TECHNICAL NOTE 66062

Fast LC-HRAM-MS quantification of 36 antidepressants in human plasma using the Orbitrap Exploris 120 mass spectrometer for clinical research

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Application benefits

- Accurate and confident results, simple sample preparation, and rapid quantitation
- Robust, sensitive, and selective LC and HRAM MS platforms enable increased confidence in data
- Quantification of 36 antidepressants in human plasma in a single method

Goal

Implementation of an analytical method for the quantification of 36 antidepressant drugs in human plasma on a Thermo Scientific™ Orbitrap Exploris™ 120 mass spectrometer

Introduction

Antidepressants are commonly prescribed to alleviate symptoms of depression and anxiety. There are different types of antidepressants, based on their mode of action. In addition to the classical tricyclic antidepressants (TCAs), a variety of newer antidepressants (ADP) are available for the treatment of major depressive disorders (MDD). These



include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs, NRIs) as well as tetracyclic antidepressants (TeCAs). Therapeutic drug monitoring (TDM) research, i.e., the quantification of serum/plasma concentrations of medications for dose optimization, is required to ensure a matched psychopharmacotherapy and to avoid side effects.

In this study, a fast and robust analytical method for clinical research for the quantification of 36 antidepressants in human plasma is reported. Samples were extracted by protein precipitation followed by chromatographic separation on a Thermo Scientific™ Vanquish™ Flex Binary UHPLC system. Detection was performed using an Orbitrap Exploris 120 mass spectrometer with heated electrospray ionization (HESI) operated in positive ion mode. Method performance was evaluated using the ClinMass™ LC-MS/MS calibrators, controls and internal



standards from RECIPE Chemicals + Instruments GmbH (Munich, Germany) in terms of linearity of response, accuracy, and intra- and inter-assay precision for all analytes.

Experimental

Target analytes

A list of the 36 antidepressant drugs, their internal standards, and their corresponding exact masses is presented in Table 1.

Table 1. Compounds, internal standards, chemical formulas, and exact masses of the protonated ion [M+H]*

