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Discovery and Optimization of Dibenzodiazepinones as Allosteric Mutant-selective EGFR Inhibitors

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ABSTRACT: Allosteric kinase inhibitors represent a promising new therapeutic strategy for targeting kinases harboring oncogenic driver mutations in cancers. Here, we report the discovery, optimization, and structural characterization of allosteric mutant-selective EGFR inhibitors comprising a 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one scaffold. Our structure-based medicinal chemistry effort yielded an inhibitor (**3**) of the EGFR(L858R/T790M) and EGFR(L858R/T790M/C797S) mutants with an IC_{50} of ~10 nM and high selectivity, as assessed by kinome profiling. Further efforts to develop allosteric dibenzodiazepinone inhibitors may serve as the basis for new therapeutic options for targeting drug-resistant EGFR mutations.

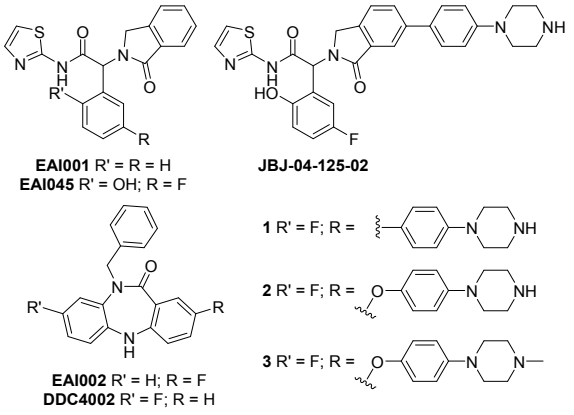


Fig. 1. Chemical structures of EAI001, EAI045, JBJ-04-125-02 and 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one allosteric EGFR inhibitors described in this work.

Activating mutations of the epidermal growth factor receptor (EGFR), e.g. L858R and in-frame exon 19 deletions, give rise to non-small cell lung cancer and confer sensitivity to EGFR-targeted tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib.[1-2] Acquired resistance to these TKIs occurs predominantly by the acquisition of a T790M 'gatekeeper' mutation, which enhances ATP binding to the EGFR kinase.[3-4] Selective inhibition of T790M-positive tumors is accomplished with third-generation TKIs (e.g. WZ4002, osimertinib) that irreversibly form a covalent bond with C797 at the edge of the ATP binding site.[5-6] Tumors acquire resistance to these inhibitors, in ~20-25% of cases, by the further acquisition of a C797S mutation rendering these inhibitors ineffective by preventing the formation of the potency-conferring covalent bond.[7-8] Therefore, continued development of inhibitors is required to address mutations that confer resistance to first- and third-generation EGFR targeting TKIs.

Accordingly, we sought to discover small-molecule inhibitors of activating EGFR mutations that act through an alternative, allosteric binding mode.[9] To that end, we recently reported a mutant-selective EGFR allosteric inhibitor (**EAI001 Fig. 1**) which binds a pocket adjacent to the ATP-binding site, affording exquisite selectivity for the mutant kinase compared to WT EGFR.[10] Initial optimization of this hit produced **EAI045** (Fig. 1), which exhibited 1000-fold selectivity for L858R/T790M EGFR compared to WT. However, **EAI045** showed minimal cellular activity owing to this compounds inability to bind the allosteric pocket of the active state, where the αC-helix is positioned inward, on the receiver subunit of the active EGFR asymmetric kinase dimer.[11] **EAI045** was rendered effective at regressing L858R/T790M/C797S tumors *in vivo* upon co-treatment with the EGFR monoclonal antibody cetuximab, which disrupts the formation of active EGFR dimers.[10] Further efforts produced a more potent analog (**JBJ-04-125-02**, Fig.

