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Structure–Odor Correlations in Homologous Series of Mercapto Furans and Mercapto Thiophenes Synthesized by Changing the Structural Motifs of the Key Coffee Odorant Furan-2-ylmethanethiol

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ABSTRACT.

Furan-2-ylmethanethiol (2-furfurylthiol; 2-FFT); **1**, is long-known as a key odorant in roast and ground coffee, and was also previously identified in a wide range of thermally treated foods, such as meat, bread, and roasted sesame seeds. Its unique coffee-like odor quality elicited at very low concentrations, and the fact that only a very few compounds showing a similar structure have previously been described in foods make **1** a suitable candidate for structure–odor activity studies. To gain insight into the structural features needed to evoke a coffee-like odor at low concentrations, 46 heterocyclic mercaptans and thio ethers were synthesized, 32 of them for the first time, and their odor qualities and odor thresholds were determined. A movement of the mercapto group to the 3-position kept the coffee-like aroma, but led to an increase in odor threshold. A separation of the thiol group from the furan ring by an elongation of the carbon side chain caused a loss of the coffee-like odor and also led to an increase in odor thresholds, especially for *ω*-(furan-2-yl)alkane-1-thiols with six or seven carbon atoms in the side chain. A displacement of the furan ring by a thiophene ring had no significant influence on the odor properties of most of the compounds studied, but the newly synthesized longer-chain 1-(furan-2-yl)- and 1-(thiophene-2-yl)alkane-1-thiols elicited interesting passion fruit-like scents. In total, only four out of the 46 compounds also showed a coffee-like odor quality like **1**, but none showed a lower odor threshold. Besides the odor attributes, also retention indices, mass spectra and NMR data of the synthesized compounds were elaborated, which are helpful in possible future identification of these compounds in trace levels in foods or other materials.

KEYWORDS. 2-furfurylthiol, coffee, odor quality, odor threshold, structure–odor activity studies, mercaptan, furan, thiophene, thio ether, *ω*-(furan-2-yl)alkane-1-thiols, 1-(furan-2-yl)alkane-1-thiols

INTRODUCTION

Mercaptans or thiols, respectively, are a very interesting class of food constituents, and up to now over 100 volatile compounds have been identified, among them several very potent aroma compounds. Although usually occurring in low concentrations, thiols can be key contributors to food aromas due to their often extremely low odor thresholds, because the human odorant receptors are quite sensitive for some sulfur compounds.

Among the most interesting thiols occurring in foods, furan-2-ylmethanethiol (2-furfurylthiol; **1**) exhibiting a pleasant coffee-like odor quality at very low concentrations, was first identified in roast and ground coffee by Reichstein and Staudinger.[1] Since then several studies have confirmed its importance in the overall aroma of roasted coffee and coffee brew.[2-3] **1** has also been found in a wide range of other thermally treated foods like cooked beef,[4] pork,[5] and chicken[6] as well as roasted sesame seeds,[7] popcorn,[8] white bread,[9] roasted hazelnuts,[10] but also in fermented products such as wine.[11]

Interestingly, only a very few additional aroma-active mercapto furans have been reported in foods so far. In particular 2-methylfuran-3-thiol, with a meat-like smell, is another very well-known compound in this substance class, which was identified, e.g., in cooked beef,[12] chicken broth,[6] and yeast extract.[13] In addition, 5-methyl-2-furfurylthiol and 2,5-dimethylfuran-3-thiol were characterized as aroma compounds in coffee[14] and cooked beef,[6] and 1-(furan-2-yl)ethane-1-thiol[15] and 2-methylfuran-3-ylmethanethiol[16] were reported to occur in coffee and wine.

A smaller amount of structurally related mercapto thiophenes was also previously described as food constituents, for example, 2-thienylthiol was reported to contribute to the aroma of roasted hazelnuts[17] and roasted sesame seeds.[18] In addition, also 2-methylthiophene-3-thiol was reported as constituent of roasted sesame seeds.[18]

Their importance in many food aromas make mercaptans suitable candidates for structure–odor activity studies, i.e., to clarify the structural elements or odotopes, respectively, needed to cause these interesting aroma attributes. Polster and Schieberle[19,20] were among the first to perform a comprehensive study on such relationships in alkane thiols, e.g. 3-mercapto-2-methylalkan-1-ols, of which 3-mercapto-2-methylpentan-1-ol is one of the most important odorants in processed onions.[21] For this purpose, several homologous series of alkane thiols and thio ethers were synthesized and their odor qualities and thresholds were determined. In all homologous series a minimum of thresholds was observed for compounds with five to seven carbon atoms. However, longer-chain thiols showed an exponential increase in thresholds and also lost the typical sulfury, onion-like or passion-fruit like odor attributes elicited by the shorter chain mercaptans. The authors also demonstrated that a substitution of the thiol group either by a hydroxyl or a thiomethyl group led to a significant increase in odor thresholds.

In a study on the influence of changes in the structural motifs of the potent grapefruit-like smelling 1-*p*-menthene-8-thiol, it was found that the double bond in the *p*-menthane structure and a tertiary thiol group in the side chain are crucial factors for the grapefruit-like odor and the very low threshold. In most cases, however, small changes in the molecular structure of structurally related mercaptans led to a strong increase in odor thresholds and a loss of the characteristic grapefruit-like odor quality. The natural aroma compound 1-*p*-menthene-8-thiol showed the lowest odor threshold among the sulfur compounds synthesized.[22] Based on this result, it was speculated that odorant receptor structures must have been shaped by naturally available aroma-active volatiles.[22] Recently it was shown that only one out of 390 human odorant receptors was activated by 3-mercapto-2-methylpentan-1-ol corroborating the assumption that receptors for detection of thiols are specialists.[23]

Following the concept of our previous study on structure-activity relationships in 1-*p*-menthene-8-thiol, the aim of this investigation was to find out which structural features are responsible for the coffee-like odor quality as well as the very low odor threshold of **1**. To verify the assumption that the naturally occurring compounds within one substance class are the most potent odorants among the structurally related components, over 40 hetero aromatic sulfur-containing compounds were synthesized with a structural relationship to **1**. Their odor qualities and odor thresholds were determined to check whether **1** also shows the lowest threshold among a series of homologues and whether its coffee-like scent is also unique among its homologues. Because potent mercaptans are often present in foods in trace amounts, it was another purpose of the study to generate analytical data, such as retention indices, mass spectra, and NMR data to facilitate their potential identification in foods in future studies.

MATERIALS AND METHODS

Chemicals and Reference Odorants. Furan-2-ylmethanethiol (2-furfurylthiol; **1**) and 2-thenylthiol (**8**) were purchased from Sigma-Aldrich (Steinheim, Germany) and TCI Europe Laboratory Chemicals (Eschborn, Germany), respectively. Further chemicals for syntheses were supplied by ABCR, Alfa-Aesar (both Karlsruhe, Germany), Sigma-Aldrich (Steinheim, Germany), TCI Europe Laboratory Chemicals (Eschborn, Germany), and VWR (Darmstadt, Germany). Solvents were obtained from VWR and deuterated solvents were purchased from Euriso-top (Saarbruecken, Germany). Diethyl ether and pentane were distilled prior to use.

Syntheses. In total 44 sulfur compounds were synthesized. The reactions were carried out in dry glassware under an atmosphere of pure argon. Detailed synthetic

procedures as well as mass spectra, NMR spectra and retention indices are given for each compound in the Supporting Information.

Synthesis of ω-(furan-2-yl)alkane-1-thiols **2-7 (**Figure 1). First, the corresponding alcohols were prepared following the method by Baciocchi et al.[24] starting from furan and the appropriate ethyl iodo alkanoic acid as shown in Figure 2. As exemplified for *2*-(furan-2-yl)ethane-1-thiol in Figure 2, the target compounds were then synthesized from the alcohols by substituting the hydroxyl by the mercapto group using a slightly modified method[25] consisting of tosylation, thio acetylation, and finally a reduction.

Synthesis of the ω-(thiophene-2-yl)alkane-1-thiols **9-12** (Figure 1). The compounds were synthesized as described above for the furan derivatives, but substituting furan by thiophene in the reaction pathway shown in Figure 2.

