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Copper catalysed Cross-Dehydrogenative Coupling (CDC) reaction of 4-thiazolidinone with terminal alkyne

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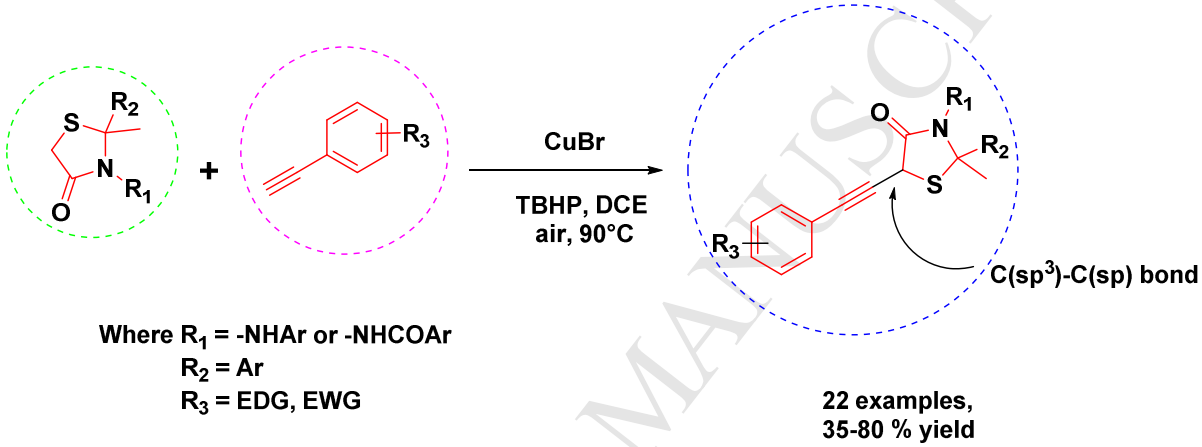
▪ GRAPHICAL ABSTRACT



▪ ABSTRACT

Cross dehydrogenative coupling (CDC) strategy has been employed for C-alkynylation of 4-thiazolidinone with terminal alkyne under copper catalysis. Present reaction involves coupling of C(sp^3) adjacent to sulfur of 4-thiazolidinone with C(sp) of terminal alkyne under CDC strategy is unprecedented to the best of our knowledge. Significant functional group tolerance, considerable yield and DFT study for mechanism make this synthetic task more interesting and compatible.

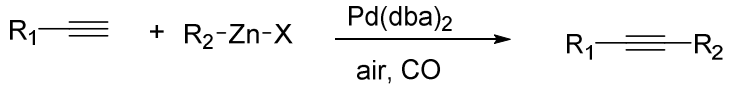
▪ **Key words:** Cross dehydrogenative coupling (CDC), sp^3(C)-sp(C) bond, 4-thiazolidinone, DFT study

▪ INTRODUCTION

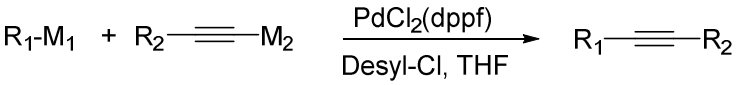
Over the past few decades transition metal catalyzed cross coupling reactions have retain their identity as revolutionary synthetic tool to streamline synthesis of numerous organic molecules.[1-4] Although classical cross coupling reactions were exclusively studied and widely applied for coupling of C(sp^2)-C(sp^2), C(sp^2)-C(sp), C(sp)-C(sp) and C(sp^2)-X (X = hetero atom)

it remains challenging for C(sp^3)-C(sp) coupling due to some mechanistic aspects[5]. In order to remove barriers of C(sp^3)-C(sp) coupling, concept of oxidative coupling has arisen which enables desired coupling through slightly different mechanistic route (Figure 1)[6]. However, oxidative C(sp^3)-C(sp) coupling reactions generally require either organometallic precursor or prefunctionalized substrate[5,7,8]. In context to atom economy as well as green chemistry perspectives, functionalization of C-H bond to install various organic motif through cross dehydrogenative coupling (CDC) emerged as a promising pathway to construct carbon-carbon bond without need of prefunctionalized substrate[9-16]. In the past few years, remarkable progress has been achieved for the activation of relatively inert C(sp^3)-H by employing CDC tactics[17-20]. Although in several cases late transition metal like palladium, platinum, ruthenium and rhodium were used as heroic catalysts, nowadays, majority of chemists shifting their attention towards utilization of inexpensive and non-toxic first row transition metal such as copper and iron were reported to exhibits remarkable catalytic activity[21-25]. Alkyl group substituted with alkynyl counterpart are of interest for pigment, pharmaceutical as well as material science industries[26,27]. Hence, development of methods for straight forward C-alkynylation of sp^3 C-H carbon is an emerging field of organic chemistry[28-31]. Beside few available other methods like nucleophilic as well as electrophilic alkynylation to form sp^3-sp carbon-carbon bond, radical mediated direct installation of alkyne group is comparatively less explored[18,32]. However, copper/iron catalysed CDC reactions have been widely investigated for oxidative functionalization of C(sp^3)-H adjacent to nitrogen or oxygen[33-37], functionalization of C(sp^3)-H adjacent to sulfur was comparatively less reported[38-41]. Keeping this in mind and to continue our efforts in transition metal catalysed C-H functionalization[42-49], herein we report an efficient synthetic protocol for functionalization of C(sp^3)-H of 4-thiazolidinone with terminal alkyne to further explore C-alkynylation. We chose 4-thiazolidinone because of its well known bioactive profile[50-51] as well as our expertise in synthesis and activation on it[43,48]. In past, we have reported C-alkynylation on same C-H bond of 4-thiazolidinone through palladium catalysis[48] (Figure 2) but here we are reporting alkynylation through CDC pathway and further we have studied reaction possibilities through DFT study. We have synthesised 4-thiazolidinones of hydrazines or hydrazides with different ketones via Schiff base pathway. Slightly more acidic C-H bond adjacent to sulfur was chosen for functionalization with terminal alkyne through CDC strategy. However, proposed pathway could not give remarkable quantity of yield.

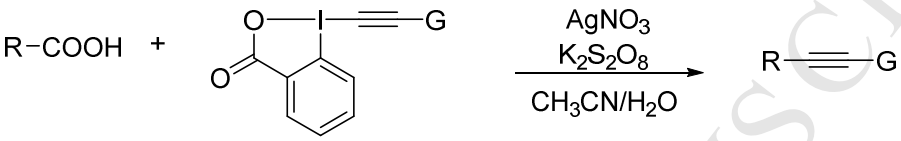
Figure -1: Oxidative coupling reaction for C(sp^3)-C(sp) coupling[5,7,8].

1. 

Where R_1 = alkyl, aryl
R_2 = alkyl
X = Cl, Br

2. 

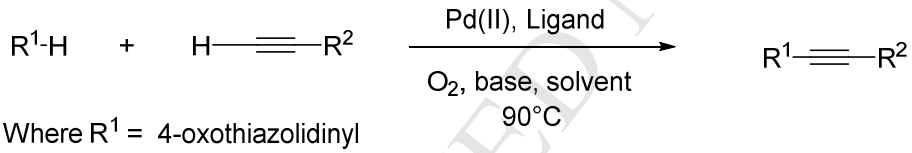
Where R_1 = alkyl
M_1, M_2 = metal salt
R_2 = alkyl, aryl

3. 

