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Regioselective *O*-glycosylation of flavonoids by fungi *Beauveria bassiana, Absidia coerulea* and *Absidia glauca*

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ABSTRACT

In the present study, the species: *Beauveria bassiana, Absidia coerulea* and *Absidia glauca* were used in biotransformation of flavones (chrysin, apigenin, luteolin, diosmetin) and flavanones (pinocembrin, naringenin, eriodictyol, hesperetin). The *Beauveria bassiana* AM 278 strain catalyzed the methylglucose attachment reactions to the flavonoid molecule at positions C7 and C3′. The application of the *Absidia* genus (*A. coerulea* AM 93, *A. glauca* AM 177) as the biocatalyst resulted in the formation of glucosides with a sugar molecule present at C7 and C3′ positions of flavonoids skeleton. Nine of obtained products have not been previously reported in the literature.

1. Introduction

The presence of glycosyl moiety is usually crucial for the biological activity of many important natural biomolecules such as glycans, lipids, peptides and small molecules [1].

Glycosylation can increase the diversity of structure and function of natural product, the sugar moieties can improve water-solubility of natural products, enhance their bioactivity, stability, bioavailability and decrease their toxicity [2]. From the reasons listed here, a lot of effort was put into development of efficient production methods of the glycosylated natural products.

Although the extraction from native producers, mainly plants, appears to be the easiest method to obtain natural glycosides, this approach has many limitations e.g. low yield as a reason of low concentration in a biomass and strict dependence on seasonal vegetation conditions. Production of specific glycosides by means of the organic synthesis is generally recognized as a challenging task, uneconomical in a large scale. It often requires protection of reactive groups in substrates and application of expensive catalysts, generates toxic wastes and efficiency is generally low [3–5].

In addition to synthetic methods and isolation from natural sources, biotransformations are an attractive alternative. Enzymes (or whole cells as biocatalysts) can be utilized to perform glycosylation reaction, additionally resulting in specific products and operating under mild conditions. From many natural products which can be decorated with carbohydrates by glycosyltransferases, flavonoids are of special interest due to their high biological activities, such as anti-inflammatory, anticancer, anti-obesity, antioxidant and antimicrobial ones [6,7]. Microbial catalysts are useful tool for production of flavonoid glycosides in a cheap, simple one-step processes. The most literature reports on this topic concern the use of filamentous fungi [8,9].

In our previous studies fungal strains belonging to species *Beauveria bassiana*, *Absidia coerulea* and *Absidia glauca* have been proven to be a useful glycosylation catalysts toward a isoflavones [10], flavonols [11] as well as prenylated chalcones, flavanones and aurones [12–16]. The objective of the present research was to obtain glycosylated derivatives of four common natural flavones and their four flavanone derivatives, using the above-mentioned biocatalysts, and to determine the influence of the structure of flavonoids used on glycosylation regioselectivity and yield.

2. Materials and methods

2.1. Compounds

Chrysin (**1**) and naringenin (**6**) were purchased from Sigma-Aldrich (St. Louis, MO, USA), hesperetin (**8**) from Alfa-Aesar (Thermo Fisher, Karlsruhe, Germany), apigenin (**2**), luteolin (**3**) and diosmetin (**4**) from

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Carbosynth (Berkshire, UK).

Pinocembrin (**5**) was obtained by hydrogenation of chrysin (**1**) using hydrogen and 10% Pd/C according to the method described by Popłoński et al. [17]. The mixture of **1** (500 mg, 1.97 mmol) and 10% Pd/C (100 mg) in methanol (75 mL) was stirred at room temperature, bubbled with nitrogen for 10 min and then with hydrogen. The progress of reaction was monitored by HPLC. The reaction was performed for 2 h. After filtration, the solvent was evaporated and the resultant residue was chromatographed by flash chromatography using an Interchim PF-15SIHP 40 g, 15 μm flash column in isocratic elution program of a chloroform:ethyl acetate (19:1, v/v) mixture at the flow rate 26 mL/min to afford 139 mg of **5** with 28% yield and purity greater than 99% (according to HPLC).