Synthesis of 1-(furan-2-yl)alkane-1-thiols **13-18** (Figure 3). These were synthesized from the corresponding ketones and/or alcohols, respectively. After reduction, the alcohols were transformed into the thiols as described previously[26] and as briefly shown for 1-(furan-2-yl)propane-1-thiol in Figure 4.

Synthesis of 1-(thiophene-2-yl)alkane-1-thiols (**19-24;** Figure 3). The corresponding thiophene derivatives were synthesized from the corresponding alcohols whith a thiophene ring following closely the reaction pathway shown for the respective furans in Figure 4. The longer chain alcohols 1-(thiophene-2-yl)hexan-1-ol (intermediate for **23**) and 1-(thiophene-2-yl)heptan-1-ol (intermediate for **24**) were synthesized as described by Fuller et al.[27]

Synthesis of alkyl substituted 2-furfuryl- (**25-28;** Figure 5) and 2-thenylthiols (**29-32;** Figure 5). These compounds were synthesized from the corresponding ketones and/or alcohols, respectively. After a reduction of the ketones, the alcohols were transformed into the thiols following the same method as described for the 1-(furan-2-yl)alkane-1-thiols in Figure 4.[26]

131 The synthesis of 3-furfurylthiol (**33**) and 3-thienylthiol (**34**) followed a slightly
132 modified strategy published previously.[26]

133 *Synthesis of* **35-46**. Thio ethers of **1** and **8** were synthesized from the respective
134 thiols and iodo alkanes following a slightly modified method described by Nolan and
135 Cohen,[28] as briefly shown in Figure 6.

136 **Gas Chromatography–Flame Ionization Detection (GC-FID) and Gas**
137 **Chromatography–Olfactometry (GC-O)**. Analyses by GC-FID coupled with
138 olfactometry were carried out by means of a Trace GC Ultra gas chromatograph
139 (Thermo Scientific, Bremen, Germany) using helium as the carrier gas. A J&W
140 Scientific DB-5 and a DB-FFAP capillary column (each 30 m × 0.32 mm i.d., 0.25 µm
141 film thickness, 75 kPa head pressure) (Chromatographie-Handel Mueller, Fridolfing,
142 Germany) were used. Samples were injected by the cold-on-column technique
143 (injection volume: 1 µL) at 40 °C. After 2 min, the temperature of the oven was raised
144 at 8 °C/min to 230 °C (DB-FFAP) or 240 °C (DB-5), respectively, and then held for
145 5 min. At the end of the capillary, the effluent was split 1:1 using a deactivated Y-
146 shaped glass splitter into an FID (250 °C) and the sniffing port (200 °C) using two
147 deactivated fused silica capillaries (50 cm × 32 mm i.d.). The FID was operated with
148 hydrogen (20 mL/min) and air (200 mL/min); nitrogen (30 mL/min) was used as the
149 makeup gas. During a GC-O run, the panelist's nose was placed above the sniffing
150 port and the odor was evaluated. If an odor quality was recognized, the retention time
151 was marked in the chromatogram, and the odor quality was annotated. Data obtained
152 by three panelists were averaged. Retention indices were calculated using a series of
153 *n*-alkanes.

154 **Gas Chromatography–Mass Spectrometry (GC-MS)**. Mass spectra were
155 recorded by means of a 5890 series II gas chromatograph (Hewlett-Packard,
156 Waldbronn, Germany) connected to an MAT 95 S sector field mass spectrometer

(Finnigan, Bremen, Germany). Mass spectra in the electron ionization mode (MS-EI) were recorded at 70 eV ionization energy and mass spectra in the chemical ionization mode (MS-CI) at 115 eV with isobutane as the reactant gas.

Determination of Odor Thresholds in Air. Thresholds in air were determined by aroma extract dilution analysis of a mixture containing known amounts of the respective odorant and the internal standard (*E*)-2-decenal with an odor threshold in air of 2.7 ng/L.[29] Thresholds of the compounds were calculated from the flavor dilution (FD) factors determined by using the method previously reported. [19,20,22,30]

NMR-Spectroscopy. The ^{1}H, ^{13}C, and 2D NMR experiments (COSY, HMBC, HSQC) were performed using a 400 MHz Avance III spectrometer (Bruker, Rheinstetten, Germany) at 297 K with deuterated chloroform (+ 0.03% tetramethylsilane) as the solvent.

RESULTS AND DISCUSSION

Previous results obtained in studies on structure-odor relationships of the natural grapefruit aroma compound 1-*p*-menthene-8-thiol have shown that the thiol showed the lowest odor threshold among the sulfur compounds synthesized. Based on this result, it was speculated that human odorant receptors must have been shaped by naturally available aroma-active volatiles.[22] To check whether the same is true for the natural coffee aroma compound furan-2-ylmethanethiol (2-furfurylthiol); **1**, over 40 structurally related hetero aromatic sulfur-containing compounds were synthesized. Their odor qualities and odor thresholds were determined to check whether **1** also shows the lowest threshold among the structurally related sulfur compounds considered, and whether its coffee-like scent is also unique among them.

Elongation of the Side Chain in 1. To investigate the influence of the distance between the furan ring and the thiol group, six further *ω*-(furan-2-yl)alkane-1-thiols (**2-7**) were synthesized up to an alkyl chain length of seven carbon atoms (Figure 1).

The mass spectrum of **1** (Figure 7A) was compared to the spectrum of compound **5** (Figure 7B) bearing a seven carbon side chain. While **1** only revealed two distinct signals, the molecular ion (M^+) (*m/z* 114) and a strong signal *m/z* 81, caused by the so called furan-2-ylmethylium cation ($C_5H_5O^+$), 5-(furan-2-yl)pentane-1-thiol (**5**) showed additional fragments generated by degradation of the side chain. The furan-2-ylmethylium cation (*m/z* 81) was the major ion in all longer-chain homologues. Although the molecular ions were always detectable in **2-7**, their intensities decreased with increasing the length of the alkyl chain.

Among the *ω*-(furan-2-yl)alkane-1-thiols only **1** showed the characteristic burned, roasty, and coffee-like odor quality, while the other homologues were described as onion-like, mushroom-like, and/or rubber-like (Table 1). The very low odor threshold of **1** (0.0084 ng/L in air) was similar in the three homologues up to four carbon atoms in the side chain (**2-4**), but then a strong increase in thresholds was observed with 7-(furan-2-yl)heptane-1-thiol (**7**) exhibiting an odor threshold of 350 ng/L, which was higher by a factor of over 45 000 than that of **1** (Table 1).

Substitution of the Furan Ring by a Thiophene Ring. In a second series of experiments, the furan ring in the *ω*-(furan-2-yl)alkane-1-thiols was replaced by a thiophene ring. Besides the commercially available 2-thenylthiol (**8**), four *ω*-(thiophene-2-yl)alkane-1-thiols (**9-12**; Figure 1) were synthesized.

Compound **8** showed a signal for the molecular ion (*m/z* 130) and for the thiophene-2-ylmethylium cation (*m/z* 97) (Figure 8) generated by elimination of the thiol group. In all homologues (**9-12**), the most intense signal was the thiophene-2-ylmethylium cation ($C_5H_5S^+$). 2-(Thiophene-2-yl)ethanethiol (**9**) and 3-(thiophene-2-

yl)propane-1-thiol (**10**) exhibited also a signal for the fragment $[M - H_2S]^+$ (*m/z* 112 and 126, respectively), while the longer-chain homologues showed signals for $[M - SH]^+$.

A burned, roasty, and coffee-like odor was only elicited by 2-thienylthiol (**8**), while **9** was described as onion-like, burned, and rubber-like (Table 2). Instead, the longer-chain homologues exhibited rubber-like and mushroom-like scents. While **8**, **9**, **10**, and 4-(thiophene-2-yl)butane-1-thiol (**11**) exhibited very similar odor thresholds between 0.012 and 0.036 ng/L in air, for 5-(thiophene-2-yl)pentane-1-thiol (**12**) an increase by two orders of magnitude was determined (1.2 ng/L)(Table 2).

Insertion of an Alkyl Chain into the Side Chain of 1. 1-(Furan-2-yl)ethane-1-thiol (**13**) naturally occurs in coffee,[15] and was also identified in model reactions of a thermally treated mixture of glucose and cysteine[31] and in further meat model systems.[32] Besides the elongation of the carbon chain between the furan ring and the thiol group, also an insertion of an additional alkyl chain is possible, thus generating 1-(furan-2-yl)alkane-1-thiols (**13-18**; Figure 3).

