SYNTHESIS OF 5-BENZIMIDAZOLYLBENZOFURAN DERIVATIVES OF EXPECTED BIOLOGICAL ACTIVITY

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Abstract:
The benzimidazole starting material 5-(1*H*-benzo[*d*]imidazol-2-yl)-4,7-dimethoxybenzofuran-6-ol (**2**)was synthesized. The Mannich bases **3a-k** were formed using formaldehyde and primary or secondary amines.(**2)** was subjected to Mannich reaction using 1,4-phenylenediamine or piperazine to lead to the 1,4-disubstituted benzenes **4a** or 1,4-disubstituted piperazines **4b**.
The compounds were screen for their antimicrobial activities

Key Words: 5-Benzimidazolylbenzofuran Derivatives, Biological Activity

Introduction

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. Several promising antitumor active agents were found to contain the benzimidazole ring system[1-11]. They were found to exert their antitumor activity by acting mainly as topoisomerases inhibitors [12-13]. Benzimidazoles belonging to the fused heterocyclic system prepared from amino acids are associated with diverse pharmaceutical activities such as antibacterial[14], insecticidal[15], fungicidal[16], antimicrobial[17], antagonist[18], anthelmintic[19-21] and anti-inflamonatary[22] *etc*. also Benzofuran derivatives posses a wide range of biological activities. They have been reported to possess antimicrobial[23-26], antitumour[27, 28], anti-inflammatory[29] activity *etc.* Hence it was though interesting to prepare the combined molecule having benzimidazole-benzofurane with expected biological activity.

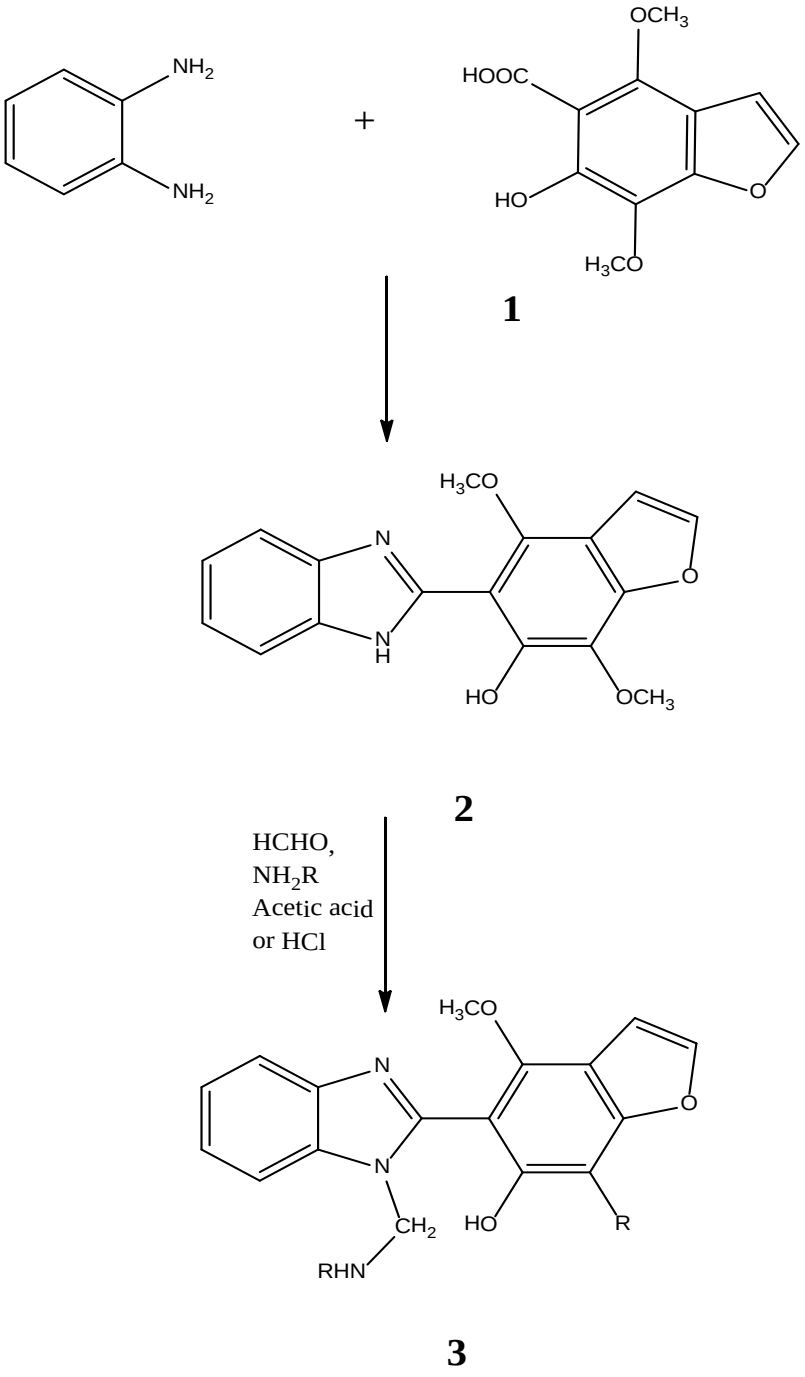
Chemistry

The benzimidazole starting material 5-(1*H*-benzo[*d*]imidazol-2-yl)-4,7-dimethoxybenzofuran-6-ol (2) was synthesized using Philips' [30] method starting from o-phenylenediamine and 6-hydroxy-4,7-dimethoxybenzofuran-5-carboxylic acid (1)

