Building Blocks

Robust Solutions for Critical Issues in Medicinal Chemistry

Acetylene Group in Medicinal Chemistry

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The acetylene group has been broadly exploited in drug discovery and development. It has become recognized as a privileged structural feature for targeting a wide range of therapeutic targets. Furthermore, a terminal alkyne is frequently introduced in chemical biology probes as a click handle to identify molecular targets and to assess target engagement. The continued widespread popularity of acetylene group in medicinal chemistry is also apparent from the number of examples of approved drugs and those in clinical evaluations that containing a terminal or internal acetylene group (**Figure 74**). There are lots of roles that acetylene group can play in drug discovery, including potency enhancement by a complementary fit into a protein binding pocket, reactive warhead for irreversible inhibition of a target protein, nonpolar linear rigid spacer which can direct pharmacophore appendages in a favorable geometry, bioisostere of a wide range of functional groups such as cyano, chloro, iodo, carboxamide, phenyl, and modulation of drug metabolism pharmacokinetic (DMPK) profile. [1]

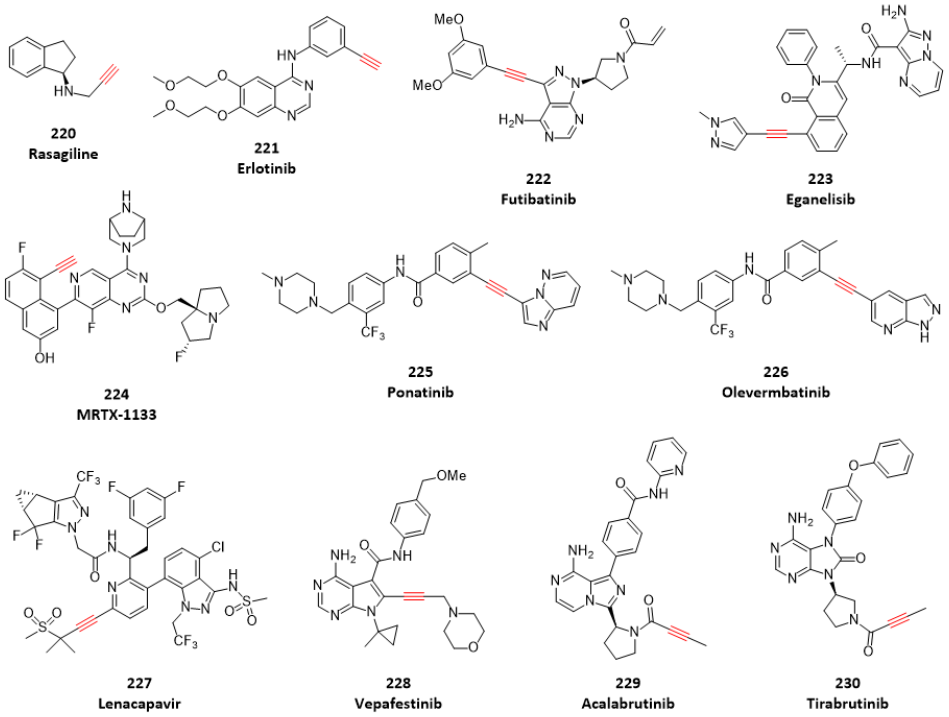

Figure 74. Drug and clinical candidate molecules containing terminal or internal alkyne.

In the medicinal campaign of discovery KRAS G12D inhibitor MRTX-1133, it was recognized that a conserved water molecule makes hydrogen bond interactions with both Gly10 and Thr58, and the team envisioned that a hydrogen bond donor from the 8-position of the naphthyl group in compound **231** might further stabilize this hydrogen bond network (**Figure 75**). The initial attempt with the introduction of a canonical hydroxyl group was unsuccessful. A careful examination suggested that an 8-ethynyl substitution would not only fill the hydrophobic space well, but also engage the conserved water molecule via a non-classical hydrogen bond. Indeed, comparing compound **231** and compound **232**, the 8-ethynyl group in the latter increased potency by 120-fold than the former. The same trend was also observed in paired compound **233** and compound **234** with the latter at 13-fold more potent than the former due to 8-ethynyl group. The X-ray structure of compound **234** in KRAS G12D revealed that the 8-ethynyl group is nicely positioned in a

hydrophobic pocket formed with Val9, Thr58, Phe78, Met72, Tyr96 and Ile100. The conserved water molecule is hydrogen-bonded to two hydrogen bond acceptors, the hydroxyl from Thr58 and the carbonyl oxygen from Gly10, and two hydrogen bond donors, the alkynyl proton of the ligand and NH of Gly10, forming a well-organized hydrogen bond network. [2]