The mass spectra of **13** and 1-(furan-2-yl)propane-1-thiol (**14**) with a short alkyl chain showed the strongest signals at *m/z* 95 and *m/z* 109, respectively, for ($[M - SH]^+$). In Figure 9 the mass spectrum of 1-(furan-2-yl)butane-1-thiol (**15**) is shown. Interestingly, all longer-chain homologues (**15-18**) showed the highest signal at *m/z* 81 representing the furan-2-ylmethylium cation. In addition, the furan-2-yl(mercapto)methylium cation (*m/z* 113), $[M - SH]^+$ and the molecular ions were always present.

While the short-chain 1-(furan-2-yl)ethane-1-thiol (**13**) showed a sulfury, meaty odor quality, the scent of the longer-chain homologues changed to catty and passion fruit-like (Table 3). For compounds **13** to **16** the thresholds were quite similar, but for

the longer chain 1-(furan-2-yl)hexane-1-thiol (**17**) and 1-(furan-2-yl)heptane-1-thiol (**18**) an increase to 0.51 and 9.0 ng/L, respectively, was observed (Table 3).

Insertion of an Alkyl Chain into the Side Chain of 2-Thienylthiol (8)

1-(Thiophene-2-yl)ethanethiol (**19**) was reported as constituent of a thermally treated mixture of glucose and cysteine[31] and thus, the homologous series of **20** to **24** (Figure 3) also represent very interesting structural modifications of **1**. The thiophene homologues showed a very similar mass spectrometric fragmentation pattern compared to the furan derivatives except that, of course, all signals were shifted by 16 mass units.

The odor qualities of the thiophene derivatives **19-24** were similar to those of the furan derivatives. While 1-(thiophene-2-yl)ethane-1-thiol,**19**, and the corresponding propane-1-thiol homologue,**20**, smelled sulfury, meaty, in the longer chain homologues a catty, passion-fruit like odor notes predominated (Table 4). Also the threshold values of the thiophene derivatives were comparable to those of the furan derivatives and showed a similar trend. While **19** revealed a threshold of 0.0075 ng/L, the longer chain 1-(thiophene-2-yl)heptane-1-thiol (**24**) showed a threshold, which was higher by a factor of 500 (Table 4).

Insertion of Additional Alkyl Chains into the Heteroaromatic Ring of 2-Furfurylthiol and 2-Thienylthiol, respectively. 5-Methyl-2-furfurylthiol (**25;** Figure 5) has been identified in coffee[14] and yeast extract,[33] and thus, it could be possible that also other alkylated 2-furfurylthiols or 2-thienylthiols, respectively may occur in thermally processed foods. Therefore, either the side chain in the 5-position of 2-furfurylthiol was extended as ethyl (**26**) or propyl group (**27**) or the methyl group was shifted from the 5- to the 3-position in **28**. Furthermore, the ring oxygen was substituted by sulfur in the thiophene derivatives with a methyl group in the 5-, **29**, as

well as the 3-,**31**, and the 4-position in 4-methyl-2-thenylthiol (**32**). In addition, the methyl group in 5-methyl-2-thenylthiol was replaced by an ethyl group (**30**; Figure 5).

As an example, the mass spectrum of the 5-propyl-2-furfurylthiol (**27)** is shown in Figure 10. Without exception, all alkyl-substituted 2-furfurylthiols showed a clear signal of the molecular ion in their mass spectra, but the highest signal was always the fragment generated by $[M - SH]^+$, e.g., *m/z* 95 for **25** or *m/z* 123 for **27**. The mass spectra of the respective thiophene derivatives showed the same fragmentation pattern.

Compared to **1,** an insertion of an alkyl chain at position 5 in the furan ring (**25-27**) led to a clear change to an onion-like and rubber-like odor quality (Table 5). However, the characteristic burned, roasty, and coffee-like odor quality of **1** was also elicited by **28** in which an additional methyl group was present in the 3 position. This compound also showed a very low odor threshold.

The respective 2-thienylthiols with the methyl or ethyl group in the 5 position (**29,30**) showed rubber-like and minty scents, while the 2-thienylthiols with the methyl group in either the 3- or the 4-position (**31**,**32**) exhibited burned, rubber-like, and garlic-like odors, respectively.

3-Furfurylthiol and 3-Thienylthiol (Figure 11). Because of the structural similarity to the parent compound **1**, 3-furfurylthiol (**33**) and 3-thienylthiol (**34**) were also synthesized. The mass spectra were nearly identical with that of 2-furfurylthiol (**1**) and 2-thienylthiol (**8**), respectively. Both thiols showed a burned, roasty, and coffee-like odor quality like **1** (Table 5). The odor thresholds of both, however, were higher by factors of 10 or 20, respectively, compared to **1** and **8** (Table 5).

Loss of the Free Thiol Group of 2-Furfurylthiol and 2-Thienylthiol. In a last series of experiments the influence of the free thiol group on the odor attributes of **1** and further homologues were evaluated. Thus, the respective alkyl thio ethers of **1**

(**35-40**) as well as **8** (**41-46**) were synthesized (Figure 12) and their odor properties were determined.

As exemplified for 2-((butylthio)methyl)furan, **38**, (Figure 13), the mass spectra of 2-((alkylthio)methyl)furans (and also of 2-((alkylthio)methyl)thiophenes) only contained very few signals. The most distinct signal was always the furan-2-ylmethylium cation (*m/z* 81) or the thiophene-2-ylmethylium cation (*m/z* 97), respectively, together with a small signal at *m/z* 53, which is caused by $C_4H_5^+$, only the molecular ion showed a considerable intensity.

Except for **35**, the odors of the 2-((alkylthio)methyl)furans were characterized by fatty and deep fried notes (Table 6) which was also true for the 2-((alkylthio)methyl)thiophenes (Table 7). In both series of thio ethers, the odor thresholds increased with increasing the molecular weight. For example, 2-((methyl-thio)methyl)furan, **35 (**Table 6), and 2-((methylthio)methyl)thiophene, **41** (Table 7), showed thresholds of 1.4 and 0.42 ng/L, respectively, and constantly increased to 59 or 84 ng/L, respectively for 2-((hexylthio)methyl)furan, **40**; **(**Table 6) and 2-((hexylthiol)methyl)thiophene **46**; (Table 7), respectively.

2-Furfurylthiol (**1**) known as a key aroma compound in roast and ground coffee exhibits a unique coffee-like flavor at the very low odor threshold of 0.0084 ng/L in air, but none of the 45 mercaptans or the derived thio ethers investigated in this study showed a significantly lower threshold. Only 3-(furan-2-yl)propane-1-thiol, **3**, and 1-(thiophene-2-yl)ethanethiol,**19**, also revealed low threshold values of 0.0080 and 0.0075 ng/L, respectively, which were in the same order of magnitude. Furthermore, only four homologues, i.e., 2-thienylthiol (**8**), 3-methyl-2-furfurylthiol (**28**), 3-furfurylthiol (**33**), and 3-thienylthiol (**34**) elicited a similar coffee-like aroma attribute as **1**.

Extending the distance between the furan ring and the thiol group resulted in a strong increase in odor thresholds for mercaptans with longer “distances” (chain length) (Table 1). Although the very low threshold value of **1** was kept for the smaller homologues, the coffee-like scent was always lost. Thus, despite the similar low thresholds, it can be assumed that 2-(furan-2-yl)ethanethiol (**2**) and **3** as well as 4-(furan-2-yl)butane-1-thiol (**4**) are not detected by the same odorant receptor as **1**. However, odor qualities and even odor thresholds of longer-chain *ω*-(furan-2-yl)alkane-1-thiols were comparable to those of the C9 and C10 alkane thiols investigated by Polster and Schieberle[19,20] who also found mushroom-like odors for such long-chain thiols.

A displacement of the furan ring by a thiophene ring had almost no influence on odor properties. As illustrated in Figures 14-16, the tendencies of thresholds with respect to chain length were nearly identical for furan and thiophene derivatives, and the odor qualities were often also the same.

