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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of coumarin clubbed thiazines scaffolds as antimicrobial and antioxidant

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Abstract

A new series of 4-methyl-6-nitro-2-oxo-2*H*-chroman-7yl-2-(4-(4-fluorophenyl)-6-phenyl-2*H*-1,3-thiazin-2-yl-amino)acetates **5a–j** were synthesized from 6-nitro-4-methyl coumarinyl chloroacetate (5) and 2-amino thiazines (**IIIa–j**). The structure of the final compounds was adequately confirmed via spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, Mass) and characterization of physical properties. Final compounds were screened for their antimicrobial, antitubercular, and antioxidant activities. Compounds **5c** and **5h** found to have antibacterial potency against *E. coli* with MIC values 50 µg/mL compared to standard drugs. Compound **5d** demonstrated better antifungal potency (MIC = 200 µg/mL) against *C. albicans* when compared with griseofulvin. Compounds **5b** and **5h** found to be encouraging antitubercular (MIC = 62.5 µg/mL with 98–99% inhibition) against *M. tuberculosis* $H_{37}Rv$. The newly synthesized **5h** and **5b** were appeared to have high radical scavenging efficacies as 33.99 ± 0.301 and 35.35 ± 0.470 µg/mL ± SD of IC_{50} values, respectively, in DPPH and ABTS bioassay.

Keywords 1,3-thiazine-2-amines · Coumarin · Antibacterial · Antioxidant and antitubercular

Introduction

The natural compound such as coumarin has served as valuable leads for the development of newer biological potent analogs (Kostova et al. 2011; Patel et al. 2017). Coumarins form an elite class of compounds, which exhibit a variety of therapeutic activities including antibacterial (Bhat et al. 2009; Muratovic et al. 2013), antimalarial (Patel et al. 2012), antioxidant (Kostova 2006; Nagamallu et al. 2016), anticancer (Sashidhara et al. 2010; Thakur et al. 2015), antiplatelet (Roma et al. 2003), antithrombotic (Kontogiorgis et al. 2015), analgesic (Keri et al. 2010), antifungal (Al-Amiery et al. 2012; Rehman et al. 2005), antiviral (Hassan et al. 2016), anticoagulant (Rost et al. 2005), anti-inflammatory (Bansal et al. 2013), and anti-tumor (Chen et al. 2013). On the other hand, the nitrogen and sulfur heterocyclic ring families are very interesting due to their physicochemical properties, especially in the sense of design of new drugs and new materials. The core moiety of 1,3-thiazines has N-C-S linkage have been used as antimicrobial activity (Koketsu et al. 2002), antitumor (Wang et al. 2012), antituberculosis (Tiwari et al. 2016), analgesic and anti-inflammatory (Jupudi et al. 2013), and antioxidant (Jeleń et al. 2015).

The development of coumarins as antioxidant agents has attracted much attention in recent years. Coumarins afford an opportunity for the discovery of new antioxidants with truly novel mechanisms of action. The present article deals with the rational design of coumarin clubbed thiazine motif with an understanding of the mechanisms of existing synthetic and natural coumarins. Antimicrobial activity of 4- and 7-hydroxy and nitrocoumarins has been reviewed extensively (Debeljak et al. 2007; Dekić et al. 2011) and it has been observed that when it has been nitrated, its antimicrobial activities is

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enhanced. Additionally, a recent Quantitative Structure Activity Relationship (QSAR) study of the antimicrobial activity of some 3-nitrocoumarins has put forward some new arguments in this direction. With this consideration and continuation of our ongoing interest in the synthesis of the thiazine clubbed coumarin derivatives, we have been prompted to synthesize newer, possibly more potent, pharmacologically active compounds. We have condensed chloroacetate of 4-methyl-7-hydroxy-6-nitrocoumarin with substituted amino derivatives of thiazines obtained via chalcone derivatives. The synthesized compounds were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The in vitro evaluation of these derivatives viz., antimicrobial activity on four different bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes*) and three different fungi (*Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*), antitubercular activity on *Mycobacterium tuberculosis* ($H_{37}Rv$) virulent strain is presented. Antioxidant acticity of these derivatives have been evaluated by DPPH (2,2'-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-Azino-bis-3-ethylbenzthiazoline-6-sulfonic acid) radical scavenging assay.

Materials and methods

All solvents, chemicals, and reagents were purchased from Sigma-Aldrich with the highest purity and used without further purification. Melting points were determined with an open capillary method on ''Equiptronics'' digital melting point apparatus, model no. EQ-730 and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrophotometer (KBr pellets) instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz NMR Spectrometer using DMSO-d_6 as solvent and TMS as an internal standard. All chemical shifts were reported as δ values (ppm). Mass spectra were recorded using Expression CMS from Advion, USA using ESI as ion source (mobile phase 0.1% formic acid in 80:20, Methanol: Water). Analytical thin-layer chromatography (TLC) was performed with Merck silica gel plates and visualized with ultraviolet (UV) irradiation (254 nm) or iodine.

Experimental procedure

Chemistry

4-Methyl-7-hydroxy-coumarin (3) has been prepared as described in literature

Yield: 85%, mp: 183 to 185 °C. IR (KBr, cm^{-1}): 3493 (–OH), 3098, 2817 (–CH_3, asym, sym), 1735 (>C=O str), 1148 (–C–O–C). ^{1}H NMR (DMSO-d_6) δ (ppm): 10.35 (s, 1H, phenolic -OH), 7.48 (d, 1H, aromatic) 6.76 (d,1H,aromatic), 6.69 (s, 1H,aromatic), 2.37 (s, 3H, –CH_3) (Furniss et al. 1989).

