Acta Poloniae Pharmaceutica – Drug Research, Vol. 66 No. 6 pp. 625–632, 2009 ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

SYNTHESIS OF TRIAZOLOTHIAZOLIDINONE DERIVATIVES OF COUMARIN WITH ANTIMICROBIAL ACTIVITY

MASHOOQ A. BHAT[1]*, NADEEM SIDDIQUI[2], SUROOR A. KHAN[2], and MOHAMED IBRAHIM MOHAMED[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Khartoum College of Medical Science, Aljerief West, 1st Block Number 398, P.O. Box 10995, Khartoum, Sudan

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University) Hamdard Nagar, New Delhi-110062, India

Abstract: A series of 2-(substituted phenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones, **8a-n,** were synthesized and evaluated for their antimicrobial activity. The structures of the compounds were confirmed on the basis of their elemental analysis and spectral data. Compounds **8k, 8l** and **8m** showed significant inhibition against *S. aureus*, compound **8m** showed significant inhibition against *E. coli* and compounds **8b, 8e 8i, 8j, 8k, 8l** and **8m** showed significant inhibition against *C. albicans*.

Keywords: coumarin, 1,2,4-triazole, 1,3,4-thiazolidinone, antimicrobial activity

Coumarins are reported to possess important pharmacological activities like antitumor (1), anticonvulsant (2) and anti-inflammatory (3). The 1,2,4-triazole derivatives are reported to show a broad spectrum of biological activities which include antibacterial (4), anti-inflammatory (5) antifungal (6) and anticonvulsant (7). The 1,3,4-thiazolidinone derivatives also possess activities like antibacterial (8), anticonvulsant (9), antifungal (10), antihistaminic (11) and anti-HIV (12). This prompted us to synthesize and study the antimicrobial activity of compounds incorporating coumarin, 1,2,4-triazole and 1,3,4-thiazolidinone moieties.

EXPERIMENTAL

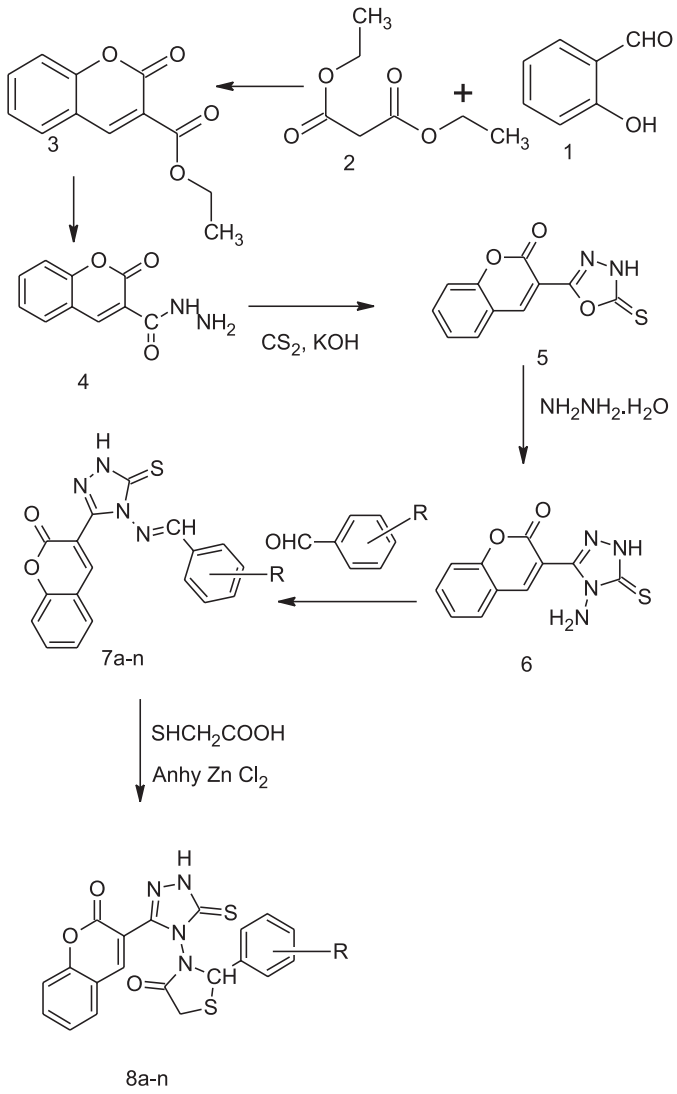
All the solvents were of LR grade and were obtained from Merck, CDH and s. d. Fine Chemicals. Melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. The elemental analysis (C, H, N and S) of all compounds were performed on the CHNS Elementar (Analysen systeme GmbH, Germany) and Vario EL III (Elementar Americas Corporation) and were within a limit of ± 0.4% and ± 0.3%, respectively, of the theoretical values. The homogeneity of the compounds was checked by TLC performed on Silica gel G coated plates (Merck). Iodine chamber was used for visualization of TLC spots. The FT-IR spectra were recorded in KBr pellets on (BIO-RAD FTS135) WIN-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker model DPX 300 FT NMR spectrometer (in $CDCl_3$) using tetramethylsilane (Me_4Si, TMS) as an internal standard. The chemical shifts are reported in δ ppm values. Mass spectra were recorded on Jeol JMS-D instrument fitted with a JMS 2000 data system at 70 eV and are expressed as (m/z). The physical constants of the synthesized compounds are given in Table 1**.**

