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# Structural descriptors and antioxidant activity markers of 4-[4-(2-aminoetoxy)benzyl]aniline

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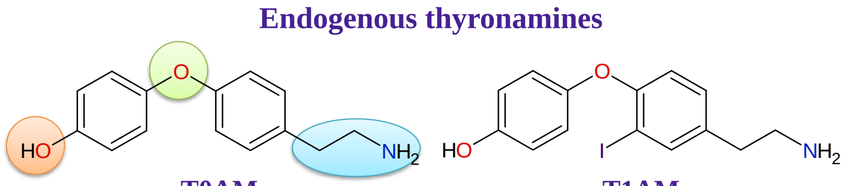
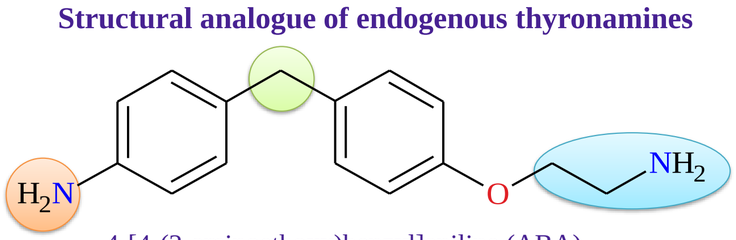
## INTRODUCTION & AIM

The release of reactive oxygen species accompanying oxidative stress is one of the most important damaging mechanisms during brain ischemia. Despite some failures in clinical trials, antioxidant therapy remains one of the best strategies for neuroprotection. Thyroid hormone signaling pathways can control redox status; however, the antioxidant effects of their bioactive metabolites are still less well known, especially for thyronamines.

**Endogenous thyronamines**




**Structural analogue of endogenous thyronamines**




4-[4-(2-aminoethoxy)benzyl]aniline (ABA)

At this study, we consider the following frameworks of the problem:

- antioxidant activity of the 4-[4-(2-amino-ethoxy)benzyl]-aniline (ABA) during brain ischemia (determination of markers of lipid peroxidation (LPO) in brain tissue and content of brain damage marker (neuroglobin (NGB));
- appropriate models of ABA for the investigation of its structure features and properties by DFT methods.

## METHODS

Synthesis of ABA was carried out in accordance with the procedure reported by Chiellini G. and coworkers [1]. Experimental NMR $^{1}H$ and $^{13}C$ spectra of the 4-[4-(2-aminoethoxy)benzyl]aniline were recorded on a Bruker Avance instrument (400 MHz) in DMSO-$d_6$ and discussed in our recent work [2]. DFT methods were used for structure investigations of ABA. All calculations were carried out at B3LYP/6-31G(d,p) level of theory. Magnetic shielding constants were calculated by the gauge-independent atomic orbital (GIAO) method.

To study the content of NGB and markers of LPO in the brain tissue, 30 rats were divided into two equal groups, in which craniotomy was performed with the application of $FeCl_3$ to the dura mater of the brain. After 60 minutes, 0.5 ml of a vehicle was administered intraperitoneally to the first group, and a solution of an ABA (75 mg/kg) to the second. 3 day after the experiment, the animals were decapitated, and the tissue of the cerebral cortex - separately intact and ischemic – was used to determine markers of LPO and NGB by the ELISA method.