The furans and thiophenes studied have a relatively high number of carbons, e.g., up to eleven in compounds **7**, **18** and **24**. However, alkane thiols with the same number of carbons have shown significantly higher thresholds,[19] e.g., compared to the furan or thiophene derivatives. Obviously the hetero aromatic moiety leads to a decrease in odor thresholds compared to alkanes with the same number of carbon atoms. At a certain chain length, however, also in the hetero atomic mercaptans, the thiol group loses its ability to generate low odor thresholds. Obviously from a certain chain length onwards it is no longer relevant which functional group is located in the molecule. This agrees with findings of Polster and Schieberle.[19] As illustrated in Figure 17, 2-((pentylthio)methyl)furan (**39**) and 2-((hexylthio)methyl)furan (**40**) showed thresholds lower than 6-(furan-2-yl)hexane-1-thiol (**6**) and 7-(furan-2-

yl)heptane-1-thiol (**7**), while significant differences were observed for the shorter-chain homologues.

Very interesting passion fruit-like odor qualities were found for longer-chain 1-(furan-2-yl)alkane-1-thiols and their respective thiophene homologues. These compounds have not been synthesized before, and their odor properties are described here for the first time. The fact that these different, but very similar ring systems, with the same side chain generate the same odors and even very similar thresholds (Figure 17), suggests that this is a structural motif activating one or more specific odorant receptors. However, the longer-chain compounds have not yet been reported as food constituents or naturally occurring aroma compounds.

1-(Furan-2-yl)alkane-1-thiols showed only slightly higher odor thresholds than the *ω*-(furan-2-yl)alkane-1-thiols for compounds with two to four carbon atoms in the side chain, but a slower increase in thresholds with increasing molecular weight was observed (Figure 15). Meilgaard[34] found that tertiary thiols generally show lower thresholds than primary and secondary ones, which was confirmed by Polster and Schieberle.[19] However, our results show that this is also possible for secondary thiols.

As expected, the loss of the free thiol group led to a significant increase in odor thresholds. In comparison to the corresponding thiols, 2-((methylthio)methyl)furan (**35**) and 2-((methylthio)methyl)thiophene (**41**) showed thresholds which were higher by factors of approximately 170 and 35, respectively. Within the homologous series of thio ethers the thresholds then increased significantly (Figure 16). Thus, the thiol group plays a very important role in the generation of low odor thresholds also for the heterocycles examined in this study. However, as mentioned before, suddenly a molecular weight is reached causing a significant increase in thresholds of the thiols.

As mentioned above, only four out of 45 homologues showed the same coffee-like odor quality as **1**: these were **8**, **28**, **33**, and **34**, while in most cases structural variations in the side chain, e.g., an elongation, led to a loss of the characteristic coffee-like scent. The odor quality was only maintained when the furan ring was replaced by a thiophene ring or if a methyl group was present at position 3 of the furan ring, respectively. Also, moving the mercapto methylene group from position 2 to position 3 in either 2-furfuryl- or 2-thenylthiol (**33** and **34**) gave a coffee-like scent. Thus, the coffee-like scent was kept only by thiols with a very similar structural motif, but the thresholds clearly increased with an increasing deviation from the structure. Therefore, it can be concluded that the odorant receptor responsible for the perception of **1** seems to be very specific.

In general, however, a relatively large number of thiols showed similar or only slightly higher thresholds than **1**. These include lower-weight *ω*-(furan-2-yl)alkane-1-thiols, *ω*-(thiophene-2-yl)alkane-1-thiols, 1-(furan-2-yl)alkane-1-thiols, and 1-(thiophene-2-yl)alkane-1-thiols as well as **28** and 3-methyl-2-thenylthiol (**31**). The basis structural motif of **1** thus seems to be a suitable one for the generation of low odor thresholds. Besides the improved perception of thiols in general,[35,36] a possible explanation for this could be the appearance of so called *π*-*π* molecular interactions. As also aromatic and hetero aromatic amino acids can occur within the respective olfactory receptors, enhanced interactions and perception are possible.

None of the homologues showed a significantly lower odor threshold than **1**, and only a very few structurally related mercaptans elicited the same odor attribute. This result is perfectly in line with data of our study on structural homologues of 1-*p*-menthene-8-thiol (1-*p*MT).[22] It can, therefore, be speculated that within evolutionary development the odorant receptors that came in contact with naturally occurring aroma compounds may have shaped them. Also compounds which are generated by

thermal treatment of raw foods may be seen as “natural”, because fire was used by humans since about 1 million years. Therefore, synthetically generated analogues are probably not perceived with the same low detection limit, because the odorant receptors are not tailor-made for them. In contrast to the results for 1-*p*MT showing that no homologue reached its low odor threshold by far, a relatively large number of the structurally related mercaptans of **1** showed similar or slightly higher thresholds. The fact that, in comparison to 1-*p*MT, furane and thiophene thiols often showed thresholds in the range of **1**, can be explained by the natural occurrence of several further hetero aromatic thiols in foods.[6, 12-18] Therefore, these odorant receptors are probably more broadly tuned.

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Notes. The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data (NMR, MS) of the 46 synthesized compounds and intermediates. In Figures S1, S22, and S67 the synthetic routes are illustrated. Figures S2-S21, S23-S66, and S68-S95 show the NMR spectra of the synthesized sulfur compounds.

This material is available free of charge via the Internet at http://pubs.acs.org.

411 **Notes.** The authors declare no competing financial interest.

412

413 **ABBREVIATIONS USED.** FD, flavor dilution; FFAP, free fatty acid phase; FFT, 2-

414 furfurylthiol; M_r, relative molecular mass; 1-*p*MT, 1-*p*-menthene-8-thiol;

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FIGURE CAPTIONS

Figure 1. Structures of 2-furfurylthiol (**1**), further *ω*-(furan-2-yl)alkane-1-thiols (**2-7**) and *ω*-(thiophene-2-yl)alkane-1-thiols (**8-12**).

Figure 2. Synthetic route used for the preparation of *ω*-(furan-2-yl)alkane-1-thiols shown for 2-(furan-2-yl)ethanethiol.

Figure 3. Structures of 1-(furan-2-yl)alkane-1-thiols (**13-18**) and 1-(thiophene-2-yl)alkane-1-thiols (**19-24**).

Figure 4. Synthetic route used for the preparation of 1-(furan-2-yl)alkane-1-thiols shown for 1-(furan-2-yl)propane-1-thiol.

Figure 5. Structures of alkylated 2-furfurylthiols (**25-28**) and 2-thenylthiols (**29-32**).

Figure 6. Synthetic route used for the preparation of 2-((alkylthio)methyl)furans shown for 2-((methylthio)methyl)furan.

Figure 7. Mass spectrum (MS-EI) of (A) 2-furfurylthiol (**1**) and (B) 5-(furan-2-yl)pentane-1-thiol (**5**).

Figure 8. Mass spectrum of 2-thenylthiol (**8**).

Figure 9. Mass spectrum (MS-EI) of 1-(furan-2-yl)butane-1-thiol (**15**).

Figure 10. Mass spectrum (MS-EI) 5-propyl-2-furfurylthiol (**27**).

Figure 11. Structural formulas of 3-furfurylthiol (**33**) and 3-thenylthiol (**34**).

Figure 12. Structures of 2-((alkylthio)methyl)furans (**35-40**) and -thiophenes (**41-46**).

Figure 13. Mass spectrum (MS-EI) 2-((butylthio)methyl)furan (**38**).

Figure 14. Influence of different heterocyclic ring systems on the odor thresholds of homologous series of *ω*-substituted alkane-1-thiols.

Figure 15. Influence of different heterocyclic ring systems at position C1 on the odor thresholds of homologous series of alkane-1-thiols.

Figure 16. Influence of different ring systems on the odor thresholds of homologous series of heterocyclic thio ethers.

Figure 17. Influence of different structural modifications on the odor thresholds homologous series of 2-furfurylthiol derivatives.

