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Complementary use of gas chromatography–mass spectrometry, gas chromatography–atomic emission detection and nuclear magnetic resonance for identification of pharmaceutically related impurities of unknown structures

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Abstract

The complementary use of gas chromatography–mass spectrometry (GC–MS), gas chromatography–atomic emission detection (GC–AED) and nuclear magnetic resonance (NMR) spectroscopy is demonstrated by the identification of four major by-products in a sample from an exploratory attempt to synthesise 1,3-dichloro-5-(difluoromethoxy)benzene. GC–MS was used for straightforward identification of the target compound and one of the impurities. By employing GC–AED, the sample was screened for heteroatoms in the analysed molecules and determination of the partial empirical formula of one sample component was carried out. The combined spectroscopic data obtained from the MS and AED experiments facilitated structure elucidation of two of the additional by-products. Finally, identification of the last unknown component could be obtained by combining spectral information from GC–MS, GC–AED and NMR data acquired after isolation of the impurity from the sample.

Keywords: Pharmaceutical analysis; Dichloro(difluoromethoxy)benzene

1. Introduction

Drug substance process research and development involves innovative chemistry focused on novel synthetic routes that can be scaled-up and developed into commercially viable chemical processes able to produce up to several hundred tonnes of active pharmaceutical ingredient per annum. Strict control of impurities and by-products formed in the synthetic route is crucial during the development phase and the whole life cycle of a drug product. This is achieved by the use of validated analytical methods that controls the impurity levels in raw materials, intermediates and the drug substance.

Identification of organic impurities at and above 0.1% is required for the drug substance. Impurities may be carried through from the raw materials, formed as by-products during synthesis or arise as degradation products during storage. Identification of unknown organic compounds, amenable to gas chromatography (GC), can be carried out very conveniently by hyphenating GC to different detection techniques, such as mass spectrometry (MS), atomic emission detection (AED) and Fourier-transformed infrared spectroscopy (FT-IR). GC–MS provides information about molecular weight and structural data by interpretation of fragmentation patterns of the analysed substances [1–4]. GC–AED verifies the occurrence of individual elements in the compounds as well as possible empirical formulas [5–9]. Results obtained by GC–FT-IR can be used for confirmation of functionalities in the analysed molecules [10,11].

The complementary use of GC–MS, GC–AED and GC–FT-IR for efficient structure elucidations of unknown organic compounds in pharmaceutical analysis has been demonstrated in a previous publication [12]. The current paper describes the analytical approach for a sample of 1,3-dichloro-5-(difluoromethoxy)benzene involving identification of four major by-products by the complementary use of GC–MS, GC–AED and nuclear magnetic resonance (NMR) data.

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2. Experimental

2.1. Sample preparation

The sample of 1,3-dichloro-5-(difluoromethoxy) benzene was dissolved in dichloromethane and analysed by GC–FID (flame ionisation detection), GC–MS and GC–AED.

One of the impurities, compound E, was isolated by precipitation upon washing the original sample, dissolved in dichloromethane, three times with acetonitrile and then filtering. The isolated solid white substance was dried under a stream of nitrogen gas. For GC–MS analysis the isolated material was dissolved in dichloromethane (analytical-reagent grade) and for ^{1}H NMR and ^{13}C NMR analyses in deuterochloroform (>99.95 at.% ^{2}H).

2.2. Instrumentation

2.2.1. GC analyses

A Hewlett-Packard (HP) gas chromatograph 6890 series was used, equipped or coupled with:

1. flame ionisation detector,
2. MS-1: HP model 5973, electron impact ionisation (EI), 70 eV (GC–EI-MS).
3. MS-2: HP model 5972, chemical ionisation (CI), reagent gas: CH_4 (GC–CI-MS),
4. AED: HP model G2350A.

2.2.2. NMR analyses

A Bruker Avance 400 MHz system with a QNP gradient probe was used.

2.3. GC conditions

Carrier gas: helium (He), 99.9999%.

2.3.1. Split injection mode

Capillary columns: cross-linked 5% phenylmethylsiloxanes: HP-Ultra 2, 25 m × 0.32 mm, 0.52 μm film thickness (GC–FID) and HP-5MS, 30 m × 0.25 mm, 0.25 μm film thickness (GC–MS).

Methylsiloxanes: HP-1, 25 m × 0.32 mm, 0.17 μm film thickness (GC–AED).

Oven temperature profiles: 50 °C for 2 min, 10 °C/min, and 300 °C for 10 min (GC–FID, GC–MS), or 60 °C for 2 min, 20 °C/min, and 300 °C for 20 min (GC–AED).

Inlet:

Temperature 250 °C (GC–FID, GC–MS, GC–AED).
He pressure 70 kPa (GC–FID, GC–MS).

Mode: constant pressure (GC–FID, GC–MS).
Mode: constant flow 4.5 ml/min (GC–AED).
Injection volume: 1 μl (GC–FID, GC–MS, GC–AED).

2.3.2. On-column injection mode

Capillary columns: HP-1, 15 m × 0.53 mm, 0.15 μm film thickness (GC–FID), and HP-5MS, 30 m × 0.25 mm, 0.25 μm film thickness (GC–EI-MS).

Oven temperature profiles: 50 °C for 2 min, 10 °C/min, and 300 °C for 5 min (GC–FID), and 50 °C for 2 min, 10 °C/min, and 300 °C for 10 min (GC–EI-MS).

Inlet:

Temperature: oven track (i.e. oven temperature + 3 °C).
He pressure: 20 kPa (GC–FID), and 80 kPa (GC–EI-MS).

Mode: constant pressure (GC–FID, GC–EI-MS).
Injection volume: 0.5 μl (GC–FID, GC–EI-MS).

