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Synthesis and fluorescent properties of novel chiral 1,2-diaminocyclohexanesubstituted ligands and their complexes

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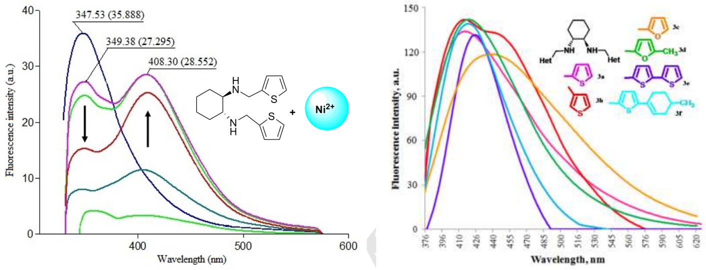
Graphical abstract



Abstract

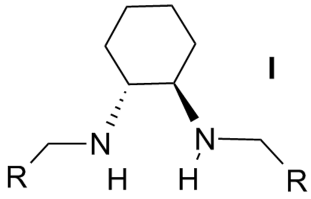
A series of novel chiral 1,2-diaminocyclohexane derivatives bearing heterocyclic units were synthesized via improved methods under ultrasonic irradiation. The photophysical properties of compounds were studied in ethanol, methanol and chloroform. The sensitivity of these amines toward Cu^{2+}, Cd^{2+} and Ni^{2+} was studied by the UV-Vis and fluorescent methods. The π-electron structure of thiophene and bithiophene containing sensors is the most active toward all above mentioned metal ions and is highly selective for Ni^{2+} and Cd^{2+}.

Keywords

Fluorescent Chiral Ligand; Heterocyclic Schiff Base; UV/Vis Spectroscopy; Diaminocyclohexane Ligand; Ultrasonic Activation

1. Introduction

Fluorescent compounds represent an important type of organic compounds due to their properties and variety of applications with strong potential as photochromic azo dyes, chromophores and *in vitro* fluorescent imaging probes for biodiagnosis.[1-5] Push-pull substituted heterocyclic compounds are of great interest due to their non-linear optical properties which are useful for opto-electronic devices.[6,7] Fluorophores based on a bithiophene structure are used in excitation chirality method for determining the absolute configurations of chiral molecules on a microscale level and the recognition of chiral molecules.[8,9] In recent years, the research work of chemical sensors for ions began to develop rapidly and to replace traditional analytical methods due to their advantages such as high sensitivity, selectivity and detection simplicity.[10] The chiral recognition method involves the application of chiral structures with optical properties. The structure of non-racemic *trans*-1,2-diaminocyclohexane satisfies requirements mentioned above. Thus new chiral sensors for ions and biomolecules based on the 1,2-diaminocyclohexane moiety have become a fast-growing research field.[8,11-14] Fluorescent receptors based on 1,2-diaminocylohexane with thiophene units indicate good results for recognition of fluoride ions.[15] Three decades ago, asymmetric reactions began to play an important role in modern organic synthesis.[16-18] The synthesis of new chiral ligands in asymmetric reactions is the subject of ongoing scientific research.[16-18] Complexes based on chiral 1,2-diaminocyclohexane with aromatic fragments are widely used in some asymmetric reactions: epoxidation of alkenes,[19] asymmetric allylic alkylation,[20] Henry reaction and Michael addition.[17,18,21] It has been shown that the properties of metal complexes depend on the structure and metal-specific binding site of the ligand.[22] The chiral unit of 1,2-diaminocyclohexane has the most suitable geometry parameters and commercial availability therefore it is the one of the important parts of the ligand structure.[23,24] It is found that thiophene containing ligands (**I**) have very good coordinating ability therefore vacant transition metal orbitals and π-rich heteroatoms of the thiophene fragment are involved in complex formation.[18] Suitable catalysts, such as complexes of **I** Cu(II), have been found to greatly increase enantioselectivity in the Henry reaction.[18]



I

R = -Ar, -Het

High enantioselectivity and good yields made this research field ripe for further exploration, and a series of thiophene containing ligands was synthesized.[23,25] The best results in allylic alkylation were obtained by using palladium complexes with two or three thiophene units in the coordination sphere of the ligand structure [23,26] Synthesis, catalytic activity and spectroscopic properties of thiophene, furan ligands and their derivatives, especially the nickel complexes, have been insufficiently studied.[21,27] In addition, the development of chiral ligands allows them to be used as highly sensitive, selective and effective metal ion sensors and opens a wide spectrum for their application.[10,13]

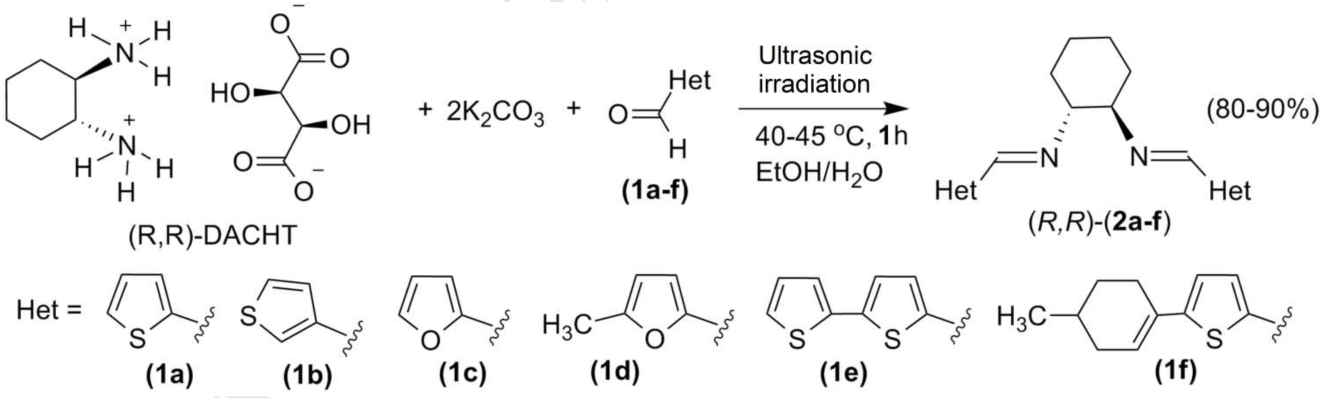
To research optical properties and the potential applications, a series of new heterocyclic chiral structures based on 1,2-diaminocyclohexane were synthesized in this work. The aim of this work was the synthesis of a series of heterocyclic ligands based on 1,2-diaminocyclohexane as a chiral unit, and to study and compare optical properties of ligands and their metal complexes.

2. Results and discussion

2.1. Chemistry

In recent years several methods for the synthesis of chiral ligands based on 1,2-diaminocyclohexane have been reported. One of the methods for azomethine synthesis from the free (*R,R)*-1,2-diaminocyclohexane and aromatic aldehydes was carried out in dichloromethane or ethanol as solvent at presence of anhydrous magnesium sulfate for 32 h at ambient temperature.[11,22,23,31-33] Significant improvement in some experiments was achieved using of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (DACHT) to avoid the use of water-soluble air-sensitive free diamine in the reaction and the use of water-removing reagents ($MgSO_4$, Na_2SO_4, molecular sieves). [11,23,28,29,32] Thereby the reaction time was decreased and the requirement to change reaction conditions depending on the aldehyde structure was excluded.[11,23,28,29,32] However, for isolation of free diamine from DACHT, base is required.[29] Condensation of aromatic aldehydes with DACHT at reflux in water-ethanol mixture in presence of potassium carbonate produced azomethines with good yields.[23,30] New methods for reaction stimulation such as microwave and ultrasonic irradiation may facilitate some reactions.[24] The most studied heterocyclic diimines and their complexes are based on thiophene-2-carbaldehyde, however, there is no data about thiophene-3-carbaldehyde and a lack information about furan ligands, their complexes and spectroscopic properties.