1), which incorporates a phenylpiperazine on the C6 position of the **EAI045** isoindolinone moiety and is capable of acting as a single-agent inhibitor in EGFR L858R/T790M/C797S cells and genetically engineered mouse models.[12] Furthermore, dual targeting of EGFR with **JBJ-04-125-02** and osimertinib was found to be more effective *in vitro* and *in vivo* than either single agent alone.[12]

In this study, we sought to evaluate a second series of allosteric mutant-selective EGFR inhibitors. As previously described, **EAI001** was discovered in a screen for mutant-selective inhibitors of EGFR(L858R/T790M).[10, 13] The same screen also yielded **EAI002** comprising of a 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one scaffold (Fig. 1), which selectively inhibited L858R/T790M with a biochemical IC_{50} of 52 nM compared to >1000 nM for WT. Subtle optimization of this hit compound via a fluorine shift afforded **DDC4002** (Fig. 1), which exhibited mutant-selective nanomolar biochemical IC_{50} values against L858R/T790M and L858R/T790M/C797S compared to WT (Table 1). Intriguingly, **DDC4002** resembles previously reported ATP-competitive, selective checkpoint kinase 1 (Chk1) inhibitors,[14] however, selective benzylation of the core amide precludes active site binding by abrogating critical hydrogen bonding contacts to the hinge likely favoring redirection to the allosteric site.

To define the inhibitor binding mode, we determined crystal structures of EGFR(T790M/V948R) in complex with **EAI002** and **DDC4002** (Fig. 2 & S1-4). Expectedly, both inhibitors are bound to the kinase domain in an allosteric pocket adjacent to the ATP-binding site (Fig. 2A), as observed previously for **EAI001**[10] and **JBJ-04-125-02**[12]. The 7-membered diazepinone ring of **DDC4002** is puckered inward toward the αC-helix (Fig. 2B) with the 8-fluorobenzene ring bound within the hydrophobic back pocket and the unsubstituted benzene ring along the αC-helix positioned out toward solvent. The benzyl substituent extends toward the kinase N-lobe, bound in between AMP-PNP and side chains of K745, L788, and the T790M gatekeeper mutation. While the inhibitor mostly forms hydrophobic interactions, the diazepinone N-H forms a H-bond with the backbone carbonyl of F856 in the DFG motif (red dotted line Fig. 2B). Additionally, the crystal structure of **EAI002** contains four EGFR chains in the asymmetric unit all with **EAI002** bound in the allosteric site, but with only one AMP-PNP and three AMP bound in the ATP site, presumably from AMP-PNP hydrolysis. The binding of either AMP-PNP or AMP does not impact the **EAI002** binding mode.

Additionally, we determined a crystal structure of EGFR(T790M/V948R) in complex with the phenylglycine **EAI045** (Fig. S1B and S4**)**. Similar to **EAI001**[10] and **JBJ-04-125-02**,[12] **EAI045** binds exclusively in the *R* configuration. Structural alignment of the kinase domains reveals that, despite distinct chemical structures, the binding mode of the dibenzodiazepinone inhibitors has significant overlap with that of the phenylglycines (Fig. 2C and S3). Specifically, both scaffolds exhibit H-bonding to the backbone carbonyl of F856 as well as fluorobenzene moieties positioned toward the hydrophobic cleft at the back of the pocket. These conserved interactions confirm that these apparently unrelated scaffolds are anchored to the allosteric site through conserved interactions. Additionally, a recent **EAI045** crystal structure bound to T790M/C797S/V948R in the absence of AMP-PNP shows limited variance in **EAI045** binding mode indicating that allosteric inhibitor binding to EGFR is structurally agnostic to the presence of ATP binding.[15]

To swiftly access the selectively substituted fused [6-7-6] tricyclic core, we streamlined our original route (Route A, Scheme 1) to a versatile, concise 2-step synthesis involving a tandem copper(I)-catalyzed intramolecular Ullmann condensation (Route B, Scheme 1).[16] Based on the binding mode of **DDC4002** (Fig. 2B), we hypothesized that functionalization at the C2 position would be capable of enhancing biochemical potency of these inhibitors, in a similar manner to that observed for **EAI045** and **JBJ-04-125-02**.[12] Following the latter example, coupling of a 4-(piperazinyl)phenyl substituent to C2 (**1**, Scheme 1) productively enhanced the potency of this scaffold. Structure-activity relationships revealed that engineering flexibility at this position via an Ullmann biaryl ether linkage (**2** and **3**, Scheme 1**)** modestly improved the effectiveness of these inhibitors, with **3** exhibiting biochemical potencies similar to **EAI045** against L858R/T790M and L858R/T790M/C797S.

