ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

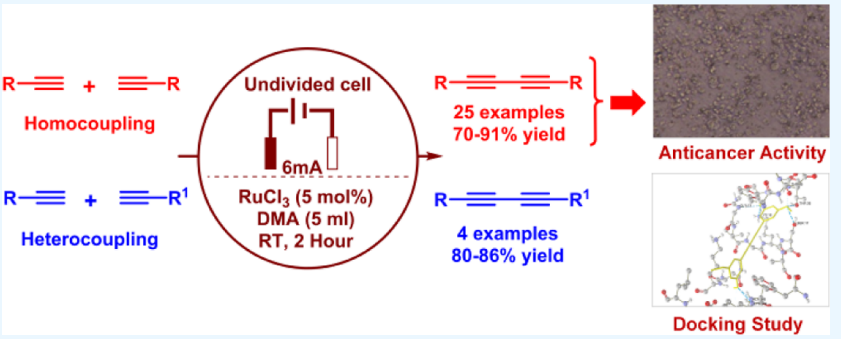
Efficient Ru-Catalyzed Electrochemical Homo- and Heterocoupling Reaction of Terminal Alkynes: Synthesis, *In Vitro* Anticancer Activity, and Docking Study

Kashyap J. Tamuli, Bardwi Narzary, Surovi Saikia, and Manobjyoti Bordoloi*

Cite This: *ACS Omega* 2023, 8, 32635−32642

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: With the objective to identify novel anticancer leads, herein ruthenium-catalyzed electrochemical homo- and heterocoupling reactions of terminal alkynes have been developed for the synthesis of the desired products. Among the synthesized 1,3-diynes, some of them were rigorously examined for possible *in vitro* anticancer activity against HeLa (human cervical cancer) and L6 normal (rat skeletal muscle) cell lines. Additionally, the docking study was also performed toward 16 ovarian cancer targets with binding affinity calculations with respect to the standard. To the best of our knowledge, this is the first scientific report on the ruthenium-catalyzed electrochemical homocoupling reaction between terminal alkynes with its *in vitro* anticancer and *in silico* docking studies.

1. INTRODUCTION

After cardiovascular disease, cancer is considered as the second deadliest disease over the world. According to the World Health Organization (WHO) factsheet 2020, an estimated 10 million people have died from cancer. In the same year, the most common cancers were breast (2.26 million), lung (2.21 million), colon and rectum and prostate (1.93 million) cancers. In 2018, almost 311,000 women died from life-threatening cervical cancer.[1] Despite the fact, present remedial treatments of cancer are effective in treating early stages, the survival rates remain limited. If it happens like this till 2025, new cancer cases could further rise up to 19.3 million.[2] Additionally, for the treatment of such life-threatening diseases, the development of expensive drug resistance has created major havoc. A review of literature study depicts that, small molecules can be established as an anticancer analogue through target-based drug discovery and phenotype-based drug discovery (PDD) methods.[3,4] Among them, PDD is gaining new momentum in drug discovery schemes with the hope that such approaches may enliven drug discovery and boost the progress rate of drug approval to novel drug targets *via* identification of viable appropriate drug candidates.[5]

According to various reports, no anticancer leads are available with 100% potency without any side effects around the globe. Therefore, there is a dire need for researchers for the development of new chemical entities, which can prevent drug resistance with maximum efficacy to provide a better therapeutic environment. In this context, small molecules, like alkynes played an important role in pharmacological and physiological activities due to their diverse biological significance. Among them, 1,3-conjugated diyne analogues exhibited numerous physiological and pharmacological activities, such as, anti-inflammatory, antibacterial, anti-viral, anticancer, antifungal, and anti-HIV activities.[6,7] Many bioactive compounds like falcarindiol, phosphoiodyns A, placotylene A, debilisone C and so on bearing the 1,3-conjugated diynes as their core moieties are isolated from different natural sources having a wide range of diverse biological efficacy.[8−15] In

Received: May 14, 2023
Accepted: June 15, 2023
Published: August 30, 2023

addition to their significant biological activities, these 1,3-diynes are found to have pronounced applications in designing complex compounds, biomolecules, supramolecular switches, macrocyclic annulenes, molecular machines, and other carbon-rich components.[16,17]

In the organic chemistry domain, alkynes are one of the most established and suitable building blocks to transform useful functionalities *via* nucleophilic substitution and nucleophilic addition reactions. The coupling of terminal alkynes could achieve a diyne fragment substituted with various functionalities attached to both sides resulting in symmetrical or unsymmetrical 1,3-diynes. The straightforward synthesis of homocoupled 1,3-diynes was reported by Glaser–Eglinton–Hay–Cadiot–Chodkiewicz with adequate results.[18−25] In the standard synthesis of 1,3-diynes, copper is assigned to be an outstanding catalyst.[26−34] Apart from that, some bimetallic metal additives with copper were used for the preparation of 1,3-diynes from different alkyne sources.[35−40] In addition to that, some nanocomposites,[41−45] charge-transfer catalysts,[46] and visible light-induced[47,48] reaction media acted as active catalysts to afford these diyne building blocks. Likewise, there are numerous methodologies that exist in the literature for the synthesis of 1,3-diyne moieties.[49−52] However, the push for this methodology is still continuing and under strong consideration by various academia along with pharmaceutical industries. Some years ago, Stelzer and co-workers reported a complex ruthenium-catalyzed homocoupling reaction for terminal acetylenes.[53] But the main limitations of that pathway were the use of air-sensitive complicated ruthenium catalysts and formation of oligo or polymeric byproducts of alkynes during the reaction. In this regard, we were keen to examine if some mild, cost effective, and potentially more versatile ruthenium catalysts could exhibit superior activity to the synthesis of 1,3-diynes.

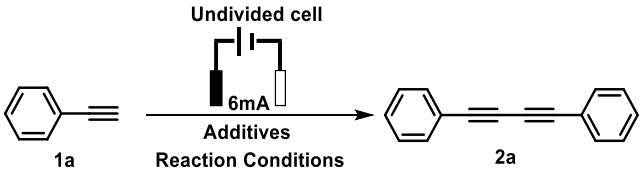
Moreover, in recent days, electrochemical synthesis achieves an attractive synthetic protocol with traceless electric current in the organic chemistry domain.[54−58] Such reactions have generally led to the improvement of numerous oxidant-free coupling reactions.[59−63] Notably, these methodologies comprise various divided cells to avert the decomposition of the used metal catalysts during cathodic deactivation. Among the metal catalysts, ruthenium is an alluring metal catalyst used for various bond activation due to its exemplary catalytic reactivity. In general, ruthenium catalysts are cost effective compared to Rh and Pd. Recently, Ru-catalyzed organic reactions *via* electrochemical pathways have been developed for the synthesis of diverse heterocyclic analogues including building blocks.[64−68]

In an effort to search for new lead molecules having potent anti-cancer activity, our approach is structural modification to central moieties of 1,3-diynes. At first, we have primarily focused on development of a mild and adequate methodology for the synthesis of 1,3-conjugated diyne moieties and then exploration of their *in vitro* anticancer activity. With the results of anticancer activity of synthesized compounds making us further examine the molecular interaction docking pattern. Herein, we have also studied the affinities of these compounds toward 16 ovarian cancer targets by considering doxorubicin as the standard drug.

