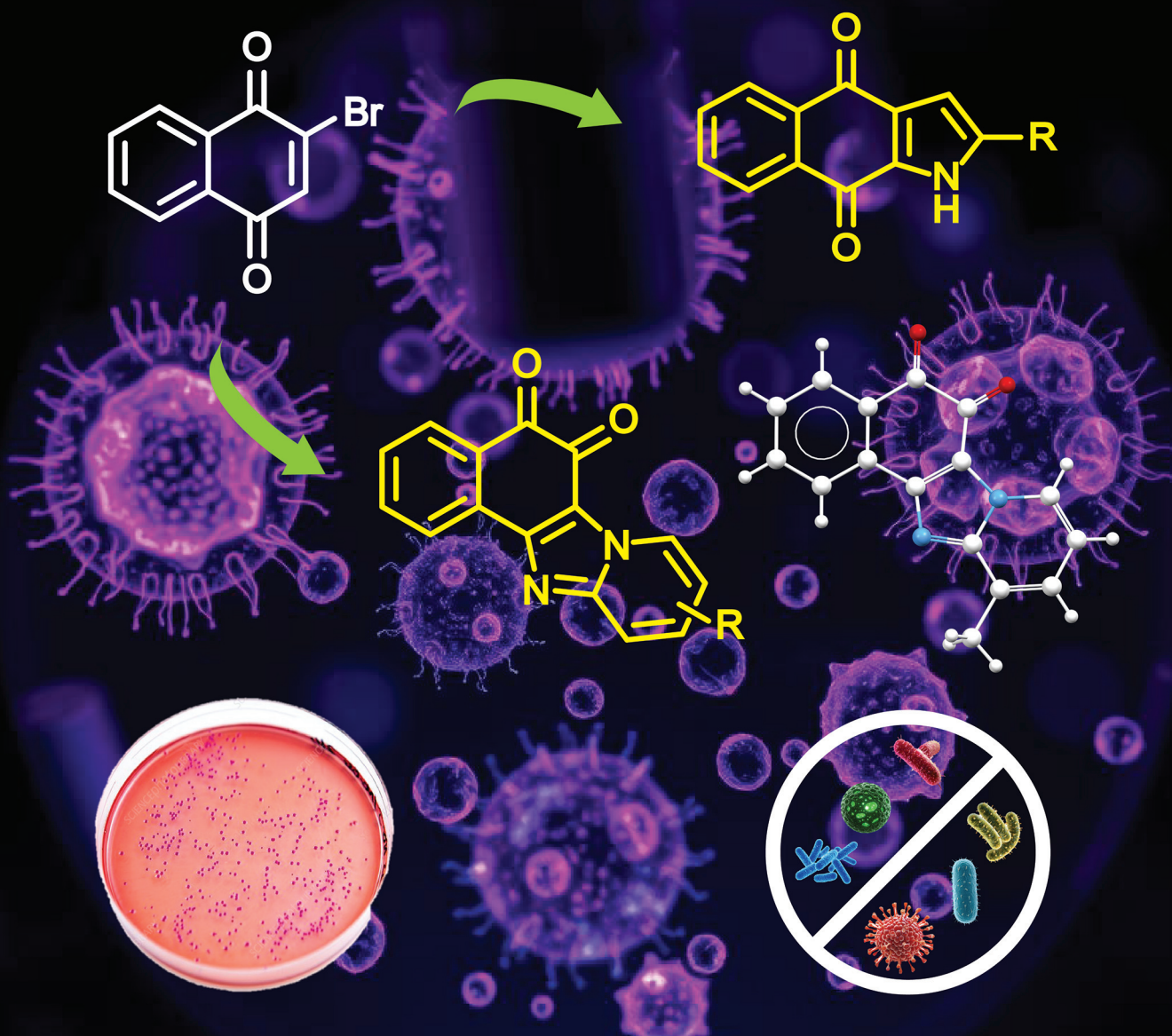


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## PAPER

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# Synthesis and biological evaluation of naphthoquinone-fused pyrrole and imidazopyridinedione heterocycles†

Rabindra Nath Sana,<sup>a,b</sup> Sudipta Chakraborty,<sup>c</sup> Vageesh M.,<sup>d</sup> Soumen Adak,<sup>e</sup> Tanurima Bhaumik,<sup>\*b</sup> Raju Dey<sup>†d</sup> and Susanta Kumar Manna<sup>†\*a</sup>

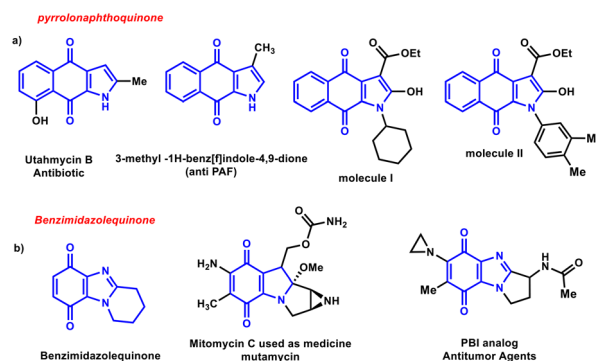
We have developed an efficient and straightforward synthetic route to obtain naphthoquinone-fused pyrrole derivatives (up to 93% yield) *via* an intramolecular cyclization of 2-(arylethynyl)naphthalene-1,4-dione derivatives with NH<sub>4</sub>OAc in methanol at ambient temperature. Furthermore, imidazopyridinedione derivatives were synthesized *via* coupling between 2-bromonaphthalene-1,4-dione and 2-amino pyridine through condensation and rearrangement under neat conditions in the presence of a catalytic amount of AcOH. A series of functionalized pyrrolonaphthoquinone and imidazopyridinedione derivatives were synthesized in high yields. Additionally, one of the synthesized pyrrolonaphthoquinones was selected as the model substrate for evaluating cytotoxicity and antimicrobial activity against both Gram-positive and Gram-negative biofilm bacteria.