Eriodictyol (**7**) was obtained according to the same procedure as **5**, using 100 mg of luteolin (**3**) (0.3 mmol) as a substrate and 45 mg of Pd/C. The progress of reaction was monitored by HPLC. Reaction was carried out for 48 h. After purification by flash chromatography using an Interchim PF-30SIHP 12 g, 30 μm flash column in isocratic elution program of a hexane:ethyl acetate:formic acid (2:5:0.003, v/v/v) mixture at the flow rate 15 mL/min 41.5 mg of **7** was obtained with the yield of 41% and purity greater than 99% (according to HPLC).

2.2. Microorganisms

The fungal strains used for biotransformation, i.e., *Absidia coerulea* AM 93, *Absidia glauca* AM 177 and *Beauveria bassiana* AM 278 were obtained from the collection of the Department of Biology and Pharmaceutical Botany, Medical University of Wrocław, Poland.

2.3. Cultivation of fungi

The fungi were maintained on Sabouraud agar slants and grown on a Sabouraud medium (glucose 3%, peptone 1%). The fungal cultures were cultivated on rotary shakers (130 rpm, 6.5 amplitude) at 28 °C in 100 mL Erlenmeyer flasks containing 30 mL of the medium in the screening studies and in 300 mL Erlenmeyer flasks with 100 mL of the medium in the preparative scale biotransformation.

2.4. Screening procedure

A substrate (5 mg) was dissolved in 0.5 mL dimethyl sulfoxide (DMSO) and added to the grown fungal culture. The reactions were carried out for seven days. Appropriate controls (the substrate in sterile medium and incubation of fungal strains without a substrate) were run along with the above experiments.

2.5. Preparative biotransformation

In the preparative biotransformations 60 mg of a substrate was dissolved in 6 mL of DMSO and distributed between four flasks of 4-days fungal cultures. The reactions were carried out for ten days.

2.6. Reaction work-up and product analysis

After incubation, the reaction mixtures were acidified with 1 M HCl to pH about 5 (if necessary) and extracted with organic solvent. In the screening experiments the cultures were extracted with 15 mL of ethyl acetate. In preparative biotransformations the cultures were extracted three times with 25 mL of ethyl acetate. Extracts were dried over anhydrous magnesium sulfate. Residues obtained by evaporation of solvent were dissolved in methanol and analyzed by TLC and HPLC. Crude product mixtures were separated by column chromatography on silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany) using chloroform:methanol mixture (7:1, v/v) as eluent.

The structures of the obtained products were determined by means of NMR (^{1}H NMR, ^{13}C NMR, HMBC, HSQC) and HR-ESIMS analysis.

The purity of obtained biotransformation products were greater than 96% (according to HPLC and NMR).

2.7. Analytical methods

TLC was carried out on Merck silica gel 60, F_{254} (0.2 mm thick) plates using chloroform:methanol (7:1, v/v) as eluent. Products were detected by inspecting plates under UV irradiation.

HPLC analysis were performed on Dionex Ultimate 3000 UHPLC + instrument system (Thermo Scientific, Waltham, MA, USA) equipped with C-18 analytical column (ZORBAX Eclipse XDB, 5 μm, 4.6 mm × 250 mm, Agilent, Santa Clara, CA, USA). The mobile-phase components were: 0.05% formic acid (A) and methanol containing 0.05% formic acid (B). The mobile-phase gradient was as follows: 0–2 min: 50% B, 2–12 min: 50–95% B, 12–14 min: 95% B. Flow rate was 1 mL/min.

The NMR spectra were recorded on a DRX 600 MHz Bruker spectrometer and measured in DMSO-d_6.

Negative-ion HR-ESIMS spectra were measured on a Bruker ESI-Q-TOF, maXis impact Mass Spectrometer (Bruker Daltonics). The mass spectrometer was operated in negative ion mode with the potential between the spray needle and the orifice 3000 V, nebulizer pressure of 0.4 bar, and a drying gas flow rate of 4 L/min at 200 °C. The sample flow rate was 3–5 μL/min. Ionization mass spectra were collected at the ranges *m/z* 50–1400. The instrument was calibrated with an Agilent electrospray calibration solution (ESI-L Low Concentration Tunemix Agilent USA, score = 100%, SD < 1 ppm).

