Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2014, 5(6):74-78

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and structural determination of novel heterocyclic derivatives of coumarin isothiocyanates

Sanjay K. Patil and Hrushikesh P. Deokar

C. K. Thakur A. C. S. College, New Panvel, Raigad, Maharashtra

---

ABSTRACT

The aim of present work is to synthesize new coumarin heterocycles and elucidates their biological activity. For the synthesis, methyl substituted 1,2,4-triazole coumarin molecule was treated with CS_2gives coumarin isothiocyanate, which is used as precursor molecule. This resultant coumarin isothiocyanates further condensed with thioglycolic acid, glycine, anthranilic acid, o-amino thiophenol and o-aminophenol which forms various heterocyclic derivatives like 1,3-thiazolidin, 2-thioxoimidazolidin, quinazolin, benzothiazol and benzoxazol. The synthesized compounds were confirmed by the spectral techniques. All the compounds were screened for their antimicrobial activities and have been found to exhibited significant activities.

Keywords: 1,3-thiazolidin, 2-thioxoimidazolidin, quinazolin, benzothiazol, benzoxazol

---

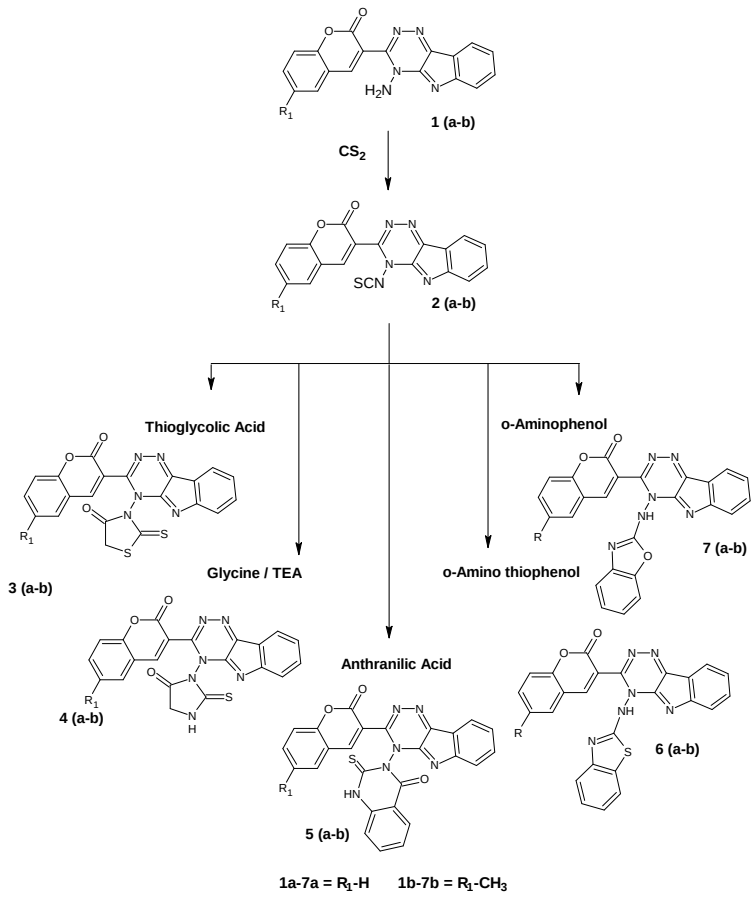
INTRODUCTION

It is well known that heterocyclic compounds are found as a major contributing entity to the structure of many biological active compounds. There has been considerable interest during past decades in the synthesis of coumarin derivatives. Coumarin (2*H*-chromen-2-one) and its derivatives are widely distributed in nature and exhibit a broad pharmacological profile which includes activities like anti-inflammatory [1], antimicrobial [2], antitubercular [3], antipyretic [4], analgesic [5], antioxidant [6] and cytotoxic activities[7]. Similarly isothiocyanates are also found to be an important class of compounds in organic chemistry. Isothiocyanates are key intermediates in the synthesis of various heterocycles [8]. It undergoes reaction with bifunctional compounds to yield heterocyclic derivatives[9]. Benzthiazole is having potent biological properties such as antitumor[10] and antibacterial[11]. By observing the biological importance of the above heterocycles, we thought to incorporate five membered heterocyclic moieties on coumarin isothiocyanate and examine them for antimicrobial activity.

