

Kojic Acid Derivatives

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1. Introduction

Melanin is one of the most important pigments which exist ubiquitously from microorganisms to plants and animals. It is secreted by melanocyte cells and determines the color of skin and hair in mammals. It protects the skin from photocarcinogenesis by absorbing UV sunlight and removing reactive oxygen species (ROS) (Gupta, 2006; Kim, 2005; Sapkota, 2011). It is formed by enzymatically catalyzed chemical reactions (Chang, 2009). The modifications in melanin biosynthesis occur in many disease states. The excessive level of melanin pigmentation causes various dermatological disorders including hyperpigmentations such as senile lentigo, melasma, postinflammatory melanoderma, freckles, ephelide, age spots and sites of actinic damage which can give rise to esthetic problems (Briganti, 2003; Curto, 1999). Hyperpigmentation usually becomes a big problem as people age because darker spots will start to be seen on the face, arms and body. Also, hormonal changes such as pregnancy and drugs manipulating hormone levels may cause hyperpigmentation.

Inhibitors of the enzyme tyrosinase (EC 1.14.18.1, syn.polyphenol oxidase, PPO; monophenol; dihydroxy-L-phenylalanin; oxidoreductase) can be used to prevent or treat melanin hyperpigmentation disorders. Therefore, they have become increasingly important in cosmetic and medical products. Besides being used in the treatment of some dermatological disorders associated with melanin hyperpigmentation, tyrosinase inhibitors are found to have an important role in cosmetic industry for their skin lightening effect and depigmentation after sunburn (Briganti, 2003; Chang, 2009; Khan, 2007; Parvez, 2007; Seo, 2003). Tyrosinase is a common multifunctional copper-containing enzyme from the oxidase superfamily found in plants, animals and fungi. It is responsible for melanin biosynthesis, which determines the color of skin, hair and fur. It is at the moment a well-characterized enzyme. As an enzyme that produces pigment, tyrosinase catalyzes two key reactions in the melanin biosynthesis pathway: the addition of a hydroxyl group (-OH) to the amino acid tyrosine, which then becomes 3,4-dihydroxyphenylalanine (L-DOPA). The tyrosinase enzyme then converts L-DOPA into *o*-dopaquinone by an oxidation reaction. Following these two main steps, melanin is then generated after further enzymatic steps (Scheme 1) (Gupta, 2006; Parvez, 2007). Melanin formation is considered to be deleterious to the color quality and flavor, and loss of nutritional and market values of foods. So, it causes the enzymatic

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based on naturally occurring compounds have opened up this research to a broad range of possible tyrosinase inhibitors (Diaz, 2009). There are several inhibition mechanisms of tyrosinase but only two types' inhibitors are regarded as "true inhibitors". These are specific tyrosinase inactivators and specific tyrosinase inhibitors. Specific tyrosinase inactivators such as mechanism-based inhibitors are also called suicide substrates. These inhibitors can be catalyzed by tyrosinase and form covalent bond with the enzyme, thus irreversibly inactivating the enzyme during catalytic reaction. They inhibit tyrosinase activity by inducing the enzyme catalyzing "suicide reaction." Specific tyrosinase inhibitors reversibly bind to tyrosinase and reduce its catalytic capacity (Chang, 2009). Therefore, the inhibition of tyrosinase is very essential in controlling the economy of foods and agriculture. Development of high-performance tyrosinase inhibitors is currently needed for these fields (Parvez, 2007).

Mushroom tyrosinase is popular among researchers as it is commercially available and inexpensive. It plays a critical role in tyrosinase inhibitor studies for its use in cosmetics as well as in food industries, and many researches have been conducted with this enzyme, which is well studied and easily purified from the mushroom *Agaricus bisporus*. No matter in terms of inhibitory strength, inhibitory mechanism, chemical structures, or the sources of the inhibitors, the search for new inhibitors based on mushroom tyrosinase has been so successful that various different types of inhibitors have been found in the past 20 years (Chang, 2009; Parvez, 2007; Seo, 2003).

In cosmetic products, tyrosinase inhibitors are used for skin-whitening effect, preventing formation of freckles and skin depigmentation after sunburn. Use of them is becoming increasingly important in the cosmetic and medicinal industries due to their preventive effect on pigmentation disorders. A number of tyrosinase inhibitors have been reported from both natural and synthetic sources, but only a few of them are used as skin-whitening agents, primarily due to various safety concerns, e.g. high toxicity toward cells, and low stability toward oxygen and water, resulting with their limited application (Chang, 2009; Kim, 2005).

Inhibitors of tyrosinase enzyme have a huge impact on industry and economy. Therefore, researchers around the world are studying on the discovery of several classes of these inhibitors. Although a large number of tyrosinase inhibitors have been reported from both natural resources or semi- and full synthetic pathways, only a few of them are used as skin lightening agents, primarily due to various safety concerns. For example, kojic acid and catechol derivatives, well-known hypopigmenting agents, inhibit enzyme activity but also exhibit harmful side effects (Fig. 1) (Seo, 2003).

Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) (Fig. 1, 4) and arbutin (4-hydroxyphenyl- β -D-glucopyranoside), extracted from leaves of common bearberry, are often used in skin care products as a lightening agent (Fig. 1). It has been shown to be safe and effective for topical use (Burdock, 2001). Recently, bibenzyl analogues are reported to have potent anti-tyrosinase activity with almost 20-fold stronger than kojic acid. However, the inhibitory activity of kojic acid is not sufficiently potent or unstable for storage for use in cosmetics. Kojic acid, a well-known tyrosinase inhibitor, alone or together with tropolone and L-mimosine are often used as the positive control in the literature for comparing the inhibitory strength of the newly inhibitors (Briganti, 2003; Chang, 2009; Khan, 2007; Parvez, 2007). L-mimosine, kojic acid and tropolone, having structural similarity to phenolic

substrates and showing competitive inhibition with respect to these substrates, are known as slow binding inhibitors (Seo, 2003). In addition, most tyrosinase inhibitors listed below are not currently commercially available, especially those from natural sources, and this limits their further evaluation in an *in vivo* study, where usually a large amount is needed for a tested inhibitor (Chang, 2009).

