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Review

Recent progress in small molecule fluorescent probes for nitroreductase

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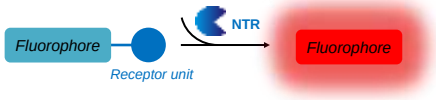
Graphical abstract



This review aims to provide a summary of the progress in fluorescent probes for nitroreductase (NTR) in recent years and displays the main fluorescent mechanisms that have been applied to design probes

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ABSTRACT

Nitroreductase (NTR) is a member of flavin-containing enzymes that exists widely in bacteria. Hypoxia, which is a characteristic of locally advanced solid tumors, resulting from an imbalance between oxygen consumption and supply, can result in NTR overexpression. Using either nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) as a source of reducing equivalents, NTR can catalyze the reduction of nitroaromatic compounds to the corresponding amines. Based on this reduction mechanism, NTR can be applied not only in the bioremediation and degradation of organic nitrogen compounds, but also in the development of NTR-targeted fluorescent probes to detect the hypoxic status of cancer cells. This review aims to provide a summary of the progress in fluorescent probes for NTR in recent years and elucidate the main fluorescent mechanisms that have been applied to design probes.

1. Introduction

Nitroreductases (NTRs) belong to the family of flavin-containing enzymes [1], which can reduce the nitroaromatic compounds to corresponding nitrite, hydroxylamine or amino derivatives with reduced NADH as an electron donor [2,3]. These flavin-associated enzymes can be divided into two types [4-6]. Type I NTRs are oxygen-insensitive, *i.e.*, capable of reduction in the presence of molecular oxygen, whereas type II NTRs are oxygen-sensitive and only function under extreme hypoxia environment [7]. The mechanistic basis of this distinction is that the type II enzymes reduce nitro groups *via* successive single-electron transfers, which yield nitro radical anion intermediates that are rapidly back-oxidized by molecular oxygen to their original forms, with the concomitant production of superoxide anion in a futile redox cycle [8]. In contrast, type I NTRs proceed *via* concerted two-electron transfers, which allow them to achieve their reduced end-product(s) independent of the oxygen status of their environment [9].

It has been proved that the activity of NTR is related to hypoxia status in the cells [10]. Hypoxia is a common feature of solid tumors, which can cause an increase in reductive stress. Under hypoxic conditions, overexpression of NTRs has been observed [11,12]. As a result, the level of O_2 in the tumors can be reflected by the activity of NTR [13]. In addition, NTR has a promising application in the field of clinical diagnosis and drug screening [14-17].