ACES Asian Chemical Editorial Society

doi.org/10.1002/asia.202300031

CHEMISTRY AN ASIAN JOURNAL Research Article

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Thiourea-Based Tritopic Halogen-Bonding Acceptors

Lauri Happonen, Milla Mattila, Ivan Peshev, Arttu Lehikoinen, and Arto Valkonen*[a]

Dedicated to the memory of our friend Dr. Jari Sinkkonen (Stora Enso), who passed away in early January 2023 at the age of 47.

Abstract: A series of thiourea-based tritopic receptor molecules were synthesized to be used as building blocks for halogen-bonded assemblies. Here, 16 new receptor molecules were synthesized from two different 2,4,6-trialkyl-1,3,5-tris(bromomethyl)benzene starting materials via tris(isothiocyanatomethyl)benzene intermediates. The alkyl substituents in the benzene ring proved to be important for isothiocyanate group formation instead of competing thiocyanate group. The synthesis route allowed us to synthesize the isothiocyanate intermediates and further the receptor molecules without the typically used and highly toxic thiophosgene. The synthesized receptor molecules were used to study their halogen-bond acceptor properties with diiodotetrafluorobenzene donors by single-crystal X-ray diffraction method. We were able to obtain five new crystal structures of halogen-bonded complexes, in which all receptors showed two to four accepted C–I···S halogen bonds. The observed halogen bonds were highly directional and showed large variation in C=S···I acceptor angles, indicating flexible acceptor properties of sulfur.

Introduction

Thiourea based tritopic assemblies have shown a lot of promise, for example, as an ionophores transferring ions and small molecules across hydrophobic membrane.[1] Incompletely *N*-substituted thiourea units offer interesting capabilities to these molecules acting as anion receptors due to their ability to form hydrogen bonds via NH-groups.[2–4] Previous studies have shown that thiourea moieties are rather rigid and well suited to form halogen bonds, which offers possibilities to these molecules to form larger assemblies trough intermolecular weak interactions.[5–7] Recent studies have also shown that halogen bonding can be used as tool to form reversible capsules.[8–11] Inspired by these facts we decided to synthesize a series of thiourea based tritopic building blocks and to experimentally research their halogen bonding capabilities. Herein we report 16 new tritopic thiourea based receptors derived from commercially available 2,4,6-trialkyl-1,3,5-tris(bromomethyl)benzenes (alkyl = methyl or ethyl). Those starting materials have been shown to be effective scaffolds to construct molecular receptor molecules, which have suitable structures to enable formation of capsular entities by non-covalent forces.[1]

Typically, isothiocyanate groups have been synthesized from primary amines with thiophosgene or carbon disulfide, which are highly toxic reagents. With this in mind we searched other possible ways to synthesize benzylic isothiocyanates, which were proposed to be intermediates in the synthesis of desired thiourea based receptors. We found quite usable reaction from the literature,[1] where potassium thiocyanate (KSCN) reacts with benzylic bromides in *N*,*N*-dimethylformamide (DMF) forming isothiocyanate group(s). This method can be generally considered to be less hazardous even though in the presence of acid a release of toxic gasses is expected and hence it is not ideal. In any case, it should be much safer than the use of thiophosgene. However, this reaction has a severe drawback, which was also observed in the present study, and which is the simultaneous formation of isomeric thiocyanates. The crude product of the reaction contains both isomers. The structure of the major product depends on the substituents (at least in *ortho*-position) in aromatic ring of the benzylic bromide and used conditions. This is not well-discussed in the literature. The reaction of isothiocyanates with primary amines is straightforward and rather easy way to prepare molecules containing thiourea groups.[1]

Halogen bonding (XB) is a non-covalent, highly directional interaction between halogen atom and Lewis base, which has a lot of similarity with hydrogen bonding (HB) as both are based of charge transfer between atoms. Both have also rather high directionality. Studies has shown that directionality on XB is strict, much stricter than in HB,[12,13] meaning that the linear interaction geometry is vital for the occurrence of XB. This makes XB one of the key interactions in supramolecular chemistry,[14–16] crystal engineering,[17–19] material sciences,[20,21] medicinal chemistry[22,23] and organocatalysis.[24,25] Halogen bond can occur between dihalogens (such as I_2 or Br_2) and electron donor (= XB acceptor). Halogen atoms can also form halogen bonds when they are bound to organic moiety, where usually some electron withdrawing atoms are introduced to make halogen atom more polarized. More polar the halogen atom is the larger is the σ-hole, which dictates how strongly halogen atom can bind to XB acceptor.[12,15,26,27] Good examples of highly polarized organic halogen bond donors are diiodotetrafluor-

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/asia.202300031

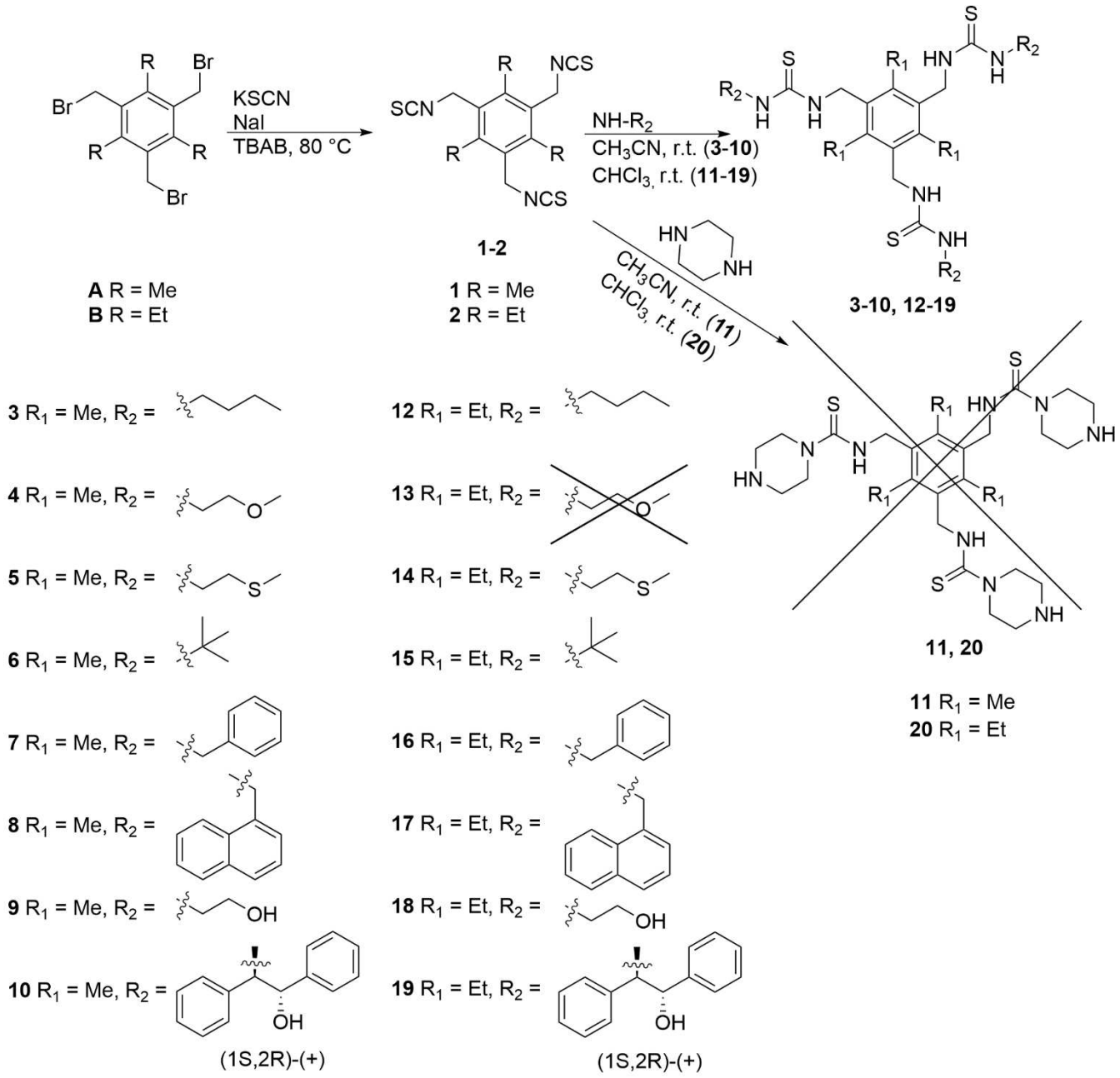
This manuscript is part of a special collection on Halogen Bonding.

obenzenes (DITFBs).[28–31] Rather recently found type of XB are three-center-four-electron bonds with highly polarized halogen (X) and two acceptor (A) atoms in $[A_1\cdots X\cdots A_2]^+$ system.[32–35]

In this experimental study our aim was to synthesize tritopic thiourea based receptor molecules, which have three XB acceptor sites and to utilize them in further XB studies to understand better the behavior and capacities of sulfur in XB. Here we used 1,3,5-tris(bromomethyl)-2,4,6-alkylbenzenes as starting materials to prepare first the corresponding isothiocyanates, which were further reacted with amines to obtain a series of tritopic target molecules. These target molecules were then mixed with diiodotetrafluorobenzenes to obtain XB complexes. The reaction of seven different di- tri- and tetratopic benzylic bromides with KSCN in DMF were also shortly examined to observe and prove the influence of *orto*-alkyl substituents in isothiocyanate formation.

