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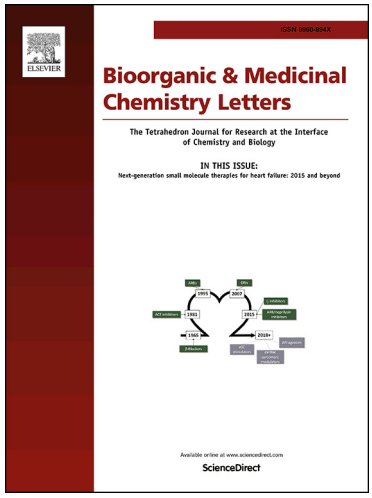

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Synthesis of *N*-arylindazole-3-carboxamide and *N*-benzoylindazole derivatives and their evaluation against α-MSH-stimulated melanogenesis

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ABSTRACT

We have designed and synthesized twenty-six *N*-arylindazole-3-carboxamide (**3a-p**) and *N*-benzoylindazole (**6a-j**) derivatives to discover with excellent inhibition activities of α-MSH-stimulated melanogenesis. In the bio evaluation studies of these compounds, we discovered eighteen compounds, out of twenty-six exhibited more potent inhibition than the positive control arbutin. From the SAR studies, we identified **3k** and **6g** as lead compounds which displayed almost 5 and 9 times more potent inhibition of α-MSH-stimulated melanogenesis respectively than the reference arbutin. It is also evident the presence of electron withdrawing group at para position (R^3) for the compounds (**3a-p**) and presence of +M group at ortho position (R^5) for the compounds (**6a-j**) were crucial for their excellent inhibition activities of α-MSH-stimulated melanogenesis.

Melanin is the key source and responsible for the pigmentation of human skin, eyes and hair which is produced from epidermis melanocytes with basal keratinocytes.[1] Upon ultraviolet B (UVB)-irradiation, melanocyte synthesizes the melanin through melanogenesis process.[2] Melanogenesis is a complex process involves the combination of biochemical and enzymatic reactions in which melanocytes produce two kinds of melanin pigments such as eumelanin (brown-black) and pheomelanin (red-yellow) formed by the conjugation of cysteine or glutathione.[3-5] At normal physiological conditions, melanin protects the skin against harmful UV irradiation and acts a vital evolutionary role in camouflage and animal mimicry.[6] But irregular production of melanin that leads to pigmented acne scars, age spots, melasma, postinflammatory melanoderma, and freckles,[7-11] as well as cancer.[12] It is also reported that abnormal melanogenesis associated with Parkinson's, Alzheimer's, and Huntington's diseases.[13-17] Thus, this area has been extensively focused by the researchers to control the abnormal production of melanin as well as the development of skin whitening agents including skin medication. Around the globe, approximately 15% world population is anticipated to invest for skin whitening products and by 2020; the global market is expected to reach around U.S. $23 billion.[18] Most of the marketed skin whitening products inhibit the melanin synthesis by overactive melanocytes. In that process several inhibitors such as arbutin, kojic acid (Fig. 1) and various herbal extracts have been developed.[19-20]

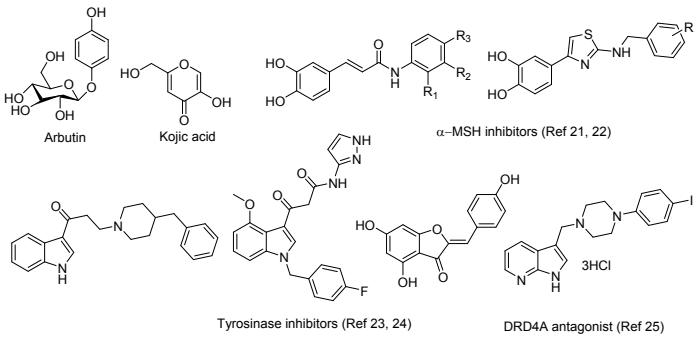


Figure 1. The representative potent inhibitors of melanogenesis.