2. RESULTS AND DISCUSSION

2.1. Chemistry. Despite the advancements in Cu-catalyzed alkyne homocoupling reaction, to the best of our knowledge, the Ru-catalyzed electrochemical reaction has not been realized so far. At first, we began our investigation by optimizing the reaction conditions for the synthesis of symmetrical 1,3-conjugated diynes electrochemically. An undivided cell consists of a Pt plate as the cathode and a reticulated vitreous carbon (RVC) as the anode with 6 mA constant current at room temperature. Herein, the metal salts and solvents were served as supporting electrolytes. Initially, the model reaction was conducted by using phenyl acetylene **1a** for its homocoupling product **2a** in the absence of solvents; no product was observed up to 24 h of reaction time (Table 1, entry 1). Some improved results were found when we used acetonitrile as the solvent, but the yield percentage of the desired product was not excessively high for 12−24 h (Table 1, entry 2). While ensuring the optimization with other solvents like toluene, ethanol, and dimethylformamide (DMF), the desired product was formed with an excellent yield of 90% while DMA was used as a solvent in just 2 h (Table 1, entry 6). Moreover, even with the addition of more amount of $RuCl_3$ catalyst (10−15 mol %), it did not enhance the yield percentage (Table 1, entries 7, 8). Afterward, some more additional optimizations were also performed to enhance the yield percentage by changing the Ru catalyst (Table 1, entries 9, 10, and 11). Unfortunately, no significant change was observed during the reaction. Further for optimization of the reaction by altering the metal catalysts like copper and palladium with their best compatible solvent system, it provided slightly lower yields with long reaction time (Table 1, entries 10−16). After all the detailed tuning of the reaction conditions, 5 mol % of $RuCl_3$ with DMA as the solvent in open air conditions was selected as the optimized reaction conditions.

Table 1. Optimization of Reaction Conditions for the Synthesis of 1,3-Diynes[a]



entry	catalyst (mol %)	solvents (mL)	time (h)	yield (%)[b]
1	$RuCl_3{\cdot}3H_2O$ (5)		24	NR[c]
2	$RuCl_3{\cdot}3H_2O$ (5)	CH_3CN	12	28, (37)[d]
3	$RuCl_3{\cdot}3H_2O$ (5)	toluene	12	41
4	$RuCl_3{\cdot}3H_2O$ (5)	EtOH	8	44, (51)[d]
5	$RuCl_3{\cdot}3H_2O$ (5)	DMF	8	47, (52)[d]
6	**$RuCl_3{\cdot}3H_2O$ (5)**	**DMA**	**2**	**90**
7	$RuCl_3{\cdot}3H_2O$ (10)	DMA	2	89
8	$RuCl_3{\cdot}3H_2O$ (15)	DMA	2	86
9	$RuCl_2{\cdot}H_2O$ (5)	DMF	4	73
10	$RuCl_2{\cdot}H_2O$ (10)	DMF	4	69
11	$[RuCl_2(p\text{-cymene})]_2$ (10)	^{t}BuOH	6	77
12	$CuCl_2{\cdot}H_2O$ (5)	DMF	8	81
13	$Cu(OAc)_2{\cdot}H_2O$ (5)	DMSO	8	84
14	CuBr (5)	CH_3CN	8	80
15	$PdCl_2$ (10)	H_20	12	68
16	$Pd(OAc)_2$ (10)	THF	12	72

[a]Reaction conditions: phenyl acetylene **1a** (1 mmol), solvents (5 mL). [b]Isolated yields. [c]NR: no reaction. [d]The reaction time in 12 h.

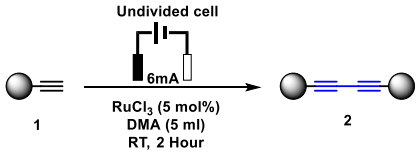
https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642

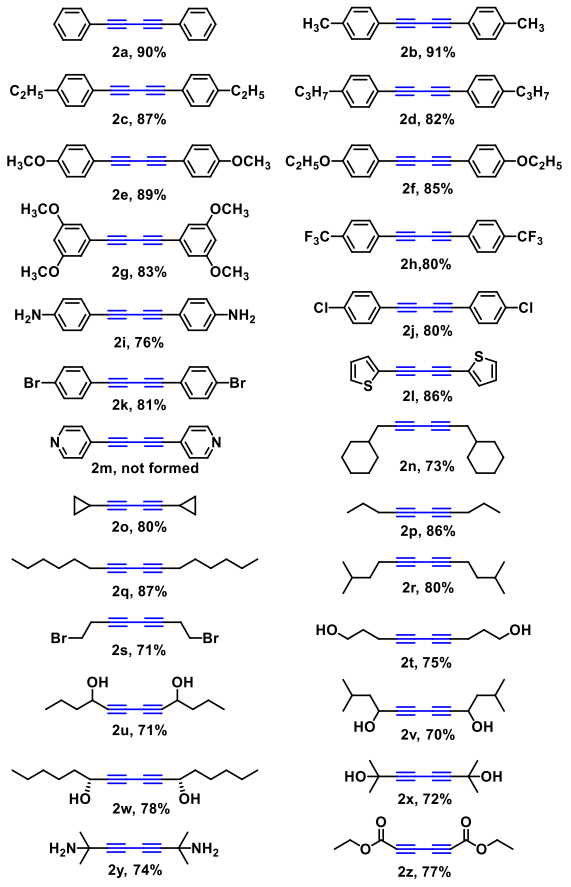
After identifying the optimum reaction conditions, we next set out to broaden the substrate tolerance by using a variety of substituted terminal alkynes (Table 2). We have tested a wide range of substituted terminal alkyne-bearing electron-withdrawing or electron-donating groups to the aromatic rings and simple aliphatic compounds. The final products were formed in moderate to excellent yields in the optimum condition. The substrates having methyl, ethyl, propyl, methoxy, and ethoxy to the aromatic ring was well tolerable to the desired homocoupled products (**2a**−**2g**) with up to 91% of yields. The resilience of para-substituted $-CF_3$ and $-NH_2$ to the phenyl ring with halide functionalities is noticeable to give the resultant products (**2h**−**2k**). Moreover, the heterocycles, furan-substituted terminal alkyne, were also shown to be very effective in producing 1,3-diynes **2l** in high yields. But, the indole moiety did not proceed under these optimized conditions. When 4-ethynylpyridine **1m** was used as the substrate, we did not achieve the desired product **2m**. The reason may be the nitrogen atom attached to the phenyl ring of the indole may coordinate to the Ru-metal catalyst which prevents the reaction. In the current study, we have also evaluated the scope of simple cyclic alkynes **1n** and **1o** as well as aliphatic long-chain terminal alkynes. It was fascinating to see that long-chain aliphatic alkynes and bromo-, hydroxy-, amine-substituted terminal alkynes exhibited the corresponding homocoupled products in good yields. Conspicuously, ethyl propiolate **1z** functionality and the sterically demanding substrate (*R*)-oct-1-yn-3-ol **1w** also successfully obtained the desired product in good yields. Hence, from our study, it was observed that all the substituted terminal alkynes were well compatible with our electrolytic homocoupling reaction.

