MICROWAVE-ASSISTED SYNTHESIS OF TETRAZOLE BASED BIPHENYLS DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

An environmentally friendly method has been developed for substituted (*E*)-(3-(4-(1*H*-tetrazole-5-yl)styryl)benzofuran-2-yl)([1,1'-biphenyl]-4-yl)methanone scaffolds by Suzuki cross-coupling reaction in an aqueous medium under both microwave irradiation and conventional heating methods. The structures of the synthesized scaffolds were characterized by IR, NMR, and mass spectral analysis. Furthermore, the synthesized scaffolds were screened for their *in-vitro* antibacterial, antifungal activities and most of the scaffolds exhibited better activity compared to standard drugs.

Keywords: Aromatic Boronic Acid, Suzuki Cross-coupling Reaction, Microwave Irradiation, Antimicrobial Activity

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INTRODUCTION

Tetrazole is a key structural motif in heterocyclic chemistry, it has been found in many drug molecules¹⁻² and these possess wide a range of biological activities.³⁻¹⁰ Aryl-aryl bond development is very significant in organic synthesis and has a broad range of applications in industrial interest, as well as the synthesis of pharmaceuticals, polymers, herbicides and other material.¹¹ The palladium-catalyzed by aryl halides with aryl boronic acid known as Suzuki cross-coupling reaction, is one of the most important and potent methods for the construction of biphenyl and polyaryls,¹²⁻¹⁴ due to the broad functional group tolerance and the low toxic reagents and the probability of using of green solvents as reaction medium.

The current years, organic synthesis is carried out in aqueous phase or containing water or mixture of organic/water as the solvent has been traditional in the field of organic chemistry. One of the most significant techniques is microwave irradiation^{16,17} which useful in organic synthesis and has been the eco-friendly, inflammable, enhanced rate of reaction, reduced side products, improved product yield as compared to conventional heating.¹⁸ Consequently, the microwave-assisted reactions using green solvents like water, to easily achieve the aim of green chemistry.

Encourage of biological activity and microwave irradiation techniques; we decided the synthesis of novel tetrazole containing benzofuran scaffolds **5a-5h** and respective aryls **7a-7j** carried out under both conventional heating, microwave irradiation methods and evaluated their antimicrobial activity.

EXPERIMENTAL

Materials and Methods

Melting points were determined in an open glass capillary tube on a Gallen-Kamp MFB-595 apparatus and are uncorrected. The IR spectra were taken on a Perkin-Elmer FT-IR-8400s, using samples in KBr

Rasayan J. Chem., 13(1), 601-609(2020)

<http://dx.doi.org/10.31788/RJC.2020.1315490>

disks. Microwave reactions were carried out in the milestone multi SYNTH microwave system. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Avance II 400 spectrometer. Mass spectra were recorded on SHIMADZU LCMS 2020 mass spectrometer.

RESULTS AND DISCUSSION

The compounds **3a-3g** on reaction with different substituted phenacyl bromides in the presence of anhydrous potassium carbonate as a base in dry acetone as a solvent and refluxed to obtained new compounds **5a-5h**. Latter compound **5h** on treated with substituted aryl boronic acids **6a-6j** in presence of $\text{Pd}(\text{PPh}_3)_4$ as catalyst and Na_2CO_3 as a base to obtain the target molecules **7a-7j** represented in Scheme-1. All Synthesised scaffolds **5a-5h** and **7a-7j** produced better yield along with shorter reaction duration using microwave irradiation method as compared to the conventional heating method (Table-1).

Scheme-1: The Synthetic Pathway for Compounds **5a-5h** and **7a-7j**.

Table-1: The Comparison of Yields and Reaction Times of the Synthesized Compounds **5a-5h** and **7a-7j**

Compounds	Conventional Heating		Microwave Irradiation		Compounds	Conventional Heating		Microwave Irradiation	
	Time (hr)	Yield (%)	Time (min)	Yield (%)		Time (hr)	Yield (%)	Time (min)	Yield (%)
5a	8	60	20	80	7b	7	62	21	76
5b	6	65	22	72	7c	6	63	23	73
5c	8	62	23	75	7d	8	50	20	80
5d	9	63	20	73	7e	9	62	23	79
5e	9	50	20	76	7f	9	65	20	80
5f	8	62	23	80	7g	8	60	23	74
5g	7	65	20	72	7h	7	65	20	75
5h	8	61	20	78	7i	8	62	23	78
7a	8	69	23	75	7j	7	63	21	80

We carefully studied for the Suzuki coupling reaction with $\text{Pd}(\text{PPh}_3)_4$ as catalyst and Na_2CO_3 as a base, from the screening studies Table-2. Finally, its confirmed the enhancement of the amount of catalyst ($\text{Pd}(\text{PPh}_3)_4$) to obtain better yield. We successfully achieved, 15mol% of $\text{Pd}(\text{PPh}_3)_4$ as an optimal condition to get 80% of desired compounds (**7a**)

Table-2: Screening Studies for the Catalyst Loading.