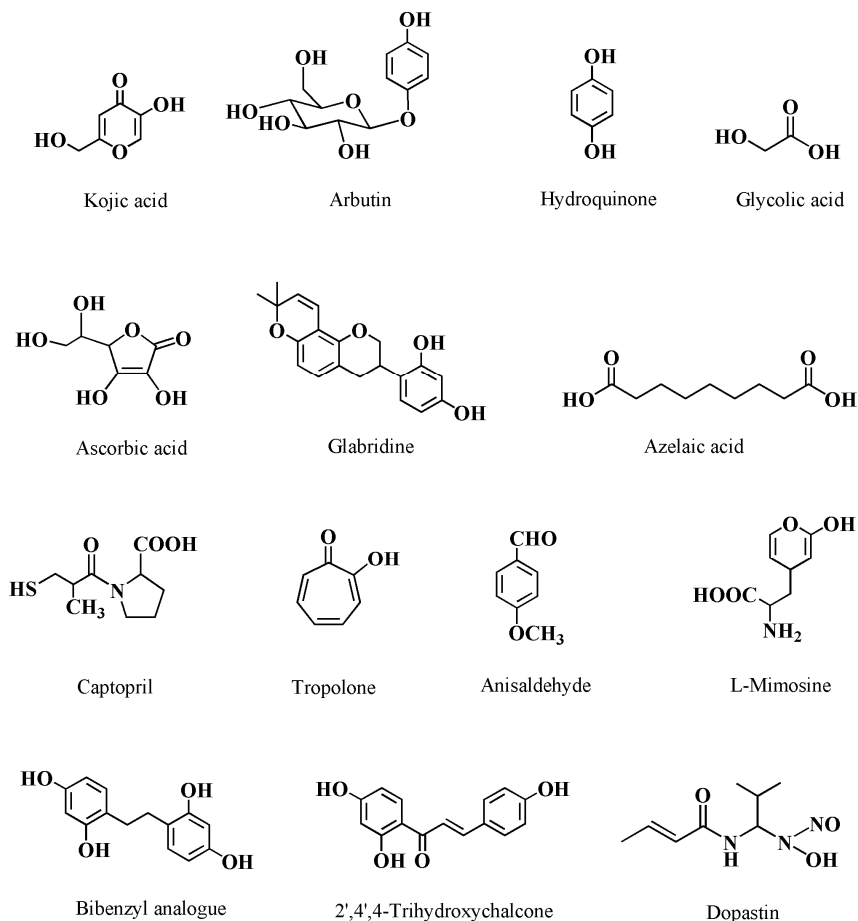


Fig. 1. Some tyrosinase inhibitors.

To treat hyperpigmentation through chemical treatments or bleaching creams are used. Most of the inhibitors are phenol or catechol derivatives, structurally similar to tyrosine or DOPA (Briganti, 2003). Hydroquinone (Fig. 1), a widely used skin lightening agent, is probably the most used bleaching cream on the market but it has a laundry list of warnings, including risk of hepatotoxicity. However, it is the most widely used bleaching cream in the world, despite the potential health side effects. It is also a reliable treatment for melasma. Kojic acid is used as an antioxidant and alternative to hydroquinone for skin lightening by the cosmetic industry (Gupta, 2006).

Although the huge number of reversible inhibitors has been identified, rarely irreversible inhibitors of tyrosinase have been found until now. Captopril, used as an antihypertensive drug, is able to prevent melanin formation as a good example of irreversible inhibitors (Khan, 2007). Another example for tyrosinase inhibitor azelaic acid, has anti-inflammatory, antibacterial, and antikeratinizing effects, which make it useful in a variety of dermatologic conditions (Briganti, 2003; Gupta, 2006). Besides, 4,4'-biphenyl derivative exhibited strong tyrosinase inhibitory activity and also assessed for the melanin biosynthesis in B16 melanoma cells (Kim, 2005).

2. Kojic acid

Kojic acid, the most intensively studied inhibitor of tyrosinase, was discovered by K. Saito in 1907. Since the early twentieth century, it has been known as an additive to prevent browning of food materials such as crab, shrimp, and fresh vegetables in food industry (e.g., as an antioxidant or antibrowning agent) in order to preserve their freshness and to inhibit discoloration. It shows a competitive inhibitory effect on monophenolase activity and a mixed inhibitory effect on the diphenolase activity of mushroom tyrosinase. The ability of kojic acid to chelate copper at the active site of the enzyme may well explain the observed competitive inhibitory effect. In addition, it is reported to be a slow-binding inhibitor of the diphenolase activity of tyrosinase (Cabanis, 1994). It is a biologically important natural antibiotic produced by various fungal or bacterial strains such as *Aspergillus oryzae*, *Penicillium* or *Acetobacter spp.* in an aerobic process from a wide range of carbon sources (Bentley, 2006; Brtko, 2004; Burdock, 2001). It plays an important role in iron-overload diseases such as β -thalassemia or anemia, since it possesses iron chelating activity (Brtko, 2004; Moggia, 2006; Stenson, 2007; Sudhir, 2005; Zborowski, 2003). Also, it forms stable complexes of metal kojates via reaction of kojic acid with metal acetate salts such as tin, beryllium, zinc, copper, nickel, cobalt, iron, manganese, chromium, gold, palladium, indium, gallium, vanadium, and aluminium (Fig. 2) (Barret, 2001; Cecconi, 2002; Emami, 2007; Finnegan, 1987; Hryniewicz, 2009; Masoud, 1989; Moggia, 2006; Naik, 1979; Sudhir, 2005; Yang, 2008; Zaremba, 2007; Zborowski, 2005). They were used as new drugs in the therapy of some diseases such as diabetes, anemia, fungal infections and neoplasia (Brtko, 2004; Song, 2002; Wolf, 1950). Tris(kojic acid) aluminium(III) and -gallium(III) complexes have lipid solubility; therefore, they can cross the blood-brain barrier with considerable facility (Finnegan, 1987).

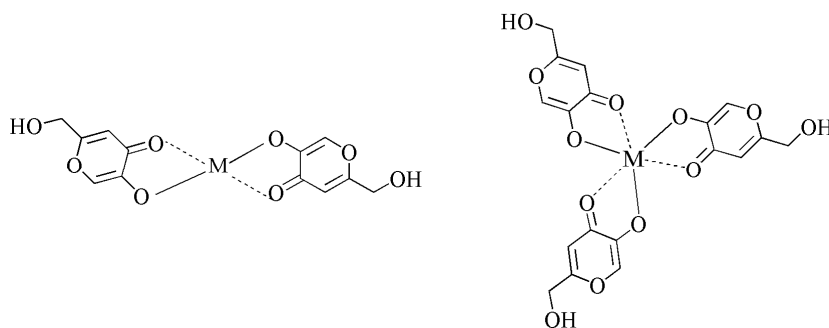


Fig. 2. $M(\text{Kojic acid})_n$ ($n=2,3$) metal complexes.

Kojic acid has weaker activity than ethylmaltol (2-ethyl-3-hydroxy-4H-pyran-4-one) against the convulsions induced by pentetrazole and strychnine. It is generally accepted that the lipid solubility of a drug is an important factor in connection with its transfer into the central spinal fluid and brain. The increase of inhibitory effect of 2-alkyl-3-hydroxy-4H-pyran-4-ones on the pentetrazole-induced convulsion with increasing carbon number of the alkyl group might be due to the enhancement of lipid solubility (Aoyagi, 1974; Kimura, 1980).

In acute, chronic, reproductive and genotoxicity studies, kojic acid was not found as a toxicant. Due to slow absorption into the circulation from human skin, it would not reach the threshold at tumor promotion and weak carcinogenicity effects were seen. The Cosmetic Ingredient Review (CIR) Expert Panel concluded that it is safe for use in cosmetic products up to a concentration level of 1%. The available human sensitization data support the safety of kojic acid at a concentration of 2% in leave-on cosmetics, suggesting that a limit of 2% might be appropriate. In an industrial survey of current use concentrations, it is used at concentrations ranging from 0.1% to 2%. The European Commission's Scientific Committee on Consumer Products (SCCP) determined that, based on a margin of safety calculation, the use of kojic acid at a maximum concentration of 1.0% in skin care formulations poses a risk to human health due to potential systemic effects (thyroid side effects). The SCCP also found it to be a potential skin sensitizer (Burnett, 2011).

