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An Unusual Intramolecular Halogen Bond guides Conformational Selection

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Abstract: PIK-75 is a phosphoinositide-3-kinase (PI3K) α-isoform-selective inhibitor with high potency. Although published SAR data show the importance of the NO_2 and the Br substituents in PIK-75, none of the published studies could correctly assign the underlying reason for their importance. In this publication, we report the first X-ray crystal structure of PIK-75 in complex with the kinase GSK-3β. The structure shows an unusual U-shaped conformation of PIK-75 within the active site of GSK-3β that is likely stabilized by an atypical intramolecular Br···NO_2 halogen bond. NMR and MD simulations show that this conformation presumably also exists in solution and leads to a binding competent pre-configuration of the PIK-75 molecule, thus explaining its high potency. We therefore suggest that the site-specific incorporation of halogen bonds could be generally used to design conformationally restricted bioactive substances with increased potencies.

The selective inhibition of kinases involved in a variety of signaling cascades has attracted increasing attention within the last 20 years. Major efforts undertaken by the pharmaceutical industry and academic research have led to highly potent inhibitors that are used in patients and have increased our understanding of the molecular mechanisms of kinases involved different diseases.[1] The small molecule PIK-75 (Figure 1) is one example of a small molecule inhibitor with high potency and selectivity toward the α-isoform of the catalytic subunit of phosphoinositide-3-kinases (PI3Ks) and glycogen synthase kinase-3β (GSK-3β, IC_{50} = 10 nM)[2], but also inhibits several other kinases (data from a kinase profiling are provided in Supplementary Table 1). PI3Ks constitute a family of kinases involved in production of the second messenger phosphatidylinositol-3,4,5-triphosphate and mutations have been shown to be important in the development of cancer and other diseases,[3] thus making available inhibitors attractive targets for structure-guided improvement of their potency and selectivity.

Several studies have attempted to predict the binding mode of PIK-75 within the active site of kinases, but they have led to different conclusions[2c, 4] (and none has correctly predicted the conformation of PIK-75 within the active site as outlined below). In this publication, we present the first co-crystal structure of PIK-75 in complex with GSK-3β, a kinase acting downstream of PI3Ks that phosphorylates many intracellular targets[3] and has been studied as a potential target in e.g. type II diabetes and Alzheimer disease. [5] We show that PIK-75 adopts a conformation that is stabilized by an intramolecular halogen bond of a type that has not been described before. MD simulations show that this binding-competent conformation is also present in solution, thus explaining the high potency of the inhibitor.

In order to gain insight into the structural interplay within the kinase domain of GSK3, we co-crystallized PIK-75 in complex with GSK-3β (residues 26–393). A dataset was collected from a single crystal and the structure solved by molecular replacement (resolution 2.6 Å, R_{work} = 22.2%, R_{free} = 25.9%, **Supplementary Table 2**). The asymmetric unit consists of two molecules of GSK-3β, both of which are phosphorylated at Tyr216 and show a very similar overall conformation (one molecule is shown in **Figure 1, A**). Additional electron density observed within the active site could be clearly and unambiguously modelled with PIK-75. The correct orientation of PIK-75 (**Figure 1, B**) was furthermore verified by the strong anomalous signal resulting from the Br atom present in the inhibitor (**Figure 1, C**).

