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Identification of nicotinamide aminonaphthyridine compounds as potent RET kinase inhibitors and antitumor activities against RET rearranged lung adenocarcinoma

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ABSTRACT

RET rearrangement is a recently identified oncogenic mutation in lung adenocarcinoma (LADC) that accounts for approximately 2% of all NSCLCs. More than six fusion partners have been identified in NSCLC, such as KIF5B, CCDC6, NCOA4, TRIM33, CLIP1 and ERC1. Many RET inhibitors have been reported and some have progressed to the clinic. Similar to most kinase inhibitors, patients often respond to current RET inhibitors but relapse can occur due to the emergence of mutant RET kinases, such as RET (S904F) and (V804L/M), which are resistant to inhibition. Our group previously reported that the benzamide aminonaphthyridine HSN356, a multikinase inhibitor, also inhibited RET. In this study, we prepared various nicotinamide analogs of HSN356 and investigated RET inhibition to uncover the salient moieties on HSN356 that are important for kinase inhibition and to also evaluate if HSN356 and analogs thereof could inhibit mutant RET kinases, such as RET (S904F) and (V804L/M). Compound **3** (HSN608), the nicotinamide analog of HSN356, inhibits RET and mutant forms better than reported RET inhibitors such as Alectinib, Sorafenib, Vandetanib and Apatinib, and comparable to BLU667. HSN608 inhibited the growth of CCDC6-RET driven LC-2/ad cell line with IC50 of ~3 nM. Under similar conditions, BLU667 and vandetanib (two drugs being evaluated against RET-driven cancers in the clinic) inhibited the growth of LC-2/ad with IC50 values of ~10 and 328 nM respectively.

1. Introduction

The RET gene is located on chromosome 10 and encodes a receptor tyrosine kinase, which plays important roles in the development of kidneys and enteric nervous system during embryogenesis [1]. RET also regulates key aspects of cellular proliferation and survival. Glial cell-line-derived neurotrophic factor (GDNF) family ligands (GFLs) bind to GDNF family receptor-α co-receptors and induce receptor dimerization and subsequent phosphorylation of the intracellular tyrosine residues, resulting in the activation of downstream signaling for cell survival and proliferation (Fig. 1) [2]. Mutations of RET lead to constitutive activation of the receptor itself in the absence of ligand binding [3]. RET rearrangements lead to the formation of a chimeric gene product, called RET fusion protein kinases, which have transforming and oncogenic properties [4]. Rearrangements of the proto-oncogene RET are newly identified as potential driver mutations in several human malignancies, such as thyroid [5] or lung [6,7] cancer. Several RET fusions have been identified in lung adenocarcinoma (LADC), including kinesin family member 5B (KIF5B)-RET, coiled-coil domain containing 6 (CCDC6)-RET, tripartite motif-containing (TRIM33)-RET, and nuclear receptor coactivator 4 (NCOA4)-RET [8]. The overexpression of RET fusion products in NIH3T3 cells resulted in anchorage-independent growth and tumorigenicity in nude mice [9]. Lung adenocarcinoma-derived cell lines, such as LC-2/ad cells, which harbor RET fusion gene CCDC6-RET [10], are sensitive to RET inhibitors [11].

Several small molecule inhibitors of RET tyrosine kinase have been described and some are in clinical development. Sorafenib [12,13], vandetanib [14], cabozantinib [15], ponatinib [16], apatinib [17] and BLU-667 [18] are RET inhibitors, which have been evaluated in the clinic. Sorafenib was evaluated in the clinic as treatment for RET-driven NSCLC but response rate was poor [19]. During the NSCLC clinical trials of carbozantinib (NCT01639508), vandetinib (UMIN000010095 and NCT01823068) and lenvatinib (NCT01877083), overall response rates of 16–50% and overall survival rates up to 11.6 months were

