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A one pot, three component synthesis of coumarin hybrid thiosemicarbazone derivatives and their antimicrobial evolution

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Abstract   A convenient, one-pot, multi-component protocol for the preparation of 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide derivatives has been achieved. Here, firstly we have reported the synthesis of 3-acetyl-2*H*-chromen-2-one using starch sulfuric acid and cellulose sulfuric acid as biodegradable catalysts. Subsequently, we also carried out the reaction of isothiocynates, hydrazine hydrate and 3-acetyl-2*H*-chromen-2-one in the presence of catalytic amount of glacial acetic acid in refluxing ethanol to afford corresponding 2-(1-(2-oxo-2*H*-chromen-3-yl)ethyli dene)hydrazinecarbothioamide derivatives in high to excellent yields. All synsized compounds were screened for antimicrobial activity. All compounds were found to show good to excellent activity against *Escherichia coli* MTCC 443.

1. Introduction

The design and green synthesis of biological active compounds as well as drug intermediates in the field of medicinal chemistry can be considered as an attractive research option, because these syntheses have various benefits such as waste reduction, energy savings, atom economy, easy work-up processes and avoiding the use of hazardous chemicals. (Kumar et al., 2012; Anastas and Kirchhoff, 2002). The development of a green, clean and eco-friendly reaction methodology for the preparation of highly potent biological active compounds is an interesting and to be explored area of medicinal chemistry (Vekariya and Patel, 2015). Multi-component reactions (MCRs) have been shown to be powerful tools in the field of green chemistry for developing various medicinally important scaffolds and intermediates (Chanda and Fokin, 2009).

Coumarin derivatives are an important class of heterocycles, which occupy an important place in the domain of natural products and synthetic organic chemistry (Vekariya and Patel, 2014). A wide range of organic compounds containing the coumarin moiety have also been found to exhibit many useful applications, which include antibacterial (Fan et al., 2001), antifungal (Zaha and Hazem, 2002), antioxidant (Vazquez-Rodriguez et al., 2013), analgesic (Khode et al., 2009),

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anticancer (Wu et al., 2014), anti-HIV (Bhavsar et al., 2011), anti-inflammatory (Timonen et al., 2011), antibiotic (Chimenti et al., 2006), anticoagulant (Van Schie et al., 2009) and antitumor (Gouda et al., 2012). Some synthetic analogs of 3-substituted coumarin derivatives (Fig. 1I and II) were reported in the literature. They shows antibacterial and anticonvulsant activities respectively (Chimenti et al., 2010).

Thiosemicarbazone derivatives, a large group of thiourea derivatives, exhibit various biological activities and have therefore attracted considerable pharmaceutical interest (Hu et al., 2006). They have been evaluated over the last 50 years as antiviral (Garcia et al., 2003), antibacterial (Kasuga et al., 2003), anticancer agents (Dilovic et al., 2008), anti-malarial (Divatia et al., 2014), anti-HIV (Patel et al., 2013), whose biological activities are a function of the parent aldehyde or ketone moiety (Yuan et al., 2004). Moreover, compounds with thiosemicarbazone structure are known to possess tranquilizing, analgesic, hypnotic, anti-tumor, anti-depressant, muscle relaxing, anti-fungal and anti-inflammatory properties (Beraldo and Gambinob, 2004; Singh et al., 2006, 2005). Indeed, many thiosemicarbazones exhibit promising antiprotozoan activity through the inhibition of cysteine proteases and other targets (Chiyanzu et al., 2003; Greenbaum et al., 2004; Fujii et al., 2005). Heterocyclic thiosemicarbazones are important because of their possible beneficial biological activity (El-Sharief and Moussa, 2009). Some synthetic analogs of thiosemicarbazone already exist in the market like, Triapine and Marboran (Fig. 1III and IV). Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) is a potent ribonucleotide reductase inhibitor and is used in the treatment of cancer (Tsimberidou et al., 2002). Marboran (1-N-methylisatin-β-thiosemicarbazone) is a good anti-viral agent. It has activity against Pox viruses, Maloney leukemia viruses and recently against HIV (Sebastian et al., 2008).
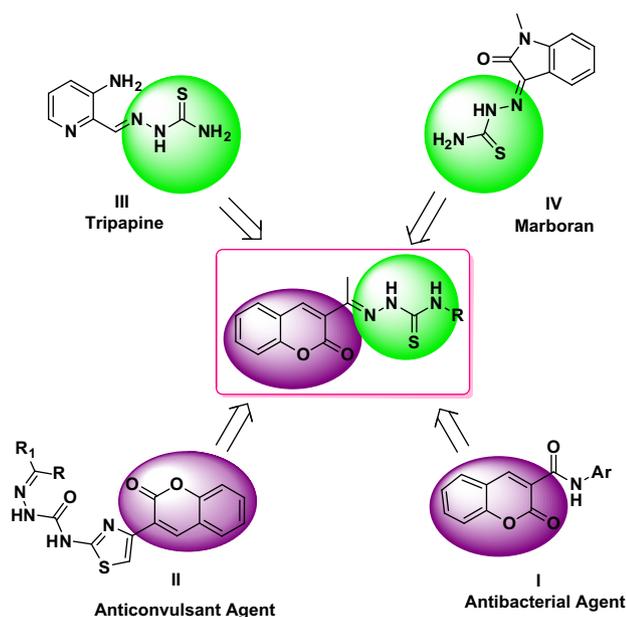
Despite many significant progresses in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to rapid development of resistance to the existing antibacterial and antifungal drugs. Thiosemicarbazone derivatives have been the focus of medicinal chemists because of their potential biological activities (Tsimberidou et al., 2002). Thiosemicarbazones were studied for their antibacterial and antifungal properties (Chohan et al., 2005). Recently, many of these derivatives were synthesized and described for their activity against bacterial species; and this can indicate that many derivatives, in-between, are useful in the therapy, prophylaxis of bacterial infections and can represent a template for the development of novel antibacterial drugs (Bermudez et al., 2003; Sriram et al., 2006).