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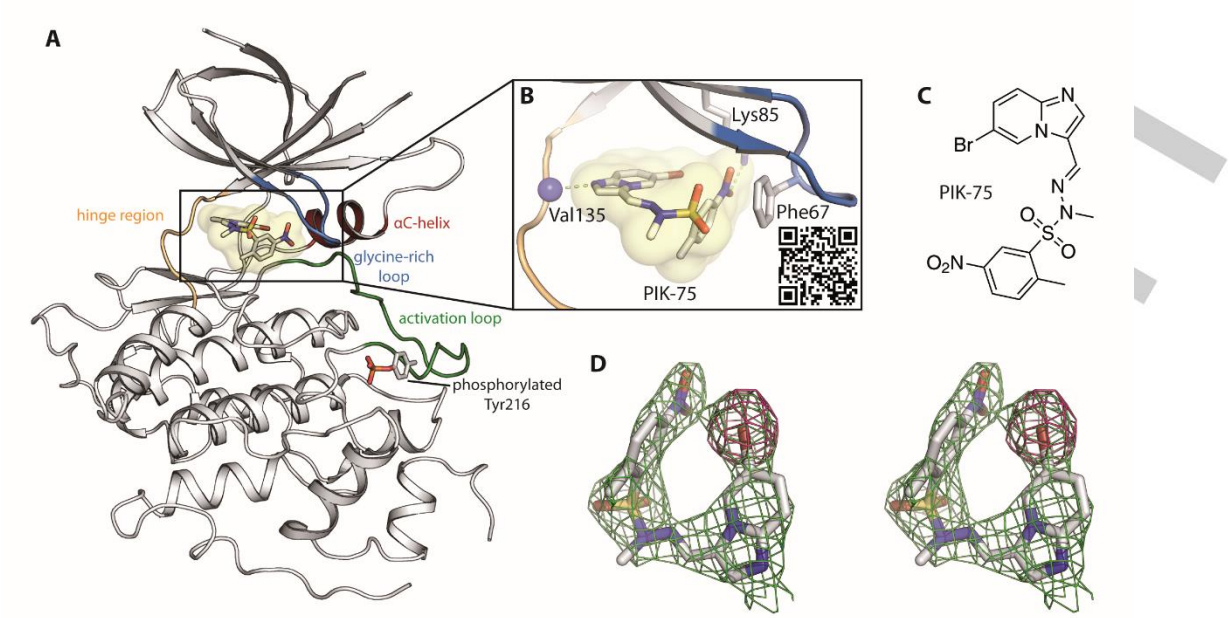

Figure 1. Structure of PIK-75 in complex with the kinase GSK-3β. (A) Overview of GSK-3β (amino acids 26–393, uniprot ID P49841). The hinge region (orange), glycine-rich loop (blue), αC-helix (red) and the activation loop (green) as well as PIK-75 (yellow) are highlighted. (B) The major interactions of PIK-75 with Phe_{67}, Lys_{85} and Val_{135} are indicated (the QR-code can be used to visualize the structure in augmented reality[6]). (C) Chemical structure of PIK-75. (D) Stereo view of PIK-75, the F_O-F_C simulated annealing omit map (σ = 3.0, green) as well as the anomalous map (σ = 5.0, magenta; diffraction data was collected close to the Br absorption edge at λ = 0.91883 Å) are shown.

Interactions were observed between one of the PIK-75 imidazo[1,2-*a*]pyridine nitrogen atoms and the GSK-3β Val135 backbone NH-group (hinge region), similarly to the adenine ring of ATP and other ATP competitive inhibitors.[7] Additionally, the NO_2 group of PIK-75 interacts with the charged ε-amino group of the catalytic residue Lys85 and its 2-methyl-5-nitrophenyl group interacts via π-stacking with the Phe67 ring within the glycine-rich loop (**Figure 1, A**). Most notable, however, is the unusual U-shaped conformation of PIK-75 within the active site that was not predicted by any of the modelling studies performed previously to predict the binding mode of the inhibitor within the active site of kinases.[2c, 4] This unusual conformation of PIK-75 allows for the C-Br bond to point toward the NO_2 group plane with an C–Br···N angle of ~120° and a 3.3 Å distance between the bromine and nitrogen atoms. This value is less than the sum of their van der Waals radii (**Supplementary Fig. 1**), indicating a previously unknown type of intramolecular halogen bond between the Br and the NO_2 group.

In C-X···NO_2 (X = F, Cl, Br, I) intermolecular interactions previously reported in the literature, the halogen atom is in close proximity to one or both of the oxygen atoms to give a three-centered bifurcated system. The type of interaction can be further characterized as symmetric bifurcated, asymmetric bifurcated or mono-coordinated.[8] The intramolecular C-Br···NO_2 interaction observed in the current study does not fit any of these categories because of restricted possible relative orientations of the Br and the NO_2 due to the connecting molecular scaffold.

Recently, Zhang and co-workers emphasized the importance of intramolecular halogen bonds and their role in stabilizing a particular conformation of a molecule.[9] We thus speculated that PIK-75 might adopt the same U-shaped conformation in solution as compared to the conformation observed within the active site of GSK-3β. To test this hypothesis, we first determined the crystal structure of PIK-75 by X-ray powder diffraction[10]. PIK-75 crystallized in a monoclinic ($P2_1/n$) crystal system with $Z = 4$ and $Z' = 1$ (data statistics are shown in **Supplementary Table 3**) and indeed adopted a similar U-shaped conformation (**Figure 2 and Supplementary Fig. 1**), indicating that this conformation is also preferred in the absence of the enzyme. It should be noted, however, that we observed a difference of ~10° between the angle of the C-Br···NO_2 in the GSK-3β bound and unbound structures (**Supplementary Fig. 2 and Supplementary Table 4)**. The prearrangement of the inhibitor was additionally validated by two-dimensional NMR experiments (**Figure 2 and Supplementary Fig. 3**), and the observed nuclear correlation between the benzyl moiety and the pyridine further validates the presence of the U-shaped conformer.

