FINAL REPORT ON PROJECT PD104618

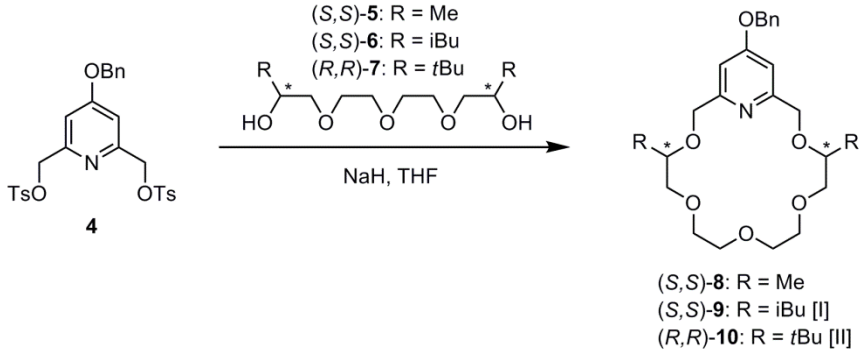
1 INTRODUCTION

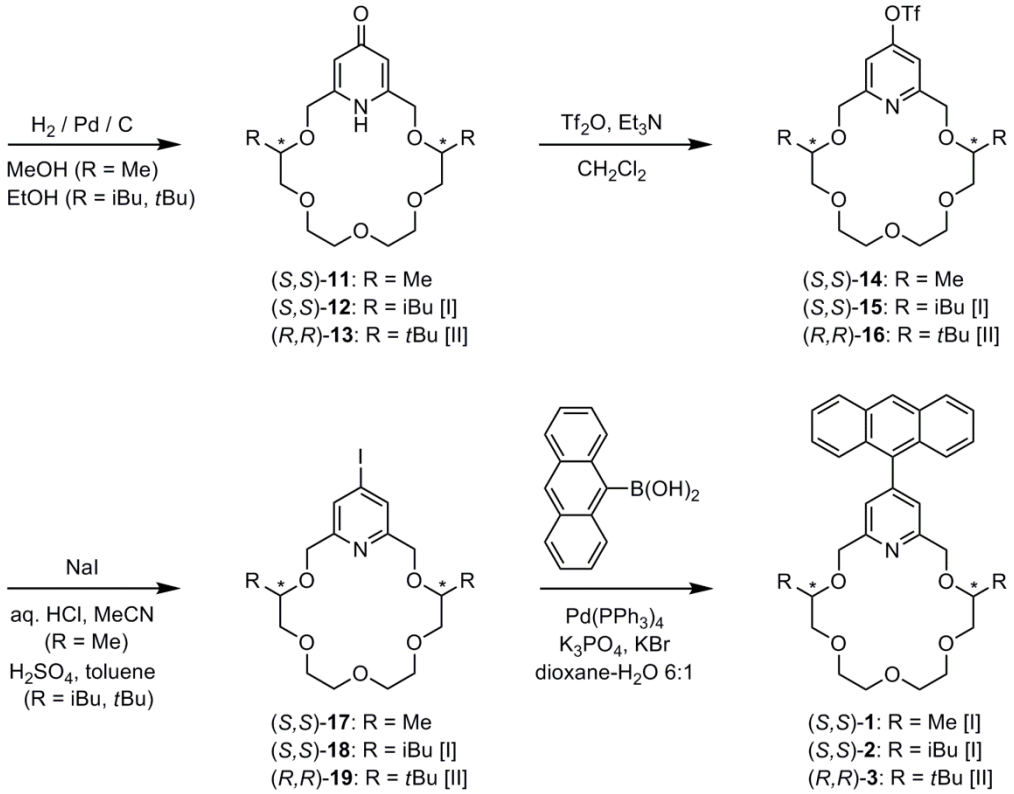
Enantiomeric recognition as a special case of molecular recognition is a widespread and important phenomenon in nature. Since the individual enantiomers of a biologically active compound have different pharmacological and toxicological properties, the determination of the enantiomeric compositions of chiral organic compounds has a great significance in pharmaceutical, pesticide, food and cosmetic industries as well as in environmental analysis.

