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Microperspective

Molecular Basis of c-MET Inhibition by Approved Small Molecule Drugs: A Structural Perspective

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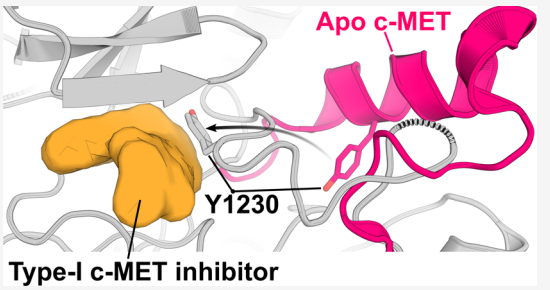
ABSTRACT: The c-MET kinase is a driver of many cancers, and as such, there are a number of small molecule inhibitors of this kinase approved for clinical use. In this Microperspective, we provide a structural overview of the molecular basis by which these drugs inhibit c-MET, focusing on key features contributing to activity, selectivity, and drug resistance. Where necessary, relevant crystal structures not publicly available were determined and are discussed here alongside existing structural data.



KEYWORDS: *c-MET, kinase inhibitor, non-small cell lung cancer, NSCLC, small molecule drug*

c-MET is a receptor tyrosine kinase that plays a key role in cell growth, survival, and migration, and as a consequence, the upregulation of this kinase is known to drive a number of cancers, including but not limited to renal, gastric and non-small cell lung cancer (NSCLC).[1−3] As well as being the primary driver of many cancers, in some cases, upregulation of c-MET has also emerged as an acquired drug-resistance mechanism to the treatment of EGFR-driven cancers with EGFR inhibitors.[4] While c-MET overactivity can be a result of *MET* amplification or activating *MET* mutations, the most clinically relevant cause of c-MET overactivity is the exon 14 skipping genetic alteration.[1] Exon 14 of the *MET* gene codes for a degron recognition sequence in the expressed protein for the c-CBL ubiquitin ligase, which, when present, is thought to result in the negative regulation of cellular c-MET protein levels via the ubiquitin-proteasome system.[5,6] When this degron is absent in the expressed protein, as in the exon 14 skipping state, cellular levels of c-MET protein are unnaturally high, and thus the pathways regulated by c-MET (such as growth or differentiation) are overactivated.

Due to the well-studied role of c-MET in cancer, a considerable number of preclinical small molecule c-MET inhibitors have been reported,[7−9] with, to the best of our knowledge, seven of these approved for clinical use to date (see Table 1 and Figure 1). There exist many excellent reviews that have covered the biology,[10,11] chemistry,[7−9] and clinical efficacy[1−3,12] of both preclinical and clinical c-MET inhibitors. In this Microperspective, we will focus on approved small molecule inhibitors of c-MET, and we will specifically be concerned with the molecular basis by which these drugs recognize and inhibit the function of c-MET based on available crystallographic data. Where this data was not available, we generated the necessary crystal structures, reporting nine new high resolution c-MET structures. We highlight common features and differences between the binding modes of approved c-MET inhibitors, emphasizing key residues and interactions that contribute to affinity, activity, and selectivity. We also provide a structural perspective on the emergence of on-target, acquired, clinically observed drug-resistant mutant forms of c-MET such as D1228V and Y1230H.

Clinically approved small molecule c-MET inhibitors can be broadly divided into two classes—"type-I" or "type-II"—based on the manner by which they are known, or assumed, to bind to and inhibit c-MET. Type-I inhibitors bind to the ATP-binding site of c-MET but do not displace the conserved tripeptide "DFG" motif of the activation loop ("A-loop") (Figure 2). Type-II inhibitors also localize to the ATP-binding site but extend further into the ATP pocket and displace the DFG motif. We will consider each class in turn, followed by an exploration of the various acquired mutant structures (many reported here for the first time) in complex with clinical c-MET inhibitors.