Agomelatine C _u H ₁ ,NO ₂ 244.1332 Agomelatine-d _u 247.1520 Atomoxetine C _u H ₁ ,ON 256.16996 Atomoxetine-d _u 259.1824 Bupropion C _u H ₂ ,CINO 240.1150 Bupropion-d _u 249.1715 Citalopram C _u H ₂ ,FN _Q 325.1711 Citalopram-d _u 331.2097 Clomethizoole C _u H ₂ ,FN _Q 325.1711 Citalopram-d _u 331.2097 Clomethizoole C _u H ₂ ,FN _Q 311.1554 Desmethylicitalopram-d _u 311.713 Desmethylicitalopram C _u H ₂ ,FN _Q 296.1257 Desmethylicitalopram-d _u 301.1571 Desmethylminasarine C _u H ₂ ,FN _Q 251.1543 Reboxetine-d _u 301.1571 Desmethylminasarine C _u H ₃ ,RN _Q 282.1495 Mirtazapine-d _u 299.1840 Desmethylsertraline C _u H ₁ ,SN _Q 292.0654 Desmethylsertraline-d _u 299.1840 Desmethylsertraline C _u H ₁ ,SN _Q 298.1260 Duloxetine-d _u 299.1666 Duloxetine C _u H ₁ ,SN _Q 298.1260 Duloxetine-d _u 290.9156 </th <th>Compound name</th> <th>Formula</th> <th>Exact mass [M+H]⁺ (<i>m/z</i>)</th> <th>Internal standard name</th> <th>Exact mass [M+H]⁺ (m/z)</th>	Compound name	Formula	Exact mass [M+H] ⁺ (<i>m/z</i>)	Internal standard name	Exact mass [M+H] ⁺ (m/z)
Bupropion C _{tt} H _m QNO 240.1150 Bupropion-d ₉ 249.1715 Citalopram C _m H _m EN,O 325.1711 Citalopram-d ₀ 331.2087 Clomethiazole C _u H _m CINS 162.0139 Three-Dihydrobupropion-d ₉ 251.1871 Desmethylidiozetine C _u H _m EN,O 311.1564 Desmethylidioxotine-d ₉ 301.1571 Desmethyllimirazopine C _u H _m P,N 251.1843 Reboxetine-d ₉ 301.1571 Desmethylmiritazopine C _u H _m N,N 252.1495 Mirazapine-d ₉ 269.1840 Desmethylsertraline C _u H _u NOIN 292.0654 Desmethylsertraline-d ₄ 290.0905 Dosulepin C _u H _u NS 296.1468 Dosulepin-d ₃ 299.1656 Duloxetine G _u H _u NOS 298.1260 Duloxetine-d ₄ 305.1700 Ery-dihydro-bupropion C _u H _u S,NO 310.1413 Fluoxetine-d ₃ 315.1727 Fluoxetine C _u H _u S,NO 319.1628 Fluoxetine-d ₃ 315.1727 Fluoxetine C _u H _u C,NO 246.0195 Tramadol-d ₆ 270.2335 Hydrox	Agomelatine	C ₁₅ H ₁₇ NO ₂	244.1332	Agomelatine-d ₃	247.1520
Citalopram C ₂₀ H ₂₁ FN ₂ O 325.1711 Citalopram-d ₀ 331.2087 Clomethiazole C ₂ H ₄ ,CINS 162.0139 Threo-Dhydrobupropion-d ₉ 251.1871 Desmethylicitatoram C ₁₀ H ₁₀ FN ₂ O 311.554 Desmethylcitatopram-d ₃ 314.1743 Desmethylimoxatine C ₁₀ H ₁₀ FNO 296.1257 Desmethylimoxatine-d ₆ 301.1571 Desmethylmirtazapine C ₁₀ H ₁₀ NS 251.1543 Reboxetine-d ₆ 319.2065 Desmethylmirtazapine C ₁₀ H ₁₁ CIN 292.0654 Desmethylfertraline-d ₃ 269.1840 Desmethylsertraline C ₁₀ H ₁₁ CIN 292.0654 Desmethylfertraline-d ₄ 296.0905 Dosulepin C ₁₀ D ₂ INS 296.1468 Dosulepin-d ₃ 299.1656 Duloxetine C ₁₀ H ₁₁ NOS 298.1260 Duloxetine-d ₄ 305.1700 Ery-dihydro-burropion C ₁₀ H ₁₁ F ₁ NO 310.1413 Fluoxetine-d ₃ 315.1727 Fluoxetine C ₁₀ H ₁₂ F ₁ NO 319.1628 Fluoxetine-d ₃ 322.1816 Guarfacine C ₁₁ H ₁₂ CINO 246.0195 Tramadol-d ₃	Atomoxetine	C ₁₇ H ₂₁ NO	256.1696	Atomoxetine-d ₃	259.1884
Clomethiazole C _B H _S CINS 162.0139 Three-Dihydrobupropion-d _g 251.1871 Desmethylidialopram C _B H _B F _B NO 311.1554 Desmethylidiuoxetine-d _g 314.1743 Desmethylimiararine C _B H _B F _B NO 296.1257 Desmethylituoxetine-d _g 301.1571 Desmethylminararine C _B H _B N _B 251.1543 Reboxetine-d _g 319.2065 Desmethylmirlazapine C _B H _B N 252.1495 Mirtazapine-d ₃ 269.1840 Desmethylsertraline C _B H _B OLN 292.0654 Desmethylsertraline-d _g 296.0905 Dosulopin C _B H _B NS 298.1260 Duloxetine-d _g 305.1700 Duloxetine C _B H _B OLNO 242.1306 Threo-Dihydrobupropion-d _g 251.1871 Fluoxetine C _B H _B CNO 310.1413 Fluoxetine-d _g 315.1727 Fluoxetine C _B H _B CNO 310.1413 Fluoxetine-d _g 315.1727 Fluoxoximine C _B H _B CNO 246.0195 Tramadol-d _g 270.2335 Hydroxybupropion C _B H _B CNO 256.1099 Hydroxybupropion-d _g 262.1475	Bupropion	C ₁₃ H ₁₈ CINO	240.1150	Bupropion-d ₉	249.1715
Desmethylcitalopram C ₁₀ H _m FN _y O 311.1554 Desmethylfluoxetine d ₁₀ 314.1743 Desmethylfluoxetine C ₁₀ H _m F _m NO 296.1257 Desmethylfluoxetine-d ₈ 301.1571 Desmethylmintarapine C ₁₀ H _m N _y 251.1543 Reboxetine-d ₈ 319.2065 Desmethylsertraline C ₁₀ H _m N _y 251.1543 Reboxetine-d ₃ 269.1840 Desmethylsertraline C ₁₀ H _m N _y N 252.1495 Mirtazapine-d ₃ 296.0905 Desmethylsertraline C ₁₀ H _m ClN 292.0654 Desmethylsertraline-d ₄ 296.0905 Dosulepin C ₁₀ H _m R _m NS 298.1260 Duloxetine-d ₆ 305.1700 Ery-dihydro-bupropion C ₁₀ H _m R _m NOS 298.1260 Duloxetine-d ₆ 305.1700 Ery-dihydro-bupropion C ₁₀ H _m R _m NOS 298.1260 Duloxetine-d ₆ 315.1727 Fluoxatine C ₁₀ H _m R _m NOS 319.1628 Fluoxatine-d ₆ 315.1727 Fluoxatine C ₁₀ H _m R _m NO ₂ 319.1628 Fluoxatine-d ₆ 322.1816 Guanfacine C ₁₀ H _m R _m NO ₂ 256.109 Hydroxybupropio	Citalopram	C ₂₀ H ₂₁ FN ₂ O	325.1711	Citalopram-d ₆	331.2087
Desmethylfluoxetine C ₁₂ H ₁₆ F ₁ NO 296.1257 Desmethylfluoxetine-d ₅ 301.1571 Desmethylmiansarine C ₇₇ H ₁₈ N ₂ 251.1543 Reboxetine-d ₅ 319.2065 Desmethylmirtazapine C ₁₆ H ₁ N ₃ 252.1495 Mirtazapine-d ₅ 269.1840 Desmethylsertraline C ₁₆ H ₁₆ Cl ₆ N 292.0654 Desmethylsertraline-d ₄ 296.0905 Desulopin C ₁₆ H ₂ NS 296.1488 Dosulepin-d ₃ 299.1666 Duloxetine C ₁₆ H ₂ NS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₃ H ₂₀ CINO 242.1306 Threo-Dihydrobupropion-d ₀ 251.1871 Fluoxatine C ₁₆ H ₂₁ F ₃ N ₂ O ₂ 319.1628 Fluoxamine-d ₃ 322.1816 Guanfacine C ₁₆ H ₂₁ Cl _N Q ₀ 246.0195 Tramadol-d ₆ 270.2335 Hydroxybupropion C ₁₂ H ₂₂ Cl _{NQ} Q 256.1099 Hydroxybupropion-d ₆ 262.1475 Methylphenidate O ₁₆ H ₂₂ N ₂ Q 265.1699 Mianserin-d ₃ 268.1888 Milnacipran C ₁₆ H ₂₂ NQ 247.1805 Minacipran-d ₉	Clomethiazole	C ₆ H ₈ CINS	162.0139	Threo-Dihydrobupropion-d ₉	251.1871
