In situ evaluation of the biological active poly functionalized novel amino-1,8-naphthyridine derivatives as DNA-electrochemical biosensor

Muhammad Tariq Riaz, Muhammad Yaqub, Shumaila Javed, Dilshad Hussain, Muhammad Naeem Ashiq and Zahid Shafiq

Institute of Chemical Sciences, Bahauddin Zakariya University, Multan, Pakistan

ABSTRACT
A one-pot three-component protocol was designed for cascade synthesis of novel heterocyclic amino-1,8-naphthyridines. Materials synthesis is confirmed by NMR (1H and 13C) and structures are verified by computational models. The in vitro phytotoxic and urease enzyme inhibition studies with IC50 ranges from 23.76 ± 0.027 μM to 67.46 ± 3.93 indicating significant pharmacological activity of synthesized compounds. Osiris calculations results confirm the non-mutagenicity and non-irritating patterns. Molinspiration calculations values of 3.49–3.94 indicate the permeability of the derivatives through membranes. Amino-1,8-naphthyridines are used for the first time in electrochemical sensing of DNA. The mechanism of interaction between DNA and amino-1,8-naphthyridine derivatives is evaluated via a constant current potentiometric method. Different electrochemical parameters such as scan rate, binding time, and effect of concentration of DNA are optimized. The strong interaction of these compounds with the human DNA under physiological conditions justified their potential applications as biosensors after further optimization.

1. Introduction
Different types of interactions are associated with synthesized biologically active organic compounds that bind human DNA like electrostatic furrow interactions, covalent interactions, cross-linking, and DNA cleaving [1–5]. During complex formation, the interactive forces may cause certain variations in DNA as a well synthesized organic compound [6]. Highly functionalized organic compounds have some surface moieties which can form additional bonds with DNA double-helix or ends of nitrogenous base pairs [7]. The interaction between such organic compounds is either electrostatic interactions or hydrogen bonding [8]. Several techniques that have been applied to evaluate the interactions between synthesized organic compounds and DNA include nuclear magnetic resonance spectroscopy, Fourier transforms infrared spectroscopy, and molecular docking techniques [9].

Recently, electrochemical techniques have gained tremendous attention in research [10–12]. Applications of electrochemical methods are not limited to fundamentals research but these techniques have been frequently used in pragmatic applications because of their high selectivity, ease of operation, and low instrumental and operational cost [13,14]. Several electrochemical techniques have been used to study the interactive forces between synthesized organic compounds and DNA [15,16]. Cyclic voltammetry (CV) is a versatile electrochemical technique that is most commonly applied to explore the binding interaction of DNA with organic compounds [17,18].

Structural and physicochemical characteristics of DNA contribute significantly towards disease. So, DNA acts as a potent molecule for biologically active compounds predominantly for antibiotics [19,20]. It is important to understand the mechanism of antiviral, antifungal, antioxidant, and anticancer activity to design novel and more effective DNA besieged organic compounds [21,22]. The interaction between synthesized organic compounds and DNA is the basic tool for biological applications to improve the medicinal applications of organic compounds [23]. Amino-1,8-Naphthyridines have a celestial attraction with DNA due to poly functionalized structure and these electrostatic interactions can be studied by cyclic voltammetry [24,25].

In this study, the synthesis of polyfunctionalized 1,8-naphthyridines has been reported. Heterocyclic amino-1,8-naphthyridines are used for the first time

CONTACT Zahid Shafiq zahidshafiq@bzu.edu.pk; Muhammad Yaqub maya2@yahoo.com Institute of Chemical Sciences, Bahauddin Zakariya University, Multan 60800, Pakistan

Supplemental data for this article can be accessed here. https://doi.org/10.1080/16583655.2021.1991718

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as electrochemical sensors for DNA. Moreover, the one-pot synthesis method is easy, versatile, and reproducible. Besides these characteristics, synthesized heterocyclic amino-1,8-naphthyridines also show phytotoxic and urease inhibition activities [26,27]. Biological applications, as well as the interaction with DNA, urease inhibition study, and phytotoxic application of the 1,8-naphthyridines, are also studied. Furthermore, the electrochemical activities using cyclic voltammetry of the synthesized 1,8-naphthyridines are also determined.