Where R = alkyl
G = Aryl, TIPS

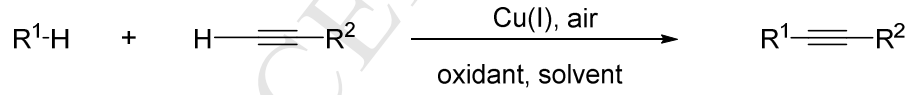
Figure -2: Previous work

Our previous work[40]



Where R^1 = 4-oxothiazolidinyl
R^2 = aryl

Present work



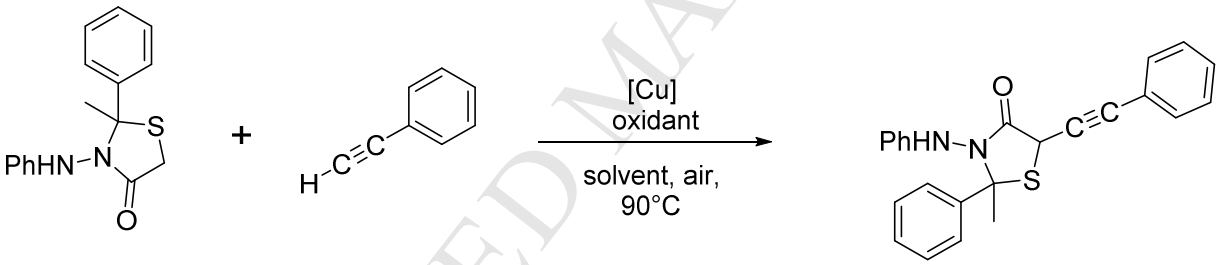
Where R^1 = 4-oxothiazolidinyl
R^2 = aryl

▪ RESULTS AND DISCUSSION

In order to get preliminary practical information, we began our study with 2-methyl-2-phenyl-3-(phenylamino)thiazolidin-4-one (1a) and phenyl acetylene (2a) as a model reactants in presence of DDQ as an oxidant along with CuBr catalyst in toluene for 8.0 hour at 90°C under air. The result of this experiment indicate desired coupling product in moderate proportion (table 1, entry no. 4). Hence, to get aimed product in satisfactory proportion we screened series of catalyst, oxidant as well as solvent. Among tested catalysts, CuBr was found best compared to other like

CuI, CuCl, CuOAc to transform proposed reaction (entry no. 1-4). Furthermore, utilization of copper(II) catalysts instead of copper(I) could not work well and gives trace product (entry no. 13-14). After catalyst, we have examined different oxidants and from the results we came to know that *tert*-Butyl hydrogen peroxide (TBHP) was appeared to be best along with CuBr (entry no. 7). Other tested oxidants like Benzoquinone (BQ), Di-ter-butylhydrogen peroxide (DTBP), 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), Potassium persulfate ($K_2S_2O_8$), O_2(g) (entry no. 5-9) were found to provide desired product in poor to moderate quantity. For solvents, DCE was found as best among other tested solvents like xylene, toluene and acetonitrile (entry no. 7, 10-12). Moreover proposed transformation could not found fruitful enough when performed under N_2 (balloon) condition (entry no. 15). In addition, reaction without oxidant was found to provide trace amount of yield (entry no. 16). In summary, catalytic system of CuBr and TBHP in DCE at 90°C under air was chosen as optimized condition (entry no. 10).

Table 1: Reaction Optimization[a]



1a **2a** **3a**

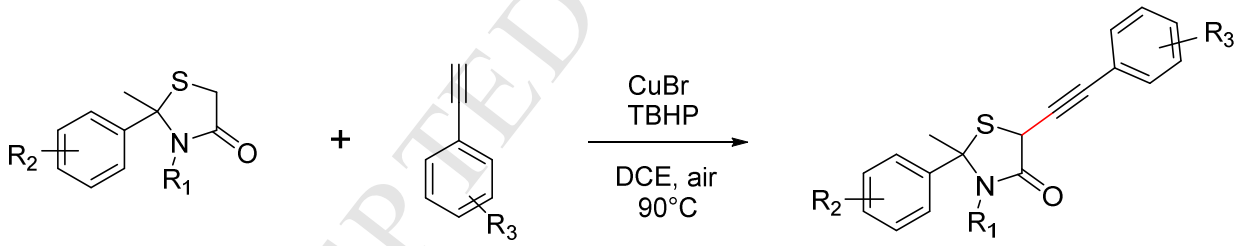
Entry	Catalyst	Oxidant	Solvent	[b]Yield
1	CuCl	DDQ	Toluene	31%
2	CuI	DDQ	Toluene	30%
3	CuOAc	DDQ	Toluene	35%
4	CuBr	DDQ	Toluene	50%
5	CuBr	BQ	Toluene	40%
6	CuBr	$K_2S_2O_8$	Toluene	25%
7	CuBr	TBHP	Toluene	60%
8	CuBr	DTBP	Toluene	50%
9	CuBr	O_2(g)	Toluene	20%
10	**CuBr**	**TBHP**	**DCE**	**70%**

11	CuBr	TBHP	Xylene	60%
[c]12	CuBr	TBHP	Acetonitrile	50%
13	$CuCl_2$	TBHP	DCE	Trace
14	$Cu(OAc)_2$	TBHP	DCE	Trace
[d]15	CuBr	TBHP	DCE	15%
16	CuBr	-	DCE	Trace

[a]Reaction Condition: 1a: 1.0 mmol, 2a: 1.5 mmol, catalyst: 10 mol%, oxidant: 2.0 mmol, solvent: 5 ml per mmol, 8.0 hours, under air. [b]Isolated Yield. [C]at 80°C. [d]under N_2 gas.

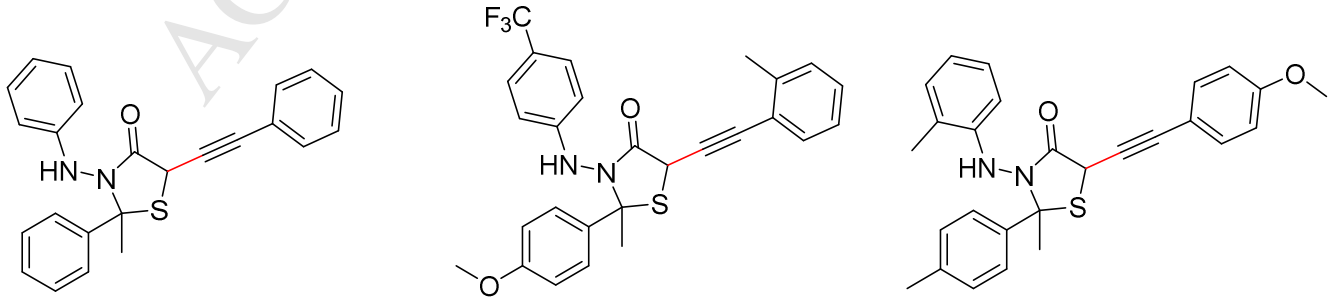
Having optimized condition in hand, we shifted our attention toward examination of substrate scope. Initially, different 4-thiazolidinones (made from various phenylhydrazine or aryl hydrazide with aromatic ketone via Schiff base route) were allowed to react with different terminal aryl alkynes under optimized condition (table-2). Both electron withdrawing and donating groups were found to tolerate employed optimized system in more or less proportion. Although, synthesis of 3b, 3f, 3m, 3p, 3q and 3r took more time to complete whereas formation of 3g, 3h, 3n and 3o were completed in relatively short time with best yield.

Table 2: Scope for the reaction of various 4-thaizolidinone with different terminal alkynes[a]

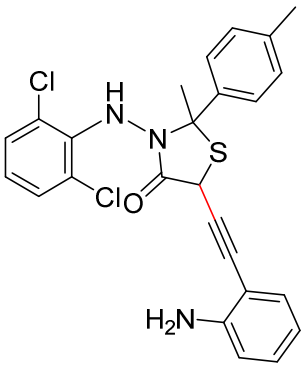


1(a-g) **2(a-g)** **3 (a-h)**

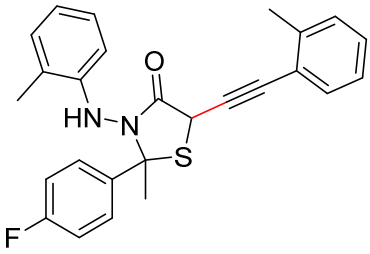
Where R_1 = -NH-Ar or –NHCO-Ar



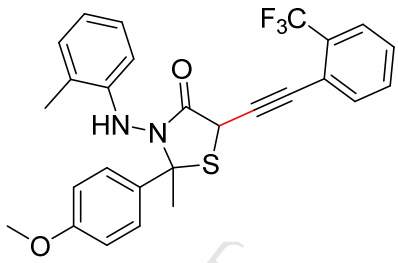
3a (70%) [b]**3b** (65%) **3c** (72%)



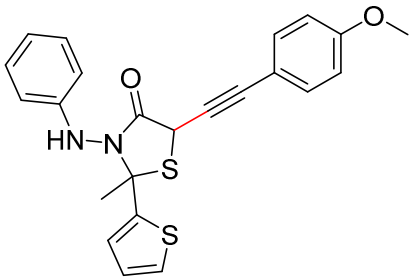
3d (77%)



