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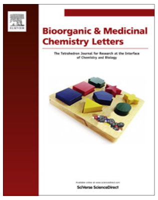

New strigolactone mimics: Structure–activity relationship and mode of action as germinating stimulants for parasitic weeds

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ABSTRACT

Strigolactones (SLs) are new plant hormones with varies important bio-functions. This Letter deals with germination of seeds of parasitic weeds. Natural SLs have a too complex structure for synthesis. Therefore, there is an active search for SL analogues and mimics with a simpler structure with retention of activity. SL analogues all contain the D-ring connected with an enone moiety through an enol ether unit. A new mechanism for the hydrolysis SL analogues involving bidentate bound water and an α,β-hydrolase with a Ser-His-Asp catalytic triad has been proposed. Newly discovered SL mimics only have the D-ring with an appropriate leaving group at C-5. A mode of action for SL mimics was proposed for which now supporting evidence is provided. As predicted an extra methyl group at C-4 of the D-ring blocks the germination of seeds of parasitic weeds.

Strigolactones (SLs) are new plant hormones that are currently much in focus.[1–10] The predominant activities of these SLs are stimulation of germination of seeds of parasitic weeds,[1–10] branching factor of AM fungi,[4,11,12] and inhibition of shoot branching and bud outgrowth.[13–15] This Letter deals primarily with the activity of SLs as germination stimulants.

Naturally occurring SLs are present in the root exudates of many plants, especially host plants for the parasitic weeds. They invariably contain three annulated rings, the ABC scaffold, connected with a butenolide ring (D-ring) via an enol ether unit.[1,2,7–10] Typical examples are (+)-strigol (**1**)[16] and (−)-*ent*-2′-*epi*-orobanchol (**2**)[17–19] (Fig. 1). For practical application these natural SLs have a too complex structure, and therefore, SL analogues have been developed with a much simpler structure but with retention of the essential bioactivity.[9,10] The most well known analogue is GR24 (**3**)[9,10,20,21] (Fig. 1).

For germination stimulants a model compound was used for the design and preparations of new bioactive analogues. This model (Fig. 2) was based on a structure–activity analysis combined with a tentative mode of action for germination.[9,10,22] It was shown that the bioactiphore of SLs resides in the CD part of the SL molecules, implying that the α,β-unsaturated carbonyl moiety connected via an enol ether unit with the D-ring is predominantly responsible for the bioactivity.[9,10,22] Illustrative examples of such SL analogues designed on the basis of the modelcompound shown in Figure 2 are Nijmegen-1 (**4**)[23] and analogues derived from tetralone (**5**),[24,25] hydroxy coumarin (**6**)[26] and saccharin (**7**)[27] (Fig. 1).

Although the full details of the germination process are not known yet, it is assumed that on a molecular level germination is triggered by an initial reaction of water with the enol ether moiety in a Michael fashion whereby the water molecule is bound in a bidentate manner.[10] In a subsequent retro-Michael reaction a cleavage process gives the hydroxy butenolide and the formylated ABC scaffold.[9,10,22] There is some evidence that this hydrolytic cleavage is catalyzed by an α/β hydrolase having a Ser-His-Asp canonical catalytic triad at the active site that is capable of accommodating an SL molecule.[28] This newly proposed mechanism of hydrolytic cleavage reaction is depicted in Figure 3, whereby histidine serves as the base to initiate the Michael addition of water.

Recently, we reported our serendipitous finding that compounds lacking the enol ether unit, such as the saccharine D-ring derivative **8** and the aroyloxy substituted butenolides **9** (Fig. 4) which are not in accordance with the model shown in Fig. 2, are active as germinating agents for parasitic weeds.[27] These compounds are named as SL mimics.

A structurally related SL mimic is butenolide **10**, which shows a moderate germination activity at a relative high concentration.[29]

In order to rationalize the activity of the SL mimics a mode of action shown in Figure 5 was tentatively proposed.[27] An essential feature of this proposal is a proton shift prior to the elimination

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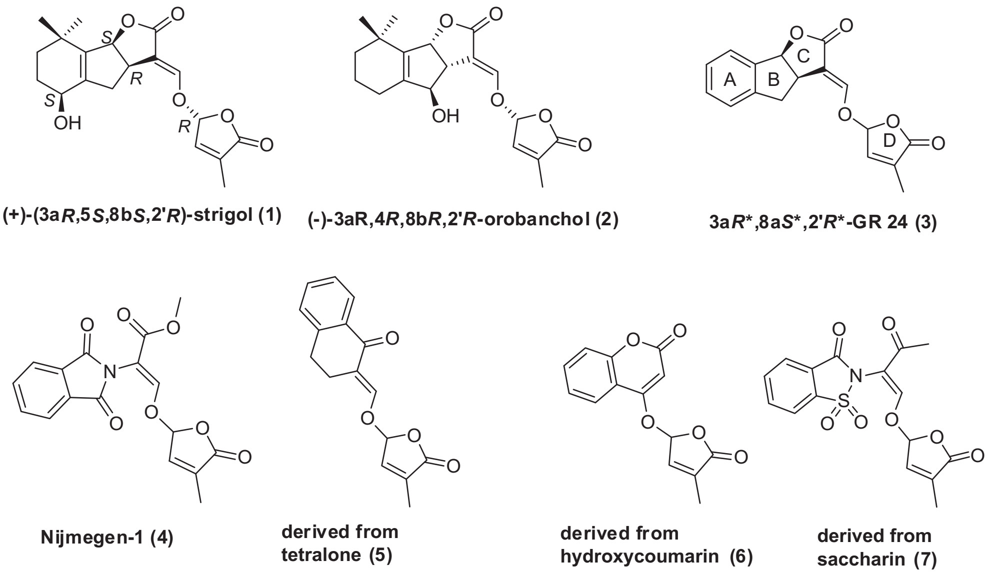


(+)-(3a*R*,5*S*,8b*S*,2'*R*)-strigol (1) **(-)-3aR,4*R*,8b*R*,2'*R*-orobanchol (2)** **3a*R**,8a*S**,2'*R**-GR 24 (3)**

Nijmegen-1 (4) **derived from tetralone (5)** **derived from hydroxycoumarin (6)** **derived from saccharin (7)**

Figure 1. Structures of some natural SLs, analogue GR24 and newly designed SL analogues.

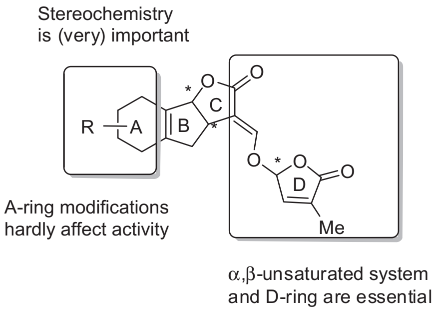
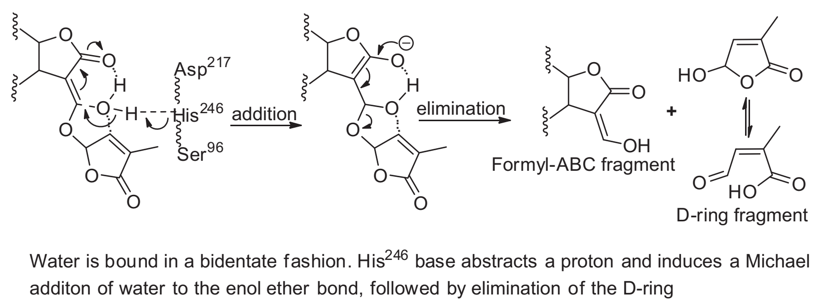


Figure 2. Model for the design of new bioactive SL analogues with germinating activity.

of the leaving group L. In the SL mimics a benzoate and a saccharide ion serve as L.

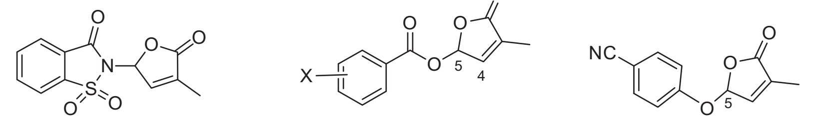
In this Letter we provide supporting evidence for this mode of action. By replacing the hydrogen atom at C-4 by a methyl group a modified SL mimic is obtained in which the essential proton transfer cannot take place anymore and accordingly these modified SL mimics are predicted to be inactive as germinating agents.

The synthesis of such C-4 methyl containing SL mimics is straightforward. A set of 4 SL mimics with a C-4 hydrogen and 3 mimics with a C-4 methyl was prepared as shown in Figure 6. The SL mimics **9** were readily obtained by a coupling of bromo-butenolide with an appropriate sodium carboxylate.[30] Coupling of a suitable acid chloridewith 3,4-dimethyl hydroxy butenolide in the presence of pyridine resulted in the SL mimics **11**. [32] There



Water is bound in a bidentate fashion. His246 base abstracts a proton and induces a Michael additon of water to the enol ether bond, followed by elimination of the D-ring

Figure 3. Proposal for the hydrolysis mechanism of SLs in the catalytic triad of Ser^{96}-His^{246}-Asp^{217}.



saccharin-butenolide (8) **5-benzoyloxy-butenolides (9)** **a**: X = H; **b**: X = *o*-OH **5-*p*-cyanophenoxy-butenolide (10)**

Figure 4. SL mimics.