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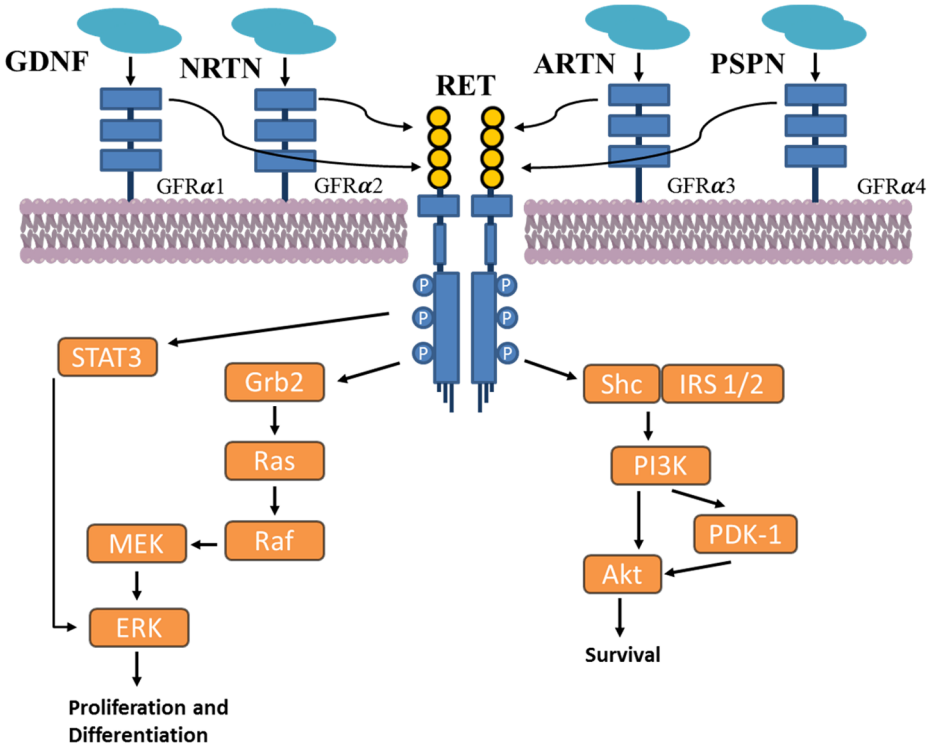


Fig. 1. Schematic represent of RET signaling in cell proliferation and survival.

recorded, [8] indicating that RET is an actionable target. One of the mechanisms that limits RET inhibitor efficacy is the emergence of drug-resistant mutants, such as the gatekeeper mutants V804M/L as well as RET S904F [20,21]. Recent efforts have therefore focused on the development of RET inhibitors, such as BLU-667, which are active against mutant RET kinases that emerge upon prolonged treatment with RET inhibitors [18].