2. Experimental

2.1. Chemicals and instrumentation

All chemicals, reagents, and solvents used for synthesis, phytotoxicity, enzyme inhibition activity, and electrochemical measurements were purchased from Merck, Fluka, and Sigma Aldrich and were used without any further pre-treatment. Melting points of synthesized organic compounds were measured by a melting point apparatus of Fisher-Johns using slips. Proton and Carbon-13 NMR spectra were determined by using the spectrometer Bruker (Rhenistetten-Forchheim, Germany) at 300 MHz. The measurements were carried out in DMSO-$d_6$ by using TMS as a standard. The advancement of the process was assessed on TLC plates layered with silica gel 60 GF254 (Merck).

For electrochemical measurements on DNA, a three-electrode system was employed consisting of a glassy carbon electrode GCE (Metrohm6.1204.110, diameter 1/42 mm), a counter electrode made of a glassy carbon rod, and a reference electrode of Ag/AgCl (Metrohm 6.0733.100). The oxidation of guanine was recorded with the help of the CCPS method on an electrochemical workstation (Auto lab PGSTAT 12) purchased from Eco Chemie, The Netherlands and all the experiments were performed by using the GPES 4.9 software. Switzky and Golay method (level 4) was applied during these measurements for baseline correction (peak width 1/40.001) and smoothing during data treatment.

2.2. Synthesis of amino-1,8-naphthyridines derivatives

1,8-naphthyridines derivatives were synthesized by previously reported procedure with slight modifications [28]. Briefly, 0.01 M malononitrile and 0.01 M aldehyde derivative were mixed in a round bottom flask and refluxed in 20 mL of dry tetrahydrofuran for 30 min in the presence of pyridine as a catalyst. A solution of 0.01 M 2-aminopyridine derivative was prepared in 5 mL of dry solvent tetrahydrofuran and added to the reaction mixture dropwise. For the confirmation of arylamine intermediate formation, a TLC experiment was carried out. Then, the mixture was further refluxed for three hours under continuous stirring. Finally, precipitates were obtained after cooling the mixture to room temperature. 1,8-naphthyridines derivatives were filtered, washed with methanol, and vacuum dried.

2.3. Phytotoxic activity (in vitro) study of amino-1,8-naphthyridines

Phytotoxic activity of 1,8-naphthyridines was evaluated by using the reported procedure of *Lemna minor* [29]. Briefly, the cultured medium was developed by the addition of different constituents in 1 L of Milli-Q water. The pH of the cultured medium was maintained at 5.5–6.5 with the help of potassium hydroxide solution and autoclaved at 120°C for 20 min. A stock solution (56 mM) of synthesized organic compound was prepared in DMSO. Then, different concentrations ranging from 28 μM to 2.8 mM were prepared from the stock solution. Under sterile conditions, the solvent was evaporated by standing overnight. Three fronds of *Lemna minor* L. were added to each flask containing 20 mL of cultured medium and placed for 7 days in the growth cabinet. Then the growth regulation (%) was calculated as follows;

\[
\text{Mortality} (\%) = \frac{\text{Growth regulation} (\%)}{\text{number of fronds in the negative control}} \times 100
\]

Positive and negative controls were also assessed with Paraquat as a standard drug for further justification of the growth regulation results.

