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(2-(6-Methyl-2-*P*-tolyl-l*H*-imidazo[1,2-a]pyridin-3-yl)핵종을 가지고 있는 불소화된 아조화합물의 합성과 항균활성의 스크리닝

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Synthesis and Antimicrobial Screening of Some Fluorinated Azoles Containing (2-(6-Methyl-2-*P*-tolyl-l*H*-imidazo[1,2-a]pyridin-3-yl) Nucleus

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요약. 일련의 불소화된 티아디아졸 3, 트리아졸 4, 그리고 옥사디아졸 5이 (2-(6-Methyl-2-*P*-tolyl-l*H*-imidazo[1,2-a]pyridin-3-yl)핵종을 가지고 있는 티오세미카르바지드로 부터 합성되어진다. 초음파조사 방법 뿐만 아니라 일반적인 방법에 의해 반응이 진행되었다. 모든 생성물들은 IR, 1H NMR, MS로 구조가 결정되었고, 이들 화합물의 항균활성을 스크닝하였다.
주제어: 불소화된 아졸, 트리아졸, 티아디아졸, 옥사티아졸, 초음파, 항균활성

ABSTRACT. The synthesis of a series of fluorinated thiadiazoles **3**, triazoles **4** and oxadiazoles **5** are synthesized from thiosemicarbazides **2** containing (2-(6-methyl-2-*p*-tolyl-l*H*-imidazo[1,2-a]pyridin-3-yl nucleus. These reactions were carried out by conventional method as well as ultra sound irradiation method. All products have been characterized by IR, ^{1}H NMR, MS study and screened for their antimicrobial activity.
Keywords: Fluorinated azoles, Triazoles, Thiadiazoles, Oxadiazoles, Ultrasound, Antibacterial activity

INTRODUCTION

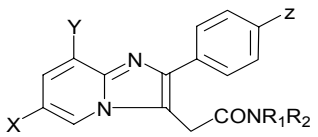
Fluorinated compounds have been of great interest to synthetic and medicinal chemists due to unique physical and biological properties imparted by fluorine.[1] Fluorinated drugs are used as anesthetics, antibiotics, anticancer, anti-inflammatory agents, psychopharmaceuticals and in many other applications.[2] 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*.

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS of vertebrates. The three types of GABA receptors denoted $GABA_A$, $GABA_B$ and $GABA_C$, have so far been characterized. The most abundant $GABA_A$ receptors are ligand-gated chloride ion channels and are characterized by the presence of several allosteric modulatory sites that regulates GABA affinity.[21] These sites include distinct ones for barbiturates, benzodiazepines (BZs), nuerosteroids and ethanol. Molecular biological studies have demonstrated that several

receptor subunits (α_1- α_6, β_1- β_3, γ_1- γ_3, δ) combine to form the $GAGA_A$ receptor complex.[22] Of the chemical classes, which have binding sites on this macromolecular ionophore, the benzodiazepines are the most widely studied. Although the exact nature of the BZ/chloride ionophore receptor complex remains to be established, expression of α, β and γ subunits results in a channel assembly that favor ligands of the BZ receptor complex. Using classical BZ_1/BZ_2 nomenclature,[23] the Bz_1 receptors are probably formed by the combination of subunits $\alpha_1\beta_2\gamma_2$, whereas a mixture of subunits α_2-, α_3- and $\alpha_5\beta_2\gamma_2$ represents BZ_2 receptors,[24] The third type, namely the BZ_3 receptors, constitute the "peripheral" receptors since they have been identified in the brain as well as in a wide range of peripheral tissues; their sub cellular location has been reported to be mainly mitochondrial,[25] and hence, this receptor is also termed "mitochondrial benzodiazepine receptor".[26] Although the pharmacological role of the BZ_3 receptors remains fully clarified, some evidence indicates their involvement in important cellular functions such as the production of neurosteroids.[26]

Among the known ligands, the N, N-dialkyl-2-phenylacetamidoimidazo[1,2-α]pyridines **A** (Alpidem) and **B** (Zolpidem) showed both high affinity and selectivity towards non-BZ_2 receptors.[27] Thus, Alpidem has high affinity for BZ_1 and BZ_3 sites while zolpidem possesses high affinity for BZ_1 but neither for BZ_2 nor peripheral sites.



