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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 $Pd(PPh_3)_4$ as catalyst, and Na_2CO_3 as a base. The structures of the newly synthesized compounds were assigned by ^1H, ^{13}C and 2D NMR spectroscopic techniques.

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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 benzodiazepines such as diazepam, flurazepam, and short term lorazepam, oxazepam [4,5]. Mechanism of action act on mide-brain ascending reticular formation and limbic system. This chemical reaction stimulates gamma-amino-butyric 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, itraconazole, 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 schistosomicidal [14], anti-HIV [15], antagonists for the Bradykinin [16], anti-arrhythmic 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]. Anderw *et al.* [21] have prepared compound **1** (Figure 1) using Suzuki coupling reaction under standard aqueous conditions and conceder it a new method to prepared 1,4-benzodiazepines. In

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2003, Nadin *et al.* [22] synthesized BDZs compound **2** (Figure 1) via Suzuki coupling reaction as a vital stage for synthesis of the active compound **3** (Figure 1) as γ-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 arylclonazepm via Suzuki Cross-coupling reaction [23,24].

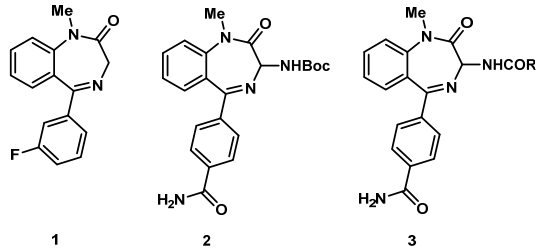


Figure 1. Some benzodiazepine derivatives.

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 (^{1}H) and 150.91 MHz (^{13}C) spectrometers (Avance III, Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Heteronuclear assignments were verified by ^{1}H, ^{13}C HMBC and ^{1}H, ^{13}C HSQC NMR experiments. Micro-analytical data were obtained with a Vario, Elemental analyzer (Shimadzu, Japan). Analytical silica gel TLC plates 60F_{254} 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 boronic acid (0.2 mmol) was added, then the mixture was stirred for 15 min at suitable temperature then adding Pd(0)(PPh_3)$_4$ (100 mg, 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% Na_2CO_3 (3 × 10 mL), and dried with sodium sulfate and then evaporated in vacuum. The residue was then filtered on a short SiO_2 column using hexane: ethyl acetate (3:2, *v*:*v*) as eluent to get the desired product [26] (Scheme 1).

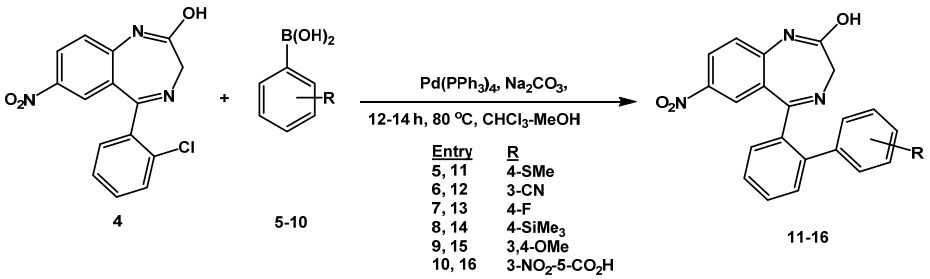
5-(4'-(Methylthio)-[1,1'-biphenyl]-2-yl)-7-nitro-3H-benzo[e][1,4]diazepin-2-ol (**11**): From 4-methylthiophenyl boronic acid (80 mg). Yield: 40 mg (67%) as a light brown powder. M.p.: 248-250 °C. R_f : 0.58. ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 2.38 (s, 3H, SMe), 7.00 (br s., 1H, $H_{arom.}$-6'), 7.43 (m, 4H, $H_{arom.}$-5' + H-3(CH_2)+ $H_{arom.}$-6), 7.56 (m, 3H, $H_{arom.}$-9 + $H_{arom.}$-3" + $H_{arom.}$-5''), 7.62 (m, 4 H, $H_{arom.}$-2" + $H_{arom.}$-6"+$H_{arom.}$-4' + $H_{arom.}$-3'), 7.98 (d, 1H, $J_{8,9}$ = 8.6 Hz, $H_{arom.}$-8). ^{13}C NMR (150.91 MHz, DMSO-d_6, δ, ppm): 15.2 (SMe), 49.7 (C-3), 124.9 ($C_{arom.}$-3'), 126.9 ($C_{arom.}$-9), 127.2 ($C_{arom.}$-2" + $C_{arom.}$-6"), 127.7 ($C_{arom.}$-3'' + $C_{arom.}$-5"), 129.2-129.7 ($C_{arom.}$-6+$C_{arom.}$-5'+$C_{arom.}$-8), 131.9-132.0 ($C_{arom.}$-2'+ $C_{arom.}$-6'), 132.5 ($C_{arom.}$-4'), 135.3 ($C_{arom.}$-5a), 137. 8 ($C_{arom.}$-4"), 141.1 ($C_{arom.}$-1' + $C_{arom.}$-1"), 147.8 ($C_{arom.}$-7), 156.8 ($C_{arom.}$-9a), 162.8 (C-2), 167.65 (C-5). Anal. calcd. for $C_{22}H_{17}N_3O_3S$: C, 65.49; H, 4.25; N, 10.42. Found: C, 65.22; H, 4.11; N, 10.20%.

