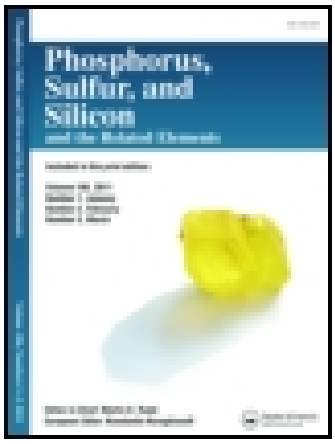

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Synthesis and Characterization of Phosphoramide Piperazine Analogues of Paeonol

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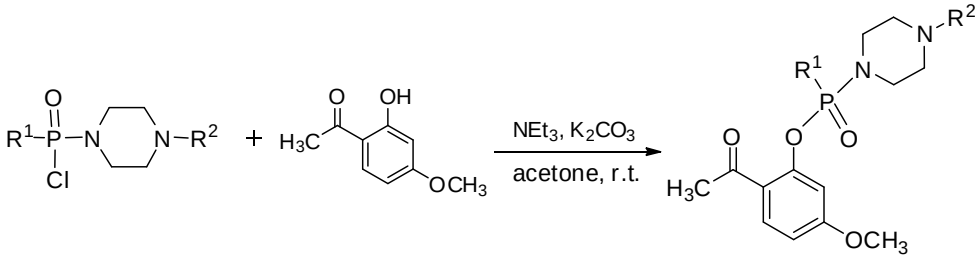
Abstract: Based on the phosphorylated reaction, an efficient general synthetic approach that provide facile, rapid and cheap access to a wide range of novel phosphoramide derivatives of paeonol has been developed. These analogues of paeonol are synthesized in high yields and elucidated by IR, HR MS and NMR.



***Keywords*:** paeonol, piperazine, phosphoramide, synthesis

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INTRODUCTION

Paeonol, 2-hydroxyl-4-methoxyacetophenone (**Fig. 1**), is one of the main components of Moutan Cortex. It is a traditional Chinese medicine with analgesic,[1] antiallergic,[2] antioxidative,[3] Antitumor,[4,5] anti-inflammatory and antimicrobial[6] properties and has been used as a remedy for cardiovascular and female genital diseases.[7, 8] But the nature of water insolubility and volatility of paeonol makes it difficult to exert its efficiency sufficiently. The impressive wide range of biological activities of paeonol has generated great research interest in the synthesis of various paeonol derivatives.[9, 10]

The piperazine scaffold has been classified as a privileged structure and is frequently found in biologically active compounds across a number of different therapeutic areas. Some of these therapeutic areas include antifungal, HIV protease inhibitor,[11] antitumor,[12] and antiviral therapy.[13] *N*-substituted piperazine pharmacophores are found in numerous drug molecules. Furthermore, an alkylating nitrogen mustard, representing one of the earliest design strategies in cancer chemotherapy, is usually used as an antineoplastic agent.[14] Phosphates and phosphoramidates were widely used as prodrug moieties to enhance desired biological activities and have proven to be exceedingly important agents for anticancer and antiviral therapy.[15,16] Moreover, the introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes to the polarization and intermolecular bonding characteristics of that molecule.[17]

The insertion of different biologically active groups into a single molecule already became an important strategy in finding new medicinal preparations. We have previously reported the synthesis of phosphoramide derivatives of coumarin[18] and quinoline,[19] etc. To the best of our

knowledge, there are no reports concerning phosphoramide derivatives of paeonol. As a continuation of our previous work, we reported here the synthesis of a novel type of phosphoramide piperazine derivatives of paeonol, in which two pharmic groups, piperazine and mustard were smoothly coupled with paeonol (**Scheme 1**), to improve their desirable physicochemical and biological properties. The structures of compounds **4a-h** are elucidated by IR, HR MS and NMR for the first time.

