Bioorganic & Medicinal Chemistry Letters 20 (2010) 7200–7204

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Green synthesis and biological evaluation of some novel azoles as antimicrobial agents

Sharad Shelke [a,*], Ganesh Mhaske [a], Sunil Gadakh [a], Charnsingh Gill [b]

[a] Department of Chemistry, S.S.G.M. College, Kopargaon, Dist-Ahmednagar (MH) 423601, India
[b] Department of Chemistry, Dr. B.A.M. University, Aurangabad (MH) 423601, India

ARTICLE INFO

Article history:
Received 19 August 2010
Revised 21 September 2010
Accepted 22 October 2010
Available online 27 October 2010

Keywords:
Ultrasound irradiation
Microwave-assisted synthesis
Triazole
Thiadiazole
Antifungal activity

ABSTRACT

A series of novel fluorine-containing triazoles **3**, thiadiazoles **4**, and oxadiazoles **5** were synthesized from thiosemicarbazides **2**. These reactions were carried out by green technique such as ultrasonication and microwave. All products have been characterized by IR, ^{1}H NMR, and Mass spectral study and screened for their antimicrobial activity.

It has known that introduction of fluorine atom in molecule may lead to significant influence on the biological and physical properties of compounds due to increase of membrane permeability, hydrophobic bonding, stability against metabolic oxidation, etc.[1] Since fluorine-containing compound is of promising pharmacological activities which are originated from their unique high thermal stabilities and lipophilicity.[2] Therefore the development of synthetic methods for fluorine-containing compounds has been an important field in both organofluorine chemistry syntheses.

Triazoles and their derivatives have enhanced considerable attention for the past few decades due to their chemotherapeutical value.[3] In particular fluorinated triazoles are of significant interested because they possess antitubercular[4] and anticancer[5] activity. Literature survey indicates that thiosemicarbazide are found to associate with antibacterial,[6] antifungal[7] activities. Compounds containing 1,3,4-thiadiazole nucleus has been reported to be a variety of biological activities like fungitoxic,[8] CNS stimulant,[9] anticholinergic,[10] and anticonvulsant.[11] Several oxadiazoles and thiadiazoles also exhibit anti-tubercular,[12] antifungal,[13] and herbicidal[13] properties. Recently literature survey reveals that fluorinated 1,3,4-oxadiazole derivatives possesses anticancer[14] and antibacterial[15] activity.

The advantageous use of ultrasound irradiation technique for activating various reactions is well documented in the literature such as synthesis of azoles and diazenes,[16] Reformatsky reaction,[17] oxidation of substrates like hydroquinones,[18] Pinacol coupling,[19] Suzuki cross-coupling,[20] etc.

Commercial microwave-assisted organic reactions occurs more rapidly, safely and with higher chemicals yields,[21–23] render the microwave method superior to conventional method. The growing number of publication in microwave-assisted synthesis includes virtually all types of synthesis like Knoevenagel condensation.[24]

Triazoles are synthetic compounds with a chemical structure comprising one or more five-membered azole rings that contain three nitrogen atoms. They have a higher affinity for fungal than mammalian target enzymes, which makes them less toxic, for instance, than imidazole compounds like ketoconazole and miconazole. The currently available systemic triazoles are fluconazole, itraconazole, voriconazole, and posaconazole. Ravuconazole, albaconazole, and isavuconazole are in advanced stages of clinical development and will not be discussed in this article. In selecting the optimal triazole agent for therapy, it is important to consider not only its spectrum of activity, but also several other pharmacokinetic and pharmacodynamic parameters. There are limited data on pharmacodynamic properties of antifungal agents, but animal models suggest that killing of fungi with triazoles is optimized with maximal drug exposure over time (time-dependent killing).[25–27]

Biological activities associated with azoles and advantages of green techniques and in continuation of our work.[28,29] We have prompted us to prepare some fluorinated azoles by conventional as well as sonochemical and microwave method.

Chemistry: In the present work, we herein report the synthesis of fluorinated azoles. Scheme for the synthesized compound has been shown in Scheme 1.

