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ORIGINAL ARTICLE

Design, synthesis and biological evaluation of new substituted 5-benzylideno-2-adamantylthiazol[3,2-b][1,2,4]triazol-6(5*H*)ones. Pharmacophore models for antifungal activity

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Abstract As a part of our ongoing studies in developing new derivatives as antimicrobial agents we describe the synthesis of novel substituted 5-benzylideno-2-adamantylthiazol[3,2-b][1,2,4]triazol-6 (5H)ones.The twenty-five newly synthesized compounds were tested for their antimicrobial and antifungal activity. All compounds have shown antibacterial properties with compounds **1–9** showing the lowest activity, followed by compounds **10–14** while compounds **15–25** the highest antibacterial activity. Specific compounds appeared to be more active than ampicillin in most studied strains and in some cases more active than streptomycin. Antifungal activity in most cases also was better than that of reference drugs ketoconazole and bifonazole. Elucidating the relation of

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molecular properties to antimicrobial activity as well as generation of pharmacophore model for antifungal activity of two fungal species *Aspergillus fumigatus* and *Candida albicans* were performed.

1. Introduction

During the past 50 years the significant efforts in the diagnosis and treatment of microbial diseases (Fernandes, 2006) led to impressive gains in the treatment of microbial diseases introducing a range of therapeutic strategies in clinical practice. However, in spite of a large number of antibiotics and chemotherapeutics available for medical use there is still an urgent medical need for new classes of antibacterial agents, due to the emergence of old and new antibiotics' resistance created in the last decades. A potential approach that addresses this issue of resistance is the design of novel agents with different mode of action in order to avoid the occurrence of cross resistance with the present therapeutics.

Five member heterocycles with two of three heteroatoms, such as imidazoles, thiazoles, triazoles and others are key structural units in many pharmaceutical preparations.

Specifically, 1,2,4-triazoles and their heterocyclic derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities. A large number of 1,2,4,-triazole derivatives containing ring systems exhibit antibacterial (Gabriela et al., 2010; Upmanyu et al., 2011; Prasad et al., 2012; Taj et al., 2013; Kumar et al., 2014; Gupta et al., 2015), antifungal (Sangshetti et al., 2009; Zoumpoulakis et al., 2012; Barbuceanu et al., 2009, 2012; Sahu et al., 2014; Gupta et al., 2015) antitubercular (Gill et al., 2008; Kumar et al., 2010; Cristophe et al., 2011; Godhani et al., 2015), analgesic (Amir et al., 2008;Tozkoparan et al., 2012; Khanage et al., 2013; Sarigol et al., 2015), anti-inflammatory (Pattan et al., 2012; Ayse et al., 2012; Ashour et al., 2013; Sarigol et al., 2015), anticancer (Romagnoli et al., 2010; Wang et al., 2011; Bai et al., 2012), anticonvulsant (Siddiqui et al., 2010; Dayanand et al., 2011; Botros et al., 2013; Plech et al., 2013; Kamboj et al., 2015), antiviral (Abdel-Aal et al., 2008; Jordao et al., 2009; El-Etrawy et al., 2010), antimalarial (Mishra et al., 2008; Gujjar et al., 2009) central nervous system (Kamboj et al., 2015) and other activities (Puthiyapurayil et al., 2012; Iqbal et al., 2012).

Additionally, the thiazolyl group bears great importance in biological systems. In this context, thiazole derivatives find a variety of applications such as bacteriostatics (Abdel-Wahab et al., 2009; Dawane et al., 2010; Kouatly et al., 2010; Zablotskaya et al., 2013; Haroun et al., 2016), antibiotics (Mostafa and Abd El-Salam, 2013), antifungal (Bharti et al., 2010), CNS regulants of high selling diuretics (Sucman et al., 2011), local anaesthetics (Geronikaki et al., 2009), anti-inflammatory (Lagunin et al., 2008; Kouatly et al., 2009; Pattan et al., 2009; Apostolidis et al., 2013), analgesic and antipyretics (Pattan et al., 2009; Saravanan et al., 2011), HIV infections (Pitta et al., 2010, 2013), antiallergic (Hargrave et al., 1983), antihypertensives (Abdel-Wagab et al., 2008), against schizophrenia (Gupta, 2013**),** antidiabetic (Lino et al., 2009), anthelminthic (Amnerkar and Bhusari, 2011), anticancer (Luzina and Popov, 2009; Liu et al., 2009) and antioxidant (Gouda et al., Geronikaki et al., 2013). Furthermore, the thiazole ring is also found in many potent biologically active molecules. In particular, Thiabendazole and 2-(p-chlorophenyl) thiazole-4-acetic acid are widely used as anti-inflammatory drugs (van Arman and Campbell, 1975). Meloxicam is a new NSAID with a thiazolyl group in its structure (Kumar and Mishra, 2006). Some other thiazole derivatives are antiulcer (Nizatidine), antiretroviral (Ritonavir) (De Souza and De Almeida, 2003) agents, while others (Van Arman and Campbell, 1975; Ramachandran et al., 2011; Vicini et al., 2008) as well as Niridazole (Kilpatrick et al., 1982) have been found to exhibit antimicrobial antifungal/antihelminthic activities.