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## Introduction

N-containing heterocycles fused with a quinone or naphthoquinone framework have received significant attention due to their wide range of biological and pharmacological activities, including anti-inflammatory,<sup>1</sup> anticancer,<sup>2</sup> anti-hyperproliferative, and antifungal activities.<sup>3a</sup> This motif is embedded in various natural and bioactive molecules.<sup>3b</sup> It also acts as a building block in the formation of many bioactive molecules. The pyrrole fused naphthoquinone utahmycin B, a natural product isolated from *Streptomyces albus* J1704, shows excellent antibiotic properties.<sup>4</sup> 3-Methyl-1*H*-benz[*f*]indole-4,9-dione (antiPAF) is a natural product obtained from the bark of *G. tapis* and *G. uvaroides*. This molecule has potential inhibitory effects against platelet-activating factor (PAF).<sup>5</sup> Even recently, the synthesized molecule **I** (Fig. 1a) showed better cytotoxicity than the chemotherapy drug doxorubicin,<sup>6</sup> while

molecule **II** (Fig. 1a) showed specific cytotoxicity towards lung cancer cells, comparable to that shown by doxorubicin.<sup>7</sup> Benzimidazole quinones exhibit cytotoxicity towards human skin fibroblast cells within the nanomolar range under hypoxic conditions (low pO<sub>2</sub>).<sup>8a</sup> Mitomycin C (Fig. 1b), a commercially available medicine, which has a pyrroloquinone moiety, has been effectively used as a chemotherapeutic drug.<sup>8b</sup> It prevents anal cancers, gastro-intestinal cancers (*e.g.* esophageal carcinoma) and breast cancers. Analogues of pyrrolo [1,2-*a*]benzimidazole (PBI) also act as antitumor agents.<sup>8c</sup> Thus, numerous synthetic methods have been developed to synthesize benzo[*f*]indole-4,9-dione derivatives.<sup>9</sup> This inspired us to develop a convenient route to access naphthoquinone fused pyrrole and imidazopyridinedione derivatives



**Fig. 1** Representative examples of medicinally important naphthoquinone-fused pyrrole and benzimidazole fused quinone derivatives.

<sup>a</sup>Department of Chemistry, Bidhannagar College, Kolkata-700064, India. E-mail: Smanna19@gmail.com

<sup>b</sup>Department of Chemistry, Jadavpur University, Kolkata-700032, India. E-mail: tanurima.bhaumik@jadavpuruniversity.in

<sup>c</sup>Department of Microbiology, Government General Degree College, Narayanagarh, West Bengal-721437, India

<sup>d</sup>Department of Chemistry, National Institution of Technology, Calicut-673601, India. E-mail: rajudey@nitc.ac.in

<sup>e</sup>Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, WestBengal 741246, India

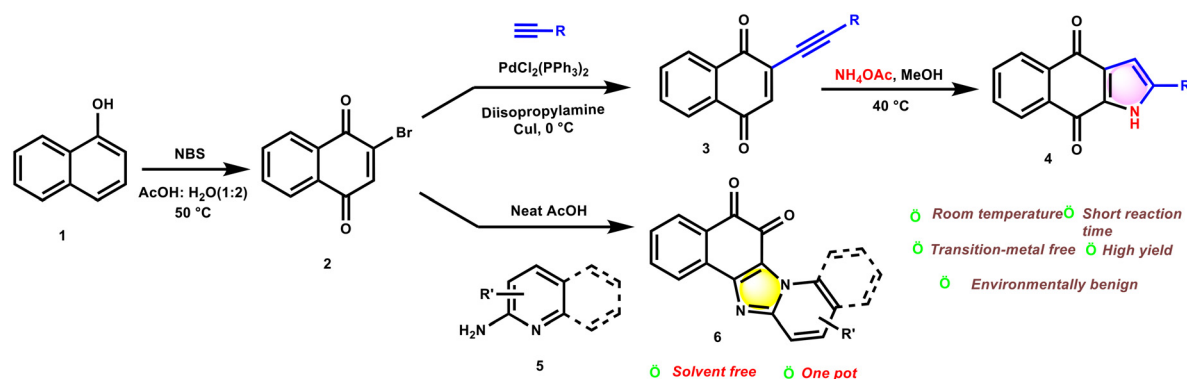
† Electronic supplementary information (ESI) available. CCDC 2431475. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5ob00564g>



