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Synthesis and Bioactivity of New Chalcone Derivatives as Potential Tyrosinase Activator Based on the Click Chemistry

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A new series of (*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenylprop-2-en-1-one **1a**—**15a** and (*E*)-3-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl) methoxy)phenyl)-1-phenylprop-2-en-1-one **1b**—**15b** were designed, synthesized based on click chemistry, and biologically evaluated for their activity on tyrosinase. The result showed that most of prepared compounds **1a**—**15a** have potent activating effect on tyrosinase, especially for **3a**, **8a**—**10a** and **14a**—**15a**. Among them, compounds **10a** and **14a** demonstrated the best activity with EC_{50}=1.71 and 5.60 μmol•L^{-1} respectively, even better than the positive control 8-MOP (EC_{50}=14.8 μmol•L^{-1}). Conversely, compounds **3b**, **5b**—**6b**, **9b**—**10b**, and **15b** induced enzymatic inhibition on tyrosinase.

Keywords enzyme, chalcone, heterocycles, synthesis, structure-activity relationship

Introduction

Tyrosinase (monophenol monooxygenase, EC: 1.14.18.1), also known as polyphenol oxidase,[1] is a copper-containing enzyme widely distributed in nature. Tyrosinase could catalyze the first two reactions in the melanin synthesis, the two steps in the pathway are the hydroxylation of monophenol to *o*-diphenol (monophenolase or cresolase activity) and the oxidation of diphenol to *o*-quinones (diphenolase or catecholase activity), both using molecular oxygen followed by a series of nonenzymatic steps resulting in the formation of melanin,[2-4] which plays a crucial protective role against skin photocarcinogenesis. Some dermatological disorders, such as Vitiligo, arise from the destruction and disappearance of melanocytes.

The *Ver-nohia anthelmintica* L. is a kind of plant growing only in the high altitude localities of southern Xinjiang and minority regions of Pakistan and India. Its fruits extract is one of the most popular Uygur medicines used for Vitiligo and initially recorded in '*Yao Yong Zong Ku*' around 300 years ago.[5-7] Some important chalcone compounds were isolated from the plant as well (Figure 1). It was believed that these compounds played an important role in this treatment. since it may activate tyrosinase and improve the melanin production.[8,9]

Chalcones which are major classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soy based foodstuff are very versatile for physiologically activity, such as antitumoral,[10,11] antioxidant,[12] antimicrobial,[13] antibacterial,[14] anti-inflammatory[15,16] and anti-HIV.[17] Until now, most chalcones and their derivatives have been described as potent inhibitors on tyrosinase.[18-20]

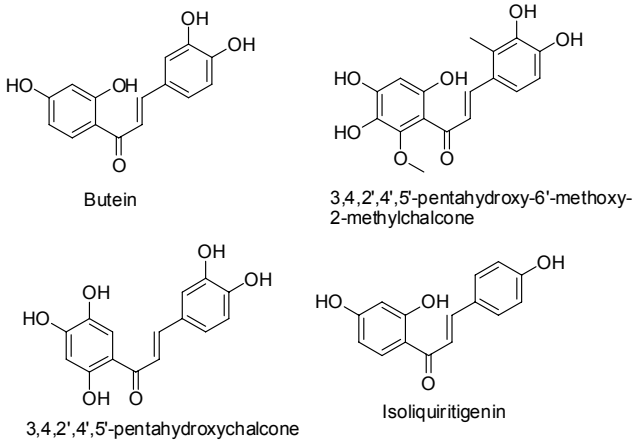

Figure 1 Structures of the chalcones in *Vernonia anthelmintica* Wild.

A few agonist of tyrosinase have been reported. Currently, only four derivatives of carbazole substituted chalcone urea[21] and 4'-(phenylurenyl/thiourenyl)chalcone derivatives[22] were discovered as activator of the tyrosinase. Unfortunately, all these compounds bore a

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poor activity.

Our group has been interested in the chalcones with activator effect on tyrisinase all along.[23-26] Inspired by above results and the literature, we introduced the 1,2,3-triazole group into chalcone ring A or B to improve the activity. 1, 4-Linked triazoles possess a high dipole moment and the nitrogen atoms at the 2 and 3 positions can act as hydrogenbond acceptors.[27,28] Thus, a new series compounds of (*E*)-1-(4-((1-benzyl-1*H*-1,2,3-triazole-4-yl)methoxy)phenylriazo)-3-phenylprop-2-en-1-one **1a**—**15a** and (*E*)-3-(4-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1-phenylprop-2-en-1-one **1b**—**15b** were synthesized and the effects of them on tyrosinase have been evaluated in this letter.

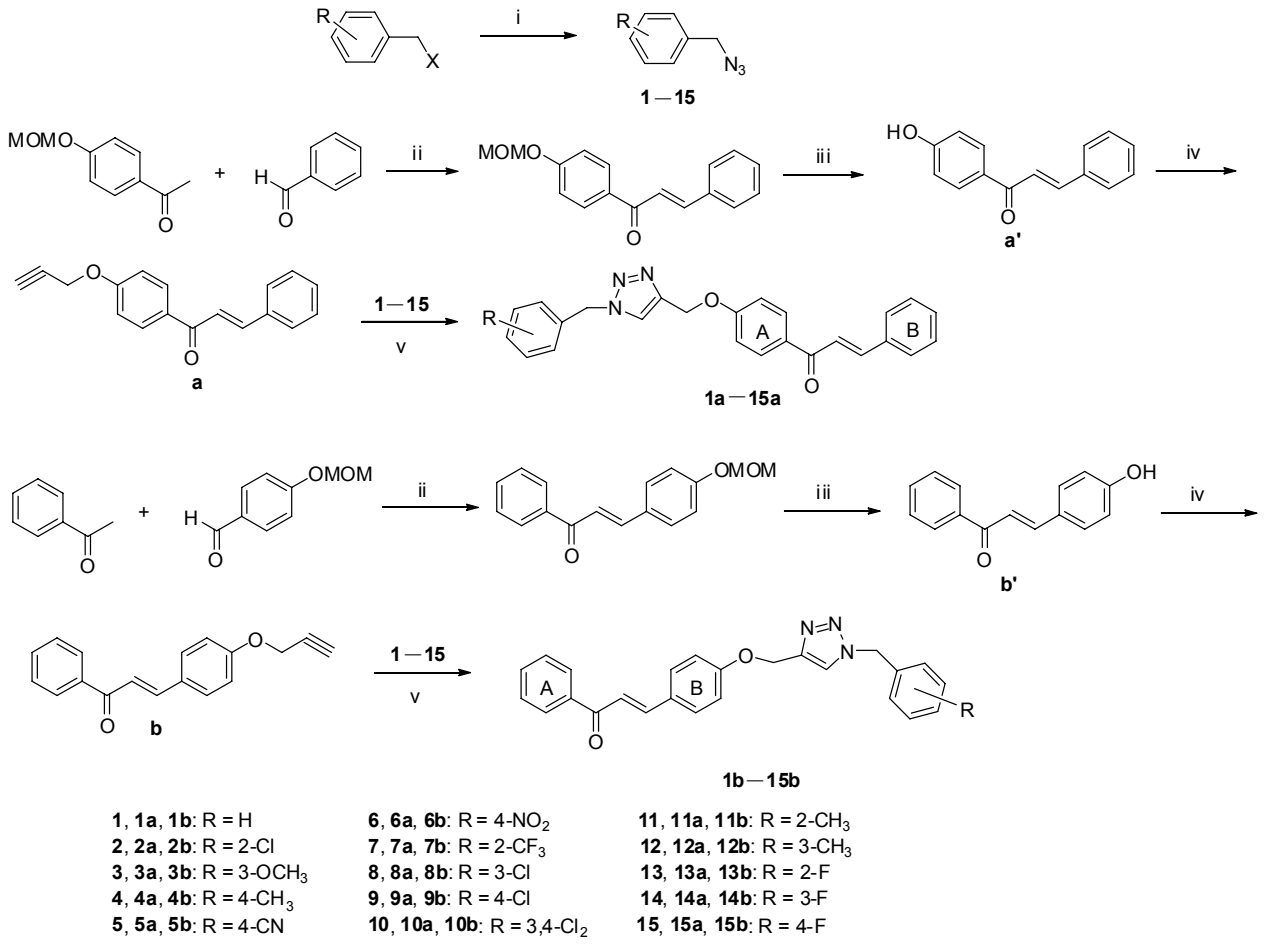
The synthetic route of compounds **1**—**15**, **1a**—**15a** and **1b**—**15b** is outlined in Scheme 1. Compounds **1**—**15** were obtained from substituted benzyl chloride or benzyl bromide in DMSO with the presence of NaN_3.[29] The 1,2,3-triazole **1a**—**15a**, **1b**—**15b** were prepared in a four-steps synthetic pathway based on click chemistry.[30,31] The hydroxyl-substituted chalcones were prepared through the Claisen-Schmidt condensation of the corresponding acetopheones and benzaldehydes with NaOH as base, followed by deprotection with HCl in ethanol.[32,33] After that, **a'** or **b'** was treated with propargyl bromide to afford **a** or **b** according to the known procedure,[34] which in the last step reacted with compounds **1**—**15**, catalyzed by $CuSO_4$/Na-Ascorbate to yield the desired compounds.