Recently Jung, J-K et al have reported the caffeic acid and chlorogenic acid derivatives (Fig. 1) as potent α-MSH induced melanogenesis inhibitors.[21-22] Different heterocycles (Fig. 1) such as indoles,[23] aurones[24] and pyrrolo[2,3-b]pyridines[25] were also found to be acts as inhibitors of tyrosinase, melanin in B16, and human melanocytes[25] respectively. To the best of our knowledge, this is the first report on *N*-benzoylindazoles and *N*-arylindazole-3-carboxamides as potent inhibitors of α-MSH-stimulated melanogenesis. As a part of our exploration of the synthesis of novel heterocyclic systems as medicinally and pharmaceutically important scaffolds, [26-29] in this report we disclosed the design

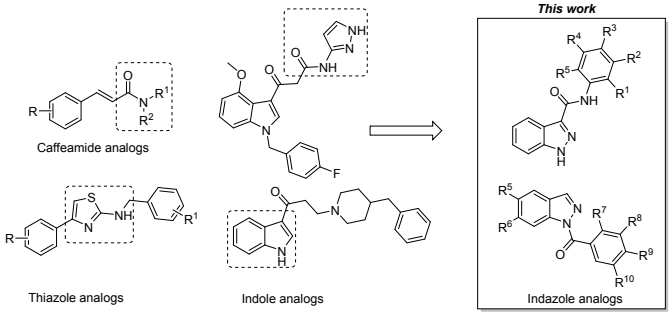
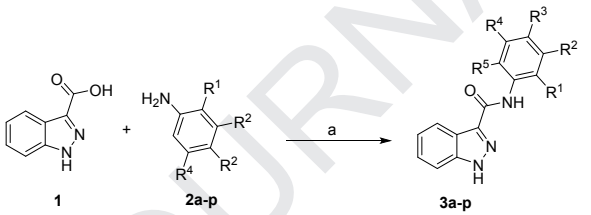


Figure 2. Design of our target molecules by using molecular modification.

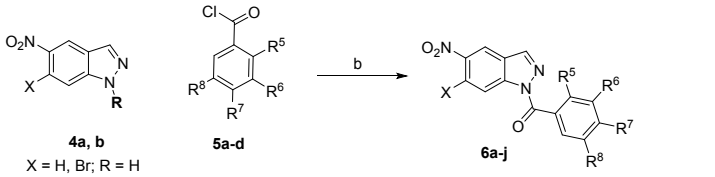
(Fig. 2) and synthesis of total twenty-six *N*-benzoylindazole and *N*-arylindazole-3-carboxamide derivatives and tested their inhibitory activities against α-MSH-stimulated melanogenesis. The assay determined the inhibitory activity of melanin formation in B16 melanoma cells in the presence of α-MSH (100nM) during three-day incubation. The quantity of melanin produced into the culture media was determined by measuring sample absorbance against synthetic melanin standard. [30-31]

Our studies commenced toward the synthesis of various *N*-arylindazole-3-carboxamide (**3a-p**) and *N*-benzoylindazole derivatives (**6a-j**) as shown in Schemes 1 and 2. The synthesis of *N*-arylindazole-3-carboxamide (**3a-p**) derivatives was achieved by the addition of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole hydrate (HOBt.H_2O) to a solution of indazole-3-carboxylic acid (**1**) in DMF and aniline derivatives (**2a-p**). The resulting mixture was stirred at 100°C for overnight provided the desired compounds **3a-p** (Scheme 1). As depicted in scheme 2, the *N*-benzoylindazole derivatives (**6a-j**) were synthesized by the treatment of 5-nitroindazole derivatives (**4a-b**) in DCM with mixture of triethylamine and benzoyl chloride derivatives (**5a-d**) at 0 ℃ and then stirred at room temperature for overnight furnished the corresponding *N*-benzoylindazole derivatives (**6a-j**). All the synthesized products **3a-p** & **6a-j** were confirmed by ^{1}H, ^{13}C NMR and mass spectra. After the synthesis



R^1=R^2=R^3=R^4= R^5= H ; **3a,** 81%
R^1=R^2=R^4=R^5=H ; R^3= OCH_3; **3b,** 68%
R^2=R^3=R^4=R^5= H ; R^1= OCH_3; **3c,** 70%
R^1=R^3=R^4=R^5= H ; R^2= OCH_3; **3d,** 65%
R^1=R^2=R^4=R^5= H ; R^3= CH_3; **3e,** Quant.
R^1=R^3=R^4=R^5= H ; R^2= CH_3 ; **3f,** 57%
R^1=R^3=R^5=CH_3; R^2=R^4=H; **3g,** 70%
R^1=R^2=R^4=R^5= H ; R^3= CF_3; **3h,** 76%
R^1=R^3=R^4=R^5= H ; R^2= CF_3; **3i,** 57%
R^2=R^3=R^4=R^5= H ; R^1= CF_3; **3j,** 69%
R^1=R^2=R^4=R^5= H ; R_3= OCF_3; **3k,** 72%
R^2=R^3=R^4=R^5= H ; R_1= OH; **3l,** 19%
R^1=R^3=R^4=R^5= H ; R^2= OH; **3m,** 49%
R^1=R^2=R^4=R^5= H ; R^3= OH; **3n,** 41%
R^1=R^2=R^4=R^5= H ; R^3= Cl; **3o,** Quant
R^1=R^2=R^4=R^5= H ; R^3= $COOCH_3$; **3p,** Quant