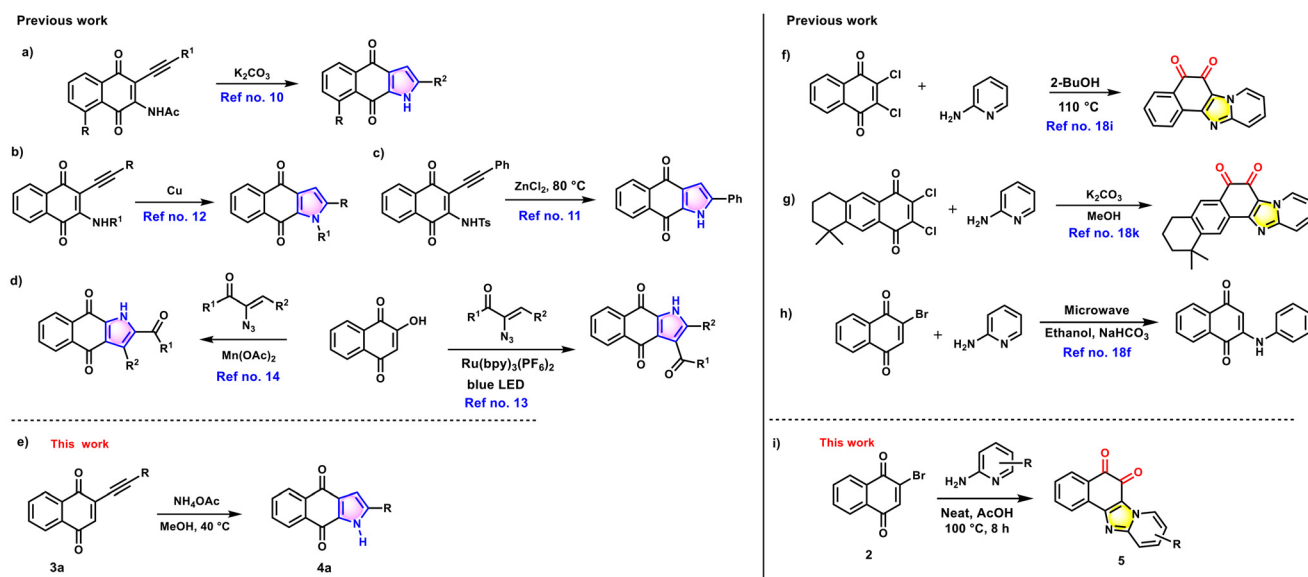
(Scheme 1). Shvartsberg *et al.* developed a method for the synthesis of pyrrolonaphthoquinone, wherein a Sonogashira derivative bearing an acetamine substituent undergoes intramolecular cyclization using  $K_2CO_3$  in acetonitrile solvent at 80 °C (Scheme 2a).<sup>10</sup> Annulation of naphthoquinones bearing acetylenic and amido substituents in the presence of  $ZnCl_2$  yielded bioactive 2-phenyl-1*H*-benzo[*f*]indole-4,9-dione (Scheme 2c).<sup>11</sup> A mild strategy for constructing indolequinone motifs involved the Sonogashira reaction and a copper-catalyzed intramolecular cyclization (Scheme 2b).<sup>12</sup> Maurya *et al.* documented the synthesis of highly functionalized naphthoquinones with 2,3-fused pyrrole through the coupling of  $\alpha$ -azidochalcones with 2-hydroxy 1,4-naphthoquinone using  $Ru(bpy)_3(PF_6)_2$  as the catalyst under blue LED light irradiation (Scheme 2d).<sup>13</sup> Here, the azide group serves as a source of pyrrole nitrogen. A novel, convenient, and economical protocol to prepare polyfunctionalized benzo[*f*]indole-4,9-diones catalyzed by  $Mn(II)$  acetate from vinyl azides and 2-hydroxy-naphthoquinone has also been achieved (Scheme 2d).<sup>14</sup> Very

recently naphthoquinone with 3,4-fused pyrrole was synthesized by Deng *et al.*, wherein they utilized naphthoquinone with aromatic aldehyde and ammonia as the nitrogen source.<sup>15</sup> Starting from 2-substituted (attached to isoxazolones) 1,4-naphthoquinones, Brogini *et al.* synthesized pyrrolonaphthoquinones using  $[Ru(p\text{-cymene})_2Cl_2]_2$  as the catalyst in DMSO at 100 °C.<sup>16</sup> Here, the nitrogen of the pyrrole comes from the isoxazole ring.

Choudhury *et al.* synthesized naphthoquinone-fused pyrroles attached to a pyrimidine moiety through a multicomponent reaction. The nitrogen from 2-amino-1,4-naphthoquinone is the source of the pyrrole nitrogen.<sup>17a</sup> Previous work also reports  $NaN_3/NH_4Cl$  mediated synthesis of pyrroles and isoquinolines through a transmolecular *aza-exo-trig* and *aza-endo-dig* cyclization of an aldehyde with an alkene or alkyne scaffold.<sup>17b</sup> Moreover, the synthesis of another interesting heterocycle benzimidazolequinone/imidazopyridinedione, was reported here by employing 2-bromo-1,4-naphthoquinone/2,3-dibromo-1,4-naphthoquinone and 2-aminopyridine under neat conditions



**Scheme 1** Outline of the synthesis of naphthoquinone-fused pyrrole and benzimidazole-fused quinone products.



**Scheme 2** State of the art in the synthesis of pyrrolonaphthoquinone and 1,2-naphthoquinone bearing fused-heterocycle rings.



with catalytic AcOH (Scheme 2i). Mosby and Boyle<sup>18a,b</sup> synthesized, for the first time, *ortho*-quinone fused benzimidazoles from 2,3-dichloro-1,4-naphthoquinone and 2-aminopyridine, and after that, several other groups<sup>18c-h</sup> have synthesized similar molecular frameworks by varying the reaction conditions. Anusevičius *et al.*<sup>18i,j</sup> and Castro *et al.*<sup>18k</sup> also developed this heterocyclic motif using various substituted *o*-aminopyridines and dichloronaphthoquinones/anthraquinones (Scheme 2f & g). Based on literature survey, this is the first documented synthesis of an *o*-quinone-fused imidazopyridine from 2-bromo naphthoquinone<sup>18f</sup>/2,3-dibromonaphthoquinone and *o*-aminopyridine (Scheme 1).