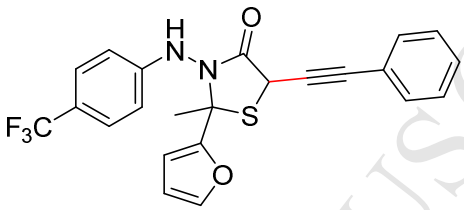
3e (65%)



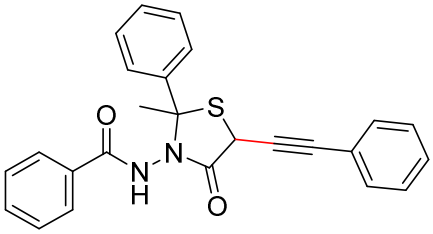
[b]**3f** (70%)



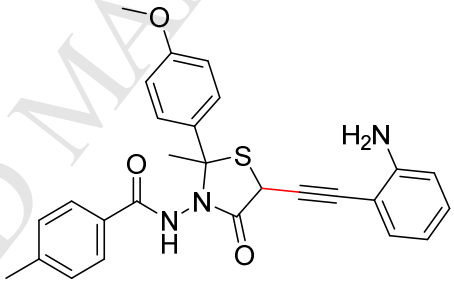
[c]**3g** (77%)



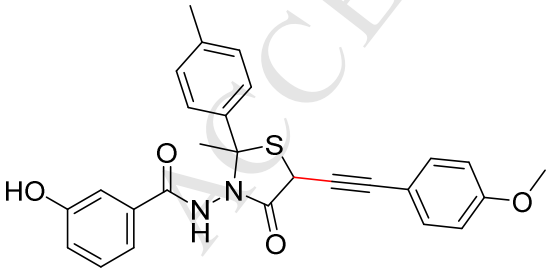
[c]**3h** (80%)



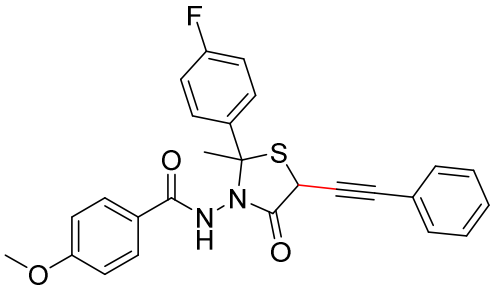
3i (65%)



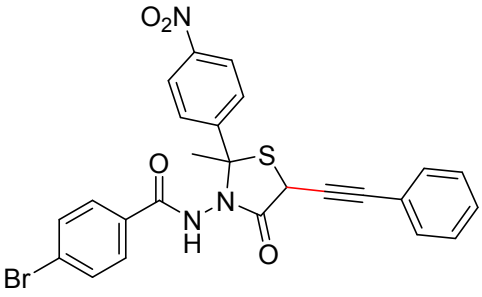
3j (72%)



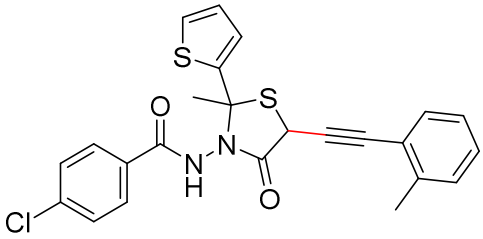
3k (70%)



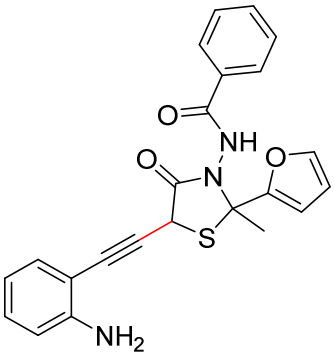
3l (70%)



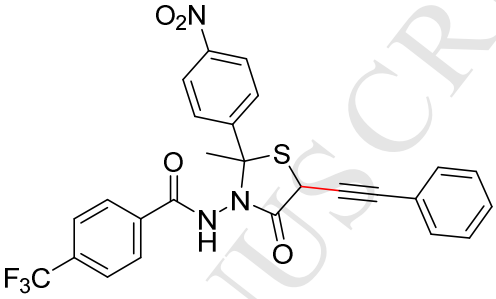
[b]**3m** (65%)



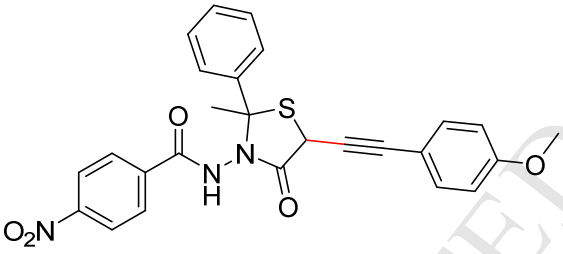
[c]**3n** (77%)



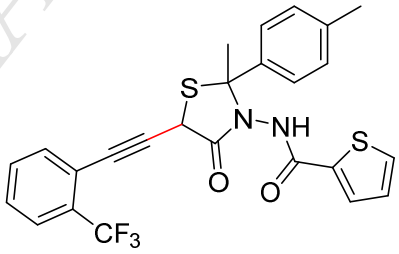
[c]**3o** (75%)



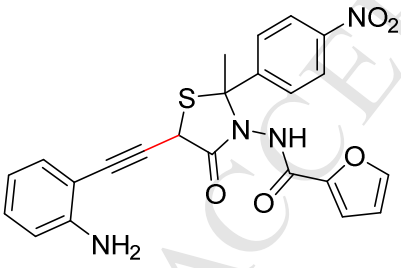
[b]**3p** (68%)



[b]**3q** (70%)



[b]**3r** (70%)

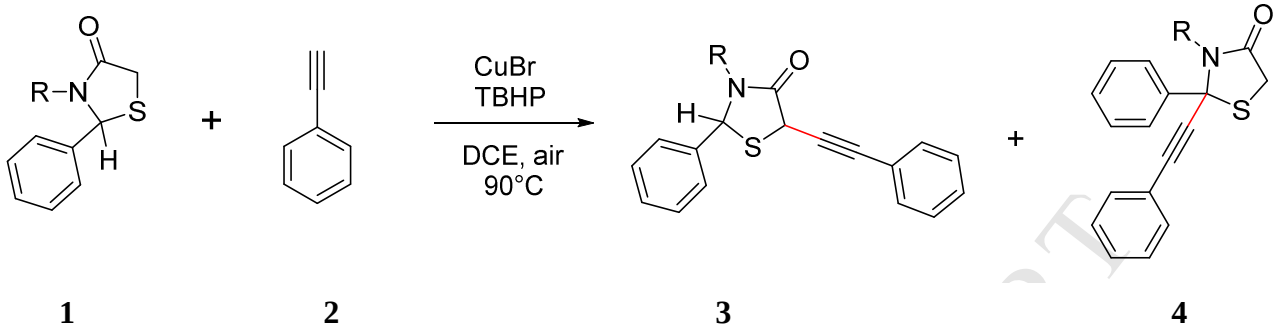


3s (70%)

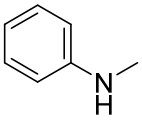
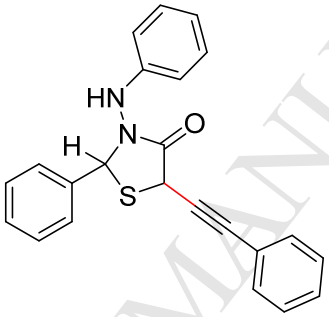
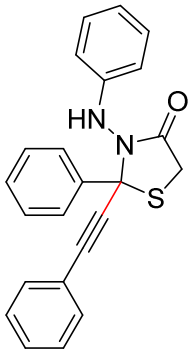
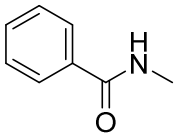
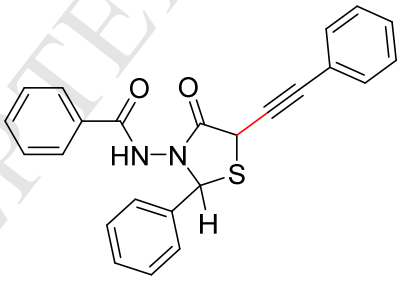
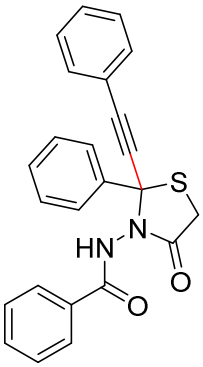
[a]Reaction Condition: 1a: 1.0 mmol, 2a: 1.5 mmol, catalyst: 10 mol%, oxidant: 2.0 mmol, solvent: 5 ml per mmol 8.0 hours, under air. [b]Completed in 10 hours, [c]Completed in 6.5 hours.

