Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2021, 13(8): 33-48
(http://www.derpharmachemica.com/archive.html)

DMAP Catalysed Selective Synthesis of Thiopyrano[2,3-B]Quinoline Derivatives through Cascade Protocol

Sreenivas Avula*, Srikanth Reddy Narra

Fluoroorganics Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad, Telangana-500607, India

***Corresponding author:** Sreenivas Avula, Fluoroorganics Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad, Telangana-500607, India, Tel: +91-9346676343; E-mail: srinu.avula343@gmail.com*

ABSTRACT

A convenient and rapid synthesis of hitherto unknown Thiopyrano[2,3-b]quinoline derivatives (3) from β-aroyl-thioacetanilides (1) and 2-chloro quinoline-3-carbaldehyde (2) in the presence of simple organic bases. Initially, β-aroyl-thioacetanilides undergo condensation with 2-chloro quinoline-3-carbaldehyde (2) and followed by intramolecular cyclization (SNAr) to obtained the Thiopyrano[2,3-b]quinoline derivatives (3a-3o). For this transformation, we have found that DMAP is the best catalyst for chemo-selective synthesis of Thiopyrano[2,3-b]quinolones derivatives in high yields. All the final compounds were well characterized by ^{1}H NMR, ^{13}C NMR and HRMS, further confirmed by single X-ray crystallography for 3a and 4a compounds.

Keywords: Thiopyrano [2,3-b]quinoline, β-aroyl-thioacetanilides, 2-chloro quinoline-3-carbaldehyde.

INTRODUCTION

Construction of new heterocyclic ring systems by using new synthetic techniques is very important in synthetic and medicinal chemistry. From the past several decades quinoline derivatives received the great attention in medicinal chemistry as an active pharmacophores [1] and the fused quinoline derivatives also have the good biological profile such as antibacterial [2,3] antimalarial [4-8] antifungal [9] anti-inflammatory [10] antihypertensive [11] antiproliferative [12] and anticancer [13] agents. The thiopyran fused quinoline framework which have structural similarities with MT477 (potential anticancer drug with a high activity against protein kinase C (PKC) isoforms [14] also possess a remarkable biological activities such as antagonistic activity [15-17] and antioxidant [18] agents. Some representative examples are outlined in Figure 1. In view of the importance of thiopyrano [2,3-b]quinoline it is necessary to develop an efficient method for the construction of this heterocyclic skeleton containing analogues.

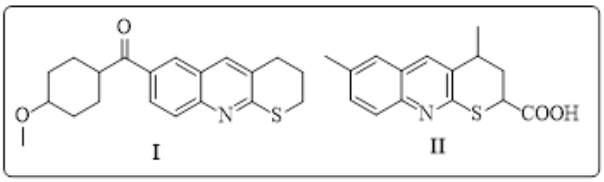


Figure 1: Some biological important 2H-thiopyrano[2,3-b]quinolones.

There are few reports available in literature on the synthesis of thiopyrano [2,3-*b*] quinoline derivatives. In 2009,wang and co-workers [19] reported the synthesis of thiopyran fused quinoline derivatives starting from aromatic aldehydes, naphthalen-2- amine and tetrahydrothiopyran-4-one in the presences of I_2 (Figure 2a). After that, Singh and co-workers [20] pioneered the synthesis of fused thiopyranquinolone from 2-thione analogs of 3-formylquinolines and acrylonitrile (*via* Domino Michael addition followed by cyclization reaction) in the presences of triethylamine (Figure 2b). In 2014, Patel and co-workers [21] synthesized 4*H*-substituted thiopyrano [2,3-b]quinolines derivatives from 2-mercaptoquinoline-3-carbaldehyde, malononitrile and thiol-based nucleophiles in the presences of L-Proline (Figure 2c). However to the best of our knowledge DMAP annulation reaction of β -ketothioamides and 2-chloroquinoline-3-carbaldehydes has not reported before, In continuation of our efforts on synthesis of novel

heterocyclic compounds, by utilizing *β*-aroyl-thioacetanilides [22-25] we report here the synthesis of novel thiopyrano [2, 3-b] quinoline (**3**) derivatives from 2-chloro quinoline-3-carbaldehyde in very good yields using DMAP as a catalyst.

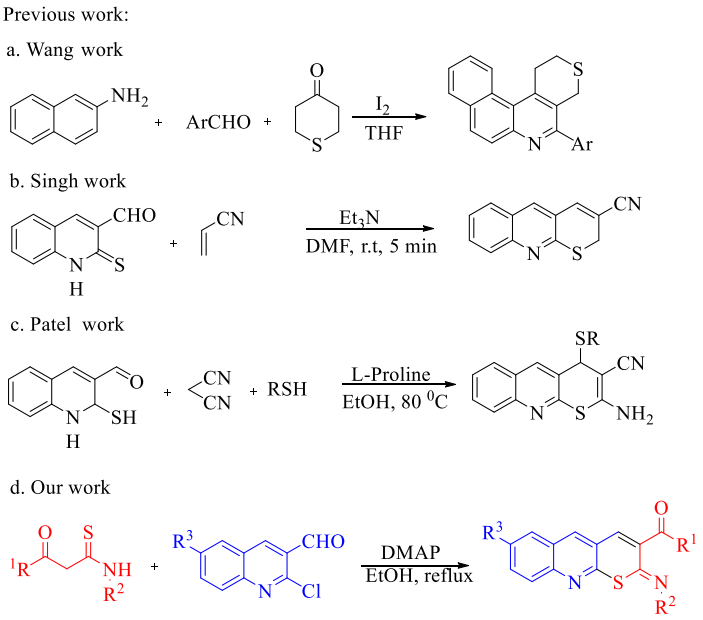


Figure 2: Previous approaches *Vs*. current approach for Synthesis of Thiopyranoquinolines.

MATERIALS AND METHODS

General

Melting points were recorded on a Veego programmable melting point apparatus and are uncorrected. IR spectra were recorded on a PerkineElmer FT-IR 240-Cspectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300 MHz in $CDCl_3$ using TMS as internal standard. Electron Spray Ionization (ESI) and high-resolution mass spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA). All the reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60F254 (mesh); spots were visualized under UV light. The crystallographic data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

General method for Synthesis of the thiopyrano[2,3-*b*]quinoline derivatives (3a-3o)

An equimolar mixture of 3-(4-ethylphenyl)-3-oxo-*N*-phenylpropane thioamide **1a** (283 mg, 1.0 mmol)) and 2-chloro-6-methoxy quinoline-3-carbaldehyde **2b** (221 mg, 1.0 mmol)) was stirred under refluxed in ethanol (15mL) containing DMAP (N,N-dimethy,4- amino pyridine) (12.2mg, 0.1mmol) for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to room temperature, and ethanol was evaporated under reduced pressure then the reaction mixture was diluted with water (15mL) and extracted with ethyl acetate (2*15mL), the combined organic layers were washed with brine (2*15mL) dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude was purified by column chromatography to afford (*Z*)-(4-Ethyl phenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)methanone (**3a**) (378.9 mg, 90%).
Similar procedure is adopted to prepare remaining compounds (**3a-3o**).

(Z)-(4-Ethylphenyl)(2-(phenylimino)-2*H*-thiopyrano [2,3-b]quinolin-3-yl)methanone (3a)

Yellow solid; Yield: 90%; R_f (30% EtOAc/hexane) 0.50; mp < 250^{o}C ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.5 Hz, 3H), