Solubilization of new analgesic thiowurtzine by γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin

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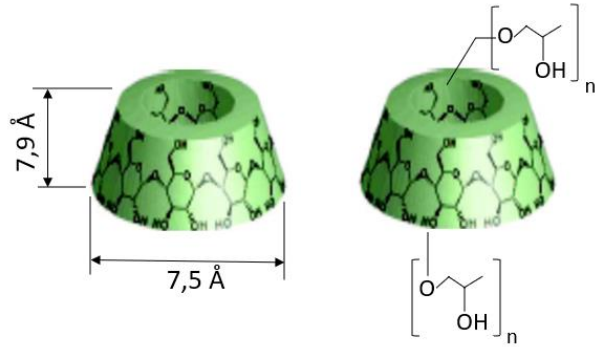
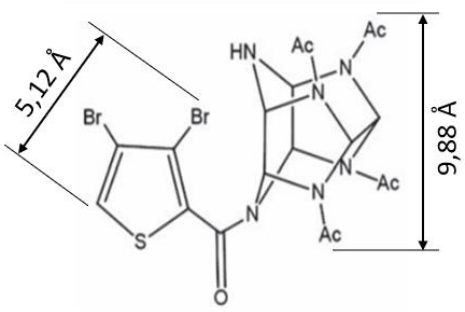
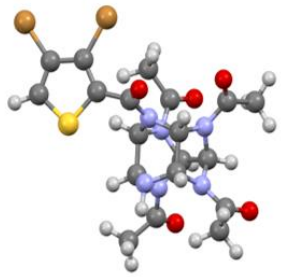
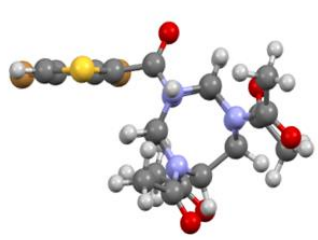
Thiowurtzine (TW) is a new analgesic based on hexaazaizowurtzitane. Thiowurtzine is successfully applied in the treatment of chronic pain syndrome caused by rheumatoid arthritis, and as an analgesic in cancer treatment.

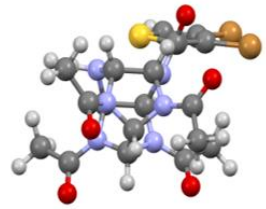
The objective of the research: to increase the water solubility of pharmaceutical form for more affinity to biological media by complex formation with γ-cyclodextrin (γ-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD).

