Supplementary material

1. Chemical synthesis of compounds 3a-3m and 4a-4m

All chemical reagents were obtained from Sigma-Aldrich, Fluka, and Aladdin (Beijing, People's Republic of China). Silica gel (GF254) for thin-layer chromatography and column chromatography (100-200 and 200-300mesh) were obtained from Aladdin. Melting points were tested on a Fisher-Johns melting apparatus. Electron-spray ionization mass spectra (ESI-MS) data were determined on a Bruker Esquire HCT spectrometer. The ^{1}H NMR spectra data was recorded on a 600 MHz spectrometer (Bruker Corporation, Switzerland).

All compounds were furnished by the aldol condisation of substituted aromatic aldehydes and intermediators (*E*)-4-(o-hydroxy)but-3-en-2-one (2a) or (*E*)-4-(p-chlorine)but-3-en-2-one (2b) from commercial available o-hydroxybenzaldehyde (1a) and p-chlorobenzaldehyde (1b) under base condition, respectively. The general procedure for synthesis of these compounds was described below. All reactions were monitored by the silica gel TLC. At the end of the reaction, water is added into the reaction mixture to precipitate the product. All compounds were purified by re-crystallization or column chromatography. Their structures were determined by spectral data from ESI–MS, and ^{1}H-NMR. The spectral data of new or unreported compounds are shown in supplementary materials.

Synthesis of 2a or 2b

To a solution of **1a or 1b** (10 mM) in acetone (25 mL) was added 1.2 mM NaOH dropwise, and the mixture was stirred at room temperature for overnight. The resulting solution was then neutralized with dilute hydrochloric acid to PH=6.0, filtered, and purified by chromatography over silica gel using petroleum ether/ethyl acetate as the eluent to give intermediate **2a or 2b**.

General procedure for synthesis of asymmetric MACs 3a-m and 4a-m

A solution of **2a** or **2b** (1 mM) and different benzaldehydes (1 mM) in 6 ml ethanol and 4 ml water was added 1.2 mM NaOH dropwise, and the mixture was stirred at room temperature for overnight. The resulting solution was then neutralized with dilute hydrochloric acid to PH=6.0, filtered, and

purified by chromatography over silica gel using petroleum ether/ethyl acetate as the eluent to get compounds **3a-m** or **4a-m**.

(1*E*,4*E*)-1-(2-Bromophenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3c)

Yellow powder, 95.4% yield, mp 145-147.3^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 8.11 (d, *J* = 16.0 Hz, Ar-CH=, 2H), 7.71 (d, *J* = 7.8 Hz, Ar(OH)-H^{6}, 1H), 7.64 (d, *J* = 8.0 Hz, Ar(Br)-H^{3}, 1H), 7.57 (d, *J* = 7.7 Hz, Ar(Br)-H^{5}, 1H), 7.35-7.22 (m, Ar(Br)-H$^{4, 6}$, Ar(OH)-H^{4}, 3H), 7.06 (d, *J* = 15.9 Hz, CO-CH=, 2H), 6.96 (d, *J* = 7.5 Hz, Ar(OH)-H^{5}, 1H), 6.93 (d, *J* = 8.1 Hz, Ar(OH)-H^{3}, 1H). ESI-MS m/z: 327.1$(M-1)^{-}$, calcd for $C_{17}H_{13}BrO_2$: 328.01.

(1*E*,4*E*)-1-(3,4-Dimethoxyphenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3d)

Yellow powder, 63.7% yield, mp 138-140^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.86 (s, OH, 1H), 8.10 (d, *J* = 16.1 Hz, Ar(OH)-CH=, 1H), 7.86 (d, *J* = 16.4 Hz, Ar(OCH_3)-CH=, 1H), 7.80 (d, *J* = 7.4 Hz, Ar(OH)-H^{6}, 1H), 7.73 (d, *J* = 15.8 Hz, CO-CH=, 2H), 7.57-7.42 (m, Ar(OH)-H^{4}, Ar(OCH_3)-H^{2,6}, 3H), 7.02-6.87 (m, Ar(OH)-H$^{3, 5}$, Ar(OCH_3)-H^{5}, *3*H), 3.94 (s, -OCH_3, 6H). ESI-MS m/z: 309.0$(M-1)^{-}$, calcd for $C_{19}H_{18}O_4$: 310.12.

