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Synthesis and Spectral Studies of Hydantoin Derivatives of Imidazo [2,1-b][1,3,4] Thiadiazoles

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Abstract: ***The present article describes the synthesis of Imidazo[2,1-b][1,3,4]thiadiazoles bearing pharmacologically important hydantoin molecules. To synthesize the targeted molecules several imidazothiadiazoles were prepared by condensation of 2-Amino-5-(4-fluorobenzyl)-1,3,4thiadiazole with phenacyl bromides. Which were subsequently subjected to Knoevenagel condensation to afford the hydantoin derivatives. Structures of newly synthesized molecules were confirmed by IR, NMR and Mass spectral studies.***

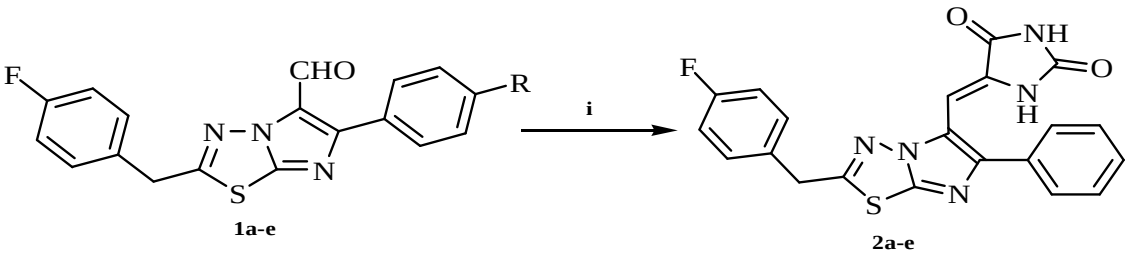
Keywords: Thiadiazole, Imidazothiadiazole, hydantoin, Vilsmeier Haack reaction

I. INTRODUCTION

Heterocyclic compounds have diverse range of applications. They have been predominantly used as pharmaceuticals [1], agrochemicals and veterinary products. They are also used as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, dye stuff [2] etc. In particular, fused heterocycles are important constituents of many available therapeutics agents. Naturally heterocyclic aromatic compounds are widely distributed in animal and plant tissues. Heterocyclic compounds possess diversified biological activities, because they are having ability to bind reversibly to proteins. Medicinal chemistry involves great utilization of heterocyclic compounds by converting them into potent biological agents. Recently many researchers work to synthesize and screen fused heterocyclic compounds against variety of different receptors, yielding several active compounds. Among such cyclic systems is imidazole fused with 1,3,4-thiadiazole moiety, imidazo[2,1-*b*][1,3,4]-thiadiazoles [3], which contains a bridgehead nitrogen atom. Imidazo[2,1-*b*] [1,3,4]thiadiazoles exhibit a diverse array of biological activities, such as anticancer [4], antitubercular [5], antibacterial [6], antifungal [7], anticonvulsant, and antitumor [8,9]. Imidazo[2,1-*b*] [1,3,4]thiadiazole is somewhat structurally close to Levamisole , a well- known potential antitumor agents and immunomodulator [10]. Further, hydantoin nucleus is integral part of many biologically active compounds such as anti-arrhythmic, anti-convulsive and antitumor agents.[11,12] The observed activities do not arise from the hydantoin nucleus itself but from different substituents that have been appended to it. In the light of above observations and facts, efforts were made to combine the two afore mentioned moieties in a single frame work to exploit the expected biological outcome.

II. RESULT AND DISCUSSIONS

The synthetic approach followed for the preparation of said heterocycle derivatives is depicted in the following scheme.



1a-e **2a-e**

a, R = H; **b,** R = Cl; **c,** R = NO_2; **d,** R = Br; **e,** R = OMe
i. hydantoin, sod.acetate, AcOH, reflux.

Scheme

The work carried out in the present investigation includes preparation of 5-formyl imidazo[2,1-b] [1,3,4]thiadiazoles and the Knoevenagel condensation with active methylene compound: hydantoin. For the preparation of formyl derivatives of imidazo[2,1-b][1,3,4]thiadiazoles **(1a-e)** literature procedure is followed in which, Imidazothiadiazoles were subjected to Vilsmeier Haack reaction in DMF and $POCl_3$ mixture.

