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Deep-cavity basket as potential DNA protective agent against oxidative damage

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pharmaceuticals MDPI

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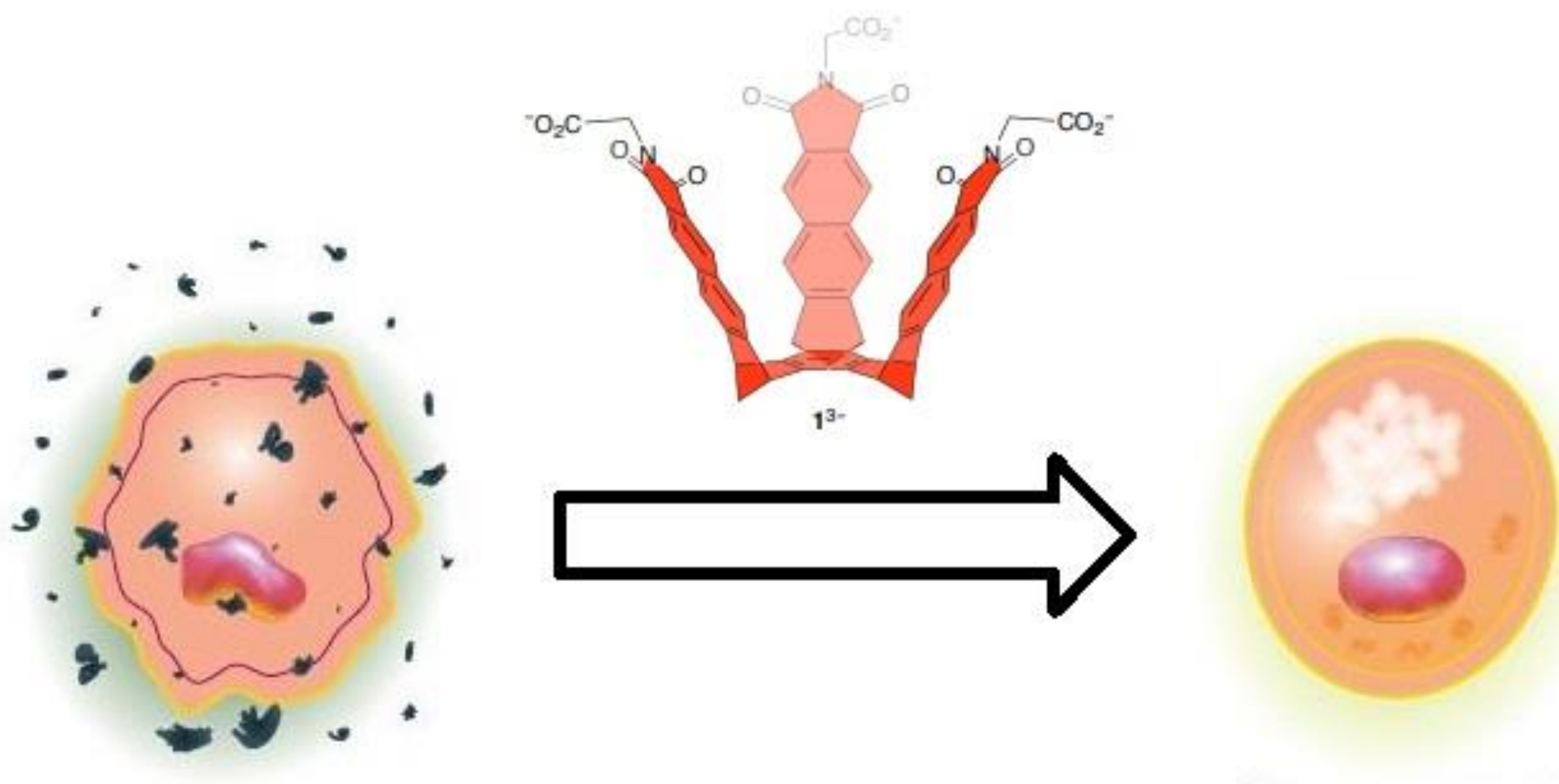
Graphical Abstract