A = Alpidem X=Z=Cl; Y=H; R1=R_2=C_3H_7
B = Zolpidem X=Z= CH_3; Y=H; R_1=R_2= CH_3

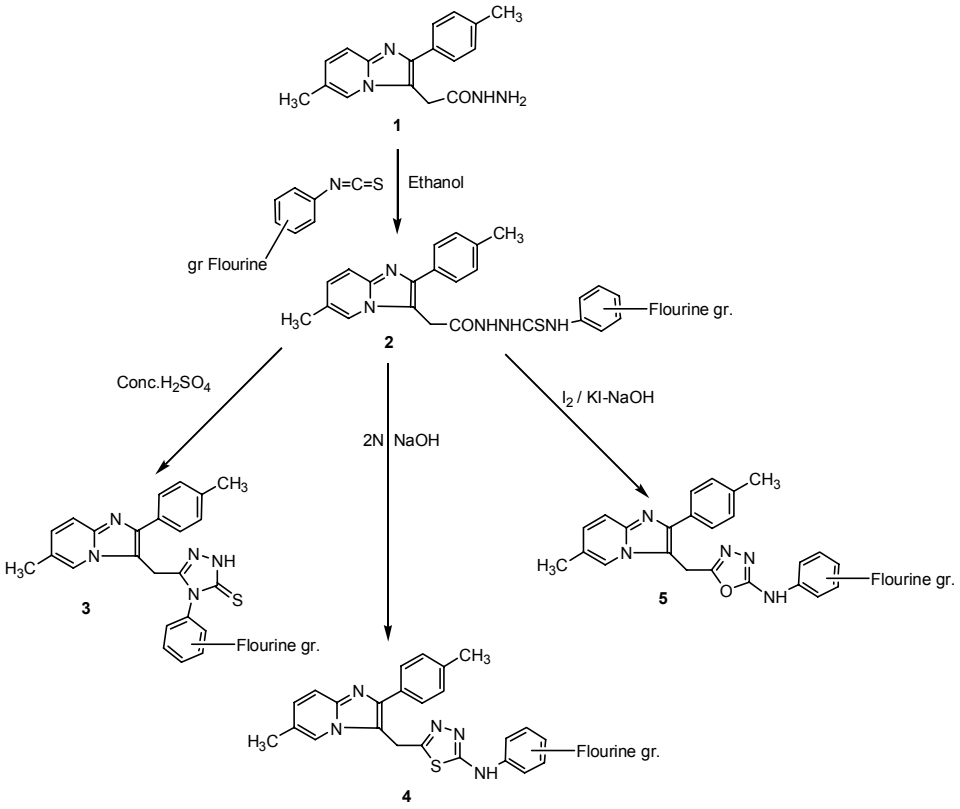
Biological activities associated with azoles and advantages of sonochemical synthesis and in continuation of our work.[28] have prompted us to prepare some fluorinated triazoles, oxadiazoles and thiadiazoles with zolpidem nucleus by conventional as well as sonochemical method.

RESULTS AND DISCUSSION

Chemistry

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

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** i.e. triazoles and in conc. H_2SO_4 gave



***Scheme* 1.** Synthesis of thiosemicarbazides **2**, triazoles **3**, thiadiazoles **4**, and oxadiazoles **5**.

compounds **4** i.e. thiadiazoles. These compounds **2** on treatment with I_2/KI & NaOH gave compounds **5** i.e. oxadiazoles. These compounds were synthesized by conventional method as well as ultra sound irradiation method. Compounds **3** and **4** were obtained in good yield within 25 - 30 min under ultrasonication. Each experiment was repeated three times to confirm the consistency of the results. The efficiency of ultrasonic method was evaluated by comparison with the same reaction in acidic or basic medium. The later method required 90 min for completion of the reaction and yields are found to be comparatively poor.