To further explore the applicability of our optimized reaction environment, we next explored the reaction scope by varying both coupling substrates to synthesize unsymmetrical 1,3-diynes (Table 3). Surprisingly, Csp−Csp cross-coupling products were obtained between phenylacetylene **1a** and alternative electron-deficient moieties of aromatic terminal alkynes **3**. Herein, methoxy, methyl, and halo-substituted to aryl alkynes and simple cyclic alkynes also resulted in the desired cross-coupling products (**4a**−**4d**) with phenylacetylene **1a** in excellent yields. These unsymmetrical 1,3-diyne functionalities can be effectively suitable for further synthetic conversions in pharmaceutical or medicinal domains.

Furthermore, we broadened our preliminary systematic study by examining some control experiments to establish the correct mechanism (Scheme 1). Because the reactions were strongly influenced by the solvent, thus few catalytic systems under optimized reaction conditions were studied by taking the model reaction. Hence, some other methylene precursors like dimethylsulfoxide and tetramethylurea were used to synthesize the desired products. By using these aprotic solvents, the reaction proceeded sluggishly to obtain resultant products in lower yields with long reaction times. To gather a more mechanistic vision into this transformation, we conducted the reaction in the presence of nitrogen and oxygen balloon. But, the desired products were formed in 3 h with no significant change in terms of yield and reaction time. Markedly, the constant current affected the reaction adequately, either decreasing or increasing the constant current

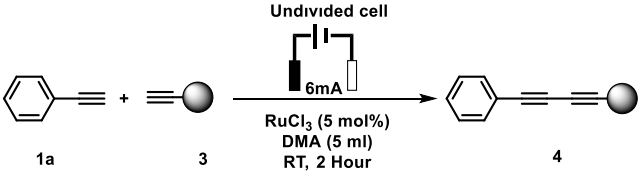
Table 2. Substrate Scope for the Synthesis of Symmetrical 1,3-Diynes[a,b]

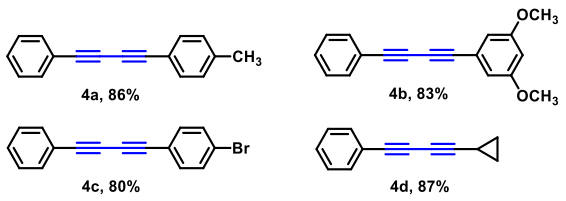




[a]Reaction conditions: phenylacetylene **1a** (1 mmol), other terminal alkyne **3** (1 mmol), DMA (5 mL), time: 2 h, room temperature. [b]Isolated yields.

Table 3. Substrate Scope for the Synthesis of Unsymmetrical 1,3-Diynes[a,b]

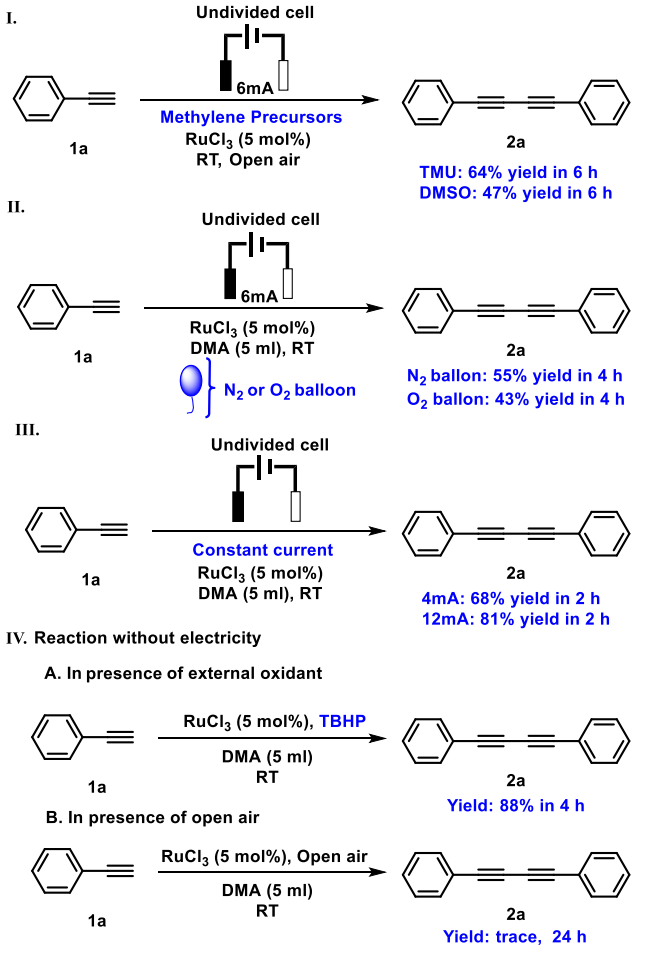




[a]Reaction conditions: phenyl acetylene **1a** (0.5 mmol), other substituted alkynes **3** (0.5 mmol), DMA (5 mL), time: 2 h, room temperature. [b]Isolated yields.

https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642

Scheme 1. Preliminary Mechanistic Studies

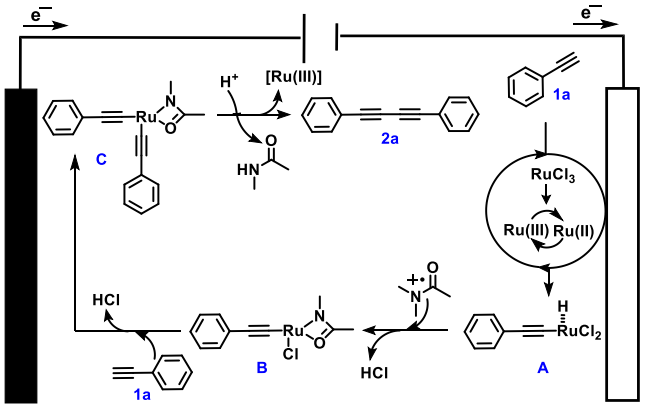


resulted in a low amount of yield. Subsequently, we treated this reaction without the electricity, but afforded 88% of yield in the presence of TBHP at first. Then, we examined our model reaction again without any electrochemical input or external oxidant but it resulted in trace amounts of final products after long reaction times when we took open air as a blank. Hence, these results implied that the electric current offered to regenerate or to active the ruthenium catalyst.

