

Analytical methods for etoxazole and its metabolites R3 and R13 in soil and method for etoxazole metabolites R4, R7, R8, and R11 in soil

Reports: ECM: EPA MRID No.: 45621721. Assaf, N. 2002. Terrestrial Field Dissipation of Etoxazole on Bare Ground in California. Laboratory Project ID: 20271. Report prepared by Valent U.S.A. Corporation, Dublin, California, and Plant Sciences, Inc., Watsonville, California, and sponsored and submitted by Valent U.S.A. Corporation, Dublin, California; 662 pages (including a duplicate of p. 3). Final report issued February 4, 2002.

ILV 1: EPA MRID No. 45621719. Stearns, J.W. 2002. Independent Laboratory Validation of Valent Method RM-37S-2, "Determination of Etoxazole, R3 and R13 Metabolites in Soil". Laboratory Project ID: V-23157. Report prepared, sponsored and submitted by Valent U.S.A. Corporation, Dublin, California; 49 pages. Final report issued January 10, 2002.

ILV 2: EPA MRID No. 45621720. Stearns, J.W. 2002. Independent Laboratory Validation of Valent Method RM-37SM, "Determination of Etoxazole Metabolites R4, R7, R8 and R11 in Soil". Laboratory Project ID: V-24045. Report prepared, sponsored and submitted by Valent U.S.A. Corporation, Dublin, California; 84 pages. Final report issued January 10, 2002.

Document No.: MRIDs 45621721 & 45621719 & 45621720

Guideline: 850.6100

Statements: ECM: The study was conducted in accordance with USEPA FIFRA Good Laboratory Practice (GLP) standards (40 CFR Part 160), with the exception of several terrestrial field dissipation field procedures (p. 3 of MRID 45621721). Signed and dated No Data Confidentiality, GLP, Quality Assurance, and Authenticity statements were provided (pp. 2-3, 5-7).

ILV 1: The study was conducted in accordance with USEPA FIFRA GLP standards (p. 3 of MRID 45621719). Signed and dated No Data Confidentiality, GLP, Quality Assurance, and Authenticity statements were provided (pp. 2-3, 5-6).

ILV 2: The study was conducted in accordance with USEPA FIFRA GLP standards (p. 3 of MRID 45621719 & 45621720). Signed and dated No Data Confidentiality, GLP, Quality Assurance, and Authenticity statements were provided (pp. 2-3, 5-6).

Classification: This analytical method is classified as unacceptable. It could not be determined that ILVs MRID 45621719 & MRID 45621720 were conducted independently of ECM MRID 45621721. No ECM performance data was submitted for the 10×LOQ fortification level for Valent Analytical Methods RM-37SM and RM-37S-2. For Valent Analytical Method RM-37SM, an insufficient number of samples (n = 3) were prepared for all soil/fortification level experiments in the ECM. ILV linearity could not be determined for Valent Analytical Method RM-37S-2. ECM linearity could

not be determined for Valent Analytical Methods RM-37SM and RM-37S-2. It could not be determined that the ILV were provided with the most difficult matrix with which to validate the methods. ILV soil matrix composed of uncharacterized homogenized soil matrix from two terrestrial field dissipation studies. The LOQ and LOD were not reported in the ILV. ECM representative chromatograms were not submitted for all fortifications. A second soil study with associated ILV should be submitted.

PC Code: 107091

Reviewed By: Zoe Ruge, M.S., Physical Scientist

Signature: 

Date: 7/3/19

Dena Barrett, PhD., Chemist

Signature: 

Date: 7/3/19

Lisa Muto, M.S.,
Environmental Scientist

Signature: 

Date: 02/01/2019

**CDM/CSS-
Dynamac JV**

Reviewers: Mary Samuel, M.S.,
Environmental Scientist

Signature: 

Date: 02/01/2019

This Data Evaluation Record may have been altered by the Environmental Fate and Effects Division subsequent to signing by CDM/CSS-Dynamac JV personnel. The CDM/CSS-Dynamac Joint Venture role does not include establishing Agency policies.

Executive Summary

The analytical method, **Valent Analytical Method RM-37S-2**, is designed for the quantitative determination of etoxazole and its metabolites R3 and R13 in soil at the LOQ of 0.02 mg/kg using LC/MS/MS. The analytical method, **Valent Analytical Method RM-37SM**, is designed for the quantitative determination of etoxazole metabolites R4, R7, R8, and R11 in soil at the LOQ of 0.01 mg/kg using LC/MS/MS. The LOQs are less than the lowest toxicological level of concern in soil for etoxazole (0.0882 mg/kg). The ECM validated the method using a soil matrix composed of characterized bulk soil samples from a terrestrial field dissipation study; ILV soil matrix composed of uncharacterized homogenized soil matrix from two terrestrial field dissipation studies. **It could not be determined that ILVs MRID 45621719 & MRID 45621720 were conducted independently of ECM MRID 45621721 since all validations were conducted at the same facility.** It could not be determined that the ILV were provided with the most difficult matrix with which to validate the method. For **Valent Analytical Method RM-37S-2**, the ILV validated the method in the second trial with the insignificant modifications including the preconditioning of the Florisil column with acetone and hexane, as well as the use of a different GC/MS system. The study author reported that the first trial had highly variable recoveries which were presumed to be due to uncontrolled evaporation in the rotary evaporator. Additional care was taken in the second trial to control the evaporation of the samples and

