Synthesis of 1-Substituted 1H-1,2,3,4-Tetrazoles Using Biosynthesized Ag/Sodium Borosilicate Nanocomposite

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ABSTRACT: An expedient solvent-free methodology has been developed to produce 1-substituted 1H-1,2,3,4-tetrazoles using sodium borosilicate glass-supported silver nanoparticles (Ag NPs) as a novel heterogeneous catalyst. A cost-efficient, facile, and greener method was deployed for the creation of Ag/sodium borosilicate nanocomposite (ASBN) catalyst by using Aleurites moluccana leaf extract as a stabilizing and reducing agent. The ASBN catalyst was identified using the latest microscopic and spectroscopic techniques such as FT-IR, TEM, FESEM, XRD, EDS, and elemental mapping. The deployment of this new catalyst enables the preparation of assorted 1-substituted tetrazoles in good to high yields via an easy work-up procedure in a relatively short reaction time under environmentally friendly conditions without using harmful and toxic reducing agents. The ASBN catalyst can be recycled and reused multiple times without meaningful loss of activity. To extend the application of the ASBN, the performance of the quantitative structure−activity relationships model was investigated for protein binding and toxicity hazard considerations.

INTRODUCTION

Tetrazoles are a significant class of heterocyclic compounds with wide-ranging applications in diverse areas of industry and science.1 Recently, they have attracted considerable attention because of their extensive utility in coordination chemistry,2−4 medicinal chemistry and pharmaceutical sciences,5−14 and also in materials science including oxygen-containing fuels.15−17 Tetrazoles can be utilized as precursors for diverse nitrogen-containing compounds (e.g., triazoles, thiazoles, and oxazolidones).18,19 Due to their broad applications, the investigation on the catalytic preparation of tetrazoles has been of immense interest, and especially, 1-substituted tetrazole derivatives have been the subject of fundamental research in view of their biological20 and medical applications.5

Although a wide variety of 5-substituted tetrazoles have been documented, only a handful attempts have been made to empower the greener preparative procedures for 1-substituted tetrazoles.21,22 Most reported protocols entail acid-catalyzed cycloaddition of isocyanides with hydrazoic acid23,24 and trimethyl azide,25 and cyclization among primary amines and their salts, triethyl orthoformate, and sodium azide by using catalysts such as Yb(OTf)3,26 AcOH,27 In(OTf)3,17 [HBIm]BF4,28 and more recently, natrolite.29

Scheme 1. Synthesis of 1H-1,2,3,4-Tetrazoles Using the ASBN Catalyst

Scheme 2. Biosynthesis of Ag NPs Using the Aqueous Extract of A. moluccana Leaves

Among the published synthetic procedures, a number of them have several drawbacks such as the use of N,N'-dimethylformamide as a solvent, refluxing for an extended period, tedious work-up of the reactions, the use of expensive and toxic reagents, under “dry” reaction conditions, lower yields, difficulty in separation and recovery of the catalyst, and the use of volatile, highly toxic, and explosive hydrazoic acid. Therefore, the development of straightforward catalytic procedures and eco-friendly approaches for the preparation of
1-substituted tetrazoles to circumvent these drawbacks is highly desirable.

Figure 1. UV−Vis spectra for leaf extract from plant and synthesized Ag NPs.

Figure 2. FT-IR spectrum of greener biosynthesized Ag NPs.

Figure 3. FT-IR spectrum for the ASBN catalyst.

Figure 4. XRD pattern of the synthesized ASBN catalyst.

Scheme 3. Proposed Structure of the Ag/Sodium Borosilicate Nanocomposite
Over the decades, the usage of heterogeneous catalysts has grown for the production of tetrAzoles due to superior catalytic activity, low noxiousness and cost, simple recovery, and ease of handling;21,29−31 metal nanoparticles (NPs), namely, Pd, Pt, Au, Cu, and Ag, have also been investigated.31,32 Among metal NPs, Ag NPs have been deployed as proficient catalysts for their unique properties such as their high surface energy and high catalytic activity. Although the clustering of metal NPs through the reaction process is usually unavoidable,33−37 its prevention has been attempted by immobilizing Ag NPs on a suitable solid prop such as TiO2,33 Fe3O4,8,34,35 SiO2,36 and graphene,37 among others.

