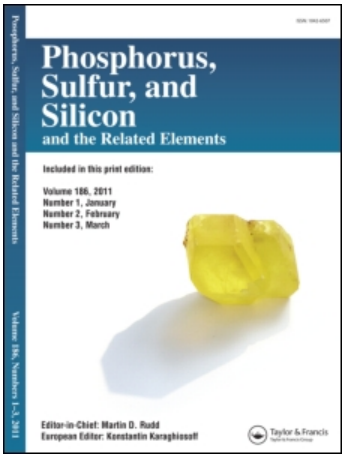


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# Synthesis of Novel Piperazine Phosphoramidate Analogues of 2-Arylquinolones

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# SYNTHESIS OF NOVEL PIPERAZINE PHOSPHORAMIDATE ANALOGUES OF 2-ARYLQUINOLONES

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***A series of novel piperazine phosphoramidate derivatives of 2-arylquinolones were synthesized to improve their physicochemical and biological properties through a facile phosphorylating reaction. Their structures were elucidated by NMR, ESI MS, and HRMS.***

**Keywords** 2-Arylquinolones; piperazine phosphoramidate; synthesis



## INTRODUCTION

2-Arylquinolones are a class of molecules used as aza analogues of flavones. Consequently, synthesis and structural modification of the derivatives of 2-arylquinolone have attracted much interest. Pharmacological research has demonstrated that 2-arylquinolones exhibit many important physiological activities, to act as potent cytotoxic, antimitotic, antibacterial, and antiplatelet agents, and have cardiovascular protecting properties.[1–4]

The introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes of the polarization and intermolecular bonding characteristics.[5–7] Moreover, phosphates and phosphoramidates have been widely used as prodrug moieties to enhance the water solubility and have proven to be exceedingly important agents for anticancer and antiviral therapy.[8–13] Piperazines also exhibits many physiological activities. They can act as platelet-activating factor antagonists, potential antipsychotic agents, dopamine transporter inhibitors, and antitumor agents.[14–17] Our interest was to synthesize a series of phosphoryl piperazine linked 2-arylquinolone derivatives to improve their physicochemical and biological properties. A novel type of

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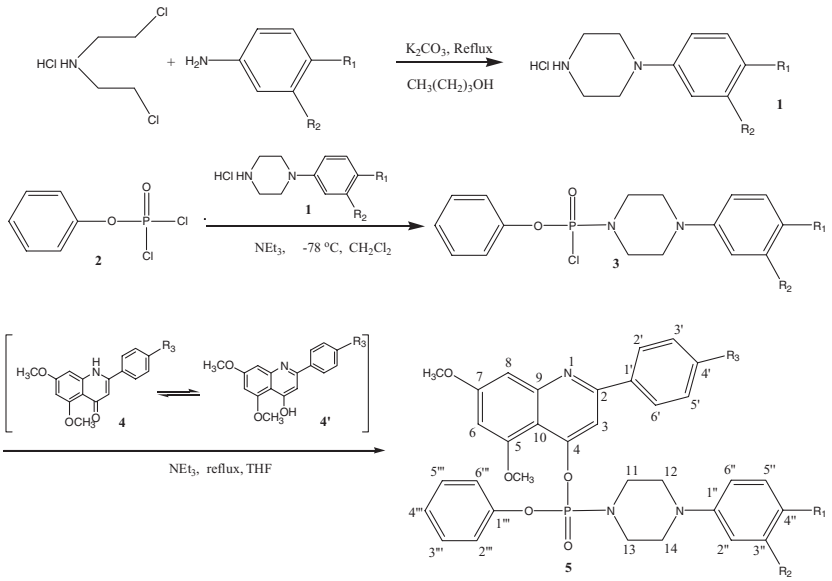


| 5 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| $R_1$ | H | H | H | H | Cl | Cl |
| $R_2$ | H | H | H | $CH_3$ | H | H |
| $R_3$ | H | $CH_3$ | Cl | $CH_3$ | $CH_3$ | Cl |

**Scheme 1** Synthesis of piperazine phosphoramide analogues of 2-arylquinolones **5a–f**.



phosphoramidate derivatives of 2-arylquinolones was synthesized by a facile phosphorylating reaction (Scheme 1).