Synthesis of ethyl-2-oxo-2*H*-chromene-3-carboxylate (**3**) (m.p. 120-122°C) and 2-oxo-2*H*-chromene-3-carbohydrazide (**4**) (m.p. 136-138°C) were carried out by standard procedures (13). The synthesis of 3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one **5** (m.p. 200-202°C) was also carried out by standard method (14).

Synthesis of 3-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**6)**

Compound **5** (2.46 g, 0.01 mol) and hydrazine hydrate 99% (0.5 g, 0.01 mol) were dissolved in

* Corresponding author: e-mail: mashooqbhat@rediffmail.com, phone: 00249-924015393, fax: 00249-228766



8a: R = 3-NO_2, **8b**: R = 4-$N(CH_3)_2$, **8c**: R = 4-OH, **8d**: R = 3-OH, **8e**: R = 2-NO_2, **8f**: R = 4F, **8g**: R = 3,4-$(OCH_3)_2$, **8h**: R = 2-OH, **8i**: R = 4-OCH_3, **8j**: R = 2-Cl, **8k**: R = 3-Cl, **8l**: R = 4-Cl, **8m**: R = H, **8n**: R = 4-NO_2

Scheme 1. Synthetic pathway for compounds **8a-n**

absolute alcohol (50 mL) to give clear solution which was refluxed for 10 h. The reaction mixture was concentrated to half volume and allowed to cool. The solid mass which separated out on cooling was filtered and washed with small amount of ice-cooled ethanol. The product was crystallized from ethanol. Yield: 70%, m.p.: 210-212°C; IR (KBr, cm^{-1}): 3451 (NH str.), 2923 (C-H str., 1620 (C=O str., coumarin), 1572 (C=N str.), 1271 (C=S str.), 1198 (C-O str.), 749 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 5.45 (s, 2H, NH_2, D_2O exchange), 6.95 (m, 2H, H-6, H-8, *J* = 7.2 Hz, Ar-H), 7.12 (m, 1H, H-7, *J* = 7 Hz, Ar-H), 7.23 (m, 1H, H-5, *J* = 7.5 Hz, Ar-H), 7.9 (s, 1H, H-4, Ar-H), 11.07 (s, 1H, NH).

General method of synthesis of 3-(4-{[(substituted phenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-ones **(7a-n)**

Compound **6** (2.38 g, 0.01 mol), appropriate aromatic aldehydes **a-n** (0.01 mol) and glacial acetic

Table 1. Physical constants of the synthesized compounds **8a-n**.

Compd.	R	M. p. (°C)	Yield (%)	Molecular formula	R_f [a]
8a	3-NO_2	110-112	60	$C_{20}H_{13}N_5O_5S_2$	0.77
8b	$N(CH_3)_2$	190-192	75	$C_{22}H_{19}N_5O_3S_2$	0.75
8c	4-OH	235-237	64	$C_{20}H_{14}N_4O_4S_2$	0.70
8d	3-OH	225-227	70	$C_{20}H_{14}N_4O_4S_2$	0.75
8e	2-NO_2	105-107	64	$C_{20}H_{13}N_5O_5S_2$	0.80
8f	4-F	180-182	62	$C_{20}H_{13}FN_4O_3S_2$	0.74
8g	3,4-$(OCH_3)_2$	240-242	50	$C_{22}H_{18}N_4O_5S_2$	0.60
8h	2-OH	190-192	66	$C_{20}H_{14}N_4O_4S_2$;	0.71
8i	4-OCH_3	200-202	65	$C_{21}H_{16}N_4O_4S_2$	0.64
8j	2-Cl	160-162	70	$C_{20}H_{13}ClN_4O_3S_2$	0.83
8k	3-Cl	150-152	75	$C_{20}H_{13}ClN_4O_3S_2$	0.84
8l	4-Cl	140-142	70	$C_{20}H_{13}ClN_4O_3S_2$	0.85
8m	H	130-132	65	$C_{20}H_{14}N_4O_3S_2$	0.5
8n	4-NO_2	170-172	70	$C_{20}H_{13}N_5O_5S_2$	0.78

[a] Eluents used in TLC were benzene : acetone (7:3, v/v) for all compounds.

acid (2 mL) were refluxed in ethanol (40 mL) for 8 h. The solvent was distilled off. The product **7** was obtained by pouring the reaction mixture in ice-cold water, filtered and recrystallized from ethanol.