With our above-mentioned control experiments and recently reported Ru(II)-catalyzed electrolytic reaction,[64−69] a plausible mechanistic pathway is described in Scheme 2. During our analysis, on the activation of alkynes by electrochemically, we found that the reaction is presumed to proceed *via* the metal-catalyzed reaction. Generally to activate the pi bonds, it requires external oxidants or transition metals.[65,66] However, in the process of the activation of terminal alkynes, the electrochemical functionalization turned out to be a mild approach, without the use of any external oxidants or additives. Initially, $RuCl_3$ is oxidized to Ru(II) in the anode. Subsequently, formation of intermediate **A** by Ru(II)-assisted metal fission with phenylacetylene.[69] With the addition of DMA, the intermediate generated **B** with the activated iminium ion. With subsequent addition of another phenylacetylene in the next step, an elimination of HCl provides **C** *via* metal fission. Finally, release of H^+ with the Ru catalyst at the cathode results in the desired final product **2a**.

2.2. Cytotoxicity Assay. The *in vitro* anticancer activity of some selected isolated compounds was screened against HeLa

Scheme 2. Probable Mechanistic Pathway for Synthesis of 1,3-Diynes



cells (human cervical cancer) and L6 normal cells (rat skeletal muscle). The results were evaluated by using tetrazolium salt MTT assays as described previously with minor modification.[70,71] The effects of the tested compounds on the proliferation of the cancer cell lines with IC_{50} values are shown in Table 4. The results depicted that most of the

Table 4. Growth Inhibition of L6 and HeLa Cell Lines When Treated with Isolated Compounds at 24 h of Exposure[a,b]

sl. no.	compounds	IC_{50} (μg/mL)	
		L6 cell[b]	HeLa[c]
1	**2a**	30.13 ± 1.72	3.77 ± 1.88
2	**2b**	3.66 ± 1.24	70.53 ± 3.50
3	**2d**	67.35 ± 1.47	42.13 ± 2.64
4	**2g**	43.14 ± 1.22	4.51 ± 1.51
5	**2i**	166.36 ± 3.49	91.2 ± 3.61
6	**2k**	18.52 ± 1.77	16.28 ± 1.75
7	**2n**	152.06 ± 2.33	116.52 ± 2.11
8	**2o**	25.55 ± 1.98	14.49 ± 4.76
9	**2p**	145.32 ± 2.52	104.74 ± 1.45
10	**2q**	31.74 ± 3.25	36.03 ± 3.44
11	**2t**	12.83 ± 1.78	39.32 ± 2.59
12	**2u**	24.47 ± 1.21	19.29 ± 3.57
13	**2w**	2.94 ± 0.45	2.48 ± 0.30
14	**2z**	3.92 ± 0.16	13.23 ± 3.40
15	**doxorubicin**	36 ± 2.07	1.71 ± 0.53

[a]IC_{50} is shown as mean ± standard deviation. The assays were performed in three independent experiments in triplicates. [b]L6 normal rat cell line. [c]HeLa human cervical cancer cell line.

compounds exhibited promising anticancer activity against the human cervical cancer (HeLa) cell lines in different concentrations at 24 h of duration. Compounds having an aromatic ring with substituents like dimethoxy **2g** and lead compound **2a** showed significant and selective antiproliferative activity on HeLa cell lines of IC_{50} = 4.51 ± 1.51 μg/mL and IC_{50} = 3.77 ± 1.88 μg/mL in contrast to normal cells, IC_{50} = 43.14 ± 1.22 μg/mL and IC_{50} = 30.13 ± 1.72 μg/mL, respectively. The IC_{50} in L6 cells are 9.56 (**2g**) and 7.99 (**2a**) fold than HeLa cells. Notably, the 1,3-diynes have an aromatic ring with propyl **2d**, bromo **2k**, and amino **2i** substituents have shown good activity against these two cell lines. Products from ethynylcyclopropane **1o** and hydroxyl-substituted alkyne **1u**

https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642

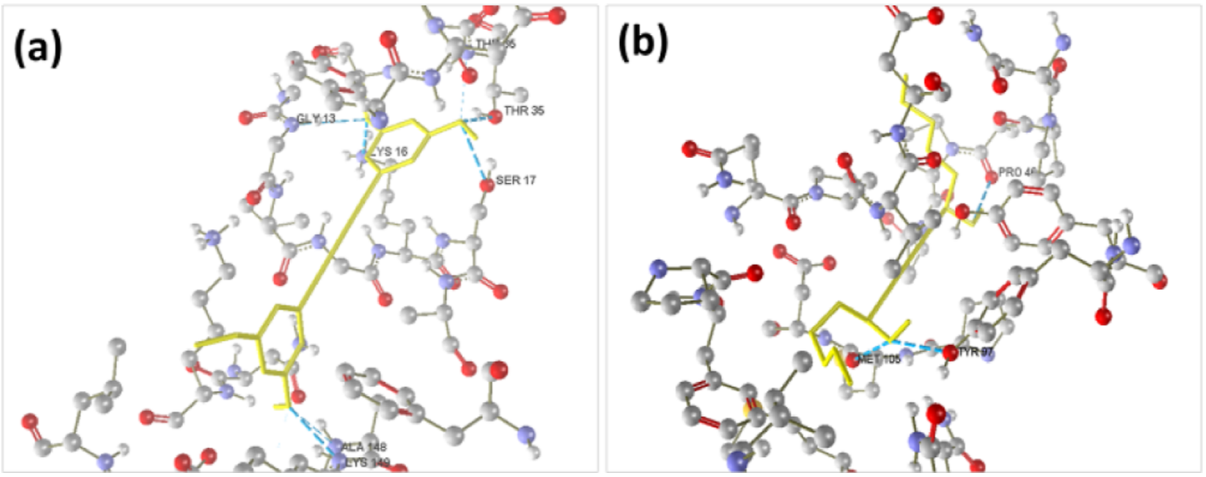


Figure 1. (a) Hydrogen bonding affinity of compound **2g** within the c-RAF1 kinase (PDB ID: 1C1Y); (b) hydrogen bonding affinity of compound **2w** within the bromo domain containing protein 4 (PDB ID: 2OOS).

and **1w** displayed moderate anticancer activity. But, prop-2-yn-1-ylcyclohexane **1n** and substituted aliphatic long chains containing substrates **1p** of 1,3-diyne exhibited poor activity. However, methyl substituents on aromatic ring **2b**, long chain alkynes **2q**, **2t**, and **2z** were toxic to L6 than HeLa cell lines. These results implies that most of the resultant compounds offer promising anticancer activity and has significant potential in further functionalization of these building blocks for drug development.