7-Hydroxy-4-methyl-6-nitro-2H-chromen-2-one (4) has been prepared as described in literature

Yield: 72%, mp: 193–195 °C (as reported). IR (KBr, cm^{-1}): 3490 (–OH), 3094, 2827 (–CH_3, asym, sym), 1745 (>C=O str), 1190 (–C–O–C), 1536, 1357 (–NO_2). ^{1}H NMR (DMSO-d_6) δ (ppm):13.26 (s, 1H, Phenolic –OH), 8.44 (s, 1H, aromatic), 7.09 (s, 1H, aromatic), 6.35 (s, 1H, aromatic), 2.37 (s, 3H, –CH_3) (Ganguly et al. 2001).

4-Methyl-6-nitro-2-oxo-2H-chromen-7-yl 2-chloroacetate (5) has been prepared as described in literature

Yield: 69%, mp: 109–112 °C. IR (KBr, cm^{-1}): 3003, 2799 (–CH_3, asym, sym), 1751, 1657 (>C=O str), 1190 (–C–O–C), 1571, 1346 (–NO_2), 831 (–C–Cl). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.38 (s, 1H, aromatic), 7.27 (s, 1H, aromatic), 6.37 (s, 1H, aromatic), 4.47 (s, 2H, –$COCH_2$), 2.48 (s, 3H, –CH_3) (Qandil and Fakhouri 2012).

General method for the synthesis of (E)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (IIa)

p-Fluoro acetophenone 6 (0.01 mol) and benzaldehyde **Ia** (0.01 mol) were dissolved in 15 mL ethanol. NaOH solution (0.02 mol) in ethanol was added slowly and the mixture was stirred at 20 °C for 2 h until the entire mixture becomes very thick. The progress of the reaction was monitored by TLC (toluene: acetone, 80:20). Then the reaction mixture was poured slowly onto 400 mL of water with stirring and kept in refrigerator for 24 h. The precipitate obtained was filtered, washed, and recrystallized from ethanol. The other compounds **IIb–j** were prepared by the same method using substituted benzaldehydes **Ib–j**.

General method for the synthesis of 4-(4-Fluorophenyl)-6-phenyl-2H-1,3-thiazin-2-amine (IIIa)

A mixture of (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **IIa** (0.01 mol), thiourea (0.01 mol) was dissolved in ethanolic sodium hydroxide (10 mL) was refluxed about 2–3 h. The progress of the reaction was monitored by TLC (ethylacetate: n-hexane (1:3)). The reacting mixture was poured onto 400 mL of cold water and stirred for an hour and then kept in refrigerator for 24 h. The precipitate of 4-(4-fluorophenyl)-6-phenyl-2*H*-1,3-thiazin-2-amine **IIIa** obtained was filtered, washed, and recrystallized with ethanol. The other compounds **IIIb–j** were prepared by the

same method using substituted chalcones **IIb–j**. Compound **IIIh**: IR (KBr, cm^{-1}): 3182 (–NH_2), 2959 (–CH_3), 1599 (–C=N), 1170 (C–F); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.76 (s, 2H, –NH_2), 6.89–7.61 (m, 8H, aromatic), 6.45 (s, 1H, aromatic), 5.28 (s, 1H, aromatic), 2.97 (t, 2H, –$\underline{CH_2}CH_2CH_3$), 1.65 (m, 2H, –$CH_2\underline{CH_2}CH_3$), 0.94 (t, 2H, –$CH_2CH_2\underline{CH_3}$).

General method for the synthesis of (5a–j)

All the reactions were carried out under nitrogen atmosphere. In a round bottom containing compound 5 (0.1 mol) and **IIIa–j** (0.1 mol), DMF and K_2CO_3 (2.4 equivalent) were added under constant stirring. Reaction Mixture was refluxed for 8–9 h. After the completion of the reaction (TLC monitored), reaction mixture was poured over crushed ice, solids that are separated out was filtered, washed with saturated solution of $NaHCO_3$ and dried. The crude product was purified by column chromatography using silica gel 100–200 mesh and gradient (0–80%) ethylacetate in hexane as eluent. The precipitate obtained was filtered, washed, and recrystallized.

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-phenyl-2H-1,3-thiazin-2-yl-amino) acetate (5a) Yellow solid, yield: 59 %, m.p.: 129–131 °C, M.F.: $C_{28}H_{19}N_3FO_6S$.