Experimental

General

Reagents and solvents were purchased from Sigma, Sodipro or VMR, and used without further purification. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co., 200—300 mesh). Melting points were determined on a Buchi B-540 apparatus and uncorrected. All the NMR spectra were recorded with a Bruker AVANCE II 400 MHz spectrometer in $CDCl_3$, using TMS as an internal standard. High-resolution mass spectra (HRMS) were recorded on AB SCIEX QSTAR Elite quadrupole

Scheme 1 Synthesis of **1a**—**15a** and **1b**—**15b**



1, **1a**, **1b**: R = H	**6**, **6a**, **6b**: R = 4-NO_2	**11**, **11a**, **11b**: R = 2-CH_3
2, **2a**, **2b**: R = 2-Cl	**7**, **7a**, **7b**: R = 2-CF_3	**12**, **12a**, **12b**: R = 3-CH_3
3, **3a**, **3b**: R = 3-OCH_3	**8**, **8a**, **8b**: R = 3-Cl	**13**, **13a**, **13b**: R = 2-F
4, **4a**, **4b**: R = 4-CH_3	**9**, **9a**, **9b**: R = 4-Cl	**14**, **14a**, **14b**: R = 3-F
5, **5a**, **5b**: R = 4-CN	**10**, **10a**, **10b**: R = 3,4-Cl_2	**15**, **15a**, **15b**: R = 4-F

Regents and condition: (i) NaN_3, DMSO, r.t.; (ii) 10% NaOH, ethanol, r.t.; (iii) 3 mol•L^{-1} HCl, ethanol, r.t.; (iv) propargyl bromide, K_2CO_3, DMF, r.t.; (v) $CuSO_4$/Na-Ascorbate, DCM/H_2O, r.t.

time-of-flight mass spectrometry. The IR data were recorded on a Thermo Fisher Scientific Nilolet 6700 FT-IR infrared spectrometer (KBr).

Synthesis of compounds 1—15

Benzyl chloride or benzyl bromide (5 mmol) and NaN_3 (6 mmol) were dissolved in 10 mL DMSO, the solution was stirred over night at room temperature until the raw materials consumed, the mixture was extracted with diethyl ether for three times, and washed with water. The organic phase was dried with $MgSO_4$, filtered, and evaporated to afford the compounds **1**—**15**.

(Azidomethyl)benzene (**1**): yield 79%, colourless oil; IR (KBr) *v*: 2089 cm^{-1}.

1-(Azidomethyl)-2-chlorobenzene (**2**): yield 83%, colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45—7.38 (m, 2H, aryl-H), 7.33—7.27 (m, 2H, aryl-H), 4.50 (s, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 133.88, 133.42, 130.12, 129.88, 129.74, 127.26, 52.38; IR (KBr) *v*: 2100 cm^{-1}.

1-(Azidomethyl)-3-methoxybenzene (**3**): yield 82%, colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30 (t, J=7.8 Hz, 1H), 6.95—6.84 (m, 3H), 4.32 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.05, 136.98, 129.98, 120.50, 113.94 113.75, 55.36, 54.85; IR (KBr) *v*: 2092 cm^{-1}.

1-(Azidomethyl)-4-methylbenzene (**4**): yield 80%, colourless oil; IR (KBr) *v*: 2080 cm^{-1}.

1-(Azidomethyl)-4-cyanobenzene (**5**): yield 86%, colourless oil; IR (KBr) *v*: 2096 cm^{-1}.

1-(Azidomethyl)-4-nitrobenzene (**6**): yield 90%, red solid; IR (KBr) *v*: 2100 cm^{-1}.

1-(Azidomethyl)-2-trifluoromethylbenzene (**7**): yield 85%, colourless oil; IR (KBr) *v*: 2105 cm^{-1}.

1-(Azidomethyl)-3-chlorobenzene (**8**): yield 76%, colourless oil; IR (KBr) *v*: 2100 cm^{-1}.

1-(Azidomethyl)-4-chlorobenzene (**9**): yield 80%, colourless oil; IR (KBr) *v*: 2085 cm^{-1}.

1-(Azidomethyl)-3,4-dichlorobenzene (**10**): yield 85%, colourless oil; IR (KBr) *v*: 2090 cm^{-1}.

1-(Azidomethyl)-4-chlorobenzene (**11**): yield 80%, colourless oil; IR (KBr) *v*: 2085 cm^{-1}.

1-(Azidomethyl)-3-methylbenzene (**12**): yield 82%, colourless oil; IR (KBr) *v*: 2091 cm^{-1}.

1-(Azidomethyl)-2-fluorobenzene (**13**): yield 75%, colourless oil; IR (KBr) *v*: 2095 cm^{-1}.

1-(Azidomethyl)-2-fluorobenzene (**14**): yield 78%, colourless oil; IR (KBr) *v*: 2100 cm^{-1}.

1-(Azidomethyl)-4-fluorobenzene (**15**): yield 74%, colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34—7.27 (m, 2H, aryl-H), 7.11—7.04 (m, 2H, aryl-H), 4.32 (s, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.00, 161.54, 131.34, 130.12, 115.89, 54.16; IR (KBr) *v*: 2093 cm^{-1}.

Synthesis of compounds a or b

4'-Hydroxychalcone or 4-hydroxychalcone (**a'** or **b'**, 0.224 g, 1 mmol), propargyl bromide (0.214 mL, 2.4 mmol) and K_2CO_3 (0.69 g, 5 mmol) were dissolved in 20 mL of DMF. This solution was stirred for 2 h at room temperature, the progress of the reaction was monitored by TLC. When the reaction was complete, 100 mL of water was poured into the solution, the reaction mixture was extracted with $CHCl_3$ for three times. The organic layer was separated and washed with distilled water and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure, and the residue was purified by a silica gel column eluted with petroleum ether/ethyl acetate (V∶V=25∶1) to give the desired compounds **a** or **b**.

