

# Synthesis and Antimicrobial Activity of 1,4-Naphthoquinones Derivatives with [1,2,4]-Triazole-3-thione Substitution

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## Shakh, *et al.*: Synthesis and Antimicrobial Property Investigation of 1,4-Naphthoquinone Derivatives

The aim of the work was the synthesis of new S-, N-containing heterocyclic naphthoquinone derivatives and evaluation of antimicrobial activity, which is important in terms of finding new drugs. The implementation of this approach can be made by nucleophilic substitution between N, S-bifunctional heterylaminothiotriazoles 2,3 and 2,3-dichloro-1,4-naphthoquinone 1. So the reaction between 2,3-dichloro-1,4-naphthoquinones and 4-amino-5-(2-methyl-furan-3-yl)-2,4-dihydro-[1,2,4]triazole-3-thione was investigated. It was established that the use of dimethylformamide as the reaction medium leads to the formation of two products with dominating yield of S-substitution products. Investigation of antimicrobial activity of the synthesized compounds showed that cultures of *Escherichia coli*, *Aspergillus niger* and *Candida tenuis* are not sensitive to 1,4-naphthoquinone heterocyclic derivatives 4, 5, 6, 7. But compounds 5, 7 showed antibacterial activity with respect to *Staphylococcus aureus* and *Mycobacterium luteum*.

**Key words:** 1,4-naphthoquinones, nucleophilic substitution, antimicrobial activity

Synthesis of new S-, N-containing heterocyclic molecules is important in terms of searching new biologically active substances. In particular, compounds with quinone moiety in their structure, show a wide range of pharmacological activity namely antibacterial, antifungal, anticancer etc.<sup>[1-4]</sup>. The most interesting is the synthesis of compounds with antitumor activity as selective inhibitors of biological targets, epidermal growth factor receptor (EGFR), apoptosis regulator (Bcl-2), induced myeloid leukaemia cell differentiation protein (Mcl-1) and others. Derivatives of quinone-containing compounds have been described as potential anticancer agents in several publications<sup>[2,5]</sup>. In some articles it was shown the synthesis and study of

antibacterial and antifungal activity series of N- and N, S-derivatives of 2,3-dichloro-1,4-naphthoquinone<sup>[6,7]</sup>. Therefore, nowadays the search and expansion of combinatorial number of compounds are necessary for further synthesis of derivatives and their biological screening.

All the chemicals were purchased from Sigma-Aldrich (USA) and were used without further purification. The

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Accepted 11 June 2017  
Revised 18 February 2017  
Received 22 October 2016  
Indian J Pharm Sci 2017;79(4):650-654

reactions were monitored by pre-coated aluminium silica gel 60F<sub>254</sub> thin layer plates (thin layer chromatography (TLC) analysis) procured from Merck (Germany). Melting points (m.p.) were determined using an SRS-EZ-Melt automated melting point instrument without correction. Infrared (IR) spectrums were recorded on a Specord-80M spectrophotometer in potassium bromide pellets. The nuclear magnetic resonance (<sup>1</sup>H-NMR and <sup>13</sup>C-NMR) spectra of the compounds were recorded in deuterated dimethyl sulfoxide (DMSO-d<sub>6</sub>) with Varian VXR (300 MHz) NMR spectrometer and chemical shifts were expressed in δ parts per million (ppm). Shifts reported are relative to the signal of the solvent used in each case and coupling constants are reported in Hz (s: singlet, bs: broad singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet).

The procedure for the synthesis of heterocyclic derivatives of 1,4-quinones is as follows. To 0.59 g (0.0026 mol) of 2,3-dichloro-1,4-naphthoquinone 1 in 10 ml of toluene was added 0.51 g (0.0026 mol) 2 in the presence of equivalent amount of triethylamine (Et<sub>3</sub>N). The reaction mass was heated to 80° and stirred for 4 h (the reaction was monitored by TLC analysis). The precipitate was filtered off and recrystallized in dimethylformamide (DMF)/ethanol (EtOH).

