# HERQUEICHRYSIN, A NEW PHENALENONE ANTIBIOTIC FROM *PENICILLIUM HERQUEI**

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Examination of the antibiotic metabolites of *Penicillium herquei* BAINIER and SARTORY showed two minor components accompanying atrovenetin, the main active substance. One of these was identified as deoxyherqueinone. The other, herqueichrysin, was a new compound. Chemical and spectroscopic investigation indicated that it was a $C_{20}H_{20}O_6$ phenalenone derivative related in structure to deoxyherqueinone. Demethylation of herqueichrysin yielded a product isomeric with, but different from, atrovenetin. The similar PMR and mass spectra of the two compounds suggest that the differences lie only in the position at which the dihydrofuran ring is fused to the phenalenone. In addition to these antibiotics physcion and physcion anthranol were present in cultures of *P. herquei*.

The presence of antibiotic substances in cultures of *Penicillium herquei* BAINIER and SARTORY was first reported by BURTON who named the active material herquein[1]. Similar activity was found by GOPALKRISHNAN and NARASIMHACHARI in an Indian isolate of the fungus[2], and NARASIMHACHARI *et al.*[3] identified one of the active factors in a third strain (strain I) as atrovenetin (**1a**). Atrovenetin monomethyl ether (**1b**, deoxyherqueinone) also showed antibiotic activity but had not then been found in the fungus culture[4]. Further studies on the antibiotic substances of *P. herquei* have shown that deoxyherqueinone is present with atrovenetin in the crude pigment fraction extracted from shaken cultures of *P. herquei* strain I. We were unable to obtain deoxyherqueinone from the mixture by fractional crystallization or chromatography, but acetylation gave a product with the PMR signals predicted for a mixture of atrovenetin triacetate and deoxyherquinone diacetate. The two derivatives were separated by column and thin-layer chromatography.

Deoxyherqueinone has recently been characterized as a metabolite of *P. herquei* by KRIEGLER and THOMAS[5] and, from further studies on the pigments of this fungus CASON *et al.*[6] have also concluded that deoxyherquinone is present in culture extracts. The basis for this conclusion was the presence of a molecular ion peak at *m/e* 356 in the mass spectrum of herqueinone and norherqueinone, and, after prolonged heating

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of the samples, a residual fragmentation pattern resembling that of deoxyherquinone. Our experience suggests that this evidence alone may not be conclusive since some herqueinone samples, even after attempted purification, contain the yellow pigment compound B[7] which has a mass spectrum similar to that of deoxyherqueinone. When these samples were methylated and examined by gas-liquid chromatography only two peaks, corresponding in retention times to the ethers of herqueinone and compound B, were present. After reduction and methylation such samples gave three peaks which now corresponded to the two ethers of deoxyherqueinone and that of compound B.

Compound B, henceforth named herqueichrysin, was previously isolated in trace amounts from the mycelium of stationary cultures of *P. herquei* strain I. Larger quantities are present along with physcion and physcion anthranol in the broth and mycelium of a fourth strain (CMI 28,809) after growth in shaken flasks, and at least part of the antibiotic activity of these cultures may be attributed to this substance. When assayed against *Bacillus subtilis* and *Staphylococcus aureus* by the serial tube dilution method it inhibited growth at a concentration of 1 $\mu$g/ml. Samples of herqueichrysin crystallized from chloroform retain solvent tenaciously, and the molecular formula deduced from earlier analyses[7] failed to take this into account. The elemental composition established by accurate mass measurement of the molecular ion at *m/e* 356 is $C_{20}H_{20}O_6$. Herqueichrysin is thus isomeric with deoxyherqueinone. The two substances can be distinguished by their chromatographic and spectral properties, and herqueichrysin differs in m.p. and other properties from the atrovenetin monomethyl ethers described by NEILL and RAISTRICK[8] as well as from a monomethyl ether (**1c**) prepared by methylation and subsequent saponification of atrovenetin triacetate. In fact, herqueichrysin cannot be any of the possible monomethyl ethers of atrovenetin because acetylation gave a triacetate, in contrast to the diacetate

Fig. 1. Electronic absorption spectra in ethanol of phenalenone and triacetylherqueichrysin.

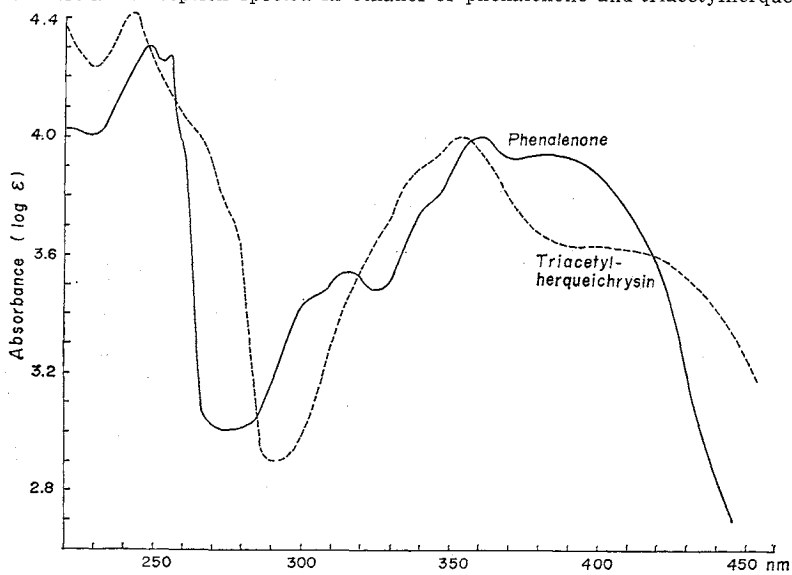


Table 1. Proton magnetic rosonance data* and assignments

| Sample | Aromatic ring | | Dihydrofuran ring | | | $OCH_3$ | $CH_3CO$ |
|---|---|---|---|---|---|---|---|
| | H | $CH_3$ | H | $CH_3$ | $(CH_3)_2$ | | |
| Atrovenetin | 2.74 | 6.97 | 4.97 q (J, 6.5) | 8.31 d (J, 6.5) | 8.29<br>8.50 | — | — |
| Triacetylatrovenetin | 2.97 d (J, 1.0) | 7.10 d (J, 1.0) | 5.25 q (J, 6.5) | 8.49 d (J, 6.5) | 8.41<br>8.65 | — | 7.60 |
| Deoxyherqueinone | 3.15 d (J, 0.8) | 7.18 d (J, 0.8) | 5.34 q (J, 6.7) | 8.53 d (J, 6.7) | 8.44<br>8.68 | 5.88 | — |
| Diacetyldeoxyherqueinone | 3.00 d (J, 1.0) | 7.11 d (J, 1.0) | 5.27 q (J, 6.5) | 8.51 d (J, 6.5) | 8.42<br>8.65 | 5.95 | 7.58<br>7.60 |
| Triacetylatrovenetin methyl ether | 3.02 d (J, 1.0) | 7.11 d (J, 1.0) | 5.32 q (J, 6.5) | 8.52 d (J, 6.5) | 8.53<br>8.75 | 6.00 | 7.50<br>7.66<br>7.68 |
| Herqueichrysin | 3.29 d (J, 0.8) | 7.11 d (J, 0.8) | 5.20 q (J, 7.0) | 8.45 d (J, 7.0) | 8.37<br>8.67 | 6.00 | — |
| Triacetylherqueichrysin | 2.82 | 7.03 | 5.47 q (J, 7.0) | 8.57 d (J, 7.0) | 8.50<br>8.72 | 6.10 | 7.59 |
| Desmethylherqueichrysin | 2.67 | 6.84 | 4.80 (J, 6.5) | 8.26 d (J, 6.5) | 8.23<br>8.47 | — | — |

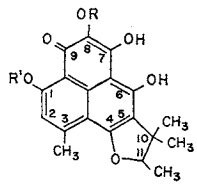
* Chemical shifts as $\tau$ values; coupling (J) in Hz; d=doublet, q=quartet. atrovenetin and desmethylherqueichrysin in trifluoroacetic acid-d, others in chloroform-$d_3$ solution.

obtained from deoxyherqueinone under comparable conditions. Since all free phenolic groups reacted, herqueichrysin evidently lacks *peri*-related carbonyl and hydroxyl functions which all atrovenetin monomethyl ethers would possess.

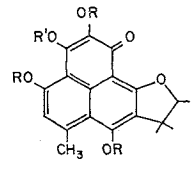
Although not derived from atrovenetin, herqueichrysin is believed to be a phenalenone derivative for several reasons. Its electronic absorption spectrum is similar to those of atrovenetin and deoxyherqueinone. Acetylation, which should cause a shift in the spectra of phenolic compounds to resemble those of the parent aromatic chromophore, changes the spectrum of herqueichrysin to resemble that of phenalenone (Fig. 1). It is noteworthy that herqueichrysin acetate lacks the series of intense maxima above 400 nm which are present in the spectrum of atrovenetin triacetate and deoxyherqueinone diacetate, and which are typical of the 9-hydroxyphenalenone chromophore[9]. The PMR spectrum of herqueichrysin is similar to those of deoxyherqueinone and the ether **1c**. All of the signals can be assigned to the protons of a tetrahydroxyphenalenone monomethyl ether fused to a trimethyldihydrofuran ring (Table 1). Formation of a triacetate accounts for the remaining hydrogen atoms in the pigment as hydroxyl functions, and the infrared spectrum of this derivative establishes the presence of a conjugated carbonyl group ($\nu_{max}$ 1660 $cm^{-1}$).

The mass spectrum of herqueichrysin is similar in many respects to that reported for deoxyherqueinone[6]. The more abundant fragment ions at *m/e* 341 ($M-CH_3$), 327 ($M-C_2H_5$), 326 ($M-2CH_3$), 323 ($M-CH_3-H_2O$) and 313 ($M-C_3H_7$), produced from herqueichrysin are common to both compounds, though their peak intensities differ. An even more striking similarity was observed in the mass spectra of atrovenetin and a product obtained from herqueichrysin by demethylation under conditions where deoxyherqueinone yielded atrovenetin. These two substances gave almost indistinguishable fragmentation patterns, although differences in their electronic, PMR,

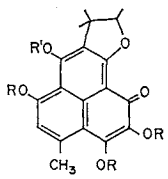
and infrared spectra, and in their chromatographic mobility showed that they were not identical. To account for their similar properties we suggest that desmethylherqueichrysin differs from atrovenetin only in the position at which the dihydrofuran and phenalenone rings are fused.



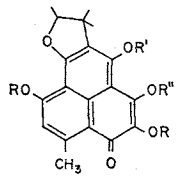
1a R=R'=H
1b R=$CH_3$, R'=H
1c R=H, R'=$CH_3$



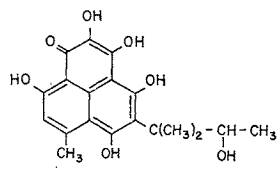
2a R=R'=H
2b R=H, R'=$CH_3$



3a R=R'=H
3b R=H, R'=$CH_3$



4a R=R'=R''=H
4b R=R''=H, R'=$CH_3$
4c R=R'=H, R''=$CH_3$



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On biogenetic grounds C-substitution of phenalenone by an isoprenoid precursor would be expected only at positions 2, 5, or 8. Substitution at position 2 can be ruled out because the PMR spectrum of herqueichrysin shows coupling between the aromatic hydrogen and methyl groups. This was confirmed by double irradiation experiments, and means that C-2, adjacent to the methyl group is the only unsubstituted position in the phenalenone nucleus. Ring closure of an isoprenoid substituent at position 2 or 5 to generate a fused furan ring could occur with any adjacent hydroxyl function, leading to structures **1a**, **2a**, **3a**, or **4a**. Closure to the 4-hydroxyl generates the atrovenetin system **1**, and the alternative mode to the 6-hydroxyl giving **2** must be considered a likely event since it implies greater biogenetic specificity in the mould than would the synthesis of **3** or **4**. After acetylation of herqueichrysin the proton at $\tau$ 3.29 shifted downfield by 0.33 ppm, and is presumed to be vicinal to a phenolic or potential phenolic function. Since this hydroxyl group cannot be *peri* to a carbonyl, position 9 would necessarily bear the methoxyl or dihydrofuran oxygen substituent, and the structure of herqueichrysin would be limited to **2b**, **3b**, **4b** or **4c**.

It has been noted[7] that ethanolic solutions of herqueichrysin are unstable and that maxima in the electronic absorption spectrum shift bathochromically to 244 and 344 nm. We have found that this change occurs only in light and is similar to the spectral changes which occur when atrovenetin is irradiated[10]. However, with atrovenetin the reaction yielding the product with $\lambda\lambda_{max}$ 259 and 340 nm is slower, and most of the atrovenetin is eventually converted *via* blue-green intermediates which are probably phenalene radicals[11] to a naphthalic anhydride with $\lambda\lambda_{max}$ 255 and 358 nm. The product with $\lambda\lambda_{max}$ 259 and 340 nm, which corresponds to the yellow compound observed by KRISHNAN *et al.*[12] in irradiated solutions of atrovenetin, has now been isolated and identified as atrovenetinone[7]. Thus the photoinduced oxidation probably follows a course similar to that postulated by MATSUURA *et al.* for dihydric phenols[13]. Herqueichrysin yields neither atrovenetinone nor the naphthalic anhydride obtained from atrovenetin and deoxyherqueinone on irradiation, confirming again that these metabolites differ by more than the pattern of substitution in ring C.

Besides the biogenetic argument which favors **4a**, the best evidence that the

difference lies in cyclization of the isoprenoid substituent to the C-6 instead of the C-4 hydroxyl is the very close correspondence in mass spectral fragmentation patterns produced from atrovenetin and desmethylherqueichrysin. In the mass spectrometer source **1a** and **2a** would be expected to interconvert readily and the equilibrium to favor the lower energy state[6]. Some support is provided by the shifts in PMR signals which occur when herqueichrysin is acetylated. Signals for the proton and methyl groups in the dihydrofuran ring were shifted upfield appreciably; this would be expected for structures **2b** or **4c** where a hydroxyl group is adjacent to the *gem* dimethyl groups of the furan ring but is less likely in **3b** and **4b** where a methoxy group occupies this position. Also, herqueichrysin is more acidic than atrovenetin or its derivatives. Its solubility in sodium bicarbonate is comparable to that of herqueinic acid which probably has structure **5**. The acidity is attributed[14] to the more stable anion generated from a phenolic group which is unable to form any intramolecular hydrogen bonds, and a similar explanation can be offered for herqueichrysin on the basis of structure **2b**.

## Experimental

Cultures

*P. herquei* strain I was obtained from Prof. C. L. PORTER, Purdue University, Lafayette, Indiana, and is maintained in the culture collection of the Prairie Regional Laboratory, National Research Council of Canada, Saskatoon, Saskatchewan, as PRL 1838. Strain CMI 28,809 was obtained from the culture collection of the Commonwealth Mycological Institute. Cultures were maintained, grown, harvested and extracted as described earlier[3,7].

Detection of deoxyherqueinone

The wet mycelium from shaken cultures of strain I was extracted with ether and the product triturated with petroleum ether (b.p. 30~60°C). The residue was crystallized once from methanol and acetylated with acetic anhydride in pyridine. It showed a PMR signal in $CDCl_3$ at $\tau$ 5.95 ($OCH_3$ of deoxyherqueinone diacetate) and broadened peaks at $\tau$ 3.00, 5.26 (quartet), 7.11, 7.61, 8.42, 8.50 (doublet) and 8.65 which were common to both atrovenetin and deoxyherqueinone acetates. Integration of the aromatic methyl and methoxyl peaks showed that the mixture contained equal amounts of each pigment. Thin-layer chromatography on silica gel (Eastman No. 6061) dipped in formamide - acetone (1 : 2) and air-dried for 10 minutes, then irrigated with benzene - petroleum ether (1 : 1), gave yellow zones corresponding to atrovenetin triacetate (Rf 0.22) and deoxyherqueinone diacetate (Rf 0.54). The two compounds were partially separated by chromatography on a column of silicic acid (Mallinckrodt SilicAR CC7) developed with benzene - chloroform (1 : 1). Deoxyherqueinone diacetate was recovered from the early fractions and identified by its infrared and mass spectra.

The mycelium from stationary cultures was extracted and herqueinone isolated as described earlier[7]. Samples in methanol were treated with excess diazomethane in ether and the product examined by gas-liquid chromatography on a 1/8 in.×6 ft. (3.18 mm× 183 cm) column of 1% methyl silicone gum rubber (SE-30) on diatomaceous earth (Applied Science Laboratories, Gaschrom Q) maintained at 230°C. Most samples of herqueinone prepared in this way gave two peaks, one corresponding in retention time to herqueinone methyl ether itself (r. t. 8.4 min.) and the other to the methyl ether of herqueichrysin (r. t. 9.6 min.). No deoxyherqueinone methyl ether was present. After reduction with zinc and acetic acid, followed by methylation and gas-liquid chromatography these samples showed only peaks corresponding to deoxyherqueinone and herqueichrysin methyl ethers.

Under the conditions used deoxyherqueinone gave two peaks with relative intensities

of 4 : 1, which were assigned from the mass spectra of samples examined in a coupled gas-chromatography-mass spectrometer system to the di- (r. t. 14.9 min.) and tri- (r. t. 11.6 min.) methyl ethers respectively. The identity of the material in peak fractions was confirmed by comparing its mass spectrum with that of reference samples.

Isolation of herqueichrysin

Shaken cultures of strain CMI 28,809 were filtered and the unadjusted filtrate (pH 4.5~5.0) was extracted with ethyl acetate. The residue from evaporation of the extract was redissolved in chloroform and herqueichrysin was extracted into aqueous sodium bicarbonate solution. The pigment was precipitated by acidification and purified by dry column chromatography on silica gel developed successively with benzene, benzene - chloroform (1 : 1) and chloroform. Herqueichrysin was eluted with chloroform as a yellow band with intense yellow fluorescence under ultraviolet light. It crystallized from chloroform as long rectangular rods, m.p. 174°C. Smaller quantities were purified by preparative thin-layer chromatography on silica gel using a chloroform - acetic acid (50 : 1) solvent mixture.

Isolation of physcion and physcion anthranol

The product obtained by ether extraction of the wet mycelium from stationary cultures of strain CMI 28,809 was triturated with petroleum-ether (b.p. 30~60°C). The soluble fraction upon concentration deposited a brown solid which was recrystallized several times to yield orange needles, m.p. 204°C, $M^+$ at *m/e* 284, identified by comparison with an authentic specimen as physcion. Physcion was also identical to fraction (d), crystallized from ether as orange yellow plates, $\lambda_{max}$ 288 and 431 nm, obtained by silicic acid chromatography of the mycelial extract from shaken cultures of *P. herquei* strain I[7] and has been reported previously as a metabolite of *P. herquei* by GALARRAGA *et al.*[15]

Subsequent extraction with benzene of the solid left after trituration of the mycelial extract with petroleum ether gave an almost colorless product, m.p. 254°C, $M^+$ at *m/e* 270, $\lambda_{max}$ in ethanol at 278 and 359 nm, which is probably physcion 10-anthranol (R. THOMAS, personal communication). A metabolite with similar properties (anthranol A, m.p. 260°C) was isolated by ASHLEY *et al.*[16] from various Aspergilli. Physcion 10-anthrone has recently been described as a metabolite of *P. herquei* by KRIEGLER and THOMAS[5].

Triacetylherqueichrysin

Herqueichrysin was heated at 100°C with acetic anhydride and pyridine for 1 hour. After ethanol had been added the solution was evaporated and the residue crystallized from methanol as needles, m.p. 185°C.

Analysis : $C_{26}H_{26}O_9$ : Calcd. : C 64.72, H 5.43.
Found : C 64.64, H 5.55.

Desmethylherqueichrysin

Herqueichrysin (100 mg) was dissolved in acetic anhydride (1 ml) and hydriodic acid (5 ml, sp. gr. 1.7) was added. The solution was heated at 120°C for 1 hour, then diluted with water. When sodium bisulfite (0.5 g) was added a yellow precipitate formed. This was removed by filtration, washed with water and crystallized from ethyl acetate as needles, m.p. 250°C (with decomposition); $\lambda_{max}$ at 254, 278 (inflexion), 350, 383 and 430 nm in ethanol; $\nu_{max}$ at 3460, 3300 (broad), 1655 and 1605 $cm^{-1}$ in potassium bromide. Thin-layer chromatography on polyamide with an acetone - acetic acid (5 : 1) solvent mixture gave a single yellow zone, Rf 0.67, for desmethylherqueichrysin, distinctly separated from that given by herqueichrysin, Rf 0.73, atrovenetin, Rf 0.29, and deoxyherqueinone, Rf 0.32. Desmethylherqueichrysin gave a deep brown color with ethanolic ferric chloride.

Atrovenetin monomethyl ether (**1c**)

Atrovenetin triacetate (200 mg) in acetone was heated under reflux for 30 hours with dimethyl sulfate (0.5 ml) and potassium carbonate (2 g). The filtered reaction mixture was evaporated and the product saponified by heating under reflux with N ethanolic sodium hydroxide (2 ml) for 15 minutes. The solution was acidified, diluted with water,

and extracted with ethyl acetate. The product after crystallization from ethanol had m.p. 239°C; $\lambda_{max}$ 280 (inflexion), 370 (inflexion), 390 and 405 nm; $\nu_{max}$ 1650 and 1600 $cm^{-1}$ in KBr.

Analysis: $C_{20}H_{20}O_6$: Calcd.: C 67.41, H 5.60, $OCH_3$ 8.7.
Found C 67.25, H 5.45, $OCH_3$ 8.1.

Irradiation of this material[10] gave a substance indistinguishable from the methoxynaphthalic anhydride obtained by oxidizing atrovenetin yellow trimethyl ether[9].

Photooxidation of atrovenetin

An ethanolic solution (1 mg/ml) of atrovenetin in a loosely covered Erlenmeyer flask was exposed to sunlight for 2 days. The product was chromatographed on a silicic acid column (SilicAR CC7 deactivated with 15 ml/100 g water) developed with benzene and then benzene-chloroform mixtures. An orange-green zone eluted with benzene - chloroform (1 : 1) contained the substance with $\lambda\lambda_{max}$ 259 and 340 nm. The material from this eluate crystallized from ethanol as amber needles, m.p. 210~215°C and was identified as atrovenetinon ethanolate by comparison (infrared, ultraviolet spectra) with an authentic specimen[7].

Mass spectra

Mass spectra were obtained with a Dupont-Consolidated Electrodynamics Corporation (CEC) model 21-491 mass spectrometer except where accurate masses were measured against a perfluorokerosene reference and a Dupont-CEC model 21-110B instrument was used. The sample was introduced directly into the source and the probe heated gradually until an ion current was detected.

Herqueichrysin

$M^+$ at *m/e* 356 (base peak) and characteristic fragment ions at *m/e* 341 (68 %), 327 (37 %), 326 (30 %), 324 (17 %), 323 (68 %), 313 (35 %), 297 (9 %), 283 (12 %), 271 (9 %), 269 (12 %), 257 (15 %), 178 (12 %), 163 (18 %). Accurate mass measurement of $M^+$, *m/e* 356.1259 (calc. for $C_{20}H_{20}O_6$, 356.1260).

Herqueichrysin triacetate

$M^+$ at *m/e* 482 (55 % of base peak) and characteristic fragment ions at *m/e* 440 (68 %), 425 (6 %), 398 (89 %), 383 (18 %), 356 (86 %), 355 (32 %), 341 (100 %), 327 (60 %), 313 (14 %), 311 (14 %), 297 (19 %), 283 (11 %).

Desmethylherqueichrysin

$M^+$ at *m/e* 342 (83 % of base peak); characteristic fragment ions at 327 (100 %), 313 (8 %), 299 (6 %), 285 (2 %), 284 (3 %), 283 (4 %), 281 (3 %), 271 (1 %), 269 (1 %), 257 (2 %), 171 (5 %), 163.5 (5 %), 163 (4 %), 156 (8 %); metastable ion at *m/e* 313.2. Accurate mass measurement of $M^+$, *m/e* 342.1099 (calcd. for $C_{19}H_{18}O_6$, 342.1103).

Atrovenetin

$M^+$ at *m/e* 342 (42 % of base peak); characteristic fragment ions at *m/e* 327 (100 %), 313 (10 %), 299 (8 %), 285 (3 %), 284 (3 %), 283 (4 %), 281 (2 %), 271 (2 %), 269 (2 %), 257 (2 %), 171 (3 %), 163.5 (4 %), 163 (3 %), 156 (13 %).

Deoxyherqueinone

$M^+$ at *m/e* 356 (50 %); characteristic fragment ions at *m/e* 341 (100 %), 327 (22 %), 326 (10 %), 323 (17 %), 313 (17 %), 311 (6 %), 297 (5 %), 283 (10 %), 269 (5 %), 257 (4 %), 178 (6 %), 163 (9 %).

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