4'-Propargyloxy chalcone (**a**): yield 81%; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J=8.7 Hz, 2H), 7.81 (d, J=15.7 Hz, 1H), 7.70—7.61 (m, 2H), 7.54 (d, J=15.7 Hz, 1H), 7.41 (d, J=4.2 Hz, 3H), 7.07 (d, J=8.7 Hz, 2H), 4.78 (d, J=2.4 Hz, 2H), 2.57 (t, J=2.4 Hz, 1H).

4-Propargyloxy chalcone (**b**): yield 85%; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.4 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.60 (d, J=8.7 Hz, 2H), 7.55 (d, J=7.4 Hz, 1H), 7.49 (t, J=7.5 Hz, 2H), 7.42 (d, J=15.7 Hz, 1H), 7.01 (d, J=8.7 Hz, 2H), 4.73 (d, J=2.4 Hz 2H), 2.55 (t, J=2.4 Hz, 1H).

Synthesis of compounds 1a—15a or 1b—15b

a or **b** (0.262 g, 1 mmol) and azide **1**—**15** (1 mmol) were dissolved in 20 mL of dry DCM. When the solid was dissolved completely, the solutions of anhydrous $CuSO_4$ (0.08 g, 0.5 mmol) and Vc-Na (0.5 g, 2.5 mmol) in water were added separately. The solution was stirred for 48 h. After the reaction was completed, 50 mL of water was added and extracted with DCM for three times. The combined organic phase was dried with $MgSO_4$, filtered, and evaporated to a residue that was purified by a silica gel column eluted with petroleum ether/ethyl acetate (V∶V , 3∶1—1∶1) to give the final compounds **1a—15a** or **1b—15b**.

1-(4-((1-Benzyl-*1H*-1,2,3-triazol-4-yl)methoxy)-phenyl)-3-phenyl-2-en-1-one (**1a**): white solid, yield 51%, m.p. 133—136 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=9.0 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.67—7.62 (m, 2H), 7.53 (d, J=15.6 Hz, 2H), 7.44—7.36 (m, 6H), 7.31—7.27 (m, 2H), 7.06 (d, J=9.0 Hz, 2H), 5.55 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.73, 161.94, 144.16, 143.88, 135.03, 134.30, 131.60, 130.83, 130.40, 129.22, 128.95, 128.93, 128.39, 128.18, 122.78, 121.80, 114.64, 62.14, 54.37; IR (KBr) *v*: 1653, 1596, 1335, 1218, 1180, 981 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{22}N_3O_2$ $[M+H]^+$ 396.1712, found 396.1690.

1-(4-((1-(2-Chlorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**2a**): white solid, yield 63%, m.p. 162—165 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=8.9 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.68—7.62 (m, 3H), 7.53 (d, J=15.7 Hz, 1H), 7.47—7.38 (m, 4H), 7.35—7.27 (m, 2H), 7.22 (dd, J=7.5, 1.8 Hz, 1H), 7.07 (d, J=8.9 Hz, 2H), 5.68 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.73,

161.95, 144.16, 143.82, 135.04, 133.59, 132.20, 131.61, 130.84, 130.52, 130.43, 130.41, 130.02, 128.95, 128.40, 127.69, 123.17, 121.81, 114.66, 62.14, 51.60; IR (KBr) *v*: 1651, 1594, 1336, 1219, 1173, 980 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1335.

1-(4-((1-(3-Methoxybenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**3a**): white solid, yield 54%, m.p. 135－137 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.03 (d, *J*＝8.9 Hz, 2H), 7.80 (d, *J*＝15.7 Hz, 1H), 7.61－7.67 (m, 2H), 7.57 (s, 1H), 7.53 (d, *J*＝15.7 Hz, 1H), 7.44－7.37 (m, 3H), 7.9 (t, *J*＝8.0 Hz, 1H), 7.06 (d, *J*＝8.9 Hz, 2H), 6.92－6.83 (m, 2H), 6.81－6.77 (m, 1H), 5.51 (s, 2H), 5.27 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.72, 161.94, 160.15, 144.15, 135.75, 135.03, 131.58, 130.83, 130.41, 130.29, 128.95, 128.40, 122.87, 121.79, 120.33, 114.64, 114.29, 113.79, 62.13, 55.33, 54.30; IR (KBr) *v*: 1660, 1602, 1253, 1216, 1167, 990 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_3$ $[M+H]^+$ 426.1818, found 426.1840.

1-(4-((1-(4-Methylbenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**4a**): white solid, yield 57%, m.p. 123－127 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.02 (d, *J*＝8.9 Hz, 2H), 7.79 (d, *J*＝15.7 Hz, 1H), 7.61－7.66 (m, 2H), 7.56－7.50 (m, 2H), 7.43－7.39 (m, 3H), 7.18 (s, 4H), 7.05 (d, *J*＝8.9 Hz, 2H), 5.49 (s, 2H), 5.24 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.69, 161.99, 144.12, 143.84, 138.87, 135.02, 131.54, 131.31, 130.83, 130.42, 129.85, 128.96, 128.40, 128.24, 122.87, 121.79, 114.64, 62.12, 54.15, 21.20; IR (KBr) *v*: 3057, 2920, 1653, 1599, 1251, 1220, 1171, 1049, 995 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1886.

1-(4-((1-(4-Cyanobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**5a**): white solid, yield 61%, m.p. 153－155 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.01 (d, *J*＝8.9 Hz, 2H), 7.77 (d, *J*＝15.7 Hz, 1H), 7.68－7.58 (m, 5H), 7.51 (d, *J*＝15.7 Hz, 1H), 7.42－7.37 (m, 3H), 7.34 (d, *J*＝8.4 Hz, 2H), 7.04 (d, *J*＝8.9 Hz, 2H), 5.60 (s, 2H), 5.26 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.66, 161.85, 144.31, 144.23, 139.61, 134.93, 132.93, 131.64, 130.84, 130.49, 128.98, 128.48, 128.41, 123.17, 121.70, 118.13, 114.61, 112.84, 62.01, 53.51; IR (KBr) *v*: 3044, 2231, 1651, 1602, 1166, 994 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}N_4O_2$ $[M+H]^+$ 421.1665, found 421.1651.

1-(4-((1-(4-Nitrobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**6a**): light yellow solid, yield 50%, m.p. 159－162 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (d, *J*＝8.8 Hz, 2H), 8.02 (d, *J*＝8.9 Hz, 2H), 7.78 (d, *J*＝15.7 Hz, 1H), 7.68 (s, 1H), 7.65－7.59 (m, 2H), 7.52 (d, *J*＝15.7 Hz, 1H), 7.44－7.37 (m, 5H), 7.05 (d, *J*＝8.9 Hz, 2H), 5.66 (s, 2H), 5.29 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 190.52, 160.07, 148.13, 144.36, 141.42, 138.38, 132.68, 130.27, 128.67, 128.62, 128.43, 128.27, 124.37, 120.20, 115.19, 62.00, 53.26; IR (KBr) *v*: 3082, 2922, 1647, 1457, 1334, 978 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}N_4O_4$ $[M+H]^+$ 441.1563, found 441.1555.