RESULT AND DISCUSSION

The title compounds were synthesized using a facile phosphorylated reaction, and the synthetic procedure was shown in **Scheme 1**. First, phosphorodichloridates **1** reacted with *N*-substituted piperazine hydrochlorides **2** in dichloromethane at low temperature to give phosphochloridates **3**, which were used without further purification in the following step to couple with paeonol at room temperature and yielded products **4**. It should be mentioned that the overall yield of the reaction was substantially affected by several factors, such as reaction temperature, molar ratio of the related reactants and their addition sequence. The results showed that for the first step, the temperature need to be kept at a relatively low temperature (-78 °C), and meanwhile the molar equivalent *N*-substituted piperazine hydrochlorides **2** must be added to the dichloromethane solution of phosphorodichloridates **1** in small portions with constant stirring. The byproducts (disubstituted phosphinamides or phosphinates) formation were therefore inhibited effectively by choosing a suitable reaction condition. For the second step, when the crude phosphochloridates **3** were couple with paeonol in the presence of triethylamine at room temperature, no products 4 were obtained. Increasing the reaction temperature to reflux condition or prolong the reaction time to 48 h afforded a small amount of products **4** . In the

structure of paeonol, there is an intramolecular hydrogen bond between H atom of hydroxyl and O atom of carbonyl, making the nucleophilic substitution reaction between the phosphochloridates **3** and paeonol difficult to occur. To obtain the products **4**, addition of a small amount of potassium carbonate was necessary. The results showed that the reaction between phosphochloridates **3** and paeonol proceeded successfully in the presence of triethylamine and potassium carbonate at room temperature, producing a series of novel phosphoramide piperazine derivatives of paeonol **4** as shown in **Table 1**.

IR spectra of phosphoramide piperazine derivatives of paeonol **4a-h** show a strong absorption band in the region 1252-1268 cm^{-1}, which are ascribed to P=O stretching vibrations. The absorption bands in the region 1021-1039 cm^{-1} could be assigned to P–O stretching vibrations. One strong absorption band of 1677-1696 cm^{-1} corresponds to the C=O stretching vibrations of paeonol group. The typical absorption band for O–H (at about 3400 cm^{-1}) group of paeonol is not observed in the IR spectra of phosphoramide piperazine derivatives of paeonol **4a-h**, which indicates that the hydroxyl group of paeonol was phosphorylated.

Several characteristic resonances are appeared in the NMR spectra of **4a-h.** The chemical shift of ^{31}P NMR in compounds **4a-e** (**Fig. 2a**) is -1.97 – -4.80 ppm, and that of compound **4f-h** (**Fig. 2b**) is about 10.5 ppm. ^{13}C NMR signals of C-1, C-2, C-6, C-10(12), C-11(13), C-14 and C-15(15′) for compound **4a-h** are split into doublet by the nearby phosphorus atom, and the values of these signal peaks and coupling constants are shown in **Table 2**. The result gave a decisive conclusion that the phosphorylation reaction occurred at 1-OH of paeonol. Notably different $^{2}J_{P\text{-}C}$ and $^{3}J_{P\text{-}C}$ coupling constants of carbon atoms were shown. $^{2}J_{(P,\,C)}$ and $^{3}J_{(P,\,C)}$ coupling constants for the aryl carbon atoms are $^{2}J_{(P,\,C\text{-}1)} \approx {}^{3}J_{(P,\,C\text{-}6)} > {}^{3}J_{(P,\,C\text{-}2)}$; $^{2}J_{(P,\,C\text{-}14)} > {}^{3}J_{(P,\,C\text{-}15(15'))}$. On the

contrary, $^{2}J_{(P, C)}$ and $^{3}J_{(P, C)}$ coupling constants for heterocyclic piperazine carbon atoms coupled with phosphorus atom are $^{3}J_{(P, C\text{-}11(13))} > {}^{2}J_{(P, C\text{-}10(12))}$. Interestingly, the signals of C-11(13) for compound **4b** and **4g** is distinctive. The chemical shifts of **4b** and **4g** shift to high-field, and the coupling constants of the peaks decrease or the split is not observed. It can be attributed to the existence of the strong electron-withdrawing $(CH_3)_3C$-O-CO group.

CONCLUSION

In summary, a highly efficient synthesis of phosphoramide derivatives of paeonol has been developed using a facile phosphorylated reaction. A novel series of phosphoramide piperazine analogues of paeonol are synthesized in high yields and their structures are elucidated by IR, HR MS and NMR. The research progress of their biological activities are ongoing.