controls. For **Valent Analytical Method RM-37SM**, the ILV validated the method in the first trial with insignificant modifications to standard solution preparation (sonication). The analytical instrumentation and all other analytical parameters were the exact same as those in the ECM, except for the insignificant extension of the mobile phase program for analysis of R4, R7, and R8. No ECM performance data was submitted for the 10×LOQ fortification level for Valent Analytical Methods RM-37SM and RM-37S-2. For Valent Analytical Methods RM-37SM and RM-37S-2, all submitted ECM and ILV data pertaining to precision, repeatability, reproducibility, and specificity was acceptable at the LOQ, except that an insufficient number of samples were prepared at the LOQ in the ECM for Valent Analytical Method RM-37SM. For Valent Analytical Methods RM-37SM and RM-37S-2, all submitted ILV data pertaining to precision, repeatability, reproducibility, and specificity was acceptable at 10×LOQ. Regarding linearity, only ILV data for Valent Analytical Method RM-37SM was acceptable; no other linearity data was provided. For both methods, the LOQ and LOD were not reported in the ILV, and ECM representative chromatograms were not submitted for 5×LOQ fortifications.

Table 1. Analytical Method Summary

Analyte(s) by Pesticide	MRID		EPA Review	Matrix	Method Date (dd/mm/yyyy)	Registrant	Analysis	Limit of Quantitation (LOQ)	
	Environmental Chemistry Method	Independent Laboratory Validation							
Etoxazole	45621721 ¹	45621719 (ILV 1) ²	Unacceptable	Soil	10/01/2002	Valent U.S.A. Corporation	GC/MS	0.02 mg/kg	
R3									
R13									
R4		45621720 (ILV 2) ³	Unacceptable		10/01/2002		LC/MS/MS		0.01 mg/kg
R7									
R8									
R11									

1 In the ECM, the soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455 of MRID 45621721). Bulk soil samples were characterized mainly as sandy loam, with one sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

2 In the ILV 1, the soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; p. 11 of MRID 45621719). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM.

3 In the ILV 2, the soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (

V-22154, 2000-2001; pp. 11-12 of MRID 45621720). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM.

I. Principle of the Method

Valent Analytical Method RM-37S-2 (Appendix V of ECM MRID 45621721)

Samples (25 ± 0.1 g) were fortified with etoxazole, R3, and R13 fortification solutions, as necessary, and extracted with 100 mL of acetone via shaking for 30-35 minutes then filtering into a 500-mL filter flask using a Whatman GF/A glass filter paper containing a bed of *ca.* 15 g celite (Appendix V, pp. 235-236 of MRID 45621721). The original flask was rinsed twice with 20 mL of acetone, and the rinsate was combined with the extract via filtering. The filtrates were transferred to a 500-mL separatory funnel. A liquid-liquid partitioning was achieved using 100 mL of 5% sodium chloride solution and 100 mL of hexane. After vigorous shaking for one minute, the hexane layer was poured through a filter funnel containing *ca.* 50 g of sodium sulfate into a 500-mL round bottom flask. The aqueous phase was further extracted twice with 50 mL of hexane in the same manner as before. After the third hexane extract was passed through the sodium sulfate, the sodium sulfate was rinsed with two 10-mL portions of hexane. The volume of the extract was reduced to *ca.* 5 mL on a rotary-evaporator with a water bath at room temperature, then transferred to a 100-mL round bottom flask with two 10-mL portions of dichloromethane and reduced to dryness on a rotary-evaporator with a water bath at room temperature. The residue was dissolved in 5 mL hexane with sonication. The sample was passed through a Florisil solid phase extraction (SPE) cartridge (pre-conditioned with 5 mL of hexane) followed by the rinse of the sample flask with 5 mL of hexane. The analytes were eluted with 10 mL followed by 15 mL portions of hexane:acetone (4:1, v:v) into a round bottom flask. The volume of the extract was reduced to dryness on a rotary-evaporator with a water bath at room temperature. The residue was reconstituted with 5 mL of ether:hexane (1:1, v:v) via sonication. The eluate was transferred to a Silica Gel SPE cartridge (pre-conditioned with 10 mL of ether, then 10 mL of 0.1% TEA in hexane) followed by the rinse of the sample flask with 5 mL and 10 mL portions of ether:hexane (1:1, v:v). The analytes were collected into a vial and reduced to dryness on a rotary-evaporator with a water bath at room temperature. The residue was reconstituted with 2.5 mL of acetone, sonicated, then stored at $\leq 0^\circ\text{C}$ until GC analysis.

Samples were analyzed for etoxazole and metabolites R3 and R13 by a Hewlett-Packard Model 6890 GC coupled to a MS detector (Appendix V, pp. 235, 237-238 of MRID 45621721). The GC/MS conditions were as follows: Rtx[®]-200 column (30 M x 320 μm column, film thickness 0.5 μm); helium carrier gas; 2 mL/minute flow rate; oven temperature program: 95°C for 2 min., 30°C/min. to 200°C for 0 min., 20°C/min. to 310°C for 5 min.; injection volume 0.1 μL ; and SIM-ESI (selective ion monitoring-electrospray ionization; source temperature 230°C) detection. Etoxazole and metabolites R3 and R13 was identified using one quantitation ion (Q) and one qualifier ion (Q1): m/z 359.3 (Q) and m/z 330.2 (Q1) for etoxazole, m/z 361.0 (Q) and m/z 346.0 (Q1) for R3, and m/z 342.0 (Q) and m/z 357.0 (Q1) for R13. Approximate retention times were 9.75, 11.04, and 10.12 minutes for etoxazole, R3, and R13, respectively.

