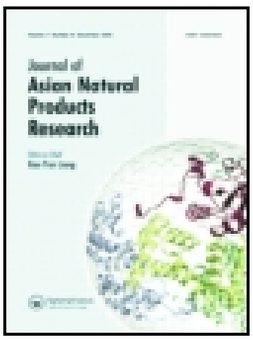

Journal of Asian Natural Products Research

ISSN: 1028-6020 (Print) 1477-2213 (Online) Journal homepage: http://www.tandfonline.com/loi/ganp20

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To cite this article: Ya-Jing Hou, Cheng Wang, Tao Wang, Li-Min Huang, Yuan-Yuan Lin & Huai-Zhen He (2017): Design, synthesis, and evaluation of new series of Imperatorin analogs with potential vasodilatory activity, Journal of Asian Natural Products Research, DOI: 10.1080/10286020.2017.1391228

To link to this article: http://dx.doi.org/10.1080/10286020.2017.1391228

Published online: 30 Oct 2017.

JOURNAL OF ASIAN NATURAL PRODUCTS RESEARCH, 2017
https://doi.org/10.1080/10286020.2017.1391228

Design, synthesis, and evaluation of new series of Imperatorin analogs with potential vasodilatory activity

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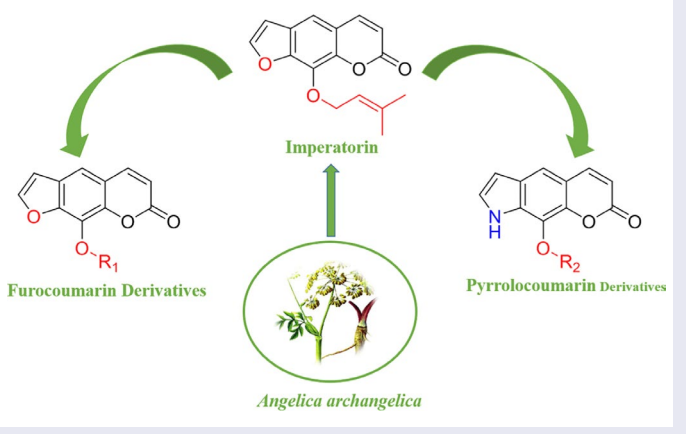
ABSTRACT

Two series of imperatorin analogs were synthesized based on our previous research and evaluated for their vasodilatation activities on *in vitro* rat mesenteric artery, basilar artery, and renal artery ring models. Target compounds were characterized by infrared, ^{1}H NMR, and mass spectra. Most derivatives possessed significant vasodilatory activity on the mesenteric artery, and compound **3a** exhibited favorable and broad vasodilatation activities on three kinds of rat artery ring models. The pharmacological results indicated that introducing nitrogen-contained ring in side chain or large steric hindrance at the distal end could increase the vasodilatory activity. Further, replacement of oxygen atom (–O–) in the skeleton of furocoumarin derivatives with nitrogen (–NH–) could cause the decrease of vasodilatory activity. The molecular docking also indicated that compound **3a** showed a best affinity with α-1C receptor (PDB ID: 3G43). All these results suggested compound **3a** would be a potential vasodilatory agent for hypertension.



ARTICLE HISTORY
Received 20 April 2017
Accepted 25 September 2017

KEYWORDS
Imperatorin; furocoumarin; pyrrolocoumarin; vasodilatation; synthesis

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1. Introduction

Hypertension is the most common cardiovascular disease [1, 2], findings from serial surveys indicate an increasing prevalence of hypertension in developing countries due to the urbanization, population ageing, changes in dietary habits, and social stress [3]. Hypertension is associated with impaired vascular, which could result in the damnification of vasodilatory capacity [4]. Furthermore, vascular damage has been recognized as one of the leading risk factors for coronary artery disease, heart failure, and renal failure [5]. Therefore, vascular studies have got much attention [6, 7], and a great deal of novel agents have been put forward for the treatment of hypertension [8, 9]. Even so, hypertension is still an incurable disease and greatly threaten human beings' health [10].

