Dyes and Pigments 113 (2015) 174–180

Contents lists available at ScienceDirect

Dyes and Pigments

journal homepage: www.elsevier.com/locate/dyepig

Synthesis, characterization and biological evaluation of fluorescent biphenyl–furocoumarin derivatives

Huaizhen He [a, 1], Cheng Wang [a, 1], Tao Wang [a], Nan Zhou [a], Zhenyi Wen [b], Sicen Wang [a], Langchong He [a, *]

[a] School of Medicine, Xi'an Jiaotong University, No. 76, Xi'an 710061, Shaanxi Province, PR China
[b] Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, The College of Chemistry & Materials Science, Northwest University, Xi'an 710069, PR China

ARTICLE INFO

Article history:
Received 19 March 2014
Received in revised form
17 June 2014
Accepted 14 July 2014
Available online 7 August 2014

Keywords:
Furocoumarin
Biphenyl
Vasodilatory activity
Fluorescence
DFT
Synthesis

ABSTRACT

A series of new biphenyl–furocoumarin derivatives were synthesized via Suzuki–Miyaura reaction as a critical step. The structures were characterized by NMR, IR and HRMS. All the derivatives presented vasodilatory activity in different degree, especially **6b**. Photoelectric properties of all derivatives were investigated by fluorescence, including the variation in different solvents and various pH of **6b**. All the ground state molecular geometries from **6a**–**6j** are fully optimized by Density Functional Theory (DFT) on gas phase, which was in accordance with the fluorescence detection. The results suggested compounds with biphenyl–furocoumarin skeleton would serve as promising vasodilatory candidates as well as fluorescent indicators.

1. Introduction

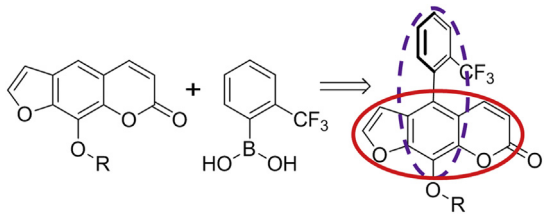
Hypertension is known as the most common cardiovascular disease, and the one which represents the major risk factor for coronary artery disease, heart failure and renal failure [1]. Due to the basis for the treatment of hypertension, a great deal of attention has been focused on vascular relaxation [2]. Coumarin and its derivatives play a significant role in pharmacological activity such as vasorelaxant activity [3], anticoagulant [4], antiflammatary [5], anti-HIV [6], anticancer [7,8] and antifungal activity [9] since it was first isolated from plants 200 years ago [10]. They also have been widely used in fluorescent probes [11,12], fluorescence labeling reagents [13], laser dyes [14] and sensors [15] because of their efficient light emission properties. Furocoumarins form a great class of coumarin compounds that occurred in nature, they also have shown to possess cardiovascular properties [16]. Our group has reported a series of furocoumarin derivatives as vasodilator agents [17,18]. For these reasons, considerable attention has focused on the preparation and application of their derivatives with various substituents at different positions.

Biphenyl derivatives present numerous applications because of their photophysical properties and pharmacological activities [19–22]. Biphenyl exhibits geometry change by internal rotation around the C–C single bond on account of environmental interaction. A statistical analysis of NMR-based screening indicates that biphenyl is identified as privileged substructure which preferentially bound to a wide range of proteins [23]. These results suggest that biphenyl-containing structure can be utilized as a template for discovery and design of potential drugs. Combining benzene moiety with furocoumarin may afford new chemical entities, which would possess simultaneously the superior properties of biphenyl and furocoumarin. Furthermore, introduction of fluorinated group into scaffold has been taken into consideration because fluorinated compounds have generally shown a dramatic increase in biological effect compared with their nonfluorinated analogs [24]. Due to an important part of fluorinated groups, amount of research had focused on trifluoromethyl group by introducing it into cyclic compounds at tactical position owing to its unique physical and biological properties [25,26].

Stemmed by above information and our further interest, we synthesized a series of biphenyl–furocoumarin derivatives (Scheme 1), aiming at obtaining new agents with stronger vasodilator activities as well as improved fluorescent properties. Biological activity evaluation indicated all the target compounds

* Corresponding author. Tel./fax: +86 29 82655451.
E-mail address: helc@mail.xjtu.edu.cn (L. He).
[1] These two people are the co-first authors.

http://dx.doi.org/10.1016/j.dyepig.2014.07.011
0143-7208/



Scheme 1. Structure design of target compounds.

possessed favorable vasorelaxant activity. The spectral properties of the title compounds were also investigated, which corresponded to theoretical studies.

