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Letter to the Editor Open Access

Imidazo[2,1-*b*] Thiazole: Introduction, Current and Perspective

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Introduction

Imidazo[2,1-*b*]thiazole (**1**) is a fused heterobicyclic system containing bridgehead nitrogen atom. Derivatives of this scaffold are especially attractive in the field of medicinal chemistry because of their broad spectrum of biological activities. The imidazo[2,1-*b*]thiazole system constitutes the core unit of the well-known anthelminthic and immunomodulatory agent Levamisole (**2**) (Figure 1), marketed under the trade name Ergamisol© and discovered at Janssen Pharmaceutica in 1966 [1].

During last decades our group synthetized some series of imidazo[2,1-*b*]thiazole derivatives active against various cancer cell lines (**3**-**8**). We discovered that, for some selected molecules, their ability to inhibit cellular proliferation was mediated by cell cycle arrest at the G2/M phase, accompanied by inhibition of ornithine

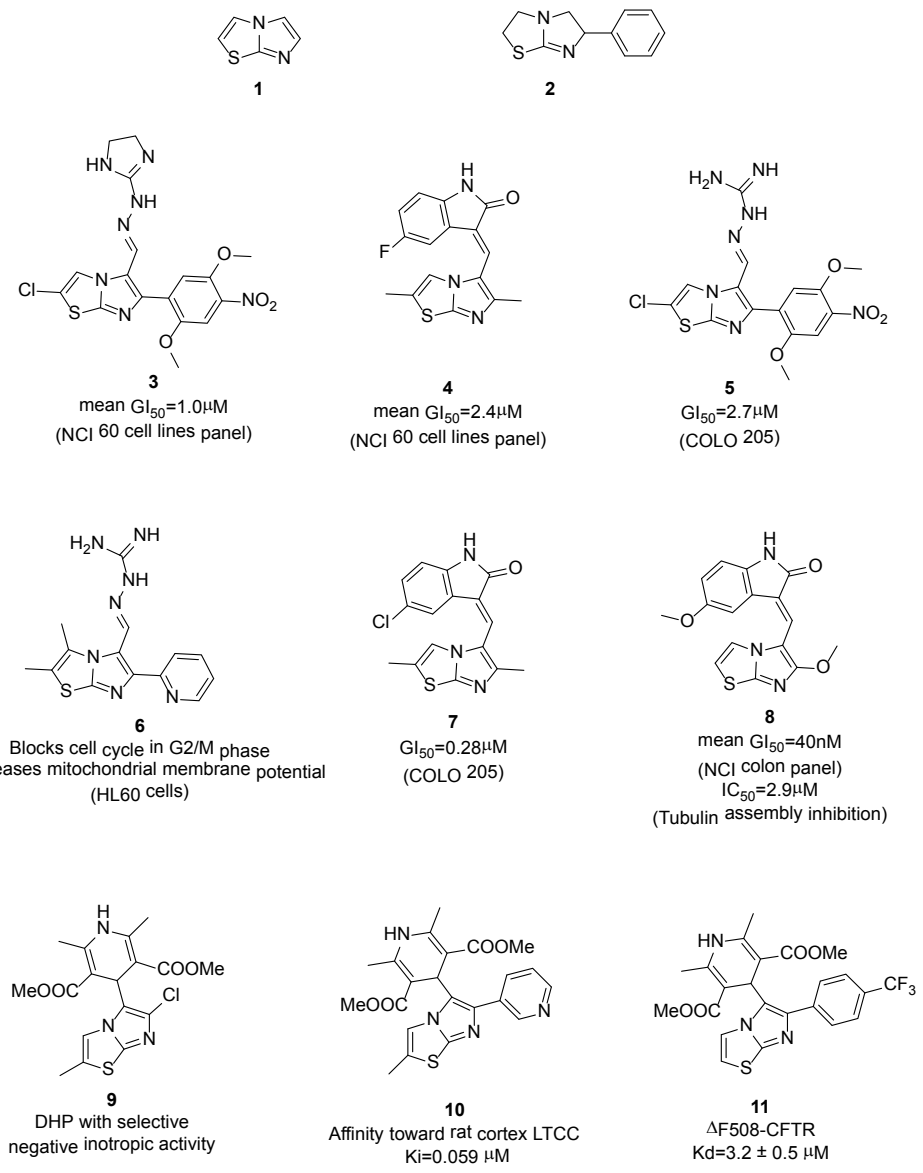

Figure 1: Imidazo[2,1-b]thiazole (1) and some derivatives (2-12).

