European Journal of Medicinal Chemistry 113 (2016) 145–166

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Mini-review

Synthetic approaches, structure activity relationship and biological applications for pharmacologically attractive pyrazole/pyrazoline–thiazolidine-based hybrids

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ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form
10 February 2016
Accepted 11 February 2016
Available online 16 February 2016

Keywords:
Synthesis
Biological activity
Pyrazole
Pyrazoline
Thiazolidine

ABSTRACT

The features of the chemistry of 4-thiazolidinone and pyrazole/pyrazolines as pharmacologically attractive scaffolds were described in a number of reviews in which the main approaches to the synthesis of mentioned heterocycles and their biological activity were analyzed. However, the pyrazole/pyrazoline–thiazolidine-based hybrids as biologically active compounds is poorly discussed in the context of pharmacophore hybrid approach. Therefore, the purpose of this review is to summarize the data about the synthesis and modification of heterocyclic systems with thiazolidine and pyrazoline or pyrazole fragments in molecules as promising objects of modern bioorganic and medicinal chemistry. The description of biological activity was focused on SAR analysis and mechanistic insights of mentioned hybrids.

1. Introduction

Pharmacophore hybrid approach is a current concept in drug design and development to produce molecules with improved affinity and efficacy. There are some reviews dealing with the concept of molecular hybridization and the promises/challenges associated with these hybrid molecules along with recent advances on anticancer hybrids [1–3]. Various heteroaryl based hybrids in particular isatin and coumarins [3] or indoline-thiazolidinones [4] have been recently reviewed as conjugates with remarkable inhibitory potential.

Design of new drug-like small molecules based on the pharmacologically attractive scaffolds of thiazolidine (4-thiazolidinone) [5–10] and pyrazole or pyrazoline [11–15] is a reasonable and promising direction in modern medicinal chemistry. The chemical approaches for the synthesis of thiazolidinone- and pyrazole-based derivatives and their pharmacological activity were described in a numerous reviews [5–12]. However, the pyrazole/pyrazoline–thiazolidine-based conjugates as biologically active compounds are poorly reviewed in the context of pharmacophore hybrid approach.

The recent synthetic studies of pyrazole–thiazolidines and related hybrids and biological investigations for their antitumor, antimicrobial, antiviral, antiparasitic, anti-inflammatory activities allowed to identify the promising drug-like compounds. Thus, the pyrazole–thiazolidinones/thiazoles have been patented as inhibitors of necroptosis [16], VHR protein tyrosine phosphatase inhibitors [17], Pin1-modulating compounds [18], compounds for modulating RNA-binding proteins [19] and activators of pro-apoptotic BAX [20]. In addition, the pyrazole–thiazolidinone hybrids have been studied for their possibility to inhibit the TNF-α–TNFRc1 interaction [21], as inhibitors of histone acetyltransferases [22] and inhibitors of COX [31,39] and ADAMTS-5 enzymes [83]. Therefore, the purpose of this review is to summarize the data about the synthesis and biological activity of heterocyclic systems with thiazolidine and pyrazole/pyrazoline fragments in molecules. The most promising pyrazole–thiazolidinone/thiazole hybrids and target heterocycles that have been reviewed as fragments of hybrid molecules are depicted in Fig. 1.

The reviewed hybrids were classified as 2-, 3- and 5-pyrazole/pyrazoline-substituted thiazolidines based on linkage of target heterocyclic cores. The basic approaches for the synthesis of

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http://dx.doi.org/10.1016/j.ejmech.2016.02.030
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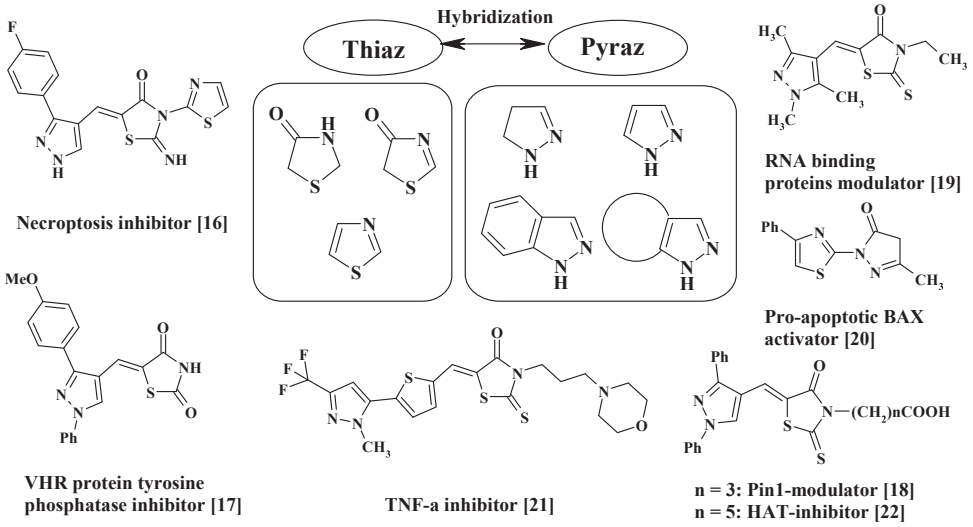

