Tyrosinase is a major enzyme of melanogenic cascade, accountable for hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) and subsequent oxidation of L-DOPA to dopaquinone, the significant steps in melanin production.\(^1\)\(^,\)\(^2\) Melanogenesis is a major defence mechanism of human skin against UV radiations. However, abnormal production and accumulation of melanin in the skin are a serious aesthetic problem, which can cause melasma, freckles, ephelede, and senile lentigines.\(^3\) In the food industry, melanin is responsible for browning reactions in fruits and vegetables, resulting in the nutritional as well as market value loss. Therefore, the development of tyrosinase inhibitors has gradually become more important as skin whitening agents and preservatives in cosmetic and food industry, respectively.\(^4\)\(^,\)\(^5\)\(^,\)\(^6\) and research in this area is continuously growing.\(^7\)\(^–\)\(^13\) Many tyrosinase inhibitors have already been reported from both synthetic and natural sources, for example hydroquinone, kojic acid, arbutin, retinol, limoleic acid, galangin, and numerous botanical products.\(^4\) However, due to undesirable side effects, many of them are banned in several countries.\(^15\)\(^,\)\(^16\)

The indole moiety is considered as a promising scaffold for tyrosinase inhibition\(^17\) and many indole group bearing compounds, such as N-p-coumaroyl serotonin, N-feruloyl serotonin, and N-cafeoyl serotonin have been described as potential tyrosinase inhibitors.\(^18\) Likewise, octapeptide containing indole scaffold has also been reported as a strong inhibitor of tyrosinase.\(^19\) The role of indole moiety and tyrosinase in melanogenesis has been depicted in Fig. 1. In the similar vein, αβ-unsaturated carbonyl compounds, the chalcones are known to possess diverse biological activities, e.g. antioxidant,\(^20\) anticancer,\(^21\) anti-inflammatory,\(^22\) antidepresive,\(^23\) antimicrobial,\(^24\) and anti-tyrosinase.\(^25\)\(^,\)\(^26\) Isoliquiritigenin chalcone as a potent inhibitor of tyrosinase was reported by Nerya et al.\(^25\) Recently, we reported (Z)-3-(2,4,6-trihydroxybenzylidene)-indolinol that suppressed the tyrosinase activity in a double-digit micro-molar range.\(^25\) Many other studies have also confirmed the tyrosinase inhibitory potential of chalcones, which can be attributed to their antioxidant capability suppressing the pigmentation resulting from auto-oxidative process.\(^27\)\(^,\)\(^28\) Furthermore, Okombi et al.\(^29\) published the report of benzylidenbenzofuran-3(2H)-ones as inhibitors of tyrosinase from human melanocytes. The lead compound (Z)-4,6-dihydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2H)-one displayed an IC\(_{50}\) of 38±2.9 µM, emerging as the remarkably potent inhibitor of tyrosinase when compared with the reference compound kojic acid. The pharmacophoric similarity between the lead tyrosinase inhibitor (Z)-4,6-dihydroxy-2-(4-hydroxybenzylidene) benzofuran-3(2H)-one and our synthesized compounds (3–10) has been presented in Fig. 2. Based on these remarks, we synthesized oxindole-based chalcones to investigate their tyrosinase inhibitory potential for their applications as skin whitening agents in cosmetics and as preservatives in food industry.

Results and Discussion

Chemistry The synthesis of oxindole-based chalcones (3–10) was carried out by Claisen–Schmidt condensation reaction of a ketone with various aldehydes. Oxindole (indolin-2-one) (1) was stirred with appropriate aldehydes (2) in the presence of ethanolic NaOH to yield the title compounds (3–10) (Chart 1). All the compounds were synthesized in fairly good yields (75–94%) and their structures were established by using UV, IR, \(^1\)H-NMR, and mass spectroscopic techniques. The UV spectra of compounds (3–10) demonstrated two typical chalcone bands, the band-I at 314.50–347.00 nm and band-II at 270.50–239.50 nm. The IR spectra of compounds (3–10) displayed peaks at 3143.97–3192.19, 1616.35–1699.29, and 1564.27–1614.42 cm\(^{-1}\) distinctive to N–H group and \(\alpha\beta\)-unsaturated carbonyl system, i.e. C=O and C=C groups, respectively. The \(^1\)H-NMR spectra of synthesized compounds showed two singlets at 9.0202–11.8558 and 7.2566–8.3317 ppm characteristic to NH and\(=\text{CH}\) (vinyllic) protons, respectively.