To date, six of the seven approved small molecule c-MET inhibitors fall into the "type-I" inhibitor class (Table 1 and Figure 1). Savolitinib,[19,20] capmatinib,[21−23] vebreltinib,[24,25]

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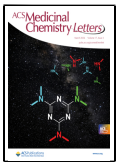

Table 1. Clinically Approved and Clinically Evaluated Small Molecule c-MET Inhibitors (Ordered by Molecular Weight)

Inhibitor	Approved clinically?	Inhibitor class	MW (Da)	AZlogD$_{7.4}$[a]	Crystal structures[b]		
					Wild-type	D1228V	Y1230H
Savolitinib	Yes	Type-I	345.4	1.71	6SDE[13]	-	-
Capmatinib	Yes	Type-I	412.4	2.38	9SXJ[f]	-	9SZJ[f]
Vebreltinib[c]	Yes	Type-I	424.4	2.64	9IVB[14]	-	-
Crizotinib[d]	Yes	Type-I	450.3	1.99	2WGJ[15]	-	-
Glumetinib[e]	Yes	Type-I	459.5	2.28	9T6K[f]	-	-
Tepotinib	Yes	Type-I	492.6	2.20	4R1V[16]	-	-
Cabozantinib	Yes	Type-II	501.5	4.59	9T2V[f]	9T3Q[f]	-
Glesatinib	No	Type-II	619.7	4.42	9T0D[f]	9T1Q[f]	-
Sitravatinib	No	Type-II	629.7	4.37	9T08[f]	9T0B[f]	-
Foretinib	No	Type-II	632.7	4.53	3LQ8[17]	6SDC[13]	-

[a]LogD predictions are generated by a multitask deep learning model developed at AstraZeneca and trained on various physicochemical properties. [b]Four-digit codes in the "Crystal structures" columns refer to Protein Data Bank (PDB) accession codes (plus relevant reference as superscript number). [c]Also referred to as bozitinib. [d]Crizotinib is a potent c-MET inhibitor and is approved for clinical use but is not currently approved for c-MET-driven cancers. See main text for further details. [e]Also referred to as glumarontinib. [f]Denotes crystal structures reported here for the first time. Further details of crystal structures reported here, including resolutions, can be found in Table S2 in the Supporting Information.

