European Journal of Medicinal Chemistry 45 (2010) 1941–1946

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological activity of *n*-butylphthalide derivatives

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ARTICLE INFO

Article history:
Received 19 September 2009
Received in revised form
15 January 2010
Accepted 15 January 2010
Available online 25 January 2010

Keywords:
Vasorelaxant effects
Synthesis
n-Butylphalide

ABSTRACT

A series of *n*-butylphthalide derivatives were designed and synthesized. The *in vitro* activities of these compounds were evaluated by a resting tension of isolated rat thoracic aorta ring assay. Compounds **4g** and **4i** were found to be more active than *n*-butylphthalide.

1. Introduction

Cardiovascular and cerebrovascular disorders are the main reason for morbidity and death in recent years. As reported, *n*-butylphthalide (NBP), the primary naphtha component from seeds of *Apium graveolens* Linn. has completed a phase 3 clinical trial and was approved by the State Food and Drug Administration of China at the end of 2002 as a new drug for the treatment of ischemic stroke in the clinic [1]. Many basic and clinical studies have shown that NBP is a potentially beneficial and promising drug for the treatment of ischemic stroke with multiple actions that affect different pathophysiological processes, such as improving microcirculation, decreasing brain infarct volume, regulating energy metabolism, inhibiting platelet aggregation, and reducing thrombus formation [2–6]. However, drug safety evaluations have demonstrated the main adverse effects of NBP to be liver dysfunction, with slight and moderate increases in the levels of alanine aminotransferase and aspartate aminotransferase, respectively [7].

Recently, Yang and co-workers have reported modifications of NBP with different substituents at the 3-position [8]. However, as platelet aggregation inhibitors, these derivatives were less active than NBP. Substitution on the phthalide aromatic ring with fluorine, to the best of our knowledge, has not been reported. Selective introduction of fluorine into biologically active molecules for modification of their pharmacological behavior is an important endeavor in drug design [9]. There are three important factors in the substitution of fluorine for hydrogen. First, fluorine is the third smallest element and can serve as a replacement for hydrogen without a large steric change; Second, fluorine is the most electronegative element, and its powerful electron withdrawing property can profoundly affect chemical reactivities [10]; Last, the introduction of fluorine into biologically active molecules often increases biological potency without increasing toxicity [11]. In this study, the fluoro analogs of the various forms of NBP were designed and synthesized for the first time, as well as some new chloro and bromo analogs [12].

2. Chemistry

Compounds **4a–i** were prepared from aminophthalide **1a–c** as shown in Scheme 1. Aminophthalide **1a–c** were subjected to standard Sandmeyer or Schieman reactions to give the halogenated derivatives **2a–i**. Treatment of **2a–i** with NBS in dry carbon tetrachloride according to literature procedure [13,14], followed by hydrolysis of the intermediates gave compounds **3a–i**. Finally, the target molecules **4a–i** were obtained by reacting **3a–i** with BuMgBr in THF.

Compounds **8a–b** were synthesized in three steps as outlined in Scheme 2. Commercially available aldehydes **5a–b** were converted to acetals **6a–b** according to a literature procedure [15]. Metalation of **6a–b** using sec-butyllithium followed by reaction with carbon dioxide and then addition of HCl solution furnished hydroxyphthalides **7a** and **7b** in 80% and 28% yield, respectively. The yields varied greatly. It was also found that treatment of *m*-bromobenzaldehyde dimethyl

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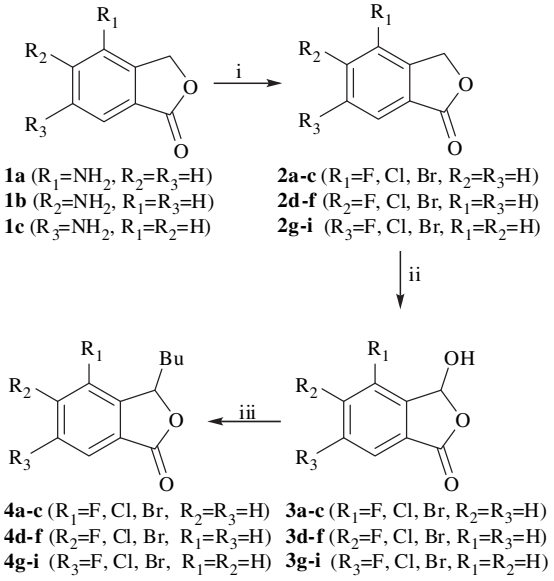
doi:10.1016/j.ejmech.2010.01.036



