Synthesis and antimicrobial screening of N-[coumarin-6-yl-amino] thiazolidinone and its derivatives

Vinata V. Mulwad* and Abid Ali Mir

Department of Chemistry, The Institute of Science, 15 Madam Cama Road, Mumbai 400 032, India

6-(2-Chloroacetyl)-aminocoumarins **2a–c** were prepared by reacting the 6-aminocoumarins **1a–c** and chloroacetylchloride in dry benzene. Compound **2a–c** on treatment with thiourea yields 6-(2'-amino-1',3'-thiazol-4'-yl)aminocoumarins **3a–c**. Compounds **3a–c** were treated with aromatic aldehydes, resulted in the formation of 6-(arylidenimino-1'-3'-thiazole-4'-yl)aminocoumarin **4a–f**. The arylidenoiminos **4a–f** on cyclisation with chloroacetylchloride/triethylamine and thioglycollic acid gave 6-[2'-(3''-chloro-2''-oxo-4''-phenyl-1''-azetidinyl)-1',3'-thiazole-4'-yl]aminocoumarins **5a–f** and 6-[2'-(2''-phenyl-4''-thiazolidinone-3''-yl)-1', 3''-thiazole-4'-yl]aminocoumarin **6a–f** respectively. Compounds **4a–f** were also treated with aniline and sodium nitrite in the presence of conc. HCl to yield 6-[2'-(1''-phenyl-3''-phenylformazane-4''-yl)-1',3'-thiazole-4'-yl]aminocoumarins **7a–f**. The structure of these compounds have been established on the basis of their analytical and spectroscopic data. All the above compounds were screened for their antimicrobial activity. Some were found to show significant antimicrobial activity.

Keywords: thiazole, Schiffs base, azetidinone, thiazolidinone, biological activity

Coumarins are an important class of heterocyclic compounds which are of synthetic and pharmacological interest because of their various biological activities[1] such as antihelminitic, anti-HIV activity, and anti oxidant activity. There have been a number of studies on the biological activities of coumarin derivatives.[2-8] Several nitrogen mustards synthesised from 6-aminocoumarin are reported as antiviral agents and are especially effective against HIV.[9]

Some thiazole derivatives have proved to be efficacious in combating various diseases, and have good antibacterial and antifungal activities.[10,11] Thiazole analogues incorporated into different skeleta have shown a range of pharmacological profiles such as anticancer,[12] antifungal[13] activities. Substituted derivatives of thiazole,[14-16] azetidinone[17-19] and thiazolidinone[20-23] exhibit potential pesticidal, antimicrobial and antifungal activity.

The biological importance of the above heterocycles led us to introduce a thiazole ring onto the nitrogen atom of 6-aminocoumarin, and from this aminothiazoylcoumarin, heterocycles containing azetidinone and thiazolidinone rings were synthesised with an aim to increasing their biological activity (Scheme 1).

The chloroacetylchloride derivatives of 6-aminocoumarins **1a–c** were obtained by acetylation with chloroacetlychloride to yield compound 6-(2-chloro-acetyl)-aminocoumarin **2a–c**. It showed positive Beilstein and Lassaigne sodium fusion tests, indicating the presence of halogen. The IR spectrum of compound **2c** showed band at 3372 cm^{-1} for –NH stretching, at 1720 cm^{-1} for >C=O stretching, 1685 cm^{-1} for carbonyl group of amide (NH–C=O), along with other bands. The ^1H NMR spectrum of compound **2c** in $CDCl_3$ showed a singlet at δ 4.30 for two protons of a methylene group and a singlet at δ 8.43 for –NH group (D_2O exchangeable). The mass spectrum of compound **2c** showed a molecular ion peak (*m/z*%) at M + at 265 along with M + 2 at 267.

In order to prepare aminothiazole derivatives compounds **2a–c** were treated with thiourea in dry acetone to yield 6-(2'-amino-1', 3'-thiazol-4'-yl) aminocoumarins **3a–c**. These showed negative Beilstein and Lassaigne sodium fusion tests, indicating the absence of halogen. The IR spectrum of compounds **3a–c** in KBr showed peak at 1720 cm^{-1} for a carbonyl stretch. However it did not contain absorption at 1685 cm^{-1} indicating the absence of amidic carbonyl carbon. The ^1H NMR of **3c** showed the presence of signal at δ 7.30 for the proton of thiazole and singlets at δ 9.20 and δ 6.20 for the protons of –NH and $–NH_2$ group respectively. These were exchanged with D_2O. The mass spectrum of **3c** showed M^+ peak at *m/z* 287 and lacked an M + 2 peak indicating the absence of chlorine which was present in compounds **2a–c**.

