

Research Article

# Solar-Assisted Green Synthesis, Molecular Docking, Antibacterial, and Cytotoxicity Studies of Symmetrical N, N'-Alkylidene Bisamides Bearing Lower E-Factors

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## Abstract

N, N'-alkylidene bisamides show promise in biological and pharmaceutical uses. Advanced chemistry now explores cleaner and more environmentally friendly methods. One such method involves using concentrated solar radiation (CSR) to facilitate the green synthesis of N, N'-alkylidene bisamides. This approach simplifies the process by combining aldehydes and amides in a one-pot reaction. Its solvent-free nature sets it apart, aligning with environmentally friendly practices. Any regular catalyst aids the response, making it efficient. The simplicity continues with an easy filtration step to isolate the products. Notably, there's no need for column chromatography, making the purification process straightforward. In general, a mixture of aldehyde, aryl/alkylamide was taken in a round bottom flask. The reaction mass in RBF was then kept under the concentrated solar radiation (CSR) setup with continuous stirring on a magnetic stirrer. After few hours of stirring the precipitate was observed. After completion of the reaction, the precipitated product was washed with water and recrystallized from hot ethanol to afford pure product symmetrical N, N'-alkylidene bisamide. Dimethyl sulfoxide (DMSO) was used as a solvent to prepare a stock of derivatives. Luria Bertani broth (LB) used for the present study viz; *Staphylococcus aureus* MCC 2408, *Escherichia coli* MCC 2412, *Pseudomonas aeruginosa* MCC 2080 and *Klebsiella pneumoniae* MCC 2451 used to evaluate the antibacterial property of the derivatives. Indeed, this method offers an eco-friendly solution and showcases the potential of using renewable energy sources in chemical synthesis. It is a significant step towards sustainable practices in chemistry, particularly in producing complex organic compounds for biological and pharmaceutical purposes.

## Keywords

Bisamides, Antimicrobial, Anti-Cancer, CSR, One-Pot Synthesis, Green Synthesis

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## 1. Introduction

Amide derivatives have been considered valuable synthetic analog that has immense biological importance [1, 2]. Classified amide compounds are naturally identified as a typical active motif with a broad range of biological activities. They also use as an intermediate in synthesizing therapeutic agents. Several valuable frameworks are developed based on the conjugation of amide compounds with a variety of aliphatic, aromatic, and heterocycles. In this regard, several research groups have demonstrated the potential activities of amide derivatives. Sun et al. developed amide derivatives with the conjugation of sorbic acid (SAAD) or benzoic acid (BAAD). A variety of sorbic and benzoic acid amide derivatives have been synthesized, which exhibited potent antimicrobial activities [3]. Moreover, a simple and practical approach was reported by Huczynski and the group to derive amide derivatives of polyether. These derivatives were screened for *in vitro* antimicrobial activity against Gram-positive and Gram-negative bacteria [4]. Furthermore, Kaplancikli et al. introduced a novel amide derivative, N-(Benzothiazol-2-yl)-2-[(5-amino/methyl-1,3,4-thiadiazol-2-yl)thio]acetamide that showed potential cytotoxicity and anticholinesterase properties [5]. Notably, Tu and his co-workers isolated N-(3,4-dihydroxybenzoyl)-3,4-dihydroxybenzamide from *Pu-erh* tea, exhibiting a protective effect on human microvascular endothelial cells against cytotoxicity [6].

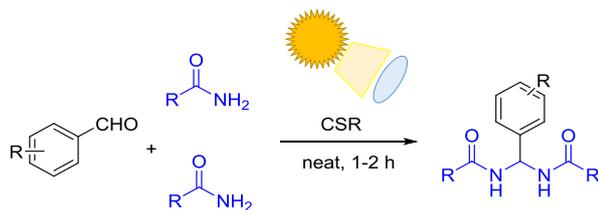
In this context, bisamide has emerged as an attractive and potent precursor with promising bio-relevant properties. Bisamides are an integral part of many biological and pharmaceutical compounds. The bisamides compounds have a characteristic role in peptidomimetic materials production [7]. Most importantly, for introducing gem-diamino alkyl residues in retro-inverse pseudo-peptide derivatives and synthesizing other biologically active and pharmaceutical scaffolds, these specified compounds have a huge application as a primary function [8-12]. Furthermore, bisamides have been applied as a cooperative ligand in the Ullmann reaction to produce biologically potent drugs [13]. Specifically, N, N' alkylidene bisamides have been widely used as HIV inhibitors,  $\alpha$ -adrenergic and neuropeptide Y antagonists and calcium channel blockers, antibacterial, antihypertensive, antitumor, anti-inflammatory, and drug release agents [14-18]. The correlation of bisamides with metal ions have effectively utilized for various purposes such as blood-pool contrasting, removal of organic dyes, bimodal imaging, recovery of fuels, etc. [19-22]. Besides, bisamides have participated in many organic syntheses as a potential reagent [23-25]. From the biological viewpoint, synthesizing bisamide derivatives has been an essential task. In literature, several methods have been reported for synthesizing symmetrical N, N' alkylidene bisamides. In general, conventional heating, ultrasound [26], and microwave [27, 28] have been associated with the synthesis of N, N' alkylidene bisamides in the presence of different metal catalysts [29, 30], Lewis or Bronsted acids [31-39], ionic liquids [40-42], graphene oxide [43], CC-activated DMSO [44]. However, implementing these methods is not environmentally friendly due to the extensive use of expensive and

