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Design and SAR of thienopyrimidine and thienopyridine inhibitors of VEGFR-2 kinase activity

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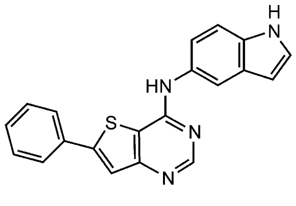
Abstract—Novel classes of thienopyrimidines and thienopyridines have been identified as potent inhibitors of VEGFR-2 kinase. The synthesis and SAR of these compounds is presented, along with successful efforts to diminish EGFR activity present in the lead series.

Angiogenesis is a critical component of human tumor growth and metastasis, and the VEGF receptor-2 (KDR, VEGFR-2) has been identified as a key component of the signaling pathway responsible for the sprouting and maturation of new blood vessels from tumors.[1,2] Additionally, disruption of VEGF signaling by a number of different approaches has resulted in inhibition of angiogenesis and tumor growth.[3,4] Moreover, with the exceptions of the female reproductive system and wound healing, angiogenesis is a relatively quiescent process, making it a very attractive target for therapeutic intervention. Our goal was to discover a small-molecule inhibitor of VEGF receptor kinase signaling.[5] In this report, we describe the structure–activity relationships of a novel series of thienopyrimidines and thienopyridines, which are potent VEGF kinase inhibitors.

Thienopyrimidine **1** (Fig. 1) was identified from high-throughput screening. Compound **1** possessed promising potency and was structurally attractive in that it contained three motifs that could be easily modified: the indole, thienopyrimidine and phenyl portions. A key driver for early chemistry efforts was to achieve selectivity versus epidermal growth factor receptor kinase (EGFR), since **1** was 26-fold more potent against this target.

In order to explore the series potential, 7-chloro-2-bromo-theino[3,2-*b*]pyrimidine (**5**, Scheme 1) was prepared by modification of a literature procedure.[6] This compound could be regioselectively functionalized at the 2 or 7- positions. Heating with amines in *t*-BuOH/DCE resulted in displacement of the chloride, whereas palladium-catalyzed couplings with boronic acids or organotin reagents, occurred exclusively at the 2-position. The 2-position could also be functionalized by Li–halogen exchange and quenching with an appropriate electrophile.[7]

We began by exploring the indole portion of **1** utilizing medium speed chemistry techniques (Table 1, examples **8**–**18**). Profiling of substituted phenyl and heterocyclic



1

VEGFR IC_{50} = 80 nM

EGFR IC_{50} = 3 nM

Figure 1. Thienopyrimidine lead.

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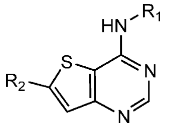
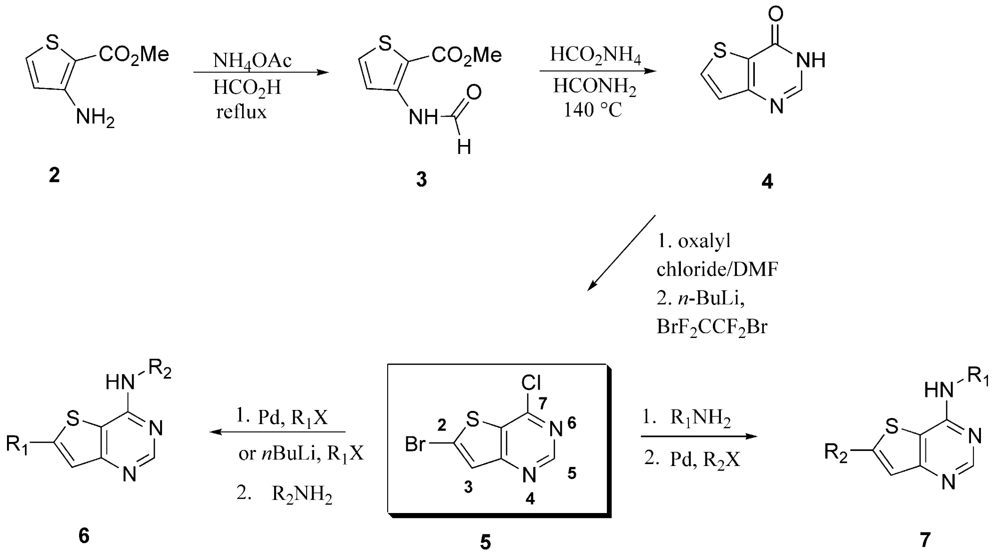
Table 1. Thienopyrimidine SAR