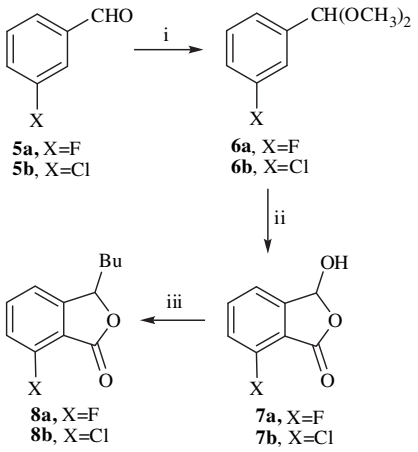
Scheme 1. Reagents and conditions: (i) HBF_4, $NaNO_2$, Δ or HCl, $NaNO_2$, CuCl, 0 °C or HBr, $NaNO_2$, CuBr, Δ; (ii) (1) NBS, CCl_4; (2) H_2O, reflux, 1 h; (iii) (1) BuMgBr, THF, reflux, 1.5 h; (2) H^+, 40 °C, 1 h.

acetal with *sec*-butyllithium followed by addition of CO_2 and then HCl solution did not afford the corresponding hydroxyphthalide. The gradual decrease in electronegativity, as well as the gradual increase in steric bulk from fluorine to bromine may account for these observations. Finally, target compounds **8a**–**b** could be obtained by reacting **7a**–**b** with BuMgBr in THF as described above.

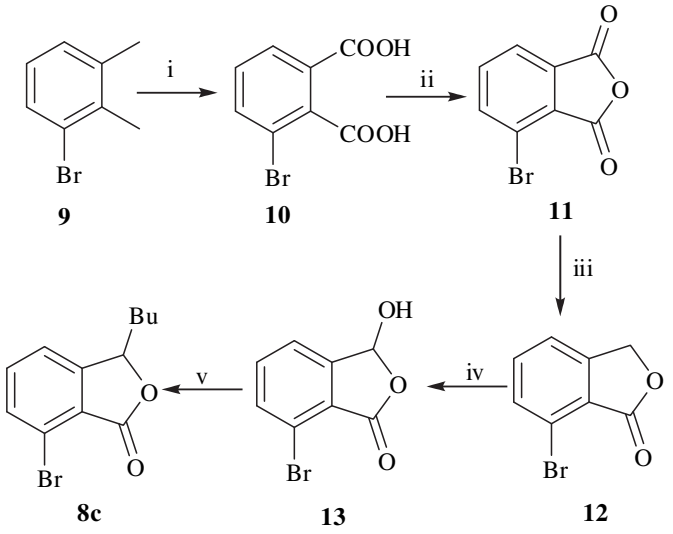
Next, we investigated an alternative method for the synthesis of 7-bromo-3-*n*-butylphthalide **8c**. As shown in Scheme 3, xylene **9** was oxidized to phthalic acid **10** with potassium permanganate. Phthalic acid **10** was refluxed with acetic anhydride to yield phthalic anhydride **11**, which was then reduced with sodium borohydride to give phthalide **12**. The target compound **8c** was prepared from **12** in a similar manner to **4a**–**i** as outlined in Scheme 1.

3. Vasorelaxant effects

The *in vitro* relaxation activities of all compounds were evaluated by a rat thoracic aorta assay. First, the thoracic aorta was quickly isolated and immersed in oxygenated K–H solution at 4 °C,



Scheme 2. Reagents and conditions: (i) trimethyl orthoformate, CH_3OH, *p*-TsOH, rt, 1 h; (ii) (1) *sec*-BuLi,THF, −70 °C; (2) CO_2, -70 °C; (3) H^+; (iii) (1) BuMgBr, THF, reflux, 1.5 h; (2) H^+, 40 °C, 1 h.



Scheme 3. Reagents and conditions: (i) $KMnO_4$, cetyl trimethylammonium bromide, H_2O, 60 °C, 4 days; (ii) Ac_2O, reflux, 1 h; (iii) $NaBH_4$, THF, 0 °C, 20 h; (iv) (1) NBS, CCl_4; (2) H_2O, reflux; (v) (1) BuMgBr, THF, reflux, 1.5 h; (2) H^+, 40 °C, 1 h.

and adherent connective tissue was cleaned. Second, the lower thoracic aorta was cut into a 3–4 mm ring, and the ring was mounted horizontally between two stirrups in an organ bath filled with 20 mL K–H solution at 37 °C, ventilated continuously with 95% O_2 and 5% CO_2. Third, the ring was equilibrated for 60 min at 1.5 g resting tension. Then, the test compound (5.0×10^{-5}–8.0×10^{-4} M) was cumulatively added into the organ bath in 10 min intervals, and the vascular tension subtracted from the resting tension was recorded. PEG-400 was also added into the organ bath as a control and the compound NBP was used for comparison.

Norepinephrine (1.0×10^{-6} M) induced a similar sustained contraction of aortic rings with a peak tension in each group. Then, the test compounds **4g**, **4i** and NBP (2.5×10^{-5}–4.0×10^{-4} M) were respective cumulatively added into the organ bath in 10 min intervals. The contractile responses were recorded as the ratio of the responses following and before the application of the test compounds (second response/first response), and the contraction induced by norepinephrine before the application of vasodilators was recorded as 100%.

All results are expressed as mean ± S.E.M. Statistical analysis was performed with repeated-measures of the ANOVA. Differences were accepted as statistically significant at P values <0.05.

4. Results

The vasorelaxant effects of **4a**–**i** and **8a**–**c** were elucidated as shown in Table 1. Compared with the PEG-400 control group, compounds **4e**, **4f**, **4g** and **4i** (5.0×10^{-5}–8.0×10^{-4} M) produced dose-dependent relaxation. As shown in Table 1, Figs. 1 and 2, compounds **4g** and **4i** are more active than NBP.

The rat thoracic aorta test also showed that compounds **4g** and **4i** can inhibit action of norepinephrine (1.0×10^{-6} M) in Ca^{2+}-free Medium. The IC_{50} of **4g** and **4i** are 131.53 μM and 106.91 μM respectively, while that of NBP is 130.06 μM (Fig. 3).

A mouse acute toxicity test by way of intraperitoneal injection gave LD_{50} for NBP and **4g** of 592.93 mg/kg and 750.89 mg/kg respectively. The LD_{50} for **4i** is more than 1000 mg/kg.

5. Conclusions

In conclusion, a series of *n*-butylphthalide derivatives was designed and synthesized. The activities of all compounds were evaluated *in vitro* by a resting tension and NE-Induced Contractile

Table 1
Effects of NBP derivatives on the resting tension of isolated rat thoracic aorta rings ($X \pm$ SEM, $n = 4$).

Group	Concentration of drugs				
	50 μM	100 μM	200 μM	400 μM	800 μM
Control group	−0.002 ± 0.009	+0.001 ± 0.020	−0.002 ± 0.018	+0.002 ± 0.021	+0.003 ± 0.018
Group NBP	−0.030 ± 0.010*	−0.043 ± 0.021*	−0.063 ± 0.035**	−0.080 ± 0.034*	−0.117 ± 0.049*
Group **4a**	−0.008 ± 0.013	−0.015 ± 0.047	−0.010 ± 0.024	−0.005 ± 0.034	−0.043 ± 0.043
Group **4b**	−0.010 ± 0.042	−0.032 ± 0.037	−0.005 ± 0.064	+0.005 ± 0.074	+0.008 ± 0.079
Group **4c**	+0.025 ± 0.038	+0.023 ± 0.040	+0.078 ± 0.094	+0.005 ± 0.053	−0.030 ± 0.049
Group **4d**	−0.003 ± 0.024	−0.013 ± 0.029	−0.020 ± 0.054	−0.020 ± 0.071	−0.003 ± 0.053
Group **4e**	−0.027 ± 0.021	−0.030 ± 0.017	−0.050 ± 0.030*	−0.100 ± 0.036*	−0.147 ± 0.025**
Group **4f**	−0.023 ± 0.017*	−0.048 ± 0.033*	−0.085 ± 0.036*	−0.115 ± 0.031**	−0.115 ± 0.039**
Group **4g**	−0.037 ± 0.015*	−0.073 ± 0.050*	−0.103 ± 0.080*	−0.110 ± 0.082*	−0.150 ± 0.131*
Group **4h**	−0.003 ± 0.013	+0.020 ± 0.056	+0.018 ± 0.081	+0.050 ± 0.054	+0.055 ± 0.076
Group **4i**	−0.027 ± 0.038	−0.105 ± 0.110*	−0.137 ± 0.123*	−0.182 ± 0.142*	−0.222 ± 0.160**
Group **8a**	+0.000 ± 0.008	−0.005 ± 0.017	−0.013 ± 0.019	−0.005 ± 0.029	+0.013 ± 0.029
Group **8b**	−0.008 ± 0.009	−0.010 ± 0.014	−0.023 ± 0.026	−0.038 ± 0.043	−0.053 ± 0.062
Group **8c**	−0.015 ± 0.031	+0.015 ± 0.017	+0.023 ± 0.026	+0.023 ± 0.040	+0.028 ± 0.053

*$P < 0.05$, **$P < 0.01$, + means contraction, − means relaxation, $n = 4$.

Responses of isolated rat thoracic aorta ring assay. Compounds **4g**, **4i** and NBP have vasorelaxant effects. Further testing of the activity of these compounds will be carried out.

6. Experimental

6.1. Materials and methods

The reagents and solvents used in this study were of analytical grade and were used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-300 spectrometers using TMS as an internal reference. Melting points were determined on a SM/XMT melting point apparatus and are uncorrected. High-resolution mass spectra (HRMS-ESI) were obtained on a Micro™ Q-TOF Mass Spectrometer.

