SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 3-(4-FLUOROPHENYL)BENZO[*g*]INDAZOLES AND 1-PYRAZOLYLTHIAZOLES

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A new series of 3-(4-fluorophenyl)benzo[*g*]indazoles derivatives have been synthesized by simple, high yielding routes. The key step in the construction of the 3-(4-fluorophenyl)benzo[*g*]indazoles nucleus involves the reaction of α-tetralone with 4-fluorobenzaldehyde followed by reaction with hydrazine or thiosemicarbazide. The newly synthesized compounds were evaluated for their antimicrobial activity and compounds **5**, **6b**, **12d** and **16b** demonstrated inhibitory effects on the growth of a wide range of microbes.

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INTRODUCTION

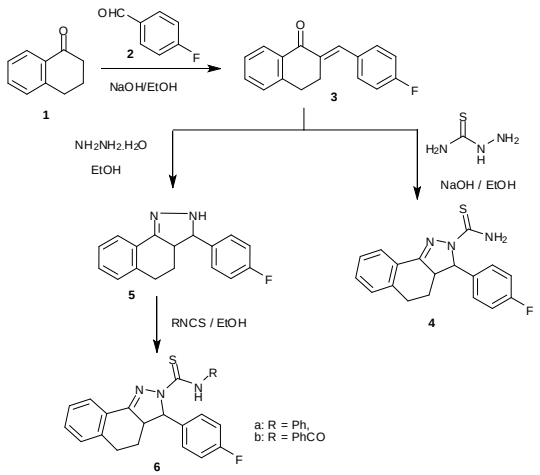
Literature survey revealed that many compounds bearing five membered rings such as pyrazoles and thiazoles show significant biological activity. Compounds containing pyrazole nucleus exhibit antibacterial,[1] antifungal,[2] anti-tubercular,[3] anti-inflammatory activities.[4] The thiazole nucleus is also present in various molecules with diverse pharmacological properties, such as antimicrobial.[5] Also, pyrazolylthiazoles showed excellent antimicrobial activities.[6-8] Keeping this observation in view and in continuation of our research on the synthesis of heterocyclic compounds containing nitrogen, sulfur and bicyclic systems with expected biological activity.[6,9] this paper presents the synthesis of several new heterocyclic compounds which contain diphenylsulfone 3-(4-fluorophenyl)benzo[*g*]indazole moiety and the study of their antibacterial and antifungal activities.

RESULTS and DISCUSSION

The compound (*E*)-2-(4-fluorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **3** was prepared by the Claisen-Schmidt condensation reaction of α-tetralone **1** and 4-flurobenzaldehyde 2 (Scheme 1).[10]

The target compounds 3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[g]indazoles **4-6** were prepared from **3** by reaction with thiosemicarbazide or hydrazine followed by isothiocyanates in anhydrous ethanol.

The structures **4-6** were fully supported by elemental analysis and spectral analysis.



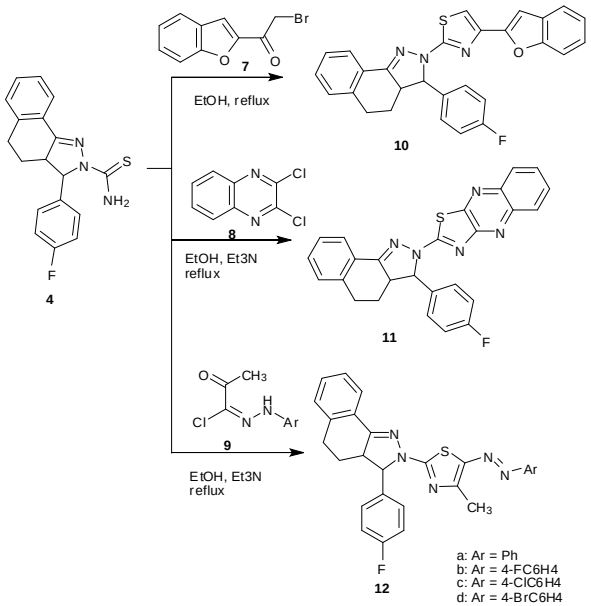
Scheme 1

In the ^{1}H NMR spectrum of **4** the NH_2 proton appears at δ 11.02 ppm. In the mass spectra of **4**, **6a** and **6b** showed the molecular ion peaks at m/z 325, 401 and 429, respectively, in agreement with the calculated masses.

