International Scholars Journals

African Journal of Chemistry ISSN 4391-3199 Vol. 6 (1), pp. 404-409, January, 2019. Available online at www.internationalscholarsjournals.org © International Scholars Journals



*Full Length Research Paper*

# Synthesis of some 2,5- diamino-3,6- dibromo - 1,4-benzoquinones

**A. E. M. Saeed[1]* and N. M. A. Omer [2]**

[1]Chemistry Department, College of Science, Sudan University of Science and Technology, P. O. Box 407 Khartoum , Sudan.

[2]Chemistry Department, Faculty of Science, University of Khartoum, P. O. Box 1996, Khartoum, Sudan.

Accepted 23 November, 2018

**A group of 19 compounds of the type 2,5-diamino-3,6-dibromo-1,4-benzoquinones were prepared and spectroscopically elucidated through IR ,UV-VIS, NMR and MS. Coupling of the intermediate 2,3,5,6-tetra bromo-benzoquinone with the required aryl amines furnished the required compounds. The prepared compounds were found to possess antimicrobial activities when tested against four standard bacterial organisms and two standard fungal organisms.**

**Key words:** *p*-quinones, synthesis, antimicrobial.

## INTRODUCTION

Quinones are wide spread in nature and many are of major industrial importance such as dyes, pigments and plant protection chemicals. Some quinones are related to more complicated aromatic systems which have been isolated from biological sources. In many cases, they seem to take part in oxidation reduction cycles as they have a vital role in electron transport in respiratory and photosynthetic elements (Pink et al., 2000; Ross et al., 2000) . Since quinones are alpha- beta - unsaturated cyclic diketones with both the oxygen atoms in simple or fused conjugated ring system, they are capable of forming 1,4- addition products. Compounds containing the thiol (SH) and amino ($NH_2$) groups react readily with quinones. These addition products are thought to be important in the inhibitory effects of quinones (Song and Jeon, 2003). *p*-Quinones were known to possess antitumor activity (long and Jaiswal, 2000), antimicrobial activity (Haraguchi, 1998) and antimalarial activity. Thio-phene ring containing quinones were reported to possess antiprotozoal activity against *Leishmania* and *Trypansoma cruize* (Valderrama et al., 1999). Alkylated hydroxy -1,4- Naphthoquinone were inhibitors of succinoxidase and NADH - oxidase (Porter et al. 1978). Hydroxy naphthoquinones inhibits parasite respiratory systems with outstanding efficacy against *Plasmodium* species (Hudson et al., 1985).

The present work reports the synthesis of some simple *p*-benzoquinone derivatives .The main objective of this work is to prepare a series of derivatives of *p*-benzo-qouinones. The basic ring was designed to be a 1,4-benzoquinone with additional derivatives as halogens. Selected amino compounds with intrinsic biological features were allowed to react with 2,3,5,6-tertabromo-1,4-benzoquinones to furnish the target 2,5- diarylamino-3,6-dibromo-1,4- benzoquinones (Scheme 1).