Results and Discussion

Synthesis of receptors. Compounds **1** and **2** were synthesized by nucleophilic substitution reaction of 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene (**A**) or 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**B**) with KSCN (Scheme 1). From these intermediate compounds **1** and **2**, the following syntheses were carried out via well-established procedure, in which the isothiocyanate



Scheme 1. Synthetic procedure of compounds **1**–**20**. Compounds **11**, **13** and **20** were not obtained.

groups react with primary amines to yield the desired thiourea-based receptors **3**–**10**, **12** and **14**–**19**.[1]

The first problematic part of this procedure was found to be the first step, where bromine is substituted with isothiocyanate group. NMR- and X-ray results showed that KSCN can react with benzylic bromide with two different ways to produce either the desired isothiocyanate or thiocyanate products. And in the case of multiple benzylic bromide sites in starting materials the reaction yields also mixed structures containing both thiocyanate and isothiocyanate forms. This is easily seen in the crystal structure of intermediate **2** (Figure 1), which shows mostly isothiocyanate substitution but also the formation of thiocyanate group (see below). However, in the case of **1** and **2** the major product is clearly the desired tris(isothiocyanate). According to NMR spectra (see Figures S1, S2, S4 and S5 in the Supporting Information, SI) both compounds contain only 4–5% of thiocyanate groups. Another problem in the first step was the complete removal of the used phase transfer catalyst tetrabutylammonium bromide (TBABr), which was proved to be challenging.

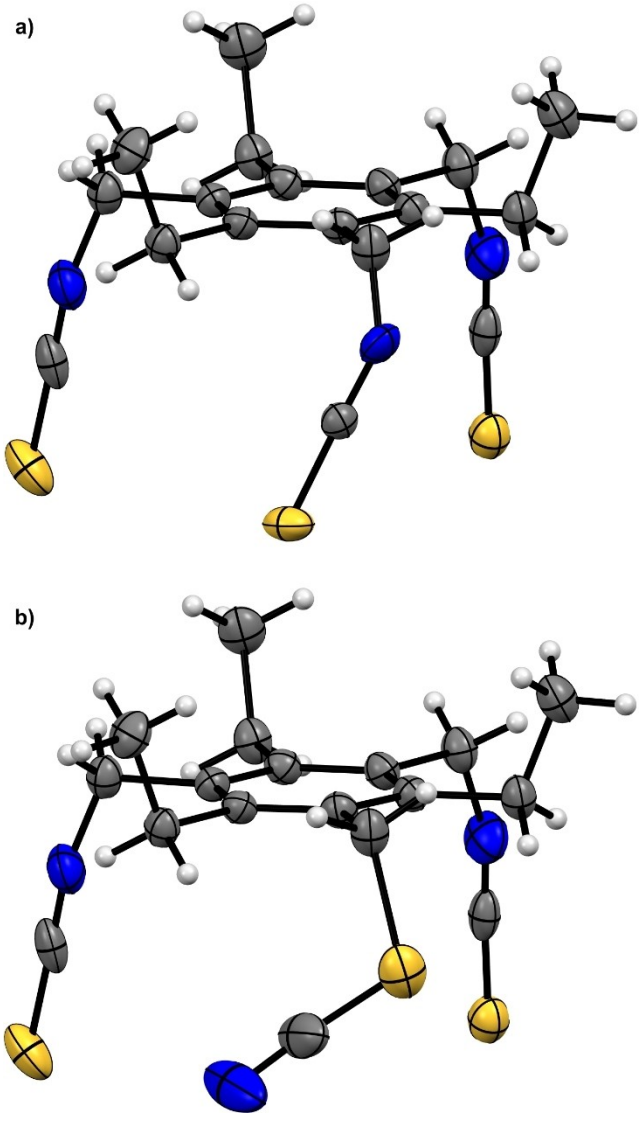


Figure 1. The crystal structure of the second molecule in the AU of **2** shows NCS/SCN disorder. a) The major component. b) The minor component.

The intermediate products **1** and **2** were used in next step without chromatographic attempts to remove thiocyanate counterparts or TBABr residues. The tritopic receptors **3**–**10** (Scheme 1) were obtained with moderate to good yields by reactions of **1** with respective primary amines in CH_3CN. The corresponding syntheses of receptors **12**–**19** from **2** in $CHCl_3$ gave poorer yields, except in the case of **15** and **17** the yield was better than with corresponding receptors **6** and **8** obtained from **1**. Unfortunately, the reaction between **2** and 2-methoxyethylamine in the same conditions did not seem to occur at all after several attempts and, thus, the receptor **13** was not obtained. The reason for this unexpected non-reactivity remained a mystery to us. The same reaction for compounds **1** and **2** was also tested with piperazine, a secondary amine to obtain trisubstituted thiourea moieties, but these reactions failed. Isothiocyanates seemed to somewhat react with piperazine, but there was no evidence of formation of compounds **11** and **20**.

The successful receptors were isolated from crude product mixtures by filtration and washed with the same solvents used in the reaction. By this simple method these tritopic receptors were obtained with adequate purity for our purposes without further purification, except for **19**, for which purification by column chromatography was necessary. Previously, similar receptors have been synthesized by opposite way starting from 1,3,5-tris(aminomethyl)-2,4,6-alkylbenzenes and monoisothiocyanates,[36,37] but as demonstrated the method in present study described by Manna and coworkers[1] a few years ago is also very much applicable.

The compounds **A** or **B** and their derivatives, where Br atoms are substituted by G (G = any atom or group), are known to be able to exist in two stable conformations, which are denoted here with 3/0 and 2/1. The 3/0 conformation, where C–G bonds of all three substituents in positions 1, 3 and 5 are directed to the same face of the central aromatic plane, is usually the desired one in supramolecular systems due to potentially better binding affinities and higher directionality. However, the improved binding affinity has been shown to depend on the groups involved.[38] The 3/0 conformation also seems to be slightly prevalent in solid-state structures derived from **B**. In the structures related to **A** the 2/1 conformation with only two C–G bonds directed to the same face, shows minor dominance.[38] In this study both conformations were best observed in the solved crystal structures of the derivatives of **A** and **B** and their XB donor complexes (see below).