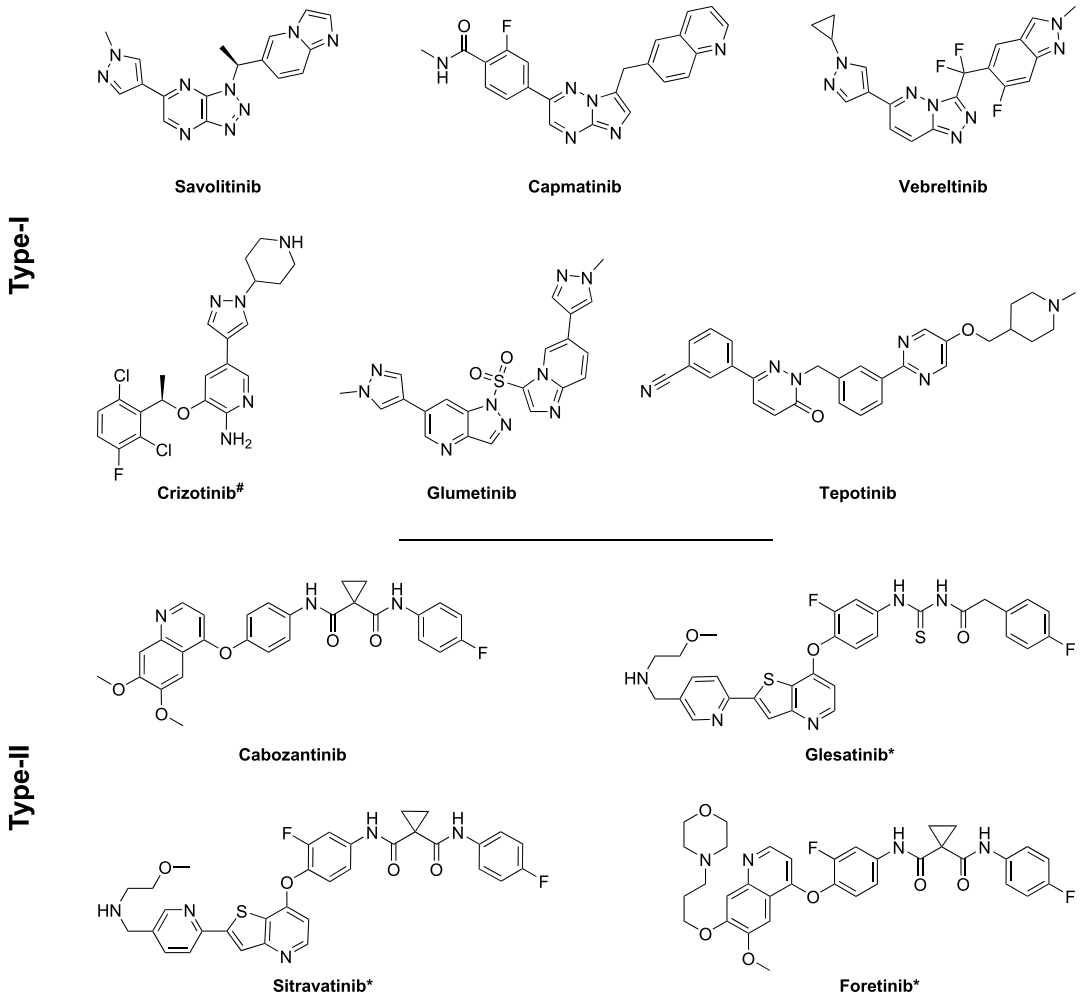

Figure 1. Chemical structures of approved type-I and type-II c-MET inhibitors. #Crizotinib is a potent c-MET inhibitor and is approved for clinical use, but is not currently approved for c-MET-driven cancers. See main text for further details. *Denotes inhibitors that have been evaluated in clinical trials but are not approved for clinical use. Inhibitors are grouped by inhibitor class/type and ordered by molecular weight.

glumetinib,[26] and tepotinib[16,27,28] are approved for the use in patients with metastatic NSCLC with tumors bearing the c-MET exon 14 skipping mutation. Crizotinib is a potent inhibitor of c-MET, and though it was one of the first compounds to show activity against c-MET driven cancers clinically[29,30] it is not currently approved for such cancers. Rather, it is approved for patients with metastatic ALK-positive tumors[31] and metastatic ROS1 rearrangement-positive NSCLC,[32] since it also potently inhibits the ALK[15] and ROS1[33,34] kinases. However, it is perhaps worth noting that,

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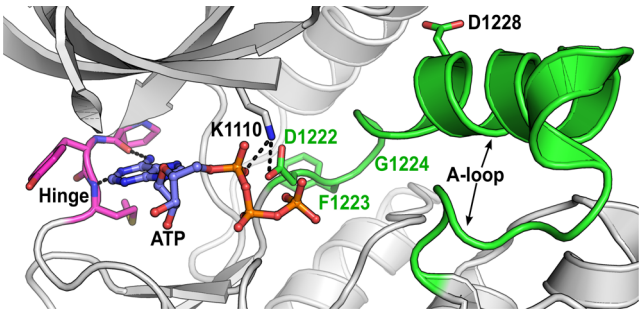

Figure 2. Crystal structure of ATP-bound c-MET (PDB entry 3DKC[18]) highlighting key features of the site to which all approved small-molecule c-MET inhibitors bind. The P-loop (phosphate-binding loop) has been partially omitted for the sake of clarity. Hinge residues colored magenta, A-loop colored green, and "DFG" motif indicated by green labels.

despite its approval status, crizotinib has purportedly been used off-label to treat c-MET exon 14 skipping cancers.[35]

