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MLN8054 and Alisertib (MLN8237): Discovery of Selective Oral Aurora A Inhibitors

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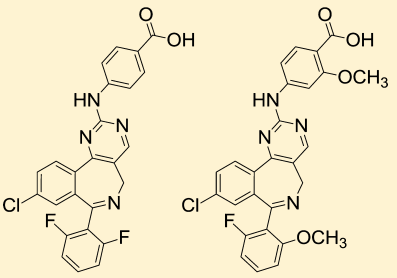
Supporting Information

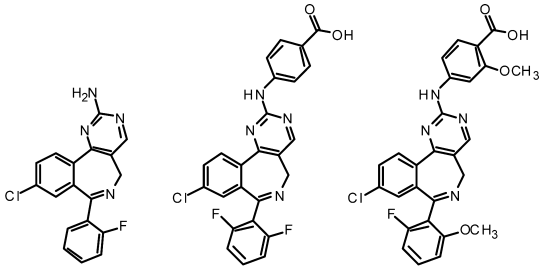
ABSTRACT: The Aurora kinases are essential for cell mitosis, and the dysregulation of Aurora A and B have been linked to the etiology of human cancers. Investigational agents MLN8054 (**8**) and alisertib (MLN8237, **10**) have been identified as high affinity, selective, orally bioavailable inhibitors of Aurora A that have advanced into human clinical trials. Alisertib (**10**) is currently being evaluated in multiple Phase II and III clinical trials in hematological malignancies and solid tumors.



KEYWORDS: *Alisertib, Aurora A kinase, MLN8054, MLN8237*

The Aurora kinases A and B are serine/threonine kinases that are essential for normal progression through mitosis. Aurora A and B overexpression occurs in both solid and hematological malignancies. Loss of function or inhibition of Aurora A or B results in aberrant mitosis that can lead to cell-cycle arrest and apoptosis. These findings have inspired numerous drug discovery efforts in search of clinically useful inhibitors of the Aurora kinases for cancer therapy.[1] While other organizations have pursued the development of Aurora B or pan-Aurora kinase inhibitors, we sought to identify a selective Aurora A kinase inhibitor. We report here the discovery of MLN8054 (**8**) and alisertib (MLN8237, **10**), selective Aurora A inhibitors that have advanced into human clinic trials.[2−4]

One of our approaches toward identifying small molecule inhibitors of Aurora A utilized a traditional high throughput screen. Scaffolds that we identified have also been identified by other groups and have been subsequently advanced into the clinic as Aurora B selective or pan Aurora kinase inhibitors.[5,6] In addition to our pursuing a traditional screening approach was our investigation of the pyrimidobenzazepine BBL22 (**1**, Figure 1), which was reported to induce G2/M cell cycle arrest and apoptosis in human tumor cell lines.[7] In an enzymatic assay, **1** inhibited Aurora A kinase activity at micromolar concentrations (Table 1).[2,3] Human tumor cell lines treated with **1** underwent cell cycle progression and mitotic defects followed by cell death, phenotypes consistent with Aurora A inhibition using RNA interference and antibody micro-injection.[3,8] Unlike the scaffolds identified in our high throughput screen, the pyrimidobenzazepines, exemplified by



	BBL22 (**1**)	MLN8054 (**8**)	Alisertib (**10**)
logP	4.1	5.2	4.9
Aurora A LE	0.34	0.31	0.34

Figure 1. Structure, logP, and Aurora A ligand efficiency (LE) of BBL22, MLN8054, and alisertib.

1, represented a unique starting point toward identifying an Aurora kinase inhibitor that meets the requirements for clinical investigation. We chose to investigate this scaffold for its potential to provide a potent and selective, orally active inhibitor of Aurora A kinase.