2. Experimental

2.1. Reagents and instruments

All the materials used for experiments were obtained from commercial suppliers without further purification. All of the solvents used were of analytical reagent grade. Water was deionized. Melting points were determined on an X-4 apparatus without correction. The infrared (IR) spectra were recorded on a Shimadzu FT-IR 440 spectrometer in the 4000–500 cm^{-1} range. The HR-ESI-MS data were obtained on a Bruker micrOTOF-Q II spectrometer (Bruker, Karlsruhe, Germany).^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCF 400 MHz instrument in $CDCl_3$ solution with TMS as internal standard. Chemical shift multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Fluorescence measurements were performed on a Shimadzu RF-5301 fluorescence spectrophotometer equipped with quartz cuvettes of 10 mm path length with a xenon lamp as the excitation source.

2.2. Synthesis

2.2.1. General procedure for the synthesis of (*3a–3h*)

Compound (**2**) was prepared according to the literature [27,28].

Anhydrous K_2CO_3 (0.99 g, 7.2 mmol) was added to a solution of compound **2** (0.50 g, 1.8 mmol) in dry acetone (30 mL). After stirring for 30 min, various substituted amine hydrochlorides were added separately. The reaction mixture was heated at reflux for 4–7 h. After cooling, the mixture was filtered and evaporated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/Ether (2:1) and EtOAc/MeOH (10:1).

3a Yield: 94.5%, white solid. M.p.: 244–245 °C. IR (KBr, cm^{-1}): 2923, 1739, 1585, 1460, 883, 829. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 9.9 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.43 (d, J = 9.9 Hz, 1H), 4.54 (t, J = 5.7 Hz, 2H), 2.83 (t, J = 5.7 Hz, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.65, 147.05, 146.83, 144.12, 142.51, 131.41, 127.74, 115.72, 115.58, 107.37, 105.93, 71.83, 58.69, 45.78. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{15}H_{14}BrNO_4$: 352.0184, found: 352.0214.

3b Yield: 95.2%, white solid. M.p.: 200–201 °C. IR (KBr, cm^{-1}): 2926, 1722, 1581, 1427, 881, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 9.9 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.45 (d, J = 9.9 Hz, 1H), 4.59 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H), 2.69 (s, 4H), 1.83–1.81 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.77, 147.15, 146.94, 144.23, 142.61, 131.59, 127.84, 115.83, 115.66, 107.45, 105.94, 72.91, 55.57, 54.62, 23.54. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{17}H_{16}BrNO_4$: 378.0341, found: 378.0380.

3c Yield: 94.2%, white solid. M.p.: 97–98 °C. IR (KBr, cm^{-1}): 3440, 2929, 1616, 1581, 1456, 872, 840. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 9.9 Hz, 1H), 7.72 (d, J = 1.9 Hz, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.45 (d, J = 9.9 Hz, 1H), 4.59 (t, J = 5.9 Hz, 2H), 2.86 (t, J = 5.9 Hz, 2H), 2.52 (s, 4H), 1.58–1.52 (m, 4H), 1.43 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.70, 147.12, 146.77, 144.16, 142.54, 131.48, 127.70, 115.71, 115.55, 107.36, 105.72, 71.46, 58.49, 54.79, 25.82, 24.08. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{17}H_{16}BrNO_5$: 392.0497, found: 392.0540.

3d Yield: 93.7%, white solid. M.p.: 129–130 °C. IR (KBr, cm^{-1}): 2956, 1735, 1583, 1446, 871, 833. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 9.9 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 9.9 Hz, 1H), 4.57 (t, J = 5.5 Hz, 2H), 3.73–3.67 (m, 4H), 2.89 (t, J = 5.5 Hz, 2H), 2.61 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.59, 147.21, 146.80, 144.27, 142.55, 131.43, 127.69, 115.73, 115.58, 107.46, 106.10, 71.10, 66.83, 58.24, 53.81. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{18}H_{18}BrNO_4$: 394.0290, found: 394.0335.

