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Research Article

# HALOGEN FREE $[HNMP]^+CH_3SO_3^-$ IONIC LIQUID MEDIATED BIFUNCTIONALIZED NAPHTHOQUINONE-DIHYDROPYRIMIDIN-(1H)-ONE HYBRIDS AND EVALUATION OF ITS ANTIMICROBIAL POTENTIAL

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## ABSTRACT

An efficient halogen free ionic liquid (HFIL) *N*-methyl-2-pyrrolidonium methane sulfonate $[HNMP]^+[CH_3SO_3]^-$ catalyzed Biginelli reaction is reported to synthesize naphthoquinone fused dihydropyrimidin-(1H)-ones (DHPM's). Diversifying this naphthoquinone constituent provides an access to new and interesting DHPM's for pharmacological profiling. A series of bifunctionalized naphthoquinone-dihydropyrimidin-(1H)-one conjugates (**4a-4l**) were synthesized and evaluated for their antimicrobial potential against selected bacterial and fungal pathogenic strains. The resulting naphthoquinone fused dihydropyrimidin-(1H)-one hybrids showed significant activities against all the tested Gram positive (*Staphylococcus aureus, Bacillus subtilis*) and Gram negative (*Escherichia coli, Pseudomonas aeruginosa*) bacterial pathogens and fungal strains of *Aspergillus niger* and *Aspergillus flavus*. Among the series, the DHPM conjugate **4k>4j>4e>4h** samples exhibited highest activities against all the tested strains that proved to be important candidates in the drug development against various life threatening diseases. Presently, one-pot, three-component methodology have been developed for the synthesis of bifunctionalized naphthoquinone linked dihydropyrimidin-(1H)-one are being explored for bio-active asymmetric Biginelli scaffolds.

**Keywords:** 3,4-dihydropyrimidin-2(1H)-ones, Naphthoquinone, Lawsone, Halogen Free Ionic Liquid (HFIL), Antimicrobial.

## 1. INTRODUCTION

The Italian chemist Pietro Biginelli reported, in 1893, Biginelli reaction is a multiple-component one-pot acid catalyzed cyclocondensation chemical reaction that resulted 3,4-dihydropyrimidin-2-(1H)-ones (DHPM's) from easily-accessible starting materials, namely, active methylene compound, an aryl aldehyde, and urea or Thiourea [1]. DHPM and related compounds have attracted considerable attention because of their important pharmacological and biological properties created renewal interest of the scientific community in recent year [2, 3]. It has been reported that 3,4-dihydropyrimidine-2(1H)-ones have prominent biological activities such as anti-tumour [4, 5], anti-viral [6, 7], anti-bacterial [8], anti-diabetic [9], antimalarial [10], anti-fungal [11] and anti-oxidant properties [12]. Moreover, other biological activities of the dihydropyrimidinone/thione moiety constitutes an active backbone in exciting medications, e.g., Mona-strol (anti-cancer agent) [13], SQ 32926, and SQ 32547 (anti-hypertensive drugs) [14, 15] shown in **fig. 1**.

Naphthoquinone (NQ) to a large extent have use in the synthesis of heterocyclic intermediates, medicinal and industrial applications as drugs [16, 17]. A large number

of naphthoquinone compounds occur naturally as plant constituents, and in the past many of these have found use as colorants and medicinal purposes. The two most important representatives for natural colorants with naphthoquinone structure are Lawsone (2-hydroxy-1, 4-naphthoquinone) and juglone (5-hydroxy-1,4-naphthoquinone). The naturally occurring 2-hydroxy-1, 4-naphthoquinone is a mono-hydroxyl naphthoquinone pigment extracted from henna plant [18, 19]. Lawsone is a special naphthoquinone one of the most important natural scaffold useful for many applications in various scientific and technological fields [20, 21]. For over 4000 years or more, Lawsone was used as a dye hair, skin (including body art) [22, 23], as well as in many interesting pharmacological activities such as anti-bacterial, anti-fungal [24, 25], anti-inflammatory [26], anti-viral [27], antioxidant [28], anti-tumor, anti-malarial, anti-proliferative, anti-inflammatory, anti-protozoal, anti-trypanosomiasis, and anti-topoisomerase activities, in addition to treatment of skin diseases and a coloring agent for wool and silk [29-33]. Naphthoquinone's are utilized in the synthesis of polyfunctionalized heterocyclic compounds have been noted as naturally occurring antibiotics, antibacterial, fungicidal, antimalarial, anti-parasitic and anti-tumor agents [34-37] shown in **fig. 2**.