Organic transformations using cellulose sulfuric acid (CSA) and starch sulfuric acid (SSA) have many advantages such as a simple work-up process, inexpensive catalyst, eco-friendliness, reusable catalyst, excellent yield of the products with high purity and shorter reaction times (Vekariya and Patel, 2015). The CSA and SSA are solid, bio-degradable catalysts and after completion of organic transformation, can be recovered and reused several times without loss of its efficiency. Various catalysts have been developed such as piperidine, L-lysine, L-proline, KSF-Clay, HZSM-5 Zeolite, heteropoly acids, $ZrOCl_2 \cdot 8H_2O$, $SnCl_2 \cdot 2H_2O$, Ionic liquids and cellulose sulfonic acid for the synthesis of 3-acetyl coumarin via Knoevenagel condensation (Vekariya and Patel, 2014). Thus, it was thought worthwhile to develop a new and mild method for the synthesis of 3-acetyl coumarin using SSA and CSA as inexpensive biopolymer-based catalysts.

Therefore, it was aimed in the present investigation to synthesize and characterize newer coumarin hybrid thiosemicarbazone derivatives for their expected antimicrobial activities. Herein, we report an efficient and green synthesis of 3-acetyl coumarin from the reaction of 2-hydroxy benzaldehyde and ethyl acetoacetate in the presence of SSA and CSA under solvent-free conditions at 100 °C. Finally we have synthesized coumarin hybrid thiosemicarbazone derivatives via one-pot reaction of a variety of isothiocynates, hydrazine hydrate and 3-acetyl coumarin in the presence of a catalytic amount of AcOH under refluxing ethanol (Scheme 1).

2. Experimental section

All the analytical grade reagents and starting materials were used. Melting points are uncorrected and were determined in automatic melting point apparatus named Optimelt MPA 100. TLC was run on Aluminum precoated ready-made thin layer chromatography (TLC) silica gel 60 F_{254} plate (Merck, Germany) and visualization was done using iodine or UV light. IR Spectra (V max in cm^{-1}) were recorded on a Perkin-Elmer FT-IR 377 spectrophotometer using KBr. Proton NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO as solvent and TMS as the internal reference. Mass spectra were recorded at Advion expression CMS, USA, Acetone is used as mobile phase, electron spray ionization (ESI) is used as ion source. Elemental analysis was performed on a CHN elemental analyzer. Starch sulfuric acid (SSA) and cellulose sulfuric acid (CSA) were prepared according to previously reported procedure (Shaabani et al., 2008).

Figure 1 Design of novel coumarin hybrid thiosemicarbazone derivatives.
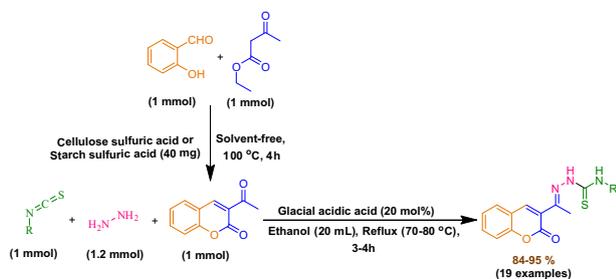
Scheme 1 Synthetic protocol of novel coumarin-thiosemicarbazone derivatives.

2.1. Typical procedure for the preparation of 3-acetyl-2H-chromen-2-one

A mixture of *ortho*-hydroxy benzaldehyde (1.0 mmol) and ethyl acetoacetate (1.0 mmol) and CSA or SSA (40 mg) was stirred at 100 °C temperature under solvent free conditions for 4 h. The reaction progress was monitored by TLC using hexane:ethyl acetate (4:6) as the mobile phase. After completion of the reaction, the reaction mixture was mixed with hot ethanol (5 ml) and filtered. SSA and CSA were recovered by filtration after the addition of ethanol to the stirred reaction mixture. Conventional elemental analysis showed the presence of sulfur, indicating sulfur had not leached out. Filtrate was cooled in ice to obtain pale yellow colored 3-acetyl coumarin with 95% yield; m.p. = 120–122 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.58 (S, 3H, —COCH$_3$), 7.44–7.78 (m, 4H, Ar-H), 8.64 (s, 1H, pyran-H). MS: m/z (%) 389.24 (M$^+$ + 1, 100%) base peak.

2.2. General procedure for the one-pot preparation of 3-acetylcoumarin thiosemicarbazone derivatives (1–19)

A solution of hydrazine hydrate (1.5 mmol, 80%) in ethanol (5 ml) was added drop wise to a stirred solution of isothiocynates (1.0 mmol) in ethanol (5 ml) at room temperature. A white precipitate starts to form immediately upon addition, the stirring was continued for 30 min. Now, 3-acetyl-2*H*-chromen-2-one (1.0 mmol) in ethanol (10 ml) was added into the reaction mixture and heated at 75–80 °C. Then, add 20 mol% of glacial acidic to the reaction mixture. The reaction mixture was refluxed for 4 h. Reaction progress was monitored on a ready-made TLC plate (Merck) every 30 min. using hexane: ethyl acetate (4:6) as the solvent system. After completion of the reaction, the reaction mixture was cooled, water was added and a yellow precipitate started to form; the solid was filtered and washed with water then with ethanol. The product was recrystallized from ethanol and dried under vacuum, which afforded the pure analytical sample in excellent yields.

2.2.1. N-(4-nitrophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (1)

IR (KBr) cm^{-1}: 3419, 3330 (NH), 1720 (C=O), 1630 (C=N), 1613, 1588 (C=S), 1375 (C=S), 1120, 1095 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 3.74 (S, 3H, CH$_3$), 7.18–8.09 (m, 8H, Ar-H), 8.60 (S, 1H, pyran-H), 10.49 (S, 1H, NH), 11.23 (S, 1H, NH). MS: m/z (%) 383.3 (M$^+$ + 1, 100%) base peak. Elemental analysis: Calc. for C$_{18}$H$_{14}$N$_4$O$_4$S

(382.39) C, 56.54%; H, 3.69%; N, 14.65%; S, 8.39%, found: C, 56.38%; H, 3.50%; N, 14.43%; S, 8.52%.