To establish that these compounds inhibit EGFR through an allosteric mechanism, biochemical IC_{50} values were measured at varying ATP concentrations spanning 1 to 1000 μM (Table S1). Indeed, compounds **2** and **3** showed no significant variance with [ATP] consistent with allosteric inhibition. This further supports that the dibenzodiazepinones are effective inhibitors of mutant EGFR, operating in an allosteric mechanism as characterized crystallographically (Fig. 2).

We additionally determined the impact of EGFR inhibition on cellular proliferation in transformed murine Ba/F3 cells. All compounds were found to be ineffective at limiting Ba/F3 proliferation due to EGFR dimer-induced resistance as we have observed previously (Table S2).[10] Co-treatment with cetuximab (1 μg/mL) establishes this to be the case and leads to productive inhibition of L858R/T790M. Consistent with their biochemical potencies, dibenzodiazepinones with biaryl ether moieties (**2** and **3**) exhibit the best effect in combination with cetuximab with IC_{50} of ~ 0.2-0.4 μM against L858R/T790M and L858R/T790M/C797S cells. Compounds **1-3** were not amenable to crystallographic characterization, but we expect that the phenylpiperazine group extends along the αC-helix to enhance the potency of **1-3** relative to **DDC4002** in a manner analogous to that observed for **JBJ-04-125-02**.[12] While these dibenzodiazepinone-based inhibitors are effective mutant-selective inhibitors of EGFR in a cellular context, they are still critically reliant on co-treatment with cetuximab.

We next sought to assess the selectivity of the best performing inhibitor (**3**) against a panel of 468 kinases via KINOME*scan* profiling (DiscoverX). At a concentration of 10 μM, **3** displayed excellent selectivity across the human kinome with S-Score(35) = 0.01 (Fig. S5, Table S4). While the KINOME*scan* shows binding of **3** to EGFR WT and mutants, the results from activity and cellular assays indicate more reliable and robust selectivity for the oncogenic mutant targets (Table 1). Except for the expected WT EGFR and EGFR mutants, only two additional targets, SLK and

KIT(V559D/V654A), were identified. We confirmed these hits to be false positives of **3** with SLK and KIT(V559D/V654A) (Kd > 10 μM; KINOME*scan* *Kd*ELECT, DiscoverX) and confirmed no impact on SLK enzymatic activity (IC_{50} > 10 μM; Invitrogen, LanthaScreen). Although it is a valuable survey tool for assessing kinase selectivity, in our experience, KINOME*Scan* profiling does not correlate with enzymatic and cellular potencies as we have recently shown in the case of **JBJ-04-125-02**.[12]

In conclusion, we have discovered and optimized an allosteric mutant-selective EGFR inhibitor based on the dibenzodiazepinone scaffold. As the presently established mutant-selective allosteric EGFR inhibitors consist of a phenylglycine scaffold,[10, 12] the compounds described here demonstrate that diverse chemical scaffolds are capable of acting as mutant-selective EGFR inhibitors while preserving essential structural elements that anchor the inhibitors to the allosteric pocket. Therefore, this discovery expands the opportunity to discover additional chemical series as allosteric EGFR inhibitors. Our structure-based medicinal chemistry effort yielded an inhibitor (**3**) of the EGFR(L858R/T790M) and EGFR(L858R/T790M/C797S) mutants with an IC_{50} of ~10 nM and high selectivity, as assessed by kinome profiling. Co-treatment with cetuximab resulted in antiproliferative activity in EGFR-mutant Ba/F3 cells. Together with the previously reported dibenzodiazepine-based inhibitors of PAK1, which bind a closely related but distinct allosteric pocket, these compounds potentially indicate a broader application of benzodiazepine compounds as allosteric kinase inhibitors.[17] Additionally, dibenzodiazepinone compounds represent new additions to the growing list of allosteric inhibitors for kinase targets, as previously explored for MEK,[18-19] BCR-ABL1,[20] and others.[21-22] We plan to further optimize physicochemical and pharmacokinetic properties to produce more effective mutant-selective allosteric EGFR inhibitors, which is the subject of on-going efforts.

