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Synthesis of 1,4-disubstituted 1,2,3-triazole Derivatives Using Click Chemistry and their Src Kinase Activities

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Abstract: A series of 1,4-disubstituted 1,2,3-triazoles derivatives (**3**) were designed and prepared as potential inhibitors for Src kinase. In this manuscript, all of the designed compounds were screened via molecular docking using PLANTS as virtual screening software to identify new inhibitors of Src kinase. As expected, the results of the docking study revealed that most of these targeted compounds possessed low binding energy. Subsequently, all of the screened compounds were synthesized via Huisgen's 1,3-dipolar cycloaddition between terminal alkynes (**1**) and methyl 2-azidoacetate (**2**) with Cu(I) in excellent yields at room temperature. The synthesized triazoles (**3**) were characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectral techniques and they were investigated as inhibitors of Src kinase.

Among these compounds, **3m** exhibited the most potent inhibitory activity against Src kinase.

Keywords: 1,2,3-triazole, molecular docking, Huisgen's 1,3-dipolar cycloaddition, PEG400, Click chemistry, Src kinase.

1. INTRODUCTION

Tyrosine kinases (TK) are enzymes that catalyze the phosphorylation of Tyrosine residues on proteins by the transfer of -phosphate moiety of ATP. TK are key regulators of various cell functions, such as cellular growth, proliferation, migration, differentiation, and apoptosis [1]. The Src family of kinases (SFKs) are non-receptor tyrosine kinases. Since Src is involved in several cell signaling pathways, inhibition of Src activity could be effective for the treatment of various diseases, including cancer [2,3]. Src mutations and/or overexpression has been correlated with tumor growth, metastasis, and angiogenesis [4,5]. Thus, the design and the discovery of novel Src kinase inhibitors remains critically important.

Quinoline carbonitriles [6–9], ATP-phosphopeptide conjugates [10], pyrazolopyrimidines [11], purines [12,13], imidazo[1,5-a]-pyrazines [14], benzotriazines [15], pyrimidoquinolines [16], pyridopyrimidinones [17], quinazolines [18] and more recently 1,4-disubstituted 1,2,3-triazoles [19] have been reported to target Src Kinase.

There has been a great interest in the development of five-membered nitrogen heterocycles in medicinal chemistry. Among them, 1,2,3-triazole heterocycles containing molecules are reported to possess a large biological spectrum as antimicrobial [20–22], antimalarial [23], antihistaminic
[24], antifungal [25,26], anti-Hiv [27,28], antitubercular [29]

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and anticancer agents [30,31]. Good stability and high aqueous solubility of these compounds in biological systems are appreciable. Moreover, this scaffold can be tuned to form powerful pharmacophores and also play an important role in bioconjugation [32].

Huisgen's cycloaddition, the general method for the synthesis of 1,4-disubstituted 1,2,3-triazoles, involves a 1,3dipolar cycloaddition between azides and alkynes under thermal conditions to afford an equal mixture of 1,4- and 1,5-disubstituted isomers [33]. Sharpless and co-workers have reported remarkable high-yielding syntheses with excellent regioselectivity [34,35]. The Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes is the model example of a click chemistry, to give only 1,4disubstituted 1,2,3-triazoles.

In the present study, we report the design and the synthesis of a series of 1,4-disubstituted 1,2,3-triazoles involving one pot condensation of methyl 2-azidoacetate and different terminal alkynes. All the synthesized triazoles were characterized by IR, ^{1}H, ^{13}C, ^{19}F NMR, and HRMS. They were investigated as inhibitors of Src kinase.

2. EXPERIMENTAL

2.1. Chemistry

All reagents were purchased from the Aldrich Chemical Co. and used without any purification. Solvents were distilled from the appropriate drying agents immediately prior to use. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 300.13 MHz, 282.37 MHz and 75.46 MHz respectively with a Brucker Avance 300 spectrometer; the chemical shifts are given in ppm relative to Me$_4$Si for the ^{1}H and ^{13}C, and CCl$_3$F for ^{19}F, as internal standards. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, dd = double doublet, dt = double of triplet, m = multiplet), coupling constants (Hz), integration. High resolution mass spectra (HRMS) were obtained by electrospray using a TOF analyzer Platform. IR spectra were obtained using a Jasco FT-IR 410 instrument (cm1) as a thin film on NaCl disc as stated. Reactions

were monitored with Merck Kieselgel 60F$_{254}$ precoated aluminium silica gel plates (0.25 mm thickness). Melting points were determined on a Stuart scientific SMP10 apparatus and are uncorrected. Flash chromatographies were performed on a Grace Reveleris X2 using 40m packed silica cartridge. Purity of the compounds were determinate by HPLC-UV at 254 nm Flash chromatographies experiments were carried out on Silica Gel premium Rf grade (40-63 m) or were performed on a Grace Reveleris X2 using 40m packed silica cartridge. HPLC analyses were obtained on the Waters Alliance 2795 using the following conditions : thermo Hypersil C18 column (3 m, 50 mm L x 2.1 mm ID), 20°C column temperature, 0.2 mL/min flow rate, photodiodearray detection (210400 nm), mobile phase consistent of a gradient of water and acetonitrile (each containing 0.1% trifluoroacetic acid).

