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Synthesis and Characterization of Some New Thiazolidinedione Derivatives Containing a Coumarin Moiety for their Antibacterial and Antifungal Activities

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Abstract

Simple coumarins and analogues are large class of compounds that have attracted their interest for a long time due to their biological activities. They have shown to be useful as anti-tumoural, anti-HIV agents and as CNS active compounds. Furthermore, they have been reported to have multiple biological activities (anti-coagulant, anti-inflammatory), although all these properties have not been evaluated systematically. In addition, their enzyme inhibition properties, antimicrobial and antioxidant activities are other foremost topics in this field of research. A new series of thiazolidinedione derivatives were synthesized by reacting with coumarin moiety and studied for their antibacterial and antifungal activities. The synthesis of compounds (**6a-9c**) was achieved through the versatile and efficient synthetic route that involved reaction of thiazolidinedione with appropriately α-bromo ketone or α-bromo oxime derivatives (**2a, 5c**). The structures of these compounds were established by means of IR, ^{1}H-NMR, ^{13}C-NMR Mass and elemental analysis.

Keywords: Antimicrobial; Chemical synthesis; Coumarin; Thiazolidinedione

Introduction

The structural and therapeutic diversity of small heterocyclic molecules coupled with their commercial viability has long fascinated organic and medicinal chemists. Heterocycles containing the coumarin ring system include some novel pharmacologically active compounds such as dicumarol, warfarin and novobiocin (Figure 1). Natural coumarins affect the formation and scavenging of ROS and influence free radical-mediated oxidative damage [1]. Azomethine group (-C=N-)-containing compounds, typically known as Schiff's bases, have been synthesized via condensation of primary amines with active carbonyls. It is well established that the biological activity of hydrazone compounds is associated with the presence of the active (-CO-NHN=C-) pharmacophore and these compounds form a significant category of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antitumoral [2,3], antifungal [4-9], antibacterial [4-11], antimicrobial [12] and anthelmintic uses [13]. Thiazolidine derivatives are reported to show a variety of biological activities. The presence of a thiazolidine ring in penicillin and related derivatives was the first recognition of its occurrence in nature [14]. Thiazolidine-4-one represents a prevalent scaffold in drug discovery [15]. Literature surveys show that thiazolinylhydrazones exhibit antitubercular and antimicrobial activities [16], and their pronounced antioxidant [17] and antifungal [18] activity has also been reported.

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widespread in nature as physiologically active constituents of plants [19-21]. In addition, coumarin derivatives have a broad range of applications in the pharmaceutical, perfume, and cosmetic industries. The diverse biological activities of coumarins is well known as anticoagulants, antithrombotics, antimicrobial, antibacterial activities, anticancer and anti-HIV activity [22-28]. Thus, coumarins containing a Schiff's base and a thiazolidinone moiety are expected to have enhanced biological activities.

Materials and Methods

Chemistry

Chemical reagents and all solvents used in this research were bought from Merck AG (Darmstadt, Germany). Melting points were determined in open glass capillaries using Bibby Stuart Scientific SMP_3 apparatus (Bibby Sterlin Ltd, U.K.) and are uncorrected. The FT-IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks; Shimadzu, Tokyo, Japan). Mass spectra were also recorded with an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmigton, USA). ^{1}H-NMR spectra were recorded using a Bruker 500 spectrometer and ^{13}C- NMR spectra were recorded using a Bruker 300 spectrometer (Bruker Bioscience, Billerica, MA, USA), and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. Merck silica gel 60 F_{254} plates were used for analytical TLC (Merck).

Experimental

The synthesis of final compounds was obtained via the useful and effective synthetic route indicated in Scheme 1. The starting with 2-hydroxy/ 2-hydroxy-3-methoxy/ 5-boromo-2-hydroxybenzaldehyd and ethylacetoacetate in methanol in the presence of piperidine to give 3-acetyl coumarin, 3-acetyl (5-bromocoumarin) and 3-acetyl (8-methoxy coumarin). Compounds 3-acetyl coumarin, 3-acetyl (5-bromocoumarin) and 3-acetyl (8-methoxy coumarin) were converted to α-bromo intermediate by refluxing with Br_2 in CH_2Cl_2

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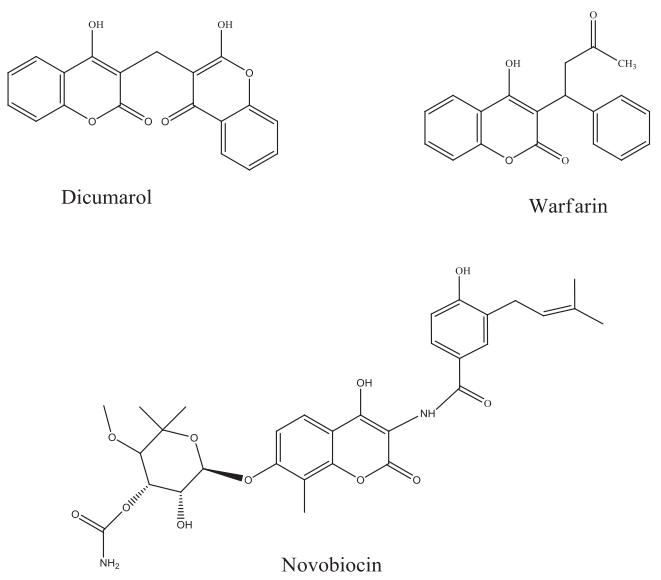


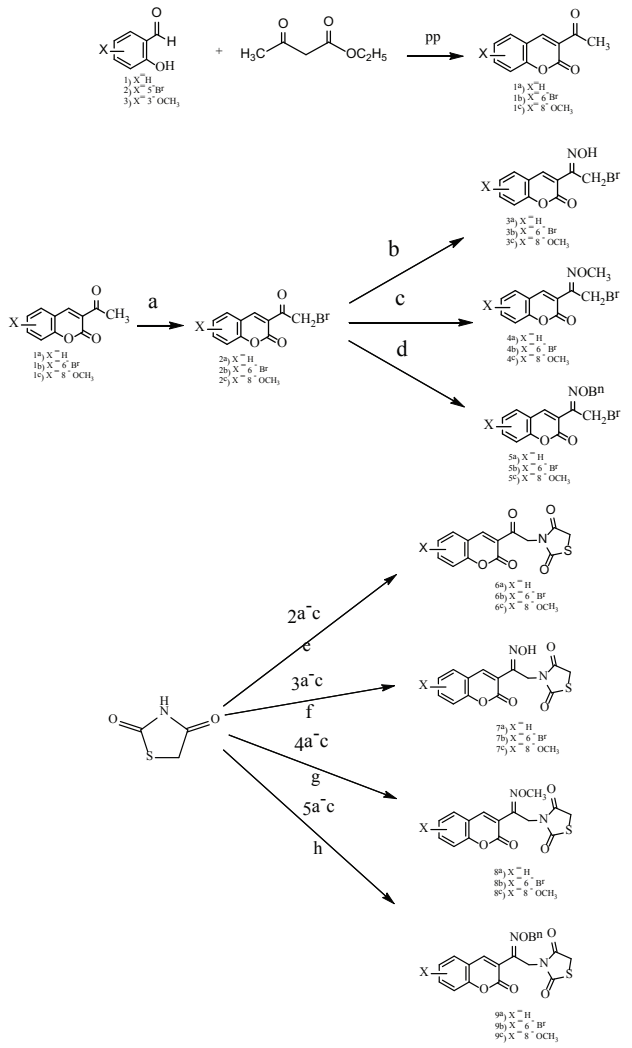
Figure 1: Heterocycles containing the coumarin ring system.