X-ray crystallographic studies

To determine molecular structures of synthesized intermediates as well as tritopic receptor molecules and their halogen bonding abilities, a series of crystallizations were carried out to produce good quality single crystals. Suitable single

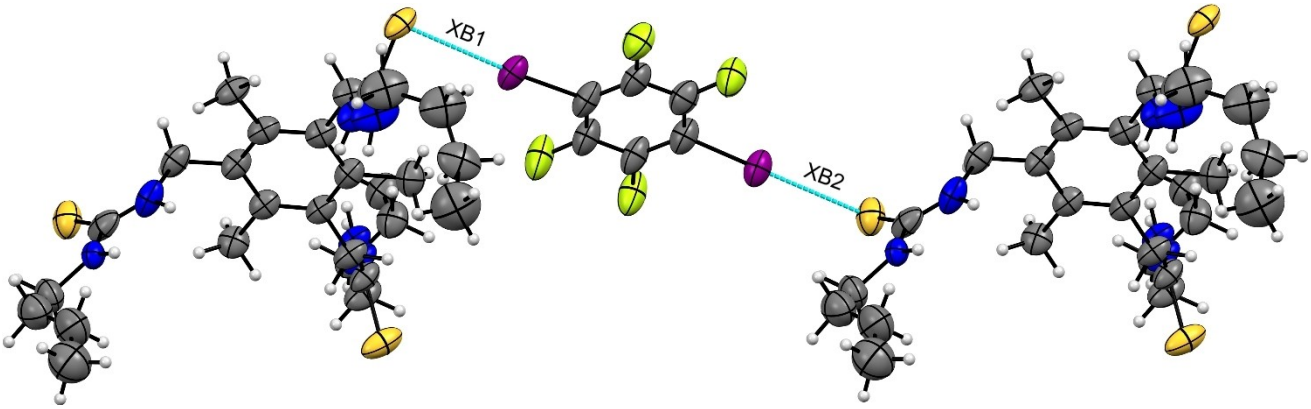


Figure 2. Two XB interactions from 1,4-DITFB donor in the crystal structure of **3**·1,4-DITFB·DMF (XB1-2 refer to Table 1). DMF molecule is excluded for clarity.

crystals of intermediate products **1** and **2** for X-ray diffraction studies were obtained from ethyl acetate. Due to low solubility nature of thiourea receptors in non-polar and low boiling point media, DMF was selected for the solvent in crystallization attempts, although the very slow evaporation rate of it makes crystallization process rather long. Most samples yielded only powder or thin film of residue in the crystallization vials. However, receptor molecules **4**, **15** and **17** yielded analyzable crystals as DMF solvates. Most importantly, receptor molecules **3**, **4**, **9** and **12** afforded single-crystalline halogen-bonded complexes with diiodotetrafluorobenzenes (DITFBs).

X-ray diffraction data of **1** and **2** structurally confirm that the first step of the planned reaction pathway works. Both structures show unsolvated product. Undisordered structure of **1** (see Figure S71 in SI) shows 2/1 conformation for isothiocyanate groups. Structure of **2** (Figures 1 and S72) confirms the findings above that in addition to isothiocyanate groups, thiocyanate groups are also formed in the synthesis. It is evident from the structure, where five out of six possible sites of two molecules in the asymmetric unit (AU) are occupied by isothiocyanate groups, but one site shows substitutional NCS/SCN disorder. The disordered site indicates 25% occupancy for thiocyanate group. According to this the percentage of thiocyanate in crystals of **2** is around 4%, which corresponds very well with the observations by NMR spectroscopy. The 3/0 conformation were observed in both molecules of the AU.

Tritopic receptor **4** crystallized with DMF molecules trapped between its arms. The crystal structure distinctly shows the 3/0 conformation (Figure S73). Total three DMF molecules are N–H···O hydrogen-bonded by both nitrogen atoms of thiourea moieties of the receptor, one DMF per arm. Thus, the overall formula in the crystal is **4**·3DMF. Corresponding structure from receptor **17** was also obtained but, as distinct from the previous, the structure of **17**·3DMF shows 2/1 conformation (Figure S74). The third DMF solvate structure obtained from receptors was **15**·DMF. In this structure the thiourea groups show 2/1 conformation (Figure S75). The first thiourea group binds the DMF molecule by two N–H···O interactions. The sulfur atom of the first thiourea group accepts two N–H···S hydrogen bonds from second thiourea of the adjacent receptor molecule. The symmetrically equivalent interactions to previous ones connect the first receptor to the adjacent one generating a hydrogen-bonded receptor dimer. The third thiourea group connect the dimers into infinite chains by $R_2^2(8)$ graph-set motifs[39] involving N–H···S hydrogen bonds.

Receptor **3** formed halogen-bonded 1:1 complex with 1,4-DITFB. In this complex one DMF molecule is also trapped by two N–H···O hydrogen bonds from one thiourea group and the overall formula of the complex is **3**·1,4-DITFB·DMF (Figure S66). Two sulfur atoms of the receptor interact by XB with separate donors generating non-covalent donor-acceptor chains. The receptor molecules show 2/1 conformation and slant stacking by N–H···S and weak π-interactions. These stacks are connected to three-dimensional network via donor molecules and by the C–I···S halogen bonds, which contain two crystallographically non-equivalent interactions (Figure 2, Table 1). It is easily discernible that aromatic rings of the receptor cores and of donors are roughly lying in the same plane.

Receptor **4** showed all in all the best capability to crystallize, because in addition to **4**·3DMF it also yielded halogen-bonded complexes with 1,2- and 1,4-DITFBs (Figure 3). Both complexes of receptor **4** show similarities, but also certain differences. The complex with 1,2-DITFB (Figure S67) shows overall structure of **4**·2(1,2-DITFB). Every arm of the receptor participates in XB and the structure shows four non-equivalent C–I···S halogen bonds donated by four different iodine atoms (Table 1). Two thiourea groups of the receptor have one halogen bond accepted by the sulfur atom whilst sulfur atom in the third arm accepts two halogen bonds. These XB interactions generate a cyclic assembly, which is illustrated in Figure 3a. As in complex **3**·1,4-DITFB·DMF aromatic moieties show distinct planarity and the receptor molecules form slant stacks by the same interactions, which are connected to next ones via XB and the donor molecules. Complex with 1,4-DITFB is, in contrast to previous, 1:1 complex or **4**·1,4-DITFB·DMF (Figure S68). Unlike in

Table 1. Found XB geometries from DITFB complexes.

Complex/XB	d(I···S) [Å]	∡(C–I···S) [°]	∡(C=S···I) [°]	R_{IS}[a]
3·1,4-DITFB·DMF				
XB1	3.2110(16)	174.4(2)	90.7(2)	0.85
XB2	3.2277(18)	179.3(2)	99.0(2)	0.85
4·2(1,2-DITFB)				
XB1	3.3671(11)	174.83(13)	95.77(14)	0.89
XB2	3.6118(13)	170.22(13)	122.36(17)	0.96
XB3	3.3344(11)	170.44(14)	90.56(14)	0.88
XB4	3.4035(12)	169.99(14)	131.98(17)	0.90
4·1,4-DITFB·DMF				
XB1	3.1867(10)	178.80(11)	89.87(12)	0.84
XB2	3.2057(10)	178.58(10)	104.08(12)	0.85
9·2(1,4-DITFB)·2DMF·0.85H_2O				
XB1	3.2284(16)	176.69(18)	100.6(2)	0.85
XB2	3.4438(17)	167.83(17)	81.9(2)	0.91
XB3	3.2434(15)	179.47(18)	86.0(2)	0.86
XB4	3.1818(17)	177.38(19)	86.3(2)	0.84
12·2(1,3-DITFB)·DMF				
XB1	3.2264(14)	175.25(14)	97.30(16)	0.85
XB2	3.3047(14)	167.85(16)	94.62(15)	0.87
XB3	3.3123(12)	170.62(16)	104.20(15)	0.88
XB4	3.3269(14)	179.33(18)	103.46(15)	0.88

[a] $R_{IS} = d(I\cdots S)/(I_{vdW} + S_{vdW})$; where $I_{vdW} = 1.98$ and $S_{vdW} = 1.80$ Å and which are van der Waals radii of I and S atoms, respectively.

4·2(1,2-DITFB) only two thiourea groups participate in XB (Figure 3b). The receptor molecules stack as in **4**·2(1,2-DITFB) and those two non-equivalent C–I···S halogen bonds (Table 1) lead to infinite donor-receptor chains crosswise to the stacks. The aromatic cores in **4**·1,4-DITFB·DMF are also coplanar. One halogen-bonded arm traps the DMF by two N–H···O hydrogen bonds and simultaneously accepts two N–H···S hydrogen bonds from thiourea of the next receptor. Non-halogen-bonded thiourea accepts similar N–H···S hydrogen bonds from the adjacent receptor. Both XB complexes of **4** show 2/1 conformations for the receptors.

Like in the case with **3** and **4** the receptor **9** also formed a corresponding complex with 1,4-DITFB (Figure 4). This **9**·2(1,4-DITFB)·2DMF·0.85H_2O is formed, when receptor **9** traps two DMF molecules and also water molecule by hydrogen bonding (Figure S69). The oxygen position of water molecule is shared in disorder with 0.85 H_2O and minor component of DMF. The DMF molecule is disordered over two sites with 0.85/0.15 (major/minor component) ratio and the major component is bound to receptor via water molecule. Water molecule is also bound by the hydrogen bond from a hydroxyl group in one arm end of the adjacent receptor. The other hydrogen bond donated by water molecule is accepted by sulfur atom of the adjacent receptor. This indicates that additional hydroxyl groups in the arm ends of **9** form strong hydrogen bonds and makes the system more hydrophilic enabling the water inclusion into the structure. The receptor **9** also shows 3/0 conformation in the complex, which deviates from the other XB complexes in the present study.