Therefore, sensor molecules capable of enantioselective recognition gained much research interest due to their potential applications. Optically active primary amines, amino acids and their derivatives are important compounds of biological relevance, of which enantiomers can be differentiated in their protonated forms by enantiopure crown ether derivatives for example. The enantiomers of α-hydroxy and α-amino acids can also be distinguished as their carboxylates by enantioselective anion sensors containing e.g., urea and thiourea units as receptor parts, which have good hydrogen bond donating ability, therefore high affinity toward anions. Sensor molecules having a fluorescent signalling unit provide a sensitive tool for the examination of their recognition ability by the use of fluorescence spectroscopy.[1,2] Organic and inorganic anions play an important role in many chemical and biological processes, so the synthesis and investigation of chemosensors for anion recognition are of great importance.[3]

2 SYNTHESIS AND STUDIES OF ENANTIOPURE FLUORESCENT CROWN ETHER-BASED SENSOR MOLECULES [I,II]

We synthesized pyridino-crown ether-based sensor molecules (*S*,*S*)-**1**–(*R*,*R*)-**3**[I,II] containing an anthracene fluorophore unit starting from ditosylate **4**[4] and the appropriate optically active tetraethylene glycol [(*S*,*S*)-**5**[5] or (*S*,*S*)-**6**[6] or (*R*,*R*)-**7**[7]]. The synthesis of crown ethers (*S*,*S*)-**9**,[I] (*R*,*R*)-**10**,[II] (*S*,*S*)-**12**,[I] (*R*,*R*)-**13**,[II] (*S*,*S*)-**15**,[I] (*R*,*R*)-**16**,[II] (*S*,*S*)-**18**[I] and (*R*,*R*)-**19**[II] containing isobutyl or *tert*-butyl groups at the stereogenic centres of their macrorings was carried out in a similar way as published for their methyl analogues (*S*,*S*)-**8**,[5] (*S*,*S*)-**11**,[5] (*S*,*S*)-**14**[8] and (*S*,*S*)-**17**[8] (*Scheme 1*). Another route for the preparation of pyridono-crown ethers (*S*,*S*)-**12** and (*R*,*R*)-**13** starting from their THP protected forms had already been reported in the literature.[9]





Scheme 1.

The enantiomeric recognition abilities of pyridino-crown ethers (*S*,*S*)-**1** and (*S*,*S*)-**2** toward the enantiomers of PhEt, NapEt, PhgOMe and PheOMe (*Fig. 1*) were studied in acetonitrile using UV–vis and fluorescence spectroscopies. Sensor molecules (*S*,*S*)-**1** and (*S*,*S*)-**2** showed remarkable "turn-off" fluorescence response upon addition of the ammonium salts with an almost total quenching of the fluorescence during the titrations (*Fig. 2*). The fluorescence spectral changes were evaluated using global nonlinear regression analysis. The sensor molecules [(*S*,*S*)-**1** and (*S*,*S*)-**2**] showed appreciable enantiomeric recognition toward NapEt, and moderate enantioselectivities in the cases of PhEt and PhgOMe. The highest enantioselectivity ($\Delta \log K = 0.60$) was experienced in the case of pyridino-crown ether (*S*,*S*)-**2** and NapEt. In this case, we recorded I_0/I as a function of the enantiomeric composition of the added chiral salt resulting in a calibration curve, which can provide an opportunity for the determination of the enantiomeric composition of NapEt (*Fig. 2*).[I]

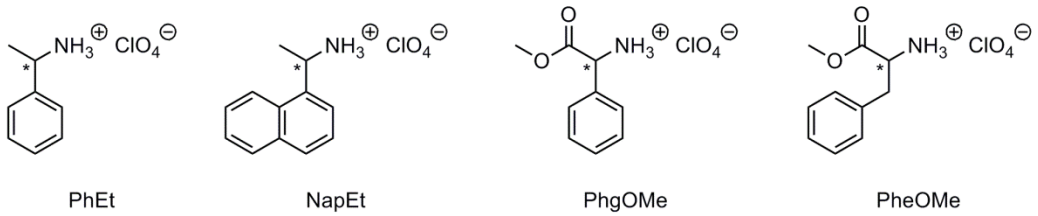


Figure 1.

