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Synthesis and Characterization of Some 2,5-Substituted 1,3,4-Oxadiazoles Derivatives

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Abstract

New 1,3,4-oxadiazoles with pharmacological potential, derived from 5-nitroindazole, have been synthesized. Their chemical structure has been established by elemental and spectral analyses (FT-IR and ^{1}H-NMR).

Keywords: 1,3,4-oxadizoles, nitroindazole.

Introduction

The interest in oxadiazole derivatives is due to their numerous pharmacological applications. Literature data offer various examples of oxadiazole ring-containing compounds with biological activity, including antimalaric, local anaesthetic, insecticide, antihypertensive, anti-inflammatory, antipyretic, analgesic, anthelmintic, antibacterialor hypoglycemiant effects.

Oxadiazoles are usually synthesised from various 4-substituted acyl-thiosemicarbazides, which suffer intramolecular cyclization by treatment with tosyl chloride and pyridine, polyphosphoric acid or trimethylphosphine and triethylamine in carbon tetrachloride. Another method described in literature for oxadiazole preparation is the cyclization reaction between a hydrazide and a carboxylic acid, in the presence of phosphorus oxychloride and aluminium oxide. Considering the pharmacological potential of substituted oxadiazoleheterocycle, our research was focused on synthesizing new 1,3,4-oxadiazoles with antipyuretic activity derived from 5-nitroindazole, through a novel method, and on their encapsulation into microparticulated systems based on sodium alginate and gelatin.

Over the past 30 years, considerable interest has been manifested for the development of polymeric micro/nanoparticulated systems as efficient drug delivery matrices. The naturally occurring polymers are attractive for drug delivery, as due to their biocompatibility, biodegradability and non-toxicity. Alginate, an anionic polymer extracted from marine brown algae, is widely used in biomedical fields. Monovalent salts, often referred to as alginates, are

hydrophilic colloids. Alginate is a linear copolymer composed of 2 monomeric units, Dmannuronic acid and L-guluronic acid. Calcium alginate hydrogel matrices usually present high water permeability, the hydrosoluble drug release being rarely controlled in an efficient manner. This drawback can be overcome by mixing alginate with other polymers, such as chitosan, pectin or even gelatin.

Experimental

Materials and method

All reagents were used as purchased Sigma, Aldrich,Merk. FT-IR spectra were recorded using a FT-IR spectrophotometer (ATR) Brucker Tensor-27; ^{1}HNMR analysis was performed on a Brucker ARX 400 spectrometer (5 mm QNP probe; 1H/13C/31P/19F) and elemental analysis – on an Exeter Analytical CE 440 elemental analyser. The melting points of the obtained compounds were determined with a MelTemp melting point module, provided with a digital thermometer. Particle morphology and size were evaluated using a VEGA-3 Tescan Scanning Electron Microscope and a laser light diffractometer (SHIMADZU – SALD 7001), respectively.

Synthesis of 2-substituted 5-aryl-amino-1,3,4 oxadiazoles

General procedure

In a reaction flask provided with a refluxing cool, 0.02 mol of anhydrous sodium acetate was added to 0.005 mol5'-nitroindazole-1'-*il*-acetyl-4-Rthiosemicarbazide (I-VI) and 0.0055 mol ethyl chloroacetate, in 50 mL ethanol. The reaction mixture was maintained under reflux on a water bath for 11 h, then filtered under vacuum. The ethanol excess was removed by distillation under vacuum, until reaching a volume of 10-15 mL. The solid product formed upon cooling was filtered under vacuum and then washed several times with ethanol. The final compound was purified by repeated recrystallization from boiling ethanol.

2-[(5'-nitroindazole-1'-methyl)]-5-phenylamino1,3,4-oxadiazole

White solid; yield: 64.28% (1.08 g); melting point: 175-177 °C. Anal. calcd. for $C_{16}H_{12}N_6O_3$: 57.14% C; 3.57% H; 25% N. Found: 57.4% C; 3.76% H; 25.35% N. FT-IR (ν cm^{-1}): 2980-3408 (NH); 1586 (NO_2 asymmetrical); 1402, 1495, 1517 (substituted oxadiazole ring); 1653 (C=N); 1170 (C-O-C); 750 (substituted benzene ring). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 5.81 (s, 2H, CH_2); 7.18-7.20 (d, 2H, Ar); 7.30-7.34 (m, 3H, Ar); 7.55 (s, 1H, Ar); 8.08 (s, 1H, Ar); 8.29-8.30 (d, 1H, Ar); 8.53-8.55 (d, 1H, Ar); 8.72 (s, 1H, NH).

