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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, X-ray characterization and biological evaluation of some new 2-(4-methy-2-oxo-2*H*-chromen-7yloxy) acetamide derivatives

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Abstract Newly designed coumarinyloxy acetamide derivatives (7**a**–7**n**) were synthesized in good yields and characterised by advanced spectroscopic studies and the XRD studies indicated that no polymorphism is observed in the molecules. Synthesized coumarinyloxy acetamides showed potent antimicrobial activity on human pathogens. Some of the analogues were found to have comparable or even more potency than the standard drugs (Ciprofloxacin for bacteria and Griseofulvin for dermatophytic fungi). Aromatic coumarinyloxy amides possess good antimicrobial activity followed by alicyclic compounds but aliphatic straight chain coumarinyloxy amides showed poor antimicrobial activity. In vitro results were correlated with docking studies.

Keywords Coumarinyloxy acetamides · Antimicrobial · Docking · Human pathogens

Introduction

Coumarin is a simple molecule and many of its derivatives have been known for more than a century. Coumarin and coumarin-related compounds have proved for many years to have significant therapeutic potential (Lacy and O'Kennedy, 2004). They come from a wide variety of natural sources and new coumarin derivatives are being discovered or synthesised on a regular basis. Their physiological, antimicrobial (Balaji *et al*., 2013; Smyth *et al*., 2009), anti-cancer (Kostova, 2005) and anti-inflammatory (Curini *et al*., 2006; Ghate *et al*., 2005) antioxidant (Nicolaides *et al*., 1998; Litinadj *et al*., 2004) activities make these compounds attractive for further backbone derivatisation and screening as novel therapeutic agents.

In recent years, multiple drug resistance has been developed due to indiscriminate use of existing antimicrobial drugs in the treatment of infectious diseases and has become a global public health problem (WHO document WHO/CDS/CSR/RMD/, 2003). The antibacterial properties of coumarins were first recognised in 1945 when Goth et al. conducted an investigation with dicoumarol and it was found to inhibit the growth of several strains of bacteria (Goth, 1945). (Smyth *et al*., 2009) reported that antimicrobial activity of 43 natural and synthetic coumarins on clinical isolates of methicillin resistant *Staphylococcus aureus* (MRSA) strains and also demonstrated their resistance modifying activity (RMA). Development of topoisomerases targeted molecules has great importance to overcome the drug resistance. Drugs that target topoisomerase I and II have become important for both cancer and bacterial therapy (Teicher, 2008; Pommier and Cushman, 2009; Larsen *et al*., 2003). A few antibiotics with the coumarin skeleton as part of their structure have been isolated. The most active of them is novobiocin, isolated from *Streptomyces niveus*, which is mainly active against Gram-positive bacteria (Kawase *et al*., 2001). These coumarin antibiotics are potent inhibitors of DNA replication

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via topoisomerase II (Bacterial gyrase) inhibition (Kalkhambkar *et al*., 2008; Flatman *et al*., 2006).

Among the various coumarin derivatives, 7-substituted coumarins constitute an important group of compounds that show various bioactivities along with other applications (Kuznetsova *et al*., 2003). Moreover, 7-amino 4-methyl coumarin is also used as laser dye and intermediate for the synthesis of bioactive compounds (Nowakowska *et al*., 2001) and the 4-methylcoumarin derivatives present in various naturally occurring compounds, are known to exhibit a wide range of biological and pharmaceutical activities (Ramesh and Raghunathan, 2008)

Previous studies have shown that combining the coumarin backbone with some nitrogen-containing heterocyclic moieties could significantly broaden the spectrum of activity of these compounds and increase their antimicrobial or anti-fungal efficiency (Keri *et al*., 2009; Raghu *et al*., 2009; Ronad *et al*., 2010).

Recent reports showed an amide moiety (i.e., –CONHAr) was thought to provide better pharmacokinetic stability rather than an ester (i.e.,–$OCOCH_2$) containing α-amino moiety. Chimenti *et al*., 2007 pointed out that a carboxamide function in the coumarin ring might play an important role leading to various biological activities.

This prompted us to synthesize and study the antimicrobial activity of compounds with coumarin and an amide linkage to get the synergistic effect. In this context, newly synthesized coumarinyloxy acetamide derivatives were characterised by X-ray crystallographic & other advanced spectroscopic studies. Furthermore, antimicrobial assay was performed on drug resistant human pathogens. In addition, in vitro studies were simulated with in silico analysis.

Experimental

Synthesis of 7-hydroxy-4-methyl-2*H*-chromen-2-one [3]

To an equivalent mixture of resorsinol (1.71 g, 15 mmol, 1 eq), ethyl acetoacetate (2.03 g, 15 mmol, 1 eq) was added to equivalents of P-TSA (0.40 g) in ethanol. The mixture is refluxed until starting material is disappeared. After complete conversion, the reaction mixture is cooled to room temperature and poured in cold water. Solid is precipitated. This solid is filtered, dried and then washed with ether to remove impurities and recrystallized from ethanol. A yellow colour solid compound is obtained in 85 % yield. The formed compound was confirmed by comparing with authentic sample (Organic Syntheses, 1955).

Synthesis of Ethyl-2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetate [4]

To the stirred mixture of **3** (1 g, 5 mmol 1.0 eq) in CH_3CN, ethylbromoacetate (0.9 g, 5 mmol, 1.2 eq) and K_2CO_3 (10 eq) are added and resulting mixture is refluxed for 4 h. After completion of reaction (monitored by TLC), reaction mixture is cooled to room temperature and filtered to remove K_2CO_3. The filtrate is concentrated under vacuum to give solid compound. This solid is washed with 10 % EtoAc and hexane to remove upper impurities and dried under vacuum and recrystallized from ethanol. The pure compound obtained in 92 % yield;

m.p: 112–114°C; IR (KBr) ν_{max}: 3080, 2950, 1732, 1709, 1613, 1568, 1504, 1217, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.56 (d, $J = 9.0$ Hz, 1H, 5-H), 6.94 (d, $J = 9.0$ Hz, 1H, 6-H), 6.78 (m,1H, 8-H), 6.17 (s, 1H, 3-H), 4.69 (s, 2H, 11-H) 4.33-4.26 (q, $J = 7.1$ Hz, 2H, 13-H) 2.41 (s, 3H, 4′-H) 1.35 (t, $J = 7.1$ Hz,3H, 14-H); ^{13}C NMR ($CDCl_3$,75 MHz) δ: 167.9 (C=O, C-2), 160.9 (C=O, C-12), 155.0 (C, C-9), 152.3 (C, C-4), 125.7 (C, C-5), 114.4 (C, C-3), 112.54 (C, C-10), 112.50 (C, C-6), 101.7 (C, C-8), 65.38 (CH_2, C-11), 61.68 (CH_2, C-13), 18.61 (CH_3, C-4′), 14.13 (CH_3, C-14); MS (ESI): (m/z): 262.26 $(M + H)^+$