[29]. α-bromoketones were converted to α-bromo oxioms by stirring with hydroxyl amine hydrochloride, methoxy amine hydrochloride and *O*-benzyl hydroxylamine hydrochloride in methanol at 22-25°C [29,30]. The final compounds consist of intermediate synthesized reaction with thiazolidinedione in EtOH, in the presence of KOH at 0°C afforded corresponding ketones and oxime derivatives (**6a-9c**), respectively (Table 1).

2, 4 thiazolidinedione ($C_3H_3NO_2S$): In a 250 ml three-necked round-bottomed flask, was placed, solution containing (56.4 g 0.6 mol) of chloracetic acid in 60 ml of water and (45.6 g, 0.6 mol) of thiourea dissolved in 60 ml of water. The mixture was stirred for 15 min. to form a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 ml of concentrated HCl from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 h at 100-110°C. On cooling the contents of the flask solidified to a cluster of white needles (Scheme 2). The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallization from ethyl alcohol. Yield: (88%); M.p: (122-124)°C.

3-acetyl-2H-chromen-2-one (1a, $C_{11}H_8O_3$): (596 mg, 3.8mmol) 2-hydroxybenzaldehyd and ethylacetoacetate (464 mg, 3.8mmol) in (14 ml) methanol in the presence of piperidine was stirred at 0-4°C for 4h. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**1a**)(869 mg). Yellow solid; M.p:(188-189)°C, yield=(82%); IR (KBr, cm^{-1}): 1734, 1630, 1601, 1572, 1459, 1434, 1363, 1282, 1128, 1094, 1043, 949, 886, 765; ^{1}H-NMR (500 MHz, DMSO-d6): δ=2.44 (s, 3H, CH_3coumarin), δ=4.45 (s, 2H,CH_2-Br), 7.42 (dt, 1H, H-6 coumarin, J=7.87 and 0.84 Hz), 7.51 (d, 1H, H-8 coumarin, J=6.91 Hz), 7.72 (dt, 1H, H-7coumarin, J=8.64 and 1.53 Hz), 7.92 (dd, 1H, H-5 coumarin, J=7.67 and 1.39 Hz), 8.41 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=32.4, 120.3, 121.8, 127.9, 131.8, 133.2, 136.2, 140.8, 157.5, 164.9, 198.1 ppm; MS (70eV) *m/z*:[M$^+$], 188 (100%); Anal. Calcd for $C_{11}H_8O_3$ 188.1794, Found 188.1785.

3-acetyl-6-bromo-2H-chromen-2-one (1b, $C_{11}H_7BrO_3$): (585 mg, 2.9mmol) 5-bromo-2-hydroxybenzaldehyd and ethylacetoacetate (378 mg, 2.9mmol) in (14 ml) methanol in the presence of piperidine was

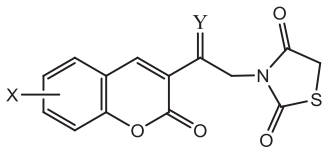


Reagents and conditions: (a) Br_2, CH_2Cl_2, 22-25°C, and then reflux; (b) hydroxylamine hydrochloride, MeOH, 22-25°C; (c) methoxy amine hydrochloride, MeOH, 22-25°C; (d) *O*-benzyl hydroxylamine hydrochloride, MeOH, 22-25°C; (e), (f), (g), (h) EtOH, KOH, 0°C.

Scheme 1: Synthesis route of compounds 6a-9c.

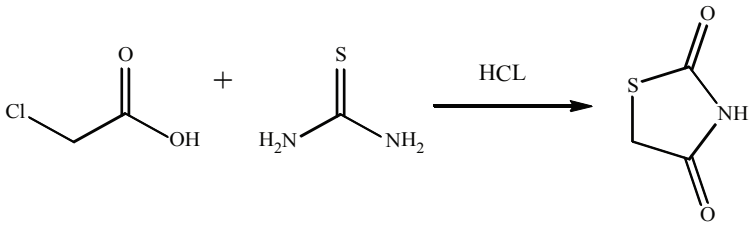
stirred at 0-4°C for 4h. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**1b**) (809 mg). Yellow solid; M.p: (225-227)°C, yield=(84%); IR (KBr, cm^{-1}): 1744, 1633, 1610, 1574, 1455, 1437, 1369, 1288, 1131, 1090, 1049, 941, 888, 671; ^{1}H-NMR (500 MHz, DMSO-d6): δ=2.41 (s, 3H, CH_3coumarin), δ=7.20-7.61 (m, 2H, H-7- H-8 coumarin), δ=7.66 (d, 1H, H-5 coumarin, J=8.85), δ=8.52 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=31.9, 120.5, 122.8, 126.6, 134.2, 136.1, 139.8, 141.4, 155.2, 164.5, 197.9 ppm; MS (70eV) *m/z*: [M$^+$],265 (100%), [M$^+$+2], 267(15%), [M$^+$+4], 269 (2%); Anal. Calcd for$C_{11}H_7{}^{79}BrO_3$ 267.0755, Found 267.0750.

3-acetyl-8-methoxy-2H-chromen-2-one (1c, $C_{12}H_{10}O_4$): (400 mg, 2.6 mmol) 2-hydroxy-3-methoxybenzaldehyd and ethylacetoacetate (335 mg, 2.6 mmol) in (14 ml) methanol in the presence of piperidine was stirred at 0-4°C for 4h. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**1c**) (605 mg). Yellow solid; M.p:(168-169)°C, yield=(78%); IR(KBr, cm^{-1}): 1738, 1641,1616, 1569, 1466, 1422, 1371, 1277, 1166, 1100, 1044, 943, 890, 766; ^{1}H-NMR (500 MHz, DMSO-d6): δ=2.46 (s, 3H, CH_3coumarin), δ=4.04 (s, 3H,



