TOMSK POLYTECHNIC UNIVERSITY

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Halogenated 2,1,3-benzoxadiazoles as potential fluorescent warheads for covalent protease inhibitors

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Background

Traditional Covalent Inhibitors of Proteases

Derivatives of:

- Alkyl halides,
- Michael acceptors,
- Alkyl boronates,
- Nitriles,
- Sulfonyl fluorides,
- Epoxides or aziridines .

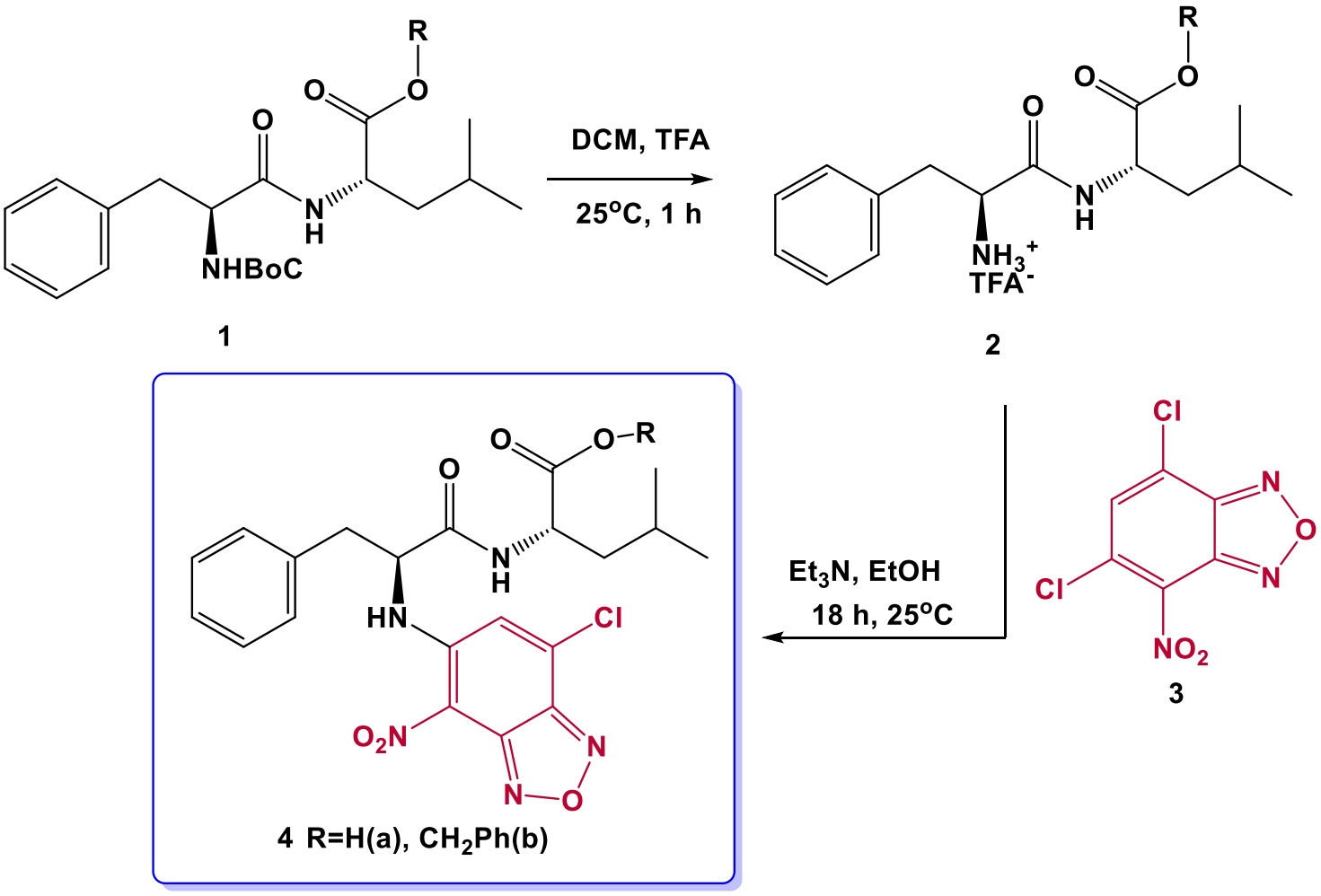
New «warheads» for Covalent Protease Inhibitors

Electrophilic Derivatives of:

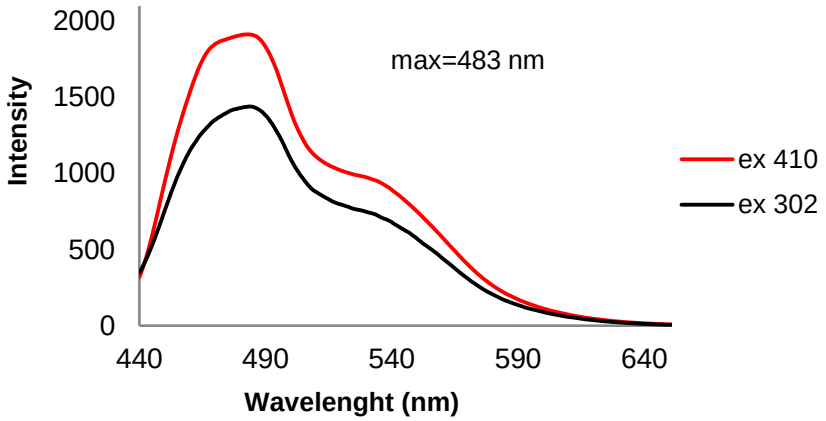
- Aromatic compounds,
- Heteroaromatic compounds,
- Quinoid compounds.

The aim is the synthesis of fluorescent S_NAr-type warheads based on halogenated 2,1,3-benzoxadiazole derivatives.

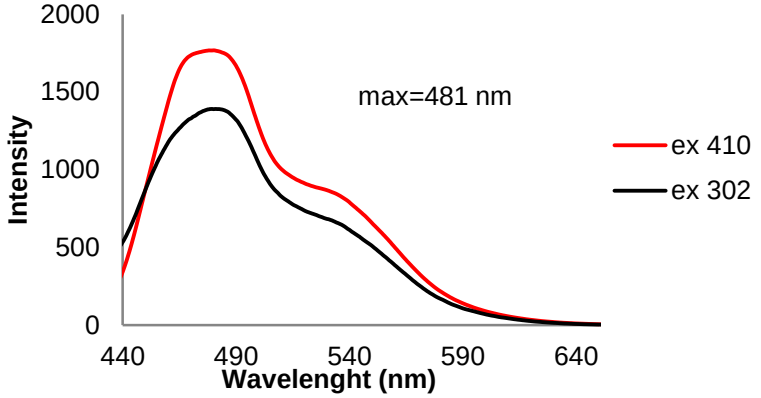
SYNTHESIS SCHEME 1



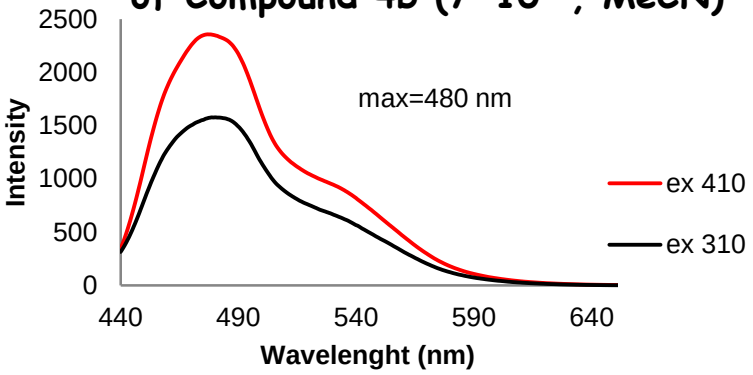
Fluorescence Spectrum of Compound 4a ($7 \cdot 10^{-5}$, MeCN)



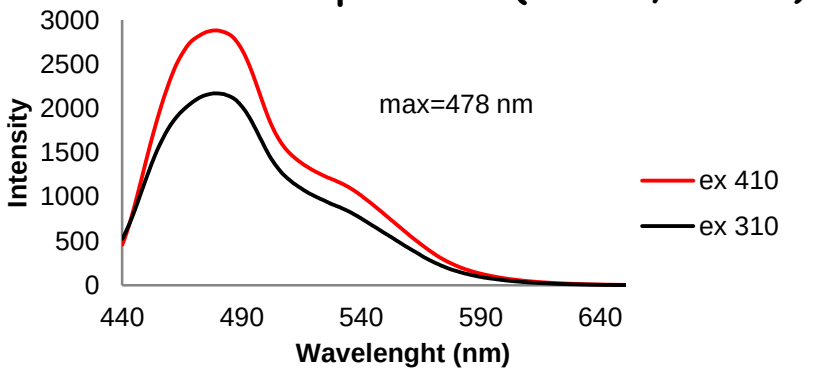
Fluorescence Spectrum of Compound 4a ($7 \cdot 10^{-5}$, MeOH)