MATERIALS AND METHODS

All commercial reagents and solvents were procured from S.D. Fine. The reactions were monitored by TLC using 0.25 mm E-Merck silica gel plates, which were visualized in Iodine Chamber and if needed in UV light. Melting points were taken in open capillaries and are uncorrected. ^{1}H spectra in DMSO-d_6 were recorded on VXR-300 MHz using TMS as internal standard.

Scheme –I



Synthesis of Compounds

3-(4′-isothiocyanato-4′*H*-[1′,2′,4′]triazino-indol-3′-yl)-2-oxo-2-*H*-benzopyran 2(a-b)

With an objective to synthesize 2(a-b), 20 cm^3mixture of iodine (0.01mol) in CS_2 was added drop wise to a solution of 3-(4′-amino-4′*H*-[1′,2′,4′]triazino-indol-3-yl)-2-oxo-2-*H*-benzopyran (0.01mol) and pyridine at 0°C. Then this reaction mixture was stirred for 3 h. Reaction mass was then treated with HCI and poured on ice pieces. Solid product obtained was filtered, washed with water and recrystalized from alcohol.

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2-thioxo-1″,3″-thiazolidin-4″-one 3(a-b)

As a strategy to synthesize3(a-b), thioglycolic acid (0.01mol) and 2(a-b) (0.01mol) were refluxed in ethanol in presence of catalytical amount of triethylamine. Reaction mixture was refluxed for 6 h. Reaction mass was neutralized using 1:1 HCl. The solid obtained was dried, washed with water and recrystalized from ethanol.

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2″-thioxoimidazolidin-4″-one 4(a-b)

Reaction mixture containing (0.01mol) of 2(a-b), glycine (0.01mol) and triethylamine 1cm^3 in ethanol were refluxed about 7 h. Reaction mass poured on ice to gain the product 4(a-b). Product then filtered, dried and recrystalized from ethanol.

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2″-thioxo-2″,3″-dihydro-*1H*-quinazolin-4″-ones 5(a-b)

In order to synthesize 5(a-b) a mixture of anthranilic acid (0.01mol) and 2(a-b) (0.01mol) was refluxed for 7 h. in ethanolic solution. The reaction mixture was cooled and poured on crushed ice; the product obtained was filtered, dried and recrystallized from ethanol.

3-[4′-(benzothiazol-2″-yl-amino)-4′*H*-[1′,2′,4′]triazino-indol-3′-yl]-2-oxo-2-*H*-benzopyran 6(a-b)
A mixture of *o*-amino thiophenol (0.01mol) and 2(a-b) (0.01mol) in DMF (20 cm^3) was refluxed for 24 h. Reaction mixture was then poured into ice cold water to obtain 6(a-b). The obtained solid was then filtered, washed with water, dried and purified by recrystallization from alcohol.

3-[4′-(benzoxazol-2″-yl-amino)-4′*H*-[1′,2′,4′]triazino-indol-3′-yl]-2-oxo-2-*H*-benzopyran 7(a-b)
An alcoholic solution of *o*-aminophenol (0.01mol) and2(a-b) (0.01mol) in presence of catalytic amount of pyridine was refluxed for 24 h. Then solvent evaporated and concentrated was poured into ice cold water. The obtained solid 7(a-b)was washed with water, dried and purified by ethanol.