Of these six type-I c-MET inhibitors, crystal structures for four were available at the time this manuscript was written, with capmatinib and glumetinib lacking crystal structures. We thus attempted to determine crystal structures of the two unavailable complexes and succeeded in determining a 1.32 Å crystal structure of wild-type c-MET in complex with capmatinib and a 1.13 Å structure for c-MET in complex with glumetinib (see Supporting Information for experimental details and Tables S1 and S2). Analysis of the crystal structures of these six type-I complexes—encompassing savolitinib,[13] capmatinib, vebreltinib,[14] crizotinib,[15] glumetinib, and tepotinib[16]—shows that all inhibitors share the common features of: 1) binding to the ATP site, wrapping around M1211; 2) anchoring to the hinge region of the kinase (residues P1158, Y1159 and M1160); 3) hydrogen bonding to the backbone NH of D1222 (with the exception of crizotinib) and, crucially; 4) π-stacking onto residue Y1230 of the A-loop (Figure 3). Indeed, comparison of these type-I complexes with apo c-MET (Figure 4A) or ATP-bound c-MET (Figure 4B) shows that the A-loop reorganizes significantly to accommodate these inhibitors, forming a "new" salt bridge between K1110 (which otherwise interacts with the α phosphate of ATP in the c-MET-ATP complex, see Figure 2) and D1228—a key interaction holding Y1230 in an orientation favorable for binding to the type-I compounds. The interaction between type-I inhibitors and Y1230 is known to be a key driver of both affinity and selectivity.[36] Indeed, *in vitro* experiments in which this residue is mutated to a residue that cannot form a π-stacking interaction with type-I inhibitors show a significant reduction in activity.[37,38]

Due to the crucial role Y1230 plays in the binding mode of type-I inhibitors, there have been numerous reports of acquired, on-target point mutations of c-MET that disrupt, or are presumed to disrupt, the type-I-Y1230 π-stacking interaction, either directly, such as Y1230H/C, or indirectly, such as the D1228V/N.[4] Clinically observed acquired, drug-resistant mutant forms of c-MET will be discussed further below.