1-(4-((1-(2-Trifluoromethylbenzyl)-*1H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3-phenyl-2-en-1-one (**7a**): white solid, yield 52%, m.p. 126－130 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.02 (d, *J*＝8.9 Hz, 2H), 7.79 (d, *J*＝15.7 Hz, 1H), 7.73 (d, *J*＝7.6 Hz, 1H), 7.62－7.65 (m, 2H), 7.60 (s, 1H), 7.57－7.43 (m, 3H), 7.43－7.39 (m, 3H), 7.22 (d, *J*＝7.7 Hz, 1H), 7.06 (d, *J*＝8.9 Hz, 2H), 5.76 (s, 2H), 5.29 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.80, 161.90, 144.23, 135.00, 132.80, 131.62, 130.85, 130.43, 130.28, 128.95, 128.92, 128.40, 128.19, 127.89, 126.29 (q, *J*＝5.6 Hz), 125.45, 123.31, 121.77, 114.64, 62.07, 50.84; IR (KBr) *v*: 1651, 1590, 1314, 1107, 989 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}F_3N_3O_2$ $[M+H]^+$ 464.1586, found 464.1572.

1-(4-((1-(3-Chlorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**8a**): white solid, yield 49%, m.p. 130－133 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.03 (d, *J*＝9.0 Hz, 2H), 7.80 (d, *J*＝15.7 Hz, 1H), 7.61－7.67 (m, 2H), 7.59 (s, 1H), 7.53 (d, *J*＝15.7 Hz, 1H), 7.44－7.39 (m, 3H), 7.35－7.26 (m, 3H), 7.16 (dt, *J*＝6.8, 1.7 Hz, 1H), 7.07 (d, *J*＝9.0 Hz, 2H), 5.53－5.51 (m, 2H), 5.31－5.27 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.72, 161.89, 144.18, 136.28, 135.11, 135.02, 131.65, 130.84, 130.51, 130.41, 129.14, 128.95, 128.39, 128.17, 126.16, 122.81, 121.79, 114.64, 62.12, 53.61; IR (KBr) *v*: 3158, 1658, 1603, 1336, 1215, 1165, 975 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1335.

1-(4-((1-(4-Chlorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**9a**): white solid, yield 60%, m.p. 153－155 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.03 (d, *J*＝8.9 Hz, 2H), 7.80 (d, *J*＝15.7 Hz, 1H), 7.67－7.60 (m, 2H), 7.58－7.50 (m, 2H), 7.38－7.45 (m, 3H), 7.35 (d, *J*＝8.5 Hz, 2H), 7.22 (d, *J*＝8.6 Hz, 2H), 7.06 (d, *J*＝8.9 Hz, 2H), 5.51 (s, 2H), 5.27 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.71, 161.90, 144.19, 144.10, 135.01, 132.83, 131.64, 130.84, 130.42, 129.48, 129.43, 128.96, 128.40, 122.71, 121.77, 114.62, 62.10, 53.59; IR (KBr) *v*: 1656, 1601, 1337, 1219, 1174, 986 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1343.

1-(4-((1-(3,4-Dichlorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**10a**): light yellow solid, yield 64%, m.p. 138－140 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.03 (d, *J*＝8.8 Hz, 2H), 7.80 (d, *J*＝15.7 Hz, 1H), 7.61－7.66 (m, 2H), 7.60 (s, 1H), 7.53 (d, *J*＝15.7 Hz, 1H), 7.35－7.48 (m, 5H), 7.11 (dd, *J*＝8.2, 2.0 Hz, 1H), 7.06 (d, *J*＝8.8 Hz, 2H), 5.50 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.70, 161.85, 144.32, 144.21, 135.00, 134.47, 133.42, 133.34, 131.67, 131.22, 130.85, 130.44, 129.98, 128.96, 128.40, 127.27, 122.81, 121.76, 114.62, 62.08, 53.02; IR (KBr) *v*: 2360, 2342, 1648, 1588, 1336, 1218, 1033, 975 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}Cl_2N_3O_2$ $[M+H]^+$ 464.0933, found 464.0937.

1-(4-((1-(2-Methylbenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**11a**): white

solid, yield 68%, m.p. 117—120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=8.9 Hz, 2H), 7.79 (d, J=15.7 Hz, 1H), 7.66—7.59 (m, 2H), 7.52 (d, J=15.7 Hz, 1H), 7.45 (s, 1H), 7.43—7.38 (m, 3H), 7.32—7.14 (m, 4H), 7.05 (d, J=8.9 Hz, 2H), 5.54 (s, 2H), 5.24 (s, 2H), 2.27 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.70, 161.97, 144.13, 136.98, 135.02, 132.26, 131.54, 131.12 130.83, 130.42, 129.51, 129.30, 128.96, 128.40, 126.74, 122.76, 121.78, 114.65, 62.13, 52.52, 21.93; IR (KBr) v: 3141, 2923, 2360, 2342, 1652, 1596, 1381, 1217, 980 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1876.

1-(4-((1-(3-Methylbenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**12a**): white solid, yield 50%, m.p. 123—126 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J=8.9 Hz, 2H), 7.79 (d, J=15.7 Hz, 1H), 7.65—7.59 (m, 2H), 7.57 (s, 1H), 7.53 (d, J=15.7 Hz, 1H), 7.42—7.37 (m, 3H), 7.25 (t, J=7.5 Hz, 1H), 7.16 (d, J=7.5 Hz, 1H), 7.10—7.02 (m, 4H), 5.48 (s, 2H), 5.25 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.64, 162.00, 144.09, 143.81, 139.03, 135.01, 134.31, 131.52, 130.83, 130.43, 129.62, 129.06, 128.96, 128.88, 128.41, 125.23, 122.98, 121.78, 114.65, 62.12, 54.30, 21.35; IR (KBr) v: 2360, 1654, 1596, 1335, 1217, 1174, 1047, 972 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1853.

1-(4-((1-(2-Fluorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**13a**): white solid, yield 55%, m.p. 127—130 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=9.0 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.68—7.61 (m, 3H), 7.53 (d, J=15.7 Hz, 1H), 7.45—7.39 (m, 3H), 7.39—7.34 (m, 1H), 7.30 (td, J=7.5, 1.5 Hz, 1H), 7.19—7.10 (m, 2H), 7.07 (d, J=9.0 Hz, 2H), 5.60 (s, 2H), 5.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.73, 161.95, 159.36, 144.15, 135.04, 131.60, 131.11 (d, J=8.3 Hz), 130.84, 130.71 (d, J=3.1 Hz), 130.40, 128.95, 128.39, 124.93 (d, J=3.7 Hz), 123.01, 121.81, 121.60, 116.03, 115.82, 114.64, 62.11, 47.90; IR (KBr) v: 1652, 1596, 1493, 1219, 1172, 997 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1625.

1-(4-((1-(3-Fluorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**14a**): white solid, yield 52%, m.p. 131—133 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=9.0 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.66—7.61 (m, 2H), 7.58 (s, 1H), 7.53 (d, J=15.7 Hz, 1H), 7.44—7.39 (m, 3H), 7.32—7.39 (m, 1H), 7.10—7.03 (m, 4H), 6.99—6.94 (m, 1H), 5.54 (s, 2H), 5.29 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.73, 164.27, 161.89, 144.18, 136.70 (d, J=7.4 Hz), 135.03, 131.65, 130.92, 130.84, 130.41, 128.95, 128.40, 123.62 (d, J=3.1 Hz), 122.82, 121.78, 116.07, 115.86, 115.20, 114.98, 114.64, 62.13, 53.68; IR (KBr) v: 1655, 1593, 1334, 1253, 1170, 997 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1605.

1-(4-((1-(4-Fluorobenzyl)-*1H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-3-phenyl-2-en-1-one (**15a**): white solid, yield 65%, m.p. 128—132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=8.9 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.63 (t, J=6.5 Hz, 2H), 7.49—7.56 (m, 2H), 7.44—7.38 (m, 3H), 7.31—7.26 (m, 2H), 7.11—7.03 (m, 4H), 5.52 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 188.72, 164.18, 161.91, 144.20, 144.04, 135.02, 131.63, 130.84, 130.42, 130.20 (d, J=3.3 Hz), 130.11, 130.03, 128.96, 128.40, 122.62, 121.77, 116.36, 116.14, 114.62, 62.13, 53.60; IR (KBr) v: 1651, 1602, 1509, 1220, 1169, 1034, 976 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1613.