Antibacterial activity

Antibacterial activities were determined by filter paper disc method against gram-ve *Bacillus cereus* and gram+ve *Klebsiella pneumoniae* bacteria. The antibiotic tetracycline (40 µgms) was used as control. The samples (40 µgms) were dissolved in dimethyl formamide (DMF) and used for the antibacterial activity. The bacterial cultures of known inoculums size (0.2 CFU/mL) of test microorganism were spread on nutrient agar plates. The watman filter paper discs of 5 mm were placed on the plate and the sample of appropriate concentrarion was added to the filter disc. The plates were further incubed for 18 - 24 hrs at 37 ^{o}C.

The investigation of antibacterial screening data revealed that all the tested compounds **3**, **4** and **5** showed moderate to excellent antibacterial activities against *Bacillus cereus and Klebsiella pneumoniae.* The **2a-c**, **3a-c**, **4a-c** and **5a-c**, are active against *Bacillus cereus and Klebsiella pneumoniae*. Among these compounds, **4e** and **5e** exhibited less active than the Tetracycline against *Bacillus cereus and Klebsiella pneumoniae* bacterial strain respectively. The most active compounds **3c** and **5c** are passive for both gram-ve *Bacillus cereus* and gram+ve *Klebsiella pneumonia*. **2a**, **2c**, **3b**, **5a**, **and 5c** compound also shows excellent activity against both bacterial strains.

EXPERIMENTAL SECTION

All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. 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 400 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 ELECTRONICS PVT.LTD, Mumbai, India has maximum power output of 100W and 33 KHz operating frequency.

The newly synthesized compounds were screened for their antibacterial activity against gram-ve *Bacillus cereus* and gram+ve *Klebsiella pneumoniae* bacteria using filter paper disc method. The antibacterial activity was evaluated by measuring the zone of inhibition in mm and results obtained are shown in *Table* 1.

1-(2-(6-Methyl-2-*p*-tolyl-l*H*-imidazo[1,2-a]pyridin-3-yl)-acetyl-4-phenyl thiosemicarbazides (2)

Acid hydrazide (0.01 mol) **1** and fluorinated aryl isothiocyanates (0.01 mol) were taken in ethanol (15 mL) and the reaction mixture was heated under reflux for 60 minutes. After completions of reaction (monitored by TLC) contents were cooled to room temperature, the white product obtained was separated by filtration. The formation of compounds **2** was confirmed by m.p, mixed m.p, spectral and analytical data. Their characterization data is given in the *Table* 2.

2a: Anal. Calcd. For $C_{25}H_{22}F_3N_5OS$: C, 60.33; H, 4.47; N, 14.10. Found: C, 60.35; H, 4.46; N, 14.08. IR (KBr) ν/cm^{-1}: 3334 (-NH), 1669 (-C=O), 1582 (-C=N), 1506 (-C=S), 1102 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H), 2.56 (s, 3H), 4.00 (s, 2H), 6.74 to 7.72 (m, 11H), 9.45 (s, 2H), 10.54 (s, 1H). MS (*m/z*): 498 (M+1).

2b: Anal. Calcd. For $C_{24}H_{22}FN_5OS$: C, 64.40; H, 4.97; N, 15.64. Found: C, 64.41; H, 4.95; N, 15.65. IR (KBr) ν/cm^{-1}: 3314 to 3278 (-NH), 1670 (-C=O), 1589 (-C=N), 1509 (-C=S), 1101 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s,