The sodium borosilicate glass can be used for the immobilization of different metal NPs as an ideal host.38 It has a considerable applicability as an effective support in catalysis because of the extremely porous and ordered structure, high specific surface area, high chemical resistance, outstanding chemical steadiness, mechanical strength, inexpensiveness, subdued thermal expansion coefficient, and superior ultraviolet clarity. Nevertheless, despite these favorable characteristics, there are still only a few examples of their use.39,40

Figure 5. FESEM images of the ASBN at different magnifications.
Various chemical and physical methods have been reported for the synthesis of metal NPs, but many of these procedures suffer from limitations. The biological synthetic methods for metal NPs avoid the use of organic solvents or harmful materials, toxic capping agents or stabilizers, higher temperature calcinations or pressure, and the formation of hazardous by-products.\(^4^1\text{--}^4^9\)

Euphorbia plants are widely distributed and range from shrubs and herbs to trees in temperate regions and tropical parts of the world, and Alerites moluccana from the family Euphorbiaceae is customarily known as possible substitute medicine for typhoid fever and diarrhea treatment. The medicinal effect of the plant is because of its rich phytochemical content including glycerides, stearic acid, palmitic acid, linoleic acid, myristic acid, protein, oil, and vitamin $B_1$, whereas the stem bark includes polyphenols, flavonoids, alkaloids, tannins, coumarins, steroids, and triterpenoids especially in plant seeds.\(^5^0\text{--}^5^3\) The phytochemical constituents of the plant and especially its polyphenolic contents encouraged us to use it for the synthesis of nanoparticles via an easy and greener protocol.

Following the literature review, there is no report on the application of the sodium borosilicate as an efficient prop for the immobilization of silver NPs by using leaf extracts. In view of our research on the preparation of tetazoles and the appliance of heterogeneous catalysts,\(^2^1^\text{--}^2^9^\) herein, we explored the A. moluccana extract from leaves for the synthesis of Ag/sodium borosilicate\(^5^4\) nanocomposite (ASBN) as a novel and efficient heterogeneous catalyst. Thus, we used this nanocomposite for catalyzing the $[2 + 3]$ cycloaddition of amines with sodium azide for the preparation of 1-substituted 1H-1,2,3,4-tetrazoles (Scheme 1).

Additionally, we examined the potential ecosystem effect in terms of protein binding and toxicity data on human health with predicted outcome for 1-substituted 1H-1,2,3,4-tetrazoles prepared by our catalyst.

### RESULTS AND DISCUSSION

**Synthesis and Identification of the ASBN Catalyst.**

In the present method, A. moluccana extract from leaves was deployed for the preparation of ASBN without using any surfactants, reductants, and hazardous or toxic materials. The extract from the leaves of the plant acted not only as a reducing agent and antioxidant source but also functioned as a stabilizer for the prepared Ag NPs adorning the surface of sodium borosilicate glass as an economical, effective, and stable support. The ensuing Ag/sodium borosilicate nanocomposites were completely analyzed by different techniques, namely, XRD, FT-IR, FESEM, EDX, TEM, and elemental mapping analyses. The catalytic activity of biosynthesized ASBN was evaluated for the preparation of 1-substituted 1H-1,2,3,4-tetrazoles via cycloaddition of amines and sodium azide. There are some compounds such as polyphenols and flavonoids in the plant extracts, which have the ability to give electrons and can undergo quick oxidation. Thus, the synthesis of Ag NPs was examined by exploiting the extract from the leaves of A. moluccana through the reduction of Ag\(^+\) ions to Ag(0) in the presence of free electrons (Scheme 2).

