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ORIGINAL ARTICLE

Synthesis and pharmacological evaluation of novel 2*H*/6*H*-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carbonitrile derivatives

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Abstract In the present study a new series of 3-hydroxy-7-isocyano-6-oxo-8-phenyl-2-(substitutedphenyl(piperidin-1-yl)methyl)-6*H*-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-*a*]-pyridine-9-carbonitrile (**5a–j**) and (*Z*)-2-(4-substitutedbenzylidene)-7-isocyano-3,6-dioxo-8-phenyl-3,6-dihydro-2*H*-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carbo-nitrile derivatives (**4a–j**) were synthesized. The newly synthesized compounds were characterized by IR, ^{1}H NMR, LC–MS mass and C, H, N analyses. All newly synthesized compounds were screened for their antibacterial (*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pyogenes* and *Klebsiella pneumoniae*) and antifungal (*Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium marneffei* and *Trichophyton mentagrophytes*) activity. The results revealed that all synthesized compounds have a significant biological activity against the tested microorganisms. Compounds **4a, 4f, 4i, 4j, 5a, 5i** and **5j** exhibited good antimicrobial activity.

1. Introduction

Triazoles are important classes of heterocyclic compounds. In particular, fused 1,2,4-triazoles express antifungal (El-Hawash et al., 1999), bactericidal (El-Hawash et al., 1999; Brown and Iwai, 1979), anxiolytic (Tarzia et al., 1988; Trust and Albrigh, 1980), anticonvulsant (Tarzia et al., 1989) or herbicidal (Peignier et al., 1991; Cantegriil et al., 1997) activities and can act as antidepressants (Sarges et al., 1990). Therefore, versatile and widely applicable methods for their synthesis are of considerable interest. Most methods for the preparation of fused 1,2,4-triazoles are mainly based on hydrazones as precursors. However, these methods have some restrictions regarding their applicability and the use of toxic reagents like lead tetraacetate (Bower and Doyle, 1957; Pollak and Tisler, 1966) and bromine (Pollak and Tisler, 1966; Gibson, 1963), also the other products were formed in low yield and isolated as salts (Hadi et al., 1992; Al-Najjar et al., 1996). Many 1,2,4-triazine derivatives are well known to possess biological activities, thus they have been found to be useful as herbicides (Neunhoeffer, 1978; Neunhoeffer, 1984). In the last decade they have been screened

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in vitro supporting for their anti-HIV and anti-cancer activities (Abdel-Rahman et al., 1999; Abdel-Rahman et al., 1994; Abdel-Rahman et al., 1999; Abdel-Rahman, 2001). However the aza-Wittig reaction is a powerful tool for the synthesis of five- to seven-membered nitrogen heterocycles (Takeuchi et al., 1989; Eguchi and Goto, 1994; Eguchi et al., 1992; Takeuchi et al., 1989; Molina and Fresneda, 1988; Molina et al., 1990; Molina and Vilaplana, 1990; Wamhoff and Schmidt, 1993; Sato et al., 1993; Molina et al., 1990a; Molina et al., 1990b). Annulation of ring systems with N-heterocycles by means of an aza-Wittig reaction has recently been widely utilized because of the availability of functionalized iminophosphoranes (Palacios et al., 2007; Eguchi, 2006; Braese et al., 2005; Eguchi, 2005; Fresneda and Molina, 2004). Many important monocyclic nitrogen heterocycles such as indole, pyridine, pyrimidine and isoquinoline derivatives have been synthesized *via* the intramolecular aza-Wittig reaction (Takeuchi et al., 1989; Eguchi and Goto, 1994; Eguchi et al., 1992; Takeuchi et al., 1989), as well as by the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocyclization (Molina and Fresneda, 1988; Molina et al., 1990; Wamhoff and Schmidt, 1993; Sato et al., 1993; Molina et al., 1990a; Molina et al., 1990b). We have previously published the synthesis of fused pyrimidines based on the tandem aza-Wittig annulation strategy (Barsy and El-Rady, 2006), and as a part of our ongoing studies we now describe a novel one-pot synthesis of 1,2,4-triazolo[1,5-*a*]pyridine and pyrido[1,2-*b*][1,2,4]triazines derivatives in good yield.

2. Experimental

2.1. Materials and reagents

All reagents and solvents were purchased and used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a Perkin–Elmer BX serried FT-IR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. LC–MS Mass spectra were recorded on a MASPEC low resolution mass spectrometer operating at 70 eV.