2.2.2. N-(4-chlorophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (2)

IR (KBr) cm^{-1}: 3408, 3335 (NH), 1722 (C=O), 1642 (C=N), 1618, 1595 (C=S), 1367 (C=S), 1107, 1085 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.34 (S, 3H, CH$_3$), 7.38–7.80 (m, 8H, Ar-H), 8.48 (S, 1H, pyran-H), 10.21 (S, 1H, NH), 10.99 (S, 1H, NH). MS: m/z (%) 370.3 (M$^+$ −1, 100%) base peak, 372.2 (M$^+$ + 2, 62%). Elemental analysis: Calc. for C$_{18}$H$_{14}$ClN$_3$O$_2$S (371.84) C, 58.14%; H, 3.79%; N, 11.30%; S, 8.62%, found: C, 58.38%; H, 3.57%; N, 11.41%; S, 8.55%.

2.2.3. 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-N-(p-tolyl) hydrazinecarbothioamide (3)

IR (KBr) cm^{-1}: 3428, 3332 (NH), 1718 (C=O), 1633 (C=N), 1610, 1598 (C=S), 1371 (C=S), 1102, 1088 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.31 (S, 3H, 4-CH$_3$), 2.51 (S, 3H, CH$_3$), 7.21–8.09 (m, 8H, Ar-H), 8.51 (S, 1H, pyran-H), 10.03 (S, 1H, NH), 10.83 (S, 1H, NH). MS: m/z (%) 352.3 (M$^+$ + 1, 100%) base peak, 353.3 (M$^+$ + 2, 54%). Elemental analysis: Calc. for C$_{19}$H$_{17}$N$_3$O$_2$S (351.42) C, 64.94%; H, 4.88%; N, 11.96%; S, 9.12%, found: C, 64.98%; H, 4.87%; N, 11.81%; S, 9.22%.

2.2.4. 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-N-propylhydrazinecarbothioamide (4)

IR (KBr) cm^{-1}: 3429, 3331 (NH), 1715 (C=O), 1637 (C=N), 1609, 1594 (C=S), 1372 (C=S), 1111, 1091 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 1.58 (t, 3H, CH$_3$, J = 10), 1.90 (q, 2H, CH$_2$), 3.35 (S, 3H, CH$_3$), 3.73 (S, 1H, NH), 6.85–7.86 (m, 4H, Ar-H), 8.24 (S, 1H, pyran-H), 10.44 (S, 1H, NH). MS: m/z (%) 304.5 (M$^+$ + 1, 100%) base peak, 305.5 (M$^+$ + 2, 27%). Elemental analysis: Calc. for C$_{15}$H$_{17}$N$_3$O$_2$S (303.38) C, 59.38%; H, 5.65%; N, 13.85%; S, 10.57%, found: C, 59.32%; H, 5.67%; N, 13.88%; S, 10.49%.

2.2.5. N-(3,4-dichlorophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (5)

IR (KBr) cm^{-1}: 3415, 3332 (NH), 1723 (C=O), 1636 (C=N), 1617, 1582 (C=S), 1378 (C=S), 1128, 1099 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.51 (S, 3H, CH$_3$), 7.40–8.04 (m, 8H, Ar-H), 8.47 (S, 1H, pyran-H), 10.29 (S, 1H, NH), 11.18 (S, 1H, NH). MS: m/z (%) 405.1 (M$^+$ −1, 100%) base peak, 407.1 (M$^+$ + 2, 86%). Elemental analysis: Calc. for C$_{18}$H$_{13}$Cl$_2$N$_3$O$_2$S (406.29) C, 53.21%; H, 3.23%; N, 10.34%; S, 7.89%, found: C, 53.32%; H, 3.43%; N, 10.58%; S, 7.69%.

2.2.6. N-(tert-butyl)-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (6)

IR (KBr) cm^{-1}: 3423, 3333 (NH), 1720 (C=O), 1627 (C=N), 1615, 1593 (C=S), 1378 (C=S), 1124, 1101 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.3 (S, 9H, t-butyl), 3.35 (S, 3H, CH$_3$), 7.18–8.09 (m, 4H, Ar-H), 8.55 (S, 1H, pyran-H), 10.03 (S, 1H, NH), 10.90 (S, 1H, NH). MS: m/z (%) 318.1 (M$^+$ + 1, 100%) base peak, 319.1 (M$^+$ + 2, 26%). Elemental analysis: Calc. for C$_{16}$H$_{19}$N$_3$O$_2$S (317.41) C, 50.54%;

H, 6.03%; N, 13.24%; S, 10.10%, found: C, 50.37%; H, 6.14%; N, 13.38%; S, 10.16%.

2.2.7. N-benzyl-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (7)

IR (KBr) cm^{-1}: 3415, 3337 (NH), 1723 (C=O), 1638 (C=N), 1619, 1579 (C=S), 1377 (C=S), 1129, 1092 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 1.95 (S, 2H, CH$_2$), 2.29 (S, 3H, CH$_3$), 4.85 (S, 2H, CH$_2$), 6.82–8.43 (m, 9H, Ar-H), 9.09 (S, 1H, pyran-H), 10.09 (S, 1H, NH). MS: m/z (%) 352.4 (M$^+$+1, 100%) base peak, 353.5 (M$^+$+2, 56%). Elemental analysis: Calc. for C$_{19}$H$_{17}$N$_3$O$_2$S (351.42) C, 64.94%; H, 4.88%; N, 11.96%; S, 9.12%, found: C, 64.97%; H, 4.94%; N, 11.89%; S, 9.15%.

2.2.8. N-(4-methoxyphenyl)-2-(1-(2-oxo-2H-chromen-3 yl) ethylidene)hydrazinecarbothioamide (8)

IR (KBr) cm^{-1}: 3418, 3331 (NH), 1721 (C=O), 1629 (C=N), 1615, 1590 (C=S), 1377 (C=S), 1125, 1098 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.5 (S, 3H, CH$_3$), 3.34 (S, 3H, OCH$_3$), 6.90–8.60 (m, 4H, Ar-H), 9.08 (S, 1H, pyran-H), 9.55 (S, 1H, NH), 11.22 (S, 1H, NH). MS: m/z (%) 368.5 (M$^+$+1, 100%) base peak, 369.5 (M$^+$+2, 21%). Elemental analysis: Calc. for C$_{19}$H$_{17}$N$_3$O$_3$S (367.42) C, 62.11%; H, 4.66%; N, 11.44%; S, 8.73%, found: C, 62.27%; H, 4.84%; N, 11.39%; S, 8.68%.

