Begala Michela (Orcid ID: 0000-0002-8213-2335)

Unexpected detection of 3-aroylbenzofuran side products in the preparation of 2-arylbenzofurans: identification, characterization and comparison with chalcone's fragmentation patterns using EI/MS^n

Michela Begala* **and Giovanna Lucia Delogu**

Department of Life and Environmental Sciences, Unit of Drug Sciences, University of Cagliari, via Ospedale 72, 09124 Cagliari, Italy

*Correspondence to Michela Begala, Department of Life and Environmental Sciences, University of Cagliari, via Ospedale 72, 09124 Cagliari, Italy. Email: michelabegala@unica.it

Running title: unexpected $[M-H]^+$ and $[M-OH]^+$ from 3-aroyl-2-arylbenzofurans

Abstract

A gas chromatography-mass spectrometry study of the intramolecular Wittig reaction revealed, together with the expected 2-phenylbenzofuran, the formation of an unexpected side product that has not been reported until now. This study reports the identification of the by-product, *i.e.* the 3-benzoyl-2-phenylbenzofuran, on the base of its mass spectrometric behaviour using a combination of electron ionization (EI), exact mass measurement, multiple stage mass spectrometry and labelled compounds. This study reports the common fragmentation pathways and discusses possible fragment structures of characteristic ions from a series of 3-aroyl-2-arylbenzofuran derivatives obtained as by-product under Wittig conditions. Emphasis is laid on the formation and structure investigation of the $[M-H]^+$ and $[M-OH]^+$ ions. Our results showed interesting analogies with the mass spectrometric behavior of chalcones.

KEYWORDS
Intramolecular Wittig reaction, 3-aroylbenzofurans, MS^n, $[M-OH]^+$, chalcone-like fragmentations

1 INTRODUCTION

2-Phenyl[*b*]benzofurans serve as core structures of many natural and artificial compounds of biological and medical importance.[1] In the course of a program directed towards the synthesis of novel monoamine oxidase (MAO) and butyrylcholinesterase (BChE) inhibitors,[2,3] we planned to synthesize 2-phenylbenzofurans using an intramolecular Wittig procedure due to the accessibility and simplicity of this methodology.[4,5] In particular, compounds **4a-g** were prepared from the appropriate triphenylphosphonium salt **2** and the commercially available aroyl chlorides **3a-g** (Scheme 1).

The reaction mixtures were analysed by gas chromatography coupled with mass spectrometry because the reaction products are susceptible to analysis by GC for their volatility and thermal stability. However, while developing this procedure, GC/MS analysis of the reaction mixture, obtained from the salt **2** and the benzoyl chloride **3a**, revealed that, together with the desired product of cyclization **4a**, the unexpected side-product **5a** was present. The same trend was observed in the crude reaction mixtures of the main products **4b-g**, obtained from the reaction of **2** with a variety of aroyl chlorides (**3b-g**). Although the Wittig reaction has been described in several papers regarding the preparation of 2-arylbenzofuran derivatives, the formation of secondary products was not mentioned.[4,5]

Identification of unknown peaks is useful to permit discovery of novel or unexpected reaction products and play an important role in comprehending the reaction mechanism by which this reaction evolves. However, isolation and purification of sufficiently large quantities of by-product compounds for their unambiguous identification and characterization by different instrumental techniques, such as infrared spectroscopy (IR) and nuclear magnetic resonance (NMR), is a very complex and time-consuming process. Nowadays, GC-MS coupled to multiple stage mass spectrometry (MS^n) is an invaluable tool for the rapid identification and structural characterization of unknown compounds, especially when low amount of analyte or not very pure samples are available for the analysis. Hence, we have undertaken a detailed investigation on the unknown side products aimed to identify their structure and to elucidate their mass spectrometric behaviour. To this aim, EI-MS^n experiments were performed using a quadrupole ion trap analyser (IT) as it is a very efficient multiple-stage mass spectrometers.[6]

2 EXPERIMENTAL

2.1 MS analysis

All experiments were performed with a Varian Saturn 2000 ion trap mass spectrometer (ITMS), operating under EI conditions (electron energy 70 eV, emission current 20 mA, ion-trap temperature 200°C, manifold temperature 80°C, automatic gain control (AGC) target 21.000) with the ion trap operating in scan mode (scan range from m/z 40-400 at a scan rate of 1 scan/s), coupled with a Varian 3800 gas chromatograph (Varian, Walnut Creek, CA).

Collision-induced dissociations (CIDs) experiments were carried out by using helium as the collision gas (gas purity (He) was 99.9999%). For MS^n experiments the supplementary rf voltage (45-55V) was varied in such a way that the relative abundance of the surviving precursor ions was 5-15 %. An isolation time of 10 msec, excitation time of 40 msec and an isolation width of 3 *m/z* for the precursor ion were used. Each MS/MS spectrum was an average of 5 scans.

Compounds **5a-g** (1 μL aliquots of 1.0 x 10^{-5} M solutions in dichloromethane) were introduced into the gas chromatographer inlet. An Agilent J&W VF-5ms Low-bleed/MS GC capillary column (30 m, 0.25 mm i.d., 0.25 mm film thickness) (Agilent Technologies Inc., Wilmington, DE, USA) was used. The oven temperature was programmed from 150°C (held for 2 min) to 310°C at 30°C/min (held for 2 min). The temperature was then ramped to 350 at

20°C/min. The transfer line was maintained at 180°C and the injector port (30:1 split) at 290°C.

HRMS: MS analyses were performed on a Agilent 6520 LC-ESI(+)-QTOF-MS operated in the positive ion mode. Compounds (1 mg) were dissolved in acetonitrile (CH_3CN, 0.5 ml) and after injection mass spectral data were acquired in the range *m/z* of 100-1,500 with an acquisition rate of 1.35 spectra/s, averaging 10,000 transients. The source parameters were adjusted as follows: drying gas temperature 250 °C, drying gas flow rate 5 L/min, nebulizer pressure 45 psi, and fragmentor voltage 150 V.

2.2 Materials and reagents

All reagents and solvents were purchased from Sigma-Aldrich (Sigma-Aldrich Srl, Milan, Italy) and Alfa Aesar (Thermo Fisher, Kandel, Germany) and used without further purification.

Compounds **4a** and **5a** were obtained by 2-benzyloxy-benzyl triphenyl phosphomium bromide **2** (1.1 mmol) and benzoyl chlorides (1.1 mmol) in the presence of Et_3N in toluene using the Wittig methodology described by Hercouet and Le Corre.[4,5] Compounds **4b-g** and **5b-g** were prepared using an adaptation of this procedure.[7]

2-(Hydroxyldideuterium-methyl) phenol **1*d*₂** was prepared starting from the methyl 2-hydroxybenzoate in THF at 0ºC using lithium aluminum deuteride, as described in literature.[8]

The reference compound 3-benzoyl-2-phenyl-benzofuran was prepared by direct Friedel-Craft acylation of the 2-phenylbenzofuran **4a** with benzoyl chloride using $AlCl_3$ as Lewis acid in anhydrous dichloromethane.[9]

3-Benzoyl-2-phenyl-d_5-benzofuran **5ad_5** was synthesized in the same way as 3-benzoyl-2-phenyl-benzofuran starting from 2-phenylbenzofuran-d_5 **4a*d*₅**.

2-Phenylbenzofuran-d_5 **4a*d*5** and 3-benzoyl-d_5-2-phenyl-d_5-benzofuran **5a*d*10** were prepared starting from 2-benzyloxy-benzyl triphenyl phosphomium bromide **2** and benzoyl chloride-d_5 in toluene and Et_3N using the procedure reported elsewhere.[7]

3-Phenyl-4H-chromen-4-one **6** (isoflavone) was prepared by Suzuki-Miyaura Cross-Coupling of 3-iodochromone with benzenboronic acid catalyzed by Pd(0)/C.[10,11]

3 RESULTS AND DISCUSSION

3.1 Identification of the by-product 5a

A typical gas chromatogram of the reaction mixture from the triphenylphosphonium salt of 2-hydroxybenzyl alcohol and the benzoyl chloride is presented in Figure 1. As can be seen, together with the desired 2-phenylbenzofuran **4a** (T_R 9.2 min) and the triphenylposphine oxide (T_R 12.5 min), one further peak is present at higher retention time (T_R 12.6 min), corresponding to the unexpected product **5a**.

By comparing the data obtained from the EI mass spectra of compounds **4a** and **5a** (Figure 1 and Figure 2A), it was enabled to define which part of the molecule of 2-phenylbenzofuran **4a** was also present in the structure of the unknown compound **5a**. In particularly, we focused our attention on the diagnostic ion at *m/z* 193 in the mass spectrum of **5a** (Figure 2A). This ion most likely corresponds to the intact 2-phenylbenzofuran molecule deprived of a H atom. In fact, under MS/MS experiments *m/z* 193 exhibits the loss of CO typical of the benzofuran nucleus to give the ion at *m/z* 165, which is also observed in the EI and MS/MS mass spectra of the 2-phenylbenzofuran **4a** ($M^{+\cdot}$ *m/z* 194).[12-14] As the sum of *m/z* value of the fragment ions at *m/z* 193 and *m/z* 105, absent in the mass spectrum of **4a**, is equal to *m/z* $M^{+\cdot}$ (*m/z* 298), these two ions could be complementary ions, representing two parts of the molecule; the rest of the structure was determined by comparison of the data achieved from the identification of the ion at *m/z* 105, with that from accurate mass measurement of the unknown compound **5a**.

Under CID experiments, the *m/z* 105 ion decomposes into ions at *m/z* 77 and 51 thus indicating the presence of a benzoyl group (C_6H_5CO) in the structure of **5a**.[15] Accordingly, accurate mass measurement for the side product **5a** reveals a $C_{21}H_{14}O_2$ (calc. 299.1066 exp. 299.1066) composition, showing that the mass difference between **5a** and the 2-phenylbenzofuran **4a** ($C_{14}H_{10}O$) was in seven carbon atoms, four hydrogen atoms and one oxygen (104 Da) suggesting the addition of a benzoyl group to the main product **4a**.

Even more, when the reaction was performed using the labeled benzoyl chloride-d_5 **3a*d*₅** in place of the benzoyl chloride **3a**, we found that the molecular ion shifted from *m/z* 298, for compound **5a**, to *m/z* 308, for the labeled compound **5a*d*₁₀**, thus confirming that two molecules of the labeled acyl chloride contribute to the structure of the side product (Figure 2B). The general structure of acylated 2-phenylbenzofuran was than proposed for the unknown compound **5a**.

The position of the acyl group was then investigated using the 2-hydroxybenzyl alcohol-d_2 **1*d*₂** as starting reagent. The Wittig reaction so performed, leads to the unlabelled acyl benzofuran **5a** at *m/z* 298. These data clearly show the lack of methine hydrogen in the furan ring of compound **5a**, thus demonstrating that the benzoyl group is attached to the C-3 position of the benzofuran nucleus. Our results indicate, therefore, that the side products **5a** most likely have the 3-aroylbenzofuran structure depicted in Scheme 1. The model 3-benzoyl-2-phenylbenzofuran was prepared by Friedel-Craft acylation of the 2-phenylbenzofuran **4a** and was analysed by MS, as a final confirmation of the proposed structure for **5a**. A detailed study aimed to provide a much deeper insight into the reaction mechanism that lead to the 3-aroyl derivative have been reported elsewhere.[7]

These findings are of particular interest since the 3-aroyl-2-arylbenzofuran scaffold constitutes the core of many pharmaceutical drug candidates such as amiodarone,[16] LY 320135,[17] benzbromarone [18] and SKF-64346.[19] Moreover, from synthetic viewpoint this procedure represents a new regioselective and versatile synthetic approach to 3-acyl derivatives.[7] However, to the best of our knowledge, mass spectrometric investigation of 3-aroylbenzofurans has received only little attention with most of the emphasis devoted to the plasma and urine detection of few biologically active compounds *i.e.* amiodarone, benziodarone, desethylamiodarone[20,21] and benzbromarone.[22]

A detailed study dealing with the fragmentation of aroyl benzofurans have also appeared, however it only covered the ESI MS/MS behavior of 2-aroyl derivatives.[23]

Therefore, as a material for further investigations, we present a systematic and detailed study on the EI induced fragmentation of 3-benzoyl-2-phenylbenzofurans. To this aim, we selected several ring substituted 3-acyl derivatives obtained by our procedure, and subjected them to EI MS^n experiments using an IT mass spectrometer.

3.2 Fragmentation typical for 3-aroyl-2-arylbenzofurans

The EI mass spectra of compounds **5a-g** are depicted in Table 1. We divided the structure into three parts: the benzofuran scaffold, the aryl group (ring A) and the aroyl group (ring B) (See Scheme 2 referred to compound **5a**, Ar = C_6H_5). Two sets of acylium ions were observed resulting from the two competing α-cleavages next to the carbonyl group, *i.e.* the $[M\text{-}Ar]^+$ ions ***a*** and the $ArC{=}O^+$ ions ***b***. Both type of acylium ions under MS/MS conditions undergo the typical loss of CO to generate, respectively, the 2-phenylbenzofuran fragment ions ***c*** (complementary to ion ***b***) and the phenylium ions ***d*** (complementary to ion ***a***) which, therefore, allow an easy identification of the original intact molecule (*vide supra*). The only exception to this trend was observed for the nitro derivatives **5b**. Under CID experiments, each of the acylium ions from **5b**, *i.e.* the $[M\text{-}Ar]^+$ ion of *m/z* 266 and the 4-nitrobenzoylcation of *m/z* 150, does not show the direct losses of CO. Instead, they both form characteristic fragment ions at *m/z* 236 and 220 and at *m/z* 120 and 104, respectively, due to the losses of $NO^{\cdot}$ and of $NO_2^{\cdot}$, which only subsequently lose CO molecule (See supplementary material).[24]

We also examined how the intensity of ions ***b*** is influenced by substituents on rings B or by heteroaromatic rings, for instance furyl and thienyl moieties. Concerning compounds **5b-e**, we found that the intensity of the acylium ions ***b*** is strongly influenced by the nature of the substituent on the benzoyl group (Table 1). In the mass spectrum of compound **5e**, bearing the methoxy group on the ring B, the *p*-methoxybenzoyl cation (*m/z* 135) is particularly intense (relative abundance, R.A. 36%). This behavior can be explained with the ability of the *p*-methoxy group to exert resonance stabilization of the *p*-methoxybenzoyl cation. The mass spectra of the heteroaryl compounds **5f** and **5g** exhibit the $ArC{=}O^+$ ions rather intense (R.A. 44 and 37%) reasonably because the 2-furyl and 2-thienyl substituents have electronic effect comparable with that of *p*-anisyl group, well recognized as an overall electron-donating system.

In the case of compounds **5b-d** bearing electron withdrawing groups, NO_2, CN and CF_3, the formation of the $ArC{=}O^+$ ions is strongly suppressed (R.A. 4-16%) in favor of the $[M\text{-}Ar]^+$ ions (R.A. 34-63%). Moreover, the stronger the electron-withdrawing effect on the ring B, the lower is the relative abundance of the benzoyl cation ***b***.

The $[M\text{-}Ar]^+$ acylium ions ***a*** constitute the most prominent fragment ions in the mass spectra of all compounds (R.A. 34-66%), with the only exception of compounds **5e-g**, for which the formation of ion ***b*** is the most favored process (*vide supra*). A possible representations of the $[M\text{-}Ar]^+$ ions is the resonance-stabilized oxonium structure ***j*** depicted in Scheme 2, which could account for the high intensities observed. We therefore thought of interest to compare the CID mass spectrum of the $[M\text{-}Ar]^+$ ions from **5a** with that of the oxonium ion at *m/z* 221 formed in the EI mass spectrum of isoflavone **6** (*m/z* 222),[25] used as reference ion (Figure 3). As can be seen, the CID mass spectra are very similar, proving that the cyclization to structure ***j*** occurs to some extents. There is, however, a difference in the relative intensity of the *m/z* 193 ion. This ion that we assign to the CO loss, is more abundant for the compound **5a** (45% *vs* 4%). These data can be rationalized by the fact that part of the *m/z* 221 ions population of **5a** posses the open structure ***a***, which undergoes easier this fragmentation.

In addition to the α-cleavages, characteristic for carbonyl compounds, some further interesting losses were observed under EI-MS and MS/MS experiments *i.e.* the losses of $H^{\cdot}$ and of $OH^{\cdot}$ radicals from the molecular ion.

3.3 Elimination of a hydrogen radical

The EI mass spectra of the 3-benzoyl-benzofurans **5a-e** show intense $[M\text{-}H]^{+}$ ions (Table 1). In the MS/MS spectra the $H^{\cdot}$ loss was even more pronounced (Figure 4). Only for compounds **5b** and **5e**, the $H^{\cdot}$ loss occurred together with the loss of the substituent or of part of it as they show the total loss of 47 and 16 amu from the molecular ion. We suggest that the first step is the loss of a hydrogen atom and that $NO_2^{\cdot}$ or $CH_3^{\cdot}$ are lost from the even-electron ion so formed. Thus, the high abundant ions at *m/z* 341 and *m/z* 342 were attributed to the $[M\text{-}H\text{-}NO_2]^{+\cdot}$ and the $[M\text{-}H\text{-}CH_3]^{+\cdot}$ for compounds **5b** and **5e**, respectively (Figure 4B and 4E).

To get insight into the structure of the $[M\text{-}H]^{+}$ specie, we first investigated the origin of the $H^{\cdot}$ lost. To this aim the MS/MS spectrum of the unsubstituted compound **5a** (*m/z* 298. Figure 4A) was compared with that of its deuterium labelled analogue **5a*d*₁₀** (rings A and B = C_6D_5; *m/z* 308. Figure 2C). Under this condition **5a** formed the stable ion at *m/z* 297, with a R.A. of 100%. The loss of 2 amu (*m/z* 306) from the molecular ion of the labelled derivatives **5a*d*₁₀** (*m/z* 308), clearly indicates that the source of the $H^{\cdot}$ eliminated is the phenyl group in position 2 (ring A) and/or the aroyl group in position 3 (ring B). MS/MS experiments on the 3-benzoyl-2-phenyl-*d*₅-benzofuran **5a*d*₅** (Figure 5B), has helped to further elucidate the origin of the $H^{\cdot}$ loss. Under MS^2 experiments the molecular ion of the labelled derivative **5ad_5** (ring A = C_6D_5; *m/z* 303) shows the preferential loss of deuterium radical from the ring A (*m/z* 301 RA 100%), rather than the loss of $H^{\cdot}$ from the benzoyl group (ring B; *m/z* 302 R.A. 25%). This result indicates that the former process requires less energy than the latter and consequently is more favoured. In fact, MS^n experiments performed using an ion trap, privilege processes with the lowest critical energies.[26] Accordingly, a different trend was observed in the full scan EI mass spectrum of **5ad_5**, which displayed the ions at *m/z* 302 and 301 with similar intensities (R.A. 29 and 34%. Figure 5A).

We supposed that the driving force for the loss of the aromatic hydrogen radical preferentially from ring A, lay in the formation of a highly resonance-stabilized ion, *i.e.* the oxonium ion ***k*** reported in Scheme 3. A possible mechanism consists in an intramolecular aromatic substitution reaction; this might occur through the interaction of the carbonyl group with the $2^{'}$ position of the phenyl ring A to form a six membered ring and consequent hydrogen radical loss, that would result in restoration of aromaticity to ring A. Analogous rearrangement process was also postulated to occur by Ronayne[27] and co-workers and by Van de Sande[28] and co-workers for chalcones and led to the formation of an oxonium ion. In fact, 3-benzoyl-2-phenylbenzofurans can be considered as benzofuran-chalcones hybrids where the C2-C3 double bond of the benzofuran nucleus fixes in the *cis* disposition the chalcones-type double bond (bold part of the ions in Scheme 3). It must be point out that the aromatic oxonium ion ***k*** could further rearrange to the structure $\boldsymbol{k_1}$, as demonstrated to occur in chalcones and 3-flavene by Traldi and co-workers.[29] Unfortunately, unlike chalcones, CID experiments on the $[M-H]^+$ ion lead to the losses of $CHO^{\cdot}$ and CO that agree with both structures ***k*** and $\boldsymbol{k_1}$.

3.4 Elimination of hydroxyl radical. 3-Aroyl-2-aylbenzofurans *vs* calchones

All compounds under investigation exhibit unusual and fairly small [M-17] peaks (Table 1). With the only exception of compounds **5a**, **5c** and **5d**, this behavior is somewhat increased in intensity under MS/MS conditions (R.A. 2-30%. Figure 4). The deuterium labeling results using the simplest 3-benzoyl-benzofuran **5a** indicate that a deuterium was involved in this process. As can be seen, in the mass spectrum the deuterated analogue **5a**d_{10} (Figure 2B), ions at *m/z* 281 shifted to *m/z* 290 reflecting the loss of OD$^{\cdot}$ from the molecular ion. The most reasonable inference is that the oxygen involved in the OH$^{\cdot}$ loss arises from the carbonyl group. In fact, compounds **5a**, as well as compounds **5f** and **5g**, have no additional substituents, which could themselves produce [M-OH]$^+$ ion. To the best of our knowledge, only few papers have been reported on the involvement of a carbonyl oxygen atom in the formation of dehydroxylated ions. Bowie and White described the formation of [M-H$_2$O]$^{+\cdot}$ and [M-OH]$^+$ ions in the mass spectra of aromatic carbonyl compounds which contain an *ortho* (or *peri*) methoxy-substituent.[30] More recently, Zenchevich and Pushkareva reported that compounds bearing -CO-CH=CH-N(CH$_3$)$_2$ structural fragments exhibit unusual peaks of [M-OH]$^+$ ions formed by a rearrangement with the migration of a hydrogen atom.[31]

To get insight into the mechanism of formation of the [M-OH]$^+$ ion, further experiments were performed on the labeled compound **5a**d_5. In the MS/MS mass spectrum of **5a**d_5 the formation of ion at *m/z* 285 [M-OD]$^+$ clearly indicates that the hydrogen lost derives from ring A (Figure 5B).

One of the possible mechanisms rationalizing these results is reported in Scheme 4. The carbonyl undergoes loss of a hydroxyl radical after abstraction of the hydrogen from ring A by McLafferty type rearrangement;[32] the ionic species so generated is plausibly represented as the ion with the structure ***y***, which contains a new five-membered ring.

In the case of *p*-nitro-derivative **5b**, some considerations have to be done. Compound **5b** has two nitro groups in the *para* positions of ring-A and B, respectively, which may be themselves involved in a M-OH process. The OH· loss is commonly observed in nitro-aromatic derivatives, due to an *ortho* effect.[33-37] However, the proximity effect described in these studies occurs between aromatic nitro function and a group in its proximity *i.e.* in *ortho* or *peri* positions, and, therefore, appears unlikely for *p*-nitro-compound **5b** where the distances between the NO_2 substituents and the phenyl rings are rather much greater.

Interestingly, Baldas and Porter[38] reported that the spectra of 3- and 4-nitrocalchones display the loss of hydroxyl radical, and that this fragmentation is initiated by the transfer of a hydrogen atom from the 2-position of the phenyl ring to the nitro group *via* a cyclized intermediate.

Considering the striking analogy between chalcone and **5a** (*vide supra*), we expected, for *p*-NO_2 derivative **5b**, a similar mechanism to that reported for nitrochalcones,[38] that involves the nitro group rather than the carbonyl. A chalcone-like mechanism was therefore proposed for compound **5b** (Scheme 5).

This behavior is in agreement with the collisional experiments performed on compound **5b** (Figure 6). Under MS^3 experiments the $[M\text{-}OH]^+$ ion (*m/z* 371) loses NO· to form the *m/z* 341. MS^4 experiments reveal that the *m/z* 341 ion fragments by the loss of a nitro radical (*m/z* 295) and of NO· (*m/z* 311). However, the sequential loses of NO· and NO_2· from the $[M\text{-}OH]^+$ ion is also consistent with the mechanism that involves the carbonyl group (Scheme 4), which, therefore, cannot be ruled out for the nitro derivative **5b**.

4 CONCLUSIONS

Electron ionization and collision induced dissociation tandem mass spectrometry have proved to be highly effective for a complete structure assignment of 3-benzoyl-2-phenylbenzofuran, a side product formed in the preparation of 2-phenylbenzofurans under Wittig conditions.

Our study showed that beside the alfa cleavages typical of carbonyl compounds, the unusual losses of $H^{\cdot}$ and of $OH^{\cdot}$ constitute diagnostic fragmentations. These losses were attributed to the interaction between the carbonyl of the 3-acyl group and the 2-phenyl ring, thus reflecting their proximity in the structure of the benzofuran nucleus. We also evidenced that 3-aroyl-2-aylbenzofurans can be considered as benzofuran-calchones hybrids and that their EI fragmentation routes have strong similarities compared with those of chalcones. However, some differences were also underlined. In particular, we found that the $OH^{\cdot}$ loss from the molecular ion of 3-aroyl-2-arylbenzofurans, involves the carbonyl group in position 3. Only nitro-chalcones were reported to show the $[M-OH]^+$ ion, and it was suggested that the source of the $OH^{\cdot}$ loss was exclusively the nitro group. In the case of the analogous 3-benzoyl-2-phenylbenzofuran derivatives bearing the NO_2 group, MS^n experiments demonstrated that a nitro-chalcone-like mechanism cannot be excluded.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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Table 1. EI (70 eV) mass spectra of compounds **5a-g**

	5a	**5a**d_{10}	**5a**d_5	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**
$M^{+\cdot}$	298 (100)	308 (100)	303 (100)	388 (100)	348 (100)	434 (100)	358 (100)	278 (100)	310 (100)
$[M\text{-}H]^+$	297 (53)	307(20)	302 (29)	387 (18)	347 (40)	433 (44)	357 (2)	277 (3)	309 (6)
$[M\text{-}D]^+$		306 (44)	301 (34)						
$[M\text{-}CH_3]^+$							343 (5)		
$[M\text{-}H\text{-}CH_3]^{+\cdot}$							342 (10)		
$[M\text{-}OH]^+$	281 (5)			371 (5)	331 (2)	417 (3)	341 (4)	261 (5)	293 (5)
$[M\text{-}OD]^+$		290 (4)	285 (3)						
$[M\text{-}F]^+$						415 (7)			
$[M\text{-}CO]^{+\cdot}$								250 (55)	282 (9)
$[M\text{-}NO]^+$				358 (5)					281 (6)
$[M\text{-}SH]^+$									277 (18)
$[M\text{-}CH_3\text{-}CO]^+$							315 (5)		
$[M\text{-}H\text{-}NO_2]^{+\cdot}$				341 (17)					
$[M\text{-}CO\text{-}CHO]^+$								221 (55)	
$[M\text{-}CF_3]^+$						365 (12)			
$[M\text{-}Ar]^+$ **a**	221 (56)	226 (66)	226 (62)	266 (34)	246 (54)	289 (63)	251 (14)	211 (7)	227 (11)
[**a**-CO]$^+$ **c**	193 (5)	198 (5)	198 (3)	-	218 (2)	261 (2)	223 (3)	183 (2)	199 (2)
[**a**-NO]$^{+\cdot}$				236 (20)					
[**a**-CH_3CO]$^{+\cdot}$							208 (4)		
[**a**-NO_2]$^{+\cdot}$				220 (5)					
[**c**-CO]$^+$	165 (20)	170 (21)	170 (20)	-	190 (15)	233 (8)	195 (9)	155 (12)	171 (6)
$ArCO^+$ **b**	105 (24)		105 (25)	150 (4)	130 (12)	173 (16)	135 (36)	95 (44)	111 (37)
$C_6D_5CO^+$ **b**		110 (25)							
[**b**-CO]$^+$ **d**	77 (31)	82 (37)	77 (38)	-	102 (20)	145 (19)	107 (13)	67 (2)	83 (7)
[**b**-NO]$^{+\cdot}$				120 (7)					
[**b**-NO_2]$^{+\cdot}$				104 (5)					

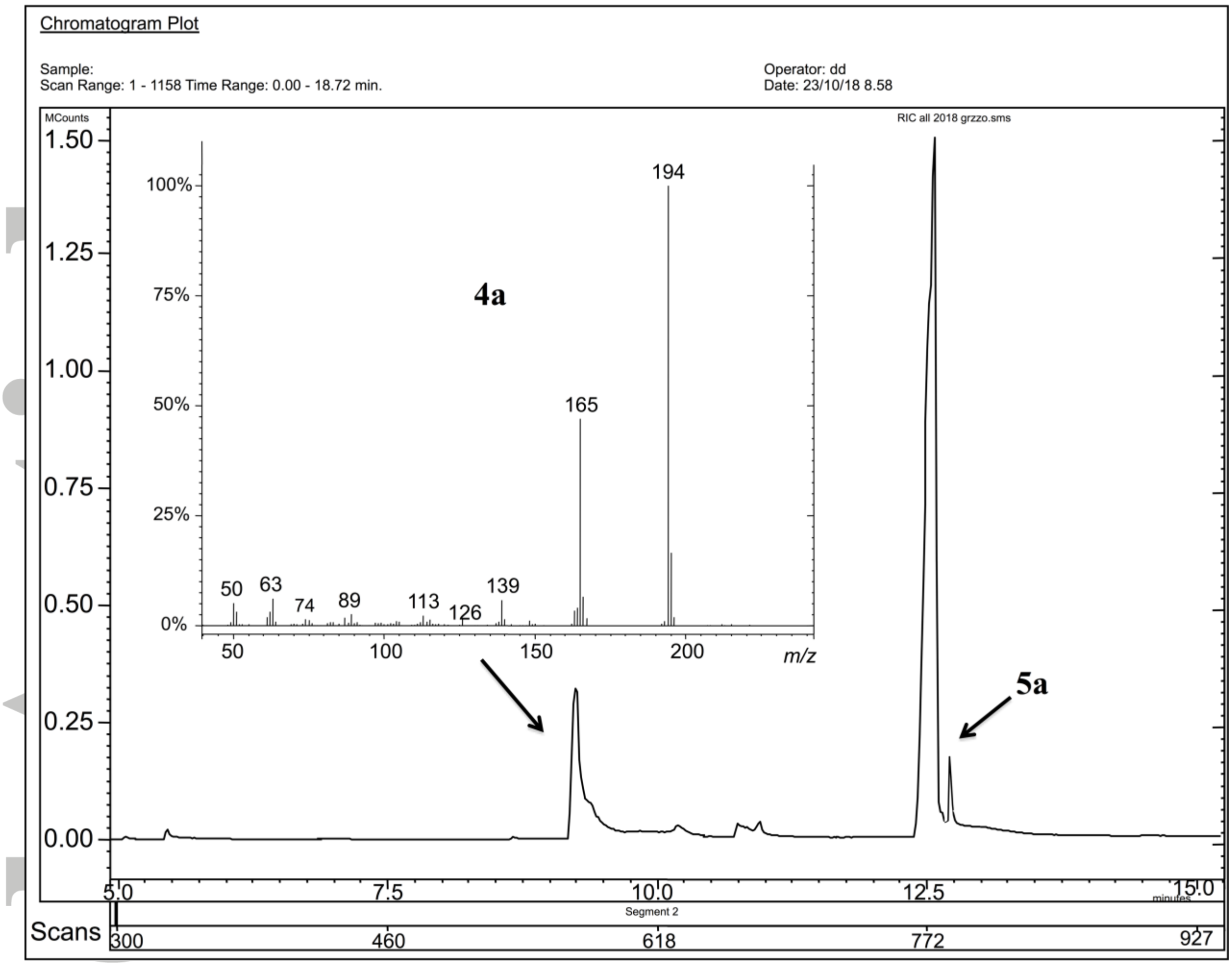


Figure 1. GC-MS analysis of the reaction mixture along with the mass spectrum of the 2-phenylbenzofurane **4a** (9.36 min)

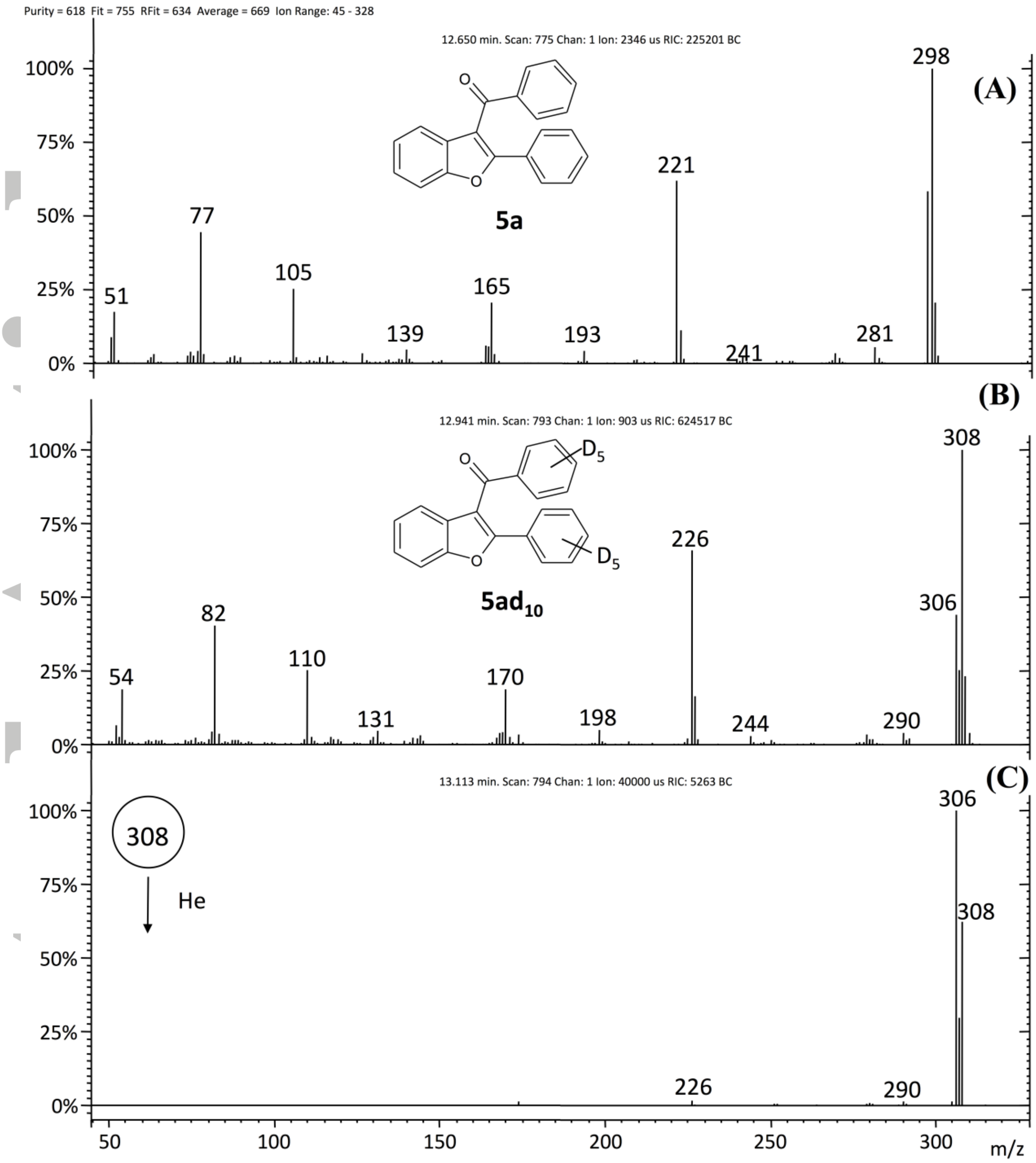


Figure 2. EI mass spectra of compounds A) **5a** (*m/z* 298) and B) the labelled **5a*d*10** (*m/z* 308). C) CID of **5a*d*10**

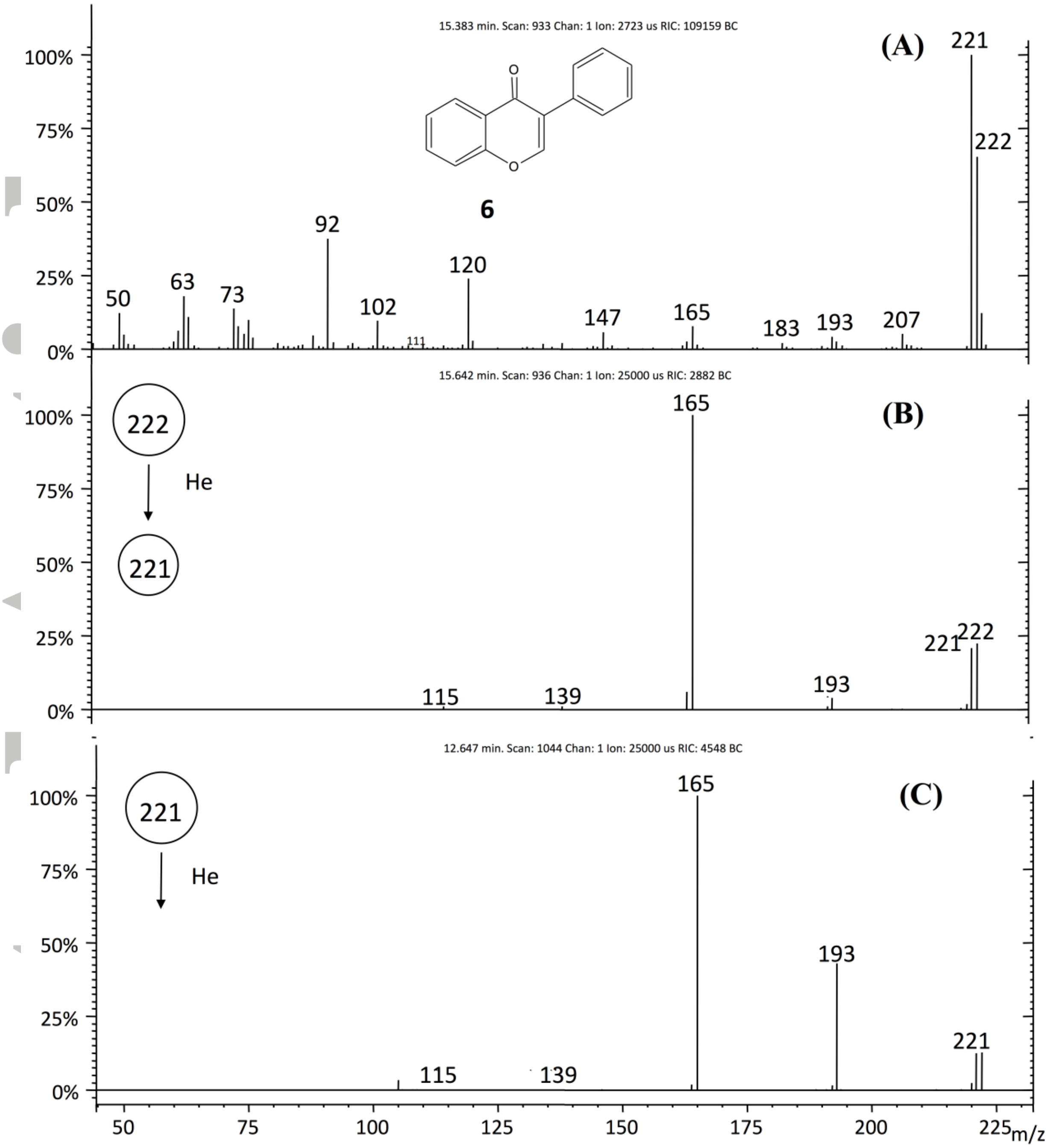


Figure 3. A) EI mass spectrum of isoflavone **6.** CID of the *m/z* 221 ions of B) isoflavone **6** and C) compound **5a**

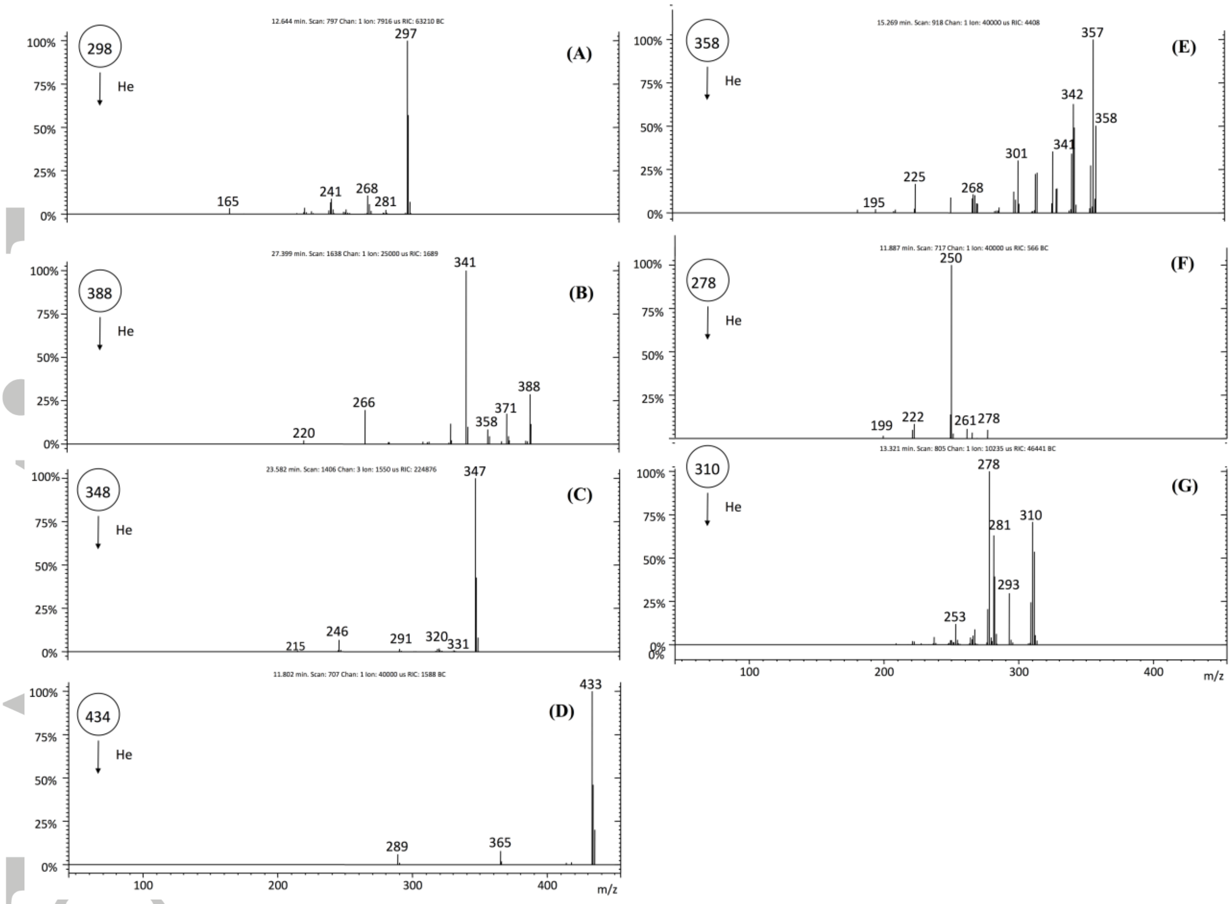


Figure 4. MS/MS of compunds **5a-g**. A) MS^2 of **5a** (*m/z* 298); (B) MS^2 of **5b** (*m/z* 388); (C) MS^2 of **5c** (*m/z* 348); (D) MS^2 of **5d** (*m/z* 434); (E) MS^2 of **5e** (*m/z* 358); (F) MS^2 of **5f** (*m/z* 278); (G) MS^2 of **5g** (*m/z* 310)

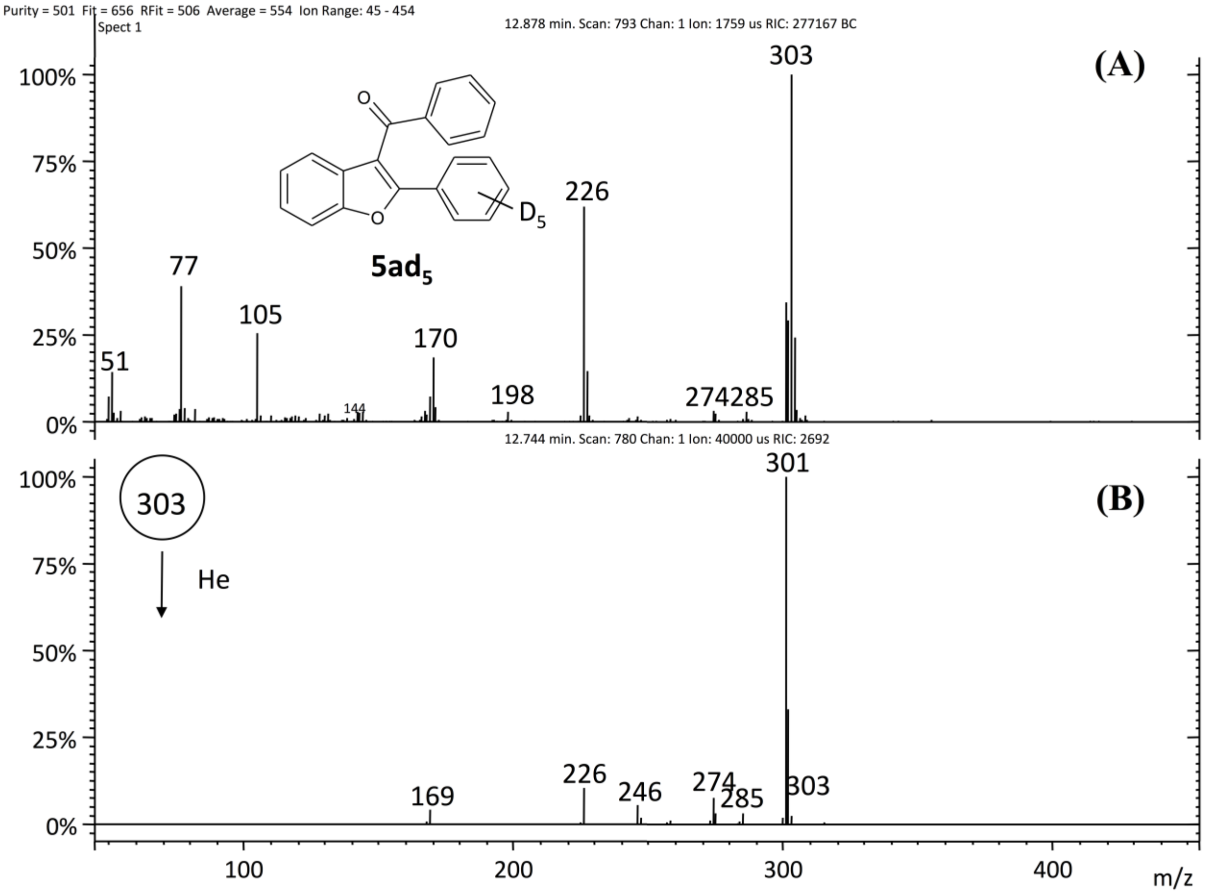


Figure 5. (A) MS^2 and (B) MS/MS of compound **5a*d*$_5$** (*m/z* 303)

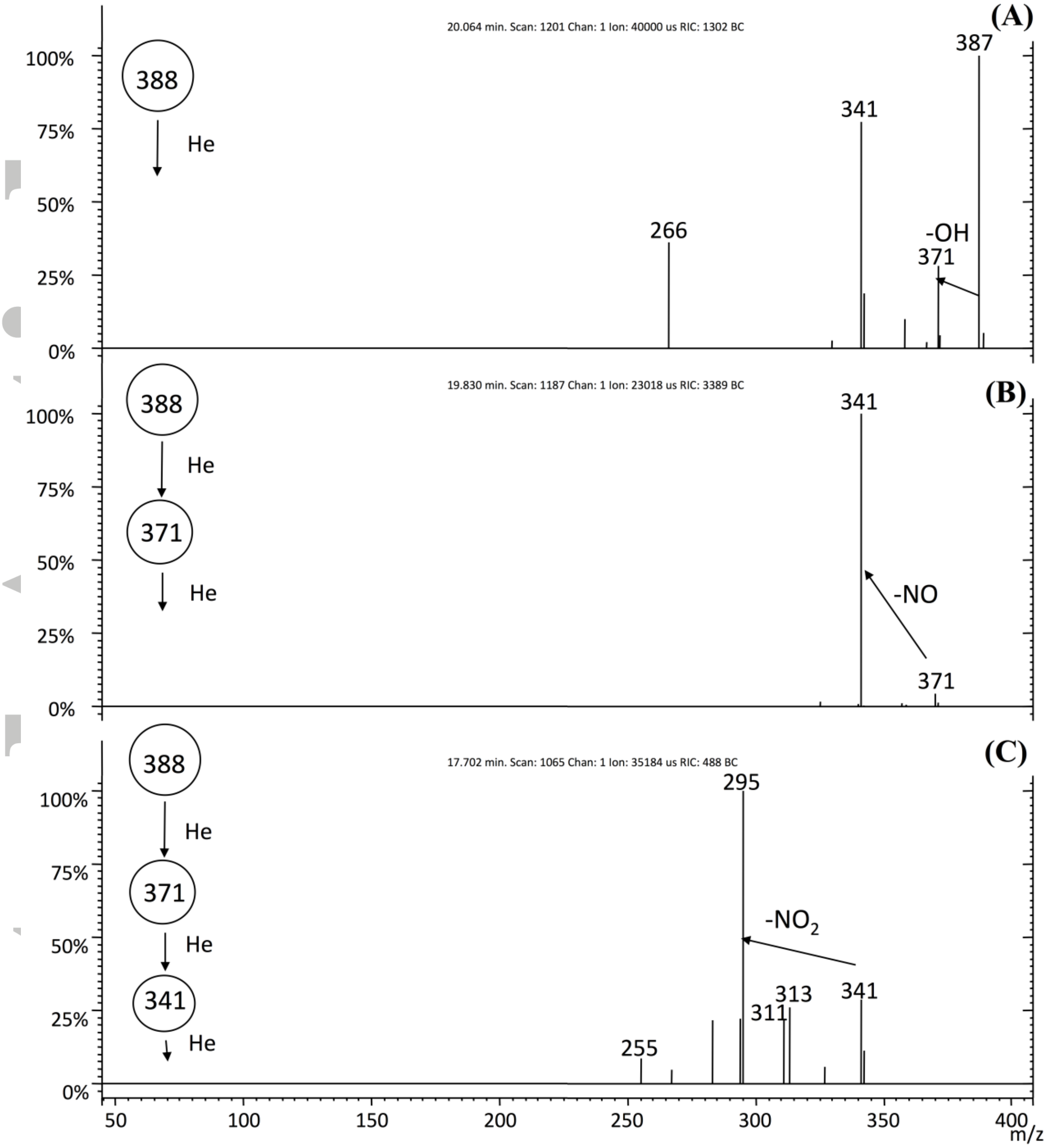
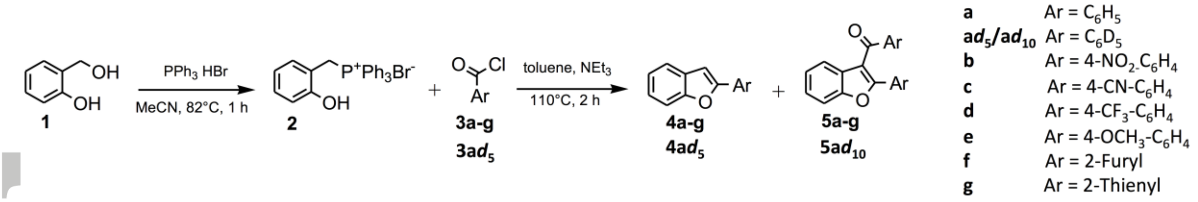
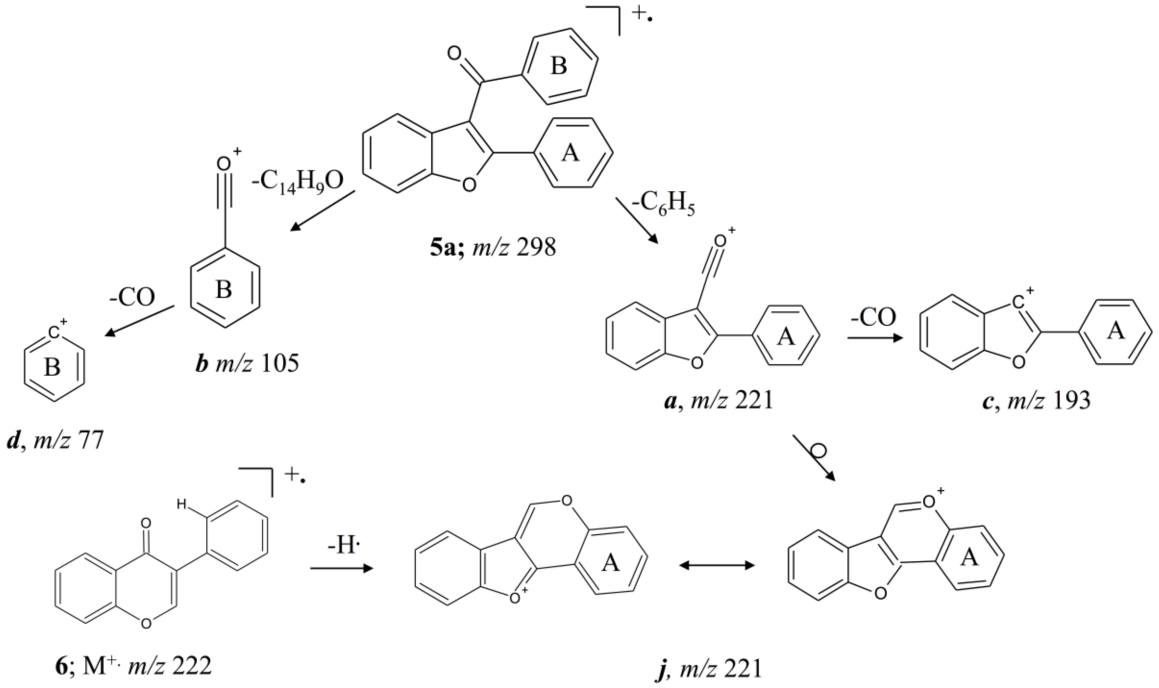


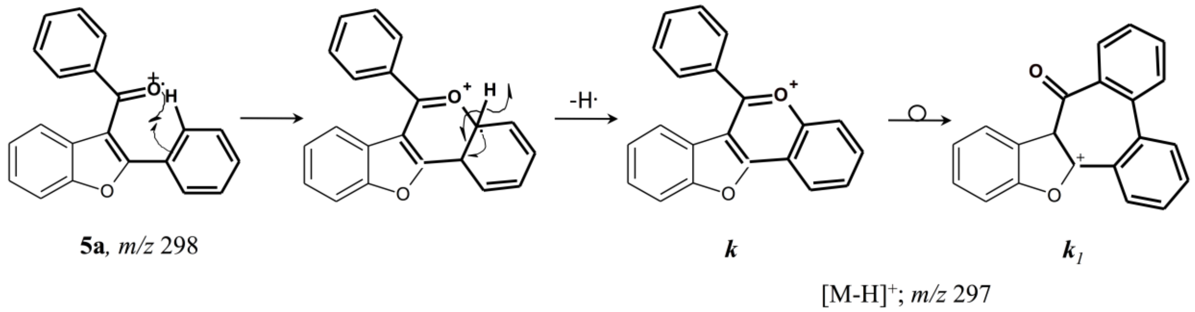
Figure 6. A) MS^2, B) MS^3 and C) MS^4 of the M$^+$. ion of compound **5c** (*m/z* 388)



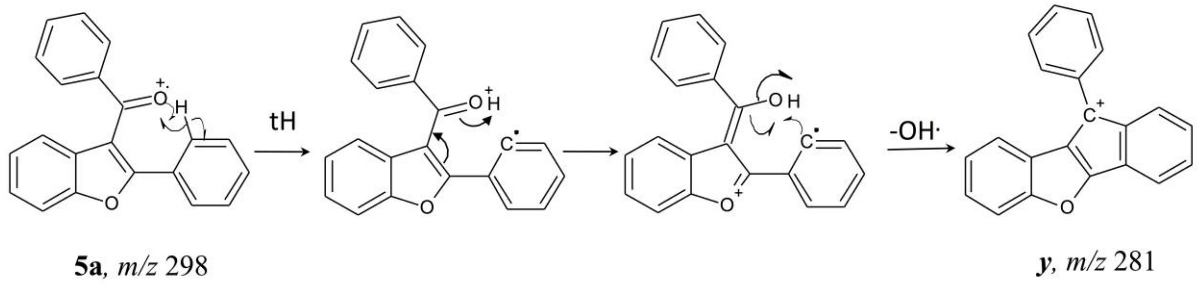
Scheme 1. Synthetic route towards 2-phenylbenzofurans **4a-g** and 3-benzoyl-2-phenylbenzofurans **5a-g**



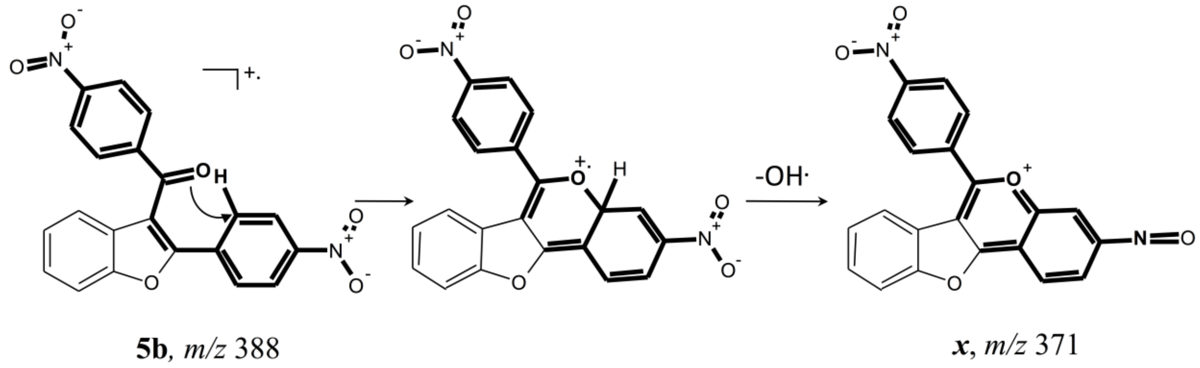
Scheme 2. Main proposed fragmentation pathways for compound **5a** on the basis of MS^2 and MS^3 spectra. Possible structures for ions at *m/z* 221



Scheme 3. Proposed mechanism of radical H. loss from compound **5a** and similarity with chalcone (bold part of the structures)



Scheme 4. Proposed mechanism of OH. loss for **5a**



Scheme 5. Chalcones-like mechanism of OH. loss for 3-benzoyl-2-phenylbenzofurans (benzofuran–calchones hybrids)