## RESULTS AND DISCUSSION

To synthesize the piperazine phosphoramidate analogues of 2-arylquinolones (**5**) (Scheme 1), bis($\beta$-chloroethyl)amine hydrochloride, the arylamine, and potassium carbonate were refluxed in *n*-butyl alcohol for 28 h. The solid was filtered off. The crystalline *N*-arylpiperazine (**1**) was obtained after the filtrate was cooled down to room temperature. Phenyl dichlorophosphates (**2**) were coupled with different *N*-arylpiperazine to achieve phenyl aminophosphorochloridates (**3**), which were used without further purification. 2-Arylquinolones (**4**) were reacted with the phenyl aminophosphorochloridates (**3**) in the presence of triethylamine in THF to form the piperazine phosphoramide analogues of 2-arylquinolones (**5**). The 2-arylquinolones (**4**) were expected to experience tautomerization to their 4-hydroquinol isomers (**4′**) under basic conditions. The structures of all newly synthesized 2-arylquinolone derivatives were confirmed by ESI MS, HRMS, and NMR.

## EXPERIMENTAL

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions. $^{1}H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded on a Bruker Avance DPX spectrometer operating at 400.13, 100.61, and 161.98 MHz, respectively, with $^{13}C$ and $^{31}P$ spectra being recorded proton-decoupled. All NMR spectra were recorded in $CDCl_3$ at room temperature ($20 \pm 3^{\circ}C$). $^{1}H$ and $^{13}C$ chemical shifts are quoted in ppm downfield from TMS. $^{31}P$ chemical shifts are quoted in ppm relative to an external 85% $H_3PO_4$ standard. Coupling constants $J$ are given in Hz, and the 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). HRMS were recorded on a Q-Tof Micro spectrometer.

### N-Arylpiperazine (1)

Bis($\beta$-chloroethyl)amine hydrochloride (6.4 g, 0.0358 mol), arylamine (3.2 mL, 0.0358 mol), and $K_2CO_3$ (5.0 g) were refluxed in *n*-butanol (60 mL) for 28 h. The excess of $K_2CO_3$ was filtered off, then the solvent was cooled to room temperature and the *N*-arylpiperazine (**1**) was crystallized.



### Phosphochloridate (3)

The phosphodichloridate (**2**) (1.05 g, 5.0 mmol) and the *N*-arylpiperazine **(1)** (1.0 g, 5.0 mmol) were suspended in anhydrous dichloromethane (30 mL). Anhydrous $NEt_3$ (1.4 mL, 10.0 mmol) was added dropwise at –50°C during 10 min, and then the reaction mixture was left to rise to room temperature. After 8 h, the solvent was evaporated under reduced pressure, and the residue was washed with anhydrous ether and filtered. The filtrate was evaporated to dryness under reduced pressure. The crude phosphochloridate (**3**) was obtained and used without further purification.[18]

### Piperazine Phosphoramidate Analogues of 2-Arylquinolones (5)

Anhydrous $NEt_3$ (0.4 mL, 3 mmol) was added dropwise to a solution of the appropriate phosphorochloridate (**3**) (0.9 g, 2.7 mmol) and 2-arylquinolone (**4**) (0.5 g, 1.8 mmol) in anhydrous THF at room temperature. The reaction mixture was refluxed for 6–10 h and then cooled to room temperature. The precipitated $NHEt_3Cl$ was filtered off, and the filtrate was evaporated under reduced pressure to give the residues as yellow powders. The crude product (**5**) was purified by column chromatography on silica gel (cyclohexane:AcOEt, 1:2).

**Compound 5a.** Yellow powder, mp 147–148°C, yield 41%. HRMS 582.2157 [M + H]$^+$ (calculated for $C_{33}H_{32}N_3O_5P$ 581.2080). $^{1}H$ NMR: $\delta$ 3.04 (t, 4 H, $^{3}J_{P\text{-}H} = 4.8$, H-11/13), 3.48–3.54 (m, 4 H, H-12/14), 3.89 (s, 3 H, 7-$OCH_3$), 3.95 (s, 3 H, 5-$OCH_3$), 6.53 (d, 1 H, $^{4}J_{H\text{-}H} = 2.3$, H-6), 6.84–6.89 (m, 3 H, H-2″/4″/6″), 7.12 (d, 1 H, $^{4}J_{H\text{-}H} = 2.3$, H-8), 7.15–7.17 (m, 1 H, H-4‴), 7.18–7.26 (m, 2 H, H-3‴/5‴), 7.29–7.36 (m, 4 H, H-3″/5″/2‴/6‴), 7.42–7.50 (m, 3 H, H-3′/4′/5′), 7.89 (d, 1 H, $^{4}J_{P\text{-}H} = 1.3$, H-3), 8.09–8.10 (m, 1 H, H-2′), 8.09–8.10 (m, 1 H, H-6′). $^{13}C$ NMR: $\delta$: 44.7 (C-12/14, d, $^{3}J_{P\text{-}C} = 1.7$), 49.7 (C-11/13, d, $^{2}J_{P\text{-}C} = 5.6$), 55.7 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.4 (C-6), 100.9 (C-8), 107.1 (C-3, d, $^{3}J_{P\text{-}C} = 3.0$), 108.4 (C-10, d, $^{3}J_{P\text{-}C} = 6.6$), 116.7 (C-2″/6″), 120.2 (C-2‴/6‴, d,