2.2.9. N-(4-iodophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (9)

IR (KBr) cm^{-1}: 3414, 3327 (NH), 1728 (C=O), 1635 (C=N), 1614, 1587 (C=S), 1379 (C=S), 1128, 1092 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.27 (S, 3H, CH$_3$), 7.06–8.09 (m, 8H, Ar-H), 8.48 (S, 1H, pyran-H), 10.19 (S, 1H, NH), 11.00 (S, 1H, NH). MS: m/z (%) 464.2 (M$^+$+1, 100%) base peak, 463.2 (M$^+$+2, 37%). Elemental analysis: Calc. for C$_{18}$H$_{14}$IN$_3$O$_2$S (463.29) C, 46.66%; H, 3.05%; N, 9.07%; S, 6.92%, found: C, 46.60%; H, 3.15%; N, 9.19%; S, 6.88%.

2.2.10. N-(3,5-dichlorophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (10)

IR (KBr) cm^{-1}: 3414, 3334 (NH), 1726 (C=O), 1637 (C=N), 1615, 1579 (C=S), 1377 (C=S), 1129, 1099 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.22 (S, 3H, CH$_3$), 6.85–7.84 (m, 10H, Ar-H), 8.47 (S, 1H, pyran-H), 10.31 (S, 1H, NH), 11.19 (S, 1H, NH). MS: m/z (%) 405.1 (M$^+$−1, 100%) base peak, 407.1 (M$^+$+2, 66%). Elemental analysis: Calc. for C$_{18}$H$_{13}$Cl$_2$N$_3$O$_2$S (406.29) C, 53.21%; H, 3.23%; N, 10.34%; S, 7.89%, found: C, 53.29%; H, 3.19%; N, 10.37%; S, 7.85%.

2.2.11. N-(2-methoxyphenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (11)

IR (KBr) cm^{-1}: 3424, 3335 (NH), 1725 (C=O), 1636 (C=N), 1618, 1594 (C=S), 1378 (C=S), 1125, 1098 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.51 (S, 3H, CH$_3$), 3.81 (S, 3H, OCH$_3$), 6.94–8.23 (m, 8H, Ar-H), 8.43 (S, 1H, pyran-H), 10.08 (S, 1H, NH), 11.23 (S, 1H, NH). MS: m/z (%) 367.3 (M$^+$+1, 100%) base peak, 368.3 (M$^+$+2, 27%). Elemental analysis: Calc. for C$_{19}$H$_{17}$N$_3$O$_3$S (367.42) C, 62.11%; H,

4.66%; N, 11.44%; S, 8.73%, found: C, 62.10%; H, 4.69%; N, 11.37%; S, 8.83%.

2.2.12. N-(3-methoxyphenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (12)

IR (KBr) cm^{-1}: 3422, 3333 (NH), 1723 (C=O), 1634 (C=N), 1616, 1590 (C=S), 1378 (C=S), 1125, 1100 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.50 (S, 3H, CH$_3$), 3.76 (S, 3H, OCH$_3$), 6.75–7.81 (m, 8H, Ar-H), 8.50 (S, 1H, pyran-H), 10.07 (S, 1H, NH), 10.92 (S, 1H, NH). MS: m/z (%) 367.2 (M$^+$+1, 100%) base peak, 368.2 (M$^+$+2, 22%). Elemental analysis: Calc. for C$_{19}$H$_{17}$N$_3$O$_3$S (367.42) C, 62.11%; H, 4.66%; N, 11.44%; S, 8.73%, found: C, 62.18%; H, 4.74%; N, 11.42%; S, 8.80%.

2.2.13. 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)-N-(3,4,5-trichlorophenyl)hydrazinecarbothioamide (13)

IR (KBr) cm^{-1}: 3414, 3339 (NH), 1728 (C=O), 1632 (C=N), 1617, 1589 (C=S), 1378 (C=S), 1129, 1098 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.42 (S, 3H, CH$_3$), 7.05–8.08 (m, 6H, Ar-H), 8.48 (S, 1H, pyran-H), 10.05 (S, 1H, NH), 10.43 (S, 1H, NH). MS: m/z (%) 367.2 (M$^+$+1, 100%) base peak, 368.2 (M$^+$+2, 22%). Elemental analysis: Calc. for C$_{18}$H$_{12}$Cl$_3$N$_3$O$_2$S (440.73) C, 49.05%; H, 2.74%; N, 9.53%; S, 7.28%, found: C, 49.09%; H, 2.86%; N, 9.46%; S, 7.35%.

2.2.14. N-(2,4-dichlorophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (14)

IR (KBr) cm^{-1}: 3422, 3327 (NH), 1728 (C=O), 1633 (C=N), 1615, 1589 (C=S), 1377 (C=S), 1122, 1097 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.51 (S, 3H, CH$_3$), 6.89–7.95 (m, 7H, Ar-H), 8.45 (S, 1H, pyran-H), 10.11 (S, 1H, NH), 11.17 (S, 1H, NH). MS: m/z (%) 406.5 (M$^+$, 100%) base peak, 407.5 (M$^+$+1, 22%). Elemental analysis: Calc. for C$_{18}$H$_{12}$Cl$_3$N$_3$O$_2$S (406.29) C, 53.21%; H, 3.23%; N, 10.34%; S, 7.89%, found: C, 53.19%; H, 3.26%; N, 10.43%; S, 7.80%.