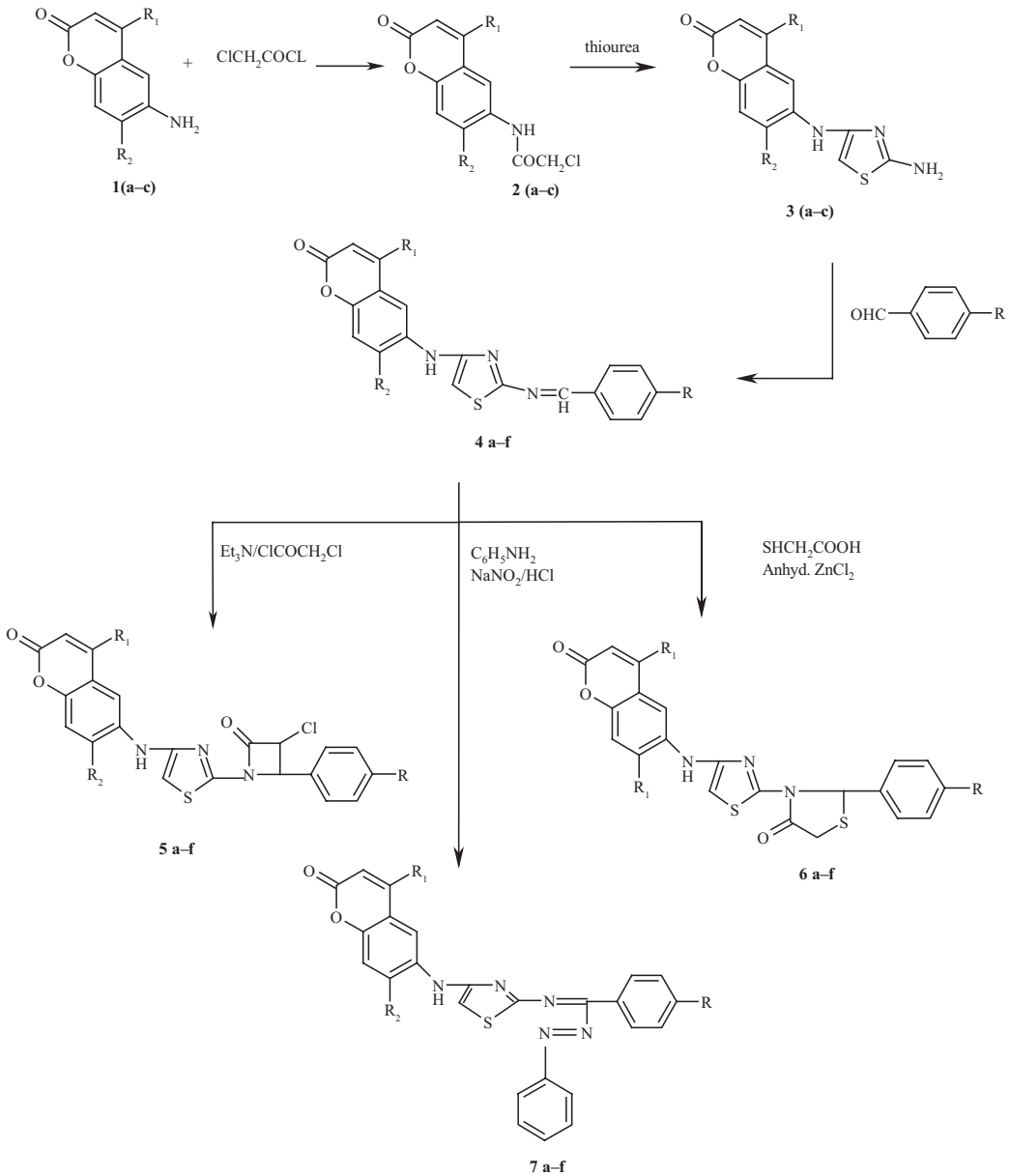
The 6-(2'-amino-1', 3'-thiazol-4'-yl)aminocoumarins **3a–c** were further treated with aromatic aldehydes to yield 6-(2'-substituted arylideneimino-1'-3'-thiazole-4'-yl)aminocoumarins **4a–f**. The IR spectra of **4a–f** in KBr showed absorption between 3300 and 3450 cm^{-1} for the –NH group and at 1725 cm^{-1} for the carbonyl carbon (>C=O). The structures of **4a–f** were in agreement with their analytical and spectroscopic data.

The cyclisation of **4a–f** was carried out with chloroacetyl chloride and thioglycollic acid[24,25] in presence of triethylamine to yield 6-[2'-(3"-chloro-2"-oxo-4"-phenyl-1"-azetidinyl)-1',3'-thiazole-4'-yl]aminocoumarin **5a–f**, and 6-[2'-(2"-phenyl-4"-thiazolidinone-3"-yl)-1',3'-thiazole-4'-yl]aminocoumarin **6a–f** respectively. The IR spectra (KBr) of compounds **5a–f** showed absorption at 3242 cm^{-1} for the –NH group and between 1720 and 1745 cm^{-1} for two carbonyls. In the ^1H NMR, there were two doublets at 3.93 and 5.30 ppm for the NCH–Ar. and CH–Cl respectively. Compound **6c** showed absorption at 3359 cm^{-1} for –NH group in the IR spectrum. The ^1H NMR spectrum contained a singlet at 3.80 for the two protions of CH_2-thiazolidinone group. The compound **4a–f** were also treated with diazotised solution of aniline, in the presence of conc. HCl to yield 6-[2'-(1"-phenyl-3"-phenyl-formazane-4"-yl)-1', 3'-thiazole-4'-yl] aminocoumarins **7a–f.**

Anti-microbial activity

All compounds have been screened for their antimicrobial activity and have found to exhibit significant biological activity (Table 1). The compounds **4a–f**, **5a–f**, and **6a–f** were screened for their antibacterial activity against *Bacillus subtilis, Escherichia coli*. and antifungal activity against *Candida albicans* and *Aspergillus niger* by the cup–plate method at different concentrations (50 and 100 ppm) using DMSO as solvent. The zone of inhibition of the growth was measured in mm. The activity was compared with the standard drugs. A commercial sample of the antibacterial agent streptomycin (50, 100 μg/ml) and the antifungal agent griseofulvin (50, 100 μg/ml) were also tested under similar conditions for comparison. The results of antimicrobial activity of coumarin derivatives (Table 1) show that, compound **5c**, **5f**, **6c** and **6f** with $–CH_3$ substitution at C-4 and C-7 in the coumarin ring have comparable activity at 50 ppm and 100 ppm concentrations. Compounds **5f** and **6f** with $–OCH_3$ group on the phenyl ring show the maximum activity amongst the compounds **4a–f** to **6a–f** which were tested.

* Correspondent. E-mail: vinata_mulwad@hotmail.com



1a: R_1=R_2=H
1b: R_1=H,R_2=CH_3
1c: R_1=R_2=CH_3

2a: R_1=R_2=H
2b: R_1=H,R_2=CH
2c: R_1=R_2=CH_3

3a: R_1=R_2=H
3b: R_1=H,R_2=CH_3
3c: R_1=R_2=CH_3

4a: R_1=R_2=R=H
4b: R_1=H,R_2=CH_3,R=H
4c: R_1=R_2=CH_3,R=H
4d: R_1=R_2=H,R=OCH_3
4e: R_1=H, R_2=CH_3,R=OCH_3
4f: R_1=R_2=CH_3,R=OCH_3

5a: R_1=R_2=H,R=H
5b: R_1=H,R_2=CH_3,R=H
5c: R_1=R_2=CH_3,R=H
5d: R_1=R_2=H,R=OCH_3
5e: R_1=H,R_2=CH_3,R=OCH_3
5f: R_1=R_2=CH_3,R=OCH_3

6a: R_1=R_2=H,R=H
6b: R_1=H,R_2=CH_3,R=H
6c: R_1=R_2=CH_3,R=H
6d: R_1=R_2=H,R=OCH_3
6e: R_1=H,R_2=CH_3,R=OCH_3
6f: R_1=R_2=CH_3,R=OCH_3

7a: R_1=R_2=H,R=H
7b: R_1=H,R_2=CH_3,R=H
7c: R_1=R_2=CH_3,R=H
7d: R_1=R_2=H,R=OCH_3
7e: R_1=H,R_2=CH_3,R=OCH_3
7f: R_1=R_2=CH_3,R=OCH_3

Scheme 1

In conclusion, we have synthesised novel 6-[2'-(3"-chloro-2"-oxo-4"-phenyl-1"-azetidinyl)-1',3'-thiazole-4'-yl] and 6-[2'-(2"-phenyl-4"-thiazolidinone-3"-yl)-1', 3'-thiazole-4'-yl] derivatives of aminocoumarin under milder conditions. The synthetic compounds showed moderate to good antimicrobial activity.

Experimental

All compounds were identified by examination of their spectral data and physical properties. Yields refer to the isolated yields of desired products. Melting points were taken in open capillaries and are uncorrected. Progress of the reaction was monitored on TLC. FT–IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 400 spectrometer using KBr discs. Elemental analyses were carried out in IIT, Mumbai. ^1H NMR spectra were recorded on JEOL NMR AL300 (300 MHz) using TMS as internal standard and mass spectra were recorded on Shimadzu GC-MS QP-2010.

Synthesis of 6-(2-chloroacetyl)-aminocoumarin (**2a–c**): Chloroacetylchloride (0.02 mole) was added to a solution of 6-aminocoumarin (0.02 mole) in dry benzene (60 ml) at 0–5°C

Table 1 Antibacterial and antifungal activities

Compounds	*B. subtilis*		*E. coli*		*C. albicans*		*A. niger*	
	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm
4a	-	+	-	+	-	+	-	+
4b	+	+ +	+	+ +	+	+ +	+	+
4c	+ +	+ +	+	+ +	+	+	+	+
4d	+	+ +	+ +	+ +	+	+ +	+	+ +
4e	+	+ +	+	+ +	+	+	+	+
4f	+	+ +	+	+ +	+	+	+	+
5a	+	+ +	+	+ +	+	+ +	+	+ +
5b	+ +	+ +	+ + +	+ + +	+	+ +	+	+ +
5c	+ +	+ + +	+ +	+ + +	+	+ +	+	+ +
5d	+ +	+ + +	+ +	+ + +	+	+ +	+	+ +
5e	+ +	+ +	+ +	+ +	-	+	+	+ +
5f	+ + +	+ + + +	+ + +	+ + + +	+ +	+ + +	+ +	+ + +
6a	+ +	+ + +	+ +	+ + +	+	+ +	+	+ +
6b	+	+ +	+	+ +	+	+ +	+	+ +
6c	+ +	+ + +	+ +	+ + +	+	+ +	+	+ +
6d	+ +	+ + +	+ +	+ + +	+ +	+ + +	+ +	+ + +
6e	+ +	+ + +	+ +	+ + +	+	+ +	+	+ +
6f	+ + +	+ + + +	+ +	+ + +	+ +	+ + +	+ +	+ + +
Sm	+ + +	+ + + +	+ + +	+ + + +				
Gf					+ + +	+ + + +	+ + +	+ + + +

Sm = Streptomycin, zone of inhibition, diameter in mm: (–) < 8, (+) 8–10, (+ +) 10–16, (+ + +) 16–22, (+ + + +) 22–27.
Gf = Griseofulvin, zone of inhibition, diameter in mm: (–) < 7, (+) 7–10, (+ +) 12–18, (+ + +) 18–22, (+ + + +) 22–28.

under stirring, which was subsequently refluxed for 6 h on water bath. The completion of the reaction was monitored by TLC. The solvent was removed under reduced pressure. The solid obtained was recrystallised by ethyl acetate–hexane to yield compound **2a–c**.

2a: M.p. 170°C, Yield 68%; IR (cm^{-1}) 3370 (–NH), 3050 (arom CH), 1682 (NH–C=O), 1720 (C=O), 689(C–Cl). ^1H NMR ($CDCl_3$): 4.25(s, 2H, CH_2), 6.40(d, 1H, J = 9 Hz, C_3–H), 7.20(d, 1H, J = 9 Hz, C_8–H), 7.25(d, 1H, J = 9 Hz, C_7–H), 7.28(s, 1H, C_5–H), 7.80(d, 1H, J = 9 Hz, C_4–H), 8.35(s, 1H, NH). Anal. Calcd. for $C_{11}H_8O_3NCl$: C, 55.6; H, 3.4, N, 5.9. Found: C, 55.6; H, 3.4; N, 5.9%.

2b: M.p. 185°C, Yield 65%; IR (cm^{-1}) 3373 (–NH), 3052 (arom–CH), 1681 (NH–C=O), 1725 (C=O), 691 (C–Cl). ^1H NMR ($CDCl_3$): 2.47(s, 3H, CH_3), 4.30(s, 2H, CH_2), 6.42(d, 1H, J = 9 Hz, C_3–H), 7.21(s, 1H, C_5–H), 7.25(s, 1H, C_8–H), 7.85(d, 1H, J = 9 Hz, C_4–H), 8.30(s, 1H, NH). Anal. Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.3; H, 4.0; N, 5.9. Found: C, 57.3; H, 4.0; N, 5.8%.

2c: M.p. 210°C, Yield 60%; IR (cm^{-1}) 3372 (–NH), 3045 (arom –CH), 1685 (NH–C=O), 1720 (C=O), 687 (C–Cl). ^1H NMR ($CDCl_3$): 2.45(s, 3H, CH_3), 2.51(s, 3H, CH_3), 4.30(s, 2H, CH_2), 6.21(s, 1H, C_3–H), 7.20(s, 1H, C_8–H), 7.36(s, 1H, C_5–H), 8.43(s, 1H, –NH). MS, *m/z* (%): (M +) 265 (100), (M + 2) 267 (34), 247(15), 216(40), 189(66), 160(44), 77(32). Anal. Calcd. for $C_{13}H_{12}O_3NCl$: C, 58.8; H, 4.55; N, 5.3. Found: C, 58.7; H, 4.5; N, 5.3%.

