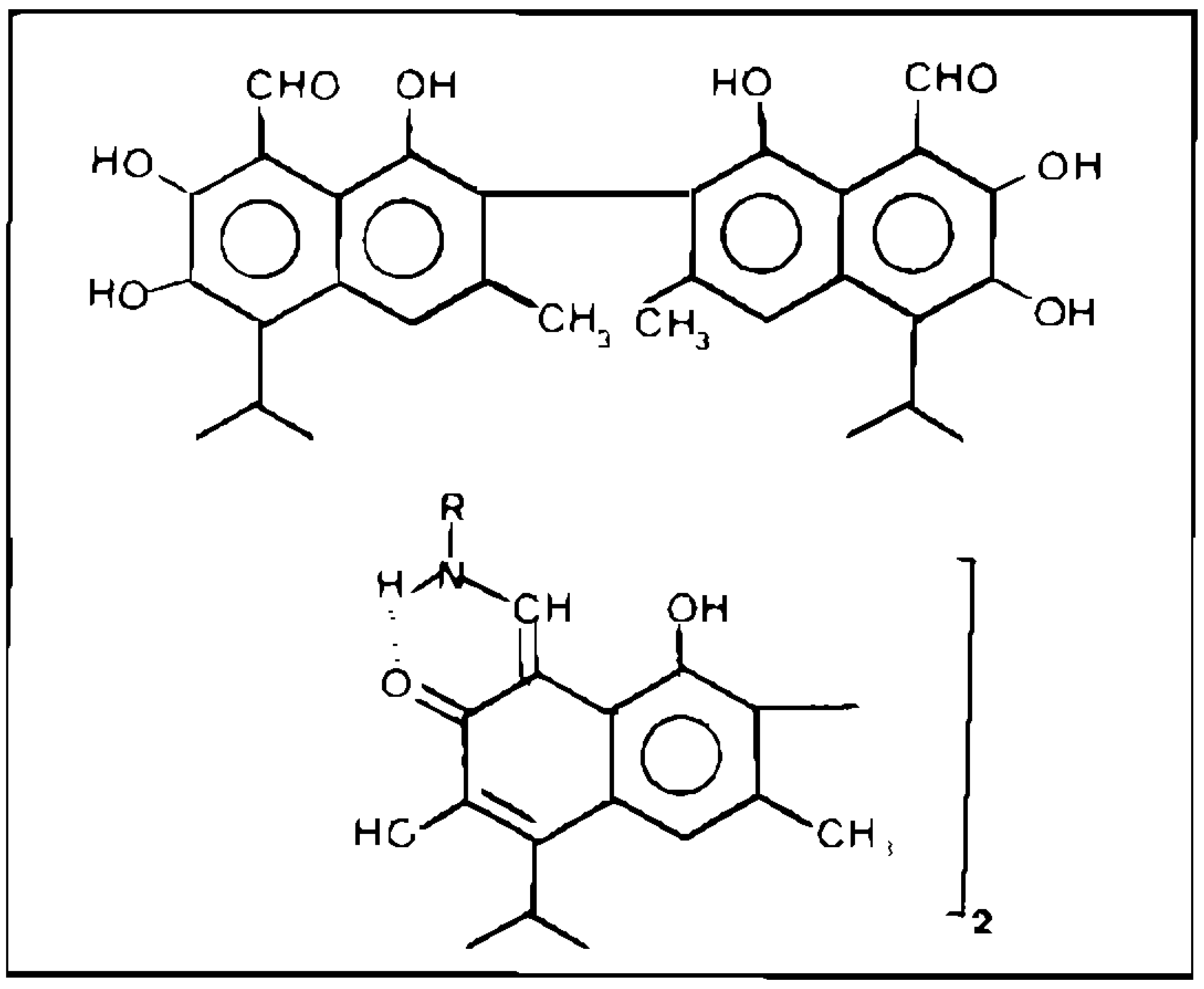


Fig. 5: gossipol.

In animal tissue, when fluorescein was used as the reagent, a very good correlation between gossipol concentration and fluorescence was observed (Cass et al., 1988).

Quinomes – Lapachol (Fig. 6) is a natural quinone, already in clinical use in Brazil. It has been widely studied in our country, particularly by A. V. Pinto et al. in Rio de Janeiro Federal University, as an antibacteria and anti *Trypanosoma cruzi* cercaria penetration. About 50 new compounds were synthetized in an attempt to improve activity. They also obtained by synthesis furanonaphthoquinones derivates. Some of these new compounds (Fig. 7) were tested in our laboratory for the evaluation of KB citotoxicity (Favaro et al., 1989).