2.1 Kojic acid as a tyrosinase inhibitor

It is well recognized that kojic acid, of high purity (99%) made by a certain pharmaceutical manufacture, began to be used extensively as a cosmetic skin-whitening product (quasi-drug) especially in Japan, for topical application. Because of its slow and effective reversible competitive inhibition of human melanocyte tyrosinase, kojic acid prevents melanin formation. So, it can play an important role at the formation of cellular melanins (Cabanes, 1994; Jun, 2007; Kahn, 1997; Kang, 2009; Kim, 2003; Lin, 2007; Noh, 2007; Raku, 2003; Saruno, 1979). Noncosmetic uses reported for kojic acid include therapeutic uses for melasma, antioxidant and preservative in foods, antibiotic, chemical intermediate, metal chelate, pesticide, and antimicrobial agents. Because of its well-documented ability to inhibit tyrosinase activity, kojic acid has been used in numerous studies as a positive control. It was showed that kojic acid have inhibitory effect on mushroom, plant (potato and apple), and crustacean (white shrimp, grass prawn, and Florida spiny lobster) tyrosinase. The inhibition mushroom, potato, apple, white shrimp and spiny lobster tyrosinase was found to be related with the kojic acid inhibited melanosis by interfering with the uptake of O₂ required for enzymatic browning (Chen, 1991). It was well-known that tyrosinase containing two copper ions in the active center and a lipophilic long-narrow gorge near to the active center. It has been reported that kojic acid inhibits the activity of tyrosinase by forming a chelate with the copper ion in the tyrosinase through the 5-hydroxyl and 4-carbonyl groups. There are several types of assays determining tyrosinase inhibition. Cabanes *et al.* stated that kojic acid is a slow-binding inhibitor of catecholase activity of frog tyrosinase in a nonclassical manner (Cabanes, 1994). In a study of several mammalian melanocyte tyrosinase inhibitors, kojic acid was considered a potent free enzyme inhibitor (Curto, 1999). Kojic acid was a positive control in a study of the inhibitory effects of oxyresveratrol and hydroxystilbene compounds on mushroom and murine melanoma B-16 tyrosinase (Kim, 2002). Melanoma-specific anticarcinogenic activity is also known to be linked with tyrosinase activity (Kim, 2005). Malignant melanoma continues to be a serious clinical problem with a high mortality

rate among the human beings (Seo, 2003). Therefore, the potential therapies targeting tyrosinase activity have a paramount importance.

The beauty industry agrees with the statement regarding kojic acid is one of the best natural based lotions as far as skin lightening agents go. The definition of beauty for some cultures consists of fair, even toned skin, so many women resort to using skin lightening products, such as kojic acid, to achieve a lighter skin tone. It has been used for years in the Far East as an alternative to hydroquinone for its bleaching effects but many women are using it to treat hyperpigmentation as well as sun spots, freckles, liver spots and a number of other pigment problems related to beauty. The majority of lightening lotions contains a healthy dose of kojic acid in it beside vitamin C (ascorbic acid), bearberry extract, licorice or mulberry; in some cases, kojic acid is the main active ingredient. Most skin lightening lotions that use kojic acid as one of their ingredients also use small amounts of hydroquinone as well as glycolic acid (Fig. 1).

In addition, kojic acid is found to prevent photodamage and subsequent wrinkling of the skin in the hairless mouse. It is a good chelator of transition metal ions and a good scavenger of free radicals therefore it is an effective agent for photoprotection (Mitani, 2001). Also, it is used as bleaching agent in cosmetics (Burdock, 2001; Lin, 2007). Current evidence suggests that it induces skin depigmentation through suppression of free tyrosinase, mainly due to chelation of its copper at the active site of the enzyme (Chen, 1991; Jun, 2007; Lee, 2006). It has been demonstrated to be responsible for therapy and prevention of pigmentation, both *in vitro* and *in vivo* and being used for topical application. Melasma is often affecting women, especially those living in areas of intense UV radiation. In treatment of melasma which continues to be a difficult problem, the addition of kojic acid in a gel containing glycolic acid and hydroquinone improved melasma. Kojic acid is found as effective as hydroquinone in reducing the pigment. The combination of both agents augments this inhibition further (Gupta, 2006).

Previous antimicrobial activity studies showed that kojic acid was more active against gram negative bacteria than against gram positive ones (Bentley, 2006). However, some of its derivatives have shown adverse effects different from kojic acid's antibacterial activity results (Aytemir, 2003a, 2003b; Fassihi, 2008; Kotani, 1978; Masoud, 1989; Petrola, 1985; Veverka, 1992). Also, its derivatives especially have significant antifungal activity against *C. albicans* and *C. krusei* (Aytemir, 2003b, 2004; Brtko, 2004; Fassihi, 2008; Kayahara, 1990; Mitani, 2001; Veverka, 1992). According to its antibacterial and fungicidal properties, kojic acid is used as a food additive (Burdock, 2001). There are several forms of kojic acid containing products including soap, cream, lotion and gel. Kojic acid also has antifungal and antibacterial properties in it, making it a perfect ingredient to be used in soap. Women who choose a kojic acid lotion tend to use it to treat smaller areas of the skin that have been affected by hyperpigmentation, age spots or hormone related skin conditions brought on by pregnancy or birth control pills. Some women favor this lotion because it absorbs directly into the skin much better than creams or soaps. One of the greatest benefits to using kojic acid is reduction of getting wrinkles when you use the lotion before exposure to the sun. So it makes this also a perfect anti-aging lotion. Based on such tyrosinase-inhibiting activity of kojic acid, there have been proposed a lot of cosmetic compositions containing kojic acid as an active ingredient. There are a variety of kojic acid creams available for purchase online and in certain specialty stores. Each one has its own unique blend of ingredients which set

them apart from one another. Some creams combine various vitamins like A and E which give them different effects. The reason many people mix these vitamins within the kojic acid creams is to help them alleviate the skin irritation that has been said to occur with kojic acid products. Another cream combines retinol, vitamin C, with kojic acid, and glycolic acid. These ingredients are added to this base to help counteract the sensitivity that is associated with prolonged use of kojic acid when it is used by itself. According to FDA kojic acid is used in a total of 16 products. Some of the trade names of kojic acid having skin-whitening usage are AEC Kojic acid, Kojic acid SL, Melanobleach-K, Oristar KA, Rita KA and Tonelite Kojic acid. Besides these there are trade name mixtures in markets Botacenta SLC 175, Dermawhite HS, Melarrest A, Melarrest L and Vegewhite (Burnett, 2011; FDA, 2009).

The development of tyrosinase inhibitors is of great concern in the medical, agricultural, and cosmetic fields. Among the many kinds of tyrosinase inhibitors, kojic acid has been intensively studied. It acts as a good chelator of transition metal ions such as Cu^{2+} and Fe^{3+} and a scavenger of free radicals. This fungal metabolite is currently applied as a cosmetic skin-lightening agent and food additive to prevent enzymatic browning. Kojic acid shows a competitive inhibitory effect on the monophenolase activity and a mixed inhibitory effect on the diphenolase activity of mushroom tyrosinase. However, its use in cosmetics has been limited, because of the skin irritation caused by its cytotoxicity and its instability during storage. Accordingly, many semi-synthetic kojic acid derivatives have been synthesized to improve its properties by converting the alcoholic hydroxyl group into an ester, hydroxyphenyl ether, glycoside, amino acid derivatives, or tripeptide derivatives (Kang, 2009; Lee, 2006).

