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Synthesis of Novel Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors—1-(3-Phthalimido-2-oxobutyl)-4-Substituted-phenylpiperazines

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Abstract: We have designed and synthesized a series of new phthalimidopiperazines, biological activity test show that the target compounds(**Ic**, **Ie**, **Ii**) can inhibit HIV-1 RT with IC_{50} 20.0, 43.8, and 63.7μM, respectively.

Keywords: Piperazine, phthalimide, HIV1-RT inhibitor.

Searching for new anti Human Immunodeficiency Virus (HIV) drug is still a hot topic of research. In this paper, we report the synthesis of novel non-nucleoside HIV-1 Reverse Transcriptase inhibitors—1-(3-phthalimido-2-oxobutyl)-4-substituted phenyl-piperazines (I).

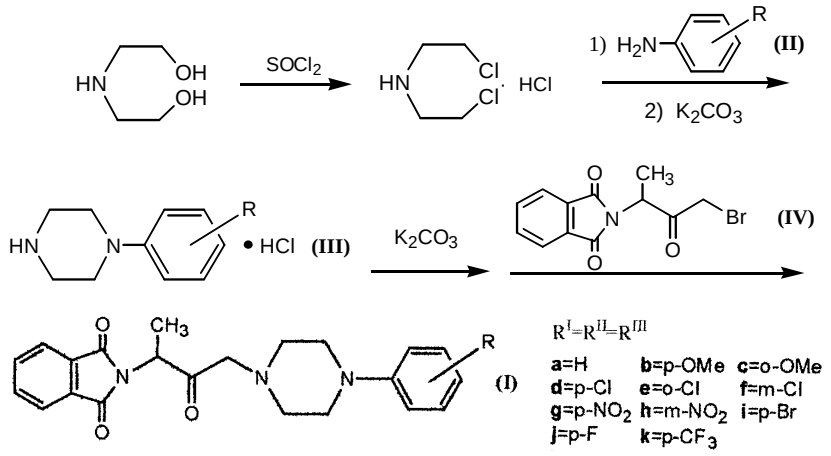
The target compounds were synthesized from diethanolamine *via* a four-step-reaction as shown in **Scheme 1**.

Diethanolamine reacted with thionyl chloride in chloroform at 70-80 °C to afford mustard hydrochloride (yield, 91%), which then refluxed with the different substituted anilines (**IIa-k**) for 62 to 137 hours in n-butanol in the presence of K_2CO_3 to give piperazine hydrochlorides (**IIIa-k**, yield 15-82%, mostly 50-60%)[1]. The resulting hydrochlorides which were firstly neutralized with alkali and then coupled with 1-bromo-3-phthalimidobutan-2-one (**IV**) to give the target com-pounds (**Ia-k**) with the yield of 14 to 95%. The last two steps—neutralization and coupling were processed as one-pot reaction[2]. The neutralization of the hydrochlorides (**IIIa-k**) were carried out in dry acetone *via* the addition of K_2CO_3, and coupling reactions were taken place by adding compound (**IV**) into the neutralized reaction mixture in ambient temperature. The target compounds (**Ia-k**) were separated *via* silica gel or alumina chromatography (column or preparative TLC), depending on the different substituent on the benzene ring. The structures of all the target compounds (**Ia-k**) were characterized by ^{1}H-NMR, IR and elemental analysis[3].

The biological activity test showed that the target compounds (**Ic, Ie** and **Ii**) possessed inhibition for human immunodeficiency virus type 1 reverse

transcriptase with IC_{50} 20.0, 43.8, 63.7μM, respectively.

Scheme 1 The synthetic route of target compounds **(I)**



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References and Notes

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3. Properties of some target compounds (**I**). Elemental analysis, data of C, H, N were all within ±0.5% of the corresponding theoretical values.
   Data of **Compound Ic:** R= *o*-Ome, mp 129-131°C, IR (KBr) 1780, 1713, 1515, 1392 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 7.76 (m, 4H, phthalimide-**H**) 6.90 (m, 4H, *ϕ*-**H**) 4.98 (q, 1H, C**H**) 3.86 (s, 3H, OC**H**$_3$) 3.30 (s, 2H, C**H**$_2$) 2.90~3.20 (m, 4H, piperazinyl-**H**) 2.50~ 2.80 (m, 4H, piperazinyl-**H**) 1.68 (d, 3H, C**H**$_3$) ppm; **Compound Id:** R= *p*-Cl, mp 132-133°C, IR (KBr) 1775, 1713, 1500cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 7.78 (m, 4H, phthalimide-**H**) 6.40-7.62 (m, 4H, *ϕ*-**H**) 4.92 (q, 1H, C**H**) 3.40 (s, 2H, C**H**$_2$) 3.10~3.30 (m, 4H, piperazinyl-**H**) 2.64~2.88 (m, 4H, piperazinyl-**H**) 1.66 (d, 3H, C**H**$_3$) ppm; **Compound Ie:** R= *o*-Cl, mp 126-127°C, IR (KBr) 1774, 1713, 1481, 1391 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 7.76 (m, 4H, phthalimide-**H**) 6.82-7.34 (m, 4H, *ϕ*-**H**) 4.92 (q, 1H, C**H**) 3.70 (s, 2H, C**H**$_2$) 2.90~3.44 (m, 8H, piperazinyl-**H**) 1.61 (d, 3H, C**H**$_3$) ppm; **Compound If:** R= *m*-Cl, mp 74-75°C, IR (KBr) 1776, 1713, 1595, 1391cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 7.76 (m, 4H, phthalimide-**H**) 6.60-7.12 (m, 4H, *ϕ*-**H**) 4.92 (q, 1H, C**H**) 3.40 (s, 2H, C**H**$_2$) 3.10~3.24 (m, 4H, piperazinyl-**H**) 2.60~2.84 (m, 4H, piperazinyl-**H**) 1.65(d, 3H, C**H**$_3$) ppm; **Compound Ii:** R= *p*-Br, mp 136-138°C, IR (KBr) 1778, 1713, 1497, 1391cm^{-1}, ^{1}H-NMR($CDCl_3$) δ 7.74 (m, 4H, phthalimide-**H**) 7.24 (d, 2H, Ar-**H**) 6.66 (d, 2H, Ar-**H**) 4.94 (q, 1H, C**H**) 3.32 (s, 2H, C**H**$_2$) 3.00~3.16 (m, 4H, piperazinyl-**H**) 2.52~ 2.68 (m, 4H, piperazinyl-**H**) 1.66 (d, 3H, C**H**$_3$) ppm; **Compound Ik:** R= *p*-CF_3, mp 139~141°C, IR(KBr) 1778, 1711, 1612, 1391 cm^{-1}, ^{1}H-NMR(Acetone-d_6) δ 7.86 (m, 4H, phthalimide-**H**) 6.84-7.56 (m, 4H, *ϕ*-**H**) 5.04 (q, 1H, C**H**) 3.08~3.60 (m, 6H, C**H**$_2$and piperazinyl-**H**) 2.44~2.64 (m, 4H, piperazinyl-**H**) 1.60 (d, 3H, C**H**$_3$) ppm.

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