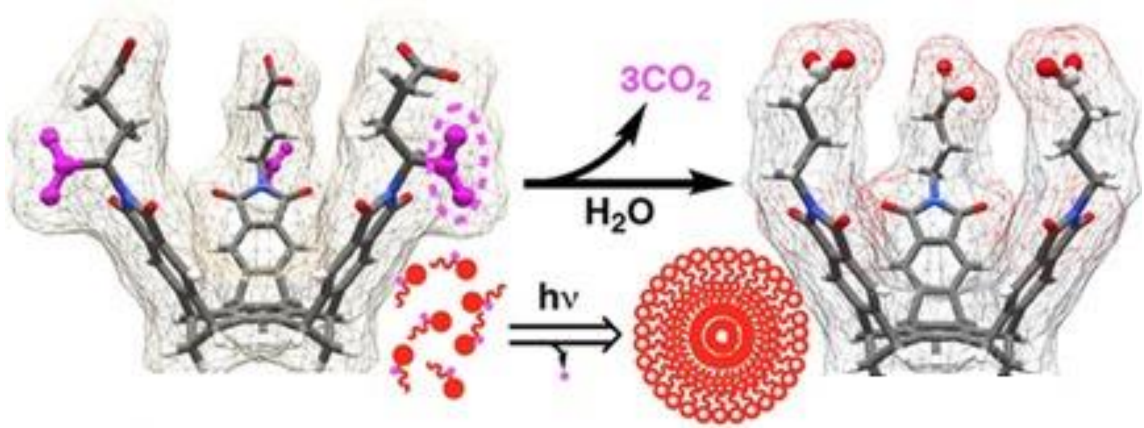
Abstract:

A novel vase-shaped molecular basket $\mathbf{1}^{3-}$, consisting of a deep nonpolar pocket of three napthalimide molecules fused to a bicyclic base, with polar glycine residues at the top was synthesized. Biocompatibility of the synthesized molecular basket was examined *in vitro*. The possible *in vitro* DNA protective potential of the newly synthesized deep-cavity basket $\mathbf{1}^{3-}$ at several concentrations (25, 50, 100, 200, and 400 µg/mL) was investigated against hydroxyl and peroxyl radicals-induced DNA damage. Basket at lower concentrations (25, 50, and 100 µg/mL) almost completely protected DNA against hydroxyl and peroxyl radicals induced DNA damage. It can be concluded that the newly synthesized molecular basket in the range of concentrations tested showed a significant DNA-protective potential against oxidative modifications of DNA caused by the harmful effects of free radicals.

Keywords: molecular baskets; cavitand; biocompatibility; DNA protection

Introduction

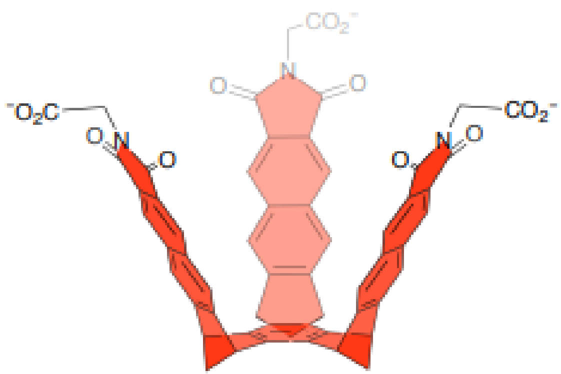
The emergence of molecular baskets in host-guest chemistry has opened doors to various interesting possible medicinal concepts, such as toxin scavenging and application of these supramolecules as drug transporters, as well as administrative antidotes in therapy (Border et al., 2019).



As presented by Border et al. (2019) the basket illustrated above undergoes chemical (decarboxylation) and conformational transformations upon irradiation, thus trapping the unwanted molecule. The transformed basket with the encapsulated molecule is less soluble and easily removed from the system.