3-(4-{[(3-Nitrophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7a**)

Yield 90%, m.p. 160-162°C. IR (KBr, cm^{-1}): 3450 (NH), 3020 (-N=CH-Ar), 2923 (C-H), 1621 (C=O str., coumarin), 1527 (C=N), 1267 (C=S), 1195 (C-O). ^{1}H NMR ($CDCl_3$, δ ppm): 7.0 (m, 2H, Ar-H, H-8, H-5'), 7.2 (m, 1H, Ar-H, H-6), 7.3 (m, 2H, Ar-H, H-7, H-6'), 7.6 (m, 1H, Ar-H, H-5,), 8.1 (m, 1H, Ar-H, H-4), 8.3 (s, 1H, N=CH-Ar), 8.7 (m, 2H, Ar-H, H-2', H-4'), 11.3 (s, 1H, NH). MS (m/z): 393 (M^+), 150.1, 146.1, 118.1, 101, 90.1,74; Analysis: calcd. for $C_{18}H_{11}N_5O_4S$: C 54.96, H 2.82, N 17.80, S 8.15%; found: C 54.92, H 2.42, N 17.60, S 8.25%.

3-[(4-{[(4-(Dimethylamino)phenyl]methylene}imino)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-2*H*-chromen-2-one (**7b**)

Yield 70%, m.p. 170-172°C. IR (KBr, cm^{-1}): 3457 (NH), 3020 (-N=CH-Ar), 2920 (C-H), 1615 (C=O, coumarin), 1531 (C=N), 1267 (C=S), 1184 (C-O), 751 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 1.8 (s, 6H, $2CH_3$), 6.5 (m, 1H, Ar-H, H-8), 6.8 (m, 2H, Ar-H, H-2', H-6'), 7.0 (m, 2H, Ar-H, H-7, H-6), 7.1 (d, 2H, Ar-H, H-3', H-5'), 7.5 (m, 1H, Ar-H, H-4), 8.5 (s, 1H, N=CH-Ar), 11.5 (s, 1H, NH). MS (m/z): 391 (M^+), 148.2, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{17}N_5O_2S$: C 61.37, H 4.38, N 17.89, S 8.19%; found: C 61.07, H 4.38, N 17.59, S 8.49%.

3-(4-{[(4-Hydroxyphenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7c**)

Yield 80%, m.p. 180-182°C. IR (KBr, cm^{-1}): 3479 (NH), 3020 (-N=CH-Ar), 2926 (C-H), 1620 (C=O, coumarin), 1512 (C=N), 1281 (C=S), 1170 (C-O), 748 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 6.9 (m, 3H, Ar-H, H-8, H-2', H-6'), 7.2 (m, 2H, Ar-H, H-6, H-7), 7.3 (m, 3H, Ar-H, H-5, H-3', H-5'), 8.7 (s, 1H, Ar-H, H-4), 11.3 (s, 1H, NH), 11.7 (s, 1H, Ar-OH). MS (m/z): 364 (M^+), 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{12}N_4O_3S$: C 59.33, H 3.32, N 15.38, S 8.80%; found: C 59.03, H 3.72, N 15.08, S 8.50%.

3-(4-{[(3-Hydroxyphenyl)methylene]amino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7d**)

Yield 72%, m.p. 175-172°C. IR (KBr, cm^{-1}): 3451 (NH), 3020 (-N=CH-Ar), 2923 (C-H), 1620 (C=O, coumarin), 1572 (C=N), 1271 (C=S), 1198 (C-O), 749 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 6.9 (m, 3H, Ar-H, H-8, H-5', H-6'), 7.2 (m, 1H, Ar-H, H-4), 7.3 (m, 3H, Ar-H, H-7, H-2', H-6'), 8.5 (s, 1H, N=CH-Ar), 8.7 (s, 2H, Ar-H, H2', H4');

MS (m/z): 364 (M^+), 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{12}N_4O_3S$: C 59.33, H 3.32, N 15.38, S 8.80%; found: C 59.03, H 3.72, N 15.08, S 8.50%.

3-(4-{[(2-Nitrophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7e**)

Yield: 75%, m.p. 165-167°C; IR (KBr, cm^{-1}): 3493 (NH), 3020 (-N=CH-Ar), 2919 (C-H), 1619 (C=O, coumarin), 1518 (C=N), 1271 (C=S), 1199 (C-O), 747 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 7.0 (m, 2H, Ar-H, H-8, H-5'), 7.2 (m, 2H, Ar-H, H-7, H-6'), 7.3 (m, 3H, Ar-H, H-6, H-5, H-6'), 7.6 (m, 1H, Ar-H, H-3'), 8.0 (m, 1H, Ar-H, H-4), 8.2 (m, 1H, N=CH-Ar), 11.4 (s, 1H, NH). MS (m/z): 393 (M^+), 150.1, 146.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{11}N_5O_4S$: C 54.96, H 2.82, N 17.80, S 8.15%; found: C 54.92, H 2.42, N 17.60, S 8.25%.