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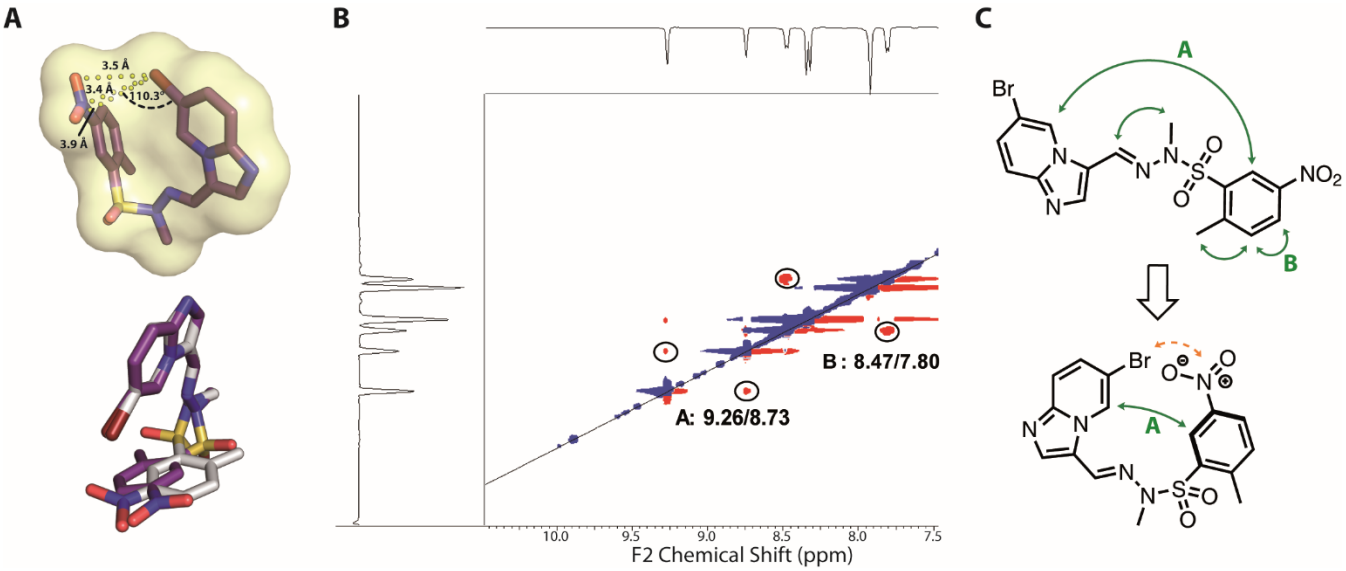

Figure 2. Small molecule crystal structure and 2D-NMR analysis of PIK-75. (A) Relative orientation and distances between the Br and the NO_2-group in the small molecule crystal structure of PIK-75 (top) and overlay of GSK-3β co-crystallized PIK-75 (gray) and the small molecule crystal structure (purple; bottom) **(B)** ^{1}H-NOESY spectra of PIK-75 observed in DMSO-d_6, which elucidates resonances from nuclei that are spatially close, rather than through direct bond connection; **(C)** NOESY cross-correlations for PIK-75 (green). The observed spatial interaction **A** indicates an intramolecular correlation between the benzylic proton at 8.73 ppm and the pyridine proton at 9.26 ppm, indicating a prearranged conformer of PIK-75.

In order to gain a better understanding of the factors that contribute to this conformation of PIK-75, we carried out *ab initio* post-Hartree-Fock calculations to evaluate existing intramolecular interactions. In addition, we also used the corresponding des-nitro analogue to determine the importance of the nitro substituent on the interaction with the bromine atom. The geometries of both compounds were fully optimized in gas-phase according to the second-order Møller-Plesset perturbation theory (MP2) using the 6-31+G* basis set[11], followed by a single point energy calculation using CAM-B3LYP/6-311G(3d) level of theory.

