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Oxazolones: New tyrosinase inhibitors; synthesis and their structure–activity relationships

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Abstract—The tyrosinase inhibitory potential of seventeen synthesized oxazolone derivatives has been evaluated and their structure–activity relationships developed in the present work. All the synthesized derivatives, **3**–**19**, demonstrated excellent in vitro tyrosinase inhibitory properties having IC_{50} values in the range of 1.23 ± 0.37–17.73 ± 2.69 μM, whereas standard inhibitors L-mimosine and kojic acid have IC_{50} values 3.68 ± 0.02 and 16.67 ± 0.52 μM,, respectively. Compounds **4**–**8** having IC_{50} values 3.11 ± 0.95, 3.51 ± 0.25, 3.23 ± 0.66, 1.23 ± 0.37, and 2.15 ± 0.75, respectively, were found to be very active members of the series, even better than both the standard inhibitors. However, compounds **3**, **9**–**11**, **13**, **14**, **16**, **17**, and **19** were found to be better than kojic acid but not L-mimosine. (2-Methyl-4-[*E*,2*Z*)-3-phenyl-2-propenyliden]-1,3-oxazol-5(4*H*)-one (**7**) bearing a cinnamyol residue at C-4 of oxazolone moiety and an IC_{50} = 1.23 ± 0.37 μM was found to be the most active one among all tested compounds. These studies reveal that the substitution of functional group (s) at C-4 and C-2 positions plays a vital role in the activity of this series of compounds. It is concluded that compound **7** may act as a potential lead molecule to develop new drugs for the treatment of tyrosinase based disorders.

1. Introduction

Tyrosinase (EC 1.14.18.1), a multifunctional copper-containing enzyme, is widely distributed in the plant and animal kingdom. It is responsible for catalyzing *ortho*-hydroxylation of phenols and *ortho*-phenol oxidation to corresponding quinones.[1–4] Tyrosinase inhibitors are clinically useful for the treatment of skin diseases associated with melanin hyperpigmentation and applied in cosmetics for whitening and depigmentation after sunburn.[5] Melanin is a heteropolymer of indole compounds and is produced inside melanosomes by the action of the tyrosinase enzyme on the tyrosinase precursor material in melanocytes. It has recently been discovered that some other factors such as metal ions and the TRP-1 and TRP-2 enzymes also contribute to the production of melanin. However, tyrosinase plays a critical role in the regulation of melanin biosynthesis. Therefore, many tyrosinase inhibitors that suppress melanogenesis have been widely studied with the aim of developing preparations for the treatment of hyperpigmentation.[6]

In insects, several enzymes have been reported[7] to generate *o*-diphenols and quinones that cure pigmentation heal wounds, encapsulate parasite or help sclerotize. Such enzymes may be an alternative target site for the control of insect pests. In food industry, tyrosinase is effective for the enzymatic browning reactions in damaged fruits during post-harvest handling and processing. Controlling enzymatic browning is essential during fruit pulp manufacturing process.

Oxazolones exhibit a wide spectrum of pharmacological activities including anticancer, antimicrobial, antifungal, antagonistic, sedative, etc. Oxazolones that are internal anhydrides of acyl amino acids make an important class of five-membered heterocycles. These are highly versatile intermediates used for the synthesis of several organic molecules, including amino acids, peptides,[8–13] antimicrobial or antitumor compounds,[14,15] immunomodulators,[16] heterocyclic precursors,[17–20] for biosen-

Keywords: Tyrosinase inhibition; Oxazolones; Structure–activity relationship; Lead compounds.
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sors coupling, and/or photosensitive composition devices for proteins.[21] Some oxazolones have shown a wide range of pharmaceutical properties.[22] These can easily be prepared from *N*-acyl amino acids by dehydration.

In continuation of our research work on oxazolone derivatives as potential lead compounds in our drug discovery program,[23–27] we synthesized a variety of oxazolones and screened them randomly for their tyrosinase inhibitory properties.

