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Synthesis and biological evaluation of 2,5-di(7-indolyl)-1,3,4-oxadiazoles, and 2- and 7-indolyl 2-(1,3,4-thiadiazolyl)ketones as antimicrobials

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ABSTRACT

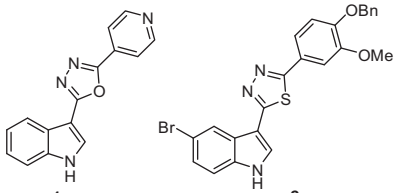
A range of novel hydrazine bridged bis-indoles was prepared from readily available indole-7-glyoxyloyl-chlorides and 7-trichloroacetylindoles and underwent cyclodehydration to produce 2,5-di(7-indolyl)-1,3,4-oxadiazoles and a 2,2′-bi-1,3,4-oxadiazolyl with phosphoryl chloride in ethyl acetate. This efficient protocol was subsequently used for the synthesis of 2- and 7-indolyl 2-(1,3,4-thiadiazolyl)ketones from related indolyl-hydrazine carbothioamides. The synthesised bis-indoles were evaluated for their antimicrobial properties, particularly the inhibition of protein–protein complex formation between RNA polymerase and σ factor and their bactericidal effect on Gram positive *Bacillus subtilis* and Gram negative *Escherichia coli*.

1. Introduction

The 1,3,4-oxadiazoles and 1,3,4-thiadiazoles are unique heterocyclic systems with importance in synthetic, medicinal and materials chemistry.[1] These five-membered heterocycles play a particularly vital role in medicinal chemistry because they display a variety of biological activities,[2–5] possess a favourable metabolic profile, and have a propensity to form hydrogen bonds. In particular, these ring systems have been found in marketed antihypertensive agents such as tiodazosin and nesapidil, antibiotics such as furamizole, and the carbonic anhydrase inhibitor acetazolamide.[6–9]

Indole linked oxadiazoles and thiadiazoles are novel classes of compounds that also exhibit a range of interesting biological activities. For example, the recently developed 2-(3-indolyl)-1,3,4-oxadiazole **1** has been screened as a potent anticancer agent and showed inhibitory activity against prostate and pancreatic cancer cell lines,[10] while the 2-(3-indolyl)-1,3,4-thiadiazole **2** displays significant cytotoxic activity against pancreatic cancer cell lines.[11]

There has been much recent interest in bis-indole amides and glyoxylamides as potent antibacterial agents. For example, compounds such as the 3-indolylglyoxylamide **3** have been shown to possess strong antibacterial activity against Gram-negative and Gram-positive bacteria.[12] We have also reported that a 7,7′-bis-indolylcarbohydrazide inhibit transcription initiation complex formation by preventing the unique bacterial σ initiation factor from binding to RNA polymerase.[13] It was therefore of interest to investigate the nature of the amide groups attached to the indole units and subsequent cyclisation of diamides and thiosemicarbazides to their bioisosters oxadiazoles and thiadiazoles respectively.



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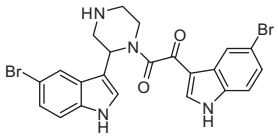

3

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Given the importance of oxadiazoles and thiadiazoles, and the extensive scope available for the development of novel indole linked oxadiazoles and thiadiazoles, we were interested in the development of 2,5-di(7-indolyl)-1,3,4-oxadiazoles, and 2- and 7-indolyl 2-(1,3,4-thiadiazolyl)ketones. A range of synthetic approaches to 1,3,4-oxadiazoles have been reported in the literature, with many of these protocols involving the cyclization of acylhydrazides using harsh reagents such as thionyl chloride,[14] triflic anhydride[15] and phosphoryl chloride.[16] Mild cyclodehydration reagents such as Burgess reagent,[17] 4-methylbenzenesulfonyl chloride (TsCl)[18] and propylphosphonic anhydride (T3P)[19] have also been used. It was therefore anticipated that the target structures could be prepared via cyclization of indole-7-acylhydrazines, which in turn could be synthesized from methoxy activated indoles which are capable of undergoing reaction at the otherwise unreactive C7 position.[20,21]

2. Results and discussion

2.1. Synthesis of 2,5-di(7-indolyl)-1,3,4-oxadiazoles

The preparation of 2,5-di(7-indolyl)-1,3,4-oxadiazoles was achieved over a convenient three-step process. The first step involved the reaction of activated indoles **4a**–**c** with trichloroacetyl chloride at reflux for 3 h, which afforded 7-trichloroacetylindoles **5a**–**c** in 27–69% yields (Scheme 1).[22] Following this, 7-trichloroacetylindoles **5a**–**c** were heated at reflux for 24 h with half an equivalent of hydrazine hydrate in the presence of triethylamine in acetonitrile to afford the 7,7′-bis-indoles **6a**–**c** in 49–81% yield.