In order to obtain further enantiopure fluorescent crown ethers, azido-substituted pyridino-crown ether (*S*,*S*)-**20**[II] and amino-substituted pyridino-crown ether (*S*,*S*)-**21**[II] as key intermediates were prepared starting from pyridino-crown ethers (*S*,*S*)-**17**[8] and (*S*,*S*)-**22**[8] (*Scheme 2*). Crown ethers (*S*,*S*)-**20** and (*S*,*S*)-**21** are planned to react with an acetylene derivative (in a click reaction) and a naphtalic anhydride derivative (to give a naphtalimide derivative), respectively.

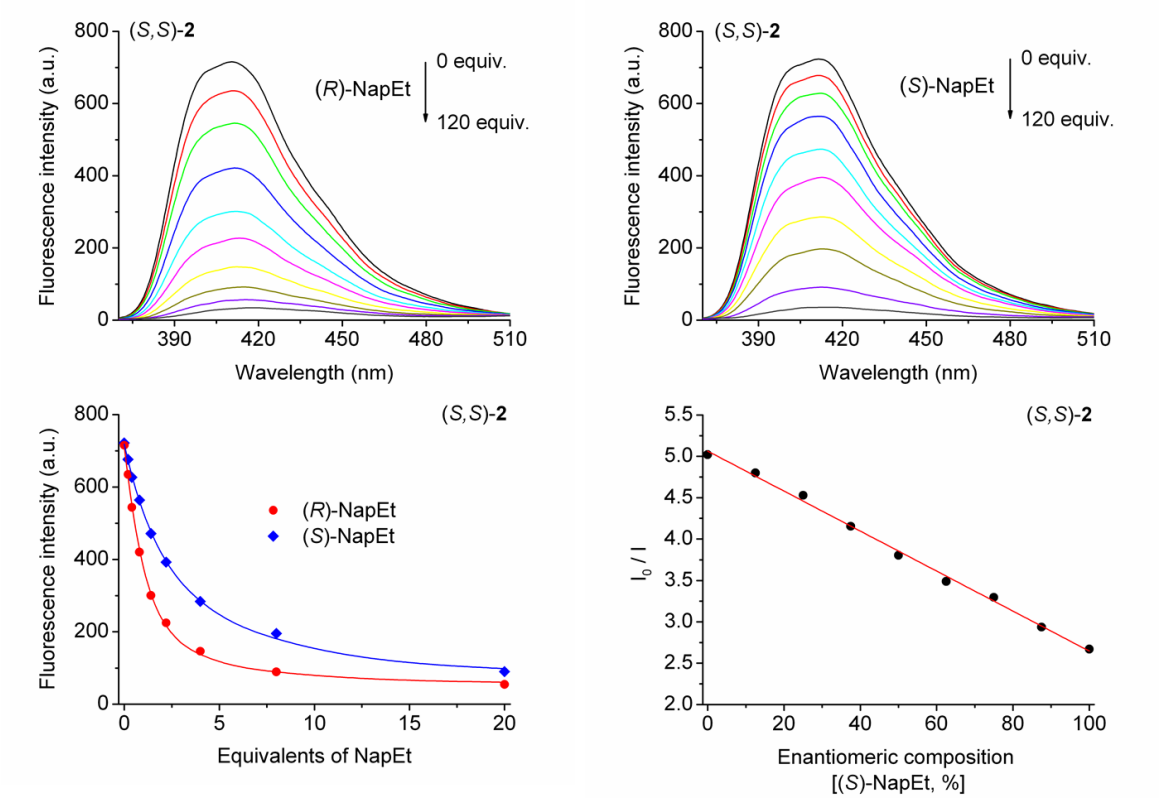
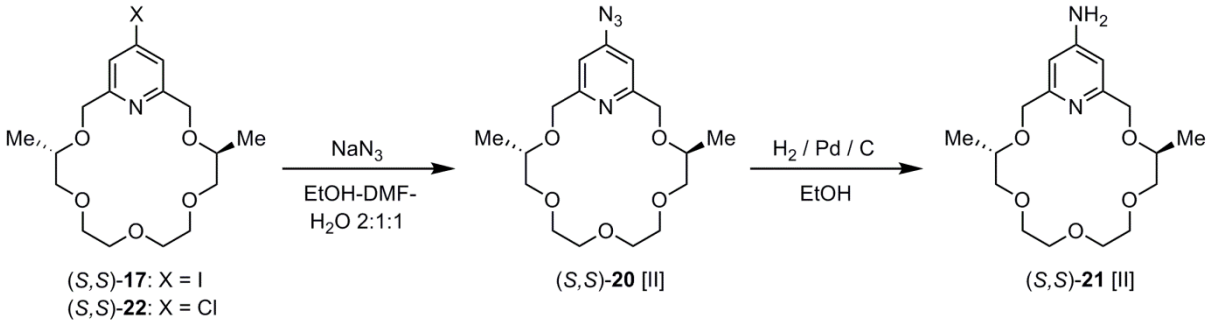
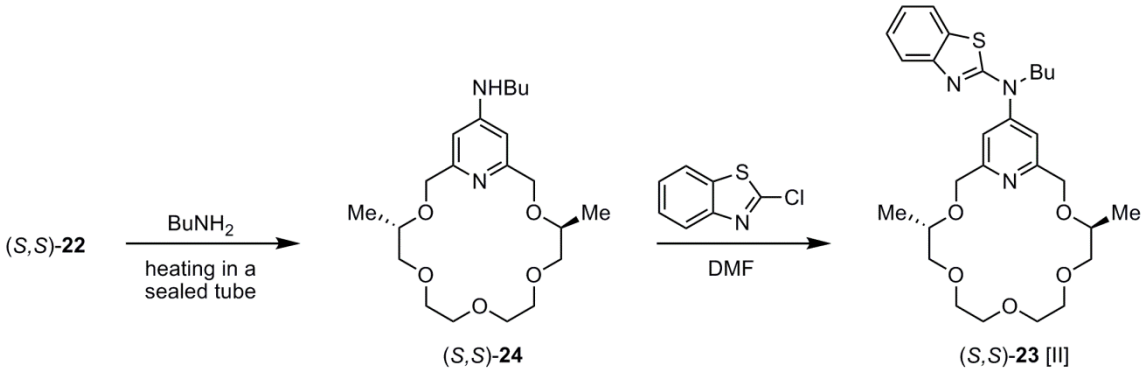


