Synthesis of new derivatives of aryl-clonazepam via Suzuki Cross-coupling reaction

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ABSTRACT

A new series of aryl clonazepam derivatives (11-16) have been synthesized by employing Suzuki Cross-coupling reaction, which includes the reaction of clonazepam with suitable derivative boronic acid at the presence of Pd(PPh3)4 as catalyst, and Na2CO3 as a base. The structures of the newly synthesized compounds were assigned by 1H, 13C and 2D NMR spectroscopic techniques.

1. Introduction

Benzodiazepine (BDZs) derivatives are considered the most important sedatives and hypnotic drugs due to their high therapeutic index number. On the other hand, BDZs have minor side effects on cardiovascular and respiratory systems due to the fact that there is no interaction between the drug and liver microsomal enzyme. All compounds of this group increase onset of sleep and hence increase total sleeping time [1-3].

Benzodiazepine, if taken in low dose, produce relaxation mode with no evident effect on patients’ physical activities. The drugs are divided into two groups based on their half-life: long term benzoazepines such as diazepam, flurazepam, and short term loraedepam, oxazepam [4,5]. Mechanism of action act on mide-brain ascending reticular formation and limbic system. This chemical reaction stimulates gamma-aminobutyric acid (GABA) ergic neurotransmission, which activates of GABA receptors which in turn leads to Cl ionophore complex and increases the opening of the Cl channel, Therefore the increase of Cl conduction will lead to decrease activation region of central nervous system [6,7]. Clonazepam is considered one of long acting benzodiazepine drugs [8]. The seven amino ring (Diazepin ring) is vital for its biding with BDZs site [9]. The lipophilic properties of BDZs play an important role in metabolism, so reach to brain through pass blood brain barrier and high interact with receptor. There are many side effects to the drug, most important of all, is addiction to the drug which occurs over a long term used, as well as deformation of the foetus in pregnant women [10]. Clonazepam is usually prescribed as control drug to acute cases of epilepsy and it is very effective in controlling non-convulsive cases of epilepticus [11]. The following drugs: erythromycin, clarithromycin, ritonavir, iraconazole, ketoconazole, nefazodone, and grapefruit juice are inhibitors of CYP3A4, an enzyme that is responsible of metabolism of the BDZs in the liver, which rise the half-life and toxicity [12].

Researchers have given immense attention to studies of benzodiazepine derivatives for its property of medical and biological activities, some of which have been used as antitumor drugs [13], antagonists of schistosomical [14], anti-HIV [15], antagonists for the Bradykinin [16], arrhythmics agents [17], cholecystokinin receptor agonists [18], and antimalaria [19]. Recent studies have shown that some BDZs compounds have been synthesized and the results have presented the important role of the drugs as therapeutic drugs used specifically as anti-hepatitis B virus [20]. Andew et al. [21] have prepared compound 1 (Figure 1) using Suzuki coupling reaction under standard aqueous conditions and conceded it a new method to prepared 1,4-benzodiazepines.
2003, Nadin et al. [23] synthesized BDZs compound 2 (Figure 1) via Suzuki coupling reaction as a vital tag for synthesis of the active compound 3 (Figure 1) as α-secretase inhibitor for the handling of case of Alzheimer. In continuation of our program on the synthesis of BDZs derivatives, we investigated the synthesis of new derivatives of arylclonazepam via Suzuki Cross-coupling reaction [23,24].

Figure 1. Some benzodiazepine derivatives.

2. Experimental

2.1. Instrumentation

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). NMR data were obtained on 400 and 600 MHz (1H) and 150.91 MHz (13C) spectrometers (Avance III, Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by 1H, 13C HSQC and HMBC and 1H, 13C HMBC NMR experiments. Micro-analytical data were obtained with a Vario Elementar analyser (Shimidzu, Japan). Analytical silica gel TLC plates 60F254 were purchased from Merck. All reagents were obtained from commercial suppliers and were used without further purification [25].

2.2. General procedure for the synthesis of the biaryl derivatives of clonazepam via Suzuki Cross-coupling reaction (11-16)

To a solution of clonazepam (4) (60 mg, 0.20 mmol) in mixture of chloroform (10 mL) with MeOH (5 mL), aryl boriconic (0.2 mmol) was added, then the mixture was stirred for 15 min at suitable temperature then adding Pd(OH)(PPh3)4 (100 mg, 0.5 mmol) and aqueous solution of 2 M sodium carbonate (5 mL). The mixture was heated under reflux for 12-14 h. After cooling phase, water (5 mL) was added and the mixture was partitioned with ethyl acetate (3 × 10 mL) and the combined organic extracts which were washed with aqueous solution of 5% Na2CO3 (3 × 10 mL) and dried with sodium sulphate and then evaporated in vacuum. The residue was then filtered on a short SiO2 column using hexane:ethyl acetate (3:2, v:v) as eluent to get the desired product [26] (Scheme 1).