Desmethylmiansarine O ₁₁ H ₁₈ N ₂ 251.1543 Reboxetine-d ₆ 319.2065 Desmethylmirtazapine C ₁₈ H ₁₁ N ₃ 252.1495 Mirtazapine-d ₃ 269.1840 Desmethylsertraline C ₁₈ H ₁₂ NS 296.0654 Desmethylsertraline-d ₄ 296.0905 Dosulepin C ₁₈ H ₂ NS 296.1468 Dosulepin-d ₄ 299.1656 Duloxetine C ₁₈ H ₂ NOS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₈ H ₂ OlNO 242.1306 Three-Dihydrobupropion-d ₆ 251.1871 Fluoxetine C ₁₈ H ₂ GINO 310.1413 Fluoxetine-d ₈ 315.1727 Fluoxetine C ₁₈ H ₂ F ₃ NO 310.1413 Fluoxetine-d ₈ 322.1816 Guardacine C ₁₈ H ₂ F ₃ N ₂ O 319.1628 Fluoxeamine-d ₈ 322.1816 Guardacine C ₁₈ H ₂ CI ₃ N ₂ O 246.0195 Tramadol-d ₈ 270.2335 Hydroxybupropion C ₃ H ₄ CI ₃ CIN ₂ O 256.1099 Hydroxybupropion-d ₉ 262.1475 Methylphenidate C ₃ H ₄ CIN ₂ N ₂ O 247.1805 Milnacipran-d ₉ 257.2433 <td>Desmethylcitalopram</td> <td>C₁₉H₁₉FN₂O</td> <td>311.1554</td> <td>Desmethylcitalopram-d₃</td> <td>314.1743</td>	Desmethylcitalopram	C ₁₉ H ₁₉ FN ₂ O	311.1554	Desmethylcitalopram-d ₃	314.1743
Desmethylmirtazapine O _{cs} H _s N _s 0 252.1495 Mirtazapine-d ₃ 269.1840 Desmethylsertraline C _{ss} H _s C _s N 292.0654 Desmethylsertraline-d ₄ 296.0905 Dosulepin C _{ss} H _s N _s NS 296.1468 Dosulepin-d ₃ 299.1656 Duloxetine C _{ss} H _s N _s NOS 298.1260 Duloxetine-d _s 305.1700 Ery-dihydro-bupropion C _{ss} H _s C _s NO 242.1306 Throe-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C _{ss} H _s SNO 310.1413 Fluoxetine-d _s 315.1727 Fluoxamine C _{ss} H _s SNO 319.1628 Fluoxetine-d _s 322.1816 Guanfacine C _{ss} H _s ClN _Q O 246.0195 Tramadol-d _g 270.2335 Hydroxybupropion C _{ss} H _s ClN _Q O 256.1099 Hydroxybupropion-d _g 282.1475 Methylphenidate C _{ss} H _{ss} NO 225.1699 Minacinan-d _{ss} 286.8188 Milliacipran C _{ss} H _{ss} NO 247.1805 Milnacipran-d _s 257.2433 Mirtazapine O _{rp} H _s N 266.1652 Mirtazapine-d _s 269.1840	Desmethylfluoxetine	C ₁₆ H ₁₆ F ₃ NO	296.1257	Desmethylfluoxetine-d ₅	301.1571
Desmethylsertraline C ₁₀ H ₁₀ Cl,N 292.0654 Desmethylsertraline-d ₄ 296.0905 Dosulepin C ₁₀ H ₂₁ NS 296.1468 Dosulepin-d ₃ 299.1656 Duloxetine C ₁₀ H ₂₀ NOS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₇ H ₂₀ ClNO 242.1306 Threo-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C ₁₇ H ₁₀ F ₃ NO 310.1413 Fluoxetine-d ₅ 315.1727 Fluvoxamine C ₁₆ H ₂₁ F ₃ N ₂ O ₂ 319.1628 Fluoxexime-d ₅ 315.1727 Fluoxamine C ₁₆ H ₂₀ N ₃ O 246.0195 Tramadol-d ₆ 270.2335 Hydroxybupropion C ₁₉ H ₁₀ ClNO ₂ 256.1099 Hydroxybupropion-d ₆ 262.1475 Methylphenidate C ₁₀ H ₁₀ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Minaserin C ₁₈ H ₂₀ N ₂ O ₂ 265.1699 Mianserin-d ₃ 268.1888 Milnacipran C ₁₈ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtzapine C ₁₇ H ₁₀ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 </td <td>Desmethylmiansarine</td> <td>C₁₇H₁₈N₂</td> <td>251.1543</td> <td>Reboxetine-d₅</td> <td>319.2065</td>	Desmethylmiansarine	C ₁₇ H ₁₈ N ₂	251.1543	Reboxetine-d ₅	319.2065
Dosulepin C ₁₉ H ₂₁ NS 296.1468 Dosulepin-d ₃ 299.1666 Duloxetine C ₁₉ H ₁₉ NOS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₉ H ₂₀ CINO 242.1306 Threo-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C ₇ H ₁₀ F ₈ NO 310.1413 Fluoxetine-d ₅ 315.1727 Fluvoxamine C ₁₉ H ₂₁ F ₈ N ₂ O ₂ 319.1628 Fluvoxamine-d ₃ 322.1816 Guarfacine C ₁₉ H ₂ CIN ₃ O 246.0195 Tramadol-d ₆ 270.2335 Hydroxybupropion C ₁₉ H ₁₉ NO ₂ 256.1099 Hydroxybupropion-d ₆ 262.1475 Methylphenidate C ₁₉ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Mianserin C ₁₉ H ₂₀ N ₂ 265.1699 Mianserin-d ₃ 268.1888 Milnacipran C ₁₉ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtazapine C ₁₉ H ₂₀ N ₂ O 269.1051 Moclobemide-d ₈ 277.1554 Nefazodone C ₂₂ H ₂₂ CIN ₂ O 269.1051 Moclobemide-d ₈ 277.1554	Desmethylmirtazapine	C ₁₆ H ₁₇ N ₃	252.1495	Mirtazapine-d ₃	269.1840
Duloxetine C ₁₈ H ₁₈ NOS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₃ H ₂₉ CINO 242.1306 Threo-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C ₁₇ H ₁₈ F ₃ NO 310.1413 Fluoxetine-d ₈ 315.1727 Fluoxamine C ₁₆ H ₂ F ₃ N ₂ O ₂ 319.1628 Fluoxamine-d ₈ 322.1816 Guanfacine C ₁₆ H ₂ Cl ₁ N ₂ O 246.0195 Tramadol-d ₈ 270.2335 Hydroxybupropion C ₁₆ H ₁₈ ClNO ₂ 256.1099 Hydroxybupropion-d ₉ 262.1475 Methylphenidate C ₁₄ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Milnacipran C ₁₆ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Milrazapine C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₆ H ₁₇ ClN ₂ O ₂ 269.1051 Moclobemide-d ₈ 277.1554 Nefazodone C ₂₆ H ₃₂ ClN ₆ O ₂ 470.2317 Nefazodone-d ₆ 476.2694 O-Desmethyltramadol C ₁₆ H ₂₅ NO ₂ 251.802 O-Desmethyltramadol-d ₆ 2	Desmethylsertraline	C ₁₆ H ₁₅ Cl ₂ N	292.0654	Desmethylsertraline-d ₄	296.0905