2.2.   General Synthetic Procedure : Huisgen's 1,3-Dipolar Cycloaddition of Azides and Alkynes

Method A: Alkyne (1.00 eq.) and azide (1.00 eq.) were dissolved in tBuOH/H$_2$O (1:1, v/v). Solid CuI was added (0.05 eq., 5 mol%) and solid sodium ascorbate (0.10 eq., 10 mol %) were added. The reaction mixture was stirred at room temperature for 12 to 72h. Reactions were monitored by TLC and when the reaction is finished ethyl acetate was added. The mixture was extracted three times with ethyl acetate, the organic phases were washed with saturated NaCl, combined and dried over MgSO$_4$. EtOAc was evaporated under reduced pressure to give the crude product. The residue was purified by flash column chromatography (silica gel, EtOAc:Cyclohexane = 1:9 ramping to EtOAc) to give the desired triazoles.

Method B: Alkyne (1.00 eq.) and azide (1.00 eq.) were dissolved PEG 400/ H$_2$O (1:1, v/v, 2 mL). Solid CuSO$_4$ was added (0.05 eq., 5 mol%) and solid sodium ascorbate (0.10 eq., 10 mol %) were added. The reaction mixture was allowed to stir at room temperature for 1-8h. After the reaction was complete, as indicated by TLC, the reaction mixture was diluted with water and filtered at the pump to collect the product or extracted with ethyl acetate (3 2 ml). The organic layer was dried over anhydrous sodium sulfate and distilled using rotary vacuum evaporator. The afforded crude product was recrystallized from cyclohexane.

2.2.1. Synthesis of methyl 2-(4-(2-aminophenyl)-1H-1,2,3triazol-1-yl)acetate (3a)

R$_f$ = 0.4 (Cyclohexane/EtOAc, 1:1, v/v); Yellow solid; mp: 113-115°C; IR: 3452 (NH), 3333 (NH), 1753 (C=O ester). Yield=99%; ^{1}H NMR (300.13 MHz, DMSO) 8.51 (s, 1H, C=C**H**-N), 7.44 (dd, J = 7.7, 1.1 Hz, 1H, **Har**), 7.16 – 6.92 (m, 1H, **Har**), 6.78 (d, J = 8.0 Hz, 1H, **Har**), 6.60 (t, J =
7.4 Hz, 1H, **Har**), 6.17 (s, 2H, C-N**H₂**), 5.48 (s, 2H, N-C**H₂**C=O), 3.74 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.6 (**C**=O), 147.3 (C-**C**-N=), 145.6 (**C**ar), 128.5 (**C**Har), 127.5 (**C**Har), 122.6 (**C**=CH-N), 116 (**C**Har), 115.8 (**C**Har), 112.4 (**C**ar), 52.6 (O-**C**H$_3$), 50.4 (N-**C**H$_2$). HRMS (M+H$^+$): 233.1039 calcd for C$_{11}$H$_{12}$N$_4$O$_2$; 233.1038 found.

2.2.2. Synthesis of methyl 2-(4-(3-aminophenyl)-1H-1,2,3triazol-1-yl)acetate (3b)

R$_f$ = 0.1 (Cyclohexane/EtOAc, 1:1, v/v); Pale brown solid; mp: 98-100°C; IR: 3431 (NH), 3350 (NH), 3135 (CHar) 1737 (C=O ester); Yield = 100%; ^{1}H NMR (300.13 MHz, DMSO) 8.39 (s, 1H, C=C**H**-N), 7.12 – 7.04 (m, J = 10.2, 5.0 Hz, 2H, **Har**), 6.93 (d, J = 7.6 Hz, 1H,
Har), 6.53 (dd, J = 7.9, 1.3 Hz, 1H, **Har**), 5.44 (s, 2H, NC**H₂**-C=O), 5.21 (s, 2H, C-N**H₂**), 3.73 (s, 3H, O-C**H₃**); ^{13}C
NMR (75 MHz, DMSO) 167.7 (**C**=O), 149.1 (C-**C**-N=), 147 (**C**ar), 131.1 (**C**ar), 129.4 (**C**Har), 122.2 (**C**=CH-N),
113.6 (**C**Har), 113.2 (**C**Har), 110.4 (**C**Har), 52.5 (O-**C**H$_3$), 50.3 (N-**C**H$_2$). HRMS (M+H$^+$): 233.1039 calcd for
C$_{11}$H$_{12}$N$_4$O$_2$; 233.1036 found.

2.2.3. Synthesis of methyl 2-(4-(4-aminophenyl)-1H-1,2,3triazol-1-yl)acetate (3c)

R_f = 0.1 (Cyclohexane/EtOAc, 1:1, v/v); Yellow solid; mp: 147-149°C; IR: 3429 (NH), 3357 (NH), 3108 (CHar) 1745 (C=O ester); Yield =70%; ^{1}H NMR (300.13 MHz, DMSO) 8.25 (s, 1H, C=C**H**-N), 7.49 (d, J = 8.4 Hz, 2H, **Har**), 6.61 (d, J = 8.4 Hz, 2H, **Har**), 5.40 (s, 2H, NC**H₂**-C=O), 5.26 (s, 2H, C-N**H₂**), 3.72 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.8 (**C**=O), 148.7 (C-**C**-N=), 147.3 (**C**ar), 126.1 (**C**Har), 120.5 (C=**C**H-N), 118 (**C**ar), 113.9 (**C**Har), 52.5 (O-**C**H₃), 50.3 (N-**C**H₂). HRMS (M+H⁺): 233.1039 calcd for $C_{11}H_{12}N_4O_2$; 233.1040 found.

2.2.4. Synthesis of methyl 2-(4-(o-tolyl)-1H-1,2,3-triazol-1yl)acetate (3d)

R_f = 0.5 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 66-68°C; IR: 3146 (CHar), 1755 (C=O ester); Yield = 27%; ^{1}H NMR (300.13 MHz, DMSO) 8.42 (s, 1H, C=C**H**N), 7.86 – 7.65 (m, 1H, **Har**), 7.44 – 7.15 (m, 3H, **Har**), 5.48 (s, 2H, N-C**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**), 2.43 (s, 3H, C-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.7 (**C**=O), 145.5 (C-**C**-N=), 134.8 (**C**ar), 130.9 (**C**Har), 129.7 (**C**ar), 128 (**C**Har), 127.8 (**C**Har), 126.1 (**C**Har), 124.7 (C=**C**H-N), 52.5

(O-**C**H₃), 50.3 (N-**C**H₂), 21.1 (Car-**C**H₃). HRMS (M+H⁺): 232.1086 calcd for $C_{12}H_{14}N_3O_2$; 232.1089 found.

2.2.5. Synthesis of methyl 2-(4-(m-tolyl)-1H-1,2,3-triazol-1yl)acetate (3e)

R_f = 0.5 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 64-66°C; IR: 3127 (CHar), 1747 (C=O ester); Yield = 60%; ^{1}H NMR (300.13 MHz, DMSO) 8.54 (s, 1H, C=C**H**N), 7.70 (s, 1H, **Har**), 7.64 (d, J = 7.7 Hz, 1H, **Har**), 7.34 (t, J = 7.6 Hz, 1H, **Har**), 7.16 (d, J = 7.5 Hz, 1H, **Har**), 5.47 (s, 2H, N-C**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**), 2.36 (s, 3H, CC**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.7 (**C**=O), 146.4 (C**C**-N=), 138.1 (**C**ar), 130.4 (**C**ar), 128.8 (**C**Har), 128.6 (**C**Har), 125.7 (**C**Har), 122.6 (C=**C**H-N), 122.3 (**C**Har), 52.6 (O-**C**H₃), 50.4 (N-**C**H₂), 21 (Car-**C**H₃). HRMS (M+H⁺):
232.1086 calcd for $C_{12}H_{14}N_3O_2$; 232.1087 found.

2.2.6. Synthesis of methyl 2-(4-(p-tolyl)-1H-1,2,3-triazol-1yl)acetate (3f)

R_f = 0.5 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp 118-120°C, lit: 116-117°C [36]; IR: 3135 (CHar), 1760 (C=O ester); Yield = 54%; ^{1}H NMR (300.13 MHz, DMSO) 8.51 (s, 1H, C=C**H**-N), 7.75 (d, J = 8.0 Hz, 2H, **Har**), 7.27 (d, J = 8.0 Hz, 2H, **Har**), 5.46 (s, 2H, N-C**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**), 2.33 (s, 3H, C-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.7 (**C**=O), 146.4 (C-**C**-N=), 137.3 (**C**ar), 129.5 (**C**Har), 127.7 (**C**ar), 125.1 (**C**Har), 122.3 (C=**C**H-N), 52.5

(O-**C**H₃), 50.4 (N-**C**H₂), 20.8 (Car-**C**H₃). HRMS (M+H⁺): 232.1086 calcd for $C_{12}H_{14}N_3O_2$; 232.1087 found.

2.2.7. Synthesis of methyl 2-(4-(2-chlorophenyl)-1H-1,2,3triazol-1-yl)acetate (3g)

R_f = 0.6 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp 69-71°C; IR: 3145 (CHar), 1741 (C=O ester); Yield = 49%; ^{1}H NMR (300.13 MHz, DMSO) 8.73 (s, 1H, C=C**H**N), 8.13 (dd, J = 7.6, 1.9 Hz, 1H, **Har**), 7.59 (dd, J = 7.8, 1.2 Hz, 1H, **Har**), 7.52 – 7.36 (m, 2H, **Har**), 5.51 (s, 2H, NC**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.7 (**C**=O), 142.5 (C-**C**-N=), 130.3 (**C**Har), 130.2 (**C**ar), 129.5 (**C**Har), 129.4 (**C**Har), 128.9 (**C**ar), 127.6 (**C**Har), 125.7 (C=**C**H-N), 52.6 (O-**C**H₃), 50.4 (N-**C**H₂). HRMS (M+H⁺): 252.0540 calcd for $C_{11}H_{11}N_3O_2Cl$; 252.0544 found.

2.2.8. Synthesis of methyl 2-(4-(3-chlorophenyl)-1H-1,2,3triazol-1-yl)acetate (3h)

R_f = 0.6 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 100-102°C; IR: 3127 (CHar), 1747 (C=O ester); Yield = 68%; ^{1}H NMR (300.13 MHz, DMSO) 8.73 (s, 1H, C=C**H**-N), 8.13 (dd, J = 7.6, 1.9 Hz, 1H, **Har**), 7.59 (dd, J = 7.8, 1.2 Hz, 1H, **Har**), 7.52 – 7.36 (m, 2H, **Har**), 5.51 (s, 2H, N-C**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.6 (**C**=O), 145.0 (C-**C**-N=), 133.7 (**C**ar), 132.5 (**C**ar), 130.9 (**C**Har), 127.7 (**C**Har), 124.7 (**C**Har), 123.7 (**C**Har), 123.5 (C=**C**H-N), 52.6 (O-**C**H₃), 50.5 (N-**C**H₂). HRMS (M+H⁺): 252.0540 calcd for $C_{11}H_{11}N_3O_2Cl$; 252.0543 found.