MDPI

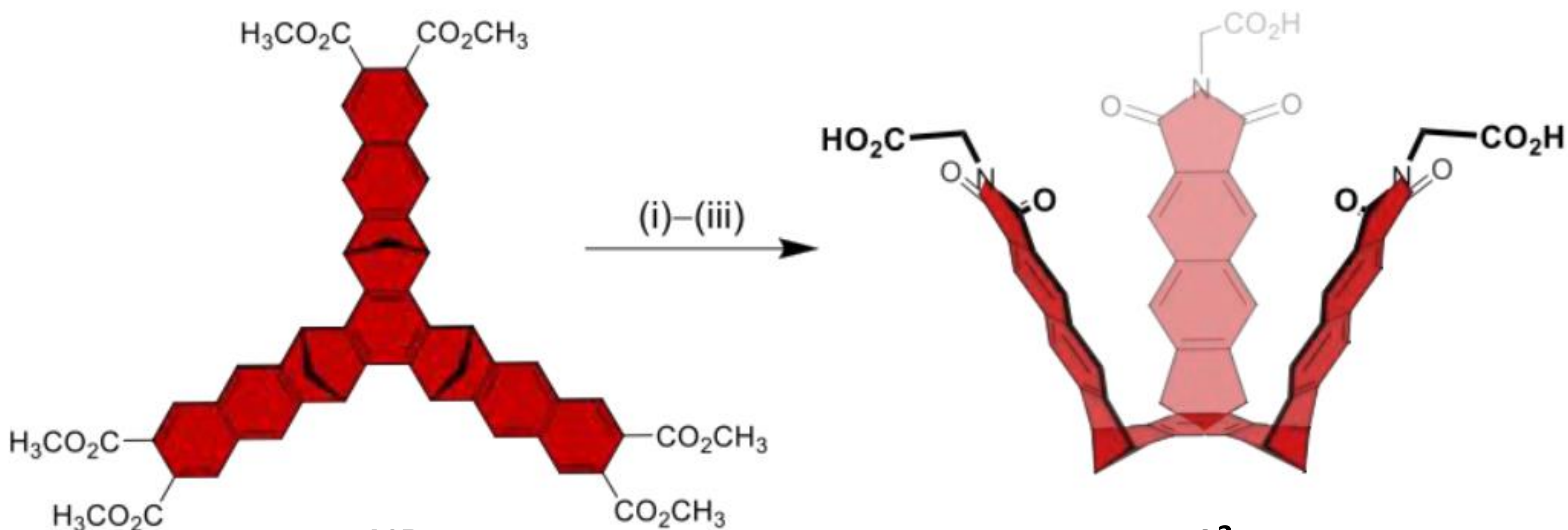
A deep cavity vase shaped molecular basket **1**$^{3-}$ was synthesized for the purpose of developing an antidote for anticancer drug mitoxantrone overdose during cancer treatment. The basket was synthesized by functionalizing and extending the sides of a previously published *tris*-naphthalene basket ***t*-NB** (Lei et al., 2020).



1^{3-}

It consists of a deep nonpolar pocket of three napthalimide molecules fused to a bicyclic base, with polar glycine residues at the top.

The methyl ester groups of ***t*-NB** were hydrolyzed and the hexaacid basket derivative was converted to *tris*-anhydride upon treatment with Ac_2O. The *tris*-anhydride was then underwent condensation with glycine to form the deep cavity basket $\mathbf{1}^{3-}$.