Figure 2.



Scheme 2.

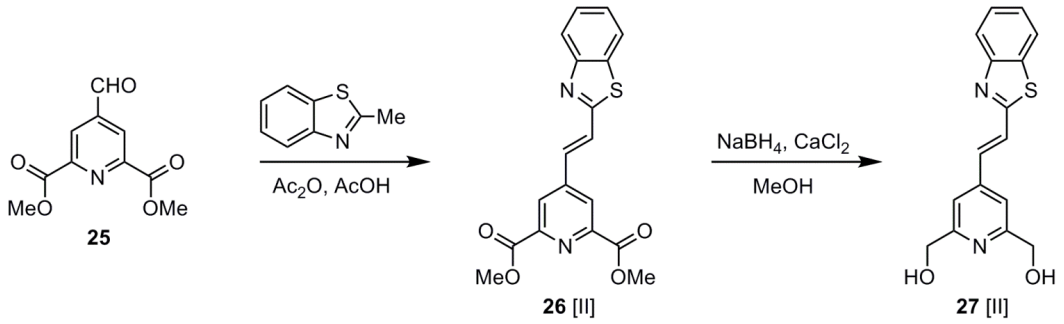


Scheme 3.

We also synthesized enantiopure pyridino-crown ether-based sensor molecule (*S*,*S*)-**23**[II] containing a benzothiazole fluorophore unit starting from butylamino-crown ether (*S*,*S*)-**24**[8] (*Scheme 3*). The enantiomeric recognition ability of pyridino-crown ether (*S*,*S*)-**23** toward the enantiomers of

PhEt, NapEt, PhgOMe and PheOMe (*Fig. 1*) was studied in acetonitrile by UV–vis and fluorescence spectroscopies. The sensor molecule showed moderate enantiomeric recognition toward the enantiomers of the selected primary ammonium salts.[II]