Interesting results were found when we used 4-thiazolidinone of aldehyde instead of ketone (table-3). Two different products were obtained each with considerable quantity.

Table 3: Scope for the reaction of 4-thaizolidinone with different terminal alkynes[a]



1 **2** **3** **4**

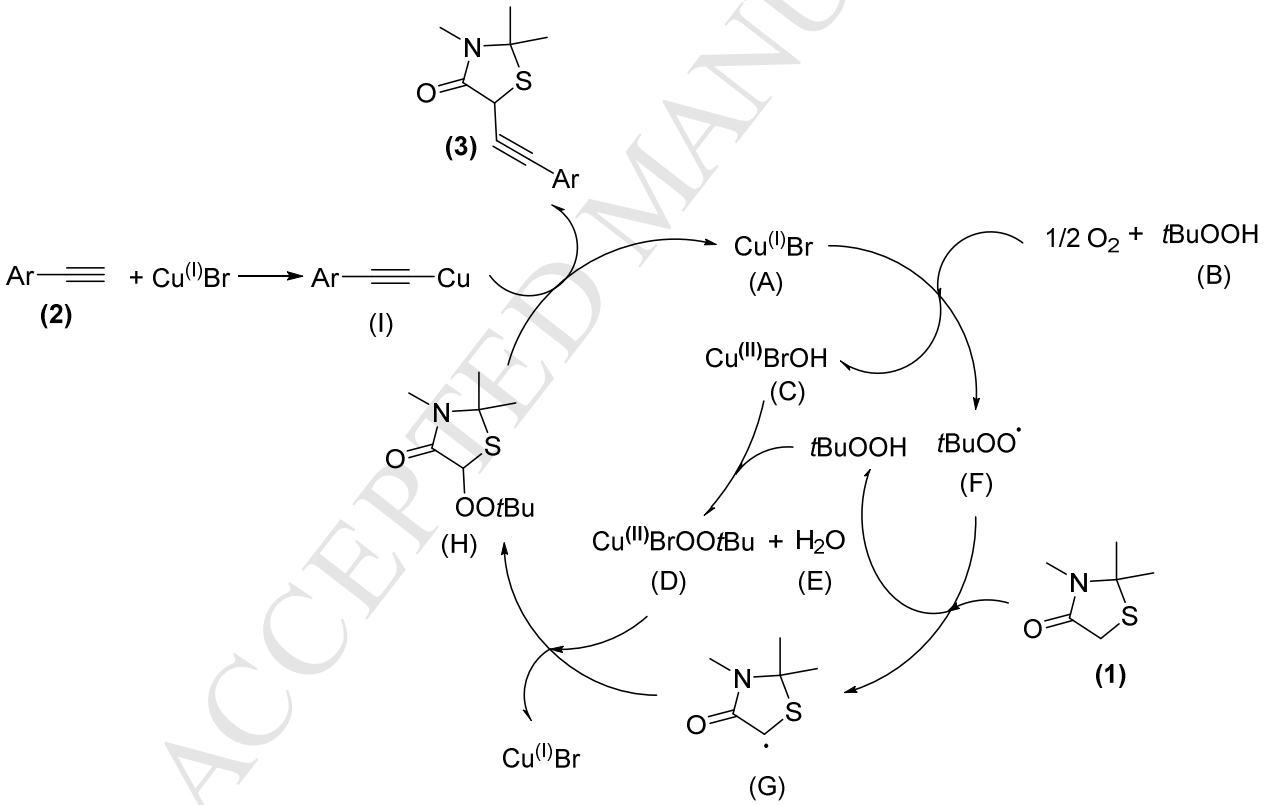
R	3	4
R = 	 **3s** (35%)	 **4a** (30%)
R = 	 **3t** (45%)	 **4b** (30%)

[a]Reaction Condition: 1: 1.0 mmol, 2: 1.5 mmol, catalyst: 10 mol%, oxidant: 2.0 mmol, solvent: 5 ml per mmol, 8.0 hours, under air.

From table-2 and 3, it can be said that optimized condition exhibits considerable functional group tolerance including $–NH_2$, -OH, -X, -OR, $-NO_2$ and $-CF_3$. After completion of substrate examination we moved to propose plausible mechanistic pathway for proposed transformation.

According to literature survey[52-63] as well as computational studies, we have proposed following mechanistic pathway for claimed reaction (scheme-2). It is generally presumed that decomposition of tert-butylhydrogenperoxide (tBuOOH) into t-butoxyl (tBuO·) and tert-butylperoxyl (tBuOO·) radicals could be achieved by CuBr as well as CuI[54,56-58]. Earlier Kochi, Kharasch and Minisci reveals some important secrets regarding reaction of Cu(I) with TBHP[57,58]. Kochi have proposed the emergence of copper peroxide complex (D) but could not figure out the participation of tBuOO·[59]. Based on hydrogen atom transfer (HAT), Minisci suggested the formation of tBuO· by the reaction of TBHP and Cu(I) which rapidly produces tBuOO· in presence of TBHP[60,61]. The mechanism presented in scheme-2 thus reveals that the key intermediate in such type of transformation is tBuOO· which react with Cu(I) to form copper peroxide complex (D).

Scheme 1: Plausible Catalytic cycle



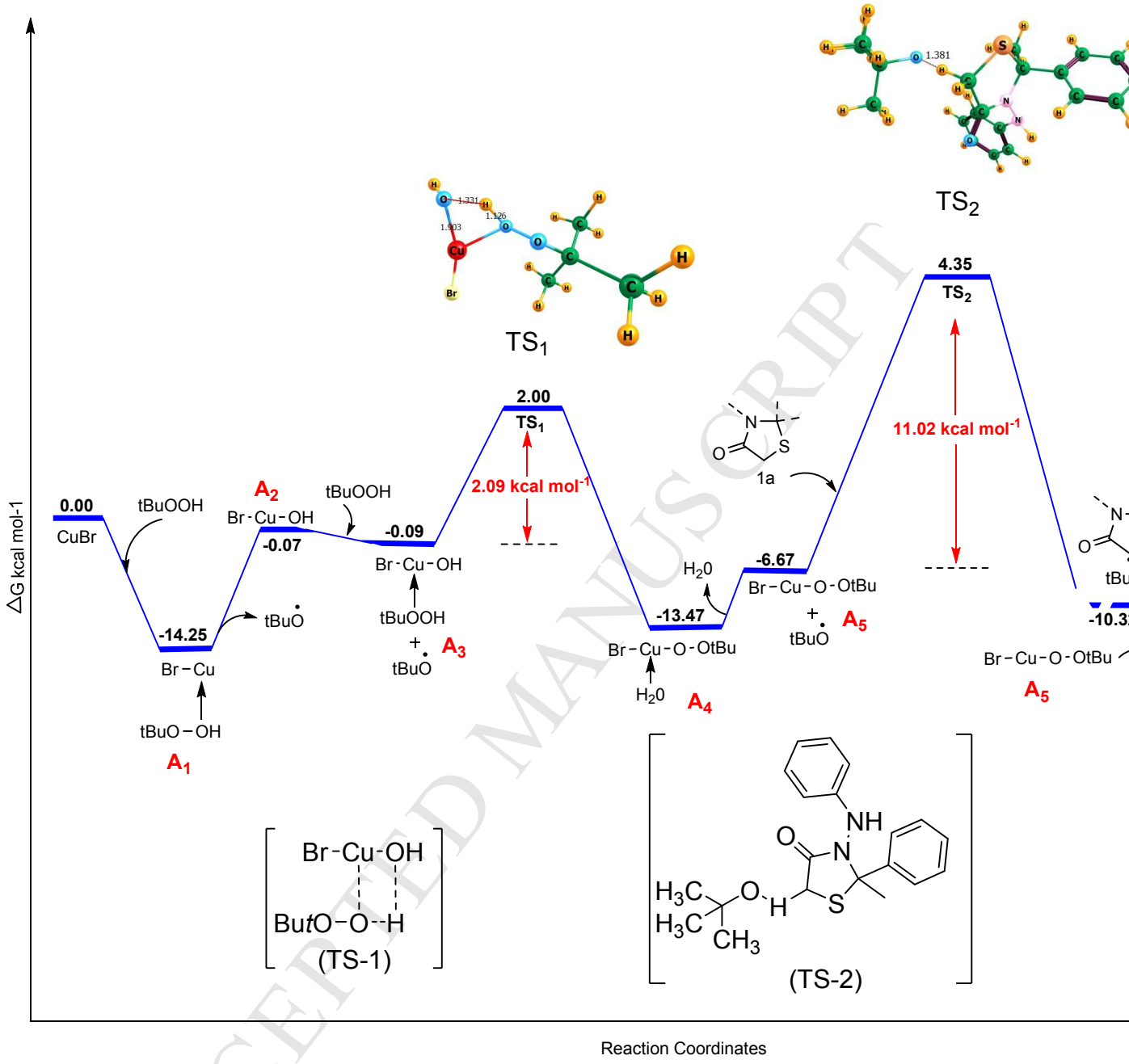
Mechanistically, CuBr **(A)** initiate the cycle by reacting with TBHP (*t*BuOOH) **(B)** and molecular oxygen to afford **(C)** and **(F)**. Obtained *t*BuOO-radical **(F)** react with 4-thiazolidinone **(1)** to provide radical of 4-thiazoldinone **(G)** with elimination of *t*BuOOH which on reaction with **(C)** to give another intermediate **(D)** and H_2O **(E)**. Later on **(G)** react with **(D)** to give another intermediate **(H)** with removal of CuBr which on reaction with terminal alkyne **(2)** to produce