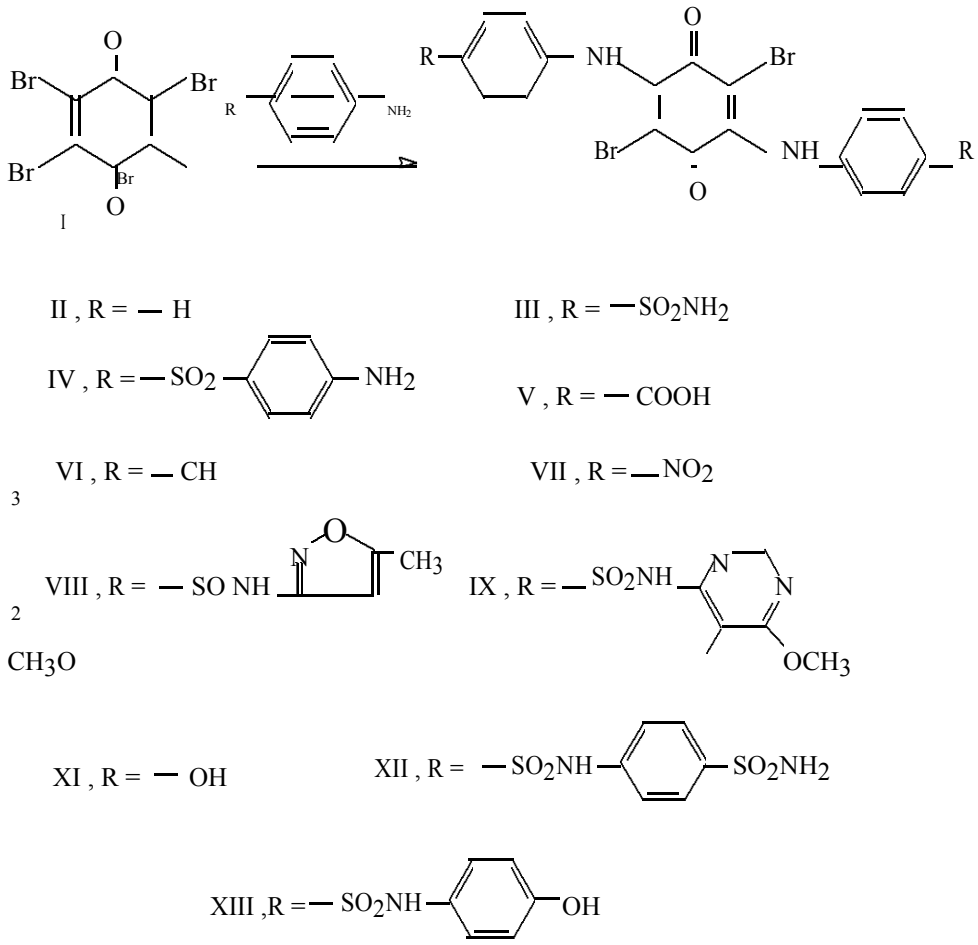
### Experimental

All chemicals and reagents were of general purpose reagent grade and were used without further purification. Melting points were uncorrected. Elemental analysis for C, H, N, S were within +/- 0.3%. IR analysis was carried out using Satellite FTIR. Spectrometer, Mattson instrument. UV/VIS was carried out using UV/VIS spectro-photometer; Jenway Model 6505. Mass spectra analysis was carried out using GC/MS model GP 5050A SHIMADZU GC-17A instrument. $^1$H- NMR analysis was carried out using JEOL ECP 400MHZ instrument. TLC was carried out with silica gel 60 GF254 (Merck, Germany) precoated plates, different mobile phases were attempted.

### Preparation of 2,3,5,6- tertrabromo-1,4-Benzoquinone (I)

To a stirred solution of hydroquinone (6 gm, 0.055 mole) in 60 ml glacial acetic acid was added 10 ml of concentrated nitric acid and the solution was further stirred for 30 min. Bromine (20 ml, 62 g,

*Corresponding author. E-mail: ahmedelsadig@yahoo.com



**Scheme 1.** Chemical structures of 2,5-diaminoaryl-3,6-dibromo-1,4-benzoquinones.

0.38.mole) was added over a period of 30 min. The reaction mixture was stirred at room temperature for one hour. The precipitated product was filtered and washed with cold water (Rec. GAA, Y = 93%, m.p. = 299 - 300°C, UV: max GAA 310.2.).

**General procedure for the preparation of 2,5-diamino -3,6-dibromo -1-4-benzoquinones (II-XX)**

To a well stirred solution of 2,3,5,6- tertrabromo-1,4-Benzoquinone (I) (0.106 g, 0.03 mole) in 2 ml EtOH, 2 ml GAA, 1 ml $H_2O$ and small amount of sodium acetate were added; the required amino compound (0.02 mole). The reaction mixture was refluxed for a period of 3 h and left overnight at room temperature. The precipitated product was filtered and recrystallized.

**2,5-di-anilino-3,6-di-bromo-1,4-benzoquinone (II)**

Y = 65%; Rec. = GAA; m.p = 225 - 257°C; IR =1625, 1599, 3230 and 1560 UV; max = THF, 278 and 298 nm.

**2,5-di-sulphanilamido-3,6-di-bromo-1,4- benzoquinone (III)**

Y= 56%; Rec.= GAA; m.p.= 279 - 280°C; IR = 1620, 1640, 1598, 3250, 3345, 1545, 1325 and 1130, $^1$HNMR= 7.00(4, d, J = 1.0 Hz); 6.69(4, d, J = 1.0 Hz), 9.58(2, s), 12.23 (4, s) MS = 306, 180, 264, 104, 281, 171, 156, 76, 608 and 606 UV: max = GAA , 289.8 nm.

