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论文

恩其明(AT-1840)开环类似物的合成和抗癌作用 1.通过光化反应合成取代-2-羟基-菲啶溴烷季铵盐

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摘要:

根据恩其明(ungeremine,1.)分子中存在次甲基N-O-O三角和内铵盐结构,这可能和其抗肿瘤活性有密切关系的设想,合成了它的开环类似物2-羟基-8,9-次甲二氧基菲啶溴甲(或乙)烷季铵盐(3a和3b)和2-羟基-8,9-二甲氧基菲啶甲(或乙)烷季铵盐(4a和4b)等有关化合物,作为抗肿瘤作用的比较,以探讨恩其明的构效关系。动物试验表明:化合物3a对小鼠艾氏腹水癌有明显抑制作用,小鼠生命时间延长130～140%,其它化合物则无明显活性。

关键词： 恩其明(曾使用石蒜碱内铵盐的名称) 抗癌作用 艾氏腹水癌 构效关系 光化反应

ANTITUMOUR ACTIVITY OF OPEN RING ANALOGUES OF UNGEREMINE (AT-1840)——PREPARTION OF SUBSTITUTED N-ALKYL PHENANTHRIDINIUM BROMIDES BY A PHOTOCHEMICAL REACTION

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Abstract:

Ungeremine(I, AT-1840), an alkaloid from *Ungernia minor*, possesses a marked inhibiting activity against the following experimental tumour systems: EAC, L1210, P388, Lewis lung carcinoma, Yoshida sarcoma and sarcoma 180.In the present investigation, a number of its open ring analogues, 2-hyroxy-8,9-methylenedioxy-N-alkyl-phenanthridinium bromides(3) and their 8, 9-dimethoxyanalogues,(4) were prepared from bromopiperonal and bromodimethoxy-benzaldehyde through a 5-step synthesis including photochemical cyclization.Bromobenzaldehydes were converted to their Schiff bases(7) with 4-isopropoxyaniline, followed by reduction to secondary amines(8) by sodium borohydride or potassium borohydride. Phenanthridines(9) were obtained by photochemical cyclization and subsequently were transformed to their quaternary ammonium iodies(10). The final products(3a, 3b, 4a and 4b) were obtained by treating compounds(10) with a mixture of hydrobromic acid and acetic acid.From the intermediates(9a) and(9b) 2-hydroxy phenanthridines(12a), (12b) and 2-isopropxy-phenanthridinium bromides were also prepared.Compound 1 with a potential betain structure(a positive quaternary amine group and a negative phenolic group) on the one hand and a methylene N-O-O triangle on the other attracted our attention to study the contribution of these features. The above compounds were thus prepared and screened on EAC in mice. The SAR was discussed as follows:1. Compounds 9 and 12, lacking phenolic group or a quaternary amine group, can not form betaine intramolecularly and thus showed no activity. 2. Although compounds(4a and 4b) are betaines, they do not have methylene N-O-O triangle in their molecules and also showed no activity.3. Compounds such as 3a and 3b do have both betaine and methylene N-O-O triangle in their structures. But 3a exhibited marked activity while 3b did not. It has been known that ethyl group at the quaternary N-atom is much easier to be eliminated. It is reasonable to assume that 3b can be converted to 12a by eliminating the ethyl group *in vivo*, thus losing its betaine forming ability.4. It seems that both betaine and methylene N-O-O triangle in ungeremine may be critical for exhibiting antitumour ability. Fission of the B ring of ungeremine will not affect its betaine forming ability and the antitumour activity of the alkaloid is maintained.

Keywords: Antitumor activity Ehrlich acites carcinoma Structureaction Relationship Photochemical reaction. Ungeremine

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