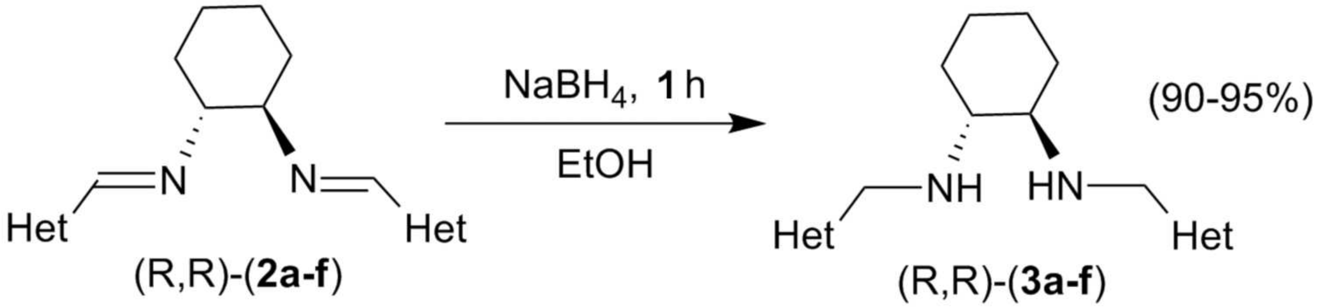
It should be mentioned that carrying out the experiment under the described conditions[30] with increase of the reaction temperature but without ultrasonic irradiation gives low yields and side products. Ultrasonic irradiation of reaction media is a useful method for preparation a series of azomethines (**3a-3f**) from corresponding aldehydes (**2a-2f**) and (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (**Scheme 1**).



Scheme 1. Synthesis of diimines (**2a-2f**)

The use of ultrasonic irradiation for reaction activation allowed the reaction time to be reduced to 1 h and the diimines to be isolated in good yields. However, the reaction time and yield are seen to be greatly affected by the absence of ultrasonic irradiation. The most suitable molar ratio of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt / aromatic aldehyde / potassium carbonate is 1:2:2 respectively.

Our interest is focused on the further reduction of the azomethines (**2a-2f**) to obtain new heterocyclic ligands for complex formation with potential uses in asymmetric catalysis. Reduction of the C=N bond in azomethines use $NaBH_4$/methanol or $NaBH_4$/THF with 10-fold excess of $NaBH_4$ and the reaction time varies up to 16 h at room temperature with good yields[11,22,23,29,34,35], but described reaction conditions lead to low yields of amines with heterocyclic fragments. We found the reaction can be carried out in ethanol with $NaBH_4$ with reflux for 1 hour of the reaction mixture. The corresponding chiral amines (**3a – 3f**) were obtained with high yields (>90%).



Scheme 2. Synthesis of amines (**3a**-**3f**)

The most suitable molar ratio of azomethine / $NaBH_4$ is 1:2:2 respectively, and the minimum volume of ethanol was used in the reaction.

2.2. Spectroscopic properties

The electronic spectra of compounds (**3a-3f**) were recorded in chloroform (10^{-3} M) and showed an intense lowest energy charge-transfer absorption band in the UV-region (**Table 1**). All compounds **(3a-3f)** exhibit an intense absorption in the UV-region and the position of this band depends on the electronic nature of the heterocyclic ring and ring substituent.

Table 1. **Yields, UV-Vis and fluorescent data of diamines (3a-3f) in chloroform (10^{-3} mole/l) and diamines 3a, 3c and 3e in ethanol ($2*10^{-6}$ mole/l)**

Compound	Solvent	λ_{abs}, nm	λ_{em}, nm (intensity, a.u.)	log ε	ν_{ss} (nm)
3a	$CHCl_3$	253, 308	416 (135)	4.19, 3.54	108
	EtOH	235	347 (142)	4.95	112
3b	$CHCl_3$	252, 300	416 (141), 443 (132)	4.16, 3.36	143
3c	$CHCl_3$	247, 309	443 (120)	4.03, 3.55	134
	EtOH	284	413 (72)	4.86	129
3d	$CHCl_3$	248, 317	423 (141)	4.20, 3.54	106
3e	$CHCl_3$	250, 355	425 (131)	4.15, 3.74	70
	EtOH	307	375 (240)	4.91	68
3f	$CHCl_3$	249, 310	423 (139)	4.09, 3.83	113

A slight bathochromic shift (8 nm) in the absorption spectrum in chloroform was observed for structure **3a** in comparison with **3b** that proves greater interaction of the α-substituent with thiophene π-system in **3a (Table 1)**. There is no significant effect on the absorption maxima of the compound **3c** with a furan moiety in comparison with **3a**. At the same time, there is a slight bathochromic shift (8 nm) for the methylfuran structure (**3d)**. The most considerable red-shift was observed for the 2,2′-bithiophene structure (**3e**) and, as with compound **3f,** it may suggest an interaction of the two π-electronic systems: thiophene and olefin moieties. The absorption spectrum of 2,2′-bithiophene-containing structure (**3e**) shows two main absorption bands in chloroform (**Table 1**). A broad band at ca. 355 nm may be ascribed to an electron transfer transition and a band of moderate intensity at ca. 250 nm may represent the π-π* local excitation transition of the heteroaromatic ring.

We measured the emission characteristics of compounds **3a**-**3f** in chloroform. All the emission spectra have a wide contour. In spite of the similar absorption maxima for **3a** and **3b,** two fluorescence maxima were observed for 3-thienyl substituted 1,2-diaminocyclohexane (**3b**). It is unexpected that the most significant bathochromic shift was noticed for the bis(2-furfuryl)diaminocyclohexane (**3c**) but not for compound (**3e**). The furan ring in comparison with thiophene has greater *π*-rich system that produces the red-shift of **3c (Table 1)**. At the same time, the furan ring is less photostable than the thiophene unit and the fluorescence intensity decreases over time for **3c**. The nature of structure (**3e**) had an apparent influence on the absorption and emission band of compound (**3e**). The wavelength maxima for absorption and emission were shifted to longer wavelengths in the structure **3e** due to the effective interaction of the two thiophene units (**Fig. 1**, **Table 1**). The presence in structure **3f** an additional chromophore group (C=C) in the cyclic olefin moiety has a slight effect on the absorption and emission maxima. The absorption and emission spectra of **3f** are similar to the corresponding spectra of **3a** and **3b** in chloroform (**Table 1**).