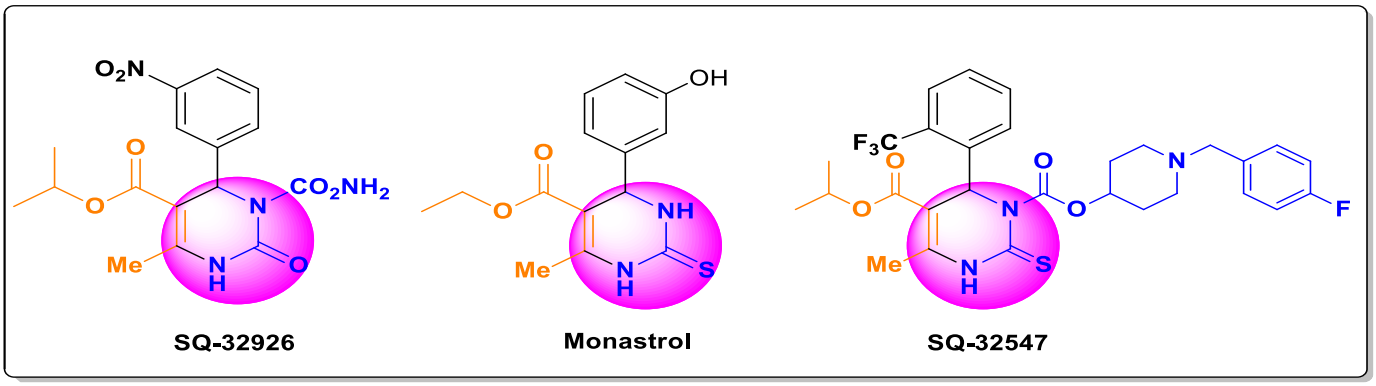



**Fig. 1: Biological active DHPM scaffold of Monastrol, SQ-32926, and SQ-32547**

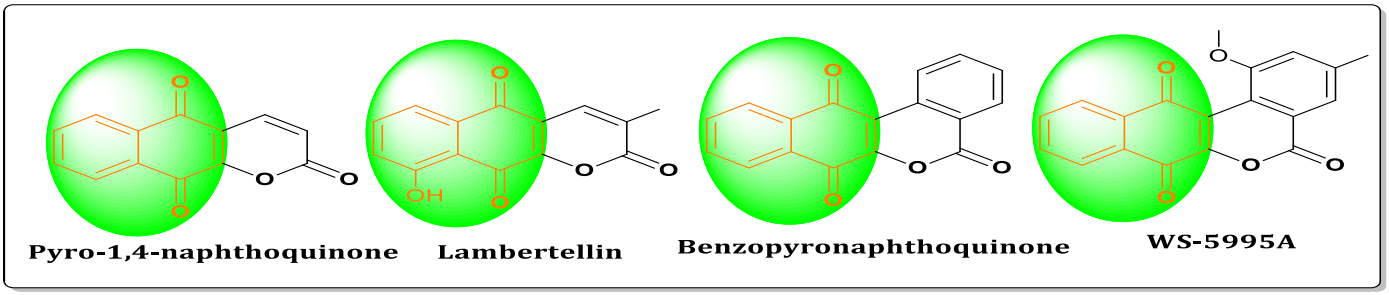
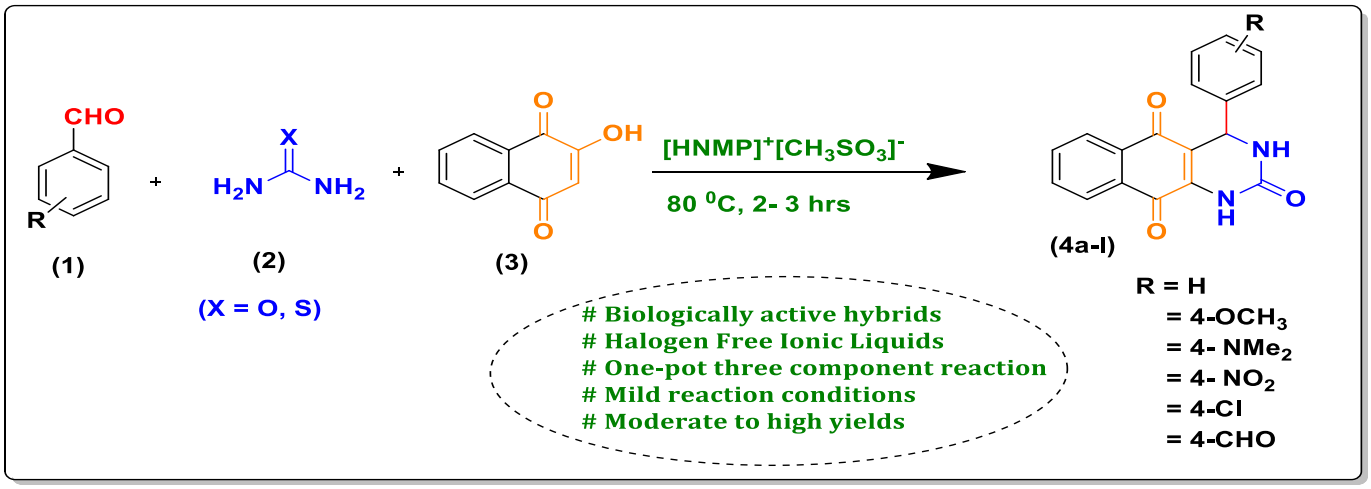