Synthesis of 6-(2'-amino-1',3'-thiazol-4'-yl) aminocoumarin (**3a–c**): A mixture of **2a–c** (0.02 mole) and thiourea (0.02 mole) in dry acetone (60 ml) was refluxed for 8 h. The excess of acetone was distilled off and the residue obtained was poured into crushed ice, filtered, dried and recrystallised from methanol to give **3a–c**.

3a: M.p. 195–197°C, Yield 55%, IR (cm^{-1}) 3383 (NH), 3047 (arom –CH), 1722 (>C=O), 1155 (C–N), 658. ^1H NMR (DMSO)d_6: 6.15(s, 1H, NH_2), 6.30(d, 1H, J = 8.5 Hz, C_3–H), 7.21(d, 1H, J = 8.5 Hz, C_8–H), 7.25(d, 1H, J = 8.5 Hz, C_7–H), 7.35(s, 1H, CH– thiazole), 7.75(d, 1H, J = 8.5 Hz, C_4–H), 9.21(s, 1H, NH). Anal. Calcd. for $C_{12}H_9O_2N_3S$: C, 55.6; H, 3.5; N, 16.2; S, 12.4. Found: C, 55.5; H, 3.6; N, 16.3; S, 12.4%.

3b: M.p. 210–212°C, Yield 50%, IR (cm^{-1}) 3337 (NH), 3044 (arom –CH), 1721 (>C=O), 655. ^1H NMR (DMSO)d_6: 2.50(s, 3H, CH_3), 6.18(s, 2H, NH_2), 6.38(d, 1H, J = 8.5 Hz, C_3–H), 7.19(s, 1H, C_8–H), 7.32(s, 1H, C_5–H), 7.34(s, 1H, CH–thiazole), 7.78(d, 1H, J = 8.5 Hz, C_4–H), 9.20(s, 1H, NH). Anal. Calcd. for $C_{13}H_{11}O_2N_3S$: C, 57.1; H, 4.1; N, 15.4; S, 11.7. Found: C, 57.0; H, 4.1; N, 15.4; S, 11.8%.

3c: M.p. 230°C, Yield 45%, IR (cm^{-1}) 3381 (NH), 3046 (arom –CH), 1723 (>C=O),1503 (–NH–deformation vib.), 657(C–S–C). ^1H NMR (DMSO)d_6: 2.32(s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.20(s, 1H, NH_2), 6.23(s, 1H, C_3–H), 7.23(s, 1H, C_8–H), 7.30(s, 1H, CH–thiazole), 7.71(s, 1H, C_5–H), 9.20 (s, 1H, NH). MS, *m/z* (%): M^+ 287(100), 263(30), 214(15), 188(50), 160(60), 116(40). Anal. Calcd. for $C_{14}H_{13}O_2N_3S$: C, 58.5; H, 4.6; N, 14.6; S, 11.2. Found: 58.8; H, 4.5; N, 14.6; S, 11.1%.

Synthesis of 6-(arylidenoimino-1'-3'–thiazole-4'-yl) aminocoumarin (**4a–f**): The aromatic aldehyde (0.02 moles) was added to a solution of **3a–c** (0.02 moles) in absolute ethanol (40 ml) and 2–3 drops of acetic acid were also added, the mixture was refluxed for 10 hr. The resulting mixture was cooled, excess alcohol was removed by distillation and the residue obtained was poured into crushed ice. The solid obtained was filtered washed with water, dried and recrystallised from methanol to give **4a–f.**

4a: M.p. 160°C, Yield 62%, IR (cm^{-1}) 3382 (–NH), 3045 (arom –CH), 1720 (>C=O),1600 (C=N). ^1H NMR ($CDCl_3$): 6.40(d, 1H, J = 9 Hz, C_3–H), 7.28(s, 1H, CH–thiazole), 7.32(d, 1H, J = 9 Hz, C_8–H), 7.40(d, 1H, J = 9 Hz, C_7–H), 7.80(m, 6H, arom–H), 7.85(d, 1H, J = 9 Hz, C_4–H), 8.10 (s, 1H, N=CH), 9.10(s, 1H, NH). Anal. Calcd. for $C_{19}H_{13}O_2N_3S$: C, 65.7; H, 3.8; N, 12.1; S, 9.2. Found: C, 65.6; H, 3.8; N, 12.2; S, 9.2%.

4b: M.p. 166°C, Yield 60%, IR (cm^{-1}) 3380 (–NH), 3043 (arom –CH), 1723 (>C=O),1600 (C=N). ^1H NMR ($CDCl_3$): 2.35(s, 3H, CH_3), 6.20(d, 1H, J = 9 Hz, C_3–H), 7.28(s, 1H, CH–thiazole), 7.70(s, 1H, C_8–H), 7.81(m, 6H, arom–H), 7.90(d, 1H, J = 9 Hz, C_4–H), 8.12(s, 1H, N=CH), 9.15(s, 1H, NH). Anal. Calcd. for $C_{20}H_{15}O_2N_3S$: C, 66.5; H, 4.2; N, 11.6; S, 8.9. Found: C, 66.4; H, 4.1; N, 11.6; S, 8.8%.

4c: M.p. 176–78°C, Yield 58%, IR (cm^{-1}), 3385 (NH), 3056 (arom –CH), 1720 (>C=O), 1622 (C=N). ^1H NMR ($CDCl_3$): 2.34 (s, 3H, $–CH_3$), 2.41 (s, 3H, $–CH_3$), 6.21(s, 1H, C_3–H), 7.10 (s, 1H, C_8–H), 7.21(s, 1H, CH–thiazole), 7.80 (s, 1H, C_5–H), 7.85 (m, 5H, arom–H), 8.07 (s,1H, N=CH), 9.10 (s, 1H, NH). MS, *m/z* (%): 375(75), 288(35), 214(30), 189(38), 160(34), 134(100), 115(20). Anal. Calcd. for $C_{21}H_{17}O_2N_3S$: C, 67.2; H, 4.6; N, 11.2; S, 8.5. Found: C, 67.1; H, 4.5; N, 11.1; S, 8.5%.