2.2. General procedure for the preparation of 1-amino-6-(triphenylphosphoranylidene-amino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (**2**)

1-Amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl -1,2-dihydro-pyridine-3,5-dicarbonitrileiminophosphorane (**2**) were synthesized according to the reported method by the reaction with triphenylphosphine/hexachloroethane and triethylamine reagent system (the Appel method, i.e., the modified Kirsanov reaction) (Appel et al., 1970). To a stirred mixture of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **1**, (0.5 g, 2.0 mmol), hexachloroethane (0.473 g, 2.0 mmol, 1.0 equiv.) and triphenylphosphine (0.52 g, 2.0 mmol, 1.0 equiv.) in anhydrous benzene (50.0 mL) triethylamine (0.4 mL, 4.0 mmol, 2.0 equiv.) were added dropwise. The resultant solution was heated at reflux for 2 h. The mixture was filtered while still hot in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid product which was crystallized from ethanol as colorless crystals; yield: 950 mg (95%); mp 170 °C, IR (KBr, cm^{-1}): 1656 (C═O), 2210 (C═N), 3229, 3259 (NH_2), ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.1–7.8 (*m*, 20H, Ar-H), 8.9 (s, 2H, NH_2); LC–MS (*m*/*z*, %): 511 $(M)^+$. Anal. Calcd for $C_{31}H_{22}N_5OP$: C, 72.79; H, 4.34; N,13.69. Found: C, 72.65; H, 4.25; N, 13.57.

2.3. Synthesis of 5-oxo-7-phenyl-2-thiol-3,5-dihydro[1,2,4]-triazolo[1,5-a]pyridine-6,8-dicarbonitrile (**3**)

To a solution of 1-amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl-1,2-dihydro-pyridine-3,5-dicarbonitrileiminophosphorane **2** (0.5 g, 1.0 mmol) in 15 mL of dry toluene an excess of carbon disulfide (7 mL) was added. The reaction mixture was heated in a closed two-neck round bottom flask at 100 °C for 3 h. The crystals that formed were collected and crystallized from a mixture of DMF and H_2O (1:1) as yellow crystals, yield: 240 mg (83%); mp 215 °C, IR (KBr, cm^{-1}): 1200 (SH), 1655 (C═O), 2210 (C═N), 3120 (NH), ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.5 (s, 1H, SH), 6.9–7.3 (*m*, 5H, Ar-H), 10.3 (s, H, NH); LC–MS (*m*/*z*, %): 293 $(M)^+$. Anal. Calcd for $C_{14}H_7N_5OS$: C, 57.33; H, 2.41; N, 23.88. Found: C, 57.11; H, 2.55; N, 23.57.

2.4. Synthesis of (Z)-2-(4-substitutedbenzylidene)-7-isocyano-3,6-dioxo-8-phenyl-3,6-dihydro-2H-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-a]pyridine-9-carbonitrile (**4**)

A mixture of 5-oxo-7-phenyl-2-thiol-3,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (**3**) (5 mmol), aromatic aldehydes (5 mmol), chloroacetic acid (5 mmol) and fused sodium acetate (10 mmol) were refluxed in acetic acid/acetic anhydride (25:5 mL) mixture for 3 h. Then the reaction mixture was cooled, filtered and crystallized from acetic acid to give the (*Z*)-2-(4-substitutedbenzylidene)-7-isocyano-3,6-dioxo-8-phenyl-3,6-dihydro-2*H*-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-*a*]pyridine-9-carbonitrile **4a–j** in 66–89% yields. The R_f values were measured using benzene/ethyl acetate mixture as an eluent in ratio (9:1). The reaction sequences were outlined in Scheme 1.

2.4.1. (Z)-2-Benzylidene-7-isocyano-3,6-dioxo-8-phenyl-3,6-dihydro-2H-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-a]pyridine-9-carbonitrile (**4a**)

White solid in a yield of 87%, mp 146–148 °C; IR (KBr, cm^{-1}): 3032 (Ar-H), 1730 (C═O), 1590 (C═N), ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H, CH), 7.60–7.55 (m, 2H, Ar-H), 7.45–7.33 (m, 6H, Ar-H), 7.19–7.17 (m, 2H, Ar-H), LC–MS (*m*/*z*, %): 422 $(M+1)^+$. Anal. Calcd for $C_{23}H_{11}N_5O_2S$: C, 64.25; H, 2.55; N, 16.57. Found: C, 65.55; H, 2.63; N, 16.62.

2.4.2. (Z)-2-(4-Chlorobenzylidene)-7-isocyano-3,6-dioxo-8-phenyl-3,6-dihydro-2H-thiazolo-[3′,2′:2,3][1,2,4]triazolo[1,5-a]pyridine-9-carbonitrile (**4b**)

White solid in a yield of 66%, mp 171–172 °C; IR (KBr, cm^{-1}): 3030 (Ar-H), 1730 (C═O), 1590 (C═N), ^{1}H NMR (300 MHz,