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Novel series of cyano-aryl porphyrazines with benzyloxy and propargyl substituents in peripheral aryl fragments for specifically personalized medicine: Optical viscosity sensing and PDT treating

Larisa Klapshina

Lobachevsky State University of Nizhny Novgorod, Russia

Abstract

Inflammation is a natural reaction of our body in response to infection or any other injury to renovate that damage. The majority of the available Non-steroidal anti-inflammatory drugs is nonselective and consequently, causes gastric irritation and ulceration. Therefore, it is a beard to design and synthesize a new series of Non-steroidal anti-inflammatory drugs with minimal gastric complications. For a long time the idea of separated diagnostic and therapeutic approaches was predominant in the development of new drugs in medicine. However, recently a significant increase has been observed in the trend to create drugs which effectively combine diagnostic and therapeutic approaches. Such the drugs termed the agents of theranostics allow to determine the tumor localization in the body and to provide a therapeutic effect on it. Furthermore, in some cases theranostic agent allows to provide the real time monitoring of individual therapeutic response to the treatment procedure. Recently we reported on the preparation and studies of the photophysical properties of new fluorescent porphyrazine pigments which have been found to be an excellent platform for drugs with the unique combination of various biomedical functions: bimodal (fluorescent/ MRI) diagnostic agents, sensitive optical sensors of intracellular viscosity and highly efficient photosensitizers in photodynamic therapy. Here we report the new series of aryl-cyano porphyrazine pigments containing n-donor oxygen atoms in the aromatic groups of peripheral frame of tetrapyrrol macrocycle. They demonstrate significantly improved photocytoxic properties and the potential for biomedical application as photosensitizers in PDT in comparison with previously reported arylcyano porphyrazine Pz1. Moreover, this series of tetrapyrrols the structural feature of which is the alternation of strongly electron withdrawing CN and π-donor aryl groups in the peripheral frame of macrocycle have been found to be novel fluorescent molecular rotor type dyes with the desirable feature of intense absorption and emission of red light that can be useful in vivo to enable deep tissue penetration in the 'tissue optical window'. High efficacy of all the series as the fluorescent sensors of local viscosity in a wide viscosity range, had been demonstrated. Furthermore, we first proposed semiempirical model describing photophysical behavior of novel porphyrazine series . The model was verified with fluorescence decay investigations for all the porphyrazine series, T. A series of novel 4-(3,4-dimethylphenyl)-2(1H)-phthalazinone derivatives were designed, synthesized and evaluated for their in vivo anti-inflammatory activity. The compounds that showed powerful anti-inflammatory activities were assessed for their in vitro COX-1/COX-2 inhibitory activity and their in vivo ulcerogenic profile. The interaction between the designated compounds and the binding pocket of the COX-2 enzyme was predicted by molecular docking stimulation.

A new series of phthalazinone derivatives were successfully synthesized and were evaluated for their in vivo anti-inflammatory activity. Six compounds (2, 4, 5, 7a, 7b, and 8b) presented powerful anti-inflammatory activity compared to celecoxib. Moreover, compounds 4, 5 and 8b were the most potent inhibitors to COX-2 and were inactive to COX-1. The screened compounds showed better ulcer protection and less gastric lesion compared to celecoxib. Compound 8b was the most promising candidate with more gastric safety.

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