toxic reagents, metal catalysts, hazardous organic solvents, and reaction conditions. Therefore, more emphasis is given to the integration of green synthesis. [45] Most importantly, the cytotoxicity, cancer and process management also received a vital task in recent trends. [46-49] Solar radiation is considered a potential and sustainable resource of energy. Globally, solar energy is considered a plentiful renewable energy source because the user does not cause the emission of CO<sub>2</sub> or other harmful gases. Because of this, light is referred to as a "clean reagent" [50-52]. Importantly, the present development has been explored accounting for the advantages of solar energy such as zero energy-production costs, less energy lost, environmentally benign, and economic. It is to say that our daily life is continuously benefited from the common uses of sunlight such as solar electricity, heating, ventilation, lighting, transportation, and many more. As time passes, many essential and advanced technologies are growing depending upon solar energy [53].

In recent chemistry, researchers have been focusing on developing less energy-consuming technologies for environmental benefits. In this account, concentrated solar radiation (CSR) is an efficient, reliable, sustainable energy source to develop a chemical transformation. The intense form of solar radiation is a renewable and green alternative compared to conventional heating techniques. UV-visible and IR radiation can occur in many thermal and photochemical processes and some previous reports affirm these consequences [54] For the last few years, many distinguished organic reactions such as Diels-alder reaction [55], Paterno-Buchi reaction [56], Hantzsch reaction [57], and Biginelli reaction [58] have been executed by concentrated solar radiation (CSR). Moreover, CSR can promote the synthesis of chalcones [59], pyrazoles [60], benzimidazoles [61], and isoxazole-5(4H)-one [62]. Besides these, CSR is effectively utilized for palladium, iron, and silver nanoparticle synthesis [53, 63, 64].

Herein, with the continuation of our sustainable research, solar energy has been utilized to synthesize N, N' alkylidene bisamide. With the assistance of concentrated solar radiation, aldehydes and amides successfully produced symmetrical N, N' alkylidene bisamide derivatives in an ethanol medium. The antibacterial activity of synthesized derivatives was evaluated against Gram-negative (*Escherichia coli* MCC 2412, *Pseudomonas aeruginosa* MCC 2080 & *Klebsiella pneumoniae* MCC 2451) and Gram-positive (*Staphylococcus aureus* MCC 2408) quality control strains. Furthermore, MTT assay was performed to evaluate the cytotoxicity of the derivatives on cancerous cell line. The MTT assay is based on the conversion of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) to formazan crystals by living cells which measures the viability of the cells to determined mitochondrial activity in living cells. This assay is vastly used to determine the cytotoxicity of the drugs or compounds on cancerous cells or primary patient cells [46]. Here,

in this study, the cytotoxicity effects of various compounds is evaluated on the highly aggressive subtype of breast cancer TNBC (Triple-Negative Breast Cancer) cell line MDAMB 231 [47, 48].



**Scheme 1.** CSR-assisted synthesis of symmetrical *N, N'* alkylidene bisamides.

## 2. Result and Discussion

**Table 1.** Optimization for the synthesis of symmetrical *N, N'*-alkylidenebisamides.

Entry	Solvent	Condition	Yield <sup>b</sup>
1	ethanol	CSR	33
2	water	CSR	< 20
3	methanol	CSR	42
4	neat	CSR	76
5	ethyl acetate	CSR	27
6	PEG-400	CSR	< 10
7	neat	without CSR	trace

<sup>a</sup>Reaction condition: benzaldehyde (1, 1 mmol) and amide (2, 2 mmol), solvent (1 mL), under concentrated solar radiation (CSR).