3-(4-((1-Benzyl-*1H*-1,2,3-triazol-4-yl)methoxy)-phenyl)-1-phenyl-2-en-1-one (**1b**): white solid, yield 57%, m.p. 132—134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=8.2 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.55—7.62 (m, 3H), 7.54 (s, 1H), 7.50 (t, J=7.4 Hz, 2H), 7.45—7.35 (m, 4H), 7.30—7.27 (m, 2H), 7.01 (d, J=8.8 Hz, 2H), 5.54 (s, 2H), 5.23 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.57, 160.21, 144.50, 144.08, 138.45, 134.36, 132.63, 130.25, 129.21, 128.91, 128.60, 128.44, 128.17, 122.73, 120.11, 115.23, 62.12, 54.34; IR (KBr) v: 1630, 1507, 1220, 1172, 980 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{22}N_3O_2$ $[M+H]^+$ 396.1712, found 396.1719.

3-(4-((1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**2b**): white solid, yield 60%, m.p. 118—120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=7.1 Hz, 2H), 7.77 (d, J=15.6 Hz, 1H), 7.65 (s, 1H), 7.62—7.55 (m, 3H), 7.50 (t, J=7.6 Hz, 2H), 7.38—7.47 (m, 2H), 7.33 (td, J=7.6, 1.8 Hz, 1H), 7.28 (dd, J=7.6, 1.2 Hz, 1H), 7.22 (dd, J=7.6, 1.8 Hz, 1H), 7.03 (d, J=8.7 Hz, 2H), 5.68 (s, 2H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.54, 160.23, 144.45, 144.02, 138.52, 133.59, 132.57, 132.28, 130.48, 130.38, 130.21, 130.01, 128.58, 128.43, 128.26, 127.66, 123.02, 120.24, 115.32, 62.19, 51.56; IR (KBr) v: 1655, 1598, 1447, 1216, 1047, 972 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1339.

3-(4-((1-(3-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**3b**): white solid, yield 63%, m.p. 116—119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.3 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.63—7.53 (m, 4H), 7.49 (t, J=7.4 Hz, 2H), 7.41 (d, J=15.7 Hz, 1H), 7.29 (t, J=7.9 Hz, 1H), 7.01 (d, J=8.6 Hz, 2H), 6.93—6.82 (m, 2H), 6.79 (s, 1H), 5.50 (s, 2H), 5.23 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.53, 160.20, 160.14, 144.47, 144.05, 138.44, 135.79, 132.60, 130.25, 130.21, 128.57, 128.41, 128.14, 122.73, 120.29, 120.11, 115.23, 114.26, 113.76, 62.12, 55.31, 54.24; IR (KBr) v: 2360, 1586, 1508, 1251, 1053, 986 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_3$ $[M+H]^+$ 426.1818, found 426.1827.

3-(4-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**4b**): white solid, yield 65%, m.p. 166—168 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.62—7.55 (m, 3H), 7.54—7.47 (m, 3H), 7.41 (d, J=15.7 Hz, 1H), 7.18 (s, 4H), 7.01 (d, J=8.8 Hz, 2H), 5.50 (s, 2H), 5.22 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (101

MHz, $CDCl_3$) δ: 190.56, 160.21, 144.50, 143.91, 138.89, 138.44, 132.62, 131.27, 130.23, 129.85, 128.59, 128.43, 128.23, 128.14, 122.63, 120.09, 115.22, 62.09, 54.17, 21.18; IR (KBr) *v*: 1646, 1561, 1508, 1253, 1174, 996 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1868.

3-(4-((1-(4-Cyanobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**5b**): white solid, yield 53%, m.p. 146－150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.76 (d, J=15.7 Hz, 1H), 7.67 (d, J=8.5 Hz, 2H), 7.64－7.54 (m, 4H), 7.49 (t, J=7.4 Hz, 2H), 7.42 (d, J=15.7 Hz, 1H), 7.35 (d, J=8.6 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 5.61 (s, 2H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.52, 160.09, 144.37, 139.57, 138.39, 132.95, 132.68, 130.27, 128.62, 128.47, 128.43, 128.27, 123.01, 120.20, 118.09, 115.18, 112.92, 62.01, 53.53; IR (KBr) *v*: 2238, 1646, 1560, 1507, 1252, 1173, 995 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}N_4O_2$ $[M+H]^+$ 421.1665, found 421.1658.

3-(4-((1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**6b**): light yellow solid, yield 48%, m.p. 148－150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, J=8.8 Hz, 2H), 8.00 (d, J=7.0 Hz, 2H), 7.76 (d, J=15.7 Hz, 1H), 7.66 (s, 1H), 7.62－7.53 (m, 3H), 7.49 (t, J=7.4 Hz, 2H), 7.38－7.45 (m, 3H), 7.01 (d, J=8.8 Hz, 2H), 5.66 (s, 2H), 5.26 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.52, 160.07, 148.13, 144.36, 141.39, 138.35, 132.68, 130.27, 128.67, 128.62, 128.43, 128.27, 124.37, 120.20, 115.19, 62.00, 53.26; IR (KBr) *v*: 1655, 1592, 1510, 1252, 1174, 986 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}N_4O_4$ $[M+H]^+$ 441.1563, found 441.1584.

3-(4-((1-(2-Trifluoromethylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-1-phenyl-2-en-1-one (**7b**): white solid, yield 50%, m.p. 122－124 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.73 (d, J=7.5 Hz, 1H), 7.63－7.45 (m, 8H), 7.42 (d, J=15.6 Hz, 1H), 7.22 (d, J=7.7 Hz, 1H), 7.02 (d, J=8.8 Hz, 2H), 5.75 (s, 2H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.54 (s), 160.16, 144.47, 138.43, 132.89 (d, J=1.5 Hz), 132.78 (d, J=0.9 Hz), 132.64, 130.25, 128.89, 128.60, 128.44, 128.21, 126.27 (q, J=5.6 Hz), 125.45, 123.33, 122.73, 120.13, 115.24, 62.05, 50.29; IR (KBr) *v*: 1654, 1590, 1314, 1098, 993 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{21}F_3N_3O_2$ $[M+H]^+$ 464.1586, found 464.1592.

3-(4-((1-(3-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**8b**): white solid, yield 57%, m.p. 142－145 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J=7.0 Hz, 2H), 7.80 (d, J=15.7 Hz, 1H), 7.65－7.57 (m, 4H), 7.52 (t, J=7.4 Hz, 2H), 7.44 (d, J=15.6 Hz, 1H), 7.37－7.28 (m, 3H), 7.18 (dt, J=6.9, 1.7 Hz, 1H), 7.04 (d, J=8.8 Hz, 2H), 5.54 (s, 2H), 5.28 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.14, 144.46, 144.36, 138.44, 136.30, 135.11, 132.64, 130.50, 130.25, 129.13, 128.60, 128.44, 128.23, 128.16, 126.15, 122.76, 120.16, 115.23, 62.10, 53.60; IR (KBr) *v*: 2988, 1586, 1509, 1336, 1222, 1176, 1003, 984 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1318.