3. Results and discussion

3.1. Flavonoids biotransformations

In this study, selected fungal strains: *Beauveria bassiana* AM 278, *Absidia coerulea* AM 93 and *Absidia glauca* AM 177 have been tested for their ability to transform common natural flavones and flavanones. For this purpose, chrysin (**1**), apigenin (**2**), luteolin (**3**), diosmetin (**4**), pinocembrin (**5**), naringenin (**6**), eriodictyol (**7**) and hesperetin (**8**) were chosen as substrates (Fig. 1). Experiments performed in a preparative scale allowed to obtain products in amounts necessary to determine its chemical structures. In the course of our study, we obtained 19 products of monoglycosylation, 9 of which, to our best knowledge, have not been reported so far in the literature (Fig. 2). The reaction yields were noted as isolated yields (Table 1).

3.1.1. Biotransformations in Beauveria bassiana AM 278 culture

The fungal strain *B. bassiana* AM 278 exhibited strict regioselective glycosylation ability towards flavonoid compounds. In the conducted studies chrysin (**1**), apigenin (**2**), luteolin (**3**), pinocembrin (**5**), naringenin (**6**) and eriodictyol (**7**) were converted to 4″-*O*-methylglucose derivatives at C7 position (**9, 11, 13, 18, 20, 22**). Our previous research also indicates that the strain *B. bassiana* AM 278 is capable of regioselective glycosylation at C7 position of daidzein, genistein and biochanin A [10]. The methoxyl group in ring B at C4′ position in diosmetin (**4**) and hesperetin (**8**) resulted in additional glycosylation products. Biotransformation of both **4** and **8** led to two glycosylated products containing 4″-*O*-methylglucose molecule attached at C7 (**15, 24**) or C3′ position (**16, 26**). In biotransformation of diosmetin (**4**) apart of methylglucose derivatives, the product of conjugation with the glucose molecule at the C3′ (**17**) was also isolated. This observation indicated that glucose methylation occurs after glucosylation, what corresponds to the discovery of Xie et al. whom indicated in other strain of *B. bassiana* that the pair of glycosyltransferase and methyltransferase are involved in the process [18]. Interestingly, the methoxyl group at C4′ position in the isoflavone biochanin A did not effect on the glycosylation reaction conducted by the same strain of *B. bassiana* [10].

The type of flavonoid skeleton has a great importance on efficiency

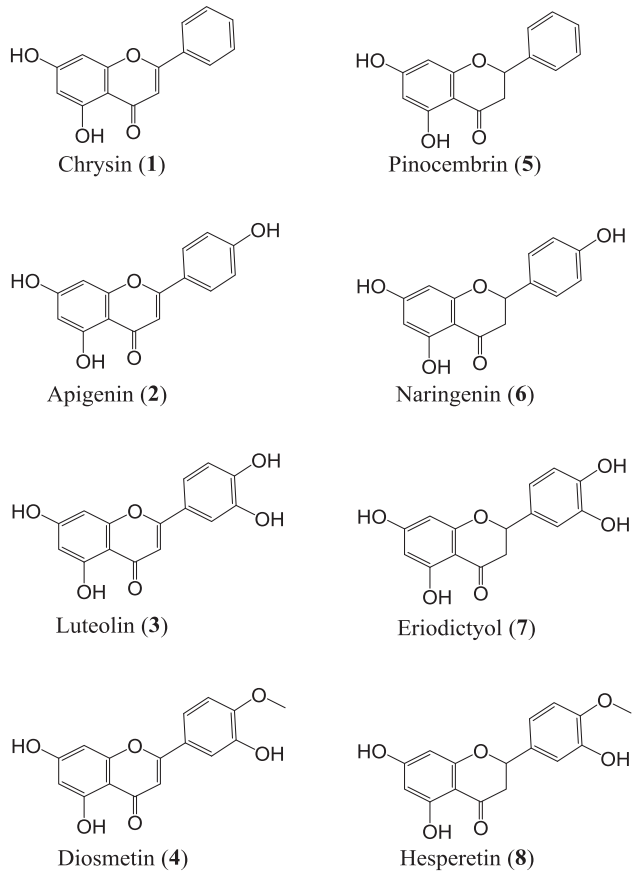


Fig. 1. Flavonoid substrates.