copper actylide complex **(I)**. Finally, reaction between intermediate **(I)** and **(H)** provide desired coupling product **(3)**.

▪ COMPUTATIONAL STUDY

For the better understanding of the feasibility and mechanistic pathway of the proposed reaction we have performed the computational studies. The critical experimental results suggested that the reaction proceed proposed radical pathway was the observation of A_9 as an intermediate. Therefore, we focused on the formation of A_9. The reaction energy profile of the radical pathway is shown in Figure. Initially, $Cu^{I}Br$ reacts with TBHP and oxidized to form $Cu^{II}Br(OH)$ (A_2) with $tBuO^{\cdot}$ radical. $Cu^{II}Br(OH)$ then reacts with another molecule of TBHP to give intermediate $Cu^{II}Br(OOtBu)$ (A_4) and H_2O via Ts1. On the other hand $tBuO^{\cdot}$ radical abstract a hydrogen molecule from the reactant 1a to generate radical A_6 through TS_2. The energy barrier for abstraction of hydrogen was calculated to be 11.02 kcal mol^{-1}. Combining radical A_6 with the doublet A_5, compound A_9 formed in conjunction with $Cu^{I}Br$. Overall, from the above energy profile we can say that the rate-determining step is hydrogen abstraction. Computational studies results reveals that reaction proceed via radical pathway to form a crucial intermediate A_9.

Table 5: Free energy profile of plausible mechanistic pathway



All calculations were performed with the Gaussian 09 package. The Kohn–Sham density functional theory (DFT) was solved with the B3LYP functional and 6-31G+(d,p) basis sets were chosen for all the atoms. The CPCM model was applied to account for solvent effects. Frequency calculations at the same level of theory were also performed to verify the stationary points as minima (no imaginary frequency) or transition states (one imaginary frequency). Transition states were located by using the Berny algorithm. Intrinsic reaction coordinates (IRCs) were calculated for the transition states to confirm that they indeed connected two relevant minima. All relative

energies (corrected with zero point energy) and Gibbs free energies (at 298.15 K and 1 atm) are reported in kcal mol^{-1}. Geometries are displayed with Chemcraft.

▪ CONCLUSION

In conclusion, we have developed a CDC approach for C-alkynylation of C(sp^3)-H using 4-thiazolidinones with terminal alkynes. Presented work contain an important idea regarding CDC coupling of sp^3(C-H) adjacent to sulfur atom which is hither to unreported as per our best knowledge. Although, reported strategy shows considerable functional group tolerance but could not increase yield in remarkable quantity and this might be limitation of this reaction. Current work could be helpful for synthesis of other similar derivatives to functionalize relatively inert C-H bond adjacent to sulfur with other C-H bond.

▪ EXPERIMENTAL SECTION

General comments: All starting materials were purchased from commercial suppliers and used without further purification. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, HRMS as well as elemental analysis. Melting point and boiling point were obtained in open capillaries on Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker400 MHz model spectrometer using $CDCl_3$ as a solvent and TMS as internal standard with ^{1}H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. HRMS spectra were recorded on XEVO G2-XS QTOF spectrophotometer. The chemical shifts of ^{1}H NMR and ^{13}C NMR were reported as parts per million (ppm) downfield from TMS (Me_4Si). The splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; m, multiplet. Elemental analyses (C, H, N) were performed using a Heraeus CarloErba 1180 CHN analyzer (Hanau, Germany).

1. General procedure for the synthesis of 1 :

According to literature[50,64,65], reaction of different amine (hydrazine or hydrazide) with different ketones in ethanol at refluxing temperature gives corresponding schiff base derivatives. Later on, as per the literature, prepared Schiff bases on reaction with thioglycolic acid in DMF results in the synthesis of 4-thiazolidinone.

2. Synthesis of 3 through CDC strategy:

Synthesised **1** (1.0 mmol) was mixed with **2** (1.5 mmol) along with CuBr (10.0 mol%), TBHP (30.0 mol%) in dichloroethane (10.0 ml) in a 25.0 ml glass tube. The reaction mixture was stirred at 90°C for 8-10 hour under air until the reaction was completed (confirmed by TLC). Finally, reaction mixture was cooled down at room temperature and poured into cold aqueous solution of $NaHCO_3$. Later on, reaction mixture was subjected to solvent extraction by adding 15-20 ml of dichloromethane. Organic layer was then separated, dried (over anhydrous Na_2SO_4) and concentrated under reduced pressure. Obtained residue was further purified by coloumn chromatography to give desired product.

2-methyl-2-phenyl-3-(phenylamino)-5-(phenylethynyl)thiazolidin-4-one (3a), white solid; Yield 70% (305 mg); mp 170-175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.58 (d, J = 4.8 Hz, 2H), 7.29 (m, 3H), 7.24-7.18 (m, 7H), 6.77 (dd, J_1 = 6.0 Hz, J_2 = 6.4 Hz, 1H), 7.62 (d, J= 5.2 Hz, 2H), 4.52 (s, 1H), 2.52 (s, 1H, D_2O exchangeable), 2.07 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.14, 40.01, 67.54, 75.73, 79.42, 115.47, 121.01, 123.80, 126.90, 128.12, 128.53, 128.59, 128.69, 129.28, 131.08, 141.76, 147.30, 179.42; **Anal. Calcd.** For $C_{24}H_{20}N_2OS$: C: 74.97; H: 5.24; N: 7.29; ***Found:*** C: 74.92; H: 5.29; N: 7.33; HRMS-ESI (m/z) calcd for $C_{24}H_{20}N_2OS$ $[M + H]^+$ 384.1296, found 384.1292.

2-(4-methoxyphenyl)-2-methyl-5-(o-tolylethynyl)-3-((4-(trifluoromethyl)phenyl)amino)thiazolidin-4-one (3b). white solid; Yield 65% (361 mg); mp 150-155 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 7.44-7.42 (m, 3H), 7.21-7.11 (m, 5H), 6.90 (d, J = 5.2 Hz, 2H), 6.57 (d, J = 5.2 Hz, 2H), 4.52 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H), 2.13 (s, 3H), 1.79 (s, 1H, D_2O exchangeable); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 20.73, 25.14, 40.01, 56.04, 66.99, 75.73, 80.63, 112.52, 124.12, 124.46, 124.93, 125.06, 125.64, 126.78, 127.97, 128.41, 129.24, 131.80, 137.33, 139.44, 152.24, 159.87, 179.42; **Anal. Calcd.** For $C_{27}H_{23}F_3N_2O_2S$: C: 65.31; H: 4.67; N: 5.64; ***Found:*** C: 65.34; H: 4.70; F: 11.44; N: 5.64; HRMS-ESI (m/z) calcd for $C_{27}H_{23}F_3N_2O_2S$ $[M + H]^+$ 496.1432, found 496.1436.