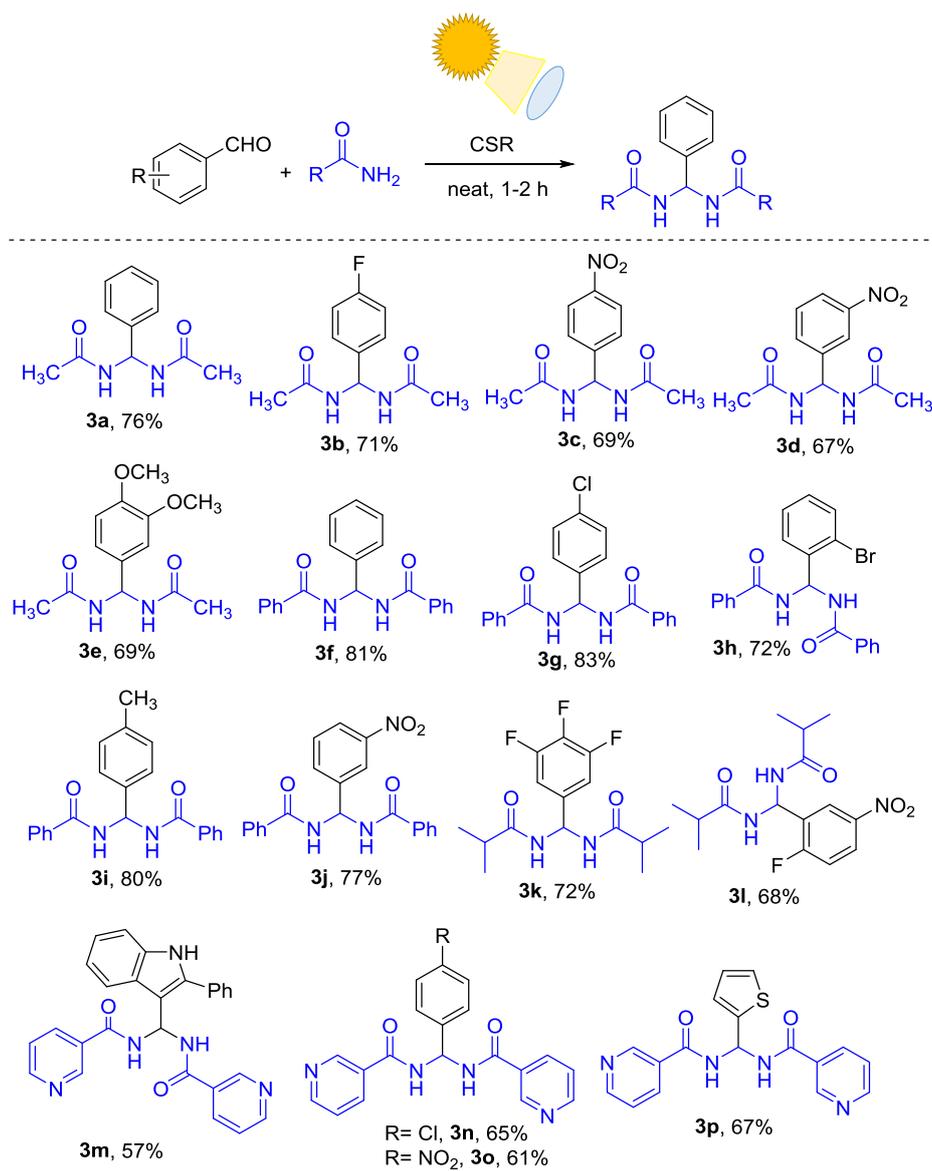
<sup>b</sup>Isolated yield.

Initially, benzaldehyde (1, 1 mmol) and acetamide (2, 2 mmol) were taken to stir without any catalyst in an ethanol medium using CSR. Surprisingly no significant amount of *N, N'*-(phenyl methylene) dibenzamide (3a) was formed after 1 h of reaction (Table 1, entry 1). Further, varying the solvents like

water and methanol. As a result, the formation of the desired product was observed at less than 20% in an aqueous medium, and in methanol, the yield was 42% (Table 1, entries 2-3). After that, our intention was shifted towards the solvent-free condition, and gratifyingly, a significant yield (76%) of 3a was generated (Table 1, entry 4). Some other commercial solvents like ethyl acetate and polyethylene glycol were also employed for the reaction. Still, they did not yield suitable results in the series of solvents (Table 1, entries 5-6). Notably, in the absence of CSR, only a trace amount of product was formed (Table 1, entry 7). Hence, in the absence of solvent, solar radiated excitation assigned the optimized reaction conditions to obtain the desired products in the best yield.