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3-(4-{[(4-Fluorophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7f**)

Yield: 65%, m.p. 190-192°C. IR (KBr, cm^{-1}): 3579 (NH), 3020 (-N=CH-Ar), 2925 (C-H), 1620 (C=O, coumarin), 1506 (C=N), 1271 (C=S), 1226 (C-O), 751 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 7.0 (m, 2H, Ar-H, H-8, H-5'), 7.2 (m, 1H, Ar-H, H-6), 7.3 (m, 2H, Ar-H, H-7, H-6'), 7.6 (m, 1H, Ar-H, H-3'), 8.1 (t, 1H, Ar-H, H-5), 8.3 (s, 1H, N=CH-Ar), 8.7 (m, 2H, Ar-H, H-2', H-3'), 11.4 (s, 1H, NH). MS (m/z): 393 (M^+), 123.1, 146.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{11}FN_4O_2S$: C 59.1, H 3.03, N 15.29, S 8.75%; found: C 59.40, H 3.30, N 15.59, S 8.95%.

3-(4-{[(3,4-Dimethoxyphenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7g**)

Yield 70%, m.p. 205-207°C. IR (KBr, cm^{-1}): 3579 (NH), 3020 (-N=CH-Ar), 2925 (C-H), 1620 (C=O, coumarin), 1506 (C=N), 1271 (C=S), 1226 (C-O), 751 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 3.8 (s, 6H, OCH_3), 6.9 (m, 1H, Ar-H, H-8), 7.1 (m, 3H, Ar-H, H-7, H-2', H-6'), 7.2 (m, 1H, Ar-H, H-6), 7.3 (m, 1H, Ar-H, H-5), 7.8 (m, 3H, Ar-H, H-3', H-5', H-4), 8.6 (s, 1H, N=CH-Ar), 11.6 (s, 1H, NH); MS (m/z): 366 (M^+), 165.1, 146.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{16}N_4O_4S$: C 58.81, H 3.95, N 13.72, S 7.85%; found: C 58.60, H 3.64, N 13.90, S 7.50%.

3-(4-{[(2-Hydroxyphenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7h**)

Yield 60%, m.p. 185-187°C. IR (KBr, cm^{-1}): 3592 (NH), 3020 (-N=CH-Ar), 2928 (C-H), 1620 (C=O, coumarin), 1508 (C=N), 1265 (C=S), 1238 (C-O), 750 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 7.0 (m, 2H, Ar-H, H-8,H-5'), 7.2 (m, 1H, Ar-H, H-6), 7.4 (m, 3H, Ar-H, H-7, H-5, H-2'), 7.7 (m, 1H, Ar-H, H-6'), 8.6 (s, 1H, N=CH-Ar), 9.7 (s, 1H, NH). MS (m/z): 408 (M^+), 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{12}N_4O_3S$: C 59.33, H 3.32, N 15.38, S 8.80%; found: C 59.03, H 3.72, N 15.08, S 8.50.

3-(4-{[(4-Methoxyphenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7i**)

Yield 75%, m.p. 220-222°C. IR (KBr, cm^{-1}): 3434 (NH), 3020 (-N=CH-Ar), 2921 (C-H), 1623 (C=O, coumarin), 1568 (C=N), 1273 (C=S), 1200 (C-O), 750 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 3.8 (s, 3H, OCH_3), 7.0 (m, 4H, Ar-H H-7, H-8, H-5, H-6'), 7.2 (s, 2H, Ar-H, H-6, H-5'), 7.4 (m, 4H, Ar-H, H-4, H-3', H-4', N=CH-Ar), 8.7 (s, 1H, Ar-OH), 11.3 (s, 1H, NH). MS (m/z): 364 (M^+), 135.1, 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{19}H_{14}N_4O_3S$: C 60.31, H 3.73, N 14.81, S 8.47%; found: C 60.70, H 3.43, N 14.61, S 8.60%.

3-(4-{[(2-Chlorophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7j**)

Yield 80%, m.p. 190-192°C. IR (KBr, cm^{-1}): 3450 (NH), 3020 (-N=CH-Ar), 2926 (C-H), 1620 (C=O coumarin), 1511 (C=N), 1252 (C=S), 1164 (C-O), 749 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 3.8 (s, 1H, N=CH-Ar), 6.8-8.0 (m, 9H, Ar-H), 8.8 (s, 1H, N=CH-Ar), 11.8 (s, 1H, NH); MS (m/z): 378 (M^+), 139.5, 121.1, 118.1, 101, 90.1,74; Anal. calcd. for $C_{18}H_{11}ClN_4O_2S$: C 56.47, H 2.90, N 14.64, S 8.38; found C 56.74, H 2.40, N 14.90, S 8.08.