Synthesis of 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetic acid [5]

Compound **4** (2.6 g, 1 eq) was treated with NaOH (3.9 g, 10 eq) in water (100 ml). The resulting mixture was refluxed at a temperature 100–108 °C for 15 h. After that the reaction mixture was left to room temperature, then transferred into ice cold water and acidified with Con. HCl up to pH ~ 2. The resulting solid was filtered off, crystallised from ethanol and dried in vacuo to yield compound **5** (95 %) as a colourless solid. m.p : 252–254 °C; IR (KBr) ν_{max}: 3,452, 3,020, 2,925, 1,718, 1,677, 1,504, 1,217, 1,073 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ: 8.04 (s, 1H, –OH), 7.89 (d, $J = 9.0$ Hz, 1H, 5-H), 7.73 (d, $J = 6.0$ Hz, 1H, 8-H), 7.56 (t, $J = 6.0$ Hz, 1H, 6-H), 6.47 (s, 1H, 3-H), 4.91 (s, 2H, 11-H), 2.50 (s, 3H, 4′-H);^{13}C NMR (DMSO-d_6, 75 MHz) δ: 170.4 (C, –COOH, C-12), 160.0 (C, C-7), 154.4 (C, –C=O, C-2), 153.7 (C, C-4), 149.8 (C, C-9), 128.1 (C, C-5), 120.9 (C, C-10), 118.2 (C, C-3), 115.9 (C, C-6), 108.7 (C, C-8), 65.7 (C, –CH_2, C-11), 19.0 (C, –CH_3, C-4′); MS (ESI): (*m*/*z*): 234.20 $(M + H)^+$.

Synthesis of amides general procedure (6–7n)

The suspension 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetic acid **5** (200 mg, 0.79 mmol) in benzene (10 mL), added thionyl chloride (1.0 mL) and refluxed for 2 h. The resulting

solution was evaporated to dryness under reduced pressure, and the residue of crude **6** was dispersed in dry benzene (10 mL). The solvent was eliminated under reduced pressure. Dispersion in dry benzene and solvent elimination was repeated twice. The residue was dissolved in benzene (10 mL) and added appropriate amine in excess and refluxing for 50–90 min, depending upon the nature of the amine, the solvent was removed by evaporation under reduced pressure and extracted threefold with $CHCl_3$ (30 mL). $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and concentrated under high vacuum. The crude product thus obtained was purified by column chromatography (60–120 mesh) to furnish corresponding amide (**7a–7n**) in good to excellent yield.

*N-ethyl-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7a)***

Yield: 85 %; colourless crystals (MeOH); m.p: 169–172 °C; IR (KBr) ν_{max}: 3373, 2984, 1717, 1650, 1553, 1538, 1211, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 1.19–1.24 (t, $J = 7.5$ Hz, 3H, H-15), 2.40 (s, 3H, H-4′), 3.37–3.46 (m, 2H, H-14), 4.53 (s, 2H, H-11), 6.66 (brs, 1H, –NH, H-13), 6.16–6.17 (s, 1H, H-3), 6.85–7.54 (m, 3H); ^{13}C NMR($CDCl_3$/TMS,75 MHz): 14.77 (C, $–CH_3$, 14-C), 18.62 (C, $–CH_3$, 4′–C), 34.07(C, $–CH_2$, 13-C), 67.53(C, $–CH_2$, 11-C), 102.63 (C, 6-C), 111.62 (C, 8-C), 112.77 (C, 5-C), 114.76 (C, 10-C), 126.01 (C, 5-C), 152.24 (C, 9-C), 155.07 (C, 4-C), 159.93 (C, –C–O, 7-C), 160.82 (C, –C=O, 2-C), 166.86 (C, –C=O, 12-C); MS [ESI]: 262.2 [M + 1].

*N-propyl-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7b)***

Yield: 83 %; colourless crystals (MeOH); m.p: 165–169 °C; IR(KBr) ν_{max}: 3377, 2986, 1720, 1656, 1550, 1539, 1211, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 0.97–0.92 (t, $J = 7.5$ Hz, 3H, H-16),1.63–1.56 (m, 2H, H-15), 2.41(s, 3H, H-4′), 3.37–3.30 (t, $J = 6.0$ Hz, 2H, H-14), 4.55 (s, 2H, H-11), 6.17 (s, 1H, H-3), 6.60 (br s, 1H, NH, H-13), 6.92–6.86 (m, 2H), 7.57–7.54 (d, $J = 8.9$ Hz, 1H, H-5); ^{13}C NMR($CDCl_3$/TMS,75 MHz):11.29 (C, $–CH_3$, C-16), 18.63 (C, $–CH_2$, C-15), 22.79 (C, $–CH_3$, C-4′), 40.85 (C, $–CH_2$, C-14), 67.57 (C, $–CH_2$, C-11), 102.67 (C, C-8), 111.60 (C, C-6), 112.83 (C, C-3), 114.80 (C, C-10), 126.01 (C, C-5), 152.19 (C, C-9), 155.09 (C, C-4), 159.91 (C, C-2), 160.81 (C, C-7), 166.98 (C, C-12); MS [ESI]: 276.2 [M + 1].

*N-isopropyl-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7c)***

Yield: 85 %; colourless crystals (MeOH); m.p: 155–157 °C; IR(KBr) ν_{max}: 3363, 2946, 1707, 1666, 1542, 1531, 1210, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 1.20–1.23(d, $J = 6.0$ Hz, 6H), 2.40 (s, 3H, H-4′), 4.14–4.25 (m, 1H, H-14), 4.50 (s, 2H, H-11), 6.16 (s, 1H, H-3), 6.38 (brs, 1H,-NH, H-13), 6.62–6.85 (m, 2H),7.56 (d, $J = 8.9$ Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.63 (C, C-15,16), 22.63 (C, C-4′), 41.34 (C, –CH, C-14), 67.55 (C, $–CH_2$, C-11), 102.64 (C, C-8), 111.69 (C, C-6), 112.81 (C, C-3), 114.78 (C, C-10), 125.99 (C, C-5), 152.22 (C, C-9), 155.07 (C, C-4), 159.91 (C, C-2), 160.82 (C, C-7), 166.14 (C, C-12); MS [ESI]: 276.2 [M + 1].

*N-isobutyl-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7d)***

Yield: 85 %; colourless crystals (MeOH); m.p: 150–153 °C; IR (KBr) ν_{max}: 3359, 2961, 1727, 1658, 1545, 1528, 1209, 1076 cm^{-1}; ^{1}H NMR (DMSO/TMS, 300 MHz): δ 1.29 (br S, 9H, H-15,16,17), 2.40 (s, 3H, H-4′), 4.54 (s, 2H, H-11), 6.22(s, 1H, H-3), 6.92 (s, 1H, –NH, H-13), 6.99 (s, 1H, H-8), 7.64 (s, 1H, H-5), 7.69 (d, $J = 8.8$ *Hz*, 1H, H-6); ^{13}C NMR (DMSO/TMS,75 MHz): 19.04 (C, C-15,16,17), 29.33 (C, C-4'), 51.35 (C, C-14), 68.14 (C, C-11), 102.36 (C, C-8), 112.24 (C, C-6), 113.32 (C, C-3), 114.37 (C, C-10), 127.38 (C, C-5), 154.33 (C, C-9), 155.44 (C, C-4), 161.02 (C, C-2), 161.86 (C, C-7), 167.05 (C, C-12); MS [ESI]: 290.2 [M + 1].