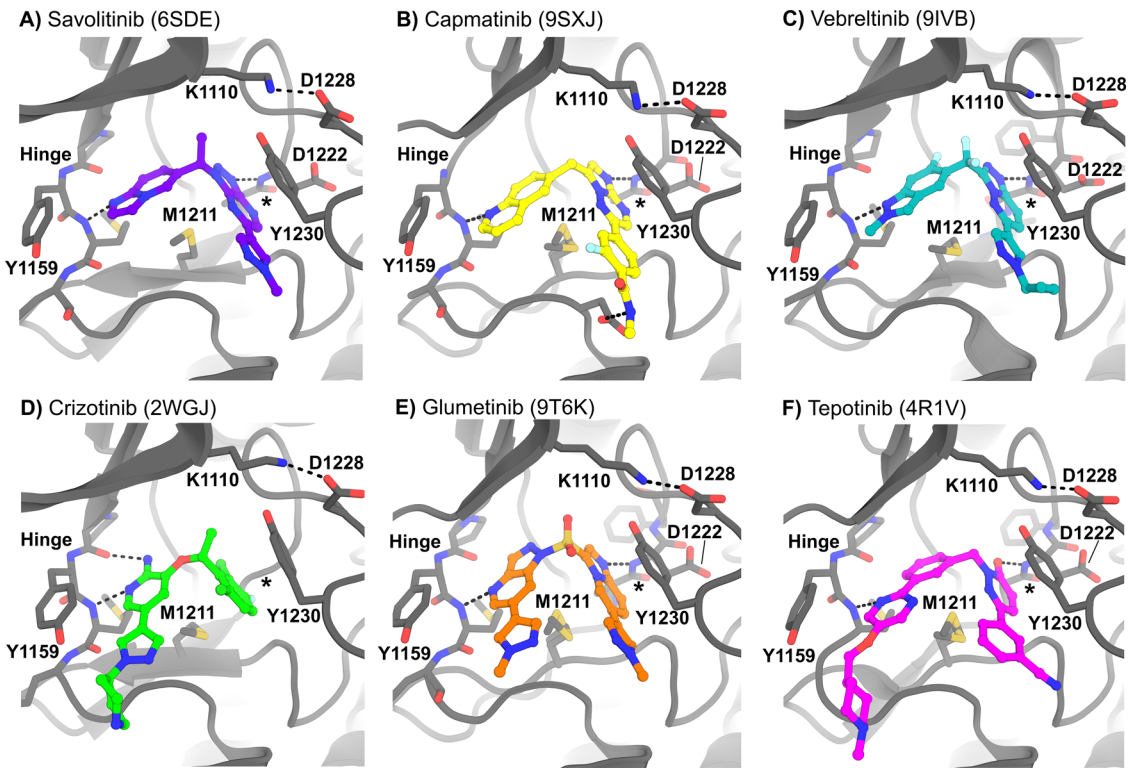

Figure 3. Binding modes of approved type-I c-MET inhibitors, highlighting shared features of: 1) binding to the ATP-binding site, wrapping around M1211; 2) hydrogen bonding to the hinge region of the kinase (residues P1158, Y1159, and M1160); 3) hydrogen bonding to the backbone NH of D1222 (with the exception of crizotinib); and 4) π-stacking onto residue Y1230 of the A-loop. Key polar interactions are shown as black dashes. *Denotes π-stacking interactions between inhibitors and Y1230. NB the fluorinated benzamide of capmatinib in panel B was modeled with two conformations but just one conformation is shown here for clarity. PDB accession codes are shown in brackets. Structures are ordered as in Table 1.

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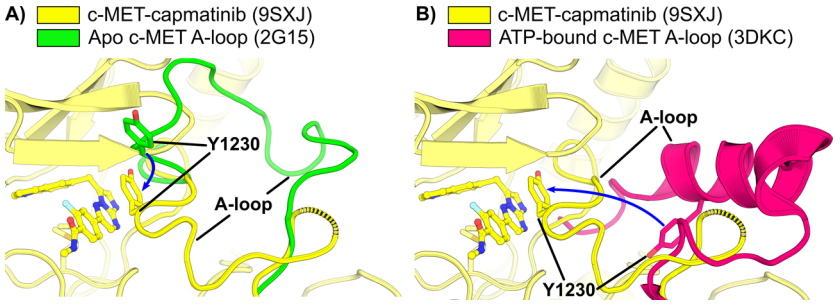

Figure 4. A-loop movement (blue arrows) induced by the binding of type-I compound capmatinib to c-MET. A) c-MET-capmatinib complex (yellow) vs apo c-MET[39] (green, for clarity, only the A-loop is shown). B) c-MET-capmatinib complex (yellow) vs ATP-bound c-MET[18] (magenta, for clarity, only the A-loop is shown). PDB accession codes are shown in brackets.

Just one of the seven approved small molecule c-MET inhibitors, cabozantinib, falls into the "type-II" inhibitor class. Alongside c-MET, it also inhibits the VEGFR2, AXL, RET, KIT, and FLT3 kinases.[40] It is approved for a number of indications but primarily for advanced renal cell carcinoma (RCC),[41] hepatocellular carcinoma[41] and metastatic medullary thyroid cancer.[42] Since there was no crystal structure available for cabozantinib in complex with c-MET, this binding mode categorization was assumed, based on the similarity of cabozantinib to other compounds, such as foretinib (see Figure 1), for which crystal structures exist.[17] In order to experimentally confirm cabozantinib's binding mode for c-MET, we generated a 1.67 Å crystal structure of this complex. This structure does indeed confirm the type-II binding mode of cabozantinib, with the inhibitor binding to the hinge region of the kinase (M1160) via its quinoline nitrogen, with the fluoro-phenyl group not interacting with Y1230 of the A-loop but rather displacing the DFG motif, thereby causing the A-loop to rearrange relative to the apo and wild-type complexes (Figure 5). Key polar contacts in addition to the hinge

