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Synthesis and antimicrobial activity of some novel 2-(substituted fluorobenzoylimino)-3-(substituted fluorophenyl)-4-methyl-1,3-thiazolines

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ABSTRACT

The synthesis of several 2-(substituted fluorobenzoylimino)-3-(substituted fluorophenyl)-4-methyl-1,3-thiazolines (**2a–t**) was carried out by base-catalyzed cyclization of corresponding 1-(fluorobenzoyl)-3-(fluorophenyl)thioureas (**1a–t**) with 2-bromoacetone in aqueous medium. The structures of the synthesized compounds were confirmed by spectral and elemental analysis. All synthesized compounds were evaluated for *in vitro* antibacterial activity using Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*). The minimum inhibitory concentration (MIC) was determined for the most active compounds. *In vitro* antifungal activity was also determined against the five fungal species (*Rhizopus oryzae*, *Fusarium oxysporum*, *Aspergillus terreus*, *A. niger* and *A. fumigatus*).

1. Introduction

There has been an increasing interest in recent years in introduction of fluorine into organic compounds [1]. Incorporation of one or several fluorine atoms into an organic molecule can enhance their biological potency, bioavailability, metabolic stability and lipophilicity. Enhanced lipophilicity may lead to easier absorption and transportation of molecules within biological systems. More than 200 fluorinated pharmaceuticals are available and still others are appearing [2]. Fluorinated compounds usually have size and shape comparable to their non-fluorinated analogues and this favors interaction at a given biological molecular recognition site. Thus they tend to have similar inherent biological activities. Moreover, the fluorinated compounds tend to be more resistant to metabolic degradation due to the high bond energies and heats of formation of the H–O and C–O bonds relative to those of the F–O bond [3]. Fluorine substitution at a certain position in a drug molecule can influence not only pharmacokinetic properties such as absorption, tissue distribution, secretion and the route and rate of biotransformation but also its pharmacodynamics, toxicology and can improve the efficacy of drugs [4].

The 2-imino-1,3-thiazoline nucleus is found in a variety of biologically active natural products and has found extensive applications in medicinal chemistry. 2-Thiazolylimino-5-arylidene-4-thiazolidinones show noticeable antimicrobial activity against bacteria, yeasts and moulds [5]. 3-Substituted 2-(cyanoimino)thiazolidines can be used in agriculture due to their neonicotinoid insecticidal activity [6]. 3-Substituted thiazolidines show radioprotective properties against γ-radiations [7]. A quantitative structural-activity relationship (QSAR) study for fungicidal activities of 2-imino-1,3-thiazoline derivatives against rice blast fungus *Pyricularia oryzae* [8] has revealed their potent use as fungicides. KHG22394, a 2-imino-1,3-thiazoline derivative, significantly inhibits melanin production in a dose-dependent manner thus acting as a skin whitening agent [9] and pifithrin-α, another imino thiazoline, is a reversible inhibitor of p53-mediated apoptosis and p53-dependent gene transcription [10]. Amidine derivatives synthesized by the condensation of 2-cyanopyridine with various 3,4-diaryl-2-imino-4-thiazolines exhibited good anti-inflammatory and analgesic activity [11]. The 3-alkyl-3-*H*-thiazoline derivative, PS 028, a GP IIb/IIIa receptor antagonist, is a lead compound for the development of orally active potent platelet aggregation inhibitors [12]. Acridinyl-thiazoline derivatives have been found to exhibit moderate CDK1 inhibition [13]. Sydnonyl substituted thiazoline derivatives exhibit potent DPPH radical scavenging activity [14]. 2-Acylimino-1,3-thiazolines show bleaching herbicidal activity against up-land weeds and selectivity against crops [15]. The above mentioned biological and synthetic significance prompted us to carry out the synthesis of some new (substituted fluorobenzoylimino)-3-aryl-4-methyl-1,3-thiazolines.

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2. Results and discussion

2.1. Synthesis

Scheme 1 outlines the synthesis of the title compounds. The cyclocondensation of 1-aroyl-3-arylthioureas with α-halocarbonyl compounds is classically achieved in the presence of bromine in basic medium in rigorously dry solvents like acetone, dichloromethane, N,N,-dimethylformamide or acetonitrile under an inert atmosphere [16–19]. However these conventional non-aqueous conditions require long reaction times (3–5 h reflux) and give only modest yields. Reaction in water not only shortens the reaction times but also increases product purities and yields compared to non-aqueous media. In recent years aqueous chemistry has fascinated the synthetic organic chemists, not only for the reason that water is the most abundant, cheapest and environmentally friendly solvent but also because water exhibits exclusive reactivity and selectivity, which is different from those obtained in conventional organic solvents. The considerable enhancement in the rate of reaction in water has been ascribed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding [20,21]. The precursor 1-(fluorobenzoyl)-3-(fluorophenyl)thioureas (**1a–t**) were prepared according to the reported procedure involving the reaction of a fluorobenzoyl chloride with potassium thiocyanate in anhydrous acetone, followed by the condensation of the resulting fluorobenzoyl isothiocyanate intermediate with a suitable fluoroaniline [22]. In their IR spectra the 1-(fluorobenzoyl)-3-(fluorophenyl)thioureas are characterized by absorptions bands at 3351, 3200 cm^{-1} for free and associated NH stretching, at 1670 for carbonyl and at 1240 cm^{-1} for thiocarbonyl functionalities; singlets at δ 9.0 and 12 for HN(1) and HN(3) and peaks at 170, 179 for carbonyl and thiocarbonyl are observed in their ^1H and ^{13}C NMR spectra, respectively.

