Integrating molecular modeling, synthesis, and biological evaluation for the design of novel pyrido[2,3-d]pyrimidine-4(3H)-one derivatives as NEK6 kinase inhibitors

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A. Semeraro *[I], P. Zardi *[II], B. Righino *[III], D. Pirolli *[III], M. Gramanzini *[III], A. Koenigs *[II], L. Đorđević *[II], M. Maggini *[II], M. Buttarelli *[IV,V], N. Cappoli *[IV,V], M. De Donato *[IV,V], D. Gallo *[IV,V,VI], G. Scambia *[IV,V], M.C. De Rosa *[III]

[I]Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185, Rome, Italy, [II]Dipartimento di Scienze Chimiche, Università di Padova, Via Marzolo 1, 35131, Padova, Italy, [III]Istituto di Scienze e Tecnologie Chimiche "Giulio Natta"; (SCITEC)-CNR, L.go F. Vito 1, 00168, Rome, Italy, [IV]Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, L.go A. Gemelli 8, 00168, Rome, Italy, [V]Dipartimento Universitario Scienze della Vita e Sanità Pubblica, Sezione di Ginecologia ed Ostetricia, Università Cattolica del Sacro Cuore, L.go F. Vito 1, 00168, Rome, Italy, [VI]Department of Toxicology & Pathology Sciences, European Research Biology Center (ERBC), Via Tito Speri 12/14 - 00071, Pomezia, Italy

The Nima-related Kinase-6 (NEK6) plays a crucial role in cell cycle regulation. Research has highlighted its overexpression in human ovarian cancer, establishing it as an adverse prognostic marker. This makes NEK6 an interesting target for anticancer therapy. Through computer-aided drug design, we identified a pyrido[2,3-d]pyrimidine-4(3H)-one derivative (21), as a potent NEK6 inhibitor with antiproliferative effects across various cancer cell lines. However, the limited water solubility of 21 raised concerns about its suitability as a drug candidate. In response to this issue, we synthesized three new derivatives of compound 21 through noninvasive structural modifications of the indenone ring system. The aim was to improve solubility while preserving the affinity for the NEK6 binding pocket. The synthetic approach was guided by molecular modeling studies and free energy perturbation (FEP) calculations. Furthermore, the LANCE Ultra TR-FRET kinase assay demonstrated that the new derivatives inhibited NEK6 at different levels. In particular, one of the three new compounds exhibited slightly higher activity in NEK6 inhibition experiments compared to the parent compound and also showed a better pharmacokinetic profile (measured through logP and ADME in silico calculations). These findings encourage further medicinal chemistry efforts, prompting ongoing modifications to the pyrido[2,3-d]pyrimidinone core to explore additional avenues for drug development.

* The authors marked with an asterisk equally contributed to the work.