We previously reported that benzamide aminonaphthyridine

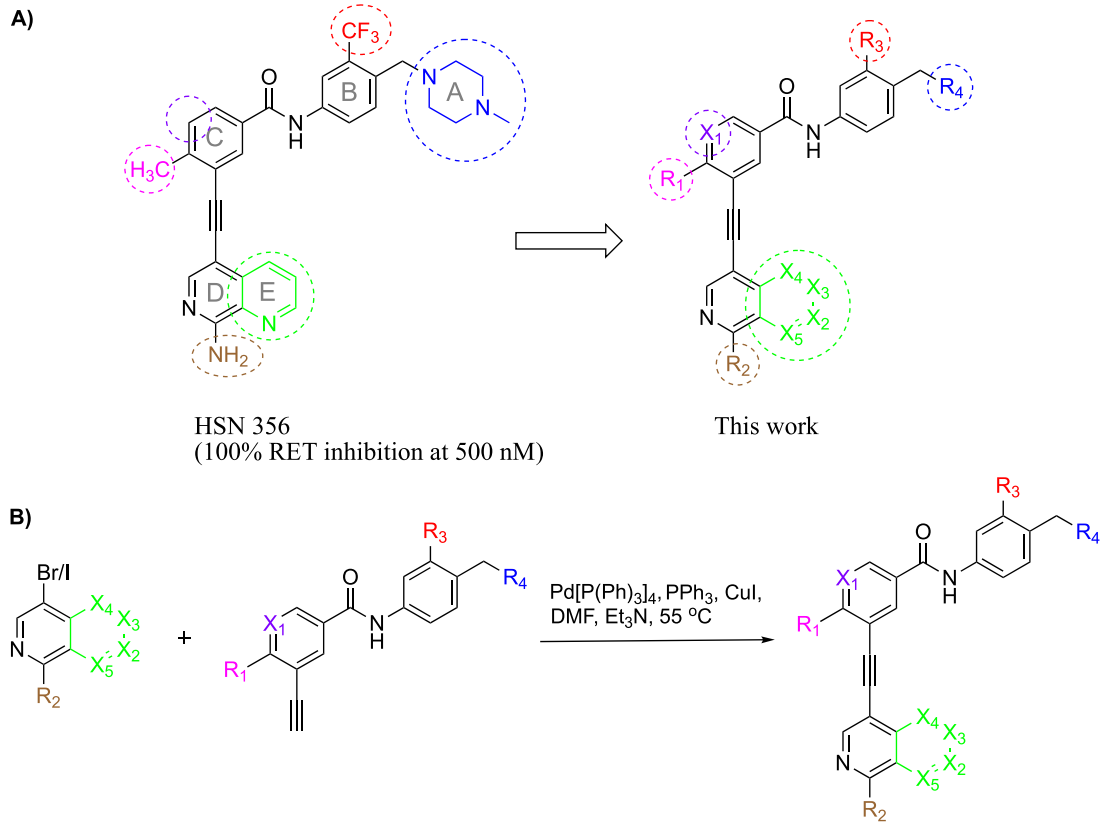


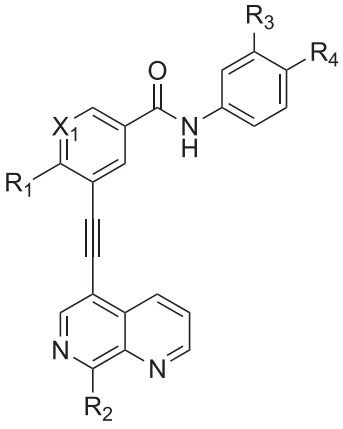
Fig. 2. (A) Parts of HSN356, which were modified to make various analogs; (B) Analogs were synthesized via Sonogashira reaction.

compound **1** (HSN356), a FLT3 kinase inhibitor, also inhibited RET [22]. At 500 nM, HSN356 completely inhibited the enzymatic activity of RET kinase in the presence of 100 μM ATP. In our previous report, the focus was on FLT3 kinase inhibition so we did not investigate in detail the potential of HSN356 to inhibit mutant RET kinases as well as the growth of RET-driven cancers. Here, we embark on a structure activity relationship study of HSN356 to uncover the salient moieties on HSN356 that are important for RET inhibition and to also evaluate if HSN356 and analogs thereof could inhibit mutant RET, such as V804M/L (Fig. 2).

2. Results and discussion

Compound **1** (HSN356) analogs were synthesized via Sonogashira reaction (Fig. 2**B**). Analogs were made to explore substitutions or replacements on/of rings A, B, C, D and E of HSN356 (see Fig. 2**A**). For example, we made analogs that replaced the methyl piperazine moiety on HSN356 with different nitrogen-containing rings while maintaining the 1,7-naphthyridin-8-amine core (compounds **3**, **9**, **10**, **11**, **12**). On ring B, we also replaced the CF_3 with Cl, H, etc. (compounds **3**, **7**, **8**).

(I) Series A: 8-naphthyridine analogs



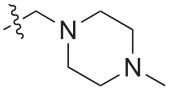
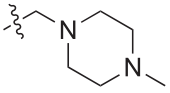
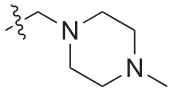
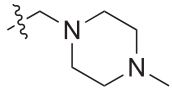
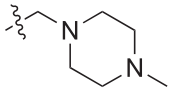
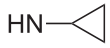
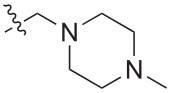
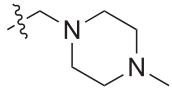
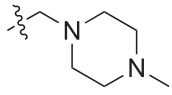
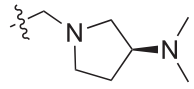
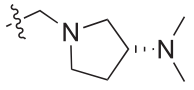
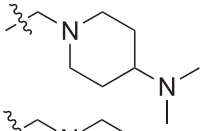
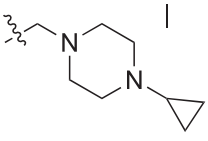
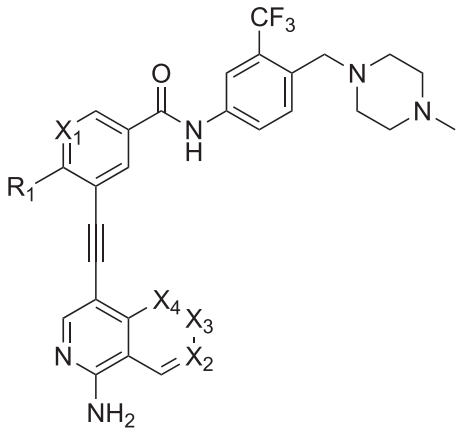
	R_1	R_2	R_3	R_4	X_1
1 (HSN356)	CH_3	NH_2	CF_3		C
2	CH_3	H	CF_3		C
3 (HSN608)	H	NH_2	CF_3		N
4	H	H	CF_3		N
5	CH_3	H	CF_3		N
6	CH_3		CF_3		N
7	H	NH_2	Cl		N
8	H	NH_2	H		N
9	H	NH_2	CF_3		N
10	H	NH_2	CF_3		N
11	H	NH_2	CF_3		N
12	H	NH_2	CF_3		N

Fig. 3. Structures of compounds, which were synthesized and screened.