2-chloro-3- {[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino} naphthalene-1,4-dione (4): yield 89%; m.p. 163-164°; Anal. calc for (C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>3</sub>S), %: C=52.79, H=2.87, Cl=9.17, N=14.48, S=8.29; found: C=52.75, H=2.91, Cl=9.14, N=14.51, S=8.32. IR (KBr), cm<sup>-1</sup>: 3224, 3180, 1650 (NH), 1720, 1680 (C=O), 1450 (C=S), 720 (C-Cl). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ, ppm: 9.76 (bs, 1H, NH); 8.43 (s, 1H, NH); 8.04-7.74 (m, 4H, HAr); 7.68 (d, 1H, J=2.0 Hz); 6.62 (d, 1H, J=2.0 Hz); 2.52 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO) δ: 12.7, 108.3, 110.1, 112.2, 119.2, 125.9, 126.7, 131.3, 131.6, 132.5, 132.7, 134.4, 140.5, 147.3, 154.8, 167.0, 175.4, 176.4.

2-Chloro-3- {[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino} naphthalene-1,4-dione (6): yield 81%; m.p. 181-182°; Anal. calc for (C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>3</sub>S), %: C=52.79, H=2.87, Cl=9.17, N=14.48, S=8.29; found: C=52.75, H=2.91, Cl=9.18, N=14.50, S=8.30. IR (KBr), cm<sup>-1</sup>: 3210, 3090, 1657 (NH), 1749, 1698 (C=O), 1455 (C=S), 708 (C-Cl). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ, ppm: 9.79 (bs, 1H, NH); 8.41 (s, 1H, NH); 7.98-7.76 (m, 4H, HAr); 7.70 (d, 1H, J=2.0 Hz); 6.63 (d, 1H, J=2.0 Hz); 2.29 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO) δ: 11.34, 116.3, 124.0,

126.3, 127.2, 130.7, 131.0, 131.3, 134.1, 134.6, 140.3, 142.7, 147.0, 151.7, 176.5, 180.1.

Heterocyclic derivatives of 1,4-quinones were synthesized by the following procedure. To 0.59 g (0.0026 mol) 1 in 10 ml of EtOH was added 0.51 g (0.0026 mol) 2 and an equivalent amount of K<sub>2</sub>CO<sub>3</sub>. The reaction mass was heated to 40° and stirred for 4 h (the reaction was monitored by TLC analysis). The precipitate was filtered off and recrystallized in DMF/EtOH.

2- {[4-Amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-3-chloronaphthalene-1,4-dione (5): yield 78%; m.p. 145-146°; Anal. calc for (C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>3</sub>S), %: C=52.79, H=2.87, Cl=9.17, N=14.48, S=8.29; found: C=52.82, H=2.86, Cl=9.16, N=14.45, S=8.24. IR (KBr), cm<sup>-1</sup>: 3550, 3475 (NH<sub>2</sub>), 1655 (NH), 1730, 1690 (C=O), 710 (C-Cl). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ, ppm: 8.12-8.00 (m, 2H, HAr); 7.85-7.79 (m, 2H, HAr); 7.74 (d, 1H, J=2.0 Hz); 6.67 (d, 1H, J=2.0 Hz); 6.27 (s, 2H, NH<sub>2</sub>); 2.54 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO) δ: 12.5, 106.5, 110.5, 112.2, 125.7, 125.9, 131.3, 131.5, 132.7, 133.8, 140.5, 147.0, 155.7, 167.0, 174.3, 175.3.

