Life Sciences, Vol. 21, pp. 1245-1248 Pergamon Press
Printed in the U.S.A.

ALLYLBENZENE ANALOGS OF Δ^9-TETRAHYDROCANNABINOL AS TUMOR GROWTH INHIBITORS

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(Received in final form July 21, 1977)

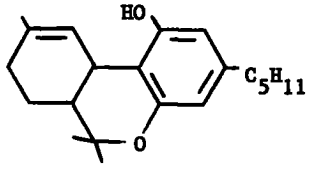
Summary

A series of substituted allylbenzene derivatives was tested in vitro for ability to inhibit cell growth in the KB cell line. None of the compounds was as active as Δ^9-tetrahydrocannabinol. It is suggested that inhibition of cell growth by cannabinoids requires a polycyclic system which may act by an intercalaction mechanism.

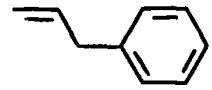
Recently a number of reports have been published which describe the ability of cannabinoids to act as tumor growth inhibitors (1-3). Cannabinoids have been shown to inhibit the synthesis of nucleic acids in human and other mammalian, in chicken, and in protozoan cells (4-11). Tetrahydrocannabinol also has been demonstrated to possess antibacterial activity (12).

Although extensive studies have been reported by many investigators relating to structure activity relationships of cannabinoids, these have dealt almost exclusively with complex polycyclic molecules which bear a very close structural similarity to Δ^9-tetrahydrocannabinol (Δ^9-THC) itself.

In 1972, Engelbrecht et al. (13) described depressant activity for a simple series of allyl benzene derivatives. These workers further suggested that the simple allyl benzene moiety might represent the pharmacophoric entity which is present in Δ^9-THC. This comparison is illustrated below. It was thus decided to investigate the possibility that this moiety might be responsible for the antitumor activity of Δ^9-THC. A series of allylbenzene derivatives was then prepared and evaluated for cytotoxicity in the KB cell line.



Δ^9-Tetrahydrocannabinol



Allylbenzene

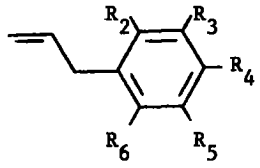
Methods

A. Chemistry. All compounds were prepared by thermal Claisen rearrangement of the appropriate allyl phenyl ethers. Compounds 1,3, and 9 were obtained commercially. New compounds were characterized by the usual physicochemical methods. In cases where the Claisen rearrangement gave two isomeric products pure samples were prepared by column chromatography over silica gel and elution with either 1,2-dichloroethane or chloroform. Structural assignments of these products were based on their nmr spectra (14).

B. Cytotoxicity Measurements. The KB cell line, derived from a human epidermoid carcinoma (15) was supplied by Arthur D. Little, Inc. to the Cell Culture Laboratory. The cell culture screen was performed according to the standard protocol (16). Drugs were dissolved in ethanol before final dilutions to 10^{-3}, 5×10^{-4}, 10^{-4}, 5×10^{-5}, and 10^{-5} molar in the growth medium. Samples were run in triplicate. The ED_{50} is the dose of drug which inhibits cell growth to 50% of the untreated control values. The ED_{50} values were obtained by extrapolation from a least squares fit of the dose response curve.

TABLE I

ED_{50} Values for in vitro Inhibition of KB Cell Growth by Substituted Allylbenzenes



Compound	R_2	R_3	R_4	R_5	R_6	$ED_{50} \times 10^4$ Molar
1	H	H	H	H	H	>10
2	OCH_3	H	H	H	H	>10
3	H	H	OCH_3	H	H	8
4	OH	H	$n\text{-}C_5H_{11}$	H	H	5.23
5	OH	H	CH_3	H	OCH_3	4.93
6	OH	H	$CH(CH_3)C_4H_9$	H	H	4.66
7	OCH_3	H	H	OCH_3	H	4.45
8	OH	H	H	OCH_3	H	3.95
9	H	OCH_3	OCH_3	H	H	3.71
10	OH	H	OCH_3	H	CH_3	3.17
11	OH	H	H	H	OCH_3	2.37
12	OH	OCH_3	H	H	H	2.19
13	OH	H	H	H	$CH(CH_3)C_4H_9$	2.12
14	OH	H	H	H	H	2.01
15	OH	H	OCH_3	H	H	1.60
16	OH	H	H	H	$n\text{-}C_5H_{11}$	1.52

Results and Discussion

The ED_{50} values for cell growth inhibition and the structures of the compounds tested are shown in Table I. For comparison, the ED_{50} values for olivetol (5-n-pentylresorcinol) and for Δ^9-THC were found to be 2.03×10^{-4}M and 6×10^{-5}M, respectively. As can be seen, none of the allylbenzene derivatives tested proved to be as potent as Δ^9-THC. It is difficult to draw meaningful conclusions about structure activity relationships, although there appear to be some trends. For example, compound 4 would seem to be more similar to THC than compound 14, and yet the latter is more potent. On the other hand, the presence of a large alkyl group adjacent to the allyl seems to increase activity, as in compound 13. This may argue in favor of an intercalation mechanism of action for THC. The presence of an ortho hydroxy also seems to be necessary, as seen from a comparison of the ED_{50} values for compounds 2 and 14. This parallels findings of requirements for psychoactive properties in the cannabinoids (17).

In summary, it would appear that the requirement for antitumor activity of cannabinoid like substances might involve a polycyclic structure. The simple allylbenzene moiety, although it may be responsible for the psychoactive properties of THC, is not sufficient to impart significant antitumor activity.

Acknowledgement

This work was supported by grants from the Purdue University Cancer Research Committee.

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