During our thorough literature survey, we did not come across any reports on the synthesis of naphthoquinone fused pyrroles in NH<sub>4</sub>OAc medium. Thus, in continuation of our synthetic efforts towards N-fused heterocycles,<sup>17b,19</sup> herein, we report a NH<sub>4</sub>OAc promoted cyclization method for indoloquinone synthesis (Scheme 1, 2e).

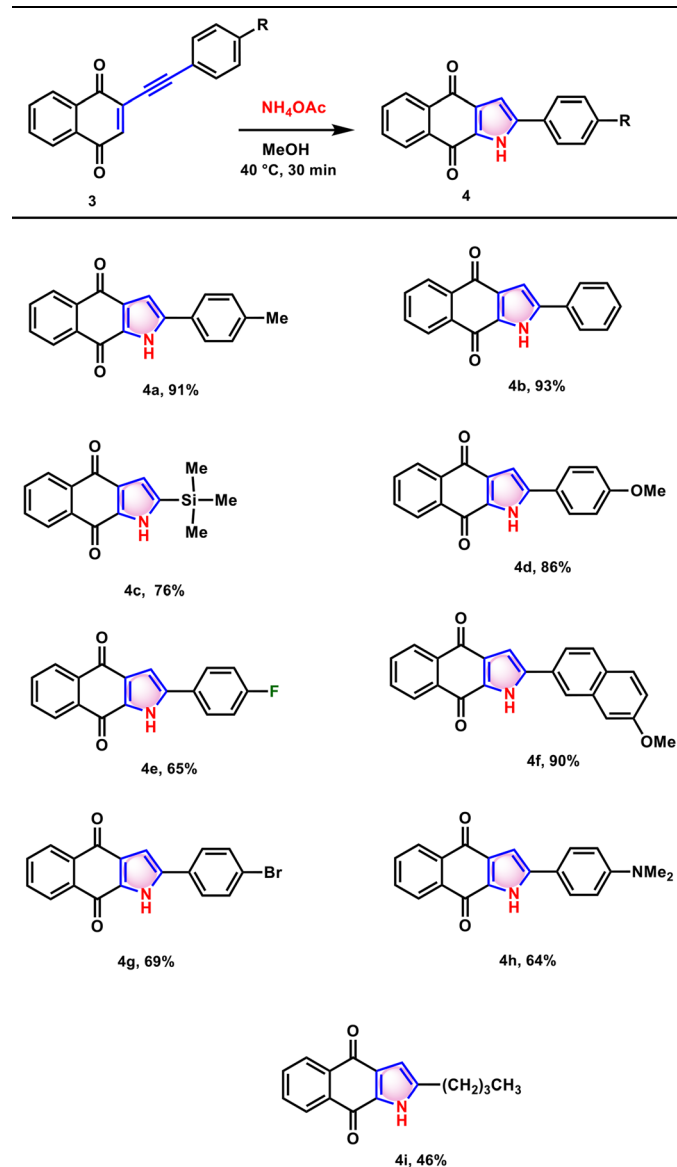
## Results and discussion

We prepared the starting materials from commercially available 1-naphthol **1**. 1-Naphthol furnished bromonaphthoquinone **2** by the treatment of NBS in an aqueous AcOH medium at 50 °C. The Sonogashira coupling of **2** with an aryl alkyne partner, in diisopropyl amine solvent at 0 °C, gave the desired 2-(arylethynyl) naphthalene-1,4-dione **3**.<sup>20</sup>

Furthermore, to optimize the reaction conditions, we carried out reactions using 2-(arylethynyl)naphthalene-1,4-dione **3a**, varying the temperature, solvent, and reaction duration. Firstly, we carried out the reaction using NH<sub>4</sub>Cl as a nitrogen source and acetonitrile as the solvent under reflux conditions, obtaining the desired product in trace amounts

(Table 1, entry 1). A similar result was observed when THF and DCM (Table 1, entries 2–4) were used as the reaction media. When methanol was used as a solvent along with an additive nitrogen source, the reaction proceeded to afford moderate to good product yields (Table 1, entries 5 and 6). Maximum yield was obtained when the reactions were carried out with NH<sub>4</sub>OAc as the nitrogen source in methanol at 40 °C for 30 minutes (Table 1, entry 7). However, alternative nitrogen sources like urea, (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and NH<sub>4</sub>SCN led to a decrease in the yield of the desired product (Table 1, entries 8–10). To establish the versatility of the protocol, the scope of the reaction was examined using different alkynyl substrates and the

**Table 2** Synthesis of pyrrole-fused naphthoquinone via NH<sub>4</sub>OAc-promoted intramolecular cyclization<sup>a,b</sup>