4d: M.p. 170°C, Yield 55%; IR (cm^{-1}) 3380 (–NH), 3040 (arom –CH), 1720 (>C=O), 1625 (C=N). ^1H NMR ($CDCl_3$): 3.78(s, 3H, OCH_3), 6.32(d, 1H, J = 9.8 Hz, C_3–H), 6.94(d, 2H, J = 7.50, arom–H), 7.23(d, 1H, J = 8.50, C_8–H), 7.26(d, 1H, J = 8.50 Hz, C_7–H), 7.28(s, 1H, CH–thiazole), 7.86(d, 2H, J = 7.50, arom–H), 7.80(s, 1H, C_5–H), 8.01(d, 1H, J = 9.8, C_4–H), 8.10(s, 1H, N=CH), 9.15(s, 1H, NH). Anal. Calcd. for $C_{20}H_{15}O_3N_3S$: C, 63.65; H, 4.0; N, 11.1; S, 8.5. Found: C, 63.6; H, 4.1; N, 11.2; S, 8.6%.

4e: M.p. 183°C, Yield 46% IR (cm^{-1}) 3385 (NH), 3040 (arom –CH), 1720 (>C=O), 1600 (C=N). ^1H NMR ($CDCl_3$): 2.23(s, 3H, CH_3), 3.80(s, 3H, OCH_3), 6.25(d, 1H, J = 9.50 Hz, C_3–H), 7.10(d, 2H, J = 7.50 Hz, arom–H), 7.30(s, 1H, CH–thiazole), 7.65(d, 2H, J = 7.50 Hz, arom–H), 7.33(s, 1H, C_8–H), 7.91(s, 1H, C_5–H), 8.05(d, 1H, J = 9.50 Hz, C_4–H), 8.15(s, 1H, N=CH), 9.15(s, 1H, NH): Anal. Calcd. for $C_{21}H_{17}O_3N_3S$: C, 64.4; H, 4.4; N, 10.7; S, 8.2. Found: C, 64.5; H, 4.3; N, 10.7; S, 8.2%.

4f: M.p. 190°C, Yield 45%, IR (cm^{-1}) 3380 (NH), 3048 (arom –CH), 1723 (>C=O),1600 (C=N). ^1H NMR ($CDCl_3$): 2.30(s, 3H, CH_3), 2.42(s, 3H, CH_3), 3.82(s,3H, OCH_3), 6.21(s, 1H, C_3–H), 6.96(d, 2H, J = 7.50 Hz, arom–H), 7.25(s, 1H, CH–thiazole), 7.55(d, 2H, J = 7.50 Hz arom–H), 7.70(s, 1H, C_8–H), 7.81(s, 1H, C_5–H), 8.15(s,

1H, N=CH), 9.05(s, 1H, NH). Anal. Calcd. for $C_{22}H_{19}O_3N_3S$: C, 65.2; H, 4.7; N, 10.4; S, 7.9. Found: C, 65.1; H, 4.7; N, 10.3; S, 7.9%.

Synthesis of 6-[2'-(3"-chloro-2"-oxo-4"-phenyl-1"-azetidinyl)-1',3'-thiazole-4'-yl]aminocoumarin (**5a–f**): Chloroacetyl chloride (0.01 moles) and triethylamine (0.01 moles) was added dropwise with constant stirring to a solution of **4a–f** (0.01 moles) in 1, 4 dioxane. The reaction mixture was then refluxed on water bath and excess of dioxane was distilled out. The resulting mixture was poured in ice cold water containing HCl, the solid obtained was filtered, dried and recrystallised from ethanol to give **5a–f**.

5a: M.p. 180°C, Yield 55%, IR (cm^{-1}) 3259 (N–H), 3046 (CH–arom), 1744 (C=O), 1721 (C=O), 1610 (C=N), 1493 (C–C arom), 1165 (C–N), 760 (C–Cl), 685. ^1H NMR ($CDCl_3$): 3.90 (d, J = *3.6* Hz, 1H, CH–arom), 5.32 (d, 1H, J = 4.8 Hz**,** CH–Cl), 6.30(d, 1H, J = 9 Hz, C_3–H), 7.31(s, 1H, CH–thiazole), 7.32(d, 1H, J = 9 Hz, C_8–H), 7.40(d, 1H, J = 9 Hz, C_7–H), 7.80(m, 6H, arom–H), 7.96(d, 1H, J = 9 Hz, C_4–H), 9.10(s, 1H, NH) Anal. Calcd. for $C_{21}H_{14}O_3N_3SCl$: C, 59.5; H, 3.3; N, 9.9; S, 7.6. Found: C, 59.5; H, 3.3; N, 9.9; S, 7.5%.

5b: M.p. 188–190°C, Yield 50%, IR (cm^{-1}) 3230 (N–H), 3040(CH–arom), 1738(C=O), 1723(C=O), 1615(C=N), 1500(C–C of aromatic), 1170 (C–N), 765 (C–Cl), 683. ^1H NMR ($CDCl_3$): 2.38(s, 3H, CH_3), 3.91 (d, J = 3.6 Hz,1H, CH–arom), 5.28 (d, 1H, J = 4.8 Hz, CH–Cl), 6.22(d,1H, J = 9 Hz, C_3–H), 7.30(s, 1H, CH–thiazole), 7.70(s, 1H, C_8–H), 7.80–7.85(m, 6H, arom), 8.01(d, 1H, J = 9 Hz, C_4–H), 9.15(s, 1H, NH). Anal. Calcd. for $C_{22}H_{16}O_3N_3SCl$: C, 60.3; H, 3.7; N, 9.6; S, 7.3. Found: C, 60.4; H, 3.6; N, 9.6; S, 7.3%.