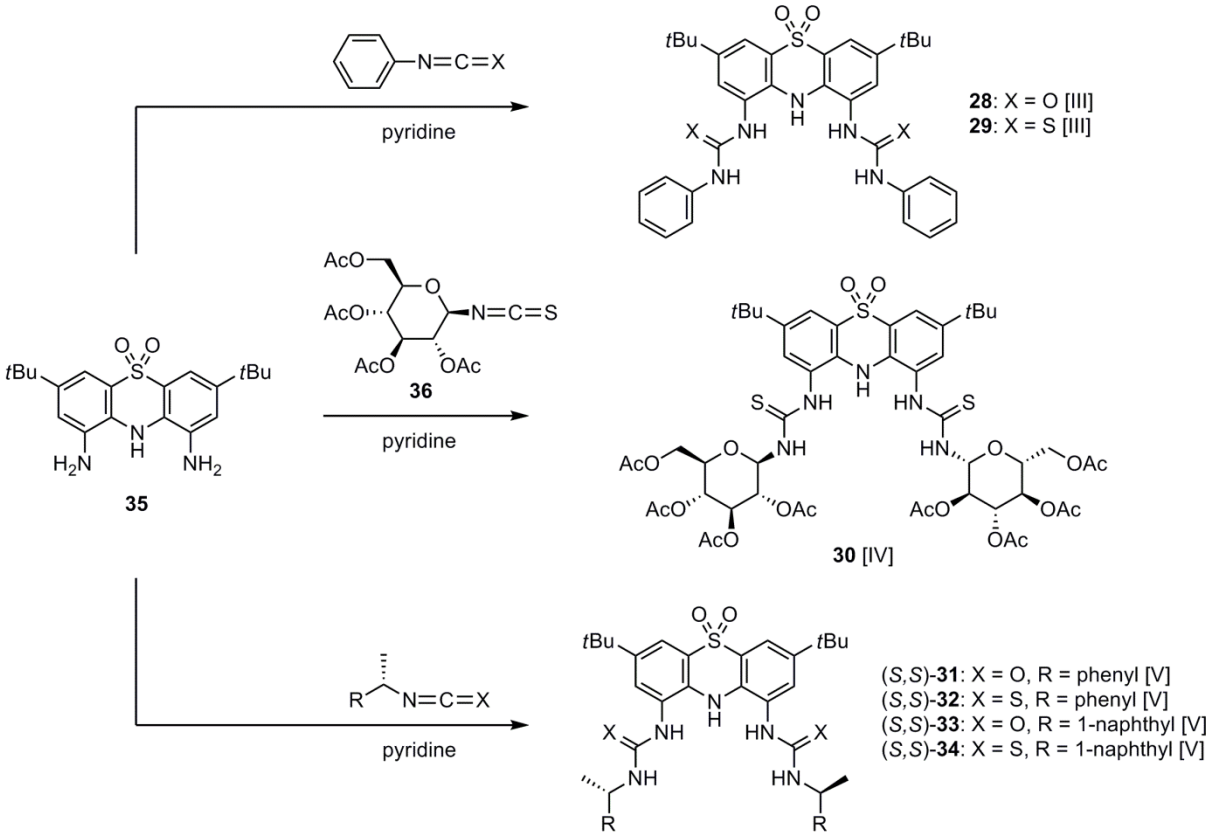
Because of the low fluorescence quantum yield of pyridino-crown ether (*S,S*)-**23**, we started to prepare a more fluorescent pyridino-crown ether in which the benzothiazole and pyridine units are conjugated. The synthesis is in progress starting from pyridine diester **25**[10] through the precursors **26**[II] and **27**[II] (*Scheme 4*).



Scheme 4.

3 SYNTHESIS AND STUDIES OF ACHIRAL AND ENANTIOPURE 5,5-DIOXOPHENOTHIAZINE- AND ACRIDONE-BASED ANION SENSORS [III–VI]

We synthesized 5,5-dioxophenothiazine-based achiral (**28** and **29**)[III] and optically active [**30**–(*S,S*)-**34**][IV,V] anion sensors starting from phenothiazine derivative **35**[11] (isothiocyanate **36** was also prepared according to the literature[12]) (*Scheme 5*).



Scheme 5.

The anion recognition properties of sensor molecules **28** and **29** toward the tetrabutylammonium salts of fluoride, chloride, bromide, iodide, nitrate, hydrogen sulfate, sulfate, dihydrogen phosphate and acetate were investigated in acetonitrile by UV–vis spectroscopy. While most of the studied anions (chloride, bromide, hydrogen sulfate, sulfate and dihydrogen phosphate) were bound only by the neutral receptors, fluoride and acetate were complexed even by the deprotonated ones (*Fig. 3*). The deprotonated receptors showed stronger complexing ability toward fluoride than acetate. The formation of the deprotonated **28**–F^- complex was also examined by ^{1}H NMR spectroscopy and X-ray crystallography (the latter was performed in cooperation with the group of Prof. Mátyás Czugler).[III]