6.2. General procedure for the synthesis of 3-butyl-4-halogen-1(3H)-isobenzofuranone (**4a–c**), 3-butyl-5-halogen-1(3H)-isobenzofuranone (**4d–f**), 3-butyl-6-halogen-1(3H)-isobenzofuranone (**4g–i**)

6.2.1. Synthesis of 3-butyl-4-fluoro-1(3H)-isobenzofuranone (**4a**)

4-aminophthalide **1a** (15.0 g, 60.0 mmo1) was dissolved in 6 M hydrochloric acid (25 mL) and stirred vigorously while cooling with an ice-salt mixture. When the temperature of the mixture has reached 5 °C or below, the diazotization is begun by the slow addition of the sodium nitrite solution (7.0 g, 60.0 mmol), the temperature being held below 5 °C. The mixture was stirred for 0.5 h. The ice-cooled solution of fluoboric acid (20%, 60.0 mL) is then poured in the diazonium solution, while maintaining the temperature below 5 °C during the addition. After 1 h stirring, the

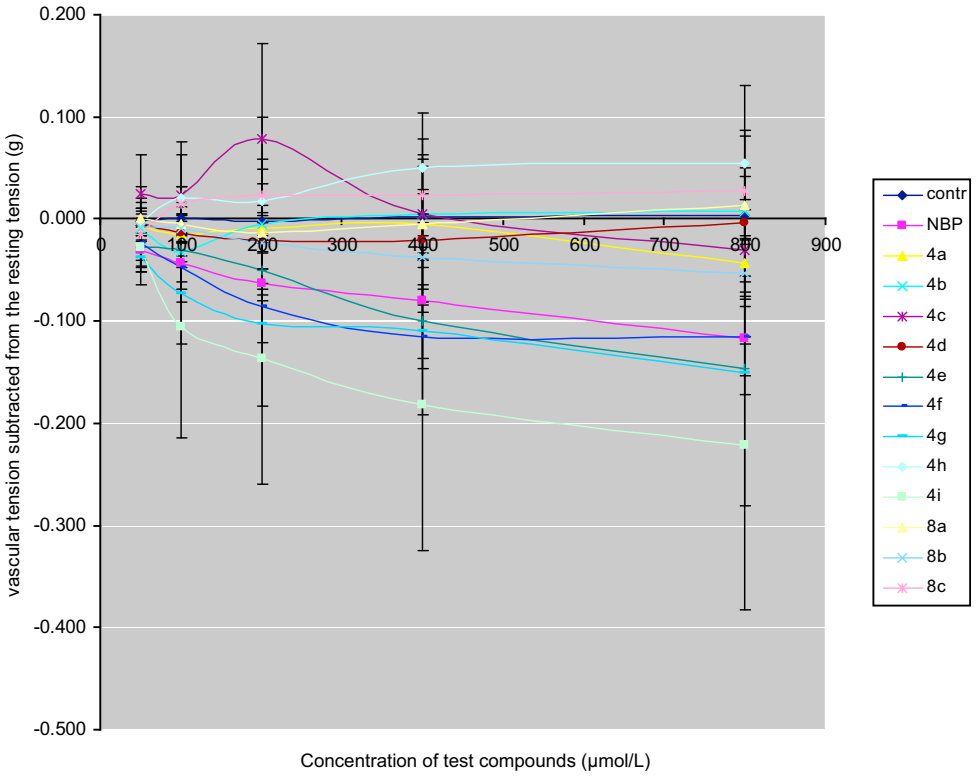


Fig. 1. Effects of NBP derivatives on the resting tension of isolated rat thoracic aorta rings. *$P < 0.05$, compared with PEG-400.

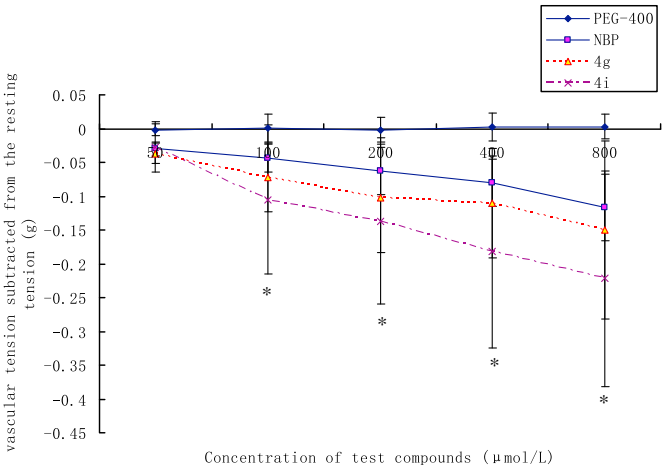


Fig. 2. Effects of compounds **4g**, **4i** and NBP (50–800 μM) on the resting tension of rat thoracic aorta rings. *$P < 0.05$, compared with PEG-400.

mixture is filtered with suction. The solid is washed with cold water, ethanol, diethyl ether and dried under vacuum. The solid is heated at 250 °C, and then the residue was purified by column chromatography to give compound **2a** (2.7 g, 17.6%), mp: 98–99 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.74 (1H, d, $J = 7.7$ Hz), 7.55 (1H, dt, $J = 4.4$, 7.9 Hz), 7.37 (1H, t, $J = 8.1$ Hz), 5.38(2H, s).