*N-(3-hydroxypropyl)-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7e)***

Yield: 85 %; colourless crystals (MeOH); m.p: 161–163 °C; IR (KBr) ν_{max}: 3360, 2924, 1722, 1649, 1558, 1220, 1082 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): 1.55–1.64 (m, 2H, H-16), 2.39 (s, 3H, H-4′), 3.16–3.23 (m, 2H, H-15), 3.41–3.45 (m, 2H, H-14), 4.44 (m, 1H, –OH, H-17), 4.59 (s, 2H, H-11), 6.21 (s, 1H, H-3), 6.94–7.02 (m, 2H, H-6,8), 7.72–7.69 (d, $J = 8.7$ Hz, 1H, H-5), 8.14 (br S, 1H, NH, H-13); ^{13}C NMR ($CDCl_3$/TMS,75 MHz): 18.59 (C, C-4'), 32.70 (C, C-15), 36.32 (C, C-14), 58.99 (C, C-16), 67.66 (C, C-11), 102.15 (C, C-8), 111.90 (C, C-6), 112.88 (C, C-3), 114.06 (C, C-10), 126.96 (C, C-5), 153.81 (C, C-9), 154.96 (C, C-4), 160.52 (C, C-2), 161.13 (C, C-7), 167.31 (C, C-12); MS [ESI]: 292.2 [M + 1].

*N-cyclohexyl-2-(4-methyl-2-oxo-2H-chromen-7yloxy) acetamide **(7f)***

Yield: 85 %; colourless crystals (MeOH); m.p: 180–182 °C; IR (KBr) ν_{max}: 3371, 2933, 1718, 1664, 1531, 1274, 1078 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 1.16–1.97 (m, 10H), 2.41 (s, 3H, H-4'), 3.85–3.93 (m, 1H, H-14), 4.52 (s, 2H, H-11), 6.17 (s, 1H, H-3), 6.39-6.41 (br s, 1H, NH), 6.85–6.92 (m, 2H. H-6, 8), 7.57 (d, $J = 8.7$ *Hz*, 1H, H-5); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.72 (C,

C-4′), 24.84 (C, C-17), 25.40 (C, C-16), 32.98 (C, C-15), 48.09 (C, C-14), 67.50 (C, C-11), 102.56 (C, C-8), 111.72 (C, C-6), 112.77 (C, C-3), 114.74 (C, C-10), 126.02 (C, C-5), 152.34 (C, C-9), 155.02 (C, C-4), 159.87 (C, C-2), 160.93 (C, C-7), 166.02 (C, C-12); MS [ESI]: 316.2 [M + 1].

4-methyl-7-(2-oxo-2-piperidin-1-yl-ethoxy) chromen-2-one ***(7g)***

Yield : 85 %; colourless crystals (MeOH); m.p: 171–174 °C;IR (KBr) ν_{max}: 2937, 2852, 2407, 1770, 1660, 1558, 1284, 1078 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300 MHz):δ 1.55–1.66 (m, 6H), 2.38(s, 3H, H-4′), 3.43–3.57 (m, 4H), 4.77 (s, 2H, H-11), 6.13(s, 1H, H-3), 6.82(d, *J = 2.5 Hz*, 1H, H-8), 6.94 (d/d, *J = 2.5 Hz,* 1H, H-6), 7.50(d, *J = 8.7 Hz*, 1H, H-5); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.62 (C, C-4′), 24.35 (C, C-16), 25.46 (C, C-15), 26.47 (C, C-14), 43.21 (C, C-17), 46.18 (C, C-13), 67.20 (C, C-11), 102.01 (C, C-8), 112.26 (C, C-6), 112.35 (C, C-3), 114.20 (C, C-10), 125.73 (C, C-5), 152.45 (C, C-9), 155.04 (C, C-4), 161.04 (C, C-2), 161.07 (C, C-7), 164.98 (C, C-12); MS [ESI]: 302.2 [M + 1].

4-methyl-7-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethoxy]-chromen-2-one ***(7h)***

Yield: 85 %; colourless crystals (MeOH); m.p: 97–99 °C; IR (KBr) ν_{max}: 3074, 2981, 1712, 1651, 1483, 1257, 1080 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300 MHz): 2.30 (s, 3H, H-16′), 2.39 (s, 3H, H-4′), 2.44–2.41 (m, 4H, H-14,15), 3.66–3.544 (m, 4H, H-17, 18), 4.77 (s, 2H, H-11), 6.14 (s, 1H, H-3), 6.82 (s, *J = 2.5 Hz*, 1H, H-8), 6.94 (d/d, *J = 2.5 Hz*, 1H, H-6), 7.53–7.50 (d, *J = 8.7 Hz*, 1H, H-5); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.70 (CH_3, C-4′), 42.00 (C, C-14), 45.00 (C, C-15), 46.01 (C, C-17), 54. 52 (C, C-18), 55.01 (C, C-16'), 67.10 (C, C-11), 101.98 (C, C-8), 112.34 (C, C-6), 112.38 (C, C-3), 114.33 (C, C-10), 125.81 (C, C-5), 152.48 (C, C-9), 155.01 (C, C-4), 160.81 (C, C-2), 161.11 (C, C-7), 165.22 (C, C-12); MS [ESI]: 317.2 [M + 1].

4-methyl-7-(2-morpholin-4-yl-2-oxo-ethoxy)-chromen-2-one ***(7i)***

Yield : 85 %; colourless crystals (MeOH); m.p: 146–148 °C; IR (KBr) ν_{max}: 3050, 2982, 1712, 1658, 1475, 1257, 1075 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300 MHz): δ 2.38 (s, 3H, H-4′), 3.57–3.67 (brm, 8H, H-14, 15, 17, 18), 4.77 (s, 2H, H-11), 6.13(s, 1H, H-3), 6.82 (d, *J = 2.5 Hz*, 1H, H-8), 6.94 (d/d, *J = 2.5 Hz*, 1H, H-6), 7.50 (d, *J = 8.7 Hz*, 1H, H-5); ^{13}C NMR ($CDCl_3$/TMS,75 MHz): 18.62 (C, C-4′), 42.39 (C, C-14), 45.66 (C, C-18), 66.59 (C, C-17), 66.75 (C, C-15), 67.17 (C, C-11), 102.00 (C, C-8), 112.28 (C, C-6), 112.45 (C, C-3), 114.42 (C, C-10), 125.84 (C, C-5), 152.39 (C, C-9), 155.05 (C, C-4), 160.68 (C, C-2), 160.98 (C, C-7), 165.52 (C, C-12); MS [ESI]: 304.2 [M + 1].