In the ILV, the ECM was performed as written, except that the Florisil column was preconditioned with acetone (1x) and hexane (2x), as well as the use of a different GC/MS

system (pp. 12-15 of MRID 45621719). An Agilent 6890 Series GC coupled with an Agilent 5973 Mass Selective Detector was used; all other analytical parameters were the same as those in the ECM. Monitored ions matched those reported in the ECM, except that only m/z 342.0 (Q) was monitored for R13. Approximate retention times were 9.7, 11.0, and 10.0 minutes for etoxazole, R3, and R13, respectively.

The Limit of Quantitation (LOQ) for etoxazole and its metabolites R3 and R13 in soil was 0.02 mg/kg in the ECM and ILV (Appendix V, p. 239 of MRID 45621721). In the ECM, the Limit of Detection (LOD) for soil was set at 0.01 mg/kg. In the ILV, the LOQ and LOD were not specifically reported.

Valent Analytical Method RM-37SM (Appendix II of ECM MRID 45621721)

Samples (20 ± 0.1 g) were fortified with R4, R7, R8, and R11 fortification solutions, as necessary, and extracted with 60 mL of acetone via shaking for 10-15 minutes then filtering into a 500-mL filter flask using a Whatman GF/A glass filter paper (Appendix II, pp. 183-184 of MRID 45621721). The filter cake (soil residue) was transferred back to the sample flask and extracted twice using 60 mL of acetone:0.05% acetic acid (9:1, v:v). Each extraction was performed by shaking for 10-15 minutes then filtering into the same 500-mL filter flask using a Whatman GF/A glass filter paper. The sample flask was rinsed twice with 10 mL of acetone which was added to the same 500-mL filter flask using a Whatman GF/A glass filter paper. After the combined extract was transferred to a 250 mL graduated cylinder and diluted to 200 mL with acetone, two separate 50-mL aliquots were transferred to separate 250-mL round bottom flasks. For R4, R7, and R8, the 50-mL aliquot was reduced to *ca.* 1.5-2 mL of aqueous extract on a rotary-evaporator with a water bath at $\leq 25^\circ\text{C}$. The residue was transferred to a 10-mL volumetric flask (important step) then 5 mL of methanol was used to rinse the 250-mL round bottom flask via sonication for *ca.* 15 seconds. The methanol rinse was combined with the aqueous extract in the 10-mL volumetric flask. The volume was adjusted to 10 mL using 0.05% acetic acid and the extract was stored in a refrigerator up to a week prior to LC/MS/MS analysis. For R11, the 50-mL aliquot was reduced to *ca.* 1.5-2 mL of aqueous extract on a rotary-evaporator with a water bath at $\leq 25^\circ\text{C}$. The residue was transferred to a 10-mL volumetric flask then 5 mL of 0.05% acetic acid was used to rinse the 250-mL round bottom flask via sonication for *ca.* 15 seconds. The 0.05% acetic acid rinse was combined with the aqueous extract in the 10-mL volumetric flask. The volume was adjusted to 10 mL using 0.05% acetic acid and the extract was stored in a refrigerator up to a week prior to LC/MS/MS analysis. The ECM noted that standards of R11 may require sonication to completely dissolve (Appendix II, p. 182).

Samples were analyzed for etoxazole metabolites R4, R7, and R8 by Hewlett-Packard 1100 Quaternary Pump HPLC system coupled with a Finnigan LCQ MS/MS (YMC ODS-AM column, 3.0 mm x 100 mm, 3 μm column; column temperature 35°C) using a gradient mobile phase of A) 0.05% acetic acid in HPLC water and B) methanol [percent A:B; 0.0 min. 70:30, 9.0-16.0 min. 30:70, 16.01-19.0 min. 0:100] with MS/MS-ESI (electrospray ionization; temperature 200°C) detection in positive ion mode and selected reaction monitoring (SRM; Appendix II, pp. 184-185 of MRID 45621721). Injection volume was 25 μL . R4, R7, and R8

were identified using one ion transition: m/z 377.8→220.9 for R4, m/z 377.8→360.9 for R7, and m/z 237.9→220.9 for R8. Approximate retention times were not reported.

Samples were analyzed for etoxazole metabolite R11 by Hewlett-Packard 1100 Quaternary Pump HPLC system coupled with a Finnigan LCQ MS/MS [Phenomenex Luna (C18) column, 3.0 mm x 50 mm, 3 μ m column; column temperature 35°C] using a gradient mobile phase of A) 0.05% acetic acid in HPLC water and B) methanol [percent A:B; 0.0 min. 70:30, 9.0 min. 30:70, 9.01-12.0 min. 70:30] with MS/MS-ESI (electrospray ionization; temperature 220°C) detection in negative ion mode and selected reaction monitoring (SRM; Appendix II, pp. 185-186 of MRID 45621721). Injection volume was 50 μ L. R11 was identified using one ion transition: m/z 156.9→113.1 for R11. Approximate retention time was not reported.

In the ILV, the ECM was performed as written, except all standard solutions required sonication, not just R11 as noted in the ECM (pp. 12-15, 17 of MRID 45621720). The analytical instrumentation and all other analytical parameters were the exact same as those in the ECM, except for the insignificant extension of the mobile phase program for analysis of R4, R7, and R8 [percent A:B; 0.0 min. 70:30, 9.0-16.0 min. 30:70, 16.01-19.0 min. 0:100, 19.01 min. 70:30]. monitored ion transitions matched those reported in the ECM. Approximate retention times were 15.2, 11.1, 7.7, and 6.3 minutes for R4, R7, R8, and R11, respectively.

The LOQ for etoxazole metabolites R4, R7, R8, and R11 in soil was 0.01 mg/kg in the ECM (Appendix II, p. 189 of MRID 45621721). In the ECM, the LOD for soil was set at 0.01 mg/kg, which was based on the lowest calibration standard. In the ILV, the LOQ and LOD were not specifically reported.