2.2 Some studies on synthetic kojic acid derivatives

Recently, it was found that kojic acid-tripeptide amides showed similar tyrosinase inhibitory activities to those of kojic acid-tripeptide free acids but exhibited superior storage stability than those of kojic acid and kojic acid-tripeptide free acids (Noh, 2007). To find further kojic acid derivatives with higher tyrosinase inhibitory activity, stability, and synthetic efficiency, a library of kojic acid-amino acid amides (KA-AA-NH_2) prepared and screened for their tyrosinase inhibitory activities. It was also confirmed that the kojic acid-phenylalanine amides reduced the amount of dopachrome production during the melanin formation. It was suggested that a tyrosinase inhibition mechanism of KA-AA-NH_2 based on the possible hydrophobic interactions between the side chain of KA-AA-NH_2 and tyrosinase active site by a docking program (Noh, 2009; Kim, 2004).

Kojic acid is a potential inhibitor of NF- κ B (transcription factor) activation in human keratinocytes, and suggests the hypothesis that NF- κ B activation may be involved in kojic acid induced anti-melanogenic effect. It was reported that the inhibitory effect of kojic acid on the activation of NF- κ B in two human keratinocytes and suggest the hypothesis that the modulation of NF- κ B in keratinocytes may be involved in anti-melanogenic effect induced by kojic acid (Moon, 2001).

The metal complexes of kojic acid-phenylalanine-amide exhibited potent tyrosinase inhibitory activity both *in vitro* enzyme test and in cell-based assay system. These results demonstrated that metal complex formation could be applied as a delivery system for hydrophilic molecules which have low cell permeability into cells. In addition, these new

materials can be used as an effective whitening agent in the cosmetic industry or applied on irregular hyperpigmentation (Kwak, 2010). Furthermore, kojic acid was shown to inhibit different enzymes relevant to the undesirable melanosis of agricultural products, which is related to its coordination ability to, e.g., copper, in the active site of tyrosinase (Naik, 1979; Stenson, 2007; Synytsya, 2008). The kojic acid scaffold was modified by a Mannich reaction with piperidine derivatives with the aim to link it to Ru(II)-arene fragments and to obtain compounds with anticancer activity (Kasser, 2010).

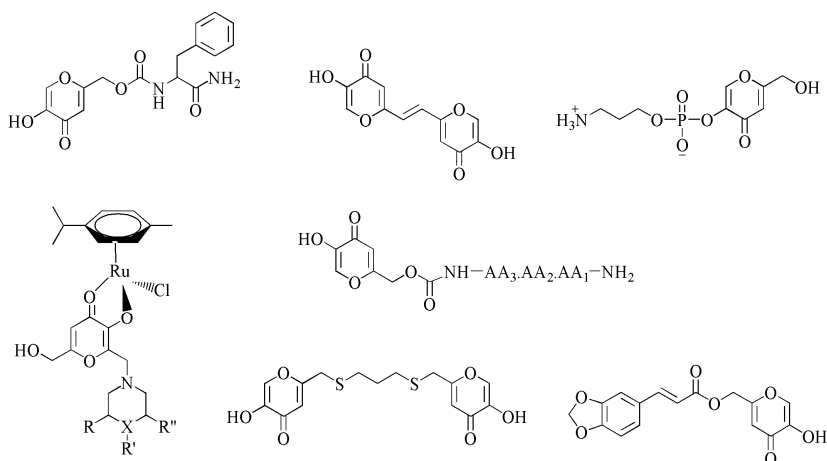


Fig. 3. Chemical structure of some synthetic kojic acid derivatives as tyrosinase inhibitors.

It was reported that compound, joining to two pyrone rings of kojic acid through an ethylene linkage, exhibited 8 times more potent mushroom tyrosinase inhibitory activity than that of kojic acid and also showed superior melanin synthesis inhibitory activity using B16F10 melanoma cell (Lee, 2006). A series of kojic acid derivatives containing thioether, sulfoxide and sulfone linkages were synthesized. Sulfoxide and sulfone derivatives decreased and kojyl thioether derivatives containing appropriate lipophilic various alkyl chains increased tyrosinase inhibitory activity (Rho, 2010). Kojic acid derivatives, containing ester linkages such as hydrophobic benzoate or cinnamate groups, increased the inhibitory activity of kojic acid. When the enolic hydroxyl group of ester derivatives was protected by a methyl group the activity was lost completely. These results indicated that the kojic acid moiety may have blocked the copper active site of tyrosinase (Rho, 2011). 5-[(3-aminopropyl)phosphinoxy]-2-(hydroxymethyl-4H-pyran-4-one (Kojyl-APPA) was showed tyrosinase inhibition effect *in situ*, but not *in vitro*. It means that Kojyl-APPA was converted to kojic acid and 3-aminopropane phosphoric acid enzymatically in cells. Kojyl-APPA was showed the inhibitory activity to same extent as kojic acid on melanin synthesis in mouse melanoma and normal human melanocytes (Kim, 2003).

In a recent study, the correlations of the inhibition of cell-free mushroom tyrosinase activity with that of cellular tyrosinase activity and melanin formation in A2058 melanoma cell line using kojic acid were evaluated. Kojic acid (10 μM) exhibited the best inhibitory effects with % inhibition values 33.3, 52.7 and 52.5 respectively against mushroom tyrosinase activity, cellular tyrosinase activity and cellular melanin formation. Also, ultraviolet A

irradiation of melanoma cells A2058 markedly improved the correlation between the inhibition of cellular tyrosinase and of melanin formation (Song, 2009).

Kojic acid contains a polyfunctional heterocyclic, oxygen containing ring with several important centers enabling additional reactions like as oxidation and reduction, alkylation and acylation, substitution nucleophilic reactions, substitution electrophilic reactions, a ring opening of the molecule, and chelation (Aytemir, 1999; Brtko, 2004; Dehkordi, 2008; O'Brien, 1960; Pace, 2004). Since kojic acid is freely soluble in water, ethanol, acetone, and sparingly soluble in ether, ethylacetate, and chloroform, its various derivatives were advantageously prepared (Brtko, 2004; Burdock, 2001; Krivankova, 1992).

Kojic acid provides a promising skeleton for development of new more potent derivatives such as chlorokojic acid (2-chloromethyl-5-hydroxy-4H-pyran-4-one), allomaltol (5-hydroxy-2-methyl-4H-pyran-4-one) and pyromeconic acid (3-hydroxy-4H-pyran-4-one) (Fig. 4). Allomaltol was synthesized from commercially available kojic acid in a two-step reaction according to the literature (Aytemir, 2004; 2010a; 2010b). Chlorination of the 2-hydroxymethyl moiety of kojic acid using thionyl chloride at room temperature afforded chlorokojic acid, with the ring hydroxyl being unaffected. Reduction of chlorokojic acid with zinc dust in concentrated hydrochloric acid resulted in the production of allomaltol (Scheme 2) (Aytemir, 2004; 2010a; 2010b; Ellis 1996).