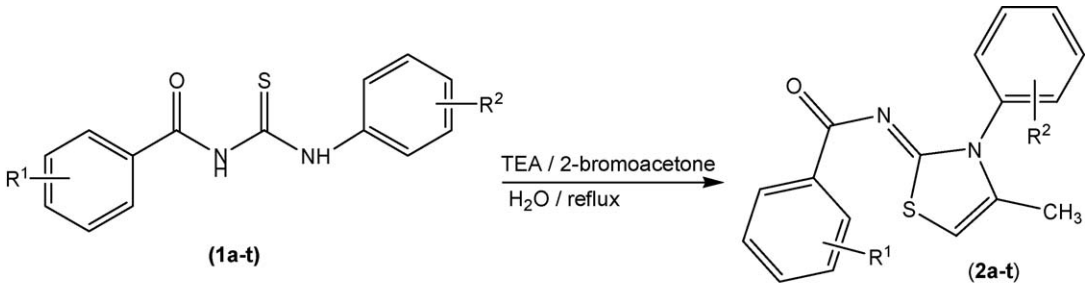
Cyclization of thioureas (**1a–t**) with 2-bromoacetone in water in basic medium led to the formation of the corresponding three series of isomeric (fluorobenzoylimino)-3-aryl-4-methyl-1,3-thiazolines. The structures were confirmed by a slight shifting of carbonyl absorption bands to 1585–1660 cm^{-1} and appearance of a characteristic C=N stretching at 1440–1480 cm^{-1} in the IR spectra, in addition to the absence of thiourea NHs absorptions. The emergence of characteristic 1H quartet for H-5 at δ 6.34–6.46 and a three-proton doublet for the 4-CH_3 of the thiazoline ring at δ 2.06–2.16, respectively, due to the mutually coupled protons with an allylic coupling constant of 0.9–1.2 Hz was noted in the ^1H NMR. ^{13}C NMR reveals the characteristic signals for olefinic carbon at δ 104.4–105.1 and for methyl carbon at δ 14.2–15.1 in conjunction with signals for aromatic protons which agreed to the proposed structures (Table 1). In the EIMS, in addition to the molecular ion peaks, the base peaks were observed at *m/z* 123, 139 and 195 corresponding to aroyl fragments $[FPhCO]^+$, $[ClPhCO]^+$ and $[(CH_3O)_3PhCO]^+$ respectively (Table 2).

2.2. Biological activities

2.2.1. Antibacterial activity

The antibacterial activities of all synthesized fluorinated iminothiazolines were investigated against four strains of bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 10197, *Bacillus subtilis* DSM 3256, *Staphylococcus aureus* ATCC 25923). The results of the antimicrobial evaluation of the tested compounds are presented in Table 3. Most of the tested compounds displayed significant efficacy against the Gram-positive bacterial strain *Bacillus subtilis* (B. S.) and the Gram-negative bacterial strain *Pseudomonas aeruginosa* (P. A.). Compound **2d** was most active against B. S., while **2o** was the least active. In the cases of P. A. **2p** exhibited highest activity and **2n** the lowest activity. Imipenem (molecular mass 299.347) was used as the standard drug. It is an intravenous β-lactam antibiotic (subgroup carbapenems) having an extremely broad spectrum of activity (Fig. 1).

Based on the results of the preliminary antimicrobial evaluation, compounds **2a**, **2b**, **2d**, **2e**, **2i**, **2n**, **2p**, **2r**, **2s** and **2t** were selected for further assessment. Significant results were obtained



a: R^1=2-Cl R^2=2-F, **b:** R^1=3,4,5-tri-OMe R^2=2-F
c: R^1=2-F R_2=2-F, **d:** R^1=3-F R^2=2-F
e: R^1=4-F R^2=2-F,

f: R^1=2-Cl R^2=3-F, **g:** R^1=3,4,5-tri-OMe R^2=3-F
h: R^1=2-F R^2=3-F, **i:** R^1=3-F R^2=3-F
j: R^1=4-F R^2=3-F,

k: R^1=2-Cl R^2=4-F, **l:** R^1=3,4,5-tri-OMe R^2=4-F
m: R^1=2-F R^2=4-F, **n:** R^1=3-F R^2=4-F
o: R^1=4-F R^2=4-F,

p: R^1=2-Cl R^2=3-Cl, 4-F, **q:** R^1=3,4,5-tri-OMe R^2=3-Cl, 4-F
r: R^1=2-F R^2=3-Cl, 4-F, **s:** R^1=4-F R^2=3-Cl, 4-F
t: R^1Ph=t-butyl R^2=3-Cl, 4-F

Scheme 1. Synthesis of some 2-(substituted fluorobenzoylimino)-3-(substituted fluorophenyl)-4-methyl-1,3-thiazolines.

Table 1
Spectroscopic data of thiazolines (**2a–t**).

