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Novel ARC-Type Inhibitors of Basophilic Protein Kinases

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Protein kinases (PKs) currently belong to the most targeted biomolecules of pharmacological industry, as the aberrant signalling of PKs triggers a variety of diseases, including diabetes and cancer. PKs catalyse the transfer of phosphoryl moiety from donor (ATP) to acceptor (protein/peptide substrate), resulting in the modification of substrate properties and alteration of its involvement in the extra-/intracellular reactions. Targeting of a PK requires a high-affinity inhibitor that binds to the enzyme and thus interfers with its functioning. The best-known PK inhibitors may be classified into those mimicking ATP and those mimicking the peptide substrate. However, humans possess 518 PKs, and achievement of both high efficacy and selectivity towards a PK of interest remains a challenge.

The ARC-type inhibitors developed in the research group of Dr. Asko Uri comprise both ATP- and peptide substrate-mimicking moieties joined by a flexible linker. Both ATP- and peptide substrate-mimicking moieties have been optimized during the previous studies,[1,2] yielding high-affinity compounds with tunable selectivity within the group of Ser/Thr-type basophilic PKs.

In the present work, a representative of ARCs (**ARC-1034**) was co-crystallized with a model PK (PKAc),[3] revealing the crucial interactions between the inhibitor and the enzyme. Based on these data, the synthesis of the new generation of ARCs was carried out.[3,4] The displacement/inhibition characteristics[5,6] of novel ARCs towards PKAc and closely related PKs (PKBγ, ROCK-II) were determined,[3] and a wider selectivity profiling of the compound with the best affinity (**ARC-1028,** K_d value below 0.5 nM towards PKAc) towards a panel of 50 PKs was performed.[3] The structural moieties of ARCs partially responsible for the selectivity patterns of inhibitors were established, and **ARC-1044** was synthesized possessing over 100-fold selectivity towards PKAc (K_d value of 1.8 nM, IC_{50} value of 21.1 nM) as compared to PKBγ or ROCK-II (K_d value of 187 nM and IC_{50} value of 2040 nM, respectively).[3] Finally, the bisubstrate character of the novel ARCs was confirmed with the aid of a fluorescent probe designed on the basis of **ARC-1028**.[3]

REFERENCES

1. Enkvist, E.; Lavogina, D.; Raidaru, G.; Vaasa, A.; Viil, I.; Lust, M.; Viht, K.; Uri, A. *J. Med. Chem.* **2006**, 49, 7150-7159.
2. Enkvist, E.; Raidaru, G.; Vaasa, A.; Pehk, T.; Lavogina, D.; Uri, A. *Bioorg. Med. Chem. Lett.* **2007**, 17, 5336–5339
3. Lavogina, D.; Lust, M.; Viil, I.; König, N.; Raidaru, G.; Rogozina, J.; Enkvist, E.; Uri, A.; Bossemeyer, D. *J. Med. Chem.* **2009**, 52, 308-21.
4. Lavogina, D.; Enkvist, E.; Uri, A. *ChemMedChem.* **2010**, 5, 23-34.
5. Vaasa, A.; Viil, I.; Enkvist, E.; Viht, K.; Raidaru, G.; Lavogina, D.; Uri, A. *Anal. Biochem.* **2009**, 385, 85-93.
6. Viht, K.; Vaasa, A.; Raidaru, G.; Enkvist, E.; Uri, A. *Anal. Biochem.* **2005**, 340, 165-170.