2- {[4-Amino-5-(3-methylfuran-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-3-chloronaphthalene-1,4-dione (7): Yield 71%; m.p. 153-154°; Anal. calc for (C<sub>17</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>3</sub>S), %: C=52.79, H=2.87, Cl=9.17, N=14.48, S=8.29; found: C=52.83, H=2.86, Cl=9.16, N=14.45, S=8.25. IR (KBr), cm<sup>-1</sup>: 3545, 3480 (NH<sub>2</sub>), 1651 (NH), 1720, 1680 (C=O), 715 (C-Cl). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ, ppm: 8.12-7.98 (m, 2H, HAr); 7.87-7.71 (m, 2H, HAr); 7.72 (d, 1H, J=2.0 Hz); 6.65 (d, 1H, J=2.0 Hz); 6.24 (s, 2H, NH<sub>2</sub>); 2.23 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO) δ: 11.34, 116.3, 124.0, 126.3, 127.2, 130.7, 131.0, 134.4, 134.2, 134.6, 140.3, 142.7, 147.0, 151.7, 176.5, 180.1.

The synthesized compounds were evaluated for antibacterial and antifungal activity against *Escherichia coli* B-906, *Staphylococcus aureus* 209-P, *Mycobacterium luteum* B-917, *Candida tenuis* VKM Y-70 and *Aspergillus niger* VKM F-1119 strains by the agar diffusion method<sup>[8]</sup>. Their activity was compared to that of the known antibacterial agent, vancomycin and the antifungal agent nystatin.

Antimicrobial and antifungal activity has been studied by diffusion in agar on solid nutrient medium (beef-extract agar for bacteria, wort agar for fungi). Petri plates containing 20 ml of nutrient medium were used for all the microorganisms that were tested. The

inoculums (the microbial loading  $10^9$  cells (spores)/ 1 ml) was spread on the surface of the solidified media and Whatman no.1 filter paper discs (6 mm in diameter) impregnated with the test compound (0.1 and 0.5%) were placed on the plates. The duration of bacteria incubation was 24 h at  $35^\circ$  and of fungi incubation 48-72 h at  $28-30^\circ$ <sup>[6]</sup>. The antimicrobial effect and degree of activity of the tested compounds were evaluated by measuring the zone diameters (Table 1). Control disk contained vancomycin (for bacteria) or nystatin (for fungi) as a standard. Every experiment was repeated three times.

All analyses were carried out in triplicate, and results are reported as the mean  $\pm$  standard deviation (SD). Significant differences were analysed by one-way ANOVA. Differences at  $P < 0.05$  were considered statistically significant.

In this communication, the synthesis of a number of new condensed heterocyclic derivatives of quinone compounds has been attempted. The implementation of this approach could be carried out by appropriate interaction of N,S-bifunctional heterylaminothiotriazoles (2, 3) and 2,3-dichloro-1,4-naphthoquinone (1) (fig. 1). Carrying out the interaction of quinone 1 with 4-amino-5-(2-methyl-furan-3-yl)-2,4-dihydro- [1,2,4] triazole-3-thione 2 in the presence of  $\text{Na}_2\text{CO}_3$  as the base at  $30-40^\circ$  in DMF for 4 h showed that the reaction takes place

with the formation of N-nucleophilic substitution product, namely 2-chloro-3-[3-(2-methyl-furan-3-yl)-5-thioxo-1,5-dihydro-[1,2,4]triazol-4-ylamino]-[1,4] naphthoquinone (4) and S-substitution product -2-[4-amino-5-(2-methyl-furan-3-yl)-4H-[1,2,4]-triazol-3-ylsulfanyl]-3-chloro-[1,4]-naphthoquinone (5) with 35 and 43% yield, respectively.