of glycosylation reaction catalyzed by *B. bassiana*. The lack of a double bond between the C2 and C3 carbon atoms in the substrate molecule contributes to an increase in transformation efficiency. The yield of the reactions catalyzed by the *B. bassiana* AM 278 enzyme system is significantly higher in the reactions in which flavanones were used as substrates, what might be associated with greater rigidity of a flavanone skeleton. The biotransformation yield was also influenced by the position of the B-ring - in comparison to the biotransformation of flavones, biotransformations of isoflavones resulted in a slightly higher yield [10]. It proves that not only state of C ring oxidation, but also B ring position at flavonoid molecules, have fundamental importance on glycosylation reaction catalyzed by *B. bassiana* AM 278.

There are several reports that described the use of filamentous fungi *B. bassiana* in flavonoid biotransformation. Attachment of 4″-*O*-methylglucose is a characteristic reaction for this species [10–16,19–21]. Chrysin 7-*O*-β-D-4″-*O*-methylglucopyranoside (**9**) was previously obtained by Herath and coworkers from chrysin using *Beauveria bassiana* strain with the yield of 44.2% [22]. To our best knowledge, other flavonoid derivatives with 4″-methylglucose molecule (**11, 13, 15, 16, 18, 20, 22, 24, 26**) obtained in our experiments are new compounds. Interestingly, attachment of 4″-*O*-methylglucopyranoside to flavonoid molecules have been also observed in biotransformation conducted by other entomopathogenic fungi belonging to *Isaria* genus [23–26].

3.1.2. Biotransformations in Absidia coerulea AM 93 and Absidia glauca AM 177 culture

Biotransformations of chrysin (**1**), apigenin (**2**) and naringenin (**6**) by *A. coerulea* AM 93 and *A. glauca* AM 177 led to derivatives with the glucose molecule attached at the C7 position of flavonoid skeleton (**10, 12, 21**). Reaction of diosmetin (**4**) – flavone with methoxyl group in ring B, with *Absidia* species led to the metabolite containing glucose molecule only at C3′ position (**17**). In turn, hesperetin (**8**) – the flavanone, derivative of diosmetin (**4**) without C2—C3 double bond, was transformed by both tested strains to hesperetin 7-*O*-β-D-glucopyranoside (**25**) and hesperetin 3′-*O*-β-D-glucopyranoside (**27**) what suggests a great importance of the C2—C3 olefin bond in a substrate recognition. Pinocembrin was converted to pinocembrin 7-*O*-β-D-glucopyranoside by *A. coerulea* AM 93 and *A. glauca* AM 177. Additionally, in the reaction medium of *A. coerulea* AM 93 the second product, containing glucose moiety at C5 position was observed, however in trace amount only. Biotransformation of luteolin (**3**) and eriodictyol (**7**) by *A. coerulea* AM 93 led to luteolin 3′-*O*-β-D-glucopyranoside (**14**) and eriodictyol 7-O-β-D-glucopyranoside (**23**) respectively. The NMR spectra analysis of **23** also confirms traces of luteolin 4′-*O*-β-D-glucopyranoside. Strain *A. glauca* AM 177 is not capable of biotransforation of luteolin (**3**) and eriodictyol (**7**).

Presented biotransformations processes performed by filamentous fungi from the *Absidia* genus are an attractive method for production of glucosylated flavonoids. Isolating of these compounds from plant material it is not a trivial task. For example, extraction yield of luteolin 3′-*O*-glucoside (**14**) from *Verbascum salviifolium* is only 0.006% [27]. In turn, Wang and coworkers isolated diosmetin 3′-*O*-glucopyranoside (**17**) from *Saussurea stella* with a yield of 0.0003% [28]. There are also examples of obtaining flavonoid glucosides by chemical synthesis [29–31]. A disadvantage of chemical glycosylation is a multistep synthesis and the necessity of selective protection of hydroxyl groups to avoid side products, what definitively results in a greater effort to obtain a final product. In addition, the catalysts and chemicals used in synthesis are harmful for the environment [32].

