European Journal of Medicinal Chemistry 84 (2014) 718–730

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

New imidazo[1,2-*b*]pyrazoles as anticancer agents: Synthesis, biological evaluation and structure activity relationship analysis

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ARTICLE INFO

Article history:
Received 24 January 2014
Received in revised form
10 July 2014
Accepted 17 July 2014
Available online 18 July 2014

Keywords:
Imidazo[1,2-b]pyrazoles
Anticancer activity
Structure–activity relationship

ABSTRACT

Synthesis and functionalization strategies of the imidazo[1,2-*b*]pyrazole core were developed giving a rapid access to three series of novel imidazo[1,2-*b*]pyrazole type derivatives: C-2/C-6/C-7 trisubstituted, C-2/C-3/C-6 tri(hetero)arylated and C-2/C-3/C-6/C-7 tetrasubstituted imidazo[1,2-*b*]pyrazoles. 39 of the synthetized products were evaluated for *in vitro* anticancer activity using the MTT colorimetric assay against 5 human and 1 murine cancer cell lines. Promising *in vitro* growth inhibitory activities were exhibited by some of the target compounds. Of the 39 evaluated products, 4 displayed an $IC_{50} \leq 10$ μM in the 6 cell lines analyzed (compounds **4d**, **4g**, **9a**, **11a**). A structure activity relationship analysis is also reported in this paper.

1. Introduction

Cancer (a group of diseases characterized by the uncontrolled growth of abnormal cells) is one of the most insidious and feared diseases. It is also one of the leading causes of death worldwide, causing almost 7 million deaths each year and studies estimate that this number is expected to double by 2030 [1]. Out of the twenty-seven types of characterized cancers, lung, stomach, colon, liver and breast cancer are mainly involved in cancer mortality. Despite the extensive effort and investment in research, the management of human malignancies still constitutes a major challenge for contemporary medicinal chemists. There is an ongoing need for discovering new and more efficient anticancer agents with minimum side effects [2].

Many synthetic small molecules from different groups of heterocycles which influence carcinogenesis have been reported and are currently in clinical trials [3]. Nitrogen bridgehead heterocycles have received considerable attention in the field of drug discovery due to their interesting biological activities [4]. In particular, imidazo[1,2-*b*]pyrazoles have been described as antifungal [5] and anti-inflammatory agents [6], and play an important role in the treatment of neurodegenerative disorders [7] or the hepatitis C virus [8]. Some imidazo[1,2-*b*]pyrazoles have also been found to be active against different types of cancer [9]. For example, Bharatam's group synthetized some imidazo[1,2-*b*]pyrazoles described as potential topoisomerase αII catalytic inhibitors (an enzyme involved in kidney and breast cancer) [9a]. 7-Carbonitrileimidazo[1,2-*b*]pyrazole derivatives are also potential spleen tyrosine kinase inhibitors and play an important role in cancer therapy [9b]. To date, very few successful methods to access this scaffold exist [5–9,10]. Based on the above findings, it was deemed of considerable interest to design and synthetize diversified libraries of imidazo[1,2-*b*]pyrazole derivatives in order to identify novel biologically relevant hits.

Based on the expertise of our group in designing nitrogen bridgehead polycyclic scaffolds [11–14] we developed synthesis and functionalization strategies of this heterocycle, giving rapid access to a large panel of tri- or tetrasubstituted imidazo[1,2-*b*]pyrazole derivatives. The activities of these new target compounds

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http://dx.doi.org/10.1016/j.ejmech.2014.07.057
0223-5234/

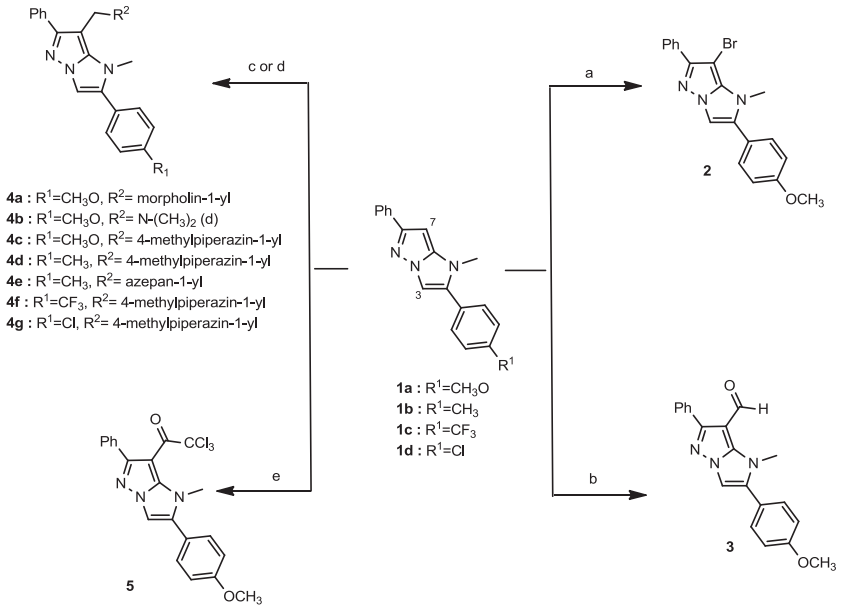
against 6 cancer cell lines as well as a structure–activity relationship (SAR) are reported in this paper.