5c: M.p. 195°C, Yield 48%, IR (cm^{-1}) 3242 (N–H), 3038 (CH–arom), 1742 (C=O), 1725(C=O), 1618 (C=N), 1486(C–C of arom), 1179 (C–N), 750 (C–Cl), 680. ^1H NMR ($CDCl_3$): 2.26(s, 3H, CH_3), 2.40(s, 3H, CH_3), 3.93 (d, J **=** 3.8 Hz**,** 1H, CH–arom), 5.30 (d, 1H, J = 4.90 Hz**,** CH–Cl), 6.23(s,1H, C_3–H), 7.17(s,1H, CH of thiazole ring), 7.20 (m, 5H, arom–H), 7.31 (s, 1H, C_8–H), 7.36 (s, 1H, C_5–H), 9.80 (s, 1H, –NH). MS, *m/z* (%): M^+ 451(100), M^{+2} 453(70), 240 (15), 160 (50), 134 (65). Anal. Calcd. for $C_{23}H_{18}O_3N_3SCl$: C, 61.1; H, 4.0; N, 9.3; S, 7.1. Found: C, 61.2; H, 4.0; N, 9.3; S, 7.1%.

5d: M.p. 176°C, Yield 50%, IR (cm^{-1}) 3250 (N–H), 3040 (CH–aroma), 1745 (C=O), 1723 (C=O), 1610 (C=N), 1495 (C–C of arom), 1165 (C–N), 765 (C–Cl), 682. ^1H NMR ($CDCl_3$): 3.80(s, 3H, OCH_3), 3.90 (d, J = 3.6 Hz,1H, CH–arom), 5.32 (d, 1H, J = 4.8 Hz, CH–Cl), 6.31(d, 1H, J = 9.80 Hz, C_3–H), 6.92(d, 2H, J = 7.50, arom–H), 7.28(s, 1H, CH–thiazole), 7.54(d, 2H, J = 7.50,arom–H), 7.25(d, 1H, J = 8.50, C_7–H), 7.26(d, 1H, J = 8.50 Hz, C_8–H), 7.80(s, 1H, C_5–H), 8.05(d, 1H, J = 9.80, C_4–H), 9.15(s, 1H, NH). Anal. Calcd. for $C_{22}H_{16}O_4N_3SCl$: C, 59.8; H, 4.2; N, 8.7; S, 6.65. Found: C, 59.9; H, 4.1; N, 8.7; S, 6.7%.

5e: M.p. 183°C Yield 48% IR (cm^{-1}) 3256 (N–H), 3042 (CH–aromatic), 1745 (C=O), 1723 (C=O), 1615 (C=N), 1490 (C–C of arom), 1167 (C–N), 762 cm1(C–Cl), 680. ^1H NMR ($CDCl_3$): 2.21(s, 3H, CH_3), 3.82(s, 3H, OCH_3), 3.89(d, 1H, J = 4.0 Hz, CH–arom.), 5.28(d, 1H, J = 5.50 Hz, CH–Cl), 6.24(d, 1H, J = 9.50 Hz, C_3–H), 7.15(d, 2H, J = 7.50 Hz, arom–H), 7.63(d, 2H, J = 7.50 Hz, arom–H), 7.30(s, 1H, CH–thiazole), 7.33(s, 1H, C_5–H), 7.91(s, 1H, C_8–H), 8.02(d, 1H, J = 9.50 Hz, C_4–H), 9.05(s, 1H, NH): Anal. Calcd. for $C_{23}H_{18}O_4N_3SCl$: C, 59.0; H, 3.9; N, 9.0; S, 6.85. Found: C, 59.0; H, 3.9; N, 9.0; S, 6.9%.

5f: M.p. 190°C, Yield 45%, IR (cm^{-1}) 3260 (N–H), 3050 (CH–arom), 1752 (C=O), 1723 (C=O), 1615 (C=N), 1486 (C–C of arom), 1170 (C–N), 760 (C–Cl). ^1H NMR ($CDCl_3$): 2.28(s, 3H, CH_3), 2.45(s, 3H, CH_3), 3.78(s, 3H, OCH_3), 3.95(d, 1H, J = 4.0 Hz, CH–arom.), 5.25(d, 1H, J = 5.50 Hz, CH–Cl), 6.23(s, 1H, C_3–H), 6.99(d, 2H, J = 7.50 Hz, arom–H), 7.22(s, 1H, CH–thiazole), 7.55(d, 2H, J = 7.50 Hz arom–H), 7.70(s, 1H, C_8–H), 7.81(s, 1H, C_5–H), 9.10(s, 1H, NH). Anal. Calcd. for $C_{24}H_{20}O_4N_3SCl$: C, 59.8; H, 4.2; N, 8.7; S, 6.65. Found: C, 59.8; H, 4.2; N, 8.8; S, 6.6%.

Synthesis of 6-[2'-(2"-phenyl-4"-thiazolidinone-3"-yl)-1', 3'-thiazole-4'-yl]aminocoumarin, (**6a–f**): A mixture of compound **4a–c** (0.01 mole), thioglycollic acid (0.01 mole) and anhydrous zinc chloride (2 grm.) was refluxed in absolute ethanol (40 ml) for 8 h. The excess alcohol was removed by distillation and the residue poured into crushed ice. The solid obtained was filtered washed with water, dried and recrystallised from ethanol to give **6a–f**.

6a: M.p. 189°C, Yield 58%, IR (cm^{-1}) 3259 (N–H), 3045 (CH–arom), 1690 (C=O of thiazolidinones), 1562 (C=N), 1721 (C=O), 1493 (C–C of arom). ^1H NMR ($CDCl_3$): 3.78 (s, 2H, CH_2 of thiazolidinone), 5.91 (s, 1H, thiazoldinone attached to aromatic ring), 6.35(d, 1H, J = 9 Hz, C_3–H), 7.17(s, 1H, CH– thiazole ring), 7.30 (s,1H, C_5–H), 7.32(d, 1H, J = 9 Hz, C_8–H), 7.38(d, 1H, J = 9 Hz, C_7–H), 7.50(m, 5H, arom–H), 7.96(d, 1H, J = 9 Hz, C_4–H), 9.40 (s, 1H, –NH). Anal. Calcd. for $C_{21}H_{15}O_3N_3S_2$: C, 59.8; H, 3.6; N, 10.0; S, 15.2. Found: C, 59.9; H, 3.6; N, 10.0; S, 15.2%.