3.2. Spectral data of obtained products

The chemical structures of synthesized substrates (pinocembrin (**5**) and eriodictyol (**7**)) and biotransformation products were determined by NMR analysis (^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC). All spectroscopic data (NMR, MS) are available in the Supplementary Materials.

Compounds **5**, **7**, **9**, **10**, **12**, **14**, **17**, **19**, **21**, **23**, **25** and **27** are known. The NMR spectroscopic data for those compounds are consistent with those reported in the literature [22,33–41].

A glucose or methylglucose molecule, in all obtained biotransformation products were confirmed by additional characteristic 6 or 7 carbon signals observed in the region from $\delta = 59$ ppm to $\delta = 102$ ppm in the ^{13}C NMR spectra, coupled with proton signals between $\delta = 3.0$–5.2 ppm in the ^{1}H NMR spectra. Exemplary spectra of aglycon - glucoside - methylglucoside forms for flavone and flavanone are presented in the Supplementary Materials (Figs. S1 and S2).

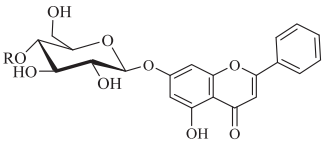
The presence of a distinctive doublets at ^{1}H NMR spectra from C1″ carbon atoms with a chemical shift in the δ 4.9–5.2 ppm range and a coupling constant of 7.7–8.0 Hz clearly indicates that the attached glucose molecules are β-anomers (Fig. S3, Supplementary Materials).

For compounds: **9, 11, 13, 15, 16, 18, 20, 22, 24, 26** a three-proton singlets between δ 3.4–3.6 ppm in the ^{1}H NMR spectrum correlated with glucose C4 carbon signals at 78–79 ppm what indicates the *O*-methylation of the sugar hydroxyl group (Fig. S4, Supplementary Materials).

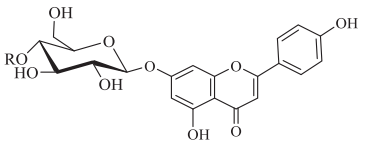
The position of glucose molecule attachment was determined by HMBC spectra processing. For the products substituted in the C7 position, the correlation of the proton bound to C1″ with the carbon atom with a chemical shift in the range of 161–165 ppm was observed. In turn, for products substituted in position C3′ the correlation of the proton from position C1″ with the carbon atom with a chemical shift in the range of 146 ppm was observed (Fig. S5, Supplementary Materials).

4. Conclusions

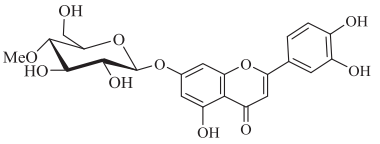
A systematic study of the application of fungi *A. glauca*, *A. coerulea* and *B. bassiana* for the preparation of natural glucosylated flavones and flavanones have been undertaken.



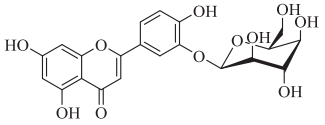
R=CH_3 Chrysin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**9**)
R=H Chrysin 7-*O*-ß-D-glucopyranoside (**10**)



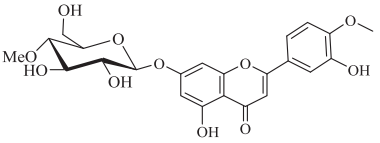
R=CH_3 Apigenin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**11**)
R=H Apigenin 7-*O*-ß-D-glucopyranoside (**12**)



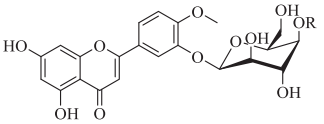
Luteolin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**13**)



