Novel 2,4-Diarylaminopyrimidine Analogues (DAAPalogues) Showing Potent c-Met/ALK Multikinase Inhibitory Activities

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Ⓢ Supporting Information

ABSTRACT: By repurposing a typical dopamine D_1/D_5 receptor agonist motif, C1-substituted-N3-benzazepine or benzazecine, into the classical RTK inhibitor 2,4-diaminopyrimidine skeleton, a series of new 2,4-diarylaminopyrimidine analogues (DAAPalogues) were developed. Compounds **7** and **8a** were identified possessing high potency against both c-Met and ALK kinases. Compound **8a** displayed appreciable antitumor efficacy at the dose of 1 mg/kg in the ALK-driven BF_3/EML4-ALK xenograft mice model.

KEYWORDS: C1-Substituted-N3-benzazepine, c-Met/ALK dual inhibitor, structure repurposing, 2,4-diarylaminopyrimidine analogues
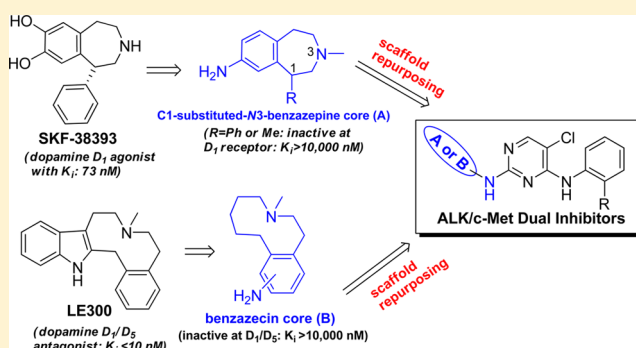
Anaplastic lymphoma kinase (ALK) is an orphan receptor tyrosine kinase (RTK), structurally belonging to the insulin receptor family.[1] In 2007, two research groups[2,3] independently disclosed the rearrangements of the ALK gene in nonsmall cell lung cancer (NSCLC), and for the first time echinoderm microtubule-associated protein-like 4-ALK translocation (EML4-ALK) was identified in lung cancer. Although many more genetic ALK-involving alterations have also been identified, only EML4-ALK fusion gene was identified specifically existing in lung cancer and recognizes a distinct molecular subset of NSCLC populations (5−6% of all NSCLCs).[4,5] This result, together with clinical outcomes resulting from aberrant ALK signaling in different human cancers, has confirmed the emergence of ALK as a novel and promising personalized molecular target against well-defined ALK-addicted NSCLCs.[6−9] The small molecule ALK inhibitor crizotinib (PF2341066) has been approved by FDA in 2011 as the new standard of care for patients with locally advanced or metastatic ALK-positive NSCLC.[10,11] This compound was originally developed as a potent inhibitor of mesenchymal epithelial transition growth factor (c-Met),[12] and ALK was found as an off-target. Crizotinib was then found possessing high potency in inhibiting ALK phosphorylation, inducing apoptosis in ALCL cells, and causing complete tumor regression in ALCL xenograft mice at oral dose of 100 mg/kg. Meanwhile, numerous other selective[13] and nonselective[14] ALK inhibitors are also being evaluated in various clinical

settings. These new inhibitors are all efficacious in the ALK-driven xenograft models, and more importantly some compounds are even effective to the newly identified crizotinib-resistant cells harboring EML4-ALK mutations (e.g., C1156Y and L1196M).[13]