The UV spectrum analysis of the extract displayed bands around 301 nm (band 1) because of the transition localized inside the cinnamoyl system of aromatics encompassing conjugation, whereas the band centered around 225 nm (band II) is associated to the $\pi \rightarrow \pi^*$ transitions, which is in agreement with absorbance for the benzoyl group of aromatic systems that are conjugated (Figure 1). Such absorbent bands are typical of flavonoids;\(^5^5\) thus, the outcomes from the UV–Vis spectrum certainly reinforce the literature precedent for the occurrence of phenolics inside the plant extract.\(^5^6\)

The UV–Vis spectrum of synthesized Ag NPs (Figure 1) described the impact of surface plasmon resonance signals on the metal ions due to noteworthy changes in the absorbance maxima at around 450 nm, revealing the interaction of constituents of leaf extract with ionic silver and the formation of nanoproducts (Scheme 2). The bioprotecting action of the adsorbed phytochemicals imparts adequate stability to the green synthesized nanoparticles with no major alteration in the symmetry of the absorption peak even after 15 days (Figure 1).

Furthermore, the FT-IR spectrum of the green Ag NPs displayed peaks at 3500, 1695, and 1465 cm\(^{-1}\), which signify the presence of free OH and OH group involved in hydrogen bond formation, the presence of carbonyl group (C=O), and stretching of C=C aromatic bonds, respectively; peaks distinctly showed the presence of phytochemicals adorning the exterior of green nanoparticles as stabilizing and capping agents (Figure 2).
Figure 7. Elemental mapping of the ASBN catalyst.
The FT-IR analysis was undertaken to learn about the potential molecules responsible for capping of the produced ASBN catalyst. As shown in Figure 3, the bands appearing ~3450 and 1647 cm\(^{-1}\) were assigned to –OH stretching and bending vibrations of molecular water present, respectively. The peaks at 1098 and 807 cm\(^{-1}\) correspond to the Si–O–Si bond and stretching B–O bond of the BO\(_4\) tetrahedral, respectively (Scheme 3). The absorption band at 477 cm\(^{-1}\) is assignable to the Si–O–Si, and peaks appear at ~1472 cm\(^{-1}\) probably due to the stretching vibrations of the B–O bonds existing in diverse boron organizational units.\(^{38,56}\) Moreover, the peak at ~949 cm\(^{-1}\) shows the stretching vibrations for the Si–O–B bond.\(^{38,56}\)

The formation of Ag NPs on the exterior of sodium borosilicate glass has been confirmed by XRD, TEM, FESEM, EDS, and elemental analyses; the crystalline structure of the ASBN was apparent from the XRD analysis (Figure 4), a broad peak at 2\(\theta\) = 21°–25° being attributed to amorphous silica. The XRD of the ASBN shows five characteristic peaks at 38.1, 44.0, 64.4, 77.3, and 85.2 corresponding to (111), (200), (220), (311), and (222) planes of the face-centered cubic (fcc) Ag crystals, respectively.

The formation of Ag NPs on the exterior of sodium borosilicate glass was verified by FESEM images (Figure 5), wherein the sodium borosilicate is covered with synthesized Ag NPs via greener method. The SEM images show that the Ag NPs appear as uniformly dispersed bright spots on the exterior of sodium borosilicate glass matrix with narrow size dispersal.

The distribution of the various elements in the ASBN was also analyzed by elemental mapping images and EDS spectrum; the EDS spectrum in Figure 6 elucidates the presence of Ag, B, C, Si, Al, Na, and O elements in the ASBN. Further, the elemental mapping pictures of the Cu/sodium borosilicate nanocomposite (Figure 7) show the dispersion of the Ag NPs on the sodium borosilicate glass surface.

**Figure 8.** TEM images of the ASBN catalyst.

**Figure 8** depicts the TEM analysis of the ASBN at varying magnifications where the spherical morphology with a narrow size distribution is apparent. Further, results from SEM, TEM, and XRD analysis for the ASBN affirmed that Ag NPs are immobilized on the surface of the sodium borosilicate.