II. Recovery Findings

Valent Analytical Method RM-37S-2

ECM (Appendix V of MRID 45621721): Mean recoveries and relative standard deviations (RSDs) were within guideline requirements (mean 70-120%; RSD \leq 20%) for analysis of etoxazole and its metabolites R3 and R13 in one soil matrix at fortification levels of 0.02 mg/kg (LOQ) and 0.10 mg/kg (5 \times LOQ; Appendix V, pp. 245-247; DER Attachment 2). No samples were prepared at 10 \times LOQ; only four samples were prepared at the LOQ. Etoxazole and its metabolites R3 and R13 were identified using one ion transition via GC/MS analysis; a confirmation method is not usually required when HPLC/MS and/or GC/MS is used as the primary method to generate study data. The soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455). Bulk soil samples were characterized mainly as sandy loam, with on sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2%

organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

ILV (MRID 45621719): Mean recoveries and RSDs were within guideline requirements for analysis of etoxazole and its metabolites R3 and R13 in one soil matrix at fortification levels of 0.02 mg/kg (LOQ) and 0.20 mg/kg (10×LOQ; p. 14; Table 2, p. 18). Etoxazole and its metabolites R3 and R13 were identified using one ion transition via GC/MS analysis. The soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; p. 11). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM. The method was validated for the soil matrix in the second trial with the insignificant modifications including the preconditioning of the Florisil column with acetone (1x) and hexane (2x), as well as the use of a different GC/MS system (pp. 12-15). The study author reported that the first trial had highly variable recoveries which were presumed to be due to uncontrolled evaporation in the rotary evaporator. Additional care was taken in the second trial to control the evaporation of the samples and controls.

Valent Analytical Method RM-37SM

ECM (Appendix II of MRID 45621721): Mean recoveries and relative standard deviations (RSDs) were within guideline requirements (mean 70-120%; RSD ≤20%) for analysis of etoxazole metabolites R4, R7, R8, and R11 in one soil matrix at fortification levels of 0.02 mg/kg (LOQ) and 0.10 mg/kg (5×LOQ; Appendix II, pp. 194-197; DER Attachment 2). No samples were prepared at 10×LOQ; an insufficient number of samples (n = 3) were prepared at the LOQ. R4, R7, R8, and R11 were identified using one ion transition via LC/MS/MS analysis; a confirmation method is not usually required when HPLC/MS and/or GC/MS is used as the primary method to generate study data. The soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455). Bulk soil samples were characterized mainly as sandy loam, with one sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

ILV (MRID 45621720): Mean recoveries and RSDs were within guideline requirements for analysis of etoxazole metabolites R4, R7, R8, and R11 in one soil matrix at fortification levels of 0.02 mg/kg (LOQ) and 0.20 mg/kg (10×LOQ; p. 17; Table 1, p. 20). R4, R7, R8, and R11 were identified using one ion transition via LC/MS/MS analysis. The soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-

22154, 2000-2001; pp. 11-12). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM. The method was validated for the soil matrix in the first trial with insignificant modifications to standard solution preparation (sonication; pp. 12-15, 17). The analytical instrumentation and all other analytical parameters were the exact same as those in the ECM, except for the insignificant extension of the mobile phase program for analysis of R4, R7, and R8.

Table 2a. Initial Validation Method Recoveries for Etoxazole and Its Metabolites R3 and R13 in Soil - Valent Analytical Method RM-37S-2

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%) ¹	Relative Standard Deviation (%) ¹
Soil ²						
GC/MS ³						
Etoxazole	0.02 (LOQ)	4	71-81	78	5	6
	0.1	6	91-96	94	2	2
R3	0.02 (LOQ)	4	76-90	82	6	8
	0.1	6	94-110	102	8	8
R13	0.02 (LOQ)	4	76-86	81	4	5
	0.1	6	90-95	93	2	2

Data (uncorrected recovery results, Appendix V, p. 239) were obtained from Appendix V, pp. 245-247 of MRID 45621721. **Red values** indicate values that are out of compliance with the guidelines.

1 Standard deviations and relative standard deviations were reviewer-calculated since these values were not reported in the study report. Rules of significant figures was followed.

2 The soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455). Bulk soil samples were characterized mainly as sandy loam, with one sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

3 Etoxazole and metabolites R3 and R13 was identified using one quantitation ion (Q) and one qualifier ion (Q1): m/z 359.3 (Q) and m/z 330.2 (Q1) for etoxazole, m/z 361.0 (Q) and m/z 346.0 (Q1) for R3, and m/z 342.0 (Q) and m/z 357.0 (Q1) for R13.

Table 2b. Independent Validation Method Recoveries for Etoxazole and Its Metabolites R3 and R13 in Soil - Valent Analytical Method RM-37S-2

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
Soil						
GC/MS						
Etoxazole	0.02 (LOQ)	5	91.2-105	102	7.0	6.9
	0.20	5	91.3-103	96.4	4.4	4.5
R3	0.02 (LOQ)	5	80.9-120	96.7	14.5	15.0
	0.20	5	86.0-101	93.3	7.2	7.7
R13	0.02 (LOQ)	5	85.7-99.9	91.5	5.3	5.8
	0.20	5	81.7-92.2	87.1	4.3	4.9

Data (uncorrected recovery results, p. 13) were obtained from p. 14; Table 2, p. 18 of MRID 45621719.