2'-(2-Hydroxy-7-nitro-3H-benzo[e][1, 4]diazepin-5-yl)-biphenyl-3-carbonitrile (**12**): From 4-cyanophenylboronic acid (80 mg). Yield: 35 mg (58 %) as a dark brown powder. M.p.: 264-266 °C. R_f: 50. ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.00 (br s, 1H, $H_{arom.}$-6'), 7.33-7.56 (m, 4H, $Ha_{rom.}$-3' + H-3(CH_2) + $H_{arom.}$-6), 7.62-7.64 (m, 3H, $H_{arom.}$-9 + $H_{arom.}$-4'+$H_{arom.}$-5'), 7.70-7.73 (m, 1H, *J* = 7.8 Hz, $H_{arom.}$-5''), 7.86-7.91 (d, 1H, *J* = 7.8 Hz, $H_{arom.}$-6''), 8.07-8.14 (m, 1H, $H_{arom.}$-8), 8.30 (br s, 1H, $H_{arom.}$-2"), 8.43 (br s, 1H, $H_{arom.}$-4"). ^{13} C NMR (150.91 MHz, DMSO-d_6, δ, ppm): 49.8 (C-3), 112.7 (CN), 119.1 ($C_{arom.}$-3"), 121.2 ($C_{arom.}$-3'), 129.1 ($C_{arom.}$-9), 129.2 ($C_{arom.}$-6), 129.3 ($C_{arom.}$-5"), 129.6 ($C_{arom.}$-5' + $C_{arom.}$-8), 129.8 ($C_{arom.}$-2"), 130.8 ($C_{arom.}$-6'), 131.9 ($C_{arom.}$-4"), 132.2 ($C_{arom.}$-6"), 132.4 ($C_{arom.}$-4'), 132.5 ($Ca_{rom.}$-2'), 135.3 ($C_{arom.}$-5a), 141.1 ($C_{arom.}$-1' + $C_{arom.}$-1"), 148.5 ($C_{arom.}$-9a), 156.8 ($C_{arom.}$-7), 162.8 (C-2), 168.1 (C-5). Anal. calcd. for $C_{22}H_{14}N_4O_3$: C, 69.10; H, 3.69; N, 14.65. Found: C, 68.82; H, 3.54; N, 14.41%.

5-(4'-Fluoro-biphenyl-2-yl)-7-nitro-3H-benzo[e][1, 4] diaze pin-2-ol (**13**): From 4-fluorophenylboronic acid (80 mg). Yield: 33 mg (55%) as a dark brown powder. M.p.: 261-263 °C. R_f: 0.67. ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 6.52 (br s, 1H, OH), 7.00 (br s, 1H, $H_{arom.}$-6'), 7.12-7.14 (dd, 1H, *J* = 7.9,1.8 Hz, $H_{arom.}$-3'), 7.32-7.45 (m, 7H, $H_{arom.}$-2" + $H_{arom.}$-6" + $H_{arom.}$-3" + $H_{arom.}$-5" + H-3(CH_2)+$H_{arom.}$-6), 7.55-7.65 (m, 3H, $H_{arom.}$-9 + $H_{arom.}$-4', $H_{arom.}$-5'), 8.09 (br s, 1H, $H_{arom.}$-8). ^{13} C NMR (150.91 MHz, DMSO-d_6, δ, ppm):49.5 (C-3), 114.6-114.8 ($C_{arom.}$-3"+$C_{arom.}$-5"), 122.2 ($C_{arom.}$-3'), 127.7 ($C_{arom.}$-9), 129.19-129.76 ($C_{arom.}$-6 + $C_{arom.}$-5'+$C_{arom.}$-8), 130.8 ($C_{arom.}$-2" + $C_{arom.}$-6"), 131.9-132.0 ($C_{arom.}$-6'+ $C_{arom.}$-2'), 132.6 ($C_{arom.}$-4'), 135.3 ($C_{arom.}$-5a), 141.04 ($C_{arom.}$-1'+$C_{arom.}$-1"), 147.0 ($C_{arom.}$-7), 156.8 ($C_{arom.}$-9a), 159.0-161.2 ($C_{arom.}$-4"), 162.81 (C-2), 168.3 (C-5). Anal. calcd. for $C_{22}H_{14}FN_3O_3$: C, 67.20; H, 3.76; N, 11.19. Found: C, 66.95; H, 3.59; N, 10.98%.