**Preparation 1-Substituted Tetrazoles Using the ASBN Catalyst.** To scrutinize the feasibility of our rationale and to identify the optimal conditions, the reaction of 1-(4-chloroaniline) with sodium azide and triethyl orthoformate was carried out in the presence of varying amounts of the ASBN catalyst (Table 1). The control test showed that no effective reaction occurred in the absence of catalyst (entry 1). Nevertheless, the supplement of the catalyst has rapidly increased the formation of the product in a high yield, the optimum amount of ASBN being 0.05 g (entry 6). Further, experimentations disclosed that heating was needed for the reaction, apparently 120 °C being the most effective temperature (Table 1, entry 6). The use of lower catalyst loadings and lower temperature did not lead to completion of reaction (entry 4). To further delineate the influence of the prepared catalyst, the model reaction was conducted in the presence of sodium borosilicate (entries 2 and 3); ASBN is highly reactive than sodium borosilicate. The sodium borosilicate as a prop inhibits the aggregation of Ag NPs, and its synergic effect is significant in this synthetic protocol. These optimal reaction conditions (amine, 2.0 mmol; sodium azide, 2.4 equiv of triethyl orthoformate, and ASBN catalyst, 120 °C. \(^{6}\)Isolated yield.

**Table 1. Optimization of Reaction Conditions for 4-Chloroaniline with Sodium Azide and Triethyl Orthoformate\(^a\)**

| entry | catalyst (g) | temperature (°C) | time (h) | yield (%) |
|-------|--------------|------------------|----------|----------|
| 1     | 0.0          | 120              | 3        | 0.0      |
| 2     | sodium borosilicate (0.03) | 120              | 8        | 77       |
| 3     | sodium borosilicate (0.05) | 120              | 8        | 82       |
| 4     | Ag/sodium borosilicate (0.03) | 90               | 5        | 60       |
| 5     | Ag/sodium borosilicate (0.03) | 120              | 3        | 85       |
| 6     | Ag/sodium borosilicate (0.05) | 120              | 3        | 94       |
| 7     | Ag/sodium borosilicate (0.05) | 100              | 3        | 77       |
| 8     | Ag/sodium borosilicate (0.07) | 120              | 3        | 94       |

\(^a\)Reaction conditions: 2.0 equiv of 4-chloroaniline, 2.0 equiv of sodium azide, 2.4 equiv of triethyl orthoformate, and ASBN catalyst, 120 °C. \(^{6}\)Isolated yield.

The products were identified by melting points, FT-IR, \(^1\)H NMR, and \(^{13}\)C NMR. The abolition of two strong and sharp absorption bands (NH\(_2\) stretching bands) and the emergence of bands in the region 1620–1680 cm\(^{-1}\) (C=\(\equiv\)N stretching band) in the FT-IR spectrum affirmed the creation of 1-substituted 1H-1,2,3,4-tetrazoles (Figure 9).\(^{29}\) The \(^1\)H NMR spectra of the products showed one proton signal at \(\delta = 7.80–8.40\) ppm for the tetrazole ring proton (Figure 10).\(^{29}\) \(^{13}\)C NMR spectra exhibited one signal for the tetrazole carbon at \(\delta = 141–157.2\) ppm (Figure 11).\(^{29}\)

The efficiency of the present synthetic method was compared with reported protocols for the synthesis of 1-(4-chlorophenyl)-1H-1,2,3,4-tetrazole (Table 3),\(^{24,26,29,57–59}\) the documented methods apparently have following drawbacks:

**Table 2. Comparison of Various Methods for Preparation of Various Tetrazoles with Sodium Azide and Triethyl Orthoformate**

| Method | Reaction Conditions | Isolated Yield (%) |
|--------|---------------------|--------------------|
| **Method A** | 4-chloroaniline, sodium azide, and triethyl orthoformate | 85 |
| **Method B** | 4-chloroaniline, sodium azide, and triethyl orthoformate | 94 |
| **Method C** | 4-chloroaniline, sodium azide, and triethyl orthoformate | 80 |
| **Method D** | 4-chloroaniline, sodium azide, and triethyl orthoformate | 77 |

**Method C** is considered to be the most effective method for the synthesis of various tetrazoles, and the outcomes are encapsulated in Table 2.