* Corresponding author. Tel.: +91 8888199853.
E-mail address: snshelke@yahoo.co.in (S. Shelke).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.10.111

The aim of the present study was to investigate the antibacterial activity of synthesized compounds. Thiosemicarbazides **2** have been prepared from acid hydrazide **1** on treatment with fluorinated aryl isothiocyanates. Thiosemicarbazides **2** in 1% NaOH gave compounds **3**, that is, triazoles and in concd H_2SO_4 gave compounds **4**, that is, thiadiazoles. These compounds **2** on treatment with I_2/KI and NaOH gave compounds **5**, that is, oxadiazoles. These compounds were synthesized by conventional method as well as green technique. Compounds **3** and **4** were obtained 72–88% yield under green technique. Each experiment was repeated three times to confirm the consistency of the results. The efficiency of green technique was evaluated by comparison with the same reaction in acidic or basic medium. The later method required 90 and 120 min. for synthesis of triazoles and thiadiazoles, respectively. Yield of conventional method are found to be 65–75% yield.

Antimicrobial activities were determined by agar diffusion assay disc method against*Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa* bacteria and *Aspergillus niger, Candida albicans* fungi. The antibiotic Nystatin (100 U/disc) and chlorampenicol (10 mcg/disc) was used as control for antibacterial and antifungal activity, respectively. The samples (100 μg/mL) were dissolved in dimethyl sulphoxide (DMSO) and used for the antimicrobial activities. The bacterial cultures of known inoculums size (1×10^8 bacteria /mL) of test microorganism were spread on Muller Hinton agar plates. While the fungial cultures of known inoculums size (1×10^6 bacteria/mL) of test microorganism were spread on potato dextrose ager plates.

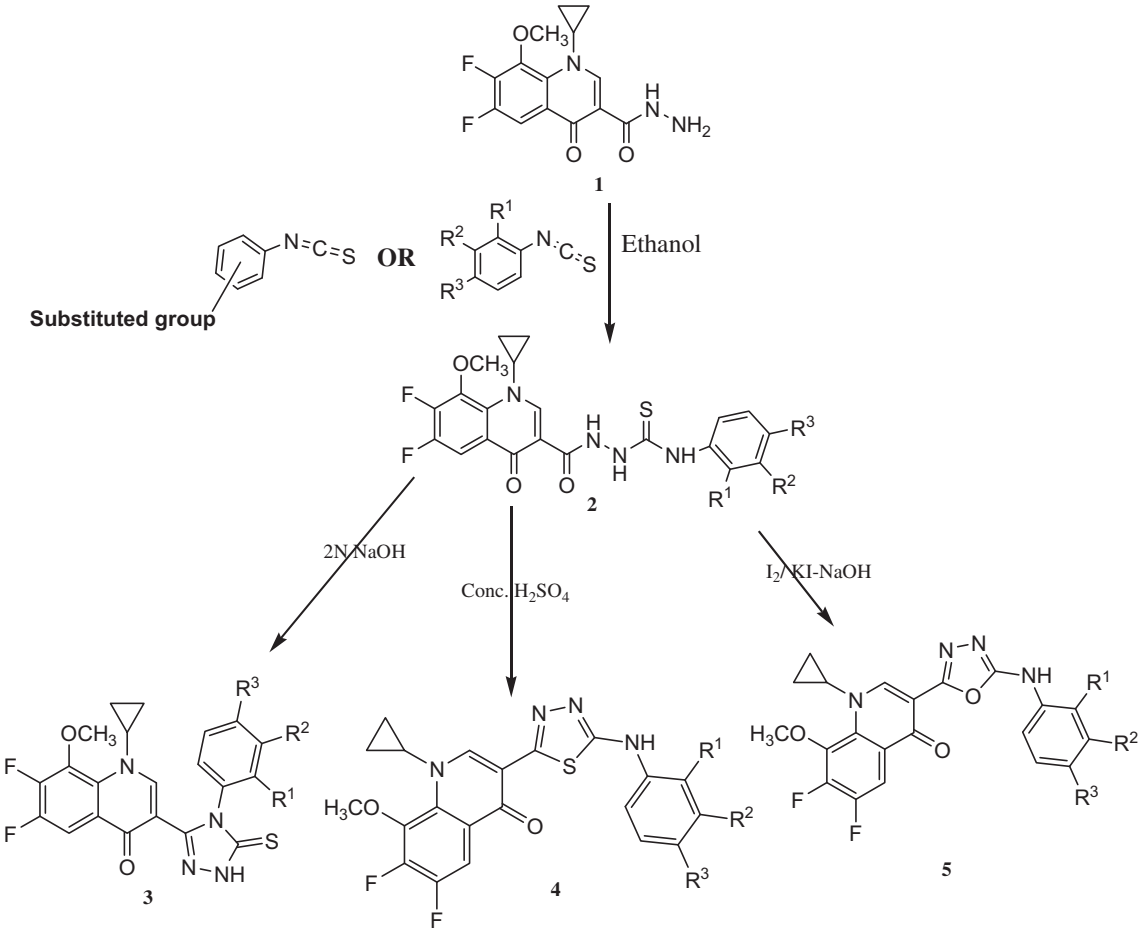
The Whatman filter paper discs of 6 mm were placed on the plate and the sample of appropriate concentration was added to the filter disc. The plates were further incubated for 18–20 h at 37 °C.