EXPERIMENTAL

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions. IR spectra were recorded with a Shimadazu IR-408 spectrophotometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer operating at 400.13, 100.61, and 161.98 MHz, respectively, with ^{13}C and ^{31}P NMR spectra being recorded with broad band proton decoupled. All NMR spectra were recorded in $CDCl_3$ at room temperature (20 ± 3 °C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. ^{31}P chemical shifts are quoted in parts per million relative to 85% H_3PO_4 as an external standard. *J* values refer to coupling constants, and signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or combinations thereof. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200-300

mesh). High resolution mass spectra (HR MS) were obtained with a Waters Micromass Q-Tof Micro instrument using the ESI technique.

General Procedure

Synthesis of Phosphodichloridates 1

Phosphodichloridates 1 were prepared according to the literature.[18,19]

Synthesis of *N*-substituted Piperazine Hydrochlorides 2

N-substituted piperazine hydrochlorides **2a-e** were synthesized following the procedures.[18,20]

Synthesis of Phosphorochloridates 3a-h

N-substituted piperazine hydrochloride salt **2** (2.0 mmol) was added to anhydrous dichloromethane (30 mL) solution of phosphodichloridate **1** (2.0 mmol) with constant stirring. Anhydrous triethylamine (1.4 mL, 10.0 mmol) was then added dropwise at -78 °C for 10 min, and the reaction mixture was left to warm up to room temperature. After 8 h, the solvent was evaporated under reduced pressure, and the residue was washed with anhydrous ether and was filtered. The filtrate was evaporated to dryness under reduced pressure. The crude phosphochloridates **3a-h** were obtained and used without further purification.

Synthesis of Phosphoramide Piperazine Analogues of paeonol (4)

The solution of phosphorochloridate **3a-h** (2 mmol) in 5 mL anhydrous acetone was added dropwise to a solution of paeonol (0.332 g, 2 mmol), anhydrous triethylamine (0.3 mL, 2.0 mmol), and potassium carbonate (0.276 g, 2mmol) in anhydrous acetone (20 mL) at room temperature. The reaction mixture was stirred for 20 h. The precipitation was filtered off, and the filtrate was evaporated under reduced pressure to give the residues as the yellow liquid. The

crude products were purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 2 : 1, v : v). The phosphoramide piperazine analogues of paeonol **4a-h** were obtained.

Compound 4a: Light yellow liquid, IR(KBr), ν(cm^{-1}): 1679 (C=O), 1604, 1455 (Ar), 1268 (P=O), 1027 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.72 (d, *J* = 8.8 Hz, 1H, 5-H), 7.29 (t, *J* = 7.8 Hz, 2H, 16, 16′-H), 7.21 (d, *J* = 7.8 Hz, 2H, 15, 15′-H), 7.13 (t, *J* = 7.6 Hz, 1H, 17-H), 7.08 (s, 1H, 2-H), 6.70 (d, *J* = 8.8 Hz, 1H, 4-H), 3.79 (s, 3H, 9-H), 3.29 (m, 4H, 10, 12-H), 2.51 (s, 3H, 8-H), 2.23 (m, 4H, 11, 13-H), 2.17 (s, 3H, N$C\underline{H}_3$). ^{13}C NMR ($CDCl_3$) δ: 196.3 (7-C), 163.5 (3-C), 151.1 (d, *J* = 7.1 Hz, 1-C), 150.4 (d, *J* = 6.5 Hz, 14-C), 132.1 (5-C), 129.7 (16, 16′-C), 125.0 (17-C), 123.1 (d, *J* = 7.0 Hz, 6-C), 119.9 (d, *J* = 5.1 Hz, 15, 15′-C), 110.6 (4-C), 106.0 (d, *J* = 2.8 Hz, 2-C), 55.6 (9-C), 54.5 (d, *J* = 5.6 Hz, 11, 13-C), 46.1 (N$\underline{C}H_3$), 44.4 (d, *J* = 1.9 Hz, 10, 12-C), 30.7 (8-C). ^{31}P NMR ($CDCl_3$) δ: -1.9. HR MS 405.1570 $[M+H]^+$ (calculated for $C_{20}H_{26}N_2O_5P$ 405.1574).

