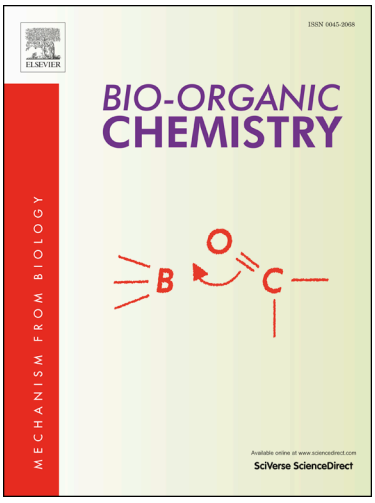

Synthesis of Imidazo-thiadiazole linked Indolinone Conjugates and evaluated their Microtubule network disrupting and Apoptosis Inducing ability

M.P. Narasimha Rao, Burri. Nagaraju, Jeshma Kovvuri, Sowjanya Polepalli, Sateesh Alavala, M.V.P.S. Vishnuvardhan, P. Swapna, Vijaykumar D. Nimbarte, Jerripothula K. Lakshmi, Nishant Jain, Ahmed Kamal

PII: S0045-2068(17)30637-5
DOI: https://doi.org/10.1016/j.bioorg.2017.11.021
Reference: YBIOO 2181

To appear in: *Bioorganic Chemistry*

Received Date: 16 August 2017
Revised Date: 4 November 2017
Accepted Date: 30 November 2017

Please cite this article as: M.P. Narasimha Rao, Burri. Nagaraju, J. Kovvuri, S. Polepalli, S. Alavala, M.V.P.S. Vishnuvardhan, P. Swapna, V.D. Nimbarte, J.K. Lakshmi, N. Jain, A. Kamal, Synthesis of Imidazo-thiadiazole linked Indolinone Conjugates and evaluated their Microtubule network disrupting and Apoptosis Inducing ability, *Bioorganic Chemistry* (2017), doi: https://doi.org/10.1016/j.bioorg.2017.11.021

Synthesis of Imidazo-thiadiazole linked Indolinone Conjugates and evaluated their Microtubule network disrupting and Apoptosis Inducing ability

M. P. Narasimha Rao,[a] Burri. Nagaraju,[a] Jeshma Kovvuri,[a] Sowjanya Polepalli,[b] Sateesh Alavala,[d] M. V. P. S. Vishnuvardhan,[a] P. Swapna,[a] Vijaykumar D. Nimbarte,[e] Jerripothula K. Lakshmi,[c] Nishant Jain,[b] and Ahmed Kamal,[a, d]*

[a]*Medicinal Chemistry and Biotechnology Division,CSIR - Indian Institute of Chemical Technology, Hyderabad 500 007, India.*

[b]*Centre for Chemical Biology Division.CSIR - Indian Institute of Chemical Technology, Hyderabad 500 007, India.*

[c]*Centre for Nuclear Magnetic Resonance & Structural Chemistry, CSIR - Indian Institute of Chemical Technology, Hyderabad 500 007, India.*

[d] *Pharmacology & Toxicology Division- CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India*

[e]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Educational & Research, Hyderabad 500 037, India.*

Abstract

A series of imidazo[2,1-*b*][1,3,4]thiadiazole linked indolinone conjugates were synthesized and investigated for antiproliferative activity in different human cancer cell lines by changing various substitutions at indolinone and phenyl ring systems. Among them conjugates **7**, **14** and **15** were exhibited potent antiproliferative activity with GI_{50} values from 0.13-3.8 μM and evaluated for cell cycle analysis, tubulin polymerization assay and apoptosis. Treatment with **7**, **14** and **15** were resulted in accumulation of cells in G2/M phase, inhibition of tubulin assembly, disruption of microtubule network. Inhibition of tubulin polymerization was further supported by Western blot analysis. In addition, the conjugates (**7, 14** and **15)** also showed apoptosis in HeLa cell line, detailed biological studies such as Hoechst 33258 staining, DNA fragmentation and caspase-3 assays suggested that these compounds induce cell death by apoptosis. Docking studies revealed that these compounds (**7**, **14** and **15)** bind with αAsn101, αThr179, αSer178, βCys241, βLys254 and βLys352 in the colchicine-binding site of the tubulin.

***Keywords*:** Imidazothiadiazoles, cell cycle, cytotoxicity, tubulin polymerization, apoptosis.

*,[a]Corresponding authors. Tel.: +91-40-27193157; fax: +91-40-27193189 (A.K.); e-mail: ahmedkamal@iict.res.in (A. Kamal).