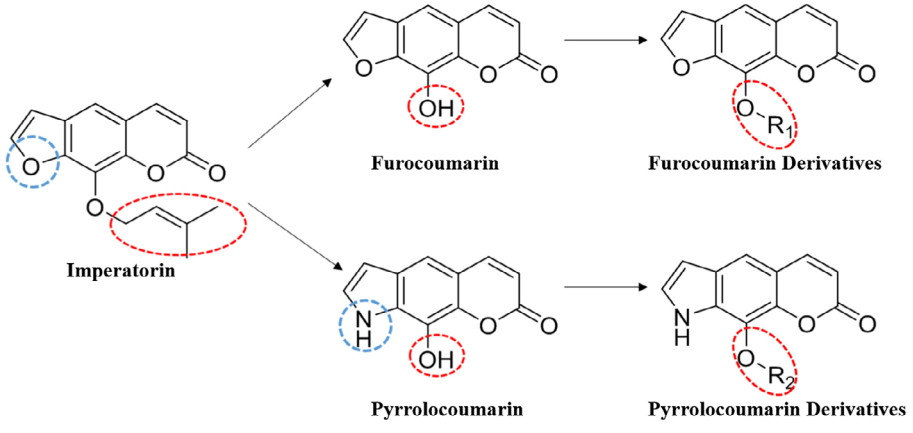
Imperatorin, a natural linear furocoumarin, is isolated from roots of *Angelica dahurica* and fruits of *Angelica archangelica* [11]. Modern researches have certified that it plays a significant role in pharmacological effects such as anti-inflammatory, antitumor, anticonvulsant, and so on [12–15]. In previous studies, we also found that imperatorin could induce vasodilatation via inhibiting voltage-dependent calcium channels and receptor mediated Ca^{2+} influx and release [16, 17]. However, the shortcomings such as its poor solubility and low bioavailability have limited its clinical application to a certain restriction [18, 19]. In order to improve its solubility and increase the structural diversity, our previous studies constructed a novel pyrrolecoumarin structure, which maintained the skeleton of imperatorin and replaced the oxygen of the furan-ring with NH [20].

In this study, six new imperatorin derivatives have been designed, synthesized (Scheme 1), and evaluated for the first time as vasorelaxant agents by isolated rat mesenteric artery (MA), basilar artery (BA), and renal artery (RA) rings models. Further, Molecule docking was performed to investigate the binding mode of these compounds with their receptor.

2. Results and discussion

2.1. Chemistry

The synthesis of compounds **1** and **2** was based on the references [20, 21]. The target compounds were prepared by Williamson reaction, the most common way of etherification



Scheme 1. Design strategy of target compounds.

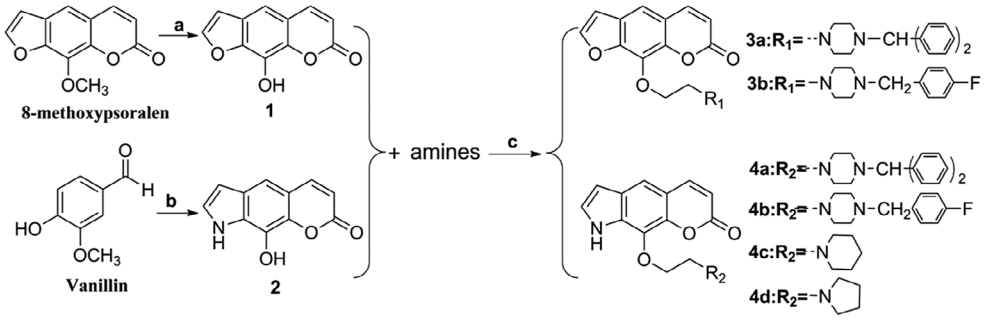
reaction, which can obtain hydrocarbyloxy derivatives. The optimization of reaction conditions is the key point of this reaction. Therefore, the effect of solvent, alkali, reaction time, and temperature was studied. At first, DMF was chosen as the solvent due to its good solubility of imperatorin intermediates, anhydrous K_2CO_3 was chosen as the acid-binding agent, and the reaction performed at 80 °C for 12 h to obtain the target product. Under this condition, the halogenated compounds will probably react with itself or the products, which resulting in an increase of by-products. In addition, DMF was difficult to remove. These all go against the yield and purification of the target compounds. For this reason, acetone is finally used as the solvent instead of DMF. With this kind of solvent, the by-products are less and crude products can be directly recrystallized from petroleum to get the target compounds (Scheme 2).

Besides, 8-hydroxypsoralen is suitable for using weak alkaline (such as K_2CO_3, Na_2CO_3) as a binding agent for the reaction rather than strong alkali (such as NaOH), which will easily lead to the degradation of pyrone. Furthermore, 9-hydroxy-8H-pyrano [3,2-*f*] indol-2-one is susceptibly photocatalytic in organic solvents and easily oxidized by acid or alkali, which could affect the further derivatization reaction.