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

Compound No.	Fluorinated group	Zone of inhibition	
		Bacillus cereus (gram-ve)	*Klebsiella neumoniae* (gram+ve)
2a	(*3*-CF_3)	13	11
2b	(*2*-F)	12	11
2c	(*3,4*-F_2)	12	12
2d	(*4*-F)	9	11
2e	(*2*-CF_3)	9	9
3a	(*3*-CF_3)	9	9
3b	(*2*-F)	12	12
3c	(*3,4*-F_2)	14	14
3d	(*4*-F)	9	9
3e	(*2*-CF_3)	9	9
4a	(*3*-CF_3)	10	9
4b	(*2*-F)	9	11
4c	(*3,4*-F_2)	9	9
4d	(*4*-F)	9	9
4e	(*2*-CF_3)	9	8
5a	(*3*-CF_3)	13	13
5b	(*2*-F)	14	14
5c	(*3, 4*-F_2)	12	12
5d	(*4*-F)	9	9
5e	(*2*-CF_3)	8	9
	Tetracycline	20	20

3H), 2.57 (s, 3H), 4.01 (s, 2H), 6.78 to 7.74 (m, 11H), 9.46 (s, 2H), 10.56 (s, 1H). MS (*m/z*): 448 (M+1).

2c: Anal. Calcd. For $C_{24}H_{21}F_2N_5OS$: C, 61.95; H, 4.54; N, 15.05. Found: C, 61.92; H, 4.55; N, 15.04. IR (KBr) ν/cm^{-1}: 3313 (-NH), 1668 (-C=O), 1615 (-C=N), 1519 (-C=S), 1110 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H), 2.38 (s, 3H), 4.08 (s, 2H), 7.06 to 8.19 (m, 10H), 9.63 (s, 2H), 10.6 (s, 1H). MS (*m/z*): 466 (M+1).

2d: Anal. Calcd. For $C_{24}H_{22}FN_5OS$: C, 64.43; H, 4.96; N, 15.64. Found: C, 64.41; H, 4.95; N, 15.65.

IR (KBr) ν/cm^{-1}: 3336 (-NH), 1672 (-C=O), 1609 (-C=N), 1409 (-C=S), 1101 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 6H), 4.08 (s, 2H), 7.02 to 8.18 (m, 11H), 9.59 (s, 2H), 10.53 (bs, 1H). MS (*m/z*): 448 (M+1).

2e: Anal. Calcd. For $C_{25}H_{22}F_3N_5OS$: C, 60.33; H, 4.42; N, 14.09. Found: C, 60.35; H, 4.46; N, 14.08.

IR (KBr) ν/cm^{-1}: 3332 (-NH), 1671 (-C=O), 1608 (-C=N), 1408 (-C=S), 1103 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 6H), 4.09 (s, 2H), 7.03 to 8.19 (m, 11H), 9.60 (s, 2H), 10.54 (bs, 1H). MS (*m/z*): 498 (M+1).

5-((6-Methyl-2-*p*-tolyl*H*-imidazo[1,2-a]pyridine-3-yl)methyl-4-phenyl-4*H*-1,2,4-triazole-3-thiols (3)

By conventional method: Thiosemicarbazide **2** (0.005) mole and 10 mL of 2N sodium hydroxide solution were taken in 100 mL RBF and the reaction mixture was heated under mild reflux for 1.5 hours. Progress of 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 compounds 3 was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the *Table* 2.

By ultrasonic irradiation: Thiosemicarbazide **2** (0.005) mole and 10 mL of 2N sodium hydroxide solution was taken in a beaker (50 mL) and the reaction mixture was subjected to ultrasonic irradiated for 30 - 35 minutes at room temperature. Progress of reaction was monitored by TLC. The reaction mixture was then 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 compounds 3 confirmed by m.p, mixed m.p, spectral and analytical data. Their Their characterization data is given in the *Table* 2.

3a: Anal. Calcd. For $C_{25}H_{20}F_3N_5S$: C, 62.61; H, 4.21; N, 14.61. Found: C, 62.62; H, 4.20; N, 14.60. IR (KBr) ν/cm^{-1}: 3425 (-NH), 3034 (=C-H), 1672 (-C=N), 1587 & 1511 (aromatic), 1374 (C=S), 1025 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H), 2.54 (s, 3H), 4.09 (s, 2H), 7.2 to 7.91 (m, 11H), 10.66 (s, 1H, -NH). MS (*m/z*): 480 (M+1).

