Bioorganic & Medicinal Chemistry Letters 25 (2015) 5495–5499

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Inhibitory kinetics of novel 2,3-dihydro-1*H*-inden-1-one chalcone-like derivatives on mushroom tyrosinase

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ARTICLE INFO

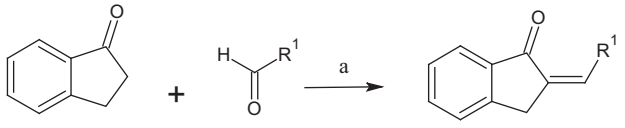
Article history:
Received 1 August 2015
Revised 20 October 2015
Accepted 23 October 2015
Available online 24 October 2015

Keywords:
Tyrosinase
Competitive
Diphenolase
Reversible

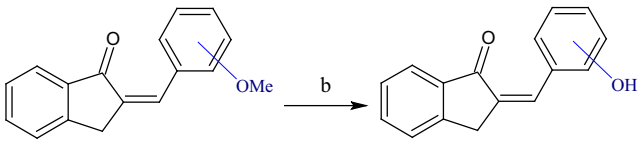
ABSTRACT

In this study, novel 2,3-dihydro-1*H*-inden-1-one chalcone-like compounds and their hydroxyl derivatives were synthesized, and their inhibitory effects on mushroom tyrosinase activity were evaluated. Two of the compounds synthesized inhibited the diphenolase activity of tyrosinase in a dose dependent manner and exhibited much higher tyrosinase inhibitory activities (IC_{50} values of 12.3 μM and 8.2 μM, respectively) than the positive control, kojic acid (IC_{50}: 27.5 μM). Kinetic analysis showed that their inhibition was reversible. Both the novel compounds displayed competitive inhibition with their K_i values of 10.3 μM and 8.7 μM, respectively. This study suggests hydroxy substituted 2,3-dihydro-1*H*-inden-1-one chalcone-like compounds to serve as promising candidates for use as depigmentation agents.

Melanin, a polymeric dark pigment is produced by melanocytes within specialized organelles called melanosomes. The melanosomes contain several enzymes that mediate the production of melanin.[1,2] The conversion of tyrosine to melanin requires tyrosinase, also known as polyphenol oxidase, a copper containing protein. Tyrosinase [EC 1.14.18.1], is the key enzyme in the melanogenic pathway responsible for the hydroxylation of L-tyrosine to 3,4-dihydroxy phenylalanine (L-DOPA) and oxidation of L-DOPA to dopaquinone.[3,4] However, an excessive accumulation of the pigment could lead to serious aesthetic issues. Alterations in tyrosinase function could culminate with serious dermatological

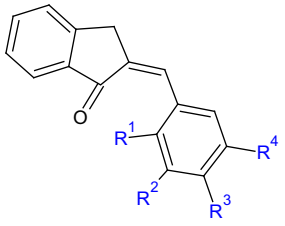


Scheme 1. General method for synthesis of 2,3-dihydro-1*H*-inden-1-one chalcones. Reagents and conditions: (a) MeOH, NaOH, 0 °C, 24 h.



Scheme 2. Dealkylation of methoxy chalcones. Reagents and conditions: (b) BBr_3, CH_2Cl_2.

Table 1
Substitution pattern and tyrosinase inhibition effects of 1-indanone derivatives



Compound	R^1	R^2	R^3	R^4	Yield (%)	Inhibition rate (%) at 50 μM
1a	H	NO_2	H	H	95.5	22.6 ± 0.44
1b	H	H	NO_2	H	87.6	19.8 ± 0.15
1c	OMe	H	NO_2	H	64.2	25.4 ± 0.55
1d	H	NO_2	OMe	H	54.1	24.2 ± 0.33
1e	OMe	H	OMe	H	85.4	30.6 ± 0.47
1f	H	OMe	OMe	H	77.2	32.2 ± 0.11
1g	H	OMe	H	OMe	70.3	38.6 ± 0.32
2a	OH	H	OH	H	51.2	65.2 ± 0.15
2b	H	OH	OH	H	45.2	74.6 ± 0.14
2c	H	OH	H	OH	42.6	50.1 ± 0.38
Kojic acid						45.2 ± 0.22

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http://dx.doi.org/10.1016/j.bmcl.2015.10.071
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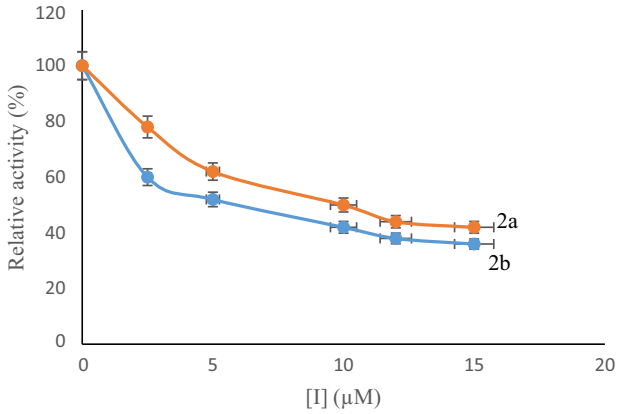