2.4. Urease inhibition (in vitro) study of amino-1,8-naphthyridines

The mixture of 100 mM urea, 55 μL of phosphate buffer, and 25 μL Jack Bean Urease was incubated with 5 μL of 0.5 mM synthesized organic compound at 25°C for 20 min. Urease inhibition was studied by the indophenols scheme [30]. Briefly, 70 μL of alkali solution (0.5% NaOH and 0.1% sodium oxychloride) and 45 μL of phenolic mixture (0.005% (Na2[Fe(CN)5NO]) and 1% phenol) were added in each plate. After 50 min the change in absorbance at 630 nm was studied in triplicate measurements with a 200 μL volume by applying a microplate reader (Spectra Max, Molecular Devices, USA). softMax Pro software (Molecular Devices, USA) was used to study the domino effects (change in absorbance per unit time). Thiourea was the compound applied as the standard urease inhibitor for the standardization of synthesized organic compounds [31]. Percentage inhibitions were calculated as;

\[
\text{Inhibition} (\%) = \frac{\text{OD test well}}{\text{OD control}} \times 100
\]
2.5. Pre-treatment of electrode and immobilization of DNA

For the refining of the glassy carbon electrode (GCE) alumina cleaning kit (Metrohm 62.80.2000) was used. After refining it was detached by ultra-sonication to obtain a clean outer surface before DNA immobilization. The deionized water was used to wash the surface of the electrode with care. By using the micropipette the DNA solution was dropped on a glassy carbon electrode (GCE) tip and upturned for immobilization of DNA and dried at room temperature for a half-hour. The potentiometric conditions were applied; potential range from 0 to +1.2 V, equilibration time one minute, and continuous current +8 μA. During the study of this technique, the concentration of immobilized DNA was assessed by plotting the graph between DNA concentrations versus guanine peak area.

2.6. Interaction of amino-1,8-naphthyridine with DNA

The electrochemical property was studied by developing the solutions of synthesized organic compounds in dimethyl sulfoxide. 10 mL of 0.1 M tetrabutylammonium perchlorate (TBAP) solution as sustaining electrolyte was used in the electrochemical cell. The surface of the glassy carbon electrode (GCE) was cleaned by alumina Kit. Before the start of the experiment, the mixture of acetone, water, and Nitrogen gas was flushed through the solution for 10 min for extensive cleaning. The DNA interactions were carried out by cyclic voltammetry with the preparation of the solutions in water and dimethyl sulfoxide at the ratio of 1:9. The DNA interaction was screened as a scan rate of 100 mV/s by a gradual increase in the concentration of DNA.

2.7. Electrochemical measurements

For electrochemical measurements, three electrodes GCE (Metrohm 6.1204.110, diameter 1/42 mm), a counter electrode, and a reference electrode of Ag/AgCl (Metrohm 6.0733.100) were used. With the help of the CCPS method on an electrochemical workstation (Auto lab PGSTAT 12), the oxidation is determined. Switzy and Golay method (level 4) was applied during these measurements for baseline correction (peak width1/40.001) and smoothing during data treatment.

3. Results and discussion

Functionalized 1,8-Naphthyridine derivatives are synthesized by treating aromatic aldehydes with malononitrile in the presence of pyridine as a catalyst and followed by the addition of 2-aminopyridine derivatives. The reaction is optimized at different conditions but dry THF is selected to get a good yield and pure product Scheme 1.

This configuration of the synthesized Amino-1,8-naphthyridines is elucidated with the help of spectroscopic (1H-NMR and 13C-NMR) and elemental analysis. (Fig S1–Fig S12). The 1H-NMR absorptions and 13C-NMR peaks are closely related to the targeted compounds of the supposed substituted Amino-1,8- naphthyridine. The proposed 3D structures of synthesized organic compounds are given in Fig. S13, S14, and S15 (Supporting Information) for compounds 5a, 5b, and 5c, respectively.

3.1. Phytotoxic activity

The novel synthesized 1,8-naphthyridines 5a-c are related to some naturally occurring compounds which can be extracted from plants and are phytotoxic. Such types of compounds are the stuff of good commercial value and gaining much attraction in pharmacology. The present report will provide the basic data in the pharmacological field for future research in exploiting the imperceptible prospective of such type of synthetic novel compounds which has not been explored so far.