5-[(4'-Methylthio)-1,1'-biphenyl-2-yl]-7-nitro-3H-benzo[e][1,4]diazepin-2-ol (13): From 4-methylthiophenyl boronic acid (90 mg). Yield: 39 mg (65%) as a dark brown powder. M.p.: 246-248 °C. Rf: 0.54. 1H NMR (600 MHz, DMSO-d6, δ ppm): 1.80-1.27 (m, 9H, SiMe3), 7.08 (br s, 1H, Harom-6'), 7.21-7.65 (m, 9H, Harom-5'), 7.74-7.75 (d, 1H, J = 7.8 Hz, Harom-3'), 7.57-7.75 (dd, 1H, J = 7.8 Hz, Harom-2'), 8.03 (br s, 1H, Harom-8), 13 C NMR (150.91 MHz, DMSO-d6, δ ppm): 49.8 (C-3), 112.7 (C arom-1'), 134.7 (C arom-2', 135.1 (C arom-3a), 140.1 (C arom-1'+C arom-1'), 148.5 (C arom-9a), 156.8 (C arom-7), 162.8 (C-2'), 168.3 (C-5). Anal. calc. for C27H24N2O4: C, 69.10; H, 3.69; N, 11.19. Found: C, 66.95; H, 3.59; N, 10.98%.

7-Nitro-5-(4'-trimethylsilyl-biphenyl-2-yl)-3H-benzo[e][1,4]diazepin-2-ol (14): Form 4-(trimethylsilyl)phenylboronic acid (90 mg). Yield: 39 mg (65%) as a dark brown powder. M.p.: 246-248 °C. Rf: 0.54. 1H NMR (600 MHz, DMSO-d6, δ ppm): 1.80-1.27 (m, 9H, SiMe3), 7.08 (br s, 1H, Harom-6'), 7.21-7.65 (m, 9H, Harom-5'), 7.74-7.75 (d, 1H, J = 7.8 Hz, Harom-3'), 7.57-7.75 (dd, 1H, J = 7.8 Hz, Harom-2'), 8.03 (br s, 1H, Harom-8), 13 C NMR (150.91 MHz, DMSO-d6, δ ppm): 49.8 (C-3), 114.9 (C arom-3'), 126.8 (C arom-3'+C arom-5'), 127.9 (C arom-5'), 129.9 (C arom-5'), 130.8 (C arom-2'), 131.9 (C arom-2'), 132.6 (C arom-1'), 135.3 (C arom-5a), 131.0 (C arom-1'+C arom-1'), 148.5 (C arom-9a), 156.8 (C arom-7), 162.8 (C-2'), 168.3 (C-5). Anal. calc. for C27H24N2O4SiC: C, 67.70; H, 3.76; N, 11.19. Found: C, 66.95; H, 3.59; N, 9.52%.

5-(3'-Dimethoxy-1,1'-biphenyl-2-yl)-7-nitro-3H-benzo[e][1,4]diazepin-2-ol (15): Form 3,4-dimethoxyphenylboronic acid (80 mg). Yield: 38 mg (65%) as a brown red powder. M.p.: 241-243 °C. Rf: 0.54. 1H NMR (600 MHz, DMSO-d6, δ ppm): 3.78 (d, 3H, OMe), 3.84 (d, 3H, OMe), 6.99-7.01 (m, 2H, Harom-5'), 7.14-7.16 (dd, 1H, J = 7.8 Hz, Harom-2'), 7.17 (d, 1H, J = 1.8 Hz, Harom-3'), 7.35-7.36 (m, 1H, Harom-6'), 7.41-7.44 (m, 4H, Harom-5'+H(3)(CH) + Harom-6'), 7.54-7.56 (dd, 1H, J = 1.8 Hz, Harom-5'), 7.61-7.63 (m, 1H, Harom-4'), 7.81-7.82 (d, 1H, J = 1.8 Hz, Harom-3'), 7.87 (br s, 1H, Harom-8), 13 C NMR (152.01 MHz, DMSO-d6, δ ppm): 50.7 (C-3'), 56.1 (2×OMe), 61.4 (C arom-5'), 112.2 (C arom-2'), 119.0 (C arom-3'), 127.7 (C arom-6'), 129.8 (C arom-9a), 131.9 (C arom-4'), 135.3 (C arom-5a), 141.1 (C arom-1'+C arom-1'), 148.5 (C arom-9a), 149.4 (C arom-7'), 151.0 (C arom-3'), 156.8 (C arom-9a), 162.8 (C-2'), 168.3 (C-5). Anal. calc. for C27H24N2O6SiC: C, 66.18; H, 4.59; N, 10.07. Found: C, 66.98; H, 3.67; N, 10.89%.
2′-(2-Hydroxy-7-nitro-3H-benzo[e][1, 4]diazepin-5-yl)-5-nitro-[1,1′-biphenyl]-3-carboxylic acid (16): From 3-nitro-5-nitrophenylboronic acid (90 mg). Yield: 39 mg (65%) as a brown powder. Mp: 258-260 °C. Rf: 0.55. 1H NMR (600 MHz, DMSO-d6, δ, ppm): 6.30 (s, 1H, NH), 6.62-6.64 (m, 3H, H_arom-3′+H_arom-4′+H_arom-5′), 6.99-7.00 (d, 1H, J = 7.8, Hz, H_arom-6), 7.41-7.43 (m, 3H, H-3(CH3)+H_arom-9), 7.60-7.63 (m, 2H, H_arom-6+H_arom-8), 8.51 (s, 1H, H_arom-4b), 8.61 (s, 1H, H_arom-6b), 8.66-8.67 (s, 1H, H_arom-2b). 12.26 (s, 1H, CO2H). 13C NMR (150.91 MHz, DMSO-d6, δ, ppm): 49.8 (C-3), 120.1 (C_arom-3′), 120.8 (C_arom-4′), 127.6 (C_arom-9), 128.3 (C_arom-6), 129.0 (C_arom-5′), 129.3 (C_arom-8), 130.03 (C_arom-6′), 131.1 (C_arom-6′), 133.4 (C_arom-2′+C_arom-3′), 134.2 (C_arom-4′), 134.5 (C_arom-5′a), 141.0 (C_arom-1′+C_arom-1′a), 147.5 (C_arom-7), 148.2 (C_arom-3′), 155.4 (C_arom-9a), 161.6 (C-2′), 168.1 (C-5′), 169.5 (CO2H). Anal. calcd. for C22H14N4O7: C, 59.20; H, 3.16; N, 12.55. Found: C, 58.98; H, 3.01; N, 12.31%.

