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# Identification of photodegradation product of amisulpride by ultra-high-pressure liquid chromatography–DAD/ESI-quadrupole time-of-flight-mass spectrometry

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ABSTRACT

Photostability of amisulpride under UVA irradiation in methanol solution was investigated and structural elucidation of its photodegradation products was performed. For the purpose of the quantitative and qualitative analysis of amisulpride and the stress degradation products elucidation, the reversed phase UHPLC–DAD system coupled with accurate mass hybrid ESI-Q-TOF mass spectrometer was used. During one run (10 min) with the use of auto MS/MS mode all essential data for the determination of photodegradation kinetics and for the structural formulas elucidation of the products was collected. Four degradation products were found and their masses with high accuracy (0.53–3.05 ppm) and formulas were obtained – 258.0666 ($C_{10}H_{14}N_2O_4S$), 367.1564 ($C_{17}H_{25}N_3O_4S$), 341.1412 ($C_{15}H_{23}N_3O_4S$) and 385.1665 ($C_{17}H_{27}N_3O_5S$). For all the analyzed compounds MS/MS fragmentation spectra were obtained (collision energy 19.8–26.1 V) allowing structural elucidation of unknown degradation products and indicating photodegradation pathways of amisulpride. UHPLC–DAD/ESI-Q-TOF system was found to be a powerful analytical tool for the fast and accurate stability analysis of pharmaceutical substances.



## 1. Introduction

Amisulpride (4-amino-N-[(1-ethylpyrrolidin-2-yl)methyl]-5-ethylsulfonyl-2-methoxy-benzamide) is an atypical antipsychotic drug whose pharmacological activity is based on the selective binding to D2 and D3 dopaminergic receptors. This drug is characterized by a lower risk of extrapiramidal side-effects (EPS) and relatively better toleration than conventional antipsychotic drugs. Nowadays, amisulpride is first of all used for the treatment of different kinds of schizophrenia [1], as well as in a low dose it can be used for the treatment of depression patients [2,3]. The newest research informs that amisulpride can also be used in the therapy of chronic fatigue syndrome (CFS) [4].

Photostability testing is an integral part of the stability study of the drugs and today it must be considered during the development and registration process of pharmaceutical products [5–7]. Photodegradation of the drugs is a very important subject of investigation because this kind of a process can result in the loss of the activity of the drug and also in adverse effects due to the formation of toxic degradation products. The knowledge what exactly is formed from the drug during this process can be very useful for the manufacturing, storage and administration of pharmaceuticals and may significantly improve the safety of therapy [8,9].

In literature data there are many papers concerning the analysis of amisulpride in biological materials [10–23] and pharmaceuticals [23,24] with the use of various methods: LC [11–20,24], TLC [24], CE [24], spectrophotometric [24], MS [21,22], RIA [10] and voltametric [23]. Nevertheless, there is no paper describing the stability study including the photostability of amisulpride and also the ultra-high-pressure liquid chromatography method and hybrid Q-TOF mass spectrometer were not used for the analysis of this drug so far.

Taking into account the above fact and our previous work [24] where it was observed during the method validation process that amisulpride is very labile under UV 254 nm radiation (UVC), that is necessary to carry out the photostability study of this substance. Taking into consideration the second fact that most of the published papers concerning the photostability investigation of the drugs required using at least a few analytical methods (LC, GC, MS, spectrophotometry, IR, etc.) [25–27] simultaneously in order to obtain satisfactory results, the aim of this work was to develop a simple, fast and accurate method enabling the whole photostability analysis during one run. For this purpose a new analytical method with the use of new generation hybrid MS/MS spectrometer combined with UHPLC–DAD including powerful auto MS/MS functions and algorithms was developed.

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## 2. Experimental

### 2.1. Materials

Amisulpride was kindly supplied by Synthelabo Groupe, Quetigny, France. Methanol hypergrade for LC–MS and 98% formic acid p.a. were purchased from Merck (Darmstadt, Germany). Water for GC and LC was obtained from Honeywell Burdick & Jackson (Muskegon, USA).

Amisulpride solution for photodegradation tests (at concentration $2.4 \times 10^{-5}$ M) was prepared in hypergrade methanol.

### 2.2. Photodegradation conditions

Amisulpride methanolic solution was placed in quartz caped cell ($l$ = 1 cm) and irradiated with UVA radiation. As a UVA source Haland HA-05 (Warsaw, Poland) ultraviolet laboratory lamp equipped with Philips TL 8W BLB tube emitting radiation at 365 nm (1.3 W of UVA radiation) was used. The distance between the UVA lamp and the sample was 10 cm and the temperature in the chamber was controlled and kept below 26 °C. The UVA intensity was controlled with MKVI Magnaflux radiometer (Athens, Greece) and the average irradiation intensity was 7 W/m$^2$. The dark control sample was used by exposing the amisulpride sample in quartz cell wrapped in aluminium foil for the same period of time.

### 2.3. UHPLC–DAD/ESI-Q-TOF-MS analysis

LC–MS/MS analysis was performed with the use of Agilent Accurate-Mass Q-TOF LC/MS G6520B system with dual electrospray (DESI) source and Infinity 1290 ultra-high-pressure liquid chromatography system consisting of: binary pomp G4220A, FC/ALS thermostat G1330B, autosampler G4226A, DAD detector G4212A, TCC G1316C module and Zorbax Eclipse-C18 (2.1 mm × 50 mm, dp = 1.8 μm) Rapid Resolution HD column (Agilent Technologies, Santa Clara, USA). A mixture of methanol (A) and water (B) with addition of 0.1% solution of formic acid in both media was used as a mobile phase. The gradient elution was carried out at constant flow 0.4 ml/min from 12%A (88%B) 0–3 min and then 12%A to 20%A 3–10 min. 1 min post time (12%A) was performed to return to initial conditions. The injection volume was 1.5 μl and the column temperature was maintained at 25 °C. MassHunter workstation software in version B.04.00 was used for the control of the system, data acquisition, qualitative and quantitative analysis.

The optimization of the instrument conditions was started with the proper tuning of Q-TOF detector in a positive mode with the use of Agilent ESI-L tuning mix in high resolution mode (4 GHz). Next, the main parameters were optimized and the following settings were applied: gas temp.: 300 °C, drying gas: 10 l/min, nebulizer pressure: 40 psig, capillary voltage: 3000 V, fragmentor voltage: 200 V, skimmer voltage: 65 V, octopole 1 RF voltage: 250 V.

In order to make the qualitative and quantitative analysis in one run, data acquisition was performed in auto MS/MS mode with spectral parameters: mass range: 50–950 $m/z$ and acquisition rate: 1.40 spectra/s (for MS and MS/MS data). In this mode the maximum data for structure elucidation was collected, and it was not necessary to repeat the analysis in different modes. Collision energy was also calculated with auto algorithm with formula: 5 V (slope) × ($m/z$)/100 + 6.8 V (offset) and in this case it ranged: 19.8 V–26.1 V. Maximum 2 precursors per cycle were selected with an active exclusion mode after 1 spectra for 0.1 min.

To ensure accuracy in masses measurements, reference mass correction was used. Mass 121.0508 and 922.0097 were used as lock masses.

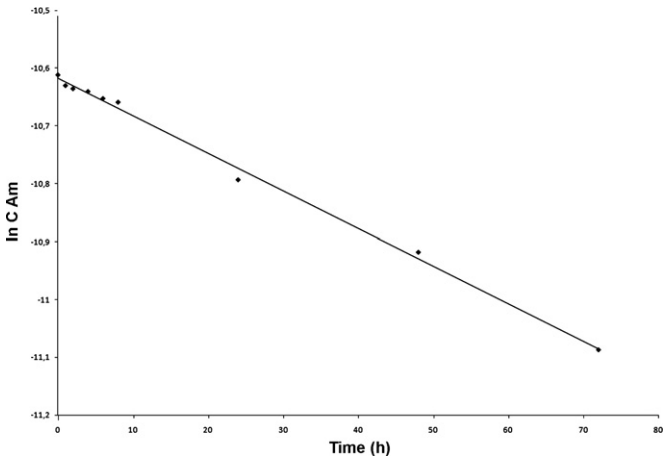


**Fig. 1.** First-order kinetics of the photodegradation of amisulpride in methanol solution.

Diode array detector collected data in the range 200–400 nm, and 270 nm was selected for the quantitative analysis of amisulpride.

### 2.4. Quantitative analysis and photodegradation kinetics

The method calibration for the determination of the concentration of amisulpride in tested samples was performed with the use of DAD detection. Calibration curve was obtained by plotting the peak area against the amount of the drug in the range: $5.4 \times 10^{-7}$ to $2.7 \times 10^{-5}$ M and studied by fitting the results to linear least-squares regression. All calibration standards were analyzed five times and the average calibration curve with statistic parameters was calculated.

The obtained calibration curve was used for the determination of photodegradation kinetics of amisulpride in methanol solution. During the irradiation procedure 100 μl of the tested solution was collected and analyzed by UHPLC–DAD/ESI-Q-TOF-MS system in the time: 0, 1, 2, 4, 6, 8, 24, 48 and 72 h of exposing to UVA radiation. The photodegradation kinetics parameters: rate constant ($k$) and $t_{1/2}$ were calculated with the use of equation:

$$\ln c = \ln c_0 - kt,$$

where $c_0$ is the concentration in the time 0, $c$ is the remaining concentration, $k$ the rate constant ($h^{-1}$) and $t$ is the time (h).

The dark control sample concentration was measured in the same time period.

## 3. Results and discussion

### 3.1. Quantitative study of the photodegradation process

The calibration of the quantitative analysis method for the determination of amisulpride was performed on DAD detector at 270 nm maximum band in the range: $5.4 \times 10^{-7}$ to $2.7 \times 10^{-5}$ M. The obtained calibration curve: $y = 2.92 \times 10^6$ ($\pm 6185$)$x - 0.9681$ ($\pm 0.0616$) was linear over the concentration range ($r = 0.9999$) and the limits of detection (LOD) and quantification (LOQ) were $1.4 \times 10^{-7}$ M and $4.1 \times 10^{-7}$ M respectively. The obtained results were used to calculate the concentration of amisulpride at proper time intervals during UVA irradiation. As shown in Fig. 1 the decomposition of amisulpride followed apparent first-order kinetics reaction according to the equation: $\ln c = \ln c_0 - kt$. The rate constant value, correlation coefficient and the half-life time of photodegradation process were respectively: $k = 6.5 \times 10^{-3}$ h$^{-1}$, $r = 0.9983$, $t_{1/2} = 103.1$ h.

**Table 1**
Exact mass measurements and elemental composition of amisulpride and its photodegradation products (D1–D4) using Q-TOF MS method.

| Comp. No. | Name | Retention time (min) | Measured mass (Da) | Theoretical mass (Da) | Mass error (ppm) | Molecular formula | DBE |
|---|---|---|---|---|---|---|---|
| 1 | D2 | 2.5 | 367.1564 | 367.1566 | 0.53 | $C_{17}H_{25}N_3O_4S$ | 7 |
| 2 | D3 | 3.7 | 341.1412 | 341.1409 | 0.79 | $C_{15}H_{23}N_3O_4S$ | 6 |
| 3 | D1 | 4.8 | 258.0666 | 258.0674 | 3.05 | $C_{10}H_{14}N_2O_4S$ | 5 |
| 4 | Amisulpride | 5.1 | 369.1732 | 369.1722 | 2.53 | $C_{17}H_{27}N_3O_4S$ | 6 |
| 5 | D4 | 8.9 | 385.1665 | 385.1671 | 1.77 | $C_{17}H_{27}N_3O_5S$ | 6 |

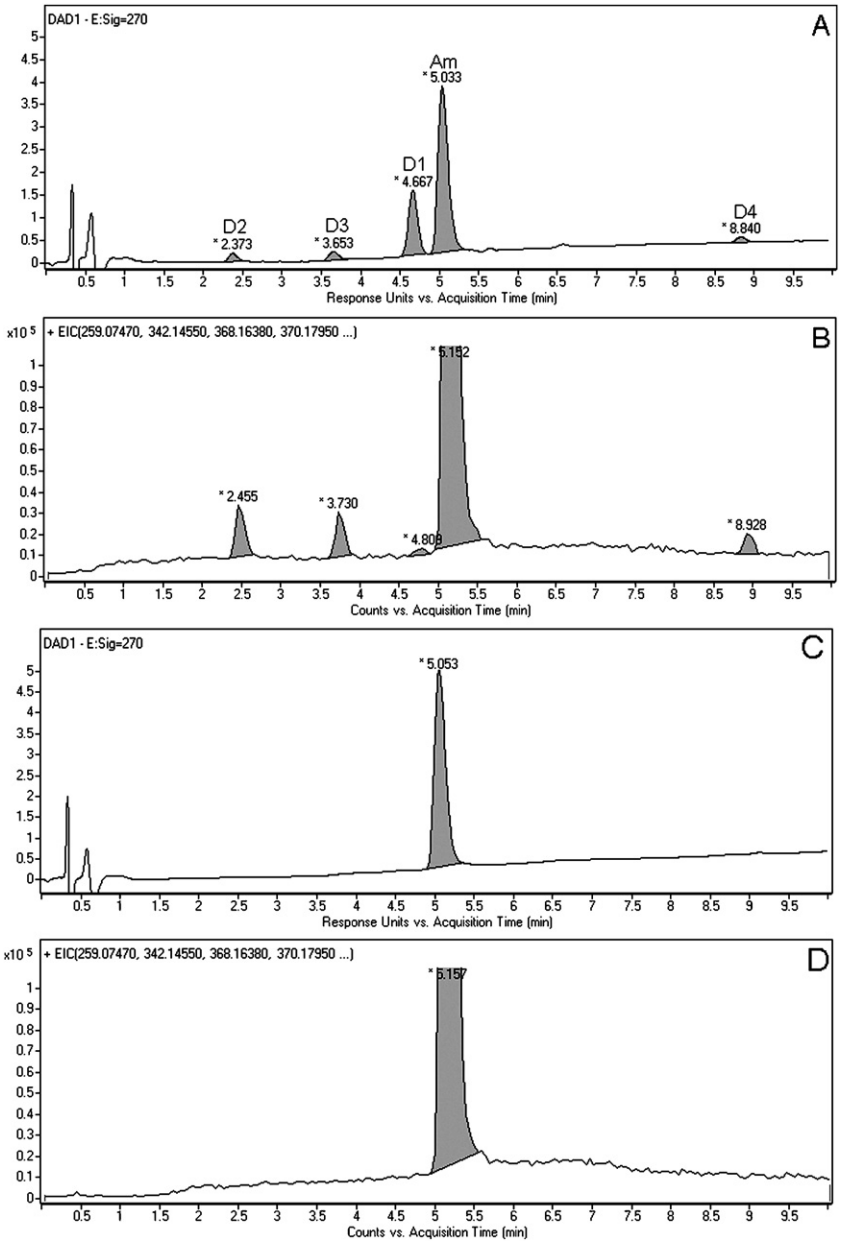


**Fig. 2.** UHPLC–DAD (A) chromatogram and Q-TOF (B) extracted ion chromatogram obtained from amisulpride (Am) methanolic solution after 72 h irradiation with UVA source and before irradiation (C and D).

The quantitative analysis of the dark control sample of amisulpride confirmed the absence of the photolysis process in this case.

### 3.2. Identification of photoproducts

The usage of hybrid LC–MS/MS system coupled with DAD detector enabled the quantitative analysis of amisulpride in the analyzed samples in order to determine kinetics parameters of the photodegradation process as well as the utmost optimization of the mass spectrometer for the qualitative analysis of the produced photodegradant. After the chromatographic and initial MS conditions optimization (Section 2.3) a good separation of all analyzed substances for both systems of detection was achieved (Fig. 2). As the Q-TOF 6520 system enabled data acquisition in three modes: MS, targeted MS/MS and auto MS/MS, the second phase of MS conditions optimization was needed. In MS mode only TOF spectras

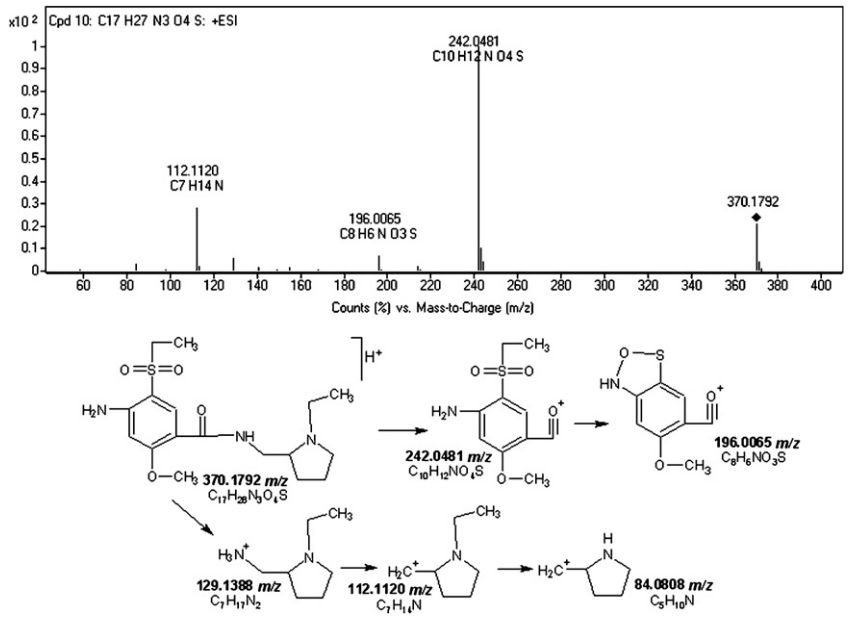


**Fig. 3.** Q-TOF MS/MS spectrum and fragmentation pathway of amisulpride.

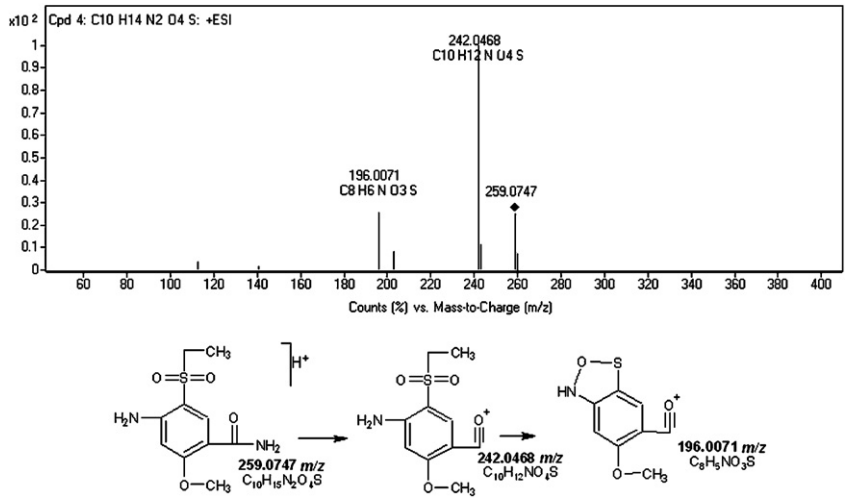


**Fig. 4.** Q-TOF MS/MS spectrum and fragmentation pathway of photodegradation product D1 ($t_R$ = 4.8 min).

are collected and fragmentation spectras are disabled. However, in targeted MS/MS the fragmentation information is enabled, the precursor ions must be selected in advance and sometimes during the analysis of an unknown compound the whole procedure must be repeated a few times for the selected ions. In this case in order to record maximum data for structure elucidation in one run analysis, auto MS/MS mode was selected. In this mode MassHunter software selects automatically precursor ions for the fragmentation and MS/MS spectras as well as MS are recorded. After the careful optimization of mass range, acquisition rate, collision energy algorithm, static exclusion range, number of precursors (Section 2.3) the analyzed ions of amisulpride and its photodegradation products were selected automatically for the fragmentation and recorded. The obtained data was next calculated with the use of MassHunter software and another auto MS/MS algorithm was used in order to find compounds and generate their formulas. The optimization of this algorithm was limited only to: the selection of retention time window (0.25 min), the selection of elements for generating formulas (limited to C, H, O, N, S) and setting a maximum mass error (5 ppm).

As shown in Table 1 the molecular ion of amisulpride was found with good accuracy (2.53 ppm) and the chemical formula was calculated in this case ($C_{17}H_{27}N_3O_4S$). Additionally, corresponding to Fig. 2 four degradation products (D1–D4) were found and their masses with accuracy 0.53–3.05 ppm as well as formulas were calculated. However, the employed auto MS/MS algorithm generated extra data for the proposed formulas in the form of fragmentation ions formulas corresponding to MS/MS fragmentation spectra of the parent ion.

In Fig. 3 MS/MS spectrum and the fragmentation pathway of amisulpride are presented. Protonated ion of amisulpride ($m/z$ = 370.1792) under the collision energy 25.3 V (Section 2.3) gave fragmentation to three main ions: $m/z$ 242.0481, 196.0065 and 112.1120. For the first two ions the generated formulas ($C_{10}H_{12}NO_4S$ and $C_8H_6NO_3S$ respectively) confirmed that the main fragmentation pathway based on the amide bond breaking. For the third main fragmentation ion $C_7H_{14}N$ formula was generated and represents pyrrolidine fragment of the parent compound. Additionally, two small fragmentation ions ($m/z$ = 129.1388 and 84.0808) which completed the fragmentation pathway of pyrro-

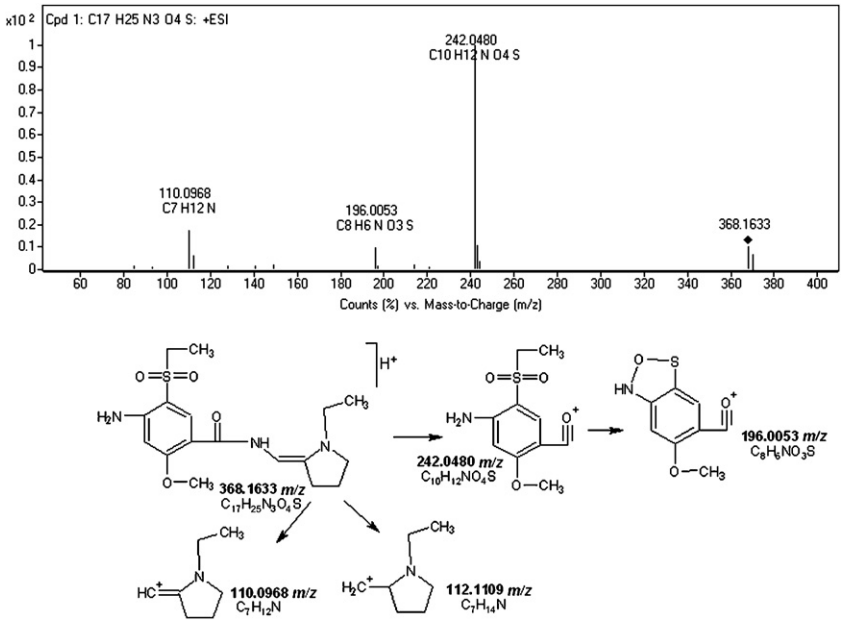


**Fig. 5.** Q-TOF MS/MS spectrum and fragmentation pathway of photodegradation product D2 ($t_R$ = 2.5 min).

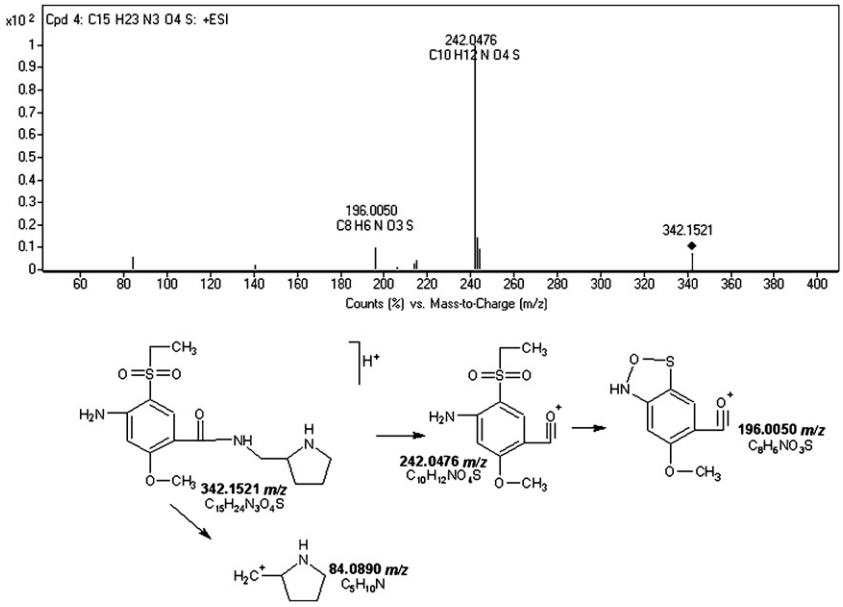


**Fig. 6.** Q-TOF MS/MS spectrum and fragmentation pathway of photodegradation product D3 ($t_R$ = 3.7 min).

lidine element were observed. Basing on this information the structure elucidation of the main photodegradation product (D1) was started. As shown in Fig. 4 MS/MS spectrum of this product is very similar to amisulpride except for the lack of the fragments of ions representing the pyrrolidine element. The measured mass (258.0666 Da), generated formula ($C_{10}H_{14}N_2O_4S$) and the presence of *m/z* 242.0469 and 196.0071 fragmentation ions in MS/MS spectrum show clearly that the analyzed compound is 4-amino-5-ethylsulfonyl-2-methoxybenzamide, because the only difference between D1 and the main fragmentation ion (*m/z* 242.0469) is the presence of $NH_2$ radical.

In Fig. 5 MS/MS spectrum of the second degradation product (D2) and the proposed fragmentation pathway are shown. In this case the measured mass was 2 Da lower than amisulpride and the generated formula has two hydrogen atoms less, and DBE (double bond equivalent) was one bound higher than in the parent compound (Table 1). The fragmentation spectrum shows that the additional double bound must be located in an alkylopyrrolidine group. A significant fragmentation ion *m/z* = 110.0968 corresponding to formula $C_7H_{12}N$ and also a lower ion *m/z* = 112.1109 ($C_7H_{14}N$) were observed which suggests that the new double bound is not placed inside the pyrrolidine ring. If the location of this double bound was in pyrrolidine ring only ion *m/z* = 110.0968 and perhaps smaller fragments of the ions might be observed in MS/MS spectrum. Ion *m/z* = 112.1109 should not be explicitly present in this case.

The measured mass of photodegradantion product D3 (341.1412 Da) enabled the generation of $C_{15}H_{23}N_3O_4S$ formula which shows that this compound lost $C_2H_4$ group in relation to amisulpride. The obtained MS/MS spectrum (Fig. 6) confirmed the presence of the same main fragmentation ions like in the case of parent compound but no *m/z* 129.1388 and 112.1120 ions

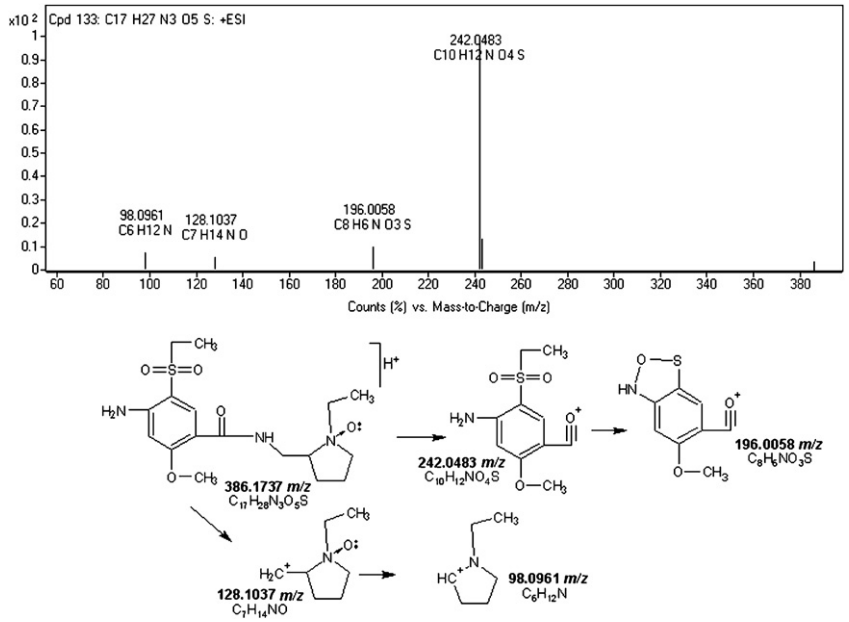


**Fig. 7.** Q-TOF MS/MS spectrum and fragmentation pathway of photodegradation product D4 ($t_R$ = 8.9 min).

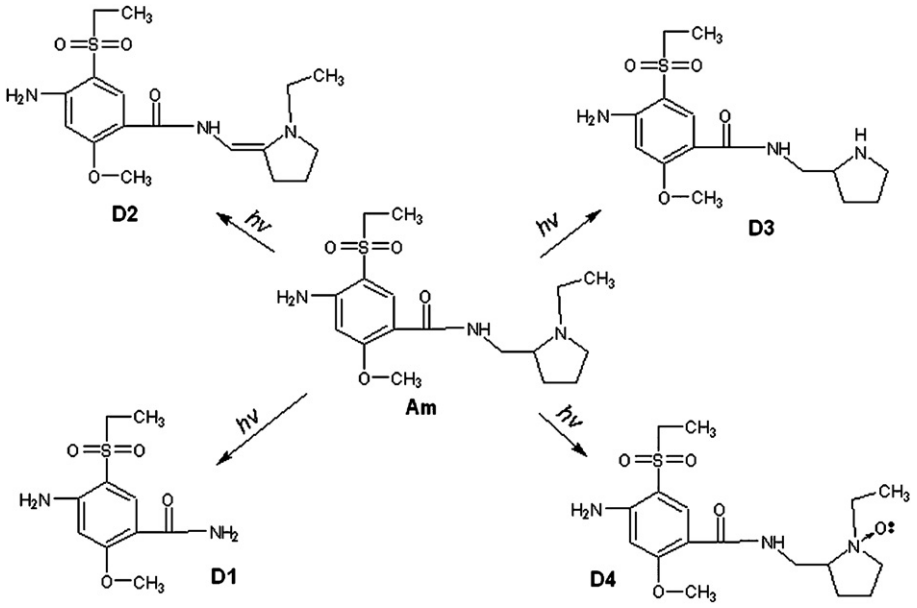


**Fig. 8.** Photodegradation pathway of amisulpride in solution.

were found. Only *m/z* 84.0809 fragmentation ion was noticed to equal $C_5H_{10}N$ formula which was elucidated early in amisulpride fragmentation pathway as 2-methylpyrrolidine ion. Taking this into account, this product (D3) has no ethyl group as a substituent in pyrrolidine ring in position 1.

The last photodegradation product (D4) was found as *m/z* = 386.1737 ion and the formula generated for it (Table 1) shows that the only difference between D4 and amisulpride is the presence of an additional oxygen element. In this situation first of all the possibility of the formation of N-oxide derivative was considered. As shown in Fig. 7 except for the characteristic ions for amisulpride MS/MS fragmentation the significant *m/z* = 128.1037 and 98.0961 ions were noticed. The generated formula for the first of these two ions ($C_7H_{14}NO$) confirmed that the N-oxide bound with nitrogen of pyrrolidine ring was formed in this case.

### 3.3. Proposed photodegradation pathway

The proposed photodegradation pathway of amisulpride in methanol solution under UVA irradiation is presented in Fig. 8. The photodegradation product D1 (4-amino-5-ethylsulfonyl-2-methoxybenzamide) was found as the main product of photolytic process. The other three photodegradation products are formed in an insignificant amount probably due to the remains of photolytic reaction to D1 product. Two of these compounds D2 (4-amino-N-[(Z)-(1-ethylpyrrolidin-2-ylidene)methyl]-5-(ethylsulfonyl)-2-methoxybenzamide) and D4 (4-amino-N-[(1-ethyl-1-oxidopyrrolidin-2-yl)methyl]-5-ethylsulfonyl-2-methoxy-benzamide) are the result of an oxidation process which is frequently observed during a photodegradation study. D3 photodegradation product (4-amino-5-(ethylsulfonyl)-

2-methoxy-N-(pyrrolidin-2-ylmethyl)benzamide) was formed as an effect of photolysis of alkylo chain from pyrrolidine ring.

## 4. Conclusion

Amisulpride is not a stable compound under UVA irradiation and yields photodegradation in accordance with a first-kinetic reaction to four products. The main photodegradation product was identified as 4-amino-5-ethylsulfonyl-2-methoxybenzamide.

UHPLC–DAD/ESI-Q-TOF system was found to be a powerful analytical tool for the fast and accurate photostability analysis of amisulpride. During one run with the use of auto MS/MS mode all essential data for the quantitative and qualitative analysis and for the structural elucidation of the photodegradation products was collected.

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