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However, in the 1H-NMR spectrum of 3-phenylallylidene substituted compound 8, =CH proton appeared upfield and as a doublet due to the presence of neighbouring Ar-CH=CH-group. The total number of protons in the 1H-NMR spectra of compounds were consistent with their respective protons of molecular formulas. The high resolution (HR)-MS electrospray ionization (ESI)-MS spectra of compounds displayed molecular ion peaks distinctive to their molecular masses. Taken together, the structures of synthesized α,β-unsaturated carbonyl compounds (3–10) were confirmed by the presence of IR and NMR peaks characteristic to α,β-unsaturation, along with the presence of molecular ion peaks corresponding to the molecular masses of the synthesized compounds.

**Tyrosinase Inhibition Activity** The tyrosinase inhibitory activity of oxindole-based chalcones (3–10) and reference compound kojic acid was investigated by using L-tyrosine and L-DOPA as the substrates in monophenolase and diphenolase activity assays, respectively. The results obtained in these assays are shown in Table 1 and Fig. 3.

Among the chalcones evaluated, compound 3 (4-hydroxy substituted) and 7 (4-hydroxy-3-methoxy substituted) ex-

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**Table 1. Tyrosinase Inhibition Activity of Oxindole-Based Chalcones (3–10)**

| Compound | l-Tyrosine (µM) | l-DOPA (µM) |
|----------|-----------------|-------------|
| 3        | 77.07           | 85.33       |
| 4        | 152.88          | 145.17      |
| 5        | 256.70          | 241.89      |
| 6        | 182.46          | 180.25      |
| 7        | 63.37           | 59.71       |
| 8        | 223.56          | 232.32      |
| 9        | 95.98           | 99.10       |
| 10       | 110.77          | 107.26      |
| Kojic acid | 22.52          | 29.74       |
hibited the most potent tyrosinase inhibitory activity with IC$_{50}$s of 77.07 and 63.37 µM in monophenolase and 85.33 and 59.71 µM in diphenolase activity assays, respectively. At the same time, the reference compound kojic acid demonstrated 50% of tyrosinase inhibition at concentrations of 22.52 and 29.74 µM in monophenolase and diphenolase activity assays, correspondingly. It is evident from the results that the hydroxyl group bearing compounds 3 and 7 displayed IC$_{50}$s much comparable to that of the reference compound kojic acid. On the other hand, compounds 4 and 6 lacking a hydroxyl group at position-4 of benzylidene moiety, showed moderate to poor activity (IC$_{50}$s of 152.88 and 182.46 µM in monophenolase and 145.17 and 180.25 µM in diphenolase activity assays, respectively). These results indicate the importance of a hydroxyl group at position 4 of benzylidene moiety for tyrosinase inhibition. However, a complete loss of activity was observed in 4-dimethylamino substituted compound 5 (neither hydroxylated nor methoxylated at position 4). Upon comparison between the inhibitory potential of compounds 3 and 7, we found that the methoxy group at position 3 of the benzylidene ring in compound 7 augments the tyrosinase inhibition. In addition, 3-phenylallylidene substituted compound 8 (chalcone prepared by reaction of cinnamaldehyde with oxindole) showed the least activity against tyrosinase; and thus, it may be assumed that this modification is not useful for the inhibition of tyrosinase. On the contrary, chalcone prepared from heterocyclic aldehydes, such as 9 (2-pyridinecarboxaldehyde) and 10 (5-ethylfurfural) exhibited moderate tyrosinase inhibitory potential with IC$_{50}$s of 95.98 and 110.77 µM in monophenolase and 99.10 and 107.26 µM in diphenolase activity assays, respectively. These results indicated that the replacement of benzylidene scaffold with 5 or 6 membered heterocyclic counterparts may retain the tyrosinase inhibitory potential of oxindole-based chalcones.

While discussing the mode of tyrosinase inhibition by our lead compound 7 or other chalcones, since our designed compounds are based on mimicking the structural part of tyrosinase substrates (Fig. 1); (i) l-tyrosine, (ii) l-DOPA, and 5,6-dihydroxyindole, we can accept that these compounds will act as competitive inhibitors of tyrosinase. Moreover, many previous studies have already reported that chalcones which bear the structural similarity with tyrosinase substrates act as the competitive inhibitors of the enzyme. 28,30)

**Molecular Docking Analysis** Before performing molecular docking studies, all the designed chalcones were assessed against the Lipinski’s Rule of Five and other drug-likeness parameters. The Lipinski’s Rule of Five states that for a chemical compound to be a successful oral drug, it should not violate more than one of the following parameters; i) Number of hydrogen bond donors (sum of OHs and NHs) should be $\leq$ 5, ii) Number of hydrogen bond acceptors (sum of Os and Ns) should be $\leq$ 10, iii) Its LogP value should be $\leq$ 5, iv) Its molecular weight should be $\leq$ 500. The calculation of Lipinski’s Rule of Five along with molar refractivity and polar surface area parameters revealed that none of the designed chalcones violated these drug-likeness parameters. Moreover, all the compounds demonstrated the values well within the proposed limits of parameters as shown in Table 2.

In order to predict the possible binding interactions that might take place between the oxindole-based chalcones and tyrosinase enzyme, all the designed compounds were docked into the active site of tyrosinase. These docked compounds showed estimated free energy of binding in the range of $-7.09$ to $-1.18$ kcal/mol (Table S1). Among them, 4-hydroxy-3-methoxybenzylidene moiety bearing compound 7 showed the lowest estimated free energy of binding, whereas 4-dimethylaminobenzylidene moiety possessing compound 5 exhibited the highest estimated free energy of binding. Close analysis of the docked complex formed between compound 7 and tyrosinase indicated the presence of three strong hydrogen bonds; where, two bondings were of 1.8 Å each, while another one was of 2.2 Å each, while another one was of 2.2 Å each. The hydroxyl oxygen of benzylidene scaffold was hydrogen bonded with the histidine (His)-60 (H–O…H–N, 1.8 Å), while carbonyl oxygen of oxindole moiety was interacting with the valine (Val)-218 (C=O…H–N, 1.8 Å) residue of tyrosinase. Additionally, the hydroxyl oxygen...
of benzylidene also formed a hydrogen bond with the His-42 residue (H–O...H–N, 2.2 Å) of the target protein. Apart from hydrogen bondings, the oxindole scaffold of compound 7 was positioned in the hydrophobic cavity created by Val-217, Val-218, and proline (Pro)-219 residues of tyrosinase (Fig. 6). Further analyses of the docked complex indicated hydrophobic and van der Waals contacts between the benzylidene part of compound 7 and methionine (Met)-61, phenylalanine (Phe)-65, leucine (Leu)-66, Phe-197 residues of tyrosinase (Fig. 6).

Taken together, the formation of three strong hydrogen bonds between compound 7 and tyrosinase (His-42, His-60, and Val-218 involved) and deep positioning of oxindole scaffold in the hydrophobic pocket of Val-217, Val-218, and Pro-219 residues might have played a central role in the tyrosinase inhibitory activity of the lead compound 7. Furthermore, the lead compound 7 has the highest polar surface area and second least LogP value among all the compounds synthesized. The compound 7 was further analysed for absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters and results of this study have been summarized in Table 3.

**Conclusion** In the present study, we report for the first time, the potential of oxindole-based chalcones as tyrosinase inhibitors. The results of this study concluded that the type and position of substitutions on benzylidene moiety are fundamental for the oxindole-based chalcones to impart tyrosinase inhibitory activity. Among the synthesized chalcones, compound 7 was emerged as the most potent tyrosinase inhibitor that possessed a hydroxyl group at position 4 and a methoxy group at position 3 of benzylidene moiety. In conclusion, this work offers an oxindole-based new scaffold for the develop-

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**Table 2. Calculation of Lipinski’s Rule of Five and Other Descriptors for Synthesized Oxindole-Based Chalcones**

| Compd. | No. of H-bond donors | No. of H-bond acceptors | LogP | Molecular weight | Molar refractivity (cm³) | Polar surface area (Å²) | Lipinski’s & other violations |
|--------|----------------------|-------------------------|------|------------------|--------------------------|-------------------------|-----------------------------|
| 3      | 2                    | 2                       | 2.96 | 237.25           | 71.71                    | 49.33                   | 0                           |
| 4      | 1                    | 2                       | 3.11 | 251.28           | 76.19                    | 38.33                   | 0                           |
| 5      | 1                    | 2                       | 3.37 | 264.32           | 84.16                    | 32.34                   | 0                           |
| 6      | 1                    | 3                       | 2.95 | 281.31           | 82.66                    | 47.56                   | 0                           |
| 7      | 2                    | 3                       | 2.80 | 267.28           | 78.18                    | 58.56                   | 0                           |
| 8      | 1                    | 1                       | 3.79 | 247.29           | 80.05                    | 29.10                   | 0                           |
| 9      | 1                    | 2                       | 2.28 | 222.24           | 67.13                    | 41.99                   | 0                           |
| 10     | 1                    | 1                       | 3.05 | 239.27           | 71.80                    | 42.24                   | 0                           |

No. of H-bond donors ≤ 5. No. of H-bond acceptors ≤ 10. LogP ≤ 5. Molecular weight ≤ 500. Molar refractivity 30–140 cm³. Polar surface area ≤ 140 Å².
ment of effective skin whitening agents. However, further research is required to optimize the lead and to understand the detailed molecular mechanism behind the tyrosinase inhibitory activity of these chalcones.

### Experimental

**Chemistry** All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and Cals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. Tyrosinase, L-DOPA, and kojic acid were purchased from Sigma Life Science Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification. All the chemicals and reagents were purchased from Sigma-Aldrich, Aldrich, Merck, Ranbaxy Fine Chemicals Ltd., Sulabh Laboratories, and Spectrochem, India, and were used without further purification.

**General Procedure for the Synthesis of Compounds (3–10)** Oxindole (0.1 mol, 1.33 g) (1) and appropriate aldehyde (0.1 mol) (2) in an ethanolic solution (80%, 25 mL) containing 2% sodium hydroxide were stirred in ice-cold conditions for about 2 h (Chart 1). The reaction mixture was kept in the refrigerator for about 10–12 h followed by neutralized with 20% HCl solution with continuous stirring. The solid product precipitated out was filtered off, washed with ample water, and dried to yield a final purified product.

### Table 3. Prediction of ADMET Profile of the Lead Compound 7

| Parameter                          | Compound 7 (Most active) | Result 7 | Probability |
|------------------------------------|--------------------------|----------|-------------|
| Blood–Brain Barrier                | BBB                      | 0.7717   |
| Human Intestinal Absorption        | HIA                      | 1.0000   |
| Caco-2 Permeability (Log P<sub>app</sub>, cm/s) | Caco-2<sup>−</sup>        | 0.6196   |
| P-Glycoprotein Substrate           | Substrate                | 0.5596   |
| P-Glycoprotein Inhibitor           | Non-inhibitor            | 0.7554   |
| Renal Organic Cation Transporter   | Non-inhibitor            | 0.8349   |

### Table 4. Calculation of ADMET Profile of the Lead Compound 7

| Parameter                          | Compound 7 (Most active) | Result 7 | Probability |
|------------------------------------|--------------------------|----------|-------------|
| Blood–Brain Barrier                | BBB                      | 0.7717   |
| Human Intestinal Absorption        | HIA                      | 1.0000   |
| Caco-2 Permeability (Log P<sub>app</sub>, cm/s) | Caco-2<sup>−</sup>        | 0.6196   |
| P-Glycoprotein Substrate           | Substrate                | 0.5596   |
| P-Glycoprotein Inhibitor           | Non-inhibitor            | 0.7554   |
| Renal Organic Cation Transporter   | Non-inhibitor            | 0.8349   |

Acute Oral Toxicity: Category III includes compounds with LD<sub>50</sub> values greater than 500 mg/kg but less than 5000 mg/kg. Probability indicates scale between 0 and 1.
Orange-yellow solid; Yield: 94%; mp: 168–170°C; UV λ_max (MeOH) nm: 260.00, 239.50. IR (KBr) cm⁻¹: 3174.83 (N–H stretch), 3068.82, 3028.24, 2899.01, 2837.29 (C–H stretch), 1699.29 (C=O stretch), 1614.42, 1462.04 (C=C stretch).

1H-NMR (mixtures of CDCl₃ & DMSO-d₆, 400 MHz) δ: 10.4208 (s, 1H, NH), 7.1079–8.5353 (10H, Ar–H & CH–CH), 6.9865–7.0242 (t, 1H, J=7.54 Hz, Ar–CH–CH(2-C=H), 6.8514–6.8706 (d, 1H, J=7.68 Hz, Ar–CH=CH(3-C=H) [calcd for C₂₀H₂₀N₂O₂: C, 75.71; H, 4.55; N, 12.58].

Anal. Calcd for C₂₀H₂₀N₂O₂: C, 75.05; H, 4.60; N, 12.58. Found: C, 75.19; H, 4.82; N, 12.85.

(Z)-3-((2-Phenylallylidene)indolin-2-one (8) Orange-yellow solid; Yield: 83%; mp: 192–195°C; UV λ_max (MeOH) nm: 358.00, 260.00. IR (KBr) cm⁻¹: 3433.29 (N–H stretch), 3057.17, 2953.02, 2810.28, 2684.91 (C–H stretch), 1616.35 (C=O stretch), 1583.56 (C=C stretch). 1H-NMR (mixtures of CDCl₃ & DMSO-d₆, 400 MHz) δ: 10.4677 (s, 1H, NH), 7.2566 (s, 1H, =CH(1-C=H), 6.1470–8.3315 (6H, Ar– and furanonyl–H), 2.8528–2.9090 (q, 2H, CH₂(1-C=H), 1.3211–1.3589 (t, 3H, J=7.56 Hz, CH₃(1–C=H)). HR-MS (ESI) m/z: 220.0112 (M+H)⁺ (calcd for C₁₄H₁₀N₂O: 219.9928). Anal. Calcd for C₁₄H₁₀N₂O: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.53; H, 4.55; N, 12.85.

Conflicts of Interest The authors declare no conflict of interest.

Supplementary Materials UV, FT-IR, ¹H-NMR, and HR-MS spectra of all the compounds (3–10) are provided as supplementary material.

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