The Mannich bases **3a-k** were formed by the reaction of compound **2** with formaldehyde and 4-chloro-2-nitroaniline or 4-fluoroaniline, 2,6-dichloroanine, n-propylamine, dimethylamine, ethylamine, isopropylamine, piperidine, 2-aminobenzoic acid, or 2-hydroxyaniline respectively.(c.f. scheme 1).

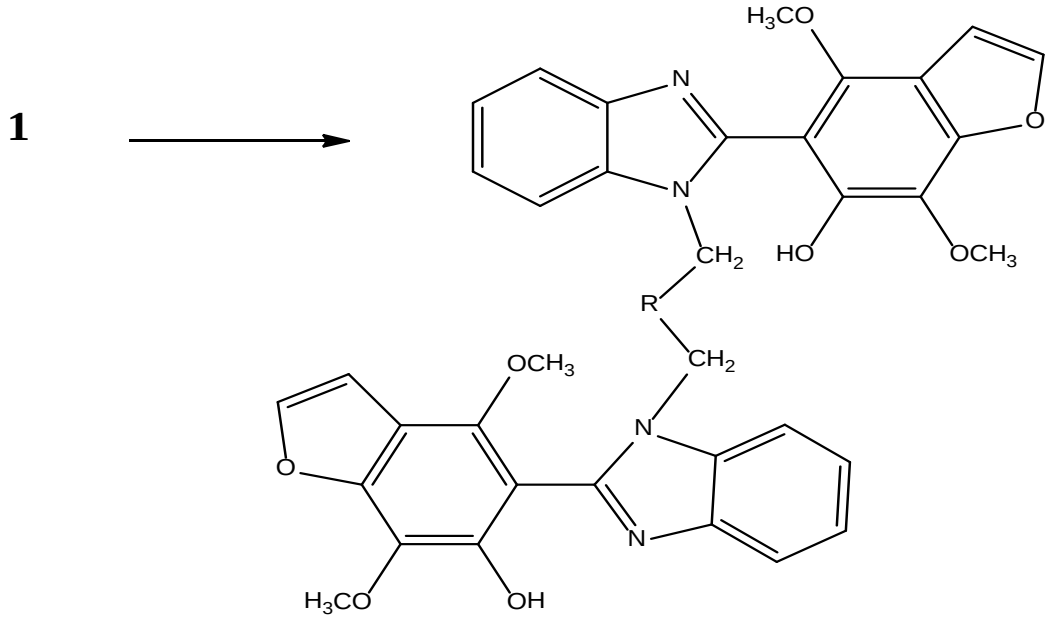
When(**2)** was subjected to Mannich reaction using 1,4-phenylenediamine or piperazine led to the 1,4-disubstituted benzenes **4a** or 1,4-disubstituted piperazines **4b**.(c.f. scheme 2).

Scheme 1:



3a, R= 4-chloro2-nitrophenyl
b, R= 4-chlorophenyl
c, R= 4-flourophenyl
d, R= 2,6-dichlorophenyl
e, R= n-propyl
f, R= dimethyl
g, R= ethyl
h, R= isopropyl
i, R= piperidyl
j, R= 2-carboxyphenyl
k, R= 2-hydroxyphenyl

Scheme 2:



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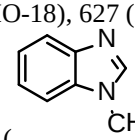
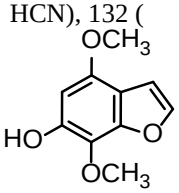
4a, R=1,4-diaminophenyl
b, R=piperazinyl

Experimental

NMR of the synthesized compounds were not performed because the great difficulty in solubility

Table1: Spectral data of compounds 2 , 3a-k, 4a,b

No.	IR (KBr) υ_{max}/cm^{-1}	MS, m/z (%)	m.p.	Color
2	3389 (br. NH & OH), 2939, 2842 (aliph. C-H stretching), 1660 (C=N), 1623 (C=C), 1592 (C=C)	328 ($M+H_2O$), 310 (M), 309 (M-1), 280 (M-HCHO), 245 (base peak), (M-HCHO-H_2O-NH_3)	240^{0}C	Black
3a	3614 (OH), 3263(OH & NH), 2943, 2839 (aliph. C-H), 1620(C=N), 1508, 1481 (C=C), 920 (C-Cl), 806 (C-NO_2)	495 (M), 497 (M+2), 456 (M-NO+1), 172 (C6H4ClN2O2), 155 (171-16-1)	>350 ^{0}C	Dark brown
3b		413 (M-HCl-H), 393 (413-18), 367, 389, 319, 281, 42 (base peak)	>350 ^{0}C	Dark brown
3c	3421 (OH & NH), 2921 (C-H stretching), 1640 (C=N), 1618 (C=C), 1482.	439 (M), 440 (M+1), 438, 437, 383, 355 (base peak), 239, 211	>350 ^{0}C	Dark brown
3d	3407 (OH & NH), 2939, 2840 (C-H stretching), 1650 (C=N), 1611 (C=C), 1482, 678 (C-Cl)	483 (M), 442 (483-Cl), 417 (447-HCHO), 389 (417-CO), 63 (base peak)	>350 ^{0}C	Dark brown
3e	3409 (NH & OH), 2939, 2841 (aliph. C-H	367 (M-CH_3+1), 339(M-n-propyl+1), 294 (M-n-propyl-NH-CH_2-17+1), 276,	>350 ^{0}C	Dark brown