2.3. Docking Study. From the results of *in vitro* anticancer activity of synthesized compounds, the molecular docking analysis has been studied to observe important structural features of these conjugated 1,3-diyne analogues in hydrogen bond formation. Molecular docking score analysis for all the compounds showed that compound **2g**, **2d**, and **2w** were the most potent candidates for all the ovarian cancer targets. Further, comparisons showed that compounds **2g** and **2w** showed the highest affinity toward c-RAF1 kinase (PDB ID: 1C1Y), which plays an important role in human ovarian cancer tumors where around 20% of them contain c-RAF mutation and bromo domain containing protein 4 (PDB ID: 2OOS), which specifically recognizes the process of epigenetics and is required for the expression of tumor driving oncogene for ovarian cancer progression (Figure 1).[72,73] Their scorings were −149.935 (kcal/mol) and −146.823 (kcal/mol) (Table S1). The former compound targeted Gly13 and Lys16 when compared with the standard (Table S1). Thus, for most of the targets considered in our study, compound **2g** displayed potential activity in docking analysis. From the *in vitro* anticancer results, compound **2g** showed significant and selective antiproliferative activity on HeLa cell lines. An outcome we can draw from here is that the structurally flexible dimethoxy substituent to aromatic alkyne moiety may have more extension to exhibit interactions through hydrogen bonding interactions. Hence, the *in vitro* anticancer results and docking analysis follow a similar trend. Additionally, with the appropriate and selective substituents of 1,3-diynes, further survey toward the improvement of new anticancer agents could be made.

3. CONCLUSIONS

In the present study, a series of 1,3-diyne derivatives were synthesized, where electric current can be used to endorse ruthenium-catalyzed homo- and heterocoupling reactions between different terminal alkynes *via* a simple undivided cell reaction setup. This novel process enabled us to obtain the desired products from various structurally diverse starting materials in excellent yields. In addition to that, the synthesized compounds *in vitro* anticancer activity against HeLa and L6 normal cell lines were further studied. Moreover, structure-based *in silico* molecular docking analysis was also performed to evaluate the structural features of these compounds with the hydrogen bond forming affinity. Among the tested compounds, methoxy substituted to phenyl ring **2g** exhibited significant antiproliferative activity on HeLa and L6 cell lines as well as the highest binding affinity for maximum targets. Such a target base study and electrochemical approach showed a great value to synthesize bioactive diyne derivatives to develop new anticancer leads.

4. EXPERIMENTAL SECTION

4.1. Materials and Methods. All the chemicals used in the experiments were purified according to standard procedures. Glasswares were used after being oven-dried or flame-dried. NMR was taken at a Bruker Avance II DPX 500 MHz instrument using tetramethylsilane as an internal standard. Fourier transform infrared (FT-IR) spectra were obtained from thin films using chloroform by using an Elmer FT-IR-2000 spectrometer. High-resolution mass spectra data were recorded by electrospray ionization with a Q-TOF mass analyzer. Melting points were measured with a Buchi-540 micro melting point apparatus. Reactions were monitored using pre-coated silica gel 60 F_{254} sheets (Merck) thin-layer chromatography (TLC).[74] For the MTT assay, cell lines were displayed and micrographed under an inverted microscope (Motic-AE30). The absorbance was recorded on an enzyme-linked immunosorbent assay plate reader (FilterMax F3 Multi-Mode Microplate Readers, Molecular Devices).[71] For the docking study, 3D structures were generated and optimized in ChemBio3D Ultra 14 (CambridgeSoft, UK) with RMS gradient 0.01 of geometry optimization. For each compound, the minimum energy structure was calculated by using the (Molecular Mechanics Alligner Force Field 2; MM2) force field. All the protein preparation were done in Molegro Virtual Docker (MVD) (6.0, Molegro-a CLC Bio Company, Denmark).[75]

https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642

4.2. Electrochemical Analysis Setup. For all electrochemical reactions, a homemade flow cell was prepared together with PowerEase 90 W Power Supply (115 VAC) from Thermo Fisher Scientific, India (Figure S1). The cell consists of a working electrode of a Pt plate as the cathode and a RVC as the anode with 6 mA constant current. The reaction vial was made up of Borosil glass with two self-made holes in the cap to put two respective electrodes, as shown in Figure S1. This results in an undivided electrochemical cell. In the cell, direct contact between the electrode surface and the reaction mixture is established.

4.3. General Experimental Procedures. *4.3.1. Experimental Procedure for Synthesis of Synthesis of Symmetrical 1,3-Diynes.* The electrolysis was carried out in an undivided cell consisting of a Pt plate as the cathode and a RVC as the anode. Substituted alkynes **1a**−**1z** (1 mmol) and $RuCl_3$ (5 mol %) were dissolved in DMA (5 mL) under an open air atmosphere. The electrolysis was performed at room temperature with a constant current of 6 mA which was then maintained for 2 h. The product formation was observed by TLC. After completion of the reaction, the mixture was transferred to a clean flask and poured into ice cold water. Then extracted the organic product with ethyl acetate (2 × 25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the desired product **2** was purified with automated flash chromatography using hexane and ethylacetate as the eluent. The RVC anode was cleaned with acetone (3 × 10 mL) in an ultrasonic bath.

4.3.2. Experimental Procedure for Synthesis of Unsymmetrical 1,3-Diynes. The electrolysis was carried out in an undivided cell consisting of a Pt plate as the cathode and a RVC as the anode. Phenyl acetylene **1a** (0.5 mmol), other substituted alkynes **3** (0.5 mmol), and $RuCl_3$ (5 mol %) were dissolved in DMA (5 mL) under an open air atmosphere. The electrolysis was performed at room temperature with a constant current of 6 mA which was then maintained for 2 h. The product formation was observed by TLC. After completion of the reaction, the mixture was transferred to a clean flask and poured into ice cold water. Then extracted the organic product with ethyl acetate (2 × 25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and purified the desired product 4 with automated flash chromatography using hexane and ethylacetate as the eluent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03129.