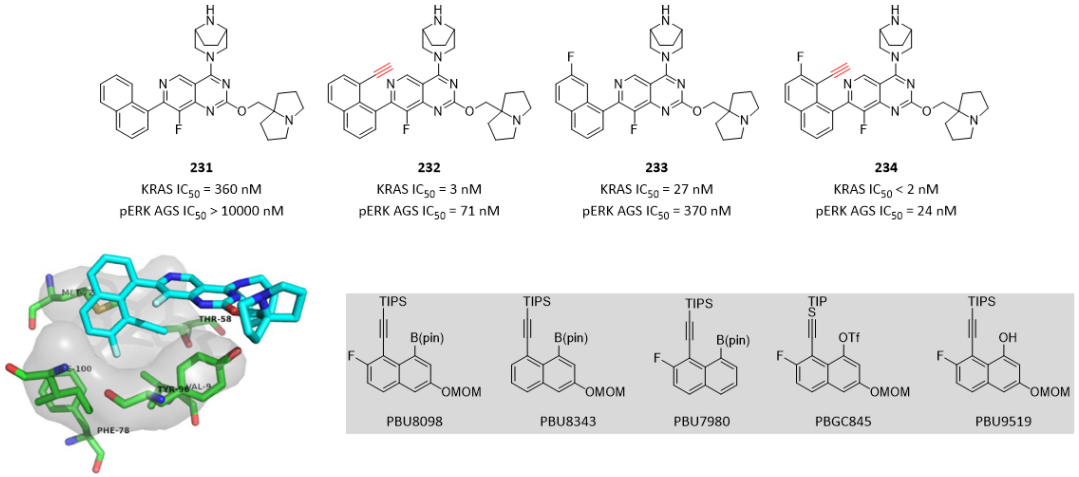

Figure 75. Alkynyl group increased potency and occupied a hydrophobic pocket. (PDB code: 7RT5)

In the course of discovery of clinical candidate **Eganelisib** (**223**) as a selective PI3Kgamma inhibitor, the team evaluated C8-substitution on compound **235** to access a nonconserved region within PI3K

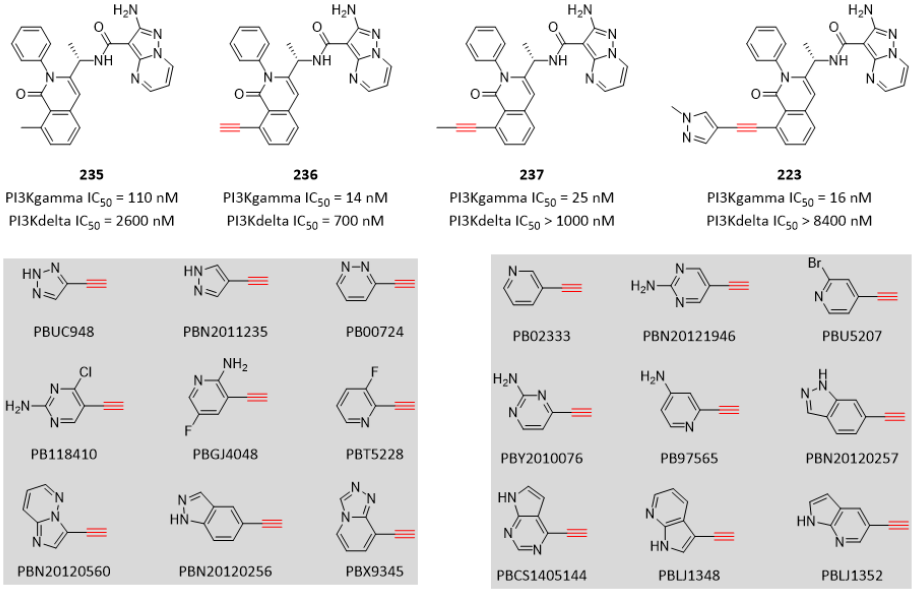

Figure 76. Alkyne group improved potency and selectivity.

Family with the aim of improving the PI3Kgamma potency and selectivity. It was found that small C8 substitution such as methyl in compound **235** did not have a profound impact on PI3Kgamma potency or selectivity. Interestingly, 8-alkyne substitutions in compound **236** and compound **237** unexpectedly provided modest improvements in potency for PI3Kgamma over compound **235**. Importantly, methyl alkyne analogue **237** also demonstrated weaker activity against PI3Kdelta compared to compound **236**, and thus compound **237** had at least 40-fold selectivity for PI3Kgamma over PI3Kdelta, suggesting that the alkyne substitution makes significant nonfavorable interactions with PI3Kdelta at the nonconserved residues adjacent to the specificity pocket (Lys802 for PI3Kgamma *vs* Thr750 for PI3Kdelta) as does the aminopyrazolopyrimidine at the hinge binding

region (**Figure 76**). Further optimization based on compound **237** successfully led to clinical candidate **Eganelisib** (**223**). [3]