All sulfur atoms of **9**·2(1,4-DITFB)·2DMF·0.85H_2O participate in XB accepting four non-equivalent C–I···S halogen bonds and each of them from different iodine atoms (Figure 4, Table 1). In contrast to complexes of **3** and **4** above the receptors do not form similar stacks, but they form pairs by $R_2^2(8)$ N–H···S motifs and additional N–H···O interactions. These pairs are connected to three-dimensional network by the halogen bonds. The coplanarity of aromatic cores and donors is observed.

Receptor **12** crystallized with 1,3-DITFB forming rather rare halogen-bonded complex structure, considering that the Cambridge Structural Database (CSD) only includes 15 earlier analyzed complexes, where sulfur is accepting halogen bond from 1,3-DITFB donor.[40–47] The complex **12**·2(1,3-DITFB)·DMF (Figure S70) seems to have similar behavior in solid state as 1,2-DITFB and 1,4-DITFB complexes presented above. DMF solvent molecule is bound to on the top of the receptor core via N–H···O hydrogen bond from thiourea group. The location of the DMF is also preventing a formation of stacks and the receptors are instead forming similar pairs to the **9**·2(1,4-DITFB)·2DMF·0.85H_2O, which are further connected to next receptor pairs via XB and N–H···S interactions. All thiourea arms in **12**·2(1,3-DITFB)·DMF with 2/1 conformation participate in the formed halogen-bonded network of receptors, which is generated by four non-equivalent C–I···S halogen bonds (Figure 5, Table 1). One sulfur accepts two XB interactions from two separate donors and the other two accept one halogen bond. This structure shows the poorest coplanarity of aromatic cores between the receptor and donors.

The obtained XB complexes in the present study showed that the formation of C–I···S halogen bonds was not excluded by presence of simultaneous N–H···O or N–H···S hydrogen bonds in the same thiourea group. For example, every thiourea group binding DMF molecule accepts one C–I···S halogen bond. Furthermore, in **9**·2(1,4-DITFB)·2DMF·0.85H_2O one thiourea group is involved in binding of DMF by one N–H···O, $R_2^2(8)$ motif formation by two N–H···S and XB by one C–I···S interactions.

The observed halogen bonds presented in Table 1 are distinctly shorter than the sum of the standard van der Waals radii of iodine and sulfur atoms (3.78 Å). They show notable variation in I···S distances, which are longest on average in the complex **4**·2(1,2-DITFB). In our previous study[7] we observed that 1,2-DITFB donor shows only slightly longer I···S distances (on average) than 1,4-DITFB and the same trend is seen in the data entries included in the CSD containing monotopic thiourea acceptors.[5,7,41,46,48–52] However, we have here only one 1,2-DITFB complex with significantly longer distances than the shortest ones reported (around 3.2 Å)[5,52] but comparable lengths (around 3.4 Å) have also been observed with thiourea acceptors.[5,7,41] Thus, any distinct conclusions about donor effects on distances cannot be made. The steric effects are, of course, more important in the case of 1,2-DITFB and especially in the presence of large acceptor molecules, but their influence in XB pattern

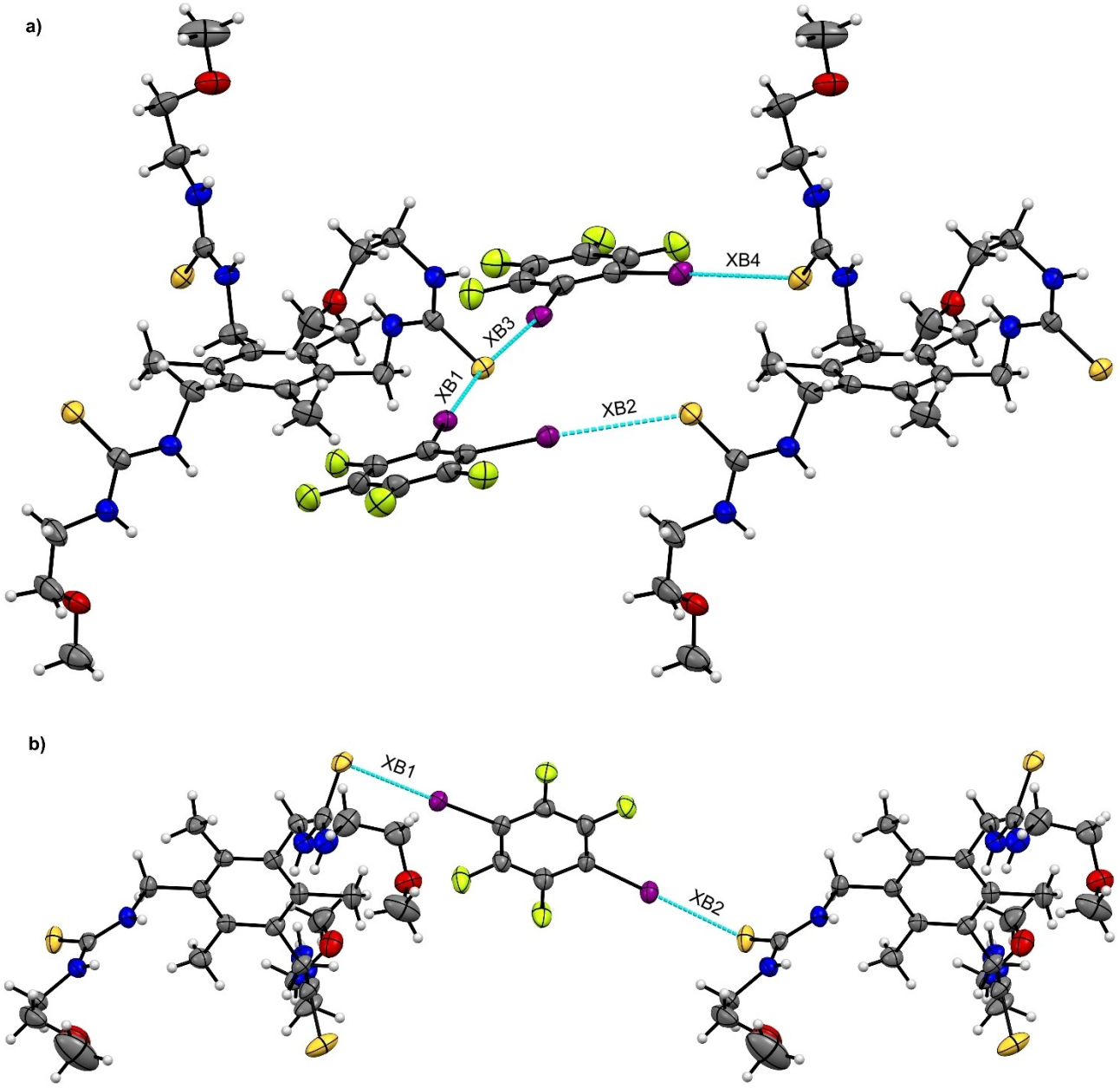


Figure 3. XB interactions in crystal structures of a) **4**·2(1,2-DITFB) and b) **4**·1,4-DITFB·DMF (DMF molecule is omitted for clarity). XB1-4 refer to Table 1.

according to present study remains unclear. Other competing interactions, like N–H···S, have also significant impact on the crystal packing. XB distances, often expressed as normalized interaction ratio (R_{IS}, Table 1), are shortest in 1,4-DITFB complexes, but values of **12**·2(1,3-DITFB)·DMF are not much longer. However, the shortest distance (3.133 Å, R_{IS} = 0.83) in the literature between DITFB and thiourea acceptor is observed with 1,3-DITFB donor.[41] Overall, the R_{IS} values are the same on average for 1,4- and 1,3-DITFB XB complexes with thioureas.[5,7,41,46,48–52] The shortest XB distances observed here are less than 0.10 Å longer than the shortest ones (R_{IS} = 0.82) found from the literature for XB contacts between DITFB and sulfur atom.[7,41,53,54]