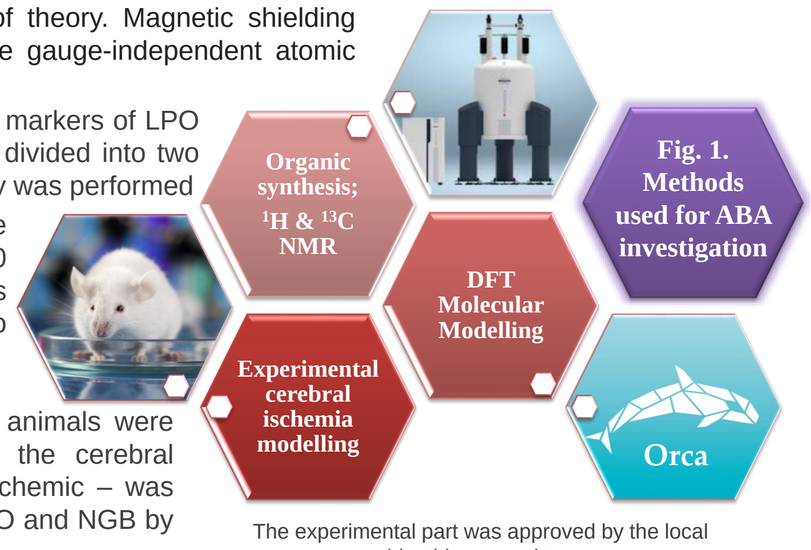



Fig. 1. Methods used for ABA investigation

The experimental part was approved by the local bioethics committee

## RESULTS & DISCUSSION

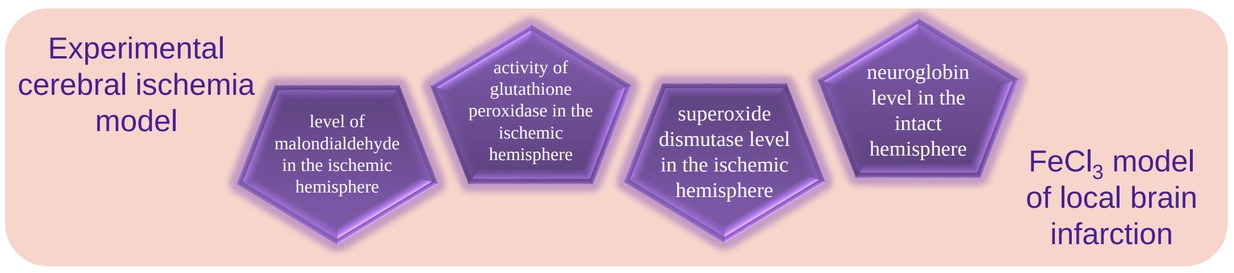



Fig. 2. Antioxidant activity markers of the ABA in models of brain damage

Some aspects of antioxidant activity of the ABA in the model of acute cerebral ischemia were experimentally studied. Considered markers are listed in Fig. 2. In rat brain ischemia model by ligation of common carotid artery administration of synthetic analogue of thyronamine T0AM (ABA) was associated with significant changes in redox-markers: lower level of malondialdehyde in the ischemic hemisphere ($p = 0.022$), increased activity of glutathione peroxidase ($p = 0.004$) and superoxide dismutase ($p = 0.042$) in the ischemic hemisphere. Also, in $FeCl_3$ model of local brain infarct administration of T0AM analog was associated with significant increase in NGB level (Fig. 3) in intact hemisphere ($p = 0.02$), which is a neuroprotective factor against hypoxia.

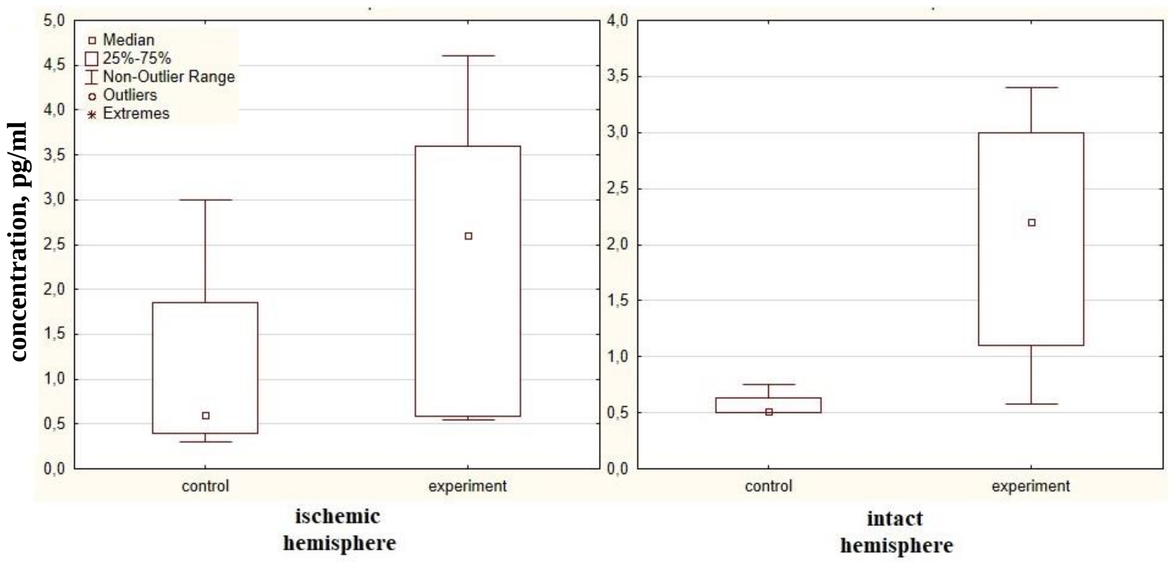



Fig. 3. The effect of ABA on the content of NGB in the intact and damaged hemispheres in rats

The chemical species distribution at different pH values for the ABA (Fig. 4) was estimated by Marvin Protonation Plugin. 2-{4-[(4-Aminophenyl)methyl]phenoxy}ethan-1-aminium cation (ABA-$H^+$) is the main species at physiological pH 6.9 - 7.2 range.