After the above experiments, the target was focused on the substrate variation by using different substituted benzaldehydes and amide compounds (Figure 1). Notably, 4-fluoro, 4-nitro, and 3-nitro substituted benzaldehyde were successfully reacted with acetamide to afford the corresponding bisamide products 3b-3d in good yields. Additionally, 3, 4-dimethoxybenzaldehyde was also reactive with acetamide to give the product 3e in 69% yield. Next, the reaction was occurred with benzamide and benzaldehyde, and as a result, 81% yield of compound *N, N'*-(phenyl methylene) dibenzamide 3f was obtained. Subsequently, the reaction was carried out with other benzaldehydes bearing 4-Cl, 2-Br, 4-CH<sub>3</sub>, and 3-NO<sub>2</sub> substituents to get the respective benzamide derivatives 3g-3j in excellent yields. Furthermore, isobutyramide was effective and reacted with highly electron-withdrawing fluoro and nitro-substituted benzaldehydes to produce 3k and 3l in 72% and 68% yields. Moreover, the reaction of 2-phenyl-1H-indole-3-carbaldehyde and nicotinamide proceeded well and gave the corresponding product 3m in moderate yield. In addition, the reaction of nicotinamide with para-substituted (Cl, NO<sub>2</sub>) benzaldehydes and thiophene-2-carbaldehyde was conducted, and the desired bisamide products 3n-3p were obtained in good yields.

**Efficacy of energy utilization:** The energy used for the synthesis of *N, N'*-(phenyl methylene)dibenzamide is the total energy consumed (KJ) per unit of *N, N'*-(phenyl methylene)dibenzamide obtained (g). The reaction time was 12 h to synthesize *N, N'*-(phenyl methylene) dibenzamide using the conventional technique [33], and for CSR, only 1 h is required. As per literature reports [65], the amount of energy needed to synthesize *N, N'*-(phenyl methylene) dibenzamide per gram is calculated at 9.10 (KJ)g<sup>-1</sup> on the other side for the CSR only 2.16 (KJ)g<sup>-1</sup> energy was required. Thus, the CSR technique is efficient in saving energy by around 76.26% compared to the conventional method.



<sup>a</sup>Reaction condition: benzaldehyde (1, 1 mmol) and amide (2, 2 mmol), under concentrated solar radiation (CSR), 1-2 h. <sup>b</sup>Isolated yield.

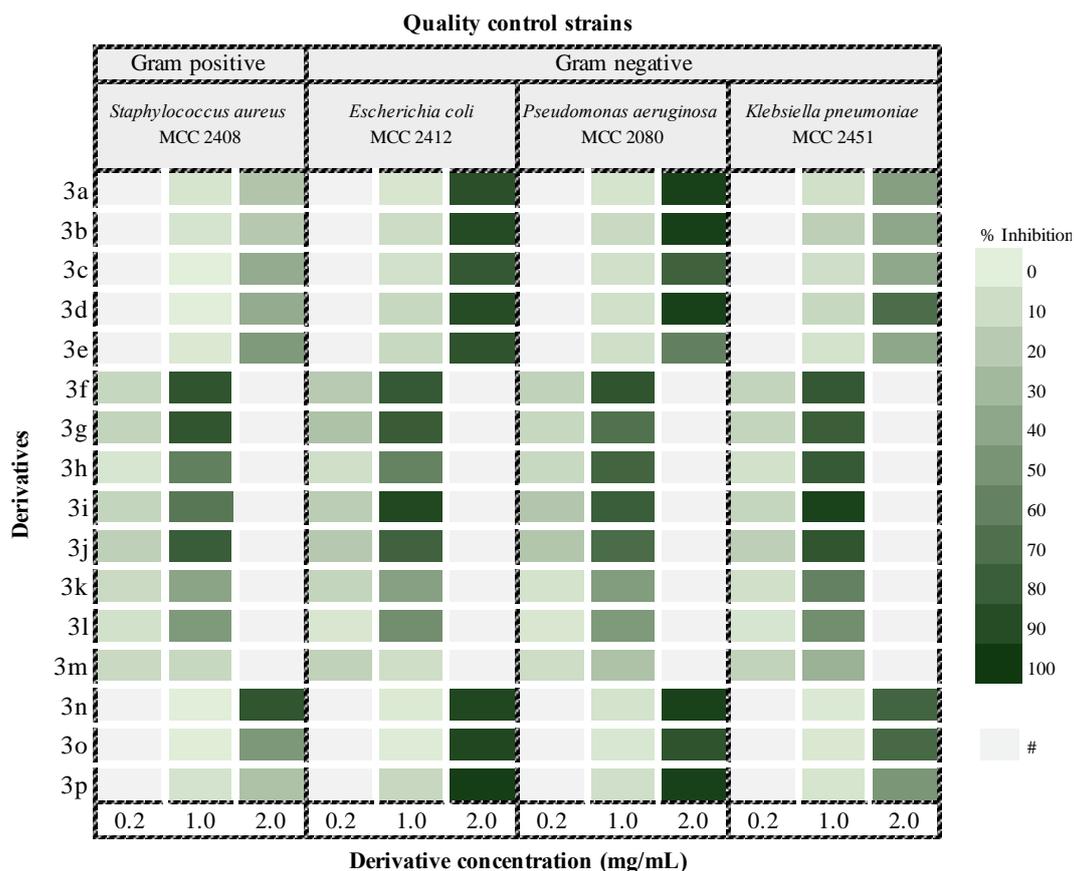
**Figure 1.** Synthesis of symmetrical *N,N'*-alkylidenebisamides<sup>a</sup>.