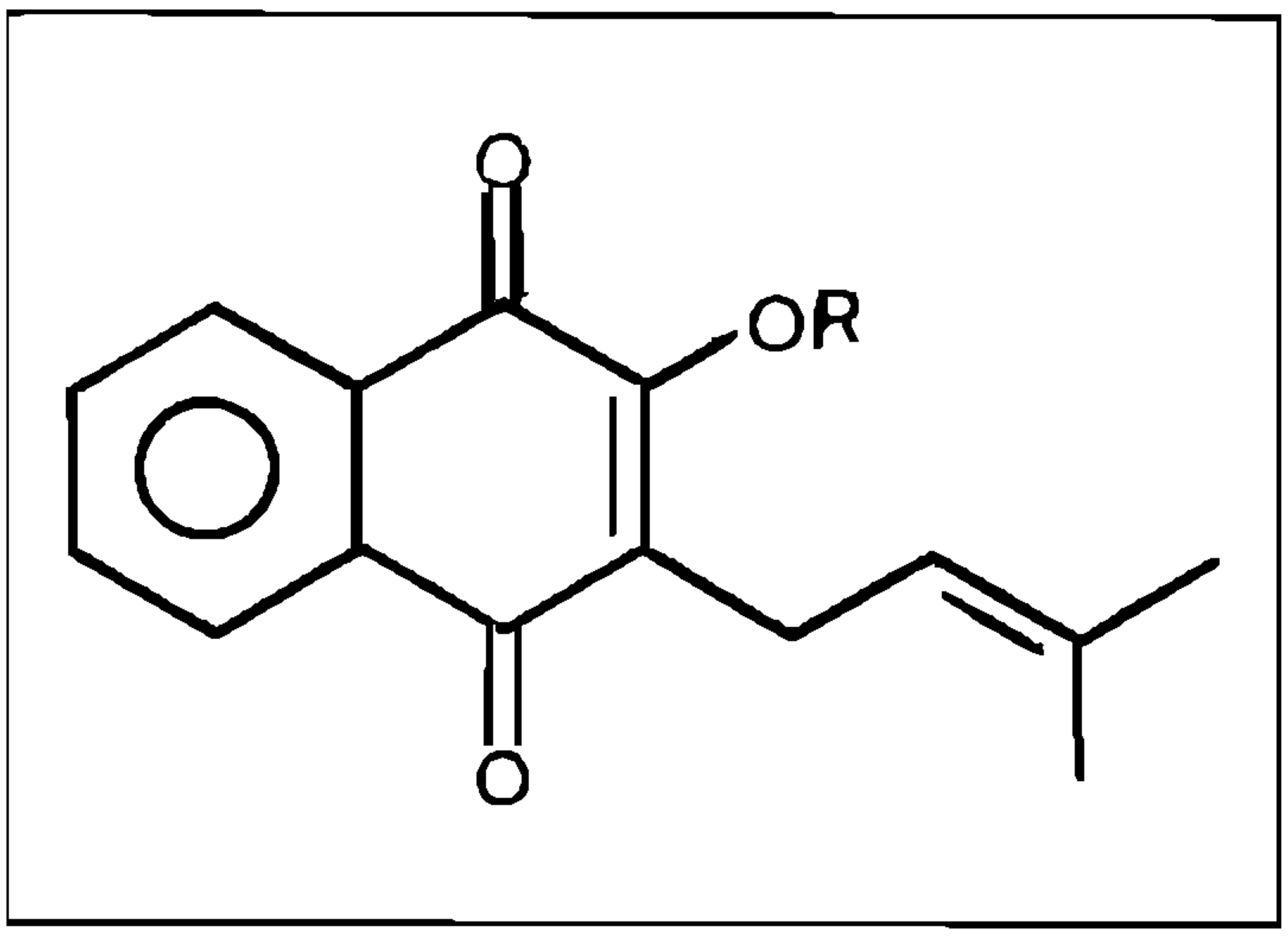


Fig. 6: lapachol.