3b: Anal. Calcd. For $C_{24}H_{20}FN_5S$: C, 67.10; H, 4.70; N, 16.32. Found: C, 67.11; H, 4.69; N, 16.31.

IR (KBr) ν/cm^{-1}: 3407 (-NH), 3036 (=C-H), 1670 (-C=N), 1589 & 1509 (aromatic), 1376 (C=S), 1023 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H), 2.57 (s, 3H), 4.11 (s, 2H), 7.1 to 7.89 (m, 11H), 10.64 (s, 1H, -NH). MS (*m/z*): 430 (M+1).

3c: Anal. Calcd. For $C_{24}H_{19}F_2N_5S$: C, 64.39; H, 4.29; N, 15.64. Found: C, 64.41; H, 4.28; N, 15.65.

IR (KBr) ν/cm^{-1}: 3379 (-NH), 2973 (=C-H), 1678 (-C=N), 1613 & 1513 (aromatic), 1363 (C=S), 1110 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H), 2.57 (s, 3H), 4.26 (s, 2H), 7.14 to 8.22 (m, 10H), 10.72 (s, 1H, -NH). MS (*m/z*): 448 (M+1).

3d: Anal. Calcd. For $C_{24}H_{20}FN_5S$: C, 67.12; H, 4.68; N, 16.32. Found: C, 67.11; H, 4.69; N, 16.31. IR (KBr) ν/cm^{-1}: 3426 (-NH), 3039 (=C-H), 1650 (-C=N), 1580 & 1508 (aromatic), 1390 (C=S), 1093 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H), 2.54 (s, 3H), 4.3 (s, 2H), 7.02 to 7.9 (m, 11H), 10.29 (s, 1H, -NH). MS (*m/z*): 430 (M+1).

3e: Anal. Calcd. For $C_{25}H_{20}F_3N_5S$: C, 62.63; H, 4.22; N, 14.62. Found: C, 62.62; H, 4.20; N, 14.60. IR (KBr) ν/cm^{-1}: 3433 (-NH), 3035 (=C-H), 1654 (-C=N), 1582 & 1518 (aromatic), 1395 (C=S), 1098 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 3H), 2.51 (s, 3H), 4.28 (s, 2H), 7.04 to 7.88 (m, 11H), 10.31 (s, 1H, -NH). MS (*m/z*): 480 (M+1).

5-(6-Methyl-2-*p*-tolyl-l*H*-imidazo[1,2-a]pyridine-3-yl)methyl-*N*-phenyl-1,3,4-thiadiazol-2-amine (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 hours. The reaction mixture was then poured over ice

Table 2. Characterization data of synthesized compounds **2** and **3**

Compound	Fluorinated group	M.P. (°C)	Conventional Method		Ultrasound Method	
			Time (min)	Yield (%)	Time (min)	Yield (%)
2a	(*3*-CF_3)	200	60	75	--	--
2b	(*2*-F)	222	60	82	--	--
2c	(*3,4*-F_2)	188	60	72	--	--
2d	(*4*-F)	220	60	78	--	--
2e	(*2*-CF_3)	210	60	67	--	--
3a	(*3*-CF_3)	300 (d)	90	58	30	85
3b	(*2*-F)	252 (d)	90	55	28	82
3c	(*3,4*-F_2)	260 (d)	90	61	32	78
3d	(*4*-F)	280 (d)	90	52	27	77
3e	(*2*-CF_3)	295 (d)	90	58	30	72

water. Product was separated by filtration and crystallized with DMF to afford the title compounds **4**. The formation of compounds **4** was confirmed by m.p, mixed m.p, spectral and analytical data. Their characterization data is given in the *Table* 3.