Amides (RCONHR) are a pivotal structural motif that can display potent biological activities. Pursuing the previous studies, our investigation has been devoted to establishing the correlation between physicochemical properties and biological activities of the synthesized derivatives. Accordingly, the studying the mentioned amide compounds to evaluate the biological interpretation.

## 2.1. Antibacterial Analysis of Synthesized Derivatives

The importance of amide-containing compounds is well

documented. Their structural analogs are frequently present in many pharmaceutical compounds which exhibit interesting biological activities, including antimicrobial, anti-inflammatory, and antioxidant [27, 66, 67]. Generally speaking, the sensitivity of symmetrical bisamides as a class of amide derivatives has received considerable attention in the chemical-biology field. Therefore, investigating such novel derivatives is highly desirable in the present research. In continuation of our research, study on the activity of the synthesized bisamides compounds was evaluated. To delight, the compounds exhibited promising activity, and the results are shown below.



**Figure 2.** Heatmap showing antibacterial activity of derivatives against selected quality control strains in terms of percent inhibition. Note: # not done.

All tested derivatives showed remarkable antibacterial activity against Gram-negative (*E. coli* MCC 2412, *P. aeruginosa* MCC 2080 & *K. pneumoniae* MCC 2451) and Gram-positive (*S. aureus* MCC 2408) quality control strains tested under this study. In general, all derivatives are more active against Gram-negative strains than Gram-positive. Derivatives with high solubility showed the highest inhibitory effect at 2 mg/ml concentration, while derivatives with low solubility are more effective at 1 mg/ml concentration.

As per the results depicted in figure 2, it is observed that less soluble derivatives are fairly active against all quality control strains with more than 60% inhibition at 1 mg/ml concentration except for the compound 3m, 3k, and 3l bearing bifunctional groups and indole ring substitutions. On the other hand, the 3f derivative with no substitution on the benzyl ring exhibited the highest antibacterial activity with more than 80% inhibition, followed by 3g and 3j with Cl- group & NO<sub>2</sub>- group substitution, respectively, having more than 70% inhibition against all tested quality control strains at 1 mg/ml concentration. In the case of highly soluble derivatives, the best activity was shown against *E. coli* MCC 2412, followed by *P. aeruginosa* MCC 2080, *K. pneumoniae* MCC 2451, and *S. aureus* MCC 2408. In particular, the 3n derivative having Cl- group substitution gave the best activity (above 75% inhibition) against all quality control strains at 2 mg/ml concentra-

tion. Similarly, 3o and 3d derivatives with NO<sub>2</sub>- group substitution at para & ortho position showed good activity (above 70% inhibition) against all three Gram-negative strains tested under this study.

In conclusion, as per the results of the antibacterial analysis, derivatives whose benzyl ring bears NO<sub>2</sub>- & Cl- groups have more outstanding antibacterial properties than the rest of the derivatives. According to the literature, the antibacterial action of chlorinated compounds is not only due to extensive membrane damage but also involves other events such as enzyme inactivation and uncoupling of electron chains either in the cell membrane or in the cell interior [65]. The NO<sub>2</sub> group has a solid electron-withdrawing effect on the benzyl ring that undergoes enzymatic reduction in biological systems, thereby forming reactive superoxide anion exhibiting antibacterial activity [66]. Therefore, this study gives six potential derivatives (Compound 3f, 3g, 3j, 3n, 3o, and 3d) for drug development. Bisamides are the core of many natural compounds and have tremendous activity against cancer cells. Many of the marketed anticancer drugs contain amides. To further study anticancer activity, an MTT assay of all the synthesized compounds were performed.

## 2.2. Cytotoxicity Assay

MTT assay is based on the conversion of MTT

(3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) to formazan crystals by living cells which measures the viability of the cells to determined mitochondrial activity in living cells. This assay is vastly used to determine the cytotoxicity of the drugs or compounds on cancerous cells or

primary patient cells [66]. Here, in this study, the cytotoxicity effects of various compounds (3a-3p) was evaluated on a highly aggressive subtype of breast cancer, TNBC (Triple-Negative Breast Cancer) cell line MDAMB 231 [67, 68].