Duloxetine C ₁₈ H ₁₈ NOS 298.1260 Duloxetine-d ₇ 305.1700 Ery-dihydro-bupropion C ₁₈ H ₂₈ CINO 242.1306 Threo-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C ₁₉ H ₁₈ F ₃ NO 310.1413 Fluoxetine-d ₈ 315.1727 Fluoxamine C ₁₉ H ₂ F ₃ N ₂ O ₂ 319.1628 Fluvoxamine-d ₈ 322.1816 Guanfacine C ₁₉ H ₂ ClNO ₂ 246.0195 Tramadol-d ₈ 270.2335 Hydroxybupropion C ₁₉ H ₁₈ ClNO ₂ 256.1099 Hydroxybupropion-d ₉ 262.1475 Methylphenidate C ₁₄ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Misnaserin C ₁₈ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₃ 268.1888 Milnacipran C ₁₈ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtazapine C ₁₇ H ₂₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₈ H ₂₂ ClN ₂ O ₂ 269.1051 Moclobemide-d ₈ 277.1554 Nefazodone C ₂₈ H ₃₂ ClN ₅ O ₂ 470.2317 Nefazodone-d ₆ 476.2694 <	Dosulepin	C ₁₉ H ₂₁ NS	296.1468	Dosulepin-d ₃	299.1656
Ery-dihydro-bupropion C ₁₀ H ₂₀ CINO 242.1306 Threo-Dihydrobupropion-d ₉ 251.1871 Fluoxetine C ₁₇ H ₁₈ F ₃ NO 310.1413 Fluoxetine-d ₆ 315.1727 Fluvoxamine C ₁₅ H ₂₂ F ₃ N ₂ O ₂ 319.1628 Fluoxamine-d ₃ 322.1816 Guanfacine C ₉ H ₂ CI ₂ N ₃ O 246.0195 Tramadol-d ₆ 270.2335 Hydroxybupropion C ₁₉ H ₂₀ CI ₂ N ₂ O 256.1099 Hydroxybupropion-d ₆ 262.1475 Methylphenidate C ₁₄ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Minaserin C ₁₈ H ₂₀ N ₂ 265.1699 Mianserin-d ₃ 268.1888 Milnacipran C ₁₈ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtazapine C ₁₉ H ₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₅ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₅ H ₂ N ₁ N ₂ O ₂ 269.1051 Moclobemide-d ₈ 277.1554 Nefazodone C ₂₈ H ₂₂ CIN ₈ O ₂ 250.1802 O-Desmethyltramadol-d ₆ 256.2	Duloxetine	C ₁₈ H ₁₉ NOS	298.1260		305.1700
Fluoxetine C ₁₁ H ₁₈ F ₃ NO 310.1413 Fluoxetine-d ₅ 315.1727 Fluvoxamine C ₁₆ H ₂₁ F ₃ N ₂ O ₂ 319.1628 Fluvoxamine-d ₃ 322.1816 Guanfacine C ₉ H ₉ Cl ₂ N ₃ O 246.0195 Tramadol-d ₆ 270.2335 Hydroxybupropion C ₁₃ H ₁₈ ClNO ₂ 256.1099 Hydroxybupropion-d ₆ 262.1475 Methylphenidate C ₁₄ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Mianserin C ₁₆ H ₂₀ NO ₂ 265.1699 Mianserin-d ₃ 268.1888 Milracipran C ₁₈ H ₂₀ NO ₂ 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtazapine C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₅ H ₂₇ ClN ₂ O ₂ 269.1051 Moclobemide-d ₆ 277.1554 Nefazodone C ₂₅ H ₃₂ ClN ₂ O ₂ 250.1802 O-Desmethyltramadol-d ₆ 276.2694 O-Desmethyltramadol C ₄₆ H ₂₂ NO ₂ 250.1802 O-Desmethyltramadol-d ₆ 284.2491 Opipramol C ₂₂ H ₂₂ NO ₃ 364.2383 Opipramol-d ₄ 368.2635	Ery-dihydro-bupropion	10 10	242.1306	Threo-Dihydrobupropion-d	251.1871
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Fluoxetine	10 20	310.1413	Fluoxetine-d ₅	315.1727
Guanfacine C _g H _g Cl ₂ N _g O 246.0195 Tramadol-d _g 270.2335 Hydroxybupropion C ₁₃ H ₁₈ ClNO ₂ 256.1099 Hydroxybupropion-d _g 262.1475 Methylphenidate C ₁₄ H ₁₉ NO ₂ 234.1489 Methylphenidate-d ₉ 243.2054 Mianserin C ₁₈ H ₂₉ N ₂ 265.1699 Mianserin-d ₃ 268.1888 Milnacipran C ₁₅ H ₂₂ N ₂ O 247.1805 Milnacipran-d ₁₀ 257.2433 Mirtazapine C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Moclobemide C ₁₇ H ₁₉ N ₃ 266.1652 Mirtazapine-d ₃ 269.1840 Mefazodone C ₂₅ H _{3c} ClN ₃ O ₂ 470.2317 Nefazodone-d ₆ 277.1554 Nefazodone C ₂₆ H _{3c} N ₃ O ₂ 250.1802 O-Desmethyltramadol-d ₆ 256.2178 O-Desmethylvenlafaxine C ₁₆ H ₂₂ NO ₂ 264.1958 Venlafaxine-d ₆ 334.1751 <	Fluvoxamine	17 10 0	319.1628	Fluvoxamine-d ₃	322.1816
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Guanfacine	10 21 0 2 2	246.0195	Tramadol-d _e	270.2335
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Hydroxybupropion	0 0 2 0	256.1099	Hydroxybupropion-d ₆	262.1475
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Methylphenidate		234.1489	Methylphenidate-d _a	243.2054
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Mianserin		265.1699	Mianserin-d ₃	268.1888
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Milnacipran		247.1805	Milnacipran-d ₁₀	257.2433
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Mirtazapine		266.1652	Mirtazapine-d ₃	269.1840
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Moclobemide	11 10 0	269.1051	Moclobemide-d _g	277.1554
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Nefazodone	10 11 2 2	470.2317	Nefazodone-d ₆	476.2694
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	O-Desmethyltramadol	20 02 0 2	250.1802	O-Desmethyltramadol-d ₆	256.2178
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	O-Desmethylvenlafaxine		264.1958	Venlafaxine-d ₆	284.2491
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Opipramol	10 20 2	364.2383	Opipramol-d ₄	368.2635
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Paroxetine	20 20 0	330.1500	Paroxetine-d ₄	334.1751
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Reboxetine		314.1751	Reboxetine-d ₅	319.2065
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Ritalinic acid		220.1332	O-Desmethyltramadol-d _e	256.2178
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	Sertraline		306.0811	Sertraline-d ₃	309.0999
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Tianeptine			0	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			264.1958	.0	270.2335
Trazodone $C_{19}H_{22}CIN_5O$ 372.1586 Opipramol- d_4 368.2635 Venlafaxine $C_{17}H_{27}NO_2$ 278.2115 Venlafaxine- d_6 284.2491	Tranylcypromine	10 20 2	134.0964	· ·	
$ Venlafaxine \qquad \qquad C_{17}H_{27}NO_2 \qquad \qquad 278.2115 \qquad \qquad Venlafaxine-d_6 \qquad \qquad 284.2491 $		0 11	372.1586		
11 21 2				7	
				0	