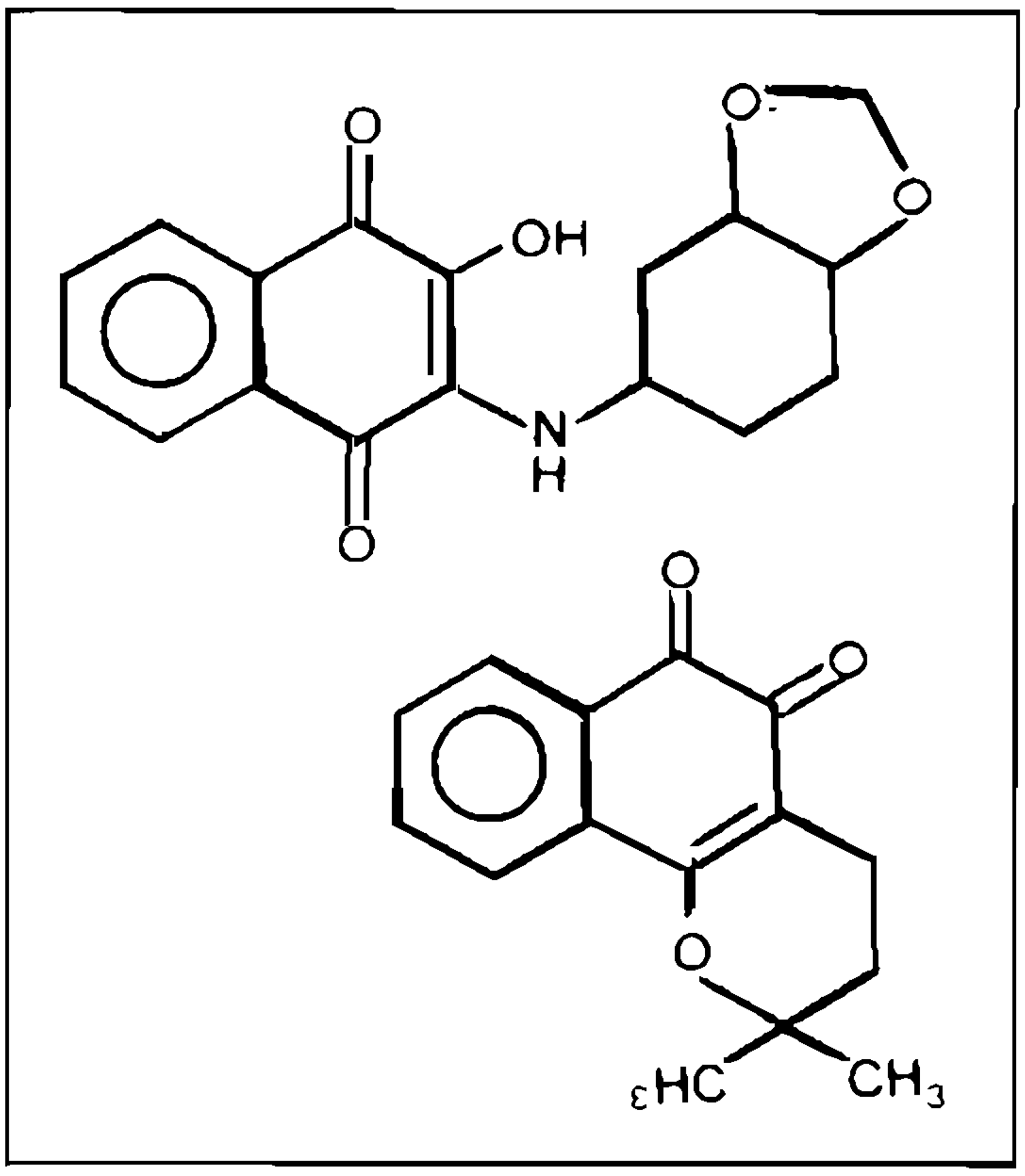


Fig. 7: KB active naphtoquinones.

Through chemical modification we could extend tumor activity of naphtoquinones such as lapachol, lawsone and juglone to ascitic neoplasias. The original substances were only active in solid experimental tumor Walker 256. Fig. 8 shows naphthoquinones glico-acetil-derivatives capable of inhibiting ascitic tumors (Linardi et al., 1975; De-Oliveira et al., 1978).