Our initial medicinal chemistry efforts were focused on establishing whether suitable Aurora A potency could be obtained with this scaffold. To enable analogue generation, we developed routes that would allow for modification of each of the aromatic rings and would also facilitate substitution on the

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Table 1. Enzyme and Cellular Activity

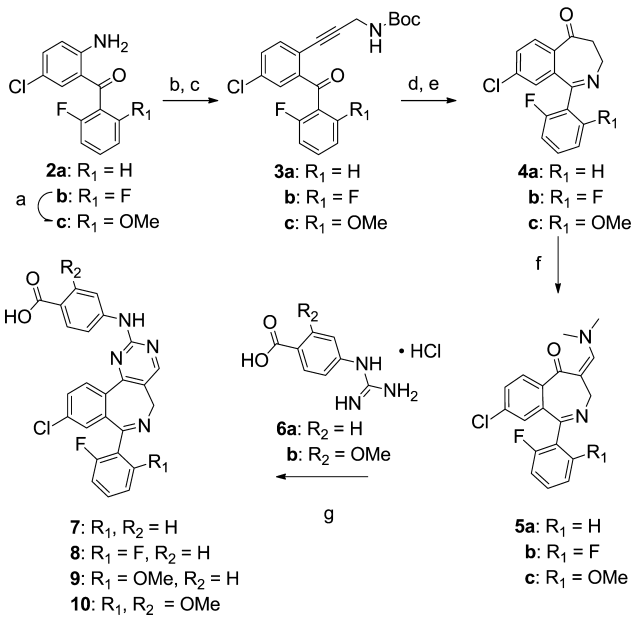
compd	AurA (nM)	pT288 (nM)[a]	pHisH3 (μM)[a]	HCT116 BrdU (μM)[b]
1	1700	6000	>10	11
7	33	170	>10	0.95
MLN8054 (**8**)	31	34	5.2	0.22
9	10	18	2.5	0.13
alisertib (**10**)	1	7	1.5	0.03

[a]IC_{50} in HCT116 cells. [b]GI_{50} values.

pyrimidine amine.[9] A screen of substitutions on the pyrimidine amine demonstrated that submicromolar affinity for Aurora A could be obtained with aryl substitutions and identified the *p*-benzoic acid containing **7** as providing a desirable low nanomolar affinity in a recombinant Aurora A enzyme assay (Table 1). As illustrated in Table 1, the selectivity of **7** for Aurora A over Aurora B was demonstrated in a cellular setting, by comparing phosphorylation of direct substrates, Aurora A autophosphorylation (pT288) and Aurora B phosphorylation of histone H3 (pHisH3) on Ser-10, in HCT116 cells.[2] The compound's effect on cellular proliferation was measured by a BrdU incorporation assay. Furthermore, **7** is cell permeable, stable in human S9 fraction, and soluble as the sodium salt.[10]

The synthetic route outlined in Scheme 1 illustrates our approach for the synthesis of **7** and related analogues.

Scheme 1. Synthesis of Analogues 7−10[a]



[a]Reagents and conditions: (a) sodium methoxide, methanol, heat; (b) HOAc, conc. HCl, $NaNO_2$, EtOAc, KI, H_2O, 10 °C; (c) prop-2-ynyl-carbamic acid *tert*-butyl ester, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_2Cl_2; (d) $HgSO_4$/formic acid or conc. HCl/DCM or TFA/H_2O; (e) K_2CO_3; (f) DMF-DMA/DCM, 35 °C; (g) **6**, K_2CO_3, MeOH, 55 °C.

Conversion of the amino-benzophenones **2a−c** to their corresponding aryl iodides allowed for Sonogashira coupling with a protected propargyl amine to provide **3a−c**. Hydration of the alkyne and deprotection of the amine was followed by exposure to basic conditions, which promoted cyclization to provide azepines **4a−c**. Conversion to the enamines **5a−c** allowed for pyrimidine ring formation through reaction with functionalized guanidines, producing the target pyrimidobenzazepines **7−10**.

