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Evaluation of the photoprotective effect of β - cyclodextrin on the emission of

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volatile degradation products of ranitidine

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Abstract

The process of the photo-excitation of ranitidine hydrochloride (RAN) in a solid state makes visible changes to its colour and generates an unpleasant odour. The purpose of the present study was to observe the protective effects of γ -cyclodextrin (CD) complexation as well as the effect of the mixture of two stoichiometries 1:1 and 1:2 (RAN:CD, IC) on the photostability of samples in a solid state. Samples of inclusion complexes (IC) and physical mixtures (PM) were prepared and irradiated for 48 h in a Suntest CPS+ chamber. Irradiated samples were analyzed using nuclear magnetic resonance (^1H NMR), infrared spectroscopy (FT-IR), the differential scanning calorimetry method (DSC) and thermogravimetry analysis (TGA). Volatiles were monitored with the use of headspace-solid phase microextraction-gas chromatography–mass spectrometry (HS-SPME-GC–MS). The protective effect of CD was noticed with respect to IC, and also PM. Achieved photostabilization of complexed RAN against photodegradation could be explained due to either the inclusion of the furan part of RAN into the CD cavity as shown by the ^1H NMR ROESY (rotation frame nuclear Overhauser effect spectroscopy) spectrum or the screening effect of CD. FT-IR spectra, DSC curves and microscope images of irradiated samples of protected RAN did not indicate any physical changes, such as phase transfer

Introduction

H₂ receptor antagonists represented by ranitidine hydrochloride (RAN) belong to a group of medicinal compounds that are very sensitive to environmental exposure, especially light and humidity [1-2]. Apart from the known problems with ranitidine taken in the form of tablets and syrup, there are still unresolved issues surrounding its use in powdered or pure substance form and any possible mechanisms of its instability in a solid state.



53 It has been documented that the process of the photo-excitation of ranitidine hydrochloride
54 causes visible colour changes and emits an unpleasant odour [3]. A number of compounds are
55 released during exposition of the solid form of RAN to light [4] and some of these have already
56 been identified [5]. The molecules produced during photodegradation may be responsible for
57 the characteristic strong odour of ranitidine powder generated during its storage and forced light
58 irradiation.

59 Studies on the photostability of medicinal substances are an important element of the
60 stability testing of drugs [6]. Photodegradation of drug compounds can contribute to a variety
61 of adverse physical effects for the medicinal product, can lead to changes in the physical and
62 chemical properties of the medicinal product and, thus, can effect changes in the
63 pharmacokinetics and eventually lead to unplanned therapeutic effects. The list of
64 environmentally sensitive pharmacological compounds constantly increases; therefore, the
65 search for newly developed methods for the improvement of drug stability is a most vital task.
66 A review of the literature suggests that one method of inhibition of drug degradation is
67 complexation with cyclodextrins – cyclic oligosaccharides (CDs) [7,8]. The photostabilization
68 effect or the photoprotection of different molecules is well documented [9-13]. Protective
69 properties of native CDs (α -, β -, γ -CD) and their derivatives are approached by incorporation
70 of a guest compound inside a cyclodextrin moiety, but this is not always so. Preparation of
71 simple physical mixtures with cyclodextrins is also effective in terms of protective activity [14].
72 For pharmaceutical applications, the improvement of drug stability and solubility, as well as
73 the biological availability of drug compounds, are necessary features. CDs are used in such
74 pharmaceuticals as the Nicorette Microtab (AB, Sweden) containing betadex (β -CD), Orungal
75 I.V. (Janssen, Belgium) containing 2-hydroxylpropyl- β -cyclodextrin, Bridion (Schering-
76 Plough, Belgium) with a modified β -CD, Flamexim (Chiesi Pharma, Poland), containing
77 piroxicam complexes with β -CD, and others.



78 In this paper, we demonstrate the influence of CDs on the emission of volatile
79 photodegradation products from ranitidine hydrochloride powder. The scope of this study is
80 only concerned with the photoprotection of RAN by β -CD, as the first step of planned and
81 parallel established general stabilization of RAN. Currently, results are demonstrated as
82 reduced amounts of compounds produced during photodegradation through either formation of
83 inclusion complexes or, the simplest form, through physical mixtures of RAN-CD in two
84 stoichiometries. The effect of supramolecular protection is investigated using the HS-SPME-
85 GC-MS method.

86 **1. Experimental**

87 *1.1. Materials*

88 The tested ranitidine hydrochloride (polymorphic Form 2) bulk powder was supplied as a
89 white crystalline powder by Polpharma Pharmaceutical Works (Poland). The β -CD CYL-3190
90 was purchased from CycloLab R&D Ltd (Budapest, Hungary). A Millipore Milli Q-plus system
91 (Millipore, Bedford, USA) was used to purify water for the preparation of complexes.

92 *1.2. Methods*

93 *1.2.1. Inclusion complexes and physical mixture preparation*

94 Ranitidine hydrochloride inclusion complexes were prepared using the encapsulation method
95 [15]. Cyclodextrin suspensions were added to the ranitidine hydrochloride solution under
96 continuous stirring. After 48 hours of stirring, solutions were filtered. The filtrate was then
97 cooled at 4 °C overnight and lyophilized using an Alpha 1-2 LD (Christ, Osterode, Germany)
98 freeze-drier. As a result, white, fluffy powders were obtained. Inclusion complexes in a molar
99 ratio of 1:1 stoichiometry of RAN:CD - IC_1:1 and 1:2 stoichiometry, IC_1:2, respectively.

100 Simultaneously, for comparative purposes physical mixtures (PM) were prepared by
101 mechanical mixing substances with the same stoichiometry as for inclusion complexes (PM_1:1
102 and PM_1:2).



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104 1.2.2. Irradiation process

105 The amount of 1g samples of IC_1:1, IC_1:2, PM_1:1 and PM_1:2 were placed in a 20 mL
106 glass vial and sealed with Parafilm. Blank samples were wrapped with aluminum foil. Samples
107 were irradiated in a Suntest CPS+ chamber (Atlas, Gelnhausen, Germany) equipped with a
108 Xenon lamp (1.1 to 1.5 kW) and an electronic device for measuring and controlling both
109 irradiation and temperature inside the box. The solar ID65 standard according to guideline ICH
110 was applied. The illuminance was set at a value of exposure power of 500 [W m⁻²] for 48 hours.

111 1.2.3. Inclusion complex and physical mixture characterization

112 Both inclusion complexes and physical mixtures were characterized using the DSC method, as
113 described previously [16], FT-IR, and nuclear magnetic resonance ¹H NMR, 2D-NOESY
114 (Nuclear Overhauser Effect Spectroscopy), 2D-TOCSY (Total Correlation Spectroscopy) and
115 2D-ROESY (Rotation Frame Nuclear Overhauser Effect Spectroscopy).

116 Differential scanning calorimeter (DSC) analyses were performed using a Netzsch Phoenix
117 DSC 204 F1 (Netzsch Gerätebau, Germany) equipped with an intercooler system. The samples
118 (1.5–4 mg) were weighed and sealed into aluminum pans. The DSC runs were conducted over
119 a temperature range of 25 – 300 °C at a rate of 10 °C min⁻¹. All tests were run under a nitrogen
120 atmosphere. Thermograms are expressed as the function °C=f(mW), i.e. the temperature of the
121 sample according to heating energy.

122 FT-IR spectra were recorded and analyzed in solid state using a Jasco 410 instrument (4000-
123 650 cm⁻¹ with 32 scans) and KBr pellets of solid samples were prepared using a minipress.

124 ¹H NMR spectra were recorded in deuterium oxide (D₂O) on a Gemini Varian 500 MHz
125 spectrometer using TMS as an internal standard at 298 and 305 K (2D-ROESY).

126 Microscope images were performed using an Opta-Tech X 2000, equipped with a 9 MP Opta-
127 Tech CMOS digital camera with Opta View software for data acquisition, version 7.1.0.4
128 (Opta-Tech, Poland). The morphology of samples was examined by means of a scanning
129 electron microscope (Hitachi TM-1000, 198 Japan), with the accelerating voltage was 15 kV.

130 1.2.4. HS-SPME-GC-MS

131 The production of volatiles was monitored using the headspace solid phase micro-
132 extraction and gas chromatography mass spectrometry method (HS-SPME-GC-MS) described
133 earlier [5].

134 Briefly, about 200 mg of the test mixture was placed in a 4 mL glass vial and then sealed
135 with Parafilm. Blank sample - vials containing the same material were wrapped with aluminum
136 foil during the irradiation process. Preconditioned fiber was exposed to the headspace for 30
137 min at 40 °C. Following extraction, fiber was retracted and introduced into the injection port of
138 a gas chromatograph for desorption (4 min).

139 Samples were extracted with the use of a carboxen/polydimethylsiloxane SPME fibre
140 (CAR/PDMS, Supelco – 57318U, $df = 75 \mu\text{m}$) conditioned before extraction in the injection
141 port of a gas chromatograph at a temperature of 290 °C for 60 minutes.