IR (KBr) ν cm^{-1}: 3192 (–NH), 1715, 1671 (–C=O), 1601 (C=N), 2961, 2840 (–CH_3), 1508, 1364 (–NO_2), 1177 (C–F); ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ ppm: 8.55 (s, 1H, –CH), 6.32–7.78 (m, 12H, aromatic), 5.23 (s, 1H, –CH), 3.71 (s, 2H, –$\underline{CH_2}$NH), 3.23 (s, 1H, –$CH_2\underline{NH}$), 2.40 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6 TMS) δ ppm: 160.11 (C-2),113.88 (C-3), 152.54 (C-4), 120.68 (C-5), 139.40 (C-6), 135.67 (C-7), 115.79 (C-8), 159.14 (C-9), 117.65 (C-10), 19.40 (C-12), 168.16 (C-14), 43.98 (C-16), 81.13 (C-18),157.35 (C-20), 95.50 (C-21), 153.11 (C-22), 134.18 (C-24), 130.12 (C-25, C-29), 115.57 (C-26, C-28), 165.09 (C-27), 136.32 (C-32), 128.55 (C-33, C-37), 129.04 (C-34, C-36), 126.32 (C-35); *m/z*: 545.54 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-2-chlorophenyl-2H-1,3-thiazin-2-yl-amino)acetates (5b) Cream yellow solid, yield: 59%, mp: 156–158 °C, M.F.: $C_{28}H_{19}ClFN_3O_6S$, IR (KBr) ν cm^{-1}: 3185 (–NH), 1720, 1667 (–C=O), 1591 (–C=N-), 2956, 2835 (–CH_3), 1514, 1354 (–NO_2), 1172 (C–F), 749 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d6, TMS) δ: 8.54 (s, 1H, –CH), 6.31–7.78 (m, 11H, aromatic), 5.39 (s, 1H, –CH), 3.69 (s, 2H, –$\underline{CH_2}$NH), 3.30 (s, 1H, –$CH_2\underline{NH}$), 2.39 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6 TMS) δ: 160.12 (C-2),113.94 (C-3), 152.51 (C-4), 120.72 (C-5), 139.44 (C-6), 135.64 (C-7), 115.77 (C-8), 159.12 (C-9), 118.67 (C-10), 19.41 (C-12), 168.17 (C-14), 40.96 (C-16), 111.13 (C-18),157.37 (C-20), 74.16 (C-21), 160.14 (C-22), 134.13 (C-24), 130.16 (C-25, C-29), 115.52 (C-26, C-28), 165.12 (C-27), 131.51 (C-32), 133.10 (C-33), 131.56 (C-37), 127.80 (C-34), 131.25 (C-36), 128.35 (C-35),; *m/z*: 563.09 (M^+), 565.09(M+2).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-4-chlorophenyl-2H-1,3-thiazin-2-yl-amino)acetates (5c) Pale yellow solid, yield: 65%, mp: 163–165 °C, M.F.: $C_{28}H_{19}ClFN_3O_6S$, IR (KBr) ν cm^{-1}: 3238 (–NH), 1740, 1669 (–C=O), 1599 (–C=N–), 3067, 2840 (–CH_3), 1538, 1358 (–NO_2), 1258, 1057 (–C–O–C–), 1170 (C–F), 758 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d6, TMS) δ: 8.54 (s, 1H, –CH), 6.30–7.77 (m, 11H, aromatic), 5.34 (s, 1H, –CH), 3.70 (s, 2H, –$\underline{CH_2}$NH), 3.23 (s, 1H, –$CH_2\underline{NH}$), 2.41 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6 TMS) δ: 160.12 (C-2),113.94 (C-3), 152.51 (C-4), 120.72 (C-5), 139.44 (C-6), 135.64 (C-7), 115.77 (C-8), 159.12 (C-9), 118.67 (C-10), 19.41 (C-12), 168.17 (C-14), 40.96 (C-16), 111.13 (C-18),157.37 (C-20), 74.16 (C-21), 160.14 (C-22), 134.13 (C-24), 130.16 (C-25, C-29), 115.52 (C-26, C-28), 165.12 (C-27), 131.51 (C-32), 133.10 (C-33), 131.56 (C-37), 127.80 (C-34), 131.25 (C-36), 128.35 (C-35); *m/z*: 563.09 (M^+), 565.09(M+2).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-2-hydroxyphenyl-2H-1,3-thiazin-2-yl-amino) acetate (5d) Pale yellow solid, yield: 61 %, m.p.: 174–176 °C, M.F.: $C_{28}H_{20}FN_3O_7S$.

IR (KBr) ν cm^{-1}: 3484 (–OH), 3190 (–NH), 1758, 1664 (–C=O), 1622 (C=N), 2965, 2842 (–CH_3), 1523, 1351 (–NO_2), 1174 (C–F);^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ ppm: 10.11 (s, 1H, –OH), 8.58 (s, 1H, –CH), 6.37–7.77 (m, 11H, aromatic), 5.22 (s, 1H, –CH), 3.71 (s, 2H, –$\underline{CH_2}$NH), 3.23 (s, 1H, –$CH_2\underline{NH}$), 2.44 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ ppm: 160.12 (C-2),113.92 (C-3), 152.50 (C-4), 120.68 (C-5), 139.46 (C-6), 135.67 (C-7), 115.72 (C-8), 159.10 (C-9), 117.64 (C-10), 19.44(C-12), 168.15 (C-14), 43.93 (C-16), 81.12 (C-18),157.35 (C-20), 95.51 (C-21), 153.12 (C-22), 134.11 (C-24), 130.12 (C-25, C-29), 115.59 (C-26, C-28), 165.15 (C-27), 122.32 (C-32), 158.54 (C-33), 117.52 (C-34), 128.35 (C-35), 121,44 (C-36), 125.02 (C-37); *m/z*: 561.54 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-4-hydroxyphenyl-2H-1,3-thiazin-2-yl-amino) acetate (5e) Pale yellow solid, yield: 69 %, m.p.: 184–186 °C, M.F.: $C_{28}H_{20}N_3FO_7S$.

