Journal of Chromatography A, 1462 (2016) 115–123

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Analysis of 4-bromo-3-fluorobenzaldehyde and separation of its regioisomers by one-dimensional and two-dimensional gas chromatography

Bo Shen [a,*], David Semin [a], Jan Fang [b], Gary Guo [c]

[a] Attribute Sciences, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, USA
[b] Quality & Regulatory Management, LLC, 2629 Townsgate Rd, Westlake Village, CA 91361, USA
[c] Commercial Analytical Operation, Gilead Sciences, 333 Lakeside Drive Foster City, CA 94404, USA

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 25 July 2016
Accepted 26 July 2016
Available online 27 July 2016

Keywords:
GC
μ-ECD
Deans switch
1D-GC
2D-GC
Chiral GC column
regioisomers
p-GTI

ABSTRACT

A starting material, 4-bromo-3-fluorobenzaldehyde, was used for active drug substance (API) AMG 369 production. The presence of the regioisomer impurities in the starting material 4-bromo-3-fluorobenzaldehyde presented significant challenges for the API synthetic route development due to the physical-chemical similarities of the impurities. These impurities significantly impact on the purity of the starting-material and final drug substance. Control of these impurities is important due to the potential genotoxicity of these impurities (*p*-GTI). Analytical development was carried out to develop GC methods with high resolving power and high sensitivity to quantify the regioisomers presented in starting material and therefore to control the purity of the starting material and the final drug substance.

In the study, complete resolution of the ten regioisomers by 1D-GC and heart-cutting two-dimensional GC (2D-GC) was achieved. A sensitive GC/micro electron capture detection (μ-ECD) method with high resolving power and sensitivity to fully resolve all the ten regioisomers of 4-bromo-3-fluorobenzaldehyde was obtained by using a CHIRALDEX GC column (1D- GC). To facilitate the systematic GC method development, heart-cutting two-dimensional gas chromatography (2D-GC) using a Deans switch was exploited for the separation of the ten regioisomers. The resulting heart-cutting 2D-GC method successfully separated all the ten regioisomers with better sensitivity and resolution. Regioisomer impurities in the starting material were identified and quantified by these GC methods. The sensitivity for the methods is in the range of 0.004 ng to 0.02 ng for the regioisomers. Linearity for the methods is: $R^2 = 0.999$ to 1.000. The methods were suitable for control of the regioisomer impurities, *p*-GTIs, in the starting material and final drug substance.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

During the route development and production of the active pharmaceutical ingredients (API), AMG 369 (see Fig. 1 for structure) [1], a starting material 4-bromo-3-fluorobenzaldehyde was used. The regioisomers of 4-bromo-3-fluorobenzaldehyde presented in the starting material can be potentially carried through to the final API due to structure similarity of these regioisomers. The starting material 4-bromo-3-fluorobenzaldehyde and its regioisomers are also potentially genotoxic impurities (*p*-GTIs) according to the "structurally alerting functional groups" [2,3] since aldehydes are known to be DNA reactive [4]. The control of these *p*-GTIs is critical for the quality of the final API and for meeting the guidelines issued by EMEA and FDA [5,6]. Last several years, extensive reviews were published for the control of genotoxic impurities [7,8].

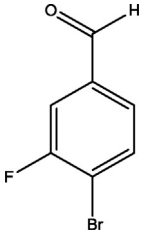
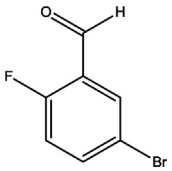
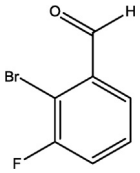
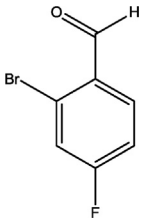
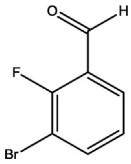
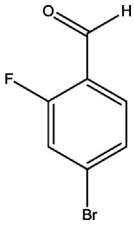
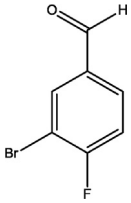
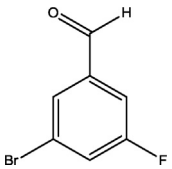
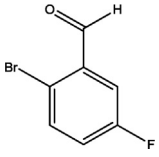
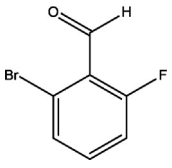
Regioisomers are the resulting compounds of different positions of functional groups or substituent attachments in parent structures that possess the same molecular formula and molecular weight. There are ten regioisomers of 4-bromo-3-fluorobenzaldehyde. A list of these compounds can be found in Table 1. Since these regiosomers possess similar range of polarity, boiling point and solubility, their elution properties are similar. The resolution of all the individual regioisomers by chromatographic separation is very challenging. It is therefore desirable to use innovative yet robust techniques that allow resolution of as many regioisomers as possible.