$^3J_{P\text{-}C} = 5.1$), 120.5 (C-4″), 125.1 (C-4‴), 127.5 (C-2′/6′), 128.8 (C-3′/5′), 129.2 (C-3″/5″), 129.6 (C-4′), 129.8 (C-3‴/5‴), 138.8 (C-1′), 150.8 (C-1‴, d, $^2J_{P\text{-}C} = 6.7$), 151.2 (C-1″), 153.6 (C-9), 155.5 (C-4, d, $^2J_{P\text{-}C} = 6.9$), 156.7 (C-5), 158.8 (C-2), 161.4 (C-7). $^{31}$P NMR: $\delta$ –2.88.

**Compound 5b.** Yellow powder, mp 151–152°C, yield 49%. HRMS 596.2312 [M + H]$^+$ (calculated for $C_{34}H_{34}N_3O_5P$ 595.2236). $^1$H NMR: $\delta$ 2.40 (s, 3 H, 4′-$CH_3$), 3.03 (t, 4 H, $^3J_{P\text{-}H} = 4.8$, H-11/13), 3.47–3.52 (m, 4 H, H-12/14), 3.87 (s, 3 H, 7-$OCH_3$), 3.94 (s, 3 H, 5-$OCH_3$), 6.51 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-6), 6.82–6.88 (m, 3 H, H-2″/4″/6″), 7.11 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-8), 7.16–7.18 (m 1 H, H-4‴), 7.27–7.36 (m, 6 H, H-2‴/3‴/5‴/6‴/3″/5″), 7.20–7.25 (m, 2 H, H-3′/5′), 7.88 (d, 1 H, $^4J_{P\text{-}H} = 1.3$, H-3), 8.00 (d, $^3J_{H\text{-}H} = 4.1$, 1 H, H-2′), 8.02 (d, $^3J_{H\text{-}H} = 4.1$, 1 H, H-6′). $^{13}$C NMR: $\delta$ 44.7 (C-12/14), 49.7 (C-11/13, d, $^2J_{P\text{-}C} = 5.5$), 55.6 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.3 (C-6), 100.9 (C-8), 106.9 (C-3, d, $^3J_{P\text{-}C} = 3.0$), 108.3 (C-10, d, $^3J_{P\text{-}C} = 6.7$), 116.7 (C-2″/6″), 120.2 (C-2‴/6‴, d, $^3J_{P\text{-}C} = 5.0$), 120.5 (C-4″), 125.1 (C-4‴), 127.3 (C-2′/6′), 129.2 (C-3′/5′), 129.5 (C-3″/5″), 129.8 (C-3‴/5‴), 136.0 (C-4′), 139.7 (C-1′), 150.8 (C-1‴, d, $^2J_{P\text{-}C} = 6.9$), 151.2 (C-1″), 153.6 (C-9), 155.4 (C-4, d, $^2J_{P\text{-}C} = 6.7$), 156.7 (C-5), 158.8 (C-2), 161.3 (C-7). $^{31}$P NMR: $\delta$ –2.63.