A mixture of **2a** (2.1 g, 13.59 mmo1), N-bromosuccinimide (2.4 g, 13.59 mmo1), and dry carbon tetrachloride (36 mL) were refluxed for 30 min, and then the reaction mixture was exposed to the light of an ordinary 100-W unfrosted light bulb placed 6–8 in. from the flask. The end of the reaction is indicated by the disappearance of N-bromosuccinimide from the bottom of the flask and accumulation of succinimide at the top of the reaction mixture. The succinimide was removed by filtration and the filtrate concentrated under vacuum. 15 mL water was added to the residue and stirred for 1 h. The reaction mixture was then placed in a refrigerator overnight. The product was filtered, washed with ice water, and dried in the air to give **3a**.

Under nitrogen atmosphere a 50 mL, three-neck, round-bottom flask, fitted with a reflux condenser, pressure-equalized addition funnel, and a thermometer, was charged with magnesium turnings (0.70 g, 28.33 mmol) and 5 mL of dry ether. The dropping funnel was charged with the 1-bromobutane. At first, 0.5 mL of 1-bromobutane was added to the flask, and the contents were stirred until the Grignard reaction has started. When the initial vigorous reaction had subsided the remainder of the 1-bromobutane solution was then added at a rate such that the mixture refluxed gently. After complete addition, reflux was continued for 1 h by heating with an oil bath. Finally, the reaction mixture was allowed to cool to room temperature. A solution of **3a** (1.74 g, 10.34 mmol) in tetrahydrofuran (17 mL) was added dropwise dropped into the Grignard solution. After completion of addition, the reaction mixture was heated at reflux for 1.5 h using an oil bath, then cooled. Saturated aqueous ammonium chloride (10 mL) was carefully added. The mixture was acidified with concentrated HCl until pH 2 and stirred for 1 h at 40 °C. The solution was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The mixture was purified by column chromatography to give the title compound **4a** (0.78 g, 36.2%), mp: 38–40 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.70 (1H, d, $J = 7.7$ Hz), 7.53 (1H, dd, $J = 4.4$, 8.1 Hz), 7.34 (1H, t, $J = 8.1$ Hz), 5.61(1H, m), 2.21 (1H, m), 1.80 (1H, m), 1.47–1.26 (4H, m), 0.91(3H, t, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$,75 MHz) δ: 169.3, 156.8, 135.8, 131.3, 129.4, 121.6, 120.7, 79.6, 33.1, 26.8, 22.6, 22.5, 13.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −119.73. ESI-TOF/MS for $C_{12}H_{13}FO_2$: calcd: 209.0978 $[M + H]^+$. Found: 209.0972 $[M + H]^+$.

6.2.2. Synthesis of 3-butyl-4-chloro-1(3H)-isobenzofuranone (**4b**)

A solution of **1a** (3.2 g, 21.45 mmo1) in 6 mL of hydrochloric acid (6 M) was placed in a three-neck flask and cooled in an ice bath. A solution of sodium nitrite (1.5 g, 21.45 mmo1) in 6 mL of water placed in the funnel was slowly added to the well-stirred mixture. The temperature of the mixture was maintained between 0 °C and 5 °C throughout the addition of the nitrite solution. The mixture was stirred for 0.5 h. A solution of CuCl (2.1 g, 21.45 mmo1) in hydrochloric acid is cooled to 0 °C. The cold diazonium solution was added to the well-stirred cuprous chloride solution portionwise. The solution was stirred for 1 h at 0 °C. The cold mixture was allowed to warm up to room temperature and stirring was continued for 1.5 h at this temperature, and then refluxed for 1.5 h. The solution was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The mixture was purified by column chromatography to give the title compound **2b** (2.4 g, 66.9%), mp: 88–89 °C.

