Available online at www.sciencedirect.com
ScienceDirect
Phytochemistry 67 (2006) 2201–2207
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

Molecules of Interest

Hyperforin

Ludger Beerhues *

Institut für Pharmazeutische Biologie, Technische Universität Braunschweig, Mendelssohnstr. 1, D-38106 Braunschweig, Germany

Received 10 August 2006; accepted 16 August 2006

Abstract

Hyperforin is a polyprenylated acylphloroglucinol derivative from *Hypericum perforatum* (St. John's wort). It exhibits antidepressant activity by a novel mechanism of action, antibiotic activity against gram-positive bacteria, and antitumoral activity *in vivo*. However, it also produces drug–drug interactions by activation of the pregnan X receptor. No total synthesis has been described. Some natural and semisynthetic analogues are available to study structure–activity relationships. Enzymatically, the skeleton of hyperforin is formed by isobutyrophenone synthase from isobutyryl-CoA and three molecules of malonyl-CoA. The first prenylation step is catalyzed by a soluble and ion-dependent dimethylallyltransferase. Hyperforin mainly accumulates in pistils and fruits where it probably serves as defensive compound.

Keywords: Hyperforin; *Hypericum perforatum*; Clusiaceae; Structure; Pharmacology; Biosynthesis

1. Introduction

In 1975, Bystrov and co-workers isolated a complex compound from *Hypericum perforatum* L. (St. John's wort) (Fig. 1) and named it hyperforin (Bystrov et al., 1975). Today, *H. perforatum* is one of the best studied medicinal plants and hyperforin its best characterized constituent. Phytomedicines based on extracts from the plant's flowering upper parts are widely used as antidepressants (Müller, 2003; Butterweck, 2003). Their efficacy in mild to moderate depression was demonstrated in a number of clinical trials versus placebo and standard antidepressants (Whiskey et al., 2001). The relatively low rate of adverse effects and the good tolerability result in high patient acceptance. The detection of additional pharmacological activities in recent years further stimulated the interest in hyperforin (Medina et al., 2006).

2. Structure elucidation

Hyperforin is a bicyclic polyprenylated acylphloroglucinol derivative (Fig. 2). Its caged structure was determined by extensive chemical degradation and derivatisation, as well as by spectroscopic means (Bystrov et al., 1978 and literature cited therein). The relative stereochemistry was concluded from X-ray data of its 3,5-dinitrobenzoic acid ester and the absolute configuration was elucidated by single crystal X-ray analysis of its *p*-bromobenzoic acid ester (Brondz et al., 1982, 1983). Hyperforin is a mixture of interconverting tautomers, as indicated by the broad shape of most ^{1}H NMR signals and the poor resolution of many ^{13}C NMR lines (Verotta et al., 2000). When the tautomeric equilibrium of the enolized β-dicarbonyl system is covalently blocked, the derivatives show sharp NMR signals. All ^{1}H and ^{13}C NMR signals of hyperforin were unequivocally assigned by one- and two-dimensional NMR experiments (Adam et al., 2002). As a pure compound, hyperforin is poorly stable when exposed to light and oxygen (Maisenbacher and Kovar, 1992a; Erdelmeier, 1998; Liu et al., 2005). As a consequence, the compound was long neglected as a pharmacologically relevant constituent in

* Tel.: +49 531 391 5689; fax: +49 531 391 8104.
E-mail address: l.beerhues@tu-bs.de.

0031-9422/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2006.08.017

Fig. 1. *Hypericum perforatum* L. (St. John's wort).

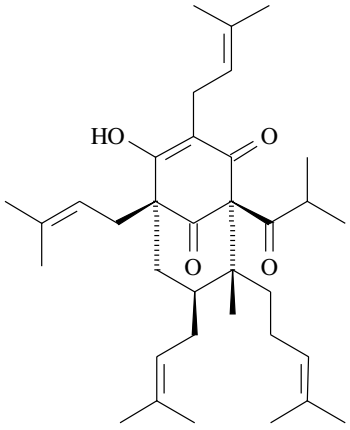

Fig. 2. Hyperforin.

commercial *H. perforatum* preparations (Chatterjee et al., 1998). Finally, the dicyclohexylammonium salt was found to be stable both at room temperature and under influence of air (Erdelmeier et al., 1999). The instability of hyperforin is due to the enolized β-dicarbonyl system because natural analogues lacking this moiety are stable (Verotta et al., 1999, 2000). The majority of commercial St. John's wort extracts prepared via aqueous alcoholic extraction contain 1–5% hyperforin (Lang et al., 2002).

3. Occurrence

The genus *Hypericum* (Clusiaceae = Guttiferae) encompasses about 450 species of trees, shrubs and herbs (Robson, 2003). *H. perforatum* is the only species to contain hyperforin as a quantitatively major constituent (Umek et al., 1999; Smelcerovic and Spiteller, 2006). In contrast to earlier studies (Berghöfer and Hölzl, 1986; Umek et al., 1999), nine *Hypericum* species have recently been found to have low hyperforin contents (*H. barbatum, H. richeri, H. rumeliacum, H. maculatum, H. tetrapterum, H. hirsutum, H. linarioides, H. olympicum*) (Smelcerovic and Spiteller, 2006). Furthermore, sepals of *H. elodes* contain hyperforin and adhyperforin (Piovan et al., 2004). In *H. perforatum*, the highest hyperforin concentrations were found in flowers and fruits. In the course of flower ontogenesis, the hyperforin content continuously increased from 2.5% in young buds (3–4 mm) to 8.5% in unripe fruits, the last developmental stage studied (Tekel'ová et al., 2000). This finding is in good agreement with the observation that hyperforin accumulates primarily in the pistil (Repčák and Mártonfi, 1997). In contrast, hypericins and flavonoids are mainly formed in sepals, petals, and stamens which fall off (Repčák and Mártonfi, 1997). In the flower of *H. calycinum*, the ovarian wall accumulates about 20% polyprenylated acyl- and benzoylphloroglucinols which act as defensive agents and protect the developing seeds against herbivores and microbes (Gronquist et al., 2001). During fruit ripening in *H. perforatum*, the content of the homologue adhyperforin increased approx. tenfold from 0.2% in flowers to 1.9% in capsules (Maisenbacher and Kovar, 1992b). In leaves, the hyperforin level was about 1.5% and did not appreciably change in response to feeding by a specialist beetle and generalists as well as mechanical wounding (Sirvent et al., 2003). Great intraspecific variation of the hyperforin content (0.3–1.3%) was observed with seedlings (Košuth et al., 2003). The hyperforin level in callus and cell cultures was about 0.15% (Kirakosyan et al., 2000), that of shoot cultures around 0.4% (Dias, 2003; Zobayed et al., 2003). Cell cultures of