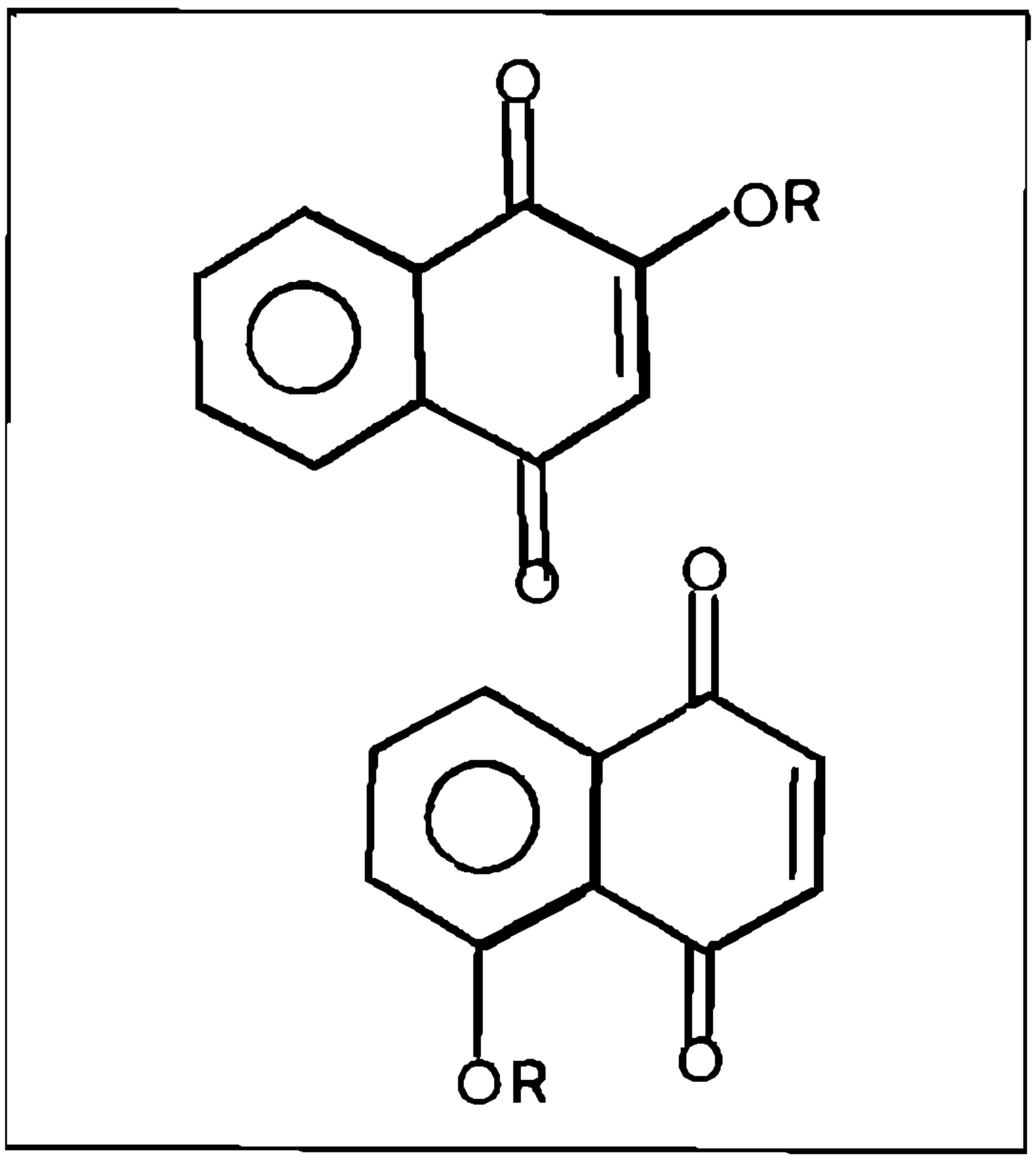
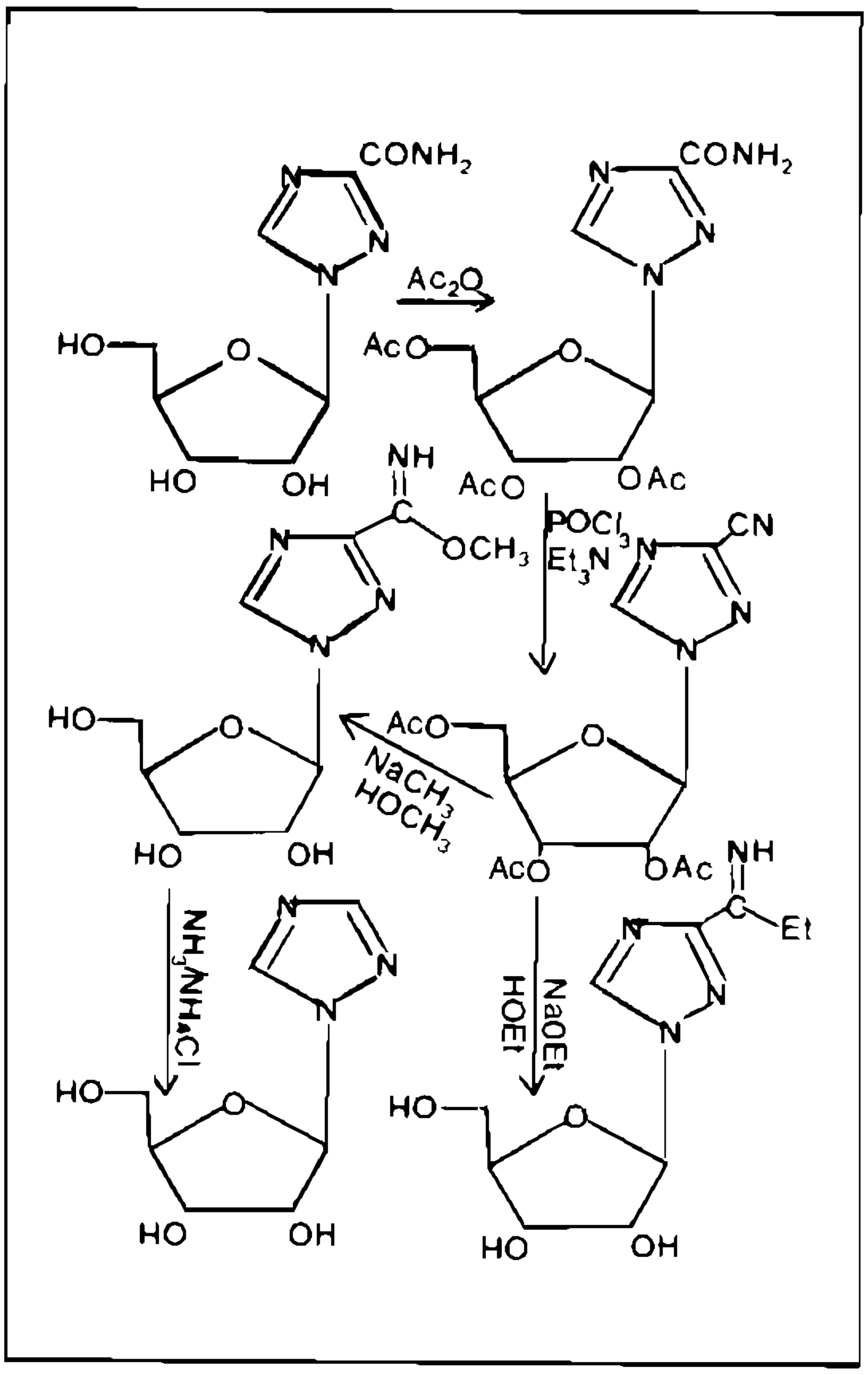