3. Results and discussion

Suzuki Cross-coupling reaction [24] has been used in the preparation of new clonazepam analogues. Thus, treatment of clonazepam (4) with the appropriate arylboronic acids (e.g.: 4-methylsulfinylphenyl, 3-cyanophenyl, 4-hlorophenyl, 4-tri methylsilylphenyl-, 3,4-dimethoxyphenyl-, 5-nitro-3-carboxyphenyl boronic acid (5-10) using palladium(0) tetrakis-triphenylphosphine (Pd(0)(Ph3P)4) and sodium bicarbonate as catalyst in mix chloroform with MeOH as solvent afforded compounds 11-16 in 55-67% (Scheme 1).

The structure of compounds 11-16 were assigned on the basis of their 1H and 13C NMR which showed similar patterns of aliphatic protons and carbon atoms. The 1H NMR spectra of compound 11-16 were characterized by the presence of additional aromatic protons and carbon atoms, indicative for arylation of clonazepam backbone. The aromatic proton appeared at the region δ 6.62-8.67 ppm, the diazepine ring protons (CH2) appeared at δ 7.32-7.56 ppm, the other aliphatic protons and substituents have been fully identified (c.f. Experimental part). The compounds 11-16 contain tautomerism in amide bond so that appeared signal OH in compounds 11-15, while signal NH in compound 16. Regarding the 1H NMR to see the OH and NH, in general, the 1H NMR spectra of some compounds do not show the OH and NH, either they appeared under the other signals or due to the use of DMSO-d6 as a solvent.

In the 13C NMR spectra of compound 11-16, the aromatic carbon atoms appeared at δ 110.9-156.9 ppm, the diazepine ring carbon atoms at δ 49.42-50.96 ppm to C-3, at δ 161.6-162.8 ppm to C-2, at δ 168.1-168.3 ppm to C-5. The other aliphatic carbon atoms and substituents have been fully analysed (c.f. Experimental part). However, compound 11 has been selected for further NMR experiments [27-29]. The HSQC NMR spectrum [30] of compound 11 showed J_C,H correlations between H_arom-3′ together with H_arom-4′ at the region δ 7.61-7.63 ppm and C-3′ at δ 124.9 ppm as well as C-4′ at δ 132.4 ppm. Furthermore, a correlation between H_arom-6′ at δ 7.00 ppm and C-6′ at δ 132.0 ppm is observed. In addition, a correlation between H-6 at δ 7.42-7.44 ppm and C-6 at the region δ 129.2-129.7 ppm is witnessed (Figure 2).

In the gradient-selected HMB spectrum [30] of compound 11, C-9a of the diazepine ring at δ 156.8 ppm showed a J_C,H coupling with H-8 of the same ring at δ 7.98 ppm. A J_C,H coupling between C_arom-2′ at δ 131.9-132.0 ppm and H_arom-6′ at δ 7.62 ppm was observed. Another J_C,H coupling was shown between C_arom-1′a at δ 141.1 ppm and H_arom-3′ at δ 7.62 ppm. The spectrum showed a J_C,H coupling between C_arom-1′ at δ 141.1 ppm and H_arom-6′ at δ 131.9-132.0 ppm well (Figure 3).

4. Conclusion

In conclusion, a new series of biaryl derivatives of aryl clonazepam by applying Suzuki Cross-coupling reaction has
been described. All the compounds were assigned by their NMR spectra. The aim of synthesis of such compounds is to
evaluate their antiviral and antitumor activity, which is in
progress, since there is a lack in study of the potency of the
related analogues of diazepine drugs.

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References