Compound	X	Y	Mp (°C)	Reaction time (h)	Yield (%)	Formula	M.W
6a	H	O	161-163	24	71	$C_{14}H_9NO_5S$	303.29
6b	6-Br	O	171-173	24	66	$C_{14}H_8BrNO_5S$	382.19
6c	8-OMe	O	165-167	24	68	$C_{15}H_{11}NO_6S$	333.32
7a	H	NOH	148-151	24	57	$C_{14}H_{10}N_2O_5S$	318.30
7b	6-Br	NOH	177-179	24	58	$C_{14}H_9BrN_2O_5S$	397.20
7c	8-OMe	NOH	153-155	24	59	$C_{15}H_{12}N_2O_6S$	348.33
8a	H	NOMe	157-159	24	58	$C_{15}H_{12}N_2O_5S$	332.33
8b	6-Br	NOMe	178-180	24	60	$C_{15}H_{11}BrN_2O_5S$	411.23
8c	8-OMe	NOMe	162-164	24	62	$C_{16}H_{14}N_2O_6S$	362.06
9a	H	NOBn	183-185	24	56	$C_{21}H_{16}N_2O_5S$	408.43
9b	6-Br	NOBn	190-192	24	55	$C_{21}H_{15}BrN_2O_5S$	487.32
9c	8-OMe	NOBn	186-188	24	54	$C_{22}H_{18}N_2O_6S$	438.45

Table 1: Structures and physicochemical data of compounds 6a-9c.



Scheme 2: Synthesis of 2, 4-thiazolidinedione.

O-CH_3coumarin), 7.39 (dt, 1H, H-6 coumarin, J=7.85 and 0.81 Hz), 7.79 (dt, 1H, H-7coumarin, J=8.70 and 1.53 Hz), 7.95 (dd, 1H, H-5 coumarin, J=7.68 and 1.40 Hz), 8.48 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=32.1, 57.4, 122.1, 124.2, 127.7, 132.6, 134.6, 140.9, 144.5, 152.4, 164.5, 198.1 ppm; MS (70eV) *m/z*: [M^+],218 (100%); Anal. Calcd for $C_{12}H_{10}O_4$ 218.2054, Found 218.2056.

3-(2-bromoacetyl)-2H-chromen-2-one (2a, $C_{11}H_7BrO_3$): To a solution of (**1a**) (500 mg, 2.7mmol) was added Br_2 (430 mg, 2.7mmol) in dichloromethane a dropwise. The completion of the reaction was monitored by TLC. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**2a**) (680 mg). Yellow crystal; M.p: (148-150)°C, yield=(82%); IR (KBr, cm^{-1}): 1733, 1630, 1600, 1562, 1452, 1434, 1366, 1277, 1163, 1094, 1043, 1001, 886, 765; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.57 (s, 2H,CH_2-Br), δ=7.33-7.76 (m, 3H, H-6 and H-7 and H-8 coumarin), δ=7.84 (d, 1H, H-5 coumarin, J=8.70 Hz), δ=8.48 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=35.8, 120.8, 121.9, 128.7, 131.5, 134.8, 136.2, 139.8, 156.2, 166.6, 197.7 ppm; MS (70eV) *m/z*: [M^+],265 (100%), [M^++2], 267(20%), [M^+ +4], 269 (1.6%); Anal. Calcd for $C_{11}H_7{}^{79}BrO_3$ 267.0755, Found 267.0752.

6-bromo-3-(2-bromoacetyl)-2H-chromen-2-one (2b, $C_{11}H_6Br_2O_3$): To a solution of (**1b**) (500 mg, 1.8mmol) was added Br_2 (287 mg, 1.8mmol) in dichloromethane a dropwise. The completion of the reaction was monitored by TLC. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**2b**) (685 mg). Yellow crystal; M.p: (235-237)°C, yield=(87%);IR (KBr, cm^{-1}): 1731, 1636,1596, 1571, 1449, 1429, 1371, 1276, 1158, 1105, 1050, 1011, 880,669; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.47 (s, 2H,CH_2-Br), δ=7.42-7.52 (m, 2H, H-7 and H-8 coumarin), δ=7.60 (d, 1H, H-5 coumarin, J=8.81), δ=8.48(s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=35.9, 120.7, 121.6, 126.3, 133.8, 135.7, 136.8, 140.9, 154.8, 164.8, 198.1 ppm; MS (70eV) *m/z*: [M^+],345 (100%), [M^++2], 347(25%), [M^+ +4], 349 (2%); Anal. Calcd for $C_{11}H_6{}^{79}Br_2O_3$ 345.9715, Found 345.9710.

3-(2-bromoacetyl)-8-methoxy-2H-chromen-2-one (2c, $C_{12}H_9BrO_4$): To a solution of (**1c**) (500 mg, 2.3 mmol) was added Br_2 (366 mg, 2.3 mmol) in dichloromethane a dropwise. The completion of the reaction was monitored by TLC. The precipitated yellow solid was filtered off, washed with cold methanol, and dried to give (**2c**) (702 mg). Yellow crystal; M.p: (178-179)°C, yield=(81%) ; IR (KBr, cm^{-1}): 1720, 1644, 1612, 1555, 1460, 1444, 1370, 1282, 1166, 1099, 1047, 1012, 890, 673; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.08 (s, 3H, O-CH_3coumarin), δ=4.51 (s, 2H,CH_2-Br), δ=7.18-7.71 (m, 2H, H-6 and H-7 coumarin), δ=7.75 (d, 1H, H-5 coumarin, J=8.66 Hz), δ=8.47 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.5, 57.3, 121.5, 122.7, 128.3, 131.8, 135.1, 142.4, 145.6, 152.5, 162.6, 198.7 ppm; MS (70eV) *m/z*: [M^+],295 (100%), [M^++2], 297(30%), [M^+ +4], 299 (5%); Anal. Calcd for $C_{12}H_9{}^{79}BrO_4$ 297.1015, Found 297.1006.

3-(2-bromo-1-(hydroxyimino)ethyl)-2H-chromen-2-one (3a, $C_{11}H_8BrNO_3$): A solution of (**2a**) (267 mg, 1.0 mmol) and hydroxylamine hydrochloride (209 mg, 3.0 mmol) in methanol (10 ml) was stirred at 22-25°C for 24 h. Then, water (25 ml) was added and the precipitate was filtered and washed with water to give compound (**3a**) (376 mg). White powder; M.p: (185-187)°C, yield=(79%); IR (KBr, cm^{-1}): 1737, 1674, 1609, 1566, 1449, 1440, 1360, 1280, 1166, 1101, 1046, 1010, 888, 761; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.42 (s, 2H,CH_2-Br), 7.46 (dt, 1H, H-6 coumarin, J=7.87 and 0.84 Hz), 7.51 (d, 1H, H-8 coumarin, J=6.91 Hz), 7.72 (dt, 1H, H-7coumarin, J=8.64 and 1.53 Hz), 7.90 (dd, 1H, H-5 coumarin, J=7.67 and 1.39 Hz), 8.28 (s, 1H, H-4 coumarin), 12.41 (s, 1H,oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6):

δ=35.7, 120.9, 123.3, 127.6, 130.2, 134.8, 136.4, 140.9, 155.5, 163.8, 198.3 ppm; MS (70eV) *m/z*: [M+], 280 (100%), [M+2], 282(35%), [M+ +4], 284 (10%); Anal. Calcd for $C_{11}H_8{}^{79}BrNO_3$ 282.0901, Found 282.0905.