The compound **4b** was prepared from **2b** (2.3 g, 13.64 mmo1) as described for compound **4a** to give a white powder (1.0 g, 33.0%), mp: 53–54 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.80 (1H, d, $J = 7.7$ Hz), 7.62 (1H, d, $J = 7.8$ Hz), 7.48 (1H, t, $J = 7.7$ Hz), 5.54 (1H, m), 2.37 (1H, m), 1.83 (1H, m), 1.45–1.29 (4H, m), 0.91(3H, t, $J = 6.9$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.3, 146.8, 134.4, 130.7, 128.7, 128.7, 124.1, 81.1, 31.7, 26.5, 22.3, 14.0. ESI-TOF/MS for $C_{12}H_{13}ClO_2$: calcd: 225.0682 $[M + H]^+$. Found: 225.0675 $[M + H]^+$.

6.2.3. Synthesis of 3-butyl-4-bromo-1(3H)-isobenzofuranone (**4c**)

A mixture of **1a** (2.3 g, 15.21 mmo1) and 8 mL hydrobromic acid (40%) in a three-neck flask was cooled in an ice bath. A solution of sodium nitrite (1.1 g, 15.21 mmo1) in 5 mL of water was added slowly, while stirring, the temperature being kept below 5 °C. In the meantime, a mixture of cuprous bromide (1.3 g, 9.13 mmo1) and 10 mL of hydrobromic acid (40%) was heated to 70–75 °C in a three-neck round-bottom flask. The diazonium solution was rapidly poured into the cuprous bromide-hydrobromic acid solution. When the addition was complete, the solution was stirred for 2 h. The solution was cooled to room temperature and extracted with ethyl acetate. The organic layer dried over anhydrous Na_2SO_4. The product was purified by column chromatography to give the title compound **2c** (1.9 g, 59.2%), mp: 102–103 °C.

The compound **4c** was prepared from **2c** (3.1 g, 14.48 mmo1) as described for compound **4a** to give a white powder (2.0 g, 46.6%), mp 39–41 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (1H, dd, $J = 1.1$,

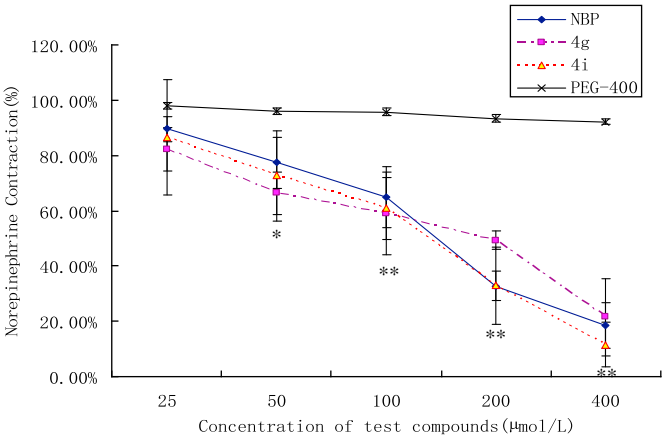


Fig. 3. Vasorelaxant effects of compounds **4g**, **4i** and NBP (25–400 μM) on Norepinephrine (1.0×10^{-6} M) – Induced Contractile Responses of Aortic Rings. *$P < 0.05$, **$P < 0.01$, compared with PEG-400.

7.7 Hz), 7.79 (1H, dd, $J = 1.1$, 7.7 Hz), 7.42 (1H, dt, $J = 0.7$, 7.7 Hz), 5.48 (1H, m), 2.38 (1H, m), 1.85 (1H, m), 1.41–1.26 (4H, m), 0.89 (3H, t, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.3, 148.8, 137.5, 130.8, 128.8, 124.7, 116.6, 82.0, 31.6, 26.5, 22.2, 13.8. ESI-TOF/MS for $C_{12}H_{13}BrO_2$: calcd: 269.0177 $[M + H]^+$. Found: 269.0172 $[M + H]^+$.

*6.2.4. Synthesis of 3-butyl-5-fluoro-1(3H)-isobenzofuranone (**4d**)*

Compound **4d** was synthesized according to the method described previously. Yield: 4.0%, yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88 (1H, dd, $J = 4.8$, 8.4 Hz), 7.24 (1H, dd, $J = 2.2$, 8.7 Hz), 7.16 (1H, dt, $J = 2.2$, 7.8 Hz), 5.46 (1H, m), 2.03 (1H, m), 1.81 (1H, m), 1.44–1.38 (4H, m), 0.89 (3H, t, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.4, 166.5, 152.8, 128.1, 122.2, 117.3, 109.1, 80.7, 32.3, 26.7, 22.4, 13.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −103.44. ESI-TOF/MS for $C_{12}H_{13}FO_2$: calcd: 209.0978 $[M + H]^+$. Found: 209.0974 $[M + H]^+$.

*6.2.5. Synthesis of 3-butyl-5-chloro-1(3H)-isobenzofuranone(**4e**)*

Compound **4e** was synthesized according to the method described previously. Yield: 14.7%, white solid. mp: 68–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82 (1H, d, $J = 8.1$ Hz), 7.49 (1H, d, $J = 8.1$ Hz), 7.43(1H, s), 5.43(1H, m), 2.03 (1H, m), 1.79 (1H, m), 1.49–1.33 (4H, m), 0.91(3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.4, 151.7, 140.7, 129.8, 126.9, 124.8, 122.2, 80.8, 34.3, 26.8, 22.4, 13.8. ESI-TOF/MS for $C_{12}H_{13}ClO_2$: calcd: 225.0682 $[M + H]^+$. Found: 225.0686 $[M + H]^+$.

*6.2.6. Synthesis of 3-butyl-5-bromo-1(3H)-isobenzofuranone (**4f**)*

Compound **4f** was synthesized according to the method described previously. Yield: 19.7%, white solid. mp: 74–76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75(1H, d, $J = 8.1$ Hz), 7.67 (1H, d, $J = 8.1$ Hz), 7.61(1H, d, $J = 0.7$ Hz), 5.44(1H, m), 2.02 (1H, m), 1.75 (1H, m), 1.41–1.26 (4H, m), 0.90(3H, t, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 146.7, 134.3, 132.6, 129.4, 127.0, 125.7, 80.7, 34.3, 26.8, 22.34, 13.8. ESI-TOF/MS for $C_{12}H_{13}BrO_2$: calcd: 269.0177 $[M + H]^+$. Found: 269.0166 $[M + H]^+$.

*6.2.7. Synthesis of 3-butyl-6-fluoro-1(3H)-isobenzofuranone (**4g**)*

Compound **4g** was synthesized according to the method described previously. Yield: 6.7%, white solid. mp: 45–47 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.56–7.38 (3H, m), 5.46(1H, m), 2.02 (1H, m), 1.74 (1H, m), 1.49–1.23(4H, m), 0.92(3H, t, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.4, 163.1, 145.6, 129.3, 123.4, 121.9, 112.0, 81.3, 34.5, 26.8, 22.4, 13.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −112.17. ESI-TOF/MS for $C_{12}H_{13}FO_2$: calcd: 231.0797 $[M + Na]^+$. Found: 231.0804 $[M + Na]^+$.

*6.2.8. Synthesis of 3-butyl-6-chloro-1(3H)-isobenzofuranone (**4h**)*

Compound **4h** was synthesized according to the method described previously. Yield: 13.7%, white solid. mp: 69–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.85 (1H, d, $J = 1.8$ Hz), 7.63 (1H, dd, $J = 1.8$, 8.1 Hz), 7.37 (1H, dd, $J = 0.7$, 8.1 Hz), 5.46(1H, m), 2.04 (1H, m), 1.76 (1H, m), 1.48–1.35 (4H, m), 0.91(3H, t, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.1, 148.2, 135.3, 134.2, 128.0, 125.6, 123.0, 81.3, 34.3, 26.8, 22.4, 13.8. ESI-TOF/MS for $C_{12}H_{13}ClO_2$: calcd: 225.0682 $[M + H]^+$. Found: 225.0674 $[M + H]^+$.

*6.2.9. Synthesis of 3-butyl-6-bromo-1(3H)-isobenzofuranone (**4i**)*

Compound **4i** was synthesized according to the method described previously. Yield: 12.9%, white solid. mp: 73–75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.02 (1H, d, $J = 1.8$ Hz), 7.77 (1H, dd, $J = 1.8$, 8.1 Hz), 7.32 (1H, d, $J = 8.1$ Hz), 5.43(1H, m), 2.03 (1H, m), 1.76 (1H, m), 1.56–1.35 (4H, m), 0.90(3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.9, 148.7, 136.9, 128.6, 128.3, 123.3, 122.9, 81.3, 34.2, 26.7, 22.3, 13.8. ESI-TOF/MS for $C_{12}H_{13}BrO_2$: calcd: 269.0177 $[M + H]^+$. Found: 269.0178 $[M + H]^+$.

*6.3. General procedure for the synthesis of 3-butyl-7-halogen-1(3H)-isobenzofuranone (**8a–c**)*

*6.3.1. Synthesis of 3-butyl-7-fluoro-1(3H)-isobenzofuranone (**8a**)*

A mixture of *m*-fluorobenzaldehyde (20.0 g, 161.2 mmol), trimethyl orthoformate (20 mL), methanol (100 mL), and *p*-toluenesulfonic acid (0.2 g) was stirred at room temperature for 1 h. The reaction mixture was quenched with 1% CH_3OH/KOH (40 mL), concentrated in vacuo, and then worked up as usual to afford after distillation the dimethyl acetal **6a**.