3-(4-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**9b**): white solid, yield 61%, m.p. 132－135 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.62－7.54 (m, 4H), 7.50 (t, J=6.6 Hz, 2H), 7.42 (d, J=15.6 Hz, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.22 (d, J=8.5 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 5.51 (s, 2H), 5.24 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.15, 144.45, 144.30, 138.43, 135.00, 132.84, 132.64, 130.25, 129.47, 129.43, 128.60, 128.44, 128.22, 122.68, 120.17, 115.22 62.06, 53.60; IR (KBr) *v*: 1587, 1561, 1253, 1174, 995 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}ClN_3O_2$ $[M+H]^+$ 430.1322, found 430.1235.

3-(4-((1-(3,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**10b**): light yellow solid, yield 66%, m.p. 120－123 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=8.5 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.63－7.55 (m, 4H), 7.50 (t, J=7.4 Hz, 2H), 7.47－7.35 (m, 3H), 7.11 (dd, J=8.2, 2.1 Hz, 1H), 7.01 (d, J=8.8 Hz, 2H), 5.50 (s, 2H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.11, 144.43, 144.39, 138.45, 134.49, 133.43, 133.33, 132.62, 131.20, 130.23, 129.96, 128.59, 128.43, 128.29, 127.24, 122.74, 120.25, 115.24, 62.08, 53.01; IR (KBr) *v*: 2923, 1656, 1593, 1248, 1175, 1106, 986 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{20}Cl_2N_3O_2$ $[M+H]^+$ 464.0933, found 464.0942.

3-(4-((1-(2-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**11b**): white solid, yield 52%, m.p. 116－119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.61－7.54 (m, 3H), 7.49 (t, J=7.4 Hz, 2H), 7.45－7.37 (m, 2H), 7.33－7.14 (m, 4H), 7.00 (d, J=8.8 Hz, 2H), 5.55 (s, 2H), 5.22 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.58, 160.21, 144.52, 143.83, 138.44, 136.99, 132.64, 132.26, 131.12, 130.24, 129.51, 129.29, 128.60, 128.44, 128.14, 126.73, 122.63, 120.09, 115.25, 62.10, 52.51, 19.00; IR (KBr) *v*: 3144, 2922, 1654, 1599, 1216, 1046, 974 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1860.

3-(4-((1-(3-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**12b**): white solid, yield 55%, m.p. 132－134 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.61－7.55 (m, 3H), 7.54 (s, 1H), 7.50 (t, J=7.4 Hz, 2H), 7.41 (d, J=15.6 Hz, 1H), 7.27 (t, J=7.9 Hz, 1H), 7.17 (d, J=7.8 Hz, 1H), 7.11－7.05 (m, 2H), 7.01 (d, J=8.8 Hz, 2H), 5.49 (s, 2H), 5.23 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.23, 144.50, 144.01, 139.07, 138.45, 134.28, 132.63, 130.24, 129.63, 129.06, 128.88, 128.60, 128.44, 128.14, 125.23, 122.75, 120.10, 115.24, 62.13, 54.33, 21.35; IR (KBr) *v*: 2360, 1659, 1591, 1512, 1253, 1215, 1015, 988 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M+H]^+$ 410.1869, found 410.1856.

3-(4-((1-(2-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**13b**): white solid, yield 50%, m.p. 116—120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.65 (s, 1H), 7.62—7.54 (m, 3H), 7.50 (t, J=7.4 Hz, 2H), 7.41 (d, J=15.7 Hz, 1H), 7.38—7.33 (m, 1H), 7.29 (td, J=7.5, 1.6 Hz, 1H), 7.18—7.09 (m, 2H), 7.02 (d, J=8.8 Hz, 2H), 5.60 (s, 2H), 5.23 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.21, 144.50, 144.06, 138.45, 132.63, 131.09 (d, J=8.3 Hz), 130.70 (d, J=3.1 Hz), 130.25, 128.60, 128.44, 128.17, 124.92 (d, J=3.7 Hz), 122.97, 121.77, 121.62, 120.12, 116.02, 115.81, 115.23, 62.07, 47.83; IR (KBr) v: 2360, 1591, 1571, 1253, 1217, 1004 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1607.

3-(4-((1-(3-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**14b**): white solid, yield 56%, m.p. 127—129 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.62—7.55 (m, 4H), 7.50 (t, J=7.4 Hz, 2H), 7.41 (d, J=15.7 Hz, 1H), 7.39—7.32 (m, 1H), 7.09—6.99 (m, 4H), 6.99—6.94 (m, 1H), 5.54 (s, 2H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.15, 144.46, 144.33, 138.44, 136.74 (d, J=7.4 Hz), 132.64, 130.87 (d, J=8.3 Hz), 130.25, 128.60, 128.44, 128.22, 123.61 (d, J=3.0 Hz), 122.78, 120.16, 116.05, 115.84, 115.23, 114.97, 62.10, 53.64; IR (KBr) v: 1589, 1509, 1250, 1175, 986 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1622.

3-(4-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)phenyl)-1-phenyl-2-en-1-one (**15b**): white solid, yield 60%, m.p. 134—136 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.0 Hz, 2H), 7.77 (d, J=15.7 Hz, 1H), 7.62—7.55 (m, 3H), 7.54 (s, 1H), 7.50 (t, J=7.4 Hz, 2H), 7.41 (d, J=15.7 Hz, 1H), 7.30—7.26 (m, 2H), 7.07 (t, J=8.6 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 5.51 (s, 2H), 5.23 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.56, 160.17, 144.46, 144.22, 138.43, 132.65, 130.25, 130.10, 130.02, 128.61, 128.44, 128.20, 122.61, 120.15, 116.34, 116.12, 115.21, 62.08, 53.58; IR (KBr) v: 2350, 1593, 1508, 1213, 1175, 1017, 987 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{21}FN_3O_2$ $[M+H]^+$ 414.1618, found 414.1505.

Biological assay (Activity on tyrosinase)

Potassium phosphate buffer (0.06 mL, 50 mmol•L^{-1}) at pH 6.5, 0.04 mL tyrosinase (250 U/mL) and 2 μL of the test compounds (0.5—300 μmol•L^{-1}), dissolved in DMSO were inserted into 96-well plates. After 5 min incubation at 25—30 ℃, 0.1 mL of *L*-tyrosine (2 mmol•L^{-1}) was added and incubated for additional 30 min. The optical density of the samples at 490 nm was measured relative to control containing DMSO (2 μL) and without inhibitor. The activity was expressed as the sample concentration that gave a 50% effect in the enzyme activity (EC_{50}).

Results and Discussion

Synthesis and structure

Dichloromethane (DCM) and *tert*-butyl alcohol (TBA) were often used as solvent in click chemistry. TBA was initially used in the preparation of compounds **1a**—**15a** and **1b**—**15b**, however, no product was obtained after 48 h. So we tried to use DCM as the solvent instead of TBA, the result was satisfactory. Click chemistry just finished in 2 h and there was no other by-product.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS (ESI). The aryl azides **1**—**15** were all identified by IR.