Detailed experimental procedures, including spectroscopic data with NMR spectra for all the isolated compounds, electrochemical experiment setup, and docking study analyses (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Manobjyoti Bordoloi − *Chemical Sciences and Technology Division, CSIR-North East Institute of Science & Technology, Jorhat 785006 Assam, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002 Uttar Pradesh, India; Department of Chemistry, Cotton University, Guwahati 781001 Assam, India;* orcid.org/0000-0003-0478-6824; Email: m.j.bordoloi.pub@gmail.com, mjb_rrljt@yahoo.co.in

Authors

Kashyap J. Tamuli − *Chemical Sciences and Technology Division, CSIR-North East Institute of Science & Technology, Jorhat 785006 Assam, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002 Uttar Pradesh, India;* orcid.org/0000-0002-3110-5644

Bardwi Narzary − *Chemical Sciences and Technology Division, CSIR-North East Institute of Science & Technology, Jorhat 785006 Assam, India*

Surovi Saikia − *Chemical Sciences and Technology Division, CSIR-North East Institute of Science & Technology, Jorhat 785006 Assam, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c03129

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank CSIR New Delhi, India for providing the financial support under the grant of CSC-0130. We also thank the Director, CSIR-NEIST for his keen interest.

■ REFERENCES

(1) World Health Organization. World Cancer Report 2020. https://www.who.int/health-topics/cancer#tab=tab_1 (accessed on Nov 13, 2021).

(2) Hamam, F. Curcumin: New Weapon against Cancer. *Food Nutr. Sci.* **2014**, *05*, 2257−2264.

(3) Moffat, J. G.; Rudolph, J.; Bailey, D. Phenotypic Screening in Cancer Drug Discovery—Past, Present and Future. *Nat. Rev. Drug Discovery* **2014**, *13*, 588−602.

(4) Hoelder, S.; Clarke, P. A.; Workman, P. Discovery of small molecule cancer drugs: successes, challenges and opportunities. *Mol. Oncol.* **2012**, *6*, 155−176.

(5) Zheng, W.; Thorne, N.; McKew, J. C. Phenotypic screens as a renewed approach for drug discovery. *Drug Discovery Today* **2013**, *18*, 1067−1073.

(6) Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. Synthesis of antibacterial 1,3-diyne-linked peptoids from an Ugi-4CR/Glaser coupling approach. *Beilstein J. Org. Chem.* **2015**, *11*, 25−30.

(7) Musza, K.; Mészáros, R.; Baán, K.; Kónya, Z.; Kukovecz, Á.; Pálinkó, I.; Sipos, P.; Szabados, M. Mechanochemical preparation of NiCuSn nanoparticles and composites in presence of cetyltrimethylammonium bromide (CTAB) and the catalytic application of the products in homocoupling and hydration of terminal alkynes. *J. Mol. Struct.* **2022**, *1262*, 132948.

(8) Garrod, B.; Lewis, B.; Coxon, D. Cis-heptadeca-1,9-diene-4,6-diyne-3,8-diol, an antifungal polyacetylene from carrot root tissue. *Physiol. Plant Pathol.* **1978**, *13*, 241−246.

(9) Kemp, M. S. Falcarindiol an antifungal polyacetylene from *Aegopodium podagraria*. *Phytochemistry* **1978**, *17*, 1002.

(10) P. Christensen, L. Aliphatic C17-Polyacetylenes of the Falcarinol Type as Potential Health Promoting Compounds in Food Plants of the Apiaceae Family. *Recent Pat. Food, Nutr. Agric.* **2011**, *3*, 64−77.

(11) Kim, H.; Kim, K. J.; Yeon, J. T.; Kim, S. H.; Won, D. H.; Choi, H.; Nam, S. J.; Son, Y. J.; Kang, H.; Placotylene, A. an Inhibitor of the Receptor Activator of Nuclear Factor-κB Ligand-Induced Osteoclast Differentiation, from a Korean *Sponge Placospongia* sp. *Mar. Drugs* **2014**, *12*, 2054−2065.