Our group has recently spent extensive efforts on the development of c-Met selective inhibitors.[15−18] The success of crizotinib as an ALK and c-Met dual inhibitor promoted us to switch our drug design strategy to the pursuit of compounds tackling both ALK and c-Met signaling pathways. The 2,4-diarylaminopyrimidine (DAAP) scaffold has long been recognized as a classical kinase inhibitor motif.[8,9] Compounds **1** (NVP-TAE226) and **2** (NVP-TAE684) were among the earliest DAAP analogues[19] (DAAPalogues) developed by Novartis showing high ALK inhibitory activities (Figure 1). With compound **2** as a starting point, extensive work has been reported by Cephalon's research team either by cyclizing the piperidinylaniline moiety (left ring) into a seven-membered bicyclic motif (benzocycloheptene,[20] C1 nonsubstituted benzazepine,[21,22] benzoxazepine,[23] or benzazepinone[22,24−26] as in compounds **3** and **4**) or by replacing the amino-benzamide/sulfonylaniline (right ring) with a bicyclo[2.2.1]-hept-5-ene motif[20,25] (as in compound **4**). Interestingly, these
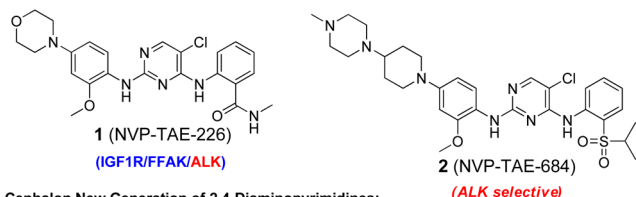
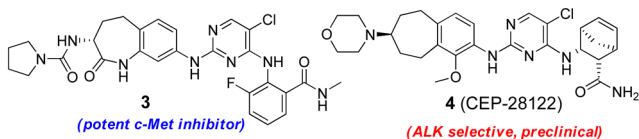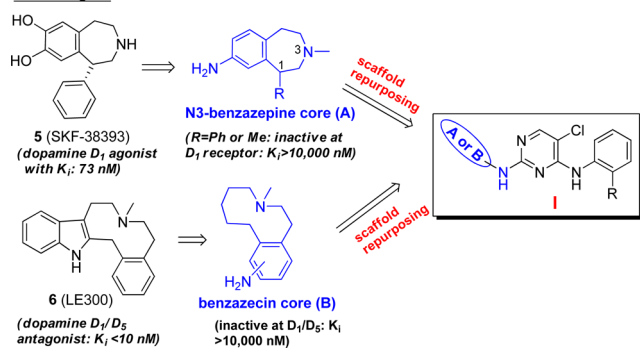**Figure 1.** Reported c-Met/ALK inhibitors and our newly designed DAAPalogues.

new DAAPalogues displayed variant potencies against either c-Met or ALK. For example, compound **3**[26] bearing a 3-amidobenzazepin-2-one component displayed an IC$_{50}$ value of 24 nM against c-Met kinase, while compound **4**[20] bearing a 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid amido fragment was found inactive against c-Met but exhibited high potency against ALK kinase.

In continuation with our recent effort[27] on incorporation of a typical G-protein coupled receptor (GPCR) agonist/antagonist motif into kinase inhibitor scaffolds, here we propose to merge a typical dopamine D$_1$/D$_5$ receptor agonist motif, C1-substituted-N3-benzazepine (**A**)[28] and benzazecine (**B**),[29] into the DAAP skeleton as the C2-arylamino substituent leading to compound series **I** (Figure 1). Through elimination of the original phenolic groups in **5** or indolic function in **6** which are critical for bindings with the dopamine receptors, these two structural motifs **A** and **B** were no longer active against the D$_1$/D$_5$ receptors.[28−30] Meanwhile, the existence of a C1-aryl or alkyl in the motif **A** not only discriminates **I** from Cephalon's C1 nonsubstituted N3-benzazepines[21,22] but also makes the skeleton **A** existing in a twisted conformation that may interact with c-Met or ALK in a different fasion.[28] Meanwhile, since DAAPalogues **1−4** are highly potent against either c-Met or ALK, we postulated that it was possible to discover novel DAAPalogues exhibiting dual inhibitory properties against both c-Met and ALK kinases, a profile similar to that of crizotinib. Herein, we report our recent effort on the synthesis and c-Met/ALK kinase activities of compounds **I**.

