Suzuki reaction of aryl halides with organo-
boron offers a facile synthetic route to synthesize
biaryls (1-2). This cross-coupling reaction is typi-
cally attractive and beneficial for the construction of
C-C bonds due to number of reasons such as high
functional group tolerance, favorable reaction kinet-
cics and easy handling of non-hazardous by-products
(1-5). The Biaryl motifs are important substructures
in pharmaceuticals as anti-arthritic, cholesterol inhi-
biting, anti-leukemic activities. These are also
potentially useful in agrochemicals, energy and
functional materials (6-7). Therefore, the synthesis
of novel biaryls with the unique therapeutic features
is gaining significant attention from the scientific
community working in the development of new
drugs. In view of the medicinal importance of bia-
ryls, the present research was carried out to synthe-
size the various functionalized biaryl derivatives via
Palladium (Pd) catalyzed Suzuki coupling reaction.
In addition to the synthesis, we have also investiga-
ted the potential pharmaceutical applications of the
newly synthesized biaryls to combat various ail-
ments.

MATERIALS AND METHODS

General

Melting point apparatus (B-540) was used for
determining the melting points of synthesized
solids. 'H-NMR was measured using CDCl₃ (Bruker

SELECTIVE ARYLATION OF PHENOL PROTECTED PROPARGYL BROMIDE VIA PD-CATALYSED SUZUKI COUPLING REACTION: SYNTHESIS, MECHANISTIC STUDIES BY DFT CALCULATIONS AND THEIR PHARMACOLOGICAL ASPECTS

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Abstract: Biaryls are the potential source of synthetic drugs. The present study describes the synthesis of a series of functionalized biphenyl derivatives (3a-3g) using Pd-catalyzed Suzuki coupling reaction. The experimental results revealed the facile synthesis of biphenyl derivatives (3a-3g) with notably high yield (80-88%). Density functional theory (DFT) studies were performed by Gaussian 09 software in order to rationalize the selectivity of coupling at C-Br bond instead of C-Cl bond. In addition of synthesis, the biological activities (biofilm inhibition, hemolytic and anti-thrombolytic) of these novel compounds were investigated. These results exhibited good biofilm inhibition (5.86-65.8%), hemolytic (1.32-30.1%) and anti-thrombolytic activities (9.64-42.5%), indicating the potential use of these compounds for pharmaceutical applications.

Keywords: Suzuki coupling, DFT, phenol, organoboron, biaryl, biofilm

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ARX at 300, 400, 500, 600 MHz). JMS-HX-110 spectrometer with a data system was used for EI-MS spectra. For column chromatography, silica gel (70–230 and 230–400 mesh) was used. TLC was used for monitoring the completion of reaction, (Merck silica gel 60 PF254 cards) and the visualization of compounds was done by UV lamp (254-365 nm).

**General procedure for the synthesis of intermediate compound 4-bromo-2-chloro-1-(prop-2-yn-1-yloxy)benzene (2)**

4-Bromo-2-chlorophenol (1.0 g, 4.83 mmol), propargyl bromide (0.688 g, 5.78 mmol), potassium carbonate (K₂CO₃) (2.33 g, 16.8 mmol) and 15 mL of dry acetone was added into Schlenk flask. Then it was refluxed at 80°C for 5 h. After that Schlenk flask cooled at room temperature. Completion of the reaction was monitored by TLC followed by the addition of distilled H₂O (10 mL) and dichloromethane (10 mL DCM). The organic layer was separated and the remaining moisture from organic layer was removed by using Sodium sulphate (Na₂SO₄). After filtration and subsequent evaporation, the product was purified by flash chromatography. Mixture of n-hexane and ethyl acetate was used as eluent (8).

**General procedure for the synthesis of biaryl compounds (3a-g)**

A mixture containing Phenol (2) (0.250 mg, 1.09 mmol), tetrakis-triphenylphosphine palladium (0.027 g, 2.5 mol%) as catalyst and 1,4-dioxane (2.5 mL) was taken in the Schlenk flask, followed by stirring at room temperature for 20 min in presence of inert atmosphere. To this mixture, respective arylboronic acid (1.54 mmol) together with a known amount of potassium phosphate (K₃PO₄) and water (0.625 mL) were added to a reaction flask. This reaction mixture was again stirred at 80-90°C for 15 h. After cooling the reaction mixture, it was further diluted with ethyl-acetate and distilled water. The organic layer was separated using a separating funnel and sodium sulfate was used to remove the remaining moisture content. The mixture was further concentrated and dried by using rota-vapour. The obtained residue was purified by the column chromatography using a mixture of ethyl acetate and n-hexane as an eluent.

**Characterization data 4-Bromo-2-chloro-1-(prop-2-yn-1-yloxy)benzene (2)**

Obtained as solid, mp = 516°C. ¹H-NMR (CDCl₃, 600 MHz) δ: 7.51 (d, J₁,₂ = 2.4 Hz, 1H), 7.33-7.18 (m, 1H), 6.95 (d, J₁,₂ = 8.4 Hz, 1H), 4.74 (d, J₁,₂ = 2.4 Hz, 2H), 2.53-2.52 (m, 1H). ¹³C NMR (CDCl₃, 150 MHz, δ, ppm): 150.1, 130.0 (m), 121.2, 118.0, 116.1, 78.7, 75.1, 54.1. EI/MS (m/z, + ion mode): [M⁺]⁺ = 246 [M+2]⁺ = 248, [M+4]⁺ = 250.

**3-Chloro-3,5'-dimethyl-4-(prop-2-yn-1-yloxy)-1,1'-biphenyl (3a)**

Obtained as solid, mp = 484°C. ¹H-NMR (CDCl₃, 600 MHz) δ: 7.51 (d, J₁,₂ = 1.8 Hz, 1H), 7.37 (dd, J₁,₂ = 8.4 Hz, 1J₁,₂ = 2.4 Hz, 1H), 7.11 (br.s, 1H), 7.04 (d, J₁,₂ = 8.4 Hz, 2H), 6.95 (br.s, 1H), 3.47 (s, 2H), 2.40 (br.s, 1H), 2.34 (s, 6H). ¹³C NMR (CDCl₃, 150 MHz, δ, ppm): 21.3, 22.0, 54.2, 76.1, 78.9, 115.3, 122.6, 125.0, 126.3, 128.4, 129.2, 133.4, 138.2, 138.9, 142.9, 153.6. EI/MS (m/z, + ion mode): [M⁺]⁺ = 271, [M+2]⁺ = 273.

**3-Chloro-3,5'-difluoro-4-(prop-2-yn-1-yloxy)-1,1'-biphenyl (3b)**

Obtained as solid, mp = 460°C. ¹H-NMR (400 MHz, CDCl₃) δ: 7.67-7.62 (m, 2H), 7.33 (dd, J₁,₂ = 8.4, J₁,₃ = 2.0 Hz, 1H), 7.08 (d, J₁,₂ = 8.4 Hz, 1H), 7.01 (d, J₁,₂ = 6.4 Hz, 1H), 6.74 (t, J₁,₂ = 8.8 Hz, 1H), 4.43 (s, 2H), 3.58 (s, 1H). ¹³C NMR (CDCl₃, 100 MHz, δ, ppm): 58.2, 76.2, 79.7, 119.0 (m), 101.2, 116.9, 122.0, 125.6, 130.9, 134.9, 140.1, 152.0, 165.8 (m) 167.0 (m). EI/MS (m/z, + ion mode): [M⁺]⁺ = 279.2, [M+2]⁺ = 281.

**3-Chloro-3,5'-difluoro-4-(prop-2-yn-1-yloxy)-1,1'-biphenyl (3c)**

Obtained as solid, mp = 454°C. ¹H-NMR (CDCl₃, 500 MHz, CDCl₃) δ: 7.52 (d, J₁,₂ = 3.0 Hz, 1H), 7.40-7.36 (m, 3H), 7.22-7.20 (m, 2H), 7.05 (d, J₁,₂ = 9.0 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (CDCl₃, 150 MHz, δ, ppm): 22.0, 116.2, 123.1, 126.2, 127.8, 129.0, 129.8, 130.1, 130.8, 132.1, 139.0, 152.9. EI/MS (m/z, + ion mode): [M⁺]⁺ = 218.0, [M+2]⁺ = 220.

**3-Chloro-4'-methyl-[1,1'-biphenyl]-4-ol (3d)**

Obtained as solid, mp = 457°C. ¹H-NMR (CDCl₃, 500 MHz, CDCl₃) δ: 7.48 (d, J₁,₂ = 2.4 Hz, 1H), 7.43-7.40 (m, 2H), 7.34 (dd, J₁,₂ = 8.4, J₁,₃ = 2.4 Hz, 1H), 7.04 (d, J₁,₂ = 8.4 Hz, 1H), 6.95-6.93 (m, 2H), 3.82 (s, 3H). ¹³C NMR (CDCl₃, 150 MHz, δ, ppm): 53.2, 112.3, 114.2, 118.2, 124.3, 128.9, 131.0, 132.9, 133.2, 135.6, 156.2, 159.2. EI/MS (m/z, + ion mode): [M⁺]⁺ = 234.0, [M+2]⁺ = 236.

**3,4'-Dichloro-[1,1'-biphenyl]-4-ol (3e)**

Obtained as solid, mp = 575°C. ¹H-NMR (CDCl₃, 500 MHz, CDCl₃) δ: 7.50 (d, J₁,₂ = 3.0 Hz, 1H), 7.44-7.33 (m, 2H), 7.06 (d, J₁,₂ = 9.0 Hz, 2H), 6.98-6.71 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz, δ, ppm): 116.2, 116.9, 123.3, 126.2, 128.4, 129.0, 129.8, 130.1, 130.8, 132.1, 139.0, 152.9. EI/MS (m/z, + ion mode): [M⁺]⁺ = 218.0, [M+2]⁺ = 220.
Selective arylation of phenol protected propargyl bromide via...


1-(3'-Chloro-4'-hydroxy-[1,1'-biphenyl]-3-yl)ethanone (3f)

Obtained as solid, mp = 516°C. 1H-NMR (600 MHz, CDCl3) δ: 8.04 (d, J1,2 = 7.2 Hz, 1H), 7.97 (d, J1,2 = 7.2 Hz, 1H), 7.53 (t, J2(1,3) = 7.2 Hz, 1H), 7.50-7.43 (m, 3H), 2.62 (s, 3H). 13C NMR (CDCl3, 150 MHz, δ, ppm): 27.0, 116.5, 125.6, 127.8, 127.9, 128.9, 129.0, 129.9, 131.2, 134.0, 136.7, 143.3, 156.0, 198.0. EIMS (m/z, + ion mode): [M+]+ = 246, [M+2]+ = 248.

3-Chloro-4'-(methylthio)-[1,1'-biphenyl]-4-ol (3g)

Obtained as solid, mp = 516°C. 1H-NMR (600 MHz, CDCl3) δ: 7.48-7.45 (m, 2H), 7.42 (d, J1,2 = 8.4 Hz, 1H), 7.36 (d, J1,3 = 8.4, J1,3 = 2.4 Hz, 1H), 7.29 (d, J1,2 = 7.2 Hz, 1H), 7.05 (d, J1,2 = 8.4 Hz, 2H), 2.53 (s, 3H). 13C NMR (CDCl3, 150 MHz, δ, ppm): 15.6, 115.6, 123.4, 126.7, 127.3, 128.1, 128.9, 129.2, 129.9, 133.2, 138.2, 139.0, 150.9. EI/MS (m/z, + ion mode): [M+]+ = 250, [M+2]+ = 252.

Computational methods

All calculations were performed by using Gaussian 09 software (9) and graphics were analyzed with the help of Gauss view 05 (10). Geometries of the transition states and intermediate products were optimized without any symmetry constraints by implementing a hybrid B3LYP method which provides nice balance between computational cost and accuracy (11-12). For geometries optimization, 6-31G (d) (13, 14) basis set was used for C, H, O, B, Br and Cl atoms and LANL2DZ pseudo potential was used for Pd atom. Every optimized geometry was confirmed by frequency analysis at the same level as a true minimum (no imaginary frequency) or as a transition state (with one imaginary frequency). The reported energies for all mechanistic steps are in kcal mol⁻¹.

Pharmacology

Biofilm inhibition assay by microtitre plate method

The novel biaryl derivatives were examined for their biofilm inhibition activity (15), where Ethylacetate was used for preparing solutions of test samples. In brief, the sample solution (100 µL) (3a–g), nutrient broth (100 µL) and the 20 µL of bacterial suspension were inoculated in 96-well plates. Rifampicin and nutrient broth were used as positive and negative controls, respectively. The incubation of well plates was done at 37°C for 24 h. Each plate was washed thrice by Phosphate-buffer solution (PBS) (220 µL), followed by shaking to remove adherent bacteria. The 95% methanolic solution (220 µL) was used to fix remaining bacteria from well plates, followed by oven drying.

Scheme 1. Synthesis of intermediate compound 4-bromo-2-chloro-1-(prop-2-yn-1-yloxy)benzene (2) and Suzuki cross coupling of (2) with various aryl boronic acids. Conditions: (i), 1 (1 g, 4.83 mmol), propargylbromide (0.68 g, 5.78 mmol), potassium carbonate (K₂CO₃) (2.33 g, 16.8 mmol), 80°C, dry acetone, reflux 5 h. (ii), 2 (0.1 g, 1 eq, 0.38 mmol) ArB(OH)₂ (1.1 eq, 0.71 mmol), K₃PO₄ (0.21 g, 1.02 mmol), Pd(PPh₃)₄ (0.011 g, 2.5 mol%), 1,4-dioxane: H₂O (4 : 1), reflux 18 h, 90°C.
For staining the plates, crystal violet (220 µL) was used (50% concentration) for 5 min. Excess stain was removed by tap water from these plates. For removing the remaining dye attached with cells, glacial acetic acid (220 µL) (33% concentration) was used. OD value of each well was examined with the help of the microplate reader (BioTek, Winooski, VT, USA) at 630 nm.

The Biofilm inhibition was quantified by measuring OD<sub>540</sub> using the following expression:

\[
\% \text{ Biofilm inhibition} = \frac{\text{OD growth control} - \text{OD sample control}}{\text{OD growth control}} \times 100
\]

**Assay of hemolytic activity**

The cytotoxicity of novel biaryl compounds (3a-g) was also tested using the previously reported method (16). In a typical procedure, a known amount of human blood (heparinized, 3 mL) was collected from the volunteers, which was centrifuged at 1000 rpm for 5 min. After discarding the plasma, chilled 5 mL (4°C) Phosphate-buffer saline (PBS) (pH ~7.4) was used to wash the cells thrice. For each assay, erythrocytes were maintained (108 cells/mL). After that, the synthesized compounds (100 µL) were mixed with blood cells separately and then the incubation of samples was done at 37°C for 35 min followed by agitation for 10 min. After incubation (for 5 min), the samples were further kept on ice, followed by centrifuge process (100 rpm for 5 min). The chilled buffer solution (4°C) was used for 10 times dilution of supernatants from each tube. As a positive control, the Triton X-100 (0.1% v/v) and as a negative control, the phosphate buffer saline (PBS) was used. Later on, the absorbance of the test solution was measured at 576 nm by using µ Quant (Biotek, USA). The percentage (%) lysis of RBCs of every sample was calculated accordingly.

**Analysis of Anti-Thrombolytic activity**

After the consent of healthy volunteers, the blood samples were collected accordingly. In the weighed micro-centrifuge, the blood (100 mL) was added to form the clots. Then in micro-tubes, the solution (100 µL) of the novel synthesized compounds with particular a concentration (1 mg/mL) was added, and incubation was done (37°C for 45 min). Streptokinase and deionized water were used as positive and negative controls respectively (16).

**RESULTS AND DISCUSSION**

**Chemistry**

The protection of aromatic amino or hydroxyl groups in the form of amine derivatives or ethers

**Table 1. Substrate scope of Suzuki coupling of 4-bromo-2-chloro-1-(prop-2-yn-1-yl)oxy benzene with variety of arylboronic acids.**

![Chemical structures of compounds 3a-g with their yields percentages.](image)
Selective arylation of phenol protected propargyl bromide via...

and their subsequent cleavage constitute a useful chemical transformation in organic synthesis. The presence of two orthogonal π-bonds in propargyl group further makes it attractive, which perhaps help in its facile cleavage in the presence of transition metal complexes (17-18).

In the present research work, we investigated the Suzuki reaction of 4-bromo-2-chloro-1-(prop-2-yn-1-yl-oxy)benzene (2) with different aryl boronic acids under optimal conditions. According to our survey, to date no such study has been reported on the synthesis and biological activities of various derivatives (3a-g) of 4-bromo-2-chloro-1-(prop-2-yn-1-yl-oxy)benzene. As presented in the Scheme 1, the first step is the synthesis of intermediate compound 4-bromo-2-chloro-1-(prop-2-yn-1-yl-oxy)
benzene (2), which was obtained in 90% yield from the reaction between 4-bromo-2-chlorophenol (1) and propargyl bromide (Scheme 1). In general, the aryl halides which are substituted with electron-withdrawing groups are appropriate substrates for the cross-coupling reaction (19). Since the hydroxyl group attached with the phenyl ring has electron donating ability, we first protected the -OH group before carrying out the Suzuki cross-coupling reaction.

In the second step, Suzuki coupling of (2) with various arylboronic acids was conducted that eventually led to the synthesis of various biaryl derivatives (3a-g) in high yields (80-88%) (Table 1). The Biaryl Compounds 3a and 3b were obtained with protected ether group; while compounds 3c-3g were de-propargylated to corresponding phenol in the reaction mixture.

In past, the Palladium catalyzed depropargylation (cleavage of C-O propargyl bond) of aryl propargyl ethers cleaved to the corresponding phenol has already been reported (17, 20). Various substituents on the phenyl ring of the starting ether (2) and aryl-boronic acids were well tolerated during the reaction. The structures of these novel synthesized compounds were characterized by Mass spectrometry, 1H-NMR, and 13C-NMR spectra.

**DFT study**

**Oxidative addition**

Recently, Huang and co-workers (21) proved that B3LYP/6-31G (d) with pseudopotential on Pd (LANL2DZ) is suitable to model the Suzuki coupling reaction. In order to confirm the selectivity of coupling at C-Br position over C-Cl, we started to form two complexes \( \text{Int1A} \) (Br) and \( \text{Int1B} \) (Cl).

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**Table 2. Biofilm inhibition (%) of Suzuki coupled compounds.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>Biofilm Inhibition%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>32.1 ± 0.25</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>65.8 ± 0.34</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>5.86 ± 0.05</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>25.8 ± 0.12</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>41.8 ± 0.21</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>54.6 ± 0.25</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>43.3 ± 0.43</td>
</tr>
<tr>
<td>8</td>
<td>Rifampicin</td>
<td>96.5 ± 0.65</td>
</tr>
</tbody>
</table>

The results are average ± S.D of three separate experiments \( p < 0.05 \)

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**Figure 3. Biofilm inhibition, Hemolytic and Anti-thrombolytic activities of novel biaryls (3a-g)**
Oxidative addition of palladium in the C-Br bond of Int1A is much more favorable than in case of Int1B (C-Cl). The oxidative addition transition state of TS1A is located at a barrier of 2.78 kcal mol\(^{-1}\) from Int1A, whereas the analogous transition state TS1B of C-Cl coupling from Int1B lies at a much more higher barrier of 9.79 kcal mol\(^{-1}\) as compared to TS1A (Fig. 1). This is in complete agreement with the experimental observation, where the products are dominantly obtained as a result of oxidative addition at C-Br bond. It is believed that the very low activation barrier for TS1A is due to the high reactivity of C-Br bond over the C-Cl bond. The C-Cl (2.07\(^{\circ}\)) and C-Pd (1.98\(^{\circ}\)) bond lengths in TS1B are shorter and stronger as compared to the C-Br (2.14\(^{\circ}\)) and C-Pd (1.99\(^{\circ}\)) bonds in case of TS1A. The oxidative addition step in both cases is exothermic by 17.2 and 17.25 kcal mol\(^{-1}\) from Int1A (Fig. 1) and Int1B (Fig. 2), respectively. Int2A and 2B (product of oxidative addition) have almost equal stability.

Transmetalation

Coordination of boronic acid with Int2A (C-Br) and Int2B (C-Cl) generates Int3A and Int3B, respectively. The intermediate Int3A, generated from the cleavage of C-Br bond is highly exothermic by 212.63 kcal mol\(^{-1}\), however, the cleavage of the Pd-Cl bond is very less exothermic by -1.31 kcal mol\(^{-1}\) and Intermediate Int3B, generated from cleavage of the Pd-Cl bond, is almost on the similar energy level compared to Int1B. The transmetalation transition state, translated form Int3A is exothermic by -179.61 kcal mol\(^{-1}\) as compared to the starting complex Int1A, whereas the analogous transition state from the Int3B is located at activation barrier of 1.86 kcal mol\(^{-1}\). Again the higher activation barrier of Pd-Cl transmetalation step is in accordance with the experimental results, that the formation of a product as a result of C-Cl bond coupling is negligible. The transmetalation product Int4A from TS3A is exothermic by -182.67 kcal mol\(^{-1}\) and Int4B from TS3B is exothermic by -32.27 kcal mol\(^{-1}\).

Reductive elimination

Very surprisingly, the reductive elimination step in both cases turned out to be the one with the very low activation barrier in the catalytic cycle for both coupling products (rate limiting step). The transition state TS5A from Int4A is exothermic and located at a barrier of -199.22 kcal mol\(^{-1}\) as compared to the Int1A. Similarly, the TS5B from Int4B is also exothermic and located at -17.30 kcal mol\(^{-1}\). From the overall computational results, it is concluded that the observed selectivity of C-Br coupling over C-Cl coupling may be attributed to the low activation barrier of the oxidative addition step of Int1A over Int1B, and to the associated with a very low activation barrier of the reductive elimination step and is complete agreement with the experimental products.

Pharmacology

Biofilm inhibition assay

The formation of biofilm by pathogenic bacteria causes various fatal infections that may lead to death in some worst cases. This film is an aggregation of bacterial cells, covered by a self-produced polymeric material (22). Inhibition of formation by novel biaryls (3a-g) was investigated against Escherichia coli, where the results revealed the moderate activity of most of the compounds (Fig. 3, Table 2). In particular, the compound 3b showed higher activity (65.8%) as compared to other compounds against E. coli, which might have its origin in the two electron withdrawing fluoro groups attached with the phenyl ring (23). On the other hand, other biaryls exhibited moderate activity, when compared with standard drug rifampicin. The biaryl 3e displayed the lowest activity 5.86%, which contains electron donating methyl moiety. Overall, the results reveal that all newly synthesized biaryls could be a potential source of biofilm inhibition at high concentrations.

Hemolytic activity

The cytotoxicity of novel biaryls (3a-g) was also studied in the present work. The biaryls 3e and 3f exhibited high hemolytic activity ~ 30.1 and 23.5%, respectively. Some of the novel biaryls viz. 3a, 3b, 3c, 3d, 3g exhibited hemolytic activity in a safe range (below 10%) (Table 3, Fig. 3). From the observed variations in the results of percentage lysis of RBCs, it is concluded that the electron withdrawing and electron donating substituents have a pronounced effect on the hemolytic activity of the compounds (24). Moreover, the cytotoxicity of the derivatives viz. 3e and 3f can be optimized by doing changes in the structure of molecules, for their practice as toxic compounds to inhibit the growth of cancer cells (25, 26).

Anti-thrombolytic Activity

Blood clot formation is a severe problem that hinders the blood circulation in the human body. Thrombus obstructs the blood flow by blocking the blood vessel, therefore hindering the tissues of normal blood flow and oxygen. These consequences led to the necrosis of tissues in that area. Many drugs
such as ticlopidine, heparin, clopidogrel, urokinase, streptokinase and plasminogen activator (t-PA) have been explored as the clot lysis agents. However, for clinical practice, only some were found of potentially beneficial (27-30). In this research work, we explored the anti-thrombolytic potential of novel biaryl derivatives (3a-g). The results showed that the compound 3f exhibited appreciable thrombolytic activity (~42.5%), while 3g and 3d displayed moderate % lysis ~ 23.4 and 21.2%, respectively. The standard drug streptokinase, however, exhibited high % lysis ~ 87.4%. The compounds 3b, 3a, and 3e exhibited reasonable % lysis, while the compound 3c was found inactive against clot lysis. The biaryls 3f, 3g, and 3d exhibited reasonable % lysis, which can be attributed to -COCH3, -SCH3 and -OCH3 substituents attached to the aromatic system. Overall, it can be seen that the anti-thrombolytic activity showed by biaryls (3a-g) have a large effect from the nature of attached substituents (23) (Table 4, Fig. 3).

CONCLUSIONS

The present study reports the synthesis of various novel biaryls (3a-g) with efficient yields under mild optimized conditions. The density functional theory studies revealed that the oxidative addition and transmetalation steps are the rate controlling steps. Energies of located transitions structures of all steps proved that C-Br coupling is preferred over C-Cl coupling. The synthesized novel biaryls exhibited good biofilm inhibition, hemolytic and anti-thrombolytic activities. From the observed variations in the results, it is concluded that the electron withdrawing and donating substituents have a pronounced effect on the biological activities of these newly synthesized biaryl derivatives. Our experimental results revealed that these compounds could be a potential source of pharmaceutical agents at higher concentrations.

Table 3. Hemolytic activity % of Suzuki coupled compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>Hemolytic activity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>2.64 ± 0.12</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>5.76 ± 0.05</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>6.32 ± 0.07</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>1.32 ± 0.09</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>30.1 ± 0.16</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>23.5 ± 0.13</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>1.59 ± 0.02</td>
</tr>
<tr>
<td>8</td>
<td>PBS</td>
<td>1.09 ± 0.01</td>
</tr>
<tr>
<td>9</td>
<td>Triton-X-100</td>
<td>98.4 ± 0.72</td>
</tr>
</tbody>
</table>

The results are average ± S.D of three separate experiments p < 0.05

Table 4. Anti-Thrombolytic activity % of Suzuki coupled compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compounds</th>
<th>% Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>12.5 ± 0.25</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>12.9 ± 0.23</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>21.2 ± 0.19</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>9.64 ± 0.09</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>42.5 ± 0.45</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>23.4 ± 0.21</td>
</tr>
<tr>
<td>9</td>
<td>Streptokinase</td>
<td>87.4 ± 0.83</td>
</tr>
</tbody>
</table>

The results are average ± S.D of three separate experiments p < 0.05
Acknowledgments

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Author contributions

HF, NR, HI, TM designed and performed the experiments, MTA, KR and KA analysed the data and contributed to the writing of the manuscript. TR, MNASZ and SI contributed in the technical refining of the data.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES


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