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Synthesis and characterization of new monocationic biphenyl derivatives: Accredited by DFT and possibility of biological activities' studies

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Abstract: Four new monocationic biphenyl derivatives 4a-d were prepared through two sequential steps. The first step involved the preparation of biphenylcarbonitrile derivatives 3a-d *via* a Suzuki coupling reaction between bromobenzonitrile derivatives 1a, b and the appropriate substituted phenylboronic acids 2a-d. The second step involved the treatment of carbonitrile derivatives 3a-d with lithium *bis*-trimethylsilylamide, followed by de-protection step and subsequent hydrochloride salt formation. Whereby, DFT calculations revealed that compounds 3a and 4a have high chemical reactivity among all the newly synthesized compounds with lower band gaps of -4.513 and -3.361 ev, respectively. Additionally, a prediction study for the biological activities was performed *via* using PASS online software which displayed promising activities of monocationic biphenyl derivatives for the treatment of tumor regression in neurocells and anticoagulanting activities**.**

keywords: Phenylboronic, Suzuki, Cationic, DFT

1. Introduction

Biaryl containing compounds are prevalent structures in a large number of pharmaceuticals, natural products, and agrochemicals [1]. For example, biphenyls possess a significant therapeutical activity in anti-cholinesterase [2], anti-diabetic [3], anti-tumor, antiproliferative [4], antifungal, anti-cancer, anti-HIV, antihepatotoxic [5], antihypertensive, and antiandrogenic [6]. Copper (II) complex of losartan, the potassium salt of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole (**I; Figure 1**), has been known for its antioxidant, antihypertensive, and antiproliferative activities [7]. It has been reported that amidine containing compounds show a broad-spectrum of biological activity including antimicrobial agents and serine protease inhibitors [8]. *Meta*-biphenyl carboxamidine (**II**) has been successfully passed the preclinical studies for their inhibition factor Xa and trypsin (Ki = 10 μM) [9]. Aryl diamidines have been long known to possess significant antiprotozoal activity. The aromatic compound bis-4,4′-amidinobiphenyl (**III)** and its terphenyl analogue showed good antiprotozoal activities [10,11]. In the present study, we report herein the preparation and characterization of four new monoamidines of substituted biphenyl derivatives.

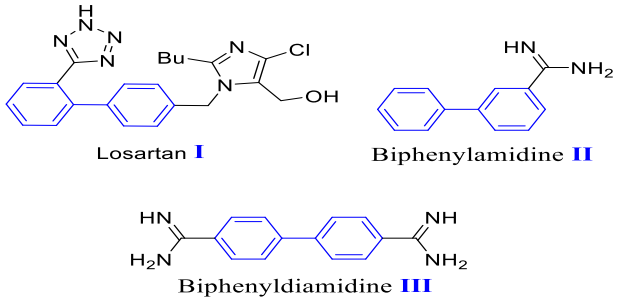


Figure 1: Biologically important biphenyl compounds

2. Materials and methods

Melting points (uncorrected) were measured in degree centigrade on Gallenkamp apparatus. Thermo Scientific Nicolet iS10 FTIR spectrometer was used to record infrared spectra (KBr). JEOL's spectrometer 500 MHz (^{1}H-NMR), 125 MHz (^{13}C-NMR) was used to measure NMR spectra in DMSO-d_6 as a solvent and an internal standard. Electron impact mass spectra were determined at 70 eV on Varian MAT 311Kratos instrument.

2.1. General methodology for preparation of biphenyl carbonitriles 3a-d.

A stirred solution of 4-bromobenzonitrile derivatives **1a, b** (**1a**: 728 mg, 4 mmol), the appropriate phenylboronic acid (4.8 mmol), Pd $(PPh_3)_4$ (160 mg), and anhydrous K_2CO_3 (4 g) in 1,4-dioxane (25 mL) was refluxed for 8-12 hrs. After completion of the reaction (monitored by TLC), 5 mL of concentrated ammonia was added, and the reaction mixture was extracted with ethyl acetate (200 mL, x3). The organic layer was evaporated to dryness under reduced pressure. The precipitate was recrystallized from the appropriate solvent to afford the desired biphenylcarbonitrile derivatives **3a-d**.

2.1.1. 4'-Fluoro-[1,1'-biphenyl]-4-carbonitrile (3a). **3a** was obtained in 72% yield as a white solid, m.p. = 107-108°C, Lit. [18] = 108.5-109°C. R_f = 0.77, EtOAc/petroleum ether (60-80 °C) (2:8). IR (KBr) ν'/cm^{-1}: 3069 (sp^2 C–H, stretch), 2224 (CN, stretch), 1600, 1518, 1490 (C=C, stretch). ^{1}H-NMR (DMSO-d_6); δ 7.31-7.34 (m, 2H, Ar-H's of *para*-fluorophenyl ring), 7.77-7.80 (m, 2H, Ar-H's of *para*-fluorophenyl ring), 7.85 (d, J = 8 *Hz*, 2H, Ar-H's of benzonitrile ring), 7.90 ppm (d, J = 8 *Hz*, 2H, Ar-H's of benzonitrile ring). MS (EI) m/e (rel.int.) for $C_{13}H_8FN$; 197 (M^+, 22), 169 (100).

2.1.2. 3',5'-Dimethoxy-[1,1'-biphenyl]-4-carbonitrile (3b). 3b was obtained in 76 % yield as a white solid, m.p. = 106-107°C. R_f = 0.58, EtOAc/petroleum ether (60-80 °C) (2:8). IR (KBr) ν'/cm^{-1}: 3096, 3058, 3001 (sp^2 C–H, stretch), 2966, 2941, 2841 (sp^3 C–H, stretch), 2221 (CN, stretch), 1593, 1557, 1514 (C=C, stretch). ^{1}H-NMR; δ 3.80 (s, 6H, *meta*-dimethoxy-H's), 6.56 (s, 1H, Ar-H of dimethoxyphenyl ring), 6.85 (s, 2H, Ar-H's of dimethoxyphenyl ring), 7.86-7.90 ppm (m, 4H, Ar-H's of benzonitrile ring). ^{13}C-NMR (DMSO-d_6); δ 55.41 (2C), 100.62, 105.18 (2C), 110.27, 118.93, 127.83 (2C), 132.76 (2C), 140.44, 144.60, 161.02 ppm (2C). MS (EI) m/e (rel.int.) for $C_{15}H_{13}NO_2$; 239 (M^+, 57), 237 (100).

2.1.3. 3',4',5'-Trimethoxy-[1,1'-biphenyl]-4-carbonitrile (3c). **3c** was obtained in 71% yield as a white solid, m.p. = 100-101°C. Lit. [19] melting point not reported. R_f = 0.39, EtOAc/petroleum ether (60-80 °C) (2:8). IR (KBr) ν'/cm^{-1}: 2996, 2925, 2842 (sp^3 C–H, stretch), 2222 (CN, stretch), 1587, 1558, 1496 (C=C, stretch). ^{1}H-NMR; δ 3.69 (s, 3H, *para*-methoxy-H's), 3.86 (s, 6H, *meta*-dimethoxy-H's), 6.70 (s, 2H, Ar-H's of trimethoxyphenyl ring), 7.89-7.93 ppm (m, 4H, Ar-H's of benzonitrile ring). MS (EI) m/e (rel.int.) for $C_{16}H_{15}NO_3$; 269 (M^+, 100), 254 (M^+- CH_3, 16).

2.1.4. 3-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carbonitrile (3d). **3d** was obtained in 84% yield as a white solid, m.p. = 125-126°C, Lit. [20] m.p. = 124.6-125.2°C, lit. [21] m.p. = 130-132°C. R_f = 0.39, EtOAc/petroleum ether (60-80 °C) (2:8). IR (KBr) ν'/cm^{-1}: 3073, 3047, 3018 (sp^2 C–H, stretch), 2998, 2970, 2941, 2842 (sp^3 CH, stretch), 2232 (CN, stretch), 1621, 1590, 1558 (C=C, stretch). ^{1}H-NMR; δ 3.70 (s, 3H, *para*-methoxy-H's), 3.87 (s, 6H, *meta*-dimethoxy-H's), 7.06 (s, 2H, Ar-H's of trimethoxyphenyl ring), 7.80 (dd, *J* = 8.5, 1.5 *Hz*, 1H, Ar-H of fluorobenzonitrile ring), 7.94-8.00 ppm (m, 2H, Ar-H's of fluorobenzonitrile ring). MS (EI) m/e (rel.int.) for $C_{16}H_{15}NO_3$; 287 (M^+, 58), 65 (100).

2.2. General methodology for preparation of biphenylcarboxamidine derivatives 4a-d:

The proper biphenylcarbonitrile derivatives **3a-d** (1.5 mmol) was allowed to react with $LiN(TMS)_2$ (1M solution in THF, 8 mL, 8 mmol) at room temperature with stirring overnight. After this, 12 mL, 1.25 M of HCl(gas)/ethanol solution was added and the reaction mixture was left to stir for 6 hours, after which, it was diluted with Et_2O, and the solid formed was filtered off. The crude biphenylcarboxamidine was neutralized with 1N NaOH and the formed monoamidine free base was filtered off, washed with water. Finally, the target biphenylcarboxamidines hydrochloride salts **4a-h** were made from their corresponding free bases on treatment with ethanolic-HCl(gas) solution for overnight, the resultant solid was filtered off after addition of Et_2O.

2.2.1.4'-Fluoro-[1,1'-biphenyl]-4-carboxamidine hydrochloride salt (4a). **4a** was obtained in 67% yield as a pale yellow solid, m.p.= 258-260°C. IR (KBr) ν'/cm^{-1}: 3356, 3308 (NH, stretch), 3137 (sp^2 C–H,

stretch), 1675, 1609, 1542 (C=N & C=C, stretch). ^{1}H-NMR; δ 7.34-7.37 (m, 2H, *para*-fluorophenyl-H's), 7.82-7.85 (m, 2H, *para*-fluorophenyl-H's), 7.92 (s, 4H, Ar-H's of benzamidine ring), 9.19 (s, 2H, NH_2 exchangeable with D_2O), 9.44 ppm (s, 2H, $^{+}NH_2$ exchangeable with D_2O). MS (EI) m/e (rel.int.) for $C_{13}H_{11}FN_2$; 214 (M^+, 47), 198 (M^++1 -NH_3, 34), 43.27 (100). Molecular Formula for the hydrochloride salt **4a** ($C_{13}H_{11}FN_2$-1.0HCl).

2.2.2. 3',5'-Dimethoxy-[1,1'-biphenyl]-4-carboxamidine hydrochloride salt (4b). **4b** was obtained in 75% yield as a pale yellow solid, m.p. = 234-236^{o}C. IR (KBr) ν'/cm^{-1}: 3467, 3398 (NH, stretch), 3052 (sp^2 C–H, stretch), 2837 (sp^3 C–H, stretch), 1676, 1602, 1544 (C=N & C=C, stretch). ^{1}H-NMR; δ 3.82 (s, 6H, *meta*-dimethoxy-H's), 6.58 (s, 1H, Ar-H of dimethoxyphenyl ring), 6.88 (s, 2H, Ar-H's of dimethoxyphenyl ring), 7.90-7.95 (m, 4H, Ar-H's of benzamidine ring), 9.17 (s, 2H, NH_2 exchangeable with D_2O), 9.43 ppm (s, 2H, $^{+}NH_2$ exchangeable with D_2O). ^{13}CNMR; δ 55.45 (2C), 100.44, 105.23 (2C), 126.94, 127.28 (2C), 128.71 (2C), 140.51, 145.14, 161.05 (2C), 162.23 ppm. MS (EI) m/e (rel.int.) for $C_{15}H_{16}N_2O_2$; 256 (M^+, 29), 238 (M^+-1 -NH_3, 10), 150 (100). Molecular Formula for the hydrochloride salt **4b** ($C_{15}H_{16}N_2O_2$ -1.0HCl).

2.2.3. 3',4',5'-Trimethoxy-[1,1'-biphenyl]-4-carboxamidine hydrochloride salt (4c). **4c** was obtained in 65% yield as an off white solid, m.p. = 242-244^{o}C. IR (KBr) ν'/cm^{-1}: 3260 (NH, stretch), 3104 (sp^2 C–H, stretch), 1667, 1590, 1541 (C=N & C=C, stretch). ^{1}H-NMR; δ 3.70 (s, 3H, *para*-methoxy-H's), 3.87 (s, 6H, *meta*-dimethoxy-H's), 7.02 (s, 2H, Ar-H's of trimethoxyphenyl ring), 7.92-7.97 (m, 4H, Ar-H's of benzamidine ring), 9.22 (s, 2H, NH_2 exchangeable with D_2O), 9.45 ppm (s, 2H, $^{+}NH_2$ exchangeable with D_2O). ^{13}C-NMR; δ 56.10 (2C), 60.13, 104.56 (2C), 126.36, 127.12 (2C), 128.63 (2C), 134.01, 138.06, 145.33, 153.37 (2C), 165.13 ppm. MS (EI) m/e (rel.int.) for $C_{16}H_{18}N_2O_3$; 286 (M^+, 79), 271 (M^+-CH_3, 30), 255 (M^++1 –CH_3 -NH_3, 13), 239 (100). Molecular Formula for the hydrochloride salt **4c** ($C_{16}H_{18}N_2O_3$-1.0HCl).

2.2.4. 3-Fluoro-3',4',5'-trimethoxy-[1,1'-biphenyl]-4-carboxamidine hydrochloride salt (4d): 4d was obtained in 71% yield as a pale brown solid, m.p.= 238-240^{o}C. IR (KBr) ν'/cm^{-1}: 3322 (NH, stretch), 3172 (sp^2 C–H, stretch), 2946 (sp^3 C–H, stretch), 1678, 1625, 1588 (C=N & C=C, stretch). ^{1}H-NMR; δ 3.69 (s, 3H, *para*-methoxy-H's), 3.88 (s, 6H, *meta*-dimethoxy-H's), 7.05 (s, 2H, Ar-H's of trimethoxyphenyl ring), 7.73-7.76 (m, 1H, Ar-H of fluorobenzamidine ring), 7.80 (d, *J* = 9.5 *Hz*, 1H, Ar-H of fluorobenzamidine ring), 7.90-7.92 (m, 1H, Ar-H of fluorobenzamidine ring), 9.43 (s, 2H, NH_2 exchangeable with D_2O), 9.53 ppm (s, 2H, $^{+}NH_2$ exchangeable with D_2O). MS (EI) m/e (rel.int.) for $C_{16}H_{17}FN_2O_3$; 304 (M^+, 100), 289 (M^+- CH_3, 28), 272 (M^+- CH_3 - NH_3, 6). Molecular Formula for the hydrochloride salt **4d** ($C_{16}H_{17}FN_2O_3$-1.0HCl).

3. Results and Discussion

3.1. Chemistry

Synthetic analyses of the target compounds biphenylcarboxamidines **4a-d** are depicted in **Figure 2**. Disconnection starts with function group interconversion (FGI) of the amidine group to its corresponding carbonitrile group. The disconnection of biphenylcarbonitriles **3a-d** may be done *via* different possible metal-catalyzed disconnections as follow; (i) a Suzuki coupling disconnection to the commercially available bromo benzonitrile derivatives **1**, and commercially available substituted phenylboronic acids **2A**, (ii) a Stille coupling disconnection to the commercially available bromo benzonitrile derivatives **1**, and commercially unavailable stannyl substituted benzene derivatives **2B**, (iii) an Ulmann coupling disconnection; this interconversion leads to the commercially available bromobenzonitrile derivatives **1**, and commercially available bromo substituted-benzene derivatives **2C**. However, Ulmann coupling reaction is allowed for symmetrical biphenyl derivatives, not for unsymmetrical biphenyls. Monocationic biphenyls **4a-d** (**Scheme 1**) were prepared starting with a Suzuki coupling reaction of each bromobenzonitriles **1a, b** with the appropriate substituted phenylboronic acids **2a-d** under the action of palladium-catalyzed, in the presence of anhydrous K_2CO_3 as a base to furnish the biphenylcarbonitrile derivatives **3a-d**. Compounds **3a-d** were allowed to react with

lithium bis-trimethylsilylamide [LiN(TMS)$_2$], followed by de-protection with HCl(gas)/EtOH. The formed precipitates were neutralized with 1N NaOH affording the corresponding free bases of biphenylcarboxamidine derivatives **4a-d**. In the same context, the hydrochloride salts of biphenylcarboxamidines **4a-d** were prepared by treatment of their free bases of monoamidine derivatives with HCl(gas) in ethanol. The chemical structures of the new carbonitrile derivatives **3a-d** were confirmed according to their spectral analyses. As IR spectra for biphenylcarbonitriles **3a-d** revealed the appearance of nitrile groups with vibrations in the range of 2221 to 2232 cm^{-1}. Whereby, ^{1}H-NMR spectrum of 3',5'-dimethoxybiphenylcarbonitrile derivative **3b** showed two singlet signals corresponding for aromatic hydrogens of 3',5'-dimethoxyphenyl ring at δ 6.56 (1H) and 6.85 (2H), in addition, one singlet signal of symmetrical two methoxy groups at δ 3.80 (*meta*-dimethoxy groups, 6H), and multiplet signal (4H) attributed to 1,4-disubstituted benzonitrile-H's. Furthermore, ^{13}C-NMR of compound **3b** displayed 10 carbon-signals of its carbon network with characteristic signal at δ 55.41 (carbon of *meta*-dimethoxy groups). Mass spectrum of **3b** displayed a molecular ion peak m/z at 239 (M^+, 57). Once more, ^{1}H-NMR of biphenylcarbonitrile **3d** gave three singlet signals at δ 3.70 (3H, *para*-methoxy-H's), 3.87 (6H, *meta*-dimethoxy-H's), and 7.06 (2H, Ar-H's of trimethoxyphenyl ring), in addition to, three aromatic hydrogens attributed to fluorobenzonitrile-H's. Mass spectrum of compound **3d** furnished m/z peak at 287 of its molecular ion peak (M^+, 58). The chemical structures of the new monocationic biphenyls **4a-d** were confirmed from their spectral analyses. IR spectra of **4a-d** revealed the disappearance of cyano group and gave new peaks corresponding to N-H stretching peaks (ν 3467, 3398 cm^{-1} for **4b**). ^{1}H-NMR of monocationic compounds **4a-d** showed the characteristic signals of the cationic groups and were D_2O exchangeable. ^{1}H-NMR of the monocationic **4b** showed two singlets at δ 9.17 (NH_2) and δ 9.43 ($^+NH_2$) characteristic for the cationic group, two singlets at δ 6.58 (1H) and 6.88 (2H) corresponding for aromatic hydrogens of 3',5'-dimethoxyphenyl ring. In addition to, one singlet signal of 3',5'-dimethoxy groups at δ 3.82 (*meta*-dimethoxy groups, 6H), and a multiplet signal (integrated for 4H) attributed to 1,4-disubstituted benzamidine-H's. ^{13}C-NMR of compound **4b** displayed ten signals corresponding to 15 carbons, in addition, the spectrum revealed characteristic signals at δ 55.45 ppm (carbon of *meta*-dimethoxy groups), and δ 165.23 ppm (carbon of cationic group). Mass spectrum of compound **4b** gave a m/z peak at 256 of its molecular ion peak (M^+, 29). ^{1}H-NMR of **4d** gave two singlets at δ 9.43 (2H) and 9.53 (2H) characteristic for the cationic group, three singlets at δ 3.69 (3H, *para*-methoxy-H's), 3.88 (6H, *meta*-dimethoxy), 7.05 (2H) of aromatic hydrogens of trimethoxyphenyl ring. In addition to, two multiplet signals at δ 7.73-7.76 (1H), and 7.90-7.92 (1H) related to fluorobenzamidine-H's, and one doublet signal at δ 7.80 (1H) corresponding to fluorobenzamidine-H's. Mass spectrum of compound **4d** gave a m/z peak at 304 of its molecular ion peak (M^+, 100).

3.2. Computational approaches

3.2.1. Molecular modeling

Computational calculations were accomplished to chemical reactivity and preliminary results of expected biological evaluation *via* using Gaussian 09 program package. In addition, the DFT approach B3LYP as function and 6-311G (d,p) basis set were applied in gaseous state for investigating the optimized structures of the synthesized compounds [12-15]. As electron density charge distributions as well as Frontier orbitals of LUMO/HOMO, of all synthesized compounds, are presented in Fig. 3 (carbonitrile compounds **3a-d**) and Fig. 4 (monocationic compounds **4a-d**). The HOMO/LUMO symbolize the highest occupied and lowest unoccupied molecular orbital energies, which indicate the chemical reactivity and stability of the prepared molecules. As the energy gap is the difference between the orbitals' energies (E_{HOMO}- E_{LUMO}) indicates the reactivity of the synthesized compounds. The molecules that have high ($\Delta E_{HOMO-LUMO}$) are called hard molecules, meaning less reactivity in the treatment biological strains. Conversably, molecules that have lower gap energies are called soft

molecules, besides have high ability as biological molecules. Calculations of the biphenyl carbonitriles **3a-d** (Fig. 3) showed that compound **3a** is the most effective and reactive molecule in the carbonitrile moieties, as it has a lower band gap (-4.513 ev) comparing to other biphenyl carbonitriles whose energies gap ranged between (-4.270-4.355 ev) (Fig. 3). On the other hand, geometrical studies for biphenylcarboxamidine derivatives **4a-d** were carried out and figure out that 4'-fluoro-[1,1'-biphenyl]-4-carboxamidine **4a** has low band gap (-3.361 ev) and it is predicted to be the most active molecule compared to other amidine derivatives **4b-d** (Fig. 4).

3.2.2. Computational prediction of biological activities: Predicted biological activity was obtained by using PASS online software for the targeted compounds which were represented in Tables 1 and 2. This tool affords predictions correlating P_i (probability to be inactive) and P_a (probability to be active) [16]. From the results of various biological activity predictions, compounds **3a-d** displayed possibility of activity towards tumor cell apoptosis and tumor regression especially in neurocells (**Table 1**). Whereby, monocationic biphenyl derivatives **4a-d** displayed completely different the possibility of biological activities of anticoagulanting activities (anticoagulant and antibacterial). Moreover, the obtained predicated biological activities are fully compatible with the theoretical studies which accomplished *via* Gaussian studies. As compound **3a** showed the best predicted having tumor cell apoptosis activity with excellent possibility of activity (P_a= 0.909) and the same time, it is the softest molecule. On the contrary, the conversion of nitrile groups in **3a-d** derivatives to amidines in compounds **4a-d** led to the creation of new biological activities completely different than the abovementioned carbonitrile compounds **3a-d** (**Table 1**). As anticoagulant activities of other biphenylcarboxamidine derivatives **4a-d** were decreased in the order of **4a** > **4b** > **4c**> **4d** (Table 2), this phenomenon is related to the presence of methoxy groups inhibiting the coagulation factors [17]. So that, compound **4a** which does not have methoxy group have a significant (P_a = 0.947 -0.876) to the anticoagulant activitie

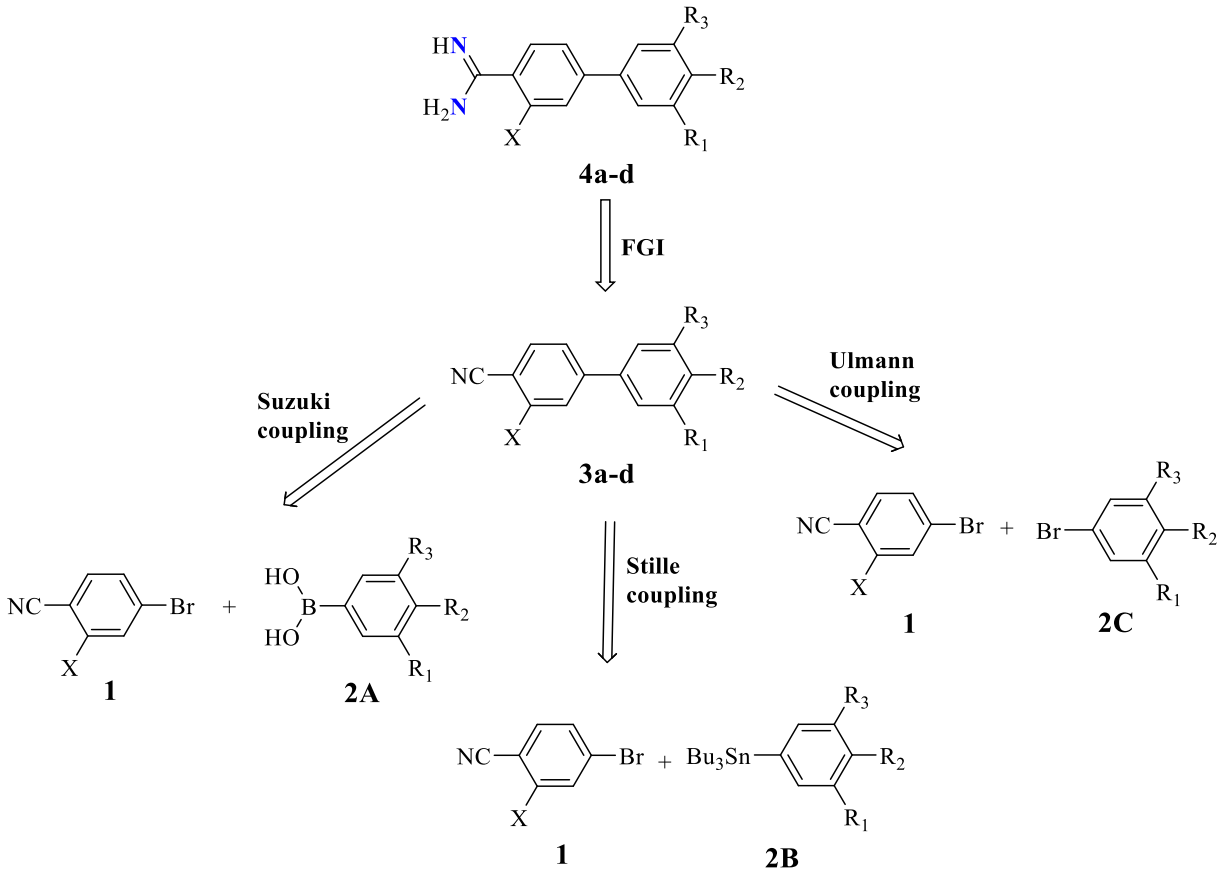
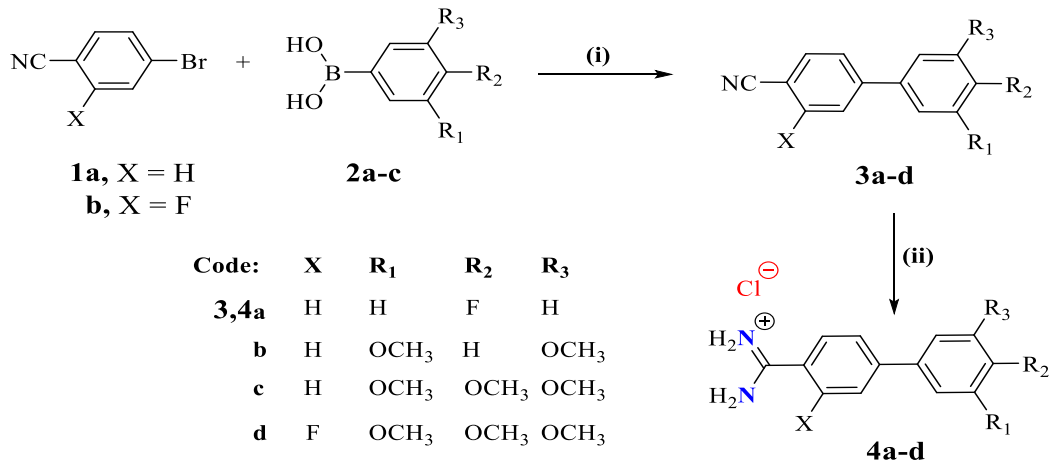


Figure 2: Retrosynthetic routes for biphenylcarboxamidines derivatives **4a-d**.



Code:	X	R_1	R_2	R_3
3,4a	H	H	F	H
b	H	OCH_3	H	OCH_3
c	H	OCH_3	OCH_3	OCH_3
d	F	OCH_3	OCH_3	OCH_3

Reagents and conditions: (i). $Pd(PPh_3)_4$, anhydrous K_2CO_3, 1,4-dioxane (ii). a) $LiN(TMS)_2$, THF; b) ethanol/hydrogen chloride.

Scheme 1: Scheme for preparation of the new biphenylcarboxamidines **4a-d**.

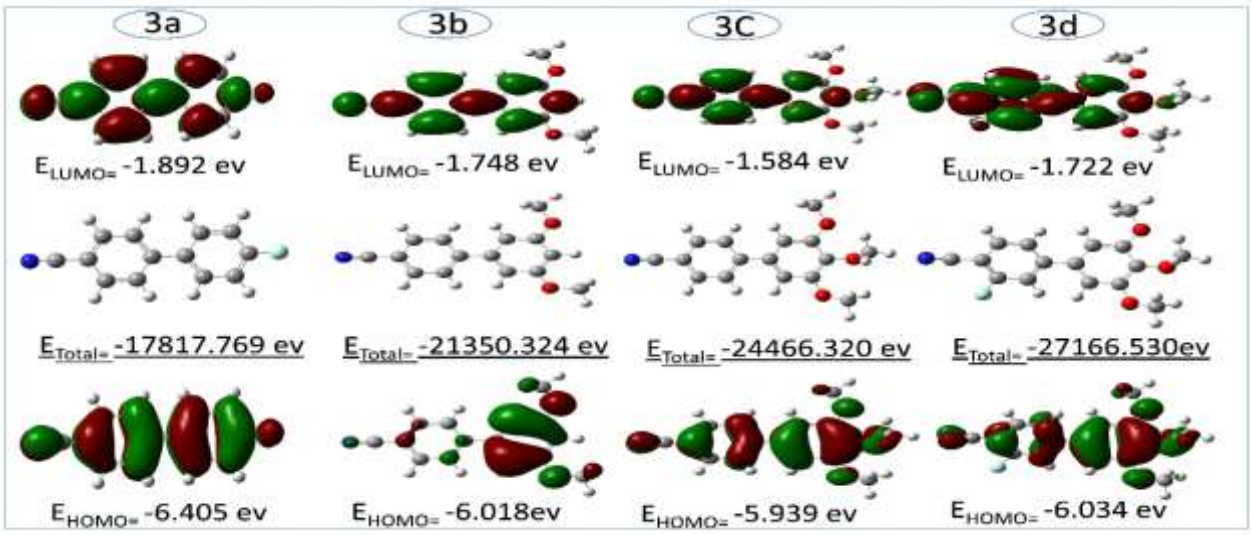


Figure 3: Geometrical optimization and spatial distributions orbitals of the derivatives **3a-d**.

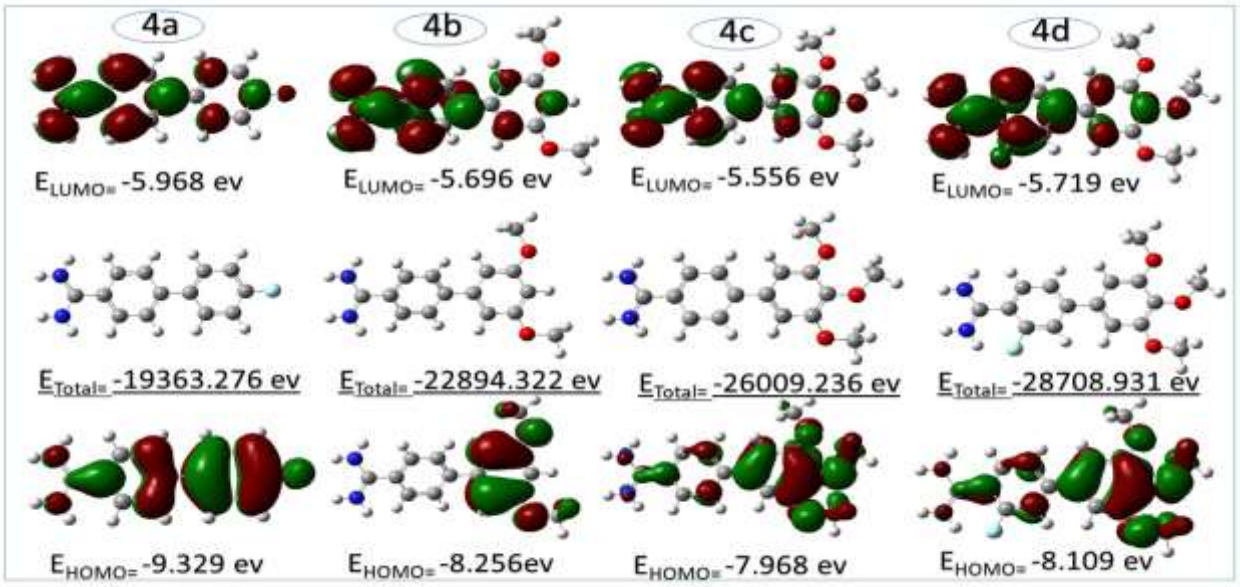


Figure 4: Geometrical optimization and spatial distributions orbitals of the derivatives **4a-d**.

Table 1: PASS online biological activities' assessments for compounds **3a-d**

Biological Activity	Compd# 3a		Compd# 3b		Compd# 3c		Compd# 3d	
	P_a	P_i	Pa	Pi	Pa	Pi	Pa	Pi
CYP2C12 substrate	0,909	0,010	0,946	0,004	0,933	0,006	0,808	0,034
Centromere associated protein inhibitor	0,900	0,002	0,740	0,005	0,740	0,005	0,618	0,014
Aspulvinonedimethylallyltransferase inhibitor	0,848	0,020	0,928	0,004	0,912	0,006	0,837	0,023
Arylmalonate decarboxylase inhibitor	0,817	0,003	NA	NA	NA	NA	NA	NA
Neurotransmitter uptake inhibitor	0,799	0,004	0,752	0,006	0,752	0,006	0,535	0,049
Antineurotic	0,787	0,019	0,773	0,024	0,711	0,038	0,658	0,053

Table 2: PASS online biological activities' assessments for compounds **4a-d**

Biological Activity	Compd# 4a		Compd# 4b		Compd# 4c		Compd# 4d	
	P_a	P_i	P_a	P_i	P_a	P_i	P_a	P_i
Anticoagulant	0,947	0,003	0,899	0,004	0,891	0,004	0,608	0,005
Venombin AB inhibitor	0,909	0,002	0,875	0,003	0,875	0,003	0,700	0,016
Platelet antagonist	0,906	0,003	0,789	0,004	0,769	0,004	NA	NA
Limulus clotting factor Binhibitor	0,889	0,002	0,795	0,005	0,826	0,004	0,656	0,019
Omptin inhibitor	0,886	0,003	0,840	0,004	0,840	0,004	0,688	0,023
Complement factor Dinhibitor	0,876	0,003	0,898	0,003	0,876	0,003	0.774	0.009

Conclusion:

To conclude, Suzuki coupling reaction of bromobenzonitriles was accomplished for the synthesis of biphenylcarbonitrile derivatives **3a-d.** After that, compounds **3a-d** were treated with lithium *bis*-trimethylsilylamide and hydrogen chloride in ethanol under stirring conditions afforded biphenylcarboxamidine derivatives **4a-d.** These compounds have been conducted with DFT simulations to check up their reactivity and stability. Eventually, the predicted biological activities for all synthesized compounds were screened through pass online software. The present study is just preliminary, whereas biological activities, studies are currently underway and will be published in the due time.

5. References

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