To a −70 °C solution of the dimethyl acetal from above (5.3 g, 31 mmol) in THF (35 mL) was added dropwise *sec*-butyllithium (22.2 mL of a 1.4 M solution in hexane), and the red solution was stirred for 0.5 h. The solution was saturated with CO_2 for 5 min with the red color disappearing to yield a light yellow solution. After 10 min the reaction mixture was allowed to warm to room temperature, and after 30 min HCl (3.5 mL) was added. After concentration the solution was made basic with 5% KOH (25 mL), the neutral material extracted with diethyl ether, the base layer acidified to pH 1 with HCl, and the product extracted with ethyl acetate. Workup as usual afforded **7a**. The compound suitable for use in the next step.

The compound **8a** was prepared from **7a** (9.1 g, 54.13 mmol) as described for compound **4a** to give a white powder (5.3 g, 46.8%), mp: 41–42 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.66 (1H, dt, $J = 4.4$, 7.7 Hz), 7.22 (1H, d, $J = 7.7$ Hz), 7.15 (1H, t, $J = 8.4$ Hz), 5.46 (1H, m), 2.04 (1H, m), 1.77 (1H, m), 1.46–1.35(4H, m), 0.91(3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.5, 161.1, 157.6, 152.6, 136.5, 117.7, 115.7, 80.9, 34.1, 26.6, 22.1, 13.6. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −115.24. ESI-TOF/MS for $C_{12}H_{13}FO_2$: calcd: 209.0978 $[M + H]^+$. Found: 209.0971 $[M + H]^+$.

*6.3.2. Synthesis of 3-butyl-6-chloro-1(3H)-isobenzofuranone (**8b**)*

Compound **8b** was synthesized according to the method described above. Yield: 9.1%, white solid. mp: 48–49 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.59 (1H, t, $J = 7.7$ Hz), 7.46 (1H, d, $J = 7.7$ Hz), 7.34 (1H, d, $J = 7.7$ Hz), 5.42 (1H, m), 2.04 (1H, m), 1.75 (1H, m), 1.49–1.33 (4H, m), 0.90(3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.5, 152.5, 134.9, 133.3, 130.4, 122.9, 120.1, 79.9, 34.4, 26.8, 22.4, 13.8. ESI-TOF/MS for $C_{12}H_{13}ClO_2$: calcd: 225.0682 $[M + H]^+$. Found: 225.0675 $[M + H]^+$.

*6.3.3. Synthesis of 3-butyl-6-bromo-1(3H)-isobenzofuranone (**8c**)*

2,3-Dimethylbromobenzene (50.8 g, 274.7 mmol), water (300 mL), cetyl trimethylammonium bromide (0.05 g) were placed in a round-bottom flask equipped with a condenser. $KMnO_4$ (174.0 g, 990.8 mmol) was added in several portions to the reaction mixture and vigorously stirred at 60 °C. The reaction took approximately 4 days. MnO_2 was filtered and the filtrate acidified at 0 °C with concentrated HCl until pH 1. Repeated extractions with ether gave **10**. The compound **10** was refluxed for 1 h with acetic anhydride (24.0 g) and then cooled in an ice bath. The formed white crystals were filtered, washed with cold ether. The suspension of crushed $NaBH_4$ (10 mmol, dried at 120 °C in vacuum), in dry tetrahydrofuran (120 mL), was refluxed for 15 min and then cooled in an ice bath. A solution of **10** (3.6 g, 16.0 mmol) in dry tetrahydrofuran (80 mL) was added dropwise to a stirred, ice-cold suspension of $NaBH_4$. The stirring was continued for 20 h. After quenching with 3 N HCl (to pH 1), 10 mL water was added and stirring continued overnight. The solution was extracted with diethyl ether and dried over anhydrous Na_2SO_4. The mixture was purified by column chromatography to give the **12**. The target compound **8c** (0.6 g, 29.7%) was prepared from **12** (1.1 g, 7.70 mmo1) in a similar manner to **4a–i** as outlined in Scheme 1. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.67 (1H, d, $J = 7.7$ Hz), 7.50 (1H, t, $J = 7.7$ Hz), 7.38 (1H, d, $J = 7.7$ Hz), 5.40 (1H, m), 2.03 (1H, m), 1.76 (1H, m), 1.61–1.35 (4H, m), 0.90 (3H, t, $J = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.9, 152.6, 134.8, 133.7, 124.5, 121.0, 120.7, 79.6,

34.4, 26.8, 22.4, 13.8. ESI-TOF/MS for $C_{12}H_{13}BrO_2$: calcd: 269.0177 $[M + H]^+$. Found: 269.0174 $[M + H]^+$.

Acknowledgement

We are indebted to the National Natural Science Foundation of China (NO. 20672030) and the Outstanding Young Scholarship of the NSFC (NO. 30825043) for funding. Finally, we are grateful to Professor Jingxi Xie for his many helpful suggestions to improve the manuscript.

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