**Table 1** Optimization of reaction conditions for pyrrole-fused naphthoquinone synthesis<sup>a</sup>

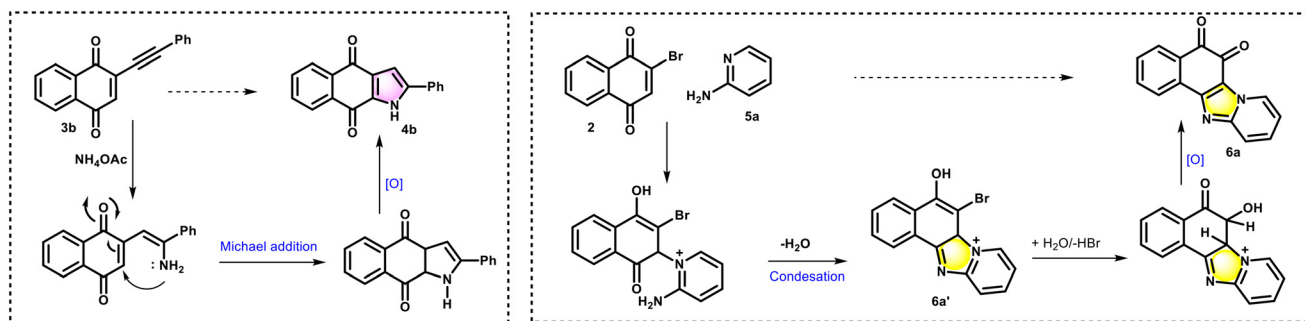
Entry	Medium	Additive	Temp. (°C)	Time	Yield <sup>b</sup> (%)
1	CH <sub>3</sub> CN	NH <sub>4</sub> Cl	Reflux	8 h	Trace
2	THF	NH <sub>4</sub> PF <sub>6</sub>	Reflux	8 h	Trace
3	CH <sub>2</sub> Cl <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	Reflux	8 h	21
4	CH <sub>2</sub> Cl <sub>2</sub>	NH <sub>4</sub> OAc	Reflux	8 h	25
5	MeOH	(NH <sub>4</sub> ) <sub>2</sub> CO <sub>3</sub>	40 °C	4 h	81
6	MeOH	NH <sub>3</sub> (1 : 1)	40 °C	4 h	80
7	<b>MeOH</b>	<b>NH<sub>4</sub>OAc</b>	<b>40 °C</b>	<b>30 min</b>	<b>93</b>
8	MeOH	Urea	Reflux	8 h	25
9	MeOH	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	Reflux	8 h	Trace
10	MeOH	NH <sub>4</sub> SCN	Reflux	8 h	Trace

<sup>a</sup> Reaction conditions: **3a** (1 mmol), additive (3 mmol), solvent (5 mL), stirred at the specified temperature for the required duration. <sup>b</sup> Yield refers to isolated yield.

<sup>a</sup> Reaction conditions: **3** (1 mmol), NH<sub>4</sub>OAc (3 mmol), MeOH (5 mL) at 40 °C. <sup>b</sup> Isolated yields of compounds characterized by <sup>1</sup>H and <sup>13</sup>C NMR and HRMS.







Scheme 3 Proposed mechanism.

results are summarised in Table 2. The reaction proceeded smoothly with both electron-donating and -withdrawing substituents (Table 2). Even halogen-substituted and alkyl-alkynyl substrates furnished the corresponding desired products in moderate to good yields (Table 2 compounds **4e**, **4g** and **4i**).

The structures of the new molecules were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectral analysis (see the ESI $^\dagger$ ). The formation of pyrrolonaphthoquinone derivatives could be explained by the nucleophilic addition of  $\text{NH}_3$  to the alkyne, followed by intramolecular Michael addition and subsequent oxidation to yield the desired molecule **4b** (Scheme 3). Our designed molecule is analogous to the core structure of the natural product utahmycin B. In addition to  $\text{NH}_4\text{OAc}$ -mediated synthesis towards pyrrolonaphthoquinones, we have also developed a method for the synthesis of benzimidazolequinones (Table 3). Herein, 2-aminopyridine **5b** reacts with 2-bromo-1,4-naphthoquinone **2** under solvent-free conditions in the presence of catalytic amounts of AcOH to afford benzimidazolequinone **6b** (Table 3, entry 10). Screening of other solvents such as acetonitrile, THF, and DCM gave trace

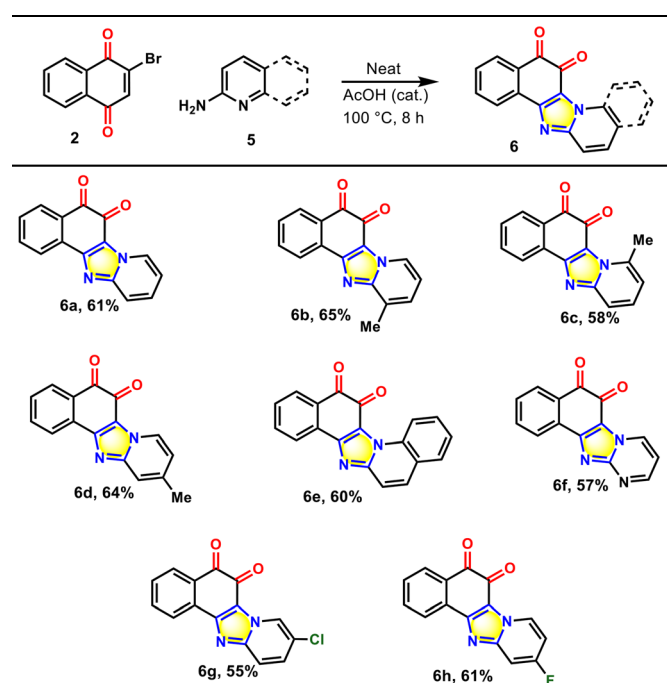
amounts of the product under reflux conditions in the presence of CuI (Table 3, entries 1–3); however, polar solvents such as DMF, MeOH, *n*-butanol and ethoxyethanol furnished moderate product yields (Table 3, entries 4–7). Moreover, the use of AcOH in ethoxyethanol (entry 8) under neat conditions in the presence of CuI afforded **6b** in moderate yield (entry 9). The reaction can be explained *via* the attack of the nucleophilic pyridyl nitrogen on the bromonaphthoquinone scaffold through a Michael addition followed by intramolecular cyclization of the carbonyl and amine, affording **6a'**, which then undergoes hydrolysis followed by air oxidation to give the desired product **6a** (Scheme 3).