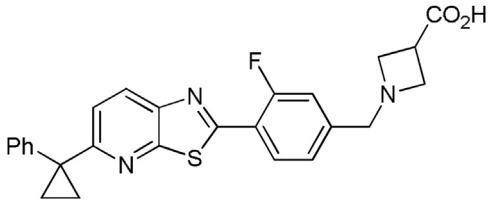
Regarding the choice of chromatographic methods, resolution of the regioisomers by HPLC methodology was found very poor.

* Corresponding author.
E-mail addresses: bshen@amgen.com, bshen@yahoo.com (B. Shen).

http://dx.doi.org/10.1016/j.chroma.2016.07.071
0021-9673/© 2016 Elsevier B.V. All rights reserved.

Table 1
Structure of 4-bromo-3-fluorobenzaldehyde and its related regioisomers.

Compound	Structure	Notes/CAS #	Compound	Structure	Notes/CAS #
4-bromo-3-fluorobenzaldehyde		(Starting Material, SM) 133059–43-5	5-bromo-2-fluorobenzaldehyde		93777–26-5
2-bromo-3-fluorobenzaldehyde		(Major Impurity in the SM)891180–59-9	2-bromo-4-fluorobenzaldehyde		59142–68-6
3-bromo-2-fluorobenzaldehyde		149947–15-9	4-bromo-2-fluorobenzaldehyde		57848–46-1
3-bromo-4-fluorobenzaldehyde		77771–02-9	3-bromo-5-fluorobenzaldehyde		188813–02-7
2-bromo-5-fluorobenzaldehyde		94569–84-3	2-bromo-6-fluorobenzaldehyde		360575–28-6



Chemical Formula: $C_{26}H_{22}FN_3O_2S$
Molecular Weight: 459.54

Fig. 1. Structure of AMG 369 drug substance.

Capillary GC usually offers significantly greater peak capacity and sensitivity [9,10]. Selection of the stationary phase for GC capillary separations is usually done with the familiar principle "like dissolves like" [11]. For complex samples, to achieve the best resolution of all the analytes could also be very difficult and time consuming. Usually, a single GC stationary phase cannot resolve all components of interest. Coupling GC columns with different polarities increases the resolution of complex samples. Multidimensional GC can greatly increase the resolution of complex samples or analytes in the sample matrix. The heart-cutting 2D-GC could provide a very large number of theoretical plates and yield a dramatic increase in the resolution. Recent reviews discuss the history, theory, and recent developments in two-dimensional gas chromatography and capillary-flow-technology (CFT)-based Deans switch (heart-cutting 2D-GC) [12–14]. For the heart-cutting 2D-GC, selected, unresolved peaks are transferred from one column to another column with different selectivity where a second separation takes place. The heart-cutting devices can easily be installed in existing GC equipment. Using the heart-cutting 2D-GC, analysts can determine trace components in a complex mixture or increase the resolving power of GC by using two different columns in the same analytical run and on the same instrument.

In this study, the very unique separation power of a chiral GC column for all ten regioisomers was demonstrated. Complete resolution of the ten regioisomers was obtained with 1D-GC by using a CHIRALDEX G-TA GC column, which was not obtained with other GC columns. Though 2D-GC is not new, the application of 2D-GC in pharmaceutical analysis is very limited. For achieving the further high separation efficiency, heart-cutting 2D-GCwas utilized for the method development. Two GC columns with dissimilar phases were coupled by using the Deans Switch [15,16], a software-controlled column flow switching device, to perform in-oven heart-cutting 2D-GC. In heart-cutting, the effluent from one

Download English Version:

https://daneshyari.com/en/article/1198626

Download Persian Version:

https://daneshyari.com/article/1198626

Daneshyari.com