Sys Rev Pharm 2020; 11(4): 719 – 724
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Synthesis and Antimicrobial Activity of New Nitric Oxide-Donor Containing Compounds

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Article History: *Submitted: 11.04.2020* *Revised: 15.05.2020* *Accepted: 20.06.2020*

ABSTRACT
This study aimed to prepare new biologically active nitric oxide compounds. A series of novel nitric oxide donor derivatives were synthesized in two steps, in light of this point. In the first step, the salt of carboxylic acid was prepared with sodium bicarbonate from the reaction of carboxylic acids(1a-e) & (2a-e), then the salts were heated with dibromoalkane to obtain haloester compounds. While, the second step, under dry and dark conditions, the compounds prepared above were treated with silver nitrate in acetonitrile as solvent. Twenty products were prepared, and their physical and spectral properties were measured. Some of these products had their antimicrobial action tested
Keywords: Amide, antimicrobial activity, Haloester, Nitric oxide donors.
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DOI: 10.31838/srp.2020.4.105

INTRODUCTION

The mechanism of action and possible effects of nitric oxide donors (NODs) were discussed in several recent papers [1-4]. There have been several studies showing that no releasing agents can kill tumor cells. Different laboratories have shown that all Nitric Oxide Synthase (NOS) isoforms have been detected from a wide variety of isolates in tumor cells [5]. The mechanisms include direct DNA damage, DNA synthesis inhibition and the rate limiting enzyme ribonucleotide reductase [6-10].

Finally, multi-drug - resistant (MDR) pathogens are increasing at an alarming rate and cause a serious problem in community and hospital-acquired infections, the role of NO as anon-specific defense mechanism against pathogenic invasion has been raised since 1990, and it has become evident that small molecules have an antimicrobial effect on different types of microorganisms such as bacteria, viruses The present study established the route of synthesis of new donors of nitric oxide for both stability products and good physical conditions (dark, dry, and cold) and their biochemical, spectroscopic, and antimicrobial activity[11]

MATERIALS AND METHODS

All chemicals were taken from and used without purification by Aldrich, Fluka, and Sigma Chemical Companies. Solvents were of high grade used for spectroscopic and other physical studies. An electrothermal IA 9300 Digital-Series apparatus had uncorrected melting points. Infrared spectra were recorded on an Alpha-platinum ATR (Germany) Burker, FT-IR spectro-photometer. On a Bruker (AS 400 MHz) at the University of Ega – Oxford, England, proton NMR spectra were recorded using TMS as an internal reference and d6–DMSO as a solvent. The following signals are given: -s = singlet; d = doublet; t = triplet; m = multiplet

2.1. Chemicals

2.1.1. General procedure for preparation of bromoalkyl esters (1a-e) and (2a-e) [12].

Dissolved in water (25 ml), a solution of carboxylic acid (0.25 mole) and sodium bicarbonate (0.025 mole, 2.1 g) was stirred at room temperature for 0.5 h. The water was completely evaporated under reduced pressure to give the salt of carboxylic acid which is used without further purification.

In a dry dimethy sulfoxide (10 ml), alkylene dibromide (0.06 mole) was added in a stirring for solution of the initial material (carboxylic acid salt) (0.02 mole). The reaction mixture was heated at 70-80 ° C for 1.5 h on water bath, then filtered hot. The volatile solvents were evaporated to yield an oily residue under reduced pressure, which was washed with acetone (30 ml) to solidify and give the desired product.

2.1.2. Nitration of terminal alkyl bromide compounds to produce organic nitrates (3a-e) and (4a-e) [13,14].

In dark cold conditions, all synthesized alkyl halide compounds ($AgNO_3$) were treated to synthesize organically compound nitrate organically in a dry mixture (acetonitrile and tetrahydrofuran).

Silver nitrate (0.005 mole, 0.85 g) was added to an alkyl halide (0.001 mole) suspension in a mixture of dry tetrahydrofuran (THF) (1:1) (15 ml) and acetonitrile (CH_3CN). Dry and dark at room temperatures, the mixture was mixed 48 hours. Under reduced pressure, the filtrate was evaporated. A dry dichloromethane washed the residue several times and filtered the organic layer, then under reduced pressure, to give organic nitrate (3a-e) and (4a-e) compounds.

2-bromoethyl acetylglycinate (1a): Pale yellow, yield 63%, m.p 52-54°C, IR (υ_{max} cm^{-1}), 3354 (N-H amid), 1741 (C=O ester), 1633 (C=O amid), 1241, 1122 (C-O-C asy,sym), 662 (C-Br) ; ^{1}H NMR (DMSO-d_6), δ ppm, 9.09 (s, 1H, NH), 4.46 (t, 2H, CH_2O), 4.11 (s, 2H, NCH_2), 3.63 (t,2H, CH_2Br), 1.86 (s, 3H, CH_3CO).

3-bromopropyl acetylglycinate (2a): yellow, yield 60%, m.p 48-50°C, IR (υ_{max} cm^{-1}), 3350 (N-H amid), 1744 (C=O ester), 1640 (C=O amid), 1236, 1118 (C-O-C asy,sym), 658 (C-Br).

2-(nitrooxy) ethyl acetylglycinate (3a): yellow, yield 57%, m.p 182-184°C, IR (υ_{max} cm^{-1}), 3358 (N-H amid), 1747 (C=O ester), 1635 (C=O amid), 1603, 1279 (O-NO_2 asy, sym) 1239, 1121 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δ ppm, 9.12 (s, 1H, NH), 4.31 (t,2H, CH_2ONO_2), 4.15(s, 2H, NCH_2), 3.78 (t, 2H, OCH_2), 1.89 (s, 3H, CH_3CO).

3-(nitrooxy) propyl acetylglycinate (4a): Pale brown, yield 54%, m.p 188-190°C, IR (υ_{max} cm^{-1}), 3355(N-H amid), 1746 (C=O ester), 1641 (C=O amid), 1591, 1274 (O-NO_2 asy, sym) 1237, 1119 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δppm, 9.11 (s, 1H, NH), 4.43 (t, 2H, CH_2ONO_2), 4.20 (s, 2H, NCH_2), 4.16 (t,2H,OCH_2), 2.01 (m, 2H , C-CH_2-C), 1.86 (s, 3H, CH_3CO).

2-bromoethyl acetylcysteinate (1b): Yellow wish, yield 67%, m.p 25-27°C (semi-solid), IR (υ_{max} cm^{-1}), 3294 (N-H amid), 2389 (SH), 1727 (C=O ester), 1638 (C=O amide), 1221, 1120 (C-O-C asy,sym), 647(C-Br).

3-bromopropyl acetylcysteinate (2b): Brown, yield 64%, m.p 26-28°C (semi-solid), IR (υ_{max} cm^{-1}), 3298 (N-H amid), 2382 (SH), 1724 (C=O ester), 1636 (C=O amid), 1224, 1123 (C-O-C asy,sym), 644 (C-Br) ; ^{1}H NMR (DMSO-d_6), δ ppm, 8.39 (s, 1H, NH), 4.73 (t,1H, SH) ,4.10 (t, 2H, CH_2O), 3.49 (t, 2H, CH_2Br), 3.12 (d, 2H, CH_2S), 1.96 (m, 2H, C-CH_2-C), 1.87 (s, 3H, CH_3CO) ,1.38(s, 1H, SH).

2-(nitrooxy) ethyl acetylcysteinate (3b): yellow, yield 51%, m.p 52-54°C, IR (υ_{max} cm^{-1}), 3291 (N-H amid), 2392 (SH), 1721 (C=O ester), 1641 (C=O amid), 1599, 1250 (O-NO_2 asy, sym), 1220, 1112 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δ ppm, 8.42 (s, 1H, NH), 4.72 (t, 1H, CH), 4.68 (t, 2H, CH_2ONO_2),4.41 (t, 2H, OCH_2), 3.06 (d, 2H, CH_2S), 1.78 (s, 3H, CH_3CO) ,1.34 (s, 1H, SH).

3-(nitrooxy) propyl acetylcysteinate(4b): Brown, yield 49%, m.p 64-66°C, IR (υ_{max} cm^{-1}), 3287 (N-H amid), 2386 (SH), 1717 (C=O ester), 1647 (C=O amid), 1587, 1248 (O-NO_2 asy, sym), 1223, 1109 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δ ppm, 8.43 (s, 1H, NH), 4.76 (t, 1H, CH), 4.47 (t, 2H, CH_2ONO_2),4.12 (t, 2H, OCH_2), 3.10 (d, 2H, CH_2S), 1.97 (m, 2H, C-CH_2-C), 1.91 (s, 3H, CH_3CO) ,1.39 (s, 1H, SH).

2-bromoethyl benzoylglycinate (1c): White, yield 69 %, m.p 39-41°C, IR (υ_{max} cm^{-1}), 3336 (N-H amid), 1739 (C=O ester), 1645 (C=O amid), 1177, 1104 (C-O-C asy,sym), 648 (C-Br) ; ^{1}H NMR (DMSO-d_6), δ ppm, 8.19 (s, 1H, NH), 7.51-7.92 (m, 5H, Ar-H), 4.48 (t, 2H, CH_2O), 4,14(s, 2H, CH_2N) 3.69 (t, 2H, CH_2Br).

3-bromopropyl benzoylglycinate (2c): Yellow, yield 75 %, m.p 34-36°C, IR (υ_{max} cm^{-1}), 3337(N-H amid), 1736 (C=O ester), 1644 (C=O amid), 1169, 1099 (C-O-C asy,sym), 641 (C-Br).

2-(nitrooxy) ethyl benzoylglycinate(3c): Pale yellow, yield 53 %, m.p 83-85°C, IR (υ_{max} cm^{-1}), 3338 (N-H amid), 1746 (C=O ester), 1647 (C=O amid), 1549, 1189 (O-NO_2 asy, sym), 1181, 1112 (C-O-C asy,sym) ; ^{1}H NMR (DMSO-d_6), δ ppm, 8.21 (s, 1H, NH), 7.45-7.77 (m, 5H, Ar-H), 4.68 (t, 2H, CH_2ONO_2), 4.18 (t, 2H, CH_2O), 4,13(s, 2H, CH_2N).

3-(nitrooxy) propyl benzoylglycinate(4c): Yellowish, yield 50 %, m.p 98-100°C, IR (υ_{max} cm^{-1}), 3340 (N-H amid), 1741 (C=O ester), 1643 (C=O amid), 1547, 1190 (O-NO_2 asy, sym), 1178, 1109 (C-O-C asy,sym).

2-bromoethyl 1-naphthoate (1d): Pale yellow, yield 71 %, m.p 63-65°C, IR (υ_{max} cm^{-1}), 1716 (C=O ester), 1186, 1107 (C-O-C asy,sym), 649 (C-Br) ; ^{1}H NMR (DMSO-d_6), δ ppm, 8.51-7.43 (m, 7H, Ar-H), 4.75 (t, 2H, CH_2O), 3.83 (t, 2H, CH_2Br).

3-bromopropyl 1-naphthoate (2d): yellow, yield 67%, m.p 68-70°C, IR (υ_{max} cm^{-1}), 1712 (C=O ester), 1189, 1113 (C-O-C asy,sym), 644 (C-Br).

2-(nitrooxy) ethyl 1-naphthoate (3d): Yellowish green, yield 53 %, m. p143-146°C, IR (υ_{max} cm^{-1}), 1718 (C=O ester), 1582, 1241 (O-NO_2 asy, sym), 1219, 1109 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δ ppm, 8.84-7.49 (m, 7H, Ar-H), 4.85 (t, 2H, CH_2ONO_2), 4.53(t, 2H, CH_2O).

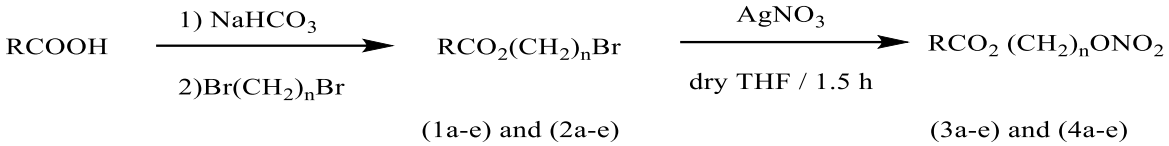
3-(nitrooxy) propyl 1-naphthoate (4d): Yellowish green, yield 54 %, m. p152-154°C, IR (υ_{max} cm^{-1}), 1717(C=O ester), 1579, 1240 (O-NO_2 asy, sym), 1220, 1120 (C-O-C asy,sym); ^{1}H NMR (DMSO-d_6), δ ppm, 9-7.43 (m, 7H, Ar-H), 4.41 (t, 2H, CH_2ONO_2), 4.30 (t, 2H, CH_2O),2.17(m, 2H, C-CH_2-C).

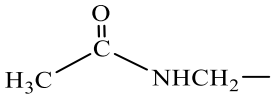
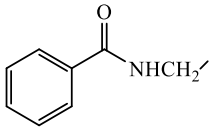
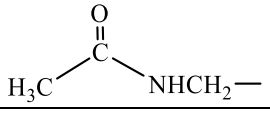
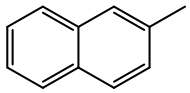
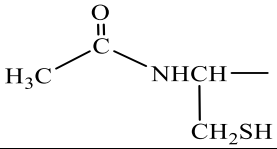
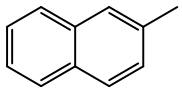
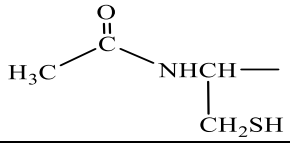
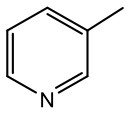
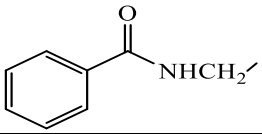
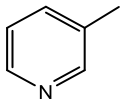
2-bromoethyl picolinate (1e): Pale brown, yield 70%, m. p 83-85°C, IR (υ_{max} cm^{-1}), 1712 (C=O ester), 1220, 1123 (C-O-C asy,sym), 639 (C-Br).

3-bromopropyl picolinate (2e): Pale yellow, yield 64 %, m. p89-91°C, IR (υ_{max} cm^{-1}), 1717 (C=O ester), 1223, 1121 (C-O-C asy,sym), 640(C-Br); ^{1}H NMR (DMSO-d_6), δ ppm, 8.91-8 (m, 4H, Ar-H), 4.33(t, 2H, CH_2O), 3.53(t, 2H, CH_2 Br), 2.21 (m, 2H, C-CH_2-C).

2-(nitrooxy) ethyl picolinate (3e): Pale orange, yield 47 %, m. p200-203°C, IR (υ_{max} cm^{-1}), 1719 (C=O ester), 1590, 1279 (O-NO_2 asy, sym), 1226, 1129 (C-O-C asy,sym).

3-(nitrooxy) propyl picolinate (4e): Grey, yield 49 %, m. p117-119°C, IR (υ_{max} cm^{-1}), 1719 (C=O ester), 1588, 1283 (O-NO_2 asy, sym), 1228, 1127 (C-O-C asy,sym) ; ^{1}H NMR (DMSO-d_6), δ ppm, 8.88-7.96(m, 4H, Ar-H), 4.48 (t, 2H, CH_2ONO_2), 4.38 (t, 2H, CH_2O), 2.19(m, 2H, C-CH_2-C).



Compound	n	R	Compound	N	R
1a, 3a	2		2c, 4c	3	
2a, 4a	3		1d, 3d	2	
1b, 3b	2		2d, 4d	3	
2b, 4b	3		1e, 3e	2	
1c, 3c	2		2e, 4e	3	

Scheme: Route of synthesis of new nitric oxide donors

2.2. Antimicrobial activity

2.2.1. Microbial strains and culture

The isolated microorganisms included in this study were gram-positive (*Staphylococcus aureus, Bacillus subtilis*), gram-negative (*Escherichia coli, Salmonella typhi, Shigella dysenteriae*) and isolated (*Candida albicans*) yeast. Standard methods for isolation and identification were used to identify the isolated microorganisms by direct examination, culture on various media, and biochemical test to be identified as *S. aureus*, *B. subtilis*, *E. coli*, *S.typhi*, *Shigella dysenteriae* and *C. albicans* [15].

2.2.2. Susceptibility test

Susceptibility testing has been applied to five varieties of Gram positive and Gram negative bacteria and one form of yeast, the susceptibility test is performed by transferring 3-5 pure culture colonies of tested bacteria into 3-5 ml Muller-Hinton broth and the inoculum density has been standardized to a chive with a final concentration of (1.5 * 108 CFU / ml) by turbid method and the turbidity has been compared with (0. The suspension inoculum was incubated for (15 minutes) at 37 ° C. A sterile cotton swab was dipped into a suspension of bacterial inoculum and then streaked over a whole dried surface (90 mm Muller-Hinton agar) plate [16].

2.2.3. Preparation the discs

Different concentrations (20 mg / ml, 10 mg / ml, 5 mg / ml, 2.5 mg / ml, 1.25 mg / ml) of each of the selected nitric oxide donor (NOD) compounds (4a, 4c, 4d, 4e, 3c, 3d) were saturated from sterile filter paper Whatman No.1 in a radius of 6 mm for 14-16 hours after dissolution in DMSO [17]. The disks were placed on the inoculated Muller-Hinton agar using a sterile forceps and then the plates were inoculated at 37 ° C for 14-16 hours. The diameter of the inhibition zone was measured for antimicrobial activity assessment, the diameter was measured in millimeter in addition to isolates' susceptibility to control antibiotic disks (chloramphenicol 30 mcg was tested for each bacterial isolate and voriconazole 1 mcg was tested for Candida isolate). The susceptibility test was conducted three times to ensure reliability and the average was determined for the three replicates of every 6 NOD compounds. Moreover, to C. The susceptibility test for albicans was carried out as Gram positive and Gram negative bacteria except that the addition of 20 grams of glucose to Muller – Hintonn agar to ensure C production. And the Albicans.

RESULTS AND DISCUSSION

In two steps Twenty compounds synthesized. In the first step, carboxylic acid sodium salt was prepared from the reaction of carboxylic acids with sodium bicarbonate, and

then the salts heated with dibromoalkane to obtain haloester (1a-e) and (2a-e) compounds. In the second process, the haloester compounds treated in acetonitrile with silver nitrate as a solvent under dry and dark conditions to obtain organic nitrate compounds (3a-e) and (4a-e). The chemical structures of title compounds using IR,1H-NMR have been described. The compounds exhibited IR stretching absorption in the regions (3358-3287), (2392-2382), (1747-1712), (1647-1633), (1241-1169), (1129-1099), (1603-1547), (1283-1189), (662-639) for N-H, S-H, C = O ester, C = O amide, C-O - C ester (asy), C-O - C ester (asy), O-NO2 (asy) and C-Br respectively. The chemical shift for N-H protons in compounds (1a,3a,4a,2b, 3b, 4b, 1c, 3c) resonated as a singlet in the range in 1H-NMR spectrum (400MHz, DMSO-d6) (9.12-8.19). The chemical change in compounds for OCH2 protons (1a,3a,4a,2b, 3b, 4b, 1c, 3c, 1d, 3d, 4d, 2e, 4e) resonated as a triplet in shift (4.75-3.78). On the other hand, the compound structures (3a, 4a, 3b, 4b, 3c, 3d, 4d, 4e) were confirmed by the disappearance of the bands for the CH2-Br for haloester compounds (1a, 2b, 1c, 1d, 2e) as a triplet band in the range (3.83-3.49) and showed the triplet bands for compounds (3a, 4a, 3b, 4b, 3c, 3d, 4d, 4e) in the range (4.85-4.31) which conform to the NOD compounds.

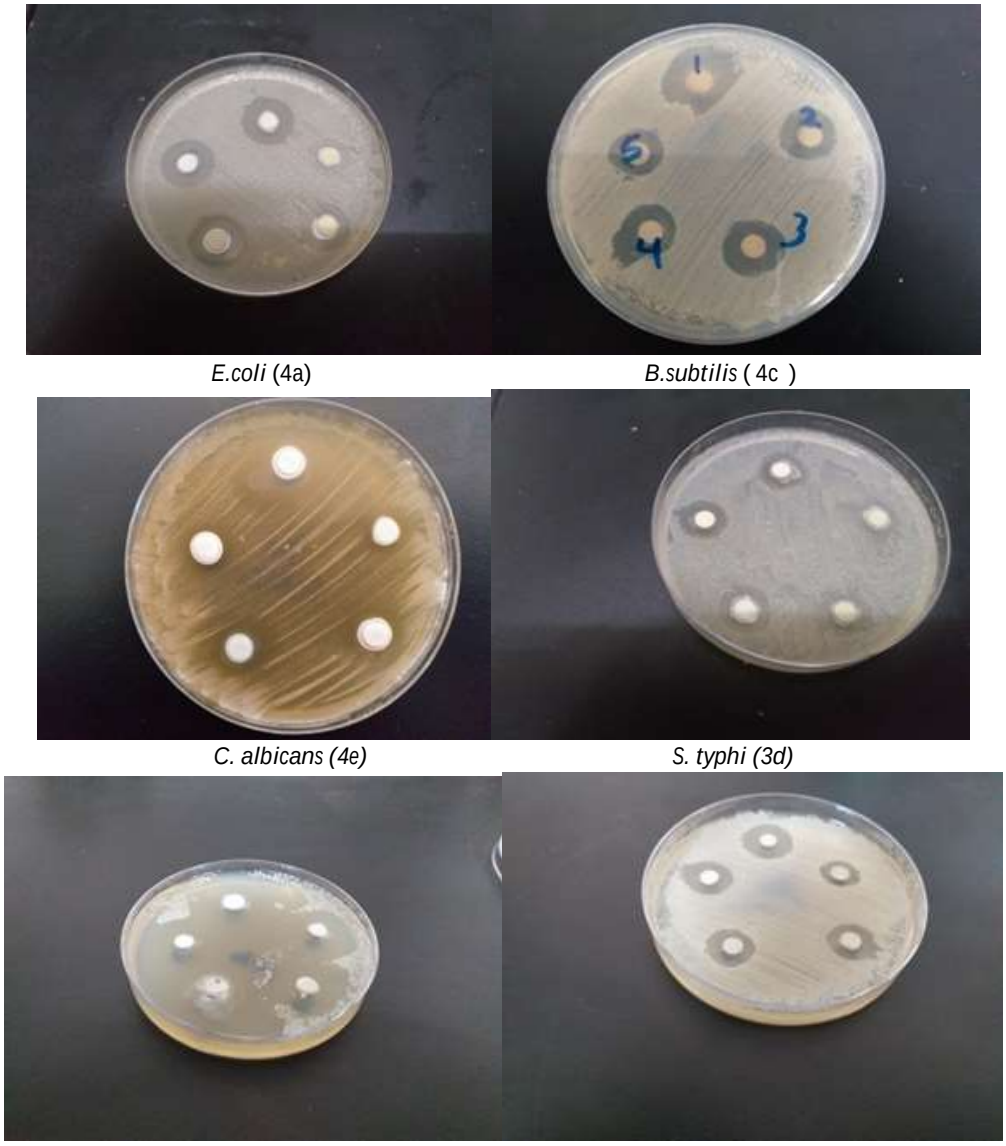
The antimicrobial activity of NOD compounds was recorded in (Fig. 1 and Table 1A & 1B). The results revealed that NOD compounds showed a good antimicrobial activity against most of microorganisms tested when compared with control antibiotic's disc in suppressing microbial growth of tested microorganisms with variable potency at concentration of NOD compounds (20mg/ml, 10mg/ml, 5mg/ml, 2.5mg/ml, 1.25mg/ml). Results of antimicrobial activity of NOD compounds its dose dependent and can suggested that for Gram positive bacteria (S. *aureus* and *B. subtilis*) the microbial growth inhibition to 4d, 4a, 4c and 4e was 100%, while growth inhibition to 3d only at concentration 20 mg/ml for both *S.aureus* and *B.subtilis* and for 3c at concentration 20mg /ml for *S.aureus* and to all concentration of *B. subtilis* except at 1.25mg/ml. In addition to microbial growth inhibition of Gram negative bacteria E. *coli* showed growth inhibition 100% for 4d and at concentration 20mg/ml for 4c and for 3d and 4a at concentration 20mg/ml, 10mg/ml and to all concentration of 4e except at concentration 1.25mg /ml and with no antimicrobial activity of 3c. However the growth inhibition of *S. typhi* was 100% for 4a, 3c and 4d except at concentration 1.25mg/ml and for 4e except at concentration of 2.5 mg/ml and 1.25mg/ml, and to 3d growth inhibition only at concentration 20 mg/ml with no antimicrobial activity of 4c,while growth inhibition of *Shigella dysenteriae* to 4d was 100% in addition to 3c, 4c at all concentration except at 1.25 mg/ml and to 4e except at concentration 2.5 mg/ml, 1.25 mg/ml and for 4a except at concentration 5mg/ml, 2.5 mg/ml and 1.25 mg/ml, with no antimicrobial activity for 3d. On the other hand, the growth inhibition of *C. albicans* was 100% for 4d and 4c and to all concentration of 4e except at 1.25 mg/ml, while for 3d to all concentration except at 2.5 mg/ml and 1.25 mg/ml, in addition to 3c except at concentration 5 mg /ml, 2.5 mg/ml and 1.25 mg/ml, with no antimicrobial activity of 4a.

Table 1A: Antimicrobial activity in millimeter to different concentrations in mg / ml of NOD compounds using disc diffusion method.

Microorganisms	3d					4d					4a				
	20	10	5	2.5	1.25	20	10	5	2.5	1.25	20	10	5	2.5	1.25
S. aureus	22	17	16	15	15	30	28	28	25	25	32	30	30	25	25
B. subtilis	20	16	15	14	14	25	20	20	20	18	25	22	20	20	18
E. coli	22	20	15	12	12	30	30	25	20	20	20	18	15	14	14
S. typhi	18	15	12	12	8	25	20	20	20	15	30	28	25	22	20
Shigella dysenteriae	14	13	13	10	10	30	25	25	20	20	20	18	15	13	10
C. albicans	30	20	20	15	15	30	25	25	25	20	12	10	10	5	0

Table 1B: Antimicrobial activity in millimeter to different concentrations in mg /ml of NOD compounds using disc diffusion method.

Microorganisms	3c					4c					4e				
	20	10	5	2.5	1.25	20	10	5	2.5	1.25	20	10	5	2.5	1.25
S. aureus	20	15	15	14	12	35	35	30	30	30	35	35	30	30	25
B. subtilis	28	25	20	20	15	28	25	25	20	18	30	20	18	18	18
E. coli	16	15	14	13	12	18	15	15	14	13	30	25	20	20	15
S. typhi	30	28	25	25	20	17	15	15	13	13	25	20	20	15	10
Shigella dysenteriae	25	23	20	20	15	25	20	20	18	15	25	20	18	15	15
C. albicans	25	20	15	12	10	30	28	20	20	18	22	20	20	18	15



E.coli (4a) *B.subtilis* (4c)

C. albicans (4e) *S. typhi (3d)*

Shigella dysenteriae (4d) *S.aureus (3c)*

Fig.1: The inhibition zone of NOD compounds against six types of microorganisms.

The antimicrobial screening test against Gram positive, Gram negative bacteria and *C.albicans* as shown in (Tables 1A& 1B). Nitric oxide donor compounds have a good antimicrobial activity against most isolated microorganisms of Gram positive and Gram negative bacteria and yeast, the lowest antimicrobial activity showed in dose 2.5mg /ml and 1.25 mg/ml and its dose dependent the inhibition effect ranged from 0% - 100%, this confirmed by other investigator how showed that , NO acts as a signaling molecule at low concentration that promotes the growth and activity of immune cells, while NO covalently binds to DNA, proteins, and lipids thereby inhibiting or killing target pathogens at high concentration [18]. Finally, our conclusion indicated that compounds 3c,4c, 3d and 4a respectively were resistant in all concentrations towards isolates of *E. coli*, *S. typhi*, *Shigella dysenteriae* and *C. albicans*, it is not surprising that few microorganisms are able to resistance the antimicrobial effect of NO [18,19].

ACKNOWLEDGMENTS

None.

FUNDING

The research is self-funded.

ETHICS APPROVAL

The research has been approved by the ethical committee of the department of pharmaceutical chemistry at the session number 6 dated 20-2-2019.

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