Fig. 8: naphthoquinones acetoglico derivatives.

Ribavirin a nucleoside was recently studied by Kini et al. (1988). Two active derivatives were obtained and tested in L1210 murine leukemia. The route to obtain these substances in shown in Scheme 2.

Our group also worked with ribavirin and its acetate, in an attempt to improve drug action. We succeded in obtaining anticancer activity in Walker 256 with both compounds, although the original drug was more active in minor doses than the prepared acetate (respectively 200-300 mg/kg and 600 mg/kg, for ribavirin acetate).

Sugar derivatives can be introduced in active molecules as a modifyer of their pharmacological action. Two groups in Brazil, led by A. B. Oliveira (Universidade Federal de Minas Gerais, Belo Horizonte, MG) and A. Massaioli (Universidade Federal de São Paulo, Unicamp, Campinas, SP) are working in this field. The former producing diaminosugars and the latter fluorosugars.



Scheme 2: Ribavarin derivatives.

An important class of pharmacological active agents is the alkaloid group. Our team is particularly interested in pyridocarbazol compounds on account of the French sucess in obtaining an ellipticine derivative which is used against human breast cancer. So we decided to synthetize olivacina (De-Oliveira, 1988) to overcome the lack of natural compound for further researches.

Despite the fact that both alkaloids, ellipticine and its isomer olivacine, are deleterious to normal and to cancer cells, as we also showed (Koseki et al., 1989), its significant *in vivo* activity points to the search of active and less toxic derivatives.

