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Preliminary communication

Novel three-component domino reactions of ketones, isatin and amino acids: Synthesis and discovery of antimycobacterial activity of highly functionalised novel dispiropyrrolidines

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ABSTRACT

One-pot three-component domino reactions of cyclic mono ketones, isatin and sarcosine/phenylglycine furnishing highly functionalised dispiropyrrolidines in moderate yields are described. The reaction when performed with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. These compounds have been screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Among thirty eight compounds screened, 1-methyl-pyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]-1″-nitrosotetrahydro-4″(1*H*)-pyridinone (**4t**) was found to be the most active with MIC of 1.98 μM against MTB and was 3.86 and 25.64 times more potent than the standard first line TB drugs, ethambutol and pyrazinamide respectively.

1. Introduction

Domino multi-component reactions offer a rapid access to highly functionalised complex molecules in a single procedural step [1,2]. The development of new methods for the synthesis of *N*-heterocycles with structural diversity is one of the major interests of modern synthetic organic chemists [3]. Indole fragment prevails in a variety of pharmacologically and biologically active compounds [4]. Oxindole derivatives are known to possess a variety of biological activities [5] such as (i) potent inhibition of monoamine oxidase (MAO) in human urine and rat tissues [6], (ii) inhibition of several enzymes such as acetylcholinestrease (AChE) [7] and atrial natriuretic peptide-stimulated guanylate cyclase and (iii) potent antagonist of *in vitro* receptor binding by atrial natriuretic peptide [8], besides possessing a wide range of central nervous system activities [9]. Schiff bases and Mannich bases of isatin were reported to possess antibacterial [10], antifungal [11], antiviral [12], anti-HIV [13], antiprotozoal [14], and antihelminthic [15] activities.

The derivatives of spirooxindole ring systems are useful as antimicrobial, antitumour agents and as inhibitors of the human NKI receptor, besides being found in a number of alkaloids like horsifiline, spirotryprostatin and (+)-elacomine [16]. Highly functionalised pyrrolidines constitute the main structural element of many alkaloids and pharmacologically active compounds [17].

Tuberculosis is an infection caused by *Mycobacterium tuberculosis* and is the leading cause of infectious disease mortality in the world [18]. Around 1.86 billion people, that is, 32% of the world's population is infected [19] with *M. tuberculosis* (MTB). World health organization estimates about 8 million new active cases of tuberculosis (TB) per year and nearly 2 million deaths each year [19,20], that is, 5000 people every day [21]. HIV positive patients are more susceptible to MTB with a 50-fold risk increase over HIV negative patients [22,23]. Similarly, the rate of progression of latent TB to active disease in HIV positive patients is higher than non-HIV infected individuals. It is pertinent to note that no new drug against tuberculosis has been developed in the last 30 years. Increasing incidence of MTB strains resistant to one or more first line TB drugs such as isoniazid [24], pyrazinamide [25] and rifampicin [26] has recently intensified the need to develop new and more efficient drugs for the treatment of mycobacterial

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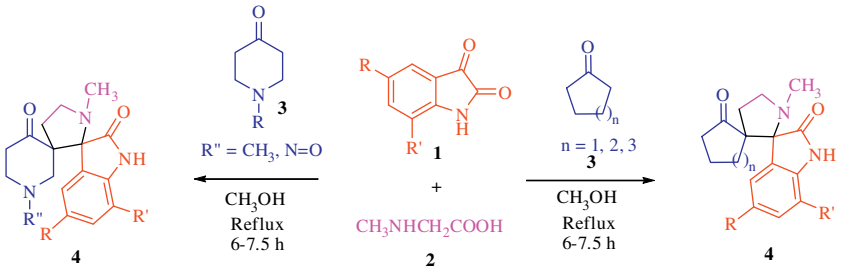
infections and this is the subject of numerous recent studies [27,28].

Recently, [29] we have communicated our preliminary results on the synthesis of dispiropyrrolidines from the novel domino reactions of isatin, sarcosine and cyclic mono ketones. This manuscript presents the results of detailed investigations on the synthetic potential of the domino protocol in the construction of (i) more dispiroheterocycles of the previously reported series [29] and (ii) novel spiroheterocycles from the reactions of isatin and cyclic mono ketones with phenylglycine. The reaction with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. The synthesized compounds were subjected to preliminary antitubercular screening against *M. tuberculosis* H37Rv (MTB) and these results are also presented in this paper.

2. Chemistry

Our previous study [29] reported the synthesis of dispiropyrrolidines **4** in moderate yields from the domino reactions of cyclic mono ketones, isatin and sarcosine in a molar ratio of 1:1:2. In the present work, this reaction has been investigated further with four more substituted isatins (Scheme 1) and amino acids, phenylglycine, proline, thiaproline and pipecolic acid. The three-component reaction of cyclic mono ketones, isatin and phenylglycine **5** in a 1:1:2 molar ratio in methanol:water (2:1) at reflux for 24 h (Scheme 2) also furnished novel dispiropyrrolidines **6** in moderate yields (32–45%) as in the case of reaction with sarcosine. After completion of the reaction (TLC), the dispiropyrrolidines **6** in pure form was obtained by column chromatographic purification.

The structure of dispiropyrrolidines **4** and **6** are in accord with their 1D and 2D NMR spectroscopic data (Figs. 1 and 2). The ^{1}H NMR spectrum of **6e** has two doublets at 4.59 and 5.37 ppm ($J = 11.3$ Hz) related by a H,H-COSY correlation assignable to H-4 and H-5 respectively. This is also supported by the HMBC correlation (Fig. 2) of the signal at 4.59 ppm with the carbonyl carbon at 207.2 ppm, besides correlating with (i) C-5 at 62.9 ppm, (ii) spiro carbon C-3 at 68.5 ppm and (iii) C-2′ at 58.9 ppm. H-4 and H-5 are *trans* to each other. The C,H-COSY correlation of H-4 assigns the



4 **3** **1** + **2** **3** **4**

Comp 3 and 4	n	R	R′	R″	Reaction time (h)	Yield of 4 (%)
a	1	H	$CH(CH_3)_2$	-	7	40
b	2	H	$CH(CH_3)_2$	-	6.5	45
c	3	H	$CH(CH_3)_2$	-	7	39
d	-	H	$CH(CH_3)_2$	CH_3	6	43
e	-	H	$CH(CH_3)_2$	N=O	10	38
f	1	CH_3	H	-	7	42
g	2	CH_3	H	-	6	40
h	3	CH_3	H	-	7.5	38
i	-	CH_3	H	CH_3	6	44
j	-	CH_3	H	N=O	10	40
k	1	Cl	H	-	7	39
l	2	Cl	H	-	7	42
m	3	Cl	H	-	6.5	38
n	-	Cl	H	CH_3	6	52
o	-	Cl	H	NO	10	40
p	1	Br	H	-	7.5	41
q	2	Br	H	-	6.5	43
r	3	Br	H	-	7	37
s	-	Br	H	CH_3	6	49
t	-	Br	H	NO	10	38

Scheme 1. Synthesis of dispiropyrrolidines.