$\text{Pd}(\text{PPh}_3)_4$ (mol %)	Conventional Heating		Microwave Irradiation	
	Time (hr)	Yield (%)	Time (min)	Yield (%)
1	7	10	20	18
4	7	12	20	16
8	7	20	20	28
12	7	25	20	40
15	7	67	20	80

The optimization of the reaction conditions was carried out by using different solvents and solvent mixtures (by using water as a co-solvent) and the results were depicted in Table-3. From these studies, it is clear that the tested solvents gave poor yields (38-65%) when the reaction was carried out without water. But, when we added water as a co-solvent in different proportions the yield of the product was increased. Among them, DMF/Water (7/3) is found to be a better solvent mixture for further studies.

Table-3: The Effect of Different Solvents on the Suzuki Coupling Reaction **7a**.

Entry	Solvent	Conventional Heating		MWI	
		Time (hr)	Yield (%)	Time (min)	Yield (%)
1	DMF	7	62	20	65
2	Dioxane	7	52	20	56
3	NMP	7	20	20	38
4	DMSO	7	25	20	40
5	EtOH	7	42	25	46
6	DMF / H_2O (6:4)	7	65	25	69
7	DMF / H_2O (7:3)	7	74	20	79
8	DMF / H_2O (1:1)	7	64	22	58

Experimental Procedure for the Synthesis of Compounds **5a-5h**

Conventional Heating Method

To a solution of compounds **3a-3g** (1 mmol), different substituted phenacyl bromides **4a, 4b** (1mmol) and anhydrous K_2CO_3 (3 mmol) in dry acetone were stirred at 70°C for 6-8 hr. The completion of the reaction was checked by TLC. The resulting reaction mixture was poured in ice-cold water and the precipitate formed was filtered, washed with water, dried in air and purified by column chromatography (using 40–60% petroleum ether/ethyl acetate) to afford desired compounds **5a-5h**.

Microwave Irradiation Method:

To a solution of compounds **3a-3g** (1 mmol), different substituted phenacyl bromides **4a, 4b** (1mmol) and anhydrous K_2CO_3 (3 mmol) in dry acetone were irradiated in the microwave at 100 W for 20-23 min. The completion of the reaction was checked by TLC. The resulting reaction mixture was poured in ice-cold water and the precipitate formed was filtered, washed with water, dried in air and purified by column chromatography (using 40–60% petroleum ether/ethyl acetate) to afford desired compounds **5a-5h**.

Characterization of Compounds **5a-5h**

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(phenyl)methanone (5a): mp $250\text{--}252^\circ\text{C}$. IR spectrum, ν , cm^{-1} : 3143, 2922, 1627 (CO), 1265; ^1H NMR spectrum, δ , ppm: 7.36-7.52 m (10H, Ar-H), 7.74 d (2H, Ar-H, $J=8.5$ Hz), 7.84 d (1H, Ha, $J=16.8$ Hz), 8.01 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 119.2, 119.6, 119.9, 122.7, 124.9, 125.3, 126.1, 127.0, 127.7, 128.4, 128.7, 129.5,