6-bromo-3-(2-bromo-1-(hydroxyimino)ethyl)-2H-chromen-2-one (3b, $C_{11}H_7Br_2NO_3$): A solution of (**2b**) (346 mg, 1.0 mmol) and hydroxylamine hydrochloride (209 mg, 3.0 mmol) in methanol (10 ml) was stirred at 22-25°C for 24 h. Then, water (25 ml) was added and the precipitate was filtered and washed with water to give compound (**3b**) (259 mg). White powder; M.p: (173-175)°C, yield=(75%); IR (KBr, cm^{-1}): 1728, 1635, 1609, 1560, 1459, 1430, 1360, 1279, 1174, 1092, 1048, 994, 892, 670; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.22 (s, 2H,CH_2-Br), δ=7.20 -7.57 (m, 2H, H-7 and H-8 coumarin), δ=7.64 (d, 1H, H-5 coumarin,J=8.78), δ=8.22 (s, 1H, H-4 coumarin), δ=12.48(s, 1H, oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.8, 121.1, 123.9, 126.4, 134.5, 136.2, 137.7, 139.8, 155.6, 164.6, 198.9 ppm; MS (70eV) *m/z*: [M+], 360 (100%), [M+2], 362(15%), [M+ +4], 364 (2%); Anal. Calcd for $C_{11}H_7{}^{79}Br_2NO_3$ 360.9862, Found 360.9855.

3-(2-bromo-1-(hydroxyimino)ethyl)-8-methoxy-2H-chromen-2-one (3c, $C_{12}H_{10}BrNO_4$): A solution of (**2c**) (297 mg, 1.0 mmol) and hydroxylamine hydrochloride (209 mg, 3.0 mmol) in methanol (10 ml) was stirred at 22-25°C for 24 h. Then, water (25 ml) was added and the precipitate was filtered and washed with water to give compound (**3c**) (389 mg). White powder; M.p: (165-167)°C, yield=(77%); IR (KBr, cm^{-1}): 1730,1723, 1677, 1615, 1444, 1361, 1258, 1171, 1025, 955, 835, 760; ^{1}H-NMR (500 MHz, DMSOd6): δ=4.06 (s, 3H,O-CH_3coumarin), δ=4.41 (s, 2H, CH_2-Br), 7.51 (dt, 1H, H-6 coumarin, J=7.91 and 0.88 Hz), 7.72 (dt, 1H, H-7coumarin, J=8.68 and 1.56 Hz), 7.93 (dd, 1H, H-5 coumarin, J=7.71 and 1.38 Hz), 8.33 (s, 1H, H-4 coumarin), 12.39 (s, 1H,oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.1, 57.6, 121.1, 123.9, 126.4, 130.5, 134.7, 141.1, 145.5, 152.6, 163.6, 197.8 ppm; MS (70eV) *m/z*: [M+], 310 (100%), [M+2], 312(20%), [M+ +4], 314 (1.6%); Anal. Calcd for $C_{12}H_{10}{}^{79}BrNO_4$ 312.1161, Found 312.1164.

3-(2-bromo-1-(methoxyimino)ethyl)-2H-chromen-2-one (4a, $C_{12}H_{10}BrNO_3$): To a stirred solution of (**2a**) (267 mg, 1.0 mmol) in MeOH (16 ml) at 22-25°C, was added 25% solution of *O*-methyl hydroxyl ammonium chloride in diluted HCl (1002 mg, 3.0 mmol). After 24 h stirring at 22-25°C, the precipitated white solid was filtered off, washed with cold methanol, and dried to give (**4a**) (977 mg). White powder; M.p: (151-153)°C, yield=(77%); IR (KBr, cm^{-1}): 1729, 1669, 1611, 1558, 1455, 1429, 1365, 1284, 1111, 1099, 1041, 995, 894, 769; ^{1}H-NMR (500 MHz, DMSO-d6): δ4.12 (s, 3H, O-CH3oxime), 4.51 (s, 2H,CH_2-Br), 7.38 (t, 1H, H-6 coumarin, J=7.39 Hz), 7.48 (d, 1H, H-8coumarin, J=8.67 Hz), 7.62-7.89 (m, 2H, H-5 and H-7 coumarin), 8.15(s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=35.4, 64.8, 120.6, 123.8, 128.3, 131.9, 134.2, 136.1, 143.1, 157.1, 165.4, 198.1 ppm; MS (70eV) *m/z*: [M+],294 (100%), [M+2], 296(35%), [M+ +4], 298 (10%); Anal. Calcd for $C_{12}H_{10}{}^{79}BrNO_3$ 296.1167, Found 296.1163.

6-bromo-3-(2-bromo-1-(methoxyimino)ethyl)-2H-chromen-2-one (4b, $C_{12}H_9Br_2NO_3$): To a stirred solution of (**2b**) (346 mg, 1.0 mmol) in MeOH (16 ml) at 22-25°C, was added 25% solution of *O*-methyl hydroxyl ammonium chloride in diluted HCl (1002 mg, 3.0 mmol). After 24 h stirring at 22-25°C, the precipitated white solid was filtered off, washed with cold methanol, and dried to give (**4b**) (996 mg). M.p: (158-160)°C, yield=(74%); IR (KBr, cm^{-1}): 1731, 1641, 1612, 1570, 1447, 1439, 1364, 1276, 1156, 1088, 1056, 1014, 896, 663; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.11 (s, 3H, O-CH_3oxime), δ=4.24 (s, 2H,CH_2-Br), δ=7.01-7.50 (m, 2H, H-7 and H-8 coumarin), δ=8.33 (d, 1H, H-5 coumarin,J=8.75), δ=8.29 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.4, 64.8, 119.9 122.6, 127.6, 130.6, 132.6, 136.1, 139.8, 156.8, 163.8, 198.3 ppm; MS (70eV) *m/z*: [M+], 374 (100%), [M+2], 376(18%), [M+ +4], 378 (2.5%); Anal. Calcd for $C_{12}H_9{}^{79}Br_2NO_3$ 375.0128, Found 375.0118.