The C–I···S angles in the investigated complexes do not deviate significantly from linear (> 167°, Table1), which is in agreement with the literature data,[5,7,41,46,48–52] and they do not correlate well with the I···S distances. On the other hand, the acceptor angle (C=S···I) values show a large variation. They do not either correlate with other geometric values in the complexes, but they show that thiourea sulfur is able to accept halogen bonds with angles, which are significantly lower than 100 degrees. A few complexes from the CSD show the same small acceptor angle characteristics.[5,7,41,50,51] This is deviating from the angles observed for urea oxygen,[40] but analogous to the ones for selenium of selenourea.[55] Sulfur and selenium have more adaptive electron configuration and are therefore more flexible XB acceptors than more extensively studied

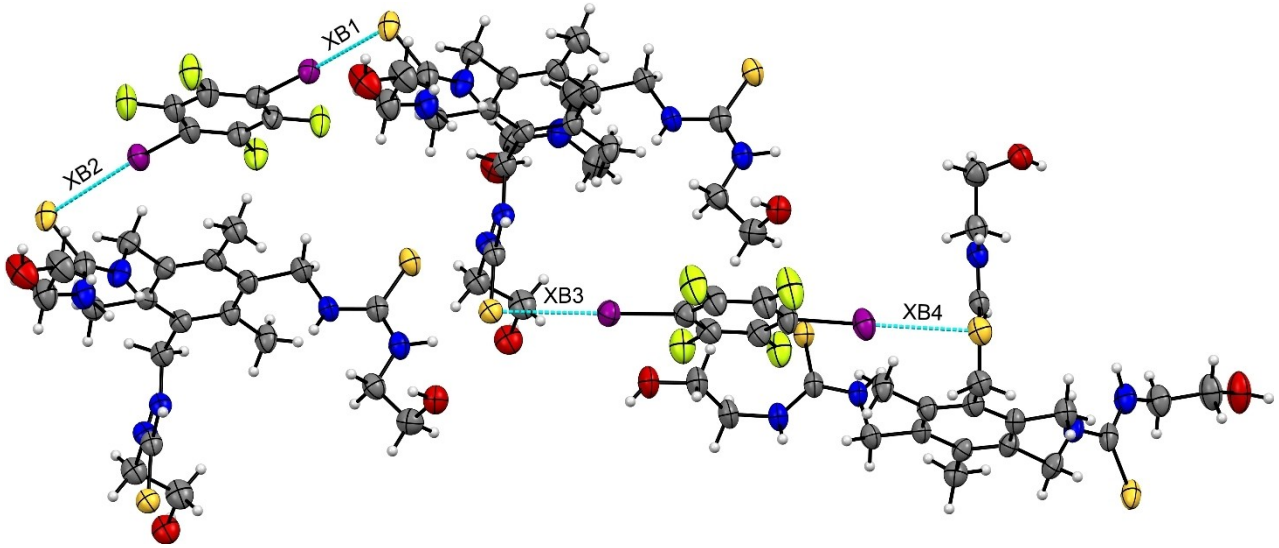


Figure 4. XB interactions in crystal structure of **9**·2(1,4-DITFB)·2DMF·0.85H_2O. DMF and water molecules are removed for clarity. XB1-4 refer to Table 1.

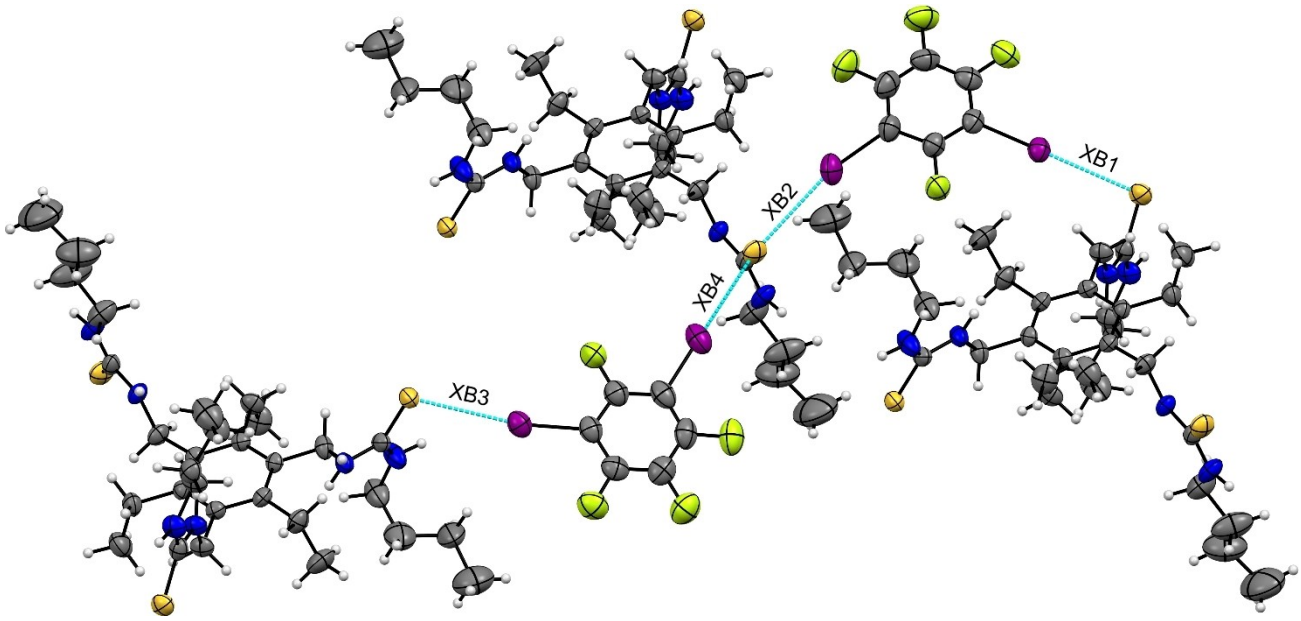


Figure 5. XB interactions donated by 1,3-DITFB molecules in crystal structure of **12**·2(1,3-DITFB)·DMF. DMF molecule is omitted for clarity. XB1-4 refer to Table 1.

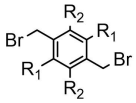
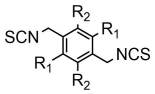
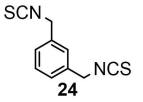
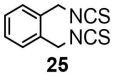
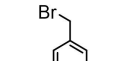
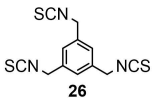
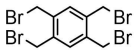
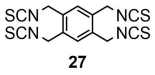
nitrogen and oxygen. This flexibility might be an advantage in design of supramolecular applications, but it may also bring on controlling problems in noncovalent network.

Previous studies have shown that thiourea-based supramolecules can efficiently bind anions.[1,2,56] We also tried to crystallize our receptors with several tetramethylammonium (TMA) and tetrabutylammonium (TBA) salts to structurally observe the anion-binding complexes. Unfortunately, none of these experiments were successful. The problem is most probably the poor solubility of our receptors in non-polar media. We had to use DMF as the solvent in the crystallizations and the crystallographic results above show that our receptors are willing to form hydrogen bonds to DMF molecules. These strong and highly competitive N–H···O hydrogen bonds are very difficult to be replaced and the anion binding is not so likely to occur. Anyway, this was not the main interest in the present study and was not further investigated.

o-Alkyl influence on benzylic bromide substitution with KSCN

Confused about the product mixtures and mixed structures in the synthesis of **1** and **2**, we decided to briefly test the related di-, tri- and tetratopic benzylic bromides in the same reaction conditions with KSCN. The performed reactions are presented in Table 2, which shows the structures of all-isothiocyanate (all-

Table 2. Reactions of selected benzylic bromides tested at the same conditions as in the synthesis of **1** and **2**. The structures of all-NCS products **21**–**27** and formed NCS/SCN product distributions for all reactions are shown.

Starting compound	Reaction conditions	Desired all-NCS product	NCS/SCN ratio[a]
	TBAB, KSCN, NaI Dry DMF, 80 °C		
$R_1=R_2=H$ $R_1=Me$, $R_2=H$ $R_1=R_2=Me$		**21** $R_1=R_2=H$ **22** $R_1=Me$, $R_2=H$ **23** $R_1=R_2=Me$	13/87 91/9 92/8
		 **24**	17/83
		 **25**	40/60
		 **26**	35/65
		 **27**	30/70

[a] Approximated from integral areas of adjacent CH_2 group ^1H NMR signals.