Scheme 1. Synthesis of *N*-arylindazole-3-carboxamide derivatives (**3a-p**). Reagents and conditions: (a) 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, HOBt.H_2O, DMF, 100 °C, Overnight. Isolated yields of (**3a-p**): 19% to quantitative.



R^5=R^6=R^7=R^8= H; X = Br ; **6a,** 47%
R^5=R^6=R^7=H; R^8= CH_3; X = Br ; **6b,** 51%
R^6=R^7=R^8=H; R^5= Cl; X = Br ; **6c,** 46%
R^5=R^6=R^8=H; R^7= Cl; X = Br ; **6d,** 35%
R^5=R^6=R^7=R^8= X =H; **6e,** 61%
R^5=R^6=R^7=H; R^8= CH_3; X = H ; **6f,** 62%
R^6=R^7=R^8=H; R^5= Cl; X = H ; **6g,** 63%
R^5=R^6=R^8=H; R^7= Cl; X = H ; **6h,** 63%
X = Br; R = $COCH_2$-2-Thiophenyl; **6i,** 61%
X = H; R = $COCH_2$-2-Thiophenyl; **6j,** 62%

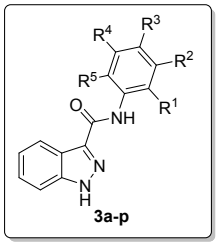
Scheme 2. Synthesis of *N*-benzoylindazole derivatives (**6a-j**). Reagents and conditions: (b) Aroyl chlorides, Et_3N, DCM, 0 °C to RT, Overnight. Isolated yields of (**6a-j**): 35-63%.

of various indazole analogs (**3a-p** & **6a-j**), we focused to examine their inhibitory activities against α-MSH-induced melanogenesis in B16 melanoma cells as shown in Table 1. As shown in Table 1, a total sixteen compounds of *N*-arylindazole-3-carboxamide derivatives (**3a-p**) were evaluated for inhibitory activities of α-MSH-induced melanogenesis with positive control arbutin which is used as reference compound in this studies.[5, 19-20, 21-22] Among all examined sixteen compounds; when compared to positive control arbutin (IC_{50}: 64±9 μM), eleven compounds such as **3a** (IC_{50}: 40±2 μM), **3b** (IC_{50}: 20±1 μM), **3c** (IC_{50}: 16±1 μM), **3d** (IC_{50}: 36±1 μM), **3e** (IC_{50}: 38±6 μM), **3f** (IC_{50}: 15±2 μM), **3h** (IC_{50}: 15±1 μM), **3k** (IC_{50}: 13±1 μM), **3l** (IC_{50}: 21±2 μM), **3m** (IC_{50}: 35±5 μM), and **3n** (IC_{50}: 18±1 μM), exhibited strong inhibitory activities against α-MSH-induced melanogenesis in B16 melanoma cells. The compounds **3p** (IC_{50}: 69±4 μM) and **3o** (IC_{50}: 93±4 μM) also displayed comparable activities with reference compound. In particular, the compound **3k** (IC_{50}: 13±1 μM) shown excellent inhibitory activity which is almost 5 times more potent inhibition than the positive control arbutin (IC_{50}: 64±9 μM). It is also noted that the compounds **3h** (IC_{50}: 15±1 μM) and **3f** (IC_{50}: 15±2 μM) exhibited almost 4 times more potent inhibition than the reference compound arbutin (IC_{50}: 64±9 μM) against α-MSH-induced melanogenesis. Next, we turned our attention to screen the inhibitory activities of *N*-benzoylindazole derivatives (**6a-j**) against α-MSH-induced melanogenesis with reference compound arbutin. As depicted in Table 1, among all ten synthesized compounds (**6a-j**); seven compounds **6a** (IC_{50}: 32±1 μM), **6b** (IC_{50}: 28±5 μM), **6c** (IC_{50}: 25±1 μM), **6e** (IC_{50}: 51±5 μM), **6g** (IC_{50}: 7±1 μM), **6h** (IC_{50}: 60±3 μM), and **6j** (IC_{50}: 55±1 μM) displayed potent inhibition than the reference arbutin (IC_{50}: 64±9 μM). The compound **6f** also shown comparable activity (IC_{50}: 77±13 μM). Especially, the compound **6g** (IC_{50}: 7±1 μM) exhibited excellent inhibition which is almost 9 times more potent inhibition than the positive control against α-MSH-induced melanogenesis.