The applicability of this protocol was explored using different 2-aminopyridine derivatives and the results are summarized in Table 4 (compounds **6a–6h**). A variety of tetracyclic

Table 3 Optimization of the reaction conditions<sup>a</sup>

Entry	Medium	Catalyst	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
1	$\text{CH}_3\text{CN}$	CuI	Reflux	12	Trace
2	THF	CuI	Reflux	12	Trace
3	$\text{CH}_2\text{Cl}_2$	CuI	Reflux	12	21
4	DMF	CuI	90	12	40
5	MeOH	CuI	Reflux	8	43
6	<i>n</i> -Butanol	CuI	110 °C	12	60
7	Ethoxyethanol	CuI	Reflux	12	53
8	Ethoxyethanol	AcOH	Reflux	12	62
9	Neat	CuI	100 °C	12	62
10	Neat	AcOH	100 °C	8	65

<sup>a</sup> Reaction conditions: **2** (1 mmol), **5** (1.1 mmol), AcOH (cat. amount), under neat conditions, heated in a preheated oil bath maintained at 100 °C for 8 h. <sup>b</sup> Yield refers to isolated yields of pure products characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and HRMS.

Table 4 Substrate scope for the synthesis of imidazopyridinedione<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **2** (1 mmol), **5b** (1.1 mmol), catalyst, solvent (5 mL), heated in a preheated oil bath maintained at the specified temperature for the required time period. <sup>b</sup> Yield refers to isolated yield.

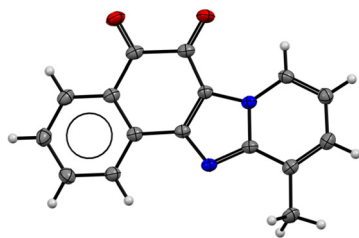


Fig. 2 ORTEP view of compound **6b** (CCDC 2431475†) drawn at 50% ellipsoidal probability.

and pentacyclic nitrogen-bridged imidazopyridine/imidazoquinoline fused *o*-quinones were furnished. The structures of the molecules were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, 2D NMR and mass spectral analysis (see the ESI†). Single crystal X-ray analysis unambiguously confirmed the polycyclic framework of **6b** (Fig. 2).

### Biological studies

To investigate the biological properties of naphthoquinone fused pyrrole derivatives, we selected **4f**, one of the synthesized compounds (Table 2), as the model compound, as **4f** showed the lowest minimum inhibitory concentration (MIC) against the tested microorganisms *S. aureus* and *E. coli* (ESI Table S3†).

#### Assessment of antimicrobial activity

**Determination of minimum inhibitory concentration (MIC).** We determined the antimicrobial activity of the compound by broth dilution assay. The compound in DMSO (70%, v/v %) at a concentration of  $5\text{ mg mL}^{-1}$  was used as the working stock solution. Cultures of *E. coli* and *S. aureus* were incubated with different concentrations of the compound separately for 24 h, and then the optical density (OD) at 600 nm was recorded. The lowest concentration of the compound that can inhibit bacterial growth after a specified incubation period was determined as the MIC value of the compound against a specific bacterial species.<sup>21</sup> ESI Fig. S1A and Table S3,† show the MIC values of the compound against *S. aureus* and *E. coli*. The results showed that the compound has potent antimicrobial activity against *S. aureus* with a MIC value of  $120\text{ }\mu\text{g mL}^{-1}$  compared to *E. coli* (MIC =  $200\text{ }\mu\text{g mL}^{-1}$ ) (see Fig. S1A†). Later, we determined the minimum bactericidal concentration (MBC) of the compound against *S. aureus* and *E. coli*.

The value of the MBC was found to be  $180\text{ }\mu\text{g mL}^{-1}$  and  $260\text{ }\mu\text{g mL}^{-1}$  for *S. aureus* and *E. coli*, respectively. We further intended to determine the MBC/MIC ratio of the compound against each tested microorganism to determine whether the compound is exhibiting bactericidal or bacteriostatic actions against them.<sup>19d</sup> Notably, the value of the MBC/MIC ratio was 1.5 and 1.3 for *S. aureus* and *E. coli*, respectively, which confirms that the compound exhibited bactericidal activity against the tested microorganisms; this activity is stronger against *S. aureus* than *E. coli*. The DMSO solvent concentration used in the experiments showed no antimicrobial activity.

