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# Adrenochrome formation during photochemical transformation of tailored epinephrine derivatives

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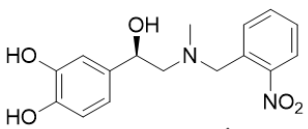
**Key words:** adrenochrome; epinephrine; photoremovable protecting group

*Motivation and Aim*: Adrenergic receptors are a class of G protein-coupled receptors that mediate the physiological effects of catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine). These receptors are widely distributed throughout the body, and their activation triggers various responses, including changes in heart rate, smooth muscle contraction, and metabolic processes.

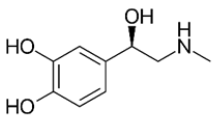
30 years ago, Muralidharan and Nerbonne reported a family of photolabile compounds capable of the release of adrenergic receptor agonists under UV light [1]. This ability is useful for light-induced modulation of receptor activity [2–4]. The compounds were prepared using 2-nitrobenzyl or substituted 2-nitrobenzyl photoremovable protecting groups. It was shown that photorelease is faster when the protective group is attached to the β-amino group rather than one of the phenolic oxygens of the catecholamine.

However, the detailed studies of the photolysis products are lacking, especially for the epinephrine analogs. On the other hand, the photooxidation of epinephrine is a common effect, and we aimed at the detailed study of the photolysis of its photolabile analogs.

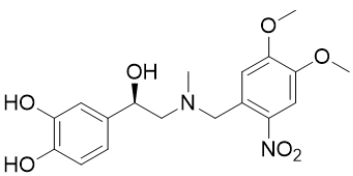
*Methods and Algorithms*: We have prepared two photolabile analogs of epinephrine, one previously described (compound 1) and one novel but structurally similar to the reported agonists (compound 2). The additional methoxy groups on the latter are aimed at shifting the excitation spectra to longer wavelengths and increasing the photorelease quantum yield. The compounds were illuminated by UV LEDS, and the photolysis products were analysed by UV-Vis spectroscopy and by high-performance liquid chromatography (HPLC).



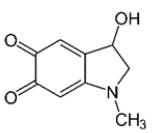

Compound 1




Epinephrine




Compound 2




Adrenochrome

*Results*: During the photolysis, we observed rapid and profound change of the absorption spectra of the compounds, which should be accompanied by the liberation of free epinephrine. Surprisingly, novel peak certainly appears in longer-wavelength region around 500 nm. HPLC analysis revealed that this product has absorption peaks at 220, 300 and 485 nm, which is characteristic for adrenochrome.

Adrenochrome is a chemical compound produced by the oxidation of epinephrine. It was the subject of limited research from the 1950s through to the 1970s as a potential cause of schizophrenia [5]. Some studies reported hallucinogenic and psychoactive properties of the compound. It has also been implicated in cardiotoxicity [6] and generally is a cytotoxic molecule. Adrenochrome can be produced by photooxidation of epinephrine. However, the process is slow and requires hours of irradiation. In contrast, the speed of adrenochrome generation observed in our experiments is quite high and cannot be explained by the photooxidation alone.

*Conclusion*: Our results indicate that aminochromes may be formed during photorelease of catecholamines from their photolabile analogs, and it should be tested before biological applications.

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*References*

1. Muralidharan S., Nerbonne J.M. Photolabile “caged” adrenergic receptor agonists and related model compounds. *J Photochem Photobiol, B Biol.* 1995;27:123-137. doi 10.1016/1011-1344(94)07063-T
2. Ellis-Davies G.C.R. Caged compounds: photorelease technology for control of cellular chemistry and physiology. *Nat Methods.* 2007;4:619-628. doi 10.1038/nmeth1072
3. Vorobev A.Yu., Moskalensky A.E. Long-wavelength photoremovable protecting groups: On the way to in vivo application. *Comput Struct Biotechnol J*. 2020;18:27-34. doi 10.1016/j.csbj.2019.11.007
4. Litunenko D.N., Karogodina T.Y., Vorob’ev A.Y., Moskalensky A.E. Novel UV-Releaser of Arachidonic Acid Based on Nitrophenyl-type Photoremovable Protecting Group. *J Biomed Photonics Eng*. 2022;8:030305. doi 10.18287/JBPE22.08.030305
5. Smythies J. The adrenochrome hypothesis of schizophrenia revisited. *Neurotox Res*. 2002;4:147-150. doi 10.1080/10298420290015827
6. Behonick G.S., Novak M.J., Nealley E.W., Baskin S.I. Toxicology update: the cardiotoxicity of the oxidative stress metabolites of catecholamines (aminochromes). *J Appl Toxicol*. 2001;21:S15-S22. doi 10.1002/jat.793