INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Volume: 2: Issue-2: April-June -2011 IJABPT *ISSN 0976-4550*

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 3-THIOCYANATO-7-HYDROXY-2-ARYL-4*H*-CHROMEN-4-ONE

M. Jeyachandran[1] and P. Ramesh[2,*]

[1] Post Graduate and Research Department of Chemistry, Sri Paramakalyani College, Alwarkurichi, Tirunelveli - 627 412, Tamil Nadu, India
E. mail : jeyachandranm@gmail.com
[2,*] Department of Natural Products Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai - 625 021, Tamil Nadu, India
E. mail : npc_ramesh@yahoo.co.in

ABSTRACT 3-Thiocyanato-7-hydroxy-2-aryl-4*H*-chromen-4-one **5 a-e** have been synthesized from 1-(2,4-dihydroxyphenyl)-2-chloroethanone **1**; this reacted with thiocyanate anion afforded 1-(2,4–dihydroxyphenyl)–2-thiocyanatoethanone **2**. Reaction of **2** with substituted benzoyl chlorides under modified Baker-Venkataraman conditions directly afforded the diketones **3 a-g**, which on cyclization furnished **4 a-g**, saponification of which afforded 3-thiocyanato-7-hydroxy-2-aryl-4*H*-chromen-4-one **5 a-g**. All of the synthesized compounds have been established by elemental analysis, IR and NMR spectral data. Compounds **5 a-g** was screened for antibacterial activity.

Keywords Thiocyanatoflavone · Modified Baker – Venkataraman reaction · Antibacterial activity ·

INTRODUCTION

Organic thiocyanates are important intermediates for the synthesis of biologically active molecules. In past several organic thiocyanates have been used as ovicidal [1], insecticidal [2] and antimicrobial agents [3]. However, their use has not been wide spread. A survey of literature revealed that there is scanty information on the synthesis and biological properties of thiocyanates derived from oxygen heterocyclic compounds. Our earlier results on the antibacterical properties of 3-substituted-2-aryl-4*H*-chromen-4-ones [4, 5] were highly encouraging. This prompted us to synthesis 3-thiocyanatochromones with a view to study their antibacterical properties.

Nucleophilic displacement of chlorine in 1-(2,4-dihydroxyphenyl)-2-chloroethanone **1** by thiocyanate anion afforded 1-(2,4–dihydroxyphenyl)–2-thiocyanatoethanone **2**. Reaction of **2** with substituted benzoyl chlorides under modified Baker-Venkataraman conditions (K_2CO_3 / dry acetone) directly afforded the diketones **3 a-g**, which on cyclization (HOAc –NaOAc) furnished **4 a-g**, saponification of which afforded 3-thiocyanato-7-hydroxy-2-aryl-4*H*-chromen-4-one **5 a-g**. Compounds **5 a-g** was screened for antibacterial activity.

MATERIALS AND METHODS

The intermediates and the final products have been characterized by elemental analysis and spectral data (IR and ^{1}H-NMR). The presence of thiocyanate moiety was established by IR bands [6] in the region 2273 - 2000 cm^{-1} (CN str.) and 700 - 600 (CS str.) cm^{-1}.

Melting points were determined on a sulphuric acid bath and are uncorrected. IR spectra were recorded on JASCO 470 FT-IR spectrometer and ^{1}H-NMR spectra was recorded on a 300 MHz on Bruker (Avance) NMR spectrometer using TMS as an internal standard. Elemental analysis of all the synthesized compounds was performed on a Perkin Elmer 2400 Series-II Elemental CHNS analyzer.

Experimental Procedures

Synthesis of 1-(2,4-dihydroxyphenyl)-2-thicyanatoethanone **(*2*)**

To a solution of 1-(2,4-dihydroxyphenyl)-2-chloroethanone **1** (0.01 mol) in dry acetone, aq. ammonium thiocyanate (0.01 mol) was added drop wise through the condenser, and the solution was refluxed for 1.5 h. The solvent was evaporated and the residue was poured into ice water and few drops of conc. HCl were added. The solid that separated was filtered and dried. Yield: 95%; m.p., 192^{0}C. IR (KBr): ν = 3453, 2148, 1635, 1452, 1349, 1290, 968, 813, 613 cm^{-1}. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 5.13 (s, 2H, -$COCH_2$), 6.27 - 7.23 (m, 3H, Ar-H), 10.12 (s, 1H, 4-OH), 12.14 (s, 1H, 2-OH) ppm.