Compound 4b: Light yellow liquid, IR(KBr), ν(cm^{-1}): 1696 (C=O), 1606, 1448 (Ar), 1263 (P=O), 1027 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.72 (d, *J* = 8.8 Hz, 1H, 5-H), 7.30 (m, 2H, 16, 16′-H), 7.20 (d, *J* = 8.8 Hz, 2H, 15, 15′-H), 7.14 (t, *J* = 7.2 Hz, 17-H), 7.06 (d, *J* = 1.2 Hz, 1H, 2-H), 6.71 (dd, *J* = 8.8, 1.6 Hz, 1H, 4-H), 3.79 (s, 3H, 9-H), 3.24 (m, 8H, 10, 11, 12, 13-H), 2.51 (s, 3H, 8-H), 1.39 (s, 9H, -C($C\underline{H}_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 196.5 (7-C), 163.6 (3-C), 154.4 (-$\underline{C}OOC(CH_3)_3$), 151.0 (d, *J* = 6.9 Hz, 1-C), 150.4 (d, *J* = 6.4 Hz, 14-C), 132.2 (5-C), 129.8 (16, 16′-C), 125.2 (17-C), 123.1 (d, *J* = 7.0 Hz, 6-C), 119.9 (d, *J* = 5.2 Hz, 15, 15′-C), 110.7 (4-C), 106.3 (d, *J* = 2.8 Hz, 2-C), 80.1 (-COO$\underline{C}(CH_3)_3$), 55.7 (9-C), 44.4 (d, *J* = 1.7 Hz, 10,12-C), 44.3 (d, *J* = 2.8 Hz, 11,13-C), 30.6 (8-C), 28.3 (-COOC($\underline{C}H_3$)$_3$). ^{31}P NMR ($CDCl_3$) δ: -2.2. HR MS 491.1939 $[M+H]^+$ (calculated for $C_{24}H_{32}N_2O_7P$ 491.1942).

Compound 4c: Colorless liquid, IR(KBr), ν(cm^{-1}): 1677 (C=O), 1604, 1450 (Ar), 1264 (P=O), 1029 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.77 (dd, *J* = 8.8, 1.0 Hz, 1H, 5-H), 7.35 (t, *J* = 8.0 Hz, 2H, 16, 16′-H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.20 (m, 3H, 15, 15′, 17-H), 7.14 (dd, *J* = 2.2, 1.0 Hz, 1H, 2-H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.76 (dd, *J* = 8.8, 2.2 Hz, 1H, 4-H), 3.85 (s, 3H, 9-H), 3.47 (m, 4H, 11, 13-H), 3.01 (t, *J* = 4.8 Hz, 4H, 10, 12-H), 2.57 (s, 3H, 8-H). ^{13}C NMR ($CDCl_3$) δ: 196.6 (7-C), 163.7 (3-C), 151.1 (d, *J* = 7.0 Hz, 1-C), 150.5 (d, *J* = 6.5 Hz, 14-C), 149.8, 132.2 (5-C), 129.9 (16, 16′-C), 129.0, 125.4 (17-C), 125.3, 123.2 (d, *J* = 6.8 Hz, 6-C), 120.0 (d, *J* = 5.1 Hz, 15, 15′-C), 117.9, 110.7 (4-C), 106.4 (d, *J* = 2.7 Hz, 2-C), 55.8 (9-C), 49.6 (d, *J* = 5.4 Hz, 11, 13-C), 44.5 (d, *J* = 1.9 Hz, 10, 12-C), 30.7 (8-C). ^{31}P NMR ($CDCl_3$) δ: -2.4. HR MS 501.1338 $[M+H]^+$ (calculated for $C_{25}H_{27}ClN_2O_5P$ 501.1341).

Compound 4d: Light yellow liquid, IR(KBr), ν(cm^{-1}): 1681 (C=O), 1603, 1482 (Ar), 1265 (P=O), 1021 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, *J* = 8.8 Hz, 1H, 5-H), 7.35 (t, *J* = 8.2 Hz, 2H, 16,16′-H), 7.26 (m, 5H), 7.15 (m, 3H), 6.76 (dd, *J* = 8.8, 2.0 Hz, 1H, 4-H), 3.85 (s, 3H, 9-H), 3.77 (s, 3H, O$\underline{C}H_3$), 3.49 (bs, 4H, 11,13-H), 2.96 (bs, 4H, 10,12-H), 2.58 (s, 3H, 8-H). ^{13}C NMR ($CDCl_3$) δ: 196.6 (7-C), 163.7 (3-C), 154.5, 151.2 (d, *J* = 7.2 Hz, 1-C), 150.5 (d, *J* = 6.3 Hz, 14-C), 132.2 (5-C), 129.8 (16, 16′-C), 125.4 (17-C), 125.2, 123.2 (d, *J* = 7.0 Hz, 6-C), 120.0 (d, *J* = 5.1 Hz, 15,15′-C), 119.0, 114.5, 110.8 (4-C), 106.3 (d, *J* = 2.7 Hz, 2-C), 55.8 (9-C), 55.5 (O$\underline{C}H_3$), 51.1 (d, *J* = 5.1 Hz, 11,13-C), 44.7 (10,12-C), 30.7 (8-C). ^{31}P NMR ($CDCl_3$) δ: -2.2. HR MS 497.1838 $[M+H]^+$ (calculated for $C_{26}H_{30}N_2O_6P$ 497.1836).

Compound 4e: Colorless liquid, IR(KBr), ν(cm^{-1}): 1677 (C=O), 1604, 1450 (Ar), 1264 (P=O), 1029 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, *J* = 8.8 Hz, 1H, 5-H), 7.36 (t, *J* = 7.9 Hz, 2H, 16, 16′-H), 7.27 (m, 5H), 7.16 (m, 3H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1H, 4-H), 3.85 (s, 3H, 9-H), 3.78 (s,

3H, OC<u>H</u>$_3$), 3.47 (bs, 4H, 11,13-H), 3.05 (bs, 4H, 10,12-H), 2.58 (s, 3H, 8-H). ^{13}C NMR ($CDCl_3$) δ: 196.6 (7-C), 163.7 (3-C), 160.6, 151.2 (d, *J* = 7.0 Hz, 1-C), 150.5 (d, *J* = 6.2 Hz, 14-C), 132.2 (5-C), 130.9, 129.8 (16, 16′-C), 128.8, 125.2 (17-C), 123.2 (d, *J* = 7.1 Hz, 6-C), 120.0 (d, *J* = 5.1 Hz, 15, 15′-C), 110.7 (4-C), 109.3, 106.3 (d, *J* = 2.7 Hz, 2-C), 103.2, 55.8 (9-C), 55.2 (O<u>C</u>H$_3$), 49.5 (d, *J* = 4.3 Hz, 11,13-C), 44.6 (10,12-C), 30.8 (8-C). ^{31}P NMR ($CDCl_3$) δ: -4.8. HR MS 497.1839 $[M+H]^+$ (calculated for $C_{26}H_{30}N_2O_6P$ 497.1836).

Compound **4f:** Light yellow liquid, IR(KBr), ν(cm^{-1}): 1679 (C=O), 1606, 1458 (Ar), 1255 (P=O), 1028 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, *J* = 8.8 Hz, 1H, 5-H), 7.28 (d, *J* = 2.4 Hz, 1H, 2-H), 6.70 (dd, *J* = 8.8, 2.4 Hz, 1H, 4-H), 3.84 (s, 3H, 9-H), 3.63 (m, 4H, 15, 17-H), 3.50 (m, 4H, 14, 16-H), 3.26 (m, 4H, 11,13-H), 2.54 (s, 3H, 8-H), 2.31 (m, 4H, 12, 14-H), 2.24 (s, 3H, NC<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$) δ: 196.5 (7-C), 163.5 (3-C), 151.2 (d, *J* = 6.4 Hz, 1-C), 132.3(5-C), 122.5 (d, *J* = 6.8 Hz, 6-C), 110.3 (4-C), 106.4 (d, *J* = 3.0 Hz, 2-C), 55.8 (9-C), 55.0 (d, *J* = 5.8 Hz, 11, 13-C), 49.5 (d, *J* = 4.4 Hz, 14, 16-C), 46.2 (N<u>C</u>H$_3$), 44.6 (d, *J* = 1.7 Hz, 10, 12-C), 42.2 (15, 17-C), 29.8 (8-C). ^{31}P NMR ($CDCl_3$) δ: 10.9. HR MS 452.1263 $[M+H]^+$ (calculated for $C_{18}H_{29}Cl_2N_3O_4P$ 452.1267).

Compound **4g:** Light yellow liquid, IR(KBr), ν(cm^{-1}): 1686 (C=O), 1605, 1456 (Ar), 1252 (P=O), 1029 (P-O). ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, *J* = 8.8 Hz, 1H, 5-H), 7.31 (dd, *J* = 2.4, 0.8 Hz, 1H, 2-H), 6.72 (dd, *J* = 8.8, 2.4 Hz, 1H, 4-H), 3.85 (s, 3H, 9-H), 3.62 (m, 4H, 15,17-H), 3.42 (m, 4H, 14,16-H), 3.30 (m, 4H, 11,13-H), 3.20 (m, 4H, 12,14-H), 2.55 (s, 3H, 8-H), 1.44 (s, 9H, -C(C<u>H</u>$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 196.5 (7-C), 163.5 (3-C), 154.5 (-<u>C</u>OOC(CH$_3$)$_3$), 151.2 (d, *J* = 6.4 Hz, 1-C), 132.4 (5-C), 122.3 (d, *J* = 6.6 Hz, 6-C), 110.2 (4-C), 106.5 (d, *J* = 2.9 Hz, 2-C), 80.1 (-<u>C</u>(CH$_3$)$_3$), 55.8 (9-C), 49.4 (d, *J* = 4.4 Hz, 14,16-C), 44.5 (d, *J* = 1.9 Hz, 10,12-C), 44.3

(11,13-C), 42.2 (15,17-C), 29.8 (8-C), 28.3 (-C(CH$_3$)$_3$). ^{31}P NMR ($CDCl_3$) δ: 10.5. HR MS 538.1631 $[M+H]^+$ (calculated for $C_{22}H_{35}Cl_2N_3O_6P$ 538.1635).

Compound **4h:** Light yellow liquid, IR(KBr), ν(cm^{-1}): 1680 (C=O), 1602, 1452 (Ar), 1256 (P=O), 1039 (P-O). ^{1}H NMR ($CDCl_3$) δ 7.69 (d, *J* = 8.8 Hz, 1H, 5-H), 7.33 (dd, *J* = 2.4, 0.8 Hz, 1H, 2-H), 6.71 (dd, *J* = 8.8, 2.4 Hz, 1H, 5-H), 3.85 (s, 3H, 9-H), 3.78 (s, 3H, OCH$_3$), 3.72 (m, 4H, 15,17-H), 3.52 (m, 4H, 14,16-H), 3.42 (m, 4H, 11,13-H), 3.05 (m, 4H, 12,14-H), 2.56 (s, 3H, 8-H). ^{13}C NMR ($CDCl_3$) δ: 196.6 (7-C), 163.6 (3-C), 160.5, 152.5, 151.2 (d, *J* = 6.5 Hz, 1-C), 132.4 (5-C), 129.9, 122.5 (d, *J* = 6.7 Hz, 6-C), 110.2 (4-C), 109.2, 106.5 (d, *J* = 3.0 Hz, 2-C), 105.2, 102.9, 55.8 (9-C), 55.2 (OCH$_3$), 49.7 (d, *J* = 5.8 Hz, 11,13-C), 49.4 (d, *J* = 4.4 Hz, 14,16-C), 44.7 (d, *J* = 2.1 Hz,10,12-C), 42.3 (15,17-C), 29.8 (8-C). ^{31}P NMR ($CDCl_3$) δ: 10.6. HR MS 544.1527 $[M+H]^+$ (calculated for $C_{24}H_{33}Cl_2N_3O_5P$ 544.1529).