(II) Series B: 7- or 6- or 5- naphthyridines



	R_1	X_1	X_2	X_3	X_4
13	CH_3	C	C	C	N
14	CH_3	N	C	N	C
15	CH_3	N	N	C	C
16	H	N	N	C	C
17	H	N	C	N	C
18	H	N	C	C	N

Fig. 3. (*continued*)

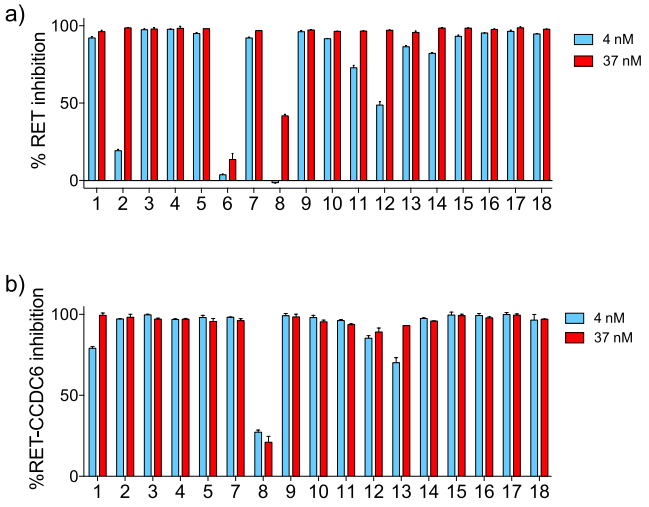


Fig. 4. Percentage inhibition of (**a**) RET and (**b**) RET-CCDC6 activity with 4 nM (in blue) and 37 nM (in red) analogs. Reactions were carried out in the presence of 100 μM ATP.

Modification of methyl group in ring C of HSN356 was also evaluated (compounds **4**, **14**, **15**, **5**, **16**, **17**). For a second series of compounds, we synthesized compounds with different naphthyridine rings [compounds **13** and **18** (1,6-naphthyridin-5-amine), **14** and **17** (2,6-naphthyridin-1-amine), **15** and **16** (2,7-naphthyridin-1-amine)], see Fig. 3.

With the series of HSN356 analogs in hand, their inhibition abilities against RET kinase were investigated via *in vitro* kinase assay at Reaction Biology Corp. (Malvern, PA) (Fig. 4**a**). Both compound **1** (HSN356) and **3** (HSN608), the nicotinamide analog of HSN356, displayed high RET inhibition (approximately 92% and 98% inhibitions at 4 nM respectively). We are more excited about **3** (HSN608) than HSN356 because HSN608 has a lower calculated LogP value than HSN356 (2.3 vs 3.9) [23]. Modification of methylpiperazine (ring A, color in blue) in HSN608 with cyclopropyl substitution (compound **12**) or replacement by 4-(dimethylamino)piperidin (compound **11**) gave compounds that were less potent at inhibiting RET phosphorylation. When the methylpiperazine in compound **3** (HSN608) was replaced with 3-(dimethylamino)pyrrolidine (compounds **9**, **10**), RET inhibition was not affected. Substitution of the CF_3 group on ring B with hydrogen, compound **8**, led to reduced inhibition of RET whereas substitution with chlorine (compound **7**) did not affect the degree of RET inhibition. Different isoforms of naphthyridin-8-amine in ring E (compounds **3**, **16**, **17**, **18** or HSN356, **13**) were all active RET inhibitors. Position-1 of the naphthyridine ring can tolerate either H (compound **4** and **5**) or NH_2 (compound **3**) but substituted amine (compound **6**) was not a good RET inhibitor. Methyl substitution of the nicotinamide moiety, compounds (**14**, **15** and **5**), did not affect RET inhibition (compare with their congener **17**, **16** and **4** respectively).