RESULTS AND DISCUSSION

Characterization of Synthesized Compounds
3-(4′-isothiocyanato-4′*H*-[1′,2′,4′]triazino-indol-3′-yl)-2-oxo-2-*H*-benzopyran (2a)
Molecular Formula: $C_{19}H_9N_5O_2S$, Melting Point: 177, Yield: 77%; Elemental Analysis% (Calculated) Found: C (61.45) 61.43, H(2.43) 2.39, N (18.86) 18.88, S (8.62) 8.55; IR (KBr): 2994 (-CH), 2141 (NCS), 1736 (C=O), 1679, 1562, 1500, 1311, 1151, 1017 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ6.88-7.30 (m, 8H, Ar), 7.78 (s, 1H, C_4)

3-(4′-isothiocyanato-4′*H*-[1′,2′,4′]triazino-indol-3′-yl)-6-methyl-2-oxo-2-*H*-benzopyran (2b)
Molecular Formula: $C_{20}H_{11}N_5O_2S$, Melting Point: 195, Yield: 71%; Elemental Analysis% (Calculated) Found: C (62.33)62.27, H (2.86)2.88, N (18.18)18.23, S (8.31) 8.28; IR (KBr): 3002 (-CH), 2136 (NCS), 1728 (C=O), 1668, 1566, 1492, 1310, 1148, 1024 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, C_6-CH_3), 6.91-7.32 (m, 7H, Ar), 7.81 (s, 1H, C_4)

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2-thioxo-1″,3″-thiazolidin-4″-one (3a)
Molecular Formula: $C_{21}H_{11}N_5O_3S_2$, Melting Point: 204, Yield: 68%; Elemental Analysis% (Calculated) Found: C (56.62)56.68, H (2.47)2.52, N (15.73)15.64, S (14.38) 14.40; IR (KBr): 3004, 1729 (C=O), 1663, 1553, 1503, 1281, 1198, 1039, 857 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 4.11 (s, 2H, CH_2), 6.96-7.38 (m, 8H, Ar), 7.89 (s, 1H, C_4)

3″-[3′-(6-methyl-2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2-thioxo-1″,3″-thiazolidin-4″-one (3b)
Molecular Formula: $C_{22}H_{13}N_5O_3S_2$, Melting Point: 220, Yield: 72%; Elemental Analysis% (Calculated) Found: C (57.51)57.58, H (2.83)2.79, N (15.25)15.30, S (13.94)13.96; IR (KBr): 3011, 1733 (C=O), 1672, 1561, 1496, 1292, 1196, 1031, 862 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, C_6-CH_3), 4.04 (s, 2H, CH_2), 6.93-7.33 (m, 7H, Ar), 7.82 (s, 1H, C_4)

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2″-thioxoimidazolidin-4″-one (4a)
Molecular Formula: $C_{21}H_{12}N_6O_3S$,Melting Point: 212, Yield: 62%; Elemental Analysis% (Calculated) Found: C (58.87)58.83, H (2.80)2.77, N (19.62)19.68, S (7.47) 7.48; IR (KBr): 3324(>NH), 3002, 1730 (C=O), 1661, 1564, 1296, 1040, 871 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 2H, CH_2), 6.95-7.37 (m, 8H, Ar), 7.76 (s, 1H, C_4), 9.85 (s, 1H, NH)

3″-[3′-(6-methyl-2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2″-thioxoimidazolidin-4″-one (4b)
Molecular Formula: $C_{22}H_{14}N_6O_3S$, Melting Point: 241, Yield: 67%; Elemental Analysis% (Calculated) Found: C (59.72)59.64, H (3.18)3.22, N (19.00)19.03, S (7.24)7.21; IR (KBr): 3332(>NH), 2997, 1725 (C=O), 1658, 1571, 1302, 1036, 867 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, C_6-CH_3), 3.69 (s, 2H, CH_2), 6.89-7.32 (m, 7H, Ar), 7.81(s, 1H, C_4), 10.01 (s, 1H, NH)

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-4′*H*-[1′,2′,4′]triazino-indol-4′-yl]-2″-thioxo-2″,3″-dihydro-*1H*-quinazolin-4″-ones (5a)
Molecular Formula: $C_{26}H_{14}N_6O_3S$, Melting Point: 235, Yield: 66%; Elemental Analysis% (Calculated) Found: C (63.67)63.71, H (2.86)2.82, N (17.14)17.16, S (6.53) 6.61; IR (KBr): 3400 (>NH), 3012, 1734 (C=O), 1662, 1618, 1279, 1160, 1016 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 6.88-7.41 (m, 12H, Ar), 7.87 (s, 1H, C_4), 10.12 (s, 1H, >NH)