129.8, 132.9, 134.7, 137.6, 139.5, 146.4, 153.0, 185.7. Mass spectrum, m/z (Irel, %): 392 [M+H]; Found, %: C 73.46; H 4.11; N 14.28. $C_{24}H_{16}N_4O_2$. Calculated, %: C 73.49; H 4.14; N 14.35.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5-fluoro benzofuran-2-yl)(phenyl)methanone (5b): mp 248–112°C. IR spectrum, ν , cm^{-1} : 3157, 2941, 1622 (CO), 1267; 1H NMR spectrum, δ , ppm: 7.50–7.66 m (9H, Ar-H), 7.79 d (2H, Ar-H, $J=8.5$ Hz), 7.86 d (1H, H_α , $J=16.8$ Hz), 8.08 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 113.7, 114.1, 119.2, 119.6, 122.7, 124.9, 125.3, 126.1, 126.9, 127.8, 128.4, 129.5, 129.8, 131.3, 132.9, 134.7, 137.6, 139.5, 146.4, 148.6, 153.0, 185.7. Mass spectrum, m/z (Irel, %): 411 [M+H]; Found, %: C 70.24; H 3.68; F 4.63; N 13.65. $C_{24}H_{15}FN_4O_2$. Calculated, %: C 70.29; H 3.77; F 4.68; N 13.69.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5-chloro benzofuran-2-yl)(phenyl)methanone (5c): mp 266–268°C. IR spectrum, ν , cm^{-1} : 3076, 2941, 1622 (CO), 1267; 1H NMR spectrum, δ , ppm: 7.45–7.57 m (9H, Ar-H), 7.78 d (2H, Ar-H, $J=7.8$ Hz), 7.88 d (1H, H_α , $J=16.8$ Hz), 8.10 d (2H, Ar-H, $J=7.8$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 113.7, 119.2, 119.6, 122.7, 124.9, 126.1, 126.9, 127.7, 128.4, 129.5, 129.8, 131.3, 132.9, 134.7, 137.6, 139.5, 146.4, 148.6, 153.0, 185.7. Mass spectrum, m/z (Irel, %): 427 [M+H]; Found, %: C 67.53; H 3.54; Cl 8.31; N 13.13. $C_{24}H_{15}ClN_4O_2$. Calculated, %: C 67.58; H 3.57; Cl 8.34; N 13.19.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5-bromo benzofuran-2-yl)(phenyl)methanone (5d): mp 248–250°C. IR spectrum, ν , cm^{-1} : 3178, 2927, 1597 (CO), 1261; 1H NMR spectrum, δ , ppm: 7.47–7.65 m (9H, Ar-H), 7.81 d (2H, Ar-H, $J=7.2$ Hz), 7.87 d (1H, H_α , $J=16.8$ Hz), 8.08 d (2H, Ar-H, $J=7.2$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 113.7, 119.2, 119.6, 122.7, 125.0, 125.3, 126.1, 126.3, 127.0, 127.7, 128.4, 129.5, 129.8, 132.9, 134.7, 137.6, 139.5, 146.4, 153.0, 185.7. Mass spectrum, m/z (Irel, %): 471 [M+H]; Found, %: C 61.16; H 3.21; Br 16.95; N 11.89. $C_{24}H_{15}BrN_4O_2$. Calculated, %: C 61.19; H 3.26; Br 16.90; N 11.87.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5-methyl benzofuran-2-yl)(phenyl)methanone (5e): mp 234–236°C. IR spectrum, ν , cm^{-1} : 3143, 2941, 1621 (CO), 1267; 1H NMR spectrum, δ , ppm: 3.22 s (3H, CH_3), 7.45–7.66 m (9H, Ar-H), 7.92 d (2H, Ar-H, $J=8.53$ Hz), 7.99 d (1H, H_α , $J=16.8$ Hz), 8.21 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 22.4, 114.0, 119.5, 119.9, 123.0, 125.2, 125.6, 126.4, 127.2, 128.0, 128.7, 129.8, 130.0, 133.2, 134.9, 137.9, 139.8, 146.7, 148.9, 153.3, 185.9. Mass spectrum, m/z (Irel, %): 407 [M+H]; Found, %: C 73.88; H 4.46; N 13.78. $C_{25}H_{18}N_4O_2$. Calculated, %: C 73.92; H 4.42; N 13.74.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5-chloro-6-methyl benzofuran-2-yl)(phenyl)methanone (5f): mp 220–222°C. IR spectrum, ν , cm^{-1} : 3076, 2941, 1622 (CO), 1267; 1H NMR spectrum, δ , ppm: 3.62 s (3H, CH_3), 7.45–7.64 m (8H, Ar-H), 7.84 d (2H, Ar-H, $J=7.28$ Hz), 7.95 d (1H, H_α , $J=16.5$ Hz), 8.23 d (2H, Ar-H, $J=7.2$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 25.0, 109.0, 114.5, 114.9, 118.0, 120.3, 120.6, 121.4, 122.2, 123.0, 123.7, 124.8, 125.1, 128.2, 130.0, 132.9, 134.8, 141.7, 143.9, 148.3, 181.0. Mass spectrum, m/z (Irel, %): 441 [M+H]; Found, %: C 68.11; H 3.89; Cl 8.04; N 12.71. $C_{25}H_{17}ClN_4O_2$. Calculated, %: C 68.17; H 3.97; Cl 8.12; N 12.77.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)-5,6-dichlorobenzofuran-2-yl)(phenyl)methanone (5g): mp 210–212°C. IR spectrum, ν , cm^{-1} : 3143, 2941, 1627 (CO), 1265; 1H NMR spectrum, δ , ppm: 7.50–7.58 m (8H, Ar-H), 7.81 d (2H, Ar-H, $J=7.2$ Hz), 7.89 d (1H, H_α , $J=16.5$ Hz), 8.17 d (2H, Ar-H, $J=7.2$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 119.1, 119.7, 121.3, 125.0, 125.8, 126.3, 127.0, 127.7, 128.1, 128.4, 129.5, 129.9, 133.1, 134.6, 137.2, 139.4, 146.4, 148.7, 149.1, 184.9. Mass spectrum, m/z (Irel, %): 461 [M+H]; Found, %: C 62.49; H 3.06; Cl 15.37; N 12.15. $C_{24}H_{14}Cl_2N_4O_2$. Calculated, %: C 62.44; H 3.16; Cl 15.39; N 12.18.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(4-bromophenyl)methanone (5h): mp 260–262°C. IR spectrum, ν , cm^{-1} : 3167, 2924, 1662 (CO), 1282; 1H NMR spectrum, δ , ppm: 7.45–7.57 m (7H, Ar-H), 7.62–7.66 m (2H, Ar-H), 7.81 d (2H, Ar-H, $J=7.8$ Hz), 7.88 d (1H, H_α , $J=16.8$ Hz), 8.10 d (2H, Ar-H, $J=7.8$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 113.7, 117.4, 119.2, 125.0, 125.3, 126.2, 127.0, 127.8, 128.4,

