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Original article

Imidazo[2,1-*b*]thiazole guanylhydrazones as RSK2 inhibitors [1]

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ABSTRACT

The activity of a series of imidazo[2,1-*b*]thiazole guanylhydrazones as inhibitors of p90 ribosomal S6 kinase 2 (RSK2) is described. It was found that a small subset of compounds show both potent inhibition of RSK2 kinase activity and tumor cell growth in vitro. Detailed study of one of the most active compounds indicates a high degree of selectivity for inhibition of RSK2 compared to a spectrum of other related kinases. Selective inhibition of the MCF-7 breast tumor cell line compared to MCF-10A non-transformed cells, as well as selective inhibition of the biomarker GSK3 provides evidence that the compounds can affect the RSK2 target in cells.

1. Introduction

We have recently reported synthesis and initial biological characterization of a series of imidazo[2,1-*b*]thiazole guanylhydrazones as potential anticancer derivatives [2]. These compounds displayed a broad range of potency as in vitro growth inhibitors and the patterns of activity generated in the NCI-60 screen were suggestive of multiple mechanisms of action.

For further studies on the antitumor activity and mechanism(s) of action, a new series has been synthesized taking into account the features which, in the previous papers, gave good results such as the 2-chloroimidazothiazole system, the 2,5-dichlorothienyl and 2,5-dimethoxy-4-nitrophenyl groups at the 6 position of the imidazothiazole system, the substitution of the imidazothiazole with analogous systems (imidazothiadiazole, imidazobenzothiazole and imidazopyridine) and the substitution of the usual guanylhydrazone chain with analogous chains. In this new series we wish to consider the following situations (see Schemes 1 and 2).

A) Substituents at the 6 position of the imidazothiazole or at the corresponding position of analogous systems:
   - 2,5-dichlorothiophene on imidazothiazole and analogous systems: **17a**, **18a**, **30a** and **34a**.
   - 2,5-dimethoxy-4-nitrophenyl group on imidazothiazole-like systems (on the imidazothiazole system it had been considered in previous papers) [2,3]: **18b**, **30b** and **34b**.
B) Replacement of the guanylhydrazone chain with a chain containing an imidazoline ring. This has been done on selected systems: **24a**, **25c**, **31a** and **35a**.
C) Fluoro derivatives were synthesized following the example of many drugs whose activity has been enhanced by incorporation of fluorine [4]: **17e,j**, **20e–l** and **21e,j**.
D) Comparison with previously published analogs: **17d,n**, **19d**, **20m**, **22o** and **23o**.

Abbreviations: RSK2, p90 ribosomal S6 kinase 2; GSK3, glycogen synthase kinase 3; NCI, National Cancer Institute; DTP, Developmental Therapeutics Program; DMSO, dimethylsulphoxide; GI, growth inhibition; TGI, total growth inhibition; LC, lethal concentration; BEC, Biological Evaluation Committee; TPA, 12-O-tetradecanoylphorbol-13-acetate; IMAP, Immobilized Metal ion Affinity-based fluorescence Polarization; PVDF, Polyvinylidene Fluoride; HRP, horseradish peroxidase.