The investigation of antimicrobial screening data revealed that all the tested compounds **2**, **3**, **4**, and **5** showed moderate to excellent antibacterial and antifungal activities against *S. aureus, E. coli, B. subtilis, P. aeruginosa*, and *A. niger*, *C. albicans*, respectively. The **2a–2e** are active against *S. aureus, E. coli, B. subtilis,* and *P.* aeruginosa. Among thiosemicarbazides **2c** are most active compounds and are passive for all bacterial species. The **3a–3e** are only active against *S. Aureus bacterial* and *A.* niger fungal species. Amoung thiadiazoles (**4a**–**4e**) **4c** and **4e** exhibited more active than the chlorampenicol against *A. niger* and Nystatin against *P. aeruginosa*, respectively.

Among oxdiazoles (**5a**–**5e**) **5a** and **5b** exhibited most activity than the chlorampenicol against *A. niger* as well as *C. albicans* and Nystatin against *P. aeruginosa,* respectively. The most active compounds **4e** and **5b** are passive for *P. aeruginosa* strains. While the most active compounds **4c, 5a** are passive for both fungal strains.

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Perkin–Elmer FTIR spectrophotometer in KBr disc. The ^{1}H NMR spectra of some of the compounds of this series were scanned on 300 MHz F spectrophotometer, respectively, using DMSO-d_6 as a solvent and TMS as an internal standard. Peak values are shown in δ ppm.

Mass spectra were obtained by Finnigan mass spectrometer. Experiment under ultrasound irradiation was carried out in ultrasonic cleaner model EN-20U-S manufactured by ENERTECH



Scheme 1. Synthesis of fluorinated azoles **2**, **3**, **4**, and **5**.

ELECTRONICS PVT. LTD, Mumbai, India has maximum power output of 100 W and 33 KHz operating frequency.

All newly synthesized compound were found to be pure (checked by thin layer chromatography).

All experiments under microwave irradiation were carried out in unmodified domestic microwave oven model 800T manufactured by BPL Appliances and Utilities Ltd, Bangalore, India having maximum power output of 800 W and 2450 MHz frequency.

The newly synthesized compounds were screened for their antimicrobial activity against *S. aureus, E. coli, B. subtilis, P. aeruginosa* bacteria and *A. niger, C. albicans* fungi using by agar diffusion assay disc method. The antimicrobial activity was evaluated by measuring the zone of inhibition in mm and results obtained are shown in Table 1.

*General procedure for synthesis of thiosemicarbazides (**2**).* Fluorinated acid hydrazide (0.01 mol) **1** and aryl isothiocyanates (0.01 mol) were taken in 100% 15 mL of ethanol and the reaction mixture was heated under reflux for 60 min. After completions of the reaction (monitored by TLC) contents were cooled to room temperature, the white product obtained was separated by filtration. The formation of the compounds **2** was confirmed by mp, mixed mp and spectral data. Their characterization data is given in the Table 2.

2a: IR (KBr) ν/cm^{-1}: 3458 (–NH), 1651 (–C=O), 1604 (C=C), 1463 (–C=S), 1240 (–C–O–C), 1178 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.08–1.20 (m, 4H), 2.25–2.31 (m, 1H), 3.31 (s, 3H), 3.33 (s, 3H), 6.88–7.40 (m, 5H), 7.97 (s, 1H), 9.66 (s, 2H), 9.89 (br s, 1H). MS (*m/z*): 475 (M+1).