Sample preparation

Reagents included three calibrators (MS9413, lot no. 1129), two controls (MS9482 lot no. 1407), and a mix of 28 deuterated internal standards (MS9412 lot no. 1478) from RECIPE. The nominal concentrations of the calibrators are given in Table 2 together with the retention times of each compound.

Samples of 50 μ L plasma were protein precipitated using 100 μ L acetonitrile containing the internal standards. Precipitated samples were vortex-mixed and kept at room temperature for 5 minutes, vortex-mixed again, and centrifuged. The supernatant was transferred to a clean vial, and 2 μ L were injected onto the LC-MS system.

Table 2. Retention time and calibration levels

Compound name	Botontion time (min)	Concentration (μg/L)				
	Retention time (min)	Li	L2	L3		
Agomelatine	3.76	5.09	122	727		
Atomoxetine	3.46	151	738	2190		
Bupropion	2.36	11.6	54.1	157		
Citalopram	3.28	16.5	86.4	259		
Clomethiazole	2.75	146	2011	6773		
Desmethylcitalopram	3.29	18.5	94.9	279		
Desmethylfluoxetine	3.84	42.7	214	656		
Desmethylmiansarine	3.19	11.8	52.7	167		
Desmethylmirtazapine	2.26	13.2	65.0	197		
Desmethylsertraline	4.09	12.4	62.5	191		
Dosulepin	3.72	16.8	83.3	244		
Duloxetine	3.79	18.5	92.5	284		
Ery-dihydro-bupropion	2.54	105	520	1568		
Fluoxetine	3.84	37.8	196	595		
Fluvoxamine	3.73	34.9	185	558		
Guanfacine	2.21	0.911	4.90	15.0		
Hydroxybupropion	2.28	145	712	2045		
Methylphenidate	2.17	3.80	18.4	51.8		
Mianserin	3.18	10.3	55.0	168		
Milnacipran	2.41	29.2	148	435		
Mirtazapine	2.29	12.0	62.0	184		
Moclobemide	2.00	156	841	2250		
Nefazodone	4.14	34.9	176	491		
O-Desmethyltramadol	1.78	83.8	422	1186		
O-Desmethylvenlafaxine	1.98	37.4	189	554		
Opipramol	3.73	41.5	205	611		
Paroxetine	3.83	19.0	96.1	299		
Reboxetine	3.42	48.0	254	753		
Ritalinic acid	1.97	24.6	116	372		
Sertraline	4.07	4.62	79.3	310		
Tianeptine	3.49	10.2	54.5	163		
Tramadol	2.10	84.5	414	1138		
Tranylcypromine	3.84	7.20	36.4	108		
Trazodone	2.99	161	1005	2752		
Venlafaxine	2.51	22.9	120	369		
Vortioxetine	4.08	8.96	41.1	119		

Liquid chromatography

LC separation was performed on a Vanquish Flex Binary UHPLC system using the following mobile phases:

Mobile phase A: 5 mM ammonium formate + 0.1% formic acid in water

Mobile phase B: 5 mM ammonium formate + 0.1% formic acid in methanol

Chromatographic separation was achieved by gradient elution on a Thermo Scientific™ Hypersil GOLD™ Phenyl 2.1 × 100 mm (1.9 μ m) analytical column (P/N 25902-102130) run at 40 °C at a flow rate of 0.5 mL/min. The chromatographic conditions are given in Table 3.

Table 3. Gradient profile

Flow rate (mL/min)	%В
0.5	10
0.5	10
0.5	50
0.5	55
0.5	95
0.5	95
0.5	10
0.5	10
	(mL/min) 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.

Mass spectrometry

Detection was performed in Full Scan acquisition mode using a resolution setting of 60,000 (FWHM) at m/z 200 and a scan range of 100–500 using an Orbitrap Exploris 120 mass spectrometer, equipped with a HESI source operated in positive ionization mode. The ion source conditions and the mass spectrometry settings are presented in Tables 4 and 5, respectively.

Data analysis

Data were acquired and processed using Thermo Scientific™ TraceFinder™ 5.1 software.

Table 4. Ion source settings

Parameter	Setting
Sheath gas	50 AU
Aux gas	10 AU
Sweep gas flow rate	0 AU
Spray voltage	3,500 V
Ion transfer tube temperature	300 °C
Vaporizer temperature	320 °C

Table 5. Mass spectrometer settings

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Method evaluation

The parameters used to evaluate the performance of the method included linearity of response, lower limit of quantification (LLOQ), intra- and inter-assay accuracy and precision for all the analytes.

Accuracy was calculated as the percent of the nominal concentrations. Precision was evaluated as the coefficient of variation (%CV). The intra-assay accuracy and precision were evaluated on two levels of QC samples extracted in replicates of five (n=5) on three different days. The interassay accuracy and precision were calculated using the same approach as for the intra-assay ones but using the full set of replicates (n=15).

The limit of quantitation (LLOQ) used in this study was set to the level of the lowest calibrator, L1. The possibility to use a lower concentration as LLOQ was investigated by dilution of the lowest calibrator.

Linearity was investigated on three calibration curves prepared and extracted on three different days by evaluation of the accuracy of the back-calculated concentration for the provided calibrators.

Results and discussion

A linear regression with 1/x weighting was used for all compounds. The mean accuracy and precision of the back-calculated calibrators are presented in Table 6. The linearity was good for all compounds in the calibrated range, with a coefficient of determination (R²) above 0.9932. The mean accuracies were within 92.9 to 106.6% and the precision was <7.3% for all compounds at all levels.

Table 6. Mean accuracy and %CV of back-calculated calibrators (n=3)

	Mean accuracy (n=3)			%CV			
	Li	L2	L3	и	L2	L3	
Agomelatine	101.5	98.2	100.3	4.3	5.1	0.8	
Atomoxetine	99.9	100.1	100.0	3.0	4.3	1.2	
Bupropion	101.9	97.4	100.8	3.1	4.4	1.3	
Citalopram	100.4	99.4	100.2	3.5	4.9	1.4	
Clomethiazole	97.8	103.0	99.2	5.3	7.3	2.1	
Desmethylcitalopram	102.0	97.2	100.8	2.7	3.9	1.1	
Desmethylfluoxetine	98.6	102.0	99.5	4.0	5.5	1.5	
Desmethylmiansarine	97.2	104.3	98.8	3.2	4.5	1.2	
Desmethylmirtazapine	100.9	103.1	99.0	5.8	4.7	1.4	
Desmethylsertraline	103.6	94.4	101.6	4.1	5.7	1.6	
Dosulepin	101.3	98.9	100.3	3.7	5.4	1.6	
Duloxetine	99.7	98.2	100.6	5.8	6.1	1.7	
Ery-dihydro-bupropion	101.4	101.3	99.5	3.0	4.5	1.4	
Fluoxetine	101.5	100.7	99.7	3.6	4.7	1.4	
Fluvoxamine	101.5	102.9	99.0	5.2	3.8	1.3	
Guanfacine	104.7	98.3	100.3	7.3	6.8	2.0	
Hydroxybupropion	101.9	99.7	100.0	3.5	4.8	1.5	
Methylphenidate	100.8	97.5	100.8	4.1	4.4	1.3	
Mianserin	102.9	100.6	99.7	5.6	5.6	1.7	
Milnacipran	101.1	99.5	100.1	2.5	4.0	1.2	
Mirtazapine	101.5	98.8	100.3	3.4	5.3	1.6	
Moclobemide	104.7	93.9	102.0	2.8	4.3	1.4	
Nefazodone	103.1	95.1	101.5	3.5	4.7	1.4	
O-Desmethyltramadol	102.1	97.9	100.6	2.5	3.7	1.2	
O-Desmethylvenlafaxine	100.8	102.8	99.1	4.4	5.3	1.7	
Opipramol	100.9	99.8	100.0	3.0	4.7	1.4	
Paroxetine	99.8	103.2	99.0	3.8	4.1	1.2	
Reboxetine	101.3	100.3	99.8	3.2	4.4	1.3	
Ritalinic acid	99.3	104.7	98.6	6.0	5.4	1.4	
Sertraline	102.4	100.9	99.7	4.5	6.1	1.5	
Tianeptine	102.8	100.9	99.6	5.5	4.6	1.5	
Tramadol	102.2	96.7	101.0	3.2	4.6	1.4	
Tranylcypromine	102.0	98.7	100.3	2.3	4.2	1.3	
Trazodone	106.6	92.9	102.2	2.9	3.9	1.3	
Venlafaxine	100.8	101.2	99.6	4.4	5.1	1.4	
Vortioxetine	99.5	97.4	100.9	5.8	4.7	1.3	

The lowest concentration of the diluted calibrators that had a mean back-calculated accuracy within 80 to 120% and a precision (CV) better than 20% are presented in Table 7. For all compounds, there is a possibility to extend the LLOQ below the lowest calibrator.

Representative chromatograms at the estimated LLOQ are presented in Figure 1, and representative calibration curves are presented in Figure 2.

The data demonstrate good accuracy and precision of the method. The intra-assay accuracy and precision results are reported in Tables 8 and 9, respectively. The intra-assay accuracy was between 85.2 and 113.9%, and the intra-assay precision was better than 6.5% for all compounds at all levels.

The inter-assay accuracy and precision results are reported in Table 10. The inter-assay accuracy was between 89.2 and 114.8%, and the inter-assay precision was better than 6.4% for all compounds at all levels.

Table 7. Estimated lower limit of quantitation (LLOQ)

Analyte	LLOQ (μg/L)
Agomelatine	0.509
Atomoxetine	15.1
Bupropion	1.16
Citalopram	1.65
Clomethiazole	48.7
Desmethylcitalopram	1.85
Desmethylfluoxetine	4.27
Desmethylmiansarine	1.18
Desmethylmirtazapine	1.32
Desmethylsertraline	4.13
Dosulepin	1.68
Duloxetine	6.17
Ery-dihydro-bupropion	10.5
Fluoxetine	3.78
Fluvoxamine	3.49
Guanfacine	0.091
Hydroxybupropion	14.5
Methylphenidate	0.380
Mianserin	1.03
Milnacipran	2.92
Mirtazapine	1.20
Moclobemide	15.6
Nefazodone	3.49
O-Desmethyltramadol	8.38
O-Desmethylvenlafaxine	3.74
Opipramol	4.15
Paroxetine	1.90
Reboxetine	4.80
Ritalinic acid	2.46
Sertraline	0.462
Tianeptine	1.02
Tramadol	8.45
Tranylcypromine	1.44
Trazodone	32.2
Venlafaxine	2.29
Vortioxetine	0.896