2. Results and discussion

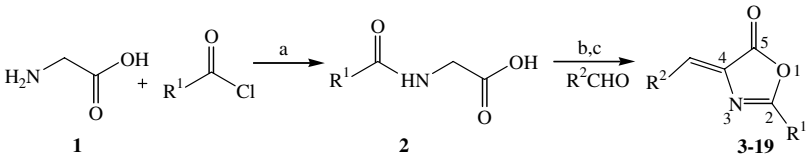
2.1. Chemistry

In recent past, we investigated a variety of classes of compounds for their potential use in medicinal chemistry. In the present study, seventeen oxazolones **3–19** were synthesized from commercially available glycine with acetic anhydride or benzoyl chloride in the presence of anhydrous sodium acetate followed by Erlenmeyer condition with appropriate aldehyde in very high yields.[28–30] All the oxazolones were isomerized by heating them with polyphosphoric acid on a water bath at 80–90 °C for 2 h according to literature procedure.[31] A general structure of oxazolone is shown in Scheme 1 along with its numbering. The structures were determined by using different spectroscopic methods like ^{1}H NMR, EI, IR, and UV, and purity was confirmed by CHN analysis.

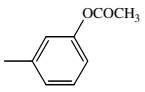
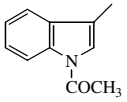
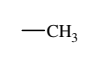
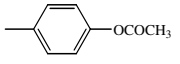
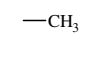
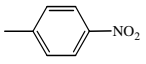
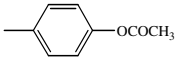
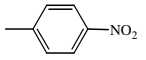
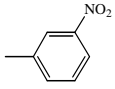
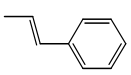
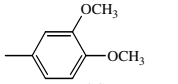
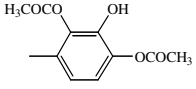
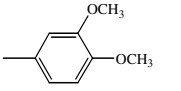
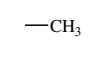
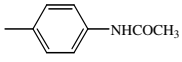
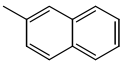
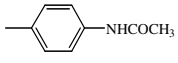
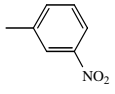
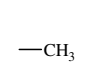
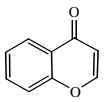
2.2. Biology

All the synthesized oxazolones were subjected to tyrosinase inhibitory assays, according to literature protocol[7] (Table 1, Fig. 1).

The oxazolones **3–19** demonstrated excellent in vitro tyrosinase inhibitory properties having IC_{50} values in the range of 1.23 ± 0.37–17.73 ± 2.69 μM, whereas standard inhibitors, L-mimosine and kojic acid, have IC_{50} values 3.68 ± 0.02 and 16.67 ± 0.52 μM, respectively. Compounds **3–8** having IC_{50} values 10.51 ± 1.04, 3.11 ± 0.95, 3.51 ± 0.25, 3.23 ± 0.66, 1.23 ± 0.37, and 2.15 ± 0.75 μM, respectively, were found to be very



a) Ac_2O or BzCl, 10% NaOH, H_2O; b) Ac_2O, NaOAc, reflux, c) PPA, 80-90 °C

Compound	R^1	R^2	Compound	R^1	R^2
3			12		
4			13		
5			14		
6			15		
7			16		
8			17		
9			18		
10			19		
11					

Scheme 1. Reagents and conditions: (a) Ac_2O or BzCl, 10% NaOH, H_2O; (b) Ac_2O, NaOAc, reflux; (c) PPA, 80–90 °C.

Table 1. Tyrosinase inhibitory activities of the oxazolones **3**–**19**, as compared to the standard inhibitors

Compound	$IC_{50} \pm SEM$[a] (μM)
3	10.51 ± 1.04
4	3.11 ± 0.95
5	3.51 ± 0.25
6	3.23 ± 0.66
7	1.23 ± 0.37
8	2.15 ± 0.75
9	8.72 ± 0.47
10	6.35 ± 1.06
11	5.21 ± 1.22
12	NA[b]
13	13.39 ± 0.99
14	6.20 ± 2.37
15	17.73 ± 2.69
16	5.67 ± 0.64
17	4.55 ± 0.55
18	NA
19	16.45 ± 1.96
Kojic acid[c]	16.67 ± 0.52
L-Mimosine[c]	3.68 ± 0.02

[a] SEM is the standard error of the mean.
[b] Not active.
[c] Standard inhibitors of the enzyme tyrosinase.

active members of the series, even better than both the standard inhibitors. However, compounds **9**–**11**, **13**, **14**, **16**, **17**, and **19** were found better than the standard kojic acid but not L-mimosine. Interestingly only compound **15** (IC_{50} 17.73 ± 2.69 μM) was found a little less active than standard kojic acid and no tyrosinase inhibitory activity was observed for compounds **12** and **18**. 2-Methyl-4-[(*E*)-3-phenyl-2-propenyliden]-1,3-oxazol-5(4*H*)-one (**7**) bearing a cinnamyol residue at C-4 of oxazolone moiety was found to be the most active one having IC_{50} = 1.23 ± 0.37 μM among all tested compounds.