The human lung adenocarcinoma cell line LC-2/ad harbors CCDC6-RET fusion product. Therefore, we also examined the inhibition of CCDC6-RET fusion kinase by the naphthyridine compounds (Fig. 4b). The results revealed that the majority of the compounds, which potently inhibited wild type RET kinase could also attenuate RET-CCDC6 activity at 4 nM (Fig. 4**b**). Interestingly compounds **2** and **12**, which inhibited RET kinase weakly at 4 nM, showed higher inhibition capability towards CCDC6-RET. In addition to RET fusion, other RET mutations have been observed in patients. Mutations of the RET gatekeeper residue V804 to other residues (such as L), impairs the binding of various kinase inhibitors (such as vandetanib, pyrazolopirimidines and ponatinib) to the ATP binding pocket and cause drug resistance [24]. RET mutation in the activation loop, RET(S904F), has been reported to confer resistance to vandetanib [21]. Since RET V804M, V804L and S904F are clinically relevant to the issue of drug resistance, we evaluated the inhibition of these mutant RET kinases by the naphthyridine compounds.

With the exception of compound **8**, all of the tested compounds were good inhibitors of RET(V804M) and RET(S905F) at 4 nM (Fig. 5 and S1). However for RET(V804L), compounds **1**(HSN356), **7**, **8**, **10**, **11**, **12**, **13**, **18** were poor inhibitors at 4 nM, displaying percentage inhibition less than 80% (see Fig. S2). Encouragingly compounds **3** (HSN608), **14**, **15**, **16** and **17** were good inhibitors of all of the tested RET kinases [Wild type, CCDC6-RET, RET (V804M, V804L and S904F)].

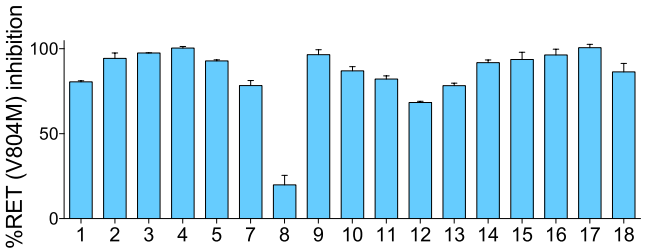


Fig. 5. Percentage inhibition of RET (V804M) activity with various analogs (4 nM). Reactions were carried out in the presence of 100 μM ATP.

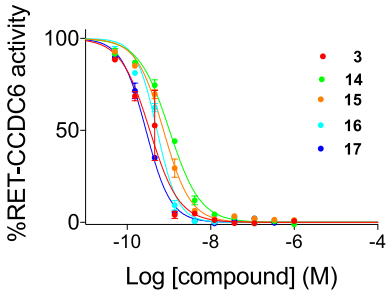


Fig. 6. Dose–response curve of CCDC6-RET inhibition by screened compounds in kinase assay. Residual kinase activity (control = 100%) was plotted as a function of compound concentration. Reactions were carried out in the presence of 100 μM ATP.

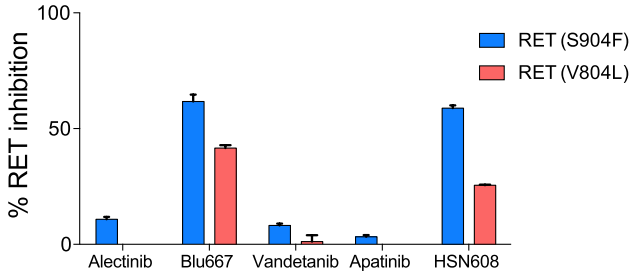


Fig. 7. Percentage inhibition of RET(S904F) and RET(V804L) activities with 1 nM Alectinib, Blu667, Vandetanib, Apatinib and compound **3** (HSN608). Reactions were carried out in the presence of 100 μM ATP.

Compounds **3** (HSN608), **14**, **15**, **16** and **17** inhibited CCDC6-RET (the driver kinase in LC-2/ad), with impressive IC50 values in the sub nanomolar range (0.31–1.19 nM, see Fig. 6). Under similar assay conditions, the IC50 of typical RET inhibitor sorafenib, is 3.54 nM. We were curious to know how compounds, such as compound **3** (HSN608) compared to current RET inhibitors in clinical trials against drug-resistant mutant RET S904F and V804L kinases. We therefore tested the inhibition of RET kinases containing S904F and gatekeeper V804L mutations using a stringent inhibitor concentration of 1 nM. Reported RET inhibitors such as Alectinib, Vandetanib and Apatinib were

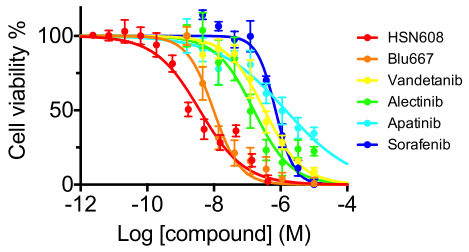


Fig. 8. Cell viability curve of LC-2/ad cell line upon treatment of indicated compounds.

