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Synthesis, characterization and antimicrobial evaluation of some novel (3-methyl-5-((3-phenylisoxazol-5-yl)methoxy)benzofuran-2-yl)(phenyl)methanones

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The synthesis and characterization of a novel class of benzofuran-isoxazole **7a-j** hybrid heterocyclic unit are described and their antimicrobial activities evaluated. The antimicrobial investigation studies reveal that the majority of the final target compounds exhibit moderate to excellent activity against tested microbes. Among the compounds screened **7b**, **7a** and **7i** have shown potent activity and compounds **7h**, **7c**, **7f** show good activity compared to standard drugs Gentamicin and Nystatin.

Keywords: Benzofuran, isoxazole, hybrid-heterocyclic, antibacterial, antifungal

Benzofuran and its derivatives either natural or synthetic have been reported[1,2] to exhibit diverse biological activities such as antibacterial[3,4], antimicrobial[5], antifungal[6], antitumor[7], anticonvulsant, anti-HIV[8], antitubercular[9], anti-inflammatory[10], antidiabetic[11], antidepressant[12], and antineophobic[13] and in the treatment of asthma, rheumatism and ulcers[14]. Furthermore, certain derivatives of benzofuran present in natural products show high cytotoxicity[15].

On other hand isoxazoles either natural or synthetic have been drawing significant interest from medicinal and organic chemists owing to their notable biological activities[16]. Isoxazoles are playing important role in heterocyclic chemistry as pharmacophores and extensively used as synthons in the field of organic chemistry. Isoxazole forms the basis for several drugs such as leflunomide, valdecoxib and zonisamide.

In continuation to our previous work in discovering potential antimicrobial benzofurans[4,3] and isoxazoles[2,16], this work directed towards the synthesis of a diverse series of novel benzofuran-isoxazole derivatives of biological interest.

Results and Discussion

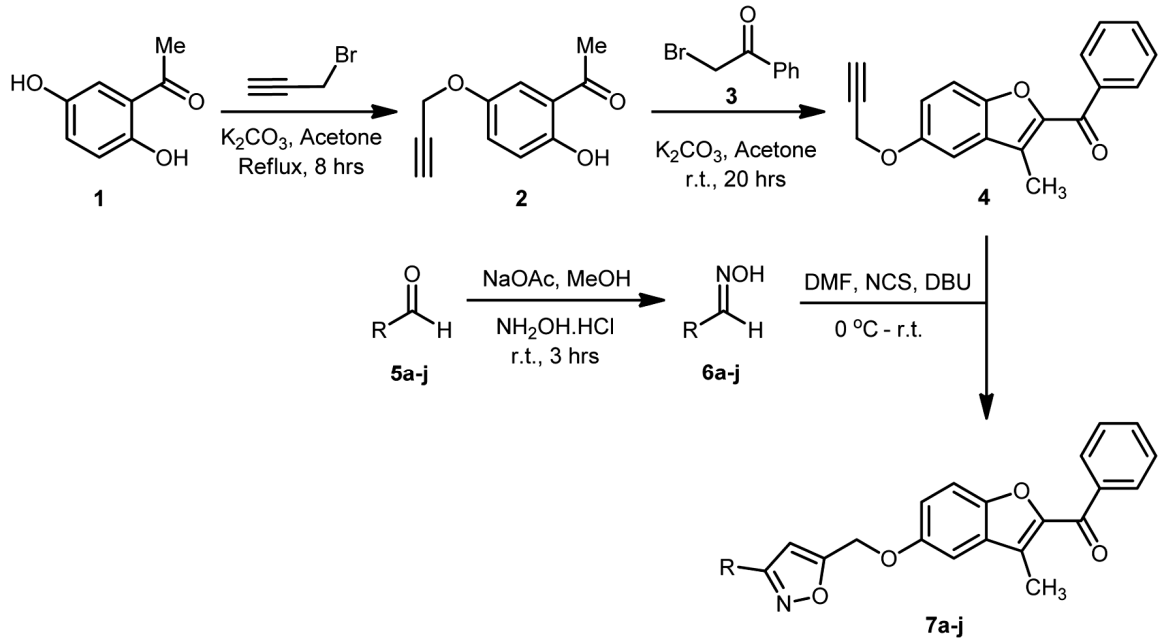
Chemistry

As shown in Scheme I, benzofuran based 3,5-disubstituted isoxazoles (**7a-j**) were synthesized by a 4-step protocol. Compound **2** was obtained by the reaction of 1-(2,5-dihydroxyphenyl)ethanone (**1**) with 3-bromoprop-1-yne in the presence of K_2CO_3 and acetone. The key intermediate compound **4** was obtained 96% yield by the reaction of acetylinic ortho hydroxyl acetophenone (**2**) with phenacylbromide (**3**). This was confirmed by ^{1}H-NMR spectra which showed characteristic peaks at δ 4.74 (d, J = 2.4 Hz, 2H) and at δ 2.53 (d, J = 2.27 Hz, 1H) indicates presence of acetylenic benzofuran. This was further confirmed by MASS spectra which gave base peak at *m/z* 291 $[M+H]^+$ corresponding to the molecular weight of compound **4**. Different substituted aldoximes (**6a-j**) were prepared by reacting aldehydes (**5a-j**) with hydroxylamine hydrochloride. The in situ generated nitrile oxides from oxime (**6a-j**) underwent a 1,3-dipolar cycloaddition with alkyne (**4**) to give the corresponding isoxazoles (**7a-j**). In ^{1}H-NMR spectra peak between δ 6.85 to δ 7.01 indicates the formation of isoxazole ring. This was also confirmed by ^{13}C-NMR spectra which showed characteristic peak of isoxazole between δ 97.2 to δ 97.4. The structures of the newly synthesized target molecules were characterized by IR, NMR and mass spectral data.

Biological activities

Antibacterial activity

The targeted novel benzofuran-isoxazoles (**7a-j**) were tested for their antibacterial activity against four



R = 3-(NO_2)Ph (**7a**), 4-(NO_2)Ph (**7b**), 4-(Cl)Ph (**7c**), 3-(Cl)Ph (**7d**), 2-(Cl)Ph (**7e**)

4-(Br)Ph (**7f**), 3-(Br)Ph (**7g**), 3-(OMe)Ph (**7h**), 4-(OMe)Ph (**7i**), 4-(Me)Ph (**7j**)

Scheme I — Synthesis of benzofuran based 3,5-disubstituted isoxazoles **7a-j**

gram positive bacteria vize *Micrococcus luteus*, Methicillin-resistant *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus* & four gram negative bacteria vize *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus vulgaris* using Gentamicin sulphate as standard drug. All the tested compounds displayed excellent to moderate activity against tested bacterial strains (Table I). Among the compounds **7b**, **7a**, **7i**, **7h** and **7c** were shown potent active. It was attracting that compounds with strong electron withdrawing group like NO_2 of phenyl ring attached to isoxazole may increasing the antibacterial activity than other aryl substituted isoxazole. The compounds **7d**, **7e**, **7f**, **7g** and **7j** were exhibited mild antibacterial activity against tested bacterial strains.

Antifungal activity

The target benzofuran-isoxazoles (**7a-j**) were also screened for antifungal activity studies against three dermatophytes vize, Microsporum *canis*, Microsporum *gypseum* and Epidermophyton *floccosum*. According to the results obtained (Table II) among all screened analogues, **7b**, **7a**, **7i**, **7h**, **7c** and **7f** have shown more active against tested fungal strains compared to standard drug Nystatin. Compounds **7d** and **7e** exhibited moderate active.

Experimental Section

The melting points were measured in open capillaries and are uncorrected. The IR spectra were recorded on a Perkin−Elmer 337 grating IR spectrophotometer for solid samples pelleted in KBr. The NMR spectra were obtained on Bruker AV-400 and AV-300 NMR spectrometers for $CDCl_3$ solutions. The chemical shifts were measured in ppm against internal TMS. Electron Spray Ionization (ESI) mass spectra were recorded on a QSTARXL hybrid MS system (Applied Bio Systems) under electro spray ionization. Thin layer chromatography was carried out on Merck TLC silica gel 60 F254 plates. The spots were visualized in UV light at 254 nm. Column chromatography was performed on a Merck silica gel 60A (100–200 mesh).

Synthesis of compound 2

Compound **1** (2 g, 0.0131 mol) was dissolved in dry acetone and was added K_2CO_3 (1.81 g, 0.0131 mol) and 3-bromoprop-1-yne (1.56 g, 0.0131 mol). This reaction mixture was heated at reflux temperature for 8 hours and monitored by TLC. After consumption of starting materials the reaction mixture was allowed to room temperature then excess acetone was removed. The crude was diluted with water and extracted with ethyl acetate. The combined organic layer was subjected to reduced pressure to remove

Table I — Antibacterial activity of the compounds **7a-j**

Compd	Conc. µg/mL	Zone of Inhibition (mm)							
		Gram +ve bacteria				Gram –ve bacteria			
		Micrococcus luteus	*MRSA*	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Klebsiella pneumonia*	*Escherichia coli*	*Proteus vulgaris*
7a	75	30	28	27	27	26	28	29	27
	100	33	31	30	30	30	32	32	31
7b	75	32	31	28	30	29	30	28	28
	100	35	34	31	33	33	34	32	32
7c	75	20	19	20	18	19	20	17	21
	100	23	23	23	21	22	24	21	24
7d	75	15	15	16	15	14	13	14	12
	100	17	18	20	18	18	17	17	16
7e	75	13	13	12	13	11	12	14	12
	100	17	16	16	16	14	15	18	15
7f	75	18	17	20	17	18	17	16	20
	100	22	20	23	21	22	22	20	23
7g	75	11	11	12	12	10	09	11	09
	100	14	13	16	15	13	13	15	12
7h	75	23	21	22	21	20	21	23	21
	100	26	24	25	24	23	24	26	24
7i	75	29	26	25	24	23	23	27	26
	100	33	29	28	27	26	26	30	29
7j	75	09	08	NA	08	07	08	NA	08
	100	12	12	NA	11	10	11	NA	10
Zentamicin	75	28	31	31	32	27	27	30	29
	100	31	33	33	35	31	30	33	32

Methicillin-resistant *Staphylococcus aureus* (MRSA), No Activity (NA).

Table II — Antifungal activity of the compounds **7a-j**

Compd	Conc. µg/mL	Zone of Inhibition (mm)		
		Microsporum canis	*Microsporum gypseum*	*Epidermophyton floccosum*
7a	75	25	20	19
	100	28	23	22
7b	75	26	23	23
	100	29	27	26
7c	75	19	16	16
	100	22	19	18
7d	75	13	11	09
	100	16	14	12
7e	75	08	05	06
	100	11	08	09
7f	75	06	08	08
	100	09	10	11
7g	75	08	12	07
	100	10	15	11
7h	75	19	17	17
	100	23	21	19
7i	75	22	18	17
	100	25	21	20
7j	75	09	11	10
	100	12	14	13
Nystatin	75	25	20	20
	100	28	24	23

excess solvent. The crude obtained was purified by column chromatography to offered 1-(2-hydroxy-5-(prop-2-yn-1-yloxy)phenyl)ethanone **2**.

IR (KBr, ν_{max} cm^{-1}): 3408, 2345, 1642. White solid, Yield 84%, mp 184-186°C. ^{1}H NMR (300 MHz, $CDCl_3$): 12.4 (s, 1H), 7.62 (dd, *J* = 7.07, 2.3 Hz, 1H), 6.40–6.40 (m, 2H), 4.73 (d, *J* = 2.3 Hz, 2H), 2.54 (s, 3H), 2.53 (d, *J* = 2.28 Hz, 1H). MS: *m/z* 191 $[M+H]^+$.

Synthesis of (3-methyl-5-(prop-2-yn-1-yloxy)benzofuran-2-yl) (phenyl)methanone, 4

In dry acetone compound **2** (2.5 g, 0.013 mol) was dissolved followed by K_2CO_3 (2.72 g, 0.019 mol), 2-bromo-1-phenylethanone (2.61 g, 0.013) was added and was stirred at room temperature for 20 hours. After completion of reaction as indicated by TLC, excess acetone was removed under reduced pressure then diluted with water and extracted with ethyl acetate. The organic layer was concentrated to get crud product which was subjected to column chromatography which offered pure compound **4** in 96% yield. IR spectrum, ν, cm^{-1}: 1664. White solid, mp 199-201°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.22 (m, 6H), 6.44–6.41 (m, 2H), 4.74 (d, *J* = 2.4 Hz, 2H), 2.56 (s, 3H), 2.53 (d, *J* = 2.27 Hz, 1H). MS: *m/z* 291 $[M+H]^+$.

Procedure for the preparation of aldoximes, 6a-j

To a solutions of aldehyde **5a-j** (1 eq) in methanol was added hydroxylamine hydrochloride (1 eq)

followed by sodium acetate (1.5 eq). The resulting reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction, the reaction mixture was quenched by adding crushed ice and the precipitate formed was isolated by filtration, washed with pet ether, and dried to afford substituted aldoximes **6a-j**.

Synthesis of benzofuran based 3,5-disubstituted isoxazoles, 7a-j

To a solution of benzaldehyde oximes **6a-j** (100 mg, 1 eq) in DMF was added N-chloro succinamide (1 eq) for chlorination, the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to 0 °C and slowly added catalytic amount of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.2eq) followed by compound **4** (1 eq). This resulting reaction mixture was stirred for 4 hours at room temperature. After consumption of the starting materials, as indicated by TLC, ice-cold water was added to the reaction mixture, precipitate so obtained was filtered, washed with water and cold MeOH to afford the pure substituted benzofuran based 3,5-disubstituted isoxazoles **7a-j** in excellent yields (Table III).

(3-Methyl-5-((3-(3-nitrophenyl)isoxazol-5-yl) methoxy)benzofuran-2-yl)(phenyl)methanone, 7a: IR (KBr, ν_{max} cm^{-1}): 1656 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.38-8.28 (m, 1H), 8.27-8.18 (m, 2H), 8.17-7.98 (m, 2H), 7.82-7.77 (m, 1H), 7.64-7.42 (m, 4H), 7.22-7.11 (m, 2H), 6.86 (s, 1H), 5.37 (s, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.7, 167.7, 159.1, 157.9, 155.8, 147.9, 145.6, 138.5, 138.0, 132.3, 129.8 (2C), 128.5 (2C), 127.5, 126.7, 125.8, 123.8, 123.3, 122.2, 120.7, 115.2, 114.2, 97.3, 61.4, 10.1. MS: *m/z* 455 $[M+H]^+$.

(3-Methyl-5-((3-(4-nitrophenyl)isoxazol-5-yl) methoxy)benzofuran-2-yl)(phenyl)methanone, 7b: IR spectrum, ν, cm^{-1}: 1653 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (d, *J* = 7.6 Hz, 2H), 8.10-7.96 (m, 4H), 7.62-7.42 (m, 4H), 7.23-7.17 (m, 2H), 6.85 (s, 1H), 5.38 (s, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.6, 167.8, 159.1, 158.8, 155.7, 147.1, 145.6, 141.1, 138.5, 133.0, 129.8 (2C), 128.6 (2C), 127.4, 125.5 (2C), 123.5, 122.2, 120.7, 120.5 (2C), 114.3, 97.3, 61.7, 10.2. MS: *m/z* 455 $[M+H]^+$.

Table III — Physical data of compounds **7a-j**

Compd	Physical State	Yield (%)	m.p. (°C)
7a	Light yellow solid	84	147-149
7b	Light yellow solid	75	157-159
7c	White solid	88	86-88
7d	White solid	90	77-79
7e	White solid	80	72-73
7f	Light yellow solid	95	104-106
7g	White solid	93	112-114
7h	White solid	90	95-97
7i	White solid	83	119-121
7j	White solid	86	126-128

(5-((3-(4-Chlorophenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7c: IR (KBr, ν_{max} cm^{-1}): 1652 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.10-8.06 (m, 2H), 7.71 (s, 1H), 7.68 (s, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55-7.46 (m, 4H), 7.45-7.42 (m, 1H), 7.23 (d, *J* = 2.2 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.90 (s, 1H), 5.39 (s, 2H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.6, 167.8, 159.0, 158.4, 155.7, 148.0, 145.5, 137.7, 138.4, 132.3, 129.9 (2C), 128.6 (2C), 128.2 (2C), 127.4, 126.6, 123.6, 122.2, 121.6 (2C), 114.2, 97.2, 61.6, 10.1. MS: *m/z* 444 $[M+H]^+$.

(5-((3-(3-Chlorophenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7d: IR (KBr, ν_{max} cm^{-1}): 1647 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.18-7.99 (m, 3H), 7.63-7.38 (m, 7H), 7.15 (s, 1H), 7.03 (d, *J* = 8.28 Hz, 1H), 6.86 (s, 1H), 5.36 (s, 2H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.6, 167.8, 159.2, 158.4, 155.6, 148.5, 145.5, 138.4, 137.6, 135.6, 132.3, 130.8, 129.9 (2C), 129.5, 129.1, 128.6 (2C), 127.4, 123.6, 122.1, 120.7, 114.2, 97.2, 61.6, 10.3. MS: *m/z* 444 $[M+H]^+$.

(5-((3-(2-Chlorophenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7e: IR (KBr, ν_{max} cm^{-1}): 1649 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.09-7.96 (m, 3H), 7.78-7.51 (m, 7H), 7.19 (s, 1H), 7.06 (d, *J* = 8.32 Hz, 1H), 6.90 (s, 1H), 5.40 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.3, 168.1, 158.9, 158.1, 157.5, 148.1, 145.2, 139.1, 137.4, 135.1, 131.9, 131.0, 130.0 (2C), 129.4, 128.9, 128.5 (2C), 127.3, 123.4, 121.9, 121.0, 114.4, 97.3, 61.5, 10.1. MS: *m/z* 444 $[M+H]^+$.

(5-((3-(4-Bromophenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7f: IR (KBr, ν_{max} cm^{-1}): 1651 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 8.09-8.05 (m, 2H), 7.70 (s, 1H), 7.67 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.53-7.46 (m, 4H), 7.45-7.41 (m, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.20 (m, *J* = 8.6, 2.3 Hz, 1H), 6.96 (s, 1H), 5.37 (s, 2H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.5, 167.9,

159.3, 158.4, 155.4, 148.6, 145.9, 145.1, 138.3, 132.6, 132.1 (2C), 129.8 (2C), 128.5 (2C), 127.4, 124.3, 123.7, 122.3, 121.6 (2C), 114.1, 97.3, 61.7, 10.4. MS: *m/z* 488 $[M+H]^+$.

(5-((3-(3-Bromophenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7g: IR (KBr, ν_{max} cm^{-1}): 1655 (C=O). ^1H NMR (400 MHz, $CDCl_3$): 8.17-8.05 (m, 2H), 7.69-7.58 (m, 5H), 7.58-7.50 (m, 2H), 7.50-7.43 (m, 1H), 7.27-7.24 (m, 1H), 7.22-7.19 (m, 1H), 7.01 (s, 1H), 5.39 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.6, 167.8, 159.2, 158.4, 155.6, 148.5, 145.5, 138.4, 137.5, 132.9, 132.8, 132.5, 132.3, 129.9 (2C), 128.6 (2C), 127.4, 123.6, 122.1, 121.9, 121.8, 114.2, 97.2, 61.6, 10.3. MS: *m/z* 488 $[M+H]^+$.

(5-((3-(3-Methoxyphenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7h: IR (KBr, ν_{max} cm^{-1}): 1654 (C=O). ^1H NMR (400 MHz, $CDCl_3$): 8.10-8.06 (m, 2H), 7.80 (s, 1H), 7.70 (s, 1H), 7.61 (t, *J* = 7.48 Hz, 1H), 7.58-7.47 (m, 4H), 7.44-7.40 (m, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.92 (s, 1H), 5.39 (s, 2H), 3.86 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.5, 166.9, 158.8, 158.1, 156.8, 147.8, 146.0, 138.7, 138.1, 132.3, 130.2 (2C), 128.6 (2C), 128.1 (2C), 127.3, 126.5, 123.4, 122.1, 121.5 (2C), 114.3, 97.3, 61.6, 56.5, 10.2. MS: *m/z* 440 $[M+H]^+$.

(5-((3-(4-Methoxyphenyl)isoxazol-5-yl)methoxy)-3-methylbenzofuran-2-yl)(phenyl)methanone, 7i: IR (KBr, ν_{max} cm^{-1}): 1653 (C=O). ^1H NMR (400 MHz, $CDCl_3$): 8.07-7.98 (m, 2H), 7.75 (s, 1H), 7.70 (s, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.56-7.47 (m, 4H), 7.39-7.36 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.95 (s, 1H),), 5.36 (s, 2H), 3.88 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.7, 167.4, 159.1, 157.2, 155.1, 148.1, 146.0, 149.9, 137.8, 132.5, 131.9 (2C), 129.8 (2C), 128.4 (2C), 127.7, 124.3, 123.6, 122.1, 121.5 (2C), 114.3, 97.4, 61.7, 56.7, 10.4. MS: *m/z* 440 $[M+H]^+$.

(3-Methyl-5-((3-(*p*-tolyl)isoxazol-5-yl)methoxy) benzofuran-2-yl)(phenyl)methanone, 7j: IR (KBr, ν_{max} cm^{-1}): 1658 (C=O). ^1H NMR (400 MHz, $CDCl_3$): 8.06-7.97 (m, 3H), 7.63-7.38 (m, 7H), 7.18 (s, 1H), 7.08 (d, *J* = 8.28 Hz, 1H), 6.90 (s, 1H), 5.35 (s, 2H), 2.58 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 185.4, 167.5, 158.9, 157.4, 155.9, 148.1, 146.2, 138.1, 137.6, 134.4, 131.2, 130.7, 129.8 (2C), 129.3, 129.3, 128.5 (2C), 127.7, 123.5, 122.2, 120.8, 113.9, 97.3, 61.5, 23.5, 10.3. MS: *m/z* 424 $[M+H]^+$.

Conclusions

A new series of benzofuran-isoxazole heterocyclics **7a-j** were synthesized in high yields and characterized by different spectroscopic techniques. These synthesized molecules were screened for antimicrobial activity and demonstrated excellent activity against tested bacterial and fungal strains. The highest activities were found for compounds **7b**, **7a**, **7i**, **7h**, **7c** and **7f**. These results positively encouraged us for further developing novel bioactive agents.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

References

1 Stevenson P C, Simmonds M S, Yule M A, Veitch N C, Kite G C, Irwin D & Legg M, *Phytochemistry*, 63 (2003) 41.

2 Sunitha V, Kumar A K, Lincoln C A, Jalapathi P & Reddy V G, *Russian J Gen Chem*, 88 (2018) 2669.

3 Sunitha V, Kumar A K, Shankar B, Kumar A A, Krishna T, Lincoln C A & Pochampalli J, *Russian J Gen Chem*, 87 (2017) 322.

4 Sunitha V, Kumar A K, Shankaraiah P, Jalapathi P & Lincoln C A, *Russian J Gen Chem*, 88 (2018) 1515.

5 Koca M, Servi S, Kirilmis C, Ahmedzade M, Kazaz C, Özbek B & Ötük G, *Eur J Med Chem*, 40 (2005) 1351.

6 Gündoğdu-Karaburun N, Benkli K, Tunali Y, Uçucu Ü & Demirayak Ş, *Eur J Med Chem*, 41 (2006) 651.

7 Pieters L, Van Dyck S, Gao M, Bai R, Hamel E, Vlietinck A & Lemiere G, *J Med Chem*, 42 (1999) 5475.

8 Rida S M, El-Hawash S A, Fahmy H T, Hazzaa A A & El-Meligy M M, *Arch Pharm Res*, 29 (2006) 826.

9 Manna K & Agrawal Y K, *Eur J Med Chem*, 45 (2010) 3831.

10 Dawood K M, Abdel-Gawad H, Rageb E A, Ellithey M & Mohamed H A, *Bioorg Med Chem*, 14 (2006) 3672.

11 Tsujihara K, Hongu M, Saito K, Kawanishi H, Kuriyama K, Matsumoto M, Oku A, Ueta K, Tsuda M & Saito A, *J Med Chem*, 42 (1999) 5311.

12 Dauzonne D, Gillardin J, Lepage F, Pointet R, Risse S, Lamotte G & Demerseman P, *Eur J Med Chem*, 30 (1995) 53.

13 Liao Y, Kozikowski A P, Guidotti A & Costa E, *Bioorg Med Chem Lett*, 8 (1998) 2099.

14 Schneiders G E & Stevenson R, *J Org Chem*, 44 (1979) 4710.

15 Banskota A H, Tezuka Y, Midorikawa K, Matsushige K & Kadota S, *J Nat Prod*, 63 (2000) 1277.

16 Sunitha V, Kumar A K, Mahesh M, Shankaraiah P, Jalapathi P & Lincoln C A, *Russian J Gen Chem*, 88 (2018) 1904.