Fig. 1. Heterocycles for pyrazole/pyrazoline–thiazole/thiazolidine hybridization and the most promising conjugates.

mentioned derivatives provide a combination of two "small" molecules in aminolysis reactions, acylation and Knoevenagel procedure or heterocyclization of monocyclic compounds *via* the [2+3]-cyclization reaction yielding the series of non-condensed bicyclic systems.

2. Synthetic approaches for 4-thiazolidinone-based hybrids with pyrazole/pyrazoline fragments in position 2

Detailed biological activity evaluation of pyrazoline–thiazolidinone conjugates **1.2**–**1.7** and pyrazoline–thiazoles **1.8**, **1.9** (Fig. 2), synthesized *via* the [2+3]-cyclocondensation of 4,5-dihydropyrazole-1-carbothioamides **1.1** as *S,N*-binucleophiles in reactions with equivalents of dielectrophilic synthon $[C2]^{2+}$, allowed to identify compounds with antimicrobial [23–28], antiviral [29,30], anti-inflammatory [31], antitumor [32–35] and insecticidal [36] activities. For synthesis of target derivatives α-halogenocarboxylic acids [31,33] and their ethyl esters [23–29,35,36], maleic anhydride [30], maleimides [30,38], β-aroylacrylic acids [30], dimethyl acetylenedicarboxylate [37], bromoacetophenones [23,24,28,29,35] and ethyl 4-chloroacetoacetate [35] were used as equivalents of dielectrophilic synthon $[C2]^{2+}$.

Three-component one-pot reaction that includes [2+3]-cyclocondensation of 4,5-dihydropyrazole-1-carbotioamides **1.1** with chloroacetic acid and the further Knoevenagel reaction with aromatic aldehydes [33,34] and isatin derivatives [32] is an effective approach for design of new anticancer agents among the pyrazoline–thiazolidinones **1.10**, **1.11** (Fig. 3).

The reaction between pyrazolyl-imines [39,40] or pyrazolyl-hydrazones [41] and thioglycolic acid or its esters is widely used approach for the synthesis of 4-thiazolidinone conjugates **1.12**, **1.13**

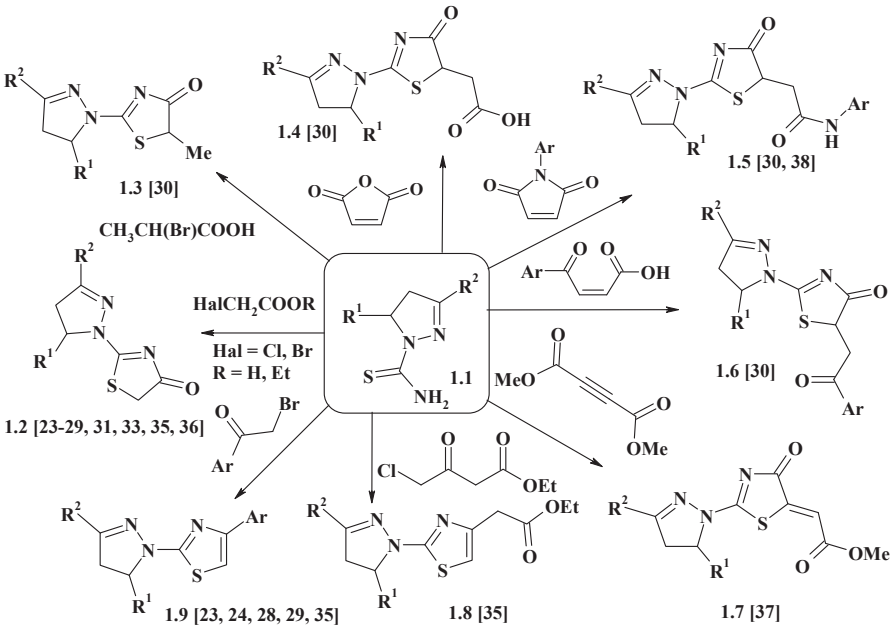

Fig. 2. Synthesis of pyrazoline–thiazolidinones *via* [2+3]-cyclization reactions.