European Journal of Medicinal Chemistry 96 (2015) 491–503

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Design, synthesis and structure–activity relationship of phthalimides endowed with dual antiproliferative and immunomodulatory activities

Marcos Veríssimo de Oliveira Cardoso [a, *], Diogo Rodrigo Magalhães Moreira [a], Gevanio Bezerra Oliveira Filho [a], Suellen Melo Tiburcio Cavalcanti [a], Lucas Cunha Duarte Coelho [a], José Wanderlan Pontes Espíndola [a], Laura Rubio Gonzalez [a], Marcelo Montenegro Rabello [a], Marcelo Zaldini Hernandes [a], Paulo Michel Pinheiro Ferreira [b], Cláudia Pessoa [c, d], Carlos Alberto de Simone [e], Elisalva Teixeira Guimarães [f, g], Milena Botelho Pereira Soares [g], Ana Cristina Lima Leite [a]

[a] Departamento de Ciências Farmacêuticas, Centro de Ciências da Saúde, Universidade Federal de Pernambuco, 50740-520, Recife, PE, Brazil
[b] Departamento de Biofísica e Fisiologia, Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal do Piauí, 64049-550, Teresina, PI, Brazil
[c] Departamento de Fisiologia e Farmacologia, Faculdade de Medicina, Universidade Federal do Ceará, 60430-270, Fortaleza, CE, Brazil
[d] Fundação Oswaldo Cruz, 60180-900, Fortaleza, CE, Brasil
[e] Departamento de Física e Informática, Instituto de Física, Universidade de São Paulo, 13560-970, São Carlos, SP, Brazil
[f] Departamento de Ciências da Vida, Universidade do Estado da Bahia, 41150-000, Salvador, BA, Brazil
[g] Hospital São Rafael, 41253-190, Salvador, BA, Brazil

ARTICLE INFO

Article history:
Received 11 November 2014
Received in revised form
15 April 2015
Accepted 18 April 2015
Available online 20 April 2015

Keywords:
Phthalimide
Thiosemicarbazone
Thiazole
Thiazolidinone
Antiproliferative
Immunosuppressive

ABSTRACT

The present work reports the synthesis and evaluation of the antitumour and immunomodulatory properties of new phthalimides derivatives designed to explore molecular hybridization and bioisosterism approaches between thalidomide, thiosemicarbazone, thiazolidinone and thiazole series. Twenty-seven new molecules were assessed for their immunosuppressive effect toward TNFα, IFNγ, IL-2 and IL-6 production and antiproliferative activity. The best activity profile was observed for the (**6a**–**f**) series, which presents phthalyl and thiazolidinone groups.

1. Introduction

Thalidomide appears to be a multi-target drug that impinges on a number of seemingly distinct cellular processes, including peptidase inhibition, glucosidase inhibition, androgen receptor antagonism and (cyclooxygenase) COX inhibition [1].

One of the most studied biological activities influenced by thalidomide is the inhibition of the expression of the pro-inflammatory cytokine tumour necrosis factor (TNFα) [2]. TNF is a central regulator of the inflammatory cascade that controls many effector pathways as anti-angiogenic, anti-inflammatory and immunomodulatory molecule. The molecular mode of action of thalidomide on TNFα expression is thought to involve the inflammatory NFjB signalling pathway, specifically inhibiting the activity of the IjB kinase, IKKa [3].

Thalidomide is also known as an inhibitor of nuclear factor kappa B (NF-κB) activation [4–7]. NF-κB is a family of structurally related transcription factors that play a major role in inflammation and immune responses. Moreover, NF-κB inhibits apoptosis, and

* Corresponding author.
E-mail address: marcosvocardoso@gmail.com (M.V.O. Cardoso).

http://dx.doi.org/10.1016/j.ejmech.2015.04.041
0223-5234/

induces proliferation and angiogenesis, suggesting that NF-κB has a pivotal role in oncogenesis and tumour progression [8,9].

Immunomodulatory drugs (IMiDs) are thalidomide derivatives with improved anti-tumour activity and safer toxicity profiles [10]. The two leading IMiD compounds, lenalidomide (CC-5013; IMiD3; Revlimid) and pomalidomide (CC-4047; IMiD1; Actimid), were the first drugs to enter into clinical trials for the treatment of multiple myeloma in 1999 [11] and are the subject of clinical evaluation in other haematological malignancies [12]. Studies on the structure–activity relationship (SAR) of the metabolites of thalidomide and its analogues have revealed that the phthalimide ring system is an essential pharmacophoric fragment [13].

In fact, substituted N-phenylphthalimides are of high interest because they have been found to inhibit TNFα [1,14] and COX [1], and have tubulin binding properties [15]. With these properties in mind, phthalimide has usually been employed in the design of potential antiinflammatory [16], immunomodulatory [17–19], antiangiogenic [20–22] and antitumour [23–26] drug candidates. In this promising scenario, the strategy of molecular hybridization using phthalimide as a pharmacophoric fragment have figured prominently and led to many successful cases [14]. On the other hand, thiosemicarbazones are compounds of considerable interest because of their important chemical properties and potentially beneficial biological activities [27–30].

In general, the synthesis of thiosemicarbazone compounds presents low cost and high atom economy because all the atoms from the reagents (except the water liberated in the condensation) are present in the final molecule.