General procedure for the synthesis of 3-hydroxy-4-(3-aryl-3-oxo-2-thiocyanatopropanoyl)-aryl benzoates (*3 a-g*)

To a solution of 1-(2,4-dihydroxyphenyl)-2-thiocyanatothanone **2** (0.01 mol) in dry acetone (75 ml), anhydrous K_2CO_3 (5.0 g) and corresponding benzoyl chlorides (0.02 mol) were added and the contents of the flask were refluxed for 24 h. The resulting orange - yellow solution was filtered and the residue was washed with hot acetone (3 x 25ml) and filtered. The combined acetone filtrate was concentrated on a water bath and the residue was treated with ice water. The solid that separated was filtered and dried. It crystallized from aq. alcohol as pale yellow needles (***3 a-g***). It gave an intense green color with alc. $FeCl_3$.

General procedure for the synthesis of 3-thiocyanato-7-(aroyloxy)-aryl-4*H*-chromen-4-one (***4 a-g***)

To a solution of 3-hydroxy-4-(3-aryl-3-oxo-2-thiocyanatopropanoyl)-aryl benzoate **3 a-g** in glacial acetic acid (25 ml), freshly fused sodium acetate (5.0 g) was added and the contents of the flask were refluxed for 3 h. The resulting solution was poured into crushed ice and the precipitated 3-thiocyanato-7-(aroyloxy)-aryl-4*H*-chromen-4-one **4 a-g** was filtered and washed with water and dried. It crystallized from aq. methanol.

3-Thiocyanato-7-(benzoyloxy)-phenyl-4H-chromen-4-one: (***4a***). Yield: 56%; m.p., 144^{0}C. IR (KBr): ν = 1976, 1741, 1608, 1440, 1149, 1056, 767, 700, 611, 468 cm^{-1}.

3-Thiocyanato-7-(4-methoxybenzoyloxy)-4-methoxyphenyl-4H-chromen-4-one: (***4b***). Yield: 61%; m.p., 132^{0}C. IR (KBr): ν = 2042, 1736, 1620, 1423, 1170, 1108, 1020, 927, 761, 607, 545 cm^{-1}.

3-Thiocyanato-7-(4-aminobenzoyloxy)-4-aminophenyl-4H-chromen-4-one: (***4c***). Yield: 58%; m.p., 126^{0}C. IR (KBr): ν = 1926, 1730, 1675, 1594, 1454, 1380, 1153, 836, 769, 701, 597, 543 cm^{-1}.

3-Thiocyanato-7-(4-nitrobenzoyloxy)-4-nitrophenyl-4H-chromen-4-one: (***4d***). Yield: 62%; m.p., 145^{0}C. IR (KBr): ν = 2240, 1750, 1610, 1450, 1370, 1300, 1100, 960, 700, 650, 590 cm^{-1}.

3-Thiocyanato-7-(4-chlorobenzoyloxy)-4-chlorophenyl-4H-chromen-4-one: (***4e***). Yield: 60%; m.p., 138^{0}C. IR (KBr): ν = 2140, 1910, 1720, 1680, 1600, 1570, 1420, 1270, 1250, 1160, 1010, 960, 910, 820, 740, 590, 480 cm^{-1}.

3-Thiocyanato-7-(3-nitrobenzoyloxy)-3-nitrophenyl-4H-chromen-4-one: (***4f***). Yield: 63%; m.p., 153^{0}C. IR (KBr): ν = 2310, 2220, 1940, 1690, 1570, 1450, 1360, 1030, 850, 700 cm^{-1}.

3-Thiocyanato-7-(3-chlorobenzoyloxy)-3-chlorophenyl-4H-chromen-4-one: (***4g***). Yield: 60%; m.p., 127^{0}C. IR (KBr): ν = 2440, 2080, 1990, 1850, 1820, 1750, 1650, 1550, 1450, 1120, 1020, 700, 650, 620 cm^{-1}.

General procedure for the synthesis of 3-thiocyanato-7-hydroxy-2-aryl-4*H*-chromen-4-one (***5 a-g***)

To a solution of 3-thiocyanato-7-(aroyloxy)-aryl-4*H*-chromen-4-one **4 a-g** in dry methanol (20 ml), sodium methoxide (0.01 g) was added and refluxed for 1 h. The solvent was removed *in vacuo* and the residue was treated with ice cold water. The compound that separated and passing CO_2 gas was extracted with ethyl acetate, which was washed with water and dried. Evaporation of the solvent *in vacuo* yielded 3-thiocyanato-7-hydroxyflavone **5 a-g**.