(12) Panthama, N.; Kanokmedhakul, S.; Kanokmedhakul, K. Polyacetylenes from the roots of *Polyalthia debilis*. *J. Nat. Prod.* **2010**, *73*, 1366−1369.
(13) Yoon, M. Y.; Choi, G. J.; Choi, Y. H.; Jang, K. S.; Cha, B.; Kim, J. C. Antifungal activity of polyacetylenes isolated from *Cirsium japonicum* roots against various phytopathogenic fungi. *Ind. Crops Prod.* **2011**, *34*, 882−887.
(14) Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. Synthesis of antibacterial 1,3-diyne-linked peptoids from an Ugi-4CR/Glaser coupling approach. *Beilstein J. Org. Chem.* **2015**, *11*, 25−30.
(15) Sari, O.; Roy, V.; Balzarini, J.; Snoeck, R.; Andrei, G.; Agrofoglio, L. A. Synthesis and antiviral evaluation of C5-substituted-(1,3-diyne)-2′-deoxyuridines. *Eur. J. Med. Chem.* **2012**, *53*, 220−228.
(16) Zhou, Y.; Zhang, Y.; Wang, J. Recent advances in transition-metal-catalyzed synthesis of conjugated enynes. *Org. Biomol. Chem.* **2016**, *14*, 6638−6650.
(17) Trost, B. M.; Masters, J. T. Transition metal-catalyzed couplings of alkynes to 1,3-enynes: modern methods and synthetic applications. *Chem. Soc. Rev.* **2016**, *45*, 2212−2238.
(18) Glaser, C. Beiträge zur Kenntniss des Acetenylbenzols. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422−424.
(19) Glaser, C. Untersuchungen über einige Derivate der Zimmtsäure. *Ann. Chem. Pharm.* **1870**, *154*, 137−171.
(20) Eglinton, G.; Galbraith, A. R. Cyclic dyines. *Chem. Ind.* **1956**, *28*, 736−737.
(21) Eglinton, G.; Galbraith, A. R. 182. Macrocyclic acetylenic compounds. Part I. Cyclotetradeca-1:3-diyne and related compounds. *J. Chem. Soc.* **1959**, 889−896.
(22) Hay, A. S. Communications-Oxidative Coupling of Acetylenes. *J. Org. Chem.* **1960**, *25*, 1275−1276.
(23) Hay, A. S. Oxidative coupling of acetylenes. II. *J. Org. Chem.* **1962**, *27*, 3320−3321.
(24) Chodkiewicz, W. Synthesis of acetylenic compounds. *Ann. Chim.* **1957**, *2*, 819−869.
(25) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647.
(26) Adimurthy, S.; Malakar, C. C.; Beifuss, U. Influence of Bases and Ligands on the Outcome of the Cu(I)-Catalyzed Oxidative Homocoupling of Terminal Alkynes to 1,4-Disubstituted 1,3-Diynes Using Oxygen as an Oxidant. *J. Org. Chem.* **2009**, *74*, 5648−5651.
(27) Yin, K.; Li, C.; Li, J.; Jia, X. CuCl-catalyzed green oxidative alkyne homocoupling without palladium, ligands and bases. *Green Chem.* **2011**, *13*, 591−593.
(28) Kusuda, A.; Xu, X. H.; Wang, X.; Tokunaga, E.; Shibata, N. Organic reaction in Solkane365 mfc: homocoupling reaction of terminal alkynes. *Green Chem.* **2011**, *13*, 843−846.
(29) Li, D.; Yin, K.; Li, J.; Jia, X. CuI/iodine-mediated homocoupling reaction of terminal alkynes to 1,3-diynes. *Tetrahedron Lett.* **2008**, *49*, 5918−5919.
(30) Zhang, S.; Liu, X.; Wang, T. An Efficient Copper-Catalyzed Homocoupling of Terminal Alkynes to Give Symmetrical 1,4-Disubstituted 1,3-Diynes. *Adv. Synth. Catal.* **2011**, *353*, 1463−1466.
(31) Zhang, L. J.; Wang, Y. H.; Liu, J.; Xu, M. C.; Zhang, X. M. Efficient and environmentally friendly Glaser coupling of terminal alkynes catalyzed by multinuclear copper complexes under base-free conditions. *RSC Adv.* **2016**, *6*, 28653−28657.
(32) Su, L.; Dong, J.; Liu, L.; Sun, M.; Qiu, R.; Zhou, Y.; Yin, S. F. Copper Catalysis for Selective Heterocoupling of Terminal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 12348−12351.
(33) Cheng, G.; Zhang, H.; Cui, X. Copper(I)-catalyzed homocoupling of terminal alkynes at room temperature under solvent and base free conditions using O_2 as an oxidant. *RSC Adv.* **2014**, *4*, 1849−1852.
(34) Wang, D.; Li, J.; Li, N.; Gao, T.; Hou, S.; Chen, B. An efficient approach to homocoupling of terminal alkynes: Solvent-free synthesis of 1,3-diynes using catalytic Cu(II) and base. *Green Chem.* **2010**, *12*, 45−48.
(35) Wityak, J.; Chan, J. B. Synthesis of 1, 3-diynes using palladium-copper catalysis. *Synth. Commun.* **1991**, *21*, 977−979.
(36) Wang, Y.; Suo, Q.; Han, L.; Guo, L.; Wang, Y.; Li, F. Copper(II)/Palladium(II) catalysed highly selective cross-coupling of terminal alkynes in supercritical carbon dioxide. *Tetrahedron* **2018**, *74*, 1918−1925.
(37) Chen, S. N.; Wu, W. Y.; Tsai, F. Y. Homocoupling reaction of terminal alkynes catalyzed by a reusable cationic 2,2′-bipyridyl palladium(II)/CuI system in water. *Green Chem.* **2009**, *11*, 269−274.
(38) Rangaraju, S. K.; Gonela, U. M.; Kavita, A.; Yadav, J. S.; Mohapatra, D. K. Synergistic Gold and Copper Dual Catalysis for Intramolecular Glaser−Hay Coupling: Rapid Total Synthesis of Ivorenolide B. *Eur. J. Org. Chem.* **2018**, 4376−4380.
(39) Mukherjee, N.; Kundu, D.; Ranu, B. C. A co-operative Ni−Cu system for Csp−Csp and Csp−Csp^2 cross-coupling providing a direct access to unsymmetrical 1,3-diynes and en-ynes. *Chem. Commun.* **2014**, *50*, 15784−15787.
(40) Bedard, A. C.; Collins, S. K. Microwave accelerated Glaser−Hay macrocyclizations at high concentrations. *Chem. Commun.* **2012**, *48*, 6420−6422.
(41) Radivoy, G.; Nador, F.; Fortunato, L.; Moglie, Y.; Vitale, C. A simple one-pot procedure for the direct homocoupling of terminal alkynes promoted by copper nanoparticles. *Synthesis* **2009**, 4027−4031.
(42) Xu, H.; Wu, K.; Tian, J.; Zhu, L.; Yao, X. Recyclable Cu/C_3N_4 composite catalysed homo-and cross-coupling of terminal alkynes under mild conditions. *Green Chem.* **2018**, *20*, 793−797.
(43) Aziz, S. T.; Islam, R. U. Polymer-supported Cu−nanoparticle as an efficient and recyclable catalyst for oxidative homocoupling of terminal alkynes. *Catal. Lett.* **2018**, *148*, 205−213.
(44) Tang, B. X.; Fang, X. N.; Kuang, R. Y.; Wu, J. H.; Chen, Q.; Hu, S. J.; Liu, Y. L. First report of a nano-Cu2O-catalyzed protocol for homo-coupling reaction of terminal alkynes in water/ionic liquid medium. *Appl. Organomet. Chem.* **2016**, *30*, 943−945.
(45) Ahammed, S.; Kundu, D.; Ranu, B. C. Cu-Catalyzed Fe-Driven Csp−Csp and Csp−Csp^2 Cross-Coupling: An Access to 1,3-Diynes and 1,3-Enynes. *J. Org. Chem.* **2014**, *79*, 7391−7398.
(46) Gonzalo Rodríguez, J.; Lafuente, A.; Martin-Villamil, R.; Martinez-Alcazar, M. P. Synthesis and structural analysis of 1,4-bis[n-(N,N-dimethylamino)phenyl]buta-1,3-diynes and charge-transfer complexes with TCNE. *J. Phys. Org. Chem.* **2001**, *14*, 859−868.
(47) Sagadevan, A.; Charpe, V. P.; Hwang, K. C. Copper(I) chloride catalysed room temperature Csp−Csp homocoupling of terminal alkynes mediated by visible light. *Catal. Sci. Technol.* **2016**, *6*, 7688−7692.
(48) Sagadevan, A.; Lyu, P. C.; Hwang, K. C. Visible-light-activated copper(I) catalyzed oxidative C_{sp}−C_{sp} cross-coupling reaction: efficient synthesis of unsymmetrical conjugated diynes without ligands and base. *Green Chem.* **2016**, *18*, 4526−4530.
(49) Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R.; Dickinson, J. M. Pd-catalysed cross coupling of terminal alkynes to diynes in the absence of a stoichiometric additive. *Chem. Commun.* **2003**, 632−633.
(50) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. Nickel-Catalyzed Oxidative Coupling Reactions of Two Different Terminal Alkynes Using O2 as the Oxidant at Room Temperature: Facile Syntheses of Unsymmetric 1,3-Diynes. *Org. Lett.* **2009**, *11*, 709−712.
(51) Li, X.; Xie, X.; Sun, N.; Liu, Y. Gold-Catalyzed Cadiot−Chodkiewicz-type Cross-Coupling of Terminal Alkynes with Alkynyl Hypervalent Iodine Reagents: Highly Selective Synthesis of Unsymmetrical 1,3-Diynes. *Angew. Chem., Int. Ed.* **2017**, *56*, 6994−6998.
(52) Thangarasu, A. K.; Yadhukrishnan, V. O.; Krishnakumar, K. A.; Varma, S. S.; Lankalapalli, R. S. Cu(I)-azidopyrrolo[3,2-d]pyrimidine Catalyzed Glaser−Hay Reaction under Mild Conditions. *ACS Org. Inorg. Au* **2022**, *2*, 3−7.
(53) Slugovc, C.; Doberer, D.; Gemel, C.; Schmid, R.; Kirchner, K.; Winkler, B.; Stelzer, F. Ruthenium Catalyzed Homocoupling of Terminal Alkynes. *Monatsh. Chem.* **1998**, *129*, 221−233.
(54) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic electrosynthesis: a promising green