3-(4-{[(3-Chlorophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7k**)

Yield 75%, m.p. 205-207°C. IR (KBr, cm^{-1}): 3504 (NH), 3030 (-N=CH-Ar), 2922 (C-H), 1620 (C=O, coumarin), 1572 (C=N), 1271 (C=S), 1198 (C-O), 750 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 6.8 (m, 2H, Ar-H, H-8, H-6'), 6.9 (m, 2H, Ar-H, H-7, H-5'), 7.1 (m, 2H, Ar-H, H-6, H-3'), 7.2 (m, 2H, Ar-H, H-5, H-4'), 7.3 (s, 1H, N=CH-Ar), 8.6 (s, 1H, Ar-H, H-4), 11.3 (s, 1H, NH). MS (m/z): 382 (M^+), 139.5, 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{11}ClN_4O_2S$: C 56.47, H 2.90, N 14.64, S 8.38%; found: C 56.74, H 2.40, N 14.90, S 8.08.

3-(4-{[(4-Chlorophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7l**)

Yield 80%, m.p. 185-187°C; IR (KBr, cm^{-1}): 3556 (NH), 3020 (-N=CH-Ar), 2923 (C-H), 1621 (C=O, coumarin), 1567 (C=N), 1269 (C=S), 1202 (C-O), 781, 748, (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 7.2 (m, 6H, Ar-H, H-8, H-7, H-6, H-5, H-6', H-5'), 7.4 (m, 2H, Ar-H, H-2', H-4'), 7.5 (m, 1H, Ar-H, H-4), 7.8 (s, 1H, Ar-H, H-4), 9.3 (s, 1H, N=CH-Ar), 11.0 (s, 1H, NH). MS (m/z): 382 (M^+), 139.5, 121.1, 118.1, 101, 90.1, 74; Analysis: calcd. for $C_{18}H_{11}ClN_4O_2S$: C 56.47, H 2.90, N 14.64, S 8.38%; found: C 56.74, H 2.40, N 14.90, S 8.08%.

3-{4-[(Phenylmethylene)imino]-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl}-2*H*-chromen-2-one (**7m**)

Yield 70%, m.p. 210-212°C; IR (KBr, cm^{-1}): 3556 (NH), 3040 (-N=CH-Ar), 2923 (C-H), 1621 (C=O, coumarin), 1567 (C=N), 1269 (C=S), 1202 (C-O), 781, 748 (=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 7.2 (m, 6H, Ar-H, H-8, H-7, H-6, H-5, H-6', H-5'), 7.4 (m, 2H, Ar-H, H-2', H-4'), 7.5 (m, 1H, Ar-H, H-4), 7.8 (s, 1H, Ar-H, H-4), 9.3 (s, 1H, N=CH-Ar), 11.0 (s, 1H, NH). MS (m/z): 382 (M^+), 105.1, 146.1, 118.1, 101, 90, 74. Analysis: calcd. for $C_{18}H_{12}N_4O_2S$: C 62.06, H 3.47, N 16.08, S 9.20%; found: C 62.36, H 3.77, N 16.48, S 9.50%.

3-(4-{[(4-Nitrophenyl)methylene]imino}-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one (**7n**)

Yield 65%, m.p. 150-152°C. IR (KBr, cm^{-1}): 3579 (NH), 3100 (-N=CH-Ar), 2925 (C-H), 1620 (C=O, coumarin), 1506 (C=N), 1271 (C=S), 1226 (C-O), 751(=C-H out of plane). ^{1}H NMR ($CDCl_3$, δ ppm): 6.9 (m, 1H, Ar-H, H-8), 7.1 (m, 3H, Ar-H, H-7, H-2', H-6'), 7.2 (m, 1H, Ar-H, H-6), 7.3 (m, 2H, Ar-H, H-5, H-4'), 7.8 (m, 3H, Ar-H, H-3', H-5', H-4), 8.6 (s, 1H, N=CH-Ar), 11.6 (s, 1H, NH); MS (m/z): 348 (M^+), 146.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{18}H_{11}N_5O_4S$: C 54.96, H 2.82, N 17.80, S 8.15%; found: C 54.92, H 2.42, N 17.60, S 8.25%.

General method for synthesis of compounds **8a-m**

Compound **7** (0.01 mol) and mercaptoacetic acid (0.9 g, 0.1 mol) were refluxed in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (40 mL) for 12 h. The reaction mixture was then cooled and poured onto crushed ice. The product **8** separated out was filtered, dried and crystallized from ethanol. The other compounds of the series were synthesized similarly.