To study the intramolecular interaction in the orbital perspective, the analysis of natural bond orbital (NBO) were focused on the second-order perturbative estimation of donor-acceptor (bonding-antibonding) interactions. The NBO analysis resulted in a table with the stabilization energy *E(2)* value between each donor-acceptor (bonding-antibonding orbitals) (see Methods online). No stabilization energy *E(2)* between the nitro group and the bromine atom were observed, suggesting that this energy is above 0.5 kcal·mol^{-1} (the threshold for printing *E(2)* in the output file). This was further verified by fragmentation of PIK-75 into two small representative parts, *i.e.* 6-bromoimidazo[1,2-a]pyridine and 2-hydrosulfonyl-1-methyl-4-nitrobenzene, and re-calculation of the NBO analysis. The result gave an *E*(2)= 0.23 kcal·mol^{-1} between a lone pair of one of the nitro group oxygen atoms and the C–Br antibonding orbital ($n_O \rightarrow \sigma_{C-Br}^*$). This type of interaction is characterized by the formation of so called "*σ*-hole", first defined in the literature as the lowest electron density region along a halogen bond C-X (X= F, Cl, Br, I)[12] that can perform attractive interaction with electron rich system (such as lone pairs and π system). The weak $n_O \rightarrow \sigma_{C-Br}^*$ interaction has led us to hypothesize that other factors could additionally contribute to the C-Br···NO_2 intramolecular interaction observed here.

The overlay of the imidazo-pyridine core of PIK-75 and its des-nitro analogue, revealed a difference and a shift of 2.2 Å of the phenyl-ring (**Figure 3, A and Supplementary Table 4**). The electrostatic potential maps around the C-Br bond showed the formation of the *σ*-hole in both molecules and using the maximal and minimal electrostatic potential on a surface map ($V_{s,max}$ and $V_{s,min}$), the nature of this noncovalent interaction was evaluated.[13] The $V_{s,max}$ in the *σ*-hole region varied by 4.3 kcal·mol^{-1} between PIK-75 and the des-nitro analogue, showing that the addition of the nitro group on PIK-75 changes the charge distribution around the *σ*-hole region (**Figure 3, B**). The electron density along the C-Br bond, as expected, also differs between PIK-75 and the des-nitro analogue as indicated by the presence of a more negatively charged region in the surface map of PIK-75 ($V_{S,min}$= -13.9 kcal·mol^{-1} vs. $V_{S,min}$= -11.0 kcal·mol^{-1} for the des-nitro analogue) (**Figure 3, C** and **D**). In PIK-75, the region around the nitrogen atom of the nitro group shows a $V_{S,max}$= 19.4 kcal·mol^{-1} and it points toward the axis of the C-X bond (**Figure 3, C**). The electrostatic potential surface map shows that the nitrogen atom could act as an electrophile interacting with the extension of C-Br bond, which has negative potential in comparison to the *σ*-hole, thus forming a classical dipole-dipole interaction. These findings are further supported by QTAIM analysis of the electron density, as the QTAIM graph features a bond critical path connecting Bromine with the Nitro-function (**Supplementary Fig. 6**)