5-((4-methoxyphenyl)ethynyl)-2-methyl-2-(p-tolyl)-3-(o-tolylamino)thiazolidin-4-one (3c). Pale yellow solid; Yield 72% (367 mg); mp 182-185 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 7.53 (d, J = 6.4 Hz, 2H), 7.14-7.13 (m, 4H), 7.01-6.73 (m, 5H), 6.59 (d, J = 5.6 Hz, 1H), 4.52 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H), 2.17 (s, 3H), 1.97 (s, 3H), 1.79 (s, 1H, D_2O exchangeable); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 17.35, 21.13, 25.14, 40.01, 56.04, 67.54, 75.73, 79.42, 114.65, 115.64, 115.74, 120.47, 125.52, 126.89, 127.20, 129.47, 130.57, 131.46, 136.27, 138.10, 146.29, 159.92, 179.42; **Anal. Calcd.** For $C_{27}H_{26}N_2O_2S$: C: 73.27; H: 5.92; N:

6.33; ***Found:*** C: 73.24; H: 5.90; N: 6.36. HRMS-ESI (m/z) calcd for $C_{27}H_{26}N_2O_2S$ $[M + H]^+$ 442.1715, found 442.1711.

5-((2-aminophenyl)ethynyl)-3-((2,6-dichlorophenyl)amino)-2-methyl-2-(p-tolyl)thiazolidin-4-one (3d), Brown solid; Yield 77% (417 mg); mp 188-192 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 7.19-7.16 (m, 5H), 7.08-7.04 (m, 3H), 6.67-6.64 (m, 2H), 6.53 (d, *J* = 5.6 Hz, 1H), 5.07 (s, 2H, D_2O exchangeable), 4.52 (s, 1H), 2.45 (s, 1H, D_2O exchangeable), 2.17 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 21.13, 25.14, 40.01, 70.93, 75.73, 82.71, 110.38, 111.93, 116.91, 122.29, 125.52, 127.75, 128.59, 119.47, 130.01, 131.43, 136.27, 138.10, 143.64, 149.41, 179.42. **Anal. Calcd.** For $C_{25}H_{21}Cl_2N_3OS$: C: 62.24; H: 4.39; N: 8.7; ***Found:*** C: 62.20; H: 4.40; N: 8.66. HRMS-ESI (m/z) calcd for $C_{25}H_{21}Cl_2N_3OS$ $[M + H]^+$ 481.0782, found 481.0787.

2-(4-fluorophenyl)-2-methyl-3-(o-tolylamino)-5-(o-tolylethynyl)thiazolidin-4-one (3e), white solid; Yield 65% (318 mg); mp 160-165 °C; **^{1}H NMR** (400 MHz, CDCl3) δ ppm: 7.42 (d, *J* = 4.8 Hz, 1H), 7.27-7.21 (m, 3H), 7.14-7.08 (m, 3H), 7.04-7.01 (m, 3H), 6.76 (dd, J_1 = 6.0 Hz, J_2 = 6.4 Hz, 1H), 6.69 (d, *J* = 6.0 Hz, 1H), 4.52 (s, 1H), 2.52 (s, 1H, D_2O exchangeable), 2.38 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 17.35, 20.73, 25.14, 40.01, 66.99, 75.73, 80.63, 114.71, 115.74, 120.47, 124.83, 126.78, 126.89, 127.20, 128.41, 129.13, 129.24, 130.57, 131.80, 139.44, 139.77, 146.29, 165.20, 179.42; **Anal. Calcd.** For $C_{26}H_{23}FN_2OS$: C: 72.53; H: 5.38; N: 6.51; ***Found:*** C: 72.50; H: 5.40; N: 6.47. HRMS-ESI (m/z) calcd for $C_{26}H_{23}FN_2OS$ $[M + H]^+$ 430.1515, found 430.1511.

2-(4-methoxyphenyl)-2-methyl-3-(o-tolylamino)-5-((2-(trifluoromethyl)phenyl)ethynyl)thiazolidin-4-one (3f), colourless oil; Yield 70% (408 mg); bp < 200°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.53 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.31-7.20 (m, 4H), 7.04-7.00 (m, 2H), 6.89 (d, *J* = 6.4 Hz, 2H), 6.70 (dd, J_1 = 5.6 Hz, J_2 = 5.4 Hz, 1H), 6.40 (d, *J* = 6.4 Hz, 1H), 4.52 (s, 1H), 3.81 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.38 (s, 1H, D_2O exchangeable); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 17.35, 25.14, 40.01, 56.04, 68.16, 75.73, 76.12, 112.52, 115.74, 120.47, 122.10, 124.01, 125.97, 126.89, 127.20, 127.97, 130.57, 130.75, 132.63, 132.64, 135.80, 137.33, 146.29, 159.87, 179.42; **Anal. Calcd.** For $C_{27}H_{23}F_3N_2O_2S$: C: 65.31; H: 4.67 N: 5.64; ***Found:*** C: 65.35; H: 4.70; N: 5.60. HRMS-ESI (m/z) calcd for $C_{27}H_{23}F_3N_2O_2S$ $[M + H]^+$ 496.1432, found 496.1435.

5-((4-methoxyphenyl)ethynyl)-2-methyl-3-(phenylamino)-2-(thiophen-2-yl)thiazolidin-4-one (3g), colourless oil; Yield 77% (376 mg); bp 175-180°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.48 (d, *J* = 6.4 Hz, 2H), 7.18 (dd, J_1 = 6.0 Hz, J_2 = 6.2 Hz, 2H), 7.05-6.86 (m, 3H), 6.80-6.76 (m, 3H), 6.66 (d, *J*= 5.2 Hz, 2H), 4.52 (s, 1H), 3.79 (s, 3H), 2.47 (s, 1H, D_2O exchangeable), 2.17 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 29.61, 40.01, 56.04, 67.54,

76.69, 79.42, 114.65, 115.47, 115.64, 121.01, 125.55, 126.38, 126.82, 129.20, 131.46, 147.36, 154.70, 159.92, 182.39; **Anal. Calcd.** For $C_{23}H_{20}N_2O_2S_2$: C: 65.69; H: 4.79; N: 6.66; ***Found:*** C: 65.67; H: 4.77; N: 6.61. HRMS-ESI (m/z) calcd for $C_{23}H_{20}N_2O_2S_2$ $[M + H]^+$ 420.0966, found 420.0962.

2-(furan-2-yl)-2-methyl-5-(phenylethynyl)-3-((4-(trifluoromethyl)phenyl)amino)thiazolidin-4-one (3h), brownish solid; Yield 80% (396 mg); mp 185-190°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.49-7.42 (m, 4H), 7.32-7.20 (m, 4H), 6.58 (d, *J* = 5.4 Hz, 2H), 6.32-6.31 (m, 2H), 4.52 (s, 1H), 2.18 (s, 3H), 1.97 (s, 1H, D_2O exchangeable); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 23.83, 40.01, 67.54, 71.20, 79.42, 104.40, 111.71, 114.12, 123.80, 124.46, 125.06, 125.64, 128.53, 128.59, 131.08, 140.65, 152.24, 155.63, 182.39; **Anal. Calcd.** For $C_{23}H_{17}F_3N_2O_2S$: C: 62.44; H: 3.87; N: 6.33; ***Found:*** C: 62.40; H: 3.90; N: 6.30. HRMS-ESI (m/z) calcd for $C_{23}H_{17}F_3N_2O_2S$ $[M + H]^+$ 442.0963, found 442.0960.

N-(2-methyl-4-oxo-2-phenyl-5-(phenylethynyl)thiazolidin-3-yl)benzamide (3i), white solid; Yield 65% (302 mg); mp 175-180°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.72 (d, *J* = 5.6 Hz, 2H), 7.46-7.45 (m, 3H), 7.39-7.21 (m, 8H), 6.63 (s, 1H), 4.52 (s, 1H), 2.17 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.14, 40.01, 67.54, 76.90, 79.42, 123.80, 126.90, 128.12, 128.28, 128.48, 128.53, 128.59, 131.08, 132.03, 132.71, 141.76, 165.41, 180.41; **Anal. Calcd.** For $C_{25}H_{20}N_2O_2S$: C: 72.79; H: 4.89; N: 6.79; ***Found:*** C: 72.76; H: 4.92; N: 6.75. HRMS-ESI (m/z) calcd for $C_{25}H_{20}N_2O_2S$ $[M + H]^+$ 412.1245, found 412.1248.