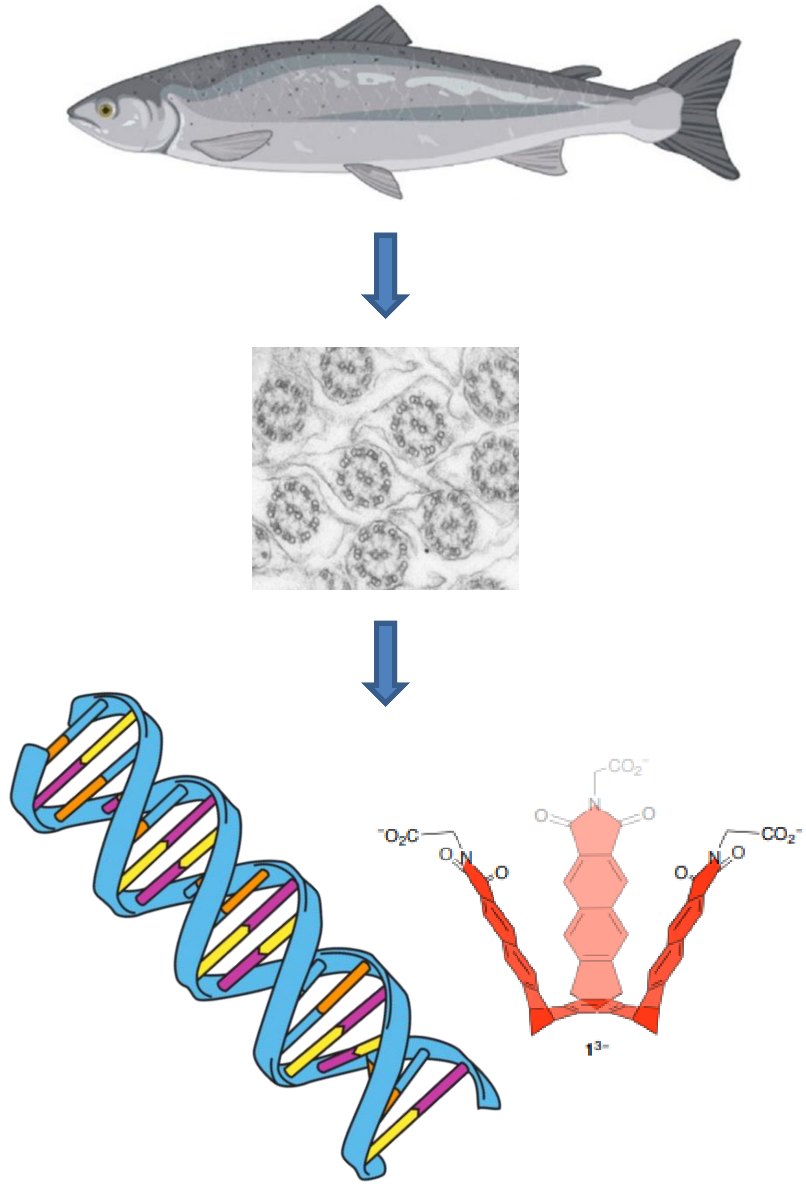
***t*-NB** $\mathbf{1}^{3-}$

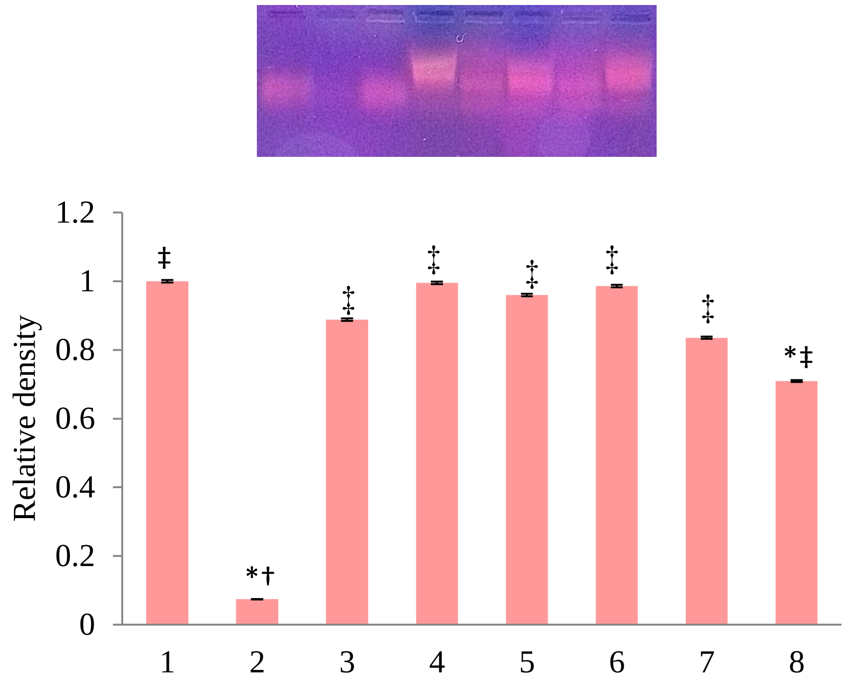
(i) LiOH/THF/Δ; (ii) Ac_2O/Δ; (iii) GlyOH/Cs_2CO_3/AcOH

Results and discussion

The purpose of this study is to determine the *in vitro* DNA protection potential of the deep cavity basket $\mathbf{1}^{3-}$ against hydroxyl and peroxyl radicals-induced DNA damage in order to assess its biocompatibility.

The protective effect of the deep cavity molecular basket **1**$^{3-}$ (25, 50, 100, 200, and 400 µg/mL) against hydroxyl radical induced DNA damage was assessed using salmon sperm DNA (Lin et al., 2008) and quercetin (100 µg/mL) as a standard drug (Poorna et al., 2013). The protective effect of newly synthesized compound (25, 50, 100, 200, and 400 µg/mL) against peroxyl radical induced DNA damage was assessed as previously described by Zhang et al. (2017).