128.4, 129.5, 129.8, 131.3, 132.9, 134.7, 137.6, 139.5, 146.5, 148.6, 153.0, 185.7. Mass spectrum, m/z (Irel, %): 471 [M+H]; Found, %: C 61.16; H 3.21; Br 16.95; N 11.89. $C_{24}H_{15}Br_2N_4O_2$. Calculated, %: C 61.19; H 3.24; Br 16.99; N 11.85.

General Experimental Procedure 7a–7j

Conventional Heating Method

A degassed solution of **5h** (1.0 mmol), arylboronic acid **6a–6j** (1.3 mmol), Na_2CO_3 (3.00 mmol), $Pd(PPh_3)_4$ (0.10 mmol) and solution of DMF/water (ratio 6:4) was introduced into a round-bottomed flask and heated it at 80°C for 6-9 hr with constant stirring under nitrogen atmosphere. The resulting solution was diluted with ice-cold water and was extracted with ethyl acetate; the combined organic layers were washed with brine, dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude thus obtained was purified using column chromatography to afford titled compounds.

Microwave Irradiation Method

A degassed mixture of **5h** (1.0 mmol), aryl boronic acid **6a–6j** (1.3 mmol), Na_2CO_3 (3.00 mmol), $Pd(PPh_3)_4$ (0.10 mmol) and a mixture of DMF/water (ratio 6:4) in a sealed pressure tube. This was introduced into CEM discover microwave reaction vessel equipped with a magnetic stirrer. The vessel was sealed and then placed into the microwave cavity. Initial microwave irradiation of 180W was used, the temperature is ramped from room temperature to the desired 80°C temperature. Once this was reached the reaction mixture was heated at this temperature for the appropriate time. The resulting solution was diluted with ice water and was extracted with ethyl acetate; the combined organic layers were washed with brine, dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude thus obtained was purified using column chromatography to afford titled compounds.