Up to this point, the conditions of the Williamson reaction are summarized. The reaction conditions for compounds **3a** and **3b** are: acetone as the reaction solvent, n (compound **1**): n (chlorinated organic amine salt): n (K_2CO_3) = 1:1.2–1.5:1.5–3, reaction at 68 °C for 8–24 h and the yield is 54–72%. The reaction conditions for compounds **4a~4d** are: acetone as the reaction solvent, n (compound **2**): n (chlorinated organic amine salt): n (K_2CO_3) = 1:1.5:3, reaction at 68 °C for 8–24 h avoiding light and oxygen, and the yield is 45–70%.

2.2. Pharmacology

At present, there are many ways to evaluate cardiovascular activity, in which the vascular ring model is a generally accepted method [22, 23]. To this end, we selected three different susceptible parts of cardiovascular disease, i.e. rat mesenteric artery (MA), renal artery (RA), and brain basilar artery (BA) as the research objects, using the vascular ring tension measurement method, to evaluate the vasodilatory activity of these six compounds. The results are displayed in Table 1.



Scheme 2. Synthesis route of target compounds. Reagents and conditions: (a) CH_2Cl_2, BF_3, −5~0 °C, 4 h; (b) The reagents and conditions of **b** were according to the literature [21]; (c) K_2CO_3, acetone, 68 °C, 8–24 h, reflux.

Table 1. Vasodilatory activity in RA, BA, and MA.

	MA		BA		RA	
Compounds	pEC_{50}	E_{max} (%)	pEC_{50}	E_{max} (%)	pEC_{50}	E_{max} (%)
Imperatorin	4.95 ± 0.14	85.6 ± 4.0	5.26 ± 0.15	65.0 ± 4.2	5.20 ± 0.09	96.0 ± 1.0
3a	6.30 ± 0.12	101.1 ± 0.67	5.93 ± 0.00	103.6 ± 4.70	5.31 ± 0.02	103.7 ± 4.49
3b	5.79 ± 0.06	105.5 ± 4.31	4.65 ± 0.07	97.9 ± 3.89	4.79 ± 0.19	102.0 ± 2.79
4a	6.00 ± 0.14	101.75 ± 4.47	4.90 ± 0.26	106.90 ± 9.38	5.04 ± 0.20	93.70 ± 6.67
4b	5.01 ± 0.14	102.3 ± 0.21	4.84 ± 0.07	100.3 ± 2.77	5.14 ± 0.12	101.9 ± 0.52
4c	4.31 ± 0.02	98.54 ± 5.12	4.60 ± 0.20	93.30 ± 8.20	4.98 ± 0.04	100.70 ± 0.44
4d	4.78 ± 0.34	97.0 ± 0.94	4.45 ± 0.04	31.0 ± 7.52	4.86 ± 0.40	103.4 ± 1.65

Introduction of the nitrogen-contained ring in side chain or large steric hindrance at the distal end is beneficial to enhance the vasodilatory activity, and it will show the best activity when the side chain ends at a diphenyl piperazine, such as compound **3a** (pEC_{50} = 6.30) and compound **4a** (pEC_{50} = 6.00). On the other hand, comparison between furocoumarin derivatives and pyrrolocoumarin derivatives with a same side chain, such as **3a** with **4a**, shows the decrease of vasodilatory activity, and comparison between **3b** with **4b** also shows the same tendency in MA, but a slight increase in BA and RA. Generally speaking, when the oxygen atom (–O–) in the nucleus of the furocoumarin derivatives is replaced with nitrogen (–NH–), it could cause the decrease of vasodilatory activity. Furthermore, most of the derivatives can exhibit significant vasodilatory activity in the MA, but in the RA and BA, most of the compounds are slightly lower or comparable than that of imperatorin. The reason may be related to the difference of three vascular tissues, i.e. vascular personality, which displays different or even opposite results for the same stimulus in different organs, tissues, or area.

2.3. Docking

The previous studies indicate that imperatorin acts on the subunits E and F of α-1C receptor in voltage-dependent L-calcium channel for its antihypertensive effect. In order to explain the different activities of the target compounds and guide further SAR studies, we proceeded to examine the interaction of compounds **3a** and **4a** with L-calcium channel (PDB code: 3G43). Molecular docking studies were conducted using the Sulflex-Dock Mode of Sybyl-X program package (New Tripos International, St. Louis, USA), and the results are shown in Figure 1.

