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The antiviral (RNA & DNA) profile of some incomplete C-nucleosides inspired from natural β- carboline (pyrido [3,4-b] indole) scaffold; pharmacology of the intermediates in the total synthesis

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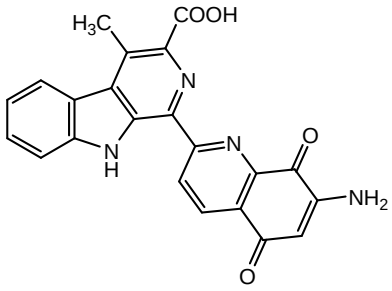
This work is presented as a dedication for the memory of Nabil M. Omar;[b] the co-supervisor of Ph D thesis (author SGA)

ABSTRACT

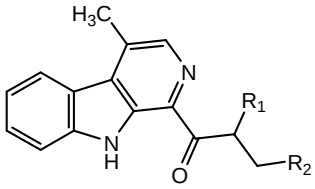
The in-vitro assessment of antiviral activity against Flu-A, HIV, RS, HSV type-1, HSV type-2, and HCMV provided that β–carboline scaffold attach to alkyl substituted with oxo, oxy or polyoxy groups can be further developed as antiviral and/or anticancer agents. Screening of the potential cytocidal properties using HL-200 and several other cell-lines was also done.

INTRODUCTION

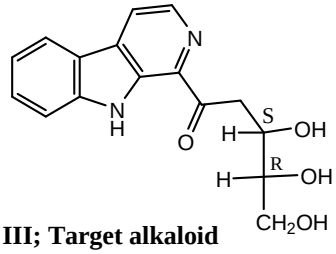
2-deoxyglucose; the radio-labeled diagnostic agent in its form (fluorine-18), was therapeutically poved as an anticancer and antiviral agent, used as an adjunct to chemotherapy and radiotherapy in the treatment of solid tumors (lung, breast, pancreas, head, neck, and gastric tumors). With respect to antiviral therapy, 2-deoxyglucose was shown to be effective against herpes simplex virus by affecting the virus' ability to penetrate cells [1]. From the alkaloids; eudistomines(natural antiviral and antitumor antibiotics) [2],[3], lavendamycin**I** and oxopropalines**II** (natural antitumor antibiotics) [4] are examples of β–carbolines; agents of high importance in medicinal chemistry. This work is realized in continuation of our interest in the design and investigation of synthetic, semi-synthetic and natural scaffolds of fused systems of the types 6-5-6 [5]-[7] and 6-5-5 [8]-[12] and verifying their different pharmacological activities. Here, it is realized the screening of potential antiviral and/or cytocidal activities for some synthetized β–carboline derivatives [5] as intermediates in the synthetic approaches to obtain a natural alkaloid **III** [13], [14]. These selected activities are basically influenced by several factors: 1- The antitumor activity of some β–carbolines.2-The relative structural coherence between some of the synthetized derivatives and oxopropalines D and G which were isolated from Streptomyces species G324 [15].3- Most of the investigated derivatives are considered as C-nucleosides with incomplete sugar moieties which render them as acceptable anti-metabolite candidates [16], [17].Differences between the reported oxopropalines D and G (**II**) with and the structure **III** are: the longer carbon chain attachment at C1, the higher number of hydroxyl groups substituents on the side chain, and the absence of methyl substituent at C4 of the skeleton.



I; Lavendamycin



II; Oxopropaline D (R^1 =OH, R^2 = OH
G (R^1 =H, R^2 =OH



III; Target alkaloid

MATERIALS AND METHODS

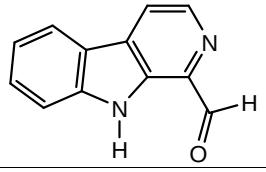
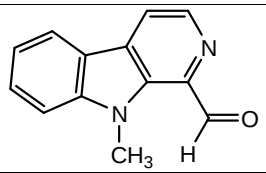
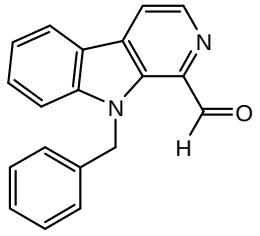
Standard cell-culture techniques were adopted by the research institute of TOSOH CO-LTD, Japan, to determine the 50% effective concentrations of the tested β–carboline derivatives (µM/ml) that arrest viral (EC50%) and cellular growth (CC50%) respectively (Table **1**). The following cell-lines were also used: MDCK, G-Hela, MT-4, and HEL. Azidothymidine (AZT) was used as a reference with the following activity characteristics: EC50 = 0.004 µM/ml, and CC50 = 131 µM/ml.