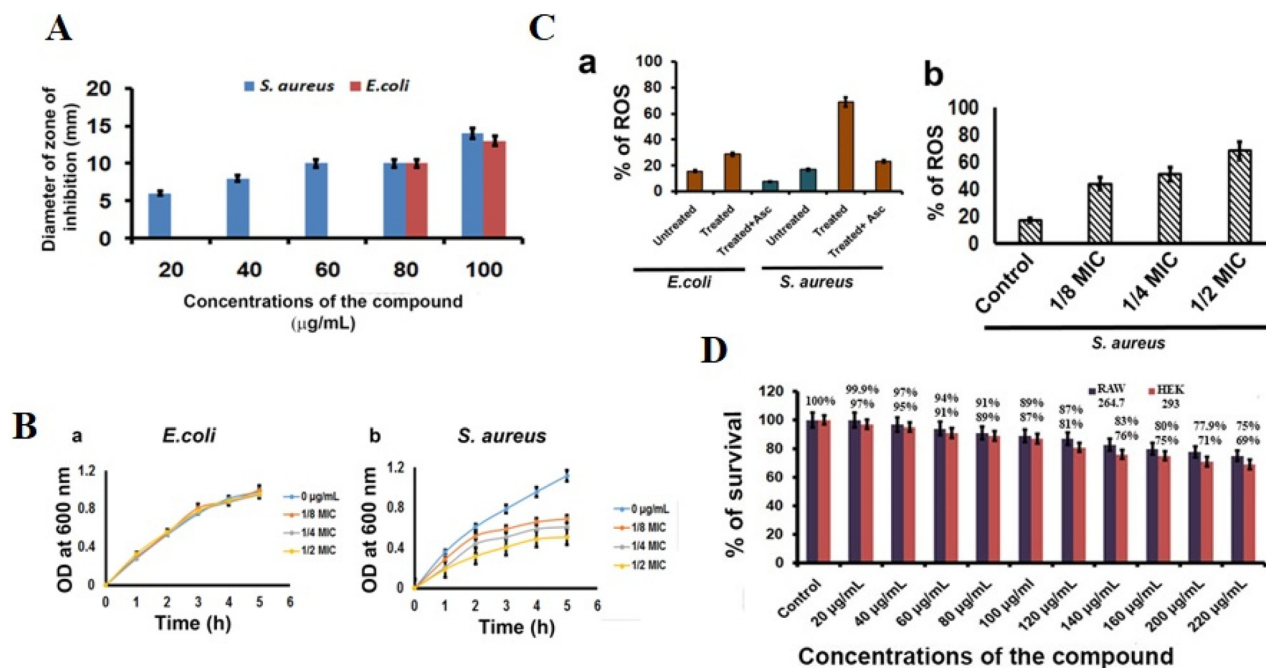
**Determination of zone of inhibition by agar diffusion assay.** To further substantiate our results, we also tested the antimicrobial activity of the compound against *S. aureus* and *E. coli* separately in solid media using the agar diffusion assay. To determine this, different concentrations of the compound were added into wells on microbial lawns followed by incubation at  $37\text{ }^\circ\text{C}$  for 24 h. A clear zone appears due to the growth inhibition of sensitive microorganisms (see ESI Fig. S1B†). The diameter of the clear zone around the wells was measured and presented as a histogram (Fig. S1A†). It was found that the compound exhibits a strong antimicrobial response against the Gram-positive bacteria *S. aureus* at lower concentrations while a similar inhibitory effect at higher concentrations was observed both for Gram-positive (*S. aureus*) and negative (*E. coli*) bacteria (see ESI Fig. S1B† and Fig. 3A). Notably, where  $60\text{ }\mu\text{g mL}^{-1}$  concentrations of the compound failed to produce any zone of inhibition in the *E. coli* plate, the same concentration produced a 10 mm zone in *S. aureus*, which must be considered as typical manifestation of selective antimicrobial effects (Fig. S1B† and Fig. 3A). From these two results, we can preliminarily conclude that the compound exhibited more promising antimicrobial action against Gram-positive bacteria than Gram-negative bacteria.

**Compound 4f treated *S. aureus* cell show reduced growth:** To further validate our results, we examined the effect of different sub-MIC doses of the compound on the growth kinetics of *S. aureus* and *E. coli* cells. For this, we compared the growth profile of the two bacterial species separately after treatment with different sub-MIC doses of the compound (1/8 MIC, 1/4 MIC, and 1/2 MIC). One set served as the untreated control. Aliquots of the microbial culture were collected aseptically from each set at regular intervals and the absorbance was measured at 600 nm.

The results demonstrated that there was no significant difference in the growth profiles of treated and untreated sets of *E. coli* cells (Panel A, Fig. 3B); in contrast, it was observed that *S. aureus* cells showed concentration-dependent growth inhibition (Panel B, Fig. 3B). Nearly 50% growth inhibition was observed after treatment with 1/2 MIC ( $60\text{ }\mu\text{g mL}^{-1}$ ) of the compound (compare Panel A with B, Fig. 3B). Collective data confirmed that the compound exhibited better antimicrobial efficacy towards *S. aureus* than *E. coli*. Thus, from these results, we can conclude the compound is more active towards Gram-positive bacteria compared to Gram-negative ones.

