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Synthesis and cytotoxic activity of heterocycle-substituted phthalimide derivatives

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Abstract

A series of heterocycle-substituted phthalimide derivatives were synthesized. Structurally diverse derivatives with heterocyclic rings, including furan, imidazo[1,2-a]pyridine, 1,3,4-thiadiazine, imidazo[2,1-b][1,3,4]thiadiazine, pyrazole, 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine, thiazole and thiazoline, were obtained by the reactions of α-bromoketone intermediate with various nucleophiles containing oxygen, nitrogen and sulfur atom. Their cytotoxic activity was also evaluated against five human cancer cell lines *in vitro*.

Keywords: Phthalimide; Heterocycle; α-Bromoketone; Cytotoxic activity

Phthalimide have been found widely use in organic synthesis and medicinal chemistry [1]. Compounds containing the phthalimide nucleus have been reported to possess diverse biological activities including anti-inflammatory [2], antimicrobial [3], antitubercular [4], antitumor [5], antivirus [6], histone deacetylase inhibitory [7], liver X receptor antagonistic [8], leukotriene D_4 receptor antagonistic [9] and angiogenesis inhibitor properties [10].

As part of our on-going studies of phthalimide derivatives [6], we designed and synthesized a series of heterocycle-substituted phthalimide derivatives. These derivatives with various heterocyclic rings, such as furan, imidazo[1,2-a]pyridine, 1,3,4-thiadiazine, imidazo[2,1-b][1,3,4]thiadiazine, pyrazole, 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine, thiazole and thiazoline, can be rapidly synthesized from α-bromoketone intermediate. This strategy permitted us to introduce great molecular diversity under mild reaction conditions, which may provide valuable leads for novel drugs.

The synthetic route to the key intermediate **3** was depicted in Scheme 1. Treatment of **1** with 3-chloro-2-butanone afforded compound **2**, which was brominated by Br_2 in AcOH to give compound **3**. The reactions of α-bromoketone **3** with oxygen, nitrogen and sulfur nucleophiles were illustrated in Scheme 2. Reactions of α-bromoketone **3** with α-naphthol [11] and 2-hydroxy-4,5,6-trimethoxyacetophenone [12] afforded furan derivatives **4** and **5**, respectively. The treatment of 2-aminopyridine with **3** produced imidazo[1,2-a]pyridine derivative **6** [13]. 1,3,4-thiadiazine derivative **7**

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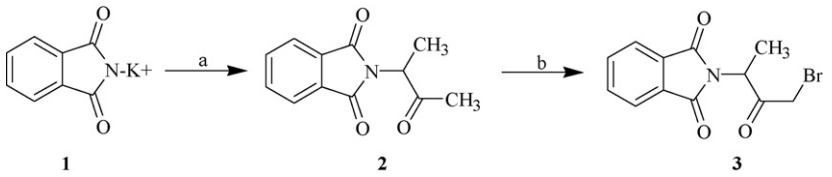
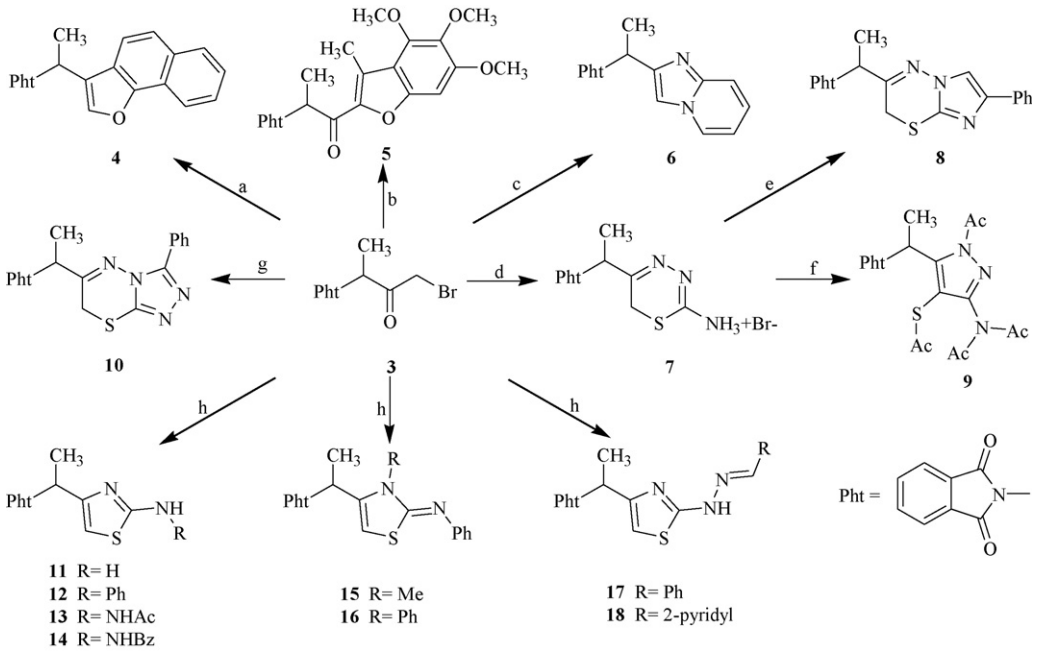


Scheme 1. Reagents and conditions: (a) 3-chloro-2-butanone, DMF, rt; (b) Br_2, AcOH, rt.