Compd.	R_1	R_2	IR spectral data (ν/cm^{-1})	^{1}H and ^{13}C NMR spectral data (δ)
2a	2-Cl	2-F	1589 (C=O), 1555 (Ar–C=C), 1448 (C=N), 1261 (C–S), 1165 (C–N)	^{1}H NMR: δ 7.81 (*dd*, 1H, *J* = 1.8, 7.65 Hz, Ar–H), 7.55–7.16 (*m*, 7H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.12 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 174.1 (C=O), 170.2 (C=N), 157.6 (*d*, ^1J = 251 Hz), 136.0, 134.3, 133.6, 131.5 (*d*, ^3J = 8.25 Hz), 131.2, 131.0, 130.7, 126.3, 125.1, 124.8 (*d*, ^3J = 12.75 Hz), 124.6 (*d*, ^4J = 3.75 Hz), 116.8 (*d*, ^2J = 19.5 Hz), 104.6 (CH=C), 14.32 (CH_3).
2b	3,4,5-triO-CH_3	2-F	1595 (C=O), 1558 (Ar–C=C), 1451 (C=N), 1273 (C–S), 1125 (C–N)	^{1}H NMR: δ 7.58–7.51 (*m*, 1H, Ar–H), 7.44 (*dt*, 1H, *J* = 1.8, 7.8 Hz, Ar–H), 7.39–7.31 (*m*, 4H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 3.86 (*s*, 3H, OCH_3), 3.77 (*s*, 6H, 2[OCH_3]), 3.23 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.6 (C=O), 169.6 (C=N), 157.7 (*d*, ^1J = 251 Hz), 152.5 (2C), 140.8, 133.9, 132.0, 131.2 (*d*, ^3J = 7.5 Hz), 130.5, 125.1 (*d*, ^3J = 12.75 Hz), 124.6 (*d*, ^4J = 3.75 Hz), 116.7 (*d*, ^2J = 19.5 Hz), 106.2 (2C), 104.3 (CH=C), 60.8 (OCH_3), 55.77 (2C, 2[OCH_3]), 14.26 (CH_3).
2c	2-F-	2-F	1606 (C=O), 1561 (Ar–C=C), 1458 (C=N), 1275 (C–S), 1130 (C–N)	^{1}H NMR: δ 7.88 (*dt*, 1H, *J* = 1.8, 7.8 Hz, Ar–H), 7.55–7.02 (*m*, 7H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.16 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.4 (C=O), 169.7 (C=N), 162.3 (*d*, ^1J = 257 Hz), 157.6 (*d*, ^1J = 251 Hz), 134.0, 132.6 (*d*, ^3J = 8.25 Hz), 132.1 (*d*, ^4J = 0.75 Hz), 131.2 (*d*, ^3J = 8.75 Hz), 130.3, 125.1 (*d*, ^3J = 7.5 Hz), 124.7 (*d*, ^4J = 3.75 Hz), 123.4 (*d*, ^4J = 3.75 Hz), 116.8 (*d*, ^2J = 19.5 Hz), 116.7 (*d*, ^2J = 22.5 Hz), 104.4 (CH=C), 14.29 (CH_3).
2d	3-F-	2-F	1598 (C=O), 1564 (Ar–C=C), 1479 (C=N), 1262 (C–S), 1128 (C–N)	^{1}H NMR: δ 7.31–7.69 (*m*, 8H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.12 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.3 (C=O), 169.6 (C=N), 162.4 (*d*, ^1J = 256 Hz), 157.9 (*d*, ^1J = 251 Hz), 134.0, 132.6 (*d*, ^3J = 8.75 Hz), 132.2 (*d*, ^4J = 0.75 Hz), 131.1 (*d*, ^3J = 9 Hz), 130.3, 125.1 (*d*, ^3J = 7.5 Hz), 124.6 (*d*, ^4J = 3 Hz), 123.3 (*d*, ^4J = 3.75 Hz), 116.9 (*d*, ^2J = 21 Hz), 116.6 (*d*, ^2J = 22.5 Hz), 105.1 (CH=C), 14.96 (CH_3).
2e	4-F-	2-F	1605 (C=O), 1569 (Ar–C=C), 1461 (C=N), 1265 (C–S), 1148 (C–N)	^{1}H NMR: δ 8.07–6.95 (*m*, 8H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.12 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.4 (C=O), 170.0 (C=N), 165.1 (*d*, ^1J = 250 Hz), 157.5 (*d*, ^1J = 251 Hz), 134.1, 133.0 (*d*, ^4J = 3 Hz), 131.7, 131.1 (*d*, 2C, ^3J = 8.25 Hz), 130.2, 124.9 (*d*, ^4J = 3 Hz), 124.8 (*d*, ^3J = 6.75 Hz), 116.9 (*d*, ^2J = 19.5 Hz), 114.8 (*d*, 2C, ^2J = 21.75 Hz), 104.5 (CH=C), 14.30 (CH_3).
2f	2-Cl-	3-F	1589 (C=O), 1554 (Ar–C=C), 1452 (C=N), 1272 (C–S), 1252 (C–N)	^{1}H NMR: δ 7.82 (*dd*, 1H, *J* = 1.8, 7.7 Hz, Ar–H), 7.57 (*q*, 1H, *J* = 8.1 Hz, Ar–H), 7.34–7.12 (*m*, 6H, Ar–H), 6.42 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.16 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 172.3 (C=O), 169.3 (C=N), 162.7 (*d*, ^1J = 247 Hz), 138.4 (*d*, ^3J = 9.75 Hz), 135.9, 134.4, 133.6, 131.8, 131.2, 130.9, 130.6 (*d*, ^3J = 9 Hz), 126.2, 123.9 (*d*, ^4J = 3.5 Hz), 116.5 (*d*, ^2J = 21 Hz), 115.9 (*d*, ^2J = 22.5 Hz), 105.0 (CH=C), 14.93 (CH_3).