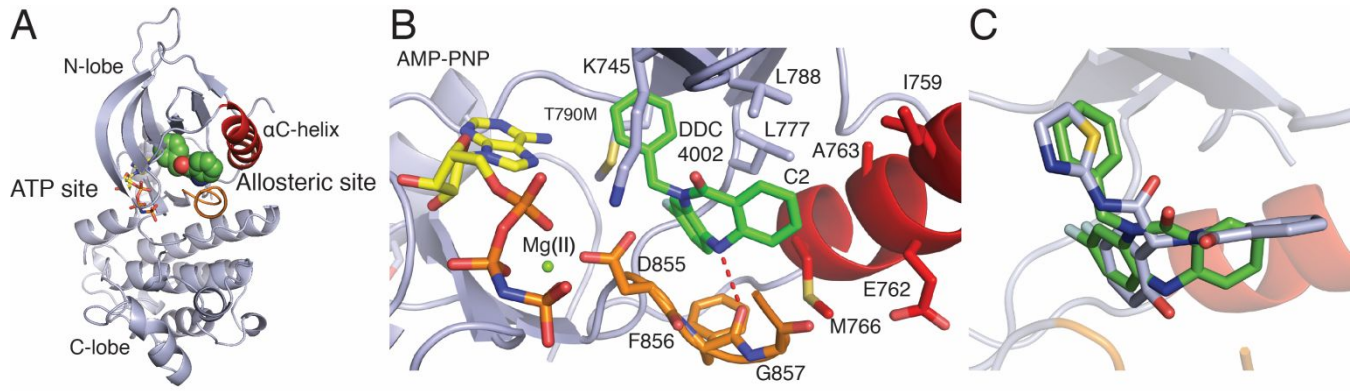
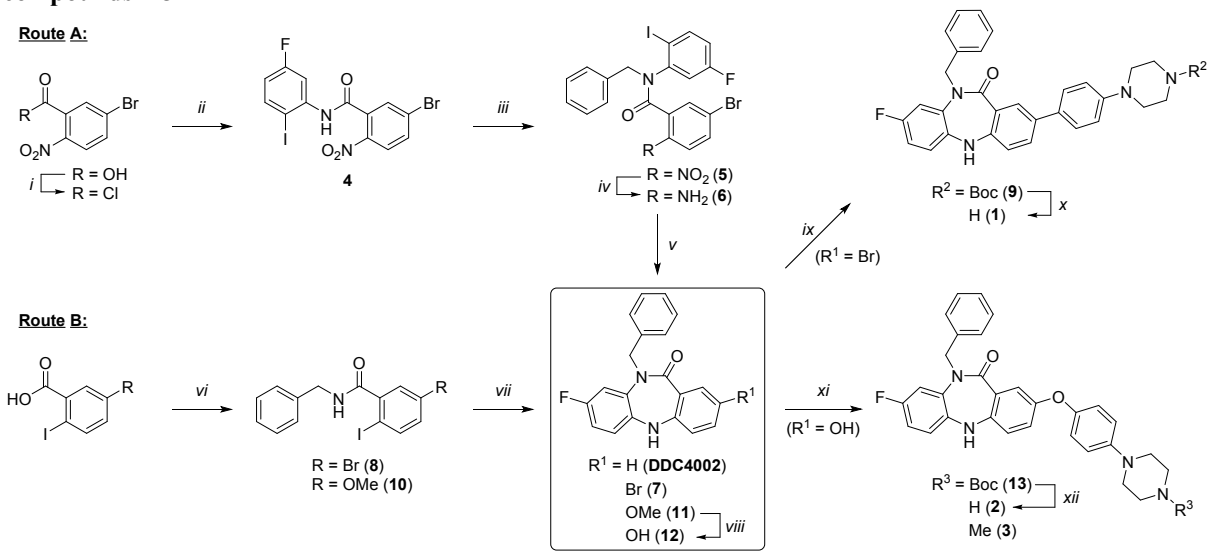


Fig. 2. Structure and binding mode of a dibenzodiazepinone EGFR allosteric inhibitor. A) Overall view of the structure of EGFR(T790M/V948R) bound to **DDC4002** and AMP-PNP (PDB 6P1D). The V948R mutation enables the kinase domain to crystallize in the inactive state. **DDC4002** is shown in CPK spheres with green carbon atoms. B) Detailed view of **DDC4002** bound to the allosteric pocket with AMP-PNP. P-loop and A-loop segments are hidden for clarity. C) View of **DDC4002** (green) and **EAI045** (PDB 6P1L, white) from the overlay of crystal structures.