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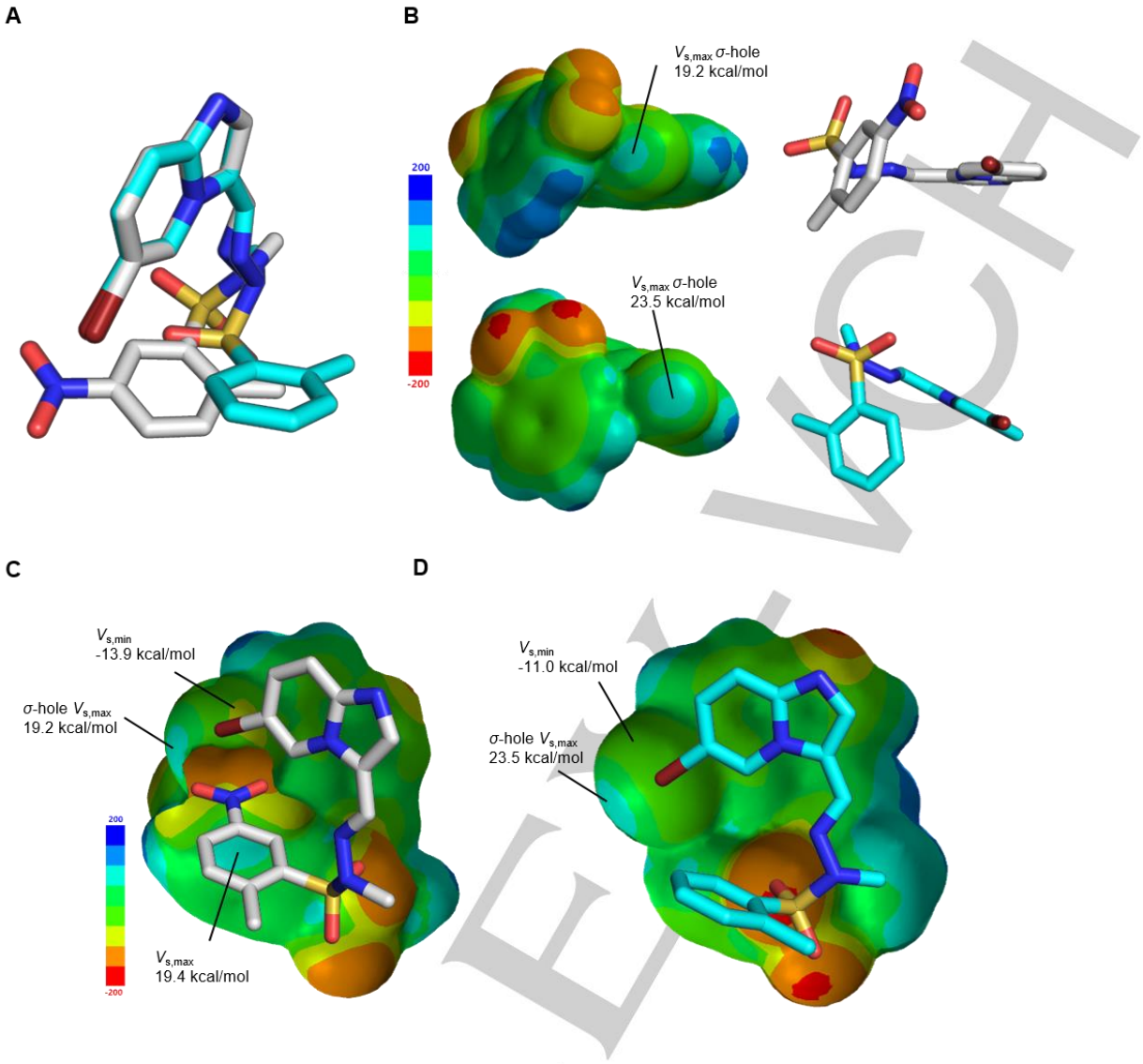

Figure 3. Electronic properties of PIK-75 and the des-nitro analogue. **(A)** Overlay of the ground-state conformations of PIK-75 (gray) and the des-nitro analogue (cyan). **(B)** Electrostatic potential maps for PIK-75 (top) and the des-nitro analogue (bottom), highlighting the shape of the σ-hole and the maximal energy values of the surface for that particular region ($V_{S,max}$). **(C)** Cross-section of the electrostatic potential surface of PIK75, highlighting the positive region of the nitro group and the influence on the σ-hole region of the bromine atom, described in terms of $V_{S,max}$. **(D)** Cross-section of the electrostatic potential surface of the des-nitro analogue, highlighting the stronger σ-hole region of the bromine atom, described in terms of $V_{S,max}$. Surfaces were calculated in the MP2/6-31+G* level of theory (IsoValue= 0.002).

After identifying that the intramolecular halogen bond in PIK-75 was also driven by classical electrostatic forces, we implemented molecular dynamics (MD) simulations for 1 μs in aqueous solution to investigate the stability of the proposed interaction of PIK-75. The statistical analysis of the distribution of torsional angles throughout the simulation revealed only two conformational populations, with a distribution of 46% and 54% for the minor and major populations, respectively. The main difference between these two ensembles is the rotation of the dihedral angle φ3 (H_3C–N–N=CH), with average angles of -10° (major) and 90° (minor) (**Figure 4, A and B**). The RMSD values calculated between each frame of the trajectory against the co-crystallized conformation of PIK-75 in complex with GSK-3β and the small molecule crystal structure (**Figure 4, C**) suggest that conformations similar to the GSK-3β co-crystallized conformation exist in solution, indicated by the high frequency of conformations with an RMSD ≤1.5 Å. Here, the minor conformational ensemble of PIK-75 is more structurally related to the co-crystallized conformation than the major ensemble (**Supplementary Fig. 4**).