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The structure of the formyl derivatives were confirmed by referring already reported data in which C-5 proton of Imidazothiadiazole disappeared and aldehydic proton appeared around 10.00 δ ppm. Formyl imidazothiadiazoles on knoevenagel condensation with hydantoins in acetic acid in presence of fused sodium acetate yielded the respective derivatives **(2a-e)**. The reaction was found to be completed in 8-10 hours to give intense yellow color solid. Furthermore these derivatives were obtained with a high degree of purity After the condensation, the reaction mixture was extensively worked up in chloroform and the solvent was distilled off when a sticky residue obtained was triturated with petroleum ether to afford orange color solid in low yield. The IR spectra of hydantoin derivative exhibited bands in the region around 1640cm^{-1}, 1730cm^{-1} and 3430cm^{-1} corresponding to –CONH, -CO and -NH groups respectively. Further the structures were established by the ^{1}H NMR spectra, where the aldehydic proton disappeared and vinylic proton resonated in the region δ 6.45-6.56 as singlet and two broad singlets were observed around at δ 11.2 and 12.3 for –NH protons which disappeared on deuteration. However in ^{1}H NMR spectra the vinyl proton was found to be merged with aromatic protons. All these derivatives were analyzed by spectral data and the results are given in the experimental part.

III. EXPERIMENTAL

Preparation of 5-[2-(4-Fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethy lene]imidazolidine-2, 4-dione (2a-e):

General method: A mixture of 2-(4-Fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4] thiadiazole-5-carbaldehydes, (0.01mol) and hydantoin (0.01mol) in glacial acetic acid (10mL) in presence of fused sodium acetate (2gm) was refluxed for 10hr. The yellow solid formed on cooling was filtered off and recrystallized from proper solvent.

5-[2-(4-Fluorobenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene] imidazolidine-2,4-dione (2a) Bright yellow color crystals (DMF), yield 92%, m.p. 263-265°C; IR (KBr) νcm^{-1}: 3443, 3214, 2924, 2853, 1735, 1642; ^{1}H NMR (300MHz, DMSO, d_6) δ: 4.50 (s, 2H, CH_2), 6.46 (s, 1H, =CH), 7.62-7.70 (m, 9H, Ar-H), 11.20 (s, 1H, NH, D_2O exchangeable).

5-[6-(4-Chlorophenyl)-2-(4-fluorobenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene] imidazolidine-2,4-dione (2b) Bright yellow color solid (DMF), yield 90%, m.p. 279-281°C; IR (KBr) νcm^{-1}: 3433 3221, 2920, 2861, 1729, 1640; ^{1}H NMR (300MHz, DMSO, d_6) δ: 4.58 (s, 2H, CH_2), 6.61 (s, 1H, =CH), 7.24-7.98 (m, 8H, Ar-H), 11.31 (s, 1H, NH, D_2O exchangeable).

5-[6-(4-Bromophenyl)-2-(4-fluorobenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]imidazolidine-2,4-dione (2c) Yellow color amorphous solid (DMF), yield 90%, m.p. 276-278°C; IR (KBr) νcm^{-1}: 3438, 3221, 2920, 2852, 1730, 1641; ^{1}H NMR (300MHz, DMSO, d_6) δ: 4.60 (s, 2H, CH_2), 6.48 (s, 1H, =CH), 7.36-7.86 (m, 8H, Ar-H), 11.20 (s, 1H, NH, D_2O exchangeable).

5-[2-(4-Fluorobenzyl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene] imidazolidine-2,4-dione (2d) Yellow color solid (DMF), yield 93%, m.p. 291-293°C; IR (KBr) νcm^{-1}: 3441, 3224, 2922, 2854, 1730, 1640; ^{1}H NMR (300MHz, DMSO, d_6) δ: 4.69 (s, 2H, CH_2), 6.71 (s, 1H, =CH), 7.26-8.12 (m, 8H, Ar-H), 11.31 (s, 1H, NH, D_2O exchangeable