**Fig. 2: Naphthoquinone fused biological active heterocycle**

Keeping this point in view, in order to consideration of DHPM and naphthoquinone derivatives diverse pharmacological significance and their potentiality, we have designed and synthesized bifunctionalized naphthoquinone-dihydropyrimidin-(1H)-one hybrids. Our previous work summarizes the synthesis of Biginelli scaffolds 4-phenyl-3,4-dihydrobenzo [h] quinazoline-2,5,10(1H)-trione in presence of halogen free ionic liquid (HFIL) *N*-methyl-2-pyrrolidonium hydrogen sulfate $[HNMP]^{+}[HSO_4]^{-}$. The resulted DHPM skeleton derived from Lawsone showed good tinctorial strength and dyeing properties on the fabrics [38]. The National Cancer Institute (NIH, United State) admitted the lawsone skeleton that contain the quinone moiety as a precursor for clinically as cytotoxic activity [1]. Benzo[g]quinonline-5, 10-dione and benzo [g] quinazoline-5, 10-dione skeletons are important pharmacophoric elements for cytotoxic activity and anticancer activity [39]. In order to consideration of its diverse pharmacological profile and their capabilities, we have extended our previous research work in the synthesis of diverse biologically relevant naphtha-

quinone fused 3, 4-dihydropyrimidin-2(1H)-ones in presence of HFIL $[HNMP]^+[CH_3SO_3]^-$. The present research article accounts dealing with the pharmacological properties and uses in medicine of naphthoquinone fused 3, 4-dihydropyrimidin-2(1H)-one hybrids (**Scheme 1**). Herein, green approaches towards asymmetric Biginelli reaction are being explored for bioactive chiral bifunctionalized naphthaquinone-dihydropyrimidin-(1H)-one hybrids.




**Scheme 1: Halogen Free Brønsted acid ionic liquid catalyzed Biginelli reaction for synthesis of DHMP conjugates 4a-4l**

## 2. EXPERIMENTAL

### 2.1. Material and instruments

The materials and solvents used in the present work were pure and laboratory prepared. All the commercial chemical reagents and spectroscopic grade solvents were procured from S.D. Fine chemicals private limited Mumbai. The solvents and reagents were used as received without further purification. The reactions were monitored on silica gel aluminum-based plates kisel gel 60 F254 Merck, India. The melting points were determined by using standard melting-point apparatus and are uncorrected. The reaction was monitored by TLC using 0.25-mm E-Merck silica-gel 60 F254 precoated plates, which were visualized with ultraviolet light. Infrared (IR) spectra were recorded on a Perkin Elmer 100 FT-IR spectrophotometer. The $^1H$ NMR spectra were recorded at a Bruker 400 (400 MHz) spectrometer with TMS as the internal standard. Mass spectra were recorded on a mass spectrometer operating at 70 eV.

### 2.2. Antimicrobial studies

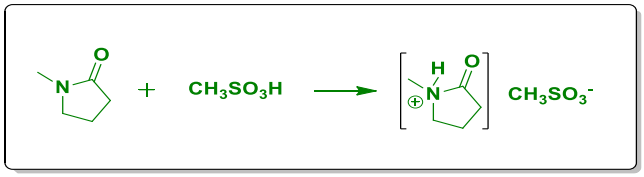
The Naphthoquinone-DHPM conjugates (**4a-4l**) synthesized above were evaluated for their antibacterial and antifungal activities against various pathogenic bacterial and fungal strains. The pure cultures of Gram positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacterial pathogens and fungal strains of *Aspergillus niger* and *Aspergillus flavus* were obtained from Department of Microbiology, R. C. Patel Arts, Commerce and Science College, Shirpur, India. The bacterial cultures were maintained on Mueller-Hinton agar slants and fungal cultures were maintained on Czapec dox agar slants at 4°C. The well diffusion method was employed for the evaluation of antimicrobial activities of test compounds (**4a-4l**) [40]. The solvent DMSO was used as the negative control. The microbial strains were rejuvenated from stock cultures by transferring into Mueller-Hinton and Czapec dox broths and incubated at 37°C for 24 h. The sterile plates of Mueller-Hinton agar and Czapec dox agar were prepared by using routine microbiological techniques. The wells of 5 mm diameter were prepared by using sterile cork borer. The bacterial and fungal strains were spread on sterile nutrient medium plates using spread plate technique [41]. Then, 50 µl of the test compounds in two different concentrations (25 and 50 µg/ml) were added into the separate wells along with negative control of DMSO. The plates of antibacterial activities were incubated at 37°C for 24 h, whereas the plates of antifungal activities were incubated at 37°C for 48 h.