6b: M.p. 195°C, Yield 55%, IR (cm^{-1}) 3255 (N–H), 3048 (CH–arom), 1685 (C=O of thiazolidinones), 1560 (C=N), 1723 (C=O), 1488 (C–C of arom). ^1H NMR ($CDCl_3$): 2.31(s, 3H, CH_3), 3.82 (s, 2H, CH_2 of thiazolidinone), 5.93 (s, 1H, thiazoldinone attached to aromatic ring), 6.22(d, 1H, J = 9 Hz, C_3–H), 7.17(s, 1H, CH of thiazole ring), 7.30 (s,1H, C_5–H), 7.45 (m, 5H, arom–H), 7.68(s, 1H, C_8–H), 8.02(d, 1H, J = 9 Hz, C_4–H), 9.25 (s, 1H, –NH). Anal. Calcd. for $C_{22}H_{17}O_3N_3S_2$: C, 60.7; H, 4.0; N, 9.65; S, 14.7. Found: C, 60.6; H, 3.9; N, 9.7; S, 14.3%.

6c: M.p. 205°C, Yield 52%, IR (cm^{-1}) 3359 (N–H), 3056 (CH–arom), 1721 cm^{-1} (C=O), 1690 (C=O of thiazolidinones), 1560 (C=N), 1491 (C–C of arom). ^1H NMR ($CDCl_3$): 2.17(s,3H, CH_3), 2.40(s, 3H, CH_3), 3.80 (s, 2H, CH_2 of thiazolidinone), 5.90 (s, 1H, thiazoldinone attached to aromatic ring), 6.23(s, 1H, C_3–H), 7.16 (s, 1H, C_8–H), 7.20(s, 1H, CH of thiazole ring), 7.35 (s,1H, C_5–H), 7.50 (m, 5H, arom–H), 9.50 (s, 1H, –NH). MS, *m/z* (%): M^+ 449(100), 421(30), 372(25), 272(15), 188(50), 160(55). Anal. Calcd. for $C_{23}H_{19}O_3N_3S_2$: C, 61.45; H, 4.3; N, 9.35; S, 14.3. Found: C, 61.5; H, 4.2; N, 9.3; S, 14.3%.

6d: M.p. 199°C, Yield 55%, IR (cm^{-1}) 3250 (N–H), 3043 (CH–arom), 1692 (C=O), 1560 (C=N), 1723 (C=O), 1490 (C–C of arom). ^1H NMR ($CDCl_3$): 3.77(s, 3H, OCH_3), 3.85(s, 2H, CH_2 of thiazolidinone), 5.82 (s, 1H, thiazoldinone attached to aromatic ring),6.30(d, 1H, J = 9.80 Hz, C_3–H), 6.88(d, 2H, J = 7.50, arom–H.), 7.54(d, 2H, J = 7.50, arom–H), 7.20(d, 1H, J = 8.50, C_7–H), 7.25(d, 1H, J = 8.50 Hz, C_8–H), 7.30(s, 1H, CH–thiazole), 7.85(s, 1H, C_5–H), 8.01(d, 1H, J = 9.80, C_4–H), 9.20(s, 1H, NH). Anal. Calcd. for $C_{22}H_{17}O_4N_3S_2$: C, 58.5; H, 3.8; N, 9.3; S, 14.2. Found: C, 58.6; H, 3.8; N, 9.4; S, 14.3%.

6e: M.p. 205–207°C, Yield 52%, IR (cm^{-1}) 3360 (N–H), 3055 (CH–arom), 1721(C=O), 1695 (C=O), 1562 (C=N), 1490 (C–C of arom). ^1H NMR ($CDCl_3$): 2.38(s, 3H, CH_3), 3.79(s, 3H, OCH_3), 3.80(s, 2H, CH_2 of thiazolidinone), 5.88 (s, 1H, thiazoldinone attached to aromatic ring), 6.45(d, 1H, J = 9.50 Hz, C_3–H), 6.96(d, 2H, J = 7.50 Hz, arom.), 7.28(s,1H, CH–thiazole), 7.60(d, 2H, J = 7.50 Hz, arom–H), 7.30 (s, 1H, C_8–H), 7.80(s, 1H, C_5–H), 8.03(d, 1H, J = 9.50 Hz, C_4–H), 9.45(s, 1H, NH) Anal. Calcd. for $C_{23}H_{19}O_4N_3S_2$: C, 59.3; H, 4.1; N, 9.0; S, 13.8. Found: C, 59.4; H, 4.1; N, 9.1; S, 13.8%.

6f: M.p. 210–212°C, Yield 50%, IR (cm^{-1}) 3240 (N–H), 3048 (CH–arom), 1695 (C=O), 1561 (C=N), 1720 (C=O), 1493 (C–C of arom). ^1H NMR ($CDCl_3$): 2.20(s,3H, CH_3), 2.39(s, 3H, CH_3), 3.77(s, 3H, OCH3), 3.85 (s, 2H, CH_2 of thiazolidinone), 5.95 (s, 1H, thiazoldinone attached to aromatic ring), 6.80(d, 2H, J = 7.50 Hz, arom–H.), 6.20(s, 1H, C_3–H), 7.10 (s, 1H, C_8–H), 7.36 (s, 1H, C_5–H), 7.27(s, 1H, CH of thiazole ring), 7.60(d, 2H, J = 7.50 Hz, arom–H.), 9.30 (s, 1H, –NH). Anal. Calcd. for $C_{24}H_{21}O_4N_3S_2$: C, 60.1; H, 4.4; N, 8.8; S, 13.4. Found: C, 60.1; H, 4.5; N, 8.8; S, 13.4%.

Synthesis 6-[2'-(1"-phenyl-3"-phenyl-formazane-4"-yl)-1',3'-thiazole-4'-yl]aminocoumarin, (**7a–f**): Conc. HCl (3 ml) was added to a solution of aniline (0.01 mole) in glacial acetic acid (10 ml), and cooled to 0–5°C. A solution of sodium nitrite (1 g) in water (5 ml) was mixed with above solution. The diazonium salt solution thus prepared was added drop by drop to a solution of compound **4a–f** (0.01 mole) in methanol (40 ml) with constant stirring at°C.The reaction mixture was kept at room temperature overnight and then poured onto ice. The resulting solid was washed with water and purified by recrystallisation to afford **7a–f**.