Table 1
K_d (nM) of HSN608 towards different kinases determined via DiscoverX K_d Elect service.

Kinase	K_d (nM)
RET	1.9
RET(V804L)	1
RET(V804M)	0.95

Table 2
Antiproliferative activity of compounds against LC-2/ad cell line.

Compound	IC_{50} (nM) in this study	IC_{50} (nM) in literature
15	2 ± 0.2	N/A
14	8 ± 0.1	N/A
16	3.03 ± 0.26	N/A
17	5.59 ± 1.80	N/A
3 (HSN 608)	3.16 ± 0.57	N/A
Sorafenib	645 ± 7.9	1100 [26]
Alectinib	156.1	~200 [27]
Blu667	9.71	3.7 [28]
Vandetanib	328	220 [26]
Apatinib	1416	N/A

ineffective at inhibiting RET S904F and V804L kinases at 1 nM. For these three compounds, less than 10% of enzymatic inhibition was observed for RET(S904F) while no inhibition was observed for RET(V804L). On the other hand, both Blu667 and HSN608 inhibited 60% of RET(S904F) activity at 1 nM inhibitor concentration (Fig. 7). For RET(V804L), at a stringent concentration of 1 nM, 40% and 25% inhibitions were recorded for Blu667 and HSN608 respectively. At 4 nM, HSN608 inhibited RET(V804L) enzymatic activity at 98% (Fig. S2).

Thus far, we had obtained the inhibition RET enzymatic activities by compound **3** (HSN608) and analogs. To provide additional insight into RET inhibition, we also obtained the binding constant of HSN608 to wild type RET and the RET mutants V804L and V804M at DiscoverX. Interestingly HSN608 binds to wild type RET, RET(V804L) and RET(V804M) with K_d values of 1.9 nM, 1 nM and 0.95 nM respectively (Table 1).

LC-2/ad is human lung adenocarcinoma cell line, which harbors CCDC6-RET fusion and is sensitive to RET inhibitors. It was used to facilitate the studies of drug treatments and the biological properties of RET fusion lung adenocarcinoma [25]. We investigated the antiproliferative activities of the best RET inhibitors in our series, compound **3** (HSN608), **14**, **15**, **16** and **17**, against LC-2/ad cell line. As shown in Fig. 8 and Table 2, these compounds displayed superior IC50 values, compared to existing RET inhibitors sorafenib, vandetanib, alectinib, apatinib and comparable IC50 with BLU667.

3. Conclusion

RET kinase has emerged as a drugable target in cancer but although a few RET inhibitors have enjoyed some degree of clinical success, kinase mutation limits drug efficacy. In this study, we synthesized a series of compounds based on the scaffold of HSN356, which was reported by our group to have inhibition effect against RET kinase [22]. We sought to improve the inhibition ability of compounds towards RET, RET-CCDC6 fusion and drug-resistant RET mutations. The nicotinamide naphthyridine compounds exhibit strong RET inhibition profiles and some of the compounds, such as compound **3** (HSN608) also inhibit RET(V804M/L) and RET(S905F) mutants, which are known to account for drug resistance in the clinic [20,21]. HSN608 inhibited the growth of LC-2/ad cell line, which harbors CCDC6-RET fusion protein, with IC50 of ~3 nM. BLU667 and vandetanib (which are being evaluated against RET-driven cancers in the clinic) inhibited the growth of LC-2/

ad with IC50 values of ~10 and 328 nM respectively under similar conditions. HSN608 is a possible clinical candidate against RET-driven tumors.

Acknowledgement

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Declaration of Competing Interest

HOS is a co-founder of KinaRx LLC, a start-up company interested in developing therapies for malignant neoplastic diseases.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103052.