3$^{//}$-[3$^{/}$-(6-methyl-2-oxo-2-*H*-benzopyran-3-yl)-4$^{/}$*H*-[1$^{/}$,2$^{/}$,4$^{/}$]triazino-indol-4$^{/}$-yl]-2$^{//}$-thioxo-2$^{//}$,3$^{//}$-dihydro-*1H*-quinazolin-4$^{//}$-ones (5b)
Molecular Formula: $C_{27}H_{16}N_6O_3S$, Melting Point: 247, Yield: 61%; Elemental Analysis% (Calculated) Found: C (64.28)64.19, H (3.19)3.16, N (16.66)16.71, S (6.35) 6.33; IR (KBr): 3394 (>NH), 3003, 1729 (C=O), 1661, 1627, 1284, 1168, 1009 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, C_6-CH_3), 6.93-7.44 (m, 11H, Ar), 7.75 (s, 1H, C_4), 10.03 (s, 1H, >NH)

3-[4$^{/}$-(benzothiazol-2$^{//}$-yl-amino)-4$^{/}$*H*-[1$^{/}$,2$^{/}$,4$^{/}$]triazino-indol-3$^{/}$-yl]-2-oxo-2-*H*-benzopyran (6a)
Molecular Formula: $C_{25}H_{14}N_6O_2S$, Melting Point: 171, Yield: 71%; Elemental Analysis% (Calculated) Found: C (64.95)64.99, H (3.03)3.05, N (18.18)18.24, S (6.93) 6.89; IR (KBr): 3441 (>NH), 3005, 1732 (C=O), 1640, 1548, 1312, 1228, 841 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 4.45 (s, 1H, NH), 6.87-7.40 (m, 12H, Ar), 7.78 (s, 1H, C_4)

3-[4$^{/}$-(benzothiazol-2$^{/}$-$^{/}$yl-amino)-4$^{/}$*H*-[1$^{/}$,2$^{/}$,4$^{/}$]triazino-indol-3$^{/}$-yl]-6-methyl-2-oxo-2-*H*-benzopyran (6b)
Molecular Formula: $C_{26}H_{16}N_6O_2S$, Melting Point: 193, Yield: 68%; Elemental Analysis% (Calculated) Found: C (65.54)65.49, H (3.36)3.39, N (17.65)17.73, S (6.72) 6.75; IR (KBr): 3437 (>NH), 3012, 1724 (C=O), 1648, 1546, 1321, 1227, 852 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, C_6-CH_3), 4.51 (s, 1H, NH), 6.84-7.35 (m, 11H, Ar), 7.75 (s, 1H, C_4)

3-[4$^{/}$-(benzoxazol-2$^{//}$-yl-amino)-4$^{/}$*H*-[1$^{/}$,2$^{/}$,4$^{/}$]triazino-indol-3$^{/}$-yl]-2-oxo-2-*H*-benzopyran (7a)
Molecular Formula: $C_{25}H_{14}N_6O_3$, Melting Point: 185, Yield: 69%; Elemental Analysis% (Calculated) Found: C (67.26)67.29, H (3.14)3.09, N (18.83)18.89; IR (KBr): 3402 (>NH), 3006, 1734 (>C=O), 1665, 1566, 1309, 1208, 1040, 880 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 1H, NH), 6.89-7.38 (m, 12H, Ar), 7.88 (s, 1H, C_4)

3-[4$^{/}$-(benzoxazol-2$^{//}$-yl-amino)-4$^{/}$*H*-[1$^{/}$,2$^{/}$,4$^{/}$]triazino-indol-3$^{/}$-yl]-6-methyl-2-oxo-2-*H*-benzopyran (7b)
Molecular Formula: $C_{26}H_{16}N_6O_3$, Melting Point: 211, Yield: 63%; Elemental Analysis% (Calculated) Found: C (67.82)67.76, H (3.48)3.53, N (18.26)18.24; IR (KBr): 3398 (>NH), 3011, 1728 (C=O), 1659, 1561, 1318, 1206, 1041, 872 $cm^{-1;}$ ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, C_6-CH_3), 3.94 (s, 1H, NH), 7.04-7.35 (m, 11H, Ar), 7.81 (s, 1H, C_4)