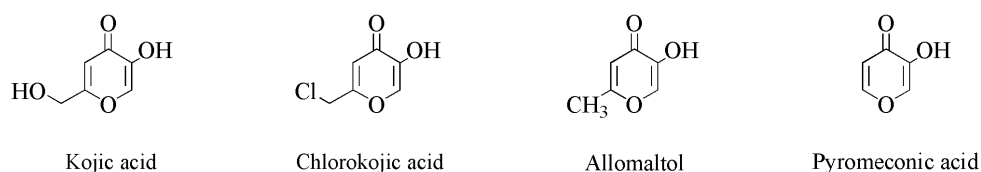
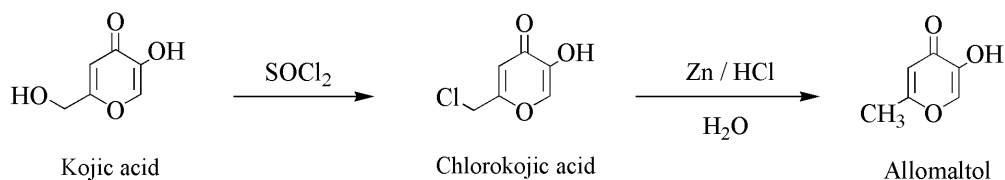


Fig. 4. Hydroxypyranone derivatives.



Scheme 2. Synthesis of some hydroxypyranone derivatives from kojic acid.

Wolf and Westveer showed that chlorokojic acid contains catechol group-inhibited *Aeromonas aerogenes*, *Micrococcus pyogenes* var. *aureus*, *Salmonella typhosa*, *Penicillium digitalum*, *Russula nigricans* and *Saccharomyces cerevisiae* (Wolf, 1950). Also, chlorokojic acid and other halogen derivatives have significant antifungal activity. Moreover, their copper(II) salts' complex derivatives were prepared and found to be more active than chlorokojic acid (Brtko, 2004). Chlorokojic acid was found to be more potent inhibitor of tyrosinase than kojic acid. Moreover, allomaltol has been described as a treatment for pigmentation disorders, sunburn prevention and as an antioxidant for oils and fats (Wempe, 2009). Ester derivatives of allomaltol were described as new tyrosinase inhibitors.

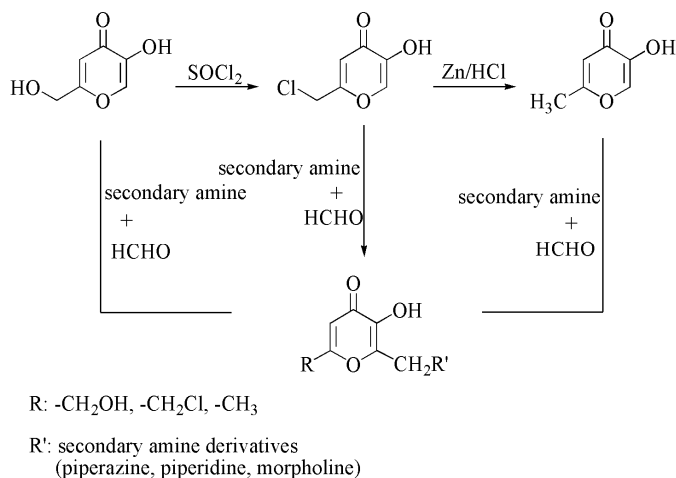
It is well known that hydroxypyranones can exist in cationic and anionic forms due to the protonation or deprotonation reactions, respectively. The hydroxyl group that is directly bound to the pyranone ring was probable more deprotonated than the hydroxymethyl group. The results of quantum mechanical investigations on tautomeric equilibria of kojic acid were determined. Because of two intramolecular hydrogen bonds, the enolic structure of neutral kojic acid is expected to be the most stable one. One of these two bonds is located between keto and hydroxyl group and the other hydrogen bond can be formed weakly between hydroxymethyl moiety and intra-ring oxygen (Beelik, 1955).

On the other hand, kojic acid and other hydroxypyranones having catechol groups are also known as effective metal chelation agents which form complexes with various metal ions that are potentially useful in medicinal therapy. These complexes have reasonable hydrolytic stability, neutral charge, and significant lipophilicity (Masoud, 1989; Thompson, 2001). Additionally, kojic acid and its derivatives have shown to possess various pharmacological activities such as herbicidal (Veverka, 1990; 1990), anti-speck (Uchino, 1988), pesticide and insecticide (Higa, 2007; Kahn, 1997; Uher, 1994), antitumor (Uher, 1994; Yamato, 1987), anti-diabetes (Xiong, 2008), slight anti-inflammatory effects (Brtko, 2004), antiproliferative properties (Fickova, 2008) antiepileptic (Aytemir, 2004, 2006, 2007, 2010a, 2010b) and antiviral (Aytemir, 2010c, 2011) activity.

3. Mannich derivatives with biological activities

Multicomponent reactions are the major parts of the synthetic organic chemistry with advantages ranging from lower reaction times and temperatures to higher yields. Mannich-type reactions are a three component condensation reaction involving carbonyl compounds, which exist as keto-enol tautomeric forms, formaline and a primary or secondary amine. Due to phenol-like properties of kojic acid readily undergoes aminomethylation in the Mannich reaction *ortho* to enolic hydroxyl group at room temperature. It was reported that di-Mannich derivatives which were formed at 3- and 6-positions, were obtained in an acidic medium by the reaction of kojic acid, formaline and aromatic amine derivatives. Woods has reported di-Mannich derivatives were obtained in an acidic medium from kojic acid, formaline and aromatic amine (Woods, 1946). However, O'Brien *et al.* showed that derivatives of Mannich bases occurred at only 6-position of kojic acid, which were synthesized using dimethylamine, diethylamine, pyrrolidine, morpholine, piperidine or 4-methylpiperazine, and chlorokojic acid. Additionally, 6-morpholino or piperidinomethyl chlorokojic acid were prepared via Mannich reaction (O'Brien, 1960). At the latter study, Mannich bases of kojic acid and pyromeconic acid were synthesized in either acidic and basic medium using aliphatic or heterocyclic secondary amines such as dimethylamine, diethylamine or morpholine, respectively (Ichimoto, 1965).

Using the methodology shown in Scheme 3, having 6-chloromethyl/hydroxymethyl/methyl-3-hydroxy-2-substituted 4*H*-pyran-4-one structure, 130 derivatives were synthesized as Mannich bases. The basic substituent was introduced in the 6-position of allomaltol/chlorokojic acid/kojic acid via a Mannich-type reaction, using formaline and an appropriate substituted piperidine, piperazine and morpholine derivatives in methanol at room temperature (Scheme 3). The reaction proceeded very rapidly (Aytemir, 2004, 2006, 2007, 2010a, 2010b, 2010c, 2011 and unpublished data).

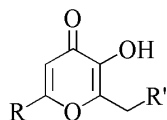


Scheme 3. Synthesis of Mannich bases of kojic acid/chlorokojic acid/allomaltol.

Structure of some Mannich bases was determined by X-Ray analysis. The conformation of the molecule is determined by intra- and intermolecular hydrogen bonds. Some weak intramolecular interactions helped to stabilize the structure. The piperazine ring displayed an almost perfect chair conformation (İskeleli, 2005; Köysal, 2004; Ocak, 2004).

3.1 Anticonvulsant activity

In our previous studies, we reported that Mannich bases of 3-hydroxy-6-hydroxymethyl/methyl-2-substituted 4*H*-pyran-4-one derivatives anticonvulsant activity (Aytemir, 2004, 2006, 2007, 2010a, 2010b). Anticonvulsant activity was examined by maximal electroshock (MES) and subcutaneous Pentylenetetrazol (scPTZ)-induced seizure tests. Substitution of different lipophilic phenyl derivatives at 4th position of piperazine ring enables penetration of the blood-brain barrier. The effects of mono substitution of an electron donating or electron-withdrawing groups at the ortho, meta and para position of the phenyl group were examined. According to the results, these compounds, especially 4-chlorophenyl and 3-trifluoromethylphenylpiperazine derivatives, had valuable anticonvulsant activity against scPTZ and MES induced seizure tests (Aytemir, 2004). When substituted piperidine derivatives and morpholine ring at 2nd positions of allomaltol (Fig. 1) were used instead of piperazine ring, anticonvulsant activity of these Mannich bases derivatives was decreased (Aytemir, 2007, 2010a). Both kojic acid and allomaltol derivatives including 4-chloro and 3-trifluoromethylphenylpiperazine were determined to be protective against all seizures. When the effect of different piperazine ring upon activity examined, kojic acid derivatives were found to be more active than allomaltol derivatives. The difference between these two starting materials is just methyl or hydroxymethyl groups at 6th positions at pyranone ring. On the other hand, when the results of the studies are compared to each other, replacement of hydroxymethyl with methyl group at 6th position at pyranone ring increases the protective effect against both tests, because of two hydrogen bonds of kojic acid, which are located between keto and hydroxyl group and/or hydroxymethyl moiety and intra-ring oxygen (Aytemir, 2010b).

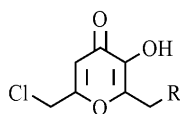


R	R'	MES		scPTZ	
		0.5 h (mg/kg)	4 h (mg/kg)	0.5 h (mg/kg)	4 h (mg/kg)
-CH ₃		30	300	-	300
-CH ₃		-	300	300	30
-CH ₃		300	30	30	-
-CH ₃		100	300	30	-
-CH ₃		100	30	-	30
-CH ₂ OH		300	-	30	30
-CH ₂ OH		300	-	-	30
-CH ₂ OH		-	-	-	30
-CH ₂ OH		-	30	100	300
-CH ₂ OH		-	300	30	100
-CH ₂ OH		-	-	30	30
-CH ₂ OH		300	-	300	30
-CH ₂ OH		30	30	100	300
-CH ₂ OH		30	300	-	-

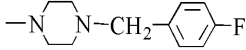
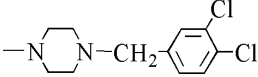
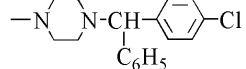
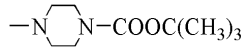
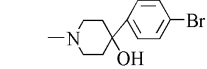
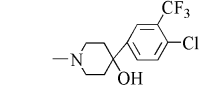
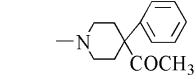
Table 1. Anticonvulsant activities of the synthesized compounds.

3.2 Antiviral activity

All compounds were assayed against both *herpes simplex virus-1 (HSV-1)* and human *parainfluenza virus type 3 (PI-3)* by using Madin Darby Bovine Kidney and Vero cell lines with the aim to capture structure relationship in each of the compounds. Acyclovir and oseltamivir were used as control agents. Correlation between toxicity on uninfected cells (Vero, MDBK) and antiviral activity of the synthesis compounds were determined in the same microtiter plate. The results of the antiviral study are presented in Table 2.



R	MDBK Cells			Vero Cells			
	MNTCs ^{a)} ($\mu\text{g/mL}$)	CPE ^{b)} Inhibitory Concentration HSV-1 ^{c)}		MNTCs ^{a)} ($\mu\text{g/mL}$)	CPE ^{b)} Inhibitory Concentration PI-3 ^{d)}		
		Max.	Min.		Max.	Min.	
1		0.8	0.8	0.05	0.8	0.4	0.025
2		0.8	0.8	0.05	0.4	0.4	0.025
3		0.8	0.8	0.05	0.8	0.2	0.025
4		0.8	0.8	0.05	1.6	0.2	0.025
5		0.8	0.8	0.2	1.6	0.2	0.05
6		0.8	0.8	0.2	1.6	0.4	0.1
7		1.6	1.6	0.1	1.6	0.8	0.05
8		1.6	0.4	0.1	0.4	0.4	0.2
9		1.6	0.8	0.1	0.8	0.8	0.025
10		1.6	0.4	0.1	0.4	0.4	0.025
11		1.6	0.4	0.1	0.4	0.4	0.05

R	MDBK Cells			Vero Cells		
	MNTCs ^{a)} ($\mu\text{g/mL}$)	CPE ^{b)} Inhibitory Concentration <i>HSV-1</i> ^{c)}		MNTCs ^{a)} ($\mu\text{g/mL}$)	CPE ^{b)} Inhibitory Concentration <i>PI-3</i> ^{d)}	
		Max.	Min.		Max.	Min.
12 	1.6	0.4	0.1	0.4	0.4	0.05
13 	0.4	-	-	0.8	0.8	0.05
14 	0.4	-	-	0.4	0.2	0.1
15 	0.8	0.8	0.4	0.4	0.4	0.2
16 	0.4	-	-	0.8	0.2	0.05
17 	0.8	0.8	0.2	0.4	0.2	0.05
18 	0.4	-	-	0.4	0.4	0.05
Acyclovir	1.6	1.6	<0.012			
Oseltamivir	-	-	-	1.6	1.6	<0.012

^{a)} MNTCs: Maximum non-toxic concentrations

^{b)} CPE: Cytopathogenic effect

^{c)} *HSV-1*: *Herpes simplex virus* Type-1

^{d)} *PI-3*: *Parainfluenza-3 virus* Max: Maximum

Min: Minimum - : Not done; activity observed

Table 2. Cytotoxicity on MDBK and Vero Cells as well as antiviral activity against *HSV-1* and *PI-3* results of the compounds **1-18**.

As given in CPE inhibitory concentration ranging, compound **7** bearing 4-methoxyphenylpiperazine substituent showed significant activity against *HSV-1* as potent as the reference compound acyclovir, but limited activity at maximum and minimum concentration ranges of 1.6-0.1 $\mu\text{g/mL}$ with the maximum non-toxic concentration (MNTCs) value of 1.6 $\mu\text{g/mL}$. Additionally, compound **9** (0.8-0.1 $\mu\text{g/mL}$) was shown anti-*Herpes simplex* activity but less potent. On the other hand, compounds **1-4** were shown as same activity as compound **7** but on higher non-toxic concentrations (MNTC: 0.8 $\mu\text{g/mL}$). Among the tested Mannich bases derivatives, compounds **5, 6, 8, 10,** and **11** were less active against DNA virus. Take into account CPE inhibitory concentration ranging against the

RNA viruses *PI-3*, compound **9** (0.8-0.025 $\mu\text{g}/\text{mL}$) and compound **13** (0.8-0.05 $\mu\text{g}/\text{mL}$) had remarkable antiviral activity in Mannich base derivatives. Furthermore, compounds **1**, **7**, **12** and **18** were less active than compounds **9** and **13**. While the activities of compounds **2** and **10** (0.4-0.025 $\mu\text{g}/\text{mL}$) against *PI-3* were in similar CPE inhibitory concentration range, compounds **3**, **4** and **11** had lower activity than those had. Also, compounds **5** and **6** were negligible values as seen in Table 2. Compounds **12** and **17** showed anti-*Herpes simplex* activity with less potency. While the activities of compounds **12** and **18** (0.4-0.05 $\mu\text{g}/\text{mL}$) against *PI-3* were in similar CPE inhibitory concentration range, compounds **5** and **6** had lower activity than those that had (Aytimir, 2010c, 2011).

3.3 Antimicrobial activity

The antibacterial and antifungal activity profiles of the newly synthesized compounds were assessed for antimicrobial activity against both standard and the isolated strains of bacteria. For antibacterial activity assessment, standard strains (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Bacillus subtilis*) and their drug-resistant isolates were tested; and for antifungal activity *Candida albicans* and *C. parapsilosis* were used. Ampicillin, vancomycin, gentamicin, ofloxacin, levofloxacin, ketoconazole, and fluconazole were also tested under identical conditions for comparison in antibacterial and antifungal assays, respectively. Tables 3 and 4 describe the *in vitro* antimicrobial activity with MIC values of compounds **1-18**.

According to our data (Table 3 and 4), the synthesized compounds showed a broad spectrum of activity against gram positive and gram negative standard strains with MIC values between 1 and 64 $\mu\text{g}/\text{mL}$. In the meantime, the synthesized compounds showed activity against drug-resistant isolated both gram positive and negative strains with MIC values of 2 to ≥ 128 $\mu\text{g}/\text{mL}$.

As given in Table 3, the antibacterial activity against gram negative bacteria of the synthesized compounds **14**, **16**, and **17** bearing (4-chlorophenyl)benzylpiperazine, 4-bromophenyl-4-hydroxypiperidine and 4-chloro-3-(trifluoromethyl) phenyl-4-hydroxypiperidine moiety respectively at the 2-position of pyran-4-one ring, was found to have significantly high antibacterial potential against standard strains of *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii* with a bacterial inhibition between 2 and 4 $\mu\text{g}/\text{mL}$. Also, these compounds showed more activity (MIC: 2 $\mu\text{g}/\text{mL}$) against *E. coli* and *P. aeruginosa* than the other gram negative bacteria compared with control drugs ampicillin (MIC: 2 $\mu\text{g}/\text{mL}$), ofloxacin (1 $\mu\text{g}/\text{mL}$) and levofloxacin (1 $\mu\text{g}/\text{mL}$). As for compounds **13** and **15**, it was found that they had the same effect against all gram negative bacteria. The MIC values of both compounds were 4 $\mu\text{g}/\text{mL}$ against *P. aeruginosa*; 8 $\mu\text{g}/\text{mL}$ against *E. coli*, *K. pneumoniae*, and *A. baumannii*; and 16 $\mu\text{g}/\text{mL}$ against *P. mirabilis*. Furthermore, in comparison, compound **18** had similar antibacterial activity with MIC values between 4 and 16 $\mu\text{g}/\text{mL}$ as these (compounds **13** and **15**). In the entire series, compounds **1-7**, **9**, **12** was less effective (MIC: 16-32 $\mu\text{g}/\text{mL}$) and compound **18** with MIC values between 4 and 16 $\mu\text{g}/\text{mL}$ towards standard strains of all gram negative bacteria. Especially, compound **13** which has 3,4-dichlorobenzylpiperazine moiety showed remarkable activity against ES β L(+)

strains of *E. coli* and *K. pneumoniae* with MIC values of 4 µg/mL, compared with the reference drugs, ampicillin (MIC: ≥128 µg/mL), ofloxacin (MIC: 0.5 µg/mL) and levofloxacin, (MIC: 0.5-1 µg/mL) respectively. As for structure-activity relationship (SAR), fluoro substitution in *para* position of the benzyl ring (compound **12**) has the worst activity with MIC values between 16 and 32 µg/mL in this series, whereas the 3,4-dichloro substitution (compound **13**) of benzyl ring increases antibacterial activity with four-folds (MIC: 4-8 µg/mL) towards isolated strains of *A. baumannii* and *P. aeruginosa* and two-folds (MIC: 8 µg/mL) against *E. coli* and *K. pneumoniae*. Moreover, antibacterial activity of the compounds **12** and **13** against *P. mirabilis* was determined to be the same. Furthermore, compounds **13** and **15** showed same activity against all bacteria except from *P. aeruginosa*. In the Mannich base derivatives bearing piperazine ring, compound **14** was the most remarkable and active one (MIC: 2-8 µg/mL). There were diphenyl rings in the structure of in which one of them was a p-chlorophenyl ring and the other a nonsubstituted phenyl ring. When compounds **13** and **15** were compared, the addition of phenyl ring on the structure of compound **14** increased the activity two-folds against all gram negative bacteria and *S. aureus*. When antibacterial activities of compounds **16-18** possessing piperidine ring were investigated, it was observed that compounds **16** and **17** were found to have the same activity and higher effect than compound **18** without halogen substitution at its structure. Hence, when hydroxy substitution at the 4-position of piperidine ring was changed with acetyl, antibacterial activity was decreased. In addition, there was no difference in the antimicrobial activity with the location and type of the halogen substituted on phenyl ring. Also, these compounds (**16** and **17**) had exactly the same activity as compound **18** possessing piperazine ring against all gram negative bacteria.

Among gram positive bacteria, *S. aureus* has been recognized for so long as one of the major resistant pathogens that can cause diseases in humans. Likewise, multi-drug resistant Enterococci have become a serious threat for public health. High level resistance for penicillin and aminoglycosides are being reported of this bacterium. According to the obtained data (Table 4), antibacterial activity results of compounds **13-18** (MIC: 1-2 µg/mL) and 8-11 (MIC: 8 µg/mL) against standard gram positive bacteria were encouraging, although compound **1-7** and **12** were found to manifest moderate (MIC: 16-64 µg/mL) activity against standard strains of *S. aureus*. Compounds **13-18** were found to be highly active against *B. subtilis* showing a bacterial inhibition value at 1 µg/mL. The antibacterial potential against *E. faecalis* was exhibited by compounds **2**, **8-11**, and **15** at concentration 8 µg/mL among the synthesized compounds. *Candida* species are the most widespread and threatening fungal pathogens today, and are responsible for many of the invasive and non-invasive fungal infections. Among all *Candida* species, *Candida albicans* is the most frequent pathogen. The results obtained clearly indicate that the series of Mannich bases discussed here are active towards growth inhibition of pathogenic fungi. In general, **1-7** (MIC: 8 µg/mL) and **13-18** (MIC: 4 µg/mL) exhibited excellent antifungal activity against *C. albicans* and at MIC values at 8 µg/mL against *C. parapsilosis* when compared to the reference drugs, ketoconazole (MIC: 1 µg/mL) and fluconazole (MIC: 2-4 µg/mL). The compounds **1-7** and **13-18** may be promoted as fungicides. In general, the compounds showed an improved antibacterial activity when compared to their antifungal activity (Aytemir, 2010c, 2011).