In general, compounds **3a** and **4a** separately formed five and four hydrogen bonds. Oxygens in pyrone of two compounds both can form hydrogen bonds with Thr110 and His107 with distances of 2.25 Å and 1.99 Å for **3a**, 2.02 Å and 2.12 Å for **4a**. After -O- change in -NH-, the H-bond donor, Lys94 was replaced with Ser81, a H-bond acceptor. And the lengths were 2.08 Å and 2.65 Å, respectively. Besides, the bonding conditions of the oxygen atom of the side chain also changed, **3a** formed two bonds with Lys94 and His107 with the distances of 2.25 Å and 1.99 Å, while **4a** formed only one with His107, and the length was 2.18 Å.

The results indicate that when the –O– in compound **3a** is replaced with -NH-, the numbers and lengths of bonds are both different, that may attribute to the changes of the electric field distribution. As a result, the dominant conformation is changed and the side

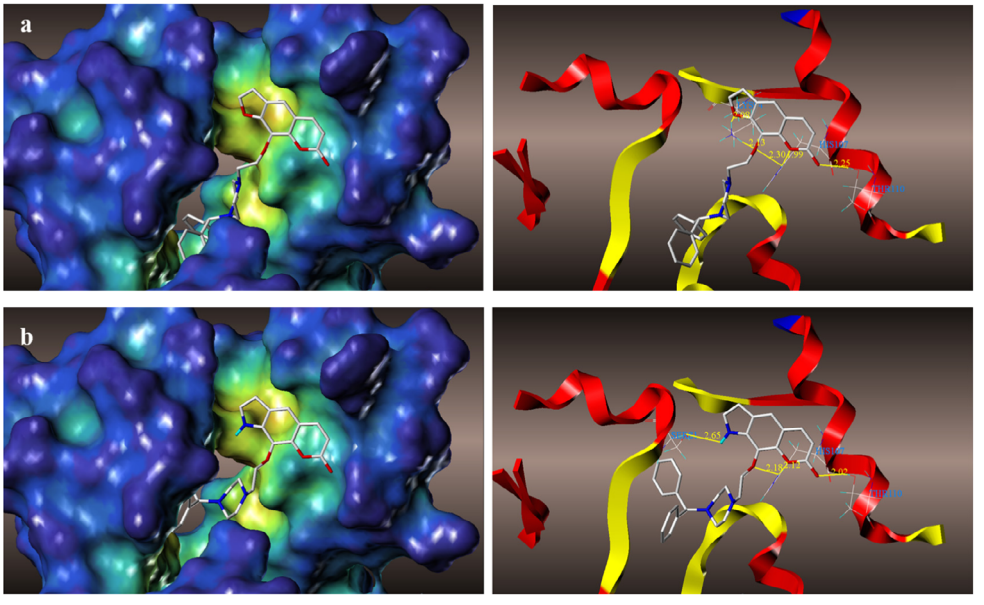


Figure 1. Binding mode of compounds **3a** (a) and **4a** (b) to L-calcium channel (PDB code: 3G43).

chain in compound **4a** cannot react with the activity cavity well. Overall, compound **3a** shows a better affinity with α-1C receptor (PDB ID: 3G43).

3. Experimental

3.1. General experimental procedures

Melting points were determined on an X-4 microscope melting point apparatus (Henan, China) and are uncorrected. IR spectra were recorded on a Shimadzu Fourier transform (FT)-IR 440 spectrometer in the 4000–500 cm^{-1} range (Shimadzu, Kyoto, Japan). NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer in $CDCl_3$ solution with TMS as internal standard (Bruker, Zurich, Switzerland). The HR-ESI-MS data were obtained on a Bruker microTOF-Q II spectrometer (Bruker, Karlsruhe, Germany). All the materials used for experiments were obtained from commercial suppliers without further purification unless otherwise stated. All of the solvents used were of analytical reagent grade. Water was deionized. The synthetic procedure was controlled by the method of thin-layer chromatography on 0.25 mm silica gel plates (60 GF-254) and visualized with UV light. The products were purified by recrystallization or flash chromatography. Column chromatography was carried out on silica gel (300–400 mesh). All other reagents were commercially available and used as received.