2.2.9. Synthesis of methyl 2-(4-(4-chlorophenyl)-1H-1,2,3triazol-1-yl)acetate (3i)

R_f = 0.4 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 143-145°C; IR: 3127 (CHar), 1743 (C=O ester); Yield = 27%; ^{1}H NMR (300 MHz, DMSO) 8.62 (s, 1H, C=C**H**-N), 8.11 – 7.77 (m, 2H, **Har**), 7.70 – 7.41 (m, 2H, **Har**), 5.49 (s, 2H, N-C**H₂**-C=O), 3.74 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.6 (**C**=O), 145.3 (C-**C**-N=), 132.4 (**C**ar), 129.4 (**C**ar), 129.0 (**C**Har), 126.8 (**C**Har), 123.1 (C=**C**H-N), 52.6 (O-**C**H₃), 50.5 (N-**C**H₂). HRMS (M+H⁺): 252.0540 calcd for $C_{11}H_{11}N_3O_2Cl$; 252.0542 found.

2.2.10. Synthesis of methyl 2-(4-(2-fluorophenyl)-1H-1,2,3triazol-1-yl)acetate (3j)

R_f = 0.6 (Cyclohexane/EtOAc, 1:1, v/v); Pale brown solid; mp: 85-87°C; IR: 3169 (CHar), 1742 (C=O ester); Yield = 10%; ^{1}H NMR (300.13 MHz, DMSO) 8.49 (d, J = 3.9 Hz, 1H, C=C**H**-N), 8.16 (td, J = 7.6, 1.6 Hz, 1H, **Har**),

7.50 – 7.28 (m, 3H, **Har**), 5.50 (s, 2H, N-C**H₂**-C=O), 3.73 (s, 3H, O-C**H₃**); ^{13}C NMR (75 MHz, DMSO) 167.6 (**C**=O),

158.4 (d, J = 247.0 Hz, F-**C**ar), 139.6 (d, J = 2.0 Hz, C-**C**N=), 129.7 (d, J = 8.4 Hz, **C**Har), 127.2 (d, J = 3.2 Hz, **C**Har), 125.2 (d, J = 11.7 Hz , C=**C**H-N), 125 (d, J = 2.9 Hz, **C**Har), 118.1 (d, J = 13.0 Hz, **C**ar), 116.0 (d, J = 21.3 Hz, **C**Har), 52.5 (O-**C**H$_3$), 50.4 (N-**C**H$_2$); ^{19}F NMR (282 MHz, DMSO) -114.8. HRMS (M+H$^+$): 236.0835 calcd for C$_{11}$H$_{11}$N$_3$O$_2$F; 236.0837 found.

2.2.11. Synthesis of methyl 2-(4-(3-fluorophenyl)-1H-1,2,3triazol-1-yl)acetate (3k)

R$_f$ = 0.3 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 113-115°C; IR: 3110 (CHar), 1745 (C=O ester); Yield = 18%; ^{1}H NMR (300.13 MHz, DMSO) 8.64 (s, 1H, C=C**H**N), 7.69 (ddd, J = 5.5, 4.0, 1.1 Hz, 2H, **Har**), 7.51 (td, J = 7.9, 6.2 Hz, 1H, **Har**), 7.25 − 7.07 (m, 1H, **Har**), 5.49 (s, 2H, N-C**H$_2$**-C=O), 3.74 (s, 3H, O-C**H$_3$**); 13C NMR (75 MHz, DMSO) 167.6 (**C**=O), 162.6 (d, J = 243.2 Hz, F-**C**ar), 145.3 (C-**C**-N=), 132.8 (d, J = 8.5 Hz, **C**ar), 131.1 (d, J = 8.5 Hz, **C**Har),123.4 (C=**C**H-N), 121.2 (d, J = 2.1 Hz, **C**Har), 114.7 (d, J = 21.1 Hz, **C**Har), 111.7 (d, J = 23.0 Hz, **C**Har), 52.6 (O-**C**H$_3$), 50.5 (N-CH2); ^{19}F NMR (282 MHz, DMSO) -112.6. HRMS (M+H$^+$): 236.0835 calcd for C$_{11}$H$_{11}$N$_3$O$_2$F; 236.0839 found.

2.2.12. Synthesis of methyl 2-(4-(4-fluorophenyl)-1H-1,2,3triazol-1-yl)acetate (3l)

R$_f$ = 0.4 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 121-123°C; IR: 3109 (CHar), 1744 (C=O ester); Yield = 66%; ^{1}H NMR (300.13 MHz, DMSO) 8.56 (s, 1H, C=C**H**N), 8.05 – 7.79 (m, 2H, **Har**), 7.47 – 7.15 (m, 2H, **Har**), 5.47 (s, 2H, N-C**H$_2$**-C=O), 3.74 (s, 3H, O-C**H$_3$**); ^{13}C NMR
(75 MHz, DMSO) 167.6 (**C**=O), 161.8 (d, J = 244.5 Hz, F**C**ar), 145.5 (C-**C**-N=), 127.2 (d, J = 8.2 Hz, **C**Har), 127 (d, J = 2.9 Hz, **C**ar), 122.6 (C=**C**H-N), 115.9 (d, J = 21.7 Hz, **C**Har), 52.6 (O-**C**H$_3$), 50.4 (N-CH2); ^{19}F NMR (282 MHz, DMSO) -113.9. HRMS (M+H$^+$): 236.0835 calcd for C$_{11}$H$_{11}$N$_3$O$_2$F; 236.0839 found.

2.2.13. Synthesis of methyl 2-(4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl)acetate (3m)

R$_f$ = 0.2 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 131-133°C; IR: 3289 (OH), 3051 (CHar), 1729 (C=O ester); Yield= 99%; ^{1}H NMR (300.13 MHz, DMSO) 9.57 (s, 1H, -O**H**), 8.49 (s, 1H, C=C**H**-N), 7.38 – 7.15 (m,
3H, **Har**), 6.85 – 6.65 (m, 1H, **Har**), 5.45 (s, 2H, N-C**H$_2$**C=O), 3.73 (s, 3H, O-C**H$_3$**); ^{13}C NMR (75 MHz, DMSO) 168 (**C**=O), 157.7 (**C**ar), 146.4 (C-**C**-N=), 131.6 (**C**ar), 130 (**C**Har), 122.6 (C=**C**H-N), 116 (**C**Har), 115 (**C**Har), 111.8 (**C**Har), 52.5 (N-**C**H$_2$), 50.4 (N-**C**H$_2$). HRMS (M+H$^+$): 234.0879 calcd for C$_{11}$H$_{11}$N$_3$O$_3$; 234.0880 found.

2.2.14. Synthesis of methyl methyl 2-(4-(thiophen-3-yl)-1H-1,2,3-triazol-1-yl)acetate(3n)

R$_f$ = 0.4 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 80-82°C; IR: 3111 (CHar), 1731 (C=O ester); Yield = 80%; ^{1}H NMR (300.13 MHz, DMSO) 8.43 (s, 1H, C=C**H**-N), 7.89 (d, J = 2.9 Hz, 1H, **Har**), 7.66 (dd, J = 5.0, 2.9 Hz, 1H, **Har**), 7.53 (d, J = 5.0 Hz, 1H, **Har**), 5.47 (s, 2H, N-C**H$_2$**-C=O), 3.73 (s, 3H, O-C**H$_3$**); ^{13}C NMR (75 MHz, DMSO) 167.7 (**C**=O), 142.9 (C-**C**-N=), 131.8 (C**3**), 127.2
(**C**Har), 125.7 (**C**Har), 122.4 (**C**Har), 120.9 (**C**Har), 52.5 (N**C**H$_2$), 50.3 (N-**C**H$_2$). HRMS (M+H$^+$): 224.0494 calcd for C$_9$H$_9$N$_3$O$_2$S; 224.0497 found.

2.2.15. Synthesis of methyl 2-(4-(pyridin-2-yl)-1H-1,2,3triazol-1-yl)acetate (3o)

White solid; mp: 77-79°C; IR: 3135 (CHar), 1752 (C=O ester); Yield =100%; ^{1}H NMR (300.13 MHz, DMSO) 8.68 – 8.46 (m, 2H, C=CH-N, Har), 8.05 (d, J = 7.9 Hz, 1H, Har), 7.90 (td, J = 7.7, 1.8 Hz, 1H, Har), 7.35
(ddd, J = 7.5, 4.9, 1.1 Hz, 1H, Har), 5.49 (s, 1H, N-CH$_2$C=O), 3.74 (s, 2H, O-CH$_3$); ^{13}C NMR (75 MHz, DMSO) 167.6 (C=O), 149.7 (C-C-N=), 149.7 (CHar), 147.2 (Car), 137.2 (CHar), 124.6 (C=CH-N), 123.0 (CHar), 119.4 (CHar), 52.6 (O-CH$_3$), 50.4 (N-CH$_2$). HRMS (M+H$^+$): 219.0882 calcd for C$_{10}$H$_{11}$N$_4$O$_2$; found 219.0883.

2.2.16. Synthesis of methyl 2-(4-(pyridin-3-yl)-1H-1,2,3triazol-1-yl)acetate (3p)

R$_f$ = 0.4 (Cyclohexane/EtOAc, 1:1, v/v); White solid; mp: 104-106°C; IR: 3110 (CHar), 1745 (C=O ester); Yield =56%; ^{1}H NMR (300 MHz, DMSO) 9.07 (s, 1H, **Har**), 8.70 (s, 1H, C=C**H**-N), 8.56 (d, J = 2.5 Hz, 1H, **Har**), 8.24 (dt, J = 7.9, 1.7 Hz, 1H, **Har**), 7.50 (dd, J = 7.9, 4.8 Hz, 1H, **Har**), 5.52 (s, 2H, N-C**H$_2$**-C=O), 3.74 (s, 3H, O-C**H$_3$**); ^{13}C NMR (75 MHz, DMSO) 167.6 (**C**=O), 149 (**C**Har), 146.3 (**C**Har), 143.6 (C-**C**-N=), 132.4 (**C**Har), 126.4 (**C**ar), 124.1 (**C**Har), 123.4 (C=**C**H-N), 52.6 (O-**C**H$_3$), 50.5 (N-**C**H$_2$). HRMS (M+H$^+$): 219.0882 calcd for C$_{10}$H$_{11}$N$_4$O$_2$; found 219.0884.

2.3.   Computational Studies: Preparation of Enzyme and Compounds for Docking

The crystal structure of Src kinase was extracted from Protein Data Bank (PDB code: 2SRC) [36]. All the water molecules and heteroatoms were removed and hydrogen atoms were added to the protein. The protein was completed and reprotonated

with SPORE [37]. The chemical structures of all the synthesized compounds were generated using MarvinSketch and were subsequently converted into 3D format using Open Babel [38]. A series of docking experiment were carried out with all the designed triazoles derivatives against Src using PLANTS [39] for possible kinase inhibition activities. The compounds were selected on the basis of their scores and those reflecting good affinity were re-scored with DSX [40]. As a parameter for the molecular docking, the ant algorithm was set to 1 (highest reliability). The binding site was defined as a 18Å radius pocket centered on hinge's E339 in order to be sure that the inhibitors could fit in the kinase active site. The number of poses was set to 10 and the AMP-PNP was used as a shape constraint. The finally obtained docked complexes were subsequently visualized using PyMol.

2.4. Biological Evaluations

Src Kinase activity assays.

The effects of synthesized compounds on the activity of src kinase was determined by Z'Lyte biochemical assay kit from Life Technologies, according to manufacturer's protocol (Invitrogen, catalogue n°P3044). Reactions were performed in 384 well low volume black non binding surface round bottom microplate (Corning n°3676). Briefly, test compounds were added to plate in the presence of ATP and specific substrates in Src kinase solution, and incubated for 1h at room temperature before the addition of Development reagent solution. After the application of stabilizer solution, fluorescence polarization values were measured at 485/530 nm using a fluorescence reader. All compounds were dissolved in DMSO and diluted in buffer, yielding a final DMSO concentration of 1% in the assay.

3. RESULTS AND DISCUSSION

3.1. Molecular Docking Analysis

To achieve this goal within a reasonable timeframe, we needed a rapid and robust docking tool. Docking studies have been used previously to find novel inhibitors with different biological properties [41–43] in particular in the discovery of Src kinase inhibitors [44–47]. Our studies were performed with the software PLANTS as virtual screening software and 16 compounds were evaluated. The analysis of the docking results showed that two of the compounds, namely **3b** and **3m**, have a good score (Fig. **1**).
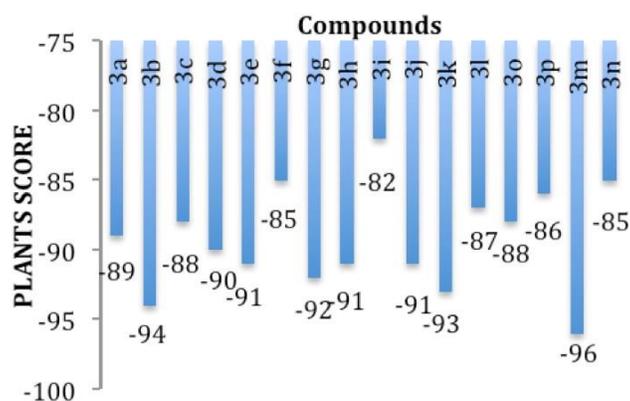

Fig. (1). Docking score of compounds (3a-3p) obtained from PLANTS.

Both compounds show a hydrogen bond donor group in the meta position of the phenyl ring. All the compounds are in the ATP binding pocket and showed two different binding types on the hinge kinases. The first binding type is for compounds **3a-c**, **3m-p**. The compounds **3a-c** and **3m** possess a hydrogen bond donor group and hence are capable of forming hydrogen bond with the hinge of Src kinase, especially with the C=O of GLU339 (Fig. **2a**) and compounds **3n-p** possess an acceptor group and show hydrogen bonding on the -NH group of MET341 (Fig. **2b**). Compounds **3b** and **3m** also possess a good DSX prediction (Fig. **3**).

The second binding mode involves the triazole moiety. Compounds **3d-i** don't have any substituent able to establish hydrogen bonds, whereas compounds **3j-l** may be able to establish hydrogen bonds thanks to the fluorine group. In this case, one of the nitrogen of the triazole group form the hydrogen bond with the -NH group of MET341 (Fig. **4**).
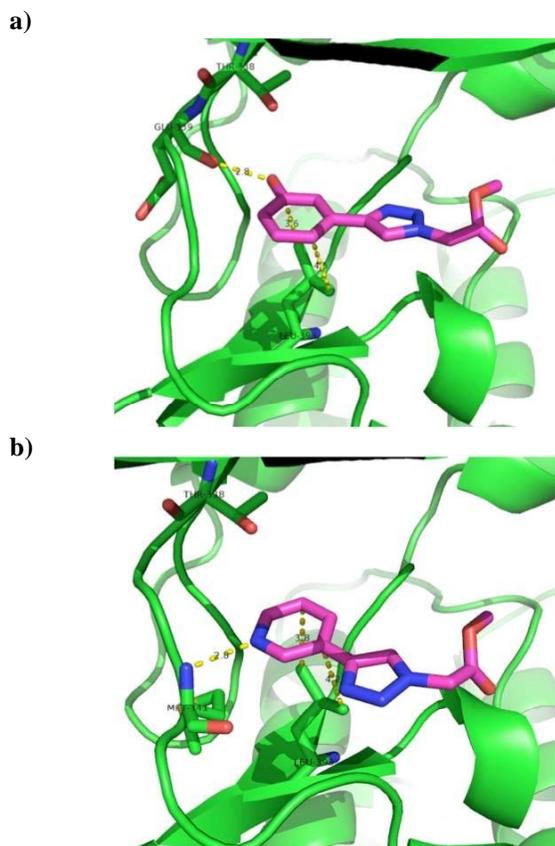
a)

b)

Fig. (2). Binding modes of compounds **3m** and **3p** calculated with PLANTS.

a) Binding mode of compound **3m** calculated with PLANTS. The ligand is shown in pink and stick, c-Src (PDB 2SRC) is represented in green and cartoon, GLU339, gatekeeper residue THR338 and ILE393 are represented in sticks. The distance between the oxygen of the phenol group and the oxygen of the –C=O of GLU339 equals to 2.8Å and hydrophobic interactions between ILE CH_3 and pyridine moiety are between 3.6 and 4.5Å. **b)** Binding mode of compound **3p** calculated with PLANTS. The ligand is shown in pink and stick, c-Src (PDB 2SRC) is represented in green and cartoon, MET341 and ILE393 are represented in stick. The distance between the nitrogen of the pyridine group and the nitrogen of the –NH of MET341 equals to 2.8Å and hydrophobic interactions between ILE CH_3 and pyridine moiety are between 3.8 and 4.2Å.

In our studies, we predicted that the synthesized molecules may be able to form hydrogen bond with the kinase hinge or with the gatekeeper residue, while earlier report showed modest inhibitory potency because of hydrophobic interactions [19].

3.2. Chemistry

For further development, we decided to synthesize the designed compounds by Huisgen's 1,3-dipolar cycloaddition (Scheme **1**).

In method A, the reaction of substituted terminal alkynes **1**, methyl 2-azidoacetate **2**, copper iodide (5 mol %) and NaAscorbate, in a mixture of solvent t-BuOH/H_2O, at room temperature, afforded the 1,4-disubstituted 1,2,3-triazoles **3a-3p** in moderate **3c-3l**, **3p** to good yield **3a-b**, **3m-o** after purification by column chromatography (Scheme **1**, Table **2**).
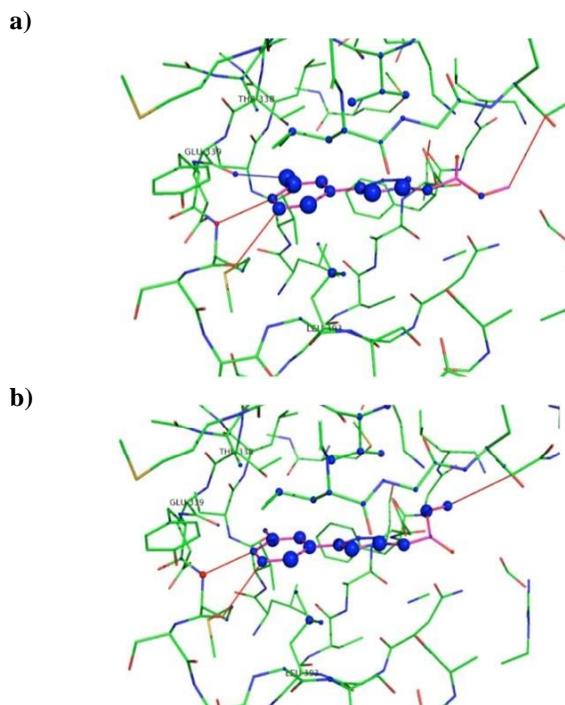
a)

b)

Fig. (3). DSX prediction for compounds **3b** (a) and **3m** (b). DSX prediction for compounds **3b** and **3m** blue spheres represents favorable interactions, red spheres represent bad interactions, blue lines represent good distances and red lines bad distances.
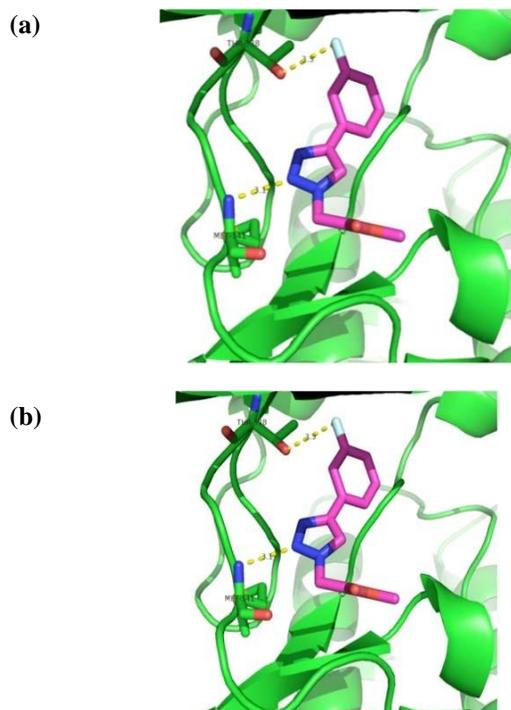
(a)

(b)