The synthesized compounds 5a-c show significant phytotoxic activity at all concentrations (Fig. S16). The results specify that phytotoxic activity is dose-dependent, i.e. compounds are low phytotoxic at low concentrations and high phytotoxic at high concentrations. At the highest concentration (1.4 mM), the maximum phytotoxic activity is shown that is 100%
Table 1. In vitro phytotoxic bioassay of different compounds 5a-c.

| Sample | Conc. of compound (mM) | No. of fronds | % Growth Regulation | Conc. of Std. Drug (mM) |
|--------|------------------------|---------------|---------------------|-------------------------|
| 5a     | 1.4                    | 0             | 17                  | 100                     |
| 5b     | 0                      | 17            | 100                 |                          |
| 5c     | 0                      | 17            | 100                 |                          |
| 5a     | 0.14                   | 10            | 17                  | 86                      |
| 5b     | 2                      | 17            | 17                  | 88                      |
| 5c     | 12                     | 17            | 17                  | 69                      |
| 5a     | 0.014                  | 11            | 17                  | 55                      |
| 5b     | 9                      | 17            | 17                  | 47                      |
| 5c     | 15                     | 17            | 17                  | 19                      |

a. Lemna minor is screened to explore the phytotoxic activity.

b. Incubation condition: 28 ± 1°C.

From the results obtained in biological activity, it is accomplished that 5a, 5b, and 5c displayed 100% inhibition at the concentration of 0.2 mM.

Table 2. Urease inhibitory activity of compounds (5a-c).

| Sample | Conc. (mM) | % Inhibition | IC50 ± SEM[μM] |
|--------|------------|--------------|----------------|
| 5a     | 0.5        | 93           | 23.76 ± 0.027  |
| 5b     | 0.5        | 88           | 28.83 ± 0.35   |
| 5c     | 0.5        | 90           | 67.46 ± 3.93   |
| Thiourea | 0.5    | 93           | 21.0 ± 0.01    |

S.E.M = Standard Error Mean, Results represent the mean of triplicate.

3.2. Urease inhibition activity

1,8-naphthyridine compounds (5a-c) are also evaluated for urease inhibition activity at a concentration of 0.5 mM (Table 2). Compound (5a) shows the maximum inhibitory activity followed by compounds 5c and 5b respectively, by taking thiourea as a reference drug. These observations suggest that synthesized compounds (5a-c) are strong inhibitors of the urease enzyme inhibition (Fig. S17). Amino-1,8-naphthyridine compound 5a has comparable inhibition at 0.5 mM concentration and IC50 values to the reference drug thiourea, whereas 5b and 5c derivatives show analogous inhibition at 0.5 mM concentration but IC50 values make less credible relative to the reference drug. The effect of various substitutions on amino-1,8-naphthyridine can be assessed by relating the urease inhibitory activity of the derivatives with that of the preliminary reacting molecules which are weak urease inhibitors. Novel compounds (5a-c) have more potential for inhibition of urease which is synthesized by treating 2-aminopyridine with appropriate derivatives of aryldines.

% Inhibition of the synthesized compounds is effective and also related with the % inhibition of standard drug thiourea in the form of a graph (Figure 1).

3.3. Theoretical calculations of 5a–c

Different researchers have used computational methodology to differentiate between naturally occurring compounds like drugs and other sources. The current study of the compounds as drugs is based on the screening of synthesized compounds against natural targets for a disease that requires a similar type of screening of the synthesized compounds containing drug-like behaviour. We also studied the known standard references (SRs) having the properties of drugs to design a strategy for the development of the particular drug-like compounds.