7-Nitro-5-(4'-trimethylsilanyl-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. R_f: 0.54. ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 0.18-0.27 (m, 9H, $SiMe_3$), 7.00 (br s, 1H, $H_{arom.}$-6'), 7.31-7.35 (dd, 1H, *J* = 7.8, 1.9 Hz, $H_{arom.}$-6"), 7.41-7.44 (m, 4H, $H_{arom.}$-5' + H-3(CH_2) +$H_{arom.}$-6), 7.47-7.48 (d, 1H, *J* = 7.8 Hz, $H_{arom.}$-3"), 7.54-7.57 (dd, 1H, *J*= 8.1, 1.8 Hz, $H_{arom.}$-9), 7.60-7.65 (m, 3H, $H_{arom.}$-4' + $H_{arom.}$-3' + $H_{arom.}$-5"), 7.75-7.77 (d, 1H, *J* = 7.8 Hz, $H_{arom.}$-2"), 8.03 (br s, 1H, $H_{arom.}$-8). ^{13} C NMR (150.91 MHz, DMSO-d_6, δ, ppm): 0.45 ($SiMe_3$), 49.4 (C-3), 119.0 ($C_{arom.}$-3') 126.8 ($C_{arom.}$-3" + $C_{arom.}$-5"), 127.9 ($C_{arom.}$-2"+$C_{arom.}$-6"), 129.4-129.9 ($C_{arom.}$-9 + $C_{arom.}$-6 + $C_{arom.}$-5'+$C_{arom.}$-8), 130.9 ($C_{arom.}$-6'), 132.2 ($C_{arom.}$-4'), 132.7 ($C_{arom.}$-2'), 135.7 ($C_{arom.}$-5a), 141.3 ($C_{arom.}$-4"), 142.4 ($C_{arom.}$-1' + $C_{arom.}$-1"), 148.5 ($C_{arom.}$-7), 156.9 ($C_{arom.}$-9a), 162.7 (C-2), 168.3 (C-5). Anal. calcd. for $C_{24}H_{23}N_3O_3Si$: C, 67.11; H, 5.40; N, 9.78. Found: C, 66.90; H, 5.38; N, 9.52%.

5-(3',4'-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 (63%) as a brown red powder. M.p.: 241-243 °C. R_f : 0.54. ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 3.78 (d, 3H, OMe), 3.84 (d, 3H, OMe), 6.99-7.01 (m, 2H, $H_{arom.}$-2"+$H_{arom.}$-6'), 7.14-7.16 (dd, 1H, *J*= 7.8, 1.8 Hz, $H_{arom.}$-3'), 7.17 (d, 1H, *J* = 1.8 Hz, $H_{arom.}$-5"), 7.35-7.36 (m, 1H, $H_{arom.}$-6"), 7.41-7.44 (m, 4H, $H_{arom.}$-5'+H-3(CH_2)+$H_{arom.}$-6), 7.54-7.56 (dd, 1H, $H_{arom.}$-9), 7.61-7.63 (m, 1H, $H_{arom.}$-4'), 7.87 (br s, 1H, $H_{arom.}$-8). ^{13}C NMR (150.91 MHz, DMSO-d_6, δ, ppm): 50.7 (C-3), 56.1 (2×OMe), 110.9 ($C_{arom.}$-5"), 112.7 ($C_{arom.}$-2"), 119.0 ($C_{arom.}$-3'), 127.7 ($C_{arom.}$-6"), 127.2 ($C_{arom.}$-9), 129.2 ($C_{arom.}$-6), 129.6 ($C_{arom.}$-5'), 129.8 ($C_{arom.}$-8'), 130.8 ($C_{arom.}$-6'), 131.9 ($C_{arom.}$-4'), 131.9 ($C_{arom.}$-2'), 135.3 ($C_{arom.}$-5a), 141.1 ($C_{arom.}$-1'+$C_{arom.}$-1"), 148.5 ($C_{arom.}$-7), 149.4 ($C_{arom.}$-4"), 151.0 ($C_{arom.}$-3"), 156.8 ($C_{arom.}$-9a), 162.8 (C-2), 168.3 (C-5). Anal. calcd. for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07. Found: C, 66.98; H, 3.67; N, 10.89%.



Scheme 1

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. M.p.: 258-260 °C. R_f : 0.55. ^{1}H NMR (600 MHz, DMSO-d_6, 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(CH_2) + $H_{arom.}$-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, CO_2H). ^{13}C NMR (150.91 MHz, DMSO-d_6, 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'), 133.44 ($C_{arom.}$-2'+$C_{arom.}$-3"), 134.2 ($C_{arom.}$-4'), 134.5 ($C_{arom.}$-5a), 141.0 ($C_{arom.}$-1'+$C_{arom.}$-1"), 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 (CO_2H). Anal. calcd. for $C_{22}H_{14}N_4O_7$: 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-methylsulfanylphenyl-, 3-cyanophenyl-, 4-fluorophenyl-, 4-trimethylsilylphenyl-, 3,4-dimethoxyphenyl-, 5-nitro-3-carboxyphenyl boronic acid (**5-10**) using palladium(0) *tetrakis*-triphenylphosphine (Pd(0)(Ph_3P)$_4$) and sodium bicarbonate as catalyst in mix chloroform with MeOH as solvent afforded compound **11-16** in 55-67% (Scheme 1).

The structure of compounds **11-16** were assigned on the basis of their ^{1}H and ^{13}C NMR which showed similar patterns of aliphatic proton and carbon atoms .The ^{1}H 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 (CH_2) 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 ^{1}H NMR to see the OH and NH, in general, the ^{1}H 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-d_6 as a solvent.

In the ^{13}C 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 subtituents 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. Furthmore, 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).

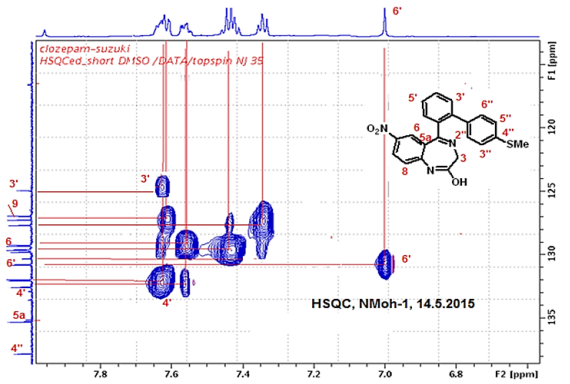


Figure 2. $J_{C,H}$ correlations in the HSQC NMR spectrum of compound **11**.

In the gradient-selected HMBC spectrum [30] of compound **11**, C-9a of the diazepin ring at δ 156.8 ppm showed a $^3J_{C,H}$ coupling with H-8 of the same ring at δ 7.98 ppm. A $^3J_{C,H}$ coupling between $C_{arom.}$-2' at δ 131.9-132.0 ppm and $H_{arom.}$-6'' at δ 7.62 ppm was observed. Another $^3J_{C,H}$ coupling was shown between $C_{arom.}$-1'' at δ 141.1 ppm and $H_{arom.}$-3' at δ 7.62 ppm. The spectrum showed a $^2J_{C,H}$ coupling between $C_{arom.}$-1' at δ 141.1 ppm and $H_{arom.}$-6' at δ 131.9-132.0 ppm well (Figure 3).

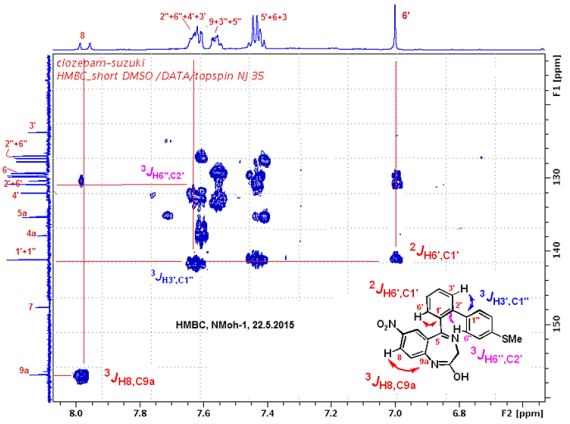


Figure 3. $J_{C,H}$ correlations in the HMBC NMR spectrum of compound **11**.