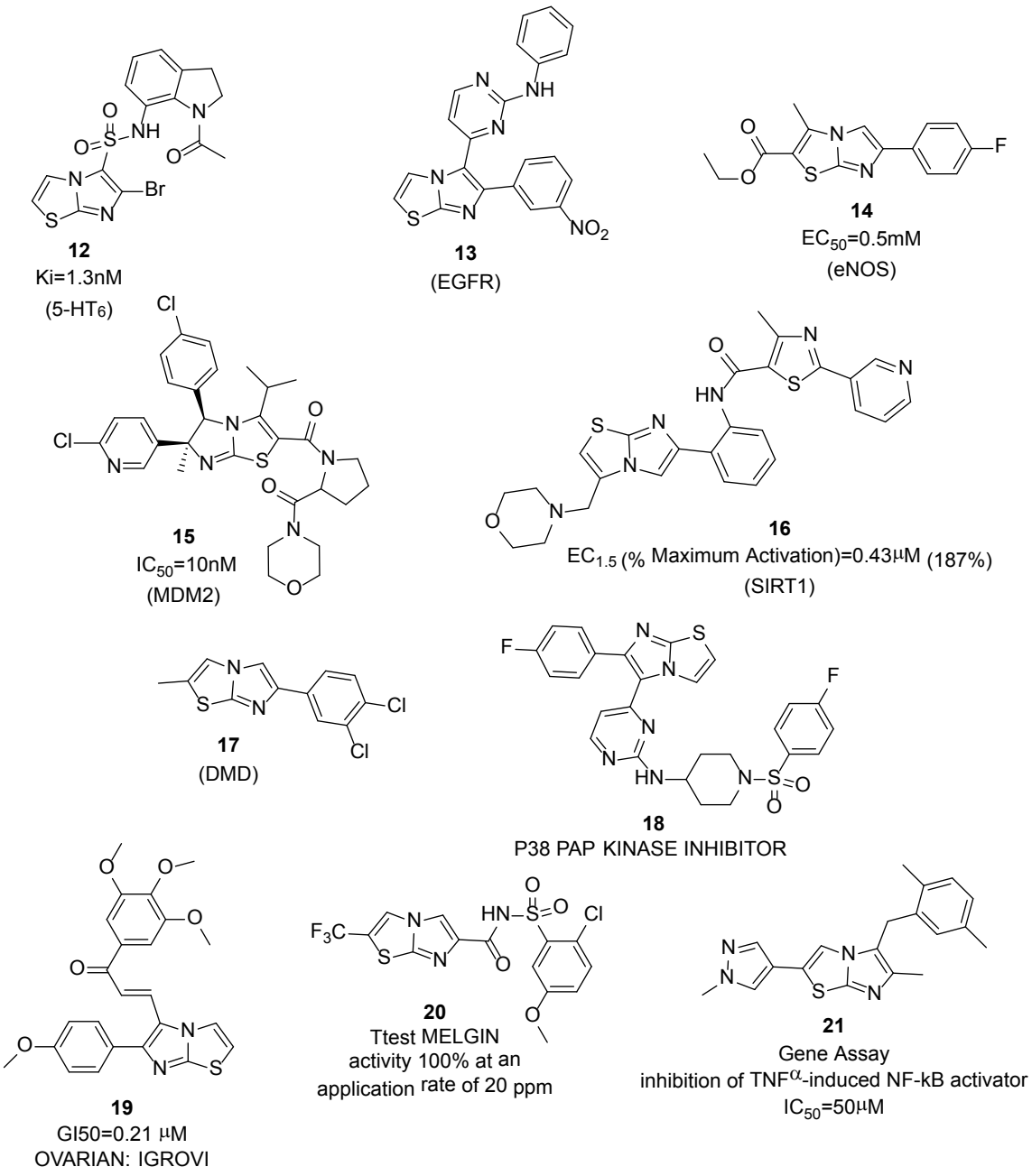

Figure 2: Patented imidazo[2,1-b]thiazole derivatives (12-21).