Encouraging progress optimizing the pyrimidobenzazepine scaffold, as demonstrated through the favorable profile observed with **7**, provided the impetus for the synthesis of numerous analogues within this series.[9,11] Of particular note from the resulting structure−activity relationship (SAR) was an improvement in cellular potency that could be obtained with an additional substituent in the ortho-position of the 7-phenyl ring. Incorporation of a fluorine at this position provided MLN8054 (**8**). In addition to an increased potency in cells, MLN8054 is 150-fold selective for Aurora A over Aurora B in HCT116 cells (Table 1). MLN8054 is a reversible, ATP competitive inhibitor of recombinant Aurora A (K_i = 7 nM, apparent K_{off} = 8 s^{-1}). Additionally, MLN8054 displayed good selectivity against a panel of known kinases.[12] MLN8054 bound to the kinase domain of Aurora A has been reported to result in an unusual activation loop conformation, which may provide a basis for selectivity over Aurora B and other kinases that cannot adopt this conformation.[13] To identify potential off-target binding activity, a screen of the PerkinElmer General SEP panel[12] was carried out with MLN8054. $GABA_A$ α-1 benzodiazapine site binding (IC_{50} = 330 nM) was the only potential off-target binding identified.

Human tumor cell lines treated with cytotoxic concentrations of MLN8054 displayed an Aurora A inhibition phenotype, which included an inhibition of Aurora A autophosphorylation (pT288), G_2/M accumulation, aneuploidy, and increased apoptosis.[2,14] An Aurora B phenotype (a decrease in histone H3 phosphorylation on Ser10 and >4 N DNA content) could be observed at concentrations >10-fold above the GI_{50}. Treatment of nude mice bearing human tumor xenografts with a single oral dose of MLN8054 (30 mg/kg) similarly resulted in a phenotype consistent with Aurora A inhibition. Significant tumor growth inhibition, with no overt toxicity, was observed in multiple xenograft efficacy models grown in immunocompromised mice.[15]

MLN8054 is highly cell permeable (Caco-2, 540 nm/s A-B, 790 nm/s B-A) and is not a substrate of P-gp in transfected MDCK cells. In vitro metabolism is predominantly through CYP1A2 and 3A4, and no CYP inhibition is observed at concentrations up to 100 μM. MLN8054 is highly protein bound (>98%), and pharmacokinetic parameters in rat (Table 2) include low clearance, a high volume of distribution, a 4 h terminal half-life and quantitative oral bioavailability. The principle route of elimination of MLN8054 is through metabolism, primarily via hydroxylation and acyl glucuronide formation. Pharmacokinetic parameters in additional preclinical models allowed for the prediction of favorable PK parameters in humans.[16]

Table 2. Pharmacokinetic Parameters in Sprague−Dawley Rat[a]

	MLN8054 (**8**)	alisertib (**10**)
CL (mL min^{-1} kg^{-1})	20.3	10.4
V_{ss} (L kg^{-1})	1.48	2.21
$T_{1/2}$ (h)	4.2	7.0
F^b (%)	100	124

[a]Administered IV (1 mg/kg) as a solution in 10% 2-HP-β-CD. [b]Sodium salts administered PO (10 mg/kg) as a solution in 10% 2-HP-β-CD with 3.5% $NaHCO_3$ (**8**) or 1% $NaHCO_3$ (**10**).

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Toxicities observed at the maximum tolerated dose in Sprague–Dawley (SD) rats given MLN8054 orally for seven consecutive days included myelosuppression and mucositis, consistent with the antiproliferative effects of Aurora A inhibition. Also observed were reversible central nervous system (CNS) effects, likely attributable to $GABA_A$ binding. In Phase I dose escalation studies in patients with advanced solid cancers, the observed dose limiting toxicity was reversible somnolence, again attributed to $GABA_A$ binding.[17,18] Dose fractionation of MLN8054 (QID), and coadministration of methylphenidate, failed to sufficiently mitigate dose limiting somnolence. Cellular phenotypes in patient skin and tumor biopsies, consistent with inhibition of Aurora A, were observed at doses above the maximum tolerated dose.[19] These studies demonstrated the need for a molecule with an improved therapeutic window with respect to CNS effects. The pharmacodynamic response demonstrating Aurora A inhibition in patients treated with MLN8054 indicated that the improvement required with regard to CNS effects might only need to be modest and that continued optimization of the pyrimidobenzazepine scaffold was warranted. Additionally, the toxicity studies in SD rats were qualitatively predictive of CNS effects observed in humans and allowed us to utilize the rat as a functional assay for the evaluation of candidate molecules that may provide this improvement.