(A) Osiris Calculations

Synthetic organic compounds are predicted for biological and molecular properties based on ADME-Tox liabilities but many drugs fail in such tests. Cytochromes P450 is a particular class of enzymes that is accountable for many ADMET tribulations. By the production of undesired molecules, there are adverse effects in the field of pharmacology. Some of the mainly imperative computational programmes, Osiris is accessible online. It is now probable to expect the biological activity and inhibition by using an electronic/structural molecular docking. The amazingly well-mannered mutagenicity of
miscellaneous synthetic organic compounds is confidential in the database of CELERON Company, Switzerland which is applied to enumerate the responsibility of different functionalities in enhancing or snooping the way where a synthesized molecule can link with DNA. The OSIRIS Property Explorer is applied in the current research is a primary element of Actelion’s in-house substance registration system. The system helps to draw the chemical structures of organic compounds and determines different features related to biologically active drugs when a structure is legal. Prophecy results and determines different features related to biologically active drugs when a structure is legal.

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Table 3. Osiris calculations of synthesized compounds (5a-c).

| Compound | MW | MUT | TUMO | IRRI | REP | CLP | S | D-L | D-S |
|----------|----|-----|------|------|-----|-----|---|-----|-----|
| 5a       | 359 | ++  | +    | +    | +   | +   | 3.5| −6.57| −9.12 | 0.25 |
| 5b       | 315 | ++  | +    | +    | +   | +   | 3.38| −6.47| −4.2  | 0.26 |
| 5c       | 339 | ++  | +    | +    | +   | +   | 3.24| −6.18| −9.34 | 0.27 |

Table 4. Molinspiration Calculations of compounds (5a-c).

| Compound | MW | cLogP | TPSA | Natoms | nON | NON | I | NV | Nrotb | VOL |
|----------|----|-------|------|--------|-----|-----|---|----|-------|-----|
| 5a       | 359.61 | 3.94 | 75.60 | 21 | 4 | 2 | 0 | 1 | 250.7 |
| 5b       | 315.16 | 3.83 | 75.60 | 21 | 4 | 2 | 0 | 1 | 246.35 |
| 5c       | 339.20 | 3.49 | 75.60 | 21 | 4 | 2 | 0 | 1 | 253.73 |

Table 5. Drug-Likeness of compounds 5(a-c).

| Compound | GPCRL | ICM | KI | NRL | PI | EI |
|----------|-------|-----|----|-----|----|----|
| 5a       | 0.07  | 0.38 | 0.57 | −0.63 | −0.47 | 0.49 |
| 5b       | 0.20  | 0.46 | 0.62 | −0.50 | −0.32 | 0.55 |
| 5c       | −0.06 | 0.13 | 0.49 | −0.53 | −0.57 | 0.35 |

3.4. Electrochemical investigations of substituted amino-1,8-naphthyridine

3.4.1. Optimization of immobilization of DNA

DNA immobilization in the electrochemical study is carried out by immobilizing 2 mL of DNA solutions on GCE and the oxidation of guanine base in DNA steadily shifted to +0.86 V from +0.89 V with increasing concentration of immobilized DNA which is the early indication of immobilization of DNA on the electrode surface. Furthermore, the peak area of oxidation guanine is determined and then the immobilized DNA concentration on the surface of the electrode is evaluated (Fig. S18-Fig S28).

Concentrations of DNA were optimized by testing different concentrations by cyclic voltammetry, and then plotting a graph of the concentration of DNA and guanine peak area. Obtained results indicate the direct relationship between DNA concentration and guanine peak area, with maximum peak area observed at 0.02 mg concentration. A similar effect is observed by changing the concentration of solutions. With increasing concentration of the solution, immobilization of DNA to the surface of glassy carbon electrode (GCE) improved up to 0.02 mg. So we can assume that this material behaves as a broad film DNA biosensor, impeding the unwanted binding of the electrode surface to the drug molecules.