142 GC-MS analyses were performed using a Varian GC-450 gas chromatograph (Varian
143 Chromatography Systems, Walnut Creek, CA, USA) equipped with a 1079 PTV injector
144 (Programmable Temperature Vaporizing) and a Varian 220-ms (Varian Chromatography
145 Systems, Walnut Creek, CA, USA) ion-trap mass spectrometer. Experimental conditions were:
146 column, 30 m \times 0.25 mm i.d. \times 0.25 μm film, VF-5ms (Varian); temperature programme: 35 °C,
147 held for 4 min, increased at a rate of 10 °C min⁻¹ to a final temperature of 290 °C and held for
148 4 min. Helium was employed as the carrier gas at a constant flow of 1 mL min⁻¹. The injector
149 was operated initially in split-less mode for 4 min and then the split vent was kept open (1:20)
150 to the end of the run. Injector temperature was held constant at 290 °C. The GC-MS transfer

151 line and ion-trap temperatures were 270 °C and 170 °C, respectively. The ion-trap mass
152 spectrometer was operated in electron impact ionization (EI) mode (70 eV). The mass range
153 scanned in full-scan acquisition mode was m/z 30–350.

154 2. Results and discussion

155 2.1. Characterization of IC and PM of ranitidine with β -cyclodextrin

156 Ranitidine susceptibility to degradation is readily noticeable when exposed to humidity or light,
157 as presented in Figs. 1 A1 and 1 A2 as the brown surface of the powder particles. There are also
158 some published reports on the color changes of RAN from white and pale yellow to dark yellow,
159 brown or russet [16,17]. The obtained inclusion complexes of RAN with CD were white and
160 puffy and remained visually unchanged after irradiation (microscope), as presented. The results
161 of SEM analysis were analyzed to investigate the morphologies of inclusion complexes and the
162 physical mixtures of RAN and β -cyclodextrin both before and after photodegradation.
163 Irregularly shaped particles are larger for IC than PM, while after photo-irradiation they both
164 become slightly shredded (Fig. 1 - B4, C4). In the case of PM after photo-exposition, the image
165 is almost the same. In contrast, a visible change in the morphology and shape of particles was
166 observed in IC_1:1 freeze-dried products of CD, revealing an apparent interaction in the solid-
167 state. Moreover, the shape of IC_1:1 (Fig. 1 - B3) confirms its amorphous form.

168 The analysis of thermograms provides interesting information about PM_1:1, for which
169 four peaks can be observed at the temperatures 92, 147, 221 and about 250 °C, respectively
170 (Table 1, Fig. 2A). The first peak (T_1) is characterized by a very high transition enthalpy of
171 about 160 J/g. The enthalpy of the other two peaks is reduced to a value of about 30 J/g for the
172 second (T_2) and to 5 J/g for the third peak (T_3). PM_1:2 (Fig. 2B) and PM_1:1 (Fig. 2A) samples
173 show a similar course for thermograms. For PM_1:2 and PM_1:2_blank, a broad endothermic
174 peak (T_1) with a maximum at about 97 °C is observed.

175

176 For the PM_1:2_UV system, the maximum transition temperature (for T₁ peak) shifted
177 approximately by 8 °C towards lower temperatures. For PM_1:2_blank and PM_1:2_UV,
178 maxima of peaks occur at about 260 °C, in turn, for PM_1:2, this maximum is shifted towards
179 lower temperatures (T₄ = 252 °C). Comparing the enthalpy of fusion for substances of PM
180 systems, for T₂ peaks a reduction was observed in the enthalpy value for PM_1:2_blank and
181 PM_1:2_UV systems as compared to PM_1:2. It is worth noting that the obtained systems are
182 characterized by a closely related course, which may indicate their high levels of stability
183 against UV radiation.

184 FT-IR spectra recorded for each sample - RAN, PM_1:1, and PM_1:2 - are presented in
185 Supplementary Materials Fig. 1S.

186 The RAN spectrum presents several characteristic bands, also observed in PM_1:1. The
187 spectrum of a physical mixture coincides with the spectrum of RAN between 2650 and 2450
188 cm⁻¹. The region of the spectrum of PM near wavenumber 1600-1100 cm⁻¹ clearly consists of
189 overlaid bands both for RAN and CD.

190 FT-IR spectra recorded for RAN and IC_1:1 are presented in Supplementary Materials Fig.
191 2S. The IC spectrum shows no characteristic bands for RAN in the ranges 3600-3200 cm⁻¹, and
192 3200-2500 cm⁻¹. Bands corresponding to CD indicate interactions between host and guest
193 compounds. A clear and sharp band characteristic for RAN from C=N stretching vibration
194 (originating from a nitro group) occurs at 1620 cm⁻¹. This may support the hypothesis that this
195 region of RAN is located outside the cyclodextrin cavity in the inclusion complex, which is also
196 confirmed by ¹H NMR ROESY. FT-IR spectra of inclusion complexes, as well as physical
197 mixtures with RAN after photodegradation are presented in Supplementary Materials Fig. 3S.
198 Samples after irradiation present no chemical damage either visually or on the infrared spectra.

199 ^1H NMR spectra were recorded for CD, RAN and IC and are presented in Fig. 3. Chemical shift
200 differences for each RAN proton in IC_1:1 and IC_1:2 are typical for such supramolecular
201 systems. Average shifts of particular protons of about 0.167 for IC_1:1 and 0.175 for IC_1:2
202 can be noted (Table 2).

203 2D-NOESY (Nuclear Overhauser Effect Spectroscopy) and 2D-TOCSY spectral plots of IC are
204 presented in Fig. 4 and do not reveal any intermolecular cross peaks confirming an inclusion
205 complex structure. Cross-peaks between protons of ranitidine itself are only observed for 4/3,
206 5/6, 3/(1 and 2), 6/7, 6/8 and 3/12 pairs of protons. Specific interaction between cyclodextrin
207 protons and incorporated ranitidine are observed only on the 2D-ROESY spectrum (Fig. 3).
208 Overlaid spectra with two specific places of interactions CD/1,2 and CD/7 (marked in green)
209 are presented in Fig. 4. RAN protons of methyl groups 1 and 2 (Fig. 4) are bonded with the CD
210 cavity, while the methylene group near the sulfur atom (number 7) is also incorporated in this
211 inclusion owing to the observed CD/7 signal of interaction. Additional weak cross-peaks
212 revealing interactions between protons of RAN (number 4 and 5) are presented in Figs. 3 and
213 4. This will probably provide an explanation for the photostability of the ranitidine inclusion
214 complex.

215 2.2. GC-MS analysis

216 GC-MS chromatograms of irradiated bulk RAN serving as a positive control for the
217 photodegradation process are presented in Fig. 5.

218 Comparing the number of peaks detected using the same methodology, we observed almost
219 clear chromatograms. Reduced amounts of degradation compounds formed during exposure to
220 light in comparison to the reference sample chromatogram of bulk RAN (Fig. 5). Significant
221 changes between chromatograms recorded for irradiated samples in comparison to blank ones

222 are presented in Fig. 6 both for 1:1 and 1:2 complex stoichiometry. The same mass spectra for
223 all peaks were noticed during photodegradation in the cases of IC_1:1 and IC_1:2.

224 In the case of inclusion complexes, both 1:1 and 1:2 stoichiometry, the most intensive peak in
225 the chromatogram was **I**, an acetaldoxime $R_t=1.65$ min. The following peaks were identified:
226 **I**, **III** - thiazole $R_t=4.60$ min, **IX** - dimethylacetamide $R_t=5.98$ min, **VI** - dimethylformamide
227 $R_t=8.07$ min and **XI** as 5-methylfurfural $R_t=9.94$ min [5].

228 In the current study, physical mixtures with the same stoichiometry as the inclusion complexes
229 were also prepared and analyzed. In the scientific literature it is documented that, in some cases,
230 even a small amount of cyclodextrins in the reaction mixtures or powders may significantly
231 influence the final effect of the reaction, and specific processes and mechanisms of different
232 chemical reactions. In such a way, it is also possible to achieve different physical or chemical
233 properties of particular chemicals.

234 Physical mixtures containing RAN and β -CD were irradiated and further analyzed by a HS-
235 SPME-GC-MS method. Surprisingly, acetaldoxime was the only product identified on the
236 chromatograms of blank and irradiated samples of PM_1:1 and also PM_1:2. Peak intensity
237 was significantly lower in PM than in IC.

238 Acetaldoxime is detected in most samples containing RAN and also the bulk one, but not in the
239 blank sample of IC and bulk RAN after the freeze-drying process, which was performed in
240 order to verify such circumstances. This effect may be related to the fact that it is so volatile
241 that during the lyophilisation process it is completely removed from samples. However, it is
242 generated during irradiation, also in blank samples (Fig. 6).

243 Reducing the amount of cyclodextrins in the physical mixtures from stoichiometry 1:1 to 1:0.1
244 was also tested in order to test photoprotective activity. These results indicate a not so

245 spectacular protection of RAN during photo-irradiation, as is the case with PM_1:1. Fewer
246 peaks are observed on the GC-MS chromatogram (Supplementary Materials Fig. 4S). It is
247 important to underline the role of cyclodextrins in the stability of the solid sample physical
248 mixture. Depending on the energetic system of the molecule occurring in the environment or
249 surrounding CD (IC & PM) in the excited state induced by e.g. radiation, both an increased and
250 an inhibited photodegradation effect can be observed [18]. The energetic system of ranitidine
251 has not been described in detail; however, it is known which part of the molecule is sensitive
252 to the quanta of electromagnetic radiation in the UV-Vis. Based on the positive photoprotection
253 results observed for the particles and blocking against the emission of volatile degradation
254 products for both IC and PM, we tend to conclude that both the change in the energy status of
255 molecule, as well as the shielding of CD play a significant role. One should also mention that
256 CDs are known for their high affinity towards volatile compounds [19]. It is therefore possible
257 to inhibit or reduce the degree of volatility of unwanted molecules through their complexation
258 [20]. It is highly probable that during the exposure of ranitidine, several photoprotection
259 mechanisms occur simultaneously.

260 In effect, not so many photodegradation products are generated.

261 The beneficial role of β -cyclodextrins towards ranitidine photostability, observed as a decrease
262 in the generation of volatile products during irradiation, is documented in this study. In physical
263 mixtures, RAN is protected more efficiently than in inclusion complexes. The number of
264 detected peaks in the PM chromatograms is lower than that for IC; moreover, these peaks are
265 less intense. The results obtained for PM_1:1 and PM_1:2 both indicate quite comparable
266 protective effects of cyclodextrins and appear very promising.

267 The results obtained in this study indicate that ranitidine hydrochloride complexes with β -CD
268 are more resistant to irradiation than free (bulk) RAN. This is a confirmation of the protective
269 properties of cyclodextrins.

270 **3. Conclusions**

271 It can be concluded that the successful photoprotection of ranitidine in solid state due to the
272 presence of cyclodextrins in the form of a physical mixture and inclusion complex was
273 achieved. In the light of the qualitative research we performed, significantly reduced emissions
274 of volatile degradation products were observed in the physical mixture of RAN compared to
275 those obtained for free ranitidine after photo-irradiation. These observations are in agreement
276 with visual and microscope images of irradiated samples of inclusion complexes and mixtures
277 with β -cyclodextrin. Protection of ranitidine against photodegradation in such supramolecular
278 systems could be explained due to the inclusion of the sulfur atom from the RAN molecule and
279 also the furan part. Nevertheless, the screening effect of β -cyclodextrin in the physical mixture
280 improved the statement of its protective properties. Moreover, no bad odor is any longer noticed
281 for samples of RAN after irradiation.

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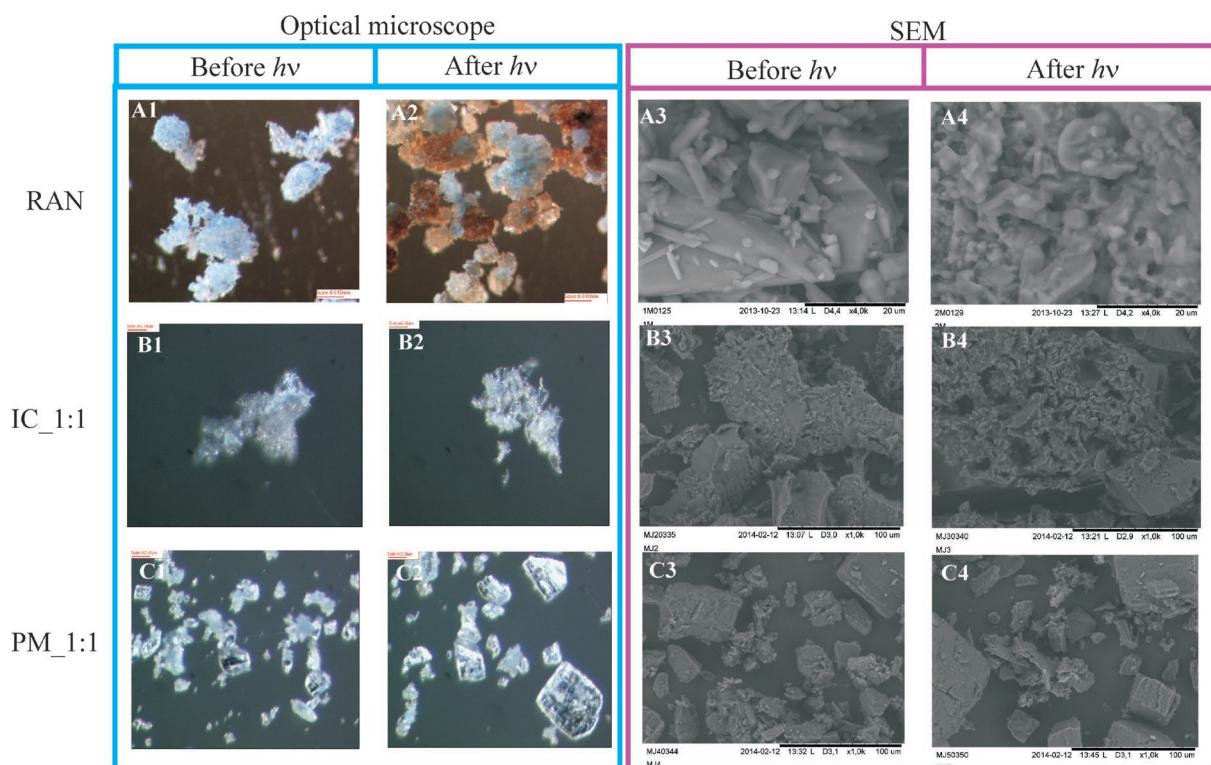


Fig. 1. Particles (1 and 2 - optical microscope; 3 and 4 - SEM) before (1,3) and after irradiation (2,4) of RAN (A), IC_1:1 (B), PM_1:1 (C).

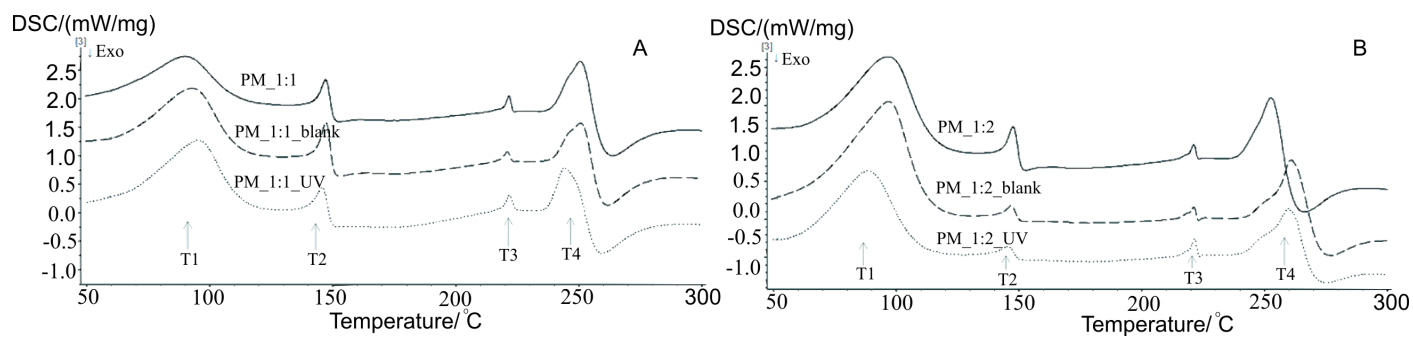


Fig. 2. DSC curves of PM_{1:1} (A) and PM_{1:2} (B) before and after irradiation.

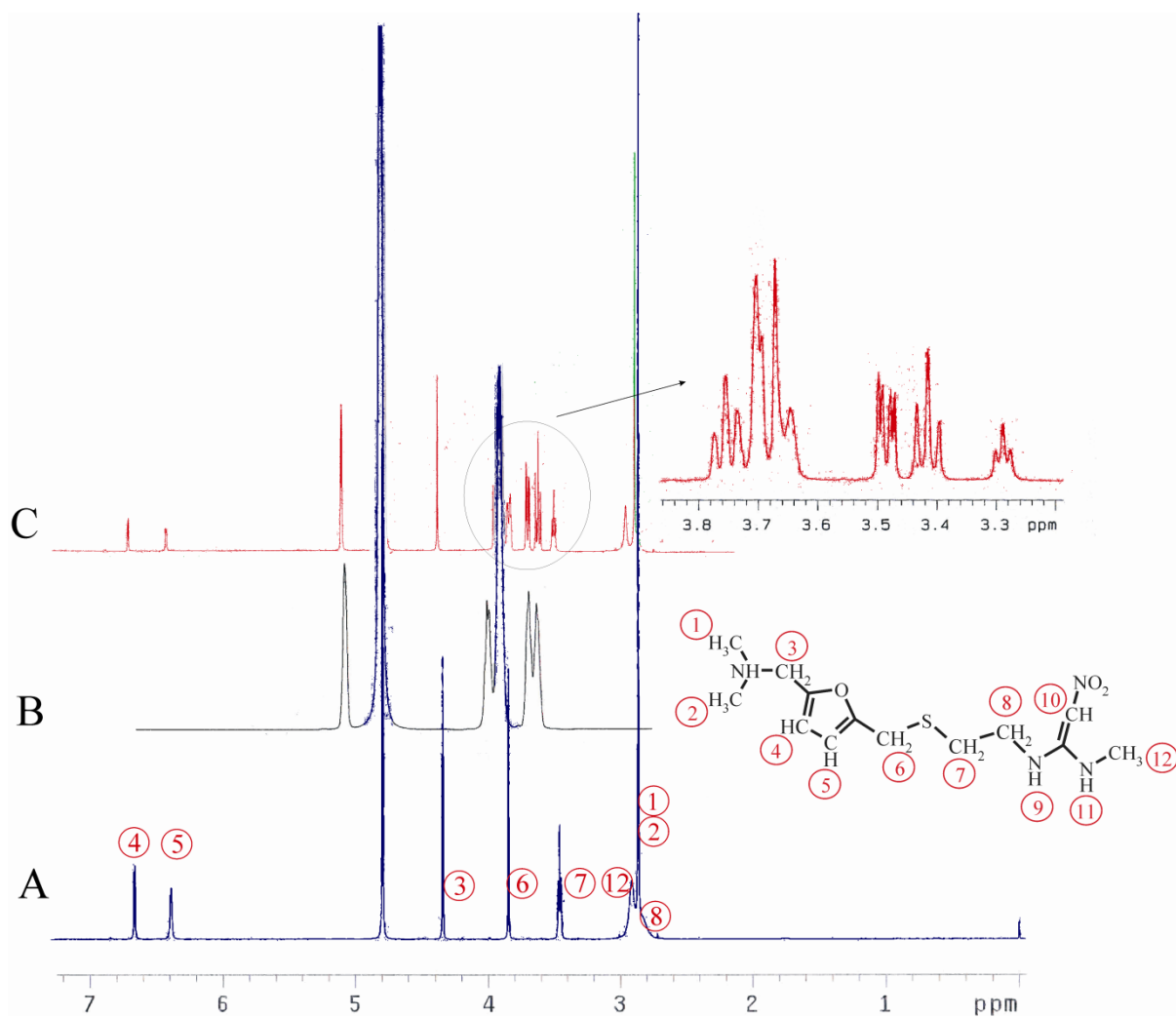


Fig. 3. ^1H NMR spectra of A) RAN, B) CD and C) IC_1:1.

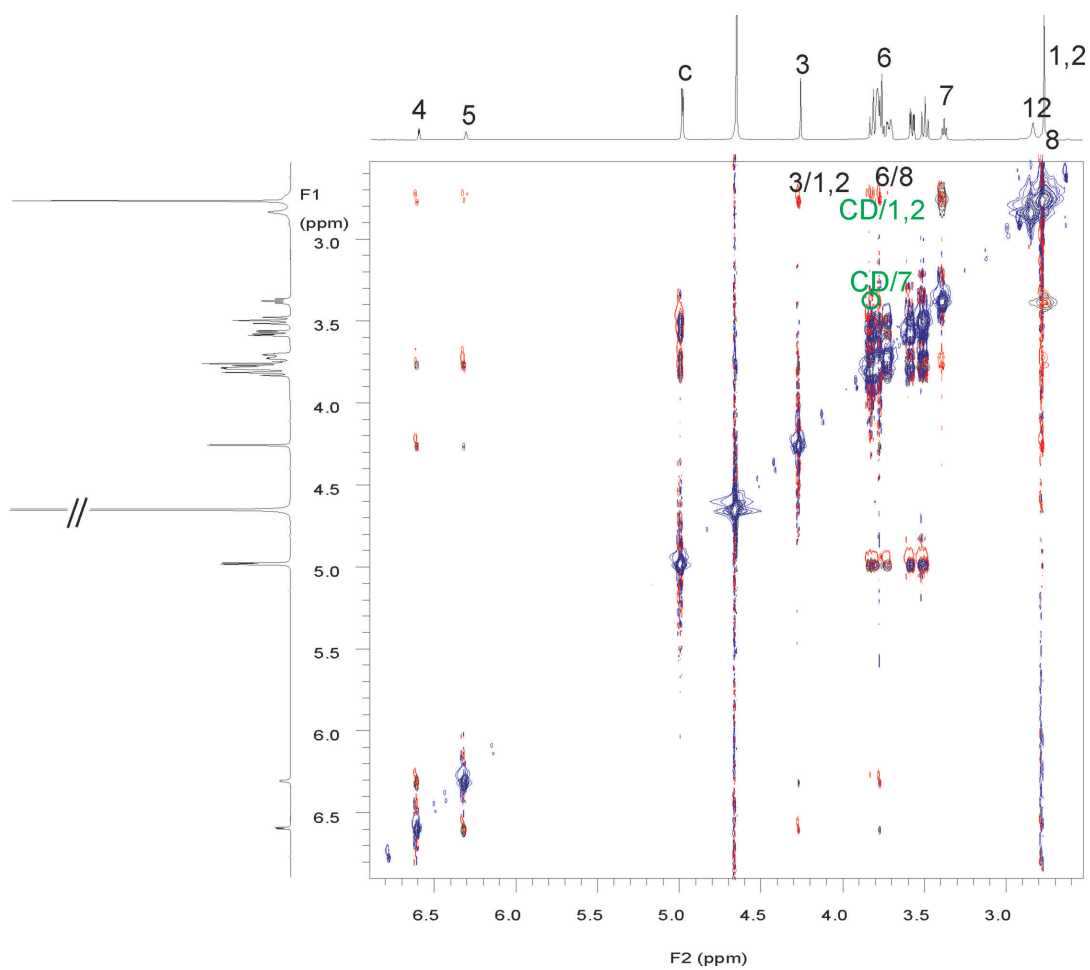


Fig. 4. Two dimensional overlaid spectra ROESY, NOESY and TOCSY of IC_{1_1} and indicated interactions.

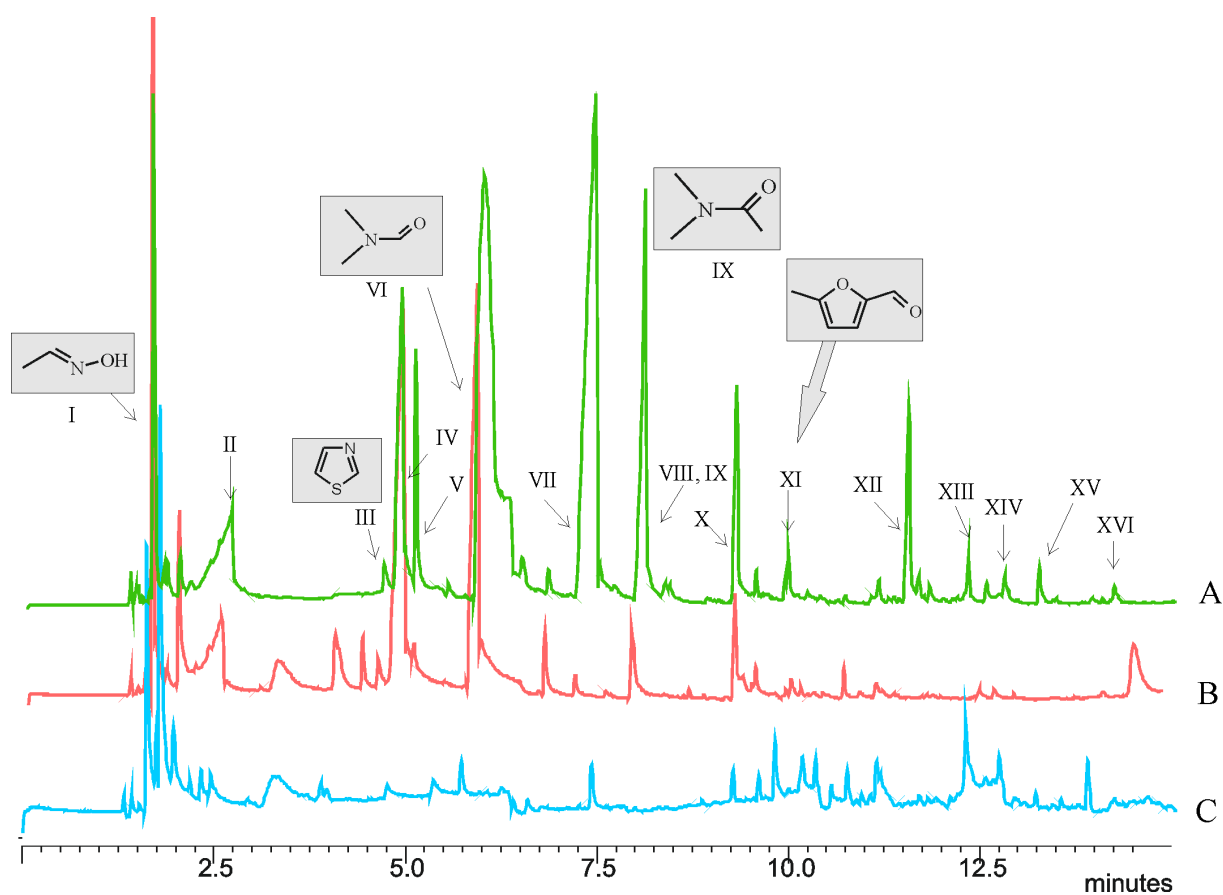


Fig. 5. GC-MS chromatogram obtained for A) bulk RAN; B) IC_1:1 and C) PM_1:1 powders after photo-exposition for 48 h in a Suntest CPS+ chamber and evaluated compounds. Roman numbers are described and identified [5].

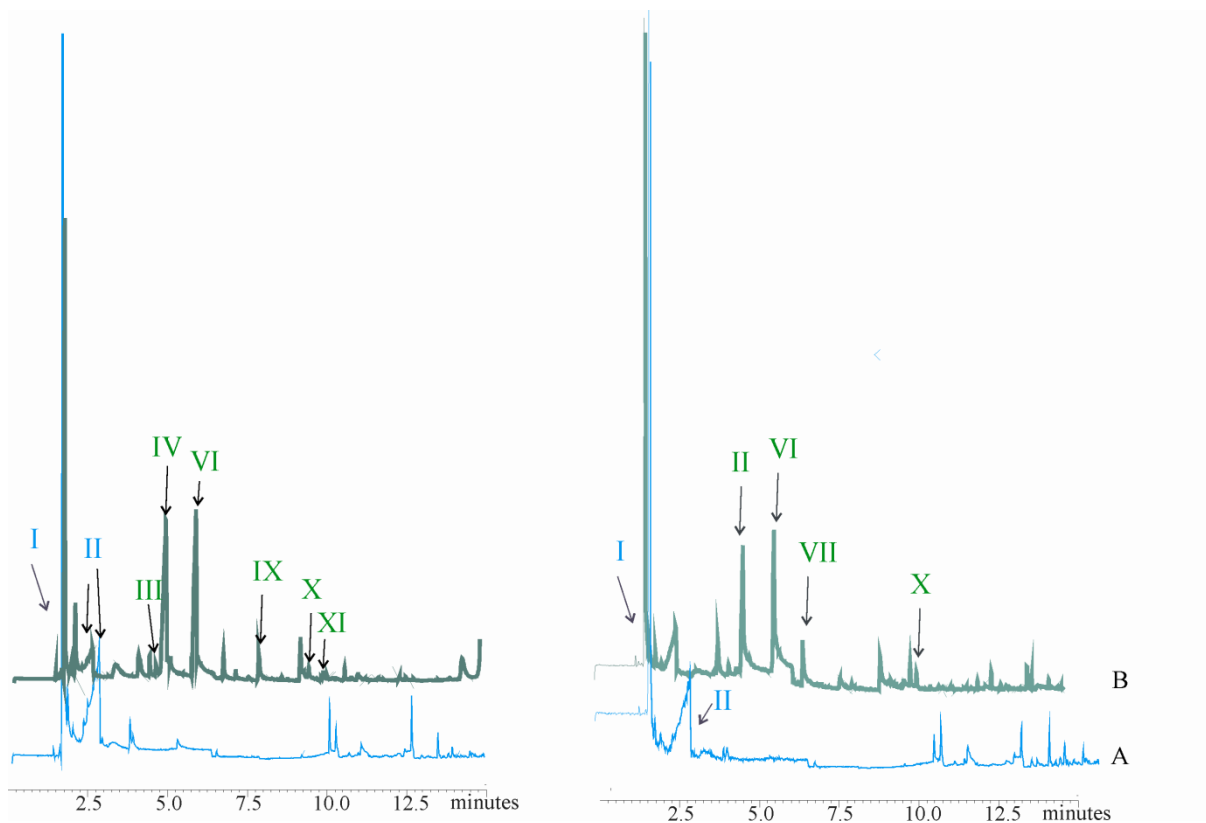


Fig. 6. GC chromatogram of organic compounds released during photo-excitation of IC_1:1 (left) and IC_1:2 (right). Roman numbers are described and identified [5].

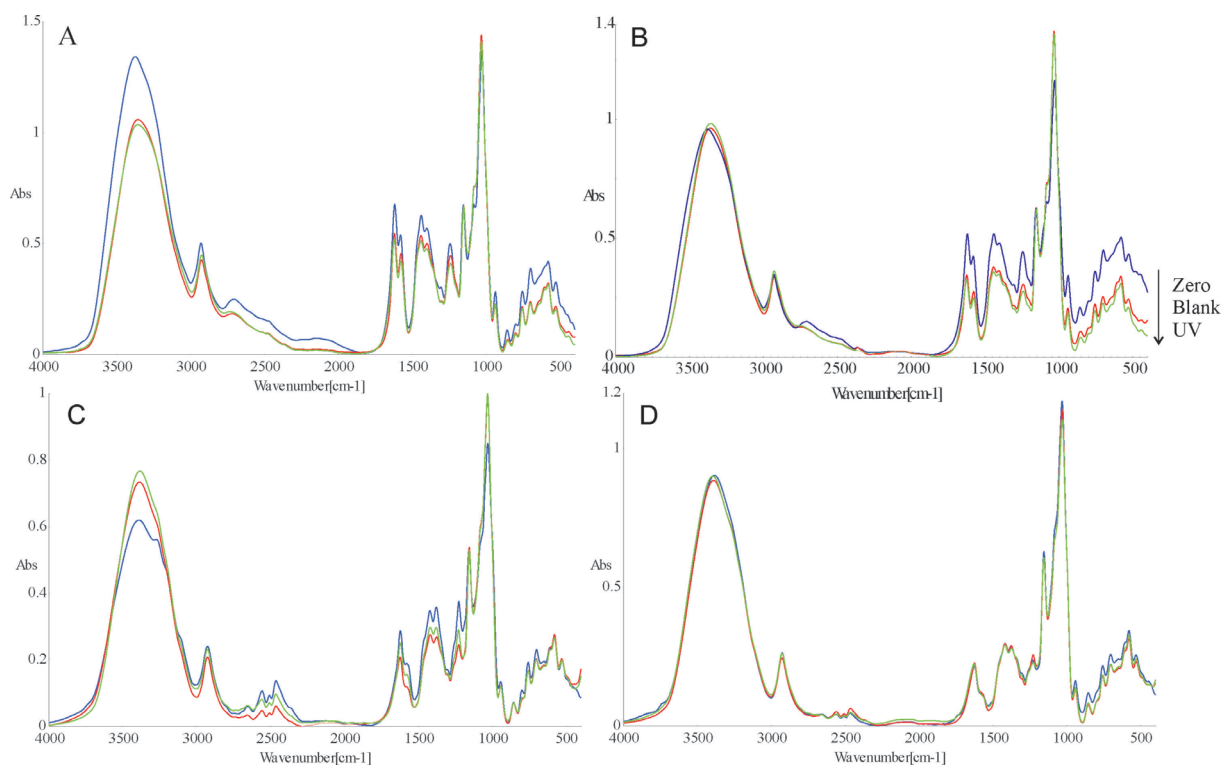


Fig. 7. FT-IR spectra of samples A) IC_1:1, B) IC_1:2, C) PM_1:1, D) PM_1:2 assigned as zero, blank and photoirradiated for 48 h.

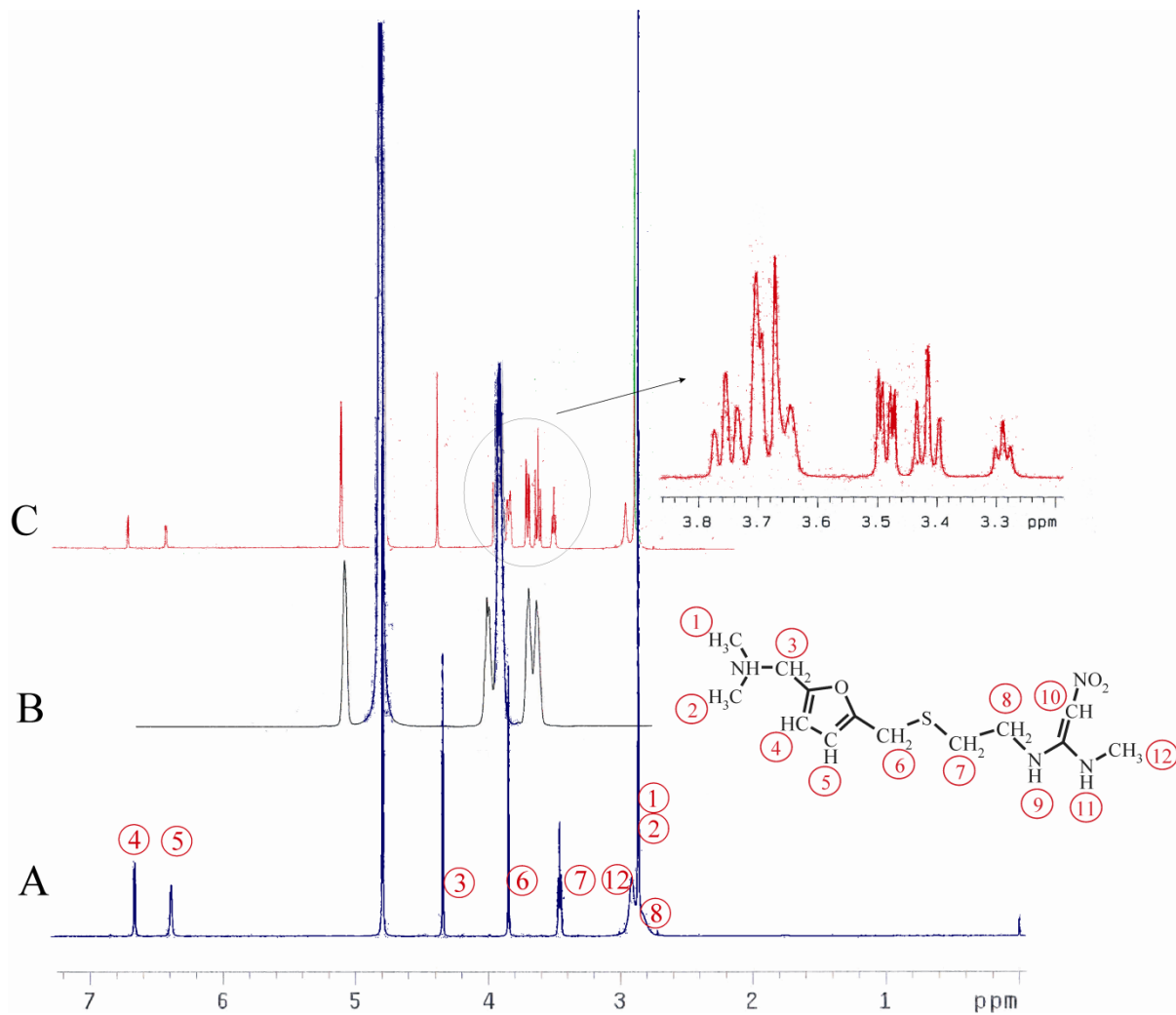


Fig. 8. ^1H NMR spectra of a) RAN, b) CD and c) IC_1:1.

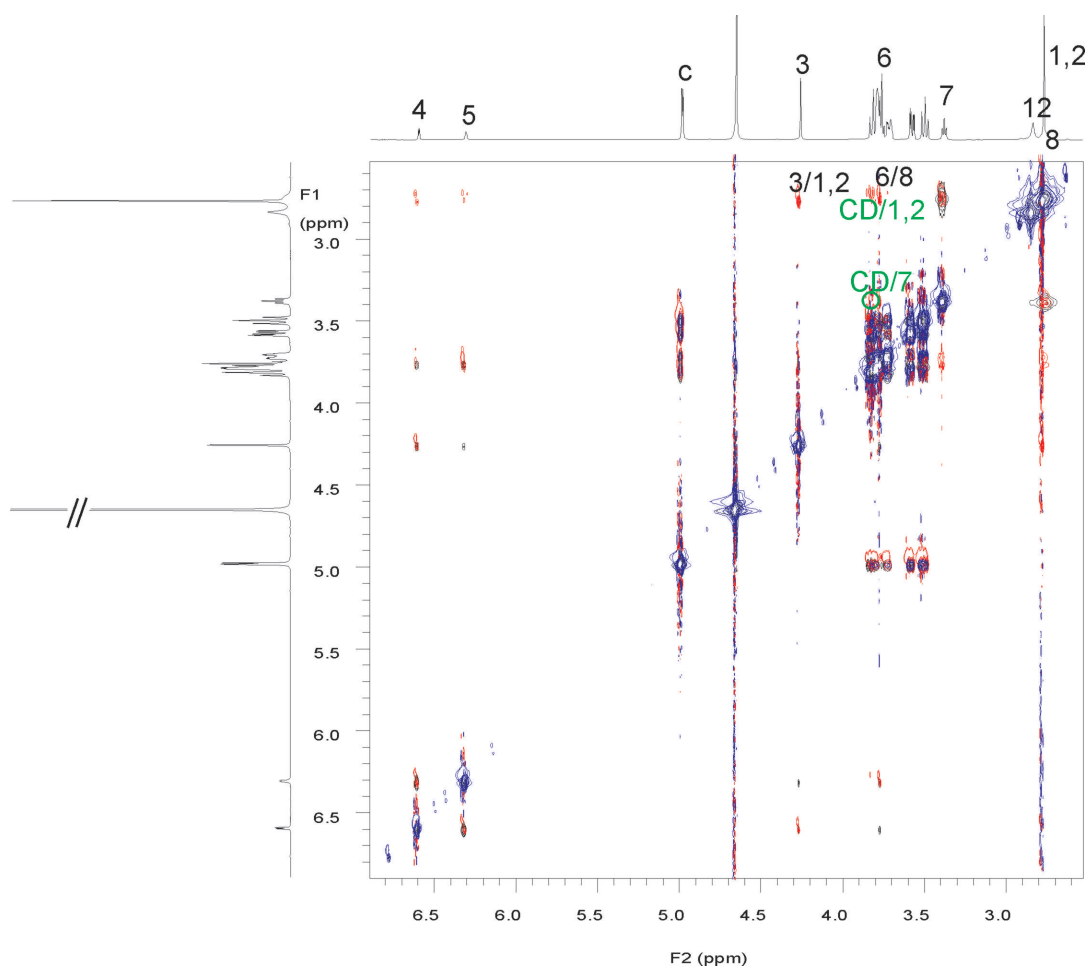


Fig. 9. Two dimensional overlaid spectra ROESY, NOESY and TOCSY of IC_{1_1} and indicated interactions.

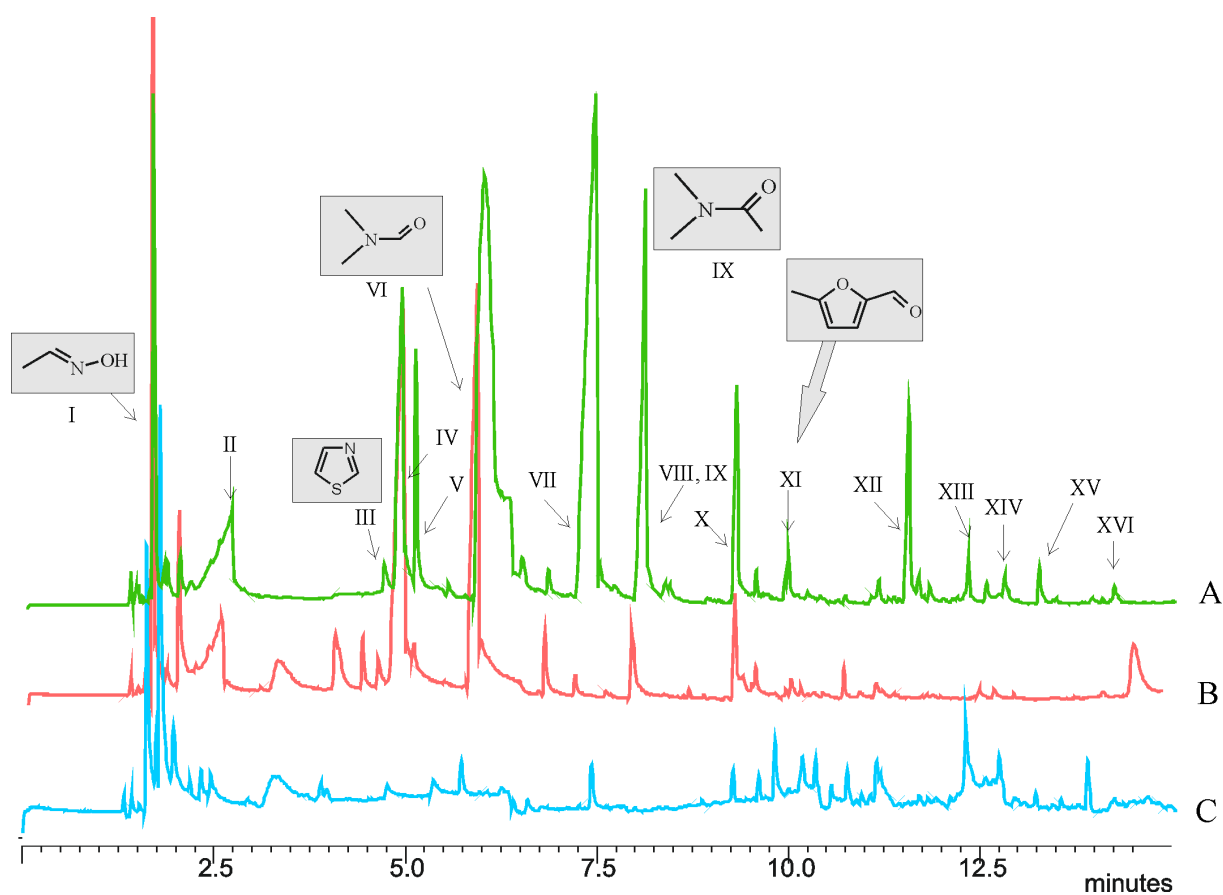


Fig. 10. GC-MS chromatogram obtained for A) bulk RAN; B) IC_1:1 and C) PM_1:1 powders after photo-exposition for 48 h in a Suntest CPS+ chamber and evaluated compounds.

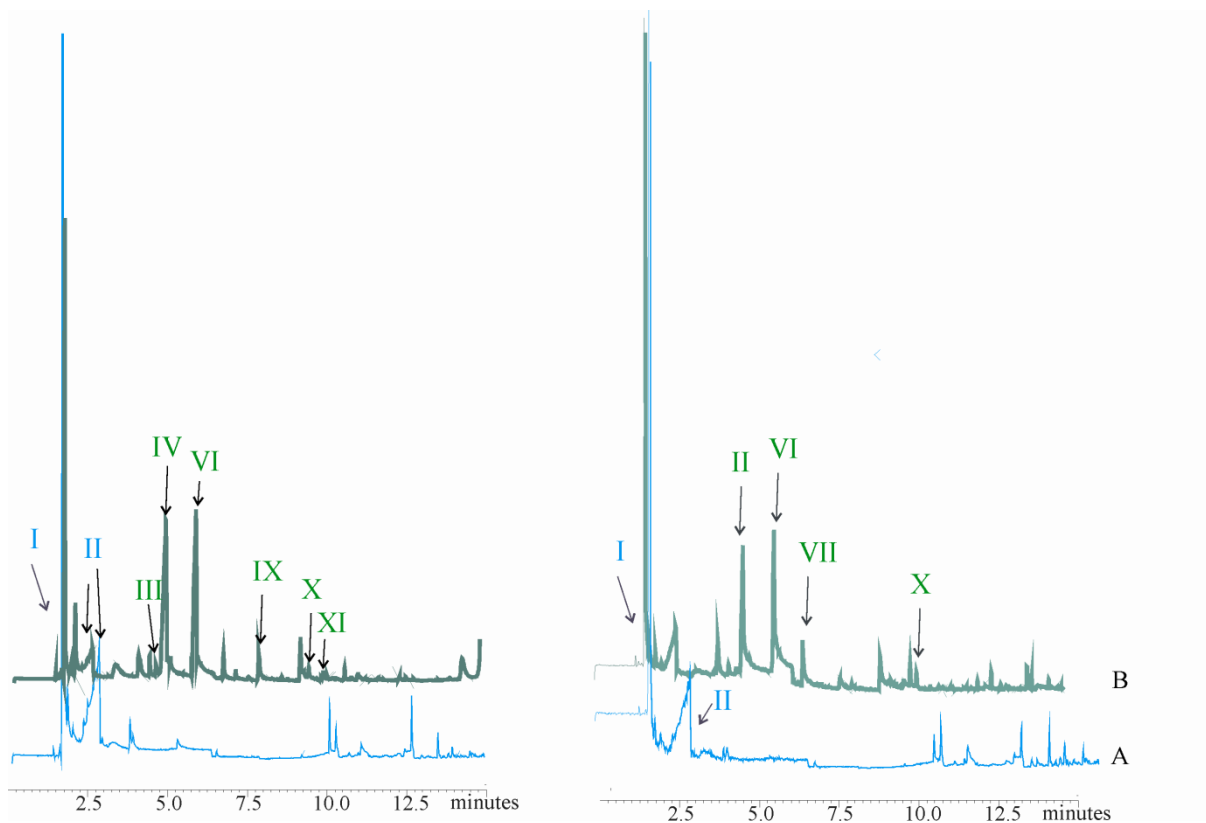


Fig. 11. GC chromatogram of organic compounds released during photo-excitation of IC_1:1 (left) and IC_1:2 (right).

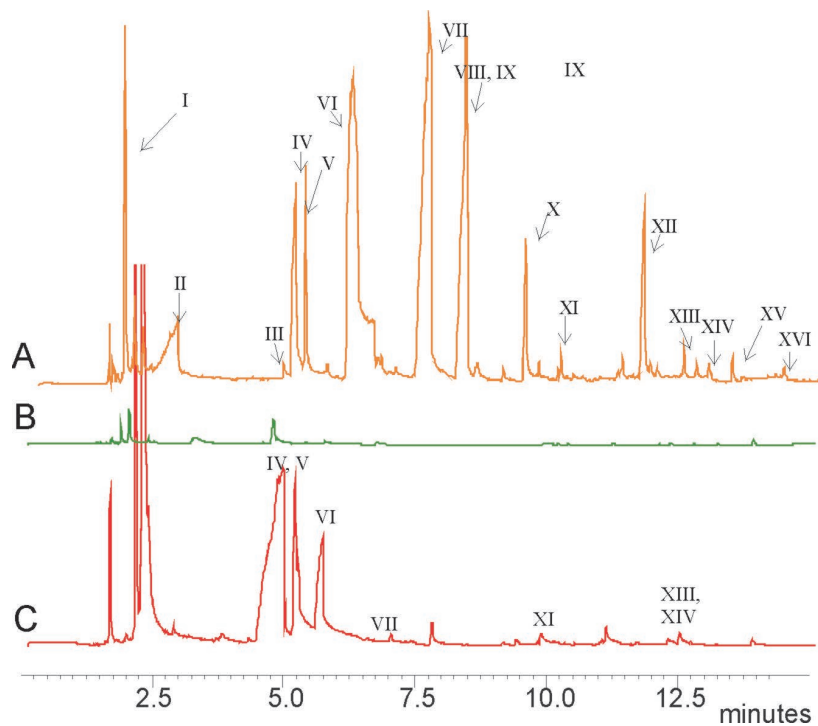


Fig. 12. GC-MS chromatogram of irradiated samples for 48h: A) RAN, B) PM_1:1 and C) PM_1:0.1

Table 1. Summary of the peak maxima and the enthalpy change for PM mixtures registered using DSC.

Sample	Peak maxima [°C] T₁; T₂; T₃; T₄	Enthalpy changes [J/g] T₁; T₂; T₃
PM_1_1	90.1; 147.2; 221.8; 250.6	155.7; 26.8; 4.6
PM_1_1_blank	92.9; 147.2; 221.2; 250.9	157.0; 32.7; 4.0
PM_1_1_uv	95.1; 145.8; 222.0; 244.2	218.4; 29.7; 6.3
PM_1_2	97.4; 147.5; 221.3; 252.9	171.7; 18.7; 3.4
PM_1_2_blank	96.8; 146.7; 221.4; 250.6	277.7; 6.6; 3.1
PM_1_2_uv	88.9; 145.4; 221.7; 259.5	137.7; 7.4; 4.2



Table 2. Chemical shifts (^1H NMR) of proton signals for RAN, inclusion complexes IC_1:1, IC_1:2 [ppm].

Assigned protons of RAN	Chemical shifts [ppm]		
	RAN	IC 1:1	IC 1:2
4	6.670	6.504	6.495
	6.663	6.498	6.490
5	6.392	6.222	6.218
3	4.343	4.168	4.159
6	3.849	3.704	3.703
	3.471	3.435	3.434
7	3.458	3.417	3.415
	3.446	3.397	3.395
12	2.914	2.751	2.746
1,2,8	2.865	2.678	2.672

Evaluation of photoprotective effect of β -cyclodextrin on the emission of volatile degradation products of ranitidine

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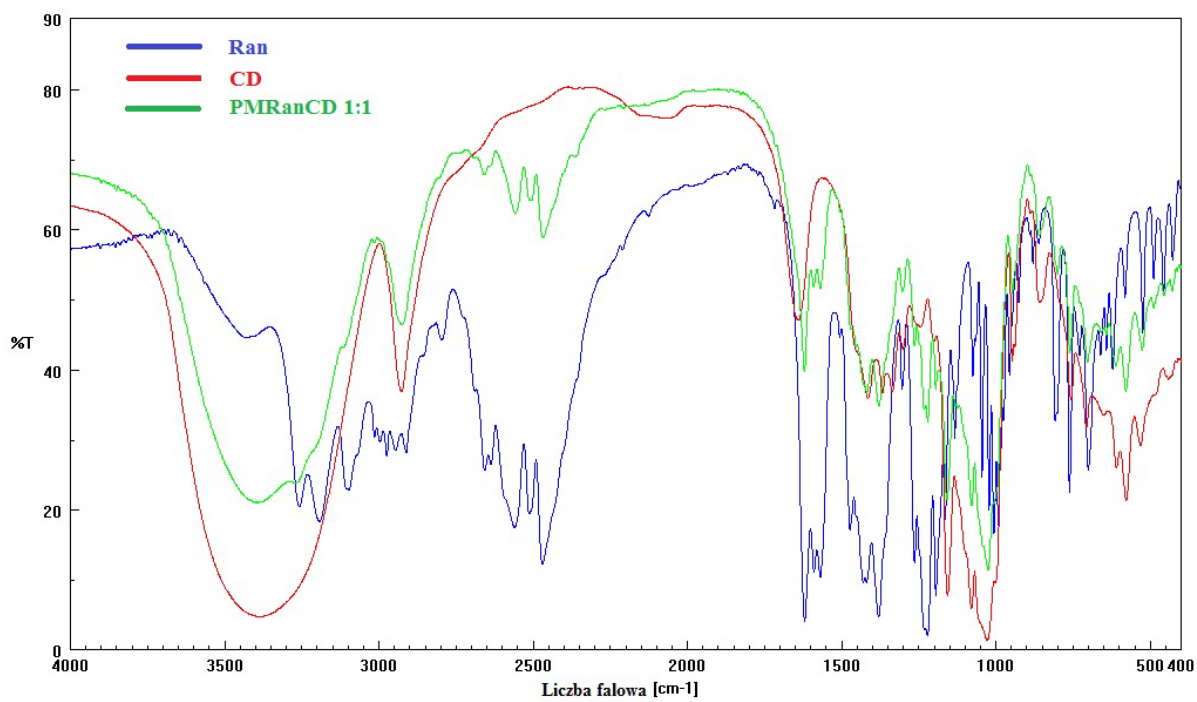


Fig. 1S. FT-IR spectra of RAN, CD and PM_1:1.

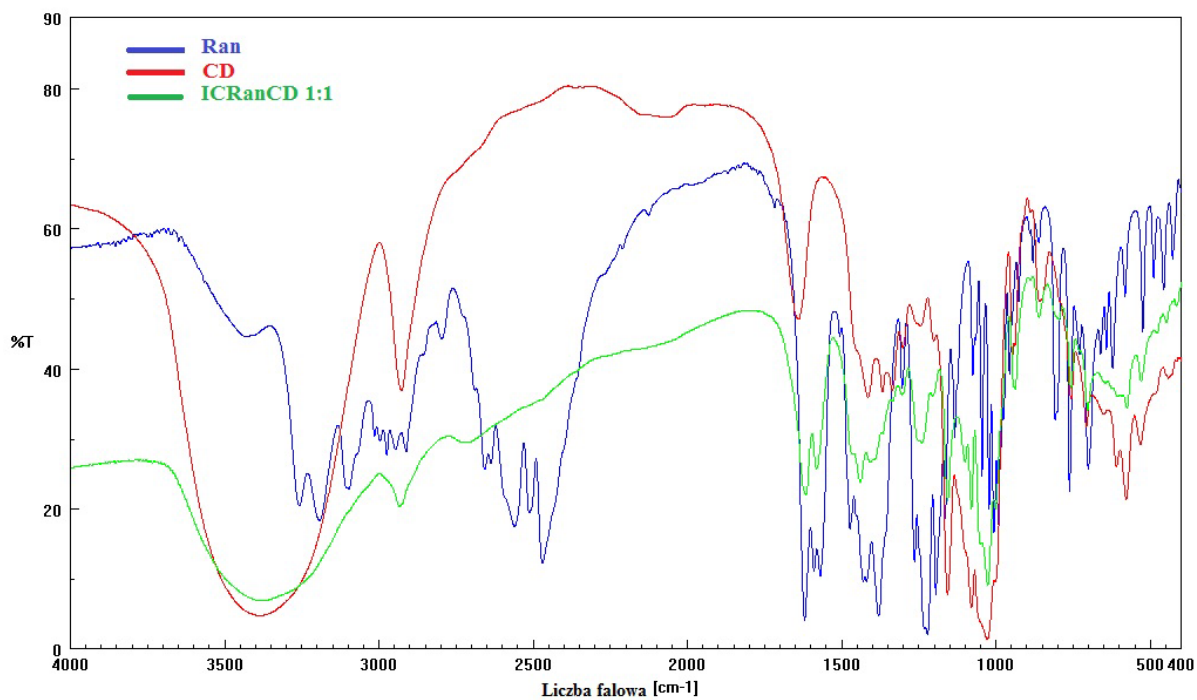


Fig.2S. FT-IR spectra of RAN, CD and IC_1:1.



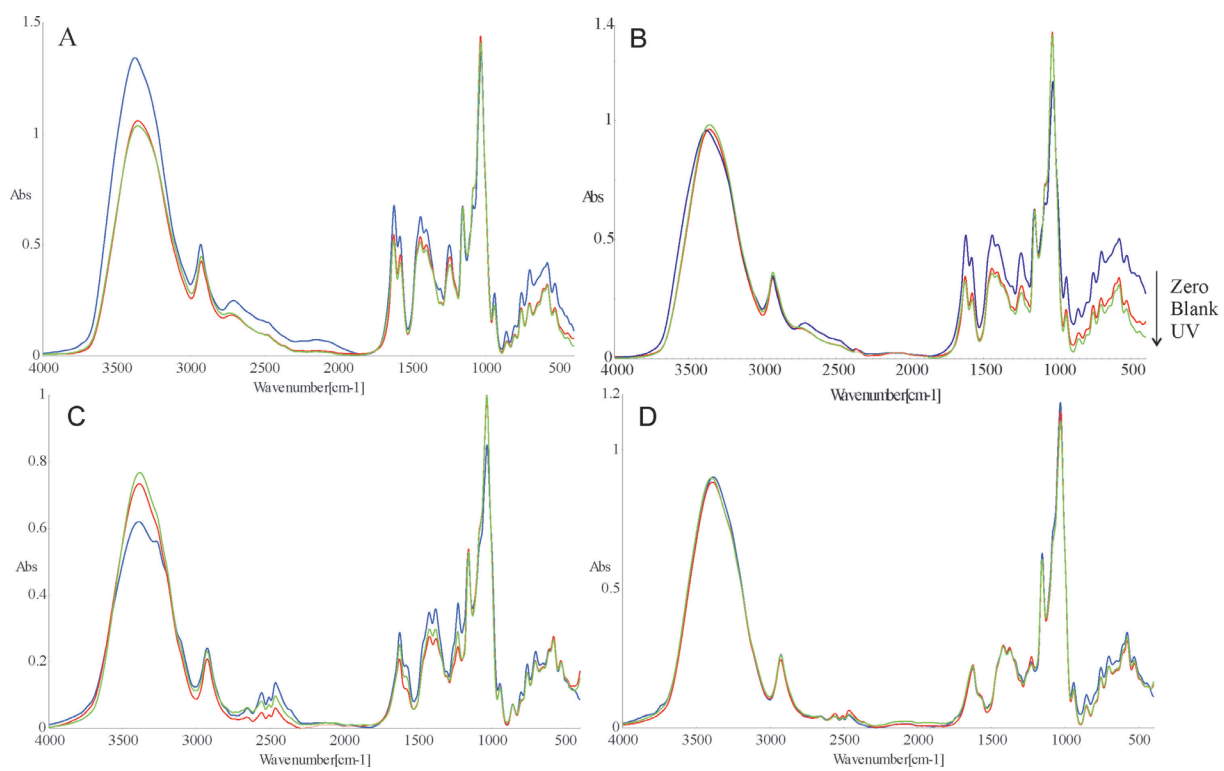


Fig. 3S. FT-IR spectra of samples A) IC_1:1, B) IC_1:2, C) PM_1:1, D) PM_1:2 assigned as zero, blank and photoirradiated for 48 h.

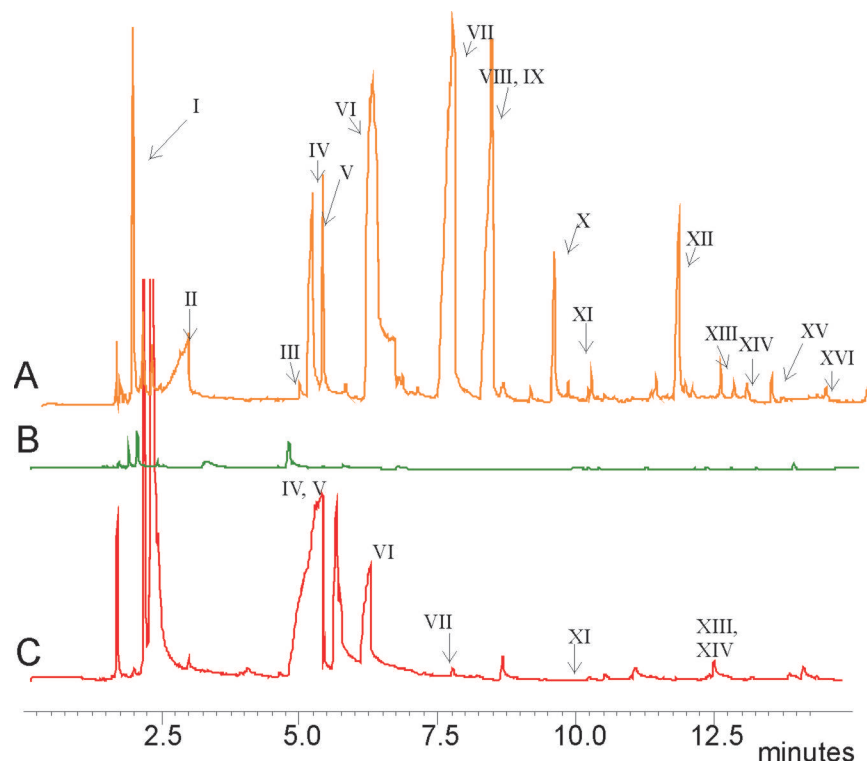


Fig. 4S. GC-MS chromatogram of irradiated samples for 48 h: A) RAN, B) PM_1:1 and C) PM_1:0.1. Roman numbers are described and identified [5].