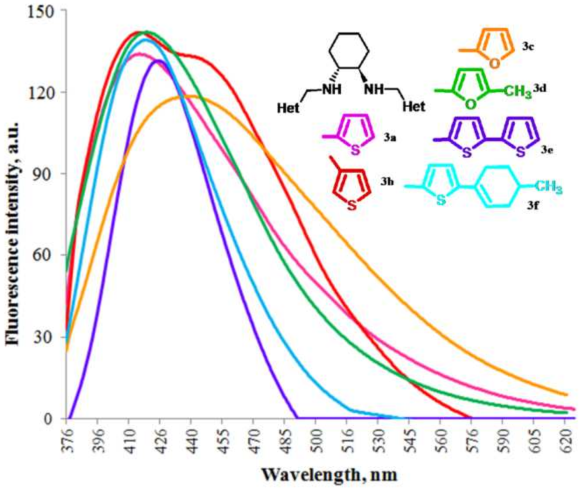


Fig. 1. Fluorescence emission spectra of compounds **3a – 3f** in chloroform (**3a** λ_{em} = 416 nm; **3b** λ_{em} = 416, 447 nm; **3c** λ_{em} = 443 nm; **3d** λ_{em} = 423 nm; **3e** λ_{em} = 430 nm; **3f** λ_{em} = 417 nm)

A comparison of UV-Vis and emission spectra of **3a** and **3e** in ethanol suggests that presence of two thiophene units in **3e** facilitates bathochromic shift of the maxima in the absorbance and fluorescence spectra (~70 nm) **(Fig. 2, Table 1)**. The use of polar solvent leads to increased red-shift of **3e** in ethanol in contrast with chloroform that is completely consistent with π* values by Kamlet et al.[36] for solvents (**Table 1**).

The recognition properties of the compounds (**3a**, **3c, 3e)** toward different metal ions: Ni^{2+}, Cd^{2+} and Cu^{2+} were studied by UV-Visible and fluorescence methods. The UV-spectra and fluorescence spectra of initial ligands (**3a, 3b, 3e**) were recorded in ethanol (**Table 1**). The UV-Vis spectrum of **3c** measured in ethanol is similar to the spectrum measured in chloroform and has a broad contour without intense maximum compared to the structures **3a** and **3e** with a stable thiophene ring (**Fig. 2**). The UV-Vis spectra of complexes compounds (**3a, 3c, 3e**) with cations have no change in either the wavelength values nor in the shapes of absorption spectra.

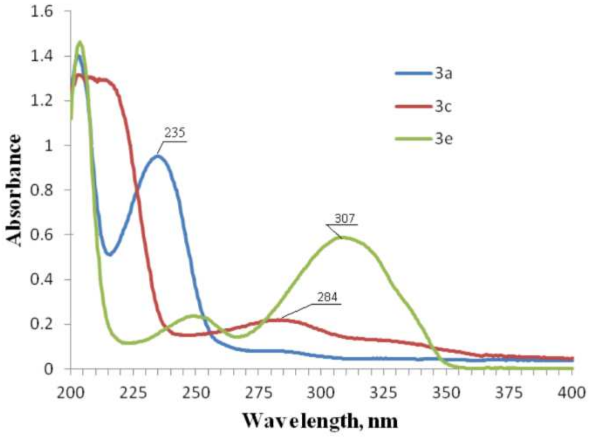


Fig. 2. UV-Vis spectra of compounds **3a, 3c, 3e** in ethanol

The interaction **3a** and **3e** with Ni^{2+} was carried out at different molar ratio of ligand and metal in ethanol-water and the intensity of fluorescence signal was measured over time. After addition of Ni^{2+} to compound **3a** at 2:1 molar ratio we observed the appearance of a new fluorescence maxima at 408 nm within 30 s that can be attributed to complex formation and a slight simultaneous increase in fluoresence intensity in contrast with the initial emission spectrum (**3a)**. Unexpected results were obtained at a 1:1 molar ratio of the compound **3a** and ion Ni^{2+} (**Table 3**). The appearance of a new intense fluorescent maxima in the longer wavelength region (408 nm) was observed and at the same time quenching of initial emission maximum (**3a**) (347 nm) during 5 min (**Fig. 3**) was observed. However the emission maxima at 347 nm of compound **3a** and new fluorescence signal of **3a**-Ni^{2+} complex at 408 nm still remain (**Table 1, 2**). It was possible to observe weak interactions between **3c** and Ni^{2+} through slight quenching of fluorescence maximum intensity and small bathocromic shift of emission maximum (8 nm) (**Table 2**).

Table 2. **Fluorescence data of complexes with diamines (3a, 3c, 3e)**[a]

Compound / ion	λ_{em}, nm (Intensity, a.u.)	Compound / ion	λ_{em}, nm (Intensity, a.u.)	Compound / ion	λ_{em}, nm (Intensity, a.u.)
3a / Ni^{2+}	408 (29)	**3a** / Cd^{2+}	349 (165)	**3a** / Cu^{2+}	355 (190)
3c / Ni^{2+}	421 (57)	**3c** / Cd^{2+}	421 (54)	**3c** / Cu^{2+}	421 (57)
3e / Ni^{2+}	376 (109)	**3e** / Cd^{2+}	375 (75)	**3e** / Cu^{2+}	377 (166)

[a]The measurement was carried out in ethanol-water 1:1 v/v (molar ratio 1:1 of compound and metal ions (10^{-6}M)).

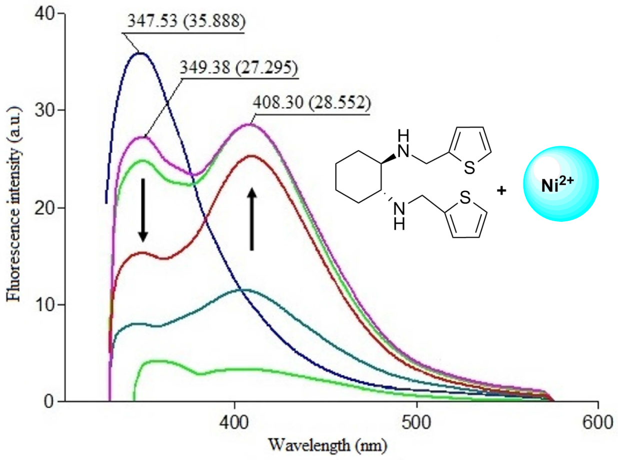


Fig. 3. Fluorescence emission spectra of complex **3a** and Ni^{2+} (at 1:1 molar ratio, ethanol-water at 1:1 v/v within 5 min). The dark blue graph represents an initial emission spectrum of **3a**

Similarly, we have studied interaction of **3e** with Ni^{2+} but there is no notable change nor in the absorption spectrum nor in the fluorescence spectrum intensity at 2:1 or 1:1 molar ratios of ligand to ion. With an excess of Ni^{2+} a hypochromic effect and increase in the fluorescence intensity of the main emission maximum were observed, also the second emission maximum was found at approx. 448 nm (**Fig. 4**). Perhaps, the molecules of solvent may take part in the external coordinating sphere at complex formation therefore red-shift is observed.

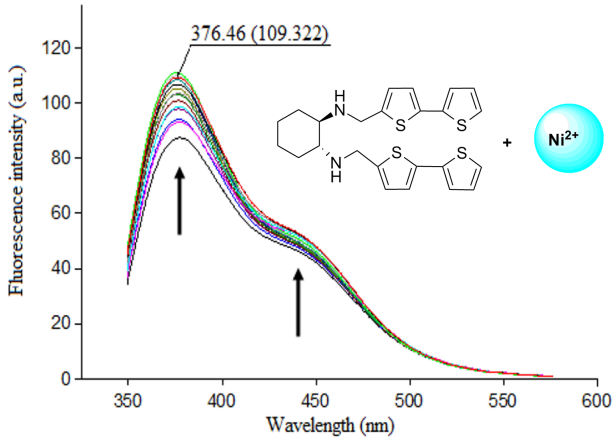


Fig. 4. Emission spectra of complex **3e** and Ni^{2+} (at 1:2 molar ratio in ethanol-water within 5 min).