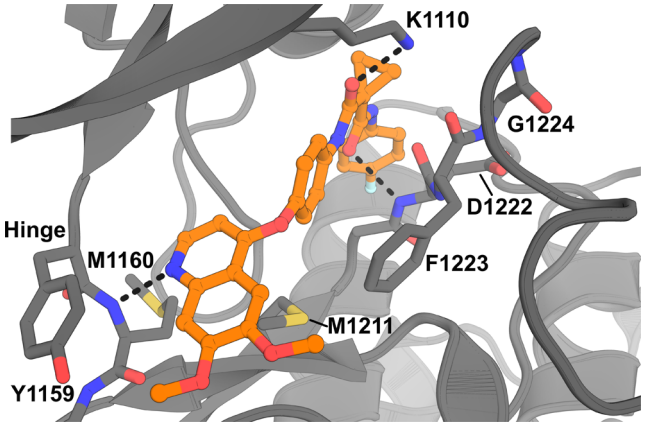

Figure 5. Crystal structure of wild-type c-MET bound by the type-II inhibitor cabozantinib. Key polar interactions are shown as black dashes. PDB entry 9T2V.

interaction are made from the carbonyl groups on either side of the cyclopropyl group to the side-chains of K1110 and the backbone NH of D1222 (Figure 5). The lack of interaction with Y1230 is assumed to be the cause of the generally lower selectivity of cabozantinib (and other type-II c-MET inhibitors such as sitravatinib, foretinib, and glesatinib, see Figure 1 for chemical structures), though the high lipophilicity of this neutral inhibitor (see calculated AZlogD$_{7.4}$ in Table 1) likely also contributes to the broader kinase activity profile of cabozantinib, along with other factors such as hinge recognition patterns, which differ across the type-I and type-II inhibitor classes. Nevertheless, lack of reliance on Y1230 π-stacking for affinity results in cabozantinib (and other clinically tested but not yet approved type-II c-MET inhibitors) being active against some of the clinically reported drug-resistant forms of c-MET, including the aforementioned D1228V and Y1230C/H mutants,[37] which will be discussed further below.

At the time of writing, no structural data was publicly available concerning clinically observed drug-resistant forms of c-MET in complex with approved c-MET inhibitors (though a small number of c-MET mutant structures exist for preclinical inhibitors[13,43−45]). To address this paucity, we determined a number of crystal structures covering the D1228V and Y1230H c-MET mutants.

The clinically reported D1228V drug-resistant form of c-MET is seen to be resistant to inhibition (compared to wild-type c-MET) by the type-I compounds listed in Table 1 where such data is available[13,37,46] (though it should be noted that such data is not available for all type-I compounds listed in Table 1) (see Table 2). As described above, the mechanism of

Table 2. Activity of c-MET Inhibitors in Wild-Type and Mutant c-MET Cell Lines

Inhibitor	Class	Wild-type	D1228V	Y1230H	Source
Savolitinib	Type-I			ND	*Collie et al., 2019 (Ref. 13)*
Capmatinib	Type-I				*Fujino et al. 2022 (Ref. 37)*
Crizotinib	Type-I			ND	*Collie et al., 2019 (Ref. 13)*
Tepotinib	Type-I				*Fujino et al. 2022 (Ref. 37)*
Cabozantinib	Type-II				*Fujino et al. 2022 (Ref. 37)*
Sitravatinib	Type-II				*Fujino et al. 2022 (Ref. 37)*
Foretinib	Type-II				*Fujino et al. 2022 (Ref. 37)*

Key: <120 nM | 120-1000 nM | >1000 nM | ND = not determined.

this resistance is understood to be due to disruption of the π-stacking surface of Y1230, which relies on a salt-bridge from D1228 to K1110 to stabilize it in a position suitable to accommodate the type-I binding mode (see Figure 3).[13] The wild-type c-MET-cabozantinib structure shows clearly why this inhibitor is active against the D1228V mutant; cabozantinib does not interact with Y1230, nor the A-loop generally and thus, unlike type-I c-MET inhibitors, does not rely on the salt bridge between D1228 and K1110. As cabozantinib is active against the D1228V drug-resistant c-MET mutant[37,46] (see Table 2), we determined a crystal structure of this complex (to a resolution of 1.63 Å). The crystal structure of the D1228V c-MET-cabozantinib complex confirms this observation further, with the binding mode of cabozantinib for wild-type and