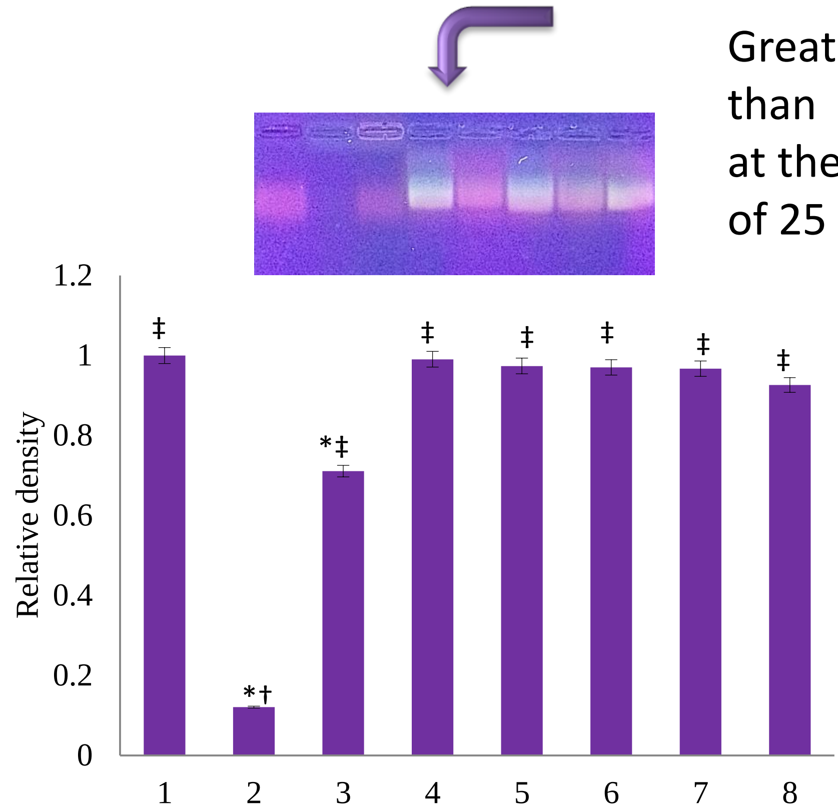
Protective effect decreases with increased concentration

Protective effect of newly synthesized molecular basket **1**$^{3-}$ against hydroxyl radical-induced DNA damage. DNA from salmon sperm (1, negative control), DNA damage control (2, positive control), quercetin (3, 100 µg/mL, standard), newly synthesized molecular basket in concentrations of 25, 50, 100, 200, and 400 µg/mL (4, 5, 6, 7, and 8).
$^{*}p < 0.05$ when compared with the negative control,
$^{\dagger}p < 0.05$ when compared with the standard, $^{\ddagger}p < 0.05$ when compared with the positive control

The *in vitro* DNA protective activity of the deep cavity molecular basket **1**$^{3-}$ at various concentrations (25, 50, 100, 200, and 400 µg/mL) against hydroxyl and peroxyl radicals-induced DNA damage decreases with the increase in concentration with the maximum effect at a concentration of 25 µg/mL and with a greater potential than the applied standard.

The results indicate the absence of a dose–response correlation, since the lower concentration was found to be more effective.

Greater protective effect than the applied standard at the lowest concentration of 25 µg/mL



Protective effect of newly synthesized molecular basket **1**$^{3-}$ against peroxyl radical-induced DNA damage. DNA from salmon sperm (1, negative control), DNA damage control (2, positive control), quercetin (3, 100 µg/mL, standard), newly synthesized molecular basket in concentrations of 25, 50, 100, 200, and 400 µg/mL (4, 5, 6, 7, and 8).
$^{*}p < 0.05$ when compared with the negative control,
$^{\dagger}p < 0.05$ when compared with the standard, $^{\ddagger}p < 0.05$ when compared with the positive control

Conclusions

It can be concluded that the deep cavity molecular basket **1**$^{3-}$ in the range of concentrations tested showed a significant DNA-protective potential against oxidative modifications of DNA caused by the harmful effects of free radicals.

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