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One-pot synthesis of 3,3'-(hexane-1,6-diyl)bis(5,5-disubstituted spiro and none spiroimidazolidine-2,4-diones): A bis-drug capability

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Abstract: An improved versatile method was applied for preparation of several new 3,3'-(hexane-1,6-diyl)bis(5,5-disubstituted spiro and none spiroimidazolidine-2,4-diones) or bis-hydantoins. In this process some ketones and aldehydes were converted to several hydantoins effectively. These hydantoins, in the presence of hexamethylene dibromide, dual alkylated and incorporated to bis-imidazolidine-2,4-diones in one step. The reactions ran click chemically and remarkable yields were achieved. The resulted compounds, to our knowledge will potentially have bis-drug behavior in comparison to mono-counterparts, as previously reported for comparable heterocycles in the literature. Spectral analysis confirmed the structures of synthesized bis-imidazolidine-2, 4-diones.

Keywords: Imidazolidine-2,4-dion, Hydantoin, Bis-hydantoin, Bis-drug, Antiepileptic, Spirohydantoin

INTRODUCTION

Discovery of new drugs and improving therapeutically usages of hydantoins in epilepsy, convulsion [1,2], tumor [2-6], arrhythmic [7], viral [8], HIV [9], cancer [5,10], Alzheimer [11], diabetes [12], migraine [13] and etc. has always caused worldwide interests among chemists. Hydantoin scaffolds are also an important structural unit found in agrochemicals [14]. These compounds are precursors to unnatural and natural α-amino acids too [9,14]. New discoveries of hydantoin derivatives as radio sensitizers and markers of oxidative cell damage in cancer, aging, and neurological disorders have also been reported [10, 14 and 15]. Recently, in a promising research way to cancer therapy, it has been revealed that substitution on N(3) of some mono-hydantoins has enhanced their pharmaceutical activities used for treating certain types of tumor cells in unique manner [16, 17]. Bis-drugs are estimated to show double therapeutic behaviours. Following the reports about superior medicinal and pharmacological activities exhibited by some bis-heterocyclic drugs and looking for developing a simple, rapid, convenient and eco-friendly method for the substituted hydantoins, encouraged us to explore bis-hydantoins as manifold medicinal agents [18]. Some potential applications such as antitumor agents [3], anticancer agents [17,19], DNA binding linkages [20] and antimicrobial agents [21] have been cited for bis-hydantoins in literature. In the current work we discuss a one-pot synthetic route for preparation of some novel 3,3'-(hexane-1,6-diyl)bis(5,5-disubstituted spiro and none spiroimidazolidine-2,4-diones) as bis-drugs.

EXPERIMENTAL OBSERVATIONS

Synthesis of 3,3'-(hexane-1,6-diyl)bis(5,5-disubstituted spiro and none spiroimidazolidine-2,4-diones) (**2a-g**). General procedure

All of mono-hydantoins (**1a-g**) were prepared through partially improved Bucherer–Bergs reaction as previously reported. Hydantoin (0.005 mol) was suspended in a solvent mixture of 1.0 M NaOH solution (5 mL) and ethanol (5 mL). The mixture was heated at reflux (60-65 ^{o}C) for 15 min. Then 1,6-dibromohexane (0.36 mL, 0.0024 mol) was added drop wise through the top of a reflux condenser to the solution and the reaction was heated for 24-72 h. The mixture was allowed to cool in ice bath, filtered, washed with water and the products **(2a-g)** were recrystallized from ethanol several times (Scheme 1 and Table 1).