Characterization of Compounds 7a–7j

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)([1,1'-biphenyl]-4-yl)methanone (7a): mp 284–286°C. IR spectrum, ν , cm^{-1} : 3072, 2922, 1740(CO), 1630, 1232; 1H NMR spectrum, δ , ppm: 7.30–7.34 m (1H, Ar-H), 7.42–7.58 m (9H, Ar-H), 7.68–7.72 m (4H, Ar-H), 7.76–7.81 m (2H, Ar-H), 7.98 d (1H, H_α , $J=16.6$ Hz), 8.21 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 112.7, 119.2, 120.4, 123.1, 124.3, 124.8, 125.0, 126.0, 126.1, 127.0, 127.3, 127.7, 129.0, 129.5, 130.5, 135.0, 136.7, 139.5, 145.5, 146.3, 147.0, 154.8, 185.4. Mass spectrum, m/z (Irel, %): 369 [M+H]; Found, %: C 76.91; H 4.30; N 11.96. $C_{30}H_{20}N_4O_2$. Calculated, %: C 76.91; H 4.30; N 11.96.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(4'-fluoro-[1,1'-biphenyl]-4-yl)methanone (7b): mp 240–242°C. IR spectrum, ν , cm^{-1} : 3071, 2922, 1741 (CO), 1631, 1235; 1H NMR spectrum, δ , ppm: 7.16–7.21 m (2H, Ar-H), 7.43–7.66 m (9H, Ar-H), 7.73 d (2H, Ar-H, $J=8.2$ Hz), 7.79 d (2H, Ar-H, $J=7.5$ Hz), 7.98 d (1H, H_α , $J=16.6$ Hz), 8.20 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 112.7, 115.8, 116.1, 119.2, 120.4, 123.1, 124.3, 124.9, 126.0, 126.1, 126.9, 127.7, 128.9, 129.1, 129.5, 130.5, 135.0, 136.1, 136.1, 136.7, 139.5, 144.4, 146.3, 147.9, 154.8, 185.3. Mass spectrum, m/z (Irel, %): 487 [M+H]; Found, %: C 74.06; H 3.94; F 3.91; N 11.52. $C_{30}H_{19}FN_4O_2$. Calculated, %: C 74.16; H 3.90; F 3.95; N 11.58.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(3'-fluoro-[1,1'-biphenyl]-4-yl)methanone (7c): mp 210–212°C. IR spectrum, ν , cm^{-1} : 3135, 2924, 1742 (CO), 1598, 1226; 1H NMR spectrum, δ , ppm: 7.18–7.20 m (1H, Ar-H), 7.33–7.58 m (12H, Ar-H), 7.69 d (2H, Ar-H, $J=8.2$ Hz), 7.74 d (1H, Ar-H, $J=16.5$ Hz), 7.99 d (2H, Ar-H, $J=8.2$ Hz). ^{13}C NMR spectrum, δ_c , ppm: 112.6, 119.2, 120.1, 123.2, 124.3, 125.0, 125.3, 125.8, 126.0, 126.0, 126.9, 127.7, 128.6, 129.5, 130.0, 130.7, 131.7, 131.9, 134.9, 136.6, 139.5, 146.3, 147.4, 152.8, 154.8, 184.6. Mass spectrum, m/z (Irel, %): 487 [M+H]; Found, %: C 74.06; H 3.94; F 3.91; N 11.52. $C_{30}H_{19}FN_4O_2$. Calculated, %: C 74.10; H 3.99; F 3.95; N 11.57.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(4'-chloro-[1,1'-biphenyl]-4-yl)methanone (7d): mp 246–246°C. IR spectrum, ν , cm^{-1} : 2923, 1738(CO), 1630, 1230; 1H NMR spectrum, δ , ppm: 7.18–7.20 m

(1H, Ar-H), 7.31-7.35 m (1H, Ar-H), 7.43-7.60 m (5H, Ar-H), 7.50-7.72 m (4H, Ar-H), 7.81 d (2H, Ar-H, $J=8.0$ Hz), 7.96 d (1H, Ha, $J=16.3$ Hz), 7.95 d (2H, Ar-H, $J=8.2$ Hz), 8.13 d (2H, Ar-H, $J=8.0$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 105.9, 109.1, 112.4, 113.4, 116.4, 117.5, 118.4, 119.1, 119.2, 119.3, 120.1, 120.5, 120.9, 121.1, 121.7, 122.7, 123.5, 123.8, 129.0, 130.9, 132.7, 136.9, 139.5, 148.0, 185.0 Mass spectrum, m/z (Irel, %): 503 [M+H]; Found, %: C 71.64; H 3.81; Cl 7.05; N 11.14. $\text{C}_{30}\text{H}_{19}\text{ClN}_4\text{O}_2$. Calculated, %: C 71.69; H 3.88; Cl 7.04; N 11.17.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(2',4'-dichloro-[1,1'-biphenyl]-4-yl)methanone (7e): mp 248-250°C. IR spectrum, ν , cm^{-1} : 3161, 2970, 1740 (CO), 1598, 1233; ^1H NMR spectrum, δ , ppm: 7.31-7.35 t (1H, Ar-H), 7.40-7.62 m (9H, Ar-H), 7.71 d (2H, Ar-H, $J=8.5$ Hz), 7.80 d (2H, Ar-H, $J=8.5$ Hz), 8.00 d (1H, Ar-H, $J=16.8$ Hz), 8.22 d (2H, Ar-H, $J=8.5$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 112.7, 119.2, 120.3, 123.2, 124.4, 124.8, 125.0, 125.2, 126.0, 126.2, 126.9, 127.0, 127.6, 127.7, 128.1, 128.6, 129.5, 130.6, 135.6, 137.7, 139.5, 142.5, 143.0, 147.7, 154.8, 179.7. Mass spectrum, m/z (Irel, %): 537 [M+H]; Found, %: C 67.05; H 3.38; Cl 13.19; N 10.43. $\text{C}_{30}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_2$. Calculated, %: C 67.10; H 3.34; Cl 14.11; N 11.03.

(E)-4'-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-carbonyl)-[1,1'-biphenyl]-4-carboxylic acid (7f): mp 240-242°C. IR spectrum, ν , cm^{-1} : 3159, 2956, 1720 (CO), 1548, 1231; ^1H NMR spectrum, δ , ppm: 7.69-7.44 m (9H, Ar-H), 7.83-7.73 m (4H, Ar-H), 7.82 d (2H, Ar-H, $J=7.8$ Hz), 7.97 d (1H, Ar-H, $J=16.56$ Hz), 8.00 d (2H, Ar-H, $J=8.3$ Hz), 8.13 d (1H, Ar-H, $J=8.0$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 112.7, 119.2, 120.2, 123.2, 124.4, 125.0, 125.3, 125.8, 126.0, 126.2, 126.7, 126.9, 127.7, 127.8, 128.6, 129.5, 131.4, 131.7, 134.9, 136.7, 139.5, 146.4, 147.4, 147.8, 154.8, 180.5. Mass spectrum, m/z (Irel, %): 513[M+H]; Found, %: C 72.65; H 3.93; N 10.93. $\text{C}_{31}\text{H}_{20}\text{N}_4\text{O}_3$. Calculated, %: C 72.64; H 3.90; N 10.99.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(4'-methyl-[1,1'-biphenyl]-4-yl)methanone (7g): mp 230-232°C. IR spectrum, ν , cm^{-1} : 3072, 2923, 1740 (CO), 1627, 1231; ^1H NMR spectrum, δ , ppm: 2.42 s (3H, CH_3), 7.18-7.20 m (1H, Ar-H), 7.28-7.33 m (2H, Ar-H), 7.42-7.63 m (8H, Ar-H), 7.75-7.79 m (4H, Ar-H), 7.96 d (1H, Ha, $J=16.6$ Hz), 8.18 d (2H, Ar-H, $J=8.3$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 22.0, 112.7, 119.1, 120.4, 123.1, 124.2, 124.7, 124.9, 126.1, 126.8, 127.2, 127.7, 128.3, 129.5, 130.5, 136.4, 137.0, 137.9, 138.2, 139.5, 145.4, 146.3, 148.0, 154.8, 185.4. Mass spectrum, m/z (Irel, %): 483 [M+H]; Found, %: C 77.16; H 4.60; N 11.61. $\text{C}_{31}\text{H}_{22}\text{N}_4\text{O}_2$. Calculated, %: C 77.06; H 4.66; N 11.64.

(E)-4'-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-carbonyl)-[1,1'-biphenyl]-4-carbaldehyde (7h): mp 265-267°C. IR spectrum, ν , cm^{-1} : 3069, 2926, 1740 (CO), 1602, 1216; ^1H NMR spectrum, δ , ppm: 6.96 d (3H, $J=8.5$, Ar-H), 7.20 t (1H, Ar-H), 7.33 t (1H, Ar-H), 7.73-7.86 m (10H, Ar-H), 8.00 (d, 1H, Ar-H, $J=16.0$ Hz), 8.24 d (2H, Ar-H, $J=8.2$ Hz), 9.84 s (1H, CHO). ^{13}C NMR spectrum, δ_{C} , ppm: 112.7, 115.9, 119.3, 120.3, 123.2, 124.4, 126.1, 126.2, 126.2, 127.0, 127.3, 127.7, 128.0, 128.6, 129.5, 130.6, 134.1, 134.9, 135.8, 137.7, 139.5, 143.7, 146.4, 154.8, 191.8, 199.1. Mass spectrum, m/z (Irel, %): 497 [M+H]; Found, %: C 74.99; H 4.06; N 11.28. $\text{C}_{31}\text{H}_{20}\text{N}_4\text{O}_3$. Calculated, %: C 74.94; H 4.11; N 11.29.

