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Synthesis and conformational studies of 5-bromo-1-[(*N*-substituted-carbamoyl)methyl]-7-azabenzimidazoles

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ABSTRACT

The Cs_2CO_3-catalysed condensation of 5-bromo-7-azabenzimidazole with a series of bromomethyl ketones has afforded a small library of ten novel 5-bromo-1-[(*N*-substututed-carbamoyl)methyl]-7-azabenzimidazoles. Rotamerism in the products as evidenced by the splitting of ^{1}H- and ^{13}C-NMR signals, is attributed to hindered internal rotation about the amide N-C(=O) bond, and has been explored using dynamic NMR (DNMR) analysis and computational methods at the GIAO B3LYP/6-311+G(2d,p) level of theory. Coalescence temperatures have been obtained for representative examples and rotational barriers determined experimentally and theoretically. A detailed theoretical analysis has been undertaken to explore conformations which may contribute to the relative populations of the *s-cis* and *s-trans* rotamers. The products have also been screened for cytotoxicity and activity against two parasitic protozoan strains (*Plasmodium falciparum* and *Trypanosoma brucei*).

1. Introduction

Substituted 7-azabenzimidazoles have been reported to exhibit broad-spectrum bioactivity. Examples include the DNA sequence-specific benzamidine derivatives **1** [1] (Fig. 1); the antihypertensive, Rho-kinase inhibiting aminofurazan derivatives containing the azabenzimidazole moiety **2** [2]; the potent allosteric AKT inhibiting pyridyl derivative **3** [3]; and the cytotoxic bis-(7-azabenzimidazole) **4** [4]. As part of our ongoing interest in the medicinal chemistry of novel systems, we have previously reported the preparation of 3-[(*N*-cycloalkylbenzamido)methyl]-2-quinolones as potential HIV-1 Integrase inhibitors [5] and *N*-substituted phosphoramidic acid esters as potential antimalarial agents [6]. We now report: i) the syntheis of a series of novel 5-bromo-1-[(*N*-substututed-carbamoyl)methyl]-7-azabenzimidazoles; ii) experimental (DNMR) and theoretical analyses of the rotamerism arising from hindered internal rotation about the amide group; and iii) evaluation of their cytotoxocity and anti-parasitic activity against *Plasmodium falciparum* (*P.falciparum*) and *Trypanosoma brucei* (*T.Brucei*).

2. Results and Discussion

2.1. Synthesis

Access to the targeted 5-bromo-1-[(*N*-substituted-carbamoyl)-methyl]-7-azabenzimidazoles **10a-j** is outlined in Scheme 1. Thus, 5-bromo-7-azabenzimidaozole **6** was prepared following a stepwise procedure [7] involving: i) reaction a mixture of 2,3-diamino-5-bromopyridine **5** with triethyl orthoformate in acetic anhydride at 110°C for 6 hours; ii) boiling a solution of the concentrated residue in 10% sodium hydroxide for 30 minutes; and iii) acidification (pH 6) to precipitate the product. The lachrymatory bromomethyl ketones **9a-j** were obtained by treating the selected amines **8a-j** with potassium carbonate (or triethylamine) and bromoacetyl bromide **7** in dichloromethane (DCM) under nitrogen. Formation of the title compounds **10a-j** in good yields (70-90 %) was readily effected by stirring mixtures of the corresponding bromomethyl ketones **9a-j** with 5-bromo-7-azabenzimidaozole **6** and Cs_2CO_3 in *N*-methyl-2-pyrrolidinone (NMP) at room temperature.

^{1}H- and ^{13}C-NMR analysis indicated the isolated products **10a-j** to be essentially pure. However, the regular splitting of certain ^{1}H- and ^{13}C-NMR signals at ambient temperature suggested hindered internal rotation about the amide N-C(=O) bond in these compounds. This was confirmed by the observed coalescence of such signals at higher temperatures, and Dynamic Nuclear Mag-

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