2.2.15. N-(2,4-difluorophenyl)-2-(1-(2-oxo-2H-chromen-3-yl) ethylidene)hydrazinecarbothioamide (15)

IR (KBr) cm^{-1}: 3418, 3329 (NH), 1718 (C=O), 1633 (C=N), 1611, 1586 (C=S), 1373 (C=S), 1117, 1092 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.51 (S, 3H, CH$_3$), 6.86–7.78 (m, 7H, Ar-H), 8.49 (S, 1H, pyran-H), 10.04 (S, 1H, NH), 11.08 (S, 1H, NH). MS: m/z (%) 374.3 (M$^+$+1, 100%) base peak, 375.3 (M$^+$+2, 42%). Elemental analysis: Calc. for C$_{18}$H$_{13}$F$_2$N$_3$O$_2$S (373.38) C, 57.90%; H, 3.51%; N, 11.25%; S, 8.59%, found: C, 57.79%; H, 3.66%; N, 11.25%; S, 8.42%.

2.2.16. N-ethyl-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (16)

IR (KBr) cm^{-1}: 3414, 3325 (NH), 1728 (C=O), 1637 (C=N), 1619, 1583 (C=S), 1379 (C=S), 1127, 1090 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.34 (S, 3H, CH$_3$), 2.51 (t, 3H, ethyl-CH$_3$, J = 4.48), 3.37 (S, 1H, NH), 7.18–7.19 (q, 2H, ethyl-CH$_2$, J = 4.12), 7.2–7.8 (m, 4H, Ar-H), 8.51 (S, 1H, pyran-H), 10.91 (S, 1H, NH). MS: m/z (%) 290.3 (M$^+$+1, 100%) base peak, 291.3 (M$^+$+2, 30%). Elemental analysis:

Calc. for C$_{14}$H$_{15}$N$_3$O$_2$S (289.35) C, 58.11%; H, 5.23%; N, 14.52%; S, 11.08%, found: C, 58.18%; H, 5.34%; N, 14.43%; S, 11.12%.

2.2.17. N-phenyl-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (17)

IR (KBr) cm^{-1}: 3416, 3336 (NH), 1724 (C=O), 1635 (C=N), 1618, 1582 (C=S), 1379 (C=S), 1126, 1098 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.35 (S, 3H, CH$_3$), 7.21–8.09 (m, 10H, Ar-H), 8.50 (S, 1H, pyran-H), 10.15 (S, 1H, NH), 10.75 (S, 1H, NH). MS: m/z (%) 338.3 (M$^+$ + 1, 100%) base peak, 339.3 (M$^+$ + 2, 28%). Elemental analysis: Calc. for C$_{18}$H$_{15}$N$_3$O$_2$S (337.4) C, 64.08%; H, 4.48%; N, 12.45%; S, 9.50%, found: C, 64.18%; H, 4.50%; N, 12.33%; S, 9.51%.

2.2.18. N-cyclohexyl-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (18)

IR (KBr) cm^{-1}: 3417, 3154 (NH$_2$), 3232 (NH), 1724 (C=O), 1633 (C=N), 1619, 1582 (C=S), 1371 (C=S), 1125, 1099 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 1.13–1.90 (m, 10H, cyclohexyl), 2.51 (S, 3H, CH$_3$), 4.20–4.21 (m, 1H, cyclohexyl), 7.38–7.83 (m, 4H, Ar-H), 8.03 (S, 1H, pyran-H), 8.31(S, 1H, NH), 10.48 (S, 1H, NH). MS: m/z (%) 344.3 (M$^+$ + 1, 100%) base peak, 345.3 (M$^+$ + 2, 38.5%). Elemental analysis: Calc. for C$_{18}$H$_{21}$N$_3$O$_2$S (343.14) C, 62.95%; H, 6.16%; N, 12.23%; S, 9.34%, found: C, 62.82%; H, 6.03%; N, 12.17%; S, 9.08%.

2.2.19. 2-(1-(2-oxo-2H-chromen-3-yl)ethylidene) hydrazinecarbothioamide (19)

IR (KBr) cm^{-1}: 3419, 3152 (NH$_2$), 3230 (NH), 1720 (C=O), 1630 (C=N), 1613, 1588 (C=S), 1375 (C=S), 1120, 1095 (C—O). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm, J Hz) 2.26 (S, 3H, CH$_3$), 7.38–7.77 (m, 4H, Ar-H), 7.99 (S, 1H, pyran-H), 8.47 (S, 2H, NH$_2$), 10.49 (S, 1H, NH). MS: m/z (%) 262.2 (M$^+$ + 1, 100%) base peak. Elemental analysis: Calc. for C$_{12}$H$_{11}$N$_3$O$_2$S (261.30) C, 55.16%; H, 4.24%; N, 16.08%; S, 12.27%, found: C, 55.11%; H, 4.29%; N, 16.23%; S, 12.16%.

2.3. Biological assay

This work has been done in, Microcare Laboratory and TRC, Surat, India as per reported method. (Hawkey and Lewis, 2003)

3. Results and discussion

Starch sulfuric acid (SSA) and cellulose sulfuric acid are readily prepared according to previously reported methods, in which drop wise addition of chlorosulfonic acid to a mixture of starch or cellulose in *n*-hexane or in dichloromethane at 0 °C was done. It is important to note that this reaction is easy and clean without any work-up procedure because HCl gas is evolved from the reaction vessel immediately. This white homogeneous, nonhygroscopic solid acid is stable under the reaction conditions.

In the present study 3-acetyl coumarin was synthesized by the reaction of salicylaldehyde (1 mmol) and ethyl acetoacetate

(1 mmol) using CSA or SSA (0.004 g) as a catalyst at 100 °C under solvent-free conditions (Scheme 1). The resultant 3-acetyl coumarin was obtained in 95% yield with high purity within 4 h. For the optimization of reaction conditions, we have carried out this synthesis using various solvents such as methanol, ethanol, chloroform, acetonitrile, ethyl acetate, dichloromethane, tetrahydrofuran (THF), dimethylformamide (DMF) and water as well as in solvent-free conditions. However, best results were obtained in solvent-free conditions in terms of product yield and reaction time. In most of previously reported methods, the reaction afforded comparatively lower product yield and also was done under some toxic and hazardous conditions. Thus, SSA and CSA promoted the reactions more effectively than the other catalysts and should be considered as one of the best choices for selecting an economically convenient, user friendly catalyst. One of the beneficial advantages of these catalysts was that they could be recovered and reused several times without loss of their efficiency. SSA and CSA were recovered by filtration after the addition of ethanol to the stirred reaction mixture. For reusability experiments, recovered catalyst was dried in an oven at 80 °C for 1 h prior before use. The results, given in (Table 1a), indicate the catalyst was reusable four times without any significant loss of activity. We have also tested this reaction with different loading of SSA and CSA at 100 °C. However, 0.004 g. catalyst (SSA or CSA) was sufficient for this conversion, this happened because 0.004 g. of catalyst is enough to carry out this transformation in the forward direction (Table 1b, Fig. 2).