IR (KBr) ν cm^{-1}: 3478 (–OH), 3186 (–NH), 1765, 1671 (>C=O), 1627 (C=N), 2959, 2851 (–CH_3), 1530, 1356 (–NO_2), 1180 (C–F);^{1}H NMR (400 MHz, DMSO-d_6, TMS):

δ ppm: 10.20 (s, 1H, –OH), 8.51 (s, 1H, –CH), 6.32–7.74 (m, 11H, aromatic), 5.27 (s, 1H, –CH), 3.69 (s, 2H, –$\underline{CH_2}$NH), 3.30 (s, 1H, –$CH_2\underline{NH}$), 2.51 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ ppm: 160.09 (C-2),113.88 (C-3), 152.46 (C-4), 120.74 (C-5), 139.41 (C-6), 135.61 (C-7), 115.72 (C-8), 159.10 (C-9), 117.64 (C-10), 19.44(C-12), 168.15 (C-14), 43.93 (C-16), 81.12 (C-18),157.35 (C-20), 95.51 (C-21), 153.12 (C-22), 134.11 (C-24), 130.12 (C-25, C-29), 115.59 (C-26, C-28), 165.15 (C-27), 122.32 (C-32), 158.54 (C-33), 117.52 (C-34), 128.35 (C-35), 121,44 (C-36), 125.02 (C-37); *m/z*: 561.45 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-4-fluorophenyl-2H-1,3-thiazin-2-yl-amino) acetate (5f) Light yellow solid, yield: 64%, m.p.: 158–160 °C, M.F.: $C_{28}H_{19}N_3F_2O_6S$.

IR (KBr) ν cm^{-1}: 3219 (–NH), 1745, 1669 (–C=O), 1619 (C=N), 2954, 2851 (–CH_3), 1168 (aryl-F), 1525, 1358 (–NO_2); ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ ppm: 8.53 (s, 1H, –CH), 6.33–7.79 (m, 11H, aromatic), 5.25 (s, 1H, –CH), 3.71 (s, 2H, –$\underline{CH_2}$NH), 3.22 (s, 1H, –$CH_2\underline{NH}$), 2.43 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ ppm: 160.11 (C-2),113.88 (C-3), 152.48 (C-4), 120.69 (C-5), 139.42 (C-6), 135.62 (C-7), 115.76 (C-8), 159.11 (C-9), 117.65 (C-10), 19.40 (C-12), 168.15 (C-14), 43.90 (C-16), 81.12 (C-18),157.33 (C-20), 95.50 (C-21), 153.10 (C-22), 134.14 (C-24), 130.12 (C-25, C-29), 115.52 (C-26, C-28), 165.16 (C-27), 131.33 (C-32), 128.51 (C-33, C-37), 115.06 (C-34, C-36), 161.34 (C-35); *m/z*: 563.53 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-p-tolyl-2H-1,3-thiazin-2-yl-amino) acetate (5g) Yellow solid, yield: 62%, m.p.: 165–167 °C, M.F.: $C_{29}H_{22}FN_3O_6S$.

IR (KBr) ν cm^{-1}: 3211(–NH), 1741, 1664 (–C=O), 1629 (C=N), 2941, 2861 (–CH_3), 1171 (aryl-F), 1517, 1353 (–NO_2); ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ ppm: 8.56 (s, 1H, –CH), 6.38–7.79(m, 11H, aromatic), 5.24 (s, 1H, –CH), 3.70 (s, 2H, –$\underline{CH_2}$NH), 3.21 (s, 1H, –$CH_2\underline{NH}$), 2.41 (s, 3H, –CH_3), 2.38 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6 TMS) δ ppm: 160.09 (C-2),113.91 (C-3), 152.54 (C-4), 120.66 (C-5), 139.46 (C-6), 135.67 (C-7), 115.79 (C-8), 159.15 (C-9), 117.65 (C-10), 19.47 (C-12), 168.18 (C-14), 43.95 (C-16), 81.11 (C-18),157.32 (C-20), 95.51 (C-21), 153.09 (C-22), 134.16 (C-24), 130.14 (C-25, C-29), 115.55 (C-26, C-28), 165.13 (C-27), 133.34 (C-32), 125.51 (C-33, C-37), 129.04 (C-34, C-36), 136.35 (C-35), 22.37 (C-38); *m/z*: 559.56 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-4-propylphenyl-2H-1,3-thiazin-2-yl-amino)acetate (5h) Dark yellow solid, yield: 68%, m.p.: 140–142 °C, M.F.: $C_{31}H_{26}$ F N_3O_6S.

IR (KBr) ν cm^{-1}: 3192 (–NH), 1715, 1671 (>C=O), 1601 (–C=N), 2961, 2840 (–CH_3), 1509, 1364 (–NO_2), 1233, 1055 (–C–O–C), 1177 (C–F); ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ ppm: 8.57 (s, 1H, –CH), 6.34–7.76 (m, 11H, aromatic), 5.23 (s, 1H, –CH), 3.74 (s, 2H, –$\underline{CH_2}$NH), 3.22 (s, 1H, –$CH_2\underline{NH}$), 2.42 (s, 3H, –CH_3), 2.99 (t, 2H, –$\underline{CH_2}CH_2CH_3$), 1.67 (m, 2H, –$CH_2\underline{CH_2}CH_3$), 0.96 (t, 2H, –$CH_2CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMSO-d_6 TMS) δ ppm: 160.10 (C-2),113.90 (C-3), 152.50 (C-4), 120.70 (C-5), 139.44 (C-6), 135.64 (C-7), 115.77 (C-8), 159.13 (C-9), 117.67 (C-10), 19.41(C-12), 168.18 (C-14), 43.94 (C-16), 81.10 (C-18), 157.34 (C-20), 95.50 (C-21), 153.10 (C-22), 134.14 (C-24), 130.14 (C-25, C-29), 115.56 (C-26, C-28), 165.10 (C-27), 133.35 (C-32), 126.52 (C-33, C-37), 128.00 (C-34, C-36), 140.34 (C-35), 34.41 (C-38), 24.01 (C-39), 13.31 (C-40); *m/z*: 587.15 (M^+).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-3-bromophenyl-2H-1,3-thiazin-2-yl-amino) acetate (5i) Pale yellow solid, yield: 62%, m.p.: 125–127 °C., M.F.: $C_{28}H_{19}BrFN_3O_6S$.