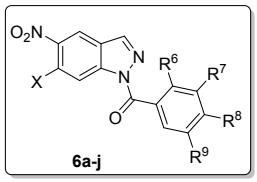
To develop the structure-activity relationship (SAR), initially we modified the indazole core unit at 1st and 3rd positions which resulted the two sets of **3a-p** and **6a-j** compounds. In the first set of *N*-arylindazole-3-carboxamide derivatives (**3a-p**), substitutions were performed at the *N*-phenyl ring (R^1, R^2, R^3, R^4, and R^5). Subsequently R^1= R^2= R^3= R^4= R^5 =H (**3a**, IC_{50}: 40±2 μM) was prepared to study the effect of core motif of *N*-phenyl-1H-indazole-3-carboxamide. We also examined the electronic influence of different groups at R^1, R^2, R^3, R^4, and R^5 including

electron withdrawing (–CF_3 –OCF_3 and –$COOCH_3$) and electron donating groups (–OCH_3 and –OH).

Table 1. Inhibitory activities of *N*-arylindazole-3-carboxamide (**3a-p**) and *N*-benzoyl indazole (**6a-j**) derivatives



3a-p



6a-j

Compounds	R^1	R^2	R^3	R^4	R^5	IC_{50} (μM)[a]	Compounds	R	X	R^6	R^7	R^8	R^9	IC_{50} (μM)[a]
Arbutin						64±9	**6a**		Br	H	H	H	H	32±1
3a	H	H	H	H	H	40±2	**6b**		Br	H	H	H	CH_3	28±5
3b	H	H	OCH_3	H	H	20±1	**6c**		Br	Cl	H	H	H	25±1
3c	OCH_3	H	H	H	H	16±1	**6d**		Br	H	H	Cl	H	--
3d	H	OCH_3	H	H	H	36±1	**6e**		H	H	H	H	H	51±5
3e	H	H	CH_3	H	H	38±6	**6f**		H	H	H	H	CH_3	77±13
3f	H	CH_3	H	H	H	15±2	**6g**		H	Cl	H	H	H	7±1
3g	CH_3	H	CH_3	H	CH_3	--	**6h**		H	H	H	Cl	H	60±3
3h	H	H	CF_3	H	H	15±1	**6i**	$COCH_2$-2-Thiophenyl	Br					--
3i	H	CF_3	H	H	H	--	**6j**	$COCH_2$-2-Thiophenyl	H					55±1
3j	CF_3	H	H	H	H	--								
3k	H	H	OCF_3	H	H	13±1								
3l	OH	H	H	H	H	21±2								
3m	H	OH	H	H	H	35±5								
3n	H	H	OH	H	H	18±1								
3o	H	H	Cl	H	H	93±4								
3p	H	H	$COOCH_3$	H	H	69±4								

[a] Data taken as a mean from three independent experiments.