3-(2-bromo-1-(methoxyimino)ethyl)-8-methoxy-2H-chromen-2-one (4c, $C_{13}H_{12}BrNO_4$): To a stirred solution of (**2c**) (297 mg, 1.0 mmol) in MeOH (16 ml) at 22-25°C, was added 25% solution of *O*-methyl hydroxyl ammonium chloride in diluted HCl (1002 mg, 3.0 mmol). After 24 h stirring at 22-25°C, the precipitated white solid was filtered off, washed with cold methanol, and dried to give (**4c**)(987 mg). White powder; M.p: (141-143)°C, yield=(76%); IR (KBr, cm^{-1}): 1726, 1636, 1601, 1576, 1461, 1429, 1368, 1251, 1123, 1097, 1053, 1014, 891, 761; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.06(s, 3H, O-CH_3coumarin), δ=4.25 (s, 2H,CH_2-Br), δ=4.15 (s, 3H, O-CH_3oxime), 7.41 (t, 1H, H-6 coumarin, J=7.42 Hz), 7.62-7.89 (m, 2H, H-5 and H-7 coumarin), 8.18(s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.3, 57.4, 65.5, 121.8, 122.7, 127.8, 131.7, 134.9, 141.7, 144.8, 152.4, 164.8, 198.1 ppm; MS (70eV) *m/z*: [M+], 324 (100%), [M+2], 326(25%), [M+ +4], 328 (2%); Anal. Calcd for $C_{13}H_{12}{}^{79}BrNO_4$ 326.1427, Found 326.1421.

3-(1-(benzyloxyimino)-2-bromoethyl)-2H-chromen-2-one (5a, $C_{18}H_{14}BrNO_3$): A solution of (**2a**) (267 mg, 1.0 mmol) and *O*-benzyl hydroxylaminehydrochloride (479 mg, 3.0 mmol) in methanol (16 mL) was stirred at 22-25°C overnight. The resulting suspension wascooled 0-4°C and the precipitated white solid was filtered off, washed with cold methanol, and dried to give (**5a**) (552 mg). White powder; M.p: (101-103)°C, yield=(74%); IR (KBr, cm^{-1}): 1711, 1617, 1600, 1459, 1370, 1241, 1172, 1101, 1061, 891, 755, 741; 1H-NMR (500 MHz, DMSO-d6) 4.47 (s, 2H, CH_2-Br), 5.29 (s, 2H, O-CH_2-Ph), 7.10-7.55 (m, 7H, H-6 coumarin, H-8 coumarin and phenyl), 7.61-7.86 (m, 2H, H-5 and H-7 coumarin), 8.01 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.6, 80.4, 122.8, 122.3, 126.1, 128.2, 129.8(2C), 130.2, 131.9(2C), 133.1, 134.6, 138.9, 143.4, 155.1, 163.2, 184.1 ppm; MS (70eV) *m/z*: [M+], 371 (100%), [M+2], 373(15%), [M+ +4], 375 (2%); Anal. Calcd for $C_{18}H_{14}{}^{79}BrNO_3$ 372.2127, Found 372.2121.

3-(1-(benzyloxyimino)-2-bromoethyl)-6-bromo-2H-chromen-2-one (5b, $C_{18}H_{13}Br_2NO_3$): A solution of (**2b**) (346 g, 1.0 mmol) and *O*-benzyl hydroxyl amine hydrochloride (0.479 g, 3.0 mmol) in methanol (16 ml) was stirred at 22-25°C overnight. The resulting suspension was cooled 0-4°C and the precipitated white solid was filtered off, washed with cold methanol, and dried to give 544 mg (**5b**). White powder; M.p: (105-107)°C, yield=(66%); IR (KBr,cm^{-1}): 1719, 1625, 1616, 1456, 1369, 1245, 1171, 1105, 1049, 888, 776, 733; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.51 (s, 2H, CH_2-Br), δ=5.39 (s, 2H, O-CH_2-Ph), δ=7.35 -7.57 (m, 7H, H7,H8coumarin and phenyl), δ=7.71 (d, 1H, H5coumarin, J=8.71), δ=8.11 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=36.9, 79.1, 122.2, 128.4, 129.7(2C), 130.8, 132.3(2C), 134.2, 135.8, 137.2, 141.5, 146.3, 153.8, 165.1, 171.9, 183.8 ppm; MS (70eV) *m/z*: [M+], 450 (100%), [M+2], 452(15%), [M+ +4], 454 (2%); Anal. Calcd for $C_{18}H_{13}{}^{79}Br_2NO_3$ 451.1087, Found 451.1081.

3-(1-(benzyloxyimino)-2-bromoethyl)-8-methoxy-2H-chromen-2-one (5c, $C_{19}H_{16}BrNO_4$): A solution of (**2c**) (297mg, 1.0 mmol) and *O*-benzyl hydroxyl amine hydrochloride (0.479 g, 3.0 mmol) in methanol (16 ml) was stirred at 22-25°C overnight. The resulting suspension was cooled 0-4°C and the precipitated white solid was filtered off, washed with cold methanol, and dried to give 527 mg (**5c**). White powder; M.p: (105-107)°C, yield=(68%); IR (KBr,cm^{-1}): 1715, 1621, 1607, 1450, 1362, 1239, 1165, 1094, 1051, 881, 765,

734^{1}H-NMR(500 MHz, DMSO-d6): δ=3.76 (s, 3H, O-CH_3coumarin), δ=4.44 (s, 2H, CH_2-Br), δ=5.36 (s, 2H, O-CH_2-Ph), δ=7.35 -7.55 (m, 7H, H-6,H7, coumarin and phenyl), δ=7.81 (d, 1H, H5-coumarin. J=7.72), δ=8.00 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=37.2, 57.8, 79.9 122.5, 125.7, 127.6, 128.7(2C), 130.9, 133.5(2C), 134.8, 136.4, 138.9, 145.1, 153.2, 163.4, 172.8, 183.1 ppm; MS (70eV) *m/z*: [M$^+$], 401 (100%), [M$^+$+2], 403(18%), [M$^+$ +4], 405 (2.5%); Anal. Calcd for $C_{19}H_{16}{}^{79}BrNO_4$ 402.2386, Found 402.2379.

General procedure for the synthesis of compounds 6a-9c

A mixture of (**2a-c**) or oxime derivatives (**3a-5c**) (0.5 mmol), thiazolidinedione (0.5 mmol), and KOH (0.5 mmol) in EtOH (10ml), was stirred at 0°C for 24h. After consumption of thiazolidinedione, water (20 ml) was added and the precipitate was filtered, washed with water, and recrystallized from methanol-chloroform (9:1) to give compounds (**6a-9c**).

3-(2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl)thiazolidine-2,4-dione(6a, $C_{14}H_9NO_5S$): Brown powder; M.p: (161-163)°C, yield=(71%); IR (KBr, cm^{-1}) : 1758, 1609, 1589, 1494, 1459, 1375, 1282, 1279 1104, 756; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.17(s, 2H, CH_2-thiazolidinedione), δ=5.26 (s, 2H,$COCH_2$), δ=7.44 (t, 1H, H-6 coumarin, J=7.76 Hz), δ=7.49 (d, 1H, H-8 coumarin, J=8.35 Hz), δ=7.77 (dt, 1H, H-7 coumarin, J=7.79 and1.46 Hz), δ=7.97 (dd, 1H, H-5 coumarin, J=6.59 and 1.36 Hz), δ=8.57 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.9, 60.4, 120.5, 122.8, 128.6, 131.2, 132.8, 135.6, 140.4, 156.4, 164.6, 171.1, 174.6, 198.7 ppm; MS (70eV) *m/z*: [M$^+$], 303 (100%); Anal. Calcd for $C_{14}H_9NO_5S$ 303.2900, Found 303.2894.