Table 1. Retention Indices and Sensory Properties of ω-(Furan-2-yl)alkane-1-thiols

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
1	2-furfurylthiol	1417	914	burned, roasty, coffee-like	0.0084
2	2-(furan-2-yl)ethanethiol	1470	996	onion-like, burned, rubber-like	0.013
3	3-(furan-2-yl)propane-1-thiol	1590	1108	burned, roasty, mushroom-like	0.0080
4	4-(furan-2-yl)butane-1-thiol	1712	1220	burned, mushroom-like	0.0088
5	5-(furan-2-yl)pentane-1-thiol	1825	1326	rubber-like, onion-like, mushroom-like	0.85
6	6-(furan-2-yl)hexane-1-thiol	1925	1423	rubber-like, burned	86
7	7-(furan-2-yl)heptane-1-thiol	2034	1527	rubber-like, burned	350

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 2. Retention Indices and Sensory Properties of ω-(Thiophene-2-yl)alkane-1-thiols

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
8	2-thenylthiol	1663	1086	burned, roasty, coffee-like	0.012
9	2-(thiophene-2-yl)ethanethiol	1723	1172	onion-like, burned, rubber-like	0.030
10	3-(thiophene-2-yl)propane-1-thiol	1845	1288	rubber-like, mushroom-like	0.036
11	4-(thiophene-2-yl)butane-1-thiol	1975	1404	rubber-like, mushroom-like	0.025
12	5-(thiophene-2-yl)pentane-1-thiol	2077	1516	rubber-like, mushroom-like	1.2

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 3. Retention Indices and Sensory Properties of 1-(Furan-2-yl)alkane-1-thiols

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
13	1-(furan-2-yl)ethanethiol	1394	961	meaty, onion-like	0.030
14	1-(furan-2-yl)propane-1-thiol	1457	1039	onion-like, passion fruit-like	0.012
15	1-(furan-2-yl)butane-1-thiol	1541	1128	catty, passion fruit-like	0.022
16	1-(furan-2-yl)pentane-1-thiol	1633	1223	catty, passion fruit-like	0.082
17	1-(furan-2-yl)hexane-1-thiol	1717	1329	catty, passion fruit-like	0.51
18	1-(furan-2-yl)heptane-1-thiol	1832	1426	catty, passion fruit-like	9.0

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 4. Retention Indices and Sensory Properties of 1-(Thiophene-2-yl)alkane-1-thiols

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
19	1-(thiophene-2-yl)ethanethiol	1643	1125	sulfury, meaty, onion-like	0.0075
20	1-(thiophene-2-yl)propane-1-thiol	1700	1207	sulfury, meaty	0.057
21	1-(thiophene-2-yl)butane-1-thiol	1782	1299	catty, passion fruit-like	0.039
22	1-(thiophene-2-yl)pentane-1-thiol	1878	1399	catty, passion fruit-like	0.088
23	1-(thiophene-2-yl)hexane-1-thiol	1977	1503	catty, passion fruit-like	0.11
24	1-(thiophene-2-yl)heptane-1-thiol	2085	1608	passion fruit-like	3.3

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 5. Retention Indices and Sensory Properties of Alkyl substituted 2-Furfurylthiols and 2-Thenylthiols as well as 3-Furfurylthiol and 3-Thenylthiol

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
25	5-methyl-2-furfurylthiol	1479	1014	onion-like, rubber-like	0.13
26	5-ethyl-2-furfurylthiol	1544	1103	onion-like, rubber-like	0.096
27	5-propyl-2-furfurylthiol	1612	1184	onion-like, rubber-like	0.36
28	3-methyl-2-furfurylthiol	1470	1002	burned, roasty, coffee-like	0.038
29	5-methyl-2-thenylthiol	1726	1183	rubber-like, minty	1.4
30	5-ethyl-2-thenylthiol	1809	1276	rubber-like, minty	0.40
31	3-methyl-2-thenylthiol	1743	1179	burned, rubber-like	0.027
32	4-methyl-2-thenylthiol	1766	1196	sulfury, garlic-like	0.19
33	3-furfurylthiol	1436	924	burned, roasty, coffee-like	0.17
34	3-thenylthiol	1688	1093	burned, roasty, coffee-like	0.12

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 6. Retention Indices and Sensory Properties of 2-((Alkylthio)methyl)furans

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
35	2-((methylthio)methyl)furan	1479	1014	cabbage-like	1.4
36	2-((ethylthio)methyl)furan	1544	1103	onion-like, fatty	2.9
37	2-((propylthio)methyl)furan	1612	1184	onion-like, fatty	5.9
38	2-((butylthio)methyl)furan	1470	1002	fatty, deep-fried	30
39	2-((pentylthio)methyl)furan	1726	1183	fatty, deep-fried	44
40	2-((hexylthio)methyl)furan	1809	1276	fatty, deep-fried	59

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

Table 7. Retention Indices and Sensory Properties of 2-((Alkylthio)methyl)thiophenes

no. [a]	compound	RI		odor quality [b]	odor threshold (ng/L in air)
		FFAP	DB-5		
41	2-((methylthio)methyl)thiophene	1691	1174	cabbage-like, green	0.42
42	2-((ethylthio)methyl)thiophene	1749	1245	onion-like, fatty	5.3
43	2-((propylthio)methyl)thiophene	1830	1351	fatty, deep-fried	10
44	2-((butylthio)methyl)thiophene	1927	1450	fatty, deep-fried	20
45	2-((pentylthio)methyl)thiophene	2033	1556	fatty, deep-fried	70
46	2-((hexylthio)methyl)thiophene	2147	1659	fatty, deep-fried	84

[a] Compound numbers correspond to the numbers in the text. [b] Odor quality as perceived at the sniffing port during GC-O at threshold level.

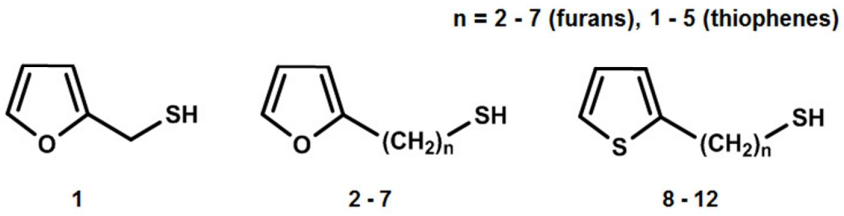
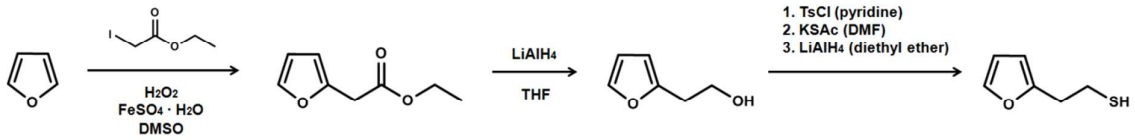


Figure 1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FeSO4 · H2O
DMSO
LiAlH4
THF
1. TsCl (pyridine)
2. KSAc (DMF)
3. LiAlH4 (diethyl ether)
OH
SH