4-N-substituted thiosemicarbazones show remarkable activity in comparison with their unsubstituted counterparts. An enhanced inhibitory effect may be attributed to the increased lipophilicity that allows the molecules to easily cross the cell membrane. The 4-N nitrogen of the thiosemicarbazone skeleton may contain: a) two hydrogen atoms (unsubstituted thiosemicarbazones); b) one hydrogen atom and one alkyl or aryl group and c) two alkyl or aryl groups or may be a part of a cyclic ring [31].

Bearing in mind the molecular pharmacophores outlined above and their structural requirements, some phthalimide derivatives were designed after exploring molecular hybridization and bioisosterism approaches between thalidomide, thiosemicarbazone, thiazolidinone and thiazole moieties (Fig. 1). These derivatives were synthesized by our group and based on the obtained biological data, and new SAR information was collected. Furthermore, a number of the derivatives exhibited potent *in vivo* activity against S-180 sarcoma cells that was comparable to that of the reference drug, thalidomide [32].

In a continuation of our work on the structure–activity relationship, twenty-seven new phthalimide derivatives were prepared to establish an appropriate SAR. Our design was based on the molecular hybridization of the phthalimide ring system with a thiosemicarbazone, thiazolidinone or thiazole subunit.

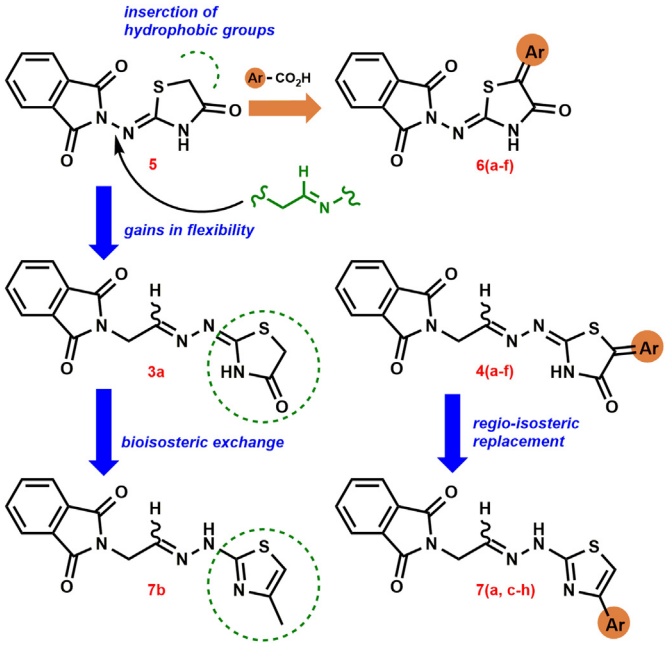

Fig. 2. Design concept of target compounds.

In the design concept, the 2-N and 4-N nitrogen of the thiosemicarbazone skeleton were then substituted by alkyl groups (**2a**–**c**) to improve the lipophilicity. A set of compounds (**3a**–**d**, **4a**–**f** and **6a**–**f**) bearing thiazolidinones was then synthesized by exploring bioisosteric relationship between thiazolidinones and thiosemicarbazones. Our approach also investigated the homologation between the phthalyl system and thiazolidinones (**3a**–**d** and **4a**–**f**) to investigate the influence of flexibility. Subsequently, a bioisosteric exchange between the thiazolidinone and thiazole nuclei was made, so that the 4-N nitrogen of the thiosemicarbazone skeleton was then converted to a thiazole ring that contained alkyl (**7b**) or phenyl groups (**7a**, **7c**–**h**) (Fig. 2).

2. Results and discussion

2.1. Chemistry

The synthesis of N-phenyl-4-(thiazol-5-yl)pyrimidin-2-amine derivatives was adapted from the method described previously [32,33] and is outlined in Scheme 1.

From the phthalic anhydride (**1**) obtained commercially, an acetal intermediate was first synthesized by imidification reaction with aminoacetaldehyde diethyl acetal reagent in the presence of DMAP. Then, this intermediate underwent acid hydrolysis to obtain the aldehyde intermediate, which was condensed with

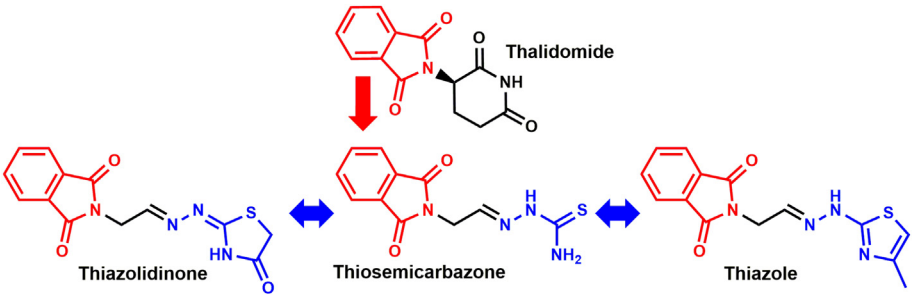

Fig. 1. Bioisosteric relationship between thalidomide and the proposed thiosemicarbazones, thiazolidinones and thiazoles.