All the compounds were synthesized and evaluated for their enzymatic inhibition against both c-Met and ALK kinases. As shown in Table 1, C1-phenyl substituted N3-benzazepine motif displayed high potency at both kinases, with marginal ALK/c-Met preference. Compared to crizotinib, it is nearly 10-fold less

Table 1. Enzymatic Inhibition of DAAPs Bearing a C1-Substituted N3-Benzazepine or Benzazecine Fragment[a]

Compd	Structure	IC$_{50}$ (nM)	
		c-Met	ALK
Crizotinib		2.4 ± 0.4	28 ± 7
2		-	1.6 ± 0.3
7		21 ± 3	14 ± 1
8a		6.0 ± 0.1	9.0 ± 1
8b		2.8 ± 0.5	7.7 ± 1
8c		6.1 ± 0.8	19 ± 0.4
8d		6.4 ± 1	60 ± 5
8e		6.5 ± 1	17 ± 8
8f		5.2 ± 0.1	13 ± 0.6
9a		710 ± 210	17 ± 1
9b		33 ± 17	36 ± 17

[a]IC$_{50}$s were calculated by Logit method from the results of at least two independent tests with eight concentrations each and expressed as means ± SD.

potent at the c-Met, whereas it is 2-fold more potent at the ALK. Interestingly, higher potency at both kinases was also observed for compound **8a** bearing a C1-methyl substituted N3-benzazepine motif. It has IC$_{50}$ values of 6.0 and 9.0 nM for c-Met and ALK, respectively. Extension of the C1-alkyl chain of the N3-benzazepine motif to the butyl (**8b**) further increased the enzymatic potency, especially at the c-Met kinase with an IC$_{50}$ value of 2.8 nM. DAAPalogues **8c−f** derived from N3-benzazepine motif bearing a C1-methylene or C1-ethylidene moiety displayed high potency at both kinases as well with 2- to 10-fold c-Met/ALK selectivity. The E- and Z-conformations in benzazepines **8e** and **8f** did not make differences to the potencies at both kinases. Significant difference was observed for DAAPalogues **9a,b** containing a benzazecine motif. Compound **9a** bearing a larger ring system has an IC$_{50}$ value of 17 nM at the ALK and is 40-fold more potent than that at

305

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the c-Met. Compound **9b** with a smaller ring system was equally potent at both c-Met and ALK showing IC$_{50}$ values of 33 and 36 nM, respectively.

To evaluate the effect of *N*3-substituent in the C1-substituted benzazepine motif on the kinase activity, DAAPalogues **8g**−**j** were designed (Table 2). Both *N*-methyl (**8a**) and *N*-H (**8g**) 1-methyl-benzazepine derivatives showed similar c-Met/ALK potency and selectivity, while higher c-Met potency and selectivity were observed for compounds **8h**−**j** bearing an *N*-acyl group in the C1-methyl-benzazepine motif indicating that an additional H-bonding might be formed favorable for the interaction with c-Met. Among them, *N*-acyl compound **8j** is the most potent c-Met inhibitor with an IC$_{50}$ value of 1.9 nM and c-Met/ALK selectivity of 28.

Nonsubstitution on the C6 position of the central pyrimidine core was found critical. Both smaller (e.g., F- or MeNH-) and larger (morpholin-4-yl) C6-substituents (**10a**−**c**) abolished the inhibitory effects on both kinases (>1 μM). Meanwhile, formation of a heterocycle at the C5 and C6 of the central pyrimidine core was not tolerated. Compounds **11a**−**c** were all inactive at both kinases. Variations at the right-side amino-benzamide fragment as the pyrimidinyl C4-substituent were investigated as well. It was found that replacing the *N*-methylcarbonyl substituent in the aminobenzamide component of **8a** with a morpholin-4-ylcarbonyl moiety yielded compound **12a** that was inactive at both kinases. While compounds **12b** and **12c** bearing an alkylsulfonyl group displayed high ALK potency with IC$_{50}$ values of 3.5 and 7.1 nM, respectively. Both compounds are 17- and 4-fold more potent at the ALK than at c-Met. Such reversed selectivity was also observed on compound **12d** bearing a (2-aminosulfonyl)-phenylamino group as the pyrimidinyl C4-substituent. It has an IC$_{50}$ value of 1.3 nM against the ALK that is 23-fold more potent than against c-Met kinase. Notably, compound **12e** bearing a 3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid amide fragment as that in preclinical ALK inhibitor **4** showed similar potency at both c-Met and ALK kinases (58 and 489 nM, respectively).