**2,5-di-(4,4-di-amino-diphenyl-sulphone)-3,6-di-bromo-1,4-benzoquinone (IV)**

Y= 78%; Rec. = THF; m.p. = 288 - 290°C; IR = 1630, 1600, 3250, 3400, 1520, 1325, 1365, 1150, 1105; HNMR = 7.59 (4, d, J = 1.0 Hz), 6.67 (4, d, J = 1.0 Hz), 9.78 (2, s), 7.79 (4, d, J = 1.0 Hz) , 7.23 (4, d, J = 1.0 Hz); MS = 248, 76, 64, 80, 140 ,91, 700 and 758 UV: max = GAA,313.7nm.

**2,5-di-(p-carboxyl phenyl amino)-3,6-di-bromo-1,4-benzoquinone (V)**

Y = 94%; Rec. = GAA; m.p.= 275-278 $^0$C; 2 IR = 1670, 1600, 3250, 1540, 3450, MS = 264, 104, 281, 136, 121, 538 and 536 UV: max =GAA 230, 220 and 260 nm.

**2,5-di-(p-toludinyl)-3,6-di-bromo-1,4- benzoquinone (VI)**

Y = 46%; Rec. = THF; IR = 1630 – 1598 – 3225 - 1525, MS = 264, 104, 106, 91, 76, 131, 332, 478 and 476 UV: max = THF, 276.5 nm.

**2,5-di-(p-nitro-phenyl amino)-3,6-di-bromo-1,4- benzoquinone (VII)**

Y = 92%; Rec. = THF; m.p. = 217 - 218°C; IR = 1640, 1600, 3235, 1525, 1350 and 1550. HNMR = 8.21(4, d, J = 1.0 Hz), 7.27(4, d, J = 1.0 Hz), 9.74(2, s) MS = 264, 104, 138, 76, 91, 146, 131, 540 and 538 UV; max = THF 281 and 371.4 nm.

**2,5-di-(Sulphamethoxazolyl)-3,6-di-bromo-1,4- benzoquinone (VIII)**

Y = 53%; Rec. = THF; m.p. = 219 - 220°C; IR = 1660, 1585, 3560, 1522, 1350, 1150, MS = 104, 76, 83, 155, 771 and 769 UV: max =THF, 295.5 and 403.6 nm.

**2,5-di-(Sulphadoxinyl)-3,6-di-bromo-1,4- benzoquinone (IX)**

Y = 73%; Rec. = THF; m.p. = 268 - 270°C; IR = 1658, 1660, 3400, 3250, 1575, 1340, 1160. HNMR = 7.92(4, d, J = 1.0 Hz), 7.25(4, d, J = 1.0 Hz), 9.80 (2, s), 3.39(6, s), 8.14(2, s)., MS = 264, 104, 273, 76, 824 and 822 UV: max = THF, 310 nm.

**2,5-di-(o-hydroxy–p-carboxyl–phenylamino)-3,6-di-bromo-1,4-benzoquinone (X)**

Y = 85%; Rec. = GAA; m.p. = 189 - 190°C; IR = 1633, 1580, 3280, 1420, 3400. HNMR = 6.79 - 7.23(6, m.), 9.40 (2, s), 9.31 (2, s), 9.81 (2, s). MS = 264, 105, 104, 76, 548, 546 UV: max = GAA, 220 and 250 nm.

**2,5-di-(p-hydroxy phenyl amino)-3,6-di-bromo-1,4-benzoquinone (XI)**

Y = 96%; Rec. = GAA; m.p. = 246 - 248°C; IR = 1622, 1600, 3220, 1513 and 3400. HNMR = 7.27(4, d, J = 1.0Hz), 7.74(4, d, m, J =1.0Hz), 9.50 (2.s.), 9.79 (2, s,), MS = 131, 264, 104, 107, 93, 76, 426, 482 and 480 UV: max = GAA 220, 240 and 260 nm.

**2,5-di-4-(4-amino-benzene sulphonamido) benzene sulphonamide (XII)**

Y = 55%; Rec. = DMSO; m.p. =284 - 286°C; IR = 1670, 1600, 3250, 3350, 1500, 1325 and 1150 UV: max = 210, 230 and 250 nm.

**2,5-di-(4-amino benzene Suphanilamido)-benzene-4-amino-phenol)3,6-dibromo-1,4-benzoquinone (XIII)**

Y = 90%; Rec. = DMSO; m.p. = 255 - 256°C; IR = 1675 - 1580 - 3225 - 2920 -1500 - 3475; MS = 264, 104, 263, 76, 425, 172, 131, 792 and 790 UV: max =220 and 240 nm.

**2,5-di-(Trimethoprim)-3,6-di-bromo-1,4- benzoquinone (XIV)**

Y=83%; Rec. GAA; m.p. = 263 - 265°C; IR = 1662.79, 1633, 1593, 0543, 1553 and 1509 UV: max = THF, 271.4.

**2,5-di-(-4-amino-phenazone)-3,6-di-bromo-1,4- benzoquinone (XV)**

Y = 79%; Rec. = GAA; m.p. = 201 - 203°C; IR = 1633, 1514, 1514, 4300, 1514, HNMR = 7.21 - 6.94 (10, m), 9.65(2, s), 2.52(12, s,), MS = 264, 104, 426, 77 and 79 UV: max = GAA, 210 and 250 nm.

$^{1}$H NMR –H . 11.65, 2.52 (6, S, 2$CH_3$).

**2, 5-di-(methylamino)-3,6-di-bromo-1,4- benzoquinone (XVI)**

Y = 89%; Rec. = GAA; m.p. = 224 - 226°C; IR = 162 3, 1655, 3350 and 1550 UV: max =GAA, 220 and 250 nm.

**2,5-di-(diethylmino)-3,6-di-bromo-1,4- benzoquinone (XVII)**

Y=82%; Rec. = GAA; m.p. = 242 - 243°C; IR = 1628,1450,3200,1507, UV: max =GAA, 220, 240 and 280 nm.

**2,5-di-(dimethyamino)-3,6-di-bromo-1,4- benzoquinone (XVIII)**

Y=75%; Rec. = GAA; m.p. = 228 - 230°C; IR = 1625, 1660, 3347, 1550, MS = 264, 104, 281 UV: max = GAA, 230 and 310 nm.

**2,5-di-( -naphthylamino)-3,6-di-bromo-1,4-benzoquinone (XIX)**

Y = 62%; Rec. = GAA; m.p. = 212-213°C; IR = 1635, 1565, 3460 and 1520 UV: max = GAA, 240 nm.

**2,5-di-(N-methyl phenyl amino)-3,6-di-bromo-1,4-benzoquinone (XX)**

Y = 49%; Rec. = GAA; m.p. = 237-239°C; IR = 1620, 1588, 3320, 1489, HNMR 6.91 - 6.96(10, m), 2.53 (6, s), MS = 264, 104, 281, 105, 80, 77 UV: max = GAA 220, 250, 230 (Scheme 2).

**Biological studies**

***Antibacterial activity***

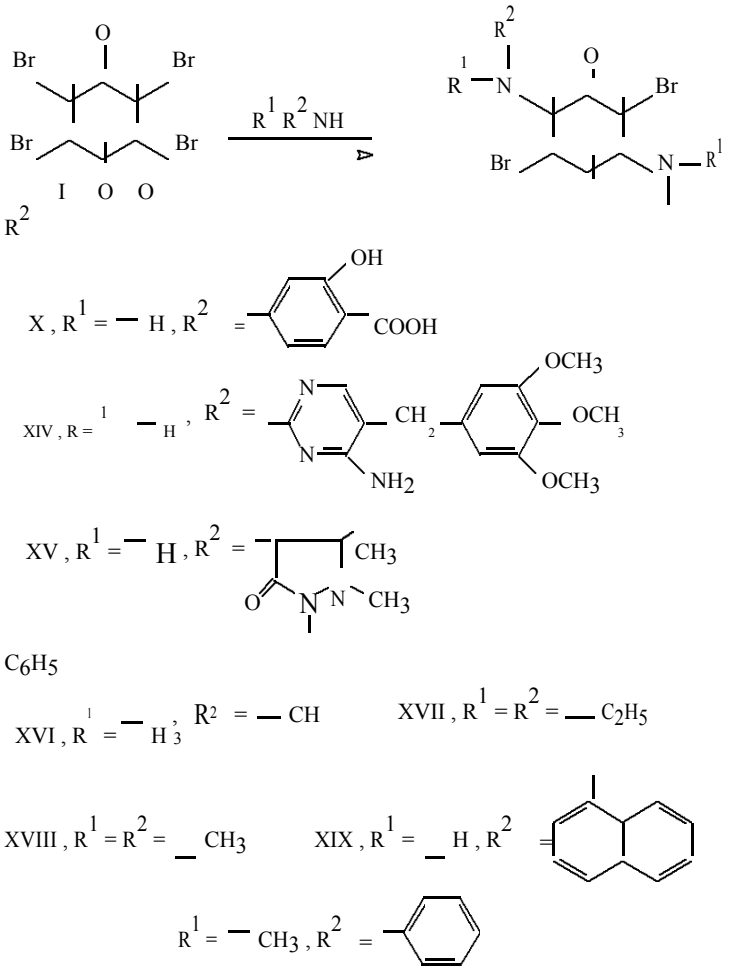
The Test Organisms used were: *Bacillus subtilis* NCTC 3610 Gram-positive Bacteria, *Staphylococcus aureus* NCTC 6571 Gram - positive Bacteria, *Escherichia coli* NCTC 10418 Gram-negative Bacteria and *Pseudomonas aeruginosa* NCTC 10662 Gram - negative Bacteria.

20 ml bottle of agar was melted and cooled at 45 - 48°C. 0.5 ml suspension of the test organism was added and mixed well with nutrient agar which was poured into a sterile Petri-dish. The plates were left to stand for 1 h to solidify. Four holes were cut out from each plate. 10 mm crock borer was used to cut discs. 0.2 ml of tested compound (1 mg/ml) was added to each hole. The plates were allowed to stand at room temperature for two hours and then incubated. The organisms were grown in nutrient agar (Oxoid) at 37°C for 18 h. After incubation period, the growth inhibition zones diameters were carefully measured in mm.

**Antifungal activity**

The Test Organisms used were *Aspergillus niger* ATCC9763 and *Candida albicans* ATTCC7596.

The fungal cultures were maintained on sabouraud agar incubated at 25°C for seven days. The fungal growth was harvested and washed with sterile normal saline and suspended in 100 ml of sterile normal saline. The suspension was stored in the refrigerator till used. 0.5 ml sample of each compound (1 mg/ml) plus 0.1 ml of the tested fungal suspension were mixed thorougly with 20 ml of pre- sterilized sabouraud dextrose agar medium , which was maintained at 45°C. The inoculated medium was poured into sterile Petri-dishes, allowed to solidify, and incubated at 25°C for seven



**Scheme 2.** Chemical structures of 2,5-diamino(N – alkyl and N-heteroaryl)-3,6-dibromo-1,4-benzoquinones.

days. The plates were examined for evidence of inhibition of growth. In the control, propylene glycol was used in place of the test compounds.

## RESULTS AND DISCUSSION

The synthetic approach developed in this work has been worked out from the retrosynthetic analysis of the target molecules. This approach involves two C- N bonds disconnection. In quinones, the ring system has lost aromatic character. Quinones are highly reactive , -unsaturated ketones and their typical behavior involves 1,4 - addition reactions. The halogen atoms adjacent to the carbonyl groups are labile and readily undergo nucleophilic substitution reaction with nucleophiles such as thiol and amino groups.

The effect of the reaction medium was investigated. The reaction between compound I and sulphanilamide was studied as a model. Ethanol, acetic acid, water and sodium acetate were selected. Sodium acetate was used in order to modify the acidity of the medium which was highly critical, because as carbonyl group became protonated, then it became more susceptible for nucleophilic attack and at the same time the lower pH was avoided to abolish the protonation of the amino groups. TLC indicated no difference in number of compounds and their yields when the effect of light was studied in dark, day light and UV irradiation. Temperature effect at 30, 50, 70 and boiling range were attempted. Higher yields were obtained at refluxing temperature. Among 1, 2 and 3 h interval periods at refluxing range, 3 h were a sufficient period to complete the reaction. Molar ratios of 1:1, 1:2, 3:2, 2:1 and 1:2 of the quinone and the amino derivative were tested respectively. Molar ratio of 3:2 gave higher yields and the number of the formed compounds was unaffected. The oxidation of 1, 4-dioxygenated benzenes remained the most widely route to benzo-1,4- quinones (Owton, 1999; Stahl et al., 2001). Accordingly, compound I was prepared from 1,4- dihydroxy benzene through nitric acid - bromine oxidation in acetic acid .

The electronic spectra, the quinoid electronic excitations and the effect of substitution on the position of the bands were in a good accord with what was reported (Singh et al., 1968).

**Table 1.** Antibacterial activity of the prepared compounds.

| Compound no. | Mean inhibition zone diameter ,"mm" | | | |
|---|---|---|---|---|
| | Test organism | | | |
| | ***B. subtits*** **(mm)** | ***S. aureus*** **(mm)** | ***E. coli*** **(mm)** | ***P. aeruginosa*** **(mm)** |
| I | 18 | 18 | 22 | 12 |
| II | 12 | 13 | 27 | 18 |
| III | 17 | 2 | 20 | 20 |
| IV | 13 | 14 | 20 | 18 |
| V | 12 | 18 | 18 | 16 |
| VI | 18 | 12 | 23 | 22 |
| VII | 19 | 17 | 13 | 22 |
| VIII | 19 | 18 | 21 | 20 |
| IX | 19 | 19 | 17 | 20 |
| X | 14 | 16 | 25 | 22 |
| XI | 22 | 23 | 18 | 16 |
| XII | 20 | 20 | 17 | 16 |
| XIII | 18 | 18 | 22 | 20 |
| VIV | 19 | 21 | 25 | 20 |
| XV | 23 | 24 | 20 | 17 |
| XVI | 20 | 20 | 20 | 21 |
| XVII | 20 | 20 | 23 | 15 |
| XVIII | 22 | 20 | 15 | 12 |
| XIX | 20 | 22 | 19 | 12 |
| XX | 17 | 16 | 19 | 18 |

The intermediate 2,3,5,6-tetrabromo - 1,4-benzoquinone showed a multiple molecular ion peaks which appeared at m/e 420, 422, 424, 426 and 428 in a relative abundance ratio of 17, 68, 100, 68 and 17%, respectively. This appearance of the ion was in a good accordance with the theoretical calculation of the isotope peaks effects, when calculated for 4 bromine atoms. The binomonal $(a + b)^n$ calculate per a = b = 1 for approximately $^{79}Br = {}^{81}Br$ in 51 : 49 was as follows : $\{ (a + b)^n = a^4 + a^3b + 6a^2b^2 + 4ab^3 + b^4 \}$, (1: 4 : 6: 4: 1), (m: m+2 : m+4 : m+6 : m+8), 420 : 422 : 424 : 426 : 428). An isolated sample of 2,3,5,6-tetrabromo-1,4-hydroxy benzene showed a Molecular ion at 422, 424, 426, 428 and 430 in the same ratio discussed above. This difference by two mass units can only be attributed to the hydroquinone form rather than the original quinone structure. Further considerations can be linked with the oxidation - reduction system required for the completion of the reaction, as the hydroquinone was the original product in sequence of the reaction which should be followed by oxidation. Examining the above mentioned fact for the case of tribromo derivative of hydroquinone, it was found that the observed m/e for the molecular ion appeared at 344, 346, 348, 350 rather than that of 342, 344, 346, 348 calculated for the quinonoid structures which were both calculated for $(a+b)^3 = a^3 + 3a^2b + 3ab^2 + b^3$, 1:3:3:1. Fragmentation led to $[M- Br]^+$ which gave rise to peaks at 241, 343, 345, 347 in a ratio of 1: 3: 3: 1 (15:45:15% RA). Pathway led to [M-2Br] which formed ions at 263, 265 and 267 in 10:20:10%. Fragmentation led to the formation of m/e 131, 133 which appeared in 50:50%. Compound III showed a peak at m/e 538 which can be attributed to M-CO-$C_2$ H $_2$N) and at m/e 458 for M-Br-CO-$C_2$ HN) which further lost Br to give m/e 379. Compound V, the p-methyl aniline derivatives showed similar spectra to that of compound XX, the N -methyl aniline derivative. Compound XX showed a peak at m/e 411 calculated for M-$C_5H_5$ and m/e 385 for –$C_6$ $H_6$N both with their observed isotope effect. The mass spectra of compound X showed a peak at m/e 262, 264, 266, which can be attributed to the lost of the two amino derivatives. Similar situation of compound X was seen in the mass spectra of compound XVIIII, the dimethylamine derivatives, a peak appeared at m/e 262, 264 and 266 in 1:2:1 ratio can be explained as M-2Nme. A peak appeared at m/e 325 due to M-HCN, M-HCN-CO at m/e 297 and M-Br $^+$ at m/e 192 which was followed by removal of HCN from M–Br-HCN at 165.