2-(3-Nitrophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one (**8a**)

IR (KBr, cm^{-1}): 3399 (NH), 2950 (C-H), 1703 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1528 (C=N), 1276 (C=S), 775 (=C-H out of plane), 697 (C-S-C str.). ^{1}H-NMR ($CDCl_3$, δ ppm): 4.0 (s, 2H, S-CH_2), 6.5 (s, 1H, S-CH), 7.1-8.1 (m, 9H, Ar-H, *J* = 10 Hz), 8.3 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 467 (M^+), 224.2, 196.2, 164.1, 146.1, 150.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}N_5O_5S_2$: C 51.39, H 2.80, N 14.98, S 13.72%; found: C 51.79, H 2.40, N 15.38, S 13.42%.

2-(4-*N*-dimethylaminophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one (**8b**)

IR (KBr, cm^{-1}): 3420 (NH), 2850 (C-H), 1700 (C=O, coumarin), 1670 (C=O, 4-thiazolidinone), 1530 (C=N), 1270 (C=S), 750 (=C-H out of plane), 677 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 2.3 (s, 6H, 2´CH_3), 3.6 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.0-8.2 (m, 9H, Ar-H, *J* = 10 Hz), 8.4 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 465 (M^+), 222.3, 194.2, 162.1, 146.1, 148.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{22}H_{19}N_5O_3S_{2\%}$: C 56.76, H 4.11, N 15.04, S 13.78%; found: C 57.16, H 4.70, N 15.44, S 14.08%.

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2-(4-Hydroxyphenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one (**8c**)

IR (KBr, cm^{-1}): 3400 (NH), 3216 (C-H), 1700 (C=O, coumarin), 1670 (C=O, 4-thiazolidinone), 1576 (C=N), 1269 (C=S), 751 (=C-H out of plane), 681 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.0 (s, 2H, S-CH_2), 6.9 (s, 1H, S-CH), 7.3-7.7 (m, 9H, Ar-H, *J* = 7.25 Hz), 9.0 (bs, 1H, NH, D_2O exchangeable), 11.1 (bs, 1H, Ar-OH, D_2O exchangeable). MS (m/z): 438 (M^+) 195.2, 167.2, 135.1, 146.1, 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{14}N_4O_4S_2$: C 54.78, H 3.22, N 12.78, S 14.63%; found: C 54.48, H 3.52, N 12.48, S 14.33%.

2-(3-Hydroxyphenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8d**

IR (KBr, cm^{-1}): 3411 (NH), 2900 (C-H), 1710 (C=O, coumarin), 1682 (C=O, 4-thiazolidinone), 1397 (C=N), 1231 (C=S), 758(=C-H out of plane), 696 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 4.0 (s, 2H, S-CH_2), 6.4 (s, 1H, S-CH), 7.0-8.0 (m, 9H, Ar-H, *J* = 7.25 Hz), 9.4 (s, 1H, NH, D_2O exchangeable), 9.6 (bs, 1H, Ar-OH, D_2O exchangeable). MS (m/z): 438

(M^+) 195.2, 167.2, 135.1, 146.1, 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{14}N_4O_4S_2$: C 54.78, H 3.22, N 12.78, S 14.63%; found: C 54.48, H 3.52, N 12.48, S 14.33%.

.

2-(2-Nitrophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8e**

IR (KBr, cm^{-1}): 3421 (NH), 2954 (C-H), 1700 (C=O, coumarin), 1690 (C=O, 4-thiazolidinone), 1400 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 4.0 (s, 2H, S-CH_2), 6.9 (s, 1H, S-CH), 7.0-7.9 (m, 8H, Ar-H, *J* = 10 Hz), 8.0 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable); MS (m/z): 467 (M^+), 224.2, 196.2, 164.1, 146.1, 150.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}N_5O_5S_2$: C 51.39, H 2.80, N 14.98, S 13.72%; found: C 51.79, H 2.40, N 15.38, S 13.42%.

2-(4-Fluorophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8f**

IR (KBr, cm^{-1}): 3410 (NH), 2930 (C-H), 1710 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1410 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.8 (s, 2H, S-CH_2), 6.7 (s, 1H, S-CH), 7.0-7.8 (m, 8H, Ar-H, *J* = 10 Hz), 8.1 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 440 (M^+), 197.2, 169.2, 154.2, 123.12, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}FN_4O_3S_2$: C 54.54, H 2.97, N 12.72, S 14.56%; found: C 54.84, H 2.57, N 12.42, S 14.26%.

2-(3,4-Dimethoxyphenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8g**

IR (KBr, cm^{-1}): 3300 (NH), 2900 (C-H), 1709 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1523 (C=N), 1274 (C=S), 757 (=C-H out of plane), 720 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.7(s, 6H, 2×OCH_3), 3.9 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.0-7.8 (m, 8H, Ar-H, *J* = 10 Hz), 8.3 (s, 1H, NH, D_2O exchangeable). MS (m/z): 482 (M^+), 263.31, 235.30, 220.28, 189.21, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{22}H_{18}N_4O_5S_2$: C 54.76, H 3.76, N 11.61, S 13.29%; found: C 54.46, H 3.36, N 11.31, S 13.59%.