The preparation of the nickel complex for enantioselective synthesis of γ-aminobutyric acid derivatives from diethylmalonate and nitroalkenes was carried out in methanol as a solvent.[27] The interest for us is to study the spectroscopic parameters of compounds **3a** and **3e** and their ability to form Ni(II) complexes with potential use as chemical sensors and catalysts in asymmetric reactions. A series of experiments with compounds **3a** and **3e** was carried out in methanol (**Table 3**). An aqueous solution of nickel (II) chloride was added to the methanol solutions of **3a** and **3e** and emission spectra were recorded.

Table 3. Fluorescence data of (3a, 3e) in methanol (10^{-3} mole/l)

Compound	λ_{abs}, nm (intensity, a.u)	λ_{ex}, nm (intensity, a.u)	λ_{em}, nm (intensity, a.u)	ε, l/mole•cm	ν_{ss}, nm
3a	307 (3.56), 241 (3.82)	342 (128)	423 (132)	141, 152	106, 172
3e	350 (3.99), 241 (3.51)	384 (247)	440 (260)	607, 533	89, 198

Along with an increase π* values by Kamlet et al.[36] for solvent polarity, a bathochromic shift is observed in **(3a)** and **(3e)**. Interaction of **3a** with Ni^{2+} lead to the hypochromic effect and hypsochromic shift of fluorescence maximum for one hour (**Fig. 5**), however the appearance of a second maximum in contrast with interaction of **3a** with Ni^{2+} in the ethanol-water mixture was not observed (**Fig. 3**).

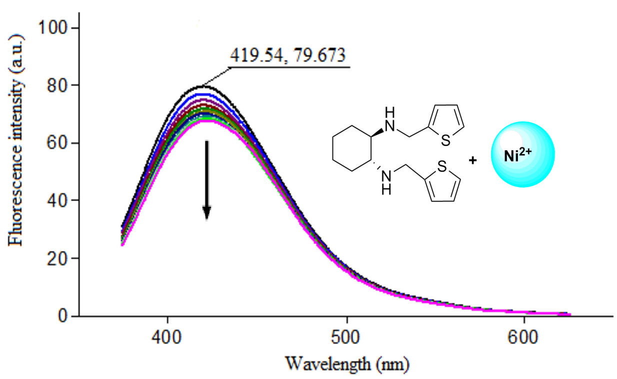


Fig. 5. The hypochromic effect in emission spectra of **3a** with Ni^{2+} in methanol (at molar ratio ligand / ion 2:1 within 1 h)

After the addition of Ni^{2+} to the methanol solution of **3e** a 9-fold increase in fluorecsence intensity was observed (**Fig. 6**) and accompanied by a small bathochromic shift (5 nm).

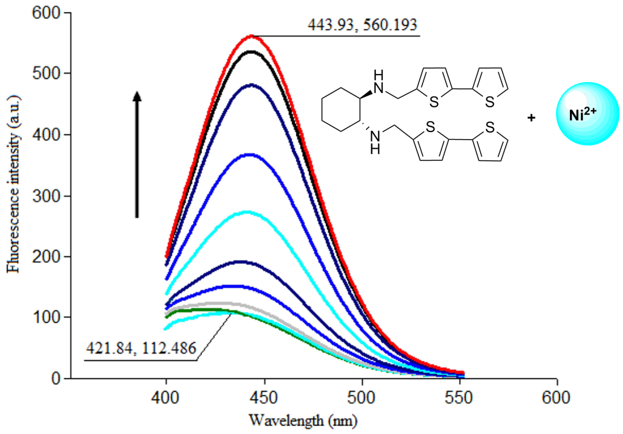


Fig. 6. The increase of fluorescence intensity in emission spectra of **3e** with Ni^{2+} in methanol (at molar ratio ligand / ion 2:1 within 10 min)

We can assume the formation of the complex **3e** with Ni^{2+} possibly facilitates the formation of a more rigid, planar configuration of ligand **3e** leading to the increase in fluorescence intensity. On the other hand, methanol may possibly form an exiplex through the compound's outer coordination sphere.[37]

The decrease in fluorescence maxima and slight bathochromic shift (10 nm) were observed for interaction of **3c** with Cd^{2+} at 1:1 molar ratio in ethanol-water solution (**Table 2**). Slight increase of the fluorescence intensity (on 16 per cent) was observed in the interaction of ligand **3a** with Cd^{2+} at 1:1 molar ratio in ethanol-water in comparison with initial emission spectrum **3a** (**Table 1, 2**). Unexpected results were obtained in the reaction of bithiophene compound **3e** with Cd^{2+} (1:1 molar ratio in ethanol-water). The significant decrease (3.2 times) of new fluorescense maximum was observed within 30 min from the starting emission value (375 nm, 134 a.u.) and to the final maximum (375 nm, 75 a.u.) (**Fig. 7**). The sensor **3e** is fluorescent in the absence of Cd^{2+}, however, after binding **3e** with Cd^{2+} an electron transfer from the fluorophore to the cation occurs. The mechanism of interaction **3e** with Cd^{2+} is photoinduced electron transfer (PET) and occurs upon complexation with a metal ion.[38]

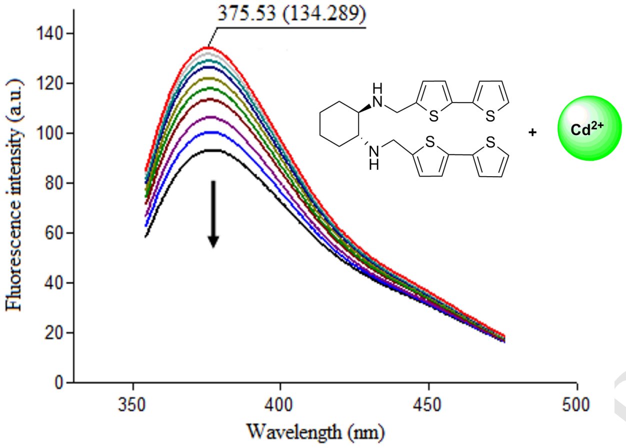


Fig. 7. The emission spectra of complex **3e** with Cd^{2+} (at molar ratio ligand / ion 1:1, water-ethanol within 30 min)

Slight changes in the fluorescence intensity were observed for compound **3c** with copper ions in ethanol-water solution (**Table 1, 2**). The interaction **3a** with Cu^{2+} in ethanol-water had practically no effect on the wavelength maxima of absorption and emission spectra. The significant decrease in intensity (in 1.5 times) of fluorescence maximum was observed in emission spectrum of compound **3e** with Cu^{2+}. Perhaps, the fluorescence signal of **3e** is quenched by the Cu^{2+} ion due to the formation of a stable complex.[39] A strong decrease of the fluorescence intensity is suggested to a chelation enhanced quenching (CHEQ effect)[40] during complex formation **3e** with Cu^{2+}. Therefore the chelated amine electron lone pairs become involved in bonding with the metal ion and they are unable to donate an electron to the excited molecule. In addition we may suggest that a short spacer such as methylene group between the bithiophene and diaminocyclohexane may be suitable for effective energy transfer.