The reaction sequences employed for synthesis of title compounds **10-12** are shown in Scheme 2. A one pot synthesis of benzo[g]indazol-2-ylthiazole derivatives **10-12** was achieved when 3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-2-carbothioamide **4** and 2-bromo-acetylbenzofuran **7** or 3,4-dichloroquinoxaline **8** were refluxed in ethanol. Also, benzo[*g*]indazol-2-yl-4-methyl-5-(phenyldiazenyl)thiazoles **12a-d** were produced in good yields by reaction of **4** with hydrazonoyl chlorides **9** in refluxing ethanol and in the presence of a catalytic amount of triethylamine.

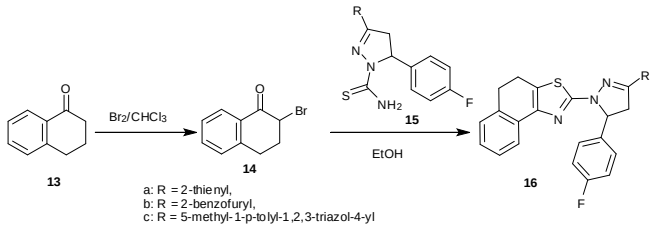
The ^{1}H NMR spectrum of **10**, a singlet at δ 8.02 was due to the thiazole-H. The protons of furan proton of benzofuran moiety resonated as singlet at δ 6.93 ppm. A characteristic singlet was observed at δ 2.49 due to the proton of the methyl group in **12**. Further evidence for the formation of benzo[g]indazol-2-ylthiazole derivatives were obtained by

recording its mass spectra. The mass spectra of compounds **10**, **11** and **12b** showed molecular ion peaks at m/z 465, 451 and 485, respectively, in conformity with their molecular formulas.



Scheme 2

Scheme 3 reports the reactions which led to pyrazol-1-yl-4,5-dihydronaphtho[1,2-*d*]thiazoles **16a-c**. Derivatives of pyrazol-1-yl-4,5-dihydronaphtho[1,2-*d*]thiazole series **16a-c** were obtained by a direct reaction between 2-bromo-3,4-dihydronaphthalen-1(2*H*)-one **14** and the appropriate 4,5-dihydro-1*H*-pyrazole-1-carbothioamides **15** by refluxing in neutral medium.



Scheme 3

Evidence for the formation of the pyrazol-1-yl-4,5-dihydronaphtho[1,2-*d*]thiazoles is found in the mass spectra of the **16a-c**. The molecular ion peaks of **16a-c** appeared at m/z 431, 465 and 520 respectively, which fit exactly with their calculated masses.

Antimicrobial activity

All the synthesized compounds were screened for their antibacterial and antifungal activities at 100 µg/mL concentration against four *Gram positive bacteria* (*StaphelococcusAureus*ATCC 29213; *B. subtilis ATCC6633*; *B. megaterium ATCC* 9885 and *Sarcinalutea*), three *Gram negative bacteria* (*Klebseillapeneumoniae*ATCC13883; *Pseudomonas. Aeroginosa* ATCC27953; *E. coliATCC 25922*) and two yeast (*Saccharomyces cervesia* and *Candida Albicans* NRRL Y-477).

Table 1. Characteristic data of the synthesized compounds

Entry	Mol. Formula (M. Wt)	Calcd./Found C%	H%	N%
4	$C_{18}H_{16}FN_3S$	66.44	4.96	12.91
	(325.40)	66.62	4.88	12.93
5	$C_{17}H_{15}FN_2$	76.67	5.68	10.52
	(266.31)	76.72	5.81	10.60
6a	$C_{24}H_{20}FN_3S$	71.80	5.02	10.47
	(401.50)	71.91	5.12	10.36
6b	$C_{25}H_{20}FN_3OS$	69.91	4.69	9.78
	(429.51)	70.02	4.77	9.88
10	$C_{28}H_{20}FN_3OS$	72.24	4.33	9.03
	(465.54)	72.31	4.39	9.16
11	$C_{26}H_{18}FN_5S$	69.16	4.02	15.51
	(451.52)	69.20	4.16	15.30
12a	$C_{27}H_{22}FN_5S$	69.36	4.74	14.98
	(467.56)	69.40	4.86	15.12
12b	$C_{27}H_{21}F_2N_5S$	66.79	4.36	14.42
	(485.55)	66.83	4.45	14.62
12c	$C_{27}H_{21}ClFN_5S$	64.60	4.22	13.95
	(502.01)	64.71	4.31	13.81
12d	$C_{27}H_{21}BrFN_5S$	59.34	3.87	12.82
	(546.46)	59.40	3.77	12.89
16a	$C_{24}H_{18}FN_3S_2$	66.80	4.20	9.74
	(431.55)	66.89	4.13	9.80
16b	$C_{28}H_{20}FN_3OS$	72.24	4.33	9.03
	(465.54)	72.36	4.42	9.00
16c	$C_{30}H_{25}FN_6S$	69.21	4.84	16.14
	(520.62)	69.29	4.89	16.21

Ciprofloxacin and ketoconazole were respectively used as standard antibacterial and antifungal reference, respectively. The results of antimicrobial activities were shown in Tables 2. Data in Table 2 revealed that most of compounds have superior significant antifungal potency to antibacterial potency. Compounds **5**, **6b**, **12d** and **16b** exhibited the highest potency against most of the tested organisms with respect to reference drugs. Compound **5** inhibited the growth of all the tested microorganisms with inhibition zones 28-38 mm. While compound **16b** showed excellent activity with inhibition zone 22-31mm. Also, compound **16c** showed highest activity against *B. subtilis ATCC6633* with inhibition zone 23 mm.

EXPERIMENTAL

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were carried from the microanalytical unit, CairoUniversity, Giza, Egypt. The IR spectra were recorded in potassium bromide disks on a JASCO FT/IR-6100. ^{1}H-NMR spectra were run on JOEL-ECA 500MHz in deuterateddimethylsulphoxide (DMSO-d_6). Chemical shifts values (δ) are given in parts per million (ppm). The mass spectra were performed using mass Varian MAT CH-5 spectrometer at 70eV. 1-(Benzofuran-2-yl)-2-bromoethanone **7**[11] 2,3-dichloroquinoxaline **8**[12] hydrazonoyl halides **9**,[13] 2-bromo-3,4-dihydronaphthalen-1(2*H*)-one **14**,[14] 4,5-dihydro-1*H*-pyrazole-1-carbothioamides **15a**,[15] **15b**[16] and **15c**[6] were prepared according to literature.

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Table 2. Antimicrobial activity expressed as inhibition diameter zones in millimeters (mm) of chemical compounds against the pathological strains based on well diffusion assay

No.	Gram positive bacteria				Gram negative bacteria			Yeast	
	***S. aureus* ATCC 29213**	***B. subtilis ATCC6633***	***B. megaterium ATCC* 9885**	***Sarcina lutea***	***K. pneumoniae* ATCC13883**	***P. Aeroginosa* ATCC27953**	***E. coli, ATCC* 25922**	***S. cereviase***	***C. Albicans* NRRL Y-477**
4	15	17	15	14	18	18	15	18	19
5	28	33	30	34	33	34	38	30	31
6a	19	29	18	19	16	14	15	16	19
6b	20	27	21	23	18	16	15	18	20
10	15	24	15	18	19	N.A.	14	17	15
11	15	19	15	19	N.A.	N.A.	16	19	16
12a	20	18	19	16	18	20	19	20	20
12b	15	24	15	15	19	18	20	19	18
12c	16	31	19	16	18	19	18	18	16
12d	29	17	25	23	N.A.	16	19	N.A.	N.A.
16c	18	23	17	13	14	16	15	16	15
16a	18	24	19	20	18	14	15	20	19
16b	22	29	30	31	31	30	28	31	33
16c	18	23	17	13	14	16	15	16	15
Ciproflox a-cin	20	22	24	20	25	24	23	N.A.	N.A.
Ketocona-zole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	23	22