3e Yield: 96.3%, white solid. M.p.: 180–182 °C. IR (KBr, cm^{-1}): 3427, 2929, 1585, 1460, 885, 831. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 9.9 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 1.9 Hz, 1H), 6.48 (d, J = 9.9 Hz, 1H), 4.83–4.79 (m, 2H), 3.93–3.79 (m, 2H), 2.97 (s, 2H), 1.67 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.39, 147.27, 146.61, 143.90, 142.63, 129.63, 128.03, 115.83, 115.70, 107.69, 105.83, 72.25, 60.65, 44.10, 29.60. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{16}H_{16}BrNO_4$: 366.0341, found: 366.0392.

3f Yield: 94.3%, white solid. M.p.: 184–186 °C. IR (KBr, cm^{-1}): 3456, 1722, 1590, 1460, 885, 830. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 9.9 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.46 (d, J = 9.9 Hz, 1H), 5.04–4.99 (m, 2H), 3.67–3.64 (m, 2H), 3.53–3.48 (m, 4H), 1.57 (t, J = 7.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.54, 147.29, 146.39, 143.64, 142.64, 129.61, 128.06, 115.79, 115.62, 107.60, 105.78, 68.15, 51.20, 47.44, 22.90. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{17}H_{18}BrNO_4$: 380.0497, found: 380.0549.

3g Yield: 95.5%, white solid. M.p.: 104–105 °C. IR (KBr, cm^{-1}): 3433, 1622, 1585, 1454, 883, 829. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 9.8 Hz, 1H), 7.72 (s, 1H), 6.87 (s, 1H), 6.45 (d, J = 9.8 Hz, 1H), 4.56 (t, J = 5.8 Hz, 2H), 3.04 (t, J = 5.8 Hz, 2H), 2.79–2.74 (m, 4H), 1.57–1.53 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.73, 147.07, 146.74, 144.10, 142.54, 131.70, 127.69, 115.67, 115.53, 107.35, 105.59, 71.99, 57.34, 55.75, 27.84, 26.81. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{19}H_{20}BrNO_4$: 406.0654, found: 406.0715.

3h Yield: 93.1%, white solid. M.p.: 112–113 °C. IR (KBr, cm^{-1}): 3456, 1722, 1585, 1460, 885, 829. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 9.9 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 9.8 Hz, 1H), 4.55 (t, J = 6.3 Hz, 2H), 3.76–3.70 (m, 4H), 2.68 (t, J = 7.3 Hz, 2H), 2.52 (s, 4H), 2.10–2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.71, 147.11, 146.78, 144.16, 142.57, 131.40, 127.75, 115.74, 115.61, 107.43, 105.83, 72.29, 66.81, 55.08, 53.57, 27.01. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{18}H_{18}BrNO_5$: 408.0447, found: 408.0534.

2.2.2. Synthesis of 5-br-9-(2-bromomethyl)-7H-furo[3, 2-g] chromen-7-one (*4*)

Anhydrous K_2CO_3 (0.99 g, 7.2 mmol) was added to a solution of compound **2** (0.50 g, 1.8 mmol) in dry acetone (30 mL). After stirring for 30 min, 1, 2-dibromoethane was added. The reaction mixture was heated at reflux temperature for 7 h. After cooling, the product was obtained by filtering, washing with H_2O and drying. Yield: 90.2%, white solid. M.p.: 134–135 °C. IR (KBr, cm^{-1}): 3427, 1724, 1587, 1454, 842. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 9.9 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.47 (d, J = 9.9 Hz, 1H), 4.74 (t, J = 6.6 Hz, 2H), 3.74 (t, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.48, 147.04, 146.83, 144.00, 142.53, 130.58, 127.82, 115.82, 115.66, 107.48, 106.68, 73.03, 29.07. HR-ESI-MS (m/z): calcd. for $[M+H]^+$ $C_{13}H_8Br_2O_4$: 386.8868, found: 386.8927.

2.2.3. Synthesis of 5-(2-(trifluoromethyl)phenyl)-9-(2-bromomethyl)-7H-furo[3, 2-g]chromen-7-one (*5*)

A mixture of **4**, Na_2CO_3, 2-(trifluoromethyl) phenylboronic acid, tetrakis (triphenylphosphine) palladium, dioxane and H_2O was