2g	3,4,5-triO-CH_3	3-F	1603 (C=O), 1565 (Ar–C=C), 1452 (C=N), 1273 (C–S), 1126 (C–N)	^{1}H NMR: δ 7.56 (*q*, 1H, *J* = 8.1 Hz, Ar–H), 7.37 (*s*, 2H, Ar–H), 7.29–7.20 (*m*, 1H, Ar–H), 7.14 (*dt*, 1H, *J* = 2.1, 8.1 Hz, Ar–H), 6.42 (*q*, 1H, *J* = 1.2Hz, CH=C), 3.87 (*s*, 3H, OCH_3), 3.67 (*s*, 6H, 2[OCH_3]), 2.10 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 172.4 (C=O), 169.5 (C=N), 162.7 (*d*, ^1J = 247 Hz), 152.5 (2C), 140.7, 138.6 (*d*, ^3J = 9.75 Hz), 133.9, 132.0, 130.5 (*d*, ^3J = 8.25 Hz), 123.9 (*d*, ^4J = 3.75 Hz), 116.5 (*d*, ^2J = 21.5 Hz), 115.2 (*d*, ^2J = 22.5 Hz), 106.2 (2C), 104.3 (CH=C), 60.7 (OCH_3), 55.7 (2C, 2[OCH_3]), 14.21 (CH_3).
2h	2-F-	3-F	1608 (C=O), 1569 (Ar–C=C), 1443 (C=N), 1277 (C–S), 1152 (C–N)	^{1}H NMR: δ 7.87 (*dt*, 1H, *J* = 1.8, 7.8 Hz, Ar–H), 7.60–7.01 (*m*, 7H, Ar–H), 6.43 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.10 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 172.4 (*d*, *J* = 3.3 Hz, C=O), 169.9 (C=N), 162.8 (*d*, ^1J = 247 Hz), 162.3 (*d*, ^1J = 251 Hz), 138.4 (*d*, ^3J = 9.75 Hz), 133.9, 132.7 (*d*, ^3J = 8.25 Hz), 132.2 (*d*, ^4J = 0.75 Hz), 130.7 (*d*, ^3J = 9 Hz), 125.2 (*d*, ^3J = 7.75 Hz), 123.9 (*d*, ^4J = 4.5 Hz), 123.4 (*d*, ^2J = 18.75 Hz), 116.7 (*d*, ^2J = 22.5 Hz), 116.3 (*d*, ^2J = 21 Hz), 115.9 (*d*, ^2J = 23.25 Hz), 105.1 (CH=C), 14.59 (CH_3).
2i	3-F-	3-F	1606 (C=O), 1559 (Ar–C=C), 1473 (C=N), 1260 (C–S), 1132 (C–N)	^{1}H NMR: δ 7.68–7.26 (*m*, 8H, Ar–H), 6.43 (*q*, 1H, *J* = 0.9 Hz, CH=C), 2.11 (*d*, 3H, *J* = 0.9 Hz, CH_3). ^{13}C NMR: δ 173.7 (C=O), 169.2 (C=N), 162.6 (*d*, ^1J = 257 Hz), 157.9 (*d*, ^1J = 257 Hz), 134.1, 132.5 (*d*, ^3J = 8.75 Hz), 132.1 (*d*, ^4J = 3.75 Hz), 131.2 (*d*, ^3J = 8.75 Hz), 130.4, 125.2 (*d*, ^3J = 8.75 Hz), 124.7 (*d*, ^4J = 0.75 Hz), 123.4 (*d*, ^4J = 3 Hz), 116.9 (*d*, ^2J = 18.75 Hz), 116.6 (*d*, ^2J = 21 Hz), 104.8 (CH=C), 15.01 (CH_3).
2j	4-F-	3-F	1602 (C=O), 1562 (Ar–C=C), 1450 (C=N), 1269 (C–S), 1142 (C–N)	^{1}H NMR: δ 8.08–8.05 (*m*, 2H, Ar–H), 7.57 (*q*, 1H, *J* = 8.1 Hz, Ar–H), 7.30–7.24 (*m*, 2H, Ar–H), 7.17 (*q*, 1H, *J* = 8.1 Hz, Ar–H), 7.06–6.96 (*m*, 2H, Ar–H), 6.44 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.14 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 170.4 (C=O), 169.9 (C=N), 164.9 (*d*, ^1J = 250 Hz), 162.7 (*d*, ^1J = 247 Hz), 138.4 (*d*, 1C, ^3J = 9.75 Hz), 133.9, 133.0 (*d*, 2C, ^3J = 8 Hz), 131.6, 130.3 (*d*, ^3J = 9 Hz), 124.0 (*d*, ^4J = 4.5 Hz), 116.6 (*d*, ^2J = 21 Hz), 115.9 (*d*, ^2J = 23.25 Hz), 114.8 (*d*, 2C, ^2J = 21.25 Hz), 105.1 (CH=C), 14.83 (CH_3).
2k	2-Cl-	4-F	1587 (C=O), 1503 (Ar–C=C), 1447 (C=N), 1279 (C–S), 1223 (C–N)	^{1}H NMR: δ 7.81 (*dd*, *J* = 2.1, 7.7 Hz, Ar–H), 7.36–7.15 (*m*, 7H, Ar–H), 6.44 (*q*, 1H, *J* = 1.2 Hz, CH=C), 2.06 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 174.0 (C=O), 170.2 (C=N), 162.6 (*d*, ^1J = 248 Hz), 136.0, 134.4, 133.5, 126.2, 133.1 (*d*, ^4J = 3 Hz), 131.8, 131.0, 130.8, 129.9 (*d*, 2C, $^3J_{C-F}$ = 8.25 Hz), 126.2, 116.6 (*d*, 2C, ^2J = 22.5 Hz), 104.9 (CH=C), 15.04 (CH_3).
2l	3,4,5-triO-CH_3	4-F	1603 (C=O), 1562 (Ar–C=C), 1452 (C=N), 1262 (C–S), 1151 (C–N)	^{1}H NMR: δ 7.39–7.35 (*m*, 4H, Ar–H), 7.28 (*dt*, 2H, *J* = 2.1, 8.25 Hz, Ar–H), 6.41 (*q*, 1H, *J* = 1.2 Hz, CH=C), 3.86 (*s*, 3H, OCH_3), 3.79 (*s*, 6H, 2[OCH_3]), 2.11 (*d*, 3H, *J* = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.0 (C=O), 169.9 (C=N), 162.6 (*d*, ^1J = 248 Hz), 152.5 (2C), 140.8, 134.1, 133.3 (*d*, ^4J = 3 Hz), 132.1, 130.2 (*d*, ^3J = 8.25 Hz), 116.3 (*d*, ^2J = 23 Hz), 106.1 (2C), 104.5 (CH=C), 60.85 (OCH_3), 55.77 (2C, 2[OCH_3]), 15.01 (CH_3).