In the course of discovery of **Futibatinib** (**222**) as the first covalent FGFR kinase inhibitor, the team found that alkyne compound **222**, which has an extended straight molecule, showed an approximately 200-fold increase in FGFR2 kinase inhibitory activity over compound **238** and flexible compound **239**. As an initial SAR study, only alkyne compound **222** achieved a single-digit nanomolar inhibitory activity on FGFR2. These data suggest that the straight-chain alkyne could correctly place the 3,5-dimethoxybenzene ring in the well-known unique hydrophobic pocket of FGFR (**Figure 77**). [4-5]

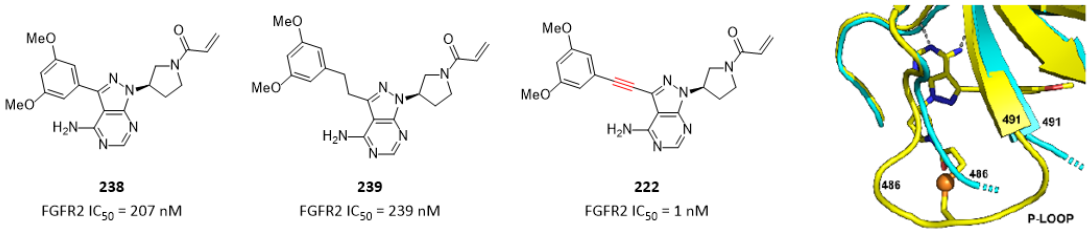

Figure 77. Alkyne group oriented 3,5-dimethoxybenzene to a hydrophobic pocket. (PDB code: 6MZQ)

The X-ray crystal structure of TACE inhibitor **240** bound to the active site of TACE indicated the binding of the phenyl-phenyl system in a shallow hydrophobic S1 pocket surrounded by residues Val314 and Leu350. Although compound **240** showed potent inhibition of TACE, it exhibited poor activity in the presence of human whole blood. Therefore, the team optimized this lead further with the assumption that internal aryl ring can be replaced with an isosteric acetylene while still projecting the terminal aryl ring in a similar orientation as observed in biaryl series. These efforts culminated in the discovery of compound **241** with comparable TACE inhibitory activity and improved activity in a human whole blood assay (**Figure 78**). [6-7]

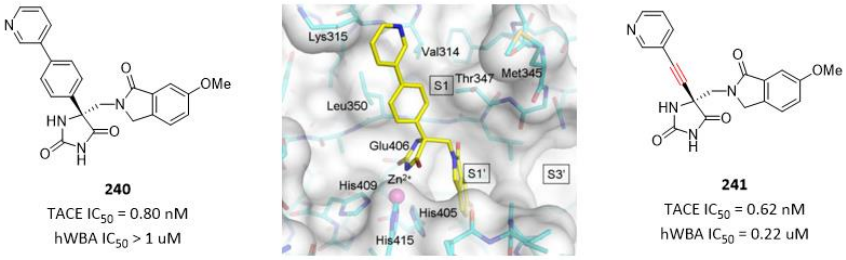

Figure 78. Alkyne group as bioisostere of phenyl ring improved hWBA. (PDB code: 3LEA)

Addition of a propargyl substituent onto the piperazine ring in compound **242** led to the discovery of compound **243** with at least 20-fold increased potency (**Figure 79**). [8] Installation of an acetylene group at the C5-position of 2-cyanopyrrolidine moiety in compound **244** to obtain compound **245** with a considerable improvement in DDP-4 selectivity over DPP-8 and DPP-9 (**Figure 79**). [9] Building blocks containing terminal or internal acetylene groups play critical roles in quick exploration of SAR and SPR.

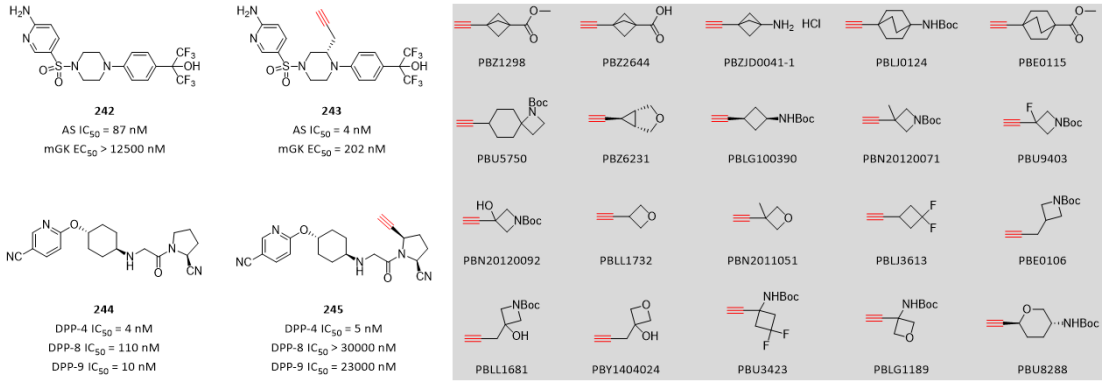

Figure 78. Two case stories where acetylene group increased potency.

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