IR (KBr) ν cm^{-1}: 3326 (–NH), 1749 (–C=O), 1623 (C=N), 2895, 2958 (–CH_3), 1514, 1331 (–NO_2); ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ: 8.57 (s, 1H, –CH), 6.38–7.77(m, 11H, aromatic), 5.25 (s, 1H, –CH), 3.73 (s, 2H, –$\underline{CH_2}$NH), 3.22 (s, 1H, –$CH_2\underline{NH}$), 2.42 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ ppm: 160.12 (C-2),113.91 (C-3), 152.50 (C-4), 120.89 (C-5), 139.43 (C-6), 135.61 (C-7), 115.72 (C-8), 159.10 (C-9), 117.66 (C-10), 19.40 (C-12), 168.16 (C-14), 43.95 (C-16), 81.12 (C-18),157.33 (C-20), 95.51 (C-21), 153.11 (C-22), 134.14 (C-24), 130.15 (C-25, C-29), 115.55 (C-26, C-28), 165.12 (C-27), 138.37 (C-32), 128.59 (C-33), 127.50 (C-37), 123.06 (C-34), 130.09 (C-36),129.35 (C-35); *m/z*: 623.32 (M^+), 625.18 (M+2), 627.15 (M+4).

4-Methyl-6-nitro-2-oxo-2H-chromen-7yl-2-(4-(4-fluorophenyl)-6-3-phenoxy-2H-1,3-thiazin-2-yl-amino) acetate (5j) Dark yellow solid, yield: 62%, m.p.: 132–134 °C., M.F.: $C_{34}H_{24}FN_3O_7S$.

IR (KBr) ν cm^{-1}: 3318 (–NH), 1749 (–C=O), 1623 (C=N), 2895, 2958 (–CH_3), 1514, 1331 (–NO_2) 1249, 1050 (–C–O–C–), 1161 (C–F); ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ: 8.57 (s, 1H, –CH), 6.38–7.77(m, 11H, aromatic), 5.25 (s, 1H, –CH), 3.73 (s, 2H, –$\underline{CH_2}$NH), 3.22 (s, 1H, –$CH_2\underline{NH}$), 2.42 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ ppm: 160.23 (C-2),113.88 (C-3), 152.65 (C-4), 120.69 (C-5), 139.51 (C-6), 135.69 (C-7), 115.66 (C-8), 159.54 (C-9), 118.56 (C-10), 19.42 (C-12), 168.21 (C-14), 40.89 (C-16), 111.56 (C-18), 157.24 (C-20), 74.19 (C-21), 160.12 (C-22), 134.18 (C-24), 130.16 (C-25, C-29),

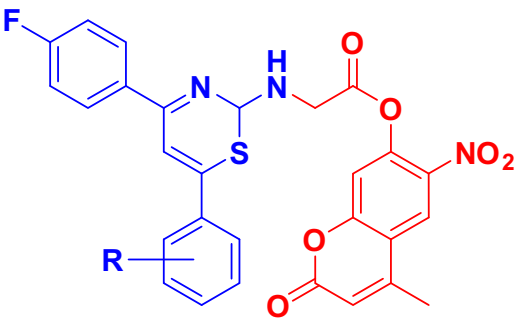


Fig. 1 General structure of 4-methyl-6-nitro-2-oxo-2*H*-chromen-7yl-2-(4-(4-fluorophenyl)-6-substituted phenyl-2*H*-1,3-thiazin-2-yl -amino) acetate **5a–j**

115.62 (C-26, C-28), 165.20 (C-27), 130.66 (C-32), 127.69 (C-33), 142.14 (C-34), 127.39 (C-35), 127.09 (C-36), 126.19 (C-37), 160.61 (C-39), 118.13 (C-40, C-44), 130.11 (C-41, C-43) 122.79 (C-42); *m/z*: 637.13 (M^+).

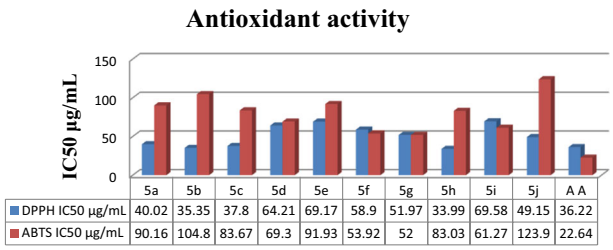
Biology

In vitro antimicrobial assay

The broth microdilution method has been employed to determine the MICs of synthesized compounds as described in the literature (Patel et al. 2010). Dimethylsulfoxide (DMSO) was used as diluent to get desired concentration of drugs to test upon standard bacterial strains. Prepare a solvent control of a 1:10 dilution of the DMSO used to dissolve the antimicrobial agent being tested. This 1:10 solution is prepared by adding 0.1 ml of solvent to 0.9 ml of the appropriate diluent. The highest dilution showing at least 99% inhibition is taken as MIC. To evaluate the antimicrobial potency of the final derivatives, they were screened against different strains viz., two Gram-positive bacteria *S. aureus* (MTCC–96) and *S. pyogenes* (MTCC–442), two Gram-negative bacteria *E. coli* (MTCC–443) and *P. aeruginosa* (MTCC–1688), and fungi, *C. albicans* (MTCC–227), *A. niger* (MTCC–282), and *A. clavatus* (MTCC– 1323), and compared with standard drugs, chloramphenicol, ciprofloxacin, and griseofulvin.

In vitro antitubercular assay

Tubercle bacilli are aerobes, grow in specially enriched media containing egg, asparagines, potatoes, serum, and meat extracts. Colonies appear in 2–6 weeks. The drug susceptibility test to determine MIC by LJ Slope method has been employed (Muralidhar and Srivastava 2004). *M. tuberculosis* $H_{37}Rv$ [acid fast bacilli] (MTCC–200) was used for screening of antitubercular activity. DMSO was used as diluents/vehicle to get desired concentration of drugs to test upon standard bacterial strains. Each synthesized compound was diluted obtaining 2000 µg/mL concentration, as a stock solution and then many dilutions were made shown as in antimicrobial activities (Fig. 1).



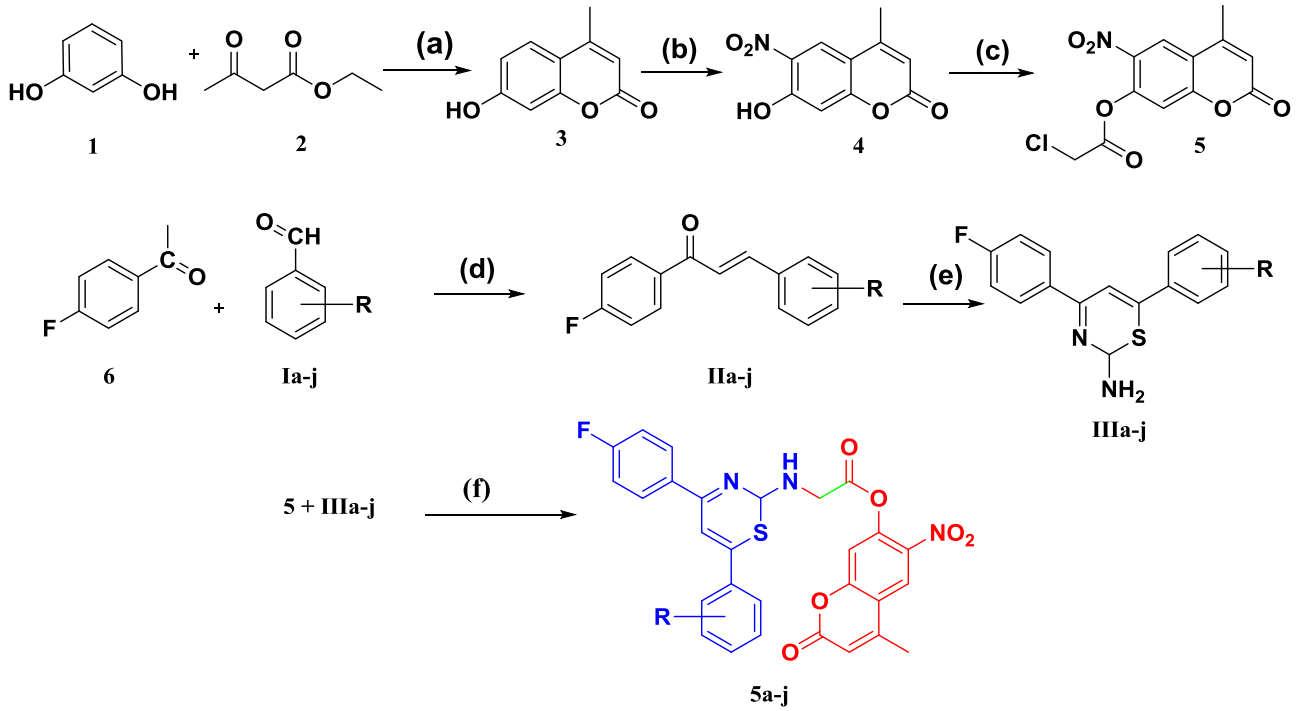
	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	A A
DPPH IC50 µg/mL	40.02	35.35	37.8	64.21	69.17	58.9	51.97	33.99	69.58	49.15	36.22
ABTS IC50 µg/mL	90.16	104.8	83.67	69.3	91.93	53.92	52	83.03	61.27	123.9	22.64

Fig. 2 The plot of antioxidant assay result of **5a–j**

Antioxidant evaluation

DPPH method Reduction of 2,2-diphenyl-1-picrylhydrazyl (free radical) is the base of the DPPH antioxidant bioassay. It has an odd electron that shows a maximum absorption band of 517 nm (deep violet color) in ethanol. The DPPH bioassay is the widely used and acceptable method for evaluating the free radical scavenging action of the tested compounds. Such substances donate a hydrogen atom when mixed with the DPPH, thereby introducing its reduced congener, diphenylpicrylhydrazine (non-radical) with the loss of violet color. In the present study, DPPH bioassay was adopted to screen the berberine-based compounds for their in vitro antioxidant profiles. The results of this bioassay investigation were introduced in the form of the percentage of radical scavenging antioxidant activity (RSA %) of each substance. The investigation of the DPPH radical scavenging activity was operated according to the methodology described by (Brand-Williams et al. 1995) with some modifications (Mistry et al. 2016). A stable free radical, DPPH, was allowed to react with test compounds in methanol as 20 µg/mL (100, 10, 1, and 0.1) quantities of title compounds were mixed up with 180 µg/mL of DPPH in methanol. Titled compounds donated hydrogen during the mixing thereby introduced the reduction of DPPH and hence a change in the color was observed from deep violet to light yellow at 517 nm after 25 min of reaction in a UV–Visible spectrophotometer (Perkin Elmer). The blank reading was also performed using the mixture of methanol (20 µg/mL) and sample (180 µg/mL of DPPH). Ascorbic acid served as a control drug in this assay, and its solution was prepared by mixing methanol (20 µg/mL) and DPPH radical solution (180 µg/mL). The results of this bioassay, RSA % was determined according to (Mensor et al. 2001) as described in the below equation.