Table 1 (*Continued*)

Compd.	R_1	R_2	IR spectral data (ν/cm^{-1})	^{1}H and ^{13}C NMR spectral data (δ)
2m	2-F-	4-F	1602 (C=O), 1563 (Ar–C=C), 1455 (C=N), 1269 (C–S), 1153 (C–N)	^{1}H NMR: δ 7.89–7.01 (*m*, 8H, Ar–H), 6.43 (*q*, 1H, J = 0.9 Hz, CH=C), 2.09 (*d*, 3H, J = 0.9 Hz, CH_3). ^{13}C NMR: δ 172.4 (*d*, J = 3 Hz, C=O), 170.1 (C=N), 162.6 (*d*, ^1J = 248 Hz), 162.3 (*d*, ^1J = 257 Hz), 134.2, 133.1 (*d*, ^4J = 3 Hz), 132.7 (*d*, ^3J = 9 Hz), 132.1 (*d*, ^4J = 0.75 Hz), 129.9 (*d*, 2C, ^3J = 9 Hz), 125.2 (*d*, ^3J = 8.25 Hz), 123.4 (*d*, ^4J = 3.75 Hz), 116.7 (*d*, ^2J = 22.5 Hz), 116.6 (*d*, 2C, ^2J = 22.5 Hz), 104.9 (CH=C), 15.04 (CH_3).
2n	3-F-	4-F	1599 (C=O), 1566 (Ar–C=C), 1454 (C=N), 1259 (C–S), 1154 (C–N)	^{1}H NMR: δ 7.71–7.30 (*m*, 8H, Ar–H), 6.46 (*q*, 1H, J = 1.2 Hz, CH=C), 2.11 (*d*, 3H, J = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.8 (C=O), 169.5 (C=N), 162.7 (*d*, ^1J = 251 Hz), 157.8 (*d*, ^1J = 257 Hz), 134.1, 132.5 (*d*, ^3J = 9 Hz), 132.2 (*d*, ^4J = 3.75 Hz), 131.2 (*d*, ^3J = 9 Hz), 130.3, 124.6 (*d*, ^4J = 3 Hz), 125.1 (*d*, ^3J = 8.75 Hz), 123.3 (*d*, ^4J = 3.75 Hz), 116.9 (*d*, ^2J = 22.5 Hz), 116.7 (*d*, ^2J = 22.5 Hz), 104.6 (CH=C), 15.04 (CH_3).
2o	4-F-	4-F	1660 (C=O), 1566 (Ar–C=C), 1453 (C=N), 1275 (C–S), 1148 (C–N)	^{1}H NMR: δ 8.07–7.35 (*m*, 4H, Ar–H), 7.28 (*dt*, 2H, J = 2.1, 7.8 Hz, Ar–H), 7.02–6.95 (*m*, 2H, Ar–H), 6.42 (*q*, 1H, J = 1.2 Hz, CH=C), 2.07 (*d*, 3H, J = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.8 (C=O), 169.9 (C=N), 164.9 (*d*, ^1J = 250 Hz), 162.6 (*d*, ^1J = 248 Hz), 134.1, 133.4 (*d*, ^4J = 3 Hz), 133.0 (*d*, 2C, ^3J = 8 Hz), 131.6, 130.2 (*d*, 2C, ^3J = 8.25 Hz), 116.3 (*d*, 2C, ^2J = 23 Hz), 114.9 (*d*, 2C, ^2J = 21.75 Hz), 104.4 (CH=C), 15.02 (CH_3).
2p	2-Cl-	3-Cl, 4-F	1596 (C=O), 1555 (Ar–C=C), 1456 (C=N), 1265 (C–S), 1136 (C–N)	^{1}H NMR: δ 7.82 (*dd*, 1H, J = 2.1, 7.65 Hz, Ar–H), 7.39–7.19 (*m*, 6H, Ar–H), 6.45 (*q*, 1H, J = 0.9 Hz, CH=C), 2.11 (*d*, 3H, J = 0.9 Hz, CH_3). ^{13}C NMR: δ 174.1 (C=O), 170.2 (C=N), 158.3 (*d*, ^1J = 251 Hz), 135.9, 134.2, 133.5, 133.4 (*d*, ^4J = 3 Hz), 131.8, 130.7, 130.6, 128.2 (*d*, ^3J = 7.5 Hz), 126.3, 122.1 (*d*, ^2J = 19.5 Hz), 121.8, 117.4 (*d*, ^2J = 22.5 Hz), 105.2 (CH=C), 15.02 (CH_3).
2q	3,4,5-triO-CH_3	3-Cl, 4-F	1598 (C=O), 1565 (Ar–C=C), 1474 (C=N), 1264 (C–S), 1125 (C–N)	^{1}H NMR: δ 7.57 (*dd*, 1H, J = 2.7, 6.3 Hz, Ar–H), 7.39–7.24 (*m*, 4H, Ar–H), 6.42 (*q*, 1H, J = 1.2 Hz, CH=C), 3.87 (*s*, 3H, OCH_3), 3.82 (*s*, 6H, 2[OCH_3]), 2.14 (*d*, 3H, J = 1.2 Hz, CH_3). ^{13}C NMR: δ 173.6 (C=O), 169.9 (C=N), 158.2 (*d*, ^1J = 251 Hz), 152.6 (2C), 140.9, 133.6 (*d*, ^4J = 3.75 Hz), 133.5, 131.8, 131.0, 128.2 (*d*, ^3J = 7.5 Hz), 121.8 (*d*, ^2J = 18.75 Hz), 117.1 (*d*, ^2J = 21.7 Hz), 106.1 (2C), 104.8 (CH=C), 60.87 (OCH_3), 55.8(2C, 2[OCH_3]), 15.02 (CH_3).
2r	2-F-	3-Cl, 4-F	1600 (C=O), 1575 (Ar–C=C), 1461 (C=N), 1273 (C–S), 1152 (C–N)	^{1}H NMR: δ 7.88 (*dt*, 1H, J = 1.8, 7.8 Hz, Ar–H), 7.46 (*dd*, 1H, J = 2.4, 6.3 Hz, Ar–H), 7.42–7.02 (*m*, 5H, Ar–H), 6.43 (*q*, 1H, J = 1.2 Hz, CH=C), 2.10 (*d*, 3H, J = 1.2 Hz, CH_3). ^{13}C NMR: δ 172.4 (*d*, J = 3 Hz, C=O), 170.1 (C=N), 162.3 (*d*, ^1J = 256 Hz), 158.3 (*d*, ^1J = 255 Hz), 133.8, 133.4 (*d*, ^4J = 3.75 Hz), 132.8 (*d*, ^3J = 9 Hz), 132.1, 130.5, 128.2 (*d*, ^3J = 7.5 Hz), 125.0 (*d*, ^3J = 7.5 Hz), 123.5 (*d*, ^4J = 4.5 Hz), 122.1 (*d*, ^2J = 18.75 Hz), 117.4 (*d*, ^2J = 22.5 Hz), 116.7 (*d*, ^2J = 22.5 Hz), 104.6 (CH=C), 15.02 (CH_3).
2s	4-F-	3-Cl, 4-F	1600 (C=O), 1571 (Ar–C=C), 1452 (C=N), 1278 (C–S), 1144 (C–N)	^{1}H NMR: δ 8.08–8.01 (*m*, 2H, Ar–H), 7.46 (*dd*, 1H, J = 2.4, 6.3 Hz, Ar–H), 7.40–6.94 (*m*, 4H, Ar–H), 6.44 (*q*, 1H, J = 1.2 Hz, CH=C), 2.13 (*d*, 3H, J = 1.2 Hz, CH_3). ^{13}C NMR: δ 172.4 (C=O), 170.1 (C=N), 164.8 (*d*, ^1J = 250 Hz), 158.2 (*d*, ^1J = 255 Hz), 134.1, 133.5 (*d*, ^4J = 3.75 Hz), 133.0 (*d*, 2C, ^3J = 8.25 Hz), 131.7, 130.5, 128.3 (*d*, ^3J = 7.5 Hz), 122.1 (*d*, ^2J = 18.75 Hz), 117.4 (*d*, ^2J = 22.5 Hz), 114.6 (*d*, 2C, ^2J = 21.75 Hz), 105.1 (CH=C), 14.98 (CH_3).
2t	*t*-Butyl	3-Cl, 4-F	1588 (C=O), 1540 (Ar-C=C), 1457 (C=N), 1258 (C–S), 1178 (C–N)	^{1}H NMR: δ 7.41–7.28 (*m*, 2H, Ar–H), 7.21 (*s*, 1H, Ar–H), 6.34 (*s*, 1H, CH=C), 2.08 (*s*, 3H, CH_3), 1.11 (*s*, 9H, 3[CH_3]). ^{13}C NMR: δ 174.6 (C=O), 169.0 (C=N), 158.1 (*d*, ^1J = 251 Hz), 128.2 (*d*, ^3J = 7.5 Hz), 121.7 (*d*, ^2J = 18.5 Hz), 117.1 (*d*, ^2J = 22.5 Hz), 104.3 (CH=C), 40.7, 27.5 (3C, 3[CH_3]), 15.05 (CH_3).