N-(5-((2-aminophenyl)ethynyl)-2-(4-methoxyphenyl)-2-methyl-4-oxothiazolidin-3-yl)-4-methylbenzamide (3j), brown solid; Yield 72% (383 mg); mp 163-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.77 (d, *J* = 6.0 Hz, 2H), 7.37 (s, 1H), 7.29-7.24 (m, 4H), 7.19-6.99 (m, 4H), 6.67 (dd, J_1 = 6.4 Hz, J_2 = 6.2 Hz, 1H), 6.55 (d, J= 5.8 Hz, 1H), 5.41 (s, 2H, D_2O exchangeable), 4.52 (s, 1H), 3.79 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 21.13, 25.14, 40.01, 56.04, 70.93, 76.90, 82.71, 110.30, 111.93, 112.52, 116.91, 127.97, 128.29, 128.80, 130.01, 131.25, 131.43, 137.33, 142.80, 149.41, 159.87, 165.41, 180.41; **Anal. Calcd.** For $C_{27}H_{25}N_3O_3S$: C: 68.77; H: 5.34; N: 8.91; ***Found:*** C: 68.75; H: 5.39; N: 8.88. HRMS-ESI (m/z) calcd for $C_{27}H_{25}N_3O_3S$ $[M + H]^+$ 471.1617, found 471.1620.

3-hydroxy-N-(5-((4-methoxyphenyl)ethynyl)-2-methyl-4-oxo-2-(p-tolyl)thiazolidin-3-yl)benzamide (3k), yellow solid; Yield 70% (378 mg); mp 190-195 °C; **^{1}H NMR** (400 MHz, CDCl3) δ ppm: 7.47-7.37 (m, 4H), 7.31-7.27 (m, 3H), 7.18-7.14 (m, 3H), 6.86 (d, *J* = 6.0 Hz, 1H), 6.86 (d, *J* = 5.8 Hz, 2H), 4.52 (s, 1H), 3.89 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.09 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 21.13, 25.14, 56.00, 67.54, 76.90, 79.92, 114.31, 114.65, 115.64, 120.70, 122.16, 125.52, 129.47, 130.49, 131.46, 133.27, 136.27, 138.10, 157.29, 159.92,

165.80, 180.41. **Anal. Calcd.** For $C_{27}H_{24}N_2O_4S$: C: 68.63; H: 5.12; N: 5.93; ***Found:*** C: 68.60; H: 5.10; N: 5.95. HRMS-ESI (m/z) calcd for $C_{27}H_{24}N_2O_4S$ $[M + H]^+$ 472.1457, found 472.1459.

N-(2-(4-fluorophenyl)-2-methyl-4-oxo-5-(phenylethynyl)thiazolidin-3-yl)-4-methoxybenzamide (3l), white solid; Yield 70% (359 mg); mp 180-185°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.66 (d, *J* = 6.0 Hz, 2H), 7.39 (d, *J* = 6.2 Hz, 2H), 7.21-7.14 (m, 5H), 7.03-7.01 (m, 4H), 6.77 (s, 1H, D_2O exchangeable), 4.52 (s, 1H), 3.81 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.14, 40.01, 56.04, 67.54, 76.90, 79.42, 113.17, 114.71, 123.80, 127.02, 128.53, 128.59, 128.99, 129.13, 131.08, 139.77, 162.98, 165.26, 165.41, 180.41; **Anal. Calcd.** For $C_{26}H_{21}FN_2O_3S$: C: 67.81; H: 4.60; N: 6.08; ***Found:*** C: 67.85; H: 4.62; N: 6.10. HRMS-ESI (m/z) calcd for $C_{26}H_{21}FN_2O_3S$ $[M + H]^+$ 460.1257, found 460.1253.

4-bromo-N-(2-methyl-2-(4-nitrophenyl)-4-oxo-5-(phenylethynyl)thiazolidin-3-yl)benzamide (3m), yellow solid; Yield 65% (383 mg); mp 215-220°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.11 (d, *J* = 5.8 Hz, 2H), 7.75 (d, *J* = 5.0 Hz, 2H), 7.59 (d, *J* = 5.6 Hz, 2H), 7.51 (m, 4H), 7.30 (dd, J_1 = 5.0 Hz, J_2 = 5.2 Hz, 1H), 7.22 (dd, J_1 = 6.0 Hz, J_2 = 5.8 Hz, 2H), 4.52 (s, 1H), 4.36 (s, 1H, D_2O exchangeable), 2.19 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.14, 40.01, 67.54, 76.90, 79.42, 122.85, 123.80, 125.78, 127.96, 128.53, 128.59, 131.19, 132.05, 133.61, 144.26, 148.35, 165.41, 180.41; **Anal. Calcd.** For $C_{25}H_{18}BrN_3O_4S$: C: 55.98; H: 3.38 N: 7.83; ***Found:*** C: 55.95; H: 3.40; N: 7.80. HRMS-ESI (m/z) calcd for $C_{25}H_{18}BrN_3O_4S$ $[M + H]^+$ 535.0201, found 535.0205.

4-chloro-N-(2-methyl-4-oxo-2-(thiophen-2-yl)-5-(o-tolylethynyl)thiazolidin-3-yl)benzamide (3n), pale yellow solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.62 (d, *J* = 5.8 Hz, 2H), 7.38-7.36 (m, 3H), 7.18-7.09 (m, 4H), 6.95 (dd, J_1 = 6.0 Hz, J_2 =6.2 Hz, 1H), 7.84 (d, *J* = 6.2 Hz, 1H), 4.75 (s, 1H, D_2O exchangeable), 4.52 (s, 1H), 2.36 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 20.73, 29.61, 40.01, 66.99, 77.21, 80.63, 124.83, 125.55, 126.38, 126.78, 126.82, 128.41, 128.76, 129.11, 129.24, 131.80, 132.57, 139.25, 139.44, 154.76, 165.41, 183.56; **Anal. Calcd.** For $C_{24}H_{19}ClN_2O_2S_2$: C: 61.73; H: 4.10; N: 6.00; ***Found:*** C: 61.70; H: 4.40; N: 6.04. HRMS-ESI (m/z) calcd for $C_{24}H_{19}ClN_2O_2S_2$ $[M + H]^+$ 466.0576, found 466.0573.

N-(5-((2-aminophenyl)ethynyl)-2-(furan-2-yl)-2-methyl-4-oxothiazolidin-3-yl)benzamide (3o), pale yellow solid; Yield 75 % (358 mg); mp 205-210°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.83 (d, *J* = 6.2 Hz, 2H), 7.44 (dd, J_1 = 6.2 Hz, J_2 = 6.4 Hz, 1H), 7.36-7.31 (m, 3H), 6.19 (d, 1H), 7.03 (dd, J_1 = 5.4 Hz, J_2 =5.2 Hz, 1H), 6.83 (s, 1H), 6.66 (dd, J_1 = 6.0 Hz, J_2 = 6.2 Hz, 1H), 6.52 (d, *J* = 6.0 Hz, 1H), 6.28 (dd, J_1 = 5.8 Hz, J_2 = 6.0 Hz, 1H), 6.13 (d, *J* = 5.6 Hz, 1H), 4.81 (s, 2H, D_2O exchangeable), 4.52 (s, 1H), 2.10 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 23.83, 40.01, 70.93, 72.14, 82.71, 104.40, 110.38, 111.71, 111.93, 116.91, 128.28, 128.48,

130.01, 131.43, 132.03, 132.71, 140.65, 149.41, 155.63, 165.41, 183.5;. **Anal. Calcd.** For $C_{23}H_{19}N_3O_3S$: C: 66.17; H: 4.59; N: 10.07; ***Found:*** C: 66.20; H: 4.62; N: 10.05. HRMS-ESI (m/z) calcd for $C_{23}H_{19}N_3O_3S$ $[M + H]^+$ 417.1147, found 417.1142.