References

[1] S.E. Mole, L.M. Mulligan, C.S. Healey, B.A.J. Ponder, A. Tunnacliffe, Localisation of the gene for multiple endocrine neoplasia type 2A to a 480 kb region in chromosome band 10q11.2, Hum. Mol. Gen. 2 (1993) 247–252.
[2] A. Drilon, Z.I. Hu, G.G.Y. Lai, D.S.W. Tan, Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes, Nat. Rev. Clin. Oncol. 15 (2017) 151.
[3] Z. Du, C.M. Lovly, Mechanisms of receptor tyrosine kinase activation in cancer, Mol. Cancer 17 (2018) 58-58.
[4] Y.S. Ju, W.C. Lee, J.Y. Shin, S. Lee, T. Bleazard, J.K. Won, Y.T. Kim, J.I. Kim, J.H. Kang, J.S. Seo, A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing, Genome Res. 22 (2012) 436–445.
[5] S.A. Wells, M. Santoro, Targeting the RET pathway in thyroid cancer, Clin. Cancer Res. (2009) 1078-0432.CCR-1008-2742.
[6] F. Li, Y. Feng, R. Fang, Z. Fang, J. Xia, X. Han, X.-Y. Liu, H. Chen, H. Liu, H. Ji, Identification of RET gene fusion by exon array analyses in “pan-negative” lung cancer from never smokers, Cell Res. 22 (2012) 928.
[7] K. Takeuchi, M. Soda, Y. Togashi, R. Suzuki, S. Sakata, S. Hatano, R. Asaka, W. Hamanaka, H. Ninomiya, H. Uehara, Y. Lim Choi, Y. Satoh, S. Okumura, K. Nakagawa, H. Mano, Y. Ishikawa, RET, ROS1 and ALK fusions in lung cancer, Nat. Med. 18 (2012) 378.
[8] R. Ferrara, N. Auger, E. Auclin, B. Besse, Clinical and translational implications of RET rearrangements in non-small cell lung cancer, J. Thorac. Oncol. 13 (2018) 27–45.
[9] T. Nakaoku, K. Tsuta, H. Ichikawa, K. Shiraishi, H. Sakamoto, M. Enari, K. Furuta, Y. Shimada, H. Ogiwara, S.-I. Watanabe, H. Nokihara, K. Yasuda, M. Hiramoto, T. Nammo, T. Ishigame, A.J. Schetter, H. Okayama, C.C. Harris, Y.H. Kim, M. Mishima, J. Yokota, T. Yoshida, T. Kohno, Druggable oncogene fusions in invasive mucinous lung adenocarcinoma, Clin. Cancer Res. 20 (2014) 3087–3093.
[10] M. Suzuki, H. Makinoshima, S. Matsumoto, A. Suzuki, S. Mimaki, K. Matsushima, K. Yoh, K. Goto, Y. Suzuki, G. Ishii, A. Ochiai, K. Tsuta, T. Shibata, T. Kohno, H. Esumi, K. Tsuchihara, Identification of a lung adenocarcinoma cell line with CCDC6-RET fusion gene and the effect of RET inhibitors in vitro and in vivo, Cancer Sci. 104 (2013) 896–903.
[11] D. Matsubara, Y. Kanai, S. Ishikawa, S. Ohara, T. Yoshimoto, T. Sakatani, S. Oguni, T. Tamura, H. Kataoka, S. Endo, Y. Murakami, H. Aburatani, M. Fukayama, T. Niki, Identification of CCDC6-RET fusion in the human lung adenocarcinoma cell line, LC-2/ad, J. Thorac. Oncol. 7 (2012) 1872–1876.
[12] F. Carlomagno, S. Anaganti, T. Guida, G. Salvatore, G. Troncone, S.M. Wilhelm, M. Santoro, BAY 43–9006 inhibition of oncogenic RET mutants, JNCI, J. Natl. Cancer Inst. 98 (2006) 326–334.
[13] I. Plaza-Menacho, L. Mologni, E. Sala, C. Gambacorti-Passerini, A.I. Magee, T.P. Links, R.M.W. Hofstra, D. Barford, C.M. Isacke, Sorafenib functions to potently suppress RET tyrosine kinase activity by direct enzymatic inhibition and promoting RET lysosomal degradation independent of proteasomal targeting, J. Biol. Chem. 282 (2007) 29230–29240.
[14] K. Yoh, T. Seto, M. Satouchi, M. Nishio, N. Yamamoto, H. Murakami, N. Nogami, S. Matsumoto, T. Kohno, K. Tsuta, K. Tsuchihara, G. Ishii, S. Nomura, A. Sato, A. Ohtsu, Y. Ohe, K. Goto, Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial, TLancet Respir. Med. 5 (2017) 42–50.