Compd	R_1	R_2	VEGFR kinase	EGFR kinase
			IC_{50} μM	IC_{50} μM
1	5-Indolyl	Ph	0.08	0.003
8	H	Ph	> 1.25	ND
9	CH_2Ph	Ph	> 2.50	ND
10	4-$PhCONH_2$	Ph	0.25	> 1.00
11	4-PhNHPh	Ph	0.39	ND
12	4-PhNHMe	Ph	0.19	ND
13	4-$PhNMe_2$	Ph	0.5	0.094
14	5-Indazolyl	Ph	0.62	1.6
15	5-Benztriazolyl	Ph	0.47	ND
16	1-Methyl-5-indolyl	Ph	> 2.50	ND
17	2-Methyl-5-indolyl	Ph	0.14	0.1
18	3-Methyl-5-indolyl	Ph	0.29	0.005
19	5-Indolyl	H	1.41	0.6
20	5-Indolyl	Br	0.22	ND
21	5-Indolyl	COPh	0.77	0.009
22	5-Indolyl	C(CH)OHPh	2.21	ND
23	5-Indolyl	CONH*n*Pr	2	ND
24	5-Indolyl	2-Thiophene	0.13	0.001
25	5-Indolyl	4-$PhCH_2OH$	0.056	0.001
26	5-Indolyl	4-$PhNH(CH_2)_2$-N-pyrrolidine	0.043	0.001
27	5-Indolyl	4-$Ph(CH_2)_3$N-1-imidazole	0.036	0.001
28	5-Indolyl	4-$PhCH_2NHC(CH_3)_2CH_2OH$	0.025	0.001
29	5-Indolyl	4-$Ph(CH_2)_2NMe_2$	0.022	0.005
30	5-Indolyl	4-$PhCH_2NH_2$	0.018	0.004



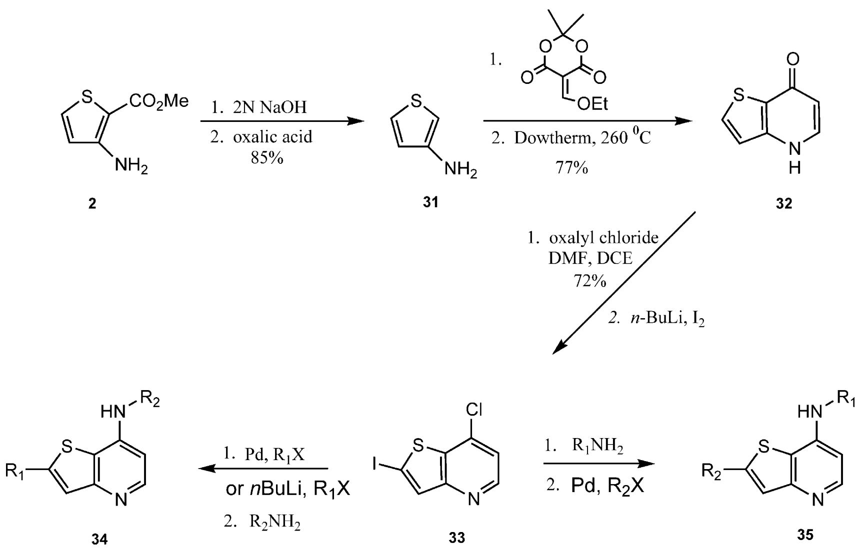
Scheme 1. Synthesis of 7-chloro-2-bromo-thieno[3,2-*b*]pyrimidine.

replacements revealed that a hydrogen bond donor or acceptor, in the region occupied by the indole nitrogen, was required. Consistent with this, alkylation of the indole nitrogen abolished activity. Attempts to substitute the indole ring were also met with limited success. Methyl groups at the 2- or 3-positions were tolerated, but larger substituents (data not shown) reduced potency considerably. Furthermore, indole and its methyl substituted analogues were the only analogues that maintained potency in cellular assays (IC_{50}'s < 1 μM). In light of the tight SAR and lack of cellular potency, no suitable replacements for the indole were identified in these early efforts.

In contrast, modifications at the 7-position of the thienopyrimidine were better tolerated. While replacement of the phenyl group with a variety of functional groups lead to modest losses in potency (Table 1, examples **19**–**24**), exploration of substitution on the phenyl ring provided an exciting finding. The *para* position of the phenyl ring was amenable to introduction of a diverse array of functionality, both in terms of size and physical properties. Presumably this portion of the pharmacophore extends out of the binding site into a solvent exposed region (Table 1, examples **25**–**30**). These modifications led to a 4-fold increase in potency, and allowed the introduction of a basic amine to enhance physical properties.

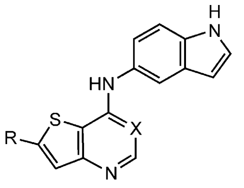
Although we had achieved moderate success in increasing potency, little improvement in EGFR selectivity was observed. As can be seen in Table 1, the compounds were still 5- to 60-fold more potent against EGFR than VEGFR. In an attempt to address this issue, we turned our attention to the thienopyrimidine core of these molecules. SAR observations in our EGFR kinase program with quinazoline leads revealed that removal of the quinazoline N-3 nitrogen resulted in a 10-fold decrease in EGFR potency. We were interested in exploring if a similar modification of the thienopyr*imidine* to the corresponding thienop*yridine* would improve EGFR selectivity, either by further increasing potency against our target, or by decreasing potency against EGFR.