2. Results and discussion

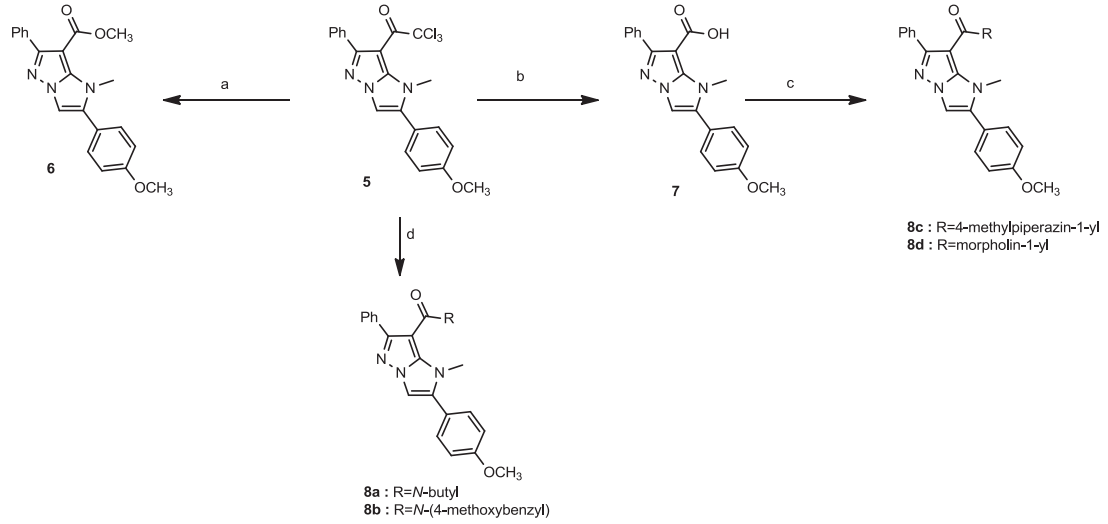
2.1. Chemistry

2.1.1. Synthesis of C-2/C-6/C-7 trisubstituted imidazo[1,2-b] pyrazoles

At the beginning of our research in this field, we developed a three-step synthesis of various imidazo[1,2-*b*]pyrazole derivatives **1a**–**d** from the commercially available 3(5)-phenyl-1*H*-pyrazol-5(3)-amine and various α-bromoacetophenones [13]. Then, a large variety of electrophiles were regioselectively introduced in position C-7 giving access to a diversified library of trisubstituted imidazopyrazole type derivatives (Scheme 1). First of all, bromination with *N*-bromosuccinimide afforded compound **2** with an excellent yield of 90%. A Vilsmeier–Haack reaction performed by using phosphorus oxychloride in presence of *N*,*N*-dimethylformamide led selectively to compound **3** (80% yield). Mannich reactions performed on products **1a**–**d** with various cyclic amines in presence of formaldehyde in acidic conditions rapidly gave the



a) NBS in $CHCl_3$, 0 °C to r.t., 15 min, 90%. b) $POCl_3$ in DMF, -30 °C, 15 min, 80%. c) amine, CH_2O, CH_3COOH in MeOH, r.t., 1-23 h, 53-77%. d) For R^2=$N(CH_3)_2$: Eschenmoser salt, CH_3COOH in MeOH, r.t., 1h, 65%. e) $ClCOCCl_3$, pyridine in 1,4-dioxane, r.t., 1 h, 90%.



a) MeONa in MeOH, r.t., 1 h, 81% b) NaOH, THF/H_2O 8/2, r.t., 1 h, 84%. c) $SOCl_2$ in dry DCM, r.t., 1 h, then amine, Et_3N, in DCM, r.t., 12 h, 56-80%. d) amine in DMF, t.a., 12 h, 70-88%.

Scheme 1. Synthetic pathway to C-2/C-6/C-7 substituted imidazo[1,2-*b*]pyrazoles.