Upon incubation, the plates were observed for the formation of zone of inhibition around the wells. All the experiments were performed in triplicates.

### 2.3. Experimental Procedure

#### 2.3.1. *Preparation of halogen free ionic liquid N-methyl-2-pyrrolidonium methane sulfonate [HNMP]$^+$[CH$_3$SO$_3$]$^-$*

*N*-Methyl-2-pyrrolidone (10 mmol) was charged into a 250 ml three necked flask with magnetic stirrer. Then equimolar concentrated methane sulfonic acid was added dropwise slowly into the flask and then mixture heated at 80°C for 2 h. The mixture was washed with ether three times to remove non-ionic residues and dried in vacuum by a rotary evaporator to obtain the viscous clear [HNMP]$^+$[$CH_3SO_3$]$^-$ **(Scheme 2).**




**Scheme 2: Synthesis of HFIL N-methyl-2-pyrrolidonium methane sulfonate**

#### 2.3.2. *Preparation of 4-phenyl-3, 4-dihydrobenzo [g] quinazoline-2,5,10(1H)-trione derivatives*

The mixture of aryl aldehyde (10 mmol), urea/thiourea (10 mmol), and 2-hydroxy-1, 4-napthaquinone (Lawsone) in presence of Brønsted acid ionic liquid [HNMP]$^+$[$CH_3SO_3$]$^-$ (10 ml) was stirred and heated at 80°C for 2-3 hrs. The mixture became solid at the end of reaction; product was crushed and poured into crushed ice and stir for 15-20 min. The crude product was isolated by filtration and that further purified by recrystallisation with hot aqueous ethanol to afford pure DHPM derivatives. The combined aqueous filtrate was heated at 80°C under reduced pressure (10 mmHg) to leave behind the ionic liquid in near complete recovery, pure enough to recycle. The recovered ionic liquid mixture was found to be equally effective for at least four recycles in the synthesis of DHPMs.

#### 2.3.3. *Spectral data for the representative molecules of Naphthoquinone-DHPM conjugates*

*2.3.3.1. 4-Phenyl-3, 4-dihydrobenzo[g]quinazoline-2, 5, 10 (1H)-trione (4a)*

Yellow powder; yield = 95%; melting point = 202-204°C. FT-IR (KBr) cm$^{-1}$ = 3398, 3349, 3110, 2980, 1668, 1636, 1571, 1533, 1358, 1277, 950; $^1$H-NMR (500 MHz, $CDCl_3$) = δ/ppm 8.1 (4H, m), 8.5 (3H, m), 8.9 (2H, dd), 7.2 (1H, s), 6.2 (2H, s); $^{13}$C-NMR (126 MHz, $CDCl_3$) = δ/ppm δ 54.22, 123.43, 126.71, 128.54, 129.45, 132.28, 142.49, 147.94, 178.37, 181.76; MS (ESI)m/z calcd for C18H12N2O3 = 304.29, found: 305.23 [M$^+$+H]; UV-Vis: λmax (nm) [ε (M$^{-1}$cm$^{-1}$)] 490 (19456.912) in DMF.

*2.3.3.2. 4-(2-Methoxyphenyl)-3, 4-dihydrobenzo [g] quinazoline-2, 5, 10(1H)-trione (4b)*

Yellow powder; yield = 90%; melting point = 172-174°C. FT-IR (KBr) cm$^{-1}$ = 3228, 3092, 2978, 1726, 1682, 1509, 1460, 1290, 868; $^1$H-NMR (500 MHz, $CDCl_3$) = δ/ppm 8.304-7.762 (8H, m), 5.15 (2H, s), 6.10 (1H, s), 3.31 (3H, s); $^{13}$C-NMR (126 MHz, $CDCl_3$) = δ/ppm 45.84, 57.03, 114.27, 120.87, 126.74, 127.76, 135.09, 149.25, 179.28, 184.15; MS (ESI)m/z calcd for C19H14N2O4: 334.07, found: 335.36 [M$^+$+H]; UV-Vis: λmax (nm) [ε (M$^{-1}$cm$^{-1}$)] 472 (12418.788) in DMF.