Scheme 2. Reagents and conditions: (a) i, α-naphthol, K_2CO_3, acetone, reflux; ii, TsOH, DCM, reflux; (b) 2-hydroxy-4,5,6-trimethoxyacetophnone, K_2CO_3, acetone, reflux; (c) 2-aminopyridine, $NaHCO_3$, *n*-BuOH, reflux; (d) thiosemicarbazide, EtOH, rt, then HBr, reflux; (e) α-bromoacetophenone, $NaHCO_3$, EtOH, reflux; (f) Ac_2O, reflux; (g) 4-amino-3-mercapto-5-phenyl-1,2,4-triazole, $NaHCO_3$, EtOH, reflux; (h) substituted thioureas, thiosemicarbazides or thiosemicarbazones, $NaHCO_3$, EtOH, reflux.

was obtained from the reaction of α-bromoketone **3** with thiosemicarbazide as a hydrobromide salt [14], which was then treated with α-bromoacetophenone to give imidazo[2,1-b][1,3,4]thiadiazine derivative **8** [15]. Upon boiling **7** with acetic anhydride, pyrazole derivative **9** was formed [16]. Condensation of **3** with 4-amino-3-mercapto-5-phenyl-1,2,4-triazole in refluxing ethanol gave 1, 2, 4-triazolo[3,4-b][1,3, 4]thiadiazine derivative **10**. Thiazole and thiazoline derivatives **11–18** were prepared by reacting α-bromoketone **3** with substituted thioureas, thiosemicarbazides and thiosemicarbazones, respectively. Yields of all the reactions ranged from 70% to 92%. It should be pointed out that derivatives **4–18** were all racemates. Except derivative **7**, others were new compounds.

The heterocycle-substituted phthalimide derivatives were evaluated for cytotoxic activity against five human cancer cell lines (A549, Bel7402, BGC-823, HCT-8 and A2780) *in vitro*. The results are shown in Table 1. Pyrazole

Table 1
Cytotoxic activity of phthalimide derivatives **4**, **9** and **15** *in vitro*.

Compounds	IC_{50} (μg/mL)				
	A549	Bel7402	BGC-823	HCT-8	A2780
4	>10	8.761	5.867	9.093	7.235
9	9.329	8.668	5.841	10.014	6.866
15	9.297	8.011	>10	9.563	7.499
Taxol	<0.001	0.050	<0.001	0.046	0.048

derivative **9** showed potent activity against all cell lines with IC_{50} values ranging from 5.841 to 10.014 μg/mL. Furan derivative **4** and thiazole derivative **15** displayed similar activity to derivative **9**, but lost activity against A549 and BGC-823 cell lines (IC_{50} >10 μg/mL), respectively. Others were inactive (IC_{50} >10 μg/mL). Thus activity was strongly influenced by the nature of heterocyclic rings. After comparison of **15** and **16** which share the same heterocycle, the modification at 3-position in the thiazoline ring gave an indication towards the design of new and potentially more active compounds. Additional effects will be devoted to study the influence of the chain between the phthalimide and heterocyclic rings.

In summary, we reported a series of phthalimide derivatives with various heterocyclic rings [17]. Their cytotoxic activity was evaluated against five human cancer cell lines *in vitro*. In addition, all of the reactions described herein were highly effective under mild conditions. A large number of structurally diverse phthalimide derivatives for drug development projects can be rapidly synthesized in good purity and high yield using this method. Further synthesis and biological evaluation of phthalimide derivatives are in progress.

