Synthesis and Structure-Activity Studies of Peptide-Acridine/Acridone Conjugates

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Abstract: This paper consists in information about structure, synthesis and biological activity of peptide-acridine/acridone conjugates which are potential anticancer, antiviral and antiprion drugs.

Keywords: Peptide-acridine, peptide-acridone, structure, synthesis, biological activity.

INTRODUCTION

Nowadays, the focus of attention while designing molecules is to look for compounds with a wide range of biological properties. The introduction of a new substitution to the motif of an appropriate molecule may have an influence on the activity of that compound. In the last few decades, acridines which are known as antitumor [1-5], antiviral [6-8], antiprion [9,10], antimicrobal [11], antiinflamatory and analgesic agents [12] have been in the center of interest of scientists. Those pharmaceutical properties have led scientists into modifying the acridine substitution pattern.

Amsacrine as an acridine derivative belongs to a versatile class of multitarget anticancer chemotherapeutics. The aromatic molecules demonstrate a noteworthy class of compounds which interact with biological targets such as topoisomerase I and II (topoI or II) by intercalation to double-stranded DNA (dsDNA), disturbing the synthesis of nucleic acid and inhibiting enzymes [1,13,14]. Moreover, heterocyclic molecules also play a secondary role in different biochemical protein metabolisms. Novel acridine compounds demonstrated promising results towards proteasome [14] and protein kinase [1].

In addition, acridine molecules constitute a nucleic acid selective fluorescent cationic dye which is used for cell cycle determination. Imaging agents can be applied in diagnostic methods to identify infected tissues [15]. Interestingly, bifunctional acridine molecules exhibit unusual chromophoric properties which are associated with participation in selective electron-transfer processes. This system of rings shows quantitative fluorescence yields and indicates chromophore-selective and spacer-length- and ionic-strength-dependent interactions with DNA that can have potential applications as fluorescent probes in biology [16-18].

In this paper, we wish to pay attention to a novel group of peptide-acridine/acridone conjugates, to their method of synthesis and also the wide range of biological properties of those compounds.

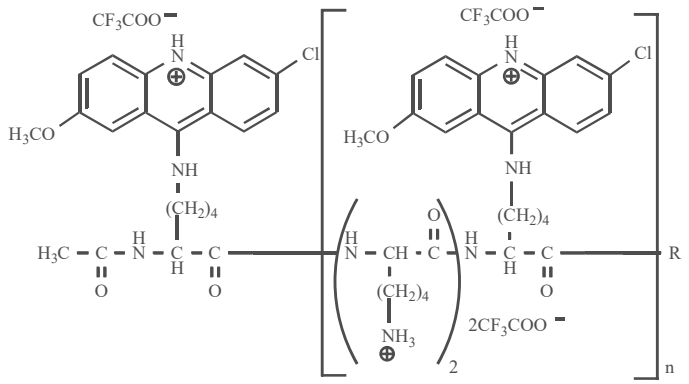
SYNTHESIS OF PEPTIDE-ACRIDINE/ACRIDONE

Nowadays, scientists have been focusing their attention on peptide-acridine/acridone conjugates. The techniques of chemical synthesis of that group of compounds are very diverse. There is the classical synthesis in solution phase and also the modern solid phase synthesis for preparing these analogues. Both strategies require different coupling agents to obtain the expected conjugates. Some of them are based on reactive acylating agents which are formed from acid in separate steps and others – where the acylating agents are generated in situ from acid in the presence of the appropriate amine-compound by the addition of coupling or activation agents [19-23]. The choice of method to synthesize acridine/acridone-conjugates varies depending on different factors e.g. the scale of synthesis, the length of the peptide and the yield.

In this article we want to present a few common methods to obtain peptide-acridine/acridone conjugates. Nowadays, the most comfortable and widespread method of synthesis of peptide conjugates is the solid support strategy.

Solid Phase Synthesis

Ueyoma *et al.* [24] synthesized a very interesting group of compounds that included some acridine in the skeleton of a molecule (Fig. (**1**)). Starting from Fmoc-Lys-OH with a 9-phenoxyacridine derivative a bond was formed between the ε-amino group of lysine and the acridine unit. Compounds **2-5** were obtained in reaction of Fmoc-Lys(Boc)-OH with previously prepared Fmoc-Lys(Acr)-OH on solid support. Synthesized polyacridine conjugates were cleaved from resin with *m*-cresol, thioanizole and trifluoroacetic acid (TFA). The same method of synthesis was used by Takenaka's group to prepare bis-acridine orange analogue (**6**) (Fig. (**2**)) [25].



1: n=0, **2**: n=1, **3**: n=2, **4**: n=3, **5**: n=4
1: R=OCH_3, **2-5**: R=NH_2

Fig. (1). Bis-, tris-, tetrakis- and pentakis-acridinyl peptides [24].

Mizuki *et al.* [26] noticed the synthesis of bis-acridine orange peptides according to Scheme **1**. Firstly, compound **9** was obtained which was used in the next step of the synthesis. The tetrapeptide was prepared on Fmoc-Sieber-PEG-resin by application of the peptide synthesizer method. The introduction of acridine orange moieties on the ε-amino group of lysine was possible because of the use of *tert*-butoxycarbonyl (Boc) and 4-methyltrityl (Mtt) protected amino groups. The selective removal of Mtt (ε-amino protected group) led to the product and then to the liberation from resin.

Carlson *et al.* [19] described the synthesis of peptide-acridine derivatives which started from an appropriate substrate: the receiving acid was used for the preparation of 9-anilinoacridine-4-carboxamide (**15**) wherein the activated product was attached to the short peptide chain through a linkage to the *N*-terminus. The needed tripeptide was prepared using standard Fmoc-strategy on *Rink* amide resin. *N*-hydroxysuccinimide (NHS) ester reacted with the free amino terminus of the solid supported peptide chain and gave compound **17** (Scheme **2**) after the cleavage with TFA, triisopropylsilane (TIS) and H_2O. The prepared library of compounds had one fixed residue (glycine) and two randomized positions Y, Z at which could be different amino acids such as alanine, glycine, serine or lysine (Fig. (**3**)).

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