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

[1]. Ashton, C. H. *Drugs* **1994**, *48*, 25-40.
[2]. Baldwin, D.; Woods, R.; Lawson, R.; Taylor, D. *Br. Med. J.* **2011**, *342*, 1-11.
[3]. Manthey, L.; Van Veen, T.; Giltay, E. J.; Stoop, J. E. , Neven, A. K.; Penninx, B. W. J. H. , Zitman, F. G. *Br. J. Clin. Pharmacol*. **2011**, *71*, 263-272.
[4]. Lader, M. *Br. J. Clin. Pharmacol*. **2012**, *77*, 295-301.
[5]. Donoghue, J.; Lader, M. *Int. J. Psychiatry Clin. Pract*. **2010**, *14*, 78-87.
[6]. Varotto, M.; Roman, G.; Battistin, L. *Boll. Soc. Ital. Biol. Sper*. **1981**, *57(8)*, 904-908.
[7]. Lehoullie, PF.; Ticku, MK. *Eu. J. Pharmacol*. **1987**, *135*, 235-238.
[8]. Griffin, C. E.; Kaye, A. M.; Bueno, F. R.; Kaye, A. D. *Ochsner J*. **2013**, *13*, 214-223.
[9]. Uddin, M. D.; Samanidou, V. F.; Papadoyannis, I. N. *Pharmac. Anal. Acta*. **2014**, *5(6)*, 1-13.
[10]. Iqbal, M. M.; Sobhan, T.; Ryals, T. *Psychiatr. Serv.* **2002**, *53*, 39-40.
[11]. Cloos, J. M. *Curr. Opin. Psychiatr.* **2005**, *18*, 45-50.
[12]. Dresser, G. K.; Spence, J. D.; Bailey, D. G. *Clin. Pharmacokinet.* **2000**, *38(1)*, 41–57.
[13]. Dourlat, J.; Liu, W. Q.; Gresh, N.; Garbay, C. *Bioorg. Med. Chem. Lett.* **2007**, *17(9)*, 2527-2530.
[14]. Menezes, C. M. S.; Rivera, G.; Alves, M. A. *Chem. Biol. Drug. Des.* **2012**, *79(6)*, 943-949.
[15]. Anwar, B.; Grimsey, P.; Hemming, K.; Krajniewskib, M.; Loukoua, C. *Tetrahedron Lett.* **2000**, *41*, 10107-10110.
[16]. Wood, M. R.; Kim, J. J.; Han, W. *J. Med. Chem.* **2003**, *46,* 1803-1806.
[17]. Butcher, J. W.; Liverton, N. J.; Claremon, D. A. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1165-1168.
[18]. Sherrill, R. G.; Berman, J. M.; Birkemo, L . *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1145-1148.
[19]. Orrling, K. M.; Marzahn, M. R.; Teran, G. *Bioorg. Med. Chem*. **2009**, *17*, 5933-5949.
[20]. Cheng, P.; Zhang, Q.; Maa, Y.; Jiang, Z.; Zhang, X.; Zhang, F.; Chen, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787-3789.
[21]. Owens, A. P.; Nadin, A.; Talbot, A. C.; Clarke, E. E.; Harrison, T.; Lewis, H. D.; Reilly, M.; Wrigley, J. D. J.; Castro, J. L. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 4143-4145.
[22]. Nadin, A.; Lopez, J. M. S.; Owens, A. P.; Howells, D. M.; Talbot, A. C.; Harrison, T. *J. Org. Chem.* **2003**, *68*, 2844-2852.
[23]. Al-Soud, Y. A.; Al-Masoudi, N. A.; Al-Suod, H. H.; Pannecouquec, *C. Z. Naturforsch.* **2012**, *67b*, 925 – 934
[24]. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
[25]. Mahdi, K. M.; Abdul-Reda, N. A.; Al-Masoudi, N. A. *Eur. J. Chem.* **2015**, *6 (1)*, 1-7.
[26]. Al-Masoudi, N. A.; Kadhim, R. A.; Abdul-Rida, N. A.; Saeed, B. A.; Engel, M. *Steroids* **2015**, *101*, 43-50.
[27]. Abdul-Reda, N. A.; Kassim, A. G.; Al-Masoudi, N. A. *Nucleos. Nucleot. Nucl.* **2014**, *33*, 141-161.
[28]. Marich, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. *Eur. J. Chem*. **2014**, *5(4)*, 588-594.
[29]. Al-Masoudi, N. A.; Abdul-Rida, N. A.; Kadhim, R. A.; Krug, S. G.; Engel, M.; Saeed, B. A. *Med. Chem. Res*. **2016**, *25*, 310-321.
[30]. Davis, A. L.; Keeler, J.; Laue, E. D.; Moskau, *D. J. Magn. Reson*. **1992**, *98*, 207-216.