3.2. General procedure for the synthesis of (3a-3b, 4a-4d)

Compound **1** (2.02 g, 10.00 mmol) and compound **2** (2.81 g, 10.00 mmol) were separately dissolved in dry acetone (150 ml), followed by adding anhydrous K_2CO_3 (12.00 mmol for **3a-3b**, 30.00 mmol for **4a-4d**). The reaction mixture was stirred under nitrogen atmosphere

for 30 min at room temperature. Then, various organic amine salts (12.00 mmol for **3a**-**3b**, 15.00 mmol for **4a**-**4d**) were added, respectively. The reaction mixture was stirred at 68 °C for 8–24 h under nitrogen atmosphere and away from light. After cooling, the mixture was concentrated *in vacuum*. The residue was dissolved with water and extracted with EtOAc or $CHCl_3$ (3 × 50 ml). The collected organic layer was washed by water (2 × 50 ml) and saturated saline (2 × 50 ml) successively, dried over Na_2SO_4, and purified by column chromatography after concentrated.

3.2.1. Compound 3a

Yield: 93%, Light yellow solid. m.p.: 77–79 °C; IR (KBr): υ_{max} 3149.5 (furan-CH), 3058.9 (ArH), 2812.0 (–CH_2–), 1730.0 (–C=O), 1587.3 (–C=C–), 1490.9 (–C=C–), 1149.5 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 9.6 Hz, 1H, H-pyrano), 7.67 (s, 1H, H-furan), 7.43 (d, J = 7.6 Hz, 4H, ArH), 7.37 (s, 1H, ArH), 7.30–7.26 (m, 4H, ArH), 7.17–7.21 (m, 2H, ArH), 6.82 (s, 1H, H-furan), 6.37 (d, J = 9.6 Hz, 1H, H-pyrano), 4.61 (t, J = 5.6 Hz, 2H, –O$\underline{CH_2}CH_2$ N), 4.23 (s, 1H, –N($CH_2\underline{CH_2}$)$_2$N$\underline{CH}$(Ph)$_2$), 2.94 (t, J = 5.4 Hz, 2H, –OCH$_2\underline{CH_2}$ N), 2.66 (s, 4H, –N($CH_2\underline{CH_2}$)$_2$NCH(Ph)$_2$), 2.43 (s, 4H, –N($\underline{CH_2}CH_2$)$_2$NCH(Ph)$_2$); EI-MS (*m/z*): 479.0 $[M]^+$.

3.2.2. Compound 3b

Yield: 56%, White solid. m.p.: 90–91 °C; IR (KBr): υ_{max} 3149.5 (furan-CH), 3064.7 (ArH), 2810.7 (–CH_2–),1714.6 (–C=O), 1587.3 (–C=C–), 1508.2 (–C=C–), 1151.4 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 9.6 Hz, 1H, H-pyrano), 7.67 (d, J = 1.6 Hz, 1H, H-furan), 7.36 (s, 1H, ArH),7.29–7.25 (m, 2H, ArH), 7.01–6.97 (m, 2H, ArH), 6.81 (d, J = 1.6 Hz, 1H, H-furan), 6.36 (d, J = 9.6 Hz, 1H, H-pyrano), 4.60 (t, J = 5.6 Hz, 2H, –O$\underline{CH_2}CH_2$ N), 3.47 (s, 2H, –N($CH_2\underline{CH_2}$)$_2$N$\underline{CH_2}$Ph-F), 2.91 (t, J = 5.6 Hz, 2H, –OCH$_2\underline{CH_2}$ N), 2.64 (s, 4H, –N($CH_2\underline{CH_2}$)$_2$NCH$_2$Ph-F), 2.45 (s, 4H, –N($\underline{CH_2}CH_2$)$_2$NCH$_2$Ph-F); HR-ESI-MS (*m/z*): 423.1 $[M + H]^+$.

3.2.3. Compound 4a

Yield: 42%, White solid. m.p.: 83–85 °C; IR (KBr): υ_{max} 3103.3 (pyrrole-CH), 3028.0 (ArH), 2810.1 (–CH_2–), 1770.5 (–C=O), 1652.9 (–C=C–), 1498.6 (–C=C–), 1188.1 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40–7.38 (m, 4H, ArH), 7.28–7.24 (m, 4H, ArH),7.19–7.15 (m, 2H, ArH), 7.07 (s, 1H, ArH), 7.05 (d, J = 5.4 Hz, 1H, H-pyrrol), 6.69 (d, J = 9.4 Hz, 1H, H-pyrano), 6.29 (d, J = 5.4 Hz, 1H, H-pyrrol), 6.13 (s, 1H, NH), 5.68 (d, J = 9.6 Hz, 1H, H-pyrano), 4.37 (s, 2H, –O$\underline{CH_2}CH_2$ N), 4.20 (s, 1H,-N($CH_2\underline{CH_2}$)$_2$ N$\underline{CH}$(Ph)$_2$), 2.70 (s, 2H, –OCH$_2\underline{CH_2}$ N), 2.53 (s, 4H, –CH_2 N($CH_2\underline{CH_2}$)$_2$NCH–), 2.40 (s, 4H, –CH_2N($\underline{CH_2}CH_2$)$_2$NCH–); EI-MS (*m/z*): 479.0 $[M]^+$.