3-(2-(6-bromo-2-oxo-2H-chromen-3-yl)-2-oxoethyl) thiazolidine-2,4-dione(6b, $C_{14}H_8BrNO_5S$): Brown powder; M.p: (171-173)°C, yield=(66%); IR (KBr, cm^{-1}) : 1760, 1608, 1580, 1490, 1455, 1379, 1291, 1284, 1119, 759; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.18 (s, 2H, CH_2-thiazolidinedione), δ=5.22 (s, 2H, $COCH_2$), δ=7.29-7.52 (m, 2H, H-7,8 coumarin), δ=7.65 (d, 1H, H-5 coumarinJ=8.80Hz), δ=8.49 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.1, 60.3, 119.8, 122.6, 127.3, 133.8, 135.6, 136.8, 140.3, 155.8, 163.8, 169.5, 174.1, 198.6 ppm; MS (70eV) *m/z*: [M$^+$], 382 (100%), [M$^+$+2], 384(18%), [M$^+$ +4], 386 (2.5%); Anal. Calcd for $C_{14}H_8{}^{79}BrNO_5S$ 382.1860, Found 382.1852.

3-(2-(8-methoxy-2-oxo-2H-chromen-3-yl)-2-oxoethyl) thiazolidine-2,4-dione(6c, $C_{15}H_{11}NO_6S$): Brown powder; M.p: (165-167)°C, yield=(68%); IR (KBr, cm^{-1}) : 1756, 1611, 1594, 1501, 1463, 1369, 1287, 1271, 1111, 767; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.09 (s, 3H, O-CH_3 coumarin), δ=4.17 (s, 2H, CH_2-thiazolidinedione), δ=5.27(s, 2H, $COCH_2$), δ=7.27-7.44 (m, 2H, H-6, H-7 coumarin), δ=7.90 (d, 1H, H-5 coumarin, J=8.71 Hz), 8.44 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=39.8, 58.6, 61.3, 121.6, 123.7, 127.3, 131.2, 135.6, 140.4, 144.4, 151.3, 163.7, 172.8, 175.1, 198.6 ppm; MS (70eV) *m/z*: [M$^+$], 333 (100%); Anal. Calcd for $C_{15}H_{11}NO_6S$ 333.3159, Found 333.3154.

3-(2-(hydroxyimino)-2-(2-oxo-2H-chromen-3-yl)ethyl) thiazolidine-2,4-dione(7a, $C_{14}H_{10}N_2O_5S$): Brown powder; M.p: (148-151)°C, yield=(57%); IR (KBr,cm^{-1}): 3428, 2926, 1755, 1611, 1587, 1493, 1464, 1377, 1280, 1279, 1106, 761; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.21(s, 2H, CH_2-thiazolidinedione), δ=4.95 (s, 2H, CNOH-CH_2), δ=7.40 (t, 1H, H-6 coumarin, J=7.62 Hz), δ=7.56 (d, 1H, H-8 coumarin, J=7.34 Hz), δ=7.66 (dt, 1H, H-7 coumarin, J=7.33 and 1.26 Hz), δ=7.77 (d, 1H, H-5 coumarin, J=7.69 Hz), δ=8.14 (s, 1H, H-4 coumarin),δ=11.26(s, 1H, oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.3, 57.3, 121.6, 122.3, 127.9, 130.8, 132.2, 133.8, 141.6, 155.9, 163.4, 171.9, 173.8, 186.6 ppm; MS (70eV) *m/z*: [M$^+$], 318 (100%); Anal. Calcd for $C_{14}H_{10}N_2O_5S$ 318.0310, Found 318.0304.

3-(2-(6-bromo-2-oxo-2H-chromen-3-yl)-2-(hydroxyimino) ethyl)thiazolidine-2,4-dione (7b, $C_{14}H_9BrN_2O_5S$): Brown powder; M.p: (177-179)°C, yield=(58%); IR (KBr, cm^{-1}) : 3352, 2929, 1760, 1609, 1592, 1491, 1455, 1371, 1294, 1205, 1118, 767; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.15 (s, 2H, CH_2-thiazolidinedione), δ=4.93(s, 2H, CNOH-CH_2), δ=7.27-7.43 (m,2H, H-7 and H-8 coumarin), δ=7.68 (d, 1H, H-5 coumarin, J=8.74Hz), δ=8.07 (s, 1H, H-4 coumarin), δ=11.28 (s, 1H, oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.3, 55.2, 120.3, 122.8, 126.8, 133.4, 134.7, 136.5, 140.8, 154.1, 164.2, 168.3, 173.5, 185.9 ppm; MS (70eV) *m/z*: [M$^+$], 397 (100%), [M$^+$+2], 399(18%), [M$^+$ +4], 401 (2.5%); Anal. Calcd for $C_{14}H_9{}^{79}BrN_2O_5S$ 397.2007, Found 397.2001.

3-(2-(hydroxyimino)-2-(8-methoxy-2-oxo-2H-chromen-3-yl) ethyl)thiazolidine-2,4-dione(7c, $C_{15}H_{12}N_2O_6S$): Brown powder; M.p:(153-155)°C, yield=(59%); IR (KBr, cm^{-1}) : 3435, 2932, 1750, 1620, 1595, 1488, 1462, 1383, 1288, 1209, 1100, 781; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.19 (s, 2H, CH_2-thiazolidinedione), δ=4.05(s, 3H, O-CH_3 coumarin), δ=4.90 (s, 2H, CNOH-CH_2), δ=7.48 (dt, 1H, H-6 coumarin, J=7.84 and 0.81 Hz), δ=7.75 (dt, 1H, H-7coumarin, J=8.71 and 1.58 Hz), δ=7.91 (dd, 1H, H-5 coumarin, J=7.69 and1.36 Hz), δ=8.25(s, 1H, H-4 coumarin), δ=11.32 (s, 1H, oxime) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=39.5, 54.1, 58.8, 121.6, 124.6, 127.9, 132.6, 136.3, 139.4, 143.6, 152.6, 164.2, 171.8, 174.3, 185.1 ppm;MS (70eV) *m/z*: [M$^+$], 348 (100%); Anal. Calcd for $C_{15}H_{12}N_2O_6S$ 348.3306, Found 348.3312.