To recognize the optimization of the reaction conditions, the reaction was studied by employing several catalysts and solvents as well as under solvent-free conditions with the hope to maximize the product yield in short reaction times (Table 2). Initially, isothiocyanatobenzene (1.0 mmol), hydrazine hydrate (1.5 mmol, 80%) and 3-acetyl coumarin (1.0 mmol) were refluxed in the presence of ethanol as the solvent without any catalyst, however, the reaction, even after 12 h, only 22% product was obtained (Table 2, Entry 1). Then the reaction was carried out in ethanol in the presence of *p*-toluenesulphonic acid (*p*-TSA) under reflux conditions for 6 h and the product was isolated in 66% yield (Table 2, Entry 2). In continuation, we have also carried out the same reaction using *p*-TSA for 8 h and 12 h, but no effective change in result was obtained (Table 2, Entries 3 and 4), while a similar reaction was carried out in the water, which did not give any improved results and only 42% product was isolated (Table 2, Entry 5). The reactions were also restrained from using hydrochloric acid (HCl) and formic acid as catalysts in ethanol and water, but they didn't give satisfactory results (Table 2, Entries 6–9). Lewis acid catalyst like Cu(OAc)$_2$was tested in

Table 1a Reusability profile of SSA and CSA.

Run	% Yield of Product (SSA)	Recovery of catalyst (%) (SSA)	% Yield of product (CSA)	Recovery of catalyst (%) (CSA)
1	95	99	95	99
2	95	98	94	97
3	93	96	92	95
4	92	94	91	93

Table 1b Screening of load of catalysts on % yield of 3-acetyl coumarin.

Entry	Catalyst	Amount of catalyst (g)	Time (h)	Yield (%)[a]
1	SSA	0.001	4	62
2	SSA	0.002	4	74
3	SSA	0.003	4	82
4	SSA	0.004	4	95
5	SSA	0.005	4	95
6	CSA	0.004	4	95
7	CSA	0.003	4	84
8	CSA	0.005	4	95

[a] All reactions were carried out at 100 °C.

ethanol and provided a trace amount of the desired product (Table 2, Entry 10). We then applied glacial acetic acid (AcOH) (20 mol%) as catalyst in ethanol, methanol and water respectively (Table 2, Entries 11–13), eventually we achieved satisfaction because the reaction proceeded well, affording the desired product in good yield. We have also, carried out this reaction using various solvents like toluene, ethyl acetate, acetonitrile, chloroform (Table 2, Entries 14–17). However, ethanol was the best solvent for this transformation in terms of the yield of the product and times of the reaction.

From the experiments to optimize reaction conditions, we have taken glacial acetic acid (AcOH) as a catalyst for these transformations. Then we concentrated our consideration on generalizing the promising conditions for the reaction. For that we scanned different amounts of glacial acetic acid. The use of 5 mol%, 7.5 mol%, 10 mol% and 15 mol% glacial AcOH was affected on the% yields of the product (Table 2, Entries 18–21), which intended that the quantity of the catalyst had a large effect on the formation of the desired product in excellent yield. In addition, no improved result was obtained, when we used 25 mol% glacial AcOH (Table 2, Entry 22).

We employed a wide range of aliphatic and aromatic isothiocynates to evaluate the generalization of this protocol. The reaction progressed smoothly and provided excellent yields in all cases (Table 3). Both electron-withdrawing and electron-donating substituents of isothiocynates reacted smoothly with this protocol to afford excellent yields of the products. The reactions were also carried out scaled up to the 10 mmol scale and it is interesting to note that all results were observed correspondingly similar to the 1 mmol scale. Furthermore, all synthesized products were easily purified by recrystallization from ethanol, thus avoiding extraction steps and chromatographic separations. The purity of the synthesized compounds was confirmed by TLC and elemental analysis.
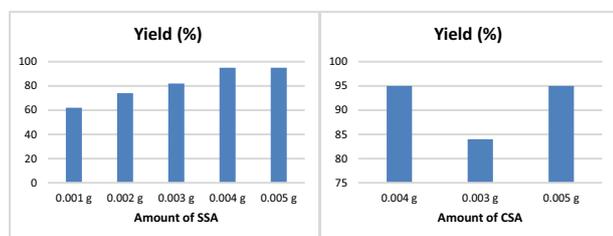
Table 2 Screening of catalysts and solvents and reaction conditions.

Entry	Conditions	Solvent	Catalyst	Time (h)	Yield (%)[a,b]
1	Reflux	Ethanol	–	12	22
2	Reflux	Ethanol	p-TSA	6	66
3	Reflux	Ethanol	p-TSA	8	70
4	Reflux	Ethanol	p-TSA	12	72
5	Reflux	Water	p-TSA	12	42
6	Reflux	Ethanol	HCl	6	62
7	Reflux	Water	HCl	6	45
8	Reflux	Ethanol	HCOOH	6	38
9	Reflux	Water	HCOOH	6	28
10	Reflux	Ethanol	Cu(OAc)$_2$	6	Trace[c]
11	Reflux	Ethanol	Gl. AcOH (20 mol%)	4	92
12	Reflux	Methanol	Gl. AcOH (20 mol%)	4	84
13	Reflux	Water	Gl. AcOH (20 mol%)	4	46
14	Reflux	CHCl$_3$	Gl. AcOH (20 mol%)	4	34
15	Reflux	Toluene	Gl. AcOH (20 mol%)	4	38
16	Reflux	Ethyl acetate	Gl. AcOH (20 mol%)	4	41
17	Reflux	Acetonitrile	Gl. AcOH (20 mol%)	4	47
18	Reflux	Ethanol	Gl. AcOH (5 mol%)	6	62
19	Reflux	Ethanol	Gl. AcOH (7.5 mol%)	6	68
20	Reflux	Ethanol	Gl. AcOH (10 mol%)	4	76
21	Reflux	Ethanol	Gl. AcOH (15 mol%)	4	80
22	Reflux	Ethanol	Gl. AcOH (25 mol%)	4	92

[a] All reactions were carried out with isothiocyanatobenzene (1.0 mmol), hydrazine hydrate (1.5 mmol, 80%) and 3-acetyl coumarin (1.0 mmol).
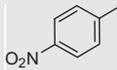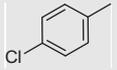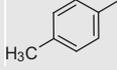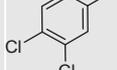[b] Yield of isolated product.
[c] Reaction failed to provide trace amount of product.

The structure of the final products were well characterized by using spectral (IR, ^{1}H NMR and HRMS) and elemental analysis data (ESI). IR spectra showed characteristic peaks of these derivatives with 3300–3500 cm^{-1} corresponding to amidic NH, while 1710–1735 cm^{-1} exhibited the cyclic ester of the coumarin nucleus and another, obse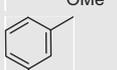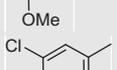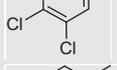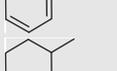rved between, 1050 and 1150 cm^{-1}, was assigned to C—O stretching frequency. The ^{1}H NMR spectrum of DMSO exhibited a singlet nearer 10 ppm, which was attributed to the —NH group, another characteristic peak of these derivatives showed nearer to 8.5 ppm, which indicated a proton of the pyran nucleus. Peaks between 7.05 and 8.70 ppm were observed for respective aromatic protons. The ESIMS spectra of compounds (**1–19**), show corresponding (M$^+$ + 1) peak and (M$^+$ + 2) peak in the case of bromo and chloro substituted compounds.

We hypothesized that mechanistically the reaction proceeds through the addition reaction between isothiocynate and hydrazine hydrate, which is very fast and produced thiosemicarbazide in excellent yields. Now, in the second step a lone

Figure 2 Screening of amount of SSA and CSA.

Table 3 One-pot solvent free synthesis of coumarin hybrid thiosemicarbazone derivatives (**1–19**).

Compound code	R	Time (h)	% Yield[a]	% Yield[b]	M.P. (°C)
1	4-O_2N-phenyl	4	85	77	192–194
2	4-Cl-phenyl	3.5	92	85	184–186
3	4-H_3C-phenyl	3.0	88	81	197–199
4	propyl chain	3.5	85	77	284–285
5	3,4-diCl-phenyl	4.0	89	80	203–205
6	tert-butyl	3.0	84	76	190–192
7	2-ethyl-phenyl	3.5	85	77	88–90
8	4-MeO-phenyl	4.0	91	82	285–287
9	4-I-phenyl	3.5	92	84	180–182
10	3,5-diCl-phenyl	4.0	87	77	215–217
11	2-OMe-phenyl	3.5	91	85	196–198
12	3-OMe-phenyl	3.5	90	80	202–204
13	3,4,5-triCl-phenyl	4.0	88	81	187–189
14	2,5-diCl-phenyl	4.0	84	77	181–183
15	2,5-diF-phenyl	4.0	88	79	186–188
16	isopropyl	3.0	87	78	293–295
17	phenyl	4.0	92	86	183–185
18	cyclohexyl	3.5	91	88	163–165
19	H	4.0	94	87	216–218

[a] Yield of the isolated product.
[b] Yield of the purified product.

pair of electrons present on the primary amine of thiosemicarbazide attacks the carbo-cation of the 3-acetyl group of coumarin, at a time when proton transfer occurs from nitrogen to oxygen. This process occurred due to the presence of acetic acid as the catalyst, because acetic acid pulls the electron from the carbonyl group of 3-acetyl to form the reactive carbo-cation. The third step is dehydrogenation, in which the proton from nitrogen and hydroxy groups at carbon are situated at adjacent positions. Thus, removal of water molecule occurred from them to form the thiosemicarbazone derivative (Fig. 3).

4. Biological evaluation

All newly synthesized coumarin hybrid thiosemicarbazone derivatives (**1–19**) were examined for antimicrobial activity against two gram-positive bacterial strains (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442), two gram-negative bacterial strains (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688) as well as three fungal strains (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 227 and *Aspergillus niger* MTCC 282) using the agar
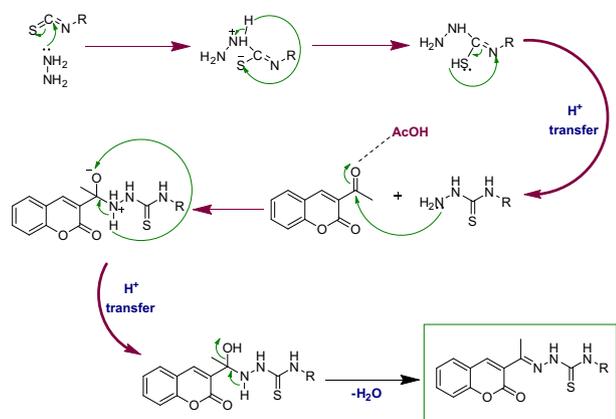
Figure 3 Proposed reaction mechanism.

dilution method (Hawkey and Lewis, 2003). Ampicillin, Ciprofloxacin and Chloramphenicol were used as standard control drugs for antibacterial activity, whereas Nystatin and Greseofulvin were used as standard control drugs for antifungal activity.