(1*E*,4*E*)-1-(3,4-Dichlorophenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3e)

Yellow powder, 91.2% yield, mp 104.3-106.4^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 7.85 (d, *J* = 16.4 Hz, Ar-CH=, 2H), 7.48-7.30(m, Ar(OH)-H^{6}, Ar(Cl)-H$^{2, 5, 6}$, 4H), 7.03 (d, *J* = 16.4 Hz, CO-CH=, 2H), 6.93 (m, Ar(OH)-H$^{3, 5}$, 2H). ESI-MS m/z: 317.1$(M-1)^{-}$, calcd for $C_{17}H_{12}Cl_2O_2$: 318.02.

(1*E*,4*E*)-1-(2-Hydroxyphenyl)-5-(2-nitrophenyl)penta-1,4-dien-3-one (3f)

Brown powder, 73.1% yield, mp 65-67^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 10.44 (s, OH), 8.14 (d, *J* = 16.2 Hz, Ar-CH=, 2H), 8.08-7.83 (m, Ar(NO_2)-H, 4H), 7.66 (d, *J* = 7.8 Hz, Ar(OH)-H^{6}, 1H), 7.32-6.79 (m, Ar(OH)-H$^{3, 4, 5}$, 3H). ESI-MS m/z: 296.1 $(M+1)^{+}$, calcd for $C_{17}H_{13}NO_4$: 295.08.

(1*E*,4*E*)-1-(2-Hydroxyphenyl)-5-phenylpenta-1,4-dien-3-one (3g)

Brown powder, 62.8% yield, mp 96-99^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 10.02 (s, OH, 1H), 8.13 (d, *J* = 16.1 Hz, Ar-CH=, 1H), 7.88 (d, *J* = 16.4 Hz, Ar-CH=, 1H), 7.77 (d, *J* = 15.9 Hz, CO-CH=, 1H), 7.62 (m, Ar-H$^{2, 6}$, Ar(OH)-H^{6}, 3H), 7.56 (d, *J* = 7.9 Hz, Ar-H^{4}, 1H), 7.50-7.38 (m, Ar-H$^{3, 5}$, Ar(OH)-H^{4}, 3H), 7.15 (d, *J* = 15.9 Hz, CO-CH=, 1H), 6.97-6.90 (m, Ar(OH)-H$^{3, 5}$, 2H). ESI-MS m/z: 249.2 $(M-1)^{-}$, calcd for $C_{17}H_{14}O_2$: 250.1.

(1*E*,4*E*)-1-(4-(Diethylamino)phenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3h)

Red brown powder, 31.2% yield, mp 125-128^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 7.86 (d, *J* = 16.4 Hz, Ar-CH=, 2H), 7.47 (d, *J* = 7.6 Hz, Ar(N)-H$^{2, 6}$, 2H), 7.42 (m, Ar(OH)-H^{6}, 1H), 7.29-7.23 (m, Ar(OH)-H$^{4, 5}$, 2H), 7.03 (d, *J* = 16.4 Hz, CO-CH=, 2H), 6.95-6.91 (m, Ar(OH)-H^{3}, Ar(N)-H$^{3, 5}$, 3H), 3.43 (m, n-CH_2-4H) , 1.43 (m, -CH_3, 6H). ESI-MS m/z: 320.5 $(M-1)^{-}$, calcd for $C_{21}H_{23}NO_2$: 321.17.

(1*E*,4*E*)-1-(2-Hydroxyphenyl)-5-(4-(pyrrolidin-1-yl)phenyl)penta-1,4-dien-3-one (3i)

Brown powder, 39.3% yield, mp 132-135^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.69 (s, 1H), 7.86 (d, *J* = 16.4 Hz, Ar-CH=, 2H), 7.74 (d, *J* = 8.6 Hz, Ar(N)-H$^{2, 6}$, 2H), 7.48 (d, *J* = 6.9 Hz, Ar(OH)-H^{6}, 1H), 7.33 (m, Ar(OH)-H$^{4, 5}$, 2H), 7.01 (d, *J* = 16.4 Hz, CO-CH=, 2H), 6.92-6.77 (m, Ar(OH)-H^{3}, Ar(N)-H$^{3, 5}$, 3H), 3.40 (m, N-CH, 4H), 2.05 (m, CH, 4H). ESI-MS m/z: 318.4 $(M-1)^{-}$, calcd for $C_{21}H_{21}NO_2$: 319.16.