3-(2-(methoxyimino)-2-(2-oxo-2H-chromen-3-yl)ethyl) thiazolidine-2,4-dione(8a, $C_{15}H_{12}N_2O_5S$): Brown powder; M.p:(157-159)°C, yield=(58%); IR (KBr, cm^{-1}) : 3425, 2934, 1757, 1615, 1595, 1488, 1468, 1382, 1278, 1221, 1114, 763; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.08 (s, 3H, O-CH_3 oxime), δ=4.17 (s, 2H, CH_2-thiazolidinedione), δ=4.87(s, 2H,C-CH_2-N), δ=7.34 (t, 1H, H-6 coumarin, J=7.52 Hz), δ=7.39 (d, 1H, H-8 coumarin, J=8.62 Hz), δ=7.56-7.62 (m, 2H, H-5 and H-7coumarin), 8.16 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=39.8, 57.1, 63.9, 120.9, 123.4, 126.5, 130.1, 133.6, 134.2, 142.3, 154.8, 164.2, 172.1, 173.6, 185.3 ppm; MS (70eV) *m/z*: [M$^+$], 332 (100%); Anal. Calcd for $C_{15}H_{12}N_2O_5S$ 332.3312, Found 332.3303.

3-(2-(6-bromo-2-oxo-2H-chromen-3-yl)-2-(methoxyimino) ethyl)thiazolidine-2,4-dione (8b, $C_{15}H_{11}BrN_2O_5S$): Brown powder; M.p: (178-180)°C, yield=(60%); IR (KBr, cm^{-1}) : 3345, 2923, 1751, 1616, 1592, 1495, 1462, 1379, 1288, 1265, 1110, 755; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.09 (s, 3H, O-CH_3 oxime), δ=4.20 (s, 2H,CH_2-thiazolidinedione), δ=4.88 (s, 2H, C-CH_2-N), δ=7.01-7.55 (m, 2H, H-7, H-8 coumarin), δ=7.75 (d,1H, H-5 coumarin, J=8.76Hz) δ=8.07 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=41.4, 57.6, 64.3, 120.9, 123.2, 127.1, 133.4, 134.7, 135.9, 141.2, 155.6, 163.6, 167.6, 172.9, 184.6 ppm; MS (70eV) *m/z*: [M$^+$], 409 (100%), [M$^+$+2], 411(18%), [M$^+$ +4], 413 (2.5%); Anal. Calcd for $C_{15}H_{11}{}^{79}BrN_2O_5S$ 411.2272, Found 411.2265.

3-(2-(8-methoxy-2-oxo-2H-chromen-3-yl)-2-(methoxyimino) ethyl)thiazolidine-2,4-dione(8c, $C_{16}H_{14}N_2O_6S$): Brown powder; M.p: (162-164)°C, yield=(62%); IR (KBr, cm^{-1}) : 3321, 2933, 1758, 1614, 1586, 1489, 1452, 1380, 1289, 1206, 1099, 758; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.03 (s, 3H, O-CH_3 coumarin),δ=4.12 (s, 3H, O-CH_3 oxime), δ=4.21 (s, 2H, CH_2-thiazolidinedione), δ=4.92 (s, 2H, 2H, C-CH_2-N), δ=7.45 (t, 1H, H-6 coumarin, J=7.45 Hz), δ=7.52-7.66 (m,

2H, H-5, H-7 coumarin), δ=8.05 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=39.9, 55.6, 57.9, 64.1, 122.9, 125.1, 128.3, 133.1, 136.6, 138.3, 145.9, 151.8, 163.8, 169.6, 171.9, 184.3 ppm; MS (70eV) *m/z*: [M$^+$], 362 (100%); Anal. Calcd for $C_{16}H_{14}N_2O_6S$ 362.3572, Found 362.3563.

3-(2-(benzyloxyimino)-2-(2-oxo-2H-chromen-3-yl)ethyl) thiazolidine-2,4-dione(9a, $C_{21}H_{16}N_2O_5S$): Brown powder; M.p: (183-185)°C, yield=(56%); IR (KBr, cm^{-1}) : 3425, 2920, 1759, 1619, 1586, 1502, 1455, 1384, 1279, 1204, 1108, 1030, 761; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=3.99 (s, 2H, CH_2-thiazolidinedione), δ=4.87(s, 2H, C-CH_2-N), δ=5.30 (s, 2H, O-CH_2-Ph), δ=7.33-7.57 (m, 7H, H-6, H-8 coumarin and phenyl), 7.61-7.77 (m, 2H, H-5 and H-7 coumarin), δ=8.05 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.1, 56.9, 80.8, 122.9, 123.4, 125.7, 127.8, 129.1(2C), 130.8, 131.2 (2C), 132.8, 134.5, 139.6, 142.3, 154.8, 162.9, 171.1, 173.6, 184.8 ppm; MS (70eV) *m/z*: [M$^+$], 408 (100%); Anal. Calcd for $C_{21}H_{16}N_2O_5S$ 408.4271, Found 408.4265.

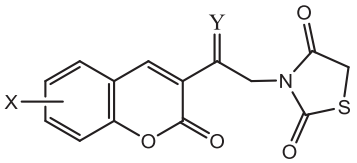
3-(2-(benzyloxyimino)-2-(6-bromo-2-oxo-2H-chromen-3yl) ethyl)thiazolidine-2,4-dione (9b, $C_{21}H_{15}BrN_2O_5S$): Brown powder; M.p: (190-192)°C, yield=(55%); IR (KBr, cm^{-1}) : 3345, 2931, 1751, 1621, 1584, 1498, 1460, 1381, 1279, 1206, 1096, 1036, 751; ^{1}H-NMR (500 MHz, DMSO-d6) : δ=4.18 (s, 2H, CH_2-thiazolidinedione) δ=5.39 (s, 2H, O-CH_2-Ph), δ=4.88 (s, 2H, C-CH_2-N), δ=5.24 (s, 2H, O-CH_2-Ph), δ=7.01-7.55 (m, 7H,H-7,H-8 coumarin and phenyl), δ=7.72 (d,1H,H-5 coumarin, J=8.82Hz), δ=8.07 (s,1H,H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.1, 56.8, 63.3, 79.8, 121.6, 123.2, 127.1, 129.6 (2C), 130.1, 131.9 (2C), 133.1, 135.1, 136.3, 140.9, 154.9, 164.2, 166.8, 171.3, 183.7 ppm; MS (70eV) *m/z*: [M$^+$], 485 (100%), [M$^+$+2], 487(18%), [M$^+$ +4], 489 (2.5%); Anal. Calcd for $C_{21}H_{15}{}^{79}BrN_2O_5S$ 487.3232, Found 487.3224.

3-(2-(benzyloxyimino)-2-(8-methoxy-2-oxo-2H-chromen3yl) ethyl)thiazolidine-2,4-dione(9c, $C_{22}H_{18}N_2O_6S$): Brown powder; M.p: (186-188)°C, yield=(54%); IR (KBr, cm^{-1}) : 3311, 2922, 1754, 1600, 1591, 1492, 1467, 1369, 1286, 1216, 1116, 1026, 758; ^{1}H-NMR (500 MHz, DMSO-d6): δ=4.02 (s, 3H, O-CH_3 coumarin), δ=4.21 (s, 2H, CH_2-thiazolidinedione), δ=4.92 (s, 2H, C-CH_2-N), δ=5.27 (s, 2H, O-CH_2-Ph), δ=7.31-7.66 (m, 7H, H-6, H-7 coumarin and phenyl), δ=7.84 (d, 1H, H5-coumarin, J=7.74Hz), δ=8.05 (s, 1H, H-4 coumarin) ppm; ^{13}C-NMR (300 MHz, DMSO-d6): δ=40.3, 54.2, 57.3, 63.8, 79.6, 122.1, 124.8, 127.3, 128.9 (2C), 130.6, 132.1 (2C), 134.6, 135.8, 138.6, 143.8, 152.4, 164.1, 168.9, 172.1, 183.5 ppm; MS (70eV) *m/z*: [M$^+$], 438 (100%); Anal. Calcd for $C_{22}H_{18}N_2O_6S$ 438.4531, Found 438.4523.

Antimicrobial and antifungal assay

The antimicrobial activity was assayed by cup-plate agar diffusion method [31,32] by measuring inhibition zones in mm. *In vitro* antimicrobial activity of all synthesized compounds and standard drugs have been evaluated against two strains of bacteria which include gram-positive bacteria such as, *Bacillus subtilis* PTCC 1207 and gram-negative bacteria such as *Escherichia coli* PTCC 1047 and fungus *Candida kefyr* ATCC 38296. The antibacterial and antifungal activity was compared with standard drugs. The purified products were screened for their antibacterial activity by using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 h old subculture of, *Bacillus subtilis* PTCC 1047, and *Escherichia coli* PTCC 1047 in separate conical flasks at 40-50°C and mixed well by gently shaking. About 25 ml of the contents of the flask was poured and evenly spread in a petri dish (90 mm in diameter) and allowed to set for 2 h. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.4 ml (400 µg / ml) solution of sample in DMSO.

The plates were incubated at 37°C for 24 h and the control was also maintained with 0.4 ml of DMSO in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and recorded in Table 2 and Figure 2. *Candida kefyr* ATCC 38296 was



Compound	X	Y	Diameter of the zone of the inhibition (mm)		
			Gram-positive organism	Gram-negative organism	Fungus
			***Bacillus subtilis* PTCC 1207**	***Escherichia coli* PTCC 1047**	***Candida kefyr* ATCC 38296**
6a	H	O	15	16	7
6b	6-Br	O	17	17	8
6c	8- OCH_3	O	16	19	7
7a	H	NOH	19	20	9
7b	6-Br	NOH	17	16	8
7c	8- OCH_3	NOH	20	15	8
8a	H	$NOCH_3$	25	21	9
8b	6-Br	$NOCH_3$	24	20	9
8c	8- OCH_3	$NOCH_3$	26	22	8
9a	H	NOBn	22	19	9
9b	6-Br	NOBn	23	21	8
9c	8- OCH_3	NOBn	21	19	8
Ciprofloxacin	-		23	26	
Ampicillin	-		15	18	-
Gentamicin	-		21	19	-
Nistatin	-		-	-	12

Table 2: *In vitro* antibacterial and antifungal activities of compounds 6a-9c.

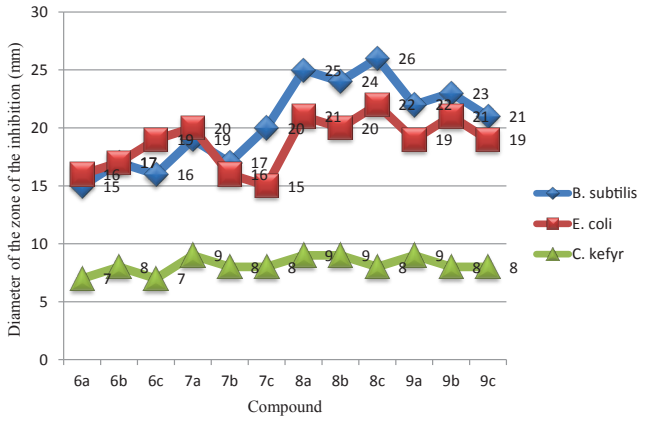


Figure 2: *In-vitro* antibacterial and antifungal activities of compounds 6a-9c.

employed for testing antifungal activity by cup-plate agar diffusion method. The culture was maintained on Sub rouse dextrose agar slants. Sterilized Sub rouse dextrose agar medium was inoculated with 72 h old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spread on a sterilized petri dish and allowed to set for 2 h. The cups (10 mm in diameter) were punched in a petri dish and loaded with 0.4 ml (400 µg/ ml) of solution of sample in DMSO. The plates were incubated at 30°C for 48 h. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm were measured. Along with the test solution in each petri dish one cup was filled up with solvent which acts as a control. The zones of inhibition are recorded in Table 2 and Figure 2.

Results and Discussion

In this study the structure of the synthesized compounds was elucidated by means of IR, ^{1}H-NMR, ^{13}C-NMR and Mass. All the compounds were evaluated for antibacterial and antifungal activities by cup-plate method. The antimicrobial activity of tested compounds against different strains of bacteria and fungus is shown in Table 2 and Figure 2. The newly synthesized compounds 6a–9c were evaluated for their in-vitro antibacterial activity against *Bacillus subtilis* PTCC 1207, *Escherichia coli* PTCC 1047 and *Candida kefyr* ATCC 38296 using conventional by cup-plate agar diffusion method [31,32]. The zone of growth inhibition values were determined by comparison to standard drugs. The zones of growth inhibition obtained for compounds 6a–9c are presented in Table 2 and Figure 2. The zone of growth inhibition values of the test derivatives indicated that most compounds exhibit good activity against gram-positive and gram-negative bacteria. Antibacterial screening of compounds 6a–9c against gram-positive and gram-negative bacteria reveals that compounds 8a, 8b and 8c exhibit the most potent in-vitro antibacterial activity. All compounds show improvement of activity against gram-negative bacteria in comparison to standard drugs. Generally, in both gram-positive and gram-negative bacteria, better results are obtained with 2-$NOCH_3$ on the ethyl spacer of coumarin. In conclusion, some of the new thiazolidinedione derivatives 6a-9c containing a carbonyl related functional groups (ketone, oxime, *O*-methyloxime, and *O*-benzyloxime) on the ethyl spacer showed considerable antibacterial activity and ethyl spacer functionality produced relatively major changes in terms of activity. In general, the results of antibacterial evaluation of the test compounds in comparison with the reference drugs indicated that compounds 8a, 8b and 8c showed comparable or more potent antibacterial activity with respect to the reference drugs against all tested species. The antifungal data reveals that all compounds have shown weak antifungal activity as compared to Nistatin.

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