Figure 2

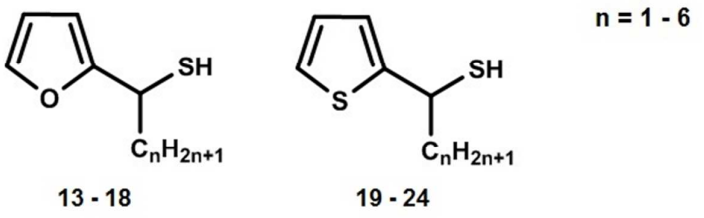


Figure 3

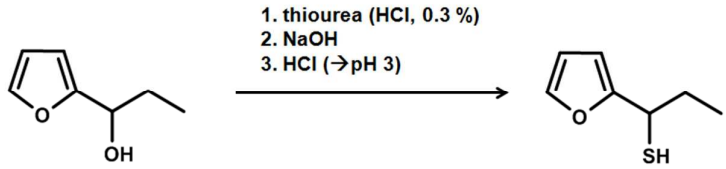


Figure 4

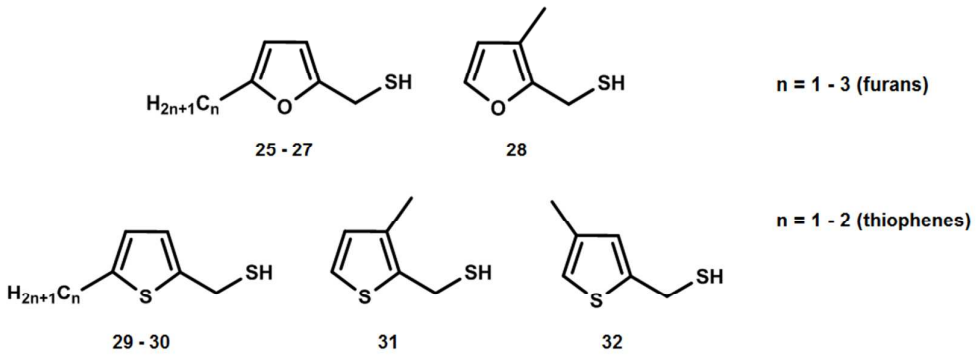


Figure 5

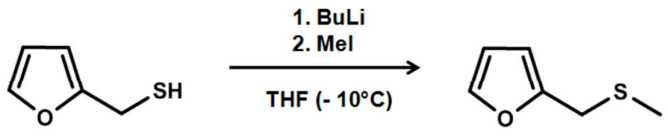
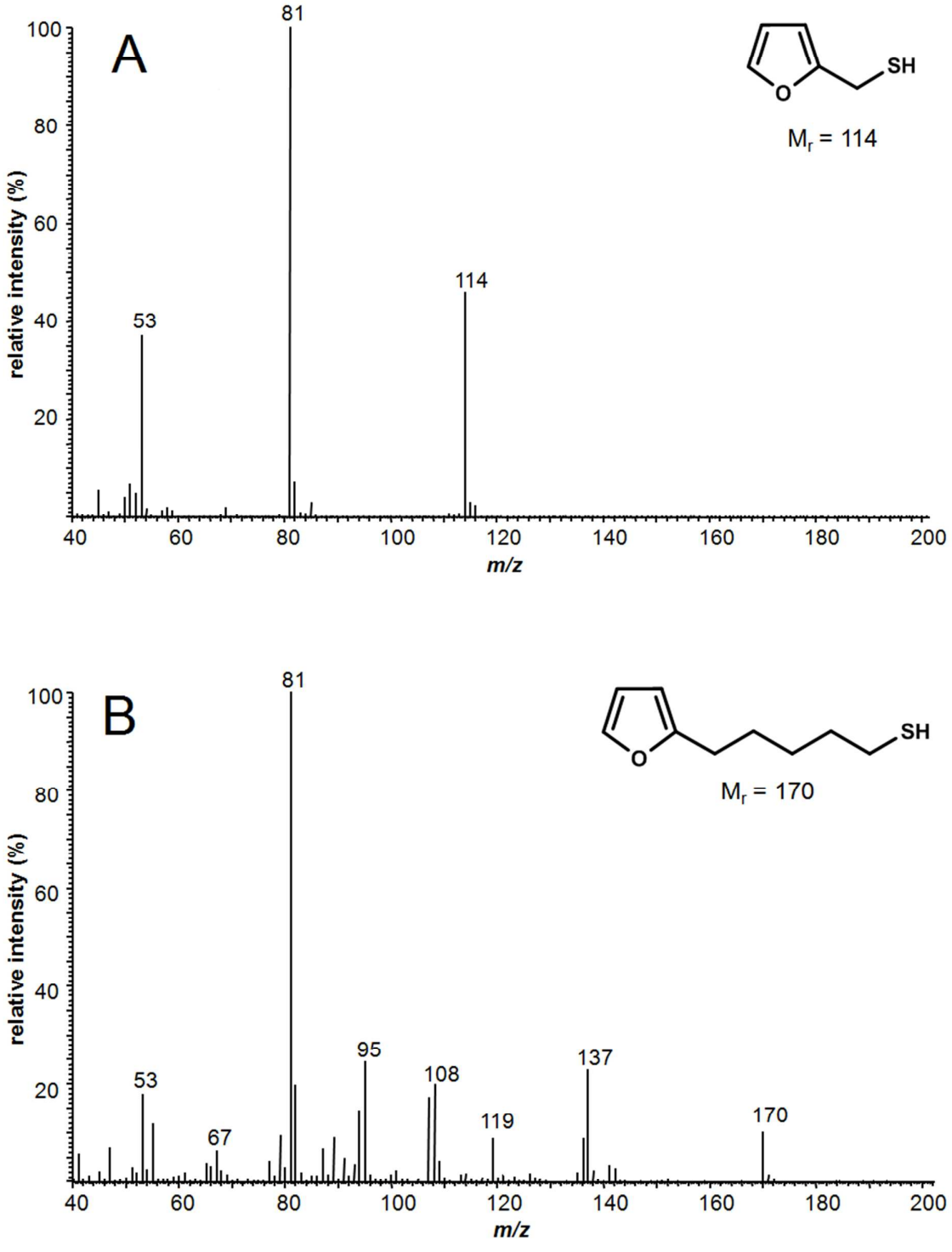


Figure 6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114
53
relative intensity (%)
m/z
SH
O
M_r = 114
B
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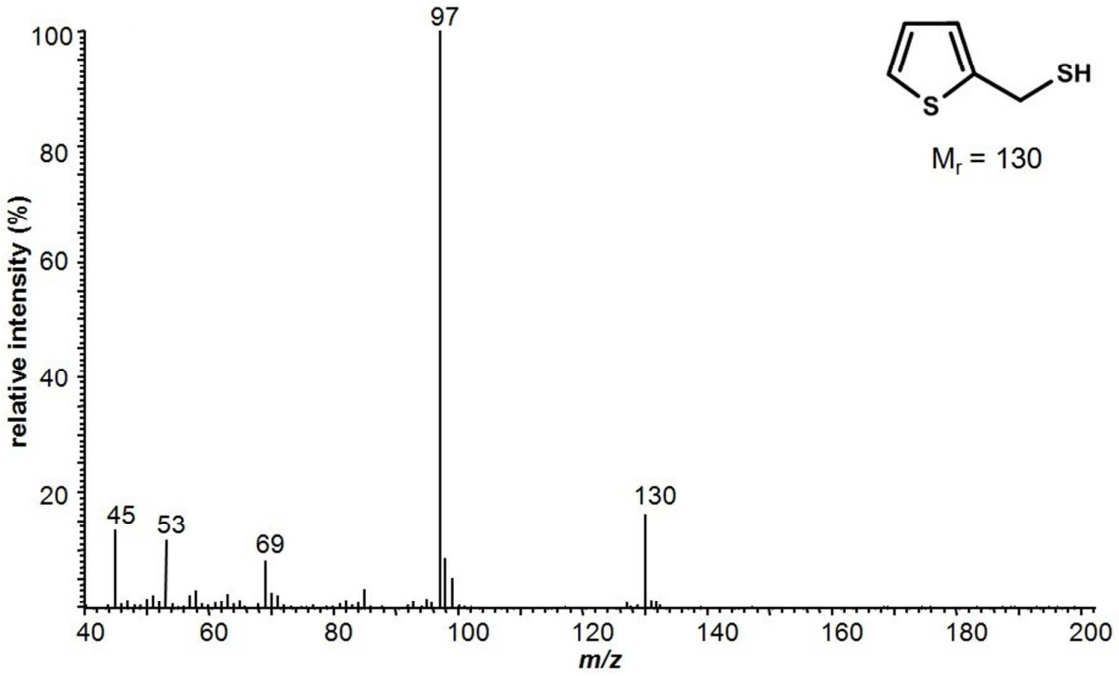
95
108
137
53
67
119
170
relative intensity (%)
m/z
SH
O
M_r = 170