[15] M. Song, Progress in discovery of KIF5B-RET kinase inhibitors for the treatment of non-small-cell lung cancer, J. Med. Chem. 58 (2015) 3672–3681.
[16] F. Carlomagno, M. Muthu, P. Buonocore, V. De Falco, M. Santoro, F. Basolo, L. Torregrossa, M. Billaud, J.M. Gozgit, Ponatinib (AP24534) is a novel potent inhibitor of oncogenic RET mutants associated with thyroid cancer, J. Clin. Endocrinol. Metab. 98 (2013) E811–E819.
[17] S.W. Chen Lin, Weiwei Xie, Rongliang Zheng, Yu Gan, Jianhua Chang, Apatinib inhibits cellular invasion and migration by fusion kinase KIF5B-RET via suppressing RET/Src signaling pathway, Oncotarget 7 (2016) 59236–59244.
[18] R. Rahal, E.K. Evans, W. Hu, M. Maynard, P. Fleming, L. DiPietro, J.L. Kim, M.P. Sheets, D.P. Wilson, K.J. Wilson, N. Stransky, J.D. Brubaker, T. Guzi, N.E. Kohl, C. Lengauer, Abstract 2641: the development of potent, selective RET inhibitors that target both wild-type RET and prospectively identified resistance mutations to multi-kinase inhibitors, Cancer Res. 76 (2016) 2641-2641.
[19] A. Horiike, K. Takeuchi, T. Uenami, Y. Kawano, A. Tanimoto, K. Kaburaki, Y. Tambo, K. Kudo, N. Yanagitani, F. Ohyanagi, N. Motoi, Y. Ishikawa, T. Horai, M. Nishio, Sorafenib treatment for patients with RET fusion-positive non-small cell lung cancer, Lung Cancer 93 (2016) 43–46.
[20] F. Carlomagno, T. Guida, S. Anaganti, G. Vecchio, A. Fusco, A.J. Ryan, M. Billaud, M. Santoro, Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors, Oncogene 23 (2004) 6056.
[21] T. Nakaoku, T. Kohno, M. Araki, S. Niho, R. Chauhan, P.P. Knowles, K. Tsuchihara, S. Matsumoto, Y. Shimada, S. Mimaki, G. Ishii, H. Ichikawa, S. Nagatoishi, K. Tsumoto, Y. Okuno, K. Yoh, N.Q. McDonald, K. Goto, A secondary RET mutation in the activation loop conferring resistance to vandetanib, Nat. Commun. 9 (2018) 625.
[22] E. Larocque, N. Naganna, X. Ma, C. Opoku-Temeng, B. Carter-Cooper, G. Chopra, R.G. Lapidus, H.O. Sintim, Aminoisoquinoline benzamides, FLT3 and Src-family kinase inhibitors, potently inhibit proliferation of acute myeloid leukemia cell lines, Fut. Med. Chem. 9 (2017) 1213–1225.
[23] Calculated using online software at www.swissadme.ch.
[24] J.E. Cortes, H. Kantarjian, N.P. Shah, D. Bixby, M.J. Mauro, I. Flinn, T. O'Hare, S. Hu, N.I. Narasimhan, V.M. Rivera, T. Clackson, C.D. Turner, F.G. Haluska, B.J. Druker, M.W.N. Deininger, M. Talpaz, Ponatinib in refractory philadelphia chromosome-positive leukemias, New Eng. J. Med. 367 (2012) 2075–2088.
[25] A. Cerrato, R. Visconti, A. Celetti, The rationale for druggability of CCDC6-tyrosine kinase fusions in lung cancer, Mol. Cancer 17 (2018) 46.
[26] H. Chang, J.H. Sung, S.U. Moon, H.-S. Kim, J.W. Kim, J.S. Lee, EGF induced RET inhibitor resistance in CCDC6-RET lung cancer cells, Yonsei Med. J. 58 (2017) 9–18.
[27] S. Arai, K. Kita, A. Tanimoto, S. Takeuchi, K. Fukuda, H. Sato, S. Yano, In vitro and in vivo anti-tumor activity of alectinib in tumor cells with NCOA4-RET, Oncotarget 8 (2017) 73766–73773.
[28] V. Subbiah, J.F. Gainor, R. Rahal, J.D. Brubaker, J.L. Kim, M. Maynard, W. Hu, Q. Cao, M.P. Sheets, D. Wilson, K.J. Wilson, L. DiPietro, P. Fleming, M. Palmer, M.I. Hu, L. Wirth, M.S. Brose, S.-H.I. Ou, M. Taylor, E. Garralda, S. Miller, B. Wolf, C. Lengauer, T. Guzi, E.K. Evans, Precision targeted therapy with BLU-667 for RET-driven cancers, Cancer Discov. 8 (2018) 836–849.