Fluorescence Spectrum of Compound 4b ($7 \cdot 10^{-5}$, MeCN)

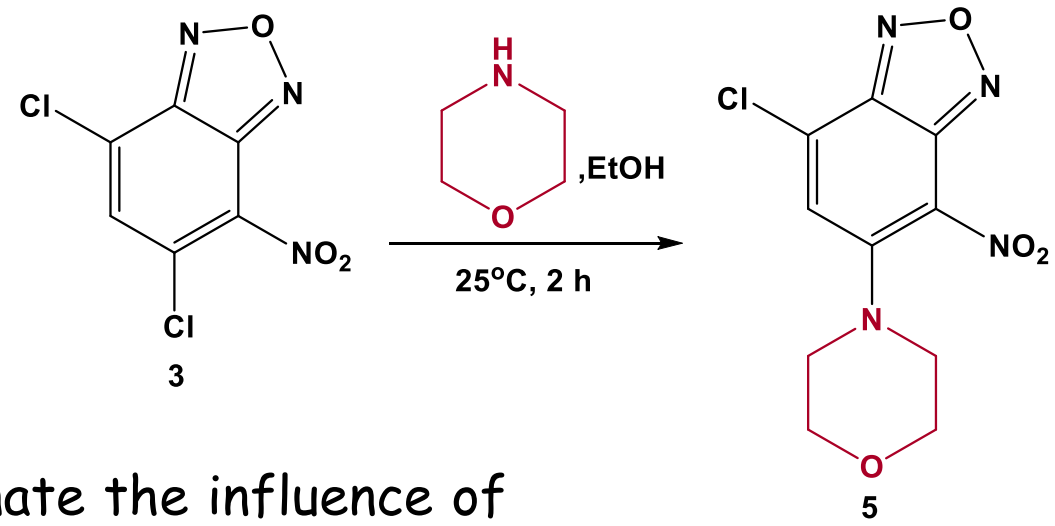


Fluorescence Spectrum of Compound 4b ($7 \cdot 10^{-5}$, MeOH)



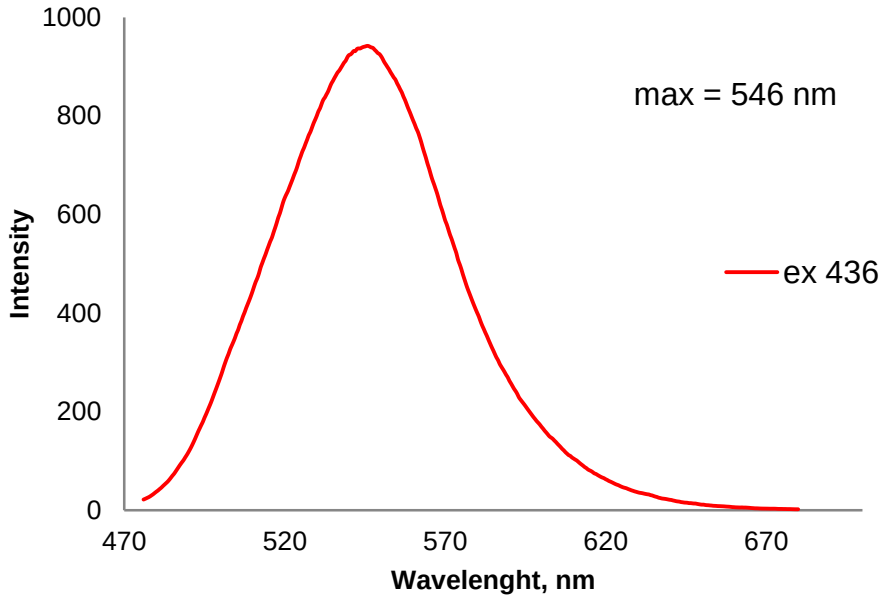
The location of the maximum emissions in a relatively narrow wavelength region can be explained by the presence of a N–H···O=N-hydrogen bond.

SYNTHESIS SCHEME 2

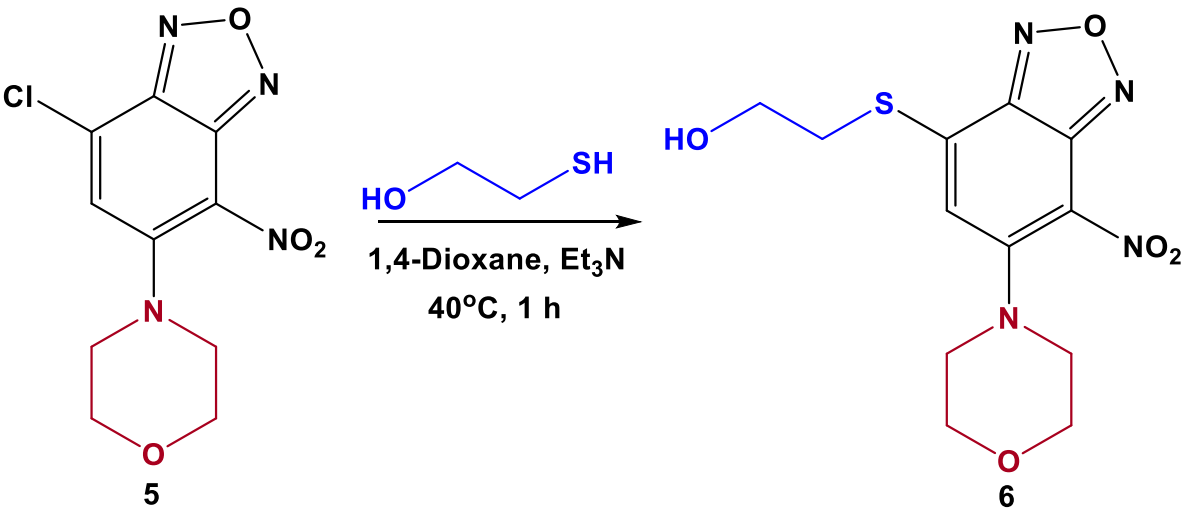


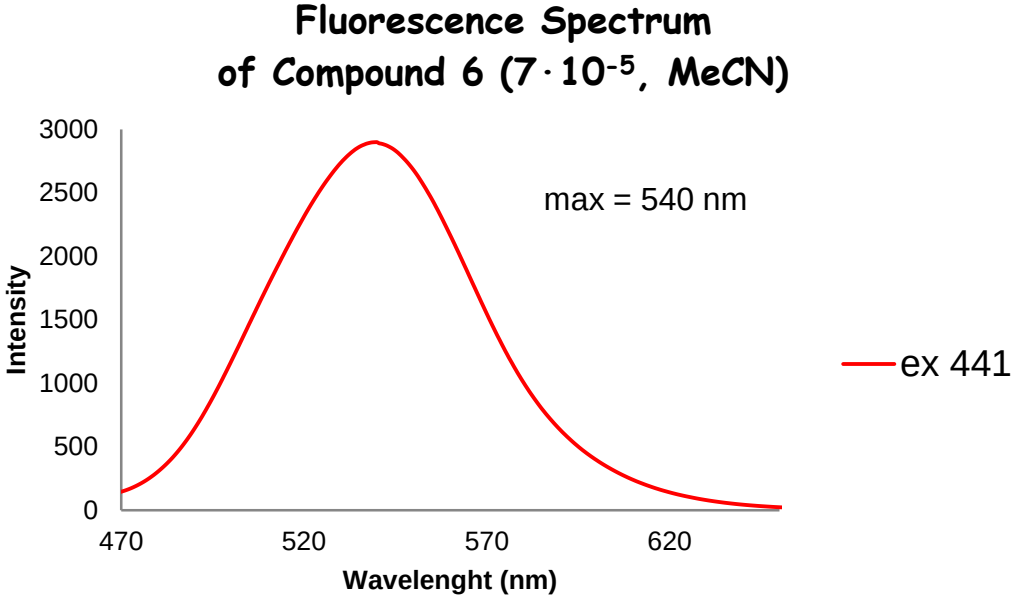
To eliminate the influence of the hydrogen bond on the fluorescent properties, we prepared a model compound from a secondary amine and studied its photophysical properties.

Fluorescence Spectrum of Compound 5 ($1 \cdot 10^{-4}$, MeOH)



THE SYNTHESIS SCHEME 3





We studied the S_NAr reaction of this compound with mercaptoethanol simulating the active cysteine residues in certain proteases and also studied the impact on the fluorescent properties.

Conclusions

- Derivatives of 2,1,3-benzoxadiazoles were synthesized as potential protease inhibitors allowing a multiparameter optical read-out and their photophysical properties were investigated.
- The emission maxima of these compounds are located at relatively short wavelengths due to the presence of an intramolecular hydrogen bond.
- Derivatives devoid of NH-protons have longer emission wavelengths and a second S_NAr reaction with a thiolate leads to an increase in the fluorescence intensity while keeping the emission wavelengths basically unchanged.

Acknowledgements

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Thank you for your attention!