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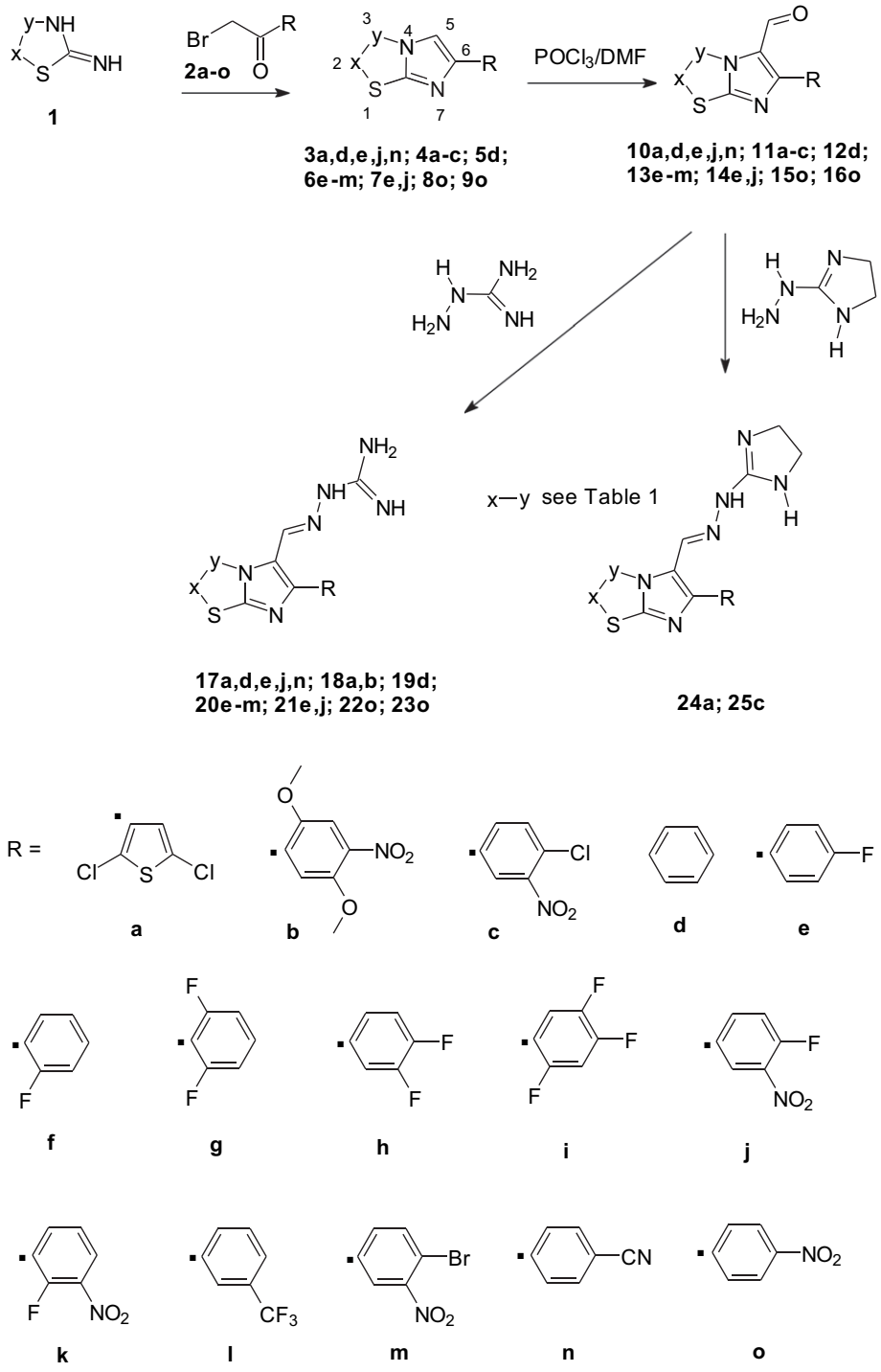

Scheme 1.

Molecular-targeted screening of the NCI chemical repository has recently led to identification of a bis-guanylhydrazone as a lead chemotype for inhibition of CHK2 kinase [5]. Based on the structural similarity of this compound to the imidazo[2,1-*b*]thiazole guanylhydrazones, we evaluated this class of compounds (those described here and others selected from previous papers) as kinase inhibitors. While no potent inhibitors of CHK2 were found, several potent and highly selective inhibitors of RSK2 were identified.

RSK2 has been identified as a potential oncology drug development target based on its role in MAP kinase signaling [6] and more recently on its importance for the RAS-ERK pathway as it effects tumor cell invasion [7]. Since only a limited number of small molecule inhibitors have been previously reported [8,9], we were interested to pursue this series in detail.

2. Chemistry

The hydrazones **17a**,**d**,**e**,**j**,**n**, **18a**,**b**, **19d**, **20e**–**m**, **21e**,**j**, **22o**, **23o**, **24a** and **25c** (Scheme 1, Table 1), **30a**,**b**, **31a**, **34a**,**b** and **35a** (Scheme