N-(2-methyl-2-(4-nitrophenyl)-4-oxo-5-(phenylethynyl)thiazolidin-3-yl)-4-(trifluoromethyl)benzamide (3p), colourless solid; Yield 68% (393 mg); mp 225-230°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.22 (d, *J* = 5.8 Hz, 2H), 7.85 (d, *J* = 5.6 Hz, 2H), 7.70-7.62 (m, 4H), 7.46 (d, *J* = 6.0 Hz, 2H), 7.25-7.24 (m, 4H), 4.52 (s, 1H), 2.10 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.19, 40.01, 67.52, 76.90, 79.42, 122.85, 123.80, 124.46, 125.78, 126.48, 128.22, 128.53, 128.59, 131.08, 132.76, 136.66, 144.26, 148.35, 165.41, 180.41; **Anal. Calcd.** For $C_{26}H_{18}F_3N_3O_4S$: C: 59.43; H: 3.45; N: 8.00; ***Found:*** C: 59.45; H: 3.48; N: 7.98. HRMS-ESI (m/z) calcd for $C_{26}H_{18}F_3N_3O_4S$ $[M + H]^+$ 525.0970, found 525.0974.

N-(5-((4-methoxyphenyl)ethynyl)-2-methyl-4-oxo-2-phenylthiazolidin-3-yl)-4-nitrobenzamide (3q), yellow solids; Yield 70% (388 mg); mp 180-185°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 8.35 (d, *J* = 6.2 Hz, 2H), 8.00 (d, *J* = 6.0 Hz, 2H), 7.63 (d, *J* = 6.4 Hz, 2H), 7.30-7.23 (m, 5H), 6.97 (d, *J* = 5.8 Hz, 2H), 6.05 (s, 1H), 4.52 (s, 1H), 3.79 (s, 3H), 2.10 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 25.14, 40.01, 56.04, 67.54, 76.90, 79.42, 114.65, 115.64, 124.04, 126.90, 128.12, 128.69, 129.08, 131.46, 138.15, 141.76, 149.21, 159.92, 165.41, 180.41; **Anal. Calcd.** For $C_{26}H_{21}N_3O_5S$: C: 64.05; H: 4.34; N: 8.62; ***Found:*** C: 64.07; H: 4.38; N: 8.60. HRMS-ESI (m/z) calcd for $C_{26}H_{21}N_3O_5S$ $[M + H]^+$ 487.1202, found 487.1205.

N-(2-methyl-4-oxo-2-(p-tolyl)-5-((2-(trifluoromethyl)phenyl)ethynyl)thiazolidin-3-yl)thiophene-2-carboxamide (3r), yellow oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.84 (d, *J* = 6.2 Hz, 1H), 7.63 (dd, J_1 = 6.0 Hz, J_2 = 6.2 Hz, 1H), 7.50 (d, *J* = 5.8 Hz, 1H), 7.42 (d, *J* = 5.8 Hz, 1H), 7.30- 7.10 (m, 8H), 4.52 (s, 1H), 2.33 (s, 3H), 2.04 (s, 3H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 21.13, 25.14, 40.01, 68.16, 76.12, 76.90, 122.10, 124.01, 125.52, 125.97, 127.41, 129.02, 129.47, 130.05, 130.75, 132.63, 132.69, 135.80, 136.27, 138.10, 139.24, 156.02, 180.41; **Anal. Calcd.** For $C_{25}H_{19}F_3N_2O_2S_2$: C: 59.99; H: 3.83; N: 5.60; ***Found:*** C: 59.96; H: 3.85; N: 5.63. HRMS-ESI (m/z) calcd for $C_{25}H_{19}F_3N_2O_2S_2$ $[M + H]^+$ 500.0840, found 500.08437.

2-phenyl-3-(phenylamino)-5-(phenylethynyl)thiazolidin-4-one (3s), white solid; Yield 35% (148 mg); mp 170-175 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.43 (d, *J* = 6.4 Hz, 2H), 7.32-7.26 (m, 5H), 7.25-7.24 (m, 4H), 7.20 (d, *J* = 5.8 Hz, 2H), 6.79 (dd, J_1 = 5.4 Hz, J_2 = 5.2 Hz, 1H), 6.68 (d, *J* = 6.0 Hz, 2H), 6.23 (s, 1H), 4.52 (s, 1H), 2.91 (s, 1H, D_2O exchangeable); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 67.94, 68.17, 115.64, 120.74, 123.80, 126.70, 127.74, 128.53, 128.59, 128.93, 129.08, 131.08, 139.96, 147.50, 179.81; **Anal. Calcd.** For $C_{23}H_{18}N_2OS$: C: 74.57;

H: 4.90; N: 7.56; O: 4.32; S: 8.65; ***Found:*** C: 74.60; H: 4.88; N: 7.58; O: 4.30; S: 8.64. HRMS-ESI (m/z) calcd for $C_{23}H_{18}N_2OS$ $[M + H]^+$ 370.1140, found 370.1144.

N-(4-oxo-2-phenyl-5-(phenylethynyl)thiazolidin-3-yl)benzamide (3t), white solid; Yield 45% (203 mg); mp 185-190 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.87 (d, *J* = 6.0 Hz, 2H), 7.50 (dd, J_1 = 6.0 Hz, J_2 = 5.8 Hz), 7.47 (d, *J* = 6.0 Hz, 2H), 7.44 (d, *J* = 5.8 Hz, 2H), 7.38-7.28 (m, 5H), 7.27 (dd, J_1 = 5.6 Hz, J_2 = 5.4 Hz), 7.24 (d, *J* = 5.6 Hz, 2H), 5.93 (s, 1H), 5.51 (s, 1H, D_2O exchangeable), 4.52 (s, 1H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 68.17, 68.66, 83.47, 123.80, 126.70, 127.74, 128.28, 128.48, 128.53, 128.59, 128.93, 131.08, 132.03, 132.71, 139.96, 160.65, 181.93; **Anal. Calcd.** For $C_{24}H_{18}N_2O_2S$: C: 72.34; H: 4.55; N: 7.03; ***Found:*** C: 72.30; H: 4.57; N: 7.05. HRMS-ESI (m/z) calcd for $C_{24}H_{18}N_2O_2S$ $[M + H]^+$ 398.1089, found 398.1085.

2-phenyl-3-(phenylamino)-2-(phenylethynyl)thiazolidin-4-one (4a), white solid; Yield 30% (127 mg); mp 210-215 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.42-7.43 (m, 4H), 7.32 (d, *J* = 6.0 Hz, 2H), 7.25 (dd, J_1 = 5.6 Hz, J_2 = 5.8 Hz, 1H), 7.25 (dd, J_1 = 6.0 Hz, J_2 = 5.8 Hz, 1H), 7.22 (d, *J* = 6.0 Hz, 2H), 7.19-6.69 (m, 5H), 4.34 (s, 1H, D_2O exchangeable), 3.83-3.80 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 35.81, 69.95, 79.06, 115.47, 121.01, 123.33, 127.00, 128.06, 128.51, 128.66, 129.28, 129.81, 131.41, 138.13, 147.36, 175.77; **Anal. Calcd.** For $C_{23}H_{18}N_2OS$: C: 74.57; H: 4.90; N: 7.56; ***Found:*** C: 74.55; H: 4.92; N: 7.53. HRMS-ESI (m/z) calcd for $C_{23}H_{18}N_2OS$ $[M + H]^+$ 370.1140, found 370.1145.

N-(4-oxo-2-phenyl-2-(phenylethynyl)thiazolidin-3-yl)benzamide (4b), white solid; Yield 30% (135 mg); mp 225-230 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 7.88 (d, *J* = 6.0 Hz, 2H), 7.49 (dd, J_1 = 5.8 Hz, J_2 = 5.6 Hz, 1H), 7.47 (d, *J* = 5.8 Hz, 2H), 7.45-7.44 (m, 4H), 7.40 (s, 1H, D_2O exchangeable), 7.33 (d, *J* = 6.0 Hz, 2H), 7.27-7.25 (m, 5H), 3.70-3.67 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ ppm: 35.81, 69.95, 79.06, 123.33, 127.00, 128.06, 128.28, 128.48, 128.51, 128.66, 129.81, 131.41, s132.03, 132.71, 138.13, 165.41, 175.55; **Anal. Calcd.** For $C_{24}H_{18}N_2O_2S$: C: 72.34; H: 4.55; N: 7.03; ***Found:*** C: 72.30; H: 4.59; N: 7.00. HRMS-ESI (m/z) calcd for $C_{24}H_{18}N_2O_2S$ $[M + H]^+$ 398.1089, found 398.1085.

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