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Microwave assisted synthesis of some novel acetazolamide cyclocondensed 1,2,3,4-tetrahydropyrimidines as a potent antimicrobial and cytotoxic agents

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ABSTRACT

A new series of some novel acetazolamide cyclocondensed 1,2,3,4-tetrahydropyrimidines was prepared by reacting of *N*-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide with urea/thiourea and appropriate aldehyde in the presence of catalytic amount of laboratory made p-toluenesulfonic acid as an efficient catalyst. Confirmation of the chemical structure of the synthesized compounds (**12a**–**n**) was substantiated by TLC, different spectral data IR, ^{1}H NMR, Mass spectra and elemental analysis were done. The synthesized compounds were evaluated for in-vitro antimicrobial and cytotoxicity against *Bacillus subtilis*, *Escherichia coli* and Vero cells. The titled compounds exhibited weak, moderate, or high in-vitro antimicrobial and cytotoxicity. Compounds **12c**, **12d**, **12g** and **12h**, exhibited potential antimicrobial and in-vitro cytotoxicity.

1. Introduction

The advent of microwave assisted technology in organic chemistry dates back to the mid 1980s and since the 1990s there has been a significant increase in the number of publications on Microwave Assisted Organic Reactions (MAOS) due to increased benefits associated with the process (Langa et al., 1997; Strauss and Trainor, 1995; Wathey et al., 2002). The promotion of microwave assisted reactions in organic

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chemistry has improved the speed, reduced cost, reduced energy spent making it a sustainable process and is widely heralded as "green chemistry" measures whose applications are promoted today to minimize the use of non renewable resources as well as polluting solvent, to reduce generation of secondary products which are often toxic and to reduce the emission of harmful gases (Prasad et al., 2012; Tucker, 2010; Wang et al., 2011). Microwave assisted reactions in organic chemistry achieve the facilitation of faster reactions under bulk conditions as well as promoting reduction of reaction time (Erdmenger et al., 2010).

Pyrimidine derivatives comprise a diverse and interesting group of drugs is extremely important for their biological activities. Dihydropyrimidine and their derivatives have attracted increasing interest owing to their therapeutic and pharmaceutical properties, such as antiviral, antitubercular (Desai et al., 2001; Singh et al., 2011; Prashantha Kumar et al., 2008), antimicrobial agent (Baldev et al., 2012; Bhuiyan et al., 2006; Shetty et al., 2009; Sharma et al., 2004; Vasudeva Rao et al., 2012; El-Sayed et al., 2012) antagonists of the human adenosine A2A receptor (Gillespie et al., 2008), cyclooxygenase-2 inhibitory activity (Orjales et al., 2008; Falcao et al., 2006), tyrosine kinase inhibitors, antiamoebic activity (Gangjee et al., 2010; Parveen et al., 2010) and cytotoxicity (Xie et al., 2009; Saritha Jyostna and Achaiah, 2010; Vasudeva Rao et al., 2012). The discovery during the 1930s that a dihydropyridine (dihydronicotinamide derivative, NADH), "hydrogen-transferring coenzyme" consequently became important in biological system, has generated numerous studies on the biochemical properties of dihydropyridines and their bioisosteres dihydropyrimidines. The search for more suitable preparation of dihydropyrimidinones continues today.

The chemical structure of acetazolamide provides a most valuable molecular template for the development of agents able to interact with a wide variety of biological activities (Karthikeyan et al., 2013; Kushwaha et al., 2012). Tetrahydropyrimidines are structurally similar to dihydropyrimidines. Hence, it was thought worthwhile to synthesize new congeners by incorporating acetazolamide with 1,2,3,4-tetrahydropyrimi dinones moieties in a single molecular frame work and to evaluate their antimicrobial and cytotoxicity.

2. Experimental

2.1. Materials and methods

All chemicals were supplied by E.Merck (Germany) and SD fine chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system ethanol, chloroform, ethylacetate (6:3:1); the spots were located under iodine vapors or UV light. IR spectrums were obtained on a Perkin–Elmer 1720 FT-IR spectrometer (KBr Pellets). ^{1}H NMR spectra were recorded or a Bruker DRX-300 (300 MHz FT-NMR) spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were obtained using Shimadzu LCMS 2010A under ESI ionization technique.

2.1.1. *Preparation of N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide (3)*

Acetazolamide **1** (0.01 M) and ethylacetoacetate **2** (0.01 M) were mixed in presence 10 ml of glacial acetic acid and refluxed for approximately 4.5 h. The colorless liquid formed was then heated on a water bath to remove the alcohol formed during the reaction. After allowing the reaction mixture to cool, crude crystals were obtained. Purification was performed by stirring crude crystals with cold diethyl ether for approximately 20 min using a mechanical stirrer. Allowing it to stand for 15 min, followed by filtration, resulted in the third compound in a pure form of N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide **3**.

2.2. General procedure

2.2.1. *Preparation of 1,2,3,4-tetrahydropyrimidines by microwave irradiation method(**12a–n**)*

The mixture of N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide (0.005 M), urea/thiourea (0.0075 M), and appropriate aldehyde (0.005 M) with catalytic amount of p-toluenesulfonic acid in 10 ml of ethanol was subjected to microwave irradiation (300 W) for 10 min at the interval of 10 s. The reactions were monitored through TLC using 25 percent ethylacetate in pet ether as solvent system. After the reaction was complete, the reaction mixture was cooled in a refrigerator and filtered. The precipitate obtained was washed thoroughly with water to remove unreacted urea/thiourea and dried. The crude solid product was recrystallized with ethanol to give the pure compounds (**12a–n**).

2.3. Analytical data

2.3.1. *N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-3-oxobutanamide (3)*

Light-bluish crystalline solid, M.P.: 188–190 °C; Yield: 74%; IR (KBr, cm^{-1}): 3332 (N–H), 2864 (AliC–H), 1734 (C=O, ketone), 1686 (C=O, amide), 1542 (C=C), 1326 (C–N); ^{1}H NMR (DMSO-d_6) δ: 2.09 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 9.44 (s, 1H, NH), 9.68 (s, 1H, NH); calculated for $C_8H_{10}N_4O_5S_2$: C, 31.37; H, 3.29; N, 18.29; found C, 31.42; H, 3.25; N, 18.35.

2.3.2. *N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-4-(3-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (12a)*

Dark-brownish solid, M.P.: 258–260 °C; Yield: 69%; IR (KBr, cm^{-1}): 3258 (N–H), 3146 (ArC–H), 2932 (AliC–H), 1663 (C=O, amide), 1571 (C=C), 1237 (O–C); ^{1}H NMR (DMSO-d_6) δ: 2.07 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 5.39 (s, 1H, CH), 7.33 (d, 2H, ArH), 7.84 (d, 2H, ArH), 8.88 (s, 1H, NH), 8.94 (s, 1H, NH), 9.62 (s, 1H, NH), 10.08 (s, 1H, NH); MS (*m*/*z*): (M + 1) calculated 472.00; Found 472.05; Calculated for $C_{16}H_{15}ClN_6O_5S_2$: C, 40.81; H, 3.21; N, 17.85; found C, 40.86; H, 3.19; N, 17.88.

2.3.3. *N-{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}-4-(3-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (12b)*

Light-ash-colored solid, M.P.: 284–287 °C; Yield: 76%; IR (KBr, cm^{-1}): 3246 (N–H), 3146 (ArC–H), 2938 (AliC–H), 1628 (C=O, amide), 1557 (C=C), 1884 (C=S), 1176 (O–C); ^{1}H NMR (DMSO-