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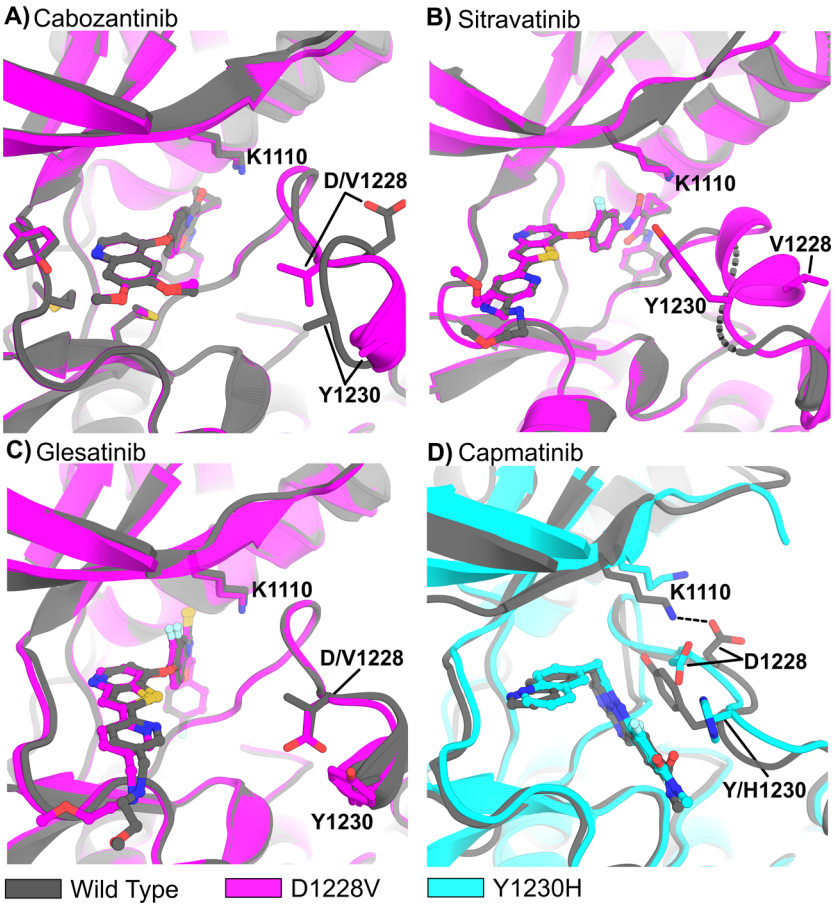

Figure 6. Crystal structures of D1228V and Y1230H c-MET-inhibitor complexes and comparison to equivalent wild-type structures. A) Overlay of crystal structures of cabozantinib in complex with wild-type (gray) and D1228V (magenta) forms of c-MET, highlighting the preserved binding mode across the two c-MET forms. NB The side-chains at position 1230 are not resolved in electron density for these structures; hence, these atoms are not present in the final models. B) Overlay of wild-type (gray) and D1228V mutant (magenta) c-MET-sitravatinib complexes. D1228 of the wild-type complex was not resolved in electron density and hence was not included in the final model. C) Overlay of wild-type (gray) and D1228V mutant (magenta) c-MET-glesatinib complexes. D) Overlay of wild-type (gray) and Y1230H (cyan) c-MET-capmatinib complexes, highlighting A-loop movement to enable π-stacking from H1230 onto capmatinib in the Y1230H complex. Where A-loops are not fully depicted in the above panels: due to dynamic disorder within the crystal lattice, these regions are not resolved in electron density and are therefore not present in the final atomic models.

D1228V c-MET being nearly identical (Figure 6A). V1228 is resolved in electron density and is clearly seen to play no role in inhibitor binding. A very similar trend was observed for the type-II inhibitors sitravatinib[47] and glesatinib,[48] for which we determined both wild-type and D1228V mutant structures (resolution range: 1.20−1.94 Å).[49] In both cases, a typical type-II binding mode was confirmed, with D1228 and V1228 shown to play no role in the binding of these compounds (Figures 6B and 6C).

