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Isoetin and its derivatives: Analytics, chemosystematics, and bioactivities

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ABSTRACT

Isoetin, 5,7,2′,4′,5′-pentahydroxyflavone, is a rare, structurally simple natural product belonging to the flavone sub-group of flavonoids. The first reports on naturally occurring isoetin derivatives were published in the 1970s though methoxy-derivatives with the same substitution pattern had already been synthesized a decade earlier. A glucoside of isoetin was first discovered in the genus *Isoetes* (Lycopodiopsida). In the forty years following the discovery of the new naturally occurring flavonoid aglycone, only a limited number of reports on isoetin and its derivatives have been published. Simple, i.e. non-methyl-ether derivatives of isoetin have been found in the Isoetaceae, Asteraceae, Ranunculaceae, Rosaceae, and Rubiaceae families; while methyl ethers and their derivatives have been found in the Lycopodiaceae, Asteraceae, Cucurbitaceae, Fabaceae, and Pedaliaceae. A total of 14 non-methyl-ether-derivatives (including isoetin) and the same number of methyl ether derivatives have been described, some methyl derivatives only as synthetic compounds, others even only as virtual compounds generated for *in silico* studies. The published NMR data of isoetin and its derivatives as well as chemosystematic studies using isoetin derivatives as markers are compiled and critically assessed. Moreover, the papers dealing with bioactivities of isoetin and its derivatives are summarized.

1. Introduction

Isoetin, compound **1** (Fig. 1) was first described in 1974 from species of the genus *Isoetes* (Isoetaceae, Isoetales, Lycopodiopsida) (Voirin and Jay, 1974; Voirin et al., 1975). Since then, surprisingly few derivatives of this flavonoid have been found (Figs. 1 and 2; Tables 1 and 2). The currently known natural derivatives of isoetin feature the following substituents: α-arabinose, α-glucose, β-glucose, β-glucuronic acid, β-xylose, 4′-*O*-acetylxylose, *O*-methyl ethers, and *p*-coumaroyl moieties (Figs. 1 and 2).

Literature on isoetin and its derivatives was retrieved with the help of the ISI web of Knowledge, the Reaxys, and the SciFinder databases. In the following sections, isoetin and its derivatives will be discussed in detail. This includes the analytical identification of the derivatives (Table 3) as well the identification of the analyzed plant material and its documentation (Table 4). Another aim of this review is to give a synopsis of the currently available NMR data of isoetin and its derivatives (Tables 5–8).

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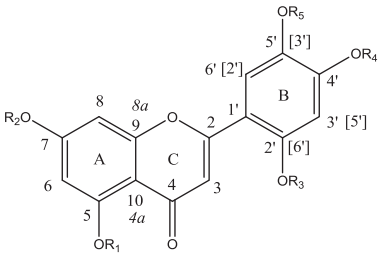

Nr.	Name	R_1	R_2	R_3	R_4	R_5	Key references
Compounds with known constitution based on NMR experiments							
1	isoetin	H	H	H	H	H	Voirin et al., 1975; Shelyuto et al., 1977a,b; Wolfbeis et al., 1984
2	isoetin 5'-*O*-β-glucoside	H	H	H	H	Glc	Voirin et al., 1975; Marco et al., 1988
3	isoetin 4'-*O*-β-glucoside	H	H	H	Glc	H	Gawrónska-Grzywacz et al., 2011
4	isoetin 4'-*O*-β-glucuronide	H	H	H	Glu	H	Pauli and Junior, 1995; Zidorn et al., 2002; Gawrónska-Grzywacz and Krzaczek, 2009
5	isoetin 2'-*O*-β-xyloside	H	H	Xyl	H	H	Gluchoff-Fiasson et al., 1991
6	isoetin 4''-*O*-acetyl-2'-*O*-β-xyloside	H	H	4-*O*-Ac-Xyl	H	H	Gluchoff-Fiasson et al., 1991
7	isoetin 7-*O*-β-glucoside	H	Glc	H	H	H	Bondarenko et al., 1978; Harborne, 1991 (Harborne, 1978); Gawrónska-Grzywacz and Krzaczek, 2009
8	isoetin 7-*O*-β-glucoside-2′-*O*-α-arabinoside	H	Glc	Ara	H	H	Shi et al., 2007; Shi et al., 2008a
9	isoetin 7-*O*-β-glucoside-2'-*O*-β-xyloside	H	Glc	Xyl	H	H	Gluchoff-Fiasson et al., 1991; Gawrónska-Grzywacz and Krzaczek, 2009[b]
10	isoetin 7-*O*-β-glucoside-4'''-*O*-acetyl-2'-*O*-β-xyloside	H	Glc	4-*O*-Ac-Xyl	H	H	Gluchoff-Fiasson et al., 1991
11	isoetin 7-*O*-β-glucoside-2′-*O*-α-glucoside	H	Glc	Glc	H	H	Shi et al., 2007; Shi et al., 2008a
12	isoetin 5-*O*-β-glucoside-2'-*O*-4''-phloridzinyl ether [≡ phloridzin-(I-4,*O*,II-2')-luteolin-5-*O*- β-D-glucoside]	Glc	H	PHL	H	H	Wang et al., 2013
Compounds with not fully established constitution/constitution only based on UV experiments							
13	isoetin 7-*O*-arabinoside	H	Ara	H	H	H	Harborne, 1978, 1991
14	isoetin 7-*O*-xylosyl-arabinosyl-glucoside[c]	H	Xyl/Ara/Glc	H	H	H	Harborne, 1978, 1991

[a] Ara = arabinosyl, Glc = glucosyl, Glu = glucuronyl, PHL = 4-phloridzinyl, Xyl = xylosyl. [b] In this publication, the linkage positions of the sugar moieties were not assigned. [c] The linkage order and linkage positions of the sugar moieties were not elucidated. * 1. Correct and current numbering followed here 1-10, 1'-6'; 2. Currently rarely used alternative numbering system *4a* and *8a;* 3. Erroneous numbering for the B-ring used in some publications [2'], [3'], [5'], and [6']. The second and third versions are only indicated if deviating from the first version.

Fig. 1. Isoetin and its naturally occurring glycosides derivatives (excluding the compounds featuring also methyl ether moieties. *,[a].

In this review, 6-hydroxy derivatives of the aglycone such as the ones found in *Juniperus thurifera* L. (Cupressaceae) (Hassani et al., 1985) and 8-prenylated derivatives such as the ones found in *Artocarpus altilis* (Parkinson) Fosberg (Moraceae) (Lan et al., 2013) will not be reviewed, because they are not considered to be isoetin derivatives but considered to represent flavonoids based on different aglyca. For the same reason, methyl ethers of the basic isoetin moiety such as the isoetin 5-*O*-methyl ether found in *Trichosanthes kirilowii* Maxim. (Cucurbitaceae) (Rahman and Moon (2007), the isoetin 7,2′,4′,5′-tetra-*O*-methyl ether reported from *Artemisia campestris* L. subsp. *glutinosa* (J.Gay ex Besser) Batt. (Asteraceae) (Tarhouni, 1996), or the isoetin 5,7,2′,5′-tetra-*O*-methyl ether e.g. reported from *Derris robusta* (Roxb. ex DC.) Benth. (Fabaceae) (Gupta et al., 1998) are discussed separately from other isoetin derivatives in this review (Fig 2, Tables 7 and 8).