Comparing the activities with the structures of compounds, it turns out that the tyrosinase activity is mainly dependent on the substituents present at C-2 and C-4 positions of oxazolone ring. When tyrosinase inhibitory activity of the most active compound **7** was compared with other compounds, it was observed that it has an extension of conjugation from distant phenyl ring passing through aliphatic double bonds and oxazolone moiety to the phenyl ring present at C-2. On the other hand, compound **12** likewise compound **18** having phenyl moieties at C-2 seemingly fulfill the requirement for extension of conjugation through indole and naphthyl residues, respectively, but found to be inactive in terms of tyrosinase inhibitory potential. This shows that extension of conjugation through an aliphatic double bond could be the prerequisite for activity rather than extension through an aromatic ring. In the case of nitrophenyl containing derivatives **5**, **6**, **15**, and **19**, the difference in their activity seems to follow supposition of extension of conjugation. The active compound **6**, containing nitrophenyl residue (IC_{50} 3.23 ± 0.66 μM), has a phenyl ring at C-2 and a 4-nitrophenyl at C-4, whereas a sharp decline in the activity of compound **5** (IC_{50} 3.51 ± 0.25 μM) might be due to the presence of methyl residue at C-2. A decrease in the activity of compound **19** (IC_{50} 16.45 ± 1.96 μM) as compared to compound **6** was due to the change in the position of nitro group in phenyl ring present at C-4. The least activity of compound **15** (IC_{50} 17.73 ± 2.69 μM) may be because of change in the position of nitro group in phenyl ring present at C-4 and substituent at C-2. Compound **8** (IC_{50} 2.15 ± 0.75 μM) was found to be second highly active member of the present series of oxazolones. Its excellent activity may be due to the presence of a phenyl group at its perfect position, that is, C-2 and the presence of an acetyl group at C-4 of second phenyl group, which meets the criteria for achieving extension of conjugation in addition to some effect of phenolic hydroxyl present at C-3 of the same phenyl ring. Though structurally similar, dramatic decline in the activities of compounds **3** (IC_{50} 10.51 ± 1.04 μM), **13** (IC_{50} 1.39 ± 0.99 μM), and **14** (IC_{50} 6.20 ± 2.37 μM) as compared to **8** may be due to either of the above-mentioned reasons. Compounds **9** (IC_{50} 8.72 ± 0.47 μM) and **10** (IC_{50} 6.35 ± 1.06 μM) are structurally similar to compound **8** except where oxygen is replaced by nitrogen. Interestingly, compounds **16** and **17** having IC_{50} values 5.67 ± 0.64 and 4.55 ± 0.55 μM, respectively, showed excellent activity. The activities may be due to the presence of methoxy groups on phenyl ring at C-4, and difference in their activity is due to the obvious reason of presence of substituents at C-2. The enhanced activity

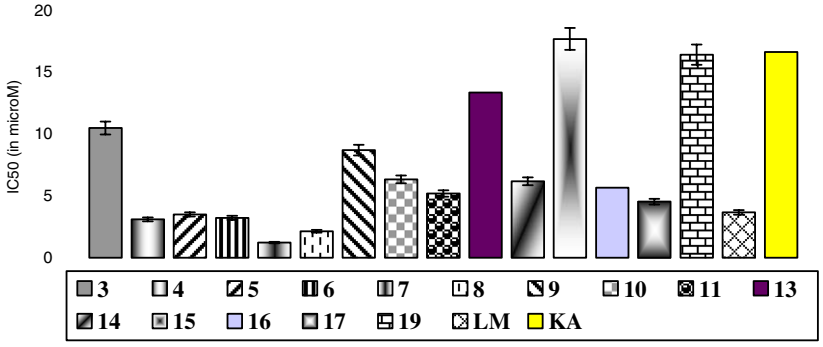


Figure 1. Comparative graphical presentation of the tyrosinase inhibitory potentials of the oxazolones **3**–**19**.

of compound **4** (IC_{50} 3.11 ± 0.95 μM) could be explained on the basis of above-mentioned reasons.