NCS) products **21**–**27**. The crude products were analyzed by NMR spectroscopy. The all-thiocyanate (all-SCN) products **21 b**, **24 b**, **25 b** and **27 b** crystallized out from the NMR-samples and their crystal structures as well as ^1H and ^{13}C NMR spectra of all crude products are shown in SI.

Each trial reaction (Table 2) according to ^1H NMR measurements showed that both isothiocyanate and thiocyanate groups were formed. That was easily seen in the spectra as there were two singlet resonances observed originating from methylene hydrogens of CH_2NCS and CH_2SCN moieties. When integrated areas of those singlets were compared the rough estimation of the formed group ratios in the reaction products could be made. However, in most cases it was not possible to be justified do the singlets originate from all-NCS (**21**–**27**) or all-SCN (**21 b**–**27 b**) compounds or were there also mixed products present. The best comparability could be achieved by inspecting the results of syntheses targeted to preparation of *p*-substituted bis-isothiocyanates **21**–**23** (Table 2), where also the effect of *o*-methyl substituents was clearly seen. In the attempt to prepare **21**, the bis-thiocyanate **21 b** was distinctly the main product and around 87% of the substituents were comprised of thiocyanate groups (see Figure S52 in SI). Does the rest 13% of isothiocyanate proportion originate from **21** or mixed structures, is not known. When two methyl groups were introduced in the benzene ring at positions 2 and 5, it was enough to result in a reverse distribution of products. In the trial synthesis of **22** it appeared, indeed, to be the main product and around 91% of the substituents were isothiocyanate groups (Figure S54). The further addition of two methyls in the benzene core did not significantly improve the proportion of formed isothiocyanate group (92%, Figure S56) in the trial synthesis of **23**.

In the preparation attempt of tritopic product **26** (Table 2) roughly 65% of the bromide were converted to thiocyanate (Figure S62). This is significantly different from the tritopic synthetic products **1** and **2**, which contained only 4–5% of thiocyanate groups. This as well as the results in synthetic efforts to prepare **21**–**23**, altogether, clearly evidenced the importance of methyl groups for isothiocyanate group formation. Furthermore, in the synthesis of non-methylated ditopic *m*-isomer **24** the formation of thiocyanate was the dominant reaction result comprising around 83% of the formed groups and **24 b** was the main product (Figure S58). However, the dominance of thiocyanate is here significantly larger than in the preparation of **26**, where the spacing of the closest substituents in the aromatic ring is similar.

The ditopic *o*-isomer **25** and tetratopic product **27** synthesis showed NCS/SCN product distribution similar to **26**, which were around 40:60 (**25**, Figure S60) and 30:70 (**27**, Figure S64). When the groups attached to benzene ring are in *o*-position, the steric effects could play a role in the reaction, but in these cases, it seems to favor thiocyanate group formation.

Our findings here showed that if the aromatic ring in these reactions is at least half *o*-alkylated the reaction produced distinctly more isothiocyanate groups. On the other hand, in the absence of introduced *o*-alkyl(s) the reaction seemed to favor the thiocyanate form over isothiocyanate one. Even though these findings were logical they are not definitive and the changes in conditions will most probably produce a deviating product distribution. These trial reactions were done and presented just to prove that the *o*-alkyl substituents are important for the final form of products.

The reason for this kind of reactivity between KSCN with *o*-alkylated benzylic bromides is another issue and understanding it needs much further investigation. One could hypothesize that steric hindrance introduced by *o*-alkyl groups could play an important role in the formation of thio- or isothiocyanate groups by S_N2 mechanism and which group becomes selected. Presumably, the higher selectivity for NCS vs SCN -substitution in the presence of *o*-alkyl(s) could be attributed to higher steric demand for the transition state in the NCS-substitution compared to SCN-substitution. The conformational free energy (A value) of the SCN substituent is significantly higher (5.2 kJ/mol) compared to the A value of the NCS substituent (1.1 kJ/mol).[57] A similar trend is observed in the product distributions: SCN-substitution is disfavored in sterically hindered settings (e.g. formation of **21 b** vs of **22** or **23**). This may be true, but it is probable that the case is not so straightforward, and, for example, electronic effects may also play a significant role. Furthermore, the fact that isothiocyanates are thermodynamically more stable and higher temperatures than 50 °C (here 80 °C) are able to cause rearrangements may have an additional effect,[58,59] although this does not seem to happen without *o*-alkyl groups. The further experimental and theoretical studies in our laboratory will hopefully give some answers in the near future.

Conclusion

The synthesized tritopic thiourea receptors seemed to have rich network of noncovalent interactions. The thiourea units were willing to bind polar solvent molecules, like DMF by N–H···O hydrogen bonds. However, the attempts to observe anion binding in polar media by these receptors unexpectedly failed. This was thought to be a result of strong hydrogen bonds between receptors and DMF solvent molecules, which were not possible to be displaced by anion-accepted interactions. On the other hand, the crystallization attempts for receptors with DITFB XB donors yielded five single-crystal structures. The inspection of the XB complexes showed that highly directional halogen bonds have a significant importance in structure stabilization. The flexible acceptor angle of sulfur enabled these complexes to obtain the found crystal structures. Sulfur atoms in all obtained complexes were accepting halogen bonds from iodine with acceptor angle (C=S···I) values significantly lower than 100°, which is not a common property for directional interactions with smaller acceptors.

The synthetic route for tritopic receptors was not significantly interfered by the competing isomeric thiocyanate group formation in the first step. The reason for this is the presence of *o*-alkyl substituents in benzene ring, which were proved here to be vital for formation of isothiocyanate isomers in used reaction conditions. Thus, the studied and rather well-known 2,4,6-trialkyl-1,3,5-tris(bromomethyl)benzene scaffolds are very practical starting materials in thiourea based receptor synthesis, also for XB applications, without highly toxic substances.

Experimental Section

General: All reagents were commercially purchased from several different chemical vendors and used as received. NMR-data was measured with either Bruker Avance III 500 MHz NMR spectrometer or Bruker Avance III HD 300 MHz spectrometer. MS data was measured with Agilent 6560 IM- QTOF and Micromass LCT (ESI/TOF) mass spectrometers equipped with ESI ion source and samples were injected from syringe pump with 5 μl/min flowrate. Intermediate compounds **1** and **2** as well as receptors **3**–**20** were synthesized using procedure described in literature (see below).[1]

Synthetic procedures of compounds 1 and 2: 1,3,5-Trimethyl-2,4,6-tris(bromomethyl)benzene (1,4700 g, 27.7 mmol, 1 eq., for compound **1**) or 1,3,5-triethyl-2,4,6-tris(bromomethyl)benzene (1.697 g, 3.84 mmol, 1 eq., for compound **2**), potassium thiocyanate (2.857 g, 29.4 mmol, 7.5 eq.), tetrabutylammonium bromide (4.400 g, 13.6 mmol, 3.7. eq.) and sodium iodide (0.565 g, 3.76 mmol, 1 eq.) were dissolved in 50 ml of DMF. Reaction mixture was refluxed 4 hours at 80 °C under Ar. After cooling the reaction mixture was filtered through a thin silica bed to remove solids and TBABr and remaining solution was diluted with 80 ml of water. The obtained solution was extracted with ethylacetate (2×50 ml), the organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed with rotatory evaporator. Yields: compound **1** 1.112 g (91.1%), compound **2** 1.179 g (81.7%).

Synthetic procedures of compounds 3–20: Compounds **3**–**20** were synthesized using the same synthetic procedure. Compound **1** or **2** was mixed with amine in 1:3 ratio in 30 ml of dry acetonitrile (**3**–**11**) or dry chloroform (**12**--**20**) and the reaction mixture was stirred at room temperature from 1.5 h to overnight depending on TLC monitoring of reaction. Formed precipitate was filtered and washed with acetonitrile or chloroform. Product **19** was purified with column chromatography 1:1 hexane:ethylacetate eluent system. Other successful products did not need any further purification besides filtering.

Synthetic procedures of trial reactions: Trial reactions to investigate the conversion of corresponding benzylic bromides to compounds **21**–**27** were carried out with similar synthetic procedure as for compounds **1** and **2**.

Compound ***1***: m.p. 125–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.72 (s, 6H), 2.48 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.4, 133.4, 131.2, 44.0, 16.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{15}N_3S_3+Na^+$: 356.0326 $[M+Na]^+$; found: 356.0319.