3.2.4. Compound 4b

Yield: 51%, Light brown solid. m.p. :172–173 °C; IR (KBr): υ_{max} 3178.5 (pyrrole-CH), 3049.3 (ArH), 2813.9 (–CH_2–), 1768.6 (–C=O), 1654.8 (–C=C–), 1510.2 (–C=C–), 1218.9 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H, ArH), 7.08–7.07 (m, 1H, ArH), 7.06 (d, J = 5.6 Hz, 1H, H-pyrrol), 7.01–6.97 (m, 2H, ArH), 6.70 (d, J = 9.6 Hz, 1H, H-pyrano), 6.30 (d, J = 5.6 Hz, 1H, H-pyrrol), 6.15–6.14 (m, 1H, NH), 5.68 (d, J = 9.6 Hz, 1H, H-pyrano), 4.43–4.30 (m, 2H, –O$\underline{CH_2}CH_2$ N), 3.46 (s, 2H, –N($CH_2\underline{CH_2}$)$_2$N$\underline{CH_2}$Ph-F),

2.68 (t, J = 6.4 Hz, 2H, –OCH$_2$CH$_2$ N), 2.51 (s, 4H, –N(CH$_2$CH$_2$)$_2$NCH$_2$Ph-F), 2.42 (s, 4H, –N(CH$_2$CH$_2$)$_2$NCH$_2$Ph-F); HR-ESI-MS (m/z): 422.1 $[M + H]^+$.

3.2.5. Compound 4c

Yield: 43%, Light brown viscous liquid. IR (KBr): υ_{max} 3176.5 (pyrrole-CH), 3105.2 (ArH), 2852.5 (–CH$_2$–), 1764.7 (–C=O), 1596.5 (–C=C–), 1500.5 (–C=C–), 1188.1 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.11–7.10 (m, 1H, ArH), 7.08 (d, J = 5.6 Hz, 1H, H-pyrrol), 6.71 (d, J = 9.2 Hz, 1H, H-pyrano), 6.30 (d, J = 5.6 Hz, 1H, H-pyrrol), 6.15 (s, 1H, ArH), 5.68 (d, J = 9.2 Hz, 1H, H-pyrano), 4.37 (t, J = 6.8 Hz, 2H, –OCH$_2$CH$_2$ N), 2.66–2.58 (m, 2H, –OCH$_2$CH$_2$ N), 2.42–2.41 (m, 4H, –N(CH$_2$CH$_2$)$_2$ CH$_2$), 1.57–1.51 (m, 4H, –N(CH$_2$ CH$_2$)$_2$CH$_2$), 1.43–1.41 (m, 2H, –N(CH$_2$CH$_2$) $_2$CH$_2$); EI-MS (m/z): 312.0 $[M]^+$.

3.2.6. Compound 4d

Yield: 34%, Light brown viscous liquid. IR (KBr): υ_{max} 3178.5 (pyrrole-CH), 3105.2 (ArH), 2875.7 (–CH$_2$–), 1770.5 (–C=O), 1652.9 (–C=C–), 1500.5 (–C=C–), 1190.0 (–C–O–C–) cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.10 (s, 1H, ArH), 7.07 (d, J = 5.6 Hz, 1H, H-pyrrol), 6.71 (d, J = 9.2 Hz, 1H, H-pyrano), 6.30 (d, J = 5.2 Hz, 1H, H-pyrrol), 6.16–6.15 (m, 1H, NH), 5.69 (d, J = 9.6 Hz, 1H, H-pyrano), 4.38 (t, J = 6.8 Hz, 2H, –OCH$_2$CH$_2$ N), 2.81 (t, J = 6.8 Hz, 2H, –OCH$_2$CH$_2$ N), 2.59–2.46 (m, 4H, –N(CH$_2$CH$_2$)$_2$), 1.82–1.67 (m, 4H, –N(CH$_2$CH$_2$)$_2$); EI-MS (m/z): 298.0 $[M]^+$.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was financially supported by the Natural Science Basic Research Plan in Shaanxi Province of China [grant number 2016JM8076].

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