3. Conclusion

Present studies suggested that the substitutions of functional group (s) at C-4 and C-2 positions of oxazolone are crucial for tyrosinase inhibitory activity of this class of compounds. It is concluded that an extension of conjugation through an aliphatic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity. Of this series, the most active compound **7** may act as a potential lead molecule for the future research in the field of tyrosinase inhibition.

4. General experimental

Melting points were determined on a Büchi 434 melting point apparatus and are uncorrected. NMR was performed on a Bruker AM 300 and 500 MHz, respectively. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Ultraviolet (UV) spectra were recorded on Perkin-Elmer Lambda-5 UV/vis spectrometer for MEOH. Infrared (IR) spectra were recorded on JASCO IR-A-302 Spectrometer. Electron impact mass spectra (EIMS) were recorded on a Finnigan MAT-311A, Germany. Thin-layer chromatography (TLC) was performed on precoated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm or by iodine vapors.

4.1. Tyrosinase inhibition assay

Tyrosinase inhibition assays were performed in 96-well microplate format using SpectraMax® 340 microplate reader (Molecular Devices, CA, USA) according to the method Hearing[7] protocol. Briefly, first the compounds were screened for the *o*-diphenolase inhibitory activity of tyrosinase using L-DOPA as substrate. All the active inhibitors from the preliminary screening were subjected to IC_{50} studies. Compounds were dissolved in methanol to a concentration of 2.5%. 30 U of mushroom tyrosinase (28 nM) was pre-incubated with the compounds in 50 nM Na-phosphate buffer (pH 6.8) for 10 min at 25 °C. Then the L-DOPA (0.5 mM) was added to the reaction mixture and the enzyme reaction was monitored by measuring the change in absorbance at 475 nm (at 37 °C) due to the formation of the DOPA chrome for 10 min. The percent inhibition of the enzyme was calculated as follows, by using MS Excel®™ 2000 (Microsoft Corp., USA) based program developed for this purpose:

$$\text{Percent inhibition}(\%) = [B - S/B] \times 100$$

Here, the *B* and *S* represent absorbance values for the blank and samples, respectively. After screening of the compounds, median inhibitory concentration (IC_{50}) was also calculated. All the experiments were carried out at least in triplicate and the results represent means ± SEM (standard error of the mean). Kojic acid and L-mimosine were used as standard inhibitors for the tyrosinase. All the chemicals and reagents were purchased from Sigma Chem. Co., MO, USA.

4.2. General procedure for the synthesis of compounds 3–19

A mixture of *N*-acylglycine or benzoyl glycine (1.2 mmol), aldehyde (1 mmol), acetic anhydride (3 mmol), and fused sodium acetate (1.5 mmol) was heated to liquification and heating was continued for additional 3–4 h. After completion of reaction (TLC analysis), EtOH (5 ml) was added and the product was left in refrigerator for overnight. It was filtered to obtain solid mass which was isomerized by mixing and heating with polyphosphoric acid on a steam bath at 80–90 °C for 2 h and finally pouring into water.[31] The resultant solid was collected, washed with cold ethanol, hot water, ethanol, and small amount of hexane and then dried to afford title compounds **3**–**19**.

4.2.1. 3-{[5-Oxo-2-phenyl-1,3-oxazol-4-(5*H*)-ylidene]methyl} phenylacetate (3). Yield: 53%; mp: 123 °C; R_f: 0.48 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 190 ($\log\varepsilon = 5.5$) nm. IR (KBr): ν_{max} 3072, 1797, 1656, 1216, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H, H-6), 8.17 (d, J = 7.2 Hz, 2H, H-2′/6′), 7.47 (t, J = 7.2 Hz, 2H, H-3′/5′), 7.53 (t, J = 7.2 Hz, 1H, H-4′), 8.16 (d, J = 1.5 Hz, 1H, H-2″), 8.17 (d, J = 7.3 Hz, 1H, H-4″), 7.61 (t, J = 7.3 Hz, 1H, H-5″), 7.84 (d, J = 7.3 Hz, 1H, H-6″), 2.35 (s, 3H, $COCH_3$); EIMS: *m*/*z* (rel. abund. %) 307 (M^+, 2.0), 265 (2.42), 105 (100), 76 (84), 51 (90); Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56; O, 20.83. Found: C, 70.39; H, 4.28; N, 4.59; O, 20.86.

