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DARK AND PHOTOCHEMICAL INTERACTIONS BETWEEN MONOFUNCTIONAL FUROCOUMARINS AND DNA.

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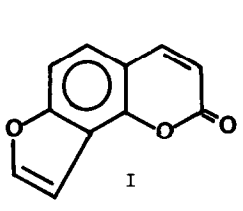
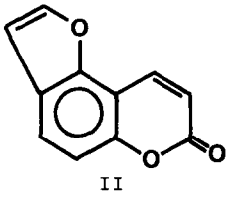


I



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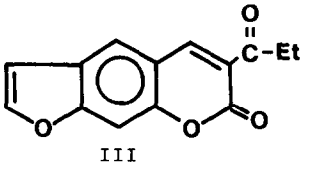

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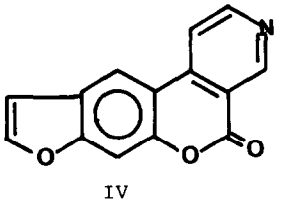
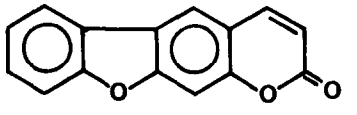


IV

Figure : molcular structure of : angelicin I;allopsoralen II; 3-CPs III; pyrydopsoralen IV;benzopsoralen V.



V

Furocoumarins are a family of naturally occurring and synthetic compounds showing marked photobiological properties. Some linear furocoumarins (psoralens) are used as drugs for the photochemotherapy of some skin diseases (1).One of the most peculiar characteristics of the furocoumarins is their ability to photobind covalently with the pyrimidine bases of DNA , forming both mono- and bi-functional adducts(inter-strand cross-links) (2). After the discovery that psoralens are able to photoinduce inter-strand cross-links in B-DNA ,a debate over the photobiological role of mono- and bifunctional cycloadducts was opened and in the last ten years the problem has been widely investigated. Over the same period, the approach has been to prepare and study new monofunctional compounds with the aim both of investigating the photobiological role of monofunctional lesions , and of obtaining new photochemotherapeutic agents safer than psoralens.

Various molecular model have been followed to obtain monofunctional agents: the angular model(angelicin and allopsoralen). These compounds ,like other furocoumarins, undergo intercalation inside duplex DNA. However , owing to their angular structure , they can photobind to the macromolecule inducing only monoadducts(3). In order to increase affinity towards DNA for the formation of the intercalated complex ,as well as to increase DNA-photobinding ,one or more methyl groups have been introduced into the angelicin molecule(3,4). Three series of methylangelicins have been prepared and studied in terms of photochemical and photobiological properties as well as, for a few compounds, therapeutical activity (4).The most promising compound is 4,6,4'-trimethylangelicin (5). In terms of clearing psoriasis it shows a terapeutical activity higher than that of 8-MOP. The furan side monoadduct 4,5'-dimethylangelicin-thymine, formed in the photoreactions between the angelicin and DNA, has been isolated; it shows a cis syn configuration similar to that shown by the cycloadducts isolated from DNA photomodified by various psoralens(4) further supporting the intercalation of the angelicin moiety inside duplex DNA.

Allopsoralen has also been methylated for the same resons as for angelicins. Methylallopsoralens undergo intercalation in duplex DNA and ,by subsequent

irradiation they photobind monofunctionally to the macromolecule. Clinically tested 4,7-dimethylallopsoralen showed poor activity in clearing psoriasis. The furan and the pyrone side monoadducts between two trimethylallopsoralens and thymine were isolated and characterized; they show a cis-syn configuration analogous to that of psoralens-thymine monoadducts (4).

A second model followed consists in utilizing psoralens which have been modified by substituents that cancel the reactivity of one of the two photoreactive sites of the psoralen molecule. The most studied is 3-carbethoxypsoralen (3-CPs). Interactions between 3-CPs and DNA have been widely studied . 3-CPs shows a relatively low affinity towards DNA for dark complex formation and by subsequent irradiation it photobinds with low efficiency to DNA in vitro. It should be noted however, that it does photobind with pyrimidine bases but also with purines(6). The furan side mono adduct between 3-CPs and thymine ,formed in the photoreaction with DNA ,was isolated . In analogy with the other furan side monoadducts isolated from DNAs photomodified by various psoralens, it shows a cis-syn configuration (6). 3-CPs show a strong oxygen-dependent lethality although this effect does not play any role in terms of mutagenicity(4). 3-CPs has been tested clinically but shows poor ability in clearing psoriasis(4).

The last model followed consists in the condensation of a fourth aromatic ring in the molecule of psoralen at the level of the furan or pyrone side thus cancelling one of the two photoreactive sites (benzopsoralens and pyridopsoralens). The most studied are the pyridopsoralens and in particular 7-methylpyridopsoralen (MePyPs) .This compound photobinds effectively to the DNA of Chinese hamster cells and shows a very strong photolethal effect on the same cells as well as on human fibroblasts(7). At equal photoaddition, MePyPs-induced monoadducts are more effective than 8-MOP-induced lesions in terms of both lethal effect and mutagenic activity. This may be due to the lower repairability of MePyPs-DNA monoadducts compared with that of 8-MOP induced lesions(7). Until recently , in order to explain the differences in antiproliferative and genotoxic activity of furocoumarins, emphasis was put mainly on the difference between mono- and bifunctional compounds, considering in general that monofunctional lesions should cause less pronounced photobiological effect. In this connection, Averbeck et al. (8) found that ,in diploid yeast, at equal degrees of photobinding of 8-MOP to the yeast DNA, the monoadducts (induced by 405 nm radiation) were less effective than the mixture of mono- and diadducts (induced at 365 nm) in terms of induction of lethal effect, mutation and mitotic gene conversion. The data obtained with MePyPs ,however, suggest that the steric parameters of the monoadducts can play an important role in terms of repairability with consequent photobiological effects. In other words it is not possible to predict a priori that the consequences of monofunctional adducts are generally less pronounced than those deriving from bifunctional lesions.In the case of the comparison of mono-and bifunctional lesions deriving from the same furocoumarin , as for 8-MOP (see above), owing to the similarity of the molecular parameters of mono- and diadducts,monoadducts are less effective than diadducts. However, for other monofunctional derivatives like benzopsoralen and pyridopsoralen , the structural properties of the monoadducts can play a more pronounced role in terms of photobiological and phototherapeutical effects. In such a way the research should be developed at molecular level studying how the structural properties of the monoadducts can affect the photobiological and the phototherapeutical effect of monofunctional furocoumarins.

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