2.4. MS acquisition parameters

2.4.1. GC–EI-MS

Mode: full scan.

Temperatures: MS quad 150 °C, MS source 230 °C.
Scan parameters: low mass 25, high mass 550.

2.4.2. GC–CI-MS

Mode: full scan.

Temperatures: MS quad 150 °C, MS source 230 °C.
Scan parameters: low mass 70, high mass 650.

2.5. AED parameters

Cavity temperature: 300 °C.
Reagent gases pressure: O_2 177 kPa, H_2 72 kPa, CH_4/N_2 (1:9) 175 kPa.

Element groups: (1) C monitored at 496 nm and Cl at 479 nm—reagent gas O_2, (2) C at 179 nm and N at 174 nm—reagent gases O_2 and H_2, (3) O at 171 nm—reagent gases H_2 and CH_4/N_2, (4) F at 690 nm—reagent gas H_2.

2.6. Determination of the empirical formula by GC–AED

1,3-Dichloro-5-methoxybenzene was used as a response standard and the calculations were carried out according to the following formula [6]:

$$(E1/E2)u = \frac{(E1/E2)k(\text{Area}\,E1/\text{Area}\,E2)u}{(\text{Area}\,E1/\text{Area}\,E2)k}$$

where ($E1/E2$) is the ratio between number of atoms of respective elements in a molecule, (Area$E1$/Area$E2$) is the peak area ratio, "u" denotes "unknown", and "k" stands for known.

2.7. NMR conditions

^{1}H NMR.
Sixteen scans were accumulated using 1 s relaxation time.

^{13}C NMR.

One thousand and twenty-four scans with 2 s relaxation time.

3. Results and discussion

The chromatogram in Fig. 1 represents a sample from a material obtained during an exploratory attempt to synthesize 1,3-dichloro-5-(difluoromethoxy)benzene. As can be seen, five major components (A–E) were detected by GC–FID instead of a desired single product in high yield. GC–FID and GC–MS analyses with on-column injection resulted in the same chromatographic pattern and relationships between peaks as for split injection, and hence, excluding analytical artefacts caused by the hot GC split inlet. Further investigation was focused on identification of the detected compounds in order to enhance the understanding of the chemistry involved.

3.1. Compounds A and B

Results from GC–EI-MS analysis were straightforward to interpret for compound A and B. The mass spectrum of the target intermediate, 1,3-dichloro-5-(difluoromethoxy)benzene, was known from earlier experiments and corresponded to compound A. Identification of compound B as 1,3-dichloro-5-methoxybenzene was facilitated by the GC–MS library (Enhanced Chemstation, G1701BA, Wiley275) Fig. 2.

3.2. Compounds C and D

The mass spectra of compound C and D were not known from previous experiments nor could the available mass spectral libraries enable identification. The structures of compound C and D could, however, be elucidated by combining spectral information from GC–MS and GC–AED experiments.

3.2.1. GC–MS analysis

GC–EI-MS analysis of compound C produced a mass spectrum containing an ion of the highest *m*/*z* value of 270, which could be the molecular ion (M^+). Furthermore, the EI mass spectrum showed the presence of two chlorine atoms in the structure, and more specific a dichlorophenyl structure (*m*/*z* 145). Additionally, an ion of *m*/*z* 59 most probably formed from a methyl ester group after α-cleavage was

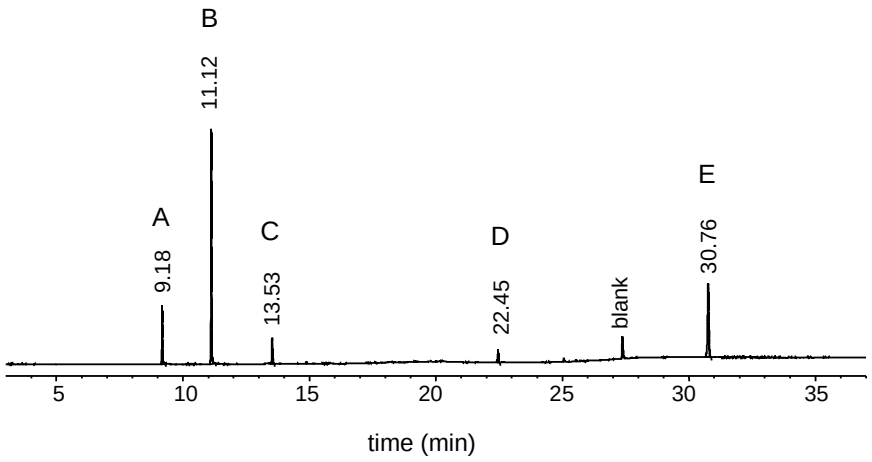

Fig. 1. GC–FID analysis of the sample obtained from the synthesis of 1,3-dichloro-5-(difluoromethoxy)benzene.