*2.3.3.3. 4, 4'-(1, 4-Phenylene)bis(3, 4-dihydrobenzo [g] quinazoline-2, 5, 10 (1H)-trione) (4f)*

Yellow powder; yield = 94%; melting point = > 300°C. FT-IR (KBr) cm$^{-1}$ =3420, 3246, 3102, 2980, 1698, 1644, 1457, 1284, 1083, 773; $^1$H-NMR (500 MHz, $CDCl_3$) = δ/ppm 8.0-7.8 (4H, m), 7.8-7.4 (4H, m), 7.4-6.7 (4H, dd), 6.1 (4H, s), 5.2 (2H, s); $^{13}$C-NMR (126 MHz, $CDCl_3$) = δ/ppm 50.04, 121.04, 126.83, 134.14, 138.38, 151.67, 178.43, 184.34; MS (ESI)m/z calcd for C30H18N4O6: 530.49, found: 531.26 [M$^+$+H]; UV-Vis: λmax (nm) [ε (M$^{-1}$cm$^{-1}$)] 460 (43991.06) in DMF.

## 3. RESULTS AND DISCUSSION

### 3.1. Chemistry

We are interested in studying Biginelli reaction with the aim to develop an operationally simple method for the synthesis of a large range of DHPMs. We started our study of the one-pot three-component Biginelli reaction examined by substituted benzaldehyde **1** was subjected to Brønsted acid ionic liquid catalyzed with Lawsone **2** and urea/thiourea **3** as co-reactants (**Scheme 1**). The corresponding resulting naphtha-quinone linked dihydropyrimidin-(1H)-one hybrids (**4a-4l**) in excellent yields shown in **Chart 1**. The mechanistic path way of the reaction can be explained on the basis of recent systemic study on reaction mechanism of multi component reactions.