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 minutes 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 compounds **4** was confirmed by m.p., mixed m.p., spectral and analytical data. Their characterization data is given in the *Table* 3.

4a: Anal. Calcd. For $C_{25}H_{20}F_3N_5S$: C, 62.61; H, 4.21; N, 14.61. Found: C, 62.62; H, 4.20; N, 14.60. IR (KBr) ν/cm^{-1}: 3469 (-NH), 2918 (=C-H), 1620 (-C=N), 1550 & 1522 (aromatic), 1034 (-C-F), 744 (-C-S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H), 2.41 (s, 3H), 4.71 (s, 2H), 6.94 to 8.46 (m, 11H), 9.92 (s, 1H, -NH). MS (m/z): 480 (M+1).

4b: Anal. Calcd. For $C_{24}H_{20}FN_5S$: C, 67.10; H, 4.71; N, 14.33. Found: C, 67.11; H, 4.69; N, 16.31.

IR (KBr) ν/cm^{-1}: 3370 (-NH), 2919 (=C-H), 1621 (-C=N), 1552 & 1521 (aromatic), 1033 (-C-F), 749 (-C-S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H), 2.39 (s, 3H), 4.74 (s, 2H), 6.95 to 8.41 (m, 11H), 9.95 (s, 1H, -NH). MS (*m/z*): 430 (M+1).

4c: Anal. Calcd. For $C_{24}H_{19}F_2N_5$: C, 64.42; H, 4.27; N, 15.65. Found: C, 64.41; H, 4.28; N, 15.65.

IR (KBr) ν/cm^{-1}: 3410 (-NH), 3055 (=C-H), 1622 (-C=N), 1574 & 1508 (aromatic), 1047 (-C-F), 776 (-C-S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.40 (s, 3H), 2.41 (s, 3H), 4.7 (s, 2H), 7.08 to 8.33 (m, 10H), 10.34 (s, 1H, -NH). MS (*m/z*): 448 (M+1).

4d: Anal. Calcd. For $C_{24}H_{20}FN_5S$: C, 67.12; H, 4.68; N, 16.34. Found: C, 67.11; H, 4.69; N, 16.31.

IR (KBr) ν/cm^{-1}: 3426 (-NH), 2958 (=C-H), 1656 (-C=N), 1565 & 1507 (aromatic), 1001 (-C-F), 755 (-C-S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.40 (s, 3H), 2.41 (s, 3H), 4.7 (s, 2H), 6.99 to 8.23 (m, 11H), 10.12 (s, 1H, -NH). MS (*m/z*): 430 (M+1).

4e: Anal. Calcd. For $C_{25}H_{20}F_3N_5S$: C, 62.63; H, 4.22; N, 16.59. Found: C, 62.62; H, 4.20; N, 14.60.

IR (KBr) ν/cm^{-1}: 3421 (-NH), 2952 (=C-H), 1653 (-C=N), 1545 & 1517 (aromatic), 1011 (-C-F), 751 (-C-S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.41 (s, 3H), 2.42 (s, 3H), 4.6 (s, 2H), 7.00 to 8.22 (m, 11H), 10.11 (s, 1H, -NH). MS (*m/z*): 480 (M+1).

Table 3. Characterization data of synthesized compounds **4** and **5**

Compound	Fluorinated group	M.P. (°C)	Conventional Method		Ultrasound Method	
			Time (min)	Yield (%)	Time (min)	Yield (%)
4a	(*3*-CF_3)	230	90	75	35	84
4b	(*2*-F)	250 (d)	90	72	32	88
4c	(*3,4*-F_2)	240	90	78	30	82
4d	(*4*-F)	198	90	76	27	85
4e	(*2*-CF_3)	285 (d)	90	75	29	86
5a	(*3*-CF_3)	275	180	59	--	--
5b	(*2*-F)	210	180	62	--	--
5c	(*3,4*-F_2)	298 (d)	180	64	--	--
5d	(*4*-F)	225	180	60	--	--
5e	(*2*-CF_3)	270	180	63	--	--