The experiment was carried out in triplicate and the average zone of inhibition was calculated

Table 3. Minimum inhibitory concentration (μg mL^{-1}) against the pathological strains based on two fold serial dilution technique

No.	Gram positive bacteria				Gram negative bacteria			Yeast	
	***Staphelococcus aureus* ATCC 29213**	***B. subtilis ATCC6633***	***B. megaterium ATCC* 9885**	***Sarcina lutea***	***Klebseillapeneumoniae*ATCC13883**	***Pseudomonas. Aeroginosa* ATCC27953**	***E. coli ATCC* 25922**	***Saccharomyces cervesia***	***CandidaAlbicans* NRRL Y-477**
4	-	200	-	-	200	200	-	200	200
5	28	50	50	25	50	25	25	50	25
6a	200	50	200	200	200	-	-	200	200
6b	200	50	100	100	200	200	-	200	100
10	-	100	-	200	200	-	-	200	-
11	-	200	-	100	-	-	200	200	200
12a	200	200	100	200	200	100	200	100	200
12b	-	100	-	-	200	200	200	100	200
12c	-	50	200	200	200	200	200	200	200
12d	50	200	50	100	-	200	200	N.A.	N.A.
16a	200	100	100	100	200	-	-	100	-
16b	100	50	50	50	50	50	50	50	50
16c	200	100	200	-	200	200	-	200	-
Ciprofloxacin	25	25	25	25	25	25	25	N.A.	N.A.
Ketoconazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	25	25

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3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-2-carbothioamide (4)

To a suspension of chalcone **3** (10 mmol, 2.52.g) and sodium hydroxide (25 mmol, 1.0 g) in ethanol (50 mL), thiosemicarbazide (12 mmol, 1.1 g) was added. The mixture was refluxed for 12 h, then left to cool; the solid product was filtered off, washed with ethanol and dried. Yield 58 %; m.p. 228-9°C; IR (KBr) ν_{max}/cm^{-1} 3465, 3325 (NH_2); ^1H NMR (DMSO-d_6) δ 1.97 (m, 2H, CH_2), 2.10 (m, H, CH), 2.95 (m, 2H, CH_2), 5.48 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.20-7.89(m, 8H, Ar-H), 11.02 (s, 2H, NH_2, D_2O-exchangeable); MS m/z (%): 325 (M^+, 36), 95 (100).

3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (5)

To a solution of chalcones **3** (2 mmol, 0.5 g) in ethanol (30 mL), hydrazine hydrate 80 % (5 mmol) was added. The reaction mixture was refluxed for 6 h. Left to cool to room temperature, and the white solid product was filtered and washed with ethanol. Yield 61 %; m.p. 108-9 °C; IR (KBr) ν_{max}/cm^{-1}, 3220 (NH); ^1H NMR (DMSO-d_6) δ 1.92 (m, 2H, CH_2), 2.12 (m, 1H, CH), 2.92 (m, 2H, CH_2), 5.44 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.20-7.89(m, 8H, Ar-H), 10.12 (s, 1H, NH, D_2O-exchangeable); MS m/z (%): 266 (M^+, 22), 95(100).

Benzo[*g*]indazole-2-carbothioamides (6a,b)

A mixture of **5** (2 mmol, 0.53 g) and phenylisothiocyante (2 mmol, 0.27 g) {or benzoylisothiocyanate (2 mmol, 0.33 g) in case of **6b**} in dry ethanol (30 mL) was refluxed for 5 h. Cool to the room temperature and the formed solid product was collected by filtration to give products **6a,b**.

3-(4-Fluorophenyl)-*N*-phenyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]-indazole-2-carbothioamide (6a)

Yield 73 %; m.p. 158-9 °C; IR (KBr) ν_{max}/cm^{-1}, 3198 (NH); ^1H NMR (DMSO-d_6) δ 1.96 (m, 2H, CH_2), 2.28 (m, H, CH), 2.99 (m, 2H, CH_2), 5.42 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.20-7.89(m, 13H, Ar-H), 9.88 (s, 1H, NH, D_2O-exchangeable); MS m/z (%): 401 (M^+, 28), 77 (100).