2-[(5'-nitroindazole-1'-methyl)]-5-(p-tolyl-amino)1,3,4-oxadiazole

White solid; yield: 72.4% (1.26 g); melting point: 169-171 °C. Anal. calcd. for $C_{17}H_{14}N_6O_3$: 58.29% C; 4% H; 24% N. Found: 58.62% C; 4.02% H; 24.41% N. FT-IR (ν cm^{-1}): 3416 (NH); 1336 (NO_2 symmetrical); 1534 (NO_2 asymmetrical); 1282 (substituted oxadiazole ring); 1623 (C=N); 1188 (C-O-C); 789, 822 (p-disubstituted benzene ring). ^{1}H-NMR

(DMSO-d_6, 400 MHz), δ (ppm): 2.26 (s, 3H, CH_3); 6.10-6.11 (s, 2H, CH_2); 7.11-7.13 (d, 2H, Ar); 7.40-7.42 (d, 2H, Ar); 8.01 (s, 1H, Ar); 8.29 (s, 1H, Ar); 8.50-8.51 (d, 1H, Ar); 8.86-8.87 (d, 1H, Ar); 10.29 (s, 1H, NH).

2-[(5'-nitroindazole-1'-methyl)]-5-(p-methoxyphenylamino)-1,3,4-oxadiazole

White solid; yield: 66.66% (1.22 g); melting point: 139-141 °C. Anal. calcd. for $C_{17}H_{14}N_6O_4$: 55.74% C; 3.82% H; 22.95% N. Found: 56.03% C; 4.01% H; 23.26% N. FT-IR (ν cm^{-1}): 3396 (NH); 1332 (NO_2 symmetrical); 1513 (NO_2 asymmetrical); 1299, 1405 (substituted oxadiazole ring); 1659 (C=N); 1175 (C-OC); 782, 812 (p-disubstituted benzene ring). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 3.70 (s, 3H, CH_3); 6.10 (s, 2H, CH_2); 6.88-6.92 (d, 2H, Ar); 7.43-7.48 (d, 1H, Ar); 8.02-8.05 (d, 1H, Ar); 8.30-8.33 (d, 1H, Ar); 8.47 (s, 1H, Ar); 8.98 (s, 1H, Ar); 10.19 (s, 1H, NH).

2-[(5'-nitroindazole-1'-methyl)]-5-(p-bromophenylamino)-1,3,4-oxadiazole

White solid; yield: 62.31% (1.29 g); meltingpt:

173-175 °C. Anal. calcd. for $C_{16}H_{11}BrN_6O_3$: 46.27% C; 2.65% H; 19.28% Br; 20.24% N. Found: 46.58% C; 2.87% H; 19.67% Br; 20.65% N. FT-IR (ν cm^{-1}): 2947, 3097 (NH); 1397 (NO_2 symmetrical); 1535 (NO_2 asymmetrical); 1136 (substituted oxadiazole ring); 1602 (C=N); 1182 (C-O-C); 898, 948 (p-disubstituted benzene ring); 748, 789 (C-Br). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 6.11 (s, 2H, CH_2); 7.43-7.47 (d, 2H, Ar); 7.53-7.55 (d, 2H, Ar); 8.01 (d, 1H, Ar); 8.49 (d, 1H, Ar); 8.85-8.86 (s, 1H, Ar); 10.59 (s, 1H, NH).

2-[(5'-nitroindazole-1'-methyl)]-5-(p-chlorophenylamino)-1,3,4-oxadiazole

White solid; yield: 62.70% (1.16 g); melting point: 181-183 °C. Anal. calcd. for $C_{16}H_{11}ClN_6O_3$: 51.75% C; 2.96% H; 9.56% Cl; 22.65% N. Found: 51.98% C; 3.32% H; 9.97% Cl; 23.05% N. FT-IR (ν cm^{-1}): 3200 (NH); 1370 (NO_2 symmetrical); 1591 (NO_2 asymmetrical); 1293 (substituted oxadiazole ring); 1625 (C=N); 1180 (C-O-C); 854, 934 (p-disubstituted benzene ring); 766 (C-Cl). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 6.11-6.13 (s, 2H, CH_2); 7.33-7.37 (d, 2H, Ar); 7.56-7.59 (d, 2H, Ar); 8.01-8.03 (d, 1H, Ar); 8.27-8.29 (d, 1H, Ar); 8.86 (s, 1H, Ar); 9.02 (s, 1H, Ar); 10.49 (s, 1H, NH).

