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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A facile synthesis of some 3-cyano-1,4,6-trisubstituted-2(1*H*)-pyridinones and their biological evaluation as anticancer agents

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Abstract The synthesis of some new 3-cyano-1,4,6-trisubstituted-2(1*H*)-pyridinones supported with various pharmacophores and functionalities at positin-1 is described. The in vitro anticancer activity of 24 of the newly synthesized compounds was evaluated according to the protocol of the NCI in vitro disease-oriented human cells screening panel assay. The results revealed that five compounds **4a–c**, **7b**, and **12b** were able to display moderate antitumor potential against some of the tested subpanel tumor cell lines at the GI_{50} and TGI levels, however, with marginal or no cytotoxic (LC_{50}) activity. The obtained data suggested that better antitumor activity was linked to derivatives with either 4-bromophenyl or 3,4-dimethoxyphenyl moieties, together with a 1-methyl-1*H*-pyrrol-2-yl counter part at positions 6 and 4, respectively. Consequently, the 3-cyano-4-(1-methyl-1*H*-pyrrol-2-yl)-6-(4-bromophenyl or 3,4-dimethoxyphenyl)-2(1*H*)-pyridinones **4a** and **4b**, could be considered as the most active members identified in this investigation as evidenced from their relative higher growth inhibitory (GI_{50} (MG-MID) 77.6 and 67.6 μM, respectively) and cytostatic (TGI (MG-MID) 85.1 and 95.5 μM, respectively) activities, when compared with the substituted thiocarbamoyl analog **7b** and the bicyclic [1,2,4]triazolo[3,4-a]pyridine derivative **12b**.

Keywords Synthesis · Chalcones · Pyridinones · Pyrrole · Thiophene · Anticancer activity

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The worldwide-ongoing efforts of research on treatment of malignancy are focused on the discovery of novel potent and effective antineoplastic agents, particularly those interacting with novel biological targets. Nevertheless, in spite of the large number of available chemotherapeutic agents, the medical need is still largely unmet due to many factors among which the lack of selectivity of conventional drugs leading to toxicity, the metastatic spreading, and the intrinsic or acquired resistance to chemotherapy developed after few therapeutic cycles (multi-drug resistance; MDR) (Braña and Ramos, 2001; Cozzi, 2003). At the same time, random screening remains one of the essential means to discover new structure leads with antineoplastic activity. The National Cancer Institute (NCI), Bethesda, USA, is still playing an articular role in this field, with special emphasis on novel chemical structures that have not had extensive clinical evaluation (Cocco *et al.*, 2000). In this respect, among the most important pharmacologically active heterocycles, pyridine-containing compounds have attracted much attention as versatile chemotherapeutic agents owing to their reported potential antimicrobial (Abdel-Aziz *et al.*, 2005; Srivastava *et al.*, 2007; Aridoss *et al.*, 2007), antitubercular (Mamolo *et al.*, 1999; Ranft *et al.*, 1999), antiamoebic (Abid *et al.*, 2005), antiparasitic (Goebel *et al.*, 2008), and antiviral activities (Dragovich *et al.*, 2002; Gudmundsson *et al.*, 2005; Allen *et al.*, 2006). As far as the antineoplastic potential is concerned, pyridine derivatives were reported to possess cytotoxic