(E)-4'-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-carbonyl)-[1,1'-biphenyl]-3-carbaldehyde (7i): mp 256-258°C. IR spectrum, ν , cm^{-1} : 3089, 2925, 1740 (CO), 1602, 1231; ^1H NMR spectrum, δ , ppm: 7.44-7.69 m (8H, Ar-H), 7.73-7.83 m (4H, Ar-H), 7.92-7.96 m (3H, Ar-H), 8.02 d (1H, Ar-H, $J=16.5$ Hz), 8.24 d (2H, Ar-H, $J=8.2$ Hz), 10.12 s (1H, CHO). ^{13}C NMR spectrum, δ_{C} , ppm: 110.6, 117.1, 118.2, 121.1, 122.3, 123.0, 124.1, 125.0, 125.5, 125.7, 126.2, 126.4, 127.5, 127.7, 128.6, 131.0, 135.0, 137.4, 138.9, 141.7, 144.3, 145.7, 152.8, 183.2, 190.0. Mass spectrum, m/z (Irel, %): 497 [M+H]; Found, %: C 74.99; H 4.06; N 11.28. $\text{C}_{31}\text{H}_{20}\text{N}_4\text{O}_3$. Calculated, %: C 74.94; H 4.11; N 11.29.

(E)-(3-(4-(1H-tetrazol-5-yl)styryl)benzofuran-2-yl)(4-(naphthalen-1-yl)phenyl)methanone (7j): mp 242-246°C. IR spectrum, ν , cm^{-1} : 3366, 2924, 1739 (CO), 1598, 1229; ^1H NMR spectrum, δ , ppm: 7.43-7.59 m (11H, Ar-H), 7.64-7.70 m (3H, Ar-H), 7.74-7.81 m (2H, Ar-H), 7.90-7.96 m (2H, Ar-H), 8.04 d (1H, Ar-H, $J=16.8$ Hz), 8.26 d (2H, Ar-H, $J=8.2$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 112.7, 115.5, 119.2,

120.2, 120.2, 120.4, 123.1, 124.3, 125.0, 125.3, 126.0, 126.1, 126.4, 127.0, 127.4, 127.7, 128.4, 128.8, 129.5, 129.9, 130.1, 131.3, 138.8, 139.5, 145.5, 151.2, 154.9, 171.7, 185.6. Mass spectrum, m/z (Irel, %): 519 [M+H]⁺; Found, %: C 78.75; H 4.28; N 10.80. C₃₄H₂₂N₄O₂. Calculated, %: C 78.79; H 4.24; N 10.87.

Biological Activity

All the synthesized compounds **5a-5h** and **7a-7j** were screened *in-vitro* for their antibacterial activity, at 20 µg/mL, and 40 µg/mL concentrations. The Zone of inhibition (in mm) was compared with standard drug *Ciprofloxacin*. Among all, the compounds **5b**, **5c**, **5e**, **7b**, **7c**, **7d**, and **7e** were exhibited better activity against all bacterial organisms and compounds **5b**, **5c**, **5e**, **7b**, **7c**, **7d**, and **7e** were shown maximum zone of inhibition. The compounds as **5a**, **5d**, **5f**, **7f**, **7h**, and **7i** shown a moderate zone of inhibition, remaining compounds have shown poor activity against bacterial strains.