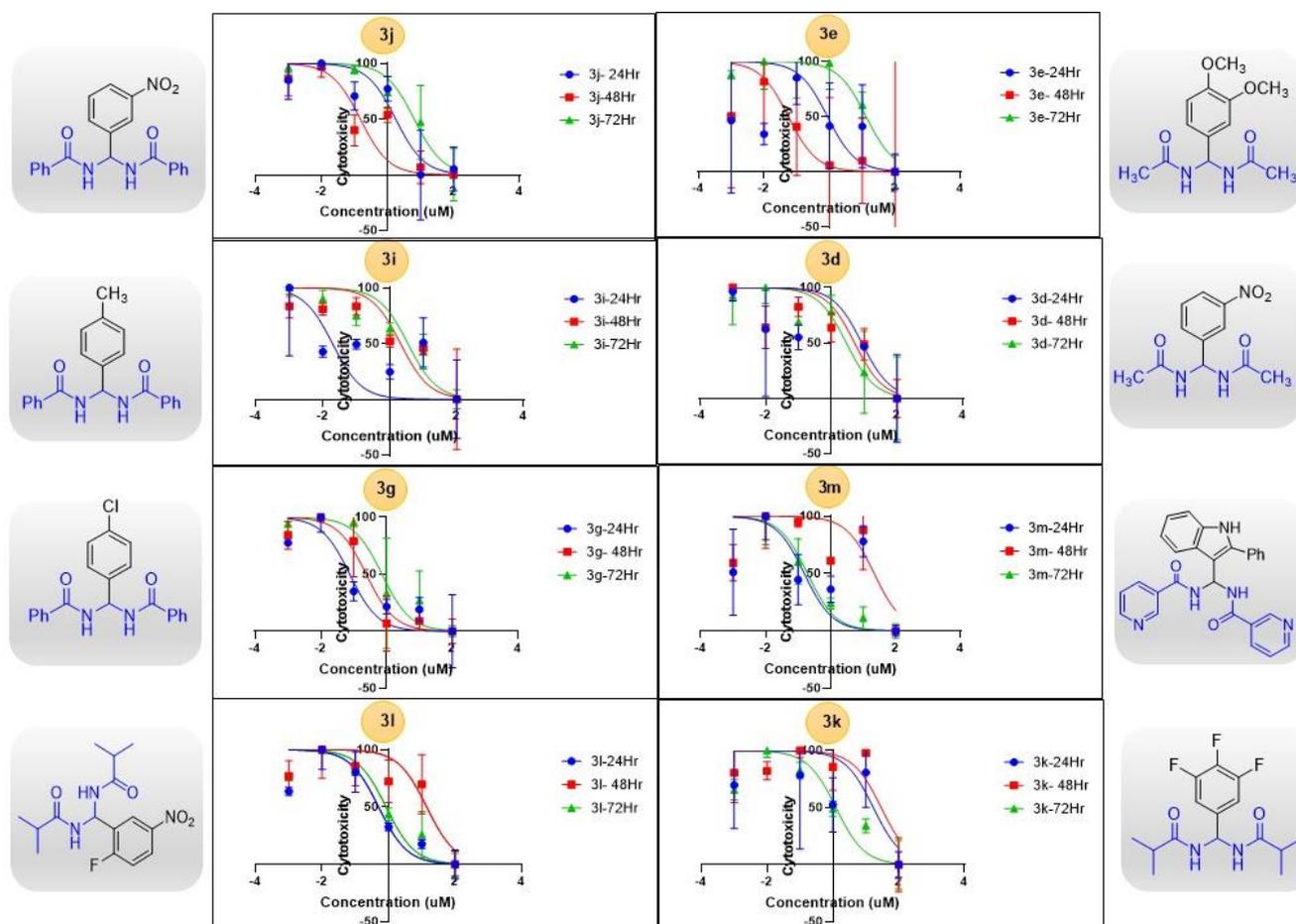


Figure 3. Dose response curve and IC<sub>50</sub> value.

As seen symmetrical bisamides of ethylene diamine underwent C–C bond cleavage to form unsymmetrical gem-bisamides. [69] In this regard, MDA-MB-231 cells were grown on Dulbecco's Modified Eagle Medium (DMEM) (Gibco) with 10% fetal bovine serum (FBS), and cells were grown at 37 °C in 5% CO<sub>2</sub>. To check the cytotoxicity of compounds, an MTT assay<sup>70</sup> was performed. Cells were seeded at 1 × 10<sup>5</sup> cells/mL in 96 well microtiter plates in Dulbecco's Modified Eagle Medium with fetal bovine serum. The cells were incubated overnight for attachment. The cells were given serum starve treatment before applying drug treatment. Applied various drug concentrations in serial ten-fold dilutions were added in triplicates and incubated for 24Hr, 48Hr, and 72Hr at 5% CO<sub>2</sub> at 37 °C (see list of drugs treated on MDAMB231 cell line) [70]. After that, the cells were treated with 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Roche). After incubation, four hours later, all of the

