STRUCTURAL OPTIMIZATION OF 4-(4-FLUOROPHENYL)-1,2,4-OXADIAZOL-5-YL-*N*-ACYLHYDRAZONES AS POTENTIAL ANTIPARASITIC AGENTS

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Introduction

N-Acylhydrazones (NAH) are of large interest, in special to Medicinal Chemistry, once the NAH framework is recognised as a privileged structure, associated to the biological response of those compounds bearing it [1]. One of the most impressive examples of the association between NAH and biological activity was found in our group, when a series of 1,2,4-oxadiazole-*N*-acylhydrazone derivatives was identified as potent trypanocides in non-citotoxic concentrations [2]. Based on such studies, several analogues were designed, synthesised and investigated as potential anti-*Trypanosoma cruzi* agents, leading to the identification of a new series of 1,2,4-oxadiazole-*N*-acylhydrazone hybrids with *in vivo* activity against the parasite [3]. Studies of structure-activity relationship (SAR) disclosed the 3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl-*N*-acylhydrazone derivatives as the most active against *T. cruzi*, eliciting further investigations on the structural modifications of this lead compounds. In order to carry out such modifications and evaluate the biological responses of the new compounds, a larger number of substituents was introduced at the hydrazone moiety of the original framework, so that 10 new molecules were synthesised and characterised by means of physical and spectroscopic analysis.

Methodology

All intermediates and target molecules were characterised by infrared spectroscopy (IV), using a Tensor27 spectroscope from Bruker. Hydrogen magnetic resonance (^{1}H NMR) analyses were performed at 300 and 400 MHz. Melting points (m. p.) were measured using a digital melting point apparatus and are uncorrected. The planned 3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl-*N*-acylhydrazone derivatives were obtained in four synthetic steps previously

developed at the Laboratory of Design and Synthesis Applied to Medicinal Chemistry-*SintMed*® [2]. Starting from 4-fluorobenzonitile, which is converted into 4-fluorobenzoamidoxime by refluxing with hydroxylamine hydrochloride and sodium carbonate in water/ethanol 1:1 mixture in 80% yield. The heterocycloaddition reaction performed between 4-fluorobenzoamidoxime and methyl oxalyl chloride led to the building of the intermediate bearing the 1,2,4-oxadiazole ring, whose ester group attached to its 5-position easily reacts with hydrazine hydrate at 0 °C, giving access to the key intermediate 3-(4-fluorophenyl)-1,2,4-oxadiazol-5-ylhydrazide. The condensation reaction between the hydrazide intermediate and the appropriate aldehydes was carried out in the presence of cerium(III) chloride catalyst under mild conditions, following the protocol developed at *SintMed*® [4]. The 3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl-*N*-acylhydrazone derivatives were isolated as *E*-isomers. The steroselectivity of the method is fundamental for the biological studies, once the evaluation of diastereomeric mixtures can lead to the misinterpretation of the outcomes.

Results and discussion

Previous attempts to obtain the target 1,2,4-oxadiazole-*N*-acylhydrazones in presence of sulfuric acid were made at *SintMed*®, always giving a mixture of *E/Z*-isomers [2]. So far, the $CeCl_3$-catalysed synthesis of *N*-acylhydrazones demonstrated to be efficient and stereoselective, so that 10 unpublished 1,2,4-oxadiazole-*N*-acylhydrazones **1-10** could be isolated as pure *E*-isomers in excellent yields. All compounds were fully characterised. The general data for the derivatives are given as follows, disclosing each substituent exploited.

Compound 1 (4-biphenyl): yield 92%, m. p. 241-243 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3263 (NH), 1689 (C=O), 1606 (C=C), 1532 (C=N);

Compound 2 (10-anthracenyl): yield 90%, m. p. 260-262 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3454 (NH), 1679 (C=O), 1607 (C=C), 1533 (C=N);

Compound 3 (2-naphtyl): yield 90%, m. p. 190-193 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3447 (NH), 1690 (C=O), 1609 (C=C), 1532 (C=N);

Compound 4 (3,4-dichlorophenyl): yield 88%, m. p. 218-220 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3420 (NH), 1692 (C=O), 1607 (C=C), 1547 (C=N);

Compound 5 (3-chlorophenyl): yield 89%, m. p. 180-183 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3312 (NH), 1710 (C=O), 1610 (C=C), 1566 (C=N);

Compound 6 (4-trifluoromethylphenyl): yield 94%, m. p. 216-218 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3168 (NH), 1682 (C=O), 1607 (C=C), 1544 (C=N);

Compound 7 (2-fluorophenyl): yield 96%, m. p. 188-200 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3216 (NH), 1695 (C=O), 1607 (C=C), 1569 (C=N);

Compound 8 (3-hydroxyphenyl): yield 95%, m. p. 244-247 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3500 (OH), 3312 (NH), 1686 (C=O), 1606 (C=C), 1549 (C=N);

Compound 9 (4-thiomethoxyphenyl): yield 90%, m. p. 205-207 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3250 (NH), 1688 (C=O), 1609 (C=C), 1592 (C=N);

Compound 10 (4-pyridinyl): yield 88%, m. p. 255-258 °C, IV (KBr, $\tilde{\nu}$, cm^{-1}) 3250, 3136 (NH), 1719 (C=O), 1603 (C=C), 1546 (C=N).

These compounds are now under investigation for their antiparasitic profile, while the synthesis of a new series of analogues has been planned in order to introduce a variety of representative chemical moieties, introducing elements to the SAR studies.

Conclusions

The planned synthesis of compounds **1-10** using de $CeCl_3$-catalysis is extremely efficient, leading to novel 1,3,4-oxadiaxole-*N*-acylhydrazones with potential antiparasitic activity. All described compounds are characterised, so that the further synthesis of other analogues can be easily achieved. The method's stereoselectivity is efficient based on the NMR analysis, which confirms the presence exclusively of the *E*-isomer.

Key words: 1,2,4-oxadiazole-*N*-acylhydrazones; $CeCl_3$-catalysis, trypanocidal activity; structural modification.

References

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