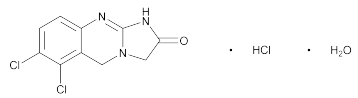
Anagrelide Hydrochloride



$C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$ 310.56
Anhydrous 292.55
[58579-51-4].
Imidazo[2,1-*b*]quinazolin-2(3*H*)-one, 6,7-dichloro-1,5-dihydro-, monohydrochloride, monohydrate;
6,7-Dichloro-1,5-dihydroimidazo[2,1-*b*]-quinazolin-2(3*H*)-one monohydrochloride, monohydrate [823178-43-4].

DEFINITION

Anagrelide Hydrochloride contains NLT 98.0% and NMT 102.0% of anagrelide hydrochloride ($C_{10}H_7Cl_2N_3O \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨**197K**⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨**191**⟩**:** Meets the requirements

ASSAY

- **PROCEDURE** Use freshly prepared standard and sample solutions and inject within 2 h.

Solution A: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.
Mobile phase: Acetonitrile and *Solution A* (1:3)
Diluent: Acetonitrile and water (1:1)
Standard stock solution: 0.5 mg/mL of anagrelide hydrochloride in acetonitrile prepared as follows. Transfer USP Anagrelide Hydrochloride RS into a suitable volumetric flask, add a small amount of 2 N hydrochloric acid (3 drops per every 50 mL of the final volume) and acetonitrile equivalent to fill about 80% of the final volume. Sonicate to dissolve, and dilute with acetonitrile to volume.
Standard solution: 0.05 mg/mL of anagrelide hydrochloride in *Diluent* from *Standard stock solution*
Sample stock solution: Weigh Anagrelide Hydrochloride, equivalent to 25 mg of anhydrous salt, into a 50-mL volumetric flask, add 3 drops of 2 N hydrochloric acid and 40 mL of acetonitrile. Sonicate to dissolve, and dilute with acetonitrile to volume.
Sample solution: Transfer 5 mL of *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 4-µm packing L11
Flow rate: 1.2 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NMT 3000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of anagrelide hydrochloride ($C_{10}H_7Cl_2N_3O \cdot HCl$) in the portion of Anagrelide Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of anagrelide from the *Sample solution*
r_S = peak response of anagrelide from the *Standard solution*
C_S = concentration of USP Anagrelide Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Anagrelide Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%
- **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 20 ppm

Change to read:

- **ORGANIC IMPURITIES**

Use freshly prepared standard and sample solutions and inject within 2 h.
Mobile phase: Proceed as directed in the *Assay*.
Diluent A: Use the *Diluent* as described in the *Assay*.
Diluent B: Acetonitrile and water (1:3)
Standard stock solution A: 0.05 mg/mL of USP Anagrelide Related Compound A RS in *Diluent A*
Standard stock solution B: 0.05 mg/mL of anagrelide related compound B in acetonitrile. Transfer USP Anagrelide Related Compound B RS into a suitable volumetric flask, add acetonitrile equivalent to fill about 50% of the final volume and a small amount of 2 N hydrochloric acid (3 drops per 200 mL of the final volume). Sonicate to dissolve, heat in the hot water bath if necessary, and dilute with acetonitrile to volume.
Standard stock solution C: 0.1 mg/mL of anagrelide hydrochloride in acetonitrile. Transfer USP Anagrelide Hydrochloride RS into a suitable volumetric flask, add acetonitrile equivalent to fill about 80% of the final volume and a small amount of 0.12 N hydrochloric acid (1 mL per 100 mL of the final volume). Sonicate to dissolve, and dilute with acetonitrile to volume.
System suitability solution: 0.25 µg/mL of each of anagrelide related compound A and anagrelide related compound B in *Mobile phase* from *Standard stock solution A* and *Standard stock solution B*
Standard solution: 0.05 µg/mL of anagrelide hydrochloride in *Mobile phase* from *Standard stock solution C*
Sample stock solution: Weigh Anagrelide Hydrochloride, equivalent to 25 mg of anhydrous salt, into a 50-mL volumetric flask. Add 45 mL of acetonitrile, sonicate, and swirl the flask until the preparation turns into a cloudy liquid. Add 1 drop of 0.12 N hydrochloric

acid, swirl the flask until the liquid turns to clear, and dilute with acetonitrile to volume.

Sample solution: Transfer 5 mL of *Sample stock solution* into a 50-mL volumetric flask, and dilute with *Diluent B* to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 4-µm packing L11

Autosampler temperature: 5°

Flow rate: 1.2 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between anagrelide related compound B and anagrelide related compound A, *System suitability solution*

Column efficiency: NLT 3000 theoretical plates, *Standard solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Anagrelide Hydrochloride, on the anhydrous basis, taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of anagrelide from the *Standard solution*

C_S = concentration of USP Anagrelide Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Anagrelide Hydrochloride (anhydrous) in the *Sample solution* (mg/mL)

F = relative response factor for each individual impurity (see *Table 1*)

Acceptance criteria See *Table 1*. Disregard any impurity peak less than 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Anagrelide related compound B[a]	0.40	0.43	0.3
Anagrelide related compound A[b]	0.55	0.37	0.15
● Anagrelide open ring methyl ester (if present)[c]	0.80	0.51	0.25 ● (RB 1-Jun-2013)
Anagrelide	1.00	1.0	—
Anagrelide related compound C[d]	1.41	0.32	0.15
Anagrelide trichloro derivative[e]	2.44	1.0	0.15
Any unspecified impurity	—	1.0	0.1
Total impurities	—	—	1.0

[a] (2-Amino-5,6-dichloroquinazolin-3(4*H*)-yl)acetic acid.

[b] Ethyl 2-(6-amino-2,3-dichlorobenzylamino)acetate.

[c] Methyl 2-(5,6 dichloro-2-imino-1,2-dihydroquinazolin-3(4*H*)-yl)acetate. ● (RB 1-Jun-2013)

[d] Ethyl 2-(5,6-dichloro-2-imino-1,2-dihydroquinazolin-3(4*H*)-yl)acetate hydrobromide.

[e] 6,7,8-Trichloro-3,5-dihydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one.

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** 4.5%–7.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store in a cold place.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Anagrelide Hydrochloride RS

USP Anagrelide Related Compound A RS
Ethyl 2-(6-amino-2,3-dichlorobenzylamino)acetate.
$C_{11}H_{14}Cl_2N_2O_2$ 277.15

USP Anagrelide Related Compound B RS
(2-Amino-5,6-dichloroquinazolin-3(4*H*)-yl)acetic acid.
$C_{10}H_9Cl_2N_3O_2$ 274.10