Compound ***2***: m.p. 109–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (s, 6H), 2.85 (q, 6H, 7.6H) 1.27 (t, 9H, 7.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.18, 132.35, 130.30, 42.84, 23.16, 15.75 ppm; HRMS (ESI): *m/z* calcd. for $C_{18}H_{21}N_3S_3+Na^+$: 398.0769 $[M+Na]^+$; found: 398.0835.

Compound ***3***: Yield 83.2%; m.p. 246–248 °C; ^{1}H NMR (500 MHz, DMF-d7): δ = 7.41 (s, 3H), 7.15 (s, 3H), 4.72 (d, 6H, 3.8 Hz), 3.54 (6H, overlap with H2O) 2.38 (s, 9H), 1.54 (m, 6H, 7.4 Hz), 1.34 (m, 6H, 7.4 Hz), 0.92 (t, 9H, 7.4 Hz) ppm; ^{13}C NMR (126 MHz, DMF-d7): δ = 183.1, 136.9, 133.2, 43.8, 34–36 (overlap with DMF), 31.3, 29.1, 19.9, 15.7 ppm; HRMS (ESI): *m/z* calcd. for $C_{27}H_{48}N_6S_3+Na^+$: 575.3001 $[M+Na]^+$; found: 575.2977.

Compound ***4***: Yield 72.0%; m.p. 192–194 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.35 (s, 3H), 7.28 (s, 3H), 4.62 (s, 6H), 3.57 (broad s, 6H), 3.40 (t, 6H, partly overlapping with H_2O, 5.1 Hz), 3.23 (s, 9H), 2.30 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 183.0, 137.0, 133.4, 71.1, 58.4, 43.9 (two overlapping CH_2 peaks), 16.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{42}N_6S_3O_3+Na^+$, $C_{24}H_{42}N_6S_3O_3+K^+$ and $C_{24}H_{42}N_6S_3O_3+Na^+$ + DMSO: 581.2379 $[M+Na]^+$, 597.2118 $[M+K]^+$ and 659.2518 $[M+DMSO+Na]^+$; found: 581.2424, 597.2465 and 659.3619, respectively.

Compound ***5***: Yield 65.3%; m.p. 219–221 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.39, 7.33 (two overlapping s, 6H, NH), 4.60 (d, 6H, 3.6 Hz), 3.62 (q, 6H, 6.4 Hz), 2.60, (t, 6H, 6.8 Hz), 2.30 (s, 9H), 2.08 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 128.3, 136.6, 132.8, 43.3, 42.7, 32.5, 16.0, 14.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{42}N_6S_6+Na^+$: 629,1693 $[M+Na]^+$; found: 629.1672.

Compound ***6***: Yield 37.5%; m.p. 189–191 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.09 (two overlapping broad singlets, 6H), 4.60 (s, 6H), 2.35 (s, 9H), 1.41 (s, 27H) ppm; ^{13}C NMR (126 MHz, DMSO-d6) δ 181.17, 137.93, 136.33, 133.61, 129.81, 128.34, 52.18, 43.88, 42.37, 28.86, 16.12, 15.83 ppm; HRMS (ESI): *m/z* calcd. for $C_{27}H_{48}N_6S_3+Na^+$ and $C_{27}H_{48}N_6S_3+K^+$: 575.2999 $[M+Na]^+$, 591.2776 $[M+K]^+$; found: 575.2998 and 591.2725 respectively.

Compound ***7***: Yield 65.9%; m.p. 233–245 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.67 (broad s, 3H) 7.34–7.23 (m, 18H), 4.66 (d, 12H, 14.6 Hz), 2.32 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 182.64, 139.18, 136.63, 132.85, 128.29, 127.28, 126.90, 47.08, 43.42, 16.01 ppm; HRMS (ESI): *m/z* calcd. for $C_{36}H_{42}N_6S_3+H^+$, $C_{36}H_{42}N_6S_3+Na^+$ and $C_{36}H_{42}N_6S_3+K^+$: 655.2711 $[M+H]^+$, 677.2531 $[M+Na]^+$ and 693,227 $[M+K]^+$; found: 655.1931, 677.2080 and 693.1304, respectively.

Compound ***8***: Yield 49.5%; m.p. 211–213 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.07 (d, 3H, 7.4 Hz), 7.96 (d, 3H, 6.9 Hz), 7.87 (d, 3H, 6.1 Hz), 7.66 (broad s, 3H), 7.53–7.59 (m, 6H, 7.2 Hz), 7.47 (d, 6H, 6.1 Hz), 7.28 (broad s, 3H), 5.128 (s, 6H), 4.67 (S, 6H), 2.32 (s, 9H), ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 128.4, 136.6, 134.4, 133.3,

132.9, 130.9, 128.5, 127.8, 126.3, 125.9, 125.5, 123.6, 45.5, 43.4, 16.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{48}H_{48}N_6S_6+H^+$ and $C_{48}H_{48}N_6S_6+K^+$: 805.3181 $[M+H]^+$ and 843,2740 $[M+Na]^+$; found: 805.9219 and 843.8578, respectively.

Compound ***9***: Yield 72.0; m.p. 199–204 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.38 (two overlapping broad s, 6H), 4.78 (broad s, 3H), 4.60 (s, 6H), 3.47 (s, 12H), 2.30 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): 182.5, 136.6, 132.9, 59.7, 46.4, 43.3, 16.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{21}H_{36}N_6O_3S_6+H^+$ and $C_{21}H_{36}N_6O_3S_6+Na^+$: 517.2089 $[M+H]^+$, 539,1909 $[M+Na]^+$; found: 517.1337 and 539.1160 respectively.

Compound ***10***: Yield 53.1%; m.p. 147–150 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.01 (broad s, 3H), 7.51 (broad s, 3H), 7.11–7.20 (m, 30H), 5.65 (s, 6H), 5.021 (s, 3H), 4.62 (s, 6H), 2.28 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 181.6, 142.6, 138.6, 136.4, 132.9, 128.5, 127.5, 127.2, 126.7, 126.6, 126.2, 74.6, 62.9, 43.2, 16.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{57}H_{60}N_6O_3S_3+H^+$, $C_{57}H_{60}N_6O_3S_3+Na^+$ and $C_{56}H_{58}N_6O_3S_3+K^+$: 973.3967 $[M+H]^+$, 995.3787 $[M+Na]^+$, 1011.3526 $[M+K]^+$; found: 973.3966, 995.3777 and 1011.3507 respectively.

Compound ***11***: Not obtained

Compound ***12***: Yield 54.5%; m.p.. 216–217 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.26 (broad s, 3H), 7.04 (broad s, 3H), 4.59 (s, 6H), 2.66 (q, 6H, 7.3 Hz), 1.43 (m, 6H, 7.2 Hz), 1.27 (m, 6H, 7.5 Hz), 1.09 (t, 9H, 7.2 Hz), 0.87 (t, 9H, 7.2 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d6) δ 182.10, 143.43, 132.32, 43.32, 42.08, 30.90, 22.67, 19.51, 16.39, 13.67 ppm; HRMS (ESI): *m/z* calcd. for $C_{30}H_{54}N_6S_3+H^+$, $C_{30}H_{54}N_6S_3+Na^+$ and $2(C_{30}H_{54}N_6S_3)+H^+$: 595.3650 $[M+H]^+$, 617,3470 $[M+Na]^+$ and 1189.7222 $[2M+H]^+$; found: 595.2642, 617.2264 and 1189.5457. respectively.

Compound ***13***: Not obtained.

Compound ***14***: Yield 54.7%; m.p.194.5–196.3 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.42 (broad s, 3H), 7.32 (broad s, 3H), 4.60 (s, 6H), 3.62–3.61 (m, 6 h), 2.66-2.60 (overlapping d and t, 12H, 7.3 and 6.9 Hz), 2.07 (s, 9H), 1.10 (t, 9H, 7.4 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 182.22, 143.55, 132.20, 42.70, 42.15, 32.55, 22.70, 16.37, 14.51 ppm; HRMS (ESI): *m/z* calcd. for $C_{27}H_{48}N_6S_6+H^+$ and $C_{27}H_{48}N_6S_6+Na^+$: 649.2343 $[M+H]^+$ and 671.2158 $[M+Na]^+$; found: 649.1185 and 671.0785, respectively.

