Synthesis and anti-HSV-1 activity of novel β-carbolines containing a substituted thiazolidin-4-one ring at C-3

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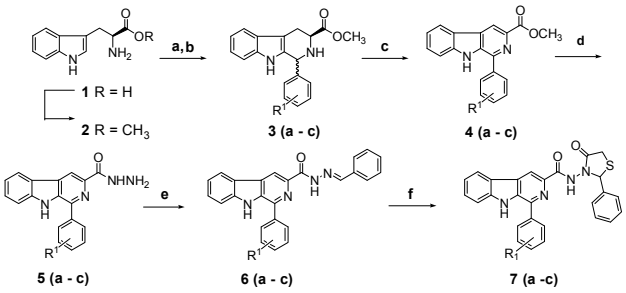
INTRODUCTION

Compounds containing heterocyclic nucleus have shown a range of pharmacological and biological properties. Our research group has demonstrated that appropriate heterocyclic groups attached to the 3-position of the β-carboline skeleton result in more active derivatives, with reduced toxicity[1, 2]. In the present work, we performed the synthesis and antiviral activity evaluation of β-carboline derivatives containing a substituted 4-thiazolidinone nucleus at 3-position.

RESULTS AND DISCUSSION

The synthetic route for preparation of the β-carboline derivatives **7a-c** is outlined in **Scheme 1**.



R^1 = a) *p*-OMe, b) H, c) *m*-NO_2

Reagents and conditions: (a) MeOH, H_2SO_4 (cat), reflux, 48 h, 92%; (b) R^1CHO, TFA, DCM, rt 80-91%; (c) S, xylene, reflux, 48 h to 0 °C, 3 h, 70-90%; (d) $NH_2NH_2.H_2O$, EtOH, reflux, 48 h, 72-91% e) PhCHO, DMF, MW 67-83%; f) $HSCH_2COOH$, *p*-TsOH (cat), toluene 68-71%.

Scheme 1. Synthetic route for β-carbolines **7a-c**

The β-carbolines containing the 4-thiazolidinone ring at 3-position (**7a-c**) were prepared from the commercial *L*-tryptophan (**1**). The Pictet Spengler condensation of the *L*-tryptophan methyl ester (**2**) with appropriate aromatic aldehydes, in acidic media, afforded the tetrahydro-β-carbolines **3a-c**. Oxidation of **3a-c** with sulfur, in xylene, followed by treatment of the β-carbolines **4a-c** with hydrazine hydrate gave the respective carbohydrazides **5a-c**, as previously reported[2]. The synthesis of the desired derivatives **7a-c** was possible by the reaction of imines **6a-c** with mercaptoacetic acid, using catalytic *p*-toluenesulphonic acid. The intermediates **6a-c** were prepared by the condensation of carbohydrazides **5a-c** with benzaldehyde, in DMF, under microwave irradiation.

The antiviral activity of the synthesized compounds was performed against *Herpes simplex* virus type 1 (HSV-1). Derivatives **7a-c** showed potent antiviral activity (EC_{50} values in the range of 0.80 to 2.02 μM), and high selectivity (SI>200) (**Table 1**).

Table 1. Antiviral activity of **7a-c** against HSV-1

Comp	EC_{50}[b] (μM)	CC_{50}[a] (μM)	SI[c]
7a	0,80±0,117	467±14,142	592,5
7b	2,15±0,424	506±6,429	235,0
7c	2,02±0,494	1080±37,859	533,9

[a] Concentration at which 50% cytotoxicity is observed
[b] Concentration at which 50% efficacy in antiviral assay is observed
[c] Selectivity index (CC_{50}/EC_{50})

CONCLUSION

In this work, we have synthesized β-carboline derivatives containing a substituted 4-thiazolidinone nucleus attached at position-3. The synthesized compounds showed potent antiviral activity and high selectivity against *Herpes simplex* virus type 1 (HSV-1).

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