medium, including MTT solution (5 mg/mL), was added solubilization buffer manually and incubated overnight. The remaining formazan crystals were dissolved in a solubilization buffer, and the absorbance was measured at 595 nm using a 96-well microplate reader (Bio-Rad mark microplate reader). The cytotoxicity index was determined using the untreated cells as a negative control. The percentage of cytotoxicity was calculated using the background-corrected absorbance. The IC<sub>50</sub> was extrapolated from the dose-response graph [71]. The drug concentration that reduced the viability of cells by 50% (IC<sub>50</sub>) was determined by plotting triplicate data points over a transforming concentration range, normalizing value, and calculating values using non-linear regression analysis of GraphPad PRISM program (version 8.0.0 for Windows, [www.graphpad.com](http://www.graphpad.com)). Calculations of confidence limits and significance testing were made at the level of p=0.05.

The cytotoxic response of the different derivatives of the

compound to the MDAMB 231 TNBC cell line to different concentrations and periods is shown in Figure 3 (a-h). The dose-response curve displayed by the derivatives of the compounds is comparable with the cancer MDAMB 231 cell line. Statistical analysis such as transforming concentration (uM) in log base 10 and normalizing value and non-linear regression analysis using graph pad PRISM shown in figure 3. Moreover, percentage-wise analysis of data in the form of a bar graph using excel is presented in supplementary.

The half-maximal effective dose deduced from the generated dose-response curve and the relative potency of the se-

lected compound derivatives, as illustrated in Table 2. Statistical analysis was done using graph pad PRISM 8.0, and in table 1, effective derivatives mentioned in descending order (3j > 3i > 3g > 3l > 3e > 3d > 3m > 3k) are comparably cytotoxic and potent. IC<sub>50</sub> is derived from the best fit value of non-linear regression analysis. 95% of the confidence interval value of IC<sub>50</sub> indicates range of half the maximum effective cytotoxic dose of the derivatives against cancer cells. Log IC<sub>50</sub> of 95% confidence interval (CI) derived concentrations which means that the relative potency of the tested derivatives in logarithmic-based value which shown in figure 3.

**Table 2.** The half-maximal effective dose is deduced from the generated dose-response curve and the relative potency of the selected compound derivatives.

Compound	Time	IC <sub>50</sub> value (uM)	IC <sub>50</sub> (uM/mL)95% Confidence Interval	Log IC <sub>50</sub> 95% confidence interval (CI)
3j	24Hr	1.769 uM	0.6404 to 4.624	-0.1935 to 0.6650
	48Hr	0.1505 uM	0.04252 to 1.290	-1.371 to 0.1107
	72Hr	0.8087 uM	0.2274 to 1.348	0.4274 to 1.148
3i	24Hr	4.527 uM	1.215 to 8.973	-2.651 to -0.1138
	48Hr	3.520 uM	0.4557 to 12.09	-0.3414 to 1.082
3g	72Hr	0.2228 uM	0.002236 to 0.7695	0.08457 to 0.9530
	24Hr	0.07634 uM	0.03186 to 0.1906	-1.497 to -0.7200
	48Hr	0.2414 uM	0.1166 to 0.5047	-0.9333 to -0.2969
3l	72Hr	0.7280 uM	0.2762 to 2.040	-0.5587 to 0.3097
	24Hr	0.5032 uM	0.1986 to 1.241	-0.7019 to 0.09381
	48Hr	14.13 uM	4.812 to 38.09	0.6823 to 1.581
3e	72Hr	3	0.3839 to 1.866	-0.4158 to 0.2708
	24Hr	0.8713 uM	0.1354 to 25.78	0.124 to 1.411
	48Hr	0.05599 uM	0.0002665 to 1.693	-3.574 to 0.2288
3d	72Hr	13.17 uM	6.291 to 27.66	0.7987 to 1.442
	24Hr	8.520 uM	1.244 to 52.41	0.09490 to 1.719
	48Hr	5.129 uM	1.127 to 16.88	0.05175 to 1.227
3m	72Hr	2.878 uM	0.8450 to 9.274	-0.07313 to 0.9673
	24Hr	0.1552 uM	0.01420 to 93.17	-1.848 to 1.969
	48Hr	21.91 uM	5.847 to 73.16	0.7670 to 1.864
3k	72Hr	0.1947 uM	0.06914 to 0.6056	-1.160 to -0.2178
	24Hr	17.08 uM	0.8775 to 108.5	-0.05673 to 2.036
	48Hr	29.59 uM	12.07 to 72.28	1.082 to 1.859
	72Hr	1.246 uM	0.4247 to 4.271	-0.3719 to 0.6305

