New kojic acid-amino acid hybrids as potential tyrosinase inhibitors

Melanogenesis is a process by which melanocytes produce melanin initiated by tyrosinase upon exposure of the skin to UV radiation. Tyrosinase plays an important role in the pathway of melanin biosynthesis from tyrosine. It catalyzes two distinct reactions involving molecular oxygen; the hydroxylation of tyrosine to L-3, 4-dihydroxyphenyl alanine (L-DOPA) as monophenolase and the oxidation of L-DOPA to dopaquinone as diphenolase. Dopaquinone is non-enzymatically converted to dopachrome and ultimately to dihydroxyindoles which cause the production of melanin pigments. Therefore, the development of tyrosinase inhibitors is of great importance in the medical, agricultural and cosmetic fields. A large number of naturally occurring as well as synthetic compounds that are tyrosinase inhibitors have been reported (Fig 1). However, only a few of them are sufficiently potent for practical use and comply with safety regulation. Kojic acid (KA) has been studied extensively for its tyrosinase activity. Its inhibitory mechanism is non-competitive one resulting from chelating with a copper ion of tyrosinase. Thus, modification of kojic acid provides a potential route for superior tyrosinase inhibitors.

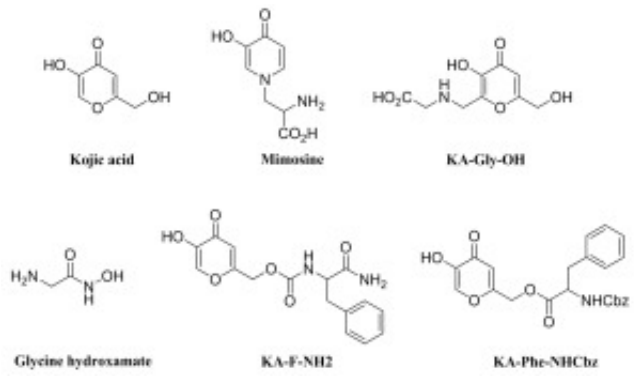

Fig. 1. Various tyrosinase inhibitors

Kojic acid (5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one) is a natural product produce by many species of fungi such as *Aspergillus*, *Acetobacter and Penicillium*. Kojic acid was discovered in Japan by Saito in 1907 who isolated the compound from mycelium of the fungi *Aspergillus oryzae* grown on steam rice (Koji in Japanese) and its structure was established by Yabuta in 1924. Kojic acid can be produce from various carbohydrate sources in an aerobic condition by a variety of microorganisms. Kojic acid has been used as food additive for preventing enzymatic discoloration of vegetables, crabs and shrimps. KA has also been used as a skin lightening or bleaching agents in cosmetic industry. Kojic acid exhibit bacteriostatic anti-inflammatory, insecticidal, antibiotic, cytotoxic and antitumor activities. Many kojic acid derivatives have shown to exhibit anti-cancer, antifungal, antibacterial, anti-microbial and anti-viral activities. Due to its vast biological activities,

the kojic acid scaffold has emerged as privileged structure in medicinal chemistry research.

Unnatural amino acids, the non-proteinogenic ?- amino acids that occur either naturally or chemically synthesized, have been used widely in ligand design and total synthesis as chiral building block. They have been also used as molecular scaffolds in constructing combinatorial libraries. They represent a powerful tool in drug discovery when incorporated into therapeutic peptidomimetics and peptide analogs. The incorporation of unnatural amino acids could enhance the resistance of peptides to enzymatic degradation and increase peptides structural diversity as well as bioactivity. The seminal work on the synthesis of unnatural amino acids has been done by O'Donnell, Maruoka and Kotha independently, which accelerated the application of this class of amino acid for practical applications. With the growing attention of functionalized peptides for pharmaceutical application, a variety of methodologies have been developed to obtain unnatural amino acids.

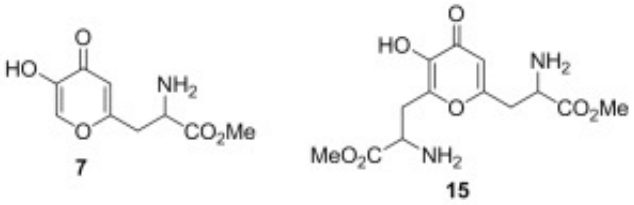

Fig. 2. Unnatural amino acid containing kojic acid

Taking into consideration these two biologically significant structure (kojic acid and ?-amino acid), we envisioned that incorporation of kojic acid moiety into ?–position of glycine would create simultaneously a new natural product-like kojic acid and unnatural amino acid (Fig 2). The resulting molecules hold great potential for biological activities and consequently the development of efficient synthetic approaches to these molecules would be needed urgently. To the best of our knowledge, unnatural amino acid containing kojic acid where kojic acid is directly linked to amino acid through a C-C bond have not been disclosed, although there are reports for the preparation of N-Kojic acid as well as O-Kojic acid ?-amino acid derivatives. In our continuation endeavor to prepare novel hybrid molecules containing variety of natural products, we developed interest in the synthesis of novel kojic acid amino acid hybrid natural products (Fig 2). Our proposed strategy was based on the protocol developed by O'Donnell starting from N-(diphenylmethylene) glycine methyl ester using chloro or bromo kojic acid. Subsequent hydrolysis of the alkylated product would provide kojic acid-amino acid hybrids 7. Using the above synthetic protocol, previously inaccessible kojic acid amino acid derivative 7 as well as di-amino acid kojic acid derivatives 15 were prepared for the first time.

The key reaction was the alkylation reaction of N-(diphenylmethylene) glycine methyl ester with bromo kojic acid derivatives. These new amino acid derivatives containing kojic acid has several

important reaction centres enabling one to perform oxidation, reduction, alkylation, acylation, chelation, nucleophilic substitution reaction and finally peptide coupling reaction. We believe that the new amino acid containing kojic acid will find widespread application as tyrosinase inhibitor as well as other biological application.

Publication

Synthesis of new kojic acid based unnatural ?-amino acid derivatives.
Balakrishna C, Payili N, Yennam S, Uma Devi P, Behera M
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