The thienopyridine was accessible through the same amino carboxylic ester used in the thienopyrimidine synthesis (Scheme 2).[6] Saponification followed by decarboxylation of methyl 3-amino-thiophene-2-carboxylate provided 3-amino thiophene. Condensation with Mander's reagent, and subsequent heating in Dowtherm,™ afforded pyridone **32**. Treatment with $POCl_3$, followed by lithiation and treatment with iodine yielded multigram quantities of 7-chloro-2-iodo-[3,2-*b*] thienopyridine (**33**). Intermediate **33** could be regioselectively functionalized at the 2- or 7- positions. Heating with amines in *t*-BuOH/DCE resulted in displacement of the chloride, whereas palladium-catalyzed couplings



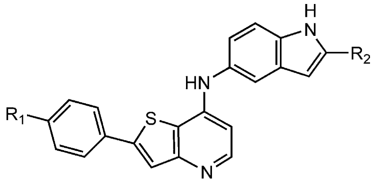
Scheme 2. Synthesis of 7-chloro-2-iodo-thieno[3,2-*b*]pyridine.

Table 2. Thienopyrimidine versus thienopyridine



Compd	R_2	X=C			Compd	X=N		
		VEGFR kinase IC_{50}, μM	EGFR kinase IC_{50}, μM	Ratio VEGFR/EGFR		VEGFR kinase IC_{50}, μM	EGFR kinase IC_{50}, μM	Ratio VEGFR/EGFR
1	Ph	0.08	0.003	26	**39**	0.048	0.068	1.4
36	2-Thiophene	0.132	0.001	132	**40**	0.055	0.039	0.7
37	4-$PhCH_2NH(CH_2)_2NHAc$	0.024	0.002	12	**41**	0.004	0.005	1.3
38	4-$PhCH_2N$-pipiperdine-4-$CONH_2$	0.017	0.001	17	**42**	0.002	0.007	3.5
27	4-$PhCH_2NH\ (CH_2)_3N$-1-imidazole	0.036	0.001	36	**43**	0.004	0.005	1.3
28	4-$PhCH_2NHC(CH_3)_2CH_2OH$	0.025	0.001	25	**44**	0.003	0.008	2.7

Table 3. Methyl versus hydrogen



Compd	R_1	$R_2 = H$			Compd	$R_2 = Me$		
		VEGFR kinase IC_{50}, μM	EGFR kinase IC_{50}, μM	Ratio EGFR/VEGFR		VEGFR kinase IC_{50}, μM	EGFR kinase IC_{50}, μM	Ratio EGFR/VEGFR
45	$CH_2NHCH_3(CH_2)_2OH$	0.004	0.003	0.8	**51**	0.003	0.14	47
46	$CH_2NH(CH_2)_2$-N-piperazine	0.007	0.003	2.3	**52**	0.003	0.25	83
47	$CH_2NH(CH_2)_3OH$	0.004	0.009	3.3	**53**	0.005	0.5	100
48	$CH_2NH(CH_2)_2O(CH_2)_2OH$	0.004	0.004	1	**54**	0.005	0.657	135
49	$CH_2NH(CH_2)_2OH$	0.006	0.002	0.3	**55**	0.004	1	250
50	CH_2-N-morpholine	0.005	0.03	5.6	**56**	0.005	1.25	250

with boronic acids, organotin, and organozinc reagents occurred exclusively at the 2-position.

The resulting thienopyridines did have improved selectivity versus EGFr (Table 2). This was a result of both increased potency against VEGFR, and diminished activity against EGFR. However, even with this improvement, most compounds were still equipotent against both targets.

Compound **17** (Table 1) suggested that the presence of a 2-methyl substituent on the indole could further diminish EGFR potency. In the thienopyrimidine series this was accompanied with an approximately 2-fold decrease in VEGFR potency as well. Much to our surprise and delight, use of the 2-methylindole group in the thienopyridine series decreased EGFR activity more than 100-fold, while having little effect on VEGFR activity (Table 3). The resulting compounds were 50- to 250-fold more selective for VEGFR, demonstrating that the effect of the methyl group on EGFR potency is amplified by removal of the thienopyrimidine nitrogen.

In summary, a new series of potent VEGFR kinase inhibitors has been developed. The synthetic routes to access these are brief and scalable, allowing for rapid analogue preparation. Interestingly, two minor modifications—adding a methyl group and removing a nitrogen atom—have inverted the selectivity of the series between EGFR and VEGFR.

References and notes

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