A cell-based assay was used to demonstrate the potency of the compound derivatives to assess their cytotoxicity effects against

an aggressive basal subtype of breast cancer cell line MDA-MB 231 by MTT assay. MTT assay is a standard colorimetric assay for measuring cellular proliferation [72]. MTT measures the extent of formazan formed is proportional to the number of living cells existing in a culture, which indicates cellular respiration. The concentration that induces 50% death of the cells due to its cytotoxic effects is denoted as the IC<sub>50</sub> value. A lower IC<sub>50</sub> value indicates more substance cytotoxicity, as described in table 1. Cytotoxic effects of derivatives are described in descending order, such as 3j > 3i > 3g > 3l > 3e > 3d > 3m > 3k. 3e shows the most cytotoxic effects on 48Hr of drug exposure against MDAMB 231 cell line is 0.05599 uM IC<sub>50</sub> concentration. Furthermore, more cytotoxic derivatives such as 3j, 3i, and 3g as increasing exposure to this compound show increasing cytotoxic effects as more effective against the TNBC cell line.

### 2.3. Computational Study

Here, a computational study and molecular docking of all the derivatives have been done. The results of the particular compounds are mentioned in the Table 3. The study shows satisfactory results against the protein 1JJJ, 3U9R and 4BK Y. Breast, prostate, and brain tumors are a few types where Maternal Embryonic Leucine Zipper Kinase (MELK) is increased. Its expression is typically linked to cell survival, proliferation, and apoptosis resistance [73, 74]. As a result, there has recently been a lot of interest in the possibility of MELK inhibitors as therapeutic drugs. Here, the original MELK complex structures with AMP-PNP and nanomolar inhibitors have been presented. Our research provides insight into the function of the MELK UBA domain, identifies critical residues for generating high potency, and characterizes the kinase active site, setting the framework for

structure-based drug design initiatives. Molecular docking analysis was used to calculate binding affinity and energies of ligand (3a-3p) binding to protein 1JJJ, 3U9R and 4BK Y using Schrodinger maestro 13.5. The 3D crystal structure of protein 1JJJ, 3U9R and 4BK Y was taken from the protein data bank (PDB) ([www.rcsb.org](http://www.rcsb.org)). The ligand used for the current study was drawn in the maestro 13.5.

### 3. Conclusion

In summary, an efficient strategy have been developed to achieve different bisamide derivatives, ensuring the sustainability and greenness of the process. The unconventional CSR technique avoids using toxic Lewis acid, catalysts, and solvents to afford the amide compounds. Notably, the products were easily isolated by simple filtration from aqueous ethanol/diethyl ether. In addition, the one-pot synthesis is attractive in terms of avoiding thermal heating, organic solvents, tedious purification, minimum wastage, that lead to operational simplicity and safe procedure to achieve the potential compounds under environmentally friendly conditions. The amide core was further studied against Gram-negative (*E. coli* MCC 2412, *P. aeruginosa* MCC 2080 & *K. pneumoniae* MCC 2451) and Gram-positive (*S. aureus* MCC 2408), showing promising antibacterial activity. On the other hand, the investigation with different doses of IC<sub>50</sub> demonstrated the effective cytotoxicity of the amide derivative. Moreover, a molecular docking study of the derivatives with higher antimicrobial activity has been featured, which can be emphasized for further evaluation in prospective chemical biology.

Table 3. Docking score of synthesized derivatives.

Compounds	1JJJ	3U9R	4BK Y
3a	-3.550	-3.190	-3.610
3b	-3.550	-3.190	-3.610
3c	-3.550	-3.190	-3.610
3d	-4.989	-3.234	-3.518
3e	-4.733	-3.816	-3.663
3f	-5.329	-2.487	-3.726
3g	-4.907	-2.510	-3.882
3h	-5.299	-2.967	-3.904
3i	-3.803	-2.104	-3.618
3j	-4.216	-2.701	-3.802
3k	-4.631	-2.838	-3.787
3l	-5.767	-3.736	-4.252
3m	-4.464	-5.629	-4.474
3n	-5.505	-3.337	-3.743

Compounds	1JJJ	3U9R	4BKY
3o	-4.048	-3.613	-4.090
3p	-5.228	-3.260	-3.259

## Abbreviations

CSR: Concentrated Solar Radiation  
 TNBC: Triple-Negative Breast Cancer  
 MTT assay: (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay  
 MCC: Microbial Culture Collection  
 MDAMB: M. D. Anderson and Metastasis Breast Cancer  
 PDB: Protein Data Bank  
 MELK: Maternal Embryonic Leucine Zipper Kinase  
 AMP-PNP: Adenylyl Imidodiphosphate

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## Conflicts of Interest

The authors declare no conflicts of interest.

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