5-(6-Methyl-2-*p*-tolyl-1*H*-imidazo[1,2-a]pyridine-3-yl)methyl-*N*-phenyl-1,3,4-oxadiazol-2-amine (5)

Thiosemicarbazide **2** (0.002 mol) was dissolved in 20 mL ethanol. To this reaction mixture 500 mg I_2 and 640 mg KI (in 20 mL H_2O) was added with 4N NaOH 2 mL and the reaction mixture was heated under mild reflux for 3 hours. Progress of reaction was monitored by TLC. Then from reaction mixture around 50% solvent was removed by distillation. Then reaction mixture was cooled and product obtained was separated by filtration and crystallized with alcohol to afford the title compounds **5**. The formation of compounds **5** was confirmed by spectral and analytical data. Their characterization data is given in the *Table* 3.

5a: Anal. Calcd. For $C_{25}H_{20}F_3N_5O$: C, 64.80; H, 4.33; N, 15.08. Found: C, 64.79; H, 4.35; N, 15.11. IR (KBr) ν/cm^{-1}: 3342 (-NH), 1651 (-C=N), 1611 & 1516 (aromatic), 1008 (-C-F). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H), 2.35 (s, 3H), 4.04 (s, 2H), 6.71 to 7.81 (m, 11H), 9.12 (s, 1H, -NH). MS (*m/z*): 463 (M+).

5b: Anal. Calcd. For $C_{24}H_{20}FN_5O$: C, 69.73; H, 4.89; N, 16.92. Found: C, 69.72; H, 4.88; N, 16.94.

IR (KBr) ν/cm^{-1}: 3343 (-NH), 1650 (-C=N), 1610 & 1509 (aromatic), 1011 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H), 2.39 (s, 3H), 4.08 (s, 2H), 6.99 to 7.80 (m, 11H), 9.13 (s, 1H, -NH). MS (*m/z*): 413 (M+).

5c: Anal. Calcd. For $C_{25}H_{22}F_3N_5OS$: C, 66.80; H, 4.42; N, 16.22. Found: C, 66.81; H, 4.44; N, 16.23.

IR (KBr) ν/cm^{-1}: 3336 (-NH), 1656 (-C=N), 1616 & 1519 (aromatic), 1017 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H), 2.38 (s, 3H), 4.38 (s, 2H), 7.03 to 7.79 (m, 10H), 8.13 (s, 1H, -NH). MS (*m/z*): 431 (M+).

5d: Anal. Calcd. For $C_{24}H_{20}FN_5O$: C, 69.70; H, 4.88; N, 16.96. Found: C, 69.72; H, 4.88; N, 16.94.

IR (KBr) ν/cm^{-1}: 3233 (-NH), 1652 (-C=N), 1619 & 1508 (aromatic), 1009 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 3H), 2.31

(s, 3H), 4.18 (s, 2H), 6.89 to 7.70 (m, 11H), 9.23 (s, 1H, -NH). MS (*m/z*): 413 (M+).

5e: Anal. Calcd. For $C_{25}H_{20}F_3N_5O$: C, 64.81; H, 4.36; N, 15.12. Found: C, 64.79; H, 4.35; N, 15.11.

IR (KBr) ν/cm^{-1}: 3340 (-NH), 1651 (-C=N), 1609 & 1511 (aromatic), 1012 (-C-F).

^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H), 2.36 (s, 3H), 4.10 (s, 2H), 6.96 to 7.81 (m, 11H), 9.12 (s, 1H, -NH). MS (*m/z*): 463 (M+).

CONCLUSION

This study reports the successful synthesis of the fluorinated azoles using ultrasonication in good yields. The newly synthesized heterocycles exhibited moderate to promising antimicrobial activity against moderate range of bacterial stains. These results make them interesting lead molecules for further synthetic and biological evaluation. It can be concluded that Ultrasonicated synthesis is very clean and 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.

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