Compound ***15***: Yield 42.1%; m.p. 225–231 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.11 (s, 3H), 7.01 (broad s, 3H), 4.55 (d, 6H, 3.7 Hz), 2.65 (q, 6H, 7.4 Hz), 1.41 (s, 27H), 1.10 (t, 9H, 7.4 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 180.87, 143.37, 132.50, 52.15, 41.21, 28.90, 22.72, 16.48 ppm; HRMS (ESI): *m/z* calcd. for $C_{30}H_{54}N_6S_3+H^+$, $C_{30}H_{54}N_6S_3+Na^+$ and $C_{30}H_{54}N_6S_3+K^+$: 595.3650 $[M+H]^+$, 617.3470 $[M+Na]^+$ and 633.3209 $[M+K]^+$; found: 595.2227, 617.1843 and 633.2003, respectively.

Compound ***16***: Yield 58.1%; m.p. 221–223 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.82 (broad s, 3H), 7.39–7.24 (m, overlapping one NH peak, 18H), 4.85 (d, 6H, 4.9 Hz), 4.79 (s, 6H), 2.80 (q, 6H, 7.3 Hz), 1.19 (t, 9H, 7.2 Hz) ppm; ^{13}C NMR (126 MHz, DMF-d7): δ = 183.6, 144.3, 139.9, 132.8, 128.6, 127.7, 127.2, 47.9, 43.1, 23.1, 16.3 ppm; HRMS (ESI): *m/z* calcd. for $C_{39}H_{48}N_6S_3+H^+$, $C_{39}H_{48}N_6S_3+Na^+$ and $C_{39}H_{48}N_6S_3+K^+$: 697.3181 $[M+H]^+$, 719.3001 $[M+Na]^+$ and 735.2740 $[M+K]^+$; found: 697.1623, 719.1829 and 735.1285, respectively.

Compound ***17***: Yield 61.2%; m.p. 199–201 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.06 (d, 3H, 7.6 Hz), 7.94 (d, 3H, 7.9 Hz), 7.86 (t, 3H, 5.1 Hz), 7.65 (broad s, 3H), 7.46–7.57 (m, 6H, 6.5 Hz), 7.46 (d, 3H, 5.1 Hz), 7.19 (broad s, 3H), 5.12 (s,6H), 4.65 (s, 6H), 2.67 (q, 6H, 7.5 Hz), 1.11 (t, 9H, 6.8 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d6) δ = 182.2, 143.5, 134.3, 133.3, 132.2, 130.9, 128.5, 127.7, 126.2, 125.8, 125.4, 123.5, 45.5, 42.3, 22.6, 16.4 ppm; HRMS (ESI): *m/z* calcd. for $C_{51}H_{54}N_6S_3+H^+$, $C_{51}H_{54}N_6S_3+Na^+$ and $C_{51}H_{54}N_6S_3+K^+$: 847.3650 $[M+H]^+$, 869.3470 $[M+Na]^+$ and 885.3209 $[M+K]^+$; found: 847.1953, 869.2011 and 885.1071, respectively.

Compound ***18***: Yield 30.3%; m.p. 190–192 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.39 (two overlapping broad s, 9H), 4.75 (broad s, 3H), 4.60 (s, 6H), 3.34 (s, 12H), 2.65 (q, 6H, 7.5 Hz), 1.11 (t, 9H, 7.3 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 182.4, 143.5, 132.3, 59.7, 45.4, 22.7, 16.4 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{42}N_6S_3+H^+$, $C_{24}H_{42}N_6S_3+Na^+$ and $C_{24}H_{42}N_6S_3+K^+$: 559.2559 $[M+H]^+$ and 581.2379 $[M+Na]^+$; found: 559.1827 and 581.1303 respectively.

Compound ***19***: Yield 21.8%; m.p. 115–121 °C; ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.02 (2 overlapping broad s, 3H), 7.50 (broad s, 3H), 7.10–7.50 (multiplet, 24H), 6.99 (s, 6H), 5.61 (s, 6H), 5.00 (s, 3H), 4.58 (two overlapping s, 6H), 2.61 (s, 6H), 1.05 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d6): δ = 181.4, 143.4, 142.6, 138.7,132.2, 128.5, 127.5, 126.7, 126.6, 126.2, 79.1, 74.6, 62.9, 42.1, 22.7, 16,4 ppm; HRMS (ESI): *m/z* calcd. for $C_{60}H_{66}N_6O_3S_3+H^+$: 1015.4437 $[M+H]^+$; found: 1015.4419

Compound ***20***: Not obtained.

Compound ***21*** *(trial)*: ^{1}H NMR (300 MHz, $CDCl_3$-d6): δ = 7.39 (s, 4H), 4.73 (s, CH_2NCS), 4.15 (s, CH_2SCN) ppm.

Compound ***22*** *(trial)*: ^{1}H NMR (500 MHz, DMF-d7): δ = 7.31 (s, 2H), 4.98 (s, CH_2NCS), 4.49 (s, CH_2SCN), 2.24 (s, 6H) ppm.

Compound ***23*** *(trial)*: ^{1}H NMR (500 MHz, DMF-d7): δ = 5.01 (s, CH_2NCS), 4.66 (s, CH_2SCN), 2.38 (s, 12H) ppm.

Compound ***24*** *(trial)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 4H), 4.72 (s, CH_2NCS), 4.14 (s, CH_2SCN) ppm.

Compound ***25*** *(trial)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (s, 4H), 4.85 (s, CH_2NCS), 4.78 (s, CH_2NCS), 4.33 (s, CH_2SCN), 4.26 (s, CH_2SCN ppm.

Compound ***26*** *(trial)*: ^{1}H NMR (500 MHz, DMF-d7): δ = 7.57 (m, 3H), 5.12 (multiple s, CH_2NCS), 4.53 (multiple s, CH_2SCN).

Compound ***27*** *(trial)*: ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.56 (m, 2H), 5.14 (multiple s, CH_2NCS), 4.53 (multiple, CH_2SCN).

Complexation studies for single crystal X-ray diffraction: To study halogen bonding properties of synthesized compounds **3**–**10, 12** and **14**–**19** crystallization samples with 1,2-, 1,3- and 1,4-DITFBs were prepared by dissolving DITFBs and receptor molecules into DMF in 3:2 (donor:acceptor) ratio (followed by mixing) in loosely sealed vials. The vials were left to stand and after several weeks suitable single crystals of XB complexes for X-ray diffraction analysis were formed with receptors **3**, **4**, **9** and **12**. The receptor **15** crystallized without XB donor (1,4-DITFB) as DMF solvate (**15**·DMF).

Other crystallizations: The intermediate compounds **1** and **2** were crystallized out from their solutions in ethyl acetate. The crystallizations of pure receptor molecules from DMF were successful for compounds **4** (**4**·3DMF) and **17** (**17**·3DMF). Also, thiocyanates **21 b**, **24 b**, **25 b** and **27 b** crystallized out from NMR samples in $CDCl_3$.

Single crystal X-ray diffraction: Three separate diffractometers were utilized to collect single crystal X-ray diffraction data. They were a Rigaku SuperNova single-source diffractometer (Eos CCD detector) using mirror-monochromated Mo–Kα (λ = 0.71073 Å), a Rigaku SuperNova dual wavelength diffractometer (Atlas CCD area detector) using mirror- monochromated Cu–Kα radiation (λ = 1.54184 Å) and a Bruker-Nonius KappaCCD diffractometer (APEX II detector) using graphite monochromatized Mo–Kα radiation (λ = 0.71073 Å). Further crystallographic details are given in the Supporting Information of this article.

Deposition Number(s) 2210850, 2210851, 2210852, 2210853, 2210854, 2210855, 2210856, 2210857, 2210858, 2210859, 2210860, 2210861, 2210862, 2210863 contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Acknowledgements

This research project was financially supported by the Academy of Finland (Grant Nos: 310975, 314343 and 335600) and the University of Jyvaskyla. Professors Kari Rissanen and Petri Pihko are gratefully acknowledged for their support and fruitful comments throughout the study. B. Sc. Risto Peltonen is also gratefully acknowledged for resynthesis of compound ***19****.*

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: halogen bonding · isothiocyanates and thiocyanates · noncovalent interactions · thiourea-based receptors · X-ray diffraction

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Manuscript received: January 13, 2023
Revised manuscript received: March 14, 2023
Accepted manuscript online: March 15, 2023
Version of record online: March 27, 2023