$$\%\,\text{Scavenging} = \frac{\text{Absorbance of blank} - \text{Absorbance of test}}{\text{Absorbance of blank}} \times 100$$



Scheme 1 **a** Cooled (5–10 °C), conc. H_2SO_4; **b** CAN, 30% H_2O_2 + 5 mL H_2O, stirred; **c** α-chloroacetyl chloride, CH_2Cl_2, triethyl amine 1 h stirred; **d** NaOH, EtOH, 2 -3 h stirred; **e** thiourea, ethanolic NaOH, 2–3 h refluxed; **f** 4-methyl-6-nitro-2-oxo-2*H*-chromen-7-yl 2-chloroacetate (5), DMF, K_2CO_3, 8-9 h refluxed. Where, **R = -H, 2-Cl, 4-Cl, 2-OH, 4-OH, 4-F, 4-CH_3, 4-C_3H_7, 3-Br, 3-OPh**

A plot of concentration (Fig. 2) of test compounds and % scavenging introduced IC_{50} in the presence of an ascorbic acid as standard.

ABTS method The ABTS• + radical cation scavenging efficacies of the test compounds was determined according to the method described earlier with some modifications (Mistry et al. 2016). Mixing of an equal amount of 7.0 mM ABTS• + stock solution with 2.45 mM potassium persulfate stock solution produces the ABTS• + cation. The mixture was kept in a dark place at 0 °C temperature for 12 h and ABTS solution was diluted with MeOH so that it gives UV absorption value of 0.700 (± 0.200) at the 734 nm. The 1000 µL stock solutions of titled compounds **5a–j** were dissolved in methanol and further dilutions of 100, 10, 1, and 0.1 µg/mL taken for test samples. In all 180 µg/mL solutions of compounds to be evaluated and 20 µg/mL of the ABTS solution were mixed in 96-well plates in a dark place and then incubated for 10 min to measure UV absorption at 734 nm. The solution of 180 µg/mL ABTS in 20 µg/mL methanol was used as a control determination, while ascorbic acid was used as a reference drug. The UV absorption data represented the radical scavenging rates that give the corresponding IC_{50s} for the test compounds.

The scavenging capability of ABTS• + radical was calculated using the following equation:

$$\%\,\text{Scavenging} = \frac{\text{Absorbance of blank} - \text{Absorbance of test}}{\text{Absorbance of blank}} \times 100$$

Results and discussion

Chemistry

The synthetic protocol for the lead molecule 4-methyl-6-nitro-2-oxo-2*H*-chromen-7-yl 2-chloroacetate (5) and final compounds (5a–j) is depicted in Scheme 1. According to the scheme, 4-methyl-7-hydroxy-coumarin (2) has been synthesized by pechmann condentation, which is followed by nitration with nitric acid and acetic acid and then reacting with chloroacetyl chloride to get 4-methyl-3-nitro-2-oxo-2*H*-chromen-7-yl 2-chloroacetate (5). For the synthesis of final compounds, key intermediate (5) was condensed with amino thiazines derivatives (**IIIa–j**) obtained from cycloaddition reaction between substituted chalcones (**IIa–j**) and thiourea. The reaction protocol is illustrated in the following scheme.

Characterizations of intermediate and final compounds were confirmed by their spectral analysis. The characteristic band of 3192 cm^{-1} of –NH, while two bands for –C=O appeared at 1715 and 1671 cm^{-1} and 1523, 1351 cm^{-1} for $–NO_2$ in IR spectrum confirmed the structure of the final compounds **5a–j**. ^1H NMR spectrum of final compounds showed singlet at 8.55 of –CH confirmed the neighboring $–NO_2$ group while $–CH_2NH$ showed two singlet at 3.71 and 3.23, respectively. ^{13}C NMR spectrum of **5a–j** showed peaks nearer at 160.10 and 168.20 for two different C=O and one peak at 19.40 for $–CH_3$ of coumarin. Peaks at

43.90, 81.10, and 111.30 were obtained for –CHNH, –CH of thiazine (C-18) ring, which confirming the structure of final compounds.

Biology

Antimicrobial activity

The minimum inhibitory concentrations (MIC) for the antimicrobial potency of **5a–j** were screened against four different bacterial strains and three different fungal strains. The susceptibility of the organisms was determined by the broth microdilution method (Rattan 2000) and compared with standard drugs; chloramphenicol, ciprofloxacin, and griseofulvin. The results of this activity are described in Table 1. Compound **5c** with a –Cl group and 5 h with $-CH_2CH_2CH_3$ at position 4 on benzaldehyde demonstrated remarkable activity (MIC = 50 µg/mL) against *E. coli*, comparable to chloramphenicol and ciprofloxacin. While other compounds showed poor activity against *S. aureus* and *S. pyogenes*. Compounds **5a** and **5b**, having substituent –H, 2-Cl, respectively, exhibited significant activity with MIC value 250 µg/mL, while compound **5d** showed encouraging potency (MIC = 200 µg/mL) against *C. albicans* compared with griseofulvin. Other compounds with very high MIC values and seem to be poor to moderately active (Table 2).

Table 1 Spectral characterization of the compounds

Comp. no.	R	Molecular Formula	M.P. °C	Yield %
5a	$-C_6H_5$	$C_{28}H_{20}FN_3O_6S$	129–131	56
5b	2-Cl	$C_{28}H_{19}FN_3O_6SCl$	156–158	59
5c	4-Cl	$C_{28}H_{19}N_3O_6SCl$	163–165	65
5d	2-OH	$C_{28}H_{20}FN_3O_7S$	174–176	61
5e	4-OH	$C_{28}H_{20}FN_3O_7S$	184–186	69
5f	4-F	$C_{28}H_{19}F_2N_3O_6S$	158–160	64
5g	$4\text{-}CH_3$	$C_{29}H_{22}FN_3O_6S$	165–167	62
5h	$4\text{-}C_3H_7$	$C_{31}H_{26}FN_3O_6S$	140–142	68
5i	3-Br	$C_{28}H_{19}BrFN_3O_6S$	125–127	62
5j	3-OPh	$C_{34}H_{24}FN_3O_7S$	132–134	69

Table 3 Antitubercular data of compounds 5**a–j**

Minimum inhibitory concentration		
Compound no.	MIC (µg/ml)	% Inhibition
5a	100	99
5b	62.5	98
5c	500	98
5d	1000	99
5e	1000	98
5f	>1000	97
5g	500	99
5h	62.5	99
5i	500	99
5j	>1000	98
Rifampicin	40	99
Isoniazid	0.2	99

Table 2 Antibacterial and antifungal data of compounds **5a–j**

Compound no.	MIC (µg/mL)						
	Antibacterial activity				Antifungal activity		
	S. aureus MTCC 96	*S. pyogenes* MTCC 442	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*C. albicans* MTCC227	*A. niger* MTCC282	*A. clavatus*MTCC 1323
5a	250	500	100	200	250	1000	1000
5b	100	100	200	200	250	200	500
5c	500	500	50	100	500	1000	>1000
5d	500	250	100	250	200	500	250
5e	250	250	250	250	1000	1000	1000
5f	200	200	125	250	1000	>1000	>1000
5g	250	250	250	250	1000	500	>1000
5h	500	500	50	100	>1000	1000	500
5i	500	500	100	100	500	1000	1000
5j	250	125	200	200	500	1000	>1000
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–
Griseofulvin	–	–	–	–	500	100	100

Table 4 Screening results of DPPH and ABTS radical scavenging activity of **5a–j**

Compd. no.	DPPH IC_{50} μg/mL ± SD	ABTS IC_{50} μg/mL ± SD
5a	40.02 ± 0.199	90.16206 ± 1.091
5b	35.35 ± 0.470	104.78 ± 0.744
5c	37.80 ± 0.246	83.67 ± 0.553
5d	64.21 ± 0.895	69.30 ± 0.893
5e	69.17 ± 0.866	91.93 ± 1.020
5f	58.90 ± 1.069	53.92 ± 0.777
5g	51.97 ± 1.098	52.00 ± 0.109
5h	33.99 ± 0.301	83.03 ± 0.713
5i	69.58 ± 0.330	61.27 ± 2.330
5j	49.15 ± 0.140	123.86 ± 1.951
Ascorbic acid	36.22 ± 0.469	22.64 ± 0.260

Antitubercular activity

The MIC of the titled compounds were tested for antituberculer activities (Andrews 2001). The results are mentioned in Table 3. Antituberculer activity results showed that, compound **5b** and **5h** having 2-Cl and 4-propyl group demonstrated better activity 62.5 μg/mL with 98–99 % inhibition against *M. tuberculosis* $H_{37}Rv$ (Table 4).

Antioxidant activity

From the antioxidant inspections, molecules **5h** and **5b** were appeared to have high radical scavenging efficacies as 33.99 ± 0.301 and 35.35 ± 0.470 μg/mL ± SD of IC_{50} values in DPPH and ABTS bioassay, respectively, and can be comparable to that of control ascorbic acid while other compounds have moderate to poor antioxidant power. The results were summarized in the following graph.

Conclusion

A new series of 4-methyl-6-nitro-2-oxo-2*H*-chromen-7yl-2-(4-(4-fluorophenyl)-6-substituted-phenyl-2*H*-1,3-thiazin-2-yl-amino) acetate has been efficiently formulated via coupling 4-methyl-6-nitro-2-oxo-2*H*-chromen-7-yl 2-chloroacetate with amino thiazine derivatives, which was obtained by treating thiourea with substituted chalcone derivatives at optimum reaction condition. All the synthesized compounds were characterized by spectral techniques. Final compounds were evaluated for their in vitro antioxidant activity using DPPH and ABTS bioassays. The presence of chloro and propyl group on phenyl ring on the chalcone system was essential to exert antioxidant effect and showed excellent free radical scavenging efficacies in DPPH and ABTS bioassays, respectively. Also, a MIC of **5a–j** using broth microdilution method towards bacterial and fungal strains was studied and the derivatives **5c** and **5h** displayed remarkable potency against *E. coli* with MIC values 50 μg/mL compare to standard drugs. It has been observed that the potent antibacterial and antitubercular candidate proved to possess significant antioxidant activity. The present of propyl group on phenyl ring plays an important role for the potency in above mentioned biological assay.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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