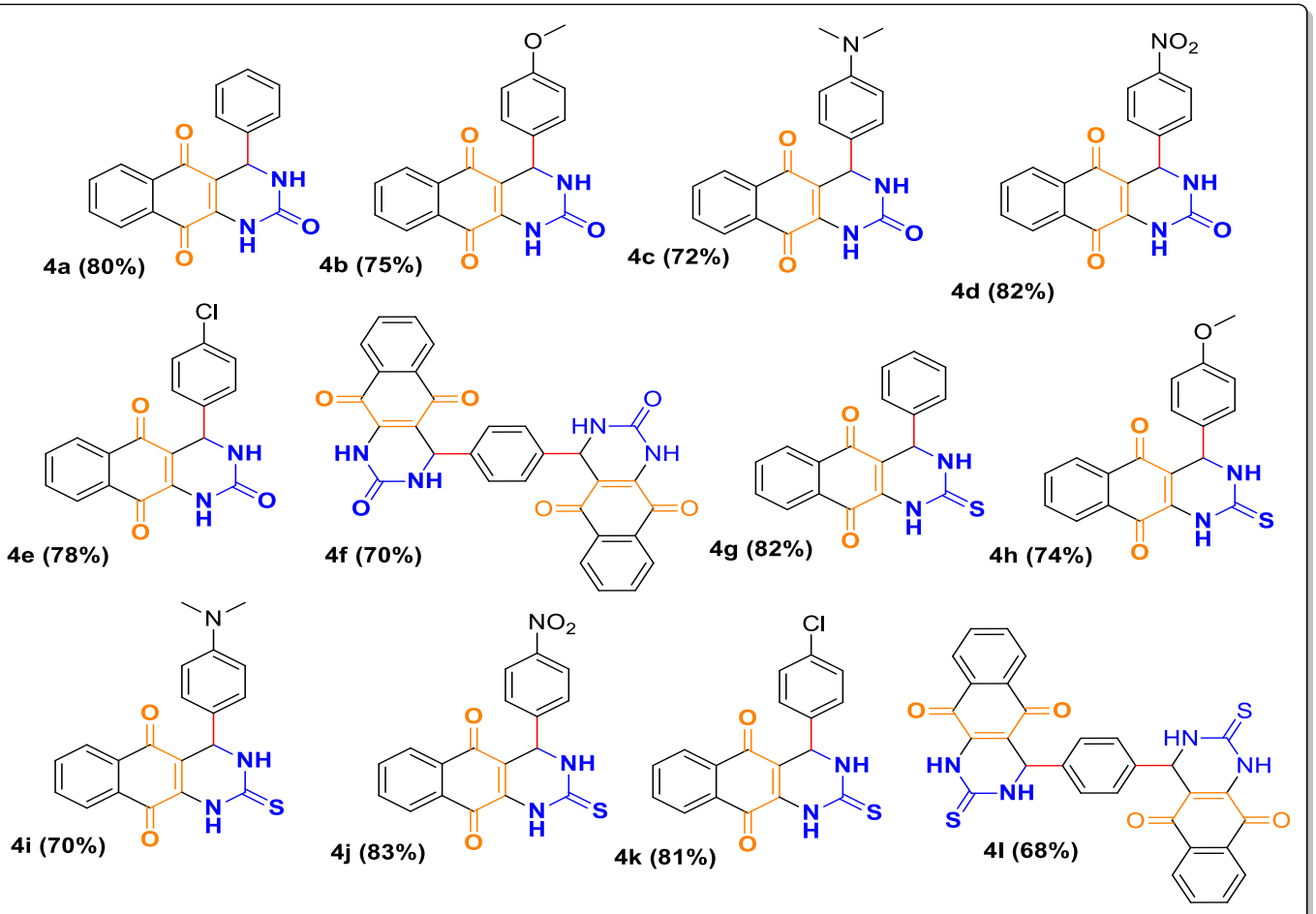



**Chart 1:** Bifunctionalized naphthoquinone - DHPM conjugates (**4a-l**).

### 3.2. Antimicrobial activity

The *in vitro* antimicrobial activities of bifunctionalized Naphthoquinone-DHPM conjugates (**4a-4l**) were studied by the well diffusion method against the Gram positive (*Staphylococcus aureus, Bacillus subtilis*) and Gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacterial pathogens and fungal strains of *Aspergillus niger* and *Aspergillus flavus*. The antimicrobial activities of these compounds were measured as the zone of inhibition around the well. The test compound under investigation interferes with the growth and reproduction of microbial cell that leads to the inhibition of growth of microbes around the well; hence the zone of inhibition appeared. The zones of inhibition for the test compounds (**4a-4l**) are depicted in **table 1.** These results revealed a strong antimicrobial potential of compounds under investigation against the selected strains of bacteria and fungi. The conjugate **4k** showed maximum zone of inhibition against all the selected strains of bacteria and fungi that indicated its extra potential to kill or inhibit the growth of various pathogenic microbes. The compounds **4j>4e>4h** also showed the significant antimicrobial activity against all the tested strains. These conjugates can serve as the potential candidates for the development of potent drugs against various human diseases. Other conjugates (**4a, 4b, 4c, 4d, 4f, 4g, 4i, 4l**) were also showed moderate activities against all the tested bacterial and fungal strains. The antimicrobial activities of conjugates (**4a-4l**) against bacterial pathogens (*S. aureus, B. subtilis, E. coli and P. aeruginosa*) and fungal pathogens (*A. niger and A. flavus*) at 25 µg/ml (blue) and 50 µg/ml (red) concentrations showed in **fig.3** and **fig.4** respectively. The compounds **(4k, 4j,** and **4h**) containing -Cl, -$NO_2$, -OMe and thione substituents, whereas compound **4e** contains -Cl and dione substituents/ chemical groups respectively that showed more potent antimicrobial activity against the bacterial and fungal strains. These results signpost towards the major role of **-Cl** and **thione** constituent in the inhibition of microbial growth around the well by leaving the clear zone of inhibition (no growth).