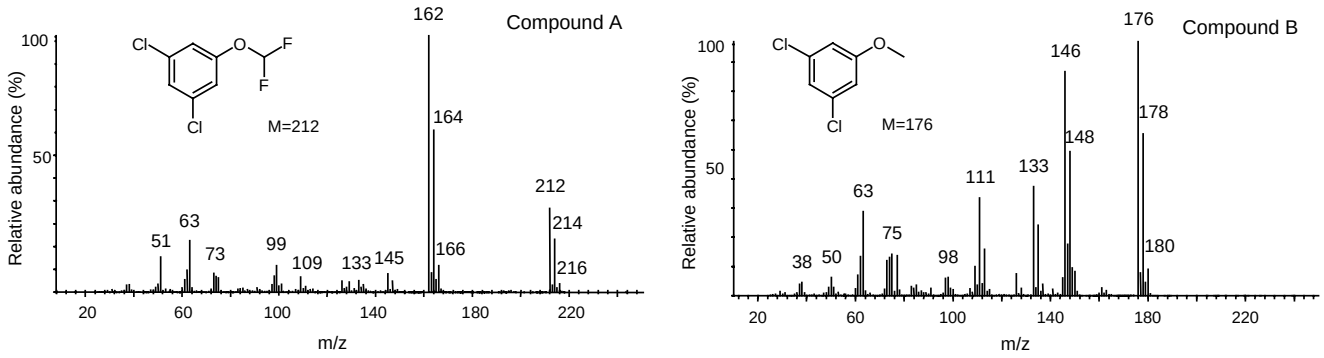

Fig. 2. GC–EI-MS mass spectra of compound A, 1,3-dichloro-5-(difluoromethoxy)benzene and compound B, 1,3-dichloro-5-methoxybenzene, respectively.

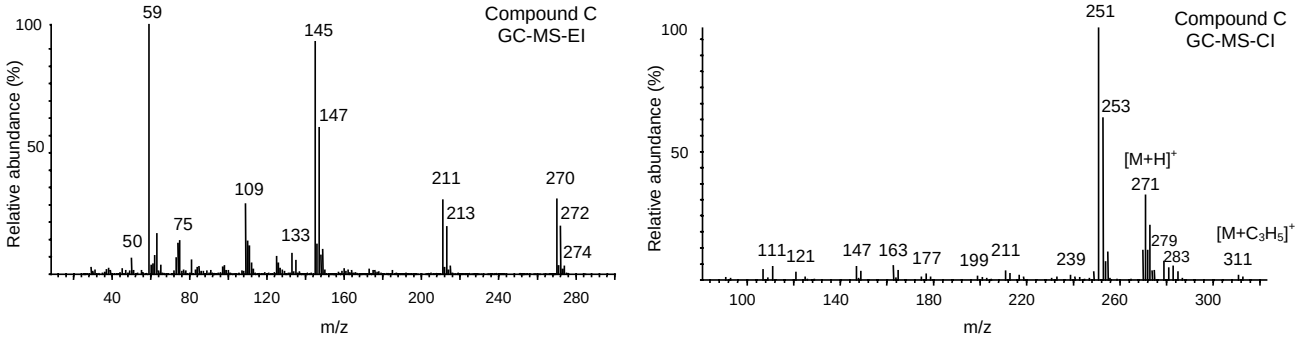

Fig. 3. Mass spectra obtained by GC–MS analysis of compound C.

identified. The ester function could be confirmed by observation of an inductive cleavage of $M-59$ (*m*/*z* 211), which is typical for methyl esters, Fig. 3. The CI mass spectrum contained *m*/*z* 271 $[M+H]^+$, and moreover the expected $[M+C_3H_5]$ or $(M+41)$. The other expected adduct, $[M+C_2H_5]$ or $(M+29)$, was not observed. Nevertheless, it was assumed that the exact mass of this compound was $M = 270$. The CI mass spectrum showed two neutral losses from $(M+41)$. The ion of *m*/*z* 283 was formed after the loss of C=O (*m*/*z* 311 − 283 = 28 u), and the occurrence of *m*/*z* 279 in the spectrum could be most probably explained by the loss of CH_3OH (*m*/*z* 311 − 279 = 32 u). Both fragments strengthened the hypothesis of the proposed methyl ester function in the molecule.

For compound D the exact mass of $M = 354$ suggested by GC–EI-MS, was partially confirmed by the CI mass spectrum with *m*/*z* 355 as $[M+H]^+$. GC–CI-MS analysis showed the formation of an ion *m*/*z* 335 probably indicating the loss of 20 amu from $[M+H]^+$, i.e. possibly neutral loss of HF. In the EI mass spectrum ion cluster *m*/*z* 354, 356, 358 and 360 with intensity pattern characteristic for four chlorine atoms was observed. Moreover, the dichlorophenyl structure (*m*/*z* 145) and another fragment with two chlorine atoms (*m*/*z* 193) were recognised, Fig. 4.

3.2.2. GC–AED analysis

The results from GC–AED analysis (Fig. 5) clearly showed that compound C contained fluorine. GC–AED also confirmed the proposed interpretation of the CI mass spectrum that fluorine occurred also in the structure of compound D. Both compounds contained oxygen, and that supported the finding from GC–MS analysis regarding the methyl ester function in compound C.

3.2.3. Identification of the structures of compounds C and D

By interpretation of results from GC–MS complemented by GC–AED analysis substance C was identified as methyl (3,5-dichlorophenoxy)(difluoro)acetate (Fig. 6). It was assumed that the dichlorophenyl structure had to be adjacent to one oxygen atom (161 u). Moreover, the methyl ester function (59 u) was identified in the molecule. Together those two fragments gave 220 u. Since the exact mass of the compound was $M = 270$, the dichlorophenyloxy fragment had to be linked with the methyl ester group by a fragment of 50 u containing carbon and fluorine, in order to correspond to the GC–AED results. It was concluded that the fragment was CF_2 (i.e. 50 u).