7a: M.p. 130–32˚C, Yield 55%, IR (cm^{-1}) 3340 (N–H), 3018 (CH–arom), 1720(C=O), 1601 (C=N), 1180 (C–N), 680. ^1H NMR ($CDCl_3$): 6.25 (d, 1H, J = 9.0 Hz, C_3–H), 7.21(d, 1H, J = 8.5 Hz, C_8–H), 7.23(d, 1H, J = 8.5 Hz, C_7–H), 7.80(s, 1H, C_5–H), 7.95(d, 1H, J = 9.0 Hz, C_4–H), 7.25–8.08 (m, 11H, arom), 9.50 (s, 1H, –NH). Anal. Calcd. for $C_{25}H_{17}O_2N_5S$: C, 66.5; H, 3.8; N, 15.5; S, 7.1. Found: C, 66.5; H, 3.8; N, 15.5; S, 7.2%.

7b: M.p. 138°C Yield 52%, IR (cm^{-1}) 3345(N–H), 3028 (CH–arom), 1722 (C=O), 1600 (C=N), 1185 (C–N), 678. ^1H NMR ($CDCl_3$): 2.45(s, 3H, CH_3), 6.21(d, 1H, J = 9.0 Hz C_3–H), 7.85(s, 1H, C_5–H), 7.30–7.80 (m, 12H, arom–H), 7.88(d, 1H, J = 9.0 Hz, C_4–H), 9.35(s, 1H, –NH). Anal. Calcd. for $C_{26}H_{19}O_2N_5S$: C, 67.1; H, 4.1; N, 15.0; S, 6.9. Found: C, 67.0; H, 4.1; N, 15.0; S, 6.9%.

7c: M.p. 150°C Yield 48%, IR (cm^{-1}) 3342 (N–H), 3036 (CH–arom), 1721 (C=O), 1605 (C=N), 1180 (C–N), 680. ^1H NMR ($CDCl_3$): 2.32 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.23 (s, 1H, C_3–H), 7.10(s, 1H, C_8–H), 7.35 (m, 11H, arom–H), 8.05(s, 1H, C_5–H), 9.40

(s, 1H, –NH). MS, *m/z* (%): M^+ 479(100), 402(20), 188(55), 160(60), 77(35). Anal. Calcd. for $C_{27}H_{21}O_2N_5S$: C, 67.6; H, 4.4; N, 14.6; S, 6.7. Found: C, 67.6; H, 4.4; N, 14.6; S, 6.7%.

7d: M.p. 138°C, Yield 50%, IR (cm^{-1}) 3340 (N–H), 3018 (CH–arom), 1721 (C=O), 1601 (C=N), 1180 (C–N), 680. ^1H NMR ($CDCl_3$): 3.79(s, 3H, OCH_3), 6.80(d, 2H, *J* = 7.50, arom–H), 7.64(d, 2H, *J* = 7.50, arom–H), 6.25 (d, 1H, *J* = 9 Hz, C_3–H), 7.25(d, 1H, *J* = 9 Hz, C_8–H), 7.30–7.50 (m, 7H, arom), 7.38(d, 1H, *J* = 9 Hz, C_7–H), 8.02(d, 1H, *J* = 9 Hz, C_4–H), 9.45 (s, 1H, –NH). Anal. Calcd. for $C_{26}H_{19}O_3N_5S$: C, 64.85; H, 3.9; N, 14.5; S, 6.7. Found: C, 64.8; H, 4.0; N, 14.5; S, 6.7%.

7e: M.p. 145°C, Yield 48%, IR (cm^{-1}) 3345 (N–H), 3028 (CH–arom), 1720 (C=O), 1600 (C=N), 1185 (C–N), 680. ^1H NMR ($CDCl_3$): 2.43(s, 3H, CH_3), 3.81(s, 3H, OCH_3), 6.21 (d, 1H, *J* = 9 Hz, C_3–H), 6.75(d, 2H, *J* = 7.50, arom–H), 7.30(d, 2H, *J* = 7.50, arom –H), 7.30–7.80 (m, 8H, arom), 7.85(d, 1H, *J* = 9.0 Hz, C_4–H), 9.35(s, 1H, –NH). Anal. Calcd. for $C_{27}H_{21}O_3N_5S$: C, 65.4; H, 4.3; N, 14.1; S, 6.5. Found: C, 65.4; H, 4.3; N, 14.1; S, 6.5%.

7f: M.p. 155–157°C, Yield 45%, IR (cm^{-1}) 3342 (N–H), 3030 (CH–arom), 1725 (C=O), 1601 (C=N), 1188 (C–N), 690. ^1H NMR ($CDCl_3$): 2.30 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.78(s, 3H, OCH_3), 6.23 (s, 1H, C_3–H), 6.40(d, 2H, *J* = 7.50, arom–H), 7.20–7.65 (m, 8H, arom), 7.40(d, 2H, *J* = 7.50, arom–H), 9.80 (s, 1H, –NH). Anal. Calcd. for $C_{28}H_{23}O_3N_5S$: C, 66.0; H, 4.55; N, 13.7; S, 6.3. Found: C, 66.1; H, 4.6; N, 13.7; S, 6.3%.

Antimicrobial activity

The cup–plate method using Hi–Media agar medium was employed to study the antibacterial activity of compounds **4a–f**, **5a–f** and **6a–f** against *Bacillus subtilis* and *Escherichia coli*. The preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done following the standard procedure.[26] Sample size for all the compounds was fixed at 0.1 ml. Using a sterilised cork borer cups were scooped out of agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 ml) was added in the cups and the petri dishes were subsequently incubated at 37°C for 24 h. Streptomycin were used as reference drugs and DMSO as control. Zones of inhibition produced by each compound was measured in mm, and the results are listed in Table 1.

The antifungal activities of compounds **4a–f**, **5a–f** and **6a–f** were tested against *Candida albicans* and *Aspergillus niger* by the agar diffusion method.[27]

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