Since compounds **7** and **8a** displayed high potency against both c-Met and ALK kinases, a profile similar to that of crizotinib, they were selected for further evaluation. First, both (+)- and (−)-enantiomers were prepared by resolution[28] of their C1-substituted benzazepine motifs followed by condensation[25] with corresponding pyrimidine fragment. As shown in Table 3, both enantiomers of **7** and **8a** were potent at both kinases, and the (+)-isomers were generally 2- to 4-fold less active than the corresponding (−)-isomers. Meanwhile, both compounds **7** and **8a**, together with their enantiomers, were evaluated for their inhibitory effects on cell proliferation against MET-amplified lung cancer EBC-1 and ALK-dependent lymphoma Karpas-299 cells. Compound **7** and its (+)-isomer showed identical IC$_{50}$ value of 29 nM against Karpas-299 cells, which is slightly more potent than that against EBC-1 cells. Compound **8a** and its two enantiomers showed IC$_{50}$ values of ∼8 nM in the EBC-1 cells that were 2-fold more potent than in the ALK-dependent lymphoma Karpas-299 cells.

DAAPalogues **7** and **8a** were further evaluated for their inhibitory activities against a panel of our in-house 20 RTKs[18] (Table S1 in Supporting Information). Besides c-Met and ALK, compound **7** also showed significant inhibition against four other kinases, including RON, RET, c-Src, and FGFR1 at the concentration of 1 μM. Similarly, inhibitory effect was also observed for compound **8a** against RON, KDR, c-Src, and

Table 2. Modification on the Pyrimidinyl Core or C4-Substituent[a]

Compd	Structure	R or R'	IC$_{50}$ (nM)	
			c-Met	ALK
8a		Me-	6.0 ± 0.1	9.0 ± 1
8g		H-	6.4 ± 2	7.9 ± 0.5
8h			7.2 ± 2	38 ± 7
8i			2.4 ± 0.3	50 ± 2
8j			1.9 ± 0.4	53 ± 0.6
10a		–	>1000	>1000
10b		–	>1000	>1000
10c		–	>1000	>1000
11a		–	>1000	>1000
11b		–	>1000	>1000
11c		–	>1000	>1000
12a			>1000	>1000
12b			63 ± 10	3.5 ± 0.1
12c			31 ± 0.1	7.1 ± 2
12d			31 ± 4	1.3 ± 0.3
12e			58 ± 9	49 ± 10

[a]IC$_{50}$s were calculated by Logit method from the results of at least two independent tests with eight concentrations each and expressed as means ± SD.

Table 3. Cell Proliferative Inhibition of Selected Compounds

	enzyme, IC$_{50}$ (nM)		cellular, IC$_{50}$ (nM)	
compd	c-Met	ALK	EBC-1 (c-Met)	Karpas-299 (ALK)
7	21 ± 7	14 ± 0.2	57	30
(+)-7	42 ± 3	39 ± 1	50	29
(−)-7	13 ± 3	14 ± 0.4	26	38
8a	5.7 ± 1.8	9.0 ± 1	7.0	14
(+)-8a	11 ± 4	24 ± 3	8.0	16
(−)-8a	6.4 ± 0.2	15 ± 2	8.4	16
crizotinib	2.4 ± 0.4	28 ± 7	6.9	200
2(TAE684)		1.6 ± 0.3		13

FGFR1 kinases. Meanwhile, compounds **7** and **8a** were further evaluated at the ALK mutations: the gate-keeper L1196 M and the C1156Y. Unfortunately, both compounds only showed significant inhibition at concentrations higher than 1 μM, different from the classical ALK inhibitor TAE684 (**2**).[19]

The pharmacokinetic properties of DAAPalogues **7** and **8a** were then evaluated (Table S2 in Supporting Information). Both compounds showed similar half-life (2.2 h) and favorable clearance (~2.0 L/h/kg). Compound **8a** showed good plasma exposure (5500 ng·h/mL) and acceptable oral bioavailability (20%), whereas DAAPalogue **7** has much higher plasma exposure (9066 ng·h/mL) and excellent oral bioavailability (73%).

Compounds **7** and **8a** were further evaluated in vivo for their antitumor efficacy in the BF$_3$-EML4-ALK xenograft mice model (Figure 2). In this model, tumor growth is specifically driven by
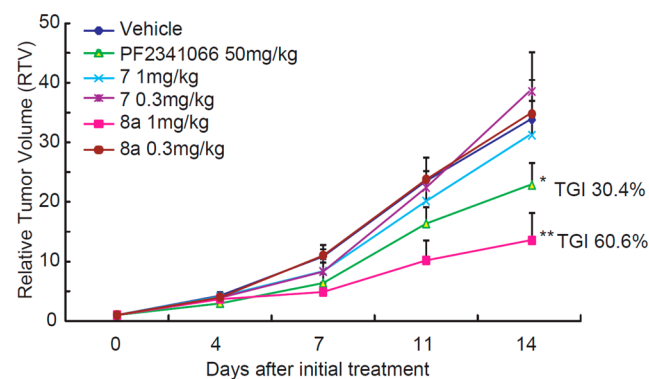
Figure 2. In vivo antitumor efficacy of DAAPalogues **7** and **8a** in BaF3/EML4-ALK xenograft model. Compounds **7**, **8a**, and PF2341066 (crizotinib) were administered orally once daily for 2 weeks after the tumor volume reached 100 to 150 mm^3. The results were shown as the mean ± standard error. *, $P < 0.05$, **, $P < 0.01$ vs control group, determined using Student's t test.

constitutively active ALK. Both compounds were orally administered with 0.5% CMC-Na (sodium carboxymethyl cellulose) at doses of 0.3 and 1.0 mg/kg for 14 days. Unfortunately, compound **7** did not show any inhibitory effect on the tumor growth at both doses. However, compound **8a** presented a significant antitumor efficacy, with an inhibitory rate of 60.6% at the doses of 1 mg/kg, which is higher than that of crizotinib (PF2341066) at a dose of 50 mg/kg.

In summary, we have developed a series of new 2,4-diarylaminopyrimidine analogues (DAAPalogues) by repurposing a typical dopamine D$_1$/D$_5$ receptor agonist motif, C1-

substituted-N3-benzazepine and benzazecine, into the classical 2,4-diaminopyrimidine skeleton. Extensive structure−activity relationships were conducted, and compounds **7** and **8a** were identified possessing high enzymatic and cellular potency against both c-Met and ALK kinases. These compounds were relatively selective within our kinase panel and showed good PK parameters. In the ALK-driven xenograft mice model, compound **7** was found inactive, while compound **8a** displayed appreciable antitumor efficacy at the dose of 1 mg/kg. Further evaluations of **8a** at higher dose regimes and on other ALK-driven mice models are undergoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
Procedures for the preparation of new compounds, analytical data, and procedure for in vitro and in vivo assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions
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Notes
The authors declare no competing financial interest.

■ ABBREVIATIONS

ALK, anaplastic lymphoma kinase; RTK, receptor tyrosine kinase; ALCL, anaplastic large-cell lymphoma; NSCLC, nonsmall cell lung cancer; EML4-ALK, echinoderm micro-tubule-associated protein-like 4-ALK translocation; c-Met, mesenchymal epithelial transition growth factor

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