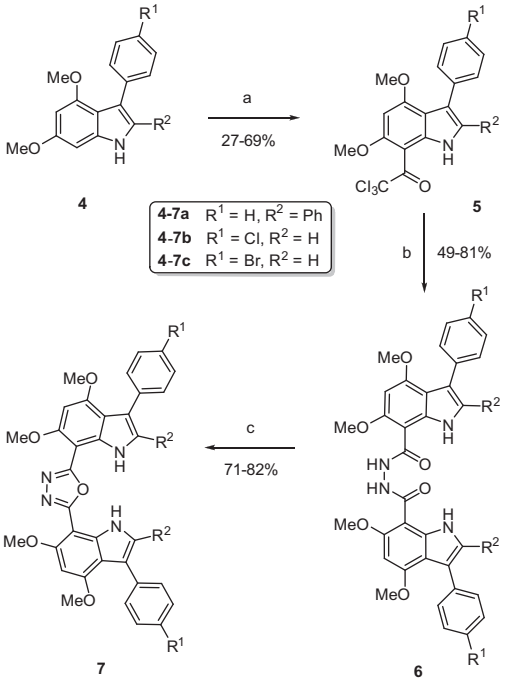
Initial attempts to generate the 2,5-di(7-indolyl)-1,3,4-oxadiazoles **7a**–**c** under mild conditions were unsuccessful. Heating bis-indoles **6a**–**c** at reflux with 1.1 equiv of T3P in the presence of triethylamine in ethyl acetate for 12 h resulted in recovery of the starting materials. Increasing the amount of T3P or base gave the same result. Similarly, no reaction was observed upon use of stronger bases such as DBU. It was therefore concluded that T3P was not strong enough to induce this dehydrative cyclization reaction.

The alternative stronger cyclodehydration reagent phosphoryl chloride was subsequently investigated. Treatment of bis-indoles **6a**–**c** with neat phosphoryl chloride at either room temperature or 50 °C resulted in formation of a black tar. Dilution of the reaction mixture with ethyl acetate as a solvent and heating bis-indoles **6a**–**c**at reflux for 2 h in the presence of excess phosphoryl chloride afforded the desired bis-indolyl-1,3,4-oxadiazoles **7a**–**c** in 71–82% yields after elimination of some baseline impurities by column chromatography.

Both bis-indoles **6a**–**c** and **7a**–**c** were poorly soluble in organic solvents, had high melting points and good stability under normal laboratory conditions. The ^{1}H NMR spectrum of the compound **7b** was characteristic for the oxadiazole compounds, showing the disappearance of hydrazide nitrogen protons of compound **6b** at 10.54 ppm, and a shift of the indole NH protons from 11.54 to 11.17 ppm. A high resolution mass spectrum further confirmed the structure, revealing the anticipated molecular ion.

2.2. Synthesis of 5,5′-di(7-indolyl)bi-2,2′-(1,3,4-oxadiazolyl) compounds

With the 2,5-di(7-indolyl)-1,3,4-oxadiazoles successfully in hand, it was of interest to extend the methodology to a related bi-2,2′-(1,3,4-oxadiazolyl) system **10**. Treatment of 7-trichloroacetylindole **5a** at room temperature for 1 h with 1.5 equiv of hydrazine hydrate in the presence of triethylamine gave the simple 7-carbohydrazide **8a** in high yield (Scheme 2).



Scheme 1. Reagents and conditions: (a) CCl_3COCl, 1,2-dichloroethane, reflux, 3 h; (b) $NH_2NH_2{\cdot}H_2O$, Et_3N, CH_3CN, reflux, 24 h; (c) $POCl_3$, EtOAc, reflux, 2 h.

Preparation of the symmetrical bis-oxalohydrazide **9a**, which possesses an extended linker between the two indole moieties, was subsequently carried out by addition of oxalyl chloride to hydrazide **8a** in dichloromethane at room temperature for 1 h.

Triturating the crude product with hot methanol gave the pure compound **9a** in 53% yield.

The tandem cyclodehydration reaction was performed using the optimized conditions described above. Notably, a prolonged reaction time was required, with the reaction reaching completion after 24 h. Formation of bi-2,2′-(1,3,4-oxadiazolyl) **10** was indicated by the disappearance of the amide nitrogen protons of compound **9a** at 9.94 ppm in the ^{1}H NMR spectrum and a shift of the indole NH protons from 11.11 to 10.79 ppm. The presence of a molecular ion in the high resolution mass spectrum further confirmed the structure.

Similar treatment of 7-trichloroacetylindoles **5b** and **5c** afforded the corresponding indole-7-carbohydrazides **8b**,**c** and bis-oxalohydrazides **9b**,**c**. However, the dehydrative cyclization of these 3-substituted analogues proved to be problematic, resulting in a mixture of inseparable products.

The next objective of interest was the development of glyoxyl derivatives related to the di(7-indolyl)-1,3,4-oxadiazoles **7**. 4,6-Dimethoxyindole **4a** undergoes exclusive C7-substitution with oxalyl chloride to afford the 7-glyoxyloyl chloride **11** which can readily react with a range of amines to produce the corresponding glyoxyl amides.[23] Therefore, treatment of acid chloride **11** with a half equivalent of hydrazine hydrate in acetonitrile gave the bis-indole glyoxyloyl hyrazide **12** in 83% yield (Scheme 3).

Cyclodehydration of the bis-indole **12** was subsequently attempted under the optimized conditions, however, only recovery of the starting material was observed. The use of different solvents such as chloroform, dichloromethane, tetrahydrofuran and neat phosphoryl chloride at either room temperature or reflux, and the use of T3P in different solvents were examined but similarly gave no reaction. Two possible reasons causing the inhibition of the dehydrative cyclization in the 7,7′-linked system **12** are postulated. Firstly, there is potentially a greater steric restriction in the