4.2.2. 2-Methyl-4-[(*E*)-2-thienylmethylidene]-1,3-oxazol-5-one (4). Yield: 62%; mp: 175 °C; R_f: 0.49 (ethyl acetate/hexane 3:7); UV (MEOH): λ_{max} 357 ($\log\varepsilon = 4.40$) nm. IR (KBr): ν_{max} 3268, 3078, 2924, 1796, 1651, 1264 cm^{-1}. ^1H NMR (400 MHz, CDCl3) δ 7.30 (s, 1H, H-6), 2.39 (s, 3H, CH_3), 7.54 (d, J = 3.5 Hz, 1H, H-3′), 7.12 (dd, J = 4.7, 3.5 Hz, 1H, H-4′), 7.66 (d, J = 4.7 Hz, 1H, H-5′); EIMS: *m*/*z* (%) 193, (M^+, 43), 165 (17), 123 (100), 96 (34), 83 (26); Anal. Calcd for $C_9H_7NO_2S$: C, 55.94; H, 3.65; N, 7.25; O, 16.56; S, 16.06. Found: C, 55.96; H, 3.68; N, 7.27; O, 16.58; S, 16.09.

4.2.3. 2-Methyl-4-[(*E*)-(4-nitrophenyl)methylidene]-1,3-oxazol-5(*4H*)-one (5). Yield: 62%; mp: 273 °C; R_f: 0.59 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 193 ($\log\varepsilon = 4.8$) nm. IR (KBr): ν_{max} 3387, 2926, 1663, 1343, 1168 cm^{-1}. ^1H NMR (400 MHz, CDCl3) δ 7.11 (s, 1H, H-6), 2.44 (s, 3H, CH_3), 8.23 (d, J = 8.9 Hz, 2H, H-2′/6′), 8.26 (d, J = 8.9 Hz, 2H, H-3′/5′); EIMS: *m*/*z* (%) 232, (M^+, 100), 204 (10), 162 (33), 132 (26), 116 (35), 89 (90), 63 (78); Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.06; O, 27.56. Found: C, 56.95; H, 3.49; N, 12.11; O, 27.60.

4.2.4. 4-[(*E*)-(4-Nitrophenyl)methylidene]-2-phenyl-1,3-oxazol-5(*4H*)-one (6). Yield: 83%; mp: 113 °C; R_f: 0.60 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 201

($\log\varepsilon = 4.1$) nm. IR (KBr): ν_{max} 3633, 3104, 2925, 1797, 1520, 1343, 1296 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 1H, H-6), 8.20 (d, $J = 7.3$ Hz, 2H, H-2′/6′), 7.5 (t, $J = 7.3$ Hz, 2H, H-3′/5′), 7.66 (t, $J = 7.3$ Hz, 1H, H-4′), 8.30 (d, $J = 7.3$ Hz, 2H, H-2″/6″), 8.36 (d, $J = 8.8$ Hz, 2H, H-3″/5″); EIMS: *m/z* (%) 294 (M^+ 10), 105 (100), 77 (54); Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52; O, 21.75. Found: C, 65.35; H, 3.49; N, 9.55; O, 21.77.

4.2.5. 2-Methyl-4-[(*E*)-3-phenyl-2-propenyliden]-1,3-oxazol-5(*4H*)-one (7). Yield: 80%; mp: 105 °C; R_f: 0.61 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 195 ($\log\varepsilon = 5.39$) nm. IR (KBr): ν_{max} 3030, 1787, 1639 1296 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.1 (s, 1H, H-6), 7.65 (d, $J = 11.6$ Hz, H-7), 7.69 (d, $J = 11.6$ Hz, 1H, H-7), 8.13 (dd, $J = 8.1$, 1.0 Hz, 2H, H-2′/6′), 7.50 (t, $J = 8.1$ Hz, 2H, H-3′/5′), 7.60 (td, $J = 8.1$, 1.0 Hz, 1H, H-4′), 8.05 (dd, $J = 8.2$, 1.5 Hz, 2H, H-2″/6″), 7.38 (m, 3H, H-3″/5″); EIMS: *m/z* (%) 275 (M^+, 32), 247 (8.0), 105 (100), 77 (64); Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09; O, 11.62: Found: C, 78.55; H, 4.79; N, 5.11; O, 11.65.