Scheme 1. Synthetic routes (A,B) for synthesis of 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-ones DDC4002 and compounds 1-3[a]



[a]Reagents and conditions: [i] $SOCl_2$, DMF, Δ; [ii] 5-fluoro-2-iodoaniline, Et_3N, CH_2Cl_2, 0 °C to RT, 81 %, two steps; [iii] BnBr, NaH, THF, 0 °C to 40 °C; [iv] Fe, NH_4Cl, THF/MeOH/H_2O, 50 °C, 72 %, two steps; [v] CuI, K_2CO_3, DMSO, 135 °C, 64 %; [vi] benzylamine, EDC.HCl, HOBt, DIEA, DMF, 87 %; [vii] 4-fluoro-2-iodoaniline, CuI, K_2CO_3, DMSO, 80 °C to 135 °C, 44 %; [viii] BBr_3, CH_2Cl_2, -20 °C to RT, 85 %; [ix] *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate, $PdCl_2$(dppf), XPhos, 2 *N* Na_2CO_3, 1,4-dioxane, 100 °C; [x] TFA, CH_2Cl_2, 45 %, two steps; [xi] 1-(4-iodophenyl)-4-methylpiperazine (**3**) or *tert*-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (**13**), CuI, L-Proline, K_2CO_3, DMSO, 80 °C, (**3** 36 %); [xii] TFA, CH_2Cl_2, 30 %, two steps.

Table 1. Biochemical activities and antiproliferative activities of a panel of EGFR allosteric inhibitors. [a]IC_{50} values were measured from a single experiment in triplicate. ATP concentration was 100 μM. Errors are reported as ± standard error. [b]IC_{50} values were measured from a single experiment with 3 replicates. Errors are reported as ± standard deviations.

Compound ID	EGFR Biochemical Activity IC_{50} (nM)[a]				Antiproliferative Activity Ba/F3 + Cetuximab IC_{50} (μM)[b]			
	WT	L858R	L858R/ T790M	L858R/ T790M/ C797S	WT	L858R	L858R/ T790M	L858R/ T790M/ C797S
EAI045	> 1000	8.8±0.9	2.0±0.5	4.7±0.3	>10	0.84±0.7	0.47±0.2	0.25±0.2
DDC4002	> 1000	690±120	39±4	59±8	9.7±0.5	>10	1.5±0.4	1.2 ± 0.3
1	> 1000	150±23	31±2	19±3	4.1±1	3.7±0.1	0.77 ± 0.1	0.93 ± 0.2
2	> 1000	130±12	12±0.9	23±4	4.0±1	3.8±0.5	0.35 ± 0.07	0.35 ± 0.2
3	> 1000	154±15	11±2	13±0.8	3.2±0.8	2.7±1	0.36 ± 0.2	0.20 ± 0.08

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Chemistry, biological assay, and X-ray crystallography data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

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Conflicts of Interest Disclosure

P.A. Jänne reports receiving commercial research grants from AstraZeneca, Boehringer Ingelheim, Astellas Pharmaceuticals, PUMA, Eli Lilly, and Takeda Oncology, has ownership interest (including stock, patents, etc.) in Gatekeeper Pharmaceuticals and LOXO Oncology, is a consultant or advisory board member for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Roche/Genentech, Pfizer, Merrimack Pharmaceuticals, Chugai Pharmaceuticals, Araxes Pharmaceuticals, Mirati, Ignyta, and LOXO Oncology, and has received other remuneration from Labcorp. M.J. Eck reports receiving a commercial research grant from Novartis Institutes for Biomedical Research, reports receiving other commercial research support from Takeda, and has been consultant for Novartis Institutes for Biomedical Research. N.S. Gray reports receiving a commercial research grant from Takeda and is a consultant or advisory board member for C4, Syros, Soltego, and B2S Bio. No potential conflicts of interest were disclosed by the other authors.

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ABBREVIATIONS

EGFR, epidermal growth factor receptor; EAI, EGFR allosteric inhibitor; TKI, tyrosine kinase inhibitor. EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. HOBt, Hydroxybenzotriazole. DIEA, N,N-Diisopropylethylamine. Dppf, 1,1'-Bis(diphenylphosphino)ferrocene. XPhos, 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. AMP-PNP, adenylyl-imidodiphosphate.

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Table of Contents Image: