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Synthesis and evaluation of dibenzo- 18 -crown -6 ether containing hydrazone derivative as antibacterial drug derivatives

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ABSTRACT

New derivatives of the macrocyclic polyether dibenzo-18-crown-6 that contain hydrazone groupings in the aromatic rings were synthesized. The biological activity of the polyether ring and the hydrazone groupings was studied. The strategy employed for the synthesis of new macromolecules containing hydrazone moiety involved formylation of dibenzo -18-crown –6 ***1*** *to yield 4, 4'- diformyl derivative of dibenzo-18-crown- 6* ***2*** *which was further reacted with different substituted hydrazides to give corresponding hydazones* ***3****. The structures of synthesized compounds have been characterized on the basis of spectroscopic data.*

Keywords:Dibenzo-18-crown-6,formylation, dibenzo-18-crown-6containing hydrazones, Antibacterial and antifungal screening.

INTRODUCTION

Macrocyclic polyethers, commonly called crown ethers, resemble natural ionophores like valinomycin, the nactins etc., in a macrocyclic structure with a hydrophobic outer sphere and a hydrophilic cavity capable of forming complexes with cations with high selectivity[1] although innumerable papers have been published concerning their chemical properties, not much work has been done regarding their biological properties. Oral toxicity in dogs and in mice was reported by Takayama et al.[2]E. I. Ivanov, A. A. Polishchuk etal reported that crown-annelated nitrogenous heterocycles, derivatives of dibenzo-18-crown-6, have antispasmodic, antiviral and pesticidal properties. Dibenzo-18-crown-6 it self and its thiazolo derivatives display antibacterial activity to a greater degree. This indicates the expedience of a drug search in this series of

dibenzo-18 crown-6 compounds [3-5]. H.Ibrahim Ugras, U Mit Cakir etal synthesized acyl-substituted crown ether derivatives were evaluated in accordance with their antimicrobial activity unfortunately, the synthesized crown ethers do not show any biological activity against the studied microorganisms. [6]. A. Kotlyar, V. P. Gorodnyuk, I. P. Konup, L. A. Konup etal reported the synthesis and antibacterial activity of aminobenzo crown ether [7]. A. Kotlyar, V. P. Gorodnyuk etal also reported synthesis and antimicrobial activity of aliphatic derivative of crown ether[8-9].Takeo tabata etal reported antifungal activity of the crown ether derivatives[8]E.I. Ivanov etal reported synthesis of xanthine derivatives containing fragments of the crown ethers: benzo-12-crown-4, benzo-15-crown-5, benzo-18-crown-6, and dibenzo-18-crown-6, to search for new biologically active substances in the purine series[11].

EXPERIMENTAL SECTION

The melting points were determined in open capillary tube and are uncorrected. Infrared spectra were recorded using KBr pellets on a Perkin Elmer Spectrum on FTIR spectrometer. The ^{1}H NMR and ^{13}CMR spectra were recorded in DMSO/$CDCl_3$ on a Jeol-JMSD-300 spectrophotometer. **(Scheme No-1)**

4, 4'-Di formyl dibenzo- 18- crown- 6 2

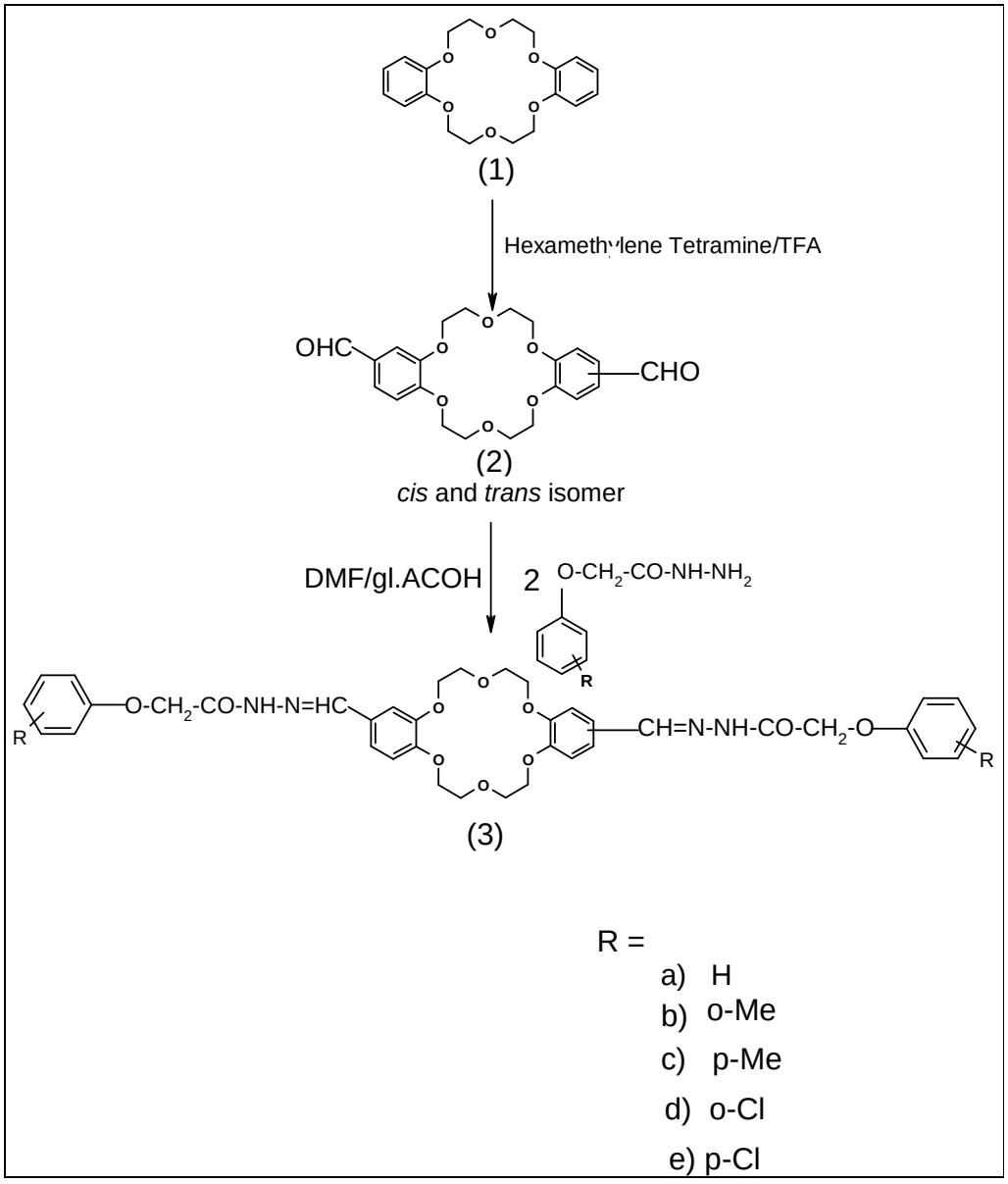
A mixture of dibenzo-18-crown-6(2.7 gm, 7.5 mmole), trifluoroacetic acid (5 mL) and hexamethylene tetramine (1.1 gm, 7.5mmole) was stirred at 90^0C for 15 hr.The reaction mixture was added to the concentrate and stirred for 1h.After completion of reaction the reaction mixture was poured on to the crushed ice brown solid separate out, which was filtered and recrystalized from ethyl alcohol. Purity of compound was checked by using TLC.

m.p. 230^0C (lit[4]: 231-233^0C); Yield: 78%; IR(KBr)**:** 3433, 2929, (CH), 1688(C=O), 1597, 1513, 1437, 1340, 1266, 1200, 1174, 1126, 1055 cm^{-1}; ^{1}H NMR (DMSO-d_6)**:** δ, 3.6-3.8 (m, 8H), 3.9-4.1 (m, 8H), 6.99-7.5(m,6H), 9.81(s,2H)ppm. $^{13}CNMR$ (DMSO-d_6), 125MHz):191.44, 177.62, 175.45, 153.30, 148.26, 129.55, 126.20, 111.74, 110.98, 109.69, 68.65, 68.56, 68.01,67.54,.

4, 4'Di (acrylophenonyl) dibenzo- 18- crown- 6 3a: (phenoxyacetic acid hydrazide)

To 0.3 gm of KOH in 10 mL ethanol taken in a round bottomed flask 4,4'-diacetyl dibenzo- 18-crown- 6 **2** (0.5 mmole) was added and the reaction mixture was stirred at room temp. Then benzaldehyde (1mmol) was added and the reaction mixture stirred for 4-5 hrs. The reaction was monitored by using TLC. After completion of reaction the reaction mixture was poured into ice water and neutralized with dil. HCl. The separated solid was filtered, dried and recrystallized by using ethanol.

m.p.210 °C; Yield: (60 %); IR (KBr): 3329,3174,3102,2873,1670 (C=O), 1575, 1466, 1371, 1328, 1284, 1198 cm^{-1}; $^{1}HNMR$(DMSOd_6): 3.84(m,8H), 4.1(m,8H), 5.1(s,4H), 6.77.3(m,14H), 7.9(s,2HNH), 8.1(s,2H,CH=N); $^{13}CNMR$(DMSOd_6,125MHz**):**194,153, 146, 141, 139, 128, 122, 118, 117, 113, 78, 67, 65, 64, 62, 42, 38, 25.Anal. calcd. for $C_{38}H_{36}0_8$ C, 73.52; H, 5.85; O, 20.63. Found: C, 73.60; H, 5.90; O, 20.60%.



4,4'Di(acrylophenonyl) dibenzo 18 Crown- 6 3b :(o-methyl phenoxy acetic acid hydrazide): m.p.230 ^{0}C; yield: (70 %); IR(KBr):3418,2925 1689, 1603, 1512, 1454, 1434, 1359, 1328, 1263, 1128, 1090, 1057; ^{1}HNMR(DMSOd_6):δ, 2.4(s,6H), 3.84(m,8H), 4.1(m,8H), 5.1(s,4H), 6.77.3(m,14H), 7.9(s,2HNH), 8.1(s,2H,CH=N)^{13}CNMR(DMSOd_6,125MHz):195.68, 193.98, 151.94, 149.04, 148.28, 147.84, 147.74, 146.41, 145.60, 134.83, 134.42, 133.87, 132.94, 130.12, 129.58, 128.80, 123.56,123.38,30.41,19.12.Anal. Calcd. for $C_{42}H_{46}N_20_8$ C, 71.35; H, 6.56; O, 18.12;N, 3.97. Found: C, 71.40; H, 6.60; O, 18.20;N, 3.95.

4, 4'Di (acrylophenonyl) dibenzo 18 Crown- 6 3c: :(p-methyl phenoxy acetic acid hydrazide):

m.p.260 ^{0}C; yield: (80 %);IR(KBr):3314, 3234, 3002, 2836, 1681, 1619, 1603, 1567, 1511, 1460, 1382, 1364, 1327, 1257, 1204, 1179, 1110,1024cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 6H), 3.8-3.9 (m, 8H), 4.1-4.2(m, 8H),5.09(s,4H),6.7-7.2(14H),7.9(s,2H,NH),8.2(s,2H, CH=N). ^{13}CNMR(DMSOd_6,125MHz):206,153,141,129,117,111.57,111.43,109.40,82,74,68,67,56,21. Anal. calcd. for $C_{38}H_{36}0_{10}$ C, 69.91; H, 5.56; O, 24.52; Found: C, 69.85; H, 5.60; O, 24.50%.

4, 4'-Di (2-amino-4-phenyl) pyrimidyl) dibenzo 18 -crown- 6 3d:(o-chloro phenoxy acetic acid hydrazide):

A mixture of chaconne **3** (1 mmole), guanidine hydrochloride (2.5 mmole), sodium methoxide (4 mmole) in 20 mL methanol was refluxed on water bath for 6-8 hrs. After completion of reaction the reaction mixture was poured into ice water and the separated solid was filtered, dried and recrystallized from ethanol.

m.p.265 ^{0}C; Yield: (67 %).IR(KBr):3314, 3171, 2982, 1667, 1610, 1575, 1509, 1462, 1392, 1372, 1331, 1285, 1269, 1252, 1196, 1182, 1122, 1027;^{1}HNMR(DMSO-d_6):.δ3.8-3.9(m,8H), 4.14.2(m,8H), 5.3(s,4H), 6.7-7.5(14H), 7.95(s,2H,NH), 8.25(s,2H, CH=N).

RESULT AND DISCUSSION

In the experimental procedure the reaction was generally run at a molar ratio i.e. in first step formylation of dibenzo- 18- crown-6 by using hexamethylene tetramine and trifluoroacetic acid i.e by duff formylation.[12] The second step involves the reaction between diformyl derivative of dibenzo 18-crown-6 **2** and different substituted hydrazides to get corresponding hydrazones derivatives of dibenzo 18- crown- 6.**3** The structures of synthesized compounds were established on the basis of IR, ^{1}H NMR, and ^{13}C NMR and elemental analysis.

Biological assessments

The synthesized dibenzo-18-crown-6 containing hydrazone derivatives 2a, 2b, 2c, ,and 2d, were tested against standard bacterial strains;E. coli ATCC 29998, S. epidermidis ATCC 12228, B.subtilis ATCC 6633, S. aureus 6538 P, S. typhimirumCCM 583, K. pneumonia CCM 2318, P. aeruginosaATCC 27853, E. feacalis ATCC 29212 and a fungi C. albicans ATCC 10239. Disc diffusion method was applied for the determination of antimicrobial activities of the samples (NCCLS, 2000). Extracts were dissolved in dimethyl formamide (DMF) and then filter-sterilized using a 0.20-lm membrane filter. A suspension of the tested microorganism (0.1 ml of 108 cells/ml) was spread over the surface of agar plates (MHA and SDA). Filter papers having a diameter of 6 mm, soaked with 10ml of extract samples and 8 ml of essential oils were placed on the inoculated agar plates. Before incubation all Petri dishes were kept in the refrigerator (4^{0}C) for 2 h. Then they were incubated at 37^0 C for 24 h for bacteria and at30^0 C for 48 h for the yeasts. The diameters of the inhibition zones were measured in millimeters

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