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Synthesis of novel isoxazolobenzimidazoles as potent antiproliferative drugs

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Isoxazole nucleus is a fundamental constituent of several natural products and synthetic products with biological activity. They are important intermediates in the synthesis of various natural products like prostanoids, vitamins, nucleosides and alkaloids. Isoxazole framework is present in several marketed drugs such as leflunomide, valdecoxib and zonisamide, cycliton and gantrisin. Also, benzothiadiazole is an important pharmacophore which has diverse biological activity and clinical applications. Therefore, we aimed at the synthesis of a few novel conjugates incorporating both the ring systems, which could provide a single molecule having tandem effect of the special characteristics of isoxazole and benzimidazole. The synthesis was carried out starting from preparation of 5-methyl-3-arylisoxazole-4-carboxylic acid chlorides from benzaldehyde in four steps. Oximation of benzaldehyde/substituted benzaldehyde with hydroxylamine hydrosulfate yields benzaldehyde oxime which was converted to chloro compound. This on reaction with methylacetoacetate forms respective methyl esters which on saponification and further reaction with PCl_5 yield 5-methyl-3-arylisoxazole-4-carboxylic acid chlorides. These acid chlorides on $La(OTf)_3$ mediated condensation with aromatic diamines form 4-(1H-benzo[d]imidazol-2-yl)-5-methyl-3-phenylisoxazoles. All the synthesized compounds were screened for cytotoxicity on C6 glioma cell lines using MTT assay. 7-(3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole)-8H-imidazo[4,5-e]-2,1,3-benzothiadiazole showed maximum cytotoxicity with an IC50 value of 100 μM.