- The soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; p. 11). Soil and soil samples were not characterized.
- Etoxazole and metabolites R3 and R13 was identified using one quantitation ion (Q) and one qualifier ion (Q1): m/z 359.3 (Q) and m/z 330.2 (Q1) for etoxazole, m/z 361.0 (Q) and m/z 346.0 (Q1) for R3, and m/z 342.0 (Q) and m/z 357.0 (Q1) for R13.

Table 3a. Initial Validation Method Recoveries for Etoxazole Metabolites R4, R7, R8, and R11 in Soil - Valent Analytical Method RM-37SM

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%) ¹	Relative Standard Deviation (%) ¹
Soil²						
LC/MS/MS ³						
R4	0.02 (LOQ)	3	84-98	91	7	8
	0.1	6	88-120	104	12	11
R7	0.02 (LOQ)	3	88-100	93	6	7
	0.1	6	91-105	98	5	5
R8	0.02 (LOQ)	3	88-109	98	11	11
	0.1	6	96-115	105	6	6
R11	0.02 (LOQ)	3	97-112	104	8	7
	0.1	6	83-94	89	5	6

Data (uncorrected recovery results, Appendix II, pp. 187-188) were obtained from Appendix II, pp. 194-197 of MRID 45621721. **Red values** indicate values that are out of compliance with the guidelines.

1 Standard deviations and relative standard deviations were reviewer-calculated since these values were not reported in the study report. Rules of significant figures was followed.

2 The soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455). Bulk soil samples were characterized mainly as sandy loam, with on sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

3 Analytes were identified using one ion transition: m/z 377.8→220.9 for R4, m/z 377.8→360.9 for R7, m/z 237.9→220.9 for R8, and m/z 156.9→113.1 for R11.

Table 3b. Independent Validation Method Recoveries for Etoxazole Metabolites R4, R7, R8, and R11 in Soil - Valent Analytical Method RM-37SM

Analyte	Fortification Level (mg/kg)	Number of Tests	Recovery Range (%)	Mean Recovery (%)	Standard Deviation (%)	Relative Standard Deviation (%)
Soil						
LC/MS/MS						
R4	0.02 (LOQ)	5	76.9-120	91.2	17.3	19.0
	0.20	5	75.2-95.2	87.8	7.9	9.0
R7	0.02 (LOQ)	5	77.0-86.9	82.7	3.6	4.4
	0.20	5	72.5-87.6	77.8	6.6	8.5
R8	0.02 (LOQ)	5	76.6-88.4	83.6	4.4	5.2
	0.20	5	72.2-85.6	77.7	6.7	8.6
R11	0.02 (LOQ)	5	68.0-87.8	76.5	7.6	10.0
	0.20	5	72.6-95.3	82.8	8.6	10.4

Data (uncorrected recovery results, pp. 15-16) were obtained from p. 17; Table 1, p. 20 of MRID 45621720.

1 The soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; pp. 11-12). Soil and soil samples were not characterized.

2 Analytes were identified using one ion transition: m/z 377.8→220.9 for R4, m/z 377.8→360.9 for R7, m/z 237.9→220.9 for R8, and m/z 156.9→113.1 for R11.

III. Method Characteristics

Valent Analytical Method RM-37S-2

The LOQ for etoxazole and its metabolites R3 and R13 in soil was 0.02 mg/kg in the ECM and ILV (Appendix V, p. 239 of MRID 45621721). In the ECM, the LOD for soil was set at 0.01 mg/kg. No calculations or comparisons to background levels were reported to justify the LOQ for the method in the ECM; no calculations were reported to justify the LOD for the method in the ECM. In the ILV, the LOQ and LOD was not specifically reported.

Valent Analytical Method RM-37SM

The LOQ for etoxazole metabolites R4, R7, R8, and R11 in soil was 0.01 mg/kg in the ECM (Appendix II, p. 189 of MRID 45621721). In the ECM, the LOD for soil was set at 0.01 mg/kg, which was based on the lowest calibration standard using the following equation:

$$\text{LOD} = [0.005 \mu\text{g/mL}] \div [0.5 \text{ g/mL}]$$

Where 0.005 $\mu\text{g/mL}$ is the lowest calibration standard and 0.5 g/mL is the matrix concentration in the sample extracts. No calculations or comparisons to background levels were reported to justify the LOQ for the method in the ECM. In the ILV, the LOQ and LOD was not specifically reported.

Table 4a. Method Characteristics - Valent Analytical Method RM-37S-2

Analyte		Etoxazole	R3	R13
Limit of Quantitation (LOQ)	ECM	0.02 mg/kg		
	ILV	Not reported		
Limit of Detection (LOD)	ECM	0.01 mg/kg		
	ILV	Not reported		
Linearity (calibration curve r^2 and concentration range)	ECM	Not reported		
	ILV	Not reported ¹		
	Range	0.1-2.0 $\mu\text{g/mL}$		
Repeatable	ECM ²	Yes at LOQ (n = 4) and 5 \times LOQ No at 10 \times LOQ; no samples prepared. (characterized bulk soil matrix)		
	ILV ^{3,4}	Yes at LOQ and 10 \times LOQ (uncharacterized homogenized soil matrix)		
Reproducible		Yes at LOQ No at 10 \times LOQ; only one set of performance data was submitted.		
Specific	ECM	Yes, no matrix interferences were quantified or observed. More baseline noise was noted in the etoxazole chromatogram than the metabolites. No 5 \times LOQ representative chromatograms were provided.		
	ILV	Representative chromatograms were small and difficult to assess.		
		Yes, no matrix interferences were quantified or observed. Two nearby contaminants (peak ht. = 50-100% of analyte peak ht.) were observed in most LOQ chromatograms.	Yes, no matrix interferences were quantified or observed.	Yes, no matrix interferences were quantified or observed. Two nearby contaminants (peak ht. = 50-100% of analyte peak ht.) were observed in most LOQ chromatograms.

Data were obtained from Appendix V, p. 239 (LOQ/LOD); Appendix V, pp. 245-247 (recovery data); Appendix V, p. 234 (calibration range); Appendix V, pp. 242-244 (chromatograms) of MRID 45621721; p. 14; Table 2, p. 18 (recovery data); Appendix III, p. 42 (calibration data); Appendix IV, pp. 44-49 (chromatograms) of MRID 45621719; DER Attachment 2. **Red values** indicate values that are out of compliance with the guidelines.

- 1 Correlation coefficients (r^2) values were not reported. Calibration and linearity response factor values were evaluated via statistics. The calibration %CV values ranged 6.1-10.8%. The linearity %CV ranged 3.9-13.8%.
- 2 In the ECM, the soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455 of MRID 45621721). Bulk soil samples were characterized mainly as sandy loam, with on sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).
- 3 In the ILV, the soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; p. 11 of MRID 45621719). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM.
- 4 The ILV validated the method for the soil matrix in the second trial with the insignificant modifications including the preconditioning of the Florisil column with acetone (1x) and hexane (2x), as well as the use of a different GC/MS system (pp. 12-15 of MRID 45621719). The study author reported that the first trial had highly variable

recoveries which were presumed to be due to uncontrolled evaporation in the rotary evaporator. Additional care was taken in the second trial to control the evaporation of the samples and controls.

Table 4b. Method Characteristics - Valent Analytical Method RM-37SM

Analyte		R4	R7	R8	R11
Limit of Quantitation (LOQ)	ECM	0.02 mg/kg			
	ILV	Not reported			
Limit of Detection (LOD)	ECM	0.01 mg/kg			
	ILV	Not reported			
Linearity (calibration curve r^2 and concentration range)	ECM	Not reported ¹			
	ILV ²	$r^2 = 0.9978$	$r^2 = 0.9994$	$r^2 = 0.9988$	$r^2 = 0.9991$
	Range	0.005-0.1 $\mu\text{g/mL}$			
Repeatable	ECM ³	Yes at LOQ, but $n = 3$ Yes at 5 \times LOQ No at 10 \times LOQ; no samples prepared. (characterized bulk soil matrix)			
	ILV ^{4,5}	Yes at LOQ and 10 \times LOQ (uncharacterized homogenized soil matrix)			
Reproducible		Yes at LOQ No at 10 \times LOQ; only one set of performance data was submitted.			
Specific	ECM	Yes, no matrix interferences were quantified or observed. More baseline noise was noted in the R11 chromatogram than the other metabolites. No 5 \times LOQ representative chromatograms were provided.			
	ILV	Yes, no matrix interferences were quantified or observed. LOQ peaks were broad.			Yes, no matrix interferences were quantified or observed. LOQ peaks were broad and non-uniform in shape. Some minor baseline noise was observed.

Data were obtained from Appendix II, p. 189 (LOQ/LOD); Appendix II, pp. 194-197 (recovery data); Appendix II, pp. 182, 187 (calibration range & graph); Appendix II, pp. 191-193 (chromatograms) of MRID 45621721; p. 17; Table 1, p. 20 (recovery data); Appendix III, pp. 44-45 (calibration data); Appendix IV, pp. 47-84 (chromatograms) of MRID 45621720; DER Attachment 2. **Red values** indicate values that are out of compliance with the guidelines.

1 Quadratic equations were used. Representative graph for R11 provided without correlation coefficient.

2 Quadratic equations were used.

3 In the ECM, the soil was obtained from the etoxazole terrestrial field dissipation study located in California and characterized by Agvise Laboratories, Northwood, North Dakota (USDA soil texture classification; Appendix X, p. 455 of MRID 45621721). Bulk soil samples were characterized mainly as sandy loam, with on sample characterized as loam: Sample ID V-20271-UTC/0-30 (sandy loam, 62% sand 25% silt 13% clay, pH 6.9, 2.4% organic matter); Sample ID V-20271-UTC/30-60 (sandy loam, 60% sand 28% silt 12% clay, pH 6.5, 1.2% organic matter); Sample ID V-20271-UTC/60-90 (loam, 32% sand 48% silt 20% clay, pH 6.7, 1.6% organic matter); Sample ID V-20271-TRT/0-30 (sandy loam, 62% sand 26% silt 12% clay, pH 6.9, 1.2% organic matter); Sample ID V-20271-TRT/30-60 (sandy loam, 64% sand 26% silt 10% clay, pH 7.1, 1.0% organic matter); and Sample ID V-20271-TRT/60-90 (sandy loam, 64% sand 28% silt 8% clay, pH 7.2, 0.9% organic matter).

4 In the ILV, the soil sample was prepared by homogenizing multiple soil samples (depth range 0-60 cm) obtained from the etoxazole terrestrial field dissipation studies located in California (V-20271, 1999-2000) and Oregon (V-22154, 2000-2001; pp. 11-12 of MRID 45621720). Soil and soil samples were not characterized. The California field dissipation study was the same one as that of the ECM.

5 The ILV validated the method for the soil matrix in the in the first trial with insignificant modifications to standard solution preparation (sonication; pp. 12-15, 17 of MRID 45621720). The analytical instrumentation and all other

analytical parameters were the exact same as those in the ECM, except for the insignificant extension of the mobile phase program for analysis of R4, R7, and R8.