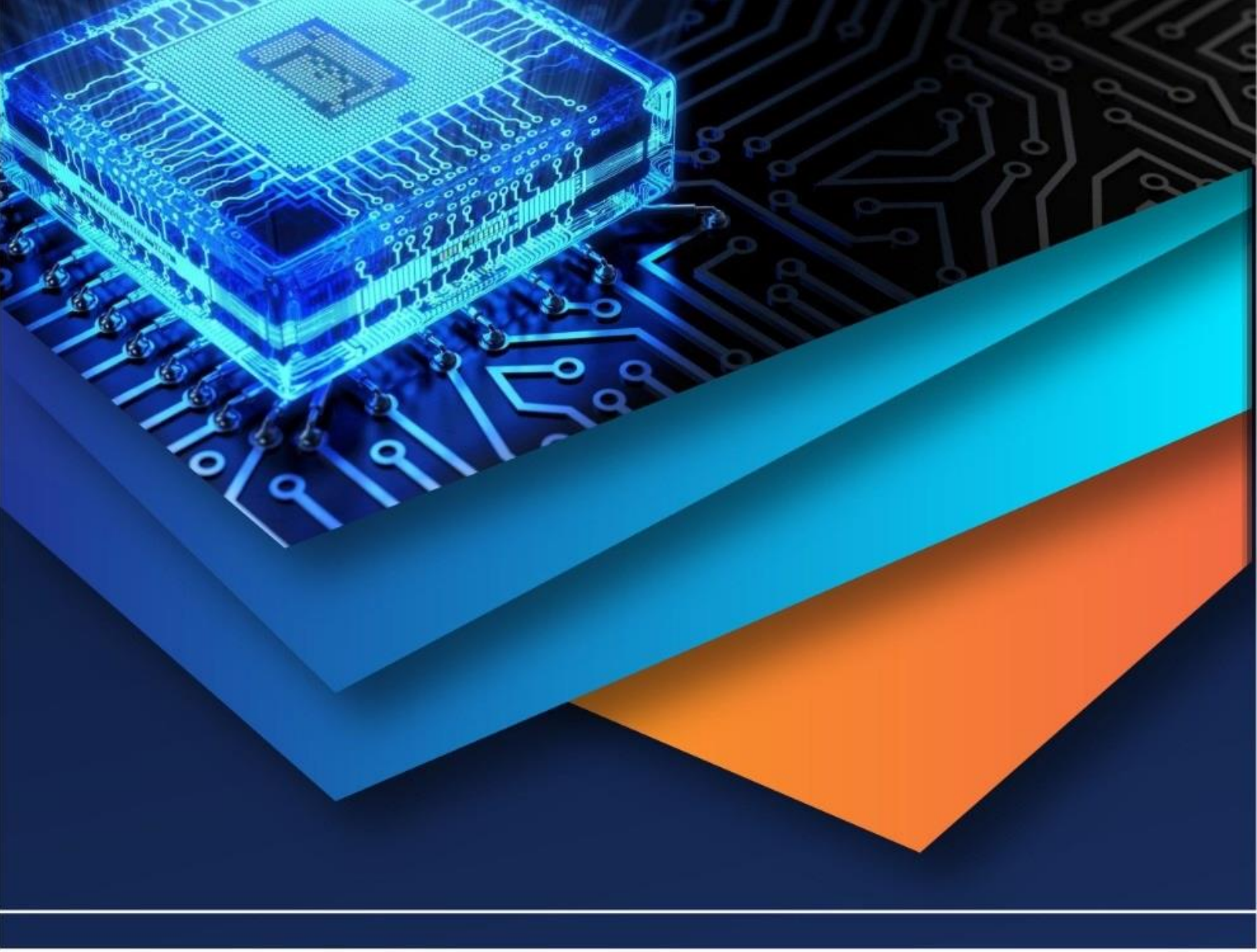
5-[2-(4-Fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene] imidazolidine-2,4-dione (2e) Yellow color granules (DMF), yield 91%, m.p. >300°C; IR (KBr) νcm^{-1}: 3434, 3219, 2920, 2854, 1730, 1641; ^{1}H NMR (300MHz, DMSO, d_6) δ: 3.86 (s, 3H, OCH_3), 4.56 (s, 2H, CH_2), 6.50 (s, 1H, =CH), 7.34-7.99 (m, 8H, Ar-H), 11.0 (s, 1H, NH, D_2O exchangeable), 11.91 (s, 1H, NH, D_2O exchangeable).

IV. CONCUSION

Keeping in view of the diverse medicinal applications of fused heterocycles and hydantoins, attempts were made to bring the two biologically potent Imidazo[2,1-b][1,3,4]thidiazles and hydantoin in a single molecular framework to see the additive and effective avtivities and its study is underway.

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