To examine the effects of diverse substituents, several 1-substituted tetrazoles were prepared under solvent-free conditions emanating from the reaction among assorted aryl amines containing electron-donating and electron-retracting groups with sodium azide and triethyl orthoformate in good to excellent yields.

The products were identified by melting points, FT-IR, \(^1\)H NMR, and \(^{13}\)C NMR. The abolition of two strong and sharp absorption bands (NH\(_2\) stretching bands) and the emergence of bands in the region 1620–1680 cm\(^{-1}\) (C=\(\equiv\)N stretching band) in the FT-IR spectrum affirmed the creation of 1-substituted 1H-1,2,3,4-tetrazoles (Figure 9).\(^{29}\) The \(^1\)H NMR spectra of the products showed one proton signal at \(\delta = 7.80–8.40\) ppm for the tetrazole ring proton (Figure 10).\(^{29}\) \(^{13}\)C NMR spectra exhibited one signal for the tetrazole carbon at \(\delta = 141–157.2\) ppm (Figure 11).\(^{29}\) The efficiency of the present synthetic method was compared with reported protocols for the synthesis of 1-(4-chlorophenyl)-1H-1,2,3,4-tetrazole (Table 3),\(^{24,26,29,57–59}\) the documented methods apparently have following drawbacks:
(1) Tiresome work-up.
(2) Use of HN₃ as a costly, toxic, and explosive reagent.
(3) Formation of impurities and by-products after longer reaction times.
(4) Usage of column chromatography for cleansing of the ensuing products.
(5) Use of homogeneous catalysts such as FeCl₃, H₂SO₄, and trifluoromethanesulfonylimide that cannot be easily recycled and recovered.
(6) Difficulties in procurement of the natrolite zeolite (entry 3).
(7) Use of organic solvents (entries 1, 2, and 5).

However, none of the aforementioned disadvantages were observed in our protocol wherein the ASBN catalyst was synthesized by deploying A. moluccana leaf extract as a renewable, nontoxic, and natural resource for the reduction of ionic silver to Ag NPs.

**Catalyst Recyclability.** The stability and recyclability of the ASBN catalyst were verified in the cycloaddition reaction for the synthesis of tetrazoles. After the reaction was completed, the ASBN catalyst was removed from the reaction medium by centrifugation, rinsed with deionized water, dried in an oven, and then reclaimed for the next cycle lacking any significant

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**Table 2. Preparation of 1-Substituted 1H-1,2,3,4-Tetrazoles Using the ASBN Catalyst at 120 °C**

| entry | amine | product | yield% | M.P. °C (Lit.) |
|-------|-------|---------|--------|----------------|
| 1     |       |         | 88     | 65-66 (65-66)⁹⁹ |
| 2     |       |         | 87     | 133-135 (133-135)⁹⁹ |
| 3     |       |         | 90     | 150-153 (150-153)⁹⁹ |
| 4     |       |         | 90     | 94-96 (94-95)⁹⁹ |
| 5     |       |         | 81     | 129-131 (127-129)⁸⁸ |
| 6     |       |         | 94     | 157-158 (156-158)⁹⁹ |
| 7     |       |         | 89     | 183-185 (183-185)⁹⁹ |
| 8     |       |         | 88     | 77-79 (76-78)⁹⁹ |
| 9     |       |         | 85     | 206-208 (207-208)⁹⁹ |
| 10    |       |         | 88     | 167-169 (167-169)⁹⁹ |

⁹⁹Reaction condition: Amine (2.0 mmol), sodium azide (2.0 mmol), triethyl orthoformate (2.4 mmol), ASBN catalyst (0.05 g), 120 °C, 3 h. ⁸⁸Yields after work-up.
decrease in catalytic activity. As shown in Scheme 4, the catalyst could be used, with unswerving activity, still after five cycles. The EDS, TEM, and FESEM analyses of the reprocessed catalyst (after five cycles) revealed that particles retain their shape and size without any obvious change in chemical composition and morphological alterations (Figures 12−14).