(1*E*,4*E*)-1-(4-(Tert-butyl)phenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3j)

Yellow powder, 89.4% yield, mp 91.2-95.8^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.98 (s, -OH, 1H), 8.12 (d, *J* = 16.0 Hz, Ar(OH)-CH=, 1H), 7.86 (d, *J* = 16.3 Hz, Ar-CH=, 1H), 7.82 (d, *J* = 8.4 Hz, Ar-($C(CH_3)_3$)-H$^{2, 6}$, 2H), 7.56-7.49 (m, Ar-($C(CH_3)_3$)-H$^{3, 5}$, Ar-(OH)-H^{6}, 3H), 7.00 (d, *J* = 15.7 Hz, CO-CH=, 2H), 6.85-6.71 (m, Ar-(OH)-H$^{3, 4, 5}$, 3H), 1.34 (s, -CH_3, 9H). ESI-MS m/z: 304.7 $(M-1)^{-}$, calcd for $C_{21}H_{22}O_2$: 306.16.

(1*E*,4*E*)-1-(4-(Benzyloxy)phenyl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3k)

Green powder, 91.6% yield, mp 75-78^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 9.89 (s, OH, 1H), 7.85 (d, *J* = 16.0 Hz, Ar-CH=, 2H), 7.49-7.36 (m, Ar-H, Ar(O)-H$^{2, 6}$, Ar(OH)-H^{6}, 8H), 7.09 (d, CO-CH=, *J* =

16.4 Hz, 2H), 7.04 (s, Ar(OH)-H^4, 1H), 7.01-6.89 (m, Ar(OH)-$H^{3, 5}$, Ar(O)-$H^{3, 5}$, 4H), 5.16 (s, -OCH_2, 2H). ESI-MS m/z: 355.5 $(M-1)^-$, calcd for $C_{24}H_{20}O_3$: 356.14.

(1*E*,4*E*)-1-(Furan-2-yl)-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (3l)

Yellow powder, 74.8% yield, mp 149-152^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 8.09 (d, *J* = 16.2 Hz, Ar-CH=, 2H), 7.55-7.41 (m, Furan-$H^{2, 4}$, Ar-H^6, 3H), 7.23 (m, Ar-H^4, 1H), 7.08 (d, *J* = 15.5 Hz, CO-CH=, 2H), 6.93-6.72 (m, Furan-H^3, Ar-$H^{3, 5}$, 3H). ESI-MS m/z: 238.6 $(M-1)^-$, calcd for $C_{15}H_{12}O_3$: 240.08.

(1E,4E)-1-(2-Hydroxyphenyl)-5-(thiophen-2-yl)penta-1,4-dien-3-one (3m)

Yellow powder, 54.3% yield, mp 141-143^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ(ppm): 8.07 (m, Thiophene-H^2, 1H), 7.89 (d, *J* = 15.5 Hz, Ar-CH=, 1H), 7.85 (d, *J* = 16.5 Hz, Thiophene -CH=, 1H), 7.57 (d, *J* = 7.6 Hz, Thiophene-H^4, 1H), 7.50 (d, *J* = 8.0 Hz, Ar(OH)-H^6, 1H), 7.42 (d, *J* = 4.9 Hz, Thiophene-H^3, 1H), 7.21 (d, *J* = 16.0 Hz, CO-CH=, 1H),7.11-6.87 (m, Ar(OH)-$H^{3, 4, 5}$, 1H). ESI-MS m/z: 255.1$(M-1)^-$, calcd for $C_{15}H_{12}O_2S$: 256.06.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(2-fluorophenyl)penta-1,4-dien-3-one (4b)

Yellow powder, 73.9% yield, mp 94-98^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.87 (d, *J* = 16.2 Hz, 1H, Ar(F)CH=), 7.71 (d, *J* = 15.9 Hz, 1H, Ar(Cl)CH=), 7.65 (td, J_1 = 7.6, J_2 = 1.5 Hz, 1H, Ar (F) -H^4), 7.58 (d, *J* = 8.5 Hz, 2H, Ar (Cl) -$H^{2,6}$), 7.42 (d, *J* = 8.5 Hz, 3H, Ar (Cl) -$H^{3,5}$, Ar (F) -H^6), 7.23 (d, *J* = 7.5 Hz, 1H, Ar (F) -H^2), 7.20 (d, *J* = 3.6 Hz, 1H, Ar (F) -H^5), 7.15 (d, *J* = 14.3 Hz, 1H, Ar(Cl)C=CH), 7.09 (d, *J* = 15.9 Hz, 1H, Ar(F)C=CH). ESI-MS m/z: 286.9$(M+1)^+$, calcd for $C_{17}H_{12}ClFO$: 286.06.