As showed in the Figure 2, the single crystals of the compounds **8a**, **10a** and **15a** (CCDC No. 1043285, 1043286 and 1043287) used for X-ray diffraction

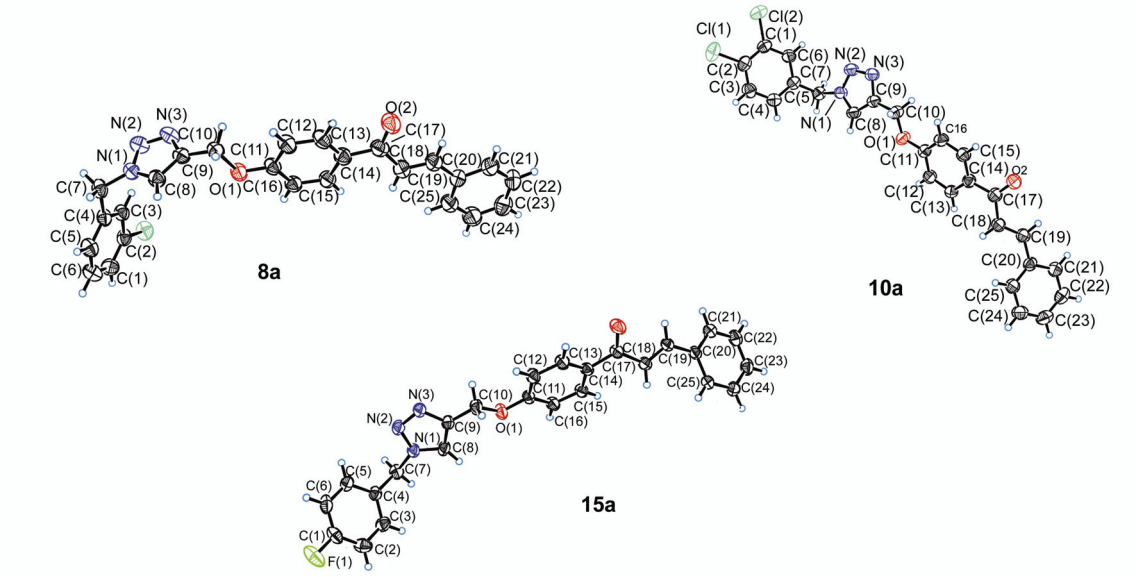


Figure 2 The crystal structures of the compounds **8a**, **10a** and **15a**.

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analysis were obtained by slow evaporation of acetone-ethanol (V ∶ V = 1 ∶ 3) mixed solution at room temperature.

Structure-activity relationship

The activities on tyrosinase of synthesized compounds **1a**—**15a**, **1b**—**15b** were performed according to a modified method,[35] with 8-MOP[36-39] and Kojic acid[40] as positive control drug. The effects of the compounds are summarized in Table 1 and Table 2.

Table 1 Activator effect on tyrosinase of compounds **1a**—**15a**

Compd.	Substrate	R	EC_{50}[a]/(μmol•L^{-1})
1a	*L*-tyrosine	H	＞100
2a	*L*-tyrosine	2-Cl	68.15±3.73
3a	*L*-tyrosine	3-OCH_3	37.42±2.18
4a	*L*-tyrosine	4-CH_3	＞100
5a	*L*-tyrosine	4-CN	＞100
6a	*L*-tyrosine	4-NO_2	95.51±4.64
7a	*L*-tyrosine	2-CF_3	75.08±4.87
8a	*L*-tyrosine	3-Cl	11.90±0.93
9a	*L*-tyrosine	4-Cl	23.85±2.63
10a	*L*-tyrosine	3,4-Cl_2	1.71±0.23
11a	*L*-tyrosine	2-CH_3	＞100
12a	*L*-tyrosine	3-CH_3	42.74±3.22
13a	*L*-tyrosine	2-F	62.65±4.36
14a	*L*-tyrosine	3-F	5.60±0.47
15a	*L*-tyrosine	4-F	14.56±1.38
8-MOP	*L*-tyrosine	—	14.8±1.50

[a] 50% effective concentration, results are the mean±SD from three independent experiments.

Table 2 Inbibitory effect on tyrosinase of compounds **1b**—**15b**

Compd.	Substrate	R	IC_{50}[a]/(μmol•L^{-1})
1b	*L*-tyrosine	H	＞100
2b	*L*-tyrosine	2-Cl	＞100
3b	*L*-tyrosine	3-OCH_3	85.76±3.17
4b	*L*-tyrosine	4-CH_3	＞100
5b	*L*-tyrosine	4-CN	66.52±2.32
6b	*L*-tyrosine	4-NO_2	43.18±1.43
7b	*L*-tyrosine	2-CF_3	＞100
8b	*L*-tyrosine	3-Cl	＞100
9b	*L*-tyrosine	4-Cl	35.64±0.71
10b	*L*-tyrosine	3,4-Cl_2	24.10±0.52
11b	*L*-tyrosine	2-CH_3	＞100
12b	*L*-tyrosine	3-CH_3	＞100
13b	*L*-tyrosine	2-F	＞100
14b	*L*-tyrosine	3-F	＞100
15b	*L*-tyrosine	4-F	31.43±0.86
Kojic acid	*L*-tyrosine	—	10.78±0.38

[a] 50% inhibitory concentration, results are the mean±SD from three independent experiments.

As shown in Table 1, most of prepared compounds **1a**—**15a** showed good to excellent activating effect on tyrosinase. The potencies of compound **8a** (EC_{50} = 11.90 μmol•L^{-1}), **10a** (EC_{50} = 1.71 μmol•L^{-1}), **14a** (EC_{50} = 5.60 μmol•L^{-1}) and **15a** (EC_{50} = 14.56 μmol•L^{-1}) were better or comparative to the positive control 8-MOP, of which EC_{50} was 14.8 μmol•L^{-1}.

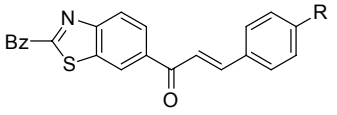
The position, number and nature of the substituent on benzene ring were varied in order to identify the most appropriate group. The compounds with halogen (X) and trifluoromethyl (CF_3) showed higher activity compared with CH_3, OCH_3 and H, which suggested that the electron-withdrawing group (EWG) may be favorable to enhance the activity. However, the activity droped rapidly when substituted with CN and NO_2, indicating that substituents with too strong electron-withdrawing ability must have no benefit to the activity.

Among these halogenated compounds **2a**, **8a**—**10a**, **14a** and **15a**, the most important factor in their efficacy was the location of the group. The shift of F substituent from the *meta* (**14a**, EC_{50} = 5.60 μmol•L^{-1}) into the *para* or *ortho* position led to **15a** (EC_{50} = 14.56 μmol•L^{-1}), which had a lower activity and **13a** (EC_{50} = 62.65 μmol•L^{-1}), which was inactive. The similar result was observed in compounds **2a**, **8a** and **9a** which were substituted with Cl group as well. It became apparent that the presence of a halogen group in the *meta* or *para* position of the phenyl ring was fundamental for activity.

The replacement of the Cl group with F contributed no enhancement to the activity. Nevertheless, the number of the halogen atom on benzene made a great influence on activity. Introduction of a second Cl to the benzene strongly increased activity. 3,4-Disubstituted compound **10a** exhibited a most promising activity than any other compounds (EC_{50} = 1.71 μmol•L^{-1}).

Compared with the benzothiazole compounds (**7b**, **7d**) in our previous research (Figure 3),[26] the active 1,2,3-triazole compounds in this work (**3a**, **8a**—**10a**, **14a**—**15a**) generally showed a better activity, which may be influenced by the preferable solubility and the characteristics of the triazole.

From the Table 2, all the compounds **1b**—**15b** slightly inhibited the tyrosinase, which was induced by the shift of the same group from A ring into the B ring of the chalcone. The result revealed that the same 1-benzyltriazol group on *para*-position of the chalcone A ring may cause a great improvement on activating effect on tyrosinase, but an inhibitor effect when it was introduced to B ring.



7a: R = H, **7b**: R = CH_3, **7c**: R = OCH_3, **7d**: R = Cl

Figure 3 The Structure of the benzothiazole compounds.