Table 2
Physicochemical and mass spectral data of thiazolines (**2a–t**).

Compound	R_1	R_2	Yield (%)	R_f[a]	Mp (°C)	Molecular formula (MW)	EIMS [M$^+$]	Analysis (Calcd./Found) (%)			
								C	H	N	S
2a	2-Cl	2-F	65	0.25	135–136	$C_{17}H_{12}N_2OSFCl$ (346.81)	346.0	58.87/58.85	3.49/3.51	8.08/8.06	9.25/9.27
2b	3,4,5-Tri-OCH_3	2-F	75	0.12	153–155	$C_{20}H_{19}N_2O_4SF$ (402.44)	402.0	59.69/59.61	4.76/4.79	6.96/6.99	7.97/7.98
2c	2-F	2-F	78	0.45	133–134	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.82	3.66/3.68	8.48/8.45	9.71/9.73
2d	3-F	2-F	73	0.53	117–119	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.86	3.66/3.64	8.48/8.47	9.71/9.73
2e	4-F	2-F	81	0.31	103–105	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.83	3.66/3.61	8.48/8.52	9.71/9.74
2f	2-Cl	3-F	65	0.22	129–131	$C_{17}H_{12}N_2OSFCl$ (346.81)	346.0	58.87/58.80	3.49/3.39	8.08/8.10	9.25/9.28
2g	3,4,5-Tri-OCH_3	3-F	68	0.11	172–173	$C_{17}H_{17}N_2O_4SF$ (364.39)	402.0	59.69/59.65	4.76/4.77	6.96/6.95	7.97/7.99
2h	2-F	3-F	76	0.43	173–174	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.85	3.66/3.69	8.48/8.43	9.71/9.68
2i	3-F	3-F	75	0.51	166–168	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.74	3.66/3.68	8.48/8.40	9.71/9.77
2j	4-F	3-F	69	0.25	147–150	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.85	3.66/3.62	8.48/8.41	9.71/9.78
2k	2-Cl	4-F	87	0.21	184–186	$C_{17}H_{12}N_2OSFCl$ (346.81)	346.0	58.87/58.82	3.49/3.45	8.08/8.11	9.25/9.27
2l	3,4,5-Tri-OCH_3	4-F	71	0.10	179–181	$C_{17}H_{17}N_2O_4SF$ (364.39)	402.0	59.69/59.71	4.76/4.73	6.96/6.91	7.97/8.08
2m	2-F	4-F	76	0.40	207–209	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.84	3.66/3.61	8.48/8.47	9.71/9.66
2n	3-F	4-F	81	0.50	174–175	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.77	3.66/3.69	8.48/8.56	9.71/9.79
2o	4-FC_6H_4	4-F	67	0.43	178–180	$C_{17}H_{12}N_2OSF_2$ (330.35)	330.0	61.81/61.80	3.66/3.61	8.48/8.45	9.71/9.73
2p	2-Cl	3-Cl-4-F	72	0.44	174–176	$C_{17}H_{11}N_2OSFCl_2$ (381.25)	380.0	53.56/53.49	2.91/2.85	7.35/7.41	8.41/8.44
2q	3,4,5-Tri-OCH_3	3-Cl-4-F	77	0.10	137–139	$C_{20}H_{18}N_2O_4SFCl$ (436.88)	436.0	54.98/54.93	4.15/4.16	6.41/6.46	7.34/7.30
2r	2-F	3-Cl-4-F	52	0.41	187–188	$C_{17}H_{11}N_2OSF_2Cl$ (364.8)	364.0	55.97/55.90	3.04/3.10	7.68/7.59	9.81/8.88
2s	4-F	3-Cl-4-F	62	0.44	185–187	$C_{17}H_{11}N_2OSF_2Cl$ (364.8)	364.0	55.97/55.96	3.04/3.07	7.68/7.65	8.79/8.77
2t	*t*-Butyl	3-Cl-4-F	82	0.56	124–125	$C_{15}H_{16}N_2OSFCl$ (326.82)	326.0	55.13/55.07	4.93/4.90	8.57/8.62	9.81/9.82

[a] Solvent system: n-hexane:ethyl acetate (6:4 v/v). Recrystallization solvent: ethanol.

Table 3
Antibacterial bioassay screening of thiazolines (**2a–t**).