**Compound 5c.** Yellow powder, mp 156–157°C, yield 32%. HRMS 616.1772 [M + H]$^+$ (calculated for $C_{33}H_{31}ClN_3O_5P$ 615.1690). $^1$H NMR: $\delta$ 3.05 (t, 4 H, $^3J_{P\text{-}H} = 4.9$, H-11/13), 3.49–3.54 (m, 4 H, H-12/14), 3.89 (s, 3 H, 7-$OCH_3$), 3.95 (s, 3 H, 5-$OCH_3$), 6.54 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-6), 6.84–6.89 (m, 3 H, H-2″/4″/6″), 7.09 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-8), 7.15–7.19 (m, 1 H, H-4‴), 7.22–7.36 (m, 6 H, H-3‴/5‴/3″/5″/2‴/6‴), 7.46 (d, 2 H, $^3J_{H\text{-}H} = 2.2$, H-3′/5′), 7.85 (d, 1 H, $^4J_{P\text{-}H} = 1.1$, H-3), 8.04 (d, 2 H, $^3J_{H\text{-}H} = 6.8$, $^4J_{H\text{-}H} = 1.7$, H-2′/6′). $^{13}$C NMR: $\delta$ 44.7 (C-12/14), 49.7 (C-11/13, d, $^2J_{P\text{-}C} = 5.5$), 55.6 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.6 (C-6), 100.9 (C-8), 106.7 (C-3, d, $^3J_{P\text{-}C} = 2.8$), 108.5 (C-10, d, $^3J_{P\text{-}C} = 6.9$), 116.7 (C-2″/6″), 120.1 (C-2‴/6‴, d, $^3J_{P\text{-}C} = 4.9$), 120.6 (C-4″), 125.2 (C-4‴), 128.7 (C-2′/6′), 128.9 (C-3′/5′), 129.2 (C-3″/5″), 129.8 (C-3‴/5‴), 135.8 (C-4′), 137.2 (C-1′), 150.8 (C-1‴, d, $^2J_{P\text{-}C} = 7.2$), 151.2 (C-1″), 153.6 (C-9), 155.7 (C-4, d, $^2J_{P\text{-}C} = 6.7$), 156.7 (C-5), 157.4 (C-2), 161.5 (C-7). $^{31}$P NMR: $\delta$ –2.59.

**Compound 5d.** Yellow powder, mp 153–154°C, yield 43%. HRMS 610.2471 [M + H]$^+$ (calculated for $C_{35}H_{36}N_3O_5P$ 609.2393). $^1$H NMR: $\delta$ 2.28 (s, 3 H, 4′-$CH_3$), 2.42 (s, 3 H, 3″-$CH_3$), 3.02 (t, 4 H, $^3J_{P\text{-}H} = 4.8$, H-11/13), 3.47–3.52 (m, 4 H, H-12/14), 3.88 (s, 3 H, 7-$OCH_3$), 3.95 (s, 3 H, 5-$OCH_3$), 6.52 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-6), 6.64–6.70 (m, 3 H, H-2″/4″/6″), 7.11 (d, 1 H, $^4J_{H\text{-}H} = 2.3$, H-8), 7.12–7.17 (m, 1 H, H-5″), 7.16–7.18 (m, 1 H, H-4‴), 7.26–7.36 (m, 6 H, H-2‴/3‴/5‴/6‴/3′/5′), 7.87 (d, 1 H, $^4J_{P\text{-}H} = 1.2$, H-3), 8.01 (d, 2 H, $^3J_{H\text{-}H} = 8.2$, H-2′/6′). $^{13}$C NMR: $\delta$ 21.3 (4′-$CH_3$), 21.7 (3″-$CH_3$), 44.7 (C-12/14), 49.8 (C-11/13, d, $^2J_{P\text{-}C} = 5.5$), 55.6 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.3 (C-6), 100.9 (C-8), 106.9 (C-3), 108.3 (C-10, d, $^3J_{P\text{-}C} = 6.7$), 117.6 (C-2″/6″), 120.2 (C-2‴/6‴, d, $^3J_{P\text{-}C} = 5.0$), 121.4 (C-4″), 125.1 (C-4‴), 127.3 (C-2′/6′), 129.5 (C-3′/5′), 129.0 (C-5″), 129.8 (C-3‴/5‴), 136.0 (C-3″), 137.7 (C-1′), 138.9 (C-4′), 150.8 (C-1‴, d, $^2J_{P\text{-}C} = 6.6$), 151.3 (C-1″), 153.6 (C-9), 155.4 (C-4), 156.7 (C-5), 157.7 (C-2), 161.3 (C-7). $^{31}$P NMR: $\delta$ –2.65.