Several organic and inorganic salts of olivacine were prepared by our group and tested in our laboratory against P388 and L1210 leukemias.

Some results with organic salts are shown in Fig. 9.

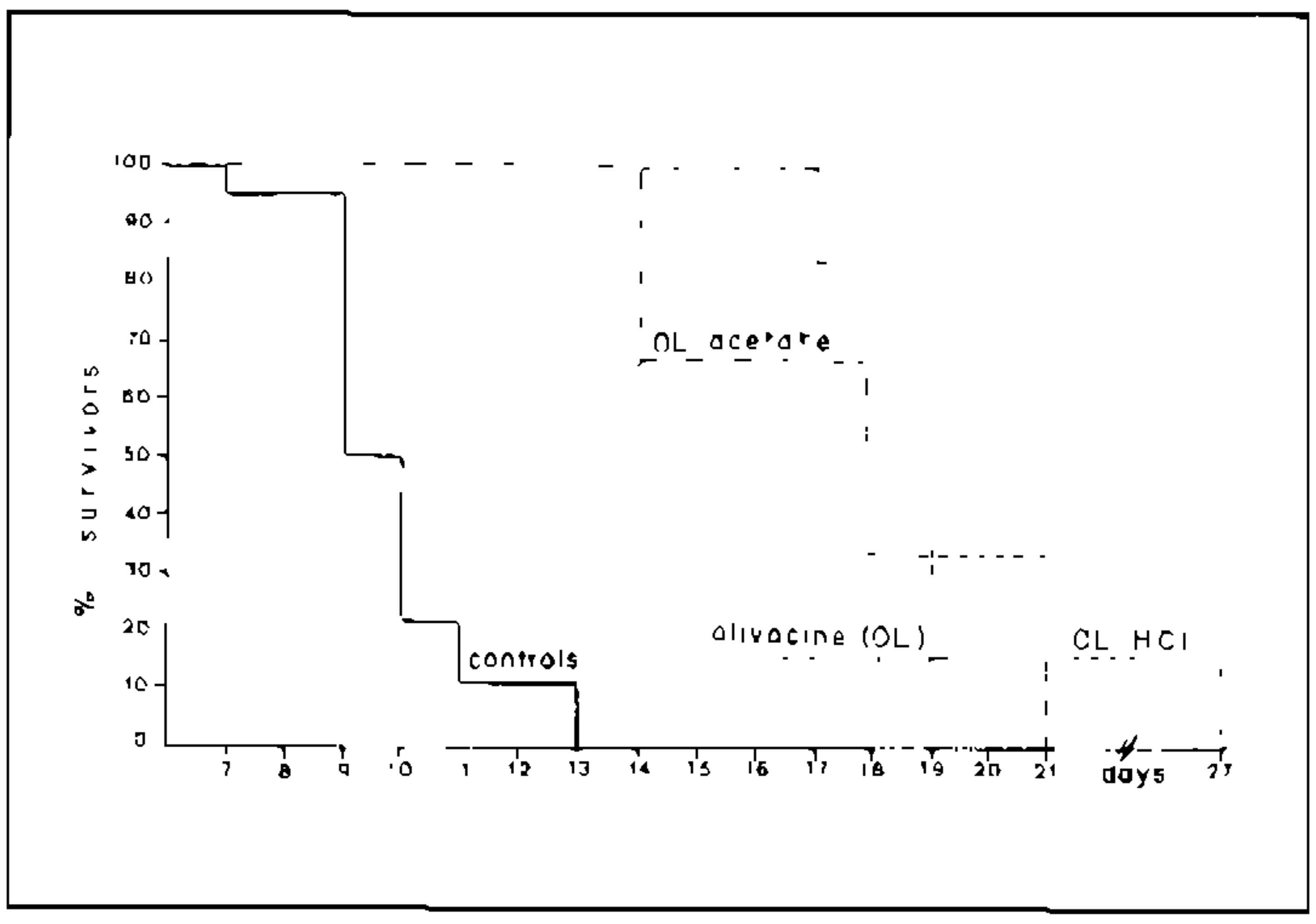


Fig. 9: survivor curves of leukemic inoculated (L1210) mice.

Olivacine and allipticine hydrobromides are more active than hydrochloride of the respective bases when tested in mice inoculated with P388 or L1210 (De-Oliveira, 1988).

A few preliminary experiences with olivacine glucoacetil derivatives also showed activity against L1210 (De-Oliveira & Linardi, 1978).

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