Compound	Antibacterial activity[a]			
	Gram positive		Gram negative	
	Staphylococcus Aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
2a	05	10	–	07
2b	–	11	–	05
2c	–	07	–	08
2d	–	15	–	06
2e	–	11	–	05
2f	–	08	–	06
2g	–	07	–	–
2h	03	08	–	09
2i	03	12	–	09
2j	–	06	–	05
2k	–	07	–	05
2l	–	08	–	–
2m	–	05	–	06
2n	–	09	–	04
2o	–	05	–	05
2p	06	12	–	15
2q	–	07	–	05
2r	–	12	–	06
2s	04	11	–	07
2t	04	08	–	09
Imipenum	21	18	16	18

Concentration used: 2 mg/1 ml. (–) = No activity.
[a] Zone of inhibition (radius, mm).

for compound **2p** that shows low minimum inhibitory concentration (MIC) against the three bacterial strains S. A., B. S. and P.A. Good results were observed for compounds **2a** and **2p** which had a value of 250 μg/ml against S. A. Compounds **2d**, **2p**, **2r**, **2s** and **2t** had same MIC value of 125 μg/ml against B. S. but compound **2p** showed this value of 125 μg/ml only against P. A. (Table 4).

2.2.2. Antifungal activity

The antifungal activities of the all synthesized fluorinated iminothiazolines have been investigated against five different fungal strains, i.e., *Aspergillus terreus*, *Rhizopus oryzae*, *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus fumigatus*. The results are summarized in Table 5. The synthesized compounds exhibit excellent *in vitro* profiles against *Aspergillus terreus* (A. T.) and *Fusarium oxysporum* (F. O), a moderate effect against *Aspergillus niger* (A. N.) and relatively poor efficacy against *Rhizopus oryzae* (R. O.) and *Aspergillus fumigatus* (A. F.) except for **2t** which showed moderate activities against R.O. and A. F. Compound **2p** having a 2-Cl substituent on the aroyl and 3-Cl, 4-F on the aryl ring showed exceptionally high activity against most of the tested strains. Moreover, the compounds **2a**, **2k** and **2p** showed significant

Table 4
Minimum inhibitory concentration (MIC) of selected compounds.

Compound	Minimum inhibitory concentration (MIC), μg/ml			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
2a	250	250	–	250
2b	–	250	–	500
2d	–	125	–	250
2e	–	250	–	500
2i	500	250	–	250
2n	–	250	–	500
2p	250	125	–	125
2r		125	–	250
2s	500	125	–	250
2t	1000	125	–	250
Imipenum	0.60	0.30	0.10	1.30

Table 5
Antifungal bioassay screening of thiazolines (**2a–t**).

Compound	Antifungal activity									
	Rhizopus oryzae		*Aspergillus terreus*		*Fusarium oxysporum*		*Aspergillus niger*		*Aspergillus fumigatus*	
	Zone of inhibition	% inhibition	Zone of inhibition	% inhibition	Zone of inhibition	% inhibition	Zone of inhibition	% inhibition	Zone of inhibition	% inhibition
2a	7.5	16.7	1.5	81.3	3.5	56.3	7.0	22.2	7.5	16.6
2b	9.0	–	5.5	31.3	5.4	32.5	6.5	27.7	6.0	33.3
2c	9.0	–	4.0	50.0	4.0	50.0	6.0	33.3	8.0	11.1
2d	8.5	5.60	4.0	50.0	3.5	56.3	9.0	–	8.0	11.1
2e	8.0	11.2	3.2	60.0	4.5	43.8	8.0	11.1	8.0	11.1
2f	8.5	5.60	5.7	28.8	4.0	50.0	9.0	–	7.0	22.2
2g	7.5	16.7	5.0	37.5	5.0	37.5	9.0	–	8.0	11.1
2h	8.0	11.2	4.0	50.0	3.5	56.3	5.0	44.4	6.0	33.3
2i	6.5	27.8	5.4	32.5	6.0	25.0	9.0	–	8.0	11.1
2j	9.0	–	5.0	37.5	5.4	32.5	7.0	22.2	7.5	16.6
2k	8.0	11.2	2.0	75.0	3.5	56.3	5	44.4	5.5	38.8
2l	8.5	5.60	4.5	43.8	6.0	25.0	9.0	–	9.0	–
2m	9.0	–	6.5	18.8	8.0	–	6.5	27.7	7.0	22.2
2n	9.0	–	5.0	37.5	3.5	56.3	4.5	50.0	5.0	44.4
2o	9.0	–	3.5	56.3	6.0	25.0	7.0	22.2	5.0	44.4
2p	7.0	22.3	0.5	93.7	2.0	75.0	2.0	77.7	4.0	55.5
2q	8.5	5.60	5.0	37.5	4.0	50.0	9.0	–	9.0	–
2r	7.5	16.7	4.5	43.8	3.5	56.3	9.0	–	9.0	–
2s	8.5	5.60	3.5	56.3	3.0	62.5	7.0	22.2	5.0	44.4
2t	3.5	61.2	3.5	56.3	3.2	60.0	5.0	44.4	4.5	50.0
Control	9.0	–	8.0	–	8.0	–	9.0	–	9.0	–
Nystatin	0	100	0	100	0	100	0	100	0	100

Zone of inhibition in cm. percentage of fungal inhibition $= \frac{100 - \text{fungal growth in test sample (cm)}}{\text{fungal growth in control (cm)}} \times 100$. Concentration used: 2 mg/1 ml. (–) = No activity.

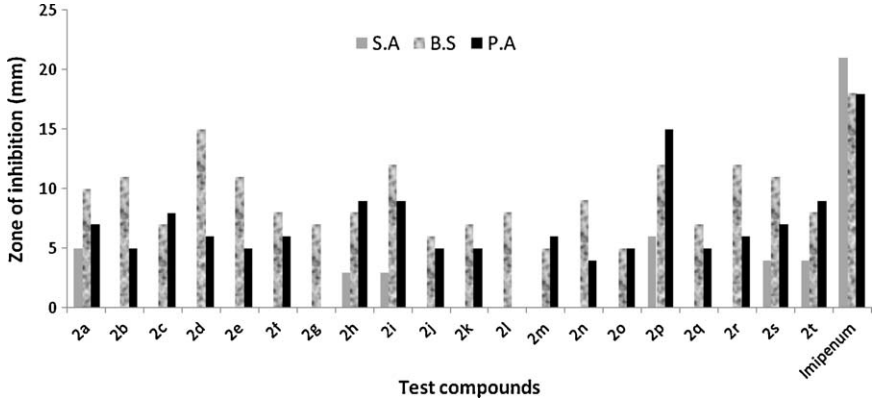


Fig. 1. Antibacterial activity of the synthesized compounds.