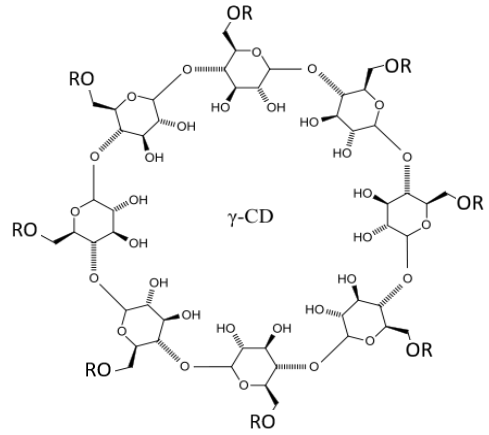








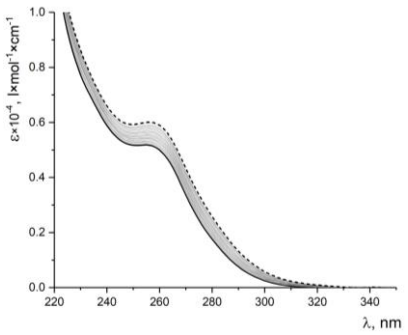


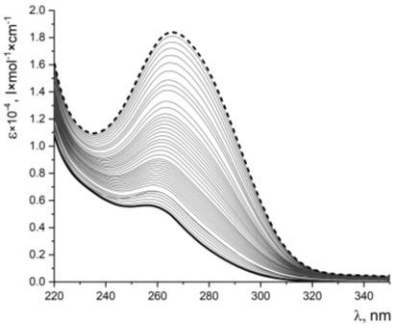


Approvement of complex formation

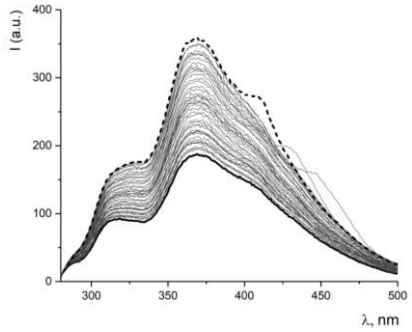
TW·γ-CD **in EtOH** TW·HP-γ-CD

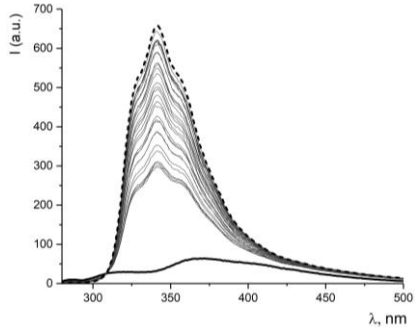
electronic absorption spectra





fluorescence spectra



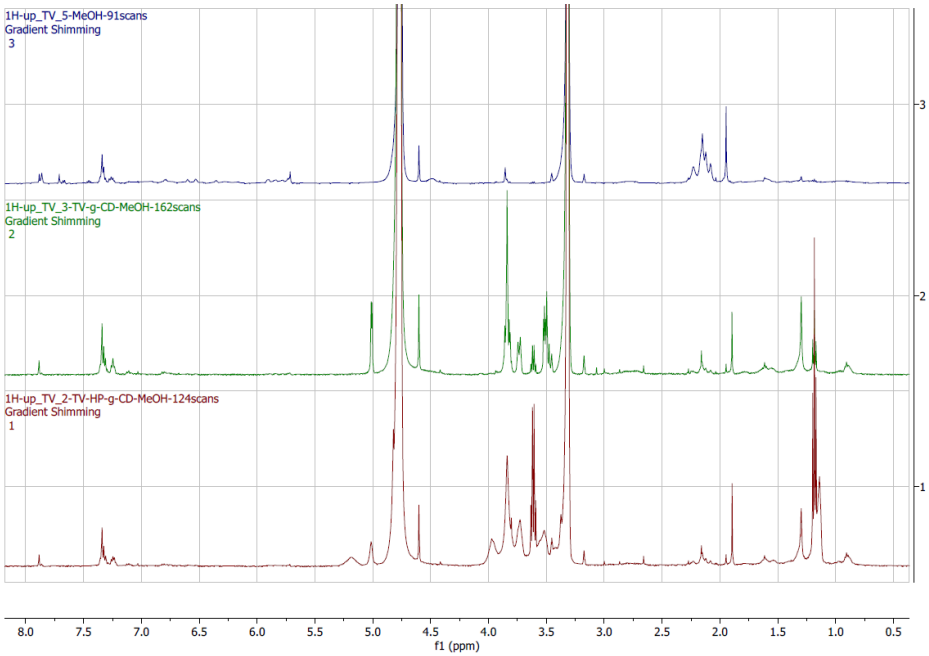


lgK (TW·γ-CD) ~ 3

lgK (TW·HP-γ-CD) = 3,1

During titration by γ-CD, an increase in absorption is observed in both systems, in case of HP-γ-CD a bathochromic shift of 11 nm is observed.

The fluorescence spectra show a significant change in the excited state of TW with the formation of complexes with a composition of 1: 1.



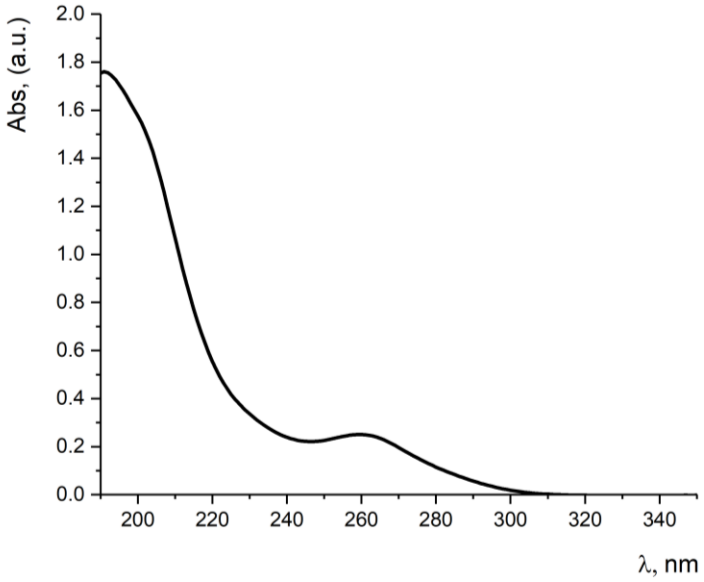
^{1}H NMR spectra of TW, TW·γ-CD and TW·HP-γ-CD

As shown by NMR spectra, the formation of complexes is accompanied by partial screening of the acetyl fragments of the molecule (2.31 - 1.99, m, 12H) and the protons of the azo cage (6.87 - 5.65, m, 8H). While there are no chemical shifts characteristic of the H thiophene ring (7.88 - 7.22, m, 1H).

Increase of solubility

Having been proved the formation of complexes, we pounded with a pestle TW with cavitands to obtain powders. We dissolved powder in spectrally pure water.

TW itself is practically insoluble in water. In composition with γ-CD and HP-γ-CD it become soluble, the 92% of solid TW goes to solution, the concentration of TW is 5×10^{-5} mol/l.



Electronic absorption spectra TW·HP-γ-CD in water

The water consisting in the (HP-)γ-CDs' cavity is replaced to the guest-molecule. The solubility of (HP-)γ-CD and its affinity to water make complexes with TW soluble in water.

- Krylova SG, Lopatina KA, Zueva EP, Safonova EA, Rybalkina OYu, Povetyeva TN, Suslov NI, Kulagina DA, Sysolyatin SV, Zhdanov VV. Hexaazaizowurtzitane derivate as a new analgesic for chronic pain syndrome relief in experimental rheumatoid artritis. Russian Journal of Pain. 2020;18(3):5–10. (In Russ.). https://doi.org/10.17116/pain2020180315
- Lopatina K.A., Krylova S.G., Safonova E.A., Zueva E.P., Kulagina D.A., Churin A.A., Fomina T.I., Sysolyatin S.V. A new analgesic agent based on hexaazaisowurzitan: feasibility of using in managing patients with cancer. Siberian Journal of Oncology. 2020; 19(2): 76–81. – doi: 10.21294/1814-4861-2020-19-2-76-81.