The Br···NO_2 interaction was also investigated during the molecular dynamics simulation. Our results revealed an average Br···NO_2 distance of ~4 Å and C–Br···N angle of ~105° for the minor population, while the major population has an average Br-NO_2 distance of ~6 Å and a C–Br···N angle of ~85°. These results reinforce the similarity between the minor population and the co-

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crystallized conformation and suggest that the proper torsions, angles and distances required for the Br···NO_2 interaction are not only possible, but frequently adopted in aqueous solution.

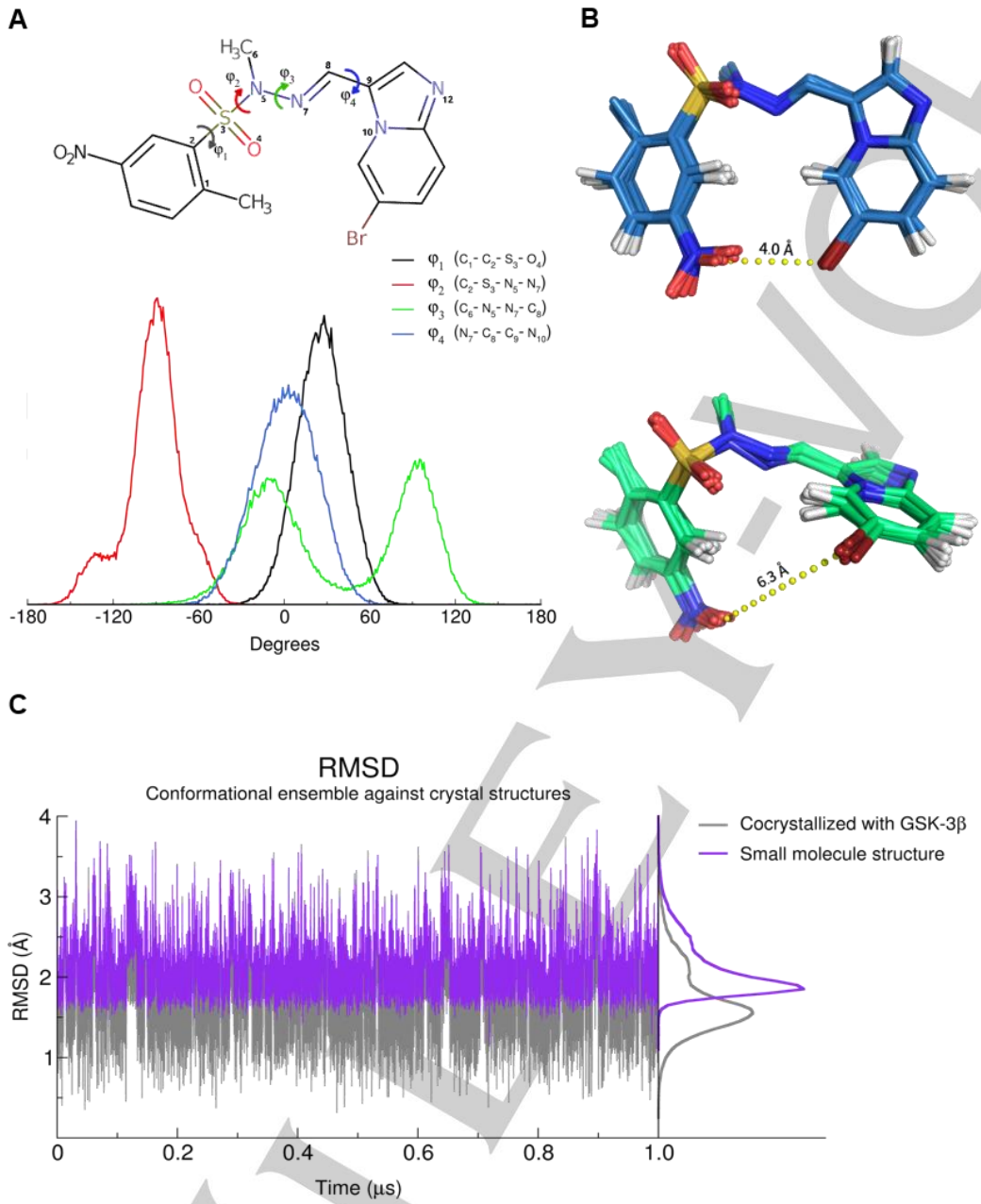

Figure 4. Molecular dynamics simulations of the conformational space adopted by PIK-75 in solution. (A) Dihedral composition of PIK-75 and relative abundance throughout molecular dynamics (MD) simulation reveals a bimodal distribution of φ_3 (green). (B) The two most prevalent conformational populations with $\varphi_3 = -10^o$ (top) and $\varphi_3 = 90$ (bottom). (C) RMSD calculations of PIK-75 structural ensemble during MD simulations compared to the conformation of PIK-75 observed in complex with GSK-3β (grey) and in the small molecule structure of PIK-75 (purple). The similarity, especially to the conformation observed in the co-crystal structure with GSK-3β, reinforces the idea that PIK-75 adopts a similar conformation also in solution.

Halogen bonding interactions have recently attracted considerable interest for the development of molecules with enhanced biological activity.[14] The International Union of Pure and Applied Chemistry (IUPAC) defines a halogen bond as an attractive interaction between an electrophilic region associated with a halogen atom and a nucleophilic region in another, or the same, molecular entity.[15] Compounds capable of forming halogen bonds can facilitate the formation of short contacts

between the carbonyl and aromatic moieties of backbone amino acid residues, leading to pronounced changes in the selectivity,[14a] as well as the conformation of the kinase.[14b] In the present study, we report a new crystal structure of GSK-3β bound to the inhibitor PIK-75 that is stabilized by an unusual intramolecular halogen bond in a binding competent conformation. In subsequent experiments, we confirm that this conformation is however not only adopted within the active site of GSK-3β, but also present in solution, in agreement with previous studies showing that small molecules frequently adopt the biologically active conformation even in the absence of the target enzyme.[16]