(1*E*,4*E*)-1-(2-Bromophenyl)-5-(4-chlorophenyl)penta-1,4-dien-3-one (4c)

Yellow powder, 70.4% yield, mp 88-90^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.10 (d, *J* = 16.0 Hz, 1H, Ar(Br)CH=),7.72 (d, *J* = 15.8 Hz, 2H, Ar(Cl)CH=), 7.67 (d, *J* = 7.8 Hz, 1H, Ar (Br) -H^3), 7.58 (d, *J* = 8.4 Hz, 3H, Ar (Cl) -$H^{2,6}$, Ar (Br) -H^5), 7.42 (d, *J* = 8.4 Hz, 3H, Ar (Cl) -$H^{3,5}$, Ar (Br) -H^6), 7.38 (d, *J* = 7.8 Hz, 1H, Ar (Br) -H^4), 7.11 (d, *J* = 15.9 Hz, 1H, Ar(Cl)C=CH), 6.99 (d, *J* = 16.0 Hz, 1H, Ar(Br)C=CH). ESI-MS m/z: 346.3$(M+1)^+$, calcd for $C_{17}H_{12}BrClO$: 345.98.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(3,4-dimethoxyphenyl)penta-1,4-dien-3-one(4d)

Yellow powder, 80.9% yield, mp 66-69^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.71 (dd, *J* = 15.9, 10.2 Hz, 2H, ArCH=×2), 7.57 (d, *J* = 8.4 Hz, 2H, Ar (Cl) -$H^{2,6}$), 7.41 (d, *J* = 8.4 Hz, 2H, Ar (Cl) -$H^{3,5}$), 7.23 (dd, J_1 = 8.3 Hz, J_2 = 1.7 Hz, 1H, Ar (OCH_3) -H^{6}), 7.16 (d, *J* = 1.7 Hz, 1H, Ar (OCH_3) -H^{2}), 7.09 (d, *J* = 15.9 Hz, 2H, ArC=CH×2), 6.92 (d, *J* = 7.7 Hz, 1H, Ar (OCH_3) -H^{5}), 3.96 (s, 6H, -OCH_3×2). ESI-MS m/z: 330.2$(M+1)^{+}$, calcd for $C_{19}H_{17}ClO_3$: 328.09.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(3,4-dichlorophenyl)penta-1,4-dien-3-one (4e)

Yellow powder, 63.4% yield, mp 134.3-136.4^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.71 (d, *J* = 15.8 Hz, 2H, ArCH=×2), 7.64 (d, *J* = 15.9 Hz, 1H, Ar (Cl_2) -H^{6}), 7.57 (d, *J* = 8.4 Hz, 2H, Ar (Cl) -$H^{2,6}$), 7.52 (d, *J* = 8.3 Hz, 1H, Ar (Cl_2) -H^{5}), 7.45 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H, Ar (Cl_2) -H^{2}), 7.42 (d, *J* = 8.5 Hz, 2H, Ar (Cl) -$H^{3,5}$), 7.05 (dd, *J* = 15.8, 15.0 Hz, 2H, ArC=CH×2). ESI-MS m/z: 336.9$(M+1)^{+}$, calcd for $C_{17}H_{11}Cl_3O$: 335.99.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(2-nitrophenyl)penta-1,4-dien-3-one (4f)

Dark green powder, 87.1% yield, mp 175.1-177.2^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.15 (d, *J* = 17.4 Hz, 1H, Ar(NO_2)CH=), 7.81-7.67 (m, 4H, Ar(Cl)CH=, Ar-H), 7.65-7.53 (m, 3H, Ar-H), 7.42 (d, *J* = 6.8 Hz, 2H, Ar (Cl) -$H^{3,5}$), 7.11 (d, *J* = 15.3 Hz, 1H, Ar(NO_2)C=CH), 6.91 (d, *J* = 16.3 Hz, 1H, Ar(Cl)C=CH). ESI-MS m/z: 313.9$(M+1)^{+}$, calcd for $C_{17}H_{12}ClNO_3$: 313.05.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-[4-(pentan-3-yl)phenyl]penta-1,4-dien-3-one(4h)

Orange red oil, 49.2% yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 9.73 (s, OH, 1H), 7.74 (d, *J* = 15.6 Hz, Ar-CH=, 1H), 7.40 (d, *J* = 8.4 Hz, Ar(N)-$H^{2, 6}$, 2H), 7.35 (d, *J* = 8.4 Hz, Ar(Cl)-$H^{2, 6}$, 2H), 7.28 (d, *J* = 7.4 Hz, Ar(Cl)-$H^{3, 5}$, 2H), 7.02 (d, *J* = 15.3 Hz, Ar(N)-CH=, 2H), 6.72 (d , *J* = 8.0 Hz,, Ar(N)-$H^{3, 5}$, 3H), 3.47 (m, NCH, 4H), 1.24 (m, CH_3, 6H). ESI-MS m/z: 340.1$(M+1)^{+}$, calcd for $C_{21}H_{22}ClNO$: 339.14.

(1*E*,4*E*)-1-(2-Hydroxyphenyl)-5-[4-(pyrrolidin-1-yl)phenyl]penta-1,4-dien-3-one (4i)

Orange red powder, 93.9% yield, mp 113-115^{o}C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.06 (d, *J* = 15.4 Hz, Ar-CH=, 2H), 7.72 (d, *J* = 8.6 Hz, Ar(N)-$H^{2, 6}$, 2H), 7.64 (d, *J* = 8.0 Hz, Ar(Cl)-$H^{2, 6}$, 7.48 (d, *J*

= 7.4 Hz, Ar(Cl)-$H^{3,5}$, 2H), 7.01 (d, *J* = 15.4 Hz, CO-CH=, 2H), 6.72 (d, *J* = 7.4 Hz, Ar(N)-$H^{3,5}$, 2H), 3.46 (m, N-CH, 4H), 2.09 (m, CH, 4H). ESI-MS m/z: 338.0$(M+1)^+$, calcd for $C_{21}H_{22}ClNO$: 337.12.

(1*E*,4*E*)-1-[4-(Tert-butyl)phenyl]-5-(2-hydroxyphenyl)penta-1,4-dien-3-one (4j)

Yellow powder, 63.3% yield, mp 141.2-145.8°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.76 (d, *J* = 15.9 Hz, Ar-CH=, 1H), 7.70 (d, *J* = 15.9 Hz, Ar-CH=, 1H), 7.58 (dd, J_1 = 7.9 Hz, J_2 = 5.3 Hz, Ar(Cl)-$H^{2,6}$, Ar-$H^{2,6}$, 4H), 7.47 (d, *J* = 7.8 Hz, Ar(Cl)-$H^{3,5}$, 2H), 7.41 (d, *J* = 8.5 Hz, Ar-$H^{3,5}$, 2H), 7.07 (dd, J_1 = 16.7 Hz, J_2 = 16.0 Hz, CO-CH=, 2H), 1.37 (s, CH_3, 9H). ESI-MS m/z: 325.1$(M+1)^+$, calcd for $C_{21}H_{21}ClO$: 324.13.

(1*E*,4*E*)-1-[4-(Benzyloxy)phenyl]-5-(4-chlorophenyl)penta-1,4-dien-3-one(4k)

Yellow powder, 72.6% yield, mp 153.3-156.8°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.73 (d, *J* = 15.9 Hz, Ar-CH=, 2H), 7.60 (d, *J* = 8.5 Hz, Ar(Cl)-$H^{2,6}$, 2H), 7.57 (d, *J* = 8.3 Hz, Ar(O)-$H^{2,6}$, 2H), 7.42 –7.06 (m, Ar-H, 9H), 6.97 (d, *J* = 15.8 Hz, CO-CH=, 2H), 5.14 (s, OCH_2, 2H). ESI-MS m/z: 375.0$(M+1)^+$, calcd for $C_{24}H_{19}ClO_2$: 374.11.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(furan-2-yl)penta-1,4-dien-3-one (4l)

Orange yellow powder, 86.5% yield, mp 92-95°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.68 (d, *J* = 16.0 Hz, Ar-CH=, 2H), 7.53 (m, Ar-$H^{2,6}$, Furan-$H^{2,4}$, 4H), 7.40 (d, *J* = 8.2 Hz, Ar(Cl)-$H^{3,5}$, 2H), 7.00 (dd, J_1 = 15.7 Hz, J_2 = 6.6 Hz, CO-CH=, 2H), 6.74 (s, Furan-H^3, 1H). ESI-MS m/z: 258.8$(M+1)^+$, calcd for $C_{15}H_{11}ClO_2$: 258.04.

(1*E*,4*E*)-1-(4-Chlorophenyl)-5-(thiophen-2-yl)penta-1,4-dien-3-one(4m)

Yellow powder, 39.5% yield, mp 109-110.9°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.89 (d, *J* = 15.5 Hz, Ar-CH=, 1H), 7.68 (d, *J* = 15.9 Hz, Ar-CH=, 1H), 7.56 (d, *J* = 8.4 Hz, Ar(Cl)-$H^{2,6}$, 2H), 7.45 (d, *J* = 5.1 Hz, Thiophen-H^2, 1H), 7.41 (d, *J* = 8.4 Hz, Ar(Cl)-$H^{3,5}$, 2H), 7.37 (d, *J* = 3.5 Hz, Thiophen-H^3, 1H), 7.12 (dd, J_1 = 4.9 Hz, J_2 = 3.8 Hz, Thiophen-H^4, 1H), 7.01 (d, *J* = 15.9 Hz, CO-CH=, 1H), 6.88 (d, *J* = 15.5 Hz, CO-CH=, 1H). ESI-MS m/z: 274.8$(M+1)^+$, calcd for $C_{15}H_{11}ClOS$: 274.02.

2. Quantitative Structure-Activity Relationship (QSAR) study for tested compounds

Descriptors calculation and selection

To obtain a QSAR model, compounds are often represented by molecular descriptors. [1] The molecular structures of all the benzimidazoles and imidazopyridines were built with Maestro (Version 9.1 Schrödinger, LLC). The full geometry optimization for the investigated molecules was carried out with MOPAC2009 version 9.0 1. All the calculations were based on the semi-empirical Parameterized model 6 (PM6) method.[2] The molecular descriptor computing were performed on MODEL (Molecular Descriptor Lab), a web-based server for computing structural and physicochemical features of compounds, according to the methods described in the literature.[3] The descriptors studied here contain the constitutional descriptors, physicochemical descriptors, topological descriptors, geometrical descriptors, charge (electronic) descriptors, and quantum chemistry descriptors. The optimized geometry of molecules was uploaded to MODEL. After the calculation of the molecular descriptors, about 4000 molecular descriptors based on molecular 3D structure were obtained. After calculation of the molecular descriptors, those that stayed constant for all molecules were eliminated and pairs of variables with a correlation coefficient greater than 0.85 were classified as inter-correlated and one in each correlated pair was deleted.

Table S1 The calculated descriptors in this work

Variables	Descriptor class	Description
Moran	Topological properties	ALOGP weighted Moran lagged 6
WHIM	Geometrical properties	1st directional WHIM shape by Atomic Mass
EEVA	Quantum Chemistry Descriptors	Electronic Eigenvalue Descriptors , EEVA(-3.00)
H-GETAWAY	Geometrical properties	Atomic mass weighted H-GETAWAY H5: H5,W
R-GETAWAY	Geometrical properties	Unweighted R-GETAWAY R+1: R+1

EEVA	Quantum Chemistry Descriptors	Electronic EEVA(-40.00)	Eigenvalue	Descriptors	,

Multiple linear regression (MLR) analysis

MLR analysis was a statistical technique that uses several explanatory variables to predict the outcome of a response variable. The goal of multiple linear regression (MLR) is to model the relationship between the explanatory and response variables. In our present study, MLR performed using R program, a powerful tool for statistical computing and graphics, to derive QSAR models. The biological data used in this study were their TNF-α- or IL-6-inhibitory rates when compared to LPS alone group. Compounds with negative values were abandoned because of their pro-inflammatory activities. The inhibition rates against TNF-α and IL-6 release, named as IRTNF-α and IRIL-6 respectively, were used as dependent variables in the linearization procedure. Subsequently, Stepwise Multiple Linear Regression (Stepwise-MLR) was used to select the significant descriptors. The most relevant descriptors were used as independent variables.

Validation of the models

Validation of the lineal models is required for testing the predictive ability and generalizing the methods by cross-validation. The leave-one-out (LOO) procedure was employed. When a data point was removed from the analyzed set, the regression was recalculated, and then the predicted value for that point was compared to its actual value. This process was repeated until each datum had been omitted once and then the sum of squares of these deletion residuals could be used to calculate q^2, an equivalent statistic to R^2.

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