**Compound 5e.** Yellow powder, mp 160–161°C, yield 47%. HRMS 630.1921 [M + H]$^+$ (calculated for $C_{34}H_{33}ClN_3O_5P$ 629.1846). $^1$H NMR: $\delta$ 2.41 (s, 3 H, 3″-$CH_3$), 2.99 (t, 4 H, $^3J_{P\text{-}H} = 4.8$, H-11/13), 3.46–3.51 (m, 4 H, H-12/14), 3.88 (s, 3 H, 7-$OCH_3$), 3.95 (s, 3 H, 5-$OCH_3$), 6.52 (d, 1 H, $^4J_{H\text{-}H} = 2.3$, H-6), 6.73–6.76 (m, 2 H, H-2″/6″), 7.11 (d, 1 H, $^4J_{H\text{-}H} = 2.3$, H-8), 7.15–7.19 (m, 2 H, H-3′/5′), 7.26–7.36 (m, 7 H, H-3″/5″/2‴/3‴/4‴/5‴/6‴), 7.86 (d, 1 H, $^4J_{P\text{-}H} = 1.3$, H-3), 7.99 (d, 2 H, $^3J_{H\text{-}H} = 1.7$, H-2′/6′). $^{13}$C NMR: $\delta$ 21.4 (4″-$CH_3$), 44.5 (C-12/14, d, $^3J_{P\text{-}C} = 2.1$), 49.7 (C-11/13, d, $^2J_{P\text{-}C} = 5.6$), 55.6 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.3 (C-6), 100.9 (C-8), 106.9 (C-3, d, $^3J_{P\text{-}C} = 3.1$), 108.3 (C-10, d, $^3J_{P\text{-}C} =$

6.4), 117.9 (C-2″/6″), 120.2 (C-2‴/6‴, d, $^3J_{P\text{-}C} = 5.0$), 125.2 (C-4″), 125.5 (C-4‴), 127.3 (C-2′/6′), 129.1 (C-3′/5′), 129.5 (C-3″/5″), 129.8 (C-3‴/5‴), 136.0 (C-4′), 139.8 (C-1′), 149.8 (C-1″), 150.8 (C-1‴, d, $^2J_{P\text{-}C} = 6.7$), 153.7 (C-9), 155.4 (C-4, d, $^2J_{P\text{-}C} = 6.5$), 156.6 (C-5), 158.8 (C-2), 161.3 (C-7). $^{31}$P NMR: $\delta$ –2.76.

**Compound 5f.** Yellow powder, mp 149–150°C, yield 32%. HRMS 650.1384 [M + H]$^+$ (calculated for $C_{34}H_{33}ClN_3O_5P$ 649.1300). $^1$H NMR: $\delta$ 2.99 (t, 4 H $^3J_{P\text{-}H} = 4.8$, H-11/13), 3.47–3.52 (m, 4 H, H-12/14), 3.89 (s, 3 H, 7-$OCH_3$), 3.95 (s, 3 H, 5-$OCH_3$), 6.53 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-6), 6.74–6.77 (m, 2 H, H-2″/6″), 7.12 (d, 1 H, $^4J_{H\text{-}H} = 2.2$, H-8), 7.16–7.19 (m, 2 H, H-3′/5′), 7.28–7.36 (m, 4 H, H-2‴/3‴/5‴/6‴), 7.43–7.50 (m, 3 H, H-3″/5″/4‴), 7.88 (d, 1 H, $^4J_{P\text{-}H} = 1.2$, H-3), 8.09 (d, 2 H, $^3J_{H\text{-}H} = 1.6$, H-2′/6′). $^{13}$C NMR: $\delta$ 44.7 (C-12/14), 49.8 (C-11/13, d, $^2J_{P\text{-}C} = 5.5$), 55.7 (7-$OCH_3$), 55.9 (5-$OCH_3$), 99.5 (C-6), 100.9 (C-8), 107.1 (C-3, d, $^3J_{P\text{-}C} = 3.0$), 108.3 (C-10, d, $^3J_{P\text{-}C} = 6.5$), 117.9 (C-2″/6″), 120.2 (C-2‴/6‴, d, $^3J_{P\text{-}C} = 5.0$), 125.2 (C-4″), 125.5 (C-4‴), 127.4 (C-2′/6′), 128.8 (C-3′/5′), 129.0 (C-3″/5″), 129.6 (C-4′), 129.8 (C-3‴/5‴), 138.8 (C-1′), 149.8 (C-1″), 150.7 (C-1‴, d, $^2J_{P\text{-}C} = 6.7$), 153.6 (C-9), 155.5 (C-4, d, $^2J_{P\text{-}C} = 6.7$), 156.6 (C-5), 158.81(C-2), 161.4 (C-7). $^{31}$P NMR: $\delta$ –2.75.



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