3. Conclusions

A series of novel chiral compounds (**3a-3f**) was synthesized in modified conditions under ultrasonic irradiation, and these new ligands have a great potential as chemosensors and catalysts for asymmetric reactions in the near future. The results showed the equal sensory ability of compound **3c** for Ni^{2+}, Cd^{2+} and Cu^{2+} in ethanol-water solution. The ligand **3a** has medium sensory ability toward Cu^{2+} and slight change in interaction with Cd^{2+} ion in ethanol-water. It was found that the interaction of compound **3a** with Ni^{2+} in ethanol-water solution leads to the formation of two maxima in its emission spectrum that may be referred to equilibrium of ligand and complex. The bithiophene unit **3e** leads to stronger sensitivity that demonstrates as for Cu^{2+} and so for Cd^{2+} where we observed the quenching of fluorescent signal, especially for Cd^{2+}. Moreover, unexpected results had been found for complex **3e** with Ni^{2+} ion in methanol, so there instead of fluorescence quenching we observed a significant increase in the emission intensity of fluorescence spectrum. The possible explanation of different sensitivity of metal ions toward ligand **3e** may be referred to the ion size or to the greater fluorescence quenching effect due to the *d*-orbitals of Cd^{2+} and Cu^{2+}.[41,42] Besides that the concentration of compounds are in the 10^{-4} – 10^{-6} mol/l range that allowed to carry out the analysis at very low ligand concentration in the water-alcohol solutions.

Thereby we can assume that the series of synthesized compounds holds promise as useful chemosensors for a variety of ions in the near future, and furthermore these compounds may be used as ligands in complexes for the catalysis of asymmetric reactions, for example, Henry reaction and Michael addition.

4. Experimental

4.1 General information and materials

Experiments with air and moisture sensitive materials were carried out under argon atmosphere. Glassware was oven dried for several hours. Silica gel 60, Merck 230-400 mesh, was used for preparative column chromatography. Reagents were commercially available from Sigma Aldrich, Merck and were used without further purification. FTIR spectra were taken on a Shimadzu IRAffinity-1 spectrophotometer in KBr pellets or thin-layer (KBr prisms). NMR spectra were recorded on a JEOL JNM ECX 400MHz spectrometer in DMSO-d_6 and $CDCl_3$ using tetramethylsilane (TMS) as an internal reference. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Elemental analysis was performed on a EuroVector EA-3000 instrument. Electron impact–mass spectrometry (EI-MS) spectra were obtained on a Finnigan Trace DSQ spectrometer (70 eV). Analytical thin-layer chromatography (TLC) was performed on aluminum-backed silica-gel plates (Merck 60 F254 and Marchery Nagel). Visualization of components was accomplished with ultraviolet light (365 nm) or exposure to I_2. Optical rotations were measured on Rudolph Research Analytical (Autopol V Plus Automatic Polarimeter) with a sodium lamp at different wavelengths (436, 589, 633 nm) at 1 cm cell and are reported as follows: $[\alpha]_D^{20°C}$ (c = g/100 ml, solvent).

Chloroform, ethanol and methanol were employed as solvents for absorption and fluorescence measurements prepared according to described methods.[43] UV/Vis absorption spectra were recorded on a Shimadzu UV mini-1240 spectrophotometer in a 1 cm quartz cell, in comparison to solvent blank, at the wavelength range 200-550 nm. Emission spectra were obtained on a Cary Eclipse Varian Fluorescence Spectrophotometer in a 1 cm quartz cell at the wavelength range 200 – 650 nm, excitation and emission slits are 5 nm. The excitation wavelength was at the maxima of excitation spectra. The emission spectra were recorded at right angle relative to the cell. Solutions of the amines (**3a-3f**) (ca. 10^{-5} - 10^{-6} M) and of the cations under study (ca. 10^{-5} - 10^{-6} M) were prepared in ethanol or in mixtures of ethanol-water equal to the molar ratios in the form of $NiCl_2 \cdot 6H_2O$, $Cd(CH_3COO)_2 \cdot 6H_2O$, $Cu(CH_3COO)_2 \cdot H_2O$. Titration of the compounds with the cations was performed by the sequential addition of the equivalents of cation in the solution to the amine solution, in a 10 mm path length quartz cuvette and emission spectra were measured by excitation at the wavelength of maximum absorption for each compound over time (varies from 5 to 60 min). The addition of metal ion solution in water to the ligand ethanol solution were made in the 3 different ratios: 1 molar equivalent of metal ion solution / 2 molar equivalents of ligand solution, 1 molar equivalent of metal ion solution / 1 molar equivalent of ligand solution, 2 molar equivalents of metal ion solution / 1 molar equivalent of ligand solution. The concentration of the samples in methanol and chloroform was in a range 2×10^{-3} - 25×10^{-3} mol/l, measurements were carried out at 25 ^{0}C over time (varies from 1 to 60 min). The aqueous solution of $NiCl_2•6H_2O$ was added to the ligand in methanol at the ratio 1 molar equivalent of metal ion / 2 molar equivalents of ligand solution.

4.2. Synthesis of the compounds

4.2.1 Synthesis of initial compounds

2,2′-Bithiophene was prepared by improved Ulmann method,[44] yield 70%, bp 102-108 °C/4 Torr.[44] Synthesis of 2-(4′-methylcyclohex-1′-en-1′-yl)thiophene was carried out by the Grignard reaction, yield 77%. 2,2′-Bithiophene-5-carbaldehyde (**1e**) was prepared by the described procedure,[45] yield 75%. Synthesis of 5-(4′-methylcyclohex-1′-en-1′-yl)thiophene-2-carbaldehyde (**1f**) was carried out by the Vilsmeier-Haack method, yield 79%. Diastereomeric pure (*1R,2R*)-(-)-1,2-diaminocyclohexane mono-(+)-tartrate (**8**) was obtained from the mixture of *trans*-1,2-diaminocyclohexanes by the described method;[28] mp 274-276°C[28].

*4.2.2 General procedure for azomethine synthesis (**2a-2f**)*

Saturated K_2CO_3 solution (0.02 mol) and (*1R,2R*)-(-)-1,2-diaminocyclohexane mono-(+)-tartrate (0.01 mole) were dispersed under ultrasonic irradiation for 5 min. The corresponding aldehyde (**1a-f**) (0.02 mol) was dissolved in 20 ml of ethanol and added dropwise to the reaction mixture. The reaction was carried out under ultrasonic irradiation for 1 h at 40-45°C. The resulting precipitate was filtered off, washed twice with distilled water and ethanol. If necessary, the azomethine (**2a-2f**) was crystallized from ethanol.

*4.2.2.1 (1R,2R)-N,N'-bis[(E/Z)-thiophen-2-ylmethylidene]cyclohexane-1,2-diamine (**2a**).* Yield 90%; mp 128-133°C. IR (KBr), cm^{-1}: 2926, 2843, 1635, 1431, 1219, 1083, 935, 854, 743, 709. ^{1}H NMR ($CDCl_3$); δ ppm: 8.25 (s, 2H, N=C$\underline{H}$), 7.27 (dd, 2H, ^{3}J 5.0 Hz, ^{4}J 1.1 Hz, 5-H), 7.12 (dd, 2H, ^{3}J 3.7 Hz, ^{4}J 1.1 Hz, 3-H), 6.94 (dd, 2H, ^{3}J 3.7 Hz, ^{3}J 5.0 Hz, 4-H), 3.27-3.35 (m, 2H, *tert*-CH), 1.72-1.84 (m, 6H, CH), 1.40-1.46 (m, 2H, CH). ^{13}C NMR ($CDCl_3$); δ ppm: 154.4, 142.6, 130.3, 128.3, 127.3, 73.5, 32.9, 31.0, 24.5. Anal. Calcd. for $C_{16}H_{18}N_2S_2$: C, 63.54; H, 6.00; N, 9.26; S, 21.20. Found: C, 63.50; H, 6.07; N, 9.21; S, 21.26.