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[17] Selected spectral data. **4**—MS (EI, *m/z*): $[M+H]^+$ 342; ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (d, 3H, *J* = 7.5 Hz), 5.88 (q, 1H, *J* = 7.5 Hz), 7.43–7.71 (m, 6H), 7.78–7.87 (m, 3H), 7.97 (d, 1H, *J* = 9.0 Hz), 8.28 (d, 1H, *J* = 8.1 Hz); **5**—MS (ESI, *m/z*): $[M+H]^+$ 424.2; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (d, 3H, *J* = 7.2 Hz), 3.82 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 5.61 (q, 1H, *J* = 7 .2 Hz), 6.60 (s, 1H), 7.69–7.72 (m, 2H), 7.83–7.86 (m, 2H); **6**—MS (ESI, *m/z*): $[M+H]^+$ 292.2; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96 (d, 3H, *J* = 6.9 Hz), 5.79 (q, 1H, *J* = 6.9 Hz), 6.75–6.80 (m, 1H), 7.13–7.18 (m, 1H), 7.56–7.62 (m, 2H), 7.69–7.71 (m, 2H), 7.82–7.84 (m, 2H), 8.06–8.08 (m, 1H); **8**—MS (ESI, *m/z*): $[M+H]^+$ 389.1; ^1H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, *J* = 6.6 Hz), 3.45 (dd, 2H, *J* = 21.9 Hz), 5.22(q, 1H, *J* = 6.6 Hz), 7.13–7.17 (m, 2H), 7.24–7.29 (m, 1H), 7.63–7.69 (m, 4H), 7.77–7.80 (m, 2H); **9**—MS (ESI, *m/z*): $[M+H]^+$ 457.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.81(d, 3H, *J* = 7.2 Hz), 2.13 (s, 3H), 2.15 (s, 3H), 2.19 (s, 3H), 2.68 (s, 3H), 5.36 (q, 1H, *J* = 7.2 Hz), 7.86–7.87 (m, 4H); **10**—MS (ESI, *m/z*): $[M+H]^+$ 390.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.76 (d, 3H, *J* = 7.2 Hz), 4.03 (dd, 2H, *J* = 18.3 Hz), 5.41 (q, 1H, *J* = 7.2 Hz), 7.31–7.45 (m, 3H), 7.84–7.94 (m, 6H); **11**—MS (ESI, *m/z*): $[M+H]^+$ 274.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.69 (d, 3H, *J* = 7.5 Hz), 5.17 (q, 1H, *J* = 7.5 Hz), 6.39 (s, 1H), 6.87 (s, 2H), 7.83 (s, 4H); 12–MS (ESI, *m/z*): $[M+H]^+$ 350.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.80 (d, 3H, *J* = 7.5 Hz), 5.33 (q, 1H, *J* = 7.5 Hz), 6.74 (m, 1H), 6.78–6.83 (m, 1H), 7.01–7.06 (m, 1H), 7.35–7.37 (m, 1H), 7.82–7.91 (m, 4H), 10.10 (s, 1H); 13–MS (ESI, *m/z*): $[M+H]^+$ 304.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.72 (d, 3H, *J* = 8.4 Hz), 2.10 (s, 3H), 5.27 (q, 1H, *J* = 8.4 Hz), 6.50 (s, 1H), 7.60–7.63 (m, 2H), 7.70–7.71 (m, 2H), 8.33 (s, 1H); 14–MS (ESI, *m/z*): $[M+H]^+$ 331.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.74 (d, 3H, *J* = 6.9 Hz), 5.25 (q, 1H, *J* = 6.9 Hz), 6.67 (m, 1H), 7.46–7.51 (m, 2H), 7.55–7.62 (m, 1H), 7.80–7.89 (m, 6H), 9.47 (s, 1H), 10.73 (s, 1H); 15–MS (ESI, *m/z*): $[M+H]^+$ 364.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.69 (d, 3H, *J* = 7.2 Hz), 3.23 (s, 3H), 5.37 (q, 1H, *J* = 7.2 Hz), 6.34 (s, 1H), 6.89–6.98 (m, 3H), 7.25–7.30 (m, 2H), 7.83–7.89 (m, 4H); 16–MS (ESI, *m/z*): $[M+H]^+$ 426.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.55 (d, 3H, *J* = 6.9 Hz), 5.39 (q, 1H, *J* = 6.9 Hz), 6.49 (s, 1H), 6.79–6.98 (m, 5H), 7.15–7.27 (m, 3H), 7.44 (m, 2H), 7.67–7.71 (m, 2H), 7.75–7.83 (m, 2H); 17–MS (ESI, *m/z*): $[M+H]^+$ 377.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.76 (d, 3H, *J* = 7.2 Hz), 5.29 (q, 1H, *J* = 7.2 Hz), 6.76 (s, 1H), 7.34–7.41 (m, 3H), 7.57–7.60 (m, 2H), 7.85–7.88 (m, 5H), 11.99 (s, 1H); 18–MS (ESI, *m/z*): $[M+H]^+$ 378.1; ^1H NMR (300 MHz, DMSO-d_6): δ 1.76 (d, 3H, *J* = 7.2 Hz), 5.30 (q, 1H, *J* = 7.2 Hz), 6.82 (s, 1H), 7.31–7.34 (m, 1H), 7.80–7.90 (m, 7H), 8.51 (d, 1H, *J* = 5.1 Hz), 12.24 (s, 1H).