Efforts to improve the therapeutic window of MLN8054 focused on attempting to decrease the $GABA_A$ binding affinity, reduce the degree of brain partitioning, and to demonstrate no discernible CNS effects in the SD rat. Accomplishing those goals within the pyrimidobenzazepine scaffold would give us the best opportunity to retain the Aurora A selectivity, oral bioavailability, and additional favorable properties imparted by this scaffold. The extent of brain partitioning of an efficacious dose of MLN8054 (30 mg/kg, PO) and selected analogues was characterized in nude mice (Table 3). The results suggested

Table 3. Brain Total Exposure in Nude Mice[a]

compd	AUC plasma[b]	AUC brain[b]	AUC ratio[b]	brain C_{max} (μg/mL)
MLN8054 (**8**)	58.2	12.5	0.22	2.6
9	54.3	3.5	0.06	0.93
alisertib (**10**)	62.3	2.0	0.03	0.42

[a]The sodium salts of **8**, **9**, and **10** administered PO (30 mg/kg) as a solution in 10% 2-HP-β-CD with 3.5% $NaHCO_3$ (**8** and **9**) or 1% $NaHCO_3$ (**10**). [b]AUC_{0-8h} (μg/mL·h), Ratio of brain $AUC_{0-8\ h}$/plasma $AUC_{0-8\ h}$.

that lower brain partitioning could be achieved while maintaining similar plasma levels. Compound **9**, in which one of the fluorine substituents on the 7-phenyl ring is replaced with a methoxy group, displayed a 3-fold brain AUC reduction. Compared to MLN8054, **9** displays comparable enzymatic and cellular Aurora A inhibition (Table 1) and has similar binding affinity for $GABA_A$ (IC_{50} = 150 nM). When an additional methoxy group was incorporated ortho to the carboxylic acid, providing alisertib (**10**),[4,11] comparable binding affinity for $GABA_A$ (IC_{50} = 490 nM) and an additional reduction in mouse brain partitioning was observed. A similar trend was observed in the SD rat with brain/plasma AUC ratios for MLN8054 (0.23) being higher than **9** (0.14) and alisertib (0.07).

While we were unable to diminish $GABA_A$ binding potency with these compounds, alisertib displayed a greater selectivity ratio of Aurora A enzyme inhibition to $GABA_A$ α-1 benzodiazepine site binding affinity compared to MLN8054 or **9**. As illustrated in Table 1, alisertib is significantly more potent in the enzymatic and cell based Aurora A assays than MLN8054 or **9** and displays similar selectivity over Aurora B in cells. Alisertib inhibition of recombinant Aurora A is competitive with ATP, and it is characterized as a slow, tight-binding inhibitor (K_i = 0.3 nM, apparent $K_{off} = 2 \times 10^{-4}\ s^{-1}$). Alisertib is highly selective against an Invitrogen kinase panel (20/204, ≥30% inhibition),[12] and no additional potential off-target binding activity was identified in the PerkinElmer General SEP panel.

Alisertib exhibits favorable pharmacokinetic parameters in the SD rat (Table 2). SD rats were dosed orally with **9** or alisertib to evaluate their potential to elicit the effects of $GABA_A$ binding. No effects attributable to $GABA_A$ binding were observed. Exposures attained with **9** ($AUC_{0-24\ h}$ = 244 μg/mL·hr, C_{max} = 46 μg/mL) and alisertib ($AUC_{0-24\ h}$ = 201 μg/mL·h, C_{max} = 48 μg/mL) in these studies were significantly higher than exposures of MLN8054 ($AUC_{0-24\ h}$= 13.8 μg/mL·h, C_{max} = 5.2 μg/mL) that are capable of eliciting CNS effects in SD rats. $GABA_A$ related effects could, however, be observed when rats were dosed with a 5 min IV infusion of alisertib, albeit at peak plasma concentrations significantly higher than those required for MLN8054 to produce CNS effects.[12] Toxicities observed at the maximum tolerated dose in SD rats given alisertib orally for seven consecutive days were myelosuppression and mucositis, consistent with Aurora A inhibition. No effects attributable to $GABA_A$ binding were observed. The mitigation of $GABA_A$ mediated effects observed with **9** and alisertib in the SD rat model provided the basis for a potential improvement in the therapeutic window in the clinic, with respect to the somnolence observed with MLN8054. In addition, alisertib has the potential for further improvement of this therapeutic window due to its greater potency against Aurora A compared to **9** and MLN8054.