IV. Method Deficiencies and Reviewer's Comments

1. It could not be determined that ILVs MRID 45621719 & MRID 45621720 were conducted independently of ECM MRID 45621721 since all validations were conducted at the same facility (Valent U.S.A. Corporation, Dublin, California) and insufficient evidence was provided to support the independence of the two laboratories (p. 1 of MRID 45621721; p. 1 of MRID 45621719; p. 1 of MRID 45621720). Although ECM MRID 45621721 was a terrestrial field dissipation study, the analytical methods which contained the internal validation data for each method were also conducted at Valent U.S.A. Corporation, Dublin, California (Appendix II, p. 180; Appendix V, p. 232 of MRID 45621721). According to OCSPP guidelines, if the laboratory that conducted the validation belonged to the same organization as the originating laboratory, the analysts, study director, equipment, instruments, and supplies of the two laboratories must have been distinct and operated separately and without collusion. Furthermore, the analysts and study director of the ILV must have been unfamiliar with the method both in its development and subsequent use in field studies. In order to support their independence claim, Valent U.S.A. Corporation showed that the study director and validation performers (chemists and other technical staff) of each validation was different (Appendix II, p. 190; Appendix V, p. 241 of MRID 45621721; p. 7 of MRID 45621719; p. 7 of MRID 45621720). The communication summary reported that communication between the staff of the initial and independent validations did not occur or was limited to request for additional analytical instrumentation parameters (p. 15 of MRID 45621719; pp. 17-18 of MRID 45621720). This reviewer notes that one of the sources of the soil samples for the homogenized ILV soil matrix which was used to validate both methods was the same one which was used in the ECM [California terrestrial field dissipation study (V-20271); Appendix IX, pp. 284-302 (field sampling data); Appendix X, p. 455 of MRID 45621721; p. 11 of MRID 45621719; pp. 11-12 of MRID 45621720].

Additionally, for Valent Analytical Method RM-37SM, the reported analytical equipment was the same in the ECM and ILV; retention times could not be compared since they were not reported in the ECM (Appendix II, pp. 183-186 of MRID 45621721; pp. 12-15, 17; Appendix I, p. 29 of MRID 45621720). Analytical instrument numbers were not reported in the ECM or ILV.

The registrant needs to provide additional information for the validations of both methods to confirm no interactions between staff and no sharing of equipment when both validations occur at the same address.

2. No ECM performance data was submitted for the 10×LOQ fortification level for Valent Analytical Methods RM-37SM and RM-37S-2; therefore, the methods were not validated at 10×LOQ. OCSPP Guideline 850.6100 states that a minimally complete sample set includes a reagent blank, two matrix blanks, five samples spiked at the LOQ, and five samples spiked at 10×LOQ for each matrix).

3. For Valent Analytical Method RM-37SM, an insufficient number of samples ($n = 3$) were prepared for the LOQ in the ECM (Appendix II, pp. 194-197 of MRID 45621721). OCSPP Guideline 850.6100 states that a minimally complete sample set includes a reagent blank, two matrix blanks, five samples spiked at the LOQ, and five samples spiked at $10\times$ LOQ for each matrix.
4. For Valent Analytical Method RM-37S-2, ILV linearity could not be determined since calibration coefficients were not reported. Calibration and linearity response factor values were evaluated via statistics (Appendix III, p. 42 of MRID 45621719). The calibration %CV values ranged 6.1-10.8%. The linearity %CV ranged 3.9-13.8%.

For Valent Analytical Methods RM-37SM and RM-37S-2, ECM linearity could not be determined since calibration coefficients were not reported, only calibration ranges were reported (Appendix II, pp. 182, 187; Appendix V, p. 234 of MRID 45621721).

5. For Valent Analytical Methods RM-37SM and RM-37S-2, it could not be determined that the ILVs were provided with the most difficult matrix with which to validate the method since only one uncharacterized homogenized soil matrix was tested. OCSPP 850.6100 guidance suggests for a given sample matrix, the registrant should select the most difficult analytical sample condition from the study (*e.g.*, high organic content versus low organic content in a soil matrix) to analyze from the study to demonstrate how well the method performs. Even though a certain number of soil matrices is not specified in the OCSPP guidelines, more than one soil/soil matrix would need to be included in an ILV in order to cover the range of soils used in the terrestrial field dissipation studies. However, the ILV soil matrix sources were reported as two terrestrial field dissipation study sites (p. 11 of MRID 45621719; pp. 11-12 of MRID 45621720).
6. ECM representative chromatograms were not submitted for the $5\times$ LOQ fortification level for Valent Analytical Methods RM-37SM and RM-37S-2. Representative chromatograms from all fortifications/matrices tested should be submitted to help assess the specificity of the methods.
7. The estimations of LOQ and LOD in ECM were not based on scientifically acceptable procedures as defined in 40 CFR Part 136 (Appendix II, p. 189; Appendix V, p. 239 of MRID 45621721). Specifically, in the ECM for Valent Analytical Method RM-37SM, the LOD was calculated as the lowest calibration standard divided by the matrix concentration in the sample extracts; no support for the LOD was provided for Valent Analytical Method RM-37S-2. No calculations for the LOQ were provided in the ECM for either method. The LOQ and LOD were not reported in the ILV. Detection limits should not be based on arbitrary values.

The registrant should conduct an additional soil study and associated ILV with appropriate LOQ and LODs, and demonstrate the independence of the laboratory validation.