To date, studies of halogen bonds in small molecule crystals have mainly focused on analysis of intermolecular interactions between donor-acceptor compounds[17] leading to the classical interpretation of the directionality of the halogen bond. However, it is not surprising that the situation is different in intramolecular interactions involving halogen bonds (some examples of intramolecular C-X$\cdots NO_2$ interactions observed in molecules retrieved from the Cambridge Structural Database CSD are shown in **Supplementary Figure 5**). In this study, we observed a mixed nature of the PIK-75 C-X$\cdots NO_2$ intramolecular halogen bond interaction, with contributions from the classical *σ*-hole interaction (although weak) in addition to a dipole-dipole interaction between the nitro group nitrogen atom and the elongation of the C-Br bond. Although the IUPAC definition of a halogen bond only accounts for interactions with the *σ*-hole region[15], Politzer and co-workers explain the nature of the halogen bond as Coulombic interactions that involve not only a direct interaction through the *σ*-hole, but also an interaction with the electron dense regions along the C-X bond.[18] Thus, our finding that the intramolecular halogen bond of PIK-75 is not driven exclusively by an interaction with the *σ*-hole region, but with the extension of the entire C-Br bond is in agreement with their work.

To our knowledge, this study on PIK-75 is the first that shows the importance of an intramolecular halogen bond to stabilize the molecule in a binding-competent conformation and reduce the entropic penalty upon binding, thus for the first time explaining the high potency of this molecule.

Experimental Section

Experimental details can be found in the supporting information.

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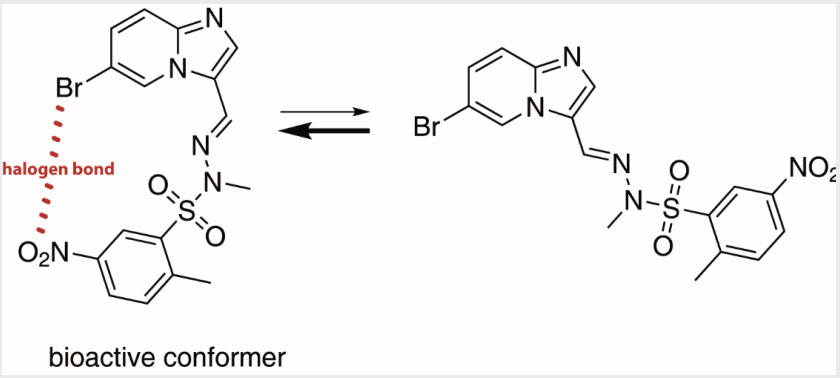

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