4.2.6. 3-(Acetoyloxy)-2-hydroxy-4-{[5-oxo-2-phenyl-1,3-oxazol-4(*5H*)-ylidene]methyl}phenylacetate (8). Yield: 75%; mp: 169 °C; R_f: 0.45 (ethyl acetate/hexane, 3:7), UV (MEOH): λ_{max} 195 ($\log\varepsilon = 5.7$) nm. IR (KBr): ν_{max} 3094, 3058, 1774, 1369, 1211 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.1 (s, 1H, H-6), 7.54 (d, $J = 7.2$ Hz, 2H, H-2′/6′), 7.44–7.31 (m, 3H, H-3′-5′), 7.9(d, $J = 7.6$ Hz, 1H, H-2″), 8.16 (d, $J = 7.6$ Hz 1H, H-3″), 2.29 (s, 3H, $COCH_3$), 2.32 (s, 3H, $COCH_3$); EIMS: *m/z* (%) 381, (M^+, 1.32), 339 (3.04), 297 (22), 105 (100), 82(42); Anal. Calcd for $C_{20}H_{15}NO_7$: C, 62.99; H, 3.96; N, 3.67; O, 29.37. Found: C, 62.98; H, 3.98; N, 3.69; O, 29.39.

4.2.7. *N*-(3-{[2-Methyl-5-oxo-1,3-oxazol-4(*5H*)-ylidene]-methyl}phenyl)acetamide (9). Yield: 52%; mp: 210 °C; R_f: 0.53 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 192 ($\log\varepsilon = 5.12$) nm. IR (KBr): ν_{max} 3822, 3302, 1799, 1659, 1552, 1260 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.1 (s, 1H, H-6), 2.40 (s, 3H, CH_3), 7.89 (d, $J = 7.5$ Hz, 2H, H-2′/6′), 8.19 (d, $J = 7.5$ Hz, 2H, H-3′/5′), 8.39 (s, 1H, NH), 2.19 (s, 3H, $COCH_3$); EIMS: *m/z* (%) 244 (M^+, 11), 202 (2.06), 174 (77), 132 (100), 82 (40); Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47; O, 19.65. Found: C, 63.95; H, 4.98; N, 11.49; O, 19.67.

4.2.8. *N*-3-{[5-Oxo-2-phenyl-1,3-oxazol-4(*5H*)-ylidene]-methyl}acetamide (10). Yield: 57%; mp: 193 °C; R_f: 0.55 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 196 ($\log\varepsilon = 6.2$) nm. IR (KBr) ν_{max} 3299, 3087, 2923, 1790, 1658, 1158 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.2 (s, 1H, H-6), 7.70 (d, $J = 7.7$ Hz, 2H, H-2′/6′), 7.42 (t, $J = 7.7$ Hz, 2H, H-3′/5′), 7.53 (t, $J = 7.7$ Hz, 2H, H-4′), 7.89 (d, $J = 7.5$ Hz, 2H, H-2″/6″), 8.19 (d, $J = 7.5$ Hz, 2H, H-3′/5′), 8.31 (s, 1H, NH), 2.22 (s, 3H, $COCH_3$); EIMS: *m/z* (%) 306 (M^+, 2.97), 105 (100), 77 (52); Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; O, 5.67. Found: C, 70.60; H, 4.64; N, 9.16; O, 5.69.

4.2.9. 2-Methyl-4-[(*E*)-(4-oxo-4H-chromen-3-yl)methylidene]-1,3-oxazol-5-one (11). Yield: 91%; mp: 239 °C; R_f: 0.58 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 194 ($\log\varepsilon = 5.1$) nm. IR (KBr): ν_{max} 3074, 2926, 1716, 1653, 1531 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H, H-6), 2.38 (s, 3H, CH_3), 8.1 (s, 1H, H-2′), 7.50 (d, $J = 8.3$ Hz, 1H, H-5′), 7.45 (td, $J = 8.0$, 1.0 Hz, 1H, H-6′), 7.70 (t, $J = 8.0$ Hz, 1H, H-7′), 8.27 (dd, $J = 8.0$, 1.6 Hz, 1H, H-8′); EIMS: *m/z* (%) 255 (M^+, 27.22), 185 (100), 120 (22), 92 (51); Anal. Calcd for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49; O, 25.07. Found: C, 65.91; H, 3.58; N, 5.52; O, 25.09.

4.2.10. 4-[(*E*)-(1-Acetyl-1H-indol-3-yl)methylidene]-2-phenyl-1,3-oxazol-5-(*4H*)-one (12). Yield: 52%; mp: 215 °C R_f: 0.59 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 194 ($\log\varepsilon = 5.6$) nm. IR (KBr): ν_{max} 3420, 2926, 1789, 1645, 1526, 1448, 1207 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H, H-6), 8.14 (d, $J = 8.6$ Hz, 2H, H-2′/6′), 7.54 (t, $J = 8.6$ Hz, 2H, H-3′/5′), 7.62 (t, $J = 8.6$ Hz, 1H, H-4′), 7.52 (s, 1H, H-2″), 8.39 (d, $J = 8.0$ Hz, 1H, H-4″), 8.27 (m, 2H, H-5″/6″), 8.48 (dd, $J = 8.6$, 1.4 Hz, 1H, H-7″), 2.81 (s, 3H, $COCH_3$); EIMS: *m/z* (%) 330, (M^+, 11.8), 288 (9.4), 105 (100), 77 (36); Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48; O, 14.53. Found: C, 72.76; H, 4.29; N, 8.50; O, 14.55.

4.2.11. 4-{[2-Methyl-5-oxo-1,3-oxazol-4(*5H*)-ylidene]-methyl} phenylacetate (13). Yield: 45%; mp: 203 °C; R_f: 0.47 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 195 ($\log\varepsilon = 5.5$) nm. IR (KBr): ν_{max} 3296, 3000, 2926, 1758, 1656, 1225, 1376 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H, H-6), 2.39 (s, 3H, CH_3), 7.16 (d, $J = 8.6$ Hz, 2H, H-2′/6′), 8.09 (d, $J = 8.6$ Hz, 2H, H-3′/5′), 2.30 (s, 3H, COCH3); EIMS: *m/z* (%) 245 (M^+, 45), 203 (100), 133 (73), 77 (47); Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71; O, 26.10. Found: C, 63.69; H, 4.56; N, 5.74; O, 26.13.

4.2.12. 4-{[5-Oxo-2-phenyl-1,3-oxazol-4-(*5H*)-ylidene]-methyl} phenylacetate (14). Yield: 56%; mp: 236 °C; R_f: 0.48 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 194 ($\log\varepsilon = 5.5$) nm. IR (KBr): ν_{max} 3423, 3075, 2923, 1795, 1656, 1217, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H, H-6), 7.59 (d, $J = 7.4$ Hz, 2H, H-2′/6′), 7.52 (m, 3H, H-3′-5′), 8.16 (d, $J = 8.7$ Hz, 2H, H-2″/6″), 8.23 (d, $J = 8.7$ Hz, 2H, H-3″/5″), 2.32 (s, 3H, CH_3); EIMS: *m/z* (%) 307, (M^+, 16), 265 (41), 104 (100), 76 (65); Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56; O, 20.83. Found: C, 70.36; H, 4.28; N, 4.57; O, 20.84.

4.2.13. 2-Methyl-4-[(*E*)-(3-nitrophenyl)methylidene]-1,3-oxazol-5(*4H*)-one (15). Yield: 40%; mp: 238 °C; R_f: 0.59 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 270 ($\log\varepsilon = 4.9$) nm. IR (KBr): ν_{max} 3086, 2930, 1801, 1662, 1351, 1296, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H, H-6), 2.44 (s, 3H, CH_3), 8.28 (s, 1H, H-2), 8.31 (d, $J = 7.8$ Hz, 1H, H-4), 8.13 (d, $J = 8.1$ Hz, 1H, H-5), 8.23 (m, 1H, H-6); EIMS: *m/z* (%) 232, (M^+, 19.6), 204 (5.4), 187 (26), 144 (100), 83 (54); Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47;

N, 12.06; O, 27.56. Found: C, 56.94; H, 3.49; N, 12.09; O, 27.59.