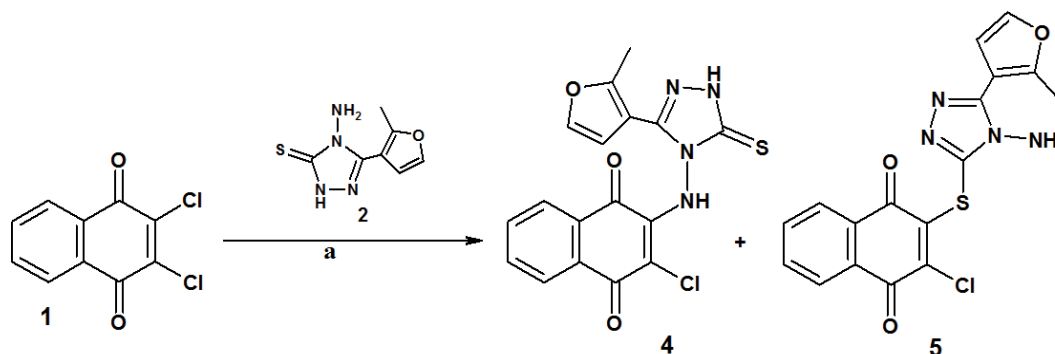
It can be explained by the nature of selected bifunctional heterylaminothiotriazoles, for which thione-thiol tautomerism is inherent. So, in neutral solvents thione tautomeric form was dominant and in alkaline solutions, thiole was dominant<sup>[9-11]</sup>. Thereby, by selecting reaction conditions, products of N-nucleophilic substitution and S-replacement of chlorine atom can be obtained in high yields, respectively.

The optimization of the reaction conditions was carried out in following solvents namely dioxane, EtOH, MeOH, toluene, benzene using a number of bases ( $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{Et}_3\text{N}$ ), at different temperatures and times of reactions (Table 2). Depending on the reaction conditions different ratio of products N- and S-substitution of chlorine atom there were obtained. While carrying out the interactions in DMF medium during 4 h highest yields were detected using as a base  $\text{K}_2\text{CO}_3$ . The highest yield of S-nucleophilic substitution product 5 (89%) was obtained using  $\text{K}_2\text{CO}_3$  at  $40^\circ$  in EtOH during 4 h. In other turn, the highest yield of N-nucleophilic substitution product 4 (78%) was received using  $\text{Et}_3\text{N}$ , at  $80^\circ$  in toluene during 4 h.

Thus, the analysis of the results of investigation allowed us to obtain selective products of N-nucleophilic substitution 4, 6 to 2,3-dichloro-1,4-naphthoquinone 1 in toluene was added 2 or 3 in the presence of  $\text{Et}_3\text{N}$ . The reaction mass was heated and maintained at  $80^\circ$  for 4 h. The precipitate was filtered off and recrystallized

**TABLE 1: EVALUATION OF RESULTS BY THE METHOD OF COMPOUND DIFFUSION IN AGAR**

| Diameter of zone of inhibition (mm) | Degree of microorganism sensitivity |
|-------------------------------------|-------------------------------------|
| 11-15                               | Low sensitive                       |
| 16-25                               | Sensitive                           |
| >25                                 | Highly sensitive                    |



**Fig. 1: Synthetic protocol of the reaction between 1,4-naphthoquinone and 4-amino-5-(2-methyl-furan-3-yl)-2,4-dihydro-[1,2,4] triazole-3-thione**

(a) DMF,  $\text{Na}_2\text{CO}_3$ ,  $30-40^\circ$ , 4 h. (1) 2,3-dichloro-1,4-naphthoquinone; (4) 2-chloro-3-[3-(2-methyl-furan-3-yl)-5-thioxo-1,5-dihydro-[1,2,4]triazol-4-ylamino]-[1,4] naphthoquinone; (5) 2-[4-amino-5-(2-methyl-furan-3-yl)-4H-[1,2,4]-triazol-3-ylsulfanyl]-3-chloro-[1,4]-naphthoquinone

and, respectively, S-substitution of chlorine atom 5, 7 to 2,3-dichloro-1,4-naphthoquinone 1 in EtOH was added 2 or 3 and an equivalent amount of  $K_2CO_3$ . The reaction mass was heated and maintained at 40° for 2 h. The precipitate was filtered off and recrystallized. It is reflected in the fig. 2.

It was established that the substitution of chlorine atom in the 2,3-dichloro-1,4-naphthoquinone 1 by 4-amino-5-(heteryl)-2,4-dihydro-[1,2,4]triazole-3-thione 2, 3 is controlled using the reaction conditions. So, in aprotic solvents there were identified only products of N-acylation, on the other hand, in alcohols, the products of S-acylation were obtained in high yields.