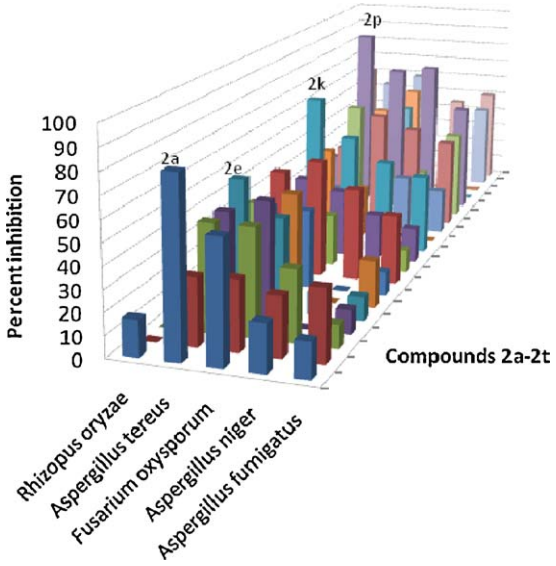


Fig. 2. Antifungal activity of the synthesized compounds.

antifungal activities against A.T. The *ortho*- and *para*-fluorine substitution on the aryl ring significantly improves the antifungal efficacy compared to the *meta*-substitution. Nystatin (mol. mass 926.09), a polyene antifungal drug isolated from *Streptomyces noursei* was used as negative control (as standard drug) with no growth (100% inhibition) of all fungal strains at the same concentration (Fig. 2).

3. Conclusion

Some new substituted fluorobenzoylimino-3-(fluoroaryl)-4-methyl-1,3-thiazolines were synthesized by base-catalyzed cyclocondensation of corresponding thioureas with 2-bromoacetone in unconventional aqueous medium. The compounds exhibit moderate to potent *in vitro* antimicrobial efficacy. In general, the antifungal activity of compounds was better than their antibacterial activity.

4. Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD BM 3.5 apparatus and are uncorrected. ^{1}H

NMR spectra were determined as $CDCl_3$ solutions at 300 MHz using a Bruker AM-300 spectrophotometer using TMS as an internal reference and ^{13}C NMR spectra were determined at 75 MHz using a Bruker 75 MHz NMR spectrometer in $CDCl_3$ solution. IR spectra were recorded using an Shimadzu IR 460 as KBr pellets; Mass Spectra (EI, 70 eV) on a GC–MS instrument Agilent technologies.

*4.1. General procedure for the preparation of 2-(substituted fluorobenzoylimino)-3-aryl-4-methyl-1,3-thiazolines (**2a–t**)*

A vigorously stirred mixture of thioureas (**1a–t**) (1 mmol), 2-bromoacetone (1 mmol) and triethylamine (1 mmol) in water (20 ml) was refluxed for 40–50 min. The progress of the reaction was followed by TLC examination using hexane ethyl acetate (6:4, v/v). On completion of the reaction the products were either filtered directly or extracted using ethyl acetate followed by drying and concentration. Recrystallization using ethanol or methanol afforded the 2-(substituted fluorobenzoylimino)-3-aryl-4-methyl-1,3-thiazolines (**2a–t**) as crystalline solids. Tables 1 and 2 give the physicochemical and characteristic spectral data (IR, ^1H, ^{13}C NMR, EIMS) of products.

5. Biological assay

5.1. Antibacterial activity

The antibacterial activity of all synthesized fluorinated iminothiazolines has been investigated against four bacterial strains by the Agar well diffusion assay. Imipenum was used as a standard antibiotic. 2 mg of compounds were dissolved in 1 ml of DMSO. In nutrient broth medium 24 h fresh bacterial was prepared. To compare the turbidity of bacterial culture McFarland 0.5% barium sulphate solution was used (as turbidity standard).

To perform the antibacterial assay, nutrient agar petri plates were prepared with sterile cotton swabs, respective bacterial colony lawns were prepared with sterile cork borrer (4 mm). Using a micropipette, 30 μl of test solution were poured into respective wells and these petri plates were incubated at 37 °C for 24 h. After 24 h of incubation, the radius of the clear zones showing no bacterial growth was measured around each well. The zones of inhibition (mm) were calculated and compared with the standard drug imipenum.

The primary screen was carried out by agar disc-diffusion method using nutrient agar medium. The minimum inhibitory concentration for the most active compounds **2a**, **2b**, **2d**, **2e**, **2i**, **2n**, **2p**, **2r**, **2s**, and **2t** against the same microorganisms used in the preliminary screening was carried out using the microdilution susceptibility method.

5.2. Antifungal activity

The antifungal activity of all the synthesized fluorinated 1-aroyl-3-aryl thioureas has been investigated against five different fungal strains, i.e., *Aspergillus terreus*, *Rhizopus oryzae*, *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus fumigatus*. 2 mg of compounds were dissolved in 1 ml of DMSO. All fungal strains were grown on saboraud dextrose agar SDA (pH 5.7) at 28 °C.

To perform the antifungal assay SDA medium petri plates were prepared. 50 μl of test samples were added to the respective petri plates using a micropipette and were dispersed using a spreader and were allowed to absorb for some time. These were inoculated with fungal strains and incubated at 30 °C. For every fungal strain, a control containing no test sample was also prepared. After 4–6 days of incubation, the diameter of the fungal strains was measured in each petri plate and percentage of fungal inhibition was calculated using the formulae:

$$\text{percentage of fungal inhibition} = \frac{100 - \text{fungal growth in test sample (cm)}}{\text{fungal growth in control (cm)}} \times 100.$$

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