2-[(5'-nitroindazole-1'-methyl)]-5-(p-iodophenylamino)-1,3,4-oxadiazole

White solid; yield: 68.39% (1.58 g); meltingpt:

177-179 °C. Anal. calcd. for $C_{16}H_{11}IN_6O_3$: 41.56% C; 2.38% H; 27.49% I; 18.18% N. Found: 41.83% C; 2.69% H; 27.88% I; 18.43% N. FT-IR (ν cm^{-1}): 3327 (NH); 1357 (NO_2 symmetrical); 1536 (NO_2 asymmetrical); 1272 (substituted oxadiazole ring); 1608 (C=N); 1183 (C-O-C); 869, 912 (p-disubstituted benzene ring); 7682 (C-I). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ (ppm): 6.12 (s, 2H, CH_2); 7.41-7.43 (d, 2H, Ar); 7.63-7.65 (d, 2H, Ar); 8.02 (d, 1H, Ar); 8.29 (d, 1H, Ar); 8.48 (s, 1H, Ar); 8.81 (s, 1H, Ar); 9.02 (s, 1H, Ar); 10.61-10.63 (d, 1H, NH).

Results and Discussion

1,3,4-oxadizoles synthesis and characterization

In the present work, oxadiazoles were synthesized by a novel method, using as starting compounds some 4-substituted acylthiosemicarbazides obtained by the addition of 5nitroindazole N-acetyl-hydrazide to various aromatic isothiocyanates.[22]

The substituted acyl-thiosemicarbazides underwent intramolecular cyclization by treatment, under heating, with ethyl bromoacetate (chloroacetate), in an ethanol solution and anhydrous sodium acetate, 2,5-disubstituted oxadiazoles (VII-XII) thus resulting.

The mechanism of cyclization probably implies, in the first step, the formation of a thioester of the thiosemicarbazidetautomeric form, which, by the nucleophilic attackof thehydroxyl oxygenon the carbon bonded to the thioester residue, followed by the elimination of ethyl mercaptoacetate, forms 2,5-disubstituted oxadiazoles.

The newly synthesized oxadiazole derivatives (VII-XII), obtained with a yield of 62-72%, are crystalline compounds, purified from ethanol, with fixed melting points. Their chemical structure was confirmed by spectral (FT-IR and ^{1}H-NMR) and elemental analyses.The main modification in the FT-IR spectra of oxadiazoles, compared to those of the corresponding thiosemicarbazides, was the appearance of a new absorption band at 1170-1188 cm^{-1},corresponding to the newly formed C-O-C bonds from the oxadiazoleheterocycle; also, the intense absorption bands at 1234-1292 cm^{-1}, specific to the C=S valence vibration in the thiourea function, no longer appeared in the spectra of oxadiazoles. Moreover, medium intense absorption bands, characteristic of C=N bond vibrations (in the 1,3,4-oxadiazole ring) and intense bands specific to N-H bond vibrations (position 5 in the oxadiazole structure) were recorded at 1602-1659 cm^{-1} and around 3300 cm^{-1}, respectively. In the FT-IR spectra of oxadiazoles (X-XII), absorption peaks specific to C-Br, C-Cl and C-I bond vibrations were registered at 748-789 cm^{-1}.

^{1}H-NMR spectra completed the analysis of the proposed chemical structures. Thus, the aromatic protons presented signals at δ = 7.11-9.02 ppm for all oxadiazoles; CH_2 protons (1' position in the indazole ring) and the NH proton could be detected as singlets at 5.81-6.13 ppm and 10.1910.63 ppm, respectively. Also, methyl protons from oxadiazolessignals as singlets at 2.26 ppm and 5.70 ppm, respectively.

Conclusions

Six new 1,3,4-oxadiazoles derived from nitroindazole were synthesized by a novel method of cyclization of some 4-substituted thiosemicarbazides. The chemical structure of the newly synthesized oxadiazoles was established by elemental and spectral analyses (FT-IR and ^{1}H-MNR).

Oxadiazoles as well as the polymeric particles encapsulating the oxadiazole, presented low acute toxicity, within admissible limits for laboratory screening. The antipyretic activity of oxadiazole, either in a free form or encapsulated into microcapsules, studied comparatively

with that of reference drugs, was remarkable against sodium nucleinateinduced pyrexia, similar to that of acetylsalicylic acid. The obtained data contribute to introducing new compounds with antipyretic activity into human clinical research.

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