Antibacterial and antifungal activity of S,N-containing derivatives of quinones has been studied in our laboratory previously<sup>[12,13]</sup>. Depending on the substituent, the results of antimicrobial activity of synthesized compounds differed in the degree of

influence on bacteria and fungi. Analysing the data of investigations, it can be summarized that products of monosubstitution of 2,3-dichloro-1,4-naphthoquinone possess higher activity than disubstituted ones.

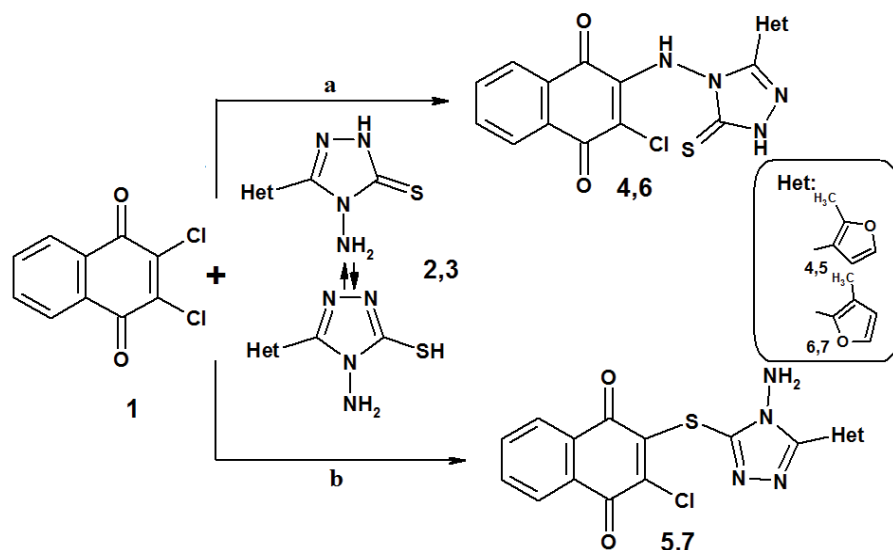
Piperazine-, morpholin, thio-, *tert*-butyl-4-hydroxyphenyl substituted naphthoquinones have been already tested on strains of bacteria such as *E. coli*, *S. aureus*, *M. luteum*, and fungi, *C. tenuis* and *A. niger*. Based on the previous research it was interesting for us to synthesize compounds that combine in one molecule bifunctional heterylaminotriazoles and naphthoquinone moiety, and then to study their antimicrobial activity.

The synthesized compounds, 4, 5, 6, 7 were evaluated for antibacterial and antifungal activity. Results of estimate diameter of microorganism growth inhibition zones according to the parameters were listed in Table 3. Antimicrobial activity data analysis of

**TABLE 2: OPTIMIZATION OF REACTION BETWEEN 1,4-NAPHTHOQUINONE AND 4-AMINO-5-(2-METHYL-FURAN-3-YL)-2,4-DIHYDRO-[1,2,4] TRIAZOLE-3-THIONE**

| Solvent  | Base       | Temperature (°) | Time (h) | Yield, %       |                |
|----------|------------|-----------------|----------|----------------|----------------|
|          |            |                 |          | N-substitution | S-substitution |
| DMF      | $K_2CO_3$  | 30-40           | 4        | 28             | 57             |
| DMF      | $Na_2CO_3$ | 30-40           | 4        | 35             | 43             |
| Dioxane  | $K_2CO_3$  | 40              | 4        | 0              | 69             |
| Dioxane  | $Na_2CO_3$ | 40              | 4        | 0              | 62             |
| Ethanol  | $K_2CO_3$  | 40              | 4        | 0              | 89             |
| Ethanol  | $Na_2CO_3$ | 40              | 4        | 0              | 77             |
| Methanol | $K_2CO_3$  | 40              | 4        | 0              | 71             |
| Methanol | $Na_2CO_3$ | 40              | 4        | 0              | 63             |
| Toluene  | $Et_3N$    | 50              | 4        | 78             | 0              |
| Benzene  | $Et_3N$    | 80              | 4        | 65             | 0              |