https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642

methodology in organic chemistry. *Green Chem.* **2010**, *12*, 2099−2119.
(55) Francke, R.; Little, R. D. Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521.
(56) Yoshida, J. I.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265−2299.
(57) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230−13319.
(58) Jiang, Y.; Xu, K.; Zeng, C. Use of Electrochemistry in the Synthesis of Heterocyclic Structures. *Chem. Rev.* **2018**, *118*, 4485−4540.
(59) Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem* **2018**, *4*, 27−45.
(60) Wang, P.; Tang, S.; Huang, P.; Lei, A. Electrocatalytic Oxidant-Free Dehydrogenative C−H/S−H Cross-Coupling. *Angew. Chem., Int. Ed.* **2017**, *56*, 3009−3013.
(61) Schulz, L.; Enders, M.; Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. Reagent- and Metal-Free Anodic C−C Cross-Coupling of Aniline Derivatives. *Angew. Chem., Int. Ed.* **2017**, *56*, 4877−4881.
(62) Xiong, P.; Xu, H. H.; Xu, H. C. Metal- and Reagent-Free Intramolecular Oxidative Amination of Tri- and Tetrasubstituted Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 2956−2959.
(63) Folgueiras-Amador, A. A.; Qian, X. Y.; Xu, H. C.; Wirth, T. Catalyst- and Supporting-Electrolyte-Free Electrosynthesis of Benzothiazoles and Thiazolopyridines in Continuous Flow. *Chem.—Eur. J.* **2018**, *24*, 487−491.
(64) Xu, F.; Li, Y. J.; Huang, C.; Xu, H. C. Ruthenium-Catalyzed Electrochemical Dehydrogenative Alkyne Annulation. *ACS Catal.* **2018**, *8*, 3820−3824.
(65) Martins, G. M.; Shirinfar, B.; Hardwick, T.; Murtaza, A.; Ahmed, N. Organic electrosynthesis: electrochemical alkyne functionalization. *Catal. Sci. Technol.* **2019**, *9*, 5868−5881.
(66) Deb, M. L.; Borpatra, P. J.; Saikia, P. J.; Baruah, P. K. Introducing tetramethylurea as a new methylene precursor: a microwave-assisted $RuCl_3$-catalyzed cross dehydrogenative coupling approach to bis(indolyl)methanes. *Org. Biomol. Chem.* **2017**, *15*, 1435−1443.
(67) Das, U. K.; Jena, R. K.; Bhattacharjee, M. Synthesis, structure and catalytic properties of $[Ru(dppp)_2(CH_3CN)Cl]$ $[BPh_4]$ and isolation of catalytically active $[Ru(dppp)_2Cl]$ $[BPh_4]$: ruthenium catalysed alkyne homocoupling and tandem alkyne−azide cycloaddition. *RSC Adv.* **2014**, *4*, 21964−21970.
(68) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C−H/Het−H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281−295.
(69) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. Ruthenium-Catalyzed Hydration of 1-Alkynes to Give Aldehydes: Insight into anti-Markovnikov Regiochemistry. *J. Am. Chem. Soc.* **2001**, *123*, 11917−11924.
(70) Mosmann, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55−63.
(71) Sahoo, R. K.; Tamuli, K. J.; Narzary, B.; Bordoloi, M.; Sharma, H. K.; Gogoi, K.; Bhattacharyya, D. R. *Clerodendrum viscosum* Vent leaf extract supported nanosilver particles: Characterization, antiplasmodial and anticancer activity. *Chem. Phys. Lett.* **2020**, *738*, 136893.
(72) Forbes, S. A.; Bindal, N.; Bamford, S.; Cole, C.; Kok, C. Y.; Beare, D.; Jia, M.; Shepherd, R.; Leung, K.; Menzies, A.; Teague, J. W.; Campbell, P. J.; Stratton, M. R.; Futreal, P. A. COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res.* **2011**, *39*, 945−950.
(73) French, C. A. Demystified molecular pathology of NUT midline carcinomas. *J. Clin. Pathol.* **2010**, *63*, 492−496.
(74) Tamuli, K. J.; Nath, S.; Bordoloi, M. In water organic synthesis: Introducing itaconic acid as a recyclable acidic promoter for efficient and scalable synthesis of quinoxaline derivatives at room temperature. *J. Heterocycl. Chem.* **2021**, *58*, 983−1002.
(75) Saikia, S.; Kolita, B.; Dutta, P. P.; Dutta, D. J.; Neipihoi; Nath, S.; Bordoloi, M.; Quan, P. M.; Thuy, T. T.; Phuong, D. L.; Long, P. Q. Marine steroids as potential anticancer drug candidates: *In silico* investigation in search of inhibitors of Bcl-2 and CDK-4/Cyclin D1. *Steroids* **2015**, *102*, 7−16.

https://doi.org/10.1021/acsomega.3c03129
ACS Omega 2023, 8, 32635−32642