Fig. (4). Binding mode of compound 3k calculated with PLANTS (a) and DSX evaluation (b).
(a) Binding mode of compound **3k** calculated with PLANTS. The ligand is shown in pink and stick, c-Src (PDB 2SRC) is represented in green and cartoon, MET341 and the gatekeeper residue THR338 are represented in sticks. The distance between the nitrogen of the triazole group and the nitrogen of the –NH of MET341 equals to 3.1Å. (b) DSX prediction for compound **3k**.
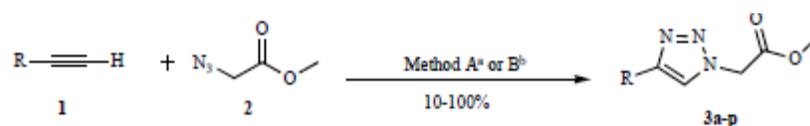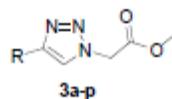
Method A : CuI (5 mol %), t-BuOH/H₂O (1:1, V/V), rt 12-72 h

[a]Method A: CuI (5mol %), NaAscorbate, tBuOH/ H₂O (1/1, V/V), rt 12-72h. [b]Method B: CuSO₄.5H₂O (5mol %), NaAscorbate (10 mol %), aq.PEG400-H₂O (1/1, V/V), rt 1-8h.
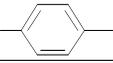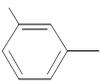
Scheme 1. Synthesis of Substituted 1,4-disubstituted 1,2,3-triazoles **3a-p**.

Table 1. Chemical structures, chemical data and purity of synthesized compounds 3.

3a-p

R-	Compound	Yield[a] (%)	Yield[b] (%)	Purity[c] (%)
	3a	99	nd	98
	3b	100	nd	98
	3c	70	78	98
	3d	27	100	97
	3e	60	100	98
	3f	54	71	98
	3g	49	40	99
	3h	68	100	99
	3i	27	76	90
	3j	10	100	98
	3k	18	100	99

Table 1. contd…

R-	Compound	Yield[a] (%)	Yield[b] (%)	Purity[c] (%)
F	3l	66	100	99
HO	3m	99	nd	98
S	3n	80	nd	99
=N	3o	100	nd	96
N	3p	56	30	99

[a] Yields obtained by method A after purification of compounds by column flash chromatography

[b] Yields obtained by method B after purification of compounds by recrystallisation

[c] HPLC Purity

In order to increase the lower yields, the reaction was conducted with aqueous polyethylene glycol (PEG) 400 and sulfate copper (Method B) (Scheme **1**, Table **1**). Benign PEG used as cosolvent, is known to enhance solubility of organic compound and therefore facilitates reactions [48]. In this reaction conditions, we were pleased to observe in most cases that 1,2,3-triazole **3** were formed more rapidly and were isolated in excellent yields after recrystallization in cyclohexane. Method B is therefore a clear improvement comparing to method A : reduced reaction time, high yield, safety.

The synthesized triazoles **3** are completely characterized by ^{1}H, ^{13}C, ^{19}F NMR, IR, HPLC and HRMS. The formation of triazole was confirmed by the presence of an absorption band in the region of 3051-3169 cm^{-1} in IR spectra due to the =CH streching of triazole ring. The presence of characteristic singlet in ^{1}H NMR due to triazolyl protons in the region of 8.25-8.73 ppm and 122.28-125.69 ppm in ^{13}C NMR due to C-5 of the triazole ring confirmed the formation of the triazole ring.

Except **3f** [49] and **3o** [50], all the other 1,2,3-triazoles have not been described before.

3.3. Biological Evaluations

The 16 diversely substituted 1,2,3-triazoles were evaluated against Src kinase (Table **2**). Dasatinib (commercially available dual SRc/Abl kinase inhibitor) was used as a positive control in the assays. The results of Src kinase inhibitory activity of compounds are shown in Table **3**. The compounds with alkyl **3d-f**, halogen **3g-l**, amines **3a-c** substituent on phenyl ring, thiophene **3n** and two pyridines **3o-p** exhibited only weak Src kinase inhibition with % inhibition value less than 10%. On the opposite, the

compound containing hydroxyl group in the meta position on the phenyl ring **3m** exhibited a more potent inhibitory activity (27%) than the rest of the compounds suggesting that prediction from the molecular docking analysis is right. On the opposite, compound **3p** showed weak inhibitory activity on Src kinase. This activity does not correlate with the docking results, since no activity was predicted. This can be explained by the limitations of the docking calculating method, which is fast and rough. More accurate results can be obtained by MM-PBSA calculations. However, this method takes much more time and computing capacity. Unfortunately, none of the synthesized compounds exhibited an activity similar to dasatinib.

Table 2. The Src kinase inhibitory activity of compounds 3a–p.

Compound	% Inhibition at 75M ±sd
3a	5 ± 2.76
3b	4 ± 0.53
3c	4 ± 0.57
3d	7 ± 1.13
3e	-1 ± 0.76
3f	3 ± 1.50
3g	0 ± 1.39
3h	0 ± 5.14
3i	-5 ± 3.63

3j	7 ± 5.84
3k	1 ± 0.61
3l	-5 ± 1.57
3m	27 ± 1.38
3n	7 ± 0.41
3o	1 ± 3.81
3p	11 ± 3.39
Dasatinib	100

4. CONCLUSION

A series of 1,4-disubstituted 1,2,3-triazole compounds were synthesized through an easy, convenient Cu(I) catalyzed click reaction and evaluated for their Src kinase activity. Compound **3m** exhibited significant inhibitory activity against Src Kinase. These results, along with molecular design docking observations, are significant evidence to demonstrate the compound **3m** could be optimized as a potential Src kinase inhibitor in further studies.

CONFLICT OF INTEREST

ACKNOWLEDGEMENTS

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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