N-(4-methoxy-phenyl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamide ***(7j)***

Yield : 86 %; colourless crystals (MeOH); m.p: 210–212 °C; IR (KBr) ν_{max}: 3354, 2912, 1708, 1668, 1539, 1247, 1082 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300 MHz): 2.39 (s, 3H, H-4′), 3.73 (s, 3H, H-17′), 4.79 (s, 2H, H-11), 6.19 (s, 1H, H-3), 6.91–6.88 (d, 2H, H-6, 8), 7.07–7.00 (d, 2H, H-16, 18), 7.54–7.51 (d, *J = 9.0 Hz,* 2H, H-15, 19), 7.72 (d, *J = 8.7 Hz*, 1H, H-5), 9.88 (d, 1H, NH, H-13); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.56 (C, C-4′), 55.63 (C, C-17′), 67.83 (C, C-11), 102.17 (C, C-8), 111.91 (C, C-6), 112.85 (C, C-3), 114.10 (C, C-10), 114.34 (C, C-18), 121.82 (C, C-15), 126.97 (C, C-16), 131.80 (C, C-17), 153.78 (C, C-14), 154.98 (C, C-9), 156.08 (C, C-4), 160.50 (C, C-2), 161.29 (C, C-7), 165.81 (C, C-12); MS [ESI]: 340.2 [M + 1].

N-(3,4,5-trimethoxy-phenyl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamide ***(7k)***

Yield: 88 %; colourless crystals (MeOH); m.p: 189–192 °C; IR (KBr) ν_{max}: 3363, 2914, 1712, 1683, 1604, 1541, 1271, 1053 cm^{-1}; ^1H NMR ($CDCl_3$/TMS,300 MHz): δ 2.39 (s, 3H, H-4′), 3.61 (s, 3H, H-14′), 3.73 (s, 6H, H-15′,16′), 4.82 (s, 2H, H-11), 6.23 (s, 1H, H-3), 7.01–7.07 (m, 3H, H-5, 6, 8), 7.70–7.73 (d, 2H, H-14, 18), 10.08 (s, 1H, –NH);^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.57 (C, C-4′), 56.21 (C, C-16′), 60.57 (C, C-14′, 15,), 67.76 (C, C-11), 97.92 (C, C-18), 102.15 (C, C-8), 111.92 (C, C-6), 112.87 (C, C-3), 114.13 (C, C-10), 127.00 (C, C-5), 134.28 (C, C-15), 134.87 (C, C-17), 153.19 (C, C-9), 153.80 (C, C-13), 154.99 (C, C-4), 160.51 (C, C-2), 161.27 (C, C-7), 166.18 (C, C-12); MS [ESI]: 400.2 [M + 1].

N-(2-hydroxy-phenyl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamide ***(7l)***

Yield : 83 %; colourless crystals (MeOH); m.p: 191–193 °C; IR (KBr) ν_{max}: 3255, 2912, 1718, 1665, 1539, 1247, 1082 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300 MHz): δ 2.39 (s, 3H, H-4'), 4.9 (s, 2H, H-11), 6.22 (s, 1H, H-3), 6.7–6.95 (m, 2H, H-6,8), 7.03–7.07 (d, 4H, H-5, 15, 16, 17), 7.6–7.7 (m, 1H, H-18), 9.3 (s, 1H, –OH), 10.04 (s, 1H, –NH). ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.58 (C, C-4′), 67.83 (C, C-11), 102.2 (C, C-8), 112.0 (C, C-6), 112.8 (C, C-3), 114.2 (C, C-10), 115.7 (C, C-15), 121.8 (C, C-18), 125.1 (C, C-17), 125.9 (C, C-16), 127.0 (C, C-5), 147.9 (C,

C-13), 148.8 (C, C-14), 153.7 (C, C-9), 155.0 (C, C-4), 160.4 (C, C-2), 160.9 (C, C-7), 166.1 (C, C-12). MS [ESI]: 326.2 [M + 1].

2-[2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetylmino]-benzoic acid ***(7m)***

Yield: 82 %; brown colour solid (MeOH); m.p: 260–262 °C; IR (KBr) ν_{max}: 3344, 3068, 2980, 1720, 1672, 1550, 1253, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 2.39 (s, 3H, H-4′), 4.88 (s, 2H, H-11), 6.22 (s, 1H, H-3), 7.03–7.08 (m, 2H, H-6,8), 7.45–7.47 (m, 1H, H-5), 7.65–7.73 (d, 2H, H–H-16,17), 7.86–7.89 (d, 1H, H-15), 7.97–7.98 (d, 1H, H-18), 8.28 (s, 1H, –NH), 10.40 (s, 1H, –COOH). ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): 18.57 (C, C-4′), 67.70 (C, C-11), 102.21 (C, C-8), 111.93 (C, C-6), 112.81 (C, C-3), 114.14 (C, C-10), 143.78 (C, C-15), 153.79 (C, C-4), 154.98 (C, C-13), 160.52 (C, C-14′), 161.25 (C, C-2), 166.64 (C, C-7), 167.52 (C, C-12). MS [ESI]: 353.2 [M + 1].

2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-Pyridin-2-yl-acetamide ***(7n)***

Yield: 80 %; colourless crystals (MeOH); m.p: 184–189 °C; IR (KBr) ν_{max}: 3398, 3072, 1732, 1676, 1521, 1263, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ 2.39 (s, 3H, H-4′), 4.94 (s, 2H, H-11), 6.21(s, 1H, H-3), 6.99–7.04 (m, 2H, H-6,8), 7.11–7.15 (m, 1H, H-5), 7.68–7.71 (d, 1H, H-15), 7.76–7.82 (d, 1H, H-16), 8.02–8.05 (d, 1H, H-14), 8.33–8.35 (d, 1H, H-17), 10.63 (s, 1H, –NH); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) : 18.57 (C, C-4′), 67.38 (C, C-11), 102.01 (C, C-8), 111.89 (C, C-6), 112.74 (C, C-3), 114.08 (C, C-10), 114.11 (C, C-3), 120.31, 127.01 (C, C-), 138.81 (C, C-15), 148.56 (C, C-17), 151.77 (C, C-9), 153.77 (C, C-4), 155.00 (C, C-13), 160.50 (C, C-2), 161.35 (C, C-7), 167.09 (C, C-12); MS [ESI]: 311.2 [M + 1]

Antimicrobial studies on human pathogens

Salmonella typhi, Vibrio cholerae, Shigella dysenteriae, Enterococcus faecalis, *Staphylococcus aureus are* isolated from blood and fecal samples of infected patients. *Trichophyton rubrum* is a dermatophytic fungus, and Staphylococcus aureus were isolated from infected skin of patients at King George Hospital, Visakhapatnam. Microscopic observations, cultural characteristics and biochemical tests were performed for organism identification (Mackie and Mac cartney, 1996; Taplin *et al*., 1969).