2b: IR (KBr) ν/cm^{-1}: 3450 (–NH), 1660 (–C=O), 1612 (C=C), 1454 (–C=S), 1247 (–C–O–C), 1186 (–C–F), 1087 (–C–Cl). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05–1.20 (m, 4H), 2.25–2.40 (m, 1H), 3.41 (s, 3H), 7.34–7.55 (m, 5H), 7.58 (s, 1H), 9.88 (s, 2H), 10.12 (br s, 1H). MS (*m/z*): 479 (M+1), 481.

2c: IR (KBr) ν/cm^{-1}: 3447 (–NH), 1661 (–C=O), 1609 (C=C), 1452 (–C=S), 1250 (–C–O–C), 1189 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.03–1.22 (m, 4H), 2.21–2.43 (m, 1H), 3.42 (s, 3H), 6.90–7.51 (m, 5H), 7.55 (s, 1H), 9.79 (s, 2H), 10.14 (br s, 1H). MS (*m/z*): 445 (M+1).

2d: IR (KBr) ν/cm^{-1}: 3436 (–NH), 1654 (–C=O), 1610 (C=C), 1462 (–C=S), 1245 (–C–O–C), 1199 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11–1.28 (m, 4H), 2.19 (s, 3H), 2.22–2.38 (m, 1H), 3.27 (s, 3H), 6.93–7.41 (m, 5H), 7.58 (s, 1H), 9.57 (s, 2H), 10.29 (br s, 1H). MS (*m/z*): 459 (M+1).

2e: IR (KBr) ν/cm^{-1}: 3437 (–NH), 1653 (–C=O), 1608 (C=C), 1463 (–C=S), 1247 (–C–O–C), 1197 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.09–1.29 (m, 4H), 2.20 (s, 3H), 2.26–2.36 (m, 1H), 3.25 (s, 3H), 6.95–7.4 (m, 5H), 7.53 (s, 1H), 9.50 (s, 2H), 10.30 (br s, 1H). MS (*m/z*): 459 (M+1).

*General procedure for synthesis of triazoles (**3**).* By conventional method: Thiosemicarbazide **2** (0.005 mol) and 10 mL of 2 N sodium hydroxide solution were taken in 100 mL RBF and the reaction mixture was heated under mild reflux for 1.5 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured over ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with DMF/water to afford the title compounds **3**. The formation of the compounds **3** was confirmed by mp, mixed mp, and spectral data. Their characterization data is given in Table 2.

By ultrasonic irradiation: Thiosemicarbazide **2** (0.005 mol) and 10 mL of 2 N sodium hydroxide solution was taken in a beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30–35 min at room temperature. Progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and acidified with dilute hydrochloric acid. Product was separated by filtration and crystallized with DMF/water to afford the title compounds **3**. The formation of the compounds **3** confirmed by mp, mixed mp, and spectral data. Their characterization data is given in Table 2.

By microwave method: Thiosemicarbazide **2** (0.005 mole) was taken in 50 mL borosilicate glass beaker with 10 mL of 2 N sodium hydroxide solution. The reaction mixture was irradiated inside a microwave oven for 1 min to 2.5 min at an output of 300 W power, with short interruption of 15 s. TLC monitored progress of reaction. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF/water to afford the titled the compounds. Their characterization data is given in Table 2.

Table 1
Antimicrobial activity of synthesized compounds **2**, **3**, **4** and **5**

Compound no.	Substituted group	Zone of inhibition					
		S. aureus	*E. coli*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Candida albicans*
2a	(*3*-OCH_3)	14.3	16.6	15.3	22.8	–	–
2b	(*3*-*Cl*)	15.9	15.0	15.1	22.6	–	–
2c	(*3*-*H*)	23.9	24.1	24.1	24.2	–	14.2
2d	(*1*-CH_3)	17.2	18.5	20.1	20.1	18	
2e	(*2*-CH_3)	–	–	–	–	–	–
3a	(*3*-OCH_3)	23.4	–	–	–	21.6	–
3b	(*3*-*Cl*)	22.2	–	–	–	21.5	–
3c	(*3*-*H*)	21.0	–	–	–	19.9	–
3d	(*1*-CH_3)	21.2	–	–	–	20.8	–
3e	(*2*-CH_3)	19.8	–	–	–	21.8	–
4a	(*3*-OCH_3)	–	–	–	–	–	–
4b	(*3*-*Cl*)	21	–	28	–	–	22
4c	(*3*-*H*)	17	24	27	22	26.1	16.3
4d	(*1*-CH_3)	–	–	–	–	–	–
4e	(*2*-CH_3)	–	23.8	–	27.1	–	–
5a	(*3*-OCH_3)	28.0	–	26.7		28.1	25.3
5b	(*3*-*Cl*)	21.06	–	24.6	26.1		22.5
5c	(*3*-*H*)	18.8	–	25.4		14.7	
5d	(*1*-CH_3)	–	–	–	–	–	–
5e	(*2*-CH_3)	–	–	21	–	–	–
Nystatin		NA	NA	NA	NA	21.12	21.96
Chlorampenicol		32.8	29.14	30.11	24.68	NA	NA

Abbreviations used: NA = not applicable, – = no zone of inhibition. * Diameter in mm calculated by digital vernier Caliper.

Table 2
Characterization data of synthesized compounds **2**, **3**, **4**, and **5**

Compound	R^1	R^2	R^3	Mp (°C)	Conventional method		Ultrasound method		Microwave METHOD	
					Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
2a	H	H	OCH_3	198	60	71	—	—	—	—
2b	H	H	Cl	204	60	73	—	—	—	—
2c	H	H	H	194	60	75	—	—	—	—
2d	CH_3	H	H	176	60	81	—	—	—	—
2e	H	CH_3	H	196	60	74	—	—	—	—
3a	H	H	OCH_3	130	90	75	28	83	3.0	80
3b	H	H	Cl	170	90	73	30	80	2.4	76
3c	H	H	H	178	90	68	30	75	2.8	72
3d	CH_3	H	H	220	90	65	28	72	2.6	68
3e	H	CH_3	H	210	90	70	26	74	2.0	71
4a	H	H	OCH_3	246	120	75	35	88	2.5	82
4b	H	H	Cl	224	120	72	25	83	3.2	77
4c	H	H	H	232	120	73	30	85	3.0	79
4d	CH_3	H	H	190	120	69	35	80	2.5	75
4e	H	CH_3	H	188	120	65	35	87	3.0	80
5a	H	H	OCH_3	214	240	70	—	—	—	—
5b	H	H	Cl	220	240	68	—	—	—	—
5c	H	H	H	200	240	72	—	—	—	—
5d	CH_3	H	H	198	240	69	—	—	—	—
5e	H	CH_3	H	212	240	65	—	—	—	—

Abbreviations used: MP = melting point, min = minute.

3a: IR (KBr) ν/cm^{-1}: 3456 (–NH), 1650 (–C=O), 1694 (–C=N), 1586 (C=C), 1445 (–C=S), 1234 (–C–O–C), 1162 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.10–1.38 (m, 4H), 3.34 (s, 3H), 3.72 (s, 3H), 3.89–4.10 (m, 1H), 6.80–7.71 (m, 5H), 8.13 (s, 1H), 11.90 (br s, 1H, exchangeable). MS (*m/z*): 457 (M+1).

3b: IR (KBr) ν/cm^{-1}: 3452 (–NH), 1651 (–C=O), 1693 (–C=N), 1580 (C=C), 1443 (–C=S), 1232 (–C–O–C), 1161 (–C–F), 1086 (–C–Cl). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.09–1.32 (m, 4H), 3.32 (s, 3H), 3.73–4.10 (m, 1H), 6.81–8.01 (m, 5H), 8.12 (s, 1H), 11.91 (br s, 1H, exchangeable). MS (*m/z*): 461 (M+1), 463.

3c: IR (KBr) ν/cm^{-1}: 3454 (–NH), 1652 (–C=O), 1692 (–C=N), 1581 (C=C), 1442 (–C=S), 1233 (–C–O–C), 1164 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.08–1.33 (m, 4H), 3.31 (s, 3H), 3.74–4.11 (m, 1H), 6.82–8.09 (m, 5H), 8.14 (s, 1H), 12.01 (br s, 1H, exchangeable). MS (*m/z*): 427 (M+1).

3d: IR (KBr) ν/cm^{-1}: 3454 (–NH), 1652 (–C=O), 1695 (–C=N), 1588 (C=C), 1447 (–C=S), 1237 (–C–O–C), 1164 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.08–1.48 (m, 4H), 2.35 (s, 3H), 3.65 (s, 3H), 3.99–4.12 (m, 1H), 6.82–7.7 (m, 5H), 8.12 (s, 1H), 12.0 (br s, 1H, exchangeable). MS (*m/z*): 441 (M+1).

3e: IR (KBr) ν/cm^{-1}: 3458 (–NH), 1656 (–C=O), 1698 (–C=N), 1589 (C=C), 1448 (–C=S), 1238 (–C–O–C), 1166 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.38–1.49 (m, 4H), 2.34 (s, 3H), 3.99 (s, 3H), 4.20–4.33 (m, 1H), 6.84–7.6 (m, 5H), 8.02 (s, 1H), 12.37 (br s, 1H, exchangeable). MS (*m/z*): 441 (M+1).

*General procedure for synthesis of thiadiazoles (**4**).* By conventional method: Thiosemicarbazide **2** (0.005 mol) and concentrated sulphuric acid (5 mL) were taken in a beaker (50 mL) and the reaction mixture was kept at room temperature for 1.5 h. The reaction mixture was then poured over ice water. Product was separated by filtration and crystallized with DMF to afford the title compounds **4**. The formation of compounds **4** was confirmed by mp, mixed mp, and spectral data. Their characterization data is given in Table 2.

By ultrasonic irradiation: Thiosemicarbazide **2** (0.005 mol) and concentrated sulphuric acid (5 mL) were taken in beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30–35 min at room temperature. Progress of reaction was monitored by TLC. The reaction mixture was then poured over ice water. Product was separated by filtration and crystallized with DMF to afford the title compounds **4**. The formation of the compounds **4** was confirmed by mp, mixed mp, and spectral data. Their characterization data is given in Table 2.

By microwave method: Thiosemicarbazide **2** (0.005 mol) was taken in 50 mL borosilicate glass beaker with 15 mL concd H_2SO_4. Reaction mixture was irradiated inside a microwave oven for 1–2.5 min at an output of 300 W power, with short interruption of 15 s. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice. Product was separated by filtration and crystallized with DMF/water to afford the titled the compounds. Their characterization data is given in Table 2.

4a: IR (KBr) ν/cm^{-1}: 3456 (–NH), 1674 (–C=O), 1616 (C=C), 1468 (–C=S), 1327 (–C–O–C), 1145 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.03–1.18 (m, 4H), 2.45–2.83 (m, 1H), 3.57 (s, 3H), 3.69 (s, 3H), 6.09–8.66 (m, 5H), 8.85 (s, 1H), 10.09 (br s, 1H, exchangeable). MS (*m/z*): 457 (M+1).

4b: IR (KBr) ν/cm^{-1}: 3445 (–NH), 1680 (–C=O), 1618 (C=C), 1469 (–C=S), 1323 (–C–O–C), 1188 (–C–F), 1097 (–C–Cl). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.01–1.16 (m, 4H), 2.26–2.83 (m, 1H), 3.75 (s, 3H), 6.12–8.65 (m, 5H), 8.86 (s, 1H), 10.35 (br s, 1H, exchangeable). MS (*m/z*): 461 (M+1), 463.

4c: IR (KBr) ν/cm^{-1}: 3455 (–NH), 1679 (–C=O), 1616 (C=C), 1467 (–C=S), 1326 (–C–O–C), 1180 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.06–1.20 (m, 4H), 2.24–2.85 (m, 1H), 3.76 (s, 3H), 6.52–8.64 (m, 6H), 9.01 (s, 1H), 10.29 (br s, 1H, exchangeable). MS (*m/z*): 421 (M+1).

4d: IR (KBr) ν/cm^{-1}: 3453 (–NH), 1672 (–C=O), 1618 (C=C), 1467 (–C=S), 1326 (–C–O–C), 1146 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.09–1.16 (m, 4H), 2.16 (s, 3H), 2.46–2.84 (m, 1H), 3.56 (s, 3H), 6.13–8.69 (m, 5H), 9.0 (s, 1H), 10.12 (br s, 1H, exchangeable). MS (*m/z*): 441 (M+1).

4e: IR (KBr) ν/cm^{-1}: 3454 (–NH), 1671 (–C=O), 1616 (C=C), 1466 (–C=S), 1325 (–C–O–C), 1150 (–C–F), ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.07–1.19 (m, 4H), 2.15 (s, 3H), 2.49–2.83 (m, 1H), 3.58 (s, 3H), 6.19–8.64 (m, 5H), 8.90 (s, 1H), 10.15 (br s, 1H, exchangeable). MS (*m/z*): 441 (M+1).

General procedure for synthesis of oxadiazoles (5). Thiosemicarbazide **2** (0.002 mol) was dissolved in 20 mL of ethanol. To this reaction mixture 500 mg of I_2 and 640 mg of KI (in 20 mL H_2O) was added with 2 mL of 4 N NaOH and the reaction mixture was heated under mild reflux for 3 h. Progress of the reaction was monitored by TLC. Then from reaction mixture around 10 mL of ethanol was removed by distillation. Then reaction mixture was cooled and product obtained was separated by filtration and crystallized with

ethanol to afford the title compounds **5**. The formation of the compounds **5** was confirmed by spectral data. Their characterization data is given in Table 2.

5a: IR (KBr) ν/cm^{-1}: 3450 (–NH), 1662 (–C=O), 1649 (–C=N), 1618 (C=C), 1246 (–C–O–C), 1176 (–C–F). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.9–1.13 (m, 4H), 2.07–2.87 (m, 1H), 3.42 (s, 3H), 3.71 (s, 3H), 6.93–7.89 (m, 5H), 8.48 (s, 1H), 10.36 (br s, 1H, exchangeable). MS (*m/z*): 441 (M+1).

5b: IR (KBr) ν/cm^{-1}: 3454 (–NH), 1662 (–C=O), 1646 (–C=N), 1617 (C=C), 1248 (–C–O–C), 1167 (–C–F), 1084 (–C–Cl). 1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05–1.15 (m, 4H), 2.21–2.87 (m, 1H), 3.70 (s, 3H), 6.92–7.95 (m, 5H), 8.52 (s, 1H), 10.30 (br s, 1H, exchangeable). MS (*m/z*): 445 (M+1), 447.

5c: IR (KBr) ν/cm^{-1}: 3454 (–NH), 1662 (–C=O), 1646 (–C=N), 1617 (C=C), 1248 (–C–O–C), 1167 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.03–1.17 (m, 4H), 2.22–2.86 (m, 1H), 3.71 (s, 3H), 6.63–7.76 (m, 6H), 8.55 (s, 1H), 10.26 (br s, 1H, exchangeable). MS (*m/z*): 411 (M+1).

5d: IR (KBr) ν/cm^{-1}: 3453 (–NH), 1664 (–C=O), 1645 (–C=N), 1615 (C=C), 1247 (–C–O–C), 1168 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.06–1.16 (m, 4H), 2.14 (s, 3H), 2.21–2.87 (m, 1H), 3.73 (s, 3H), 6.94–7.96 (m, 5H), 8.56 (s, 1H), 10.30 (br s, 1H, exchangeable). MS (*m/z*): 425 (M+1).

5e: IR (KBr) ν/cm^{-1}: 3451 (–NH), 1661 (–C=O), 1647 (–C=N), 1616 (C=C), 1247 (–C–O–C), 1166 (–C–F). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.9–1.14 (m, 4H), 2.12 (s, 3H), 2.22–2.86 (m, 1H), 3.72 (s, 3H), 6.95–7.91 (m, 5H), 8.50 (s, 1H), 10.34 (br s, 1H, exchangeable). MS (*m/z*): 425 (M+1).

This study reports the successful synthesis of the fluorinated azoles using green technique with 72–88% yield. These green techniques required less time for the completion of the reaction as compared to conventional method. The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against moderate range of bacterial and fungal stains. These results make them interesting lead molecules for further synthetic and biological evaluation. It can be concluded that ultrasonicated synthesis is very clean, while microwave method required shorter time for completion and azoles certainly hold great promise towards the pursuit of discovering novel classes of antimicrobial agents. Further studies to acquire more information concerning structure–activity relationships are in progress.

Acknowledgments

Authors are thankful to the Principal Dr. K.H. Shinde, S.S.G.M. College, Kopargaon, Ahmednagar for providing necessary facilities and constant encouragement. One of the authors (S.N.S.) thanks UGC, New Delhi for funding support (MRP).

References and notes

1. Kuznetsova, L.; Ungureanu, M. I.; Pepe, A. *J. Fluorine Chem.* **2004**, *125*, 415.
2. Haga, T.; Fujikawa, K.; Koyanag, T.; Nakajima, T.; Hayashi, K. *Heterocycles* **1984**, *22*, 117.
3. Sanghvi, Y. S.; Bhattacharya, B. K.; Kini, G. D.; Matsumoto, S. S.; Larson, S. B.; Jolley, W. B.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1990**, *33*, 336.
4. Gill, C. H.; Jadhav, G.; Shaikh, M.; Kale, R.; Ghawalkar, A.; Nagargoje, D.; Shiradkar, M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6244.
5. Lin, R.; Connolly, P. J.; Huang, S.; Wetter, S. K.; Lu, Y.; Murray, W. V.; Emanuel, S. L.; Gruninger, R. H.; Fuentes, A. R.; Rugg, C. A.; Middleton, S. A.; Jolliffe, L. K. *J. Med. Chem.* **2005**, *48*, 4208.
6. Bhamaria, R. P.; Bellare, R. A.; Deliwala, C. V. *Indian J. Exp. Biol.* **1968**, *6*, 62.
7. Vander Kerk, G. J. M. *Proc. Br. Insectic Fungic Conf. IV* **1967**, *2*, 562.
8. Giri, S.; Singh, H. *J. Indian Chem. Soc.* **1972**, *49*, 175.
9. Pandey, V. K.; Lohani, H. C.; Agarwal, A. K. *Indian J. Pharm. Sci.* **1982**, *44*, 155.
10. Muhi-eldeen, Z.; Al-Jawed, F.; Eldin, S.; Abdul-Kadir, S.; Carabet, M. *Eur. J. Med. Chem.* **1982**, *17*, 479.
11. Chapleo, C. B.; Myers, M.; Meyers, P. L. *J. Med. Chem.* **1986**, *29*, 2273.
12. El Marsi, N. N.; Smith, I. N.; William, R. T. *Biochem. J.* **1958**, *68*, 587.
13. Ernst, A.; Roeder, K. *Chem. Abstr.* **1970**, *73*, 45516_w.
14. Bhat, K. S.; Karthikeyan, M. S.; Holla, B. S.; Shetty, N. S. *Indian J. Chem., Sect. B* **2004**, *43B*, 1765.
15. Amir, M.; Khan, M. S. Y.; Zaman, M. S. *Indian J. Chem., Sect. B* **2004**, *43B*, 2189.
16. Kidwai, M.; Venkataramanan, R.; Dave, B. *J. Heterocycl. Chem.* **2002**, *39*, 1045.
17. Ross, N. A.; Bartsch, R. A. *J. Heterocycl. Chem.* **2001**, *38*, 1255.
18. Singh, V.; Sapehiyia, V.; Kad, G. L. *Synthesis* **2003**, *2*, 198.
19. Robin, M.; Pique, V.; Faure, R.; Glay, J. *J. Heterocycl. Chem.* **2002**, *39*, 1083.
20. Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, *61*, 616.
21. Maruthikumar, T. V.; Reddy, V. P.; Rao, P. H. *Indian J. Chem., Sect. B* **2005**, *44*, 1931.
22. Yakaiah, T.; Reddy, G. V.; Lingaiah, B. P. V.; Rao, P. S.; Narsaiah, B. *Indian J. Chem., Sect. B* **2005**, *44*, 1301.
23. Chornous, V. O.; Bratenko, M. K.; Vovk, M. V. *Synth. Commun.* **2004**, *34*, 79.
24. Wang, G.; Cheng, B. *ARKIVOC* **2004**, *ix*, 4.
25. Louie, A.; Drusano, G. L.; Banerjee, P. *Antimicrob. Agents Chemother.* **1998**, *42*, 1105.
26. Klepser, M. E.; Malone, D.; Lewis, R. E.; Ernst, E. J.; Pfaller, M. A. *Antimicrob. Agents Chemother.* **2000**, *44*, 1917.
27. Andes, D.; Marchillo, K.; Conklin, R. *Antimicrob. Agents Chemother.* **2004**, *48*, 137.
28. Shelke, S. N.; Gill, C. H.; Karale, B. K. *Oriental J. Chem.* **2006**, *22*, 369.
29. Shelke, S.; Salunkhe, N.; Sangale, S.; Bhalerao, S.; Jadhav, R.; Karale, B. *J. Korean Chem. Soc.* **2010**, *54*, 59.