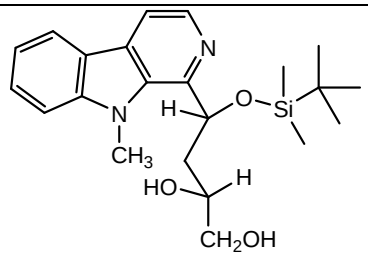
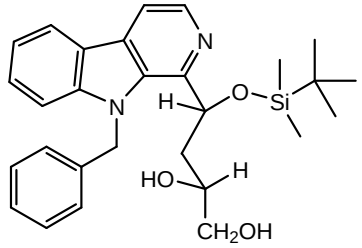
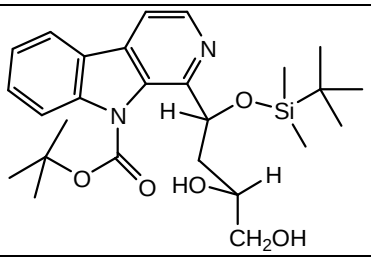
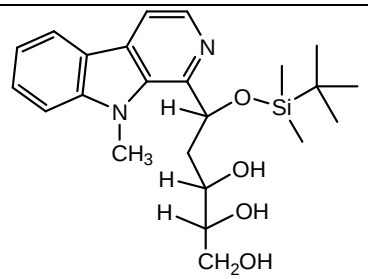
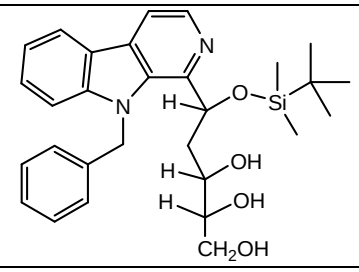
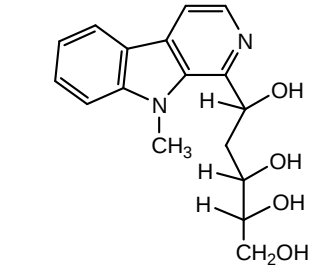
RESULTS AND DISCUSSION

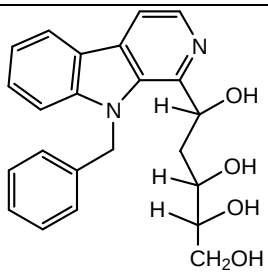
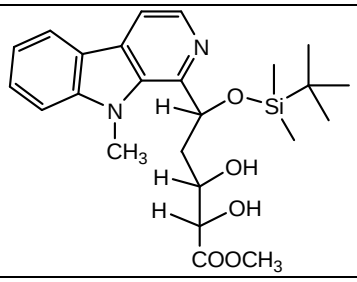
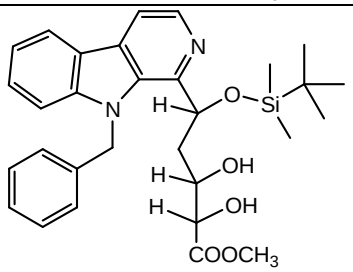
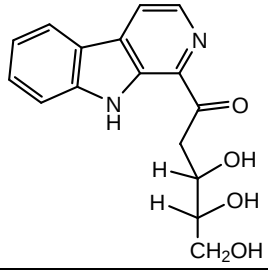
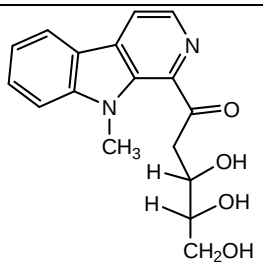
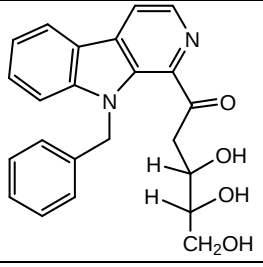
Since cellular growth arrest is usually focused on prevention of out-law replication of cellular DNA or RNA, potential antiviral and antitumor activities of several antimetabolites are not uncommon [18]. For this reason, the protocol involved in the presented work (Table **1**) for the biological evaluation of 15 derivatives comprised the following directions:

1-In vitro assessment of the antiviral activity using the following RNA and DNA viruses such as: Influenza virus type-1 (Flu-A; RNA), human immunodeficiency virus (HIV; RNA), respiratory syncytial (Rs; RNA), herpes simplex virus (HSV type-1 and HSV type-2; DNA), and human cytomegalovirus (HCMV; DNA).
2-In vitro screening of the potential cytotoxic properties using standard human promyelocytic leukemia cells (HL-60 cell line).

Table 1: The antiviral / cytotoxic effects of the derivatives (µM/ml)

No.	structure	Value	Flu-A	Rs	HIV	HSV-1	HSV-2	HCMV
1a		EC50	8.9	35,4	1.8	7.5	7.5	4.0
		CC50	35.4					
1b		EC50	9.1	6.9	0.36	1.67	1.67	0.8
		CC50	9.1					
1c		EC50	6.42	4.42	1.7	0.8	0.8	0.8
		CC50	6.42					

2b		EC50	86.6	27.7	5.5	100	100	100
		CC50	86.6					
2c		EC50	4.21	2.21	4.4	4.11	4.11	2
		CC50	4.21					
2d		EC50	8.33	4.42	7.4	6.16	6.16	4
		CC50	8.33					
3b		EC50	100	53.8	7	69	69	50
		CC50	100					
3c		EC50	8.87	3.68	4.3	1.63	1.63	2
		CC50	8.87					
4b		EC50	100	100	45.3	100	100	100
		CC50	100					

4c		EC50	10	10	10	10	10	10
		CC50	10					
5b		EC50	8.92	4.42	2	8.23	8.23	4
		CC50	8.92					
5c		EC50	100	26.8	100	100	100	100
		CC50	100					
6a		EC50	100	100	8.6	45.5	45.5	20
		CC50	100					
6b		EC50	30.53	57.8	30.2	8.81	8.81	12.7
		CC50	30.53					
6c		EC50	100	90.6	12.5	22.8	22.8	10.2
		CC50	100					

From consideration of the results listed in table**1**, it can be easily seen that most of the tested β- carbolines bearing varied levels of the antiviral estimations. Most of the tested compounds are of high activity against HIV. The activity against HSV-1 and HSV-2 appear to be equal in all derivatives.

Most of the derivatives pear good to poor antiviral activities on different types of viruses, at the same time giving good to poor cytocidal activity. None of tested compounds acquire a safe selectivity index (CC50/EC50) to be considered as antiviral agent. A generalized cytotoxic activity recommends further detailed investigation of these C-glycosides.

Meanwhile, the following empirical structure-activity relationship (SAR) can be made for the observed cytotoxic activity of the tested compounds:

1-The highest activities were manifested by two of the β-carboline-1-carbaldehydes (**1b, 1c**) and one of the triol-1-OTBS ethers (**2c**). N-9-Benzyl derivatives (**1c, 2c, 3c**) being the most active.
2-The least active derivativesare found among the β-carbolinetetrols (**4b**) and the 1-OTBS methyl ester derivatives (**5c**).
3-With few exceptions (**5c, 6c**), the N-9-benzyl derivatives are generally more cytotoxic than the corresponding N-9-methyl analogues.
4-Substitution of the 9-NH function of the tested β-carbolines by other functions such as N9-methyl, N9-benzyl or even N9-(BOC) group increases antiviral and cytotoxic activity.
5-The target 1-oxo β-carboline derivatives; the ketones (**6a, 6b, 6c**), generally show weak antiviral and cytotoxic activity. However, the N9-methyl derivative is comparably better than the other two derivatives (N9-H or N9-benzyl).
6-Bulky groups (e.g. BOC) on the substituent at C1 and at N9 (e.g. benzyl or BOC) increase both of the antiviral activity and the cytocidal activity.
Obviously, these conclusions are just approximations, and, precise quantitative structure activity relationship (QSAR) as well as further antiviral and cytological studies are needed to explore the potential utility of the candidate β-carboline derivatives as hopeful antiviral and/or antineoplastic agents

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