2-(2-Hydroxyphenyl)-3-[3-(2-oxo-2H-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8h**

IR (KBr, cm^{-1}): 3424 (NH), 2924 (C-H), 1700 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1498 (C=N), 1255 (C=S), 753 (=C-H out of plane), 666 (C-S-C). ^{1}H-NMR ($CDCl_3$, d ppm): 3.6 (s, 2H, S-CH_2), 6.7 (s, 1H, S-CH), 6.9-7.6 (m, 8H, Ar-H, *J* = 7.14 Hz), 9.5 (s, 1H, Ar-H, H-4), 10.1 (bs, 1H, NH, D_2O exchangeable), 10.9 (s, 1H, Ar-OH). MS (m/z): 438 (M^+) 195.2, 167.2, 135.1, 146.1, 121.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{14}N_4O_4S_2$: C 54.78, H 3.22, N 12.78, S 14.63%; found: C 54.48, H 3.52, N 12.48, S 14.33%.

2-(4-Methoxyphenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8i**

IR (KBr, cm^{-1}): 3394 (NH), 2926 (C-H), 1702 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1454 (C=N), 1300 (C=S), 840 (=C-H out of plane), 692 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.4 (s, 3H, OCH_3), 3.9 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.0-7.8 (m, 9H, Ar-H, *J* = 10 Hz), 8.3 (s, 1H, NH, D_2O exchangeable). MS (m/z): 452 (M^+) 209.26, 181.25, 166.24, 135.16, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{21}H_{16}N_4O_4S_2$: C 55.74, H 3.56, N 12.38, S 14.17%; found: C 55.71, H 3.86, N 12.08, S 14.27%.

2-(2-Chlorophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8j**

IR (KBr, cm^{-1}): 3410 (NH), 2930 (C-H), 1700 (C=O, coumarin), 1682 (C=O, 4-thiazolidinone), 1420 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.7 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.1-7.9 (m, 8H, Ar-H, *J* = 10 Hz), 8.1 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 456 (M^+), 213.68, 185.67, 170.65, 139.58, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}ClN_4O_3S_2$: C 52.57, H 2.87, N 12.26, S 14.04%; found: C 52.37, H 2.47, N 12.36, S 14.24%.

2-(3-Chlorophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8k**

IR (KBr, cm^{-1}): 3410 (NH), 2930 (C-H), 1700 (C=O, coumarin), 1690 (C=O, 4-thiazolidinone), 1410 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.6 (s, 2H, S-CH_2), 6.7 (s, 1H, S-CH), 7.0-8.0 (m, 8H, Ar-H, *J* = 10 Hz), 8.1 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 456 (M^+), 213.68, 185.67, 170.65, 139.58, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}ClN_4O_3S_2$: C 52.57, H 2.87, N 12.26, S 14.04%; found: C 52.37, H 2.47, N 12.36, S 14.24%.

Table 2. Antibacterial and antifungal activity of compounds **8a-n**.

Compound	Diameter of zone of inhibition (mm)			% inhibition with reference to standard		
	S. aureus	*E. coli*	*C. albicans*	*S. aureus*	*E. coli*	*C. albicans*
8a	15	14	16	60	56	80
8b	17	13	18	68	52	90
8c	14	-	16	56	-	80
8d	13	-	14	52	-	70
8e	15	13	17	60	52	85
8f	16	14	15	64	56	75
8g	15	16	13	60	64	65
8h	14	-	14	56	-	70
8i	15	17	17	60	68	85
8j	18	15	18	72	60	90
8k	19	16	17	76	64	85
8l	20	17	18	80	68	90
8m	23	20	18	92	80	90
8n	17	17	15	68	68	75
Ciprofloxacin	25	25	-	100	100	-
Ketoconazole	-	-	20	-	-	100

2-(4-Chlorophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8l**

IR (KBr, cm^{-1}): 3430 (NH), 2940 (C-H), 1700 (C=O, coumarin), 1682 (C=O, 4-thiazolidinone), 1410 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.8 (s, 2H, S-CH_2), 6.6 (s, 1H, S-CH), 7.0-7.9 (m, 8H, Ar-H, *J* = 10 Hz), 8.1 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 456 (M^+), 213.68, 185.67, 170.65, 139.58, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}ClN_4O_3S_2$: C 52.57, H 2.87, N 12.26, S 14.04%; found: C 52.37, H 2.47, N 12.36, S 14.24%.