We next turned our attention to the Y1230H clinically drug-resistant mutant. This mutation is known to significantly reduce the activity of approved type-I inhibitors (though it should be noted that *in vitro* data is not available for all type-I inhibitors listed in Table 1), yet not for the approved type-II inhibitor cabozantinib[37,50] (see Table 2). While we were unable to obtain a crystal structure of Y1230H c-MET in complex with cabozantinib, based on the equivalent wild-type and D1228V crystal structures, both showing the lack of engagement between cabozantinib and Y1230 (Figure 6A), we would expect the binding mode of cabozantinib to be isomorphous across the three c-MET forms (i.e., wild-type, D1228V and Y1230H).

Finally, while approved type-I c-MET inhibitors lose significant activity against the Y1230H mutant as stated above, we noted with curiosity that capmatinib retains some (albeit very weak, with a sub-μM IC_{50} value) activity against this mutant[37] (see Table 2). We thus attempted and succeeded in determining a crystal structure of capmatinib in complex with Y1230H c-MET (resolution, 2.29 Å). Interestingly, in this complex, the A-loop reorganizes (relative to the equivalent wild-type complex) such that the side-chain of H1230 is able to π-stack over the terminal fluorinated benzamide moiety of the inhibitor (Figure 6D), contrasting to the π-stacking interaction seen in the wild-type complex, in which the side chain of Y1230 π-stacks over the central imidazotriazine core of capmatinib. We also noted with curiosity an absence of salt-bridge between K1110 and D1228 in the Y1230H-capmatinib complex, contrasting to the equivalent wild-type complex (Figure 6D—K1110-D1228 salt bridge in wild-type-capmatinib complex shown as black dashes).

c-MET remains an important cancer drug target, as attested by the steady and continued stream of approvals targeting this kinase, as well as ongoing clinical trials.[1,3] While c-MET-targeting small molecules have received approval for a number

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of indications, there is likely a need for next-generation inhibitors that can address cancers driven by the emergent on-target acquired drug-resistant mutant forms of c-MET. While type-II c-MET inhibitors such as cabozantinib offer an option for treating such mutant-c-MET-driven cancers, the generally broader kinome activity profiles of type-II c-MET compounds (compared to type-I c-MET inhibitors) arguably offer scope for improvement. Thus, there remains a need to discover c-MET inhibitors that combine the exquisite selectivity of type-I inhibitors while retaining activity against emerging mutants. How might this be achieved? While the pursuit of type-I c-MET inhibitors with mutant activity and/or the design of type-II inhibitors with improved selectivity are unquestionably prudent routes of investigation,[43,44] it could be speculated that the discovery and exploration of inhibitors with different binding modes—such as allosteric or type-III/IV inhibitors—may yield the desired profile, and there is some evidence that this may indeed be the case.[51]

■ ASSOCIATED CONTENT

Data Availability Statement

Atomic coordinates and structure factors have been deposited in the Protein Data Bank and will be released up publication of this article. Accession codes can be found in Table 1.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.5c00713.

Experimental methods for the crystal structures reported (PDF)

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Notes

The authors declare the following competing financial interest(s): I.C.R., L.v.B., I.N.M., C.P., A.S., C.J.S., and G.W.C. are all employees of AstraZeneca. No competing interests beyond this are declared by any of the authors.
No unexpected or unusually high safety hazards were encountered throughout the experimental work conducted here.

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■ ABBREVIATIONS

ALK, anaplastic lymphoma kinase; A-loop, activation loop; ATP, adenosine triphosphate; AXL, tyrosine-protein kinase receptor UFO; c-CBL, cellular casitas B-lineage lymphoma; c-MET, cellular mesenchymal-to-epithelial transition factor; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase 3; KIT, mast/stem cell growth factor receptor Kit; MW, molecular weight; NSCLC, non-small cell lung cancer; P-loop, phosphate-binding loop; RCC, renal cell carcinoma; RET, rearranged during transfection kinase; ROS1, proto-oncogene tyrosine-protein kinase ROS; VEGFR2, vascular endothelial growth factor receptor 2

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