Nude mice bearing human tumor xenografts treated with a single oral dose of alisertib (20 mg/kg) displayed a phenotype consistent with inhibition of Aurora A.[4] MLN8054 and alisertib were evaluated in a Calu-6 human tumor xenograft growth efficacy model, see Figure 2. Alisertib displayed equivalent to superior tumor growth inhibition with a lower compound exposure than that of MLN8054. Alisertib has demonstrated

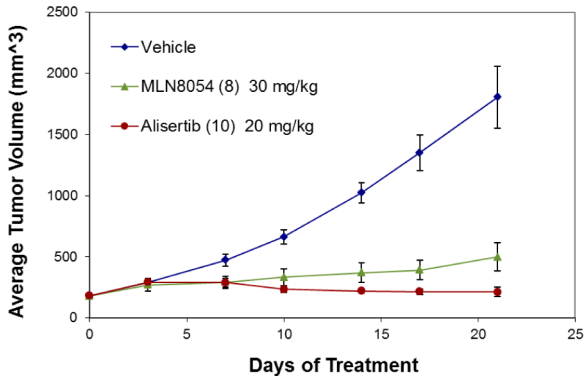

Figure 2. Growth inhibition of Calu-6 human lung tumor xenografts as measured by average tumor volume (mm^3). Mice were dosed orally twice daily for 21 consecutive days with vehicle, 30 mg/kg MLN8054 (**8**), or 20 mg/kg alisertib (**10**) as sodium salts. Error bars denote the standard error of the mean.

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significant tumor growth inhibition in multiple human tumor xenograft models.[4,20]

Alisertib retains the favorable physiochemical and PK properties observed within this scaffold. It exhibits high cell permeability in Caco-2 cells (620 nm/s A-B, 470 nm/s B-A) and is not a substrate of P-gp in transfected MDCK cells. In vitro metabolism is low and is mediated through multiple CYP isoforms and UGTs, with the predominant metabolites being hydroxylation of the azepine ring, demethylation of the 7-fluoromethoxyphenyl ring, and acylglucuronide formation. No inhibition of the major human CYP isozymes is observed (IC_{50} > 100 μM). Alisertib is highly protein bound (>97%) and pharmacokinetic parameters in preclinical models suggested favorable PK in humans.[21]

In Phase I dose escalation studies with alisertib given orally on a twice daily schedule for seven consecutive days, the maximum tolerated dose was defined predominantly by the occurrence of grade 3 or grade 4 myelosuppression and stomatitis, consistent with the antiproliferative effects of Aurora A inhibition.[22,23] In contrast to MLN8054, the incidence of somnolence observed upon administration of alisertib was not dose limiting. Additionally, pharmacodynamic effects in skin and tumor biopsies reflecting Aurora A inhibition were observed at doses below the maximum tolerated dose. These studies provided support for the continued clinical investigation of alisertib.

We have identified the pyrimidobenzazepines as a unique kinase inhibitor scaffold. From this scaffold, MLN8054 (**8**) was identified as a potent and selective inhibitor of Aurora A. Off-target somnolence was identified as the dose limiting toxicity of MLN8054 in humans. Alisertib (**10**) was discovered and identified to have a potentially greater therapeutic window due to its increased potency against Aurora A and its diminished CNS effects in a SD rat model. Alisertib appears to have a generally tolerable safety profile in humans and has advanced into multiple clinical studies including an open-label Phase III trial for patients with relapsed and refractory peripheral T-cell lymphoma.[24]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for compounds **7**–**10**, kinase selectivity data, and SD rat exposures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/ml500409n.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

Aur A, Aurora A; BrdU, 5-bromo-2′-deoxyuridine; $GABA_A$, gamma-aminobutyric acid ionotropic receptor; LE, ligand efficiency; MDCK, Madin–Darby canine kidney

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