*4.2.2.2. (1R,2R)-N,N'-bis[(E/Z)-thiophen-3-ylmethylidene]cyclohexane-1,2-diamine (**2b**).* Yield 94%, mp 128-132°C. IR (KBr), cm^{-1}: 2927, 2854, 1639, 1240, 1078, 937, 866, 800, 783. ^{1}H NMR (CDCl$_3$); δ ppm: 8.18 (s, 2H, N=C$\underline{H}$), 7.42 (dd, 2H, ^4J 1.2 Hz, ^4J 2.9 Hz, 2-H), 7.39 (dd, 2H, ^3J 5.1 Hz, ^4J 1.2 Hz, 5-H), 7.21 (dd, 2H, ^3J 5.1 Hz, ^4J 1.2 Hz, 4-H), 3.26-3.33 (m, 2H, *tert*-CH), 1.70-1.84 (m, 6H, CH), 1.44-1.51 (m, 2H, CH). ^{13}C NMR (CDCl$_3$); δ ppm: 155.5, 140.7, 130.0, 126.1, 125.9, 73.9, 33.1, 24.6. Anal. Calcd. for $C_{16}H_{18}N_2S_2$: C, 63.54; H, 6.00; N, 9.26; S, 21.20. Found: C, 63.58; H, 6.06; N, 9.27; S, 21.12.

*4.2.2.3. (1R,2R)-N,N'-bis[(E/Z)-furan-2-ylmethylidene]cyclohexane-1,2-diamine (**2c**).* Yield 85%. IR (KBr), cm^{-1}: 2931, 2858, 1647, 1485, 1068, 1014, 933, 767, 740. ^{1}H NMR (CDCl$_3$); δ ppm: 7.99 (s, 2H, N=C$\underline{H}$), 7.41 (2H, d, ^3J 1.8 Hz, 5-H), 6.55 (d, 2H, ^3J 3.4 Hz, 3-H), 6.36 (dd, 2H, ^3J 3.4 Hz, ^3J 1.8 Hz, 4-H), 3.31-3.35 (m, 2H, *tert*-CH), 1.75-1.83 (m, 6H, CH), 1.40-1.43 (m, 2H, CH). ^{13}C NMR (CDCl$_3$); δ ppm: 151.4, 149.6, 144.5, 114.4, 111.5, 74.1, 33.1, 24.5. Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.15; H, 6.78; N, 10.40.

*4.2.2.4. (1R,2R)-N,N'-bis[(E/Z)-(5-methylfuran-2-yl)methylidene]cyclohexane-1,2-diamine (**2d**).* Yield 97%. IR (KBr), cm^{-1}: 2927, 2858, 1643, 1535, 1022, 929, 786. ^{1}H NMR (CDCl$_3$); δ ppm: 7.84 (s, 2H, N=C$\underline{H}$), 6.37 (d, 2H, ^3J 3.2 Hz, 3-H), 5.90 (d, 2H, ^3J 3.2 Hz, 4-H), 3.23-3.30 (m, 2H, *tert*-CH), 2.23 (s, 6H, 2×CH$_3$), 1.68-1.74 (m, 6H, CH), 1.30-1.39 (m, 2H, CH). ^{13}C NMR (CDCl$_3$); δ ppm: 155.3, 150.1, 149.5, 116.3, 107.9, 74.1, 43.5, 33.2, 24.5, 14.0. Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N 9.39. Found: C, 72.45; H, 7.41; N, 9.41.

*4.2.2.5. (1R,2R)-N,N'-bis[(E/Z)-(2,2'-bithiophene-5-yl)methylidene]cyclohexane-1,2-diamine (**2e**).* Yield 91%, mp 110-113°C. IR (KBr), cm^{-1}: 2935, 2843, 1624, 1462, 1226, 1087, 835, 790, 696, 686. ^{1}H NMR (CDCl$_3$); δ ppm: 8.20 (s, 2H, N=C$\underline{H}$), 7.20 (dd, 2H, ^3J 5.2 Hz, ^4J 1.2 Hz, 5-H), 7.18 (dd, 2H, ^3J 3.7 Hz, ^4J 1.2 Hz, 4-H), 7.00-7.04 (m, 4H, 3-H, 3′-H), 6.99 (dd, 2H, ^3J 3.7 Hz, ^3J 5.2 Hz, 4′-H), 3.25-3.32 (m, 2H, *tert*-CH), 1.72-1.87 (m, 6H, CH), 1.40-1.46 (m, 2H, CH). ^{13}C NMR (CDCl$_3$); δ ppm: 154.3, 141.0, 140.0, 137.3, 131.1, 128.0, 125.2, 124.5, 123.6, 73.5, 32.9, 24.5. Anal. Calcd. for $C_{24}H_{22}N_2S_4$: C, 61.76; H, 4.76; N, 6.00; S, 27.48. Found: C, 61.78; H, 4.74; N, 6.02; S, 27.46.

*4.2.2.6. (1R,2R)-N,N'-bis[(E/Z)-(5-(4-methylcyclohex-1-ene-1-yl)thiophene-2-yl)methylidene]cyclohexane-1,2-diamine (**2f**).* Yield 60%, mp 147-149°C. IR (KBr), cm^{-1}: 2924, 2858, 1627, 1460, 1226, 792. ^{1}H NMR (CDCl$_3$); δ ppm: 8.15 (s, 2H, N=C$\underline{H}$), 6.98 (d, 2H, ^3J 3.7 Hz, 4-H), 6.79 (d, 2H, ^3J 3.7 Hz, 3-H), 6.19 (br, 2H, C=C$\underline{H}$), 3.24-3.28 (m, 2H, *tert*-CH), 2.20-2.46 (m, 6H, CH), 1.55-1.81 (m, 10H, CH), 1.21-1.40 (m, 4H, CH), 0.97 (d, 6H, ^3J 6.4 Hz, 2×CH$_3$). ^{13}C NMR (CDCl$_3$); δ ppm: 154.6, 149.4, 139.4, 130.9, 130.8, 125.4, 121.4, 73.5, 34.4, 33.0, 30.9, 28.1, 27.3, 24.5, 21.7. Anal. Calcd. for $C_{30}H_{38}N_2S_2$: C, 73.42; H, 7.85; N, 5.71; S, 13.07. Found: C, 73.40; H, 7.81; N, 5.72; S, 13.07.

*4.2.3 General procedure of amines synthesis (**3a-3f**)*

The corresponding azomethine (0.01 mol) is dissolved in the minimal volume of ethanol. $NaBH_4$ (0.1 mol) was added with intensive stirring at room temperature and then the mixture refluxed for 1 h. The reaction mixture is cooled to r.t. and half of the ethanol was evaporated, the residue is poured into cold water. The amine is extracted with methylene chloride (3×50 ml), dried over anhydrous $MgSO_4$. Solvent was removed with a rotary evaporator and the amines were obtained with good yields.

*4.2.3.1. (1R,2R)-N,N'-bis(thiophen-2-ylmethyl)cyclohexane-1,2-diamine (**3a**).* Yield 98%, mp 70-72°C. $[\alpha]_D^{20}$ -76.8 (c 0.05, $CHCl_3$). IR (KBr), cm^{-1}: 3298, 2924, 2850, 1450, 1111, 694. ^1H NMR ($CDCl_3$); δ ppm: 7.18 (dd, 2H, ^3J 5.0 Hz, ^4J 1.4 Hz, 5-H), 6.90-6.94 (m, 4H, 3-H, 4-H), 4.1 (d, 2H, J 14.2 Hz, C$\underline{H}$-NH), 3.88 (d, 2H, J 14.2 Hz, C$\underline{H}$-NH), 2.26-2.30 (m, 2H), 2.05-2.15 (m, 2H), 1.70-1.74 (m, 2H), 1.20-1.25 (m, 2H), 1.01-1.05 (m, 2H). ^{13}C NMR ($CDCl_3$); δ ppm: 145.2, 126.6, 124.5, 124.3, 60.5, 45.6, 31.6, 25.1. Anal. Calcd. for $C_{16}H_{22}N_2S_2$: C, 62.70, H, 7.24, N, 9.14, S, 20.92. Found: C, 62.73; H, 7.22; N, 9.15; S, 20.90.