Compound D was identified as 1,3-dichloro-5-[(3,5-dichlorophenoxy)(fluoro)methoxy]benzene (Fig. 6). GC–MS analysis detected a dichlorophenyl structure, and similarly to compound C, assumption was made about the occurrence of a dichlorophenyloxy fragment (161 u). Given that the exact mass was $M = 354$, and there were no distinct peaks in the EI mass spectrum between *m*/*z* 354 and 193, it was proposed that two dichlorophenyloxy fragments were

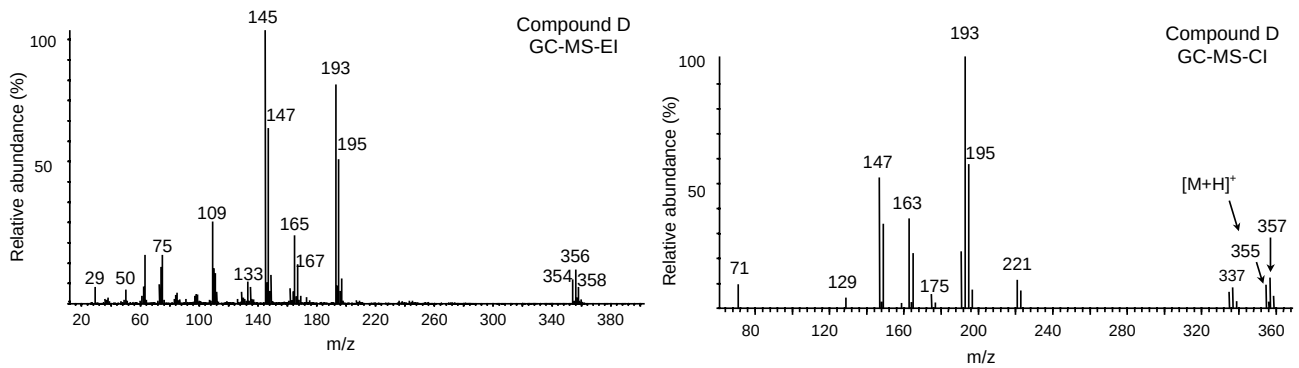

Fig. 4. Mass spectra obtained by GC–MS analysis of compound D.

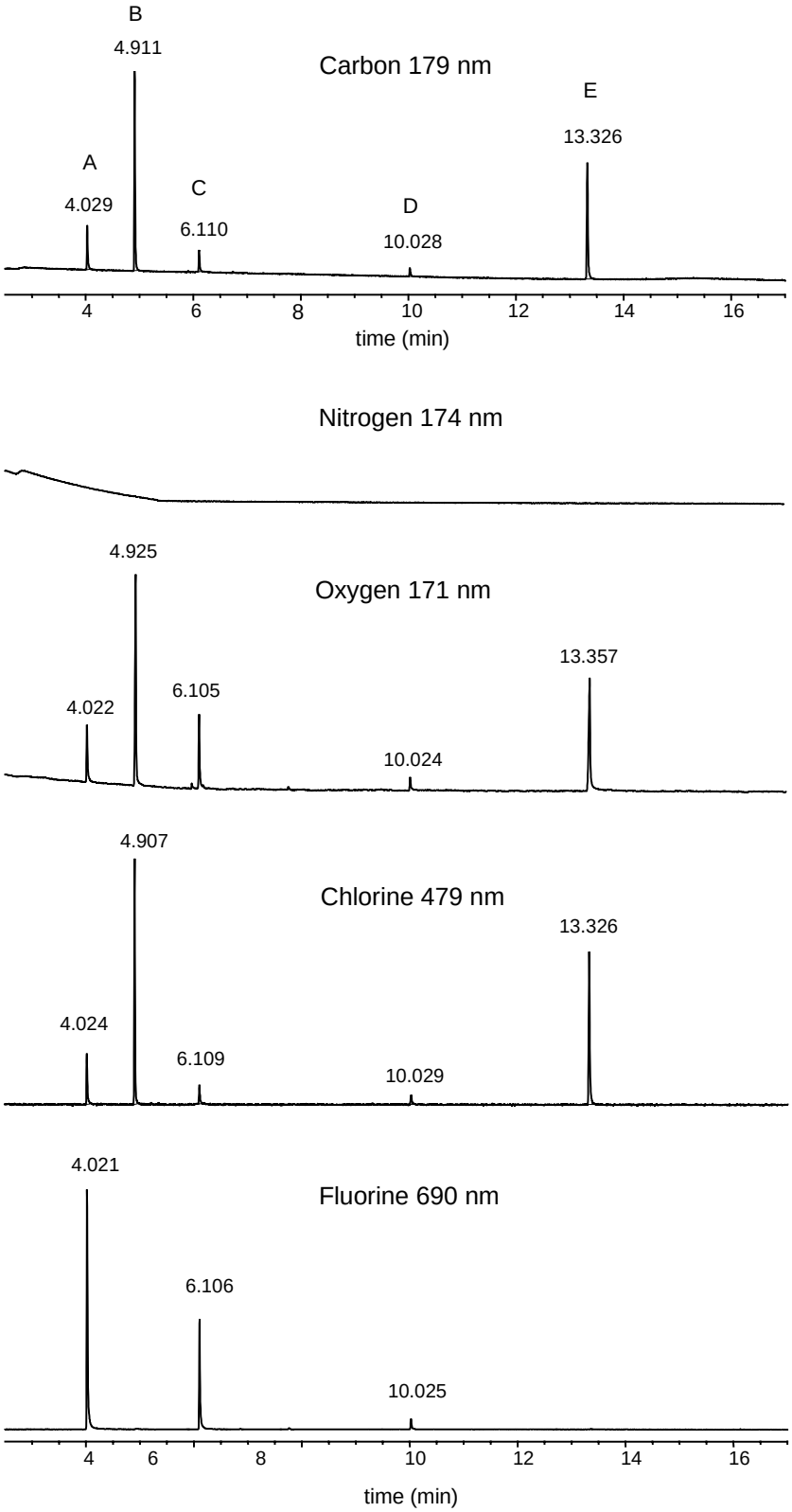

Fig. 5. GC–AED analysis of the sample of 1,3-dichloro-5-(difluoromethoxy)benzene.

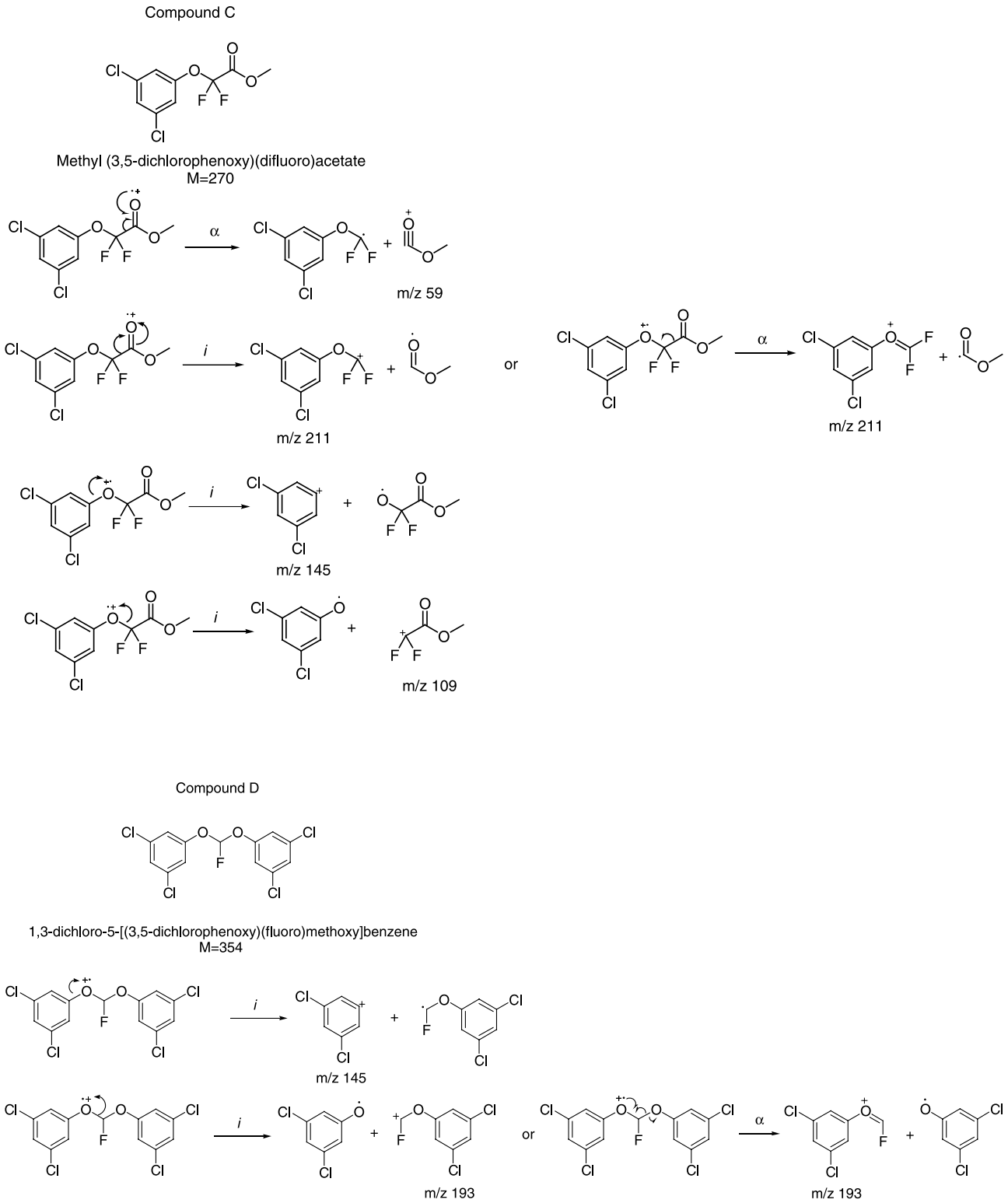

Fig. 6. The structures of compounds C and D, and their fragmentation patterns resulting in predominant peaks in EI and CI mass spectra.

present in the molecule. Hence, the fragment that connected both dichlorophenyloxy fragments was of 32 u. Since, correspondingly to the results from GC–AED analysis, compound D had to contain fluorine, the bonding fragment was resolved as CHF (i.e. 32 u).

3.3. Compound E

The target intermediate and three of the four major unknown impurities detected in the analysed sample were identified using results obtained by GC–MS analysis combined

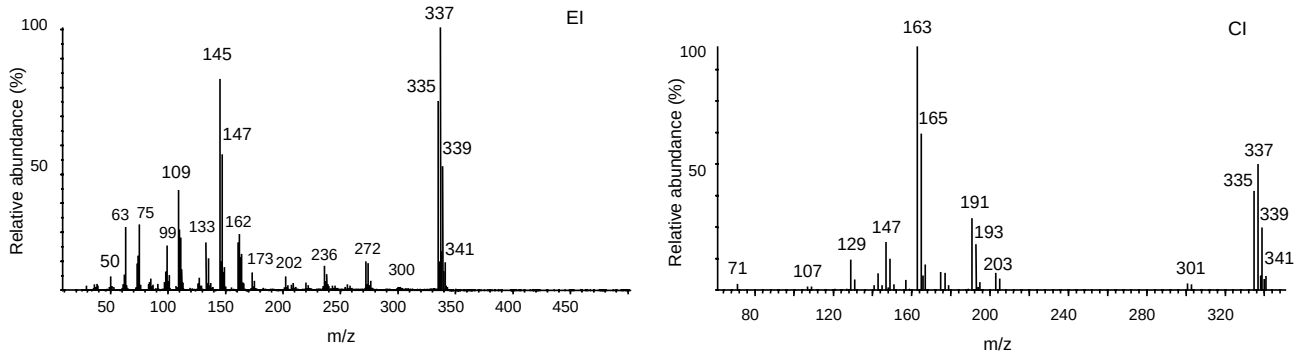

Fig. 7. Mass spectra obtained by GC–MS analysis of compound E. Ion cluster *m/z* 335, 337, 339, 341 and the ratio between the ion intensities are characteristic for four chlorine atoms.

with GC–AED. However, additional investigations were required to identify compound E.

3.3.1. GC–MS analysis

GC–EI-MS analysis suggested that the molecule contained four chlorine atoms and an exact mass of $M = 335$ (Fig. 7). This could indicate the presence of an uneven number of nitrogen atoms in the structure. However, much longer retention time in comparison to compound D ($M = 354$) indicated at this stage of investigation that compound E had to have a higher molecular mass. Similarly to compounds C and D the dichlorophenyl fragment (*m/z* 145) was formed during GC–EI-MS analysis. For determination of the exact mass the sample was analysed by GC–CI-MS. In the CI mass spectrum the cluster *m/z* 335, 337, 339, and 341 was observed as the ions of highest mass, Fig. 7. This observation, that even mild ionisation conditions caused fragmentation of the molecule and produced the same ions of highest mass as during electron impact ionisation, showed that the results of GC–MS analysis could not provide information regarding the molecular weight of the unknown compound.

3.3.2. GC–AED analysis

GC–AED was employed to study the elemental composition, and the results showed that no nitrogen or fluorine was present in the structure, Fig. 5. It was also shown that the molecule contained oxygen. The dichlorophenyl structure and the presence of oxygen could again indicate that the unknown compound E contained a dichlorophenyloxy group. This assumption was strengthened by additional interpretation of GC–EI-MS analysis, where the ion *m/z* 162, probably caused by formation of $[C_6H_3Cl_2OH]^+$, was observed. The next step was to determine a partial empirical formula by compound independent calibration (CIC). Since the AED response can sometimes be dependent on the molecular structure it is recommended to use structurally related substances for that purpose. The presence of a dichlorophenyloxy group and the absence of fluorine in the structure of compound E justified use of 1,3-dichloro-5-methoxybenzene as a response standard for CIC calculations. In Table 1 possible empirical formulae based on the outcome of the CIC experiment are shown.

The exact masses of the partial empirical formulae I and II were too low and these formulae were therefore ruled out. Partial empirical formula V was on the other hand considered having too high exact mass, taking the GC retention time of compound E into account. Consequently, all those three proposals were not further considered.

The number of chlorine atoms in formulae III and IV could suggest three dichlorophenyl units, and, moreover, three oxygen atoms could imply three dichlorophenyloxy units. In both cases the number of carbon atoms in the aromatic rings were eighteen leaving one carbon atom in formula III, and C_4Cl in formula IV, unaccounted for, respectively. Considering three substituted dichlorobenzene groups, the number of hydrogen atoms in formula III had to be at least nine. That led to the exact mass of $M = 495$ ($C_{19}H_9Cl_6O_3$), but the mass could not be uneven since the GC–AED analysis showed no presence of nitrogen. Hence, at least one more hydrogen atom was needed giving an empirical formula of $C_{19}H_{10}Cl_6O_3$, corresponding to an exact mass $M = 496$. For formula IV with nine hydrogen atoms in three rings the partial empirical formula is $C_{22}H_9Cl_7O_3$, resulting in an even exact mass of $M = 566$. However, there were still four carbon atoms not incorporated in aromatic rings, and therefore the molecule should contain at least a few more hydrogen atoms. Even though the empirical formula was not exactly determined it was concluded that the molecular mass of the compound E was around 500 u up to 600 u, and the number of hydrogen atoms was about 10–15.

3.3.3. NMR analysis

At this stage of the investigation it was concluded that the structure of compound E could not be finally identified using GC–MS and GC–AED data alone. It was found that compound E conveniently could be isolated by precipitation upon dissolving the sample in dichloromethane and

Table 1
Partial empirical formula determination of compound E using 1,3-dichloro-5-methoxybenzene as a response standard in the GC–AED analysis

Compound	Empirical formula	Retention time (min)	Peak area		
			C 179	Cl 479	O 171
1,3-Dichloro-5-methoxybenzene	$C_7H_6Cl_2O$	4.9	37.3	41.9	2.5
Compound E	?	13.3	30.6	37.4	2.0
			C/Cl	Cl/O	C/O
Peak area ratio					
1,3-Dichloro-5-methoxybenzene			0.89	16.8	14.9
Compound E			0.81	18.7	15.3
Number of atom ratio					
1,3-Dichloro-5-methoxybenzene			3.5	2.0	7.0
Compound E (calculated)			3.2	2.2	7.2
Possible number of atom ratio[a]					
1			12.8:4	4:1.8	12.8:1.8
2			16.0:5	5:2.3	16.0:2.2
3			19.2:6	6:2.7	19.2:2.7
4			22.4:7	7:3.2	22.4:3.1
5			25.6:8	8:3.6	25.6:3.6
Theoretically possible partial empirical formulae					
I			$C_{13}Cl_4O_2$		Exact mass 328
II			$C_{16}Cl_5O_2$		Exact mass 399
III			$C_{19}Cl_6O_3$		Exact mass 486
IV			$C_{22}Cl_7O_3$		Exact mass 557
V			$C_{26}Cl_8O_4$		Exact mass 656

[a] The number of chlorine atoms had to be at least four (GC–MS), and the highest number was considered as eight because of the molecular weight.

washing with acetonitrile. GC–MS analysis of the isolated material showed that the sample comprised mainly one component, the unknown impurity E. Thus, to complement MS and AED data the isolated compound E was analysed by NMR.

The results obtained by ^{1}H and ^{13}C NMR are presented in Fig. 8 and Table 2.

The signals in the ^{1}H NMR spectrum corresponded to ten hydrogen atoms and of those nine were in aromatic structures. These results supported the postulate of the occurrence of dichlorophenyl moieties in the molecule. The ^{1}H NMR detected two groups of aromatic hydrogens with six and three protons in, respectively. Since in the dichlorophenyl structure there are two different groups of hydrogens having one and two atoms, respectively, the ^{1}H NMR analysis provided the evidence that compound E comprised of three dichlorophenyl structures. Since all proton signals were singlets, it was evident that the substitution pattern in the benzene rings was 1,3,5. The total number of ten hydrogen atoms excluded the partial empirical formula IV from the GC–AED analysis. At this stage it was apparent that the most probable correct empirical formula was $C_{19}H_{10}Cl_6O_3$, and the exact mass $M = 496$. Both ^{1}H and ^{13}C NMR analysis showed a CH group adjacent to several oxygen atoms.

3.3.4. Identification of the structure of compound E

Very few signals in the NMR spectra together with a relatively high molecular mass of the compound clearly

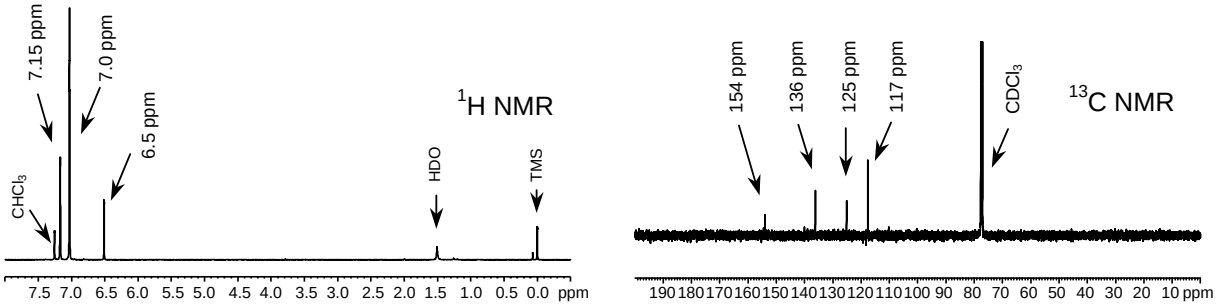

Fig. 8. ^{1}H and ^{13}C NMR spectra of the unknown impurity.

Table 2
Results of the NMR analysis of the unknown compound isolated from the sample of 1,3-dichloro-5-(difluoromethoxy) benzene

Shift (ppm)	Integral	Interpretation
^{1}H spectrum		
6.5	1 (s)	H adjacent to several O, or Ar–H, no neighbouring H; 1 proton
7.0	5.8 (s)	Ar–H, no neighbouring H; 6 protons
7.15	2.8 (s)	Ar–H, no neighbouring H; 3 protons
^{13}C spectrum		
117		C–H adjacent to several O and Ar–C
125		Ar–C
136		Ar–C
154		Ar–C substituted
C–H one-bond correlation		
H-shift	Coupled to	
6.5	117	CH adjacent to several O; 1 proton
7.0	125	Ar–CH; 6 protons
7.15	136	Ar–CH; 3 protons

indicated that the structure of the unknown compound E was symmetric. Therefore, it was evident that three dichlorophenyl groups had to be connected with each other by a structure of CHO_3. GC–MS results indicated the presence of dichlorophenyloxy groups, and GC–AED suggested an empirical formula containing three oxygen atoms. Therefore, it was presumed that three dichlorophenyloxy units are present in the unknown structure, and that they are bonded by the CH group. Moreover, due to the fact that all signals in the ^{1}H NMR spectrum were singlets, it was concluded that benzene rings were substituted in positions 1,3,5.

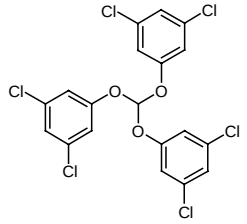

Fig. 9. The proposed structure of compound E.

Interpretation of all the results obtained by GC–MS, GC–AED and NMR enabled a proposal of the structure for compound E as 1-[bis(3,5-dichlorophenoxy)methoxy]-3,5-dichlorobenzene, Fig. 9.

The fragmentation to the dominant ion cluster, which was observed in GC–EI-MS analysis, was apparently due to α-cleavage (α) or inductive cleavage (i) according to the mechanism shown in Fig. 10.

3.4. Verification of the identity of the resolved structures D and E

In order to verify the identity of the structures of compounds D and E a survey of the literature on fluorine chemistry was performed [13]. Based on this a reaction mechanism for the formation of both identified by-products could be proposed, Fig. 11.

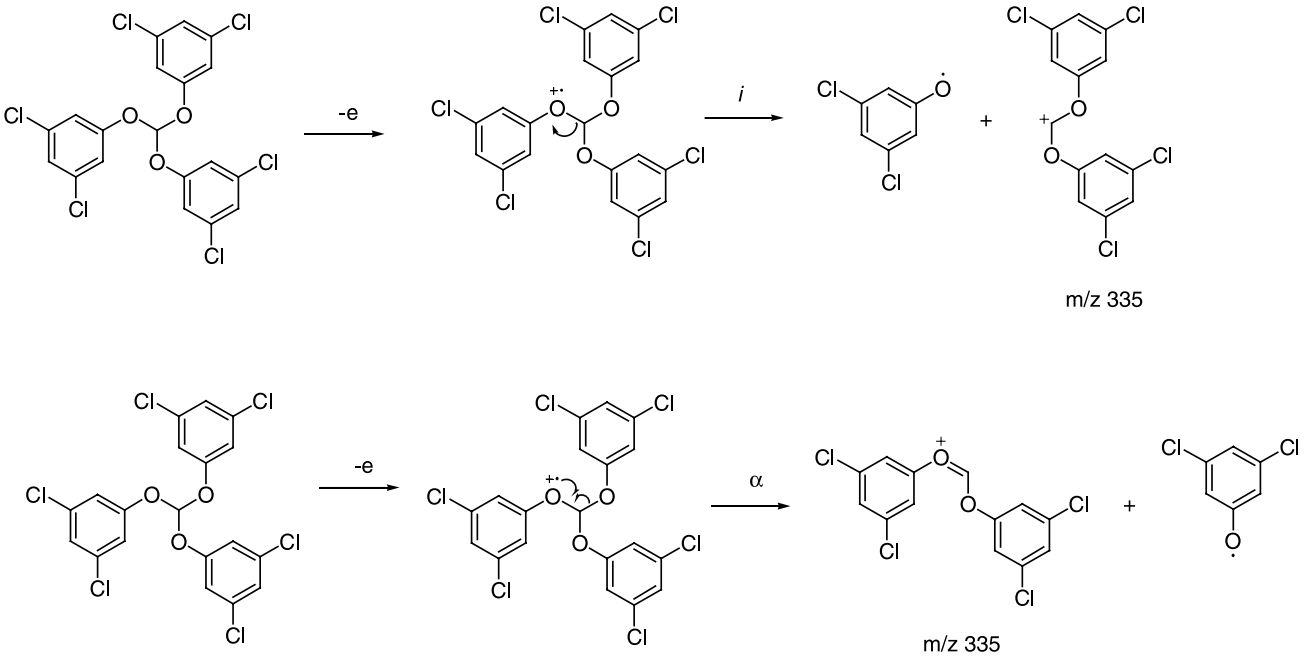

Fig. 10. Fragmentation pattern of compound E, yielding the predominant ion cluster, *m/z* 335, 337, 339 and 341, in the EI mass spectrum.

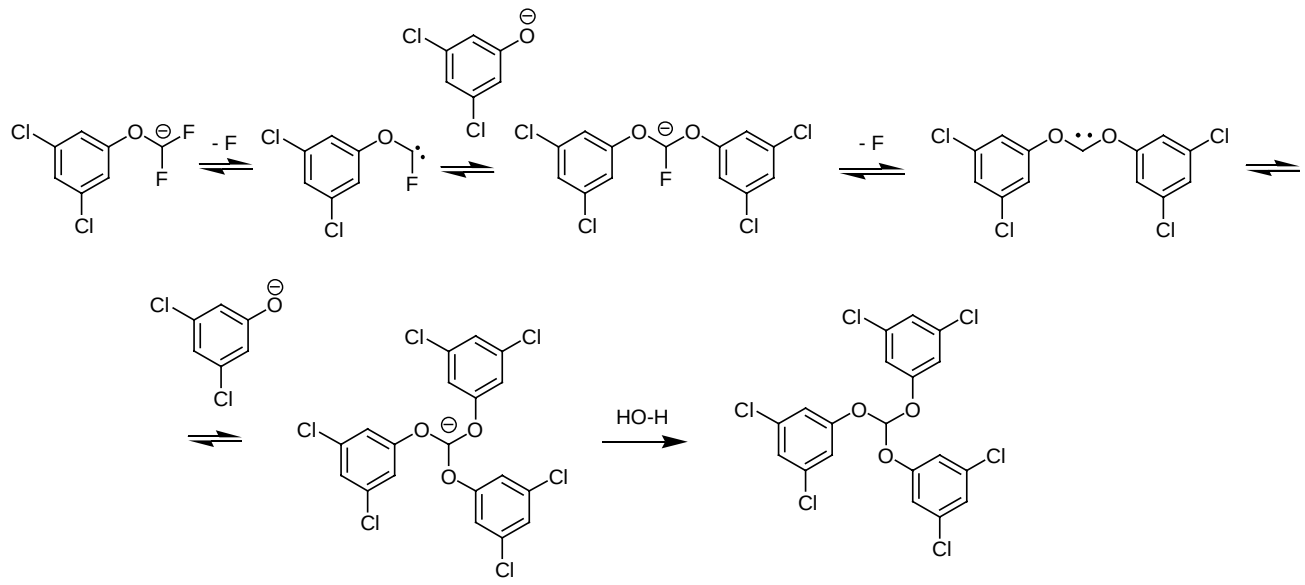

Fig. 11. Reaction mechanism for the formation of compounds D and E.

4. Conclusions

The complementary use of GC–MS, GC–AED and NMR data for efficient structure elucidation of unknown pharmaceutically related impurities has been demonstrated. GC–MS analyses provided structural information and molecular mass of the investigated compounds. GC–AED analysis showed the occurrence of heteroatoms and gave information about elemental composition of the detected compounds. Furthermore, GC–AED results confirmed findings from GC–MS analyses regarding structural fragments of the unknown compounds and, therefore enabled proposal of resolved structures. NMR supported results from GC–MS and GC–AED by providing the evidence for substitution pattern in the benzene rings of one unknown substance and showing the symmetric character of the molecule.

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