DMSO was used as a solvent in experimental NMR studies of the ABA structure and as a component of the dissolution medium for the ABA injection preparations. Spatial configuration of the ABA-$H^+$ and its solvate with DMSO were obtained at B3LYP/6-31G(d,p) level of theory (Fig. 5). The magnetic shielding constants of the $^{1}H$ and $^{13}C$ nuclei were calculated and the chemical shifts of these nuclei were estimated based on them. Linear correlations were observed between the experimental and calculated values of chemical shifts. Experimental chemical shifts of $NH_2$ groups protons are sensitive to the solvent and take part in exchange processes. Good agreement between experimental and calculated chemical shifts of these groups was obtained in the case of the ABA-$H^+$ solvate with DMSO.

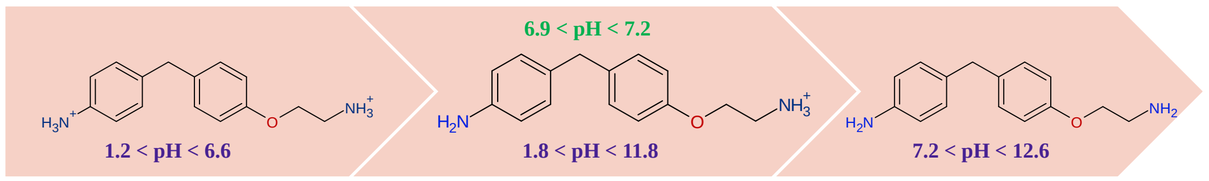



Fig. 4. The estimated chemical species distribution at different pH values for ABA (Marvin Protonation Plugin)

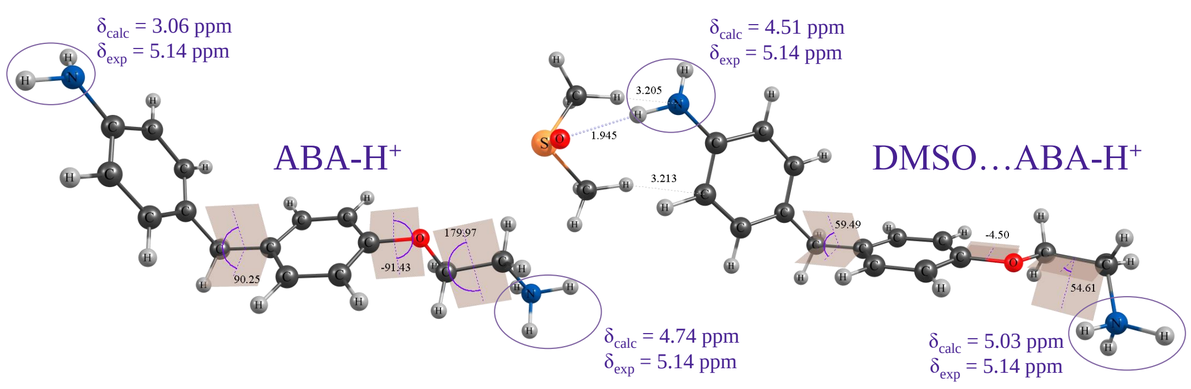



Fig. 5. Spatial configurations of the protonated form of ABA and its solvate with DMSO (B3LYP/6-36G(d,p)/PCM level of theory)

## CONCLUSIONS

It was revealed that the T0AM thyronamine analogue ABA could control redox status in acute brain ischemia condition. It also induces an increase in the level of NGB in the intact hemisphere, which may be a mechanism for neuroprotection of healthy tissues, but further experimental studies are needed to evaluate its neuroprotective potential.

Structural models of the ABA protonated form (ABA-$H^+$) and its solvate with DMSO obtained at B3LYP/6-31G(d,p) level of theory can be used for the further structural investigations by DFT methods.

## REFERENCES

1. Chiellini, G.; Nesi, G.; Digiacomo, M.; et al. *J. Med. Chem.* **2015**, *58*, 5096–5107.
2. Eresko, A.; Raksha, E.; Filimonov, D.; et al. *Russ. J. Org. Chem.* **2024**, 60, 1654-1662.

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