Fragmentation pathway that appeared consistently in the most of the prepared compounds was seen at m/e 264 and 76. These fragmentations were in a good accord with what was reported (Hassan et al., 2007).

The antibacterial activity of the prepared compounds (1 - XIX) against the two gram positive bacteria, *B. subtilis* and *S. aureus* and the two gram negative bacterial; *E. coli* and *aeruginosa* is given in Table 1. The results ob-

**Table 2.** Anti-fungal activity of the tested compound.

| Chemical agents | Test organism | |
|---|---|---|
| | ***Apergillus niger*** | ***Candida albicans*** |
| I | - | + |
| II | - | + |
| III | - | + |
| IV | - | + |
| VI | - | - |
| VII | + | + |
| IX | - | + |
| X | - | + |
| XI | + | + |
| XII | - | + |
| XIII | + | + |
| XV | + | + |
| XVIII | - | - |
| XIX | - | - |

tained indicated that all the compounds exhibited anti-bacterial activity. A significant potentiation of activity upon coupling of the intermediate compounds with I has occurred in four compounds, namely XIII, VIII, III and IX. In other cases the activity has either remained unchanged or diminished. The antifungal activity of the prepared compounds is shown in Table 2. The results were tabulated for compounds I, II, III, IV, VI, VII, IX, X, XI, XII, XIII, XV, XVIII and XIX in propylene glycol as a solvent against the two fungi *Aspergillus niger* and *C. albicans* in sabouraud dextrose agar media. Compounds VIII, XI, XIII and XV possessed activity against both *A. niger* and *C. albicans.* The following structural features seem to be necessary for antifungal activity a nitro group in compound VII, OH group in compounds XI, XII and $CH_3$ group in compounds XV and XVIII whereas compounds VI and XIX were not active against the two fungi. Compounds I, II, III, IV, IX, X and XII were inactive against *A. niger.* Generally, antifungal activity did not seem to be connected with certain chemical structures.

**REFERENCES**

Haraguchi H (1998). Recent Research Developments in Agricltural and Food Chemistry pp.259 – 268.
Hassan AA, Aly AA, El sheref EM (2007). ARKIVOC, xiv: 229 – 244.
Hudson AT, Randall AW, Fry M, Ginger CD, Hilll B, Latter VS, McHardy N, Williams RB (1985). Parasitology 90: 45-55.
Long DJ, Jaiswal AK (2000). Chem. Biol. Interact. 129: 99 – 112.
Owton WM (1999). J. Chem. Soc. Perkin Trans. 1: 2409-2420.
Pink JJ, Planchon SM, Tagliarino C, Varnes ME, Siegel D, Boothman DA (2000). J. Biol. Chem. 275: 5416 – 5424.
Porter TH, Tsai CS, Kishi T, Kishi H, Folkers K (1978). Acta Pharm.Suec.15: 97-104.
Ross D, Kepa JK, Winski SL, Beall HD, Anwar A, Siegel D (2000). Chem. Biol. Interact. 129: 77 -97.
Singh I, Ogata RT, Moore RE, Changs CW, Scheuer PJ (1968). Tetraheadron 24: 6053- 6073.
Song K, Jeon S (2003). Bull. Korean Chem. Soc. 24: 153 -154.
Stahl P, Kissau L, Mazitschek R, Huwe A, Furet P, Giannis A, Waldmann H (2001). J. Am. Chem Soc. 123(115): 86 -11593.
Valderrama J, Fourent A, Valderama C, Bastias S, Astudillo C, Arias AR, Inchausti A, Yaluff G (1999). Synthesis and in vitro antiprotozoal activity of thiophene ring containing quinines. Chem. Pharm. Bull. 47(9): 1221-1226.