decarboxylase (ODC), the limiting enzyme of polyamine synthesis, and followed by induction of apoptosis (**4**) [2,3]. We studied also the effect of the guanylhydrazone derivatives bearing the scaffold of imidazo[2,1-*b*]thiazole. We found an inhibitor of Complex III of the mitochondrial respiratory chain inducing apoptosis in the cell lines HT29 and HL60 (**5**) [4]. Varying the substitutions on the thiazole ring of the imidazothiazole skeleton we obtained some imidazothiazole guanylhydrazones that block the cell cycle progression with a marked reduction in the mitochondrial transmembrane potential $\Delta\Psi_m$ and a decrease in the intracellular ATP content (**6**) [5]. In the same period, we reported new series of substituted 3-(5-imidazo[2,1-*b*] thiazolylmethylene)-2-indolinones as anticancer agents. Among these,

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some derivatives exhibit growth inhibition in submicromolar range. Mechanistic studies of the most active compounds revealed that the apoptosis in the HT-29 cells was accompanied by caspase activation and phosphatidylserine externalization and that the most potent compounds strongly reduced Akt(Ser473) phosphorylation. Further mechanistic studies in colon adenocarcinoma (HT-29) cell line revealed that imidazo[2,1-*b*]thiazolylmethylene-2-indolinones, in some cases, are capable of blocking cells in M phase without interfering with microtubule dynamics (**7**,**8**) [6,7]. Recently we focused our attention on the synthesis and functional *in vitro* assay in cardiac and smooth muscle (vascular and nonvascular) of a library of 4-imidazo[2,1-*b*] thiazole-1,4-dihydropyridines to define their calcium blocker nature and their selectivity on Cav1.2 and Cav1.3 isoforms (**9**,**10**) [8,9]. Taking into account that 1,4-dihydropyridines that block L-type Ca^{2+} channels are also effective potentiators of the cystic fibrosis transmembrane conductance regulator (CFTR) gating able to correct the defective activity CFTR mutants, we evaluated the ability of the previously and newly synthesized 4-imidazo[2,1-*b*]thiazoles-1,4-dihydropyridines without vascular activity and inotropic and/or chronotropic cardiac effects to enhance the activity of CFTR mutants (**11**) [10].

The versatility of imidazo[2,1-*b*]thiazole nucleus has attracted the attention of many other academic researchers and of pharmaceutical companies [11,12]. In the last decade the research in this field has generated patents with heterogeneous therapeutic applications: modulators of transcription for modulators of activity at 5-HT_6 receptor **12**, inhibitors of the EGFR kinase activity **13**, endothelial nitric oxide synthase **14**, inhibitors of murine double minute 2 **15**, sirtuin modulators **16**, treatment of Duchenne muscular dystrophy **17**, inhibitors of p53 MAK kinase **18**, potential anticancer agents **19**, nematicides **20** and modulators of the tumor necrosis factor activity **21** (Figure 2) [13-22].

The framework of imidazo[2,1-*b*]thiazole allows various substitution patterns and generally, they are obtained by classical synthetic routes or more novel protocols based on multicomponent reactions [23]. In recent years, the design and synthesis of pharmacologically relevant heterocyclic molecules by combinatorial techniques have proven to be a promising strategy in the search for new pharmaceutical lead structures. Click chemistry is one of the powerful reactions for making carbon-heteroatom-carbon bonds in aqueous environment with a wide variety of chemical and biological applications in various fields and it is a newer approach to the synthesis of drug like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. Furthermore new therapeutic approaches that are currently being developed to circumvent the effectiveness of the current arsenal of anticancer agents may definitely lead to discover novel drugs having low toxicity and resistance. For example the search for a putative anticancer drug could involve a multiple-target approach to overcome potential mechanism(s) of resistance caused in part by redundancy and robustness of biological pathways and to afford compounds able to modulate multiple aspects of pathologies [24,25]. All these considerations prompt to us to continue the research based on the imidazo[2,1-*b*]thiazole core as a tool to discover small molecules that could be lead compound for anticancer therapy.

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