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Synthesis and anti-angiogenic activity of benzothiazole, benzimidazole containing phthalimide derivatives

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ABSTRACT

Benzothiazole and benzimidazole containing phthalimide derivatives (**NK037, NK041, NK042, NK0139A and NK0148**) have been synthesized and their anti-angiogenic activity was evaluated using ex vivo egg yolk angiogenesis model. A comparative study with pure thalidomide (**NKTA**) has also been performed to describe the efficacy of these derivatives in blocking angiogenesis. **NK037, NK041** and **NK042** were equally potent in blocking egg yolk angiogenesis and the anti-angiogenesis effect was higher than **NKTA** suggesting the efficacy of these three derivatives in blocking angiogenesis when compare to control. Other two derivatives **NK0139A** and **NK0148** showed effect less than **NKTA** and stronger than control in ex vivo angiogenesis.

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Angiogenesis is the process of generating new capillary blood vessels which play an important role both in health (wound healing,[1] female reproductive cycle[2]) and disease (cancer,[3] rheumatoid arthritis,[4] diabetic retinopathy[5]). The growth and maintenance of solid tumors is highly dependent on neovascularization and can be regulated by agents that interfere with either the stimulation or proliferation of endothelial cells.[6] As a result, the control of angiogenesis continues to be an attractive area for the development of novel therapeutic agent.[5]

Thalidomide (**NKTA**) is a sedative and/or hypnotic drug much used in the 1950s, which was withdrawn from clinics as its teratogenicity was discovered.[7] However, basic research on thalidomide (**NKTA**) did not come to a halt, and in earlier 1990s thalidomide (**NKTA**) proved to be an anti-angiogenic agent.[8] It has, since, been established to be effective for the treatment of various diseases, including graft-versus-host disease, cancers, AIDS, and other angiogenesis-dependent disorders.[9] The United States Food and Drug Administration (FDA) approved thalidomide (**NKTA**) for the treatment of *Erythema Nodosum Leprosum* (ENL) in 1998.[10] Furthermore, many clinical studies of thalidomide (**NKTA**) for the treatment of multiple myeloma, breast cancer, prostate cancer, and other conditions are on-going in the U.S. The side effects associated with clinically effective thalidomide (**NKTA**) treatment has led to the design and synthesis of more potent analogues with reduced toxicity.[11]

Derivatives of nitrogen and sulfur containing heterocyclic compounds such as benzimidazole, benzothiazole and benzothiadiazole have found number of application as anticancer agent.[12] We postulated that phthalimide derivatives of these heterocyclic compounds can be more active than thalidomide (**NKTA**) with less side effect. Recently, Yeh et al. reported the therapeutic effects of cantharidin derivatives with these type of heterocyclic compounds without bridging ether oxygen on human hepatocellular carcinoma cells.[13] Kok et al. have evaluated the anticancer activity of benzothiazole substituted phthalimide derivatives towards three human cancer cell lines and demonstrated the potential of these compounds as anticancer agents.[14]

Thalidomide (**NKTA**) has been shown to inhibit angiogenesis potentially in vivo.[8] Our previous study have also showed thalidomide (**NKTA**) mediated inhibition of angiogenesis by interacting with soluble guanyl cyclase.[15] The present study aims to synthesize structurally modified phthalimide derivatives and comparatively evaluate their anti-angiogenic activity.

Phthalimide derivatives were synthesized using ionic liquid as solvent and catalyst. To optimize the best reaction condition, condensation of phthalic anhydride was carried out with 2-aminobenzothiazole in different ionic liquids at variable temperature and time interval (Table 1). Full conversion was not observed without using any solvent (Table 1, entry 1). Low to moderate yield was observed in case of toluene and 1-butyl-3-methylimidazolium hydrogen sulfate ([bmim]HSO_4) (Table 1, entry 2 and 6). Comparative yield was observed in case of acetic acid, [bmim]BF_4 and

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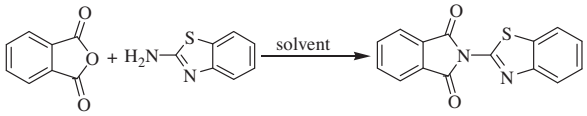
Table 1
Condensation of phthalic anhydride with 2-aminobenzothiazole under different conditions[a]



Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	Neat	110	5	32
2	Toluene	110	5	39
3	Acetic acid	110	5	76
4	[bmim]BF_4	110	5	73
5	[bmim]PF_6	110	5	83
6	[bmim]HSO_4	110	5	52
7	[bmim]PF_6	110	4	81
8	[bmim]PF_6	110	4	85[b]
9	[bmim]PF_6	110	4	72[c]
8	[bmim]PF_6	110	2	49
9	[bmim]PF_6	90	6	63
10	Silica-H_3BO_3	110	5	33
11	Silica-H_2SO_4	110	5	35

[a] Reaction conditions: A mixture of phthalic anhydride (250 mg, 1.68 mmol), 2-aminobenzothiazole (253 mg, 1.68 mmol), 5 ml of solvent were heated in round bottom 25 ml flask.
[b] Under vacuum (0.4 bar).
[c] Yield after third cycle.

