SYNTHESIS OF NEW 1,2,4-OXADIAZOLES-DERIVED DIPEPTIDOMIMETICS, A POTENTIAL CLASS OF ANTIINFLAMMATORY DRUGS

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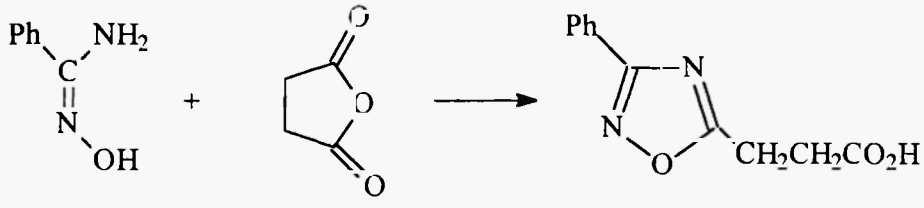
Abstract: Substituted 1,2,4-oxadiazoles containing pseudopeptide moiety as the side chain have been synthesized as part of a program of a study aiming to discover potential antiinflammatory drugs. A simple and efficient strategy for the synthesis started with Boc-protected amino acids (Phe, Asp, Val, Asp, Glu, Leu and Ile) and reactions conditions to allow the formation of dipeptidomimetics derivatives in good yields.

Introduction

1,2,4-Oxadiazoles have attracted widespread attention due to their important pharmacological properties. These include antiviral (1), fungicide (2), herbicide (3), analgesic and antiinflammatory activities (4). Some of these also exhibited pronounced β-adrenoreceptor blocking activity and moderate α-adrenoreceptor blocking properties (5). Oxadiazoles have also been used as dipeptidomimetics and their electrostatic and hydrogen bonding properties have been studied (6,7). It has been shown that therapeutically active agents with small peptides or amino acid residues reduce toxicity and enhance their therapeutic effect (8-10). Considering the potentiality of 1,2,4-oxadiazoles, we undertook the synthesis of 8a-g employing a strategy from the peptide synthesis (11). This paper reports the synthesis of six such compounds for the first time and the confirmation of their structures by spectroscopic means.

Results

1,2,4-oxadiazoles (12) are most commonly synthesized from amidoximes and acetylating agents such as carboxylic acid chlorides or anhydrides (13). In this study, benzamidoxime was obtained as previously reported (14), by reaction with hydroxylamine chloridrate and benzonitrile and was allowed to react with succinic anhydride to give 3-[3-(Aryl)-1,2,4-oxadiazol-5-yl] propionic acid 3 (15), scheme I.

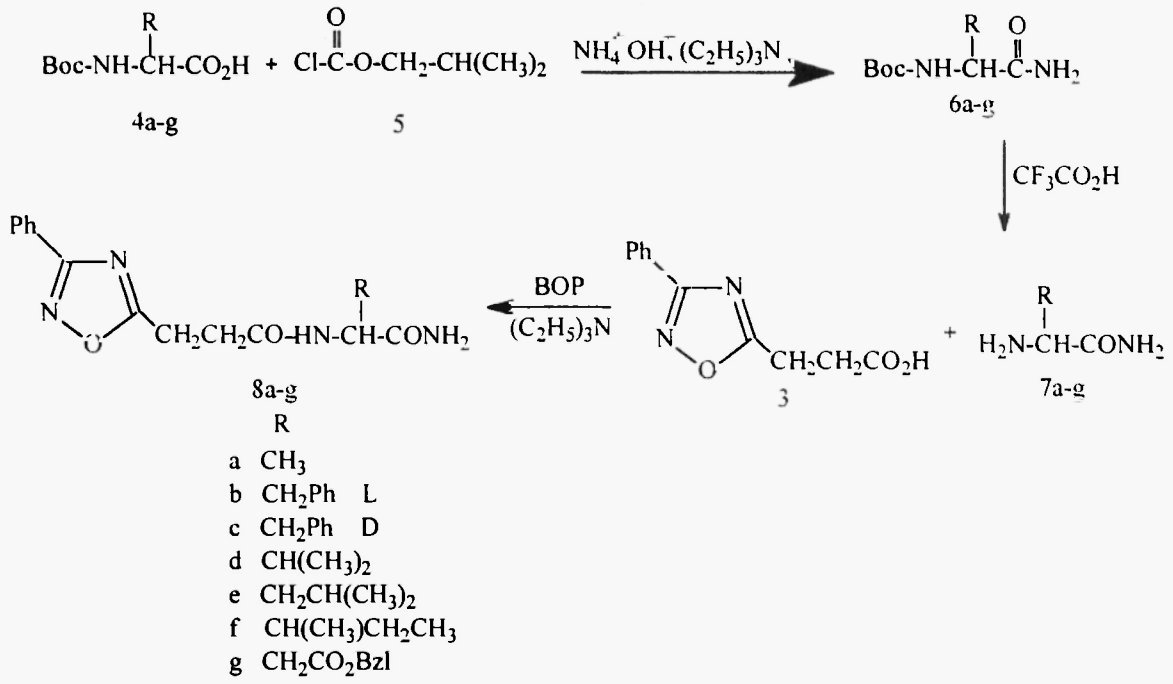


1 2 3

Scheme I

For synthesizing 1,2,4-oxadiazoles carrying a pseudopeptide chain, we firstly prepared amides 4a-g by the sequence shown in the scheme. Except from 8c (which belongs to D-series), all amino acids are of L-series. The reaction of these amino acid amides with 3 in the presence of benzotriazolyloxy-tris-(dimethylamino) phosphonium hexafluorophosphate (BOP) reagent provided 8a-g in good yields, as scheme II. 8a(55%, mp 225°C), 8b(86.3%, mp 235-7°C), 8c(99.6%, mp 235/7°C), 8d(72%, mp 181°C), 8e(90%, mp 230°C), 8f(56%, mp 101°C), 8g(66%, mp 136°C).

All compounds gave satisfactory spectrocopic data. The IR spectra showed characteristic group absorptions for NH stretch (3300 cm^{-1}), for C=O stretch, amide I band (1670 cm^{-1}), and C=N ring strectching (1573 cm^{-1}). Characteristic signals such as ^{1}H-NMR for NH_2 (δppm 7.44) and NH (δppm 8.25). Two singlets for NH_2 shown nonequivalent protons. For the NH, a characteristic duplet showed a coupling constant 8Hz with CH quiral. Different chemical shift for groups next to the chiral center are observed. The phenomenon is more pronounced with the bulky substituents.



Scheme II

Conclusions

The present work represents an efficient and facile synthesis of a novel class of pseudopeptides. The reactions producing 1,2,4-oxadiazoles having a pseudopeptide chain are versatile and can be performed starting from most of the natural amino acids. The reactions conditions used are mild for the protecting groups. We are presently employing the same procedure in the preparation of others derivatives. The 1,2,4-oxadiazoles pseudopeptides were tested in the mouse carragenan paw edema. The antiinflammatory activity of 1,2,4-oxadiazoles pseudopeptides, have shown promising preliminary results. These results will be reported in up coming.

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