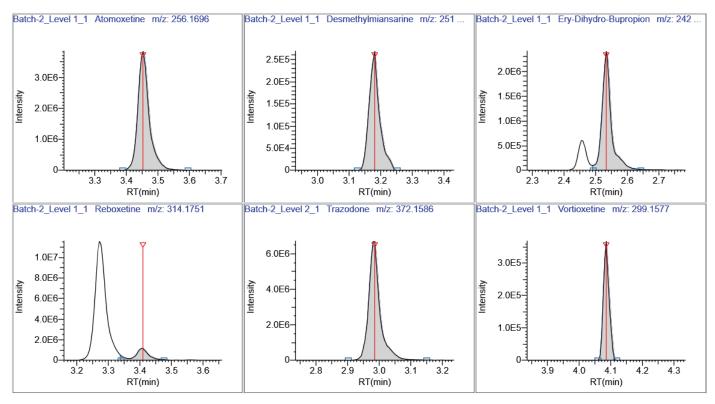


Figure 1. Representative chromatograms at the estimated LLOQ

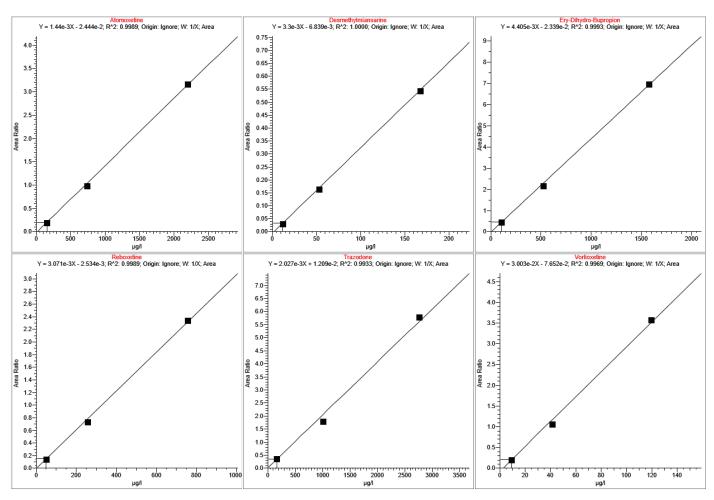


Figure 2. Representative calibration curves

Table 8. Intra-assay % accuracy of the QC samples (mean, n=5)

	QC Level 1				QC Level 2			
	Nominal conc. (μg/L)	Batch 1	Batch 2	Batch 3	Nominal conc. (μg/L)	Batch 1	Batch 2	Batch 3
Agomelatine	26.9	102.6	98.0	93.1	290	101.9	97.5	90.2
Atomoxetine	407	104.9	99.8	97.5	952	104.5	102.1	94.9
Bupropion	35.3	105.4	101.0	97.2	78.7	106.0	102.8	97.2
Citalopram	49.0	108.1	103.6	100.6	116	107.1	103.8	99.2
Clomethiazole	518	112.0	104.9	108.4	2828	114.8	111.7	101.4
Desmethylcitalopram	24.7	105.9	104.7	107.2	58.9	105.7	104.6	100.1
Desmethylfluoxetine	118	104.7	101.3	98.3	275	105.2	105.3	98.0
Desmethylmiansarine	30.0	102.3	99.3	97.5	67.6	104.8	104.3	98.3
Desmethylmirtazapine	34.9	104.4	106.1	100.5	80.6	104.2	107.8	100.2
Desmethylsertraline	34.8	113.9	108.9	113.3	82.5	109.6	106.4	111.2
Dosulepin	44.6	103.7	98.8	96.6	102	105.6	101.2	96.1
Duloxetine	50.3	100.1	99.2	95.3	115	105.4	103.5	95.4
Ery-dihydro-bupropion	279	111.1	101.6	103.8	662	108.7	102.7	100.3
Fluoxetine	105	108.9	104.2	100.2	249	107.0	104.5	98.3
Fluvoxamine	101	113.9	109.1	104.8	244	109.8	105.1	101.4
Guanfacine	2.52	104.4	103.0	95.4	5.97	106.0	105.3	95.7
Hydroxybupropion	398	104.8	99.8	97.2	903	106.1	102.3	96.8
Methylphenidate	11.1	110.9	104.9	110.4	25.3	111.4	106.8	109.2
Mianserin	29.3	108.7	104.0	98.7	69.3	107.6	106.0	98.7
Milnacipran	77.4	105.8	101.2	98.9	180	106.0	103.5	97.8
Mirtazapine	33.9	102.1	102.1	96.7	79.0	105.0	104.3	96.5
Moclobemide	474	94.9	91.6	88.6	1089	95.9	93.1	87.8
Nefazodone	103	98.1	95.1	92.4	232	102.3	98.7	92.6
O-Desmethyltramadol	227	102.1	97.8	95.7	518	103.1	99.8	94.9
O-Desmethylvenlafaxine	104	108.0	101.4	99.0	239	109.2	106.4	97.8
Opipramol	108	105.1	100.6	96.5	257	103.1	99.8	93.1
Paroxetine	50.6	110.6	103.3	102.8	121	108.0	104.4	98.7
Reboxetine	134	104.8	102.1	98.2	318	104.6	103.9	96.7
Ritalinic acid	63.2	112.6	104.3	102.2	151	110.9	105.7	97.8
Sertraline	28.9	107.2	99.4	95.6	145	110.6	105.8	99.3
Tianeptine	31.7	107.1	102.8	98.6	73.4	109.7	104.9	97.7
Tramadol	215	104.1	101.6	98.2	501	102.2	99.6	93.8
Tranylcypromine	19.6	105.7	101.2	97.2	46.9	105.8	103.2	93.5
Trazodone	548	94.1	90.2	85.2	1224	100.1	98.6	91.8
Venlafaxine	60.9	107.7	102.3	98.4	145	107.1	103.4	98.0
Vortioxetine	22.4	104.6	101.5	98.7	51.1	105.3	101.3	97.0