The inhibitory effects of *N*-arylindazole-3-carboxamide derivatives (**3a-p**) depended on the nature of the substitution at the *N*-phenyl ring (R^1, R^2, R^3, R^4, and R^5). For instance, the electron withdrawing group such as –CF_3 at para position (R^3 substitution) exhibited (**3h** IC_{50}: 15±1 μM) strong inhibitory activities than the corresponding ortho (R_1 substitution, **3i**) and meta position (R^2 substitution, **3j**) compounds respectively. It is also important to note that the electron withdrawing group –OCF_3 at para position contained compound **3k** (IC_{50}: 13±1 μM) exhibited 5 times more potent inhibition than the positive control arbutin (IC_{50}: 64±9 μM). Similarly, in the case of electron donating groups; ortho substitution is vital for better inhibitory activities. For instance, –OCH_3 group ortho substituted compound (**3c**, IC_{50}: 16±1 μM) displayed more potent inhibition than the corresponding meta (**3d,** IC_{50}: 36±1 μM) and para (**3b**, IC_{50}: 20±1 μM) substituted compounds respectively. It is also explored that the compound **3c** (IC_{50}: 16±1 μM) displayed 4 times more potent inhibition than the reference compound arbutin (IC_{50}: 64±9 μM). In the case of *N*-benzoylindazole (**6a-j**) derivatives, the structure-activity relationship (SAR) development was initiated for the indazole scaffold and it was modified at 1st, 5th and 6th positions of indazole core unit which results the ten compounds (**6a-j**). Significantly, we focused to perform different substitutions at aromatic ring (R^6, R^7, R^8, and R^9) of *N*-benzoylindazole (**6a-j**) derivatives. Consequently, R^6= R^7= R^8= R^9= H and X =Br (**6a**, IC_{50}: 32±1 μM) was prepared to study the effect of core motif of (5-nitro-1H-indazol-1-yl)(phenyl)methanone. We also screened different substitutions at R^6, R^7, R^8, R^9 and X. Especially, when we tested +M substituents like –Cl at R^6 position of aromatic ring exhibited strong inhibitory activities than the remaining substitutions. For instance, the compounds **6c** (IC_{50}: 25±1 μM) and **6g** (IC_{50}: 7±1 μM) exhibited almost 4 and 9 times more potent inhibitory activities respectively than the positive control arbutin (IC_{50}: 64±9 μM). We also observed that 2-thiophenyl substituted compound **6j** (IC_{50}: 55±1 μM) also shown good inhibitory activity than the reference compound.

In summary, a total twenty-six compounds of indazole analogs (**3a-p & 6a-j**) were designed, synthesized and evaluated their inhibitory effects on α-MSH-induced melanogenesis. Structure-activity relationship (SAR) studies of **3a-p** analogs revealed that the presence of electron withdrawing groups at para position (R^3) and electron donating groups at ortho position (R^1) were crucial for their inhibitory

effects on α-MSH-induced melanogenesis and also in the case of **6a-j** analogs +M groups at R^6 position was most important for their inhibitory activities. The screening starting from the initial lead scaffold **3k** directed to the discovery of **6g** analog which displayed 9 times more potent inhibition than the reference compound against α-MSH-induced melanogenesis. The remaining compounds also exhibited most potent inhibitions. Thus, *N*-arylindazole-3-carboxamide (**3a-p**) and *N*-benzoylindazole derivatives (**6a-j**) provided new chemical tools for development of pathway-selective α-MSH-induced melanogenesis inhibitors with excellent activity. Work on the enrichment of potency and pharmacological profiles of the lead molecules are underway.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version at http://dx.doi.org/10.1016/j.bmcl.

Graphical Abstract

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Synthesis of *N*-arylindazole-3-carboxamide and *N*-benzoylindazole derivatives and their evaluation against α-MSH-stimulated melanogenesis

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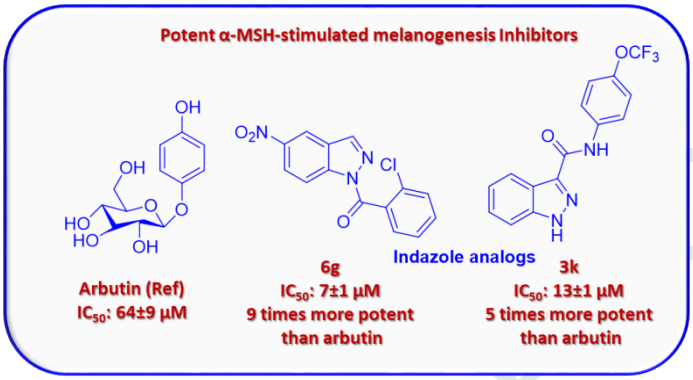
Sateesh Kumar Arepalli, Chaerim Lee, Jae-Kyung Jung, Youngsoo Kim, Kiho Lee and Heesoon Lee*



altered.

Highlights:

- Twenty-six indazole analogs were designed, synthesized and evaluated as α-MSH inhibitors.
- Eighteen compounds exhibited more potent inhibition than reference arbutin.
- The compound (**3k**) displayed 5 times more α-MSH inhibition than arbutin
- The compound (**6g**) displayed 9 times more α-MSH inhibition than arbutin
- Structure-activity relationship was developed