3-Thiocyanato-7-hydroxy-2-phenyl-4H-chromen-4-one: (***5a***). Yield: 47%; m.p., 159^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 6.42 - 7.32 (m, 8H, Ar-H), 10.12 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_9NO_3S$ (%): C, 65.07; H, 3.07; N, 4.74. Found (%): C, 65.11; H, 3.12; N, 4.76.

3-Thiocyanato-7-hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one: (***5b***).Yield: 42%; m.p., 148^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 3.76 (s, 3H, $-OCH_3$), 6.53 - 7.66 (m, 7H, Ar-H), 10.03 (s, 1H, OH) ppm. Anal. Calcd. for $C_{17}H_{11}NO_4S$ (%): C, 62.76; H, 3.41; N, 4.31. Found (%): C, 62.74; H, 3.43; N, 4.36.

3-Thiocyanato-7-hydroxy-2-(4-aminophenyl)-4H-chromen-4-one: (***5c***). Yield: 46%; m.p., 152^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 5.37 (s, 2H, NH_2), 6.38 - 7.09 (m, 7H, Ar-H), 10.11 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_{10}N_2O_3S$ (%): C, 61.93; H, 3.25; N, 9.03. Found (%): C, 61.99; H, 3.28; N, 9.08.

3-Thiocyanato-7-hydroxy-2-(4-nitrophenyl)-4H-chromen-4-one: (***5d***). Yield: 48%; m.p., 161^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 6.41 - 7.79 (m, 7H, Ar-H), 10.13 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_8N_2O_5S$ (%): C, 56.47; H, 2.37; N, 8.23. Found (%): C, 56.52; H, 2.33; N, 8.27.

3-Thiocyanato-7-hydroxy-2-(4-chlorophenyl)-4H-chromen-4-one: (***5e***). Yield: 45%; m.p., 155^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 6.41 - 7.43 (m, 7H, Ar-H), 9.89 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_8ClNO_3S$ (%): C, 58.28; H, 2.45; N, 4.25. Found (%): C, 58.33; H, 2.49; N, 4.19.

3-Thiocyanato-7-hydroxy-2-(3-nitrophenyl)-4H-chromen-4-one: (***5f***). Yield: 47%; m.p., 167^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 6.37 - 7.88 (m, 7H, Ar-H), 10.14 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_8N_2O_5S$ (%): C, 56.47; H, 2.37; N, 8.23. Found (%): C, 56.52; H, 2.33; N, 8.18.

3-Thiocyanato-7-hydroxy-2-(3-chlorophenyl)-4H-chromen-4-one: (***5g***). Yield: 48%; m.p., 148^{0}C. ^{1}H-NMR (300 MHz , $CDCl_3$) : δ = 6.38 - 7.85 (m, 7H, Ar-H), 10.11 (s, 1H, OH) ppm. Anal. Calcd. for $C_{16}H_8ClNO_3S$ (%): C, 58.28; H, 2.45; N, 4.25. Found (%): C, 58.33; H, 2.52; N, 4.19.

RESULTS AND DISCUSSION

Antimicrobial activity

The antimicrobial activity of compounds was determined by the disc diffusion method and minimum inhibitory concentrations (MICs). MICs were determined by the macrodilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards for testing purposes [7, 8]. MICs were defined as the lowest concentrations of the antimicrobial. Compounds **5 a-g** were evaluated *in vitro* activity against *S. aureus* and *P. aeruginosa* at a concentration of 10 µg/mL in meat peptone agar medium. Amecasin was used as a standard for antimicrobial screening. For each biological activity test, two to three experiments were performed and the average zone of inhibition are shown in **Table 1**.