Another interesting core in medicinal chemistry responsible for numerous pharmacological properties and biological activities is the thiazolidinone (Knutsen et al., 2007; Apostolidis et al., 2013). Many publications refer to antifungal activity of different thiazole and thiazolidinone derivatives (Amnerkar and Bhusari, 2011; Apostolidis et al., 2013; Marques et al. 2014; Gupta et al., 2016; Haroun et al., 2016).

In view of these facts the thiazolo[3,2-b]1,2,4-triazoles are compounds with broad spectrum of biological activities, such as antimicrobial (Barbuceanou et al., 2009; Karthikeyan, 2009; Gupta et al., 2015), anticancer (Lesyk et al., 2007; Kaminskyy et al., 2011), anti-inflammatory (Tozkoparan et al., 2000; Doğdaş et al., 2007; Apostolidis et al., 2013) and analgesic (Assarzadeh, 2014) as well as antihypertensive (Bhandari et al., 2009) and anti-diabetic (Calderone et al., 2009).

Moreover, adamantane derivatives have been documented for their antiviral activity against influenza A (McSharry et al., 2007; Galvão et al., 2014) and HIV viruses (Balzarini et al., 2009; Pitta et al., 2010). Several adamantane derivatives were also associated with central nervous system (Suh et al., 2005), antimicrobial (Kadi et al., 2007) and anti-inflammatory activities (Kadi et al., 2007; Tozkoparan et al., 2012; Karthikeyan, 2008; Kouatly et al., 2009).

These findings focused particular interest on the incorporation of thiazolo[3,2-b]1,2,4-triazole with adamantine ring in one frame in order to obtain compounds with improved/higher antibacterial and antifungal activities.

To this extend, twenty-five new 5-arylidene **-2**-adamatylthiazol[3,3-b]triazol-6(5H)-ones (Scheme 1,1–25) were synthesized and evaluated for their *in vitro* antimicrobial properties against Gram positive, Gram negative bacteria and fungi strains. To a step further, multivariate data analysis highlighted the relation between molecular properties to antimicrobial and antifungal activities of the synthesized compounds.

2. Results and discussion

2.1. Chemistry

The synthesis of title compounds was performed by a multistep reaction as shown in Scheme 1. Adamantane thiosemicarbizide (3) was synthesized using a procedure reported earlier starting from adamantine-1-carbonyl chloride (1) upon reaction with thiosemicarbazide (2), followed by cyclization in alkaline solution under reflux to 5-adamantyl-4H-1,2,4-trizol-3-thiole (3). The third step includes the one pot condensation of 5-adaman tyl-4H-1,2,4-triazol-3-thiole (4) with bromoacetic acid and appropriate substituted benzaldehydes in the presence of sodium acetate and acetic anhydride (Karthikeyan et al., 2008). Reactions proceed smoothly with good yields (55–88%).

All new structures of compounds **1–25** were characterized by IR, ^{1}H NMR and elemental analysis. IR spectra showed absorptions at 1724–1747 cm^{-1} (C=O) and at 1578–1654 cm^{-1} (C=N). In the ^{1}H NMR spectra the title compounds showed peaks in the region of 1.75–2.36 ppm (adamantine), 7.12–7.80 ppm (Ar—H) and 8.11–8.48 ppm (CH=).

During the reaction of 5-adamantyl-4*H*-1,2,4-trizol-3-thiole with different dielectrophiles the formation of two cyclic

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