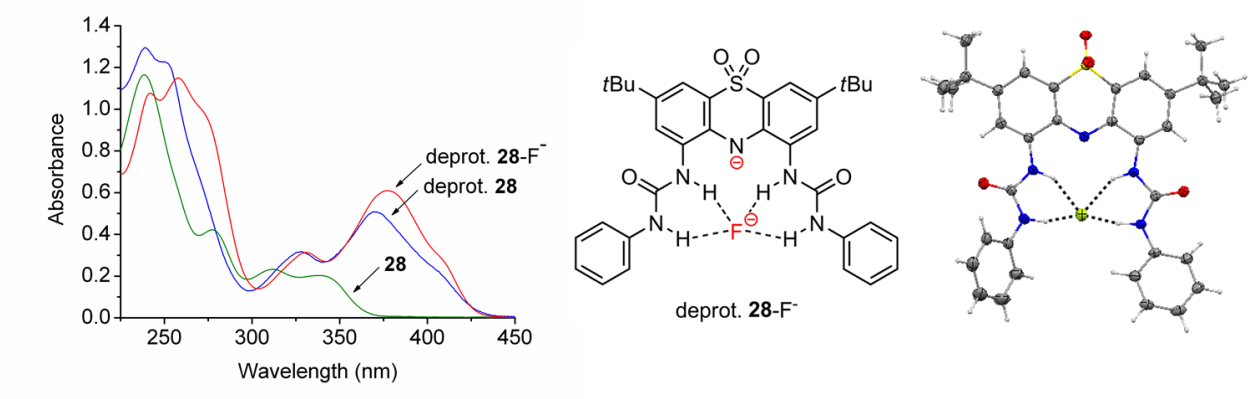


Figure 3.

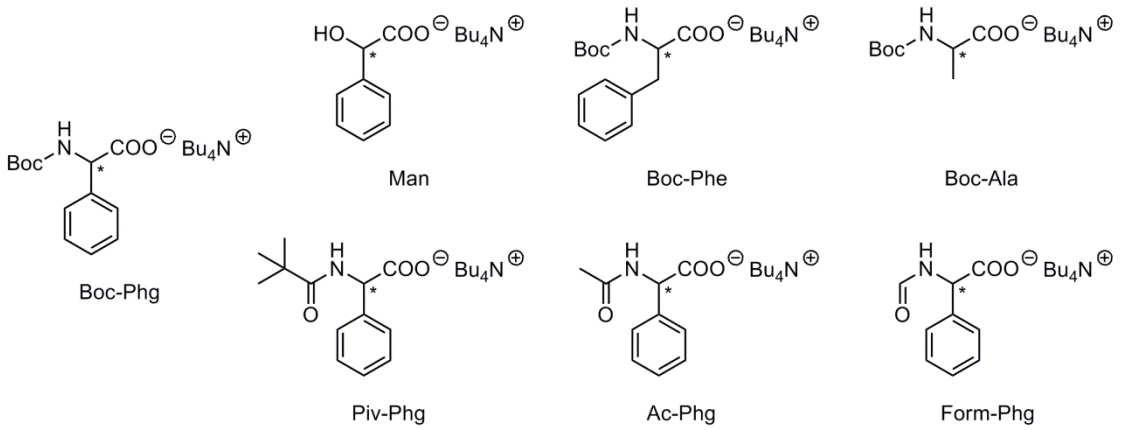


Figure 4.

The enantiomeric recognition ability of anion sensor **30** containing glucopyranosyl groups toward the enantiomers of Man, Boc-Phg, Boc-Phe and Boc-Ala (*Fig. 4*) was studied in acetonitrile using UV–vis spectroscopy. The highest enantioselectivity, which is a moderate one ($\Delta \log K = 0.22$), could be observed in the case of Boc-Phg (*Fig.5*). The effect of the size of the protecting group on enantiomeric recognition was also examined in the case of Phg with the enantiomers of Piv-Phg, Ac-Phg and Form-Phg (*Fig. 4*). The same enantioselectivity was observed in the cases of Piv-Phg and Boc-Phg, which have protecting groups of similar sizes. The complexation properties of receptor **30** with the enantiomers of Boc-Phg was also studied by ^{1}H NMR spectroscopy.[IV]

The enantiomeric recognition abilities of anion sensors (*S*,*S*)-**31**–(*S*,*S*)-**34** toward the enantiomers of Man, Boc-Phg, Boc-Phe and Boc-Ala (*Fig. 4*) were investigated in acetonitrile by UV–vis and fluorescence spectroscopies. Receptors (*S*,*S*)-**31** and (*S*,*S*)-**32** gave considerably small absorption and

fluorescence spectral changes upon addition of the carboxylates, which did not allow the accurate determination of the stability constants of these complexes. However, derivatives (*S*,*S*)-**33** and (*S*,*S*)-**34** showed larger spectral changes in the presence of the chiral carboxylates, and the enantiomeric recognition abilities were evaluated based on the fluorescence spectral changes (the sensor molecules have low fluorescence quantum yields). The highest enantioselectivity ($\Delta \log K = 0.24$) could be observed in the case of receptor (*S*,*S*)-**34** and Boc-Phg (*Fig. 5*). This preference of receptor (*S*,*S*)-**34** is similar to that of bis(thiourea) derivative **30**.[V]

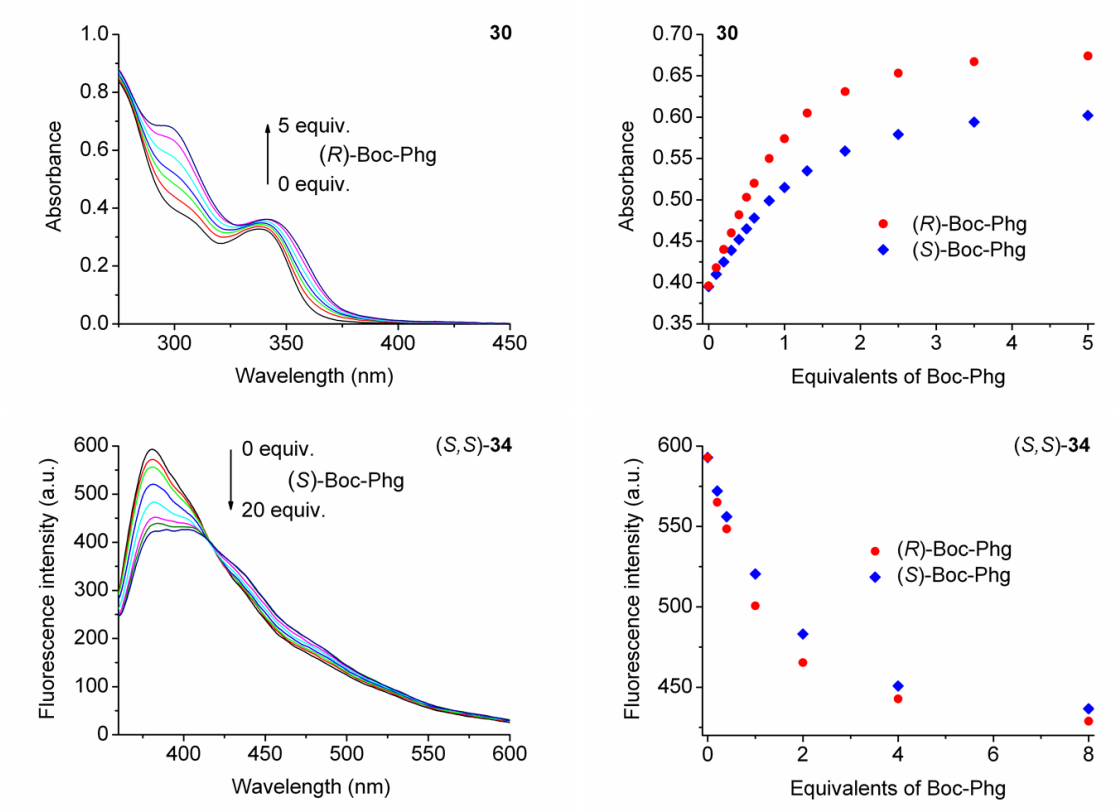
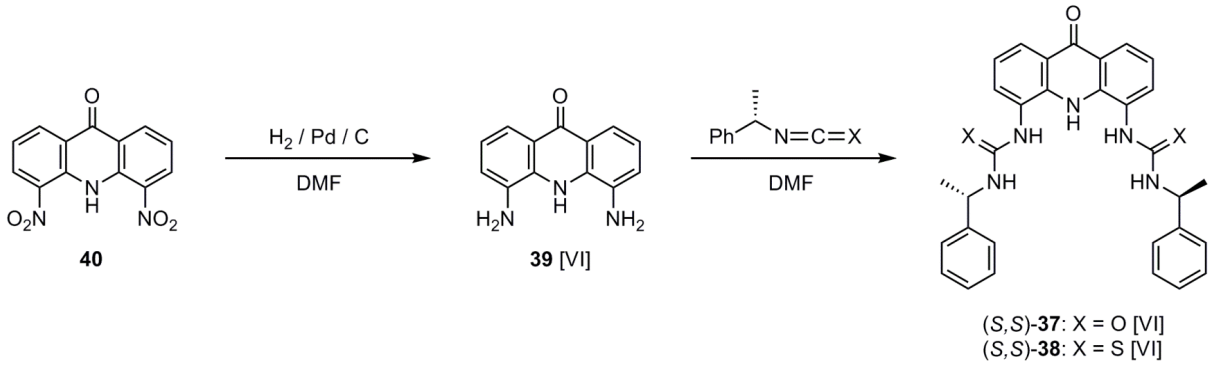


Figure 5.

We also prepared acridone-based optically active fluorescent anion sensors (*S*,*S*)-**37** and (*S*,*S*)-**38**[VI] starting from acridone derivative **39** (*Scheme 6*). Diaminoacridone **39** was synthesized from dinitroacridone **40**[13–16] with a more efficient and convenient method[VI] (*Scheme 6*) than the ones reported in the literature.[13–16]



Scheme 6.

The enantiomeric recognition abilities of anion sensors (*S*,*S*)-**37** and (*S*,*S*)-**38** toward the enantiomers of Man, Boc-Phg, Boc-Phe and Boc-Ala (*Fig. 4*) were examined in acetonitrile–DMSO 99:1 by UV–vis and fluorescence spectroscopies. Anion sensor (*S*,*S*)-**37** showed appreciable enantiomeric differentiation in the case of Boc-Ala ($\Delta \log K = -0.56$) (*Fig. 6*), and moderate enantioselectivities could be observed in the case of receptor (*S*,*S*)-**38** and Man, Boc-Phg and Boc-Ala, respectively.[VI]

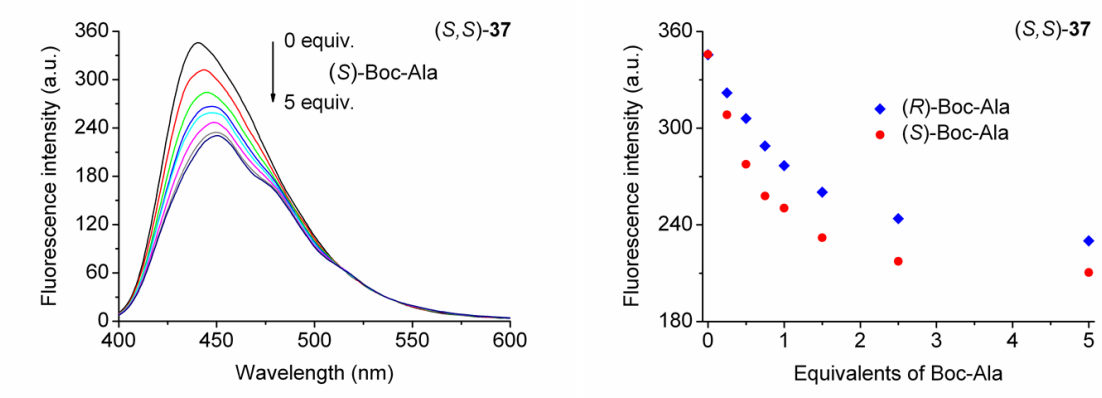


Figure 6.

The evaluation of the fluorescence and UV–vis spectroscopic measurements was carried out in cooperation with Dr. Péter Baranyai (Research Centre for Natural Sciences, HAS) and Prof. Klára Tóth (Budapest University of Technology and Economics).

The synthesized sensor molecules, which showed enantiomeric and anion recognition properties experimentally carried out in solutions, may be suitable for incorporating them into optode membranes with the aim of developing optical sensors.

The results of the research on the synthesis and studies of sensor molecules containing heterocyclic units were also presented in several conferences.[i–vi]

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