Gram-negative Standard and Clinic Isolated Strains										
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>P. mirabilis</i>	<i>K. pneumoniae</i>	<i>A. baumannii</i>					
	ATCC 35218	Isolated strain ESβL+ ATCC 10145	Isolated strain ATCC 7002	Isolated Strain ESβL+ RSKK 574	Isolated Strain ESβL+ RSKK 02026	Isolated strain	Isolated strain	Isolated strain	Isolated strain	Isolated strain
1	16	64	16	64	16	64	16	64	32	64
2	16	64	16	64	16	64	32	64	16	64
3	16	64	32	64	32	64	16	64	32	64
4	16	64	32	64	16	64	16	64	32	64
5	32	64	32	64	32	64	32	64	32	64
6	32	64	32	64	32	64	32	64	32	64
7	32	64	16	64	32	64	16	32	16	32
8	64	>128	64	>128	64	>128	64	>128	64	>128
9	32	64	32	64	32	64	32	64	32	64
10	64	>128	64	>128	64	>128	64	>128	64	>128
11	64	64	16	64	32	64	32	64	64	32
12	16	64	16	64	16	64	16	64	32	64
13	8	4	4	16	16	64	8	4	8	16
14	4	64	2	16	8	64	4	64	4	16
15	8	64	4	16	16	64	8	64	8	16
16	4	64	2	16	8	64	4	64	4	16
17	4	64	2	16	8	64	4	64	4	16
18	8	64	4	16	16	64	8	64	4	16
AMP ^{a)}	2	>128	-	-	2	>128	2	>128	2	>128
OFX ^{b)}	0.12	-	0.5	2	-	-	-	-	-	-
LVX ^{c)}	<0.12	0.5	1	64	<0.12	1	<0.12	0.5	0.12	64

^{a)} AMP: ampicillin,

^{b)} OFX: ofloxacin,

^{c)} LVX: levofloxacin

-: No activity observed, *E. coli* isolates; (resist to trimethoprim-sulfamethoxazole, cefepime, tazobactam), *P. aeruginosa* isolates (resist to Trimethoprim-Sulfamethoxazole, tazobactam), *P. mirabilis* isolates (resist to trimethoprim-sulfamethoxazole, cefepime, tazobactam), *K. pneumoniae* isolates (resist to trimethoprim-sulfamethoxazole, amoxicillin clavulonate, ceftriaxone, cefepime, aztreonam) *A. baumannii* isolates (resist to trimethoprim-sulfamethoxazole, cefepime).

Table 3. Antibacterial activity of the synthesized compounds **1-18** and the control drugs (MIC in µg/mL).

Comp.	Gram-positive standard and Clinic Isolated Strain Bacteria						Fungi	
	<i>S. aureus</i>		<i>E. faecalis</i>		<i>B. subtilis</i>	<i>C. albicans</i>	<i>C. parapsilosis</i>	
	ATCC 25923	Isolated Strain MRSA	ATCC 29212	Isolated Strain	ATCC 6633	Isolated Strain	ATCC 10231	ATCC 22019
1	32	64	16	32	32	64	8	8
2	16	64	8	32	8	64	8	8
3	16	64	16	32	8	16	8	8
4	16	64	16	32	16	32	8	8
5	64	128	64	128	16	32	8	8
6	64	128	64	128	16	32	8	8
7	32	64	32	64	32	64	8	8
8	8	>128	8	>128	16	>128	16	16
9	8	128	8	128	16	32	16	16
10	8	>128	8	>128	16	>128	16	16
11	8	64	8	64	16	64	16	16
12	32	64	16	32	32	64	16	16
13	2	128	16	128	1	2	4	8
14	1	64	16	32	1	2	4	8
15	2	128	8	128	1	2	4	8
16	1	64	16	32	1	2	4	8
17	1	64	16	32	1	2	4	8
18	2	128	64	128	1	2	4	8
AMP ^{a)}	<0.12	>128	0.5	>128	0.12	0.5	-	-
VAN ^{b)}	0.12	2	-	-	-	-	-	-
OFX ^{c)}	0.25	64	1	32	-	-	-	-
LVX ^{d)}	0.25	128	0.5	32	-	-	-	-
KET ^{e)}	-	-	-	-	-	-	1	1
FLU ^{f)}	-	-	-	-	-	-	2	4

^{a)} AMP: ampicillin,

^{b)} VAN: vancomycin,

^{c)} OFX: ofloxacin,

^{d)} LVX: levofloxacin,

^{e)} KET; ketoconazole,

^{f)} FLU: fluconazole

-: No activity observed, *S. aureus* isolates (resist to oxacillin, gentamicin, aztreonam, trimethoprim-sulfamethoxazole), *E. faecalis* isolates (resist to cephalosporins & beta-lactam), *B. subtilis* isolates (resist to ceftriaxone).

Table 4. Antibacterial and antifungal activities of the synthesized compounds **1-18** and the control drugs (MIC in µg/mL).

4. Conclusions

A number of research groups around the world are engaged and are expending much effort in the discovery of tyrosinase inhibitors. Various limitations are associated with many of these inhibitors, such as high cytotoxicity, poor skin penetration and low stability in formulations. Therefore, it is very important to discover novel and potent inhibitors with potent activity and lower side effect.

Kojic acid is currently used as tyrosinase inhibitors which are commercially available. Unfortunately, unstability during storage limits its use and new tyrosinase inhibitors of novel kojic acid derivatives are needed in cosmetics industry. More expended studies on this subject will be helpful in designing more suitable tyrosinase inhibitors for human use.

In our continuing search, a huge number of Mannich bases are being examined as inhibiting mushroom tyrosinase activity at the moment, and few of them will have confirmed in melanogenesis inhibiting activity in cell or skin models. Mannich bases compounds are more hydrophobic than kojic acid. Therefore, disadvantages of kojic acid might be decreased by increasing skin penetration and stability in formulation. In the light of these findings we will undertake further synthetic and biological studies on the new compounds in the future.

5. Acknowledgement

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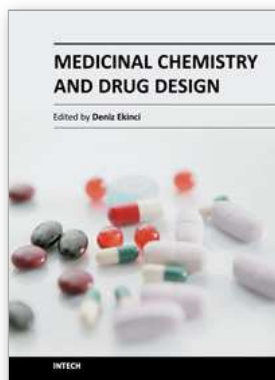
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Over the recent years, medicinal chemistry has become responsible for explaining interactions of chemical molecules processes such that many scientists in the life sciences from agronomy to medicine are engaged in medicinal research. This book contains an overview focusing on the research area of enzyme inhibitors, molecular aspects of drug metabolism, organic synthesis, prodrug synthesis, in silico studies and chemical compounds used in relevant approaches. The book deals with basic issues and some of the recent developments in medicinal chemistry and drug design. Particular emphasis is devoted to both theoretical and experimental aspect of modern drug design. The primary target audience for the book includes students, researchers, biologists, chemists, chemical engineers and professionals who are interested in associated areas. The textbook is written by international scientists with expertise in chemistry, protein biochemistry, enzymology, molecular biology and genetics many of which are active in biochemical and biomedical research. We hope that the textbook will enhance the knowledge of scientists in the complexities of some medicinal approaches; it will stimulate both professionals and students to dedicate part of their future research in understanding relevant mechanisms and applications of medicinal chemistry and drug design.

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