Conclusions

In summary, a new series of thirty chalcone compounds consisting of 1,2,3-triazol were synthesized. After screening, most chalcone compounds **1a**—**15a** with A ring substituent showed activating effect on tyrosinase. The position and the number of the halogen on benzene ring contributed the most to the activity. Among these compounds, **10a** (EC_{50}=1.71 μmol•L^{-1}) and **14a** (EC_{50}=5.60 μmol•L^{-1}) were discovered as the most promising agonist of the tyrosinase, and they might be developed as new leading compounds. The compounds described in this study offer a new templates for the design and future development of potent agonist of tyrosinase. Meanwhile, a slight inhibition on tyrosinase was observed when the same group was introduced to B ring. The contrary action raises an interesting point for future investigation concerning the mechanism of these compounds.

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References

[1] Whitaker, J. R. In *Food Enzymes*, *Structure and Mechanism*, Ed.: Wong, D. W. S., Chapman & Hall, New York, **1995**, pp. 271—307.
[2] Garcia-Molina, M. M.; Muñoz-Muñoz, J. L.; Garcia-Molina, F.; García-Ruiz, P. A.; Garcia-Canovas, F. *J. Agric. Food Chem.* **2012**, *60*, 6447.
[3] Ismaya, W. T.; Rozeboom, H. J.; Weijn, A.; Mes, J. J.; Fusetti, F.; Wichers, H. J.; Dijkstra, B. W. *Biochemistry* **2011**, *50*, 5477.
[4] Land, E. J.; Ramsden, C. A.; Riley, P. A. *Acc. Chem. Res.* **2003**, *36*, 300.
[5] Yao, L.; Li, Q.; Shang, J. *J. Xinjiang Med. U.* **2010**, *33*, 1191 (in Chinese).
[6] Sun, L.; Shang, J.; Li, H. J.; Wu, L. *J. Mod. Chin. Med.* **2006**, *8*, 10 (in Chinese).
[7] Zhou, J.; Shang, J.; Ping, F. F.; Zhao, G. R. *J. Ethnopharmacol.* **2012**, *143*, 639.
[8] Shang, J.; Xu, J. G.; Yu, L. H.; Sun, L.; Li, H. J. *CN 1778294A*, **2006** [*Chem. Abstr.* **2006**, *145*, 152560].
[9] Yan, M.; Huo, S. X.; Gao, L.; Peng, X. M. *CN 102526153A*, **2012** [*Chem. Abstr.* **2012**, *157*, 241762].
[10] Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N. E.; Huang, P.; Khan, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491.
[11] Fang, X. M.; Zhou, L. Z.; Cheng, Z.; Yang, M. P.; Yang, B. Q. *Chin. J. Org. Chem.* **2013**, *33*, 523 (in Chinese).
[12] FPérez-Cruz, F.; Vazquez-Rodriguez, S.; Matos, M. J.; Herrera-Morales, A.; Villamena, F. A.; Das, A.; Gopalakrishnan, B.; Olea-Azar, C.; Santana, L.; Uriarte, E. *J. Med. Chem.* **2013**, *56*, 6136.
[13] Go, M. L.; Wu, X.; Liu, X. L. *Curr. Med. Chem.* **2005**, *12*, 483.
[14] Batovska, D.; Parushev, S.; Stamboliyska, B.; Tsvetkova, I.; Ninova, M.; Najdenski, H. *Eur. J. Med. Chem.* **2009**, *44*, 2211.
[15] Lee, S. H.; Seo, G. S.; Kim, J. Y.; Jin, X. Y.; Kim, H. D.; Sohn, D. H. *Eur. J. Pharmacol.* **2006**, *532*, 178.
[16] Araico, A.; Terencio, M. C.; Alcaraz, M. J.; Dominguez, J. N.; Leon, C.; Ferrandiz, M. L. *Life Sci.* **2007**, *80*, 2108.
[17] Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtraku, S. *Bioorg. Med. Chem.* **2006**, *14*, 1710.
[18] Khatib, S.; Nerya, O.; Musa, R.; Shmuel, M.; Tamir, S.; Vaya, J. *Bioorg. Med. Chem.* **2005**, *13*, 433.
[19] Thanigaimalai, P.; Lee, K. C.; Sharma, V. K.; Rao, E. V.; Roh, E.; Kim, Y.; Jung, S. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1922.
[20] Jun, N.; Gao, H.; Jun, K. *Bioorg. Med. Chem.* **2007**, *15*, 2396.
[21] Nixhal, A. R.; Arslan, M.; Atalay, Y.; Gencer, N.; Ergun, A.; Arslan, O. *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 808.
[22] Sonmez, F.; Sevmezler, S.; Atahan, A.; Ceylan, M.; Demir, D.; Gencer, N.; Arslan, O.; Kucukislamoglu, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7479.
[23] Aisa, H. A.; Niu, C.; Li, G.; Madina, K. *CN 103360338A*, **2013** [*Chem. Abstr.* **2013**, *159*, 654134].
[24] Aisa, H. A.; Niu, C.; Li, G.; Tuerxuntayi, A.; Madina, K. *CN 103342653A*, **2013** [*Chem. Abstr.* **2013**, *159*, 608387].
[25] Aisa, H. A.; Tuerxuntayi, A.; Niu, C.; Madina, K. *CN 103613493A*, **2013** [*Chem. Abstr.* **2014**, *160*, 398878].
[26] Niu, C.; Li, G.; Madina, K.; Aisa, H. A. *Chem. J. Chin. Univ.* **2014**, *35*, 1204 (in Chinese).
[27] Aragao-Leoneti, V.; Campo, V. L.; Gomes, A. S. *Tetrahedron* **2010**, *66*, 9475.
[28] Li, L. J.; Zhang, Y. Q.; Zhang, Y.; Zhu, A. L.; Zhang, G. S. *Chin. Chem. Lett.* **2014**, *25*, 1161.
[29] Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, *4*, 413.
[30] Stefely, J. A.; Palchaudhuri, R.; Miller, P. A.; Peterson, R. J. *J. Med. Chem.* **2010**, *53*, 3389.
[31] Ciocoiu, C. C.; Nikolić, N.; Nguyen, H. H.; Thoresen, G. H. *Eur. J. Med. Chem.* **2010**, *45*, 3047.
[32] Rao, Y. K.; Fang, S. H.; Tzeng, Y. M. *Bioorg. Med. Chem.* **2009**, *17*, 7909.
[33] Bandgar, B. P.; Patil, S. A.; Korbad, B. L.; Nile, S. H.; Khobragade, C. N. *Eur. J. Med. Chem.* **2010**, *45*, 2629.
[34] Rajakumar, P.; Raja, S. *Synth. Commun.* **2009**, *39*, 3888.
[35] Soliman, K.; Ohad, N.; Ramadan, M.; Maayan, S.; Snait, T.; Jacob, V. *Bioorg. Med. Chem.* **2005**, *13*, 433.
[36] Lei, T. C.; Victoria, V.; Yasumoto, K.; Vieira, W. D.; Toyofuku, K.; Hearing, V. *J. Invest. Dermatol.* **2002**, *119*, 1341.
[37] Kao, C. H.; Yu, H. S. *J. Invest. Dermatol.* **1992**, *98*, 734.
[38] Marwan, M. M.; Jiang, J.; Marwan, M. M.; Jiang, J.; de Lauro Castrucci, A. M.; Hadley, M. E. *Pigm. Cell Res.* **1990**, *3*, 214.
[39] Pearl, E.; Grimes, M. D. *Clin. Dermatol.* **1997**, *15*, 921.
[40] Ley, J. P.; Bertram, H. J. *Bioorg. Med. Chem.* **2001**, *9*, 1879.

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