[bmim]PF_6 with maximum yield in [bmim]PF_6 (Table 1, entry 3–5). When the reaction was carried out under vacuum (0.4 bar) a slight increase in yield was observed (Table 1, entry 8). In the presence of silica supported boric acid and sulfuric acid low yield was recorded (Table 1, entry 10 and 11) and yield was comparable to the reaction where no solvent or catalyst were used (Table 1, entry 1).

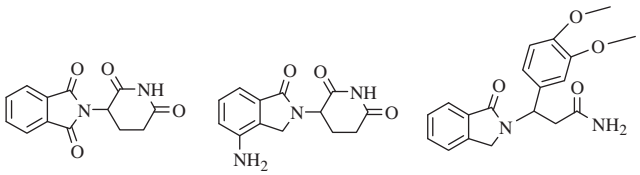


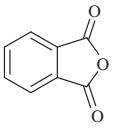
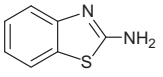
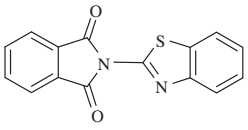
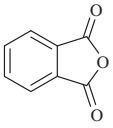
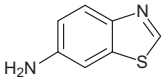
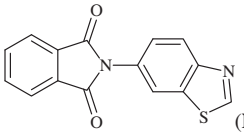
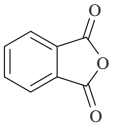
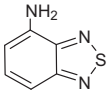
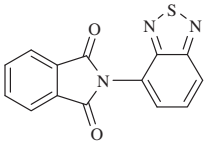
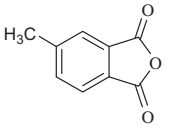
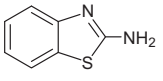
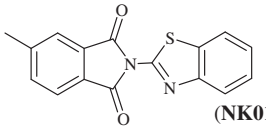
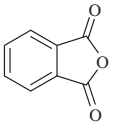
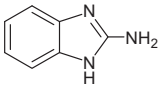
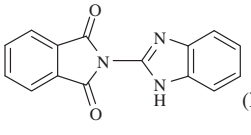
Figure 1. Structure thalidomide, lenalidomide and CC-1069.

After optimizing the best reaction conditions the scope of reaction was explored using different substrates (Table 2). Low to good yield was obtained in most of the cases.

Numerous studies have revealed that many tissues and organs like eyes and heart are affected by thalidomide (**NKTA**) during embryonic development.[16] In 1994, D'amato et al. demonstrated that orally administered thalidomide (**NKTA**) was an inhibitor of angiogenesis induced by basic fibroblast growth factor in a rabbit cornea micropocket assay.[8] Our previous study also demonstrated that thalidomide (**NKTA**) exerts inhibitory effects on nitric oxide-mediated angiogenesis by altering sub-cellular actin polymerization pattern, which leads to inhibition of endothelial cell migration.[17] Moreira et al. showed that thalidomide (**NKTA**) analogue CC–1069 (Fig. 1) significantly inhibited endothelial cell proliferation compared to thalidomide (**NKTA**).[18] There was a notable reduction in the nuclear factor activity and a sensible inhibition of NF-κB activation in nuclear extracts of endothelial cells.

The pharmacokinetics of thalidomide (**NKTA**) suggested that thalidomide (**NKTA**) having two rings where the glutarimide moiety was thought to be responsible for the teratogenic effects of the molecule.[11] These effects coupled with clinically effective thalidomide (**NKTA**) have led to the synthesis of more potent phthalimide

Table 2
Synthesis of different phthalimide derivatives[a]

Entry	Phthalic anhydride	Amine	Product	Yield (%)
1			 (**NK037**)	85.1
2			 (**NK041**)	83.9
3			 (**NK042**)	84.5
4			 (**NK0139A**)	76
5			 (**NK0148**)	72.6

[a] Conditions were not optimized separately for different substrates, reaction conditions: a mixture of phthalic anhydride (1.68 mmol), amine (1.68 mmol), 5 ml of [bmim]PF_6 were heated at 110 °C in round bottom 25 ml flask for 4 h under vacuum (0.4 bar).

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