**Tested concentrations of the compound induce ROS (reactive oxygen species) accumulation in bacterial cells.** To determine the mechanism of bactericidal activity, we made efforts to determine whether the bacterial cells accumulate ROS (reactive oxygen species) upon exposure to the compound. Intracellular ROS accumulation is one of the important mechanisms leading to bacterial cell death.<sup>22</sup> The results showed there is a considerable difference in the intracellular ROS production in *S. aureus* cells treated with the compound compared to untreated cells at their corresponding 1/2 MIC value (Panel A, Fig. 3C). On the other hand, very little difference was observed in treated and untreated sets of *E. coli* cells (Panel A,





**Fig. 3** (A) Measurement of the zone of inhibition from agar diffusion assay: diameter of the zone of inhibition (mm) measured for *Staphylococcus aureus* (■) and *E. coli* (■) from agar diffusion assay. (B) Growth curve analysis: *S. aureus* and *E. coli* were grown in media supplemented with the compound at their corresponding 1/8, 1/4, and 1/2 MIC doses, and growth was determined by measuring optical densities (OD) at 600 nm over different time periods. Error bars indicate standard deviation ( $\pm$ SD). (C) Intracellular ROS measurement assay: percentage of ROS produced by *S. aureus* (a) and *E. coli* (b) was measured after treatment with 1/2 MIC of the compound for 12 h at 37 °C. One set served as the untreated control. Ascorbic acid (Asc) was used as a ROS quencher (Panel C (a)). Gradual augmentation of ROS production by *S. aureus* cells after treatment with the compound in a concentration-dependent manner. (D) Effect of the compound on mammalian cell lines: RAW 264.7 macrophage cells and human kidney epithelial cells (HEK 293) were treated with indicated concentrations of the compound and the percentage of survival of cells was measured. Cell survival in the untreated control (0) set was considered 100%. Each column with an error bar represents the average  $\pm$  SD.

Fig. 3C). Notably, the result also revealed that with the gradual increase in the concentration of the tested compound, the intracellular ROS level of *S. aureus* increased (Panel B, Fig. 3C). Thus, the result of the ROS assay confirmed that the tested concentrations (1/8, 1/4 and 1/2 MIC) of the compound can elevate intracellular ROS in the tested microorganisms, which can be considered as one of the causes of bactericidal activity of the compound. To gain further confidence, compound **4f**-mediated ROS generation in bacteria was further confirmed using the well-known ROS quencher ascorbic acid (Fig. 3c, Panel A).

## Conclusion

We have demonstrated a new straightforward methodology for the synthesis of various pyrrolonaphthoquinone derivatives *via* a unique cyclization between alkynynaphthoquinone and ammonium acetate. We have also developed a synthetic route to obtain imidazopyridinedione derivatives *via* an unprecedented cyclization reaction. The compounds were characterized precisely by  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , and HRMS. Additionally, the potential role of these types of molecules as antimicrobial agents against *S. aureus* and *E. coli* was established using **4f** as the model compound. Surprisingly, this molecule exhibited

low cytotoxicity against two mammalian cell lines: RAW 264.7 (murine macrophages) and human kidney epithelial cell (HEK 293). We anticipate that these molecules will exhibit significant medicinal properties due to the co-existence of both naphthoquinone and pyrrole pharmacophores.

## Experimental data

### Procedure for the preparation of 2-bromonaphthalene-1,4-dione (2)

1.45 g (5 mmol) of 1-naphthol was mixed with 7.12 g (20 mmol) of *N*-bromosuccinamide (NBS) in 50 mL glacial acetic acid and 100 mL water in a 500 mL round-bottom flask. The reaction mixture was then stirred for 45 minutes at 50 °C. The progress of the reaction was monitored by TLC, in comparison with the starting material. The product formed was extracted with ethyl acetate and water. It was purified by column chromatography with petroleum ether and ethyl acetate (20 : 1, v/v) as eluent.

### Preparation of 2-(*p*-tolylethynyl)naphthalene-1,4-dione (3)

2-Bromo-1,4-naphthoquinone **2** (0.92 mmol, 220 mg) and phenylacetylene (0.143 g, 1.4 mmol, 1.5 equiv.) were mixed with CuI (19 mg, 0.1 mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (35 mg, 0.05 mmol) catalyst in 10 mL THF. Diisopropylamine (0.281 g,



2.78 mmol, 3 eq.) was added gradually in portions to the reaction mixture at 0 °C and stirred for 45 minutes. The progress of the reaction was monitored by TLC. The product formed was extracted in diethyl ether/ethyl acetate and water with the addition of 10 mL 1N HCl. The crude product was purified by column chromatography with petroleum ether and ethyl acetate (10 : 1, v/v) as eluent to obtain the desired product.

#### General procedure for the preparation of pyrrole-fused naphthoquinone derivatives (4)

2-(*p*-Tolylethynyl)naphthalene-1,4-dione (1 mmol) **3** was stirred with NH<sub>4</sub>OAc (3 mmol) in 5 mL MeOH for 30 minutes at 40 °C. The reaction was monitored by TLC. The product formed was extracted with diethyl ether and the extract was evaporate under reduced pressure using a rotary evaporator to obtain the crude product, which was further purified by column chromatography with hexane and ethyl acetate (1 : 1, v/v) as eluent to obtain the desired product.

#### General procedure for the preparation of imidazopyridinedione derivatives (6)

2-Bromo-1,4-naphthoquinone **2** (0.63 mmol, 0.150 g) and 2-aminopyridine (0.071 g, 0.75 mmol) were taken in a round-bottom flask and were heated at 100 °C in the presence of a catalytic amount of AcOH (5 mol%) for 8 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). The crude product was purified directly by column chromatography using silica gel as the stationary phase with ethyl acetate and chloroform (1 : 4, v/v) as eluent.

## Author contributions

All authors have read and agreed to the published version of the manuscript. RNS and VM performed the experiments, and SA collected the data related to the crystal structure. SC collected the data related to the biological study. SKM and RD analyzed the data. SKM, SC, TB, and RD drafted the manuscript, and supervised, reviewed, and edited the text.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data that support the findings of this study are available within the article and the ESI.†

## Acknowledgements

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