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Synthesis of Acyl Derivatives of L-Tryptophan Containing Residues of Anthranilic and Oxalic Acids

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Abstract—Oxamoyl derivatives of dipeptide, *N*-anthranoyl-L-tryptophan, were synthesized by acylation of L-tryptophan methyl ester hydrochloride with 3,1-benzoxazinone derivatives. A one-stage procedure was developed for the synthesis of esters of *N*-[2-(*N*'-R-amidooxalyl)aminobenzoyl]-L-tryptophan.

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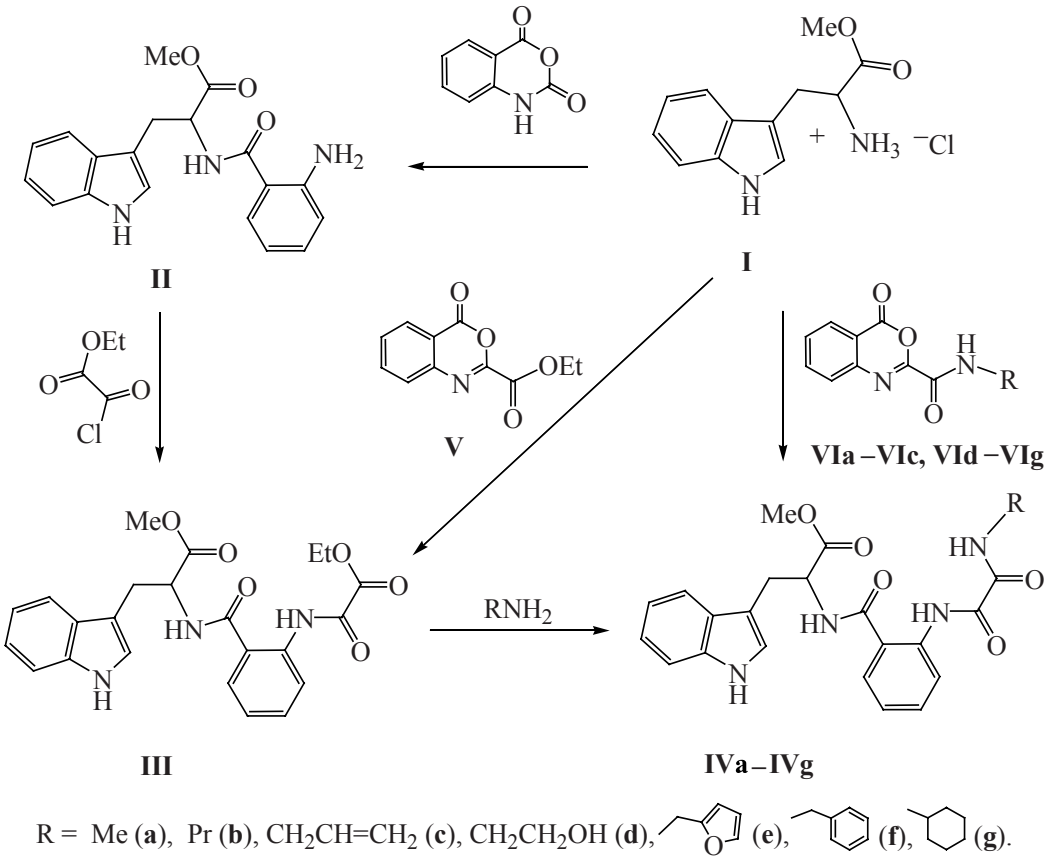
Low-molecular peptides and pseudopeptides based on L-tryptophan possess a versatile pharmacological activity. A synthetic pseudopeptide glutaryl-L-tryptophan (thymogen) exhibits an immunostimulating action [1], nonpeptide metabolite aspercillin isolated from *Aspergillus alliaceus* shows an inhibiting activity with respect to cholecystokinin receptors [2, 3]. A high affinity to some subtypes of cholecystokinin receptors was found in a series of pseudopeptides related to aspercillin and containing C-terminal fragments of anthranoyl-anthranilic acid linked to L-tryptophan [4]. The residues of the anthranilic acid and tryptophan are present in the composition of a number of metabolites: glyantrypine from *Aspergillus clavatu*s [5], fumiquinazolines F and G from *Aspergillus fumigatu*s [6], fiscalin B from *Neosartorya fischeri* and *Corynascus setosu*s [7] exhibiting high antitumor activity.

Acyl derivatives of L-tryptophan containing residues of anthranilic and oxalic acid linked in succession are unknown. Aiming at preparation of pharmacologically promising oxamoyl derivatives of *N*-(2-aminobenzoyl)-L-tryptophan we carried out their synthesis proceeding from L-tryptophan methyl ester hydrochloride (**I**) and appropriate derivatives of 3,1-benzoxazinone. The reaction of L-tryptophan alkyl esters with a 3,1-benzoxazinedione was previously described [8–10]; however, boiling in pyridine as solvent for 5 h followed by vacuum distillation [8, 9] resulted in low yields and tarring. The application of benzene as solvent [10] required a previous conversion of hydrochloride **I** into the base because of its insolubility in benzene. We used DMF as solvent in the presence of an equimolar quantity of triethanolamine and maintained the reaction mixture at 80°C for 12 h. Applying thus modified procedure we succeeded in preparation of *N*-(2-aminobenzoyl)-L-tryptophan methyl ester (**II**) in 95% yield.

The acylation of ester **II** with ethoxalyl chloride in ethyl acetate in the presence of triethanolamine led to the formation of *N*-[2-(ethoxalylamino)benzoyl]-L-tryptophan methyl ester (**III**). The reaction of diester **III** with aliphatic amines proceeded regioselectively at room temperature exclusively at the ethoxalyl fragment of the molecule, not involving the carbonyl group of the L-tryptophan residue and resulting in amidoesters **IVa–IVg**. At the use of a double excess of aliphatic amines the reaction gave the same products.

Diester **III** and amidoesters **IVa–IVc, IVe–IVg** were prepared in a single-stage process from L-tryptophan methyl ester **I** and the corresponding 3,1-benzoxazinones. Reacting ester **I** with ethyl 4-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-2-carboxylate (**V**) or with its amides **VIa–VIc, VIe–VIg** by maintaining the initial reagents in DMF at 80°C resulted in the opening of the oxazine ring and in the formation of diester **III** or amidoesters **IVa–IVg** respectively. Inasmuch as the synthesis of the corresponding N-(β-hydroxyethyl)amide of 4-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-2-carboxylic acid is difficult, the most suitable procedure for preparation of compound **IVd** is the reaction of diester **III** with aminoethanol.

Benzoxazinones **V**, **VIa–VIc, VIe–VIg** are strong electrophiles; at heating in DMF with primary aliphatic



R = Me (**a**), Pr (**b**), $CH_2CH{=}CH_2$ (**c**), CH_2CH_2OH (**d**), (**e**), (**f**), (**g**).

and aromatic amines they form *N*-(R-substituted) amides of 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid [11]. However the acylation of ester **I** with 3,1-benzoxazine **V** even at boiling the reaction mixture gave only compound **III**, most likely because of considerable steric hindrances at the benzamide moiety of molecule **II**.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian M-200 (200 MHz) from solutions in DMSO-d_6, internal reference TMS. IR spectra were recorded on a spectrophotometer Specord 75IR from KBr pellets. Mass spectra were measured on an instrument Varian 1200L with direct probe asmission into the ion source, ionization energy 70 eV, the temperature of ionization chamber 50–150°C. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 plates in a system ethyl acetate–hexane, 1:1 (development in iodine vapor).

L-tryptophan methyl ester hydrochloride (**I**) was prepared from L-tryptophan by method [12]. Ethyl 4-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-2-carboxylate (**V**) and the corresponding amides of 4*H*-3,1-benzoxazin-4-one-2-carboxylic acid **VIa–VIc, VIe–VIg** were synthesized as described in [11].

***N*-(2-Aminobenzoyl)-L- tryptophan methyl ester (II).** To 0.01 mol (2.54 g) of ester hydrochloride **I** in 10 ml of DMF was added 0.02 mol (2.98 g) of triethanolamine. The reaction mixture was stirred for 30 min, the separated triethanolamine hydrochloride was filtered off, the filtrate 0.01 mol (1.63 g) of 3,1-benzoxazinedione was added, and the solution obtained was heated at 80°C for 12 h, then it was diluted with 20 ml of water, and the precipitated oily substance was kept till it solidified. Yield 3.16 g (94%), mp 133–136°C (from ethanol). IR spectrum, cm^{-1}: 3424, 3330, 3243, 3055, 2951, 1745, 1727, 1644, 1611, 1581, 1512, 1487, 1458, 1344. ^{1}H NMR spectrum, δ, ppm: 3.25 d (2H, CH_2), 3.75 s (3H, OCH_3), 4.65 t (1H, CH), 6.25 br.s (2H, NH_2), 6.5 t ($1H_{arom}$), 6.65 d ($1H_{arom}$), 6.9–7.15 m ($3H_{arom}$), 7.18 d (1H, α-CH_{indole}), 7.35 d ($1H_{arom}$), 7.55 m ($2H_{arom}$), 8.5 d (1H, NHCO), 10.58 s (1H, NH_{indole}).

***N*-[2-(Ethoxalylamino)benzoyl]-L-tryptophan methyl ester (III).** *a.* To 0.01 mol (3.37 g) of ester **II** and 0.01 mol (1.49 g) of triethanolamine in 10 ml of ethyl acetate was added dropwise 0.01 mol (1.2 ml) of ethoxalyl

chloride, and the mixture was maintained for 12 h. Yield 3.88 g (89%), mp 145–147°C (from ethanol).

b. Using as initial compounds 2.54 g (0.01 mol) of ester hydrochloride **I** and 2.19 g (0.01 mol) of 2-ethoxycarbonyl-3,1-benzoxazine (**V**) we carried out the synthesis by the procedure described for ester **II**. Yield 2.92 g (67%), mp 145–147°C (from ethanol). IR spectrum, cm^{-1}: 3407, 1738, 1646, 1587, 1523, 1453, 1368. ^1H NMR spectrum, δ, ppm: 1.25 t (3H, $CH_2\underline{CH_3}$), 3.22 d (2H, CH_2), 3.75 s (3H, OCH_3), 4.25 q (2H, $\underline{CH_2}CH_3$), 4.65 t (1H, CH), 7.0 m ($2H_{arom}$), 7.25 m (3H, α-CH_{indole} +H_{arom}), 7.75 d (1H, H_{arom}), 8.5 d ($1H_{arom}$), 9.3 d (1H, CO<u>NH</u>CH), 10.95 s (1H, NH_{indole}), 12.5 c (1H, COCONHAr).

***N*-[2-(*N'*-R-Amidooxalyl)aminobenzoyl]-L-tryptophan methyl esters IVa–IVg.** *a*. To 0.01 mol (4.37 g) of diester **III** dissolved in 15 ml of ethanol was added 0.02 mol of an appropriate amine, the mixture was left standing for 24 h at room temperature, the separated precipitate was filtered off, recrystallized from ethyl acetate, and dried in air.

b. Using as initial compounds 2.54 g (0.01 mol) of ester hydrochloride **I** and 0.01 mol of an appropriate amide of 4-oxo-1,4-dihydro-2*H*-3,1-benzoxazine-2-carboxylic acid **VIa–VIc, VIe–VIg** the synthesis was carried out similarly to the preparation of ester **II**.

***N*-[2-(*N'*-Methylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVa).** Yield 3.45 g (82%) (*a*), 3.79 g (90%) (*b*), mp 136–138°C. IR spectrum, cm^{-1}: 3329, 1684, 1632, 1588, 1514, 1450, 1411. ^1H NMR spectrum, δ, ppm: 2.71 d (NHC<u>H</u>$_3$), 3.75 s (3H, OCH_3), 3.23 d (2H, CH_2), 4.75 q (1H, CH), 7.0 m ($2H_{arom}$), 7.25 m (3H, α-CH_{indole} + H_{arom}), 7.75 m ($2H_{arom}$), 8.0 m ($1H_{arom}$), 8.5 d ($1H_{arom}$), 8.8 d (2H, CHN<u>H</u>CO), 9.0 q (1H, CH_3N<u>H</u>COCO), 10.98 s (1H, NH_{indole}), 12.30 br.s (1H, Ar<u>NH</u>CO). Mass spectrum, *m/z* (I_{rel}, %): 421 (8.3) [*M* –1]$^+$, 390 (100) [*M* – 31]$^+$, 304 (3.6) [*M* – 117]$^+$, 292 (3.5) [*M* – 129]$^+$, 243 (3.6) [*M* – 178]$^+$, 217 (4.0) [*M* – 204]$^+$, 216 (16.9) [*M* – 205]$^+$, 215 (87.9) [*M* – 206]$^+$, 206 (5.2) [*M* – 215]$^+$, 205 (44.5) [*M* – 216]$^+$, 203 (7.7) [*M* – 218]$^+$, 202 (9.1) [*M* – 219]$^+$, 201 (35.2) [*M* – 220]$^+$, 200 (100) [*M* – 221]$^+$, 199 (4.6) [*M* – 222]$^+$, 171 (10.4) [*M* – 250]$^+$, 170 (55.0) [*M* – 251] $^+$, 159 (16.0) [*M* – 262]$^+$, 158 (9.9) [*M* – 263] $^+$, 148 (16.9) [*M* – 263] $^+$, 147 (8.9) [*M* – 262]$^+$, 146 (56.7) [*M* – 275]$^+$, 143 (7.5) [*M* – 278]$^+$, 131 (9.9) [*M* – 290]$^+$, 130 (98.9) [*M* – 291]$^+$, 120 (7.5) [*M* – 301]$^+$.

***N*-[2-(*N'*-Propylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVb).** Yield 3.24 g (72%) (*a*), 3.69 g (82%) (*b*), mp 115–117°C. IR spectrum, cm^{-1}: 3424, 3354, 3057, 1728, 1682, 1634, 1598, 1586, 1513, 1450, 1341. ^1H NMR spectrum, δ, ppm: 1.01 t (3H, $CH_2CH_2\underline{CH_3}$), 1.10 q (2H, $C\underline{H_2}CH_2CH_3$), 1.25 m (2H, $CH_2C\underline{H_2}CH_3$), 3.22 d (2H, CH_2), 3.25 C (3H, $OC\underline{H_3}$), 4,75 q (1H, C<u>H</u>), 7.0 m ($2H_{arom}$), 7.25 m (3H, α-CH_{indole} + H_{arom}), 7.6 t ($2H_{arom}$), 7.75 d ($1H_{arom}$) 8.5 d ($1H_{arom}$), 9.0 m (2H, CHN<u>H</u>CO + CH_2N<u>H</u>COCO), 10.95 s (1H, NH_{indole}), 12.25 br.s (1H, Ar<u>NH</u>CO). Mass spectrum, *m/z* (I_{rel}, %): 450 (7.5) [*M*]$^+$, 304 (3.2) [*M* – 146]$^+$, 234 (5.9) [*M* – 216]$^+$, 233 (30.6) [*M* – 217]$^+$, 216 (11.3) [*M* – 234]$^+$, 215 (100) [*M* – 235]$^+$, 202 (16.1) [*M* – 248]$^+$, 201 (68.8) [*M* – 249]$^+$, 170 (10.0) [*M* – 280]$^+$, 148 (10.0) [*M* – 302]$^+$, 147 (3.9) [*M* – 303]$^+$, 146 (35.9) [*M* – 304]$^+$, 143 (5.1) [*M* – 307]$^+$, 131 (6.3) [*M* – 302]$^+$, 130 (96.8) [*M* – 302]$^+$, 128 (3.4) [*M* – 322]$^+$, 120 (4.9) [*M* – 330]$^+$.

***N*-[2-(*N'*-Allylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVc).** Yield 3.49 g (78%) (*a*), 4.12 g (92%) (*b*), mp 152–155°C. IR spectrum, cm^{-1}: 3427, 3328, 3279, 3060, 2360, 1747, 1672, 1642, 1599, 1586, 1509, 1445, 1342. ^1H NMR spectrum, δ, ppm: 3.22 d (2H, CH_2), 3.75 s (3H, OCH_3), 3.85 t (2H, =CHC<u>H</u>$_2$NH), 4.75 q (1H, CH), 5.22 m (2H, $CH_2CH{=}C\underline{H_2}$), 5.80 m (1H, $CH_2C\underline{H}{=}CH_2$), 7.0 m ($2H_{arom}$), 7.25 m (3H, α-$CH_{indole}$ + H_{arom}), 7.75 m ($2H_{arom}$), 7.80 m ($1H_{arom}$), 8.5 d ($1H_{arom}$), 9.2 m (2H, CHN<u>H</u>CO + CH_2N<u>H</u>COCO), 10.95 s (1H, NH_{indole}), 12.30 br.s (1H, Ar<u>NH</u>CO). Mass spectrum, *m/z* (I_{rel}, %): 448 (19.5) [*M*]$^+$, 232 (3.1) [*M* – 216]$^+$, 231 (18.3) [*M* – 219]$^+$, 216 (4.5) [*M* – 232]$^+$, 215 (12.3) [*M* – 233]$^+$, 202 (17.4) [*M* – 248]$^+$, 201 (100.0) [*M* – 249]$^+$, 170 (10.0) [*M* – 302]$^+$, 159 (4.8) [*M* – 302]$^+$, 148 (3.0) [*M* – 302]$^+$, 146 (14.5) [*M* – 302]$^+$, 131 (7.9) [*M* – 302]$^+$, 330 (6.2) [*M* – 302]$^+$, 120 (3.9) [*M* – 302]$^+$.

***N*-[2-(*N'*-β-Hydroxyethylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVd).** Yield 3.25 g (72%), mp 119–123°C. IR spectrum, cm^{-1}: 3366, 3296, 2947, 1727, 1683, 1630, 1587, 1515, 1453, 1343. ^1H NMR spectrum, δ, ppm: 3.0–3.3 m (6H, CH_2 + CH_2CH_2), 3.55 s (3H, $OC\underline{H_3}$), 4.6–4.8 m (2H, C<u>H</u> + <u>H</u>OCH_2), 6.8 m ($2H_{arom}$), 7.25–7.4 m (3H, α-$CH_{indole.}$+ H_{arom}), 7.50–7.75 m ($2H_{arom}$), 7.80 m ($1H_{arom}$), 8.40 d ($1H_{arom}$), 8.75 d (2H, CHN<u>H</u>CO), 9.0 q (1H, NHCOCO), 10.95 s (1H, NH_{indole}), 12.30 br.s (1H, Ar<u>NH</u>CO). Mass spectrum, *m/z* (I_{rel}, %): 452 (4.3) [*M*]$^+$, 235 (9.9) [*M* – 217]$^+$, 217 (3.5) [*M* – 235]$^+$, 216 (5.3) [*M* – 236]$^+$, 215 (31.8) [*M* – 237]$^+$, 202 (11.9) [*M* – 250]$^+$, 201 (78.5) [*M* – 251]$^+$, 170 (9.3) [*M* – 282]$^+$, 159 (4.2) [*M* – 293]$^+$,

148 (4.0) [*M* – 304]$^+$, 147 (3.7) [*M* – 305]$^+$, 146 (17.6) [*M* – 306]$^+$, 143 (4.0) [*M* – 309]$^+$, 131 (8.2) [*M* – 321]$^+$, 130 (100) [*M* – 322]$^+$, 120 (3.9) [*M* – 332]$^+$.

***N*-[2-(*N'*-Furfurylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVe).** Yield 3.86 g (79%) (*a*), 4.00 g (82%) (*b*), mp 122–125°C. IR spectrum, cm^{-1}: 3344, 2951, 2283, 1738, 1679, 1645, 1598, 1586, 1512, 1450, 1352. ^{1}H NMR spectrum, δ, ppm: 3.10 d (2H, CH_2), 3.70 s (3H, OCH_3), 4.4 d (2H, $C\underline{H}_2NH$), 4.7 q (1H, CH), 6.10 d (1H, H^3_{fur}), 6.40 t (1H, H^4_{fur}), 7.0 m ($2H_{arom}$), 7.30 m (3H, α-CH_{indole} + H_{arom}), 7.60 m (3H, H_{arom}+ H^5_{fur}), 7.80 m ($1H_{arom}$), 8.5 d ($1H_{arom}$), 9.1 d (1H, CHN<u>H</u>CO), 9.40 t (1H, $CH_2N\underline{H}COCO$), 10.95 s (1H, NH_{indole}), 12.30 br.s (1H, Ar<u>NH</u>CO). Mass spectrum, *m/z* (I_{rel}, %): 488 (5.0) [*M*]$^+$, 215 (3.4) [*M* – 273]$^+$, 202 (6.4) [*M* – 286]$^+$, 201 (100) [*M* – 287]$^+$, 170 (8.2) [*M* – 318]$^+$, 146 (11.3) [*M* – 342]$^+$, 131 (7.5) [*M* – 357]$^+$, 130 (60.8) [*M* – 358]$^+$, 120 (3.3) [*M* – 368]$^+$.

***N*-[2-(*N'*-Benzylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVf).** Yield 4.18 g (84%) (*a*), 4.53 g (91%) (*b*), mp 96–98°C. IR spectrum, cm^{-1}: 3351, 3059, 2950, 1738, 1679, 1643, 1598, 1585, 1511, 1451, 1357. ^{1}H NMR spectrum, δ, ppm: 3.30 d (2H, CH_2), 3.60 s (3H, OCH_3), 4.4 d (2H, $C\underline{H}_2NH$), 4.7 q (1H, CH), 7.0 m ($2H_{arom}$), 7.1–7.4 m (8H, α-CH_{indole} + H_{arom}), 7.65 m ($3H_{arom}$), 7.80 d ($1H_{arom}$), 8.5 d (1H, CHN<u>H</u>CO), 8.9 br.s (1H, $CH_2N\underline{H}COCO$), 9.4 br.s (1H, Ar<u>NH</u>CO), 10.75 s (1H, NH_{indole}). Mass spectrum, *m/z* (I_{rel}, %): 498 (11.3) [*M*]$^+$, 281 (11.8) [*M* – 217]$^+$, 215 (8.4) [*M* – 283]$^+$, 202 (16.3) [*M* – 296]$^+$, 201 (100) [*M* – 398]$^+$, 130 (42.9) [*M* – 368]$^+$.

***N*-[2-(*N'*-Cyclohexylamidooxalyl)aminobenzoyl]-L-tryptophan methyl ester (IVg).** Yield 3.33 g (68%) (*a*), 2.84 g (58%) (*b*), mp 120–122°C. IR spectrum, cm^{-1}: 3339, 2932, 2855, 1737, 1675, 1648, 1585, 1511, 1450, 1350. ^{1}H NMR spectrum, δ, ppm: 1.10–1.65 m (10H, CH), 3.20 d (2H, CH_2), 3.7 s (3H, OCH_3), 4.0 m (1H, CH), 4.7 q (1H, CH), 7.0 m ($2H_{arom}$), 7.30 m (3H, α-$CH_{indole.}$+ H_{arom}), 7.60 m ($2H_{arom}$), 8.8 d (1H, CHN<u>H</u>CO), 9.0 d (1H, CHN<u>H</u>COCO), 9.2 br.s (1H, Ar<u>NH</u>CO), 10.75 s (1H, NH_{indole}). Mass spectrum, *m/z* (I_{rel}, %): 490 (7.6) [*M*]$^+$, 274 (3.4) [*M* – 216]$^+$, 273 (13.2) [*M* – 217]$^+$, 216 (10.3) [*M* – 274]$^+$, 215 (63.4) [*M* – 275]$^+$, 202 (20.5) [*M* – 288]$^+$, 201 (100) [*M* – 390]$^+$, 191 (8.2) [*M* – 299]$^+$, 170 (8.5) [*M* – 320]$^+$, 159 (6.3) [*M* – 331]$^+$, 158 (3.3) [*M* –332]$^+$, 148 (5.2) [*M* – 342]$^+$, 146 (19.4) [*M* – 344]$^+$, 143 (5.1) [*M* – 347]$^+$, 131 (8.2) [*M* – 359]$^+$, 130 (81.3) [*M* – 360]$^+$, 120 (3.3) [*M* – 370]$^+$.

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