3.4.2. Optimization of interaction time

Interaction time is considered an important parameter in the electrochemical investigation of DNA. An arrangement of three electrodes system is applied to assess cyclic voltammetric behaviour. To evaluate the effect of accumulation time of drug (methotrexate) on the DNA adapted electrode is determined by a decrease in guanine peak current. After some time, the reduction in guanine peak current levelled off and no further change is observed up to 5 min. The approach of the interface is determined by changing the peak potentials while the DNA binding constant is measured with the
help of peak currents. The formula to calculate the DNA binding constant is given in the following equation [35].

\[
\log  \left( \frac{1}{\text{[DNA]}} \right) = \log k + \log \left( \frac{I_0}{I - I} \right)
\]

In the above relationship, I and I₀ are the peak currents of DNA-bound organic compound and free synthesized organic compound, respectively and K is binding constant. From the equation, the value of (I₀ - I/I) is the ratio of experimental peak current. The binding site size is calculated by a subsequent equation [36].

\[
\frac{C_b}{C_f} = K \left( \frac{\text{[free base pair]}}{s} \right)
\]

where \(C_b\) shows the concentration of synthesized organic compound-DNA bound group, \(C_f\) is free concentration group and s is the binding site size in conditions of base pair. \(C_b/C_f\) is the experimental peak current [37].

In recent years different electrochemical sensors for DNA detection has been reported with varying efficiency. These materials include quinacrine [38], Azoimine quinoline derivatives [39], 4-methyl-5-((phenylimino)methyl)-3H-1,2-dithiole-3-thione (MPDT) and 5-(4-fluorophenyl)-3H-1,2-dithiole-3-thione (FPDT) [40], amide substituted dexibuprofen derivatives [41], and 17\(\alpha\)-Ethinylestradiol [42]. Our synthesized amino-1,8-naphthyridine derivatives also show comparable DNA interaction efficiency along with some addition benefits of phytotoxic and urease inhibition activities.

### 3.4.3. Electrochemical characterization

During the study of synthesized organic compounds, the redox behaviour of 0.5 mM \(5a\) and \(5b\) are premeditated by cyclic voltammetry (CV) at a 100 mVs⁻¹ scan rate. The CVs are primarily happening at +0.00 V and measured in the range of potential of −2.50–0.00 V. On the voltammogram, initiating in the positive path, one oxidation peak is attained at −0.4 V showing that synthesized compound \(5b\) is oxidizable under these conditions. Synthesized compound \(5b\) shows strong reduction potential at −1.5 V and between −1.0 to −0.5 V with the current −2.59 × 10⁻⁶ and −7.93 × 10⁻⁷ mA respectively. This oxidation–reduction behaviour of the synthesized compound shows that this compound is easy to oxidize and reduce at multiple scan rates. A more strong reduction at two different potentials indicates a more prominent reduction behaviour. A similar oxidation–reduction pattern is observed in oxidation and reduction at different scan rates showing that scan rate has no significant effect on oxidation and reduction of \(5b\) (Figure 2).

### 4. Conclusions

In this research, organic synthesis of substituted 1,8-naphthyridine derivatives \(5a-c\) is done in one-pot three components. 2-Aminopyridines are used as bis-nucleophile with malononitrile and substituted aromatic aldehydes to get final products. NMR results indicate the successful synthesis of the materials which are further justified by computational models. Electrochemical DNA sensing is done using cyclic voltammetry. The optimization of electrochemical parameters such as binding time, the concentration of DNA, and scan rate are optimized. The synthesized organic molecules 1,8-naphthyridine derivatives \(5a-c\) have DNA binding invariable standards in the range of 10⁻³ M. The synthesized material show significant phytotoxic and urease inhibition activities also. These results indicate that substituted 1,8-naphthyridine derivatives possess the promising potential for DNA sensing under optimized conditions and can be used for sensing applications of multiple biomolecules with some other modifications.
Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
This research is supported by Bahauddin Zakariya University, Multan, Pakistan, and the authors are thankful to Higher Education Commission, Islamabad, Pakistan for financial support through project NRPU/6975.

ORCID
Zahid Shafiq http://orcid.org/0000-0003-4088-8297

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