Determination of zone of inhibition and minimum inhibition concentration

Freshly grown microbial culture was dissolved in sterile saline solution to make different dilutions. The turbidity of the resulting suspensions was diluted with saline to obtain a transmittance of 25–70 % at 520 nm. This suspension used as inoculum. Zone of inhibition was determined by agar well diffusion method (Perez *et al*., 1990). Sterilised agar medium (MHA for bacteria, SDA for dermatophyte) poured into petri plate with inoculum by sub surface pour plate method. A 6 mm well was cut in the centre of each plate using a sterilised cork borer. 50 µl of compound and Antibiotic (Griseofulvin) for dermatophytic fungi, Ciprofloxacin for bacteria as positive control were placed into the wells. Bacteria inoculated Plates were incubated at 34 °C for 24 h. Fungal inoculated plates were incubated for 5 days at 28 °C for the observation of zones of inhibition. Zone of inhibition was expressed in milli metre with Himedia zone reader. The minimum inhibitory concentration of compounds was determined using broth dilution assay. The medium containing different concentrations of compounds viz., 100–0.1 mg per ml prepared by serial dilution (10^{-1} dilution). After inoculation of culture, the dermatophytic fungal tubes were incubated for 72 h at 28°C for anti-fungal activity, while bacteria inoculated tubes were incubated for 24 h at 37°C. The MIC of each sample was determined by measuring the optical density in the spectrophotometer at 520 nm. The experiments were conducted according to Clinical and Laboratory Standards Institutes (Previously called as NCCLS) (CLSI, 2012; Pfaller *et al*., 2010).

Molecular docking studies

X-Ray crystal structures of proteins used in docking studies are obtained from Protein Data Bank. Topoisomerase IIA (PDB ID 2XCT) (Bax *et al*., 2010) was used in docking studies for antimicrobial activity. Co-crystallised ligands and water molecules are removed from target protein using Argus lab. Ligands are prepared using Chemoffice (Cambridge). Energy minimization was done using molecular mechanics. The minimised was executed until root mean square value reached smaller than 0.001 kcal/mol. Such energy minimised ligands and receptor used for docking studies using GEMDOCK (Generic Evolutionary Method for molecular Docking) is a generic evolutionary method with an empirical scoring function for the protein–ligand docking, which is a problem of paramount importance in structure-based drug design, combines both continuous and discrete search mechanisms. A population size of 300 with 70 generations and three solutions were used in docking accuracy setting (Yang and Chen, 2004).

Structure determination

Single crystal X-ray diffraction data sets were collected on an Oxford Xcalibur (Mova) diffractometer equipped with an EOS CCD detector using Mo Kα radiation ($\lambda = 0.71073$ Å). The crystal was maintained at 120 K during data collection using the Oxford Instruments Cryojet-HT controller. All structures were solved by direct methods using SHELXS-97 and refined against F^2 using SHELXL-97. H-atoms were fixed geometrically and refined isotropically. The WinGX package was used for refinement and production of data tables and ORTEP-3 for structure visualisation and making the molecular representations. Analysis of the H-bonded and $\pi\cdots\pi$ interactions was carried out using PLATON22 for all the structures. Packing diagrams were generated by using MERCURY.

Results and discussions

Chemistry

In the present study, we described the synthesis and selective antimicrobial evaluation of different coumarinyloxy acetamide derivatives. Pechmann condensation between resorcinol and ethyl acetoacetate using p-TSA as catalyst resulted the formation of 7-hydroxy-4-methyl-2-oxo-2*H*-chromenone (**3**). Then compound **3** was treated with ethyl bromo acetate in the presence of potassium carbonate to get Ethyl 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetate (**4**) which was hydrolyzed by using aqueous NaOH and conc.HCl solution to give corresponding acid **5**. The obtained 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy) acetic acid (**5**) was then converted into acid chloride (**6**) by the reaction with thionyl chloride which was immediately treated with various amines (aromatic/aliphatic) to give corresponding 7-coumarinyloxy acetamide derivatives (**7a–7n**). All the synthesized compounds were purified by recrystallization from ethanol and were duly characterised by advanced spectral techniques.

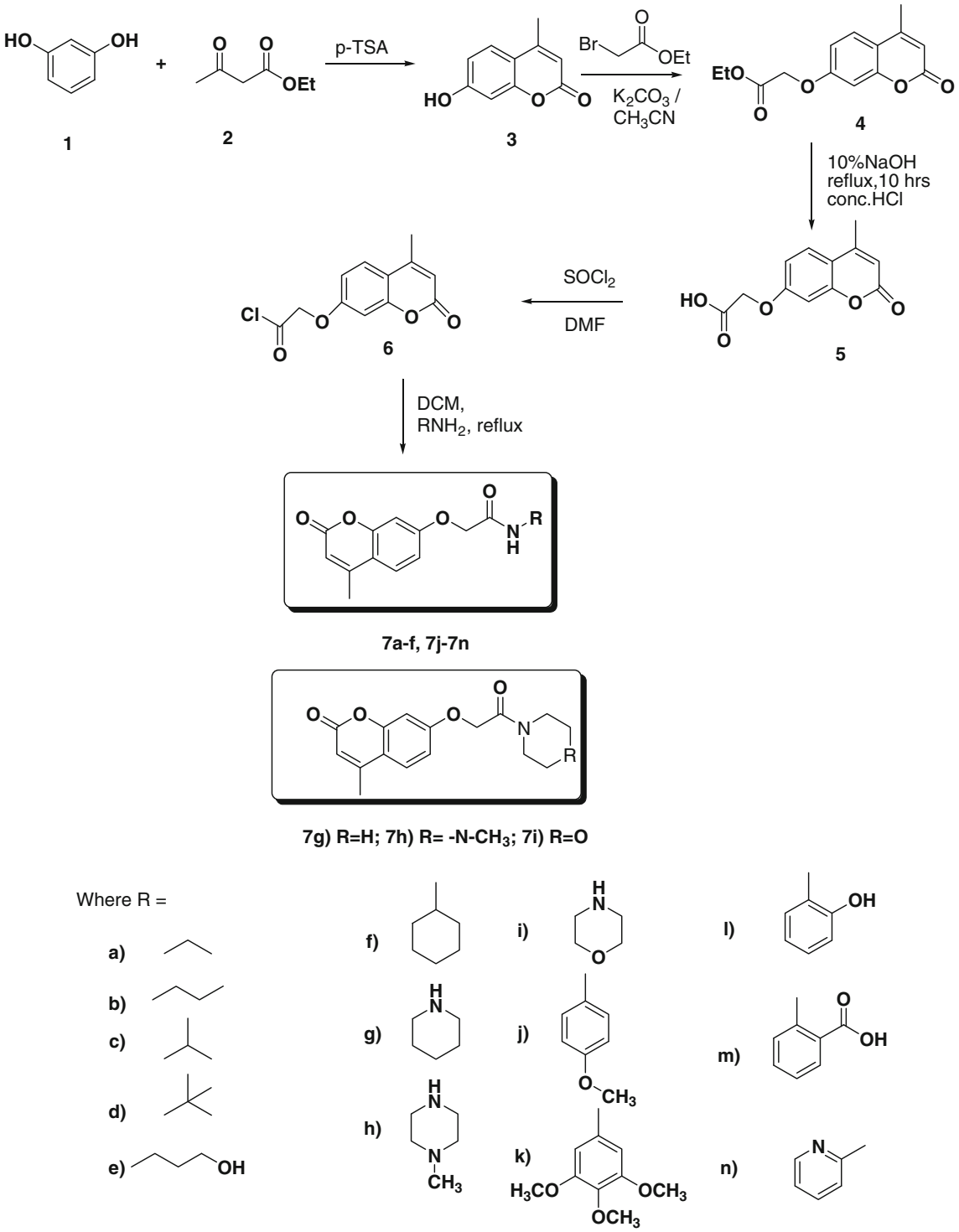
Initially, the formation of coumarinyloxy acetamide was confirmed by IR spectroscopy. The formation of amide group was confirmed by the characteristic -NH stretching at ~3,340 cm^{-1} for all the synthesized compounds and the peak at 1,700–1,732 cm^{-1} corresponds to the lactone carbonyl of coumarin and the carbonyl stretching of the amide functional was observed at 1,680–1,649 cm^{-1}. In ^{1}HNMR spectra, –NH proton appeared at δ 6.41–8.12 and δ 9.88–10.63 for aliphatic and aromatic amides, respectively. It was observed that there was decrease in the melting points with the increase in the alkyl group of the acyclic carbyloxy acetamides. But in case of substitution on the aromatic amides, the melting point is increasing. Scheme 1