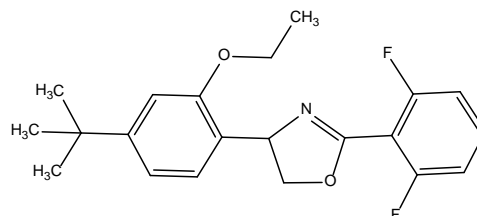
8. For Valent Analytical Method RM-37S-2, the time required to complete the sample workup was reported as *ca.* 12 hours in the ILV (p. 15 of MRID 45621719). Sample workup was conducted over a period of three days with overnight storage at room temperature. The sample analysis required *ca.* 10 hours. For Valent Analytical Method RM-37SM, the time required to complete the sample workup was reported as *ca.* 6 hours in the ILV (p. 18 of MRID 45621720). Sample workup was conducted over a period of two days with overnight storage at room temperature. The sample analysis required *ca.* 7.5 hours for R4, R7, and R8 for a set of 13 samples; two sample sets were required. The sample analysis for R11 required *ca.* 14 hours, including two hours to purge the LC/MS/MS before analysis.

V. References

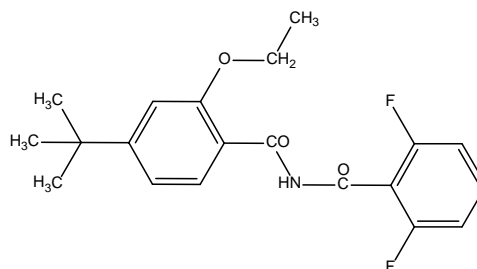
- U.S. Environmental Protection Agency. 2012. Ecological Effects Test Guidelines, OCSPP 850.6100, Environmental Chemistry Methods and Associated Independent Laboratory Validation. Office of Chemical Safety and Pollution Prevention, Washington, DC. EPA 712-C-001.
- 40 CFR Part 136. Appendix B. Definition and Procedure for the Determination of the Method Detection Limit-Revision 1.11, pp. 317-319.

Attachment 1: Chemical Names and Structures**Etoxazole (S-1283)**

IUPAC Name: (RS)-5-tert-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydrooxazol-4-yl]phenetole
CAS Name: 2-(2,6-Difluorophenyl)-4-[4-(1,1-dimethylethyl)-2-ethoxyphenyl]-4,5-dihydrooxazole
CAS Number: 153233-91-1
SMILES String: FC1=C(C(F)=CC=C1)C2=NC(C3=C(OCC)C=C(C(C)(C)C)C=C3)CO2

**R3**

IUPAC Name: 4-(tert-Butyl)-N-(2,6-difluorobenzoyl)-2-ethoxybenzamide
CAS Name: Not reported
CAS Number: Not reported
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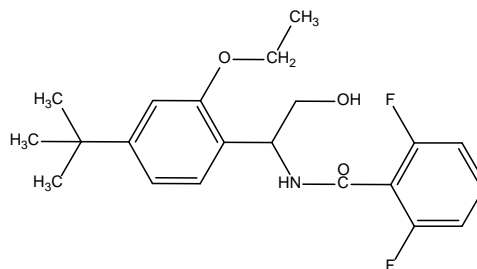
R4

IUPAC Name: N-(1-(4-(tert-butyl)-2-ethoxyphenyl)-2-hydroxyethyl)-2,6-difluorobenzamide

CAS Name: Not reported

CAS Number: Not reported

SMILES String: CC(C)(C)C1=CC(OCC)=C(C(CO)NC(C2=C(F)C=CC=C2F)=O)C=C1

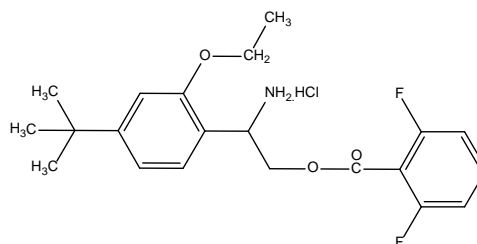
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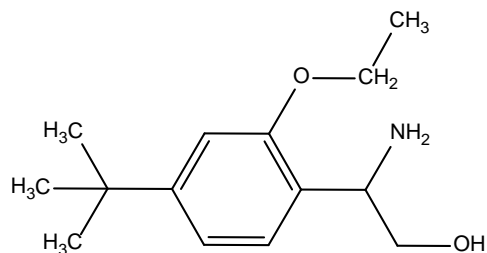
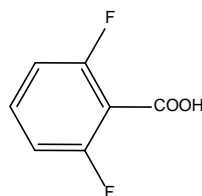
IUPAC Name: 2-Amino-2-(4-(tert-butyl)-2-ethoxyphenyl)ethyl 2,6-difluorobenzoate hydrochloride

CAS Name: Not reported

CAS Number: Not reported

SMILES String: CC(C)(C)C1=CC(OCC)=C(C(N)COC(C2=C(F)C=CC=C2F)=O)C=C1.Cl



R8**IUPAC Name:** 2-Amino-2-(4-(tert-butyl)-2-ethoxyphenyl)ethan-1-ol**CAS Name:** Not reported**CAS Number:** Not reported**SMILES String:** CC(C)(C)C1=CC(OCC)=C(C(N)CO)C=C1**R11****IUPAC Name:** 2,6-Difluorobenzoic acid**CAS Name:** Not reported**CAS Number:** Not reported**SMILES String:** FC1=C(C(O)=O)C(F)=CC=C1

R13**IUPAC Name:** 4-(4-(tert-Butyl)-2-ethoxyphenyl)-2-(2,6-difluorophenyl)oxazole**CAS Name:** Not reported**CAS Number:** Not reported**SMILES String:** CC(C)(C)C1=CC(OCC)=C(C2=COC(C3=C(F)C=CC=C3F)=N2)C=C1