*4.2.3.2. (1R,2R)-N,N'-bis(thiophen-3-ylmethyl)cyclohexane-1,2-diamine (**3b**).* Yield 86%, mp 70-72°C. $[\alpha]_D^{20}$ -76.3 (c 0.05, $CHCl_3$). IR (KBr), cm^{-1}: 3294, 2924, 2850, 1450, 1111, 856, 833, 770. ^1H NMR ($CDCl_3$); δ ppm: 7.25 (d, 2H, ^3J 5.0 Hz, 5-H), 7.08-7.11 (m, 2H, 2-H), 7.04 (d, 2H, 4-H), 3.91 (d, 2H, J 13.9 Hz, C$\underline{H}$-NH), 3.68 (d, 2H, J 13.9 Hz, C$\underline{H}$-NH), 2.22-2.27 (m, 2H), 2.04-2.15 (m, 2H), 1.65-1.74 (m, 2H), 1.19-1.25 (m, 2H), 1.00-1.10 (m, 2H). ^{13}C NMR ($CDCl_3$); δ ppm: 142.1, 127.7, 125.8, 121.2, 60.9, 46.0, 31.6, 25.1. Anal. Calcd. for $C_{16}H_{22}N_2S_2$: C, 62.70; H, 7.24; N, 9.14; S, 20.92. Found: C, 62.68; H, 7.17; N, 9.10; S, 20.85.

*4.2.3.3. (1R,2R)-N,N'-bis(furan-2-ylmethyl)cyclohexane-1,2-diamine (**3c**).* Yield 83%, $[\alpha]_D^{20}$ -42.5 (c 0.05, $CHCl_3$). IR (KBr), cm^{-1}: 3302, 2924, 2854, 1450, 1149, 1010, 732. ^1H NMR ($CDCl_3$); δ ppm: 7.20-7.22 (dd, 2H, ^3J 3.4 Hz, ^4J 1.8 Hz, 5-H), 6.16-6.17 (d, 2H, ^4J 3.4 Hz, 3-H), 6.07-6.08 (dd, 2H, ^4J 1.8 Hz, ^3J 3.4 Hz, 4-H), 3.75 (d, 2H, C$\underline{H}$-NH), 3.61 (d, 2H, C$\underline{H}$-NH), 2.10-2.18 (m, 2H), 1.90-1.94 (m, 2H), 1.56-1.64 (m, 2H), 1.05-1.11 (m, 2H), 0.90-1.00 (m, 2H). ^{13}C NMR ($CDCl_3$); δ ppm: 154.0, 141.6, 110.2, 106.8, 60.4, 43.3, 31.1, 24.9. Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.08; H, 8.11; N, 10.15.

*4.2.3.4. (1R,2R)-N,N'-bis[(5-methylfuran-2-yl)methyl]cyclohexane-1,2-diamine (**3d**).* Yield 94%, $[\alpha]_D^{20}$ -52.0 (c 0.05, $CHCl_3$). IR (KBr), cm^{-1}: 3302, 2924, 2855, 1566, 1450, 1219, 1114, 1018, 783. ^1H NMR ($CDCl_3$); δ ppm: 5.95 (d, 2H, ^3J 3.2 Hz, 3-H), 5.77 (d, 2H, ^3J 3.2 Hz, 4-H), 3.70 (d, 2H, J 14.2 Hz, C$\underline{H}$-NH), 3.54 (d, 2H, J 14.2 Hz, C$\underline{H}$-NH), 2.14 (s, 6H, 2×CH_3), 1.93-2.00 (m, 2H), 1.60-1.65 (m, 4H), 1.10-1.20 (m, 2H), 0.90-0.98 (m, 2H). ^{13}C NMR ($CDCl_3$); δ ppm: 152.8, 151.0, 107.1, 106.0, 60.6, 43.7, 31.5, 25.1, 13.6. Anal. Calcd. for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.55; H, 8.71; N, 9.25.

*4.2.3.5. (1R,2R)-N,N'-bis[(2,2′-bithiophene-5-yl)methyl]cyclohexane-1,2-diamine (**3e**).* Yield 88%, $[\alpha]_D^{20}$ -9.2 (c 0.01, $CHCl_3$). IR (KBr), cm^{-1}: 3290, 2920, 2850, 1458, 1099, 833, 798, 698. ^1H NMR ($CDCl_3$); δ ppm: 7.15 (dd, 2H, ^3J 5.0 Hz, ^4J 1.4 Hz, 5′-H), 7.08 (dd, 2H, ^3J 3.7 Hz, ^4J 1.4 Hz, 3′-H), 6.98 (d, 2H, ^3J 3.6 Hz, 4-H), 6.94 (dd, 2H, ^3J 5.0 Hz, ^3J 3.7 Hz, 3′-H), 6.81 (d, 2H, ^3J 3.6 Hz, 3-H), 4.07 (d, 2H, ^3J 14.1 Hz, $C\underline{H}$-NH), 3.86 (d, 2H, ^3J 14.1 Hz, $C\underline{H}$-NH), 2.34-2.38 (m, 2H), 2.10-2.16 (m, 2H), 1.71-1.75 (m, 2H), 1.20-1.26 (m, 2H), 1.02-1.08 (m, 2H). ^{13}C NMR ($CDCl_3$); δ ppm: 144.4, 137.9, 136.3, 127.8, 125.2, 124.0, 123.4, 123.3, 60.5, 45.7, 31.5, 29.8, 25.0. Anal. Calcd. for $C_{24}H_{26}N_2S_4$: C, 61.22; H, 5.57; N, 5.95; S, 27.25. Found: C, 61.16; H, 5.50; N, 5.97; S, 27.29.

