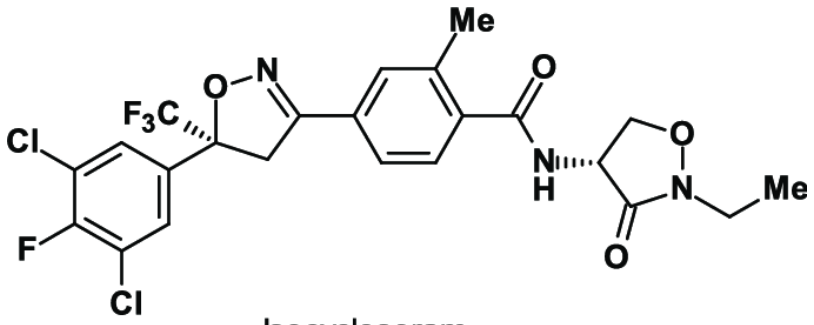
CIPAC STATUS REPORT

11.08.2024



Isocycloseram

1025 Isocycloseram

Allocated to DAPA

CIPAC methods published in: CIPAC Handbook -

CIPAC

CIPAC 66th meeting, June 2022 virtual

Isocycloseram by Mr Christian Mink (5326, 5327)

Mr Mink presented the results of a small scale collaborative study for the determination of isocycloseram in three TC and two WP formulations by reversed phase high performance liquid chromatography using UV detection at 265 nm and external standardization. The sample set was sent to four participants whereas the organizer added two independent data sets. The participating laboratories reported minor deviations which were assessed as not of influence to the results. The resulting HorRat values ranged from 0.2-0.5

Mr Mink recommended to go forward to a full scale CIPAC collaborative trial.

No comments of the meeting were received.

Closed meeting:
No further comments were received, the method can be promoted to a **full scale CIPAC trial**.

CIPAC 67th meeting, June 2023 Braunschweig

Isocycloseram by Mr Christian Mink (5349, 5350)

Mr Mink presented the results of a full scale collaborative trial for the determination of isocycloseram in two TC materials and three WP formulations after dissolving in or extraction with acetonitrile, reversed phase HPLC, UV-detection at 265 nm and external standardization. 16 Laboratories from Europe and Asia participated and all laboratories reported in time. One laboratory used a different stationary phase which could influence the outcome of the trial, the other reported deviations were assessed as not critical. The statistical evaluation resulted in HorRat values of 0.3-0.6, which included one outlier and included the laboratory which applied another stationary phase.
Mr Mink considered the method to be suitably validated and recommended that the method is considered as a provisional CIPAC method.
No questions were asked by the meeting.

Closed meeting:
It was not clear to the meeting if an identity test was available or performed.
The method can be promoted to a **provisional** CIPAC method with the remark that an identity test should be available.

CIPAC 68th meeting, June 2024 Wageningen

Isocycloseram by Mr Christian Mink (5370, 5371)

Mr Christian Mink presented the results of an isocycloseram chiral method collaborative trial for TC and WP. Isocycloseram consists of four isomers with a defined composition: 5S,4R 87.5%, 5R,4R 5.5%, 5S,4S 3.0% and 5R,4S 0.1%. The chiral analysis was performed by high performance liquid chromatography on a Chiralpak IG-3 (Daicel, 150 Å~ 4.6 mm, 3 µm) at 40ÅãC with UV detection at 265 nm and external standardization. The eluent was water : acetonitrile : methanol 25:50:25 (v/v/v) at a flow rate of 1.0 ml/min. All peaks were baseline separated. Three TC and two WP materials were sent to seven laboratories and all laboratories reported results. Three minor deviations were reported which were of no significance for the results. Excluding stragglers and outliers both WP samples returned HorRat values ranging from 0.01 – 0.02 for the 5S,4R isomer, 0.45 – 0.46 for the 5R,4R isomer, and 0.73 – 0.88 for the 5S,4S isomer. The 5R,4S isomer content was below the detection limit of both WP formulations. The three TC samples returned HorRat values ranging from 0.02 – 0.05 for the 5S,4R isomer, 0.5 – 0.96 for the 5R,4R isomer, and 0.45 – 0.69 for the 5S,4S isomer. Only in one TC the 5R,4S isomer content was above the detection limit which resulted in a HorRat value of 1.81.
Mr Christian Mink concluded that with exception of one result for the isocycloseram 5R,4S isomer the method fulfilled all the requirements. As explanation of the 5R,4S isomer deviation it was highlighted that the 5R,4S isomer content was near or below the detection limit of the method.

Questions and remarks from the meeting.

- It was not clear what the aim of the method was as it was announced as an identification method but was reported as a quantitative method.
  - The method was validated as an identifying method as the composition of the isocycloseram is strictly defined by ISO. The identification of the composition was a request of the CIPAC 2023 meeting in Braunschweig.
- Why did only seven labs participated as at least eight labs are required for a quantitative validation.
  - The method was intended as an identification method, not as a quantification method.
- Was the percentage set at 100% for the total isocycloseram content?
  - Yes
- Calculation of the relation between the different isomers based on their respective peak areas requires that the respective extinction coefficients are identical. Is this known?
  - They are equal, but it will be checked.

Closed meeting:

The reversed phase HPLC method (CIPAC/5349) for the determination of isocycloseram in TC and WP formulations was accepted as **full** CIPAC method.

Isocycloseram (5370, 5371):

Some remarks were given by the meeting.

- Provide data to prove that the extinction coefficients of the different isomers are equal.
- An elaborate discussion emerged because of the dual aspect of the interlaboratory validation procedure. The method was notified as an identification method. However, the identification required quantification of the different isomers as the composition is defined by ISO. And as the quantification method is not capable of distinguishing between the different isomers, this method can only report the total isocycloseram concentration.

Conclusion: The method was **accepted** as chiral identity method with the need of clarification of the absorption coefficient of the isomers.