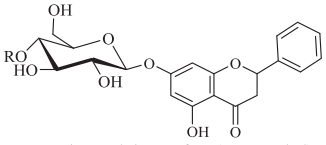
Luteolin 3'-*O*-ß-D-glucopyranoside (**14**)



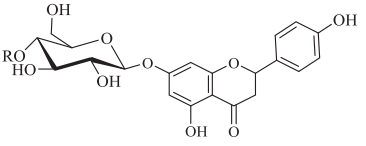
Diosmetin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**15**)



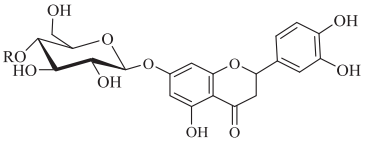
R=CH_3 Diosmetin 3'-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**16**)
R=H Diosmetin 3'-*O*-ß-D-glucopyranoside (**17**)



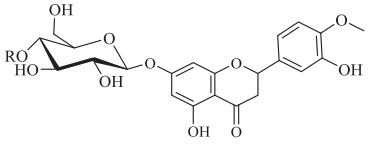
R=CH_3 Pinocembrin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**18**)
R=H Pinocembrin 7-*O*-ß-D-glucopyranoside (**19**)



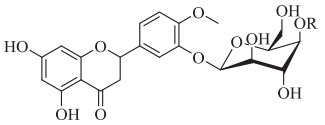
R=CH_3 Naringenin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**20**)
R=H Naringenin 7-*O*-ß-D-glucopyranoside (**21**)



R=CH_3 Eriodictyol 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**22**)
R=H Eriodictyol 7-*O*-ß-D-glucopyranoside (**23**)



R=CH_3 Hesperetin 7-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**24**)
R=H Hesperetin 7-*O*-ß-D-glucopyranoside (**25**)



R=CH_3 Hesperetin 3'-*O*-ß-D-(4"-*O*-methyl)-glucopyranoside (**26**)
R=H Hesperetin 3'-*O*-ß-D-glucopyranoside (**27**)

Fig. 2. Biotransformation products.

This and our previous studies [10–16] have shown that preferable position of glycosylation catalyzed by mentioned fungal cultures is a hydroxyl group bound to C7 in a flavonoid molecule. Moreover, low substrate specificity of enzymes involved in the reaction causes that many flavonoids of different classes including chalcones, flavanones, flavones, isoflavones, flavonols and aurones are accepted substrates for glycosylation. However, yield of glycosylation strongly depends on the type of flavonoid skeleton and substituents present in aromatic rings,

Table 1
Obtained biotransformation products with isolated yields.

Substrate	Biotransformation products (isolated yield)		
	B. bassiana AM 278	*A. coerulea* AM 93	*A. glauca* AM 177
Chrysin (**1**)	**9** (15%)	**10** (23%)	**10** (14%)
Apigenin (**2**)	**11** (15%)	**12** (8%)	**12** (2%)
Luteolin (**3**)	**13** (23%)	**14** (18%)	–
Diosmetin (**4**)	**15** (7%)	**17** (18%)	**17** (15%)
	16 (4%)		
	17 (7%)		
Pinocembrin (**5**)	**18** (37%)	**19** (45%)	**19** (38%)
Naringenin (**6**)	**20** (82%)	**21** (73%)	**21** (35%)
Eriodictyol (**7**)	**22** (36%)	**23** (30%)	–
Hesperetin (**8**)	**24** (38%)	**25** (36%)	**25** (9%)
	26 (33%)	**27** (6%)	**27** (11%)

for instance the lack of a double bond between the C2 and C3 carbon atoms in the substrate molecule (flavanones) significantly increase the transformation efficiency. Additionally, the presence of methoxyl group at C4′ and hydroxyl group at C3′ in ring B have also influence on the glycosylation process. In case of diosmetin (**4**) and hesperetin (**8**) with both mentioned groups instead of pair of C7 glycosylated products, two pairs of products were observed (C7 and C3′ glycosides).

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Sample availability

Samples of all compounds are available from the authors for possible research projects in cooperation.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.01.046. These data include MOL files and InChiKeys of the most important compounds described in this article.

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