Crystallographic studies

The structures of the compounds **7e**, **7f**, **7g** and **7j** were further confirmed by the X-ray crystallographic studies. Compounds 7e, 7f, 7g, and 7j were recrystallized 3–4 times from methanol to get 99.9 % purity and the compounds were submitted to XRD studies to understand polymorphism and space grouping. The ORTEP diagram and packing diagram of the tested compounds were presented in Figs. 1, 2, 3, 4, 5, 6, 7 and 8. These studies confirmed that these four compounds have Centro symmetric. In compound 7e, the crystals were afforded in a Centro symmetric space group *P*-1 with $Z = 2$. The packing in the crystal lattice is mainly through N–H···O interactions. The distance of N–H···O is 2.844 Å (distance of H···O is 2.111 Å) and the publication CCDC No of 7e is **912668.** In compound 7f, the crystals were afforded in a Centro symmetric space group *P*-1 with $Z = 2$. The packing in the crystal lattice is mainly through N–H···O interactions. The distance of N–H···O is 3.110 Å (distance of H···O is 2.357 Å) and the publication CCDC No of 7f is **912665**. In compound 7g, the crystals were afforded in a Centro symmetric space group $P2_1/n$ with $Z = 4$. The packing in the crystal lattice is mainly through two different C–H···O interactions. The distance of one C–H···O is 3.277 Å (distance of H···O is 2.357 Å) and the second C–H···O distance is 3.285 Å (distance of H···O is 2.355 Å) and the publication CCDC No of 7g is **912666**. In compound 7j, the crystals were afforded in a Centro symmetric space group $P2_1/n$ with $Z = 4$. The packing in the crystal lattice is mainly through two different N–H···O interactions. The distance of N–H···O is 3.299 Å and the publication CCDC No of 7j is **912667.** The crystal data (CIF data) of the synthesized compounds were depicted in Table 1.

Antimicrobial activity on human pathogens

These newly synthesized coumarinyloxy acetamide derivatives showed significant inhibitory activity on human pathogens viz*) S.typhi, V.Cholerae, S.dysentriae, E.faecalis, S.aureus, T.rubrum*. Some analogues of this series were found to have comparable or even more potency than the standard drugs (Ciprofloxacin for bacteria and Griseofulvin for dermatophytic fungi).These results were presented in Table 2. Among the in vitro tested compounds, a series of aromatic compounds (**7j–7n**) showed potent antimicrobial activity on human pathogens, especially effective on dermatophytic fungi. **7k** (3, 4, 5 tri methoxy)



Scheme 1 Synthesis of carbyloxy acetamide derivatives of 4-methyl, 7-hydroxy coumarin compounds

and **7l** (2-hydroxy) were showed 19 and 21 mm inhibitory zones (highest) and 1 μg/ml of MIC value (lowest) with *V. cholerae*. The compounds **7k** and **7l** showed good antimicrobial activity compared to other aromatic series of compounds. Aliphatic straight chain compounds (**7a–7i**) exhibited considerable inhibitory zones (8–15 mm) and

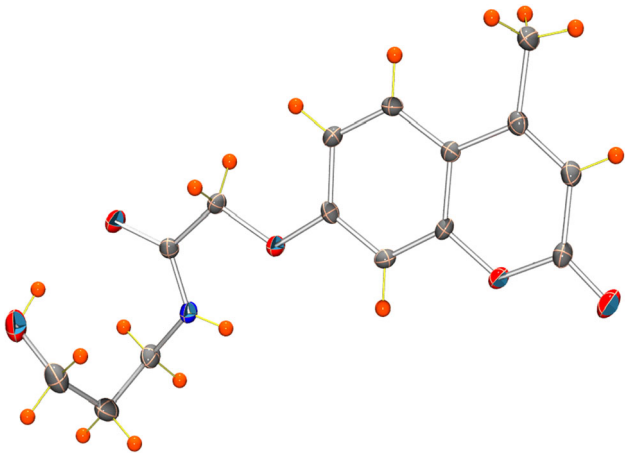


Fig. 1 ORTEP diagram of (7**e**)

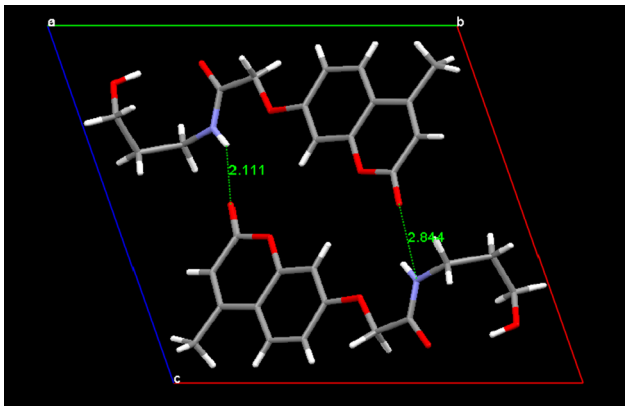


Fig. 2 Packing diagram of (7**e**) viewed along *X*-axis

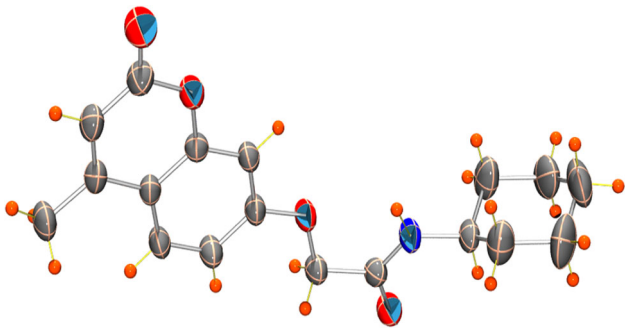


Fig. 3 ORTEP diagram of (7**f**)

MIC values found between 10–1,000 µg/ml. In alicyclic series, **7f** and **7g** showed considerable antimicrobial activity while **7h** and **7i** were poor in activity.