***N*-(3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]inda-zole-2-carbonothioyl)benzamide (6b)**

Yield 70 %; m.p. 184-6°C; IR (KBr) ν_{max}/cm^{-1}, 3198 (NH); ^1H NMR (DMSO-d_6) δ 1.95 (m, 2H, CH_2), 2.28 (m, H, CH), 2.98 (m, 2H, CH_2), 5.41 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.21-7.88(m, 13H, Ar-H), 10.21 (s, 1H, NH, D_2O-exchangeable); MS m/z (%): 429 (M^+, 33), 77 (100).

Synthesis of 10-12

General procedure

To a suspension of compound **4** (1 mmol, 0.33 g) in ethanol (20 mL) the 1 mmol of appropriate reagent {(2-bromoacetylbenzofuran, **7**) or (3,4-dichloroquinoxaline, **8**) or hydrozonoyl chlorides, **9** + Et_3N)} was added and heated under reflux for 2.5 h. After cooling, the precipitate was collected by suction filtration.

4-(Benzofuran-2-yl)-2-(3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)thiazole (10)

Yield 45 %; m.p. 218-9 °C; ^1H NMR (DMSO-d_6) δ 1.84 (m, 2H, CH_2), 2.28 (m, H, CH), 2.98 (m, 2H, CH_2), 5.95 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 6.96 (s, 1H, benzofuryl-CH), 7.17-7.97 (m, 12H, Ar-H), 8.02(s, 1H, thiazolyl-CH); MS m/z (%): 465 (M^+, 11), 85 (100).

2-(3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)thiazolo[4,5-*b*]quinoxaline (11)

Yield 42 %; m.p. 192-3°C;^1H NMR (DMSO-d_6) δ 1.84 (m, 2H, CH_2), 2.28 (m, H, CH), 2.98 (m, 2H, CH_2), 5.95 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.20-7.95(m, 12H, Ar-H); MS m/z (%): 451 (M^+, 23), 187 (100).

2-(3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-4-methyl-5-(phenyldiazenyl)thiazole (12a)

Yield 66 %; m.p. 178-9 °C;^1H NMR (DMSO-d_6) δ 1.79 (m, 2H, CH_2), 2.28 (m, H, CH), 2.49(s, 3H, CH_3), 2.93 (m, 2H, CH_2), 5.96 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.11-7.97(m, 13H, Ar-H); MS m/z (%): 467 (M^+, 19), 95 (100).

2-(3-(4-Fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-5-((4-fluorophenyl)diazenyl)-4-methylthiazole (12b)

Yield 66 %; m.p. 220-1°C;^1H NMR (DMSO-d_6) δ 1.79 (m, 2H, CH_2), 2.28 (m, H, CH), 2.45(s, 3H, CH_3), 2.93 (m, 2H, CH_2), 5.93 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.11-7.97(m, 12H, Ar-H); MS m/z (%): 485 (M^+, 60), 95 (100).

5-((4-Chlorophenyl)diazenyl)-2-(3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-4-methylthiazole (12c)

Yield 69 %; m.p. 244-5°C; ^1H NMR (DMSO-d_6) δ 1.79 (m, 2H, CH_2), 2.28 (m, H, CH), 2.51(s, 3H, CH_3), 2.93 (m, 2H, CH_2), 5.93 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.11-7.97(m, 12H, Ar-H); MS m/z (%): 501 (M^+, 56), 95 (100).

5-((4-Bromophenyl)diazenyl)-2-(3-(4-fluorophenyl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)-4-methylthiazole (12d)

Yield 73 %; m.p. 250-1°C;^1H NMR (DMSO-d_6) δ 1.79 (m, 2H, CH_2), 2.28 (m, H, CH), 2.50(s, 3H, CH_3), 2.94 (m, 2H, CH_2), 5.93 (dd, 1H, CH, J= 8.45 Hz, J= 8.45 Hz), 7.11-7.97(m, 12H, Ar-H); MS m/z (%): 546 (M^+, 66), 95 (100).

Synthesis of dihydronaphtho[1,2-*d*]thiazoles 16

General procedure

A mixture of 2-bromo-3,4-dihydronaphthalen-1(2*H*)-one **14** (1mmol) and appropriate pyrazoline-1-carbothioamide **15** (1mmol) dissolved in ethanol (30 mL) was refluxed for 4 h. The formed solid was filtered off and dried.

2-(5-(4-Fluorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4,5-dihydronaphtho[1,2-*d*]thiazole (16a)

Yield 53 %; m.p. 180-1 °C; ^{1}H NMR (DMSO-d_6) δ 2.87-2.89 (m, 4H, $2CH_2$), 4.09 (m, 1H, CH), 6.05 (dd, 2H, CH_2, J=10.8 Hz, J=10.8 Hz), 7.15-7.75 (m, 11H, Ar-H); MS m/z (%): 431 (M^+, 19), 187 (100).

2-(3-(Benzofuran-2-yl)-5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4,5-dihydronaphtho[1,2-*d*]thiazole (16b)

Yield 45 %; m.p. 170-1 °C; ^{1}H NMR (DMSO-d_6) δ 2.87-2.89 (m, 4H, $2CH_2$), 4.09 (m, 1H, CH), 6.05 (dd, 2H, CH_2, J=10.8 Hz, J=10.8 Hz), 7.15(s, 1H, benzofuryl), 7.18-7.75 (m, 12H, Ar-H); MS m/z (%): 465 (M^+, 19), 187 (100).

2-(5-(4-Fluorophenyl)-3-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4,5-dihydronaphtho[1,2-*d*]thiazole (16c)

Yield 61 %; m.p. 185-6 °C; ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.86-2.88 (m, 4H, $2CH_2$), 4.05 (m, 1H, CH), 6.05 (dd, 2H, CH_2, J= 10.8 Hz, J= 10.8 Hz), 7.15 (s, 1H, benzofuryl), 7.18-7.75 (m, 12H, Ar-H); MS m/z (%): 520 (M^+, 12), 187 (100).

Antimicrobial activity

Chemical compounds were individually tested against a panel of gram positive and gram negative bacterial pathogens, yeast and fungi. Antimicrobial tests were carried out by the agar well diffusion method,[17] using 100 µL of suspension containing $1x10^8$ CFU/mL of pathological tested bacteria and 1 $x10^6$ CFU/ml of yeast spread on nutrient agar (NA) and Sabourand dextrose agar (SDA) respectively. After the media had cooled and solidified, wells (10 mm in diameter) were made in the solidified agar and loaded with 100 µL of tested compound solution prepared by dissolving 100 mg of the chemical compound in one ml of dimethyl sulfoxide (DMSO). The inculcated plates were then incubated for 24 h at 37 °C for bacteria and 48 h at 28 °C for fungi. Negative controls were prepared using DMSO employed for dissolving the tested compound. Ciprofloxacin (50 µg mL^{-1}) and Ketoconazole (50 µg mL^{-1}) were used as standard for antibacterial and antifungal activity respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The observed zone of inhibition is presented in Table 1. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate and the average zone of inhibition was calculated.

Minimal inhibitory concentration (MIC) measurement

The bacteriostatic activity of the active compounds (having inhibition zones (IZ) ≥ 16 mm) was then evaluated using the two fold serial dilution technique.[18] Two fold serial dilutions of the tested compounds solutions were prepared using the proper nutrient broth. The final concentration of the solutions was 200, 100, 50 and 25 µg mL^{-1}. The tubes were then inoculated with the test organisms, grown in their suitable broth at 37 °C for 24 hours for bacteria (about 1×10^8 CFU/ml), each 5 ml received 0.1 ml of the above inoculum and incubated at 37 °C for 24 h. The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC).

Minimal inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) of the synthesized compounds against highly inhibited organisms is reported in Table 3.

Compounds **5** revealed the lowest MIC (25 µg mL^{-1}) against *Sarcina Lutea*, *Pseudomonas Aeroginosa* ATCC27953 and *E. coli ATCC 25922*. On the other hand, compounds **16b** exhibited high MIC (50 µg mL^{-1}) against all the tested microorganisms expect *Staphylococcus Aureus* ATCC 29213. Compound **6a**, **6b**, **12a** and **16c** showed the lowest MIC 200 µg mL^{-1} against most of the tested organisms(Table 3).

CONCLUSION

Novel 3-(4-fluorophenyl)-benzo[*g*]indazoles derivatives, with potential antimicrobial activity, were prepared from available α-tetralone. The new compounds were tested for their antimicrobial activity; some of them showed significant activities, probably due to the presence of some moieties such as benzo[*g*]indazoles and thiazole.

REFERENCES

[1]Mitchell, R. E., Greenwood, D. R., Sarojini, V. *Phytochemistry*, **2008**, *69*, 2704-7.

[2]Zhang, C. Y., Liu, X. H., Wang, B. L., Wang, S. H., Li, Z. M. *Chem. Biol. Drug. Des.*, **2010**, *75*, 489-93.

[3]Pandit, U.; Dodiya, A. *Med. Chem. Res*., **2013**, *22*, 3364-71.

[4]Tewari, A. K., Srivastava, P., Singh, V. P., Singh, A., Goel, R. K., Mohan, C. G., *Chem. Pharm. Bull.*, **2010**, *58*, 634-8.

[5]Pucci, M. J., Bronson, J. J., Barrett, J. F., Den Bleyker, K. L., Discotto, L. F., Fung-Tomc, J. C., Ueda, Y. *Antimicrob. Agents Chemother*., **2004**, *48*, 3697-701.

[6]Abdel-Wahab, B. F., Sediek, A., Mohamed, H. A., Awad, G. E. A. *Lett. Drug Des. Discov*., **2013**, *10*, 111-8.

[7]Abdel-Wahab, B. F., Mohamed, H. A., Farahat, A. A., Dawood, K. M., *Heterocycles*, *2011*, *83*, 2731-67.

[8]Abdel-Wahab, B. F., Shaaban, S., *Synthesis*, **2014,** *46*, 1709-1716.

[9]Abdel-Wahab, B. F., Abdel-Gawad, H., Awad, G. E. A., Badria, F. A., *Med. Chem. Res*., **2012**, *21*, 1418–1426.

[10]Feng, Y., Ding, X., Chen, T., Chen, L., Liu, F., Jia, X., Luo, X., Shen, X., Chen, K., Jiang, H.,Wang, H., Liu, H., Liu, D., *J. Med. Chem.*, **2010**, *53*, 3465-79.

[11]Shriner, R. L., Anderson, J., *J. Am. Chem. Soc*., **1939**, *61*, 2705-8.

[12]Krishnan, V. S. H., Chowdary, K. S., Dubey, P. K., *Indian J. Chem.*, **1999**, *38B*, 45-51.

[13]Czollner, L., Szilagyi, G., Lango, J., Janaky, J., *Arch. Pharm.*, **1990**, *323*, 225-7.

[14]Prokopowicz, M., Młynarz, P., Kafarski, P., *Tetrahedron Lett*., **2009**, *50*, 7314-7.

[15]Fun, H. K., Suwunwong, T., Chantrapromma, S., *ActaCryst*., **2012**, *68*, 259-60.

[16]Mohamed, H. A., Abdel-Latif, E., Abdel-Wahab, B. F., Awad, G. E. A., *Int. J. Med. Chem*., **2013**, 1-6.

[17]Scott, A. C., *Laboratory Control of Antimicrobial Therapy.* In: Collee, J. G., Duguid, J. P., Fraser, A. G., Marmion, B. P., *Mackie and MacCartney Practical Medical Microbiology*, 13th Ed, Churchill Livingstone. **1989,** *2*, 161–181.

[18] Perez, C., Pauli, M., Bazevque, P., *Acta Biol. Med. Exp.*, **1990**, *15*, 113–115.

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