**QSAR Toolbox Prediction for a Single Chemical.** A wide range of chemical entities are continuously released into the environment from a variety of sources. These discharges and the ensuing pollution of the atmosphere and the potential damage to existing beings and humans cause risk to human health and the ecosystem.60 To effectively reduce this exposure by instigating measures or substitutions, it is obligatory to recognize the chemical releases of concern,61,62 the main reason should be grounded on the probable undesirable impact of the chemicals rather than only the emitted amount. Chemical risk identification may be means to obtain the requisite information.63,64 The usage of quantitative structure−activity relationship (QSAR) models for the appraisal of chemicals may help accelerate the process exploration, specifically for cases where investigational statistics are lacking; the QSAR model is the co-relation between the chemical structure and biological activity in a dataset of chemicals.65 The characteristics of a chemical structure are obtained by a set of chemical descriptors that are utilized to...
forecast feature of the chemical. Relative to other data collection methods, QSARs are expeditious and have the prospect to include diverse entities that are reliant on the model domain. Additionally, the appraised facts, for example, by QSARs, are expected to upsurge in significance as authorizations such as the European Chemicals Agency promote the reduced use of animal testing. In this study, the QSAR method was explored to investigate the formation plausibility of the synthesized chemicals in Table 2 and predict the effect of different functional groups attached to the main structure for their toxicity hazard and protein binding (Figure 15).

Table 3. Comparison of the Present Procedure with Previously Documented Methods for the Synthesis of 1-(4-Chlorophenyl)-1H-1,2,3,4-tetrazole

| entry | reaction conditions | time (h) | yield (%) | reference |
|-------|---------------------|----------|-----------|-----------|
| 1     | RNC, HN\textsubscript{3}, H\textsubscript{2}SO\textsubscript{4}, Et\textsubscript{2}O, reflux | 24 | 32 | 24 |
| 2     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, NaN\textsubscript{3}, Yb(OTf)\textsubscript{3}, 2-methoxyethanol, 100 °C | 6 | 88 | 26 |
| 3     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, NaN\textsubscript{3}, natrolite zeolite, solvent-free, 120 °C | 4 | 93 | 29 |
| 4     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, NaN\textsubscript{3}, silica sulfuric acid, solvent-free, 120 °C | 8 | 89 | 57 |
| 5     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, NaN\textsubscript{3}, trifluoromethanesulfonylimide, glycerol, r.t. | 3.5 | 90 | 58 |
| 6     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, trimethylsilyl azide, FeCl\textsubscript{3}, solvent-free, 70 °C | 6 | 88 | 59 |
| 7     | RNH\textsubscript{2}, CH(OEt)\textsubscript{3}, NaN\textsubscript{3}, ASBN, solvent-free, 120 °C | 3 | 94 | this work |

“Isolated yields.

Protein Binding. The QSAR results are presented in two steps: first, the observed and recorded scientific resources are located in QSAR database; second, the prediction is created by the users. In this case, the results are shown in Figures 16 and 17. Indeed, it is possible to collect the predictions under the following titles:

(1) Protein binding warnings for skin sensitization according to GHS.
(2) Protein binding alarms for chromosomal aberration by OASIS.
(3) Protein binding alerts for skin sensitization by OASIS.
(4) Protein binding potency Cys (DPRA 13%).
(5) Protein binding potency h-CLAT.
(6) Protein binding potency GSH.
(7) Protein binding by OASIS.