*4.2.3.6. (1R,2R)-N,N'-bis[(5-(4-methylcyclohex-1-ene-1-yl)thiophene-2-yl)methyl]cyclohexane-1,2-diamine (**3f**).* Yield 91%, $[\alpha]_D^{20}$ -5.0 (c 0.01, $CHCl_3$). IR (KBr), cm^{-1}: 3290, 2924, 2862, 1624, 1454, 1357, 1111, 1022, 787. ^1H NMR ($CDCl_3$); δ ppm: 6.69-6.76 (m, 4H, 3-H, 4-H), 6.06 (br s, 2H), 4.02 (d, 2H, ^3J 14.2 Hz, $C\underline{H}$-NH), 3.80 (d, 2H, ^3J 14.2 Hz, $C\underline{H}$-NH), 2.05-2.50 (m, 12H), 1.62-1.85 (m, 8H), 1.15-1.33 (m, 6H), 0.97 (d, 6H, ^3J 4.3 Hz, $2\times CH_3$). ^{13}C NMR ($CDCl_3$); δ ppm: 145.7, 142.0, 131.0, 124.8, 123.1, 120.7, 60.2, 45.7, 34.3, 31.4, 31.0, 28.3, 27.3, 25.0, 21.8. Anal. Calcd. for $C_{30}H_{42}N_2S_2$: C, 72.82; H, 8.56; N, 5.66; S, 12.96. Found: C, 72.75; H, 8.64; N, 5.70; S, 12.97.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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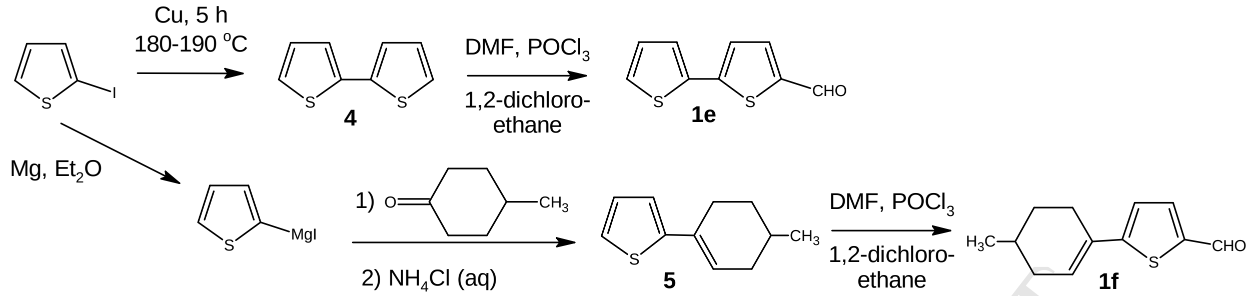
Supplementary data



2,2′-Bithiophene (**4**) was prepared by improved Ulmann method[1]: a mixture of 2-iodothiophene (82 g, 0.39 mole) and copper (50 g, 0.78 mole) was refluxed (180 - 190°C) with stirring for 3 hours. The reaction mixture was extracted with 1,2-dichloroethane (3×200 ml) and copper iodide was removed by filtration. The solvent was removed with a rotary evaporator, the fractional distillation of the residue gave the *title compound* **4** (22.7 g, 70%); bp 102-108 °C/4 Torr)[1].

*Synthesis of 2-(4′-methylcyclohex-1′-en-1′-yl)thiophene (**5**)*

A solution of 2-iodothiophene (35.7 g, 0.17 mole) in dry Et_2O (85 ml) was added dropwise from a dropping funnel to a magnesium turnings (4.34 g, 0.18 mole) in dry Et_2O (10 ml). The reaction mixture was heated on the water bath for 2.5 h (until magnesium turnings disappeared). The Grignard reagent was cooled to 0-5 °C and 4-methylcyclohexanone (14.1 g, 0.125 mole) in dry Et_2O (30 ml) was added dropwise from a dropping funnel. After ketone addition, the reaction mixture was heated for 1 h on the water bath. The solution was cooled to 0 °C and the mixture was quenched with dilute NH_4Cl solution. The ether phase was separated, washed with water and dried over anhydrous $MgSO_4$. After filtration, solvent was removed with a rotary evaporator. The crude product mixture was fractionally distilled to obtain desired *compound* **5** (17.13 g, 77%) as slight yellow liquid; bp 107-112°C/5-7 Torr. IR (KBr), cm^{-1}: 2947, 2920, 2870, 1454, 1434, 1234, 844, 802, 690. ^{1}H NMR (DMSO-d_6); δ ppm: 7.23 (dd, 1H, ^3J 4.1 Hz, ^4J 2.0 Hz, 5-H), 6.92 (dd, 2H, ^3J 4.1 Hz, ^4J 2.0 Hz, 3-H, 4-H), 6.05 (br, 1H, CH), 2.38-2.43 (m, 1H, CH), 2.25-2.34 (m, 1H, CH_2), 2.13-2.21 (m, 1H, CH_2), 1.56-1.75 (m, 3H, CH_2), 1.19-1.29 (m, 1H, *tert*-CH), 0.91 (d, 3H, ^3J 6.4 Hz, CH_3). ^{13}C NMR (DMSO-d_6); δ ppm: 146.3, 131.0, 127.8, 123.7, 123.3, 122.0. Anal. Calcd. for $C_{11}H_{14}S$: C, 74.10; H, 7.91; S, 17.98. Found C, 74.23; H, 8.01; S, 18.06.

*Synthesis of 2,2′-bithiophene-5-carbaldehyde (**1e**)*

2,2′-Bithiophene-5-carbaldehyde (**1e**) was prepared by the improved procedure.[2] To the mixture of 2,2′-bithiophene (**4**) (44 g, 0.027 mol) and *N*,*N*-dimethylformamide (3.9 g, 0.053 mol) in 1,2-dichloroethane (44 ml) was added dropwise from a dropping funnel $POCl_3$ (6.3 g, 0.042 mol) at 0-5 °C. Reaction mixture was stirred for 5 h at room temperature. The mixture was quenched with saturated $NaHCO_3$ solution (pH = 7-8). Organic phase was separated, washed several times with water, and dried over anhydrous $MgSO_4$. Solvent was removed with a rotary evaporator and the residue crystallized from *n*-hexane. Yield 3.9 g (75%); mp 52-55 °C.[2]

*Synthesis of 5-(4'-methylcyclohex-1'-en-1'-yl)thiophene-2-carbaldehyde (**1f**)*

The Vilsmeier-Haack reagent was prepared to avoid side reactions and to increase yield of compound (**5**). $POCl_3$ (7 ml, 0.075 mol) was added dropwise from a dropping funnel at 5-10 °C to the stirring *N,N*-dimethylformamide (9.67 g, 0.125 mol). To the mixture of compound (**5**) (8.9 g, 0.05 mol) in of 1,2-dichloroethane (30 ml) Vilsmeier-Haack reagent was added dropwise at 10-15 °C. The reaction mixture was allowed to warm up and kept for 10 h at room temperature. The mixture was poured into crushed ice and then neutralized with $NaHCO_3$. The aqueous layer was extracted with 1,2-dichloroethane and dried over anhydrous $MgSO_4$. The solvent was removed with a rotary evaporator, the resulting precipitate filtered off and washed with *n*-hexane to afford the pure compound **7** (7.8 g, 79%) as pale yellow needles; mp 76-78 °C. IR (KBr), cm^{-1}: 2924, 2854, 1651, 1454, 1226, 1033, 794, 671. ^1H NMR (DMSO-d_6); δ ppm: 9.80 (s, 1H, CHO), 7.61 (d, 1H, ^3J 3.9 Hz, 4-H), 7.03 (d, 1H, ^3J 3.9 Hz, 3-H), 6.40 (br, 1H, CH), 2.40-2.50 (m, 2H, CH), 2.25-2.34 (m, 1H, CH), 1.79-1.88 (m, 2H, CH), 1.68-1.77 (m, 1H, CH), 1.31-1.41 (m, 1H, *tert*-CH), 0.99 (d, 3H, ^3J 6.4 Hz, CH_3). ^{13}C NMR (DMSO-d_6); δ ppm: 182.9, 157.0, 140.5, 137.3, 130.7, 128.6, 122.3, 34.4, 30.7, 28.0, 27.4, 21.6. MS (EI) *m/z* (%): M^+ 206 (100), [M^+ -CH_3] 191 (30), [M^+ -CHO] 177 (50). Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.86; H, 6.84; S, 15.54. Found: C, 69.97; H, 6.80; S, 15.61.

References and notes

1. Wynberg, H.; Logothetis, A. *J. Am. Chem. Soc.* **1956**, *58*, 1958-1961.

2. Wei, Y.; Wang, B.; Wang, W.; Tian, J. *Tetrahedron Lett.* **1995,** *36*, 665-668.