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Table 1 Phosphoramide piperazine derivatives of paeonol

Entry	R^1	R^2	Yield (%)
4a	C_6H_5O	CH_3	80
4b	C_6H_5O	$(CH_3)_3C–O–CO$	78
4c	C_6H_5O	p-$Cl–C_6H_4$	71
4d	C_6H_5O	p-$CH_3O–C_6H_4$	77
4e	C_6H_5O	m-$CH_3O–C_6H_4$	71
4f	$(ClCH_2CH_2)_2N$	CH_3	80
4g	$(ClCH_2CH_2)_2N$	$(CH_3)_3C–O–CO$	79
4h	$(ClCH_2CH_2)_2N$	m-$CH_3O–C_6H_4$	86

Table 2. The data of ^{31}P NMR and partial ^{13}C NMR split by phosphor atom for **4a-h**

Entry	^{31}P NMR	^{13}C NMR						
		δ_{C-1}	δ_{C-2}	δ_{C-6}	$\delta_{C-10(12)}$	$\delta_{C-11(13)}$	δ_{C-14}	$\delta_{C-15, 15'}$
		^2J(Hz)	^3J(Hz)	^3J(Hz)	^2J(Hz)	^3J(Hz)	^2J(Hz)	^3J(Hz)
4a	-1.9	151.1 7.1	106.0 2.8	123.1 7.0	44.4 1.9	54.5 5.6	150.4 6.5	119.9 5.1
4b	-2.2	151.0 6.9	106.3 2.8	123.1 7.0	44.4 1.7	44.3 2.8	150.4 6.4	119.9 5.2
4c	-2.4	151.1 7.0	106.4 2.7	123.2 6.8	44.5 1.9	49.6 5.4	150.5 6.5	120.0 5.1
4d	-2.2	151.2 7.2	106.3 2.7	123.2 7.0	44.7 /	51.1 5.1	150.5 6.3	120.0 5.1
4e	-4.8	151.2 7.0	106.3 2.7	123.2 7.1	44.6 /	49.5 4.3	150.5 6.2	120.0 5.1
4f	10.9	151.2 6.4	106.4 3.0	122.5 6.8	44.6 1.7	55.0 5.8	49.5 4.4	/
4g	10.5	151.2 6.4	106.5 2.9	122.3 6.6	44.5 1.9	44.3 /	49.4 4.4	/
4h	10.6	151.2 6.5	106.5 3.0	122.5 6.7	44.7 2.1	49.7 5.8	49.4 4.4	/

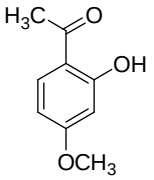
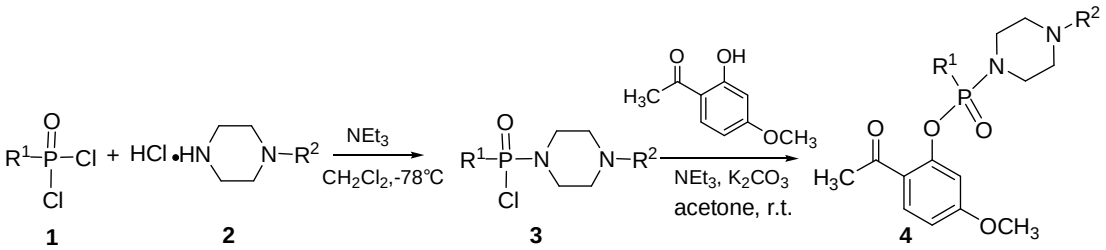
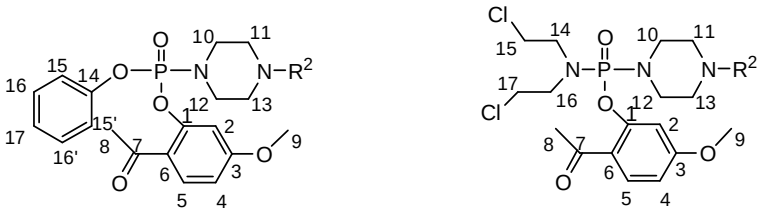


Fig. 1. The structure of paeonol



Scheme 1 Synthesis of phosphoramide piperazine analogues of paeonol **4a-h**



a **b**

Fig. 2. The structures of compounds **4a-e (a)** and **4f-h (b)**