According to the QSAR created by the use of the data in the Supporting Information, the cause of protein binding in the acquired chemicals is different depending on the existing functional groups and their positions in the chemical structure (Figure 18).
Toxicity Hazard. One of the most important aims in the QSAR study is the prediction of LD base of the chemical structures. In Figure 19, we present the effect of the different structures in terms of toxicity hazard according to the products in Table 2 as follows:

1. Acute aquatic toxicity classification by Verhaar (modified).
2. Aquatic toxicity classification by ecological structure–activity relationships.
3. Toxic hazard classification by Cramer.
4. Acute aquatic toxicity MOA by OASIS.

CONCLUSIONS

The Ag/sodium borosilicate nanocomposite has been prepared via the reduction of Ag⁺ ions to Ag(0) in attendance of A. moluccana leaf extract, and the ensuing Ag NPs were immobilized under solvent-free conditions on the sodium borosilicate glass surface. The FT-IR spectrum of Ag NPs and leaf extract from A. moluccana demonstrated that flavonoids or polyphenols present in the leaf extract were accountable for the bioreduction of Ag⁺ ions rather than using conventional toxic and hazardous reducing agents, namely, borohydrides or hydrazines. The thermally and chemically stable catalyst displayed high catalytic activity as a green and economically
recyclable heterogeneous catalyst for the preparation of 1-substituted tetrazoles in good to excellent yields. The notable benefit of this protocol is the use of an environmentally benign method for the preparation of sodium borosilicate glass and Ag/sodium borosilicate nanocomposite, thus eliminating deployment of dangerous reagents, organic solvents, and homogeneous catalysts for the facile synthesis of tetrazoles. Moreover, the Ag/sodium borosilicate nanocomposite can be recycled several times without noteworthy deactivation in its catalytic prowess. Additionally, protein binding and toxicity hazard considerations for the ensuing 1-substituted tetrazoles were investigated via the QSAR model.

■ EXPERIMENTAL SECTION

Instruments and Reagents. All high-purity chemical reagents were purchased from Merck and Sigma-Aldrich without further purification. Fourier transform infrared spectroscopy (FT-IR) was recorded by using a Spectrum One system (Perkin-Elmer) spectrometer (Nicolet 370 FT/IR spectrometer, Thermo Nicolet), using KBr pellets. The 1H NMR spectra were obtained by a Bruker Avance DPX 400 MHz spectrometer. X-ray powder diffraction (XRD) measurements were performed using a Philips powder diffractometer type PW 1373 goniometer (Cu Kα = 1.5406 Å) to investigate the crystal structures of the samples. The materialization of Ag NPs was evaluated by UV–Visible spectral analysis on a double-beam spectrophotometer (Hitachi, U-2900). The size and morphology of the Ag NPs were investigated through transmission electron microscopy (TEM, Philips EM208) and field-emission scanning electron microscopy (FESEM, Hitachi S-4700). Elemental analysis of the ASBN was performed using energy-dispersive X-ray spectroscopy (EDS) equipped in FESEM.

Preparation of A. moluccana Leaf Extract. Forty grams of powdered dried leaves of the plant was extracted by boiling in 300 mL of double-distilled water for 25 min at 80 °C. The aqueous extract was filtered and stored in a refrigerator for subsequent use.

Biosynthesis of Ag NPs Using A. moluccana Leaf Extract. The aqueous extract (10 mL) was added dropwise to aqueous solution of AgNO3 (40 mL of 0.005 M) with continuous stirring at 70 °C. After 10 min, the solution turned into a brown suspension due to the excitation of surface plasmon resonance, thereby reaffirming the generation of Ag NPs (as monitored by UV–Vis spectroscopy). Then, the suspension was centrifuged (7000 rpm) for 25 min. The green synthesized nanoparticles have adequate stability with no noteworthy alteration in the symmetry of the absorption peak even after 15 days, presumably due to the protecting influence of the adsorbed phytochemicals.