DMF: dimethylformamide



**Fig. 2: Synthetic protocol for preparation of 1,4-naphthoquinone derivatives 4-6**  
(a) Toluene,  $NEt_3$ , 80°, 4 h; (b) EtOH,  $K_2CO_3$ , 40°, 4 h

**TABLE 3: ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY OF INVESTIGATED COMPOUNDS BY AGAR DIFFUSION METHOD**

| Comp. | Diameter of the zones of microbial growth inhibition, mm; Mean±SD |         |                  |           |                  |                     |                  |           |                 |           |
|-------|---|---------|------------------|-----------|------------------|---------------------|------------------|-----------|-----------------|-----------|
|       | Antibacterial activity  |         |                  |           |                  | Antifungal activity |                  |           |                 |           |
|       | <i>E. coli</i>  |         | <i>S. aureus</i> |           | <i>M. luteum</i> |                     | <i>C. tenuis</i> |           | <i>A. niger</i> |           |
|       | 0.10%   | 0.50%   | 0.10%            | 0.50%     | 0.10%            | 0.50%               | 0.10%            | 0.50%     | 0.10%           | 0.50%     |
| 4     | 0   | 0       | 9.5±0.27         | 15.1±0.39 | 9.5±0.43         | 11.8±0.41           | 0                | 10.8±0.25 | 6.8±0.50        | 12.1±0.53 |
| 5     | 0   | 0       | 10.4±0.21        | 16.4±0.43 | 9.7±0.35         | 16.9±0.49           | 0                | 9.9±0.35  | 0               | 10.5±0.58 |
| 6     | 0   | 0       | 10.2±0.34        | 16.2±0.43 | 0                | 11.1±0.43           | 0                | 10.5±0.55 | 0               | 11.2±0.57 |
| 7     | 0   | 0       | 10.7±0.30        | 16.5±0.47 | 14.6±0.39        | 17.2±0.45           | 8.5±0.57         | 12.1±0.45 | 6.6±0.35        | 11.9±0.51 |
| C*    | 0   | 14±0.34 | 11.3±0.34        | 16.6±0.43 | 15.8±0.41        | 17.7±0.47           | 11.3±0.51        | 19.0±0.51 | 7.7±0.50        | 20.1±0.58 |

All analyses were carried out in triplicate, and results are reported as the mean±standard deviation (SD). C\*: vancomycin was used as a control in the tests of antibacterial activity of the synthesized compounds, and nystatin was used in the tests of antifungal activity

heterocyclic quinoid derivative series showed that studied microorganisms were predominantly insensitive to the synthesized derivatives. The compounds 4, 5, 6, 7 had good activity against *S. aureus* at a concentration of 0.1% and 0.5%. The strain *M. luteum* was most sensitive to compounds 5, 7 at a concentration of 0.5%. The compounds 4, 5, 6, 7 had low antibacterial activity against *C. tenuis* and *A. niger* and had no antibacterial activity against *E. coli* at 0.1 and 0.5% concentration evaluated by the diffusion method. The results obtained are presented in Table 3.

Optimized conditions of interaction showed that the reaction could be controlled in following ways. In aprotic solvents, only N-acylation products were obtained and in alcohols -S-acylation products that in general is a subject of Kornblum's rule. Investigation of antimicrobial activity of the synthesized compounds showed that cultures of *E. coli*, *A. niger* and *C. tenuis* are practically not sensitive to 1,4-naphthoquinone heterocyclic derivatives 4, 5, 6, 7, but showed medium to high activity value to *S. aureus* and *M. luteum*. Thus, compounds 5, 7 have found to possess high antibacterial activity with respect to these cultures.

#### Financial assistance:

None.

#### Conflict of interests:

None declared.

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