Figure 1. Inhibition effects of compounds **2a** and **2b** on the diphenolase activity of mushroom tyrosinase. Data are presented as means ($n = 3$).

disorders including melasma, ephelides (freckles), solar lentigo (age spots), and sites of actinic damage.[5–7] Tyrosinase is responsible for melanization in animals, cuticle formation in insects, wound healing and browning of fruits and vegetables.[8–15] Therefore, tyrosinase inhibitors have potential applications in the treatment of dermatological disorders associated with melanin hyperpigmentation, in agriculture as bio-insecticides and also in cosmetics for whitening and depigmentation after sunburn. From a structural perspective, tyrosinase has two copper ions in its active site which play a vital role in its catalytic activity. At the active site of tyrosinase, a dioxygen molecule binds in side-on coordination between two copper ions. Each of the copper ions is coordinated by three histidines in the protein matrix. The copper atoms participate directly in hydroxylation of monophenols to diphenols (cresolase activity) and in the oxidation of *o*-diphenols to *o*-quinones (catechol oxidase activity) that enhance the production of the brown color.[16,17]

Several natural and synthetic tyrosinase inhibitors have been reported, including aromatic aldehydes and acids, tropolone, arbutin, flavonoids, and kojic acid.[18,19] However, most of these compounds have been reported to be either toxic towards cells or have low stability towards oxygen and water.[20–22]

Indanones are bioactive molecules that are frequently used as precursors in the synthesis of pharmaceutical and natural product substances. Previously, indanone based curcumin analogs have been reported to have strong inhibitory effects on tyrosinase.[23] Another indanone derivative, tetrahydrocurcumin, was recommended to be used in cosmetics as a lighting agent.[24]

Although indole and its derivatives are popular medicinal agents, the related heterocycles like indene and their derivatives like substituted 1-indanones (2,3-dihydro-1*H*-inden-1-one) have much less been exploited for their biological potential. Previously we have studied the tyrosinase inhibition of azachalcone compounds.[25] Hence, we considered that it might be interesting to synthesize a series of novel 2,3-dihydro-1*H*-inden-1-one chalcone-like

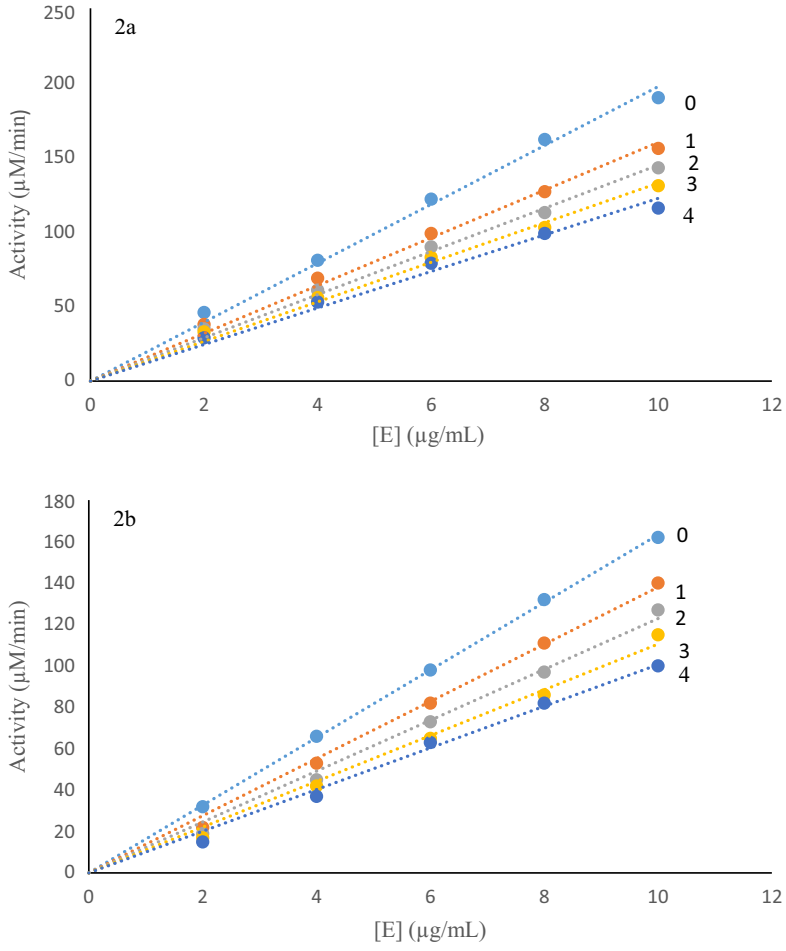

Figure 2. The inhibitory mechanism of compounds **2a** and **2b** on mushroom tyrosinase were reversible. The concentration of inhibitor used for curves 0–4 are 0, 0.25, 0.5, 1.0 and 2.0 μM, respectively.