Preparation of the Sodium Borosilicate Glass. Sodium borosilicate was prepared by a simple method using 19 g of borax (Na2B4O7·10H2O) dispersed in distilled water (200 mL) at 35 °C to make a homogeneous solution. Then, sodium silicate (Na2SiO3, 50 g) was added to distilled water (200 mL) and filtered to isolate the precipitated silica. In the next step, both
solutions were mixed to form a jelly-like polymer under a slow reaction, which ultimately dried. Last, the product is rinsed with distilled water to eliminate any excess ions.54

**Biosynthesis of the ASBN Using *A. moluccana* Leaf Extract.** For the greener synthesis of the ASBN, a mixture containing sodium borosilicate glass (1.0 g) and *A. moluccana* leaf extract (50 mL) was stirred at room temperature for 20 min. Then, 50 mL of 0.003 M AgNO₃ (99.99%) aqueous solution was added dropwise to the above mixture solution with vigorous stirring and heating. After stirring for 4 h, the prepared Ag/sodium borosilicate nanocomposite was separated from the residual solution by filtration, washed three times with water, and dried at 110 °C for 5 h in an oven.

**General Procedure for the Preparation of 1-Substituted 1H-1,2,3,4-Tetrazoles.** A mixture of amine (2 mmol), sodium azide (2 mmol), triethyl orthoformate (2.4 mmol), and Ag/sodium borosilicate glass nanocomposite (0.05 g) was taken and stirred at 120 °C for the suitable times (Table 2), with the progress of the reaction being monitored by thin-layer chromatography (TLC). After the reaction is completed, the reaction mixture was allowed to reach room temperature, then thinned with cold water (5 mL), and finally extracted with ethyl acetate (3 × 10 mL). The heterogeneous catalyst was separated by filtration. The solution was rinsed with water, dehydrated over dry MgSO₄, filtered, concentrated, and then crystallized from EtOAc-hexane to give different tetrazoles. All synthesized compounds were known and characterized through spectral analysis and melting points.29

**QSAR Prediction for Protein Binding and Toxicity Hazard Considerations.** The molecular structures were calculated using quantum chemical methods (Table 5). The predicted LD₅₀ values were 2.41 log(1/mol/kg), with a confidence range of 1.76-3.06 at 95.0%. The predicted endpoint (OECD Principle 1 - Defined endpoint) for Human Health Hazards is Acute Toxicity, with LD₅₀ for Oral exposure to *Rat* being 24 h.

Calculation approach (OECD principle 2 - Unambiguous algorithm): Linear approximation
Model equation: undefined endpoint = 2.38 (±0.114) + 0.160 (±0.0320) * log Kow, log(1/mol/kg) Active descriptor: log Kow (calculated)
Data usage: Arithmetic mean (average) value*
Statistics of the prediction model:
N = 99; count of data points
R² = 0.503; coefficient of determination
R²adj = 0.498; adjusted coefficient of determination
SSR = 10.1; sum of squared residuals
s = 0.319; sample standard deviation of residuals
F = 98.1; Fisher function
*When multiple values are available for the same chemical, their arithmetic mean (average) value is taken in prediction calculations.
Figure 16. Subcategories of protein binding processed by QSAR.

Figure 17. Subcategories of toxicity hazard processed by QSAR.

Figure 18. Protein binding based on chemicals in Table 2 obtained by QSAR.

Figure 19. LD based on chemicals in Table 2 obtained by QSAR.
imported in quantitative structure--activity relationships (QSAR), target chemicals were set by drawing the molecule and finding the CAS number (5378-52-9), and then the profilers were selected by ticking specific background information such as protein binding groups (Figure 16) and toxic hazard groups (Figure 17). We utilized inventory data from Distributed Structure-Searchable Toxicity (DSTTox), existing commercial chemical substances (EINECS), METI Japan, the original concept of the Chemical Substances Control Law (CSCL), and the diet and the Toxic Substances Control Act (TSCA) databases. We predicted the molecular structure by organic functional group subcategorization through elimination of dissimilar analogues with respect to structural functionalities. This subcategorization helps eliminate structurally dissimilar analogues such as aromatic amines.

**ASSOCIATED CONTENT**

**S Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00800.

Result components and matrix data including protein binding and toxicity hazard considerations (ZIP)

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**Notes**

The authors declare no competing financial interest.

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