Furthermore, the antifungal activity of synthesized compounds **5a-5h** and **7a-7j** were tested against three pathogenic fungi at 50 µg/mL concentrations. The zone of inhibition compares to standard drug *Amphotericin-B*. Among all, the compounds **5b**, **7b** and **7c** with flouro substitution on ring showed maximum activity. Compounds **7h**, **7i** with carbonyl substitution on a ring was active against *A. flavus*

Table-4: Antimicrobial Activity of Synthesized Compounds **5a-5h** and **7a-7j**

Compound	Zone of Inhibition (mm), Concentration (µg/mL)										
	Gram-positive Bacteria				Gram-negative Bacteria				Fungi		
	<i>S. aureus</i>		<i>B. subtilis</i>		<i>K. pneumoniae</i>		<i>E. coli</i>		<i>A. nigerzeae</i>	<i>A. flavus</i>	<i>F. oxysporum</i>
	20	40	20	40	20	40	20	40	50	50	50
5a	15	28	12	24	18	28	10	25	10	9	12
5b	14	27	15	28	22	34	15	35	13	11	13.7
5c	13	20	14	21	21	30	13	31	9	9.5	10
5d	11	20	12	25	20	29	11	27	7	8	12
5e	13	21	13	24	23	31	12	30	8	7.4	11
5f	11	19	11	21	14	30	14	28	7.5	9.2	10.4
5g	9	20	9	20	11	22	9	21	8	9	10
5h	10	21	10	21	14	21	11	17	11	10	12
7a	9	22	7	20	12	24	8	22	7	9	11
7b	13	26	15	26	19	28	14	29	13	11.7	14
7c	14	25	14	25	17	25	15	30	13	11.2	13.4
7d	12	24	14	23	16	27	15	28	11	10.4	12
7e	14	26	14	24	18	26	14	29	8	9	10
7f	11	21	11	19	14	21	15	25	11	9.8	9.4
7g	9	20	10	20	13	20	12	21	8	9	10
7h	10	21	12	21	19	28	14	24	10	14	11.4
7i	11	22	13	20	18	26	12	27	11.2	13.7	12.4
7j	8	21	13	19	18	19	14	23	7.5	8.2	11
<i>Ciproflaxacin</i>	15	28	16	30	23	35	18	35	-	-	-
<i>Amphotericin-B</i>	-	-	-	-	-	-	-	-	16.3	15.6	16.2

Biological Assay

Antibacterial Activity

The synthesized scaffolds **5a-5h** and **7a-7j** were screened for their antibacterial activity against bacterial strains such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* at a concentration of 20 µg/mL and 40 µg/mL. The cultures were diluted with 4% autoclaved saline and the final volume was made with concentration approximately 10⁵-10⁶ CFU/mL. The synthesized compounds were diluted in DMSO. According to the procedures described agar disc diffusion method¹⁹. The synthesized compounds were added to the disc and plates were incubated at 37°C for 24 hr. Zones of inhibition were measured in (mm). All experiments were carried out in triplicates.

Antifungal Activity

The antifungal activity of synthesized compounds **5a-5h** and **7a-7j** was tested against three pathogenic fungi such as *Fusarium oxysporum*, *Aspergillus niger*, and *Penicillium italicum*, by the poison plate technique at a concentration of 50 µg/mL. Three kinds of fungi were incubated in PDA at 25±1 °C for 5 days to get new mycelium for antifungal assay, then a mycelia as disks of approximately 0.45 cm diameter cut from the culture medium were picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The test compounds were dissolved in DMSO (10 mL) then added to the Potato Dextrose Agar medium (PDA, 20 mL). The final concentration of compounds in the medium was adjusted to 50µg/mL. The inoculated plates were incubated at 25±1 °C for 5 days. DMSO was diluted with sterilized distilled water and used as a control, while *Amphotericin-B*. (50 µg/mL) was used as a standard control for each treatment three replicates of experiments were carried out. The radial growth of the fungal colonies was measured on the sixth day.

CONCLUSION

In conclusion, we herein the report the new scaffolds **5a-5h** and **7a-7j** were synthesized by using a microwave irradiation method to obtained better yield as compared to conventional heating. The reaction carried out under green conditions. They evaluated their antimicrobial activity and the compounds **5b**, **5c**, **5e**, **7b**, **7c**, **7d**, and **7e** were found to be good antibacterial activity and compounds **5b**, **7b** and **7c** were exhibited good antifungal activity. The **7b** and **7c** were exhibited better antimicrobial activity.

ACKNOWLEDGMENT

We are thankful to the Head, Department of Chemistry, Osmania University, for providing laboratory facilities and CFRD OU, for providing spectral analysis. We are thankful to the University Grants Commission, New Delhi, for their financial support and one of the authors, Ravinder Dharavath is thankful to CSIR-New Delhi, India, for financial support. D. Ashok is thankful to UGC, New Delhi for the award of UGC-BSR fellowship.

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[RJC-5490/2019]