Figure 7

545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relative intensity (%)
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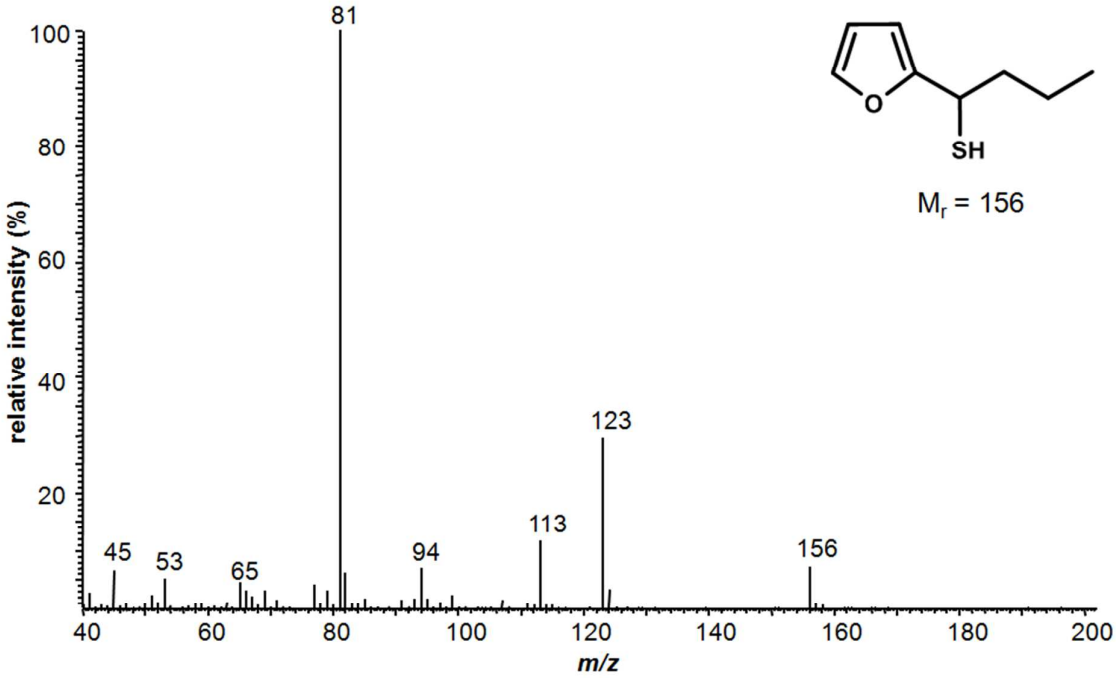
200
m/z
SH
S
M$_r$ = 130

Figure 8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40
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relative intensity (%)
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113
45
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65
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100
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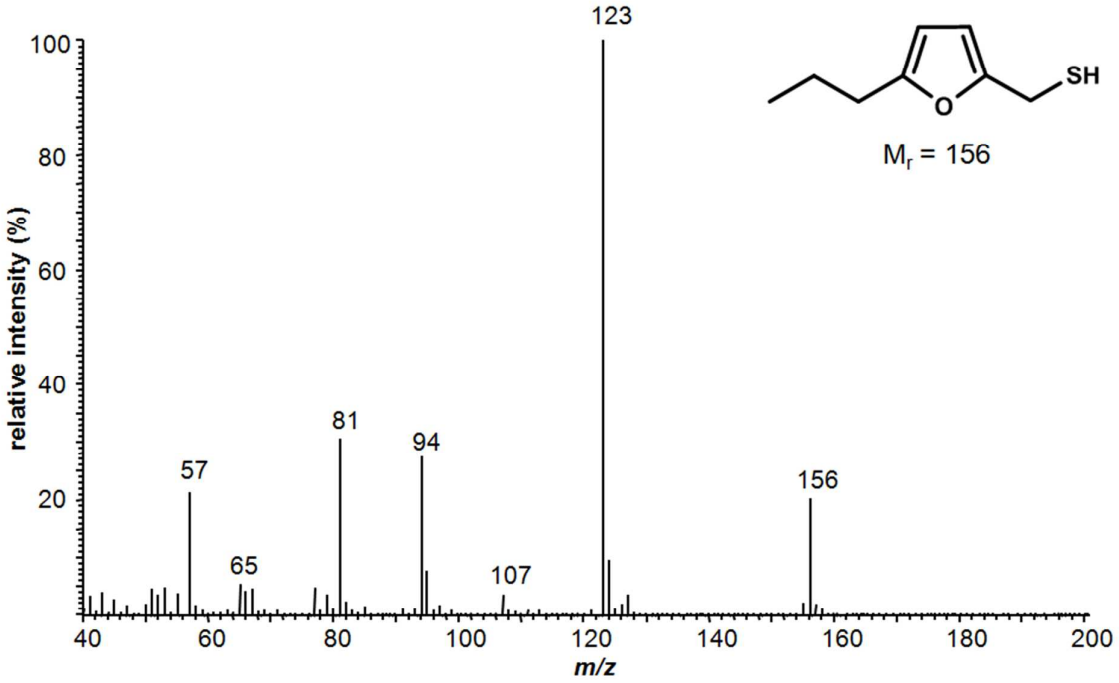
140
160
180
200
m/z
O
SH
M_r = 156

Figure 9


123
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80
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relative intensity (%)
81
94
57
156
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100
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140
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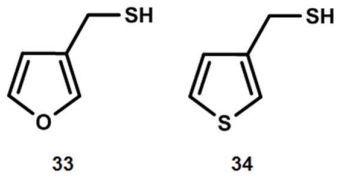
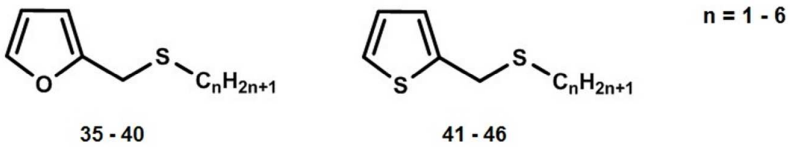
180
200
m/z
SH
O
M_r = 156

Figure 10



33 34

Figure 11



35 - 40 41 - 46

Figure 12

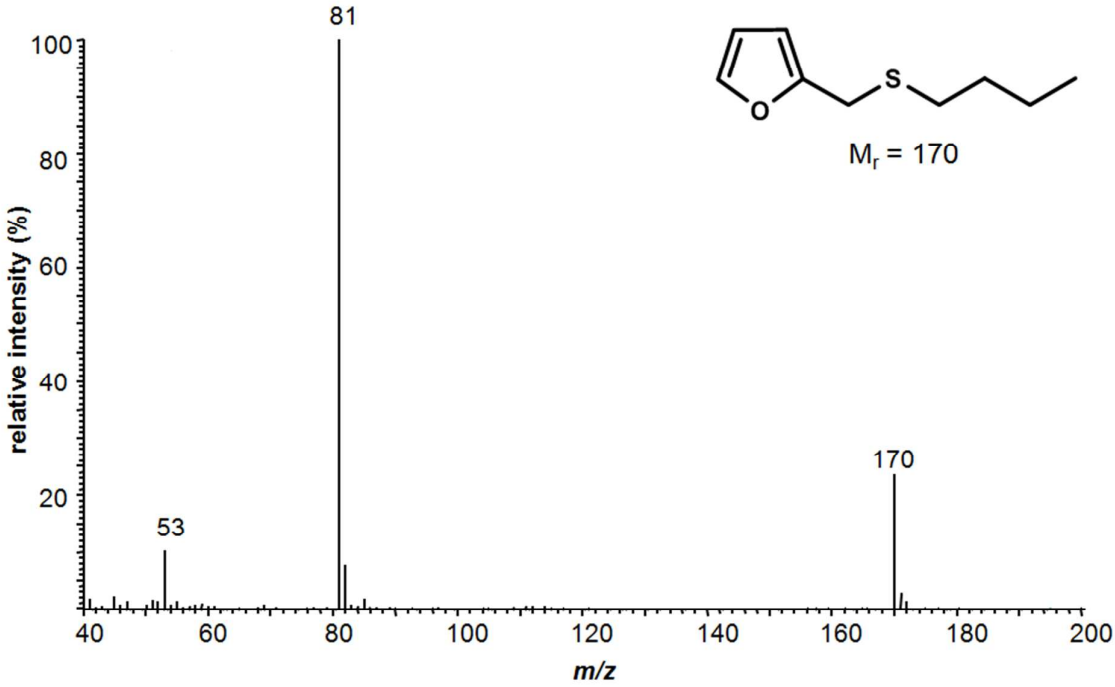

81
100
80
60
40
20
relative intensity (%)
53
170
40
60
80
100
120
140
160
180
200
m/z
O
S
M_r = 170