	stretching), 1655 (C=N), 1617 (C=C)	265		
3f	3418 (NH & OH), 2938 (aliph. C-H stretching), 1660 (C=N), 1616,1482 (C=C)	369 (M+2), 368(M+1), 367(M), 353(M-CH_2), 119 (base peak).	>350 ^{0}C	Dark brown
3g	3407, 3224 (NH & OH), 2939 (aliph. C-H stretching), 1655 (C=N), 1614, 1513 (C=C).	368 (M-CH_3+2H^+), 277, 204, 190, 57 (base peak)	>350 ^{0}C	Reddish brown
3h	3412, (NH & OH), 2971, 2937, 2846 (aliph. C-H stretching), 1640 (C=N), 1616, 1500 (C=C).	382 (M+1), 381 (M), 369 (M-CH_2 +1), 286(base peak), 204, 189, 161, 119…	>350 ^{0}C	Dark brown
3i		407 (M), 311 (M-piperidyl-2), 78, 63(base peak).	>350 ^{0}C	Dark brown
3j	3402, (OH, NH_3^+), 2937, (aliph. C-H stretching), 1700 (shoulder C=O), 1616 (C=N), 1612 (COO^-), 1481(C=C).	460 (M+1), 459 (M), 414, 397, 249, 121 (base peak)	>350 ^{0}C	Dark brown
3k	3614 (OH), 3139 (NH & OH), 2958, 2750, 2592 (aliph. C-H stretching), 1616 (C=N) 1523, 1446 (C=C).	401 (M), 254, 244, 230 (base peak), 122,109……	>350 ^{0}C	Dark brown
4a	3409 (NH & OH), 2943, 2839 (aliph. C-H stretching), 1660 (C=N), 1620, 1512 (C=C)	752 (M), 108 (base peak)	>350 ^{0}C	Dark brown
4b	3394 (NH & OH), 2947 (aliph. C-H stretching), 1635 (C=N), 1508 (C=C)	730 (M+1), 729 (M), 672 (M-2CHO), 654 (M-2CHO-18), 627 (M-2CHO-18-  HCN), 132 (), 112 (base peak), 84 (piperazine)	>350 ^{0}C	Dark brown

Biological Activity

The antimicrobial activity of material against *E. coli* was investigated as a pathogenic bacteria . Bacteriological Tests were performed in lysogeny broth (LB) (Bertani, G. (2004)) medium on solid agar plates and in liquid systems. The materials were shown to be an effective bactericide or bacteriostatic . The results show effect of 32 materials on growth of pathogenic bacteria by Growth measurements methods

Material and Methods

Bactericidal test

Escherichia coli strain was grown on (lb) broth for 24 hour were cultured on 20 ml on 50 ml falcon of lb broth by add 10 microliter from culture and supplemented with 0.3 gram from tested materials . material- free lb broth cultured under the same conditions were used as a control > the falcons was incubation in shaker incubator for 24 hour in 30 ^{c} at 150 rpm >>>the table show O.D (optical density) for control and other treatments at wave 600

Counting plates

The treatments was cultured after 24 hour incubation on lb agar plates by pour plate method to counting survival bacteria to indicator the effect of material on bacteria. The culture was diluted to 10^{-7} and then put 50 microliter on plate and then incubated for 24 hour and 30 ^{c}

Results and Discussion

The table show the Comparison between the control and other treatment on optical dencity and Counting plates and it showe the materials 3b was Active growth and materials 3a and 4b was made Percentage of death 66 % ,and material 3f was made percentage of death 33%.

Table 2: O.D for culture supplemented with 10 materials .and show plat counting result

a Material	O.D	Percentage of death %	Plate count
Cont	0.6	0	1205 cell
2	0.5	16	1020
3a	0.2	66	400
3b	0.6	X	1170
3e	0.5	16	1172
3f	0.4	33	900
3g	0.5	16	1100
3i	0.6	0	1205
3j	0.5	16	1006
4a	0.5	16	1010
4b	0.2	66	204

Acknowledgement

The authors would like to thanks Taibah University KSA ,Scientific Researches Deanship for Financial support under research number 431/430 , thanks for faculty of science, department of chemistry. And Dr. Sahar A. Zaki Head, Enverionmental Biotechnology Department Gentetic Engineering and Biotechnology Research Institute City of Scientific Research and Technological Applications.

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