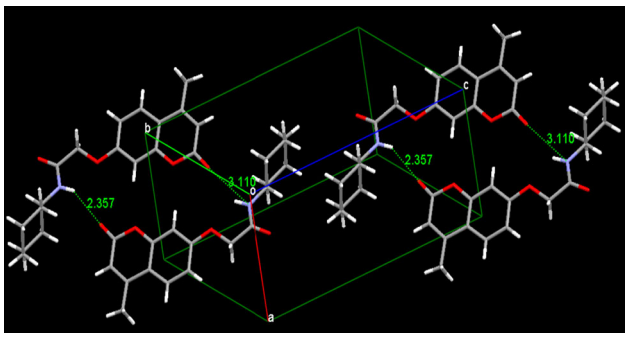


Fig. 4 Packing diagram of (7**f**) viewed along *X*-axis

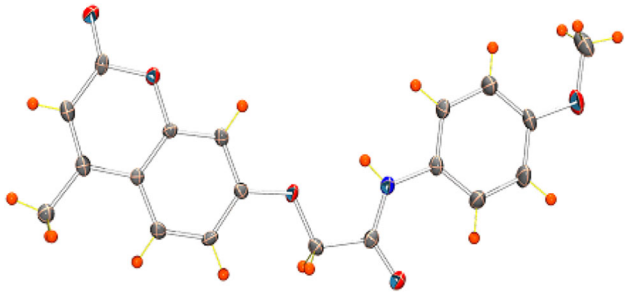


Fig. 5 ORTEP diagram of (7**g**)

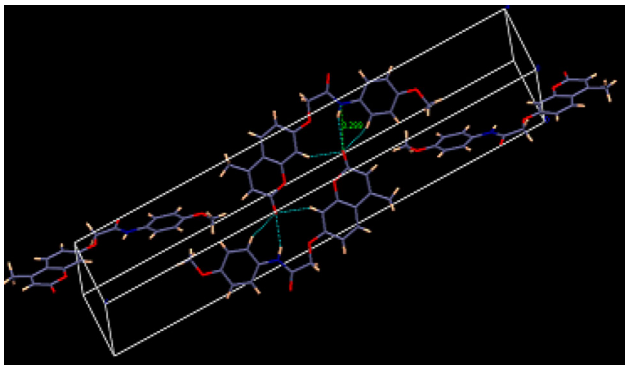


Fig. 6 Packing diagram of (7**g**)

In molecular docking studies on Topo IIA, compounds (**7j–7n**) were docked with high binding affinity comparable to Ciprofloxacin. Binding energies and interactions were demonstrated in Table 3. Binding energy or docked energy was inversely proportional to affinity towards enzyme. Lower binding energy indicated higher binding affinity. Glycine, Serine and Arginine were commonly interacted amino acids of Topo IIA. Among tested compounds, 7k bounds with topo IIA with highest binding energy (−96.1)

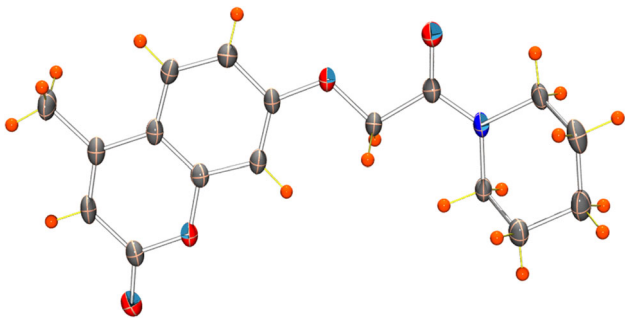


Fig. 7 ORTEP diagram of (7**j**)

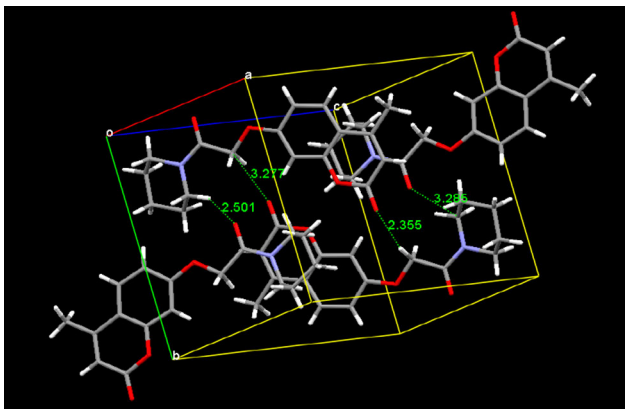


Fig. 8 Packing diagram of (7**j**)

and its binding interactions were shown in Fig. 9. In vitro and In silico studies results are correlated.

Structural antimicrobial activity relationship

In structure antimicrobial activity relationship point of view, aromatic coumarinyloxy amides are potential in antimicrobial activity followed by alicyclic analogues but aliphatic straight chain coumarinyloxy amides showed poor antimicrobial activity. Bioactivity was decreased with the addition of alkyl side chain while increased with addition of methoxy group. In vitro and in silico studies demonstrated that compounds bearing methoxy and hydroxy functional groups on the terminal benzene ring of

Table 1 Crystallographic data information table

Compound	**7e**	**7f**	**7g**	**7j**
Formula	$C_{15}H_{17}NO_5$	$C_{18}H_{21}NO_4$	$C_{17}H_{19}NO_4$	$C_{19}H_{17}NO_5$
Formula weight	291.3	315.4	301.3	339.3
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	*P*-1	$P2_1/n$	P 2_1/c
a (Å)	4.6508 (3)	6.3219 (10)	10.1404 (2)	5.2158 (6)
b (Å)	12.6001 (9)	9.7093 (13)	11.0104 (2)	8.4659 (8)
c (Å)	12.7947 (10)	14.6017 (18)	13.2401 (3)	35.5643 (27)
Volume (Å^3)	702.21 (18)	813.36 (57)	1473.28 (2)	90
α	71.770 (7)	101.296 (11)	90	91.973 (9)
β	80.437 (6)	97.960 (12)	94.703 (2)	90
γ	86.443 (6)	108.589 (13)	90	1569.47 (5)
Z	2	2	4	4
Density (gcm^{-3})	1.38	1.29	1.36	1.44
μ (mm^{-1})	0.104	0.091	0.097	0.105
F (000)	308.0	336.0	639.9	711.9
$h_{min,\ max}$	−5, 5	−8, 8	−12, 12	−6, 6
$k_{min,\ max}$	−16, 16	−12, 12	−14, 14	−10, 9
$l_{min,\ max}$	−16, 16	−18, 18	−16, 16	−42, 42
No. of measured reflections	16,790	19,491	12,751	13,185
No. of unique reflections	3,059	3,540	3,185	2,748
No. of reflections used	2,316	2,305	2,673	1,438
$R_{\_all}$, $R_{\_obs}$	0.063, 0.044	0.083, 0.055	0.048, 0.039	0.140, 0.065
wR_{2_all}, wR_{2_obs}	0.117, 0.106	0.169, 0.147	0.107, 0.102	0.148, 0.115
$\Delta\rho_{min,max}$ (e Å^{-3})	−0.245, 0.271	−0.184, 0.200	−0.195, 0.218	−0.269, 0.312
GOOF	1.079	1.078	1.037	0.961

Table 2 Anti-proliferative studies of synthesized coumarinyloxy acetamide derivatives (7a–7n)

Zone of inhibition (mm)*/MIC(μgml^{-1})							
		Gastrointestinal pathogens			Skin pathogens		
S.No	Compound	*S. typhi*	*V.cholerae*	*S.dysenteriae*	*E. faecalis*	*S.aureus*	*T.rubrum*
1	**7a**	11/100	10/100	11/100	9/1,000	10/1,000	10/1,000
2	**7b**	10/ 1,000	9/1,000	10/>1,000	NA/ >1,000	9/>1,000	10/1,000
3	**7c**	10/100	10/100	09/100	9/1000	10/1,000	11/1,000
4	**7d**	09/100	10/100	11/100	08/100	09/100	11/100
5	**7e**	10/100	11/100	10/100	11/> 1,000	10/1,000	11/1,000
6	**7f**	10/ 1,000	11/1,000	12/1,000	ND	10/1,000	12/100
7	**7g**	14/10	15/10	14/10	13/100	11/1,000	10/1,000
8	**7h**	10/100	10/100	9/100	10/1,000	9/1,000	ND
9	**7i**	9/1,000	09/1,000	10/100	ND	9/>1,000	ND
10	**7j**	13/10	10/100	10/100	10/100	10/100	10/100
11	**7k**	19/10	15/100	13/100	15/10	17/10	14/10
12	**7l**	18/10	21/1	15/10	14/10	17/10	14/10
13	**7m**	14/>10	13/10	14/10	12/10	ND	13/100
14	**7n**	13/>10	11/>10	8/>1,000	ND	11/>100	ND
15	Antibiotic	17/10	19/10	14/10	13/10	16/10	15/10

* 50 μg compound per well. Antibiotic: Ciprofloxacin for bacteria and Griseofulvin for dermatophytic fungi

ND Not Determined

Table 3 Binding energies and interactions of synthesized compounds on Topoisomerase IIA(2XCT)

Compound	Binding energy (−Kcal/mol)	Amino acids involved
7a	**−75.0**	ARG-2207, ARG-2207, GLY-2206, ARG-2210 SER-2648
7b	**−74.3**	ALA-2977, TRP-2981, GLY-2871, ASP-2978 SER-2870
7c	**−71.9**	GLY-2206, SER-2205, ARG-2207, SER-2648 ALA-2311
7d	**−71.2**	PHE-1790, GLY-582, GLY-584, GLU-585 LEU-583
7e	**−71.7**	ASP-2208, ARG-2207, GLY-2206,TRP-2315
7f	**−82.2**	ASP-2645, ARG-2207, SER-2209, GLY-2206 SER-2648
7g	**−75**	PHE-1790, GLY-582, GLU-585, GLY-584 PHE-1790
7h	**−68.2**	TRP-592, SER-445, ARG-447, GLY-446 SER-449
7i	**−71.5**	LYS-1732, ARG-1736, GLY-1076, LYS-1733
7j	**−74.6**	SER-2648, SER-2205, THR-2647, GLY-2206 ARG-2207
7k	**−96.1**	ARG-2207, SER-2648, ASP-2208, GLY-2206 ALA-2311
7l	**−90.2**	ARG-2207, GLY-2206, ASP-2208, SER-2648 ARG-2210
7m	**−77.8**	PHE-1790, GLY-582, LYS-581, GLY-584 GLU-585
7n	**−75.2**	THR-1963, ALA-588, GLY-446, GLU-1962 SER-445
[a]Standard	**−79.7**	GLY-446, ARG-447, TRP-592, ASP-448, THR-1963

[a] Ciprofloxacin for antimicrobial and Camptothecin for anti-cancer was used as standard drugs

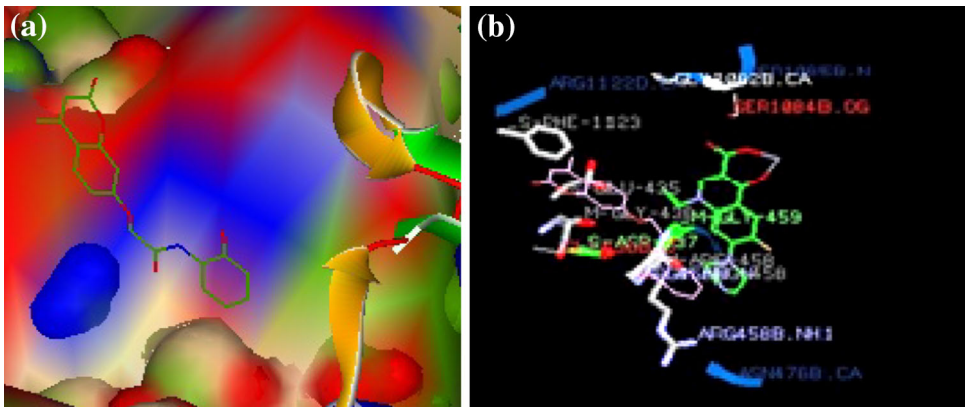


Fig. 9 **a** 7l docked with active site of Topo IIA **b** 7l & Ciprofloxacin comparative interactions with catalytic residues of Topo IIA

coumarinyloxy amides are important for antimicrobial activity.

Conclusions

In summary, the design of coumarinyloxy acetamide derivatives was synthesized in good yields and duly characterised by advanced spectroscopic studies and the XRD studies indicated that no polymorphism was observed in the molecules. The studies on clinical isolates of human pathogenic microorganisms indicated that the synthesized compounds showed observable inhibition and these results were in correlated with the in silico studies. In the antimicrobial studies on isolated pathogens showed that coumarinyloxy acetamide derivatives with phenolic (7l) and trimethoxy (7k) substitutions exhibited noticeable activity than standard.

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