Table 9. Intra-assay precision of the QC samples, %CV (n=5)

	QC Level 1			QC Level 2			
	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	
Agomelatine	2.1	2.7	3.1	3.9	2.2	2.9	
Atomoxetine	2.6	2.5	2.8	3.5	2.0	3.4	
Bupropion	2.4	2.6	2.9	3.5	1.6	3.1	
Citalopram	2.5	2.6	3.2	3.1	2.6	3.5	
Clomethiazole	2.7	2.3	4.0	2.8	2.8	4.4	
Desmethylcitalopram	3.1	4.1	3.9	3.4	2.1	2.0	
Desmethylfluoxetine	2.3	3.6	3.8	3.0	1.9	4.1	
Desmethylmiansarine	3.0	2.6	3.2	3.7	2.4	3.3	
Desmethylmirtazapine	2.1	3.0	3.8	3.2	3.6	3.5	
Desmethylsertraline	4.1	5.9	6.0	6.4	5.5	4.2	
Dosulepin	1.8	2.7	2.9	3.5	1.6	3.5	
Duloxetine	3.0	3.6	2.8	2.1	3.4	3.9	
Ery-dihydro-bupropion	2.3	3.0	3.5	3.0	2.8	3.6	
Fluoxetine	2.9	3.1	3.8	3.4	2.3	3.6	
Fluvoxamine	2.0	2.9	2.5	3.4	2.1	3.7	
Guanfacine	3.0	3.9	4.6	4.4	3.2	3.7	
Hydroxybupropion	2.5	2.7	2.9	3.4	2.1	3.4	
Methylphenidate	3.3	2.8	3.4	3.0	2.5	3.9	
Mianserin	2.3	2.5	2.8	3.4	2.2	4.4	
Milnacipran	2.2	3.0	3.9	3.5	2.7	4.2	
Mirtazapine	2.3	3.4	4.2	3.3	3.1	3.8	
Moclobemide	1.8	2.2	2.2	3.5	2.1	2.9	
Nefazodone	2.3	2.4	3.2	3.1	2.8	3.2	
O-Desmethyltramadol	2.6	2.4	3.1	3.2	2.1	2.9	
O-Desmethylvenlafaxine	3.8	3.3	3.3	3.8	2.3	4.4	
Opipramol	1.9	2.5	3.2	3.0	2.5	3.4	
Paroxetine	2.7	3.8	3.5	3.0	2.2	3.8	
Reboxetine	1.9	3.0	3.1	3.3	2.6	3.4	
Ritalinic acid	4.9	3.8	2.4	3.4	1.6	3.3	
Sertraline	2.3	2.2	3.5	3.3	2.4	3.4	
Tianeptine	3.2	2.8	3.7	3.8	3.0	3.8	
Tramadol	2.2	2.4	3.6	2.9	2.6	3.1	
Tranylcypromine	2.4	4.7	1.0	3.5	2.6	4.9	
Trazodone	2.5	2.4	3.1	2.7	2.3	2.8	
Venlafaxine	2.5	2.8	2.7	3.5	2.0	3.6	
Vortioxetine	2.6	1.4	2.9	3.5	3.1	3.8	

Table 10. Inter-assay % accuracy and precision of the QC samples, %CV (n=15)

	Ассі	Accuracy		ision
	QC1	QC2	QC1	QC2
Agomelatine	97.9	96.5	4.8	5.9
Atomoxetine	100.7	100.5	4.0	5.1
Bupropion	101.2	102.0	4.2	4.5
Citalopram	104.1	103.4	4.0	4.3
Clomethiazole	108.4	109.3	4.0	6.3
Desmethylcitalopram	106.0	103.5	3.6	3.4
Desmethylfluoxetine	101.4	102.9	4.0	4.5
Desmethylmiansarine	99.7	102.5	3.4	4.2
Desmethylmirtazapine	103.7	104.1	3.7	4.5
Desmethylsertraline	112.0	109.1	5.4	5.4
Dosulepin	99.7	101.0	3.9	4.9
Duloxetine	98.2	101.4	3.6	5.3
Ery-dihydro-bupropion	105.5	103.9	4.8	4.5
Fluoxetine	104.4	103.3	4.6	4.7
Fluvoxamine	109.3	105.5	4.2	4.5
Guanfacine	100.9	102.3	5.4	5.9
Hydroxybupropion	100.6	101.7	4.1	4.8
Methylphenidate	108.8	109.1	3.9	3.4
Mianserin	103.8	104.1	4.7	4.9
Milnacipran	101.9	102.4	4.1	4.7
Mirtazapine	100.3	101.9	4.1	5.0
Moclobemide	91.7	92.2	3.5	4.6
Nefazodone	95.2	97.9	3.5	5.1
O-Desmethyltramadol	98.5	99.3	3.8	4.4
O-Desmethylvenlafaxine	102.8	104.5	5.0	5.8
Opipramol	100.7	98.7	4.3	5.2
Paroxetine	105.6	103.7	4.7	4.7
Reboxetine	101.7	101.7	3.7	4.6
Ritalinic acid	106.4	104.8	5.7	6.0
Sertraline	100.7	105.2	5.6	5.4
Tianeptine	102.8	104.1	4.6	5.9
Tramadol	101.3	98.5	3.6	4.6
Tranylcypromine	101.4	100.8	4.6	6.4
Trazodone	89.8	96.8	4.9	4.5
Venlafaxine	102.8	102.8	4.6	4.8
Vortioxetine	101.6	101.2	3.3	4.7

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Conclusion

A fast, reproducible, accurate, and sensitive liquid chromatography-HRAM mass spectrometry method was implemented for the quantification of 36 antidepressant drugs in human plasma in less than 7 min/sample. The method was analytically validated on a Vanquish Flex Binary UHPLC system interfaced to an Orbitrap Exploris 120 mass spectrometer. It offers a rapid and simple offline protein precipitation with concomitant internal standard addition. The described method meets research laboratory requirements in terms of sensitivity, linearity of response, accuracy, and precision.

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