Figure 13

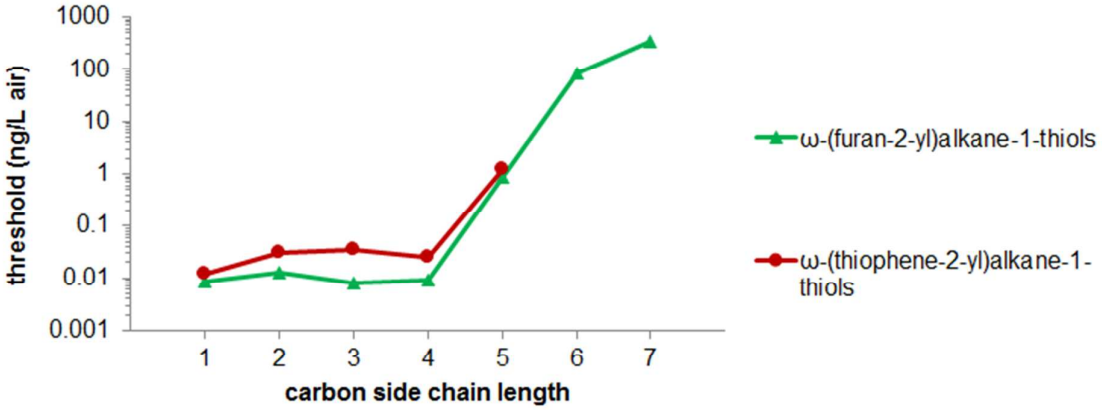

1000
100
10
1
0.1
0.01
0.001
threshold (ng/L air)
1
2
3
4
5
6
7
carbon side chain length
ω-(furan-2-yl)alkane-1-thiols
ω-(thiophene-2-yl)alkane-1-thiols

Figure 14

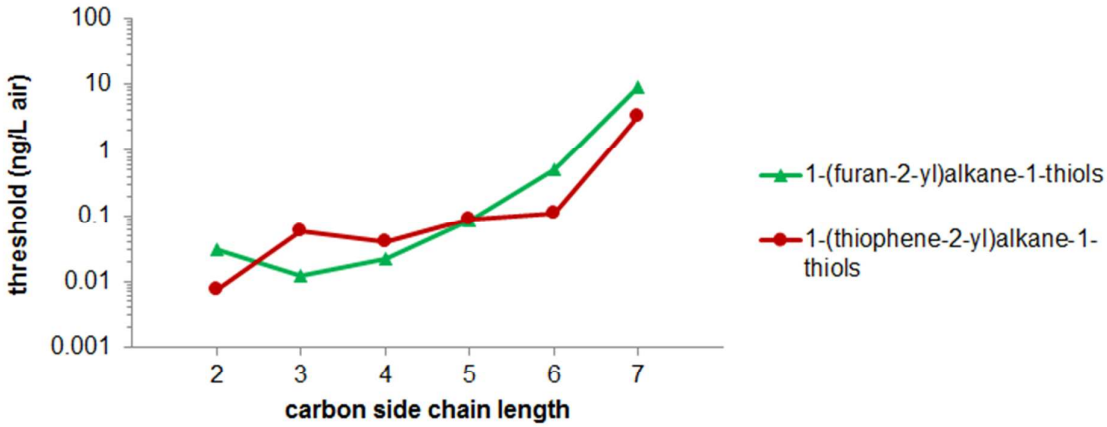

100
10
1
0.1
0.01
0.001
threshold (ng/L air)
2
3
4
5
6
7
carbon side chain length
1-(furan-2-yl)alkane-1-thiols
1-(thiophene-2-yl)alkane-1-thiols

Figure 15

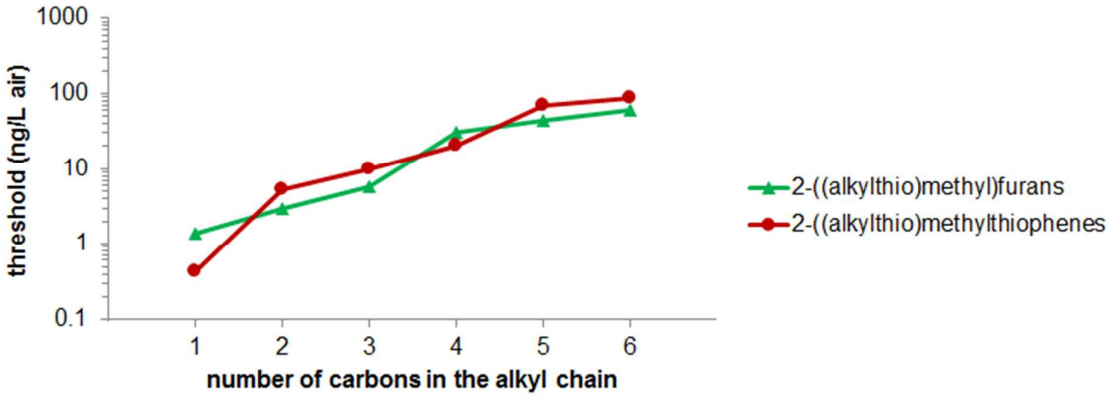

1000
100
10
1
0.1
threshold (ng/L air)
1
2
3
4
5
6
number of carbons in the alkyl chain
2-((alkylthio)methyl)furans
2-((alkylthio)methylthiophenes

Figure 16

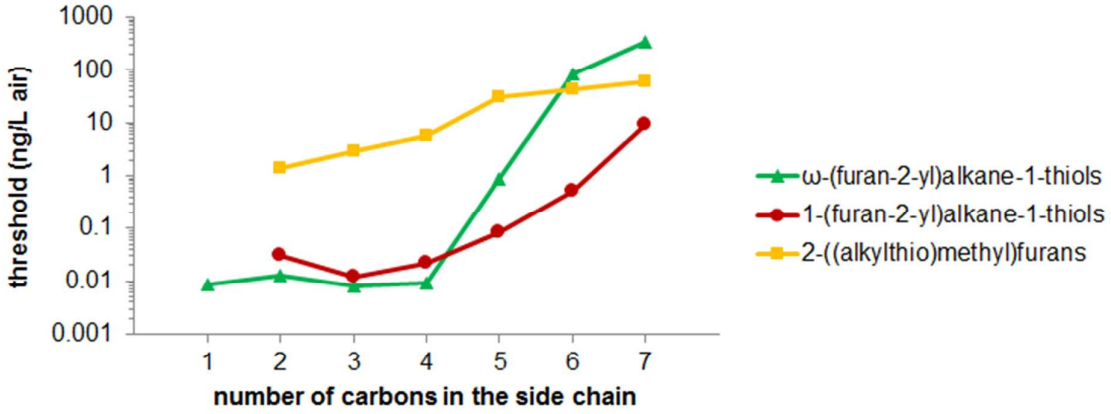
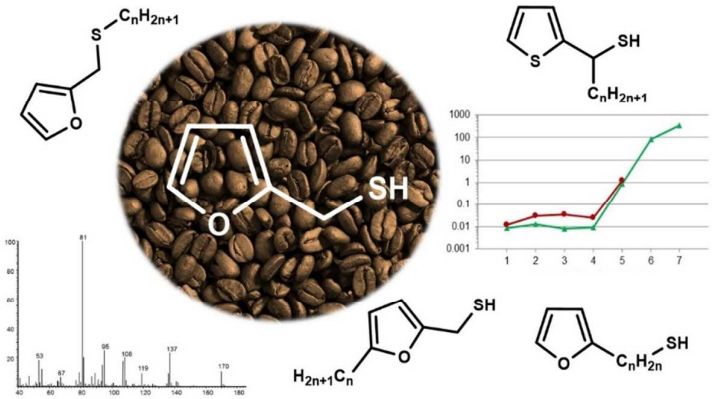

1000
100
10
1
0.1
0.01
0.001
threshold (ng/L air)
1
2
3
4
5
6
7
number of carbons in the side chain
ω-(furan-2-yl)alkane-1-thiols
1-(furan-2-yl)alkane-1-thiols
2-((alkylthio)methyl)furans

Figure 17

TOC graphic


S
C_nH_{2n+1}
O
SH
O
S
SH
C_nH_{2n+1}
1000
100
10
1
0.1
0.01
0.001
1 2 3 4 5 6 7
100
80
60
40
20
81
53
67
95
108
119
137
170
40 60 80 100 120 140 160 180
SH
O
$H_{2n+1}C_n$
O
SH
C_nH_{2n}