4.1. In vitro antibacterial activity

Reviewing the antibacterial activities of coumarin hybrid thiosemicarbazone derivatives (Table 4) indicates that all scaffolds were found to exhibit good to moderate activity against the specific microbial strain. Table 4 shows that bioassay results of the series of (1–19) compounds revealed that compound 15, bearing an electron deactivating fluoro group at 2 and 4 positions of the phenyl ring, was found to be the most active compound that inhibits the gram positive S. aureus

bacterial growth at the lowest minimum inhibitory concentration (MIC) value of 50 μg/mL. Compounds 2, 5, 10 and 13 with a chloro group on the phenyl ring showed excellent effectiveness with 125 μg/mL MIC against the same bacteria, while compound 14 exhibited more potent activity with 100 μg/mL MIC against the same bacteria. Interestingly, compound 4 having a propyl aliphatic linker, inhibits the both gram positive S. aureus and S. pyogenus bacterial growth at the lowest minimum inhibitory concentration (MIC) value of 100 μg/mL. Similarly compounds 2, 5, 8, 10, 13, 14 and 19 exhibited high potent activity against E. coli at MIC of 62.5 μg/mL, while compound 15 showed more potent activity against E. coli equivalent to Chloramphenicol. Here, compound 8 having an electron donating substituent like OMe on the phenyl ring inhibits the gram negative E. coli bacterial growth at the lowest minimum inhibitory concentration (MIC) value of 62.5 μg/mL. Furthermore, compounds 1, 8, 10, 13, 15, 18 and 19 showed good activity against gram negative P. aeruginosa equivalent to Chloramphenicol. Here, Compound 18 has an aliphatic cyclohexyl ring, while compound 19 has no substituents. Surprisingly, compound 1, bearing an electron withdrawing nitro group on the phenyl ring, was found to be the active one that inhibits gram negative P. aeruginosa and gram positive S. pyogenus bacterial growth at the minimum inhibitory concentration (MIC) value of 100 μg/mL equivalent to Ampicillin. Compounds 1, 3, 4, 6, 7, 13, 14 and 15 exhibited good activity against gram positive S. pyogenus bacterial growth at the minimum inhibitory concentration (MIC) value of 100 μg/mL equivalent to Ampicillin. It is important to note that compound 4, 6 and 7, bearing aliphatic linker substituents shows good activity against gram positive S. pyogenus bacteria. It can be noted that among the halogenated compounds with the lowest lipophilicity (Lowest Log P) showed highest activity against bacteria.

Table 4 In-vitro antibacterial activity of compounds (1–19).

MIC [μg/mL]

Sr. No.	Compound code	E. coli MTCC 443	P. aeruginosa MTCC 1688	S. aureus MTCC 96	S. pyogenus MTCC 442
1	1	100	100	250	100
2	2	62.5	200	125	250
3	3	100	125	250	100
4	4	200	200	100	100
5	5	62.5	125	125	250
6	6	250	200	200	100
7	7	100	125	200	100
8	8	62.5	100	250	250
9	9	100	200	250	500
10	10	62.5	100	125	250
11	11	125	200	250	200
12	12	200	200	250	250
13	13	62.5	100	125	100
14	14	62.5	125	100	100
15	15	50	100	50	100
16	16	100	250	500	500
17	17	250	250	250	250
18	18	100	100	500	500
19	19	62.5	100	500	500
20	Ampicillin	100	100	250	100
21	Ciprofloxacin	25	25	50	50
22	Chloramphenicol	50	50	50	50

Table 5 *In-vitro* antifungal activity of compounds (**1–19**).

MIC [μg/mL]

Sr. No.	Compound code	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
1	1	500	1000	1000
2	2	250	250	250
3	3	1000	1000	1000
4	4	1000	500	500
5	5	250	250	250
6	6	500	500	500
7	7	250	1000	> 1000
8	8	500	> 1000	> 1000
9	9	250	1000	1000
10	10	250	250	250
11	11	500	250	250
12	12	500	1000	> 1000
13	13	250	250	250
14	14	250	250	250
15	15	100	100	100
16	16	250	1000	> 1000
17	17	1000	500	500
18	18	500	1000	1000
19	19	> 1000	1000	500
20	Nystatin	100	100	100
21	Greseofulvin	500	100	100

4.2. In vitro antifungal activity

Antifungal activity data (Table 5) showed that among the (**1–19**) analogs, compound 15 bearing an electron deactivating fluoro group at 2 and 4 positions of the phenyl ring displayed excellent activity at 100 μg/mL MIC against *C. albicans* equivalent to Nystatin and greater then Greseofulvin, whereas compounds **2**, **5**, **10**, **13** and **14** with a chloro substituent on the phenyl ring also showed excellent activity at 250 μg/mL MIC against *C. albicans* fungi. In addition, compounds 7 and 16 with aliphatic substituents also exhibited potent activity at 250 μg/mL MIC against *C. albicans* fungi. Compound **9**, bearing an Iodo substituent at the *para* position of phenyl ring demonstrated superior activity at 250 μg/mL MIC against *C. albicans*. Analogues **1**, **6**, **8**, **11**, **12**, **18** exhibited good activity against *C. albicans* fungi at 500 μg/mL equivalent to Greseofulvin. Moreover, compounds (**1–19**) exerted moderate inhibitory efficiency against the *A. niger* and *A. clavatus*. Only Compound **15**, displayed excellent activity at 100 μg/mL MIC against *A. niger* and *A. clavatus* fungi, which is equivalent to Nystatin.

5. Conclusion

In this article, we have presented the initial efforts made toward the discovery of novel, potentially active 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinecarbothioamide derivatives. These derivatives were prepared through one-pot three component reaction of isothiocynates, hydrazine hydrate and 3-acetyl-2*H*-chromen-2-one in the presence of a catalytic amount of glacial acetic acid in refluxing ethanol. We have also reported an environmentally friendly synthesis of 3-acetyl-2*H*-chromen-2-one using starch sulfuric acid and cellulose sulfuric acid as a biodegradable catalyst by the reaction of

ortho-hydroxy benzaldehyde and ethyl acetoacetate under solvent-free conditions. From the bioassays it is clear that the hybridization of coumarin nuclei with different thiosemicarbazides leads to more active antimicrobial as well as antifungal activity. In the present study, compound **2**, **4**, **5**, **10**, **13**, **14** and **15** exhibited highly potent activity against most of the tested bacteria.

Conflict of interest

There is no conflict of interest.

Appendix A. Supplementary data

Proton NMR spectra and Mass spectrometry data for all compounds. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jaubas.2016.04.002.

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