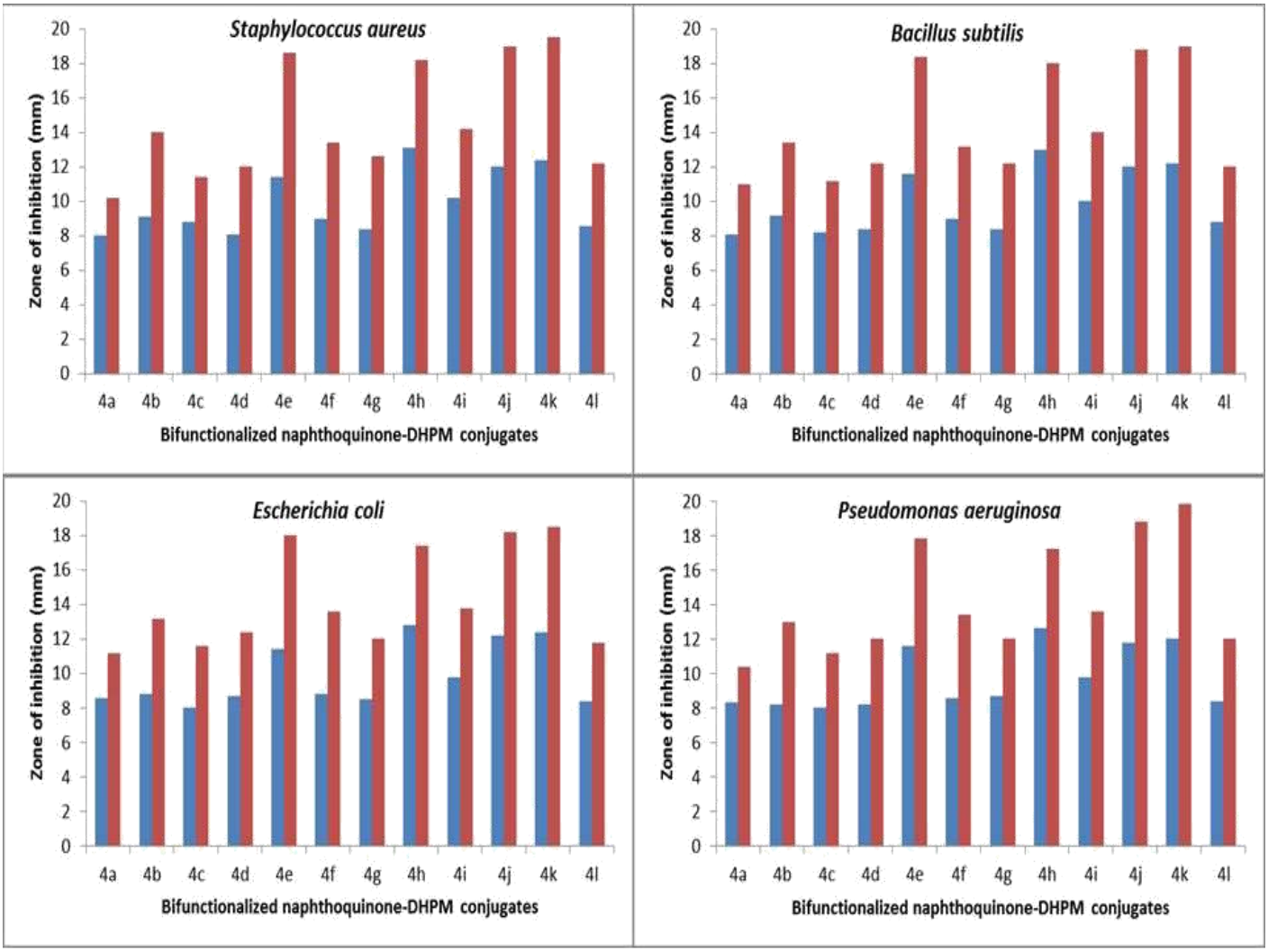



**Fig. 3: Antimicrobial activities of bifunctionalized Naphthoquinone-DHPM conjugates (4a-4l) against bacterial pathogens (*S. aureus, B. subtilis, E. coli* and *P. aeruginosa*) at 25 µg/ml (blue) and 50 µg/ml (red) concentrations**

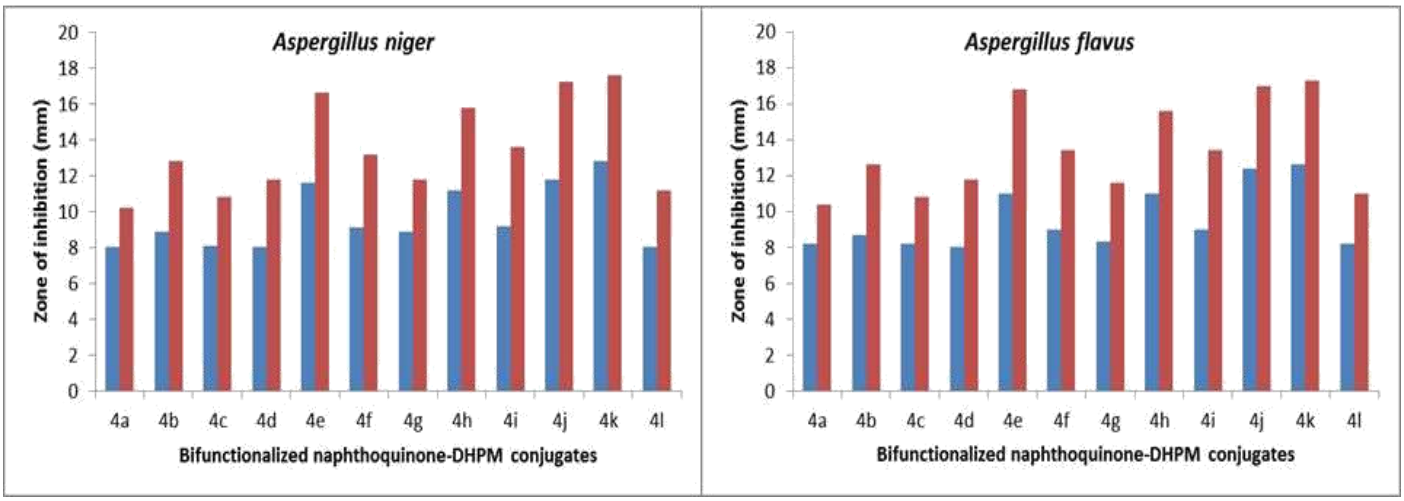



**Fig. 4: Antimicrobial activities of bifunctionalized Naphthoquinone-DHPM conjugates (4a-4l) against fungal pathogens (*A. niger* and *A. flavus*) at 25 µg/ml (blue) and 50 µg/ml (red) concentrations**