4.2.14. 4-[(*E*)-(3,4-Dimethoxyphenyl)methylidene]-2-methyl-1,3-oxazol-5 (*4H*)-one (16). Yield: 75%; mp: 190 °C; R_f: 0.50 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 194 ($\log\varepsilon = 4.8$) nm. IR (KBr): ν_{max} 3080, 3003, 2933, 1790, 1656, 1270 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 7.07 (s, 1H, H-6), 2.38 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.89 (d, $J = 8.4$ Hz, 2H, H-2′/5′), 7.50 (d, $J = 8.4$ Hz, 1H, H-6′); EIMS: *m*/*z* (%) 248, (M^+, 100), 177 (100), 162 (90), 82 (12); Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67; O, 25.88. Found: C, 63.20; H, 5.35; N, 5.69; O, 25.92.

4.2.15. 4[(*E*)-(3,4-Dimethoxyphenyl)methylidene]-2-phenyl-1,3-oxazol-5(*4H*)-one (17). Yield: 80%; mp: 196 °C; R_f: 0.52 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 197 ($\log\varepsilon = 4.9$) nm. IR (KBr): ν_{max} 3264, 3062, 2949, 1787, 1655, 1516, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1H, H-6), 8.12 (dd, $J = 8.6$ Hz, 2H, H-2″/6″), 7.44 (t, $J = 8.6$ Hz, 2H, H-3′/5′), 7.55 (t, $J = 8.6$ Hz, 1H, H-4′), 6.93 (d, $J = 8.4$ Hz, 2H, H-2″/5″), 7.50 (m, 1H, H-6″), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3); EIMS: *m*/*z* (%) 309, (M^+, 42), 177 (4.1), 105 (100), 77 (22); Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53; O, 20.69. Found: C, 69.95; H, 4.94; N, 4.56; O, 20.75.

4.2.16. 4-[(*E*)-1-Naphthylmethylidene]-2-phenyl-1,3-oxazol-5(*4H*)-one (18). Yield: 48%; mp: 278 °C; R_f: 0.60 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 203 ($\log\varepsilon = 4.4$) nm. IR (KBr): ν_{max} 3289, 3057, 1723, 1648, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.2 (s, 1H, H-6), 7.97 (d, $J = 8.1$ Hz, 2H, H-2′/6′), 7.54 (m, 3H, H-3′-5′), 8.31 (d, $J = 8.3$ Hz, 1H, H-2″), 8.20 (d, $J = 8.3$ Hz, 1H, H-3″), 7.63 (m, 4H, H-4″/7″), 8.14 (s, 1H, H-8″); EIMS: *m*/*z* (%) 298, (M^+, 43), 210 (63), 105 (100), 77 (54); Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68; O, 10.69. Found: C, 80.28; H, 4.40; N, 4.70; O, 10.62.

4.2.17. 4-[(*E*)-(3-Nitrophenyl)methylidene]-2-phenyl-1,3-oxazol-5 (*4H*)-one (19). Yield: 54%; mp: 133 °C; R_f: 0.62 (ethyl acetate/hexane, 3:7); UV (MEOH): λ_{max} 196 ($\log\varepsilon = 4.9$) nm. IR (KBr): ν_{max} 3092, 2863, 1792, 1503, 1349, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 1H, H-6), 8.21 (d, $J = 7.8$ Hz, 2H, H-2′/6′), 7.56 (t, $J = 7.8$ Hz, 2H, H-3′/6′), 7.66 (t, $J = 7.8$ Hz, 1H, H-4′), 8.28 (d, $J = 1.2$ Hz, 1H, H-2″), 8.40 (d, $J = 7.8$ Hz, 1H, H-4″), 8.21 (d, $J = 7.8$ Hz, 1H, H-5″), 8.27 (dd, $J = 7.8$ Hz, 1H, H-6″); EIMS: *m*/*z* (%) 294, (M^+, 58), 105 (100), 77 (37), 51(6.2). Anal. Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52 O, 21.75. Found: C, 65.35; H, 3.45; N, 9.60; O, 21.78.

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