Table 1 Antibacterial activity of compounds **5 a-g**

Compound	**Antibacterial activity (zone of inhibition in mm) at 10 µg/mL**	
	S. aureus	*P. aeruginosa*
5a	12	4
5b	13	5
5c	11	4
5d	10	4
5e	14	5
5f	14	6
Control (DMSO)	-	-
Amecasin	**16**	**9**

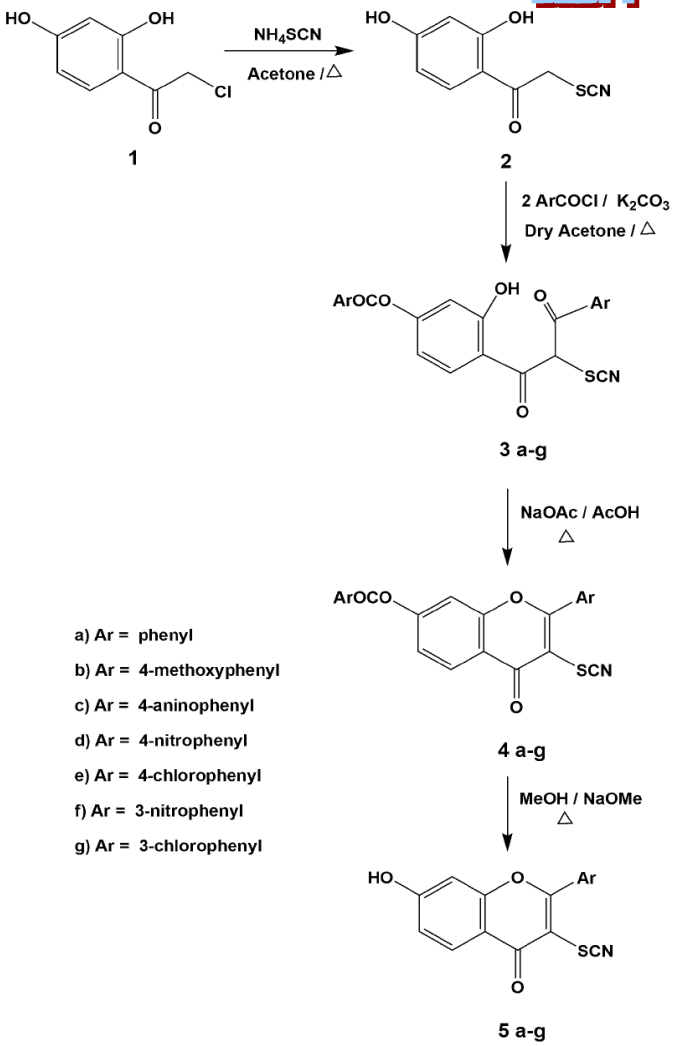
Compounds **5b, 5e** and **5f** exhibited high activity against both species *S. aureus* as well as *P. aeruginosa*. Compounds **5a, 5c** and **5b** showed moderate activity against *S. aureus* and *P. aeruginosa*. The MICs of compounds **5b, 5e** and **5f** are summarized in **Table 2**.

Table 2 Minimum inhibitory concentrations (MICs in µg)

Compounds	*S. aureus*	*E. coli*
5b	7	6
5e	5	5
5f	6	7

Acknowledgement

The authors thank School of Chemistry for providing FT-NMR (under DST-IRHPA programme) and one of the authors is grateful to Madurai Kamaraj University for USR fellowship. The authors also thankful to K. M. College of Pharmacy, Madurai for carrying out biological studies.



Scheme 1, Synthesis of compounds **5 a-g**

REFERENCES

1. Nakamura, T.; Osaka shiritsu Daigaku Igaku Zasshi. 1961, **10** (96), 387.
2. Sebae, A. H. E.; Awatef, E. K.; Alexandria J. Agric. Res. 1975, **23** (2), 333.
3. Donald, C. W.; Charles, F. H.; Develop. Ind. Microbiol. 1971, **12**, 404.
4. Ramesh, P.; Nagendran, A.; Shanmugapriya, M.; Jeyachandran, M.; Indian J. Heterocyclic Chem. 2006, **15** (4), 389.
5. Ramesh, P.; Jeyachandran, M.; Durgashankar, R.; Indian J Heterocyclic Chem. 2009, **18** (3), 211.
6. Silverstein, R. M.; Basler, G. C.; Morrill, T. C.; Spectroscopic Identification of Organic Compounds, (1983) 4th edn. John Wiley and Sons, New York.
7. NCCLS (National Committee for Clinical Laboratory Standards) Approved standard. 1997, M7-A4, NCCLS, Wayne, PA.
8. NCCLS (National Committee for Clinical Laboratory Standards) Approved standard. 1997, M27, NCCLS, Wayne, PA.