Antimicrobial Study
Synthesized Compounds **2(a-b)**, **3(a-b)**, **4(a-b)**, **5(a-b)**, **6(a-b**) and **7(a-b)** has been screened for their antimicrobial activity against *S. aureus* (Gram-positive) and *S. typhi* and *E. coli* (Gram-negative) bacterial strains at two concentration(50 µg/mL and 100 µg/mL) using DMSO as solventby drug diffusion method. Streptomycin used as a standard drug to compare activity exhibited by synthesized compounds. Activity exhibited by compounds is summarized in table no. 1.

Table 1: Antibacterial activity of compounds 2(a-b) to 7(a-b)

Compound	Zone of Inhibition in mm					
	S. aureus		*S. typhi*		*E. coli*	
	50µg	100 µg	50 µg	100 µg	50 µg	100 µg
2a	11	13	11	14	12	15
2b	12	14	13	15	15	17
3a	11	13	12	14	14	16
3b	12	14	13	14	14	17
4a	13	14	14	16	12	16
4b	14	15	15	18	14	17
5a	13	14	13	16	15	16
5b	15	19	17	19	16	18
6a	14	15	15	17	14	16
6b	16	17	18	19	16	19
7a	13	15	14	15	15	17
7b	14	15	14	16	16	18

Disc size: 6.35mm *Standard: Streptomycin* *Control: DMSO*
Duration: 24 hrs *Resistant (11mm/less)* *Intermediate(12-14mm)*
Sensitive(15mm/more)

When inhibition activity of synthesized compounds compared with standards it could be observed that compounds 5a, 5b, 6a, 6b, 7a and 7b have significant activity against used bacterial strains, where as other synthesized

compounds with moderate activity. Which means quinazolin **5(a-b)**, benzothiazol **6(a-b)** and benzoxazol **7(a-b)** heterocycles enhance the biological character of coumarin moiety.

CONCLUSION

Spectral techniques used in the scheme confirm the formation and synthetic route of newly synthesized derivatives. From the result of antibacterial activity it is seen that heterocycles like thiazolidinone, quinazolin and benzothiazol exhibited significant activity where as other with moderate activity. This confers all the newly synthesized heterocyclic derivatives of coumarin isothiocyanates are biologically active towards the tested bacteria.

Acknowledgment
The authors are grateful to Dr. S. T. Gadade, Principal, C. K. Thakur A. C. S. College, for providing laboratory and other facilities.

REFERENCES

[1] Ghate M, Manohar D, Kulkarni M V, Shoba R, *Eur. J. Med. Chem*, **2003**, 38, 297.
[2] Khan I A, Kulkarni M V, Gopal M, Shahabuddin M S, Sun C M, *Bioorg. Med. Chem. Lett*, **2005**, 15, 3584.
[3] Gupta A S, Prabhu B S, *Ind. J. Het. Chem*, **2004**, 13, 391.
[4] Shastri L A, Manjunath G D, Kulkarni M V, *Ind. J. Chem*, **2004**, 43B, 2416.
[5] Ghate M, Kusanur R A, Kulkarni M V, *Eur. J. Med. Chem*, **2005**, 40, 882.
[6] Torres R, Faini F, *Phytochemistry*, **2006**, 67, 984.
[7] Kostava I, Momekov G, *Eur. J. Med. Chem*, **2007**, 20, 1.
[8] Mukerjee A K, Ashare R, *Isothiocyanates in the chemistry of heterocycles*. *Chem. Rev*, **1991**, 91, pp 1.
[9] Ulrich H, *Cycloaddition Reactions of Heterocumulenes*, Academic Press, New York, **1967**, pp 122.
[10] Kashiyama E, Hutchinson I, Chua M S, Stinson S F, *J. Med. Chem*, **1999**, 42, 4172.
[11] Palmer P J, Trig R B, Warrington J V, *J. Med. Chem*, **1971**, 14, 248.