**Table 1: Zones of inhibition of bifunctionalized naphthoquinone-DHPM conjugates (4a-4l) against selected bacterial and fungal pathogens**

| Compound | Conc. (µg/ml) | Zone of inhibition (mm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | *S.aureus* | *B. subtilis* | *E.coli* | *P. aeruginosa* | *A. niger* | *A. flavus* |
| **4a** | 25 | 8.0 | 8.1 | 8.6 | 8.3 | 8.0 | 8.2 |
| | 50 | 10.2 | 11.0 | 11.2 | 10.4 | 10.2 | 10.4 |
| **4b** | 25 | 9.1 | 9.2 | 8.8 | 8.2 | 8.9 | 8.7 |
| | 50 | 14.0 | 13.4 | 13.2 | 13.0 | 12.8 | 12.6 |
| **4c** | 25 | 8.8 | 8.2 | 8.0 | 8.0 | 8.1 | 8.2 |
| | 50 | 11.4 | 11.2 | 11.6 | 11.2 | 10.8 | 10.8 |
| **4d** | 25 | 8.1 | 8.4 | 8.7 | 8.2 | 8.0 | 8.0 |
| | 50 | 12.0 | 12.2 | 12.4 | 12.0 | 11.8 | 11.8 |
| **4e** | 25 | 11.4 | 11.6 | 11.4 | 11.6 | 11.6 | 11.0 |
| | 50 | **18.6** | **18.4** | **18.0** | **17.8** | **16.6** | **16.8** |
| **4f** | 25 | 9.0 | 9.0 | 8.8 | 8.6 | 9.1 | 9.0 |
| | 50 | 13.4 | 13.2 | 13.6 | 13.4 | 13.2 | 13.4 |
| **4g** | 25 | 8.4 | 8.4 | 8.5 | 8.7 | 8.9 | 8.3 |
| | 50 | 12.6 | 12.2 | 12.0 | 12.0 | 11.8 | 11.6 |
| **4h** | 25 | 13.1 | 13.0 | 12.8 | 12.6 | 11.2 | 11.0 |
| | 50 | **18.2** | **18.0** | **17.4** | **17.2** | **15.8** | **15.6** |
| **4i** | 25 | 10.2 | 10.0 | 9.8 | 9.8 | 9.2 | 9.0 |
| | 50 | 14.2 | 14.0 | 13.8 | 13.6 | 13.6 | 13.4 |
| **4j** | 25 | 12.0 | 12.0 | 12.2 | 11.8 | 11.8 | 12.4 |
| | 50 | **19.0** | **18.8** | **18.2** | **18.8** | **17.2** | **17.0** |
| **4k** | 25 | 12.4 | 12.2 | 12.4 | 12.0 | 12.8 | 12.6 |
| | 50 | **19.5** | **19.0** | **18.5** | **19.8** | **17.6** | **17.3** |
| **4l** | 25 | 8.6 | 8.8 | 8.4 | 8.4 | 8.0 | 8.2 |
| | 50 | 12.2 | 12.0 | 11.8 | 12.0 | 11.2 | 11.0 |

## 4. CONCLUSION

The present research work involved the synthesis of naphthoquinone fused dihydropyrimidin-(1H)-one hybrids (**4a-4l**) to explore their antimicrobial activity. We have described an expedient and convergent four-component domino protocol for the regioselective synthesis of a library of naphthoquinone fused dihydropyrimidin-(1H)-one hybrids (**4a-4l**) in good yields from readily available simple starting materials. The naphthoquinone fused dihydropyrimidin-(1H)- one derivatives have been synthesized in presence of halogen free ionic liquid *viz*. *N*-methyl-2-pyrrolidonium methane sulfonate $\{[HNMP]^+ [CH_3SO_3]^-\}$as solvents-catalysts under conventional heating. Further, the synthesized derivatives have been explored for their antimicrobial activity. The synthesized compounds (**4a-4l**) displayed proficient antimicrobial properties against selected Gram positive bacteria (*S. aureus*, *B. subtilis*), Gram negative bacteria (*E. coli, P. aeruginosa*) and fungal strains of *A. niger* and *A. flavus*. The maximum antimicrobial activity was showed by **4k>4j>4e>4h** conjugates against all the selected microbial pathogens. The naphthoquinone fused DHPM having the wide range of medicinal applications. Hence, it is concluded that there is ample scope for further study in developing these conjugates as the lead compounds for the treatment of bacterial as well as fungal diseases. For the welfare of mankind further evaluation needs to be carried out in order to explore the practical clinical applications of naphthoquinone fused DHPMs.

## 5. ACKNOWLEDGEMENT

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### *Conflict of interests*

The authors declare no conflict of interest.

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