2-Phenyl-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8m**

IR (KBr, cm^{-1}): 3374 (NH), 2920 (C-H), 1700 (C=O, coumarin) 1670 (C=O, 4-thiazolidinone), 1474 (C=N), 1300 (C=S), 840 (=C-H out of plane), 692 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.9 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.0-7.6 (m, 9H, Ar-H, *J* = 10 Hz), 8.1 (s, 1H, Ar-H, H-4), 8.3 (s, 1H, NH, D_2O exchangeable). MS (m/z): 422 (M^+), 179.23, 151.22, 136.21, 118.1, 105.13, 101, 90.1, 74; Analysis: calcd. for $C_{20}H_{14}N_4O_3S_2$: C 56.86, H 3.34, N 13.26, S 15.18%; found: C 56.76, H 3.70, N 13.40, S 15.23%.

2-(4-Nitrophenyl)-3-[3-(2-oxo-2*H*-chromen-3-yl)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-one **8n**

IR (KBr, cm^{-1}): 3431 (NH), 2900 (C-H), 1700 (C=O, coumarin), 1674 (C=O, 4-thiazolidinone), 1400 (C=N), 1260 (C=S), 838 (=C-H out of plane), 694 (C-S-C). ^{1}H-NMR ($CDCl_3$, δ ppm): 3.8 (s, 2H, S-CH_2), 6.8 (s, 1H, S-CH), 7.0-7.9 (m, 8H, Ar-H, *J* = 10 Hz), 8.0 (s, 1H, Ar-H, H-4), 9.7 (bs, 1H, NH, D_2O exchangeable). MS (m/z): 467 (M^+), 224.2, 196.2, 164.1, 146.1, 150.1, 118.1, 101, 90.1, 74. Analysis: calcd. for $C_{20}H_{13}N_5O_5S_2$: C 51.39, H 2.80, N 14.98, S 13.72%; found C 51.79, H 2.40, N 15.38, S 13.42%.

Antimicrobial activity

The synthesized compounds were screened for their antibacterial activity against Gram positive *S. aureus* and Gram negative *E. coli* strains and antifungal activity against *C. albicans* by cup-plate method and agar diffusion method (15). Ciprofloxacin and ketoconazole were used as the standards. The test compounds and standards were evaluated at 100 µg/mL concentration. DMF (N,N-dimethylformamide) was used as solvent and control. Data are represented as % inhibition with reference to standards in Table 2.

RESULTS

Salicylaldehyde **1** and diethylmalonate **2** were reacted in the presence of piperidine in ethanol to form ethyl-2-oxo-2*H*-chromene-3-carboxylate **3** which on treatment with hydrazine hydrate 99% resulted in 2-oxo-2*H*-chromene-3-carbohydrazide **4**. Compound **4** was refluxed with potassium hydroxide and carbon disulfide until evolution of hydrogen sulfide ceased to form 3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one **5**. Compound **5** was further refluxed with hydrazine hydrate to form 3-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-2*H*-chromen-2-one **6**. This was condensed with appropriate aldehydes to furnish the Schiff bases **7a-n**, which in the presence of thioglycolic acid and a pinch of anhydrous zinc chloride were cyclized to desired 1,3-thiazolidin-4-ones **8a-n**.

The synthesized compounds were characterized by elemental analysis, FT IR, ^{1}H NMR and mass spectroscopy. The FT IR spectra of **8a-n** revealed the following bands for NH, C-H, C=O (coumarin), C=O (4-thiazolidinone), C=N, C=S groups at 3431-3300 cm^{-1}, 3216-2900 cm^{-1}, 1709-1596 cm^{-1}, 1690-1670 cm^{-1}, 1576-1397 cm^{-1}, 1300-1231 cm^{-1}, respectively. The ^{1}H NMR spectra of **8a-n** confirm the presence of aromatic protons at δ 6.9-9.5 ppm. The singlet for two protons of β-thialactam ring appears at δ 3.0-4.0 ppm. Another singlet also appears for a single proton (S-CH-Ar) at δ 6.4-6.9 ppm. A singlet for NH proton appears at δ 8.3-9.7 ppm and is D_2O exchangeable.

It has been observed that most of the compounds showed growth inhibition against *S. aureus*, *E. coli* and *C. albicans*. Compounds **8k, 8l** and **8m** showed 76%, 80% and 92% growth inhibition, respectively, against *S. aureus*. Compound **8m** showed 80% growth inhibition against *E. coli*. Compounds **8b, 8j, 8l** and **8m** showed 90% growth inhibition while compounds **8e, 8i** and **8k** showed 85% growth inhibition against *C. albicans*. Thus it was concluded that the compounds without substitution and with Cl substitution showed the highest activity against *S. aureus* and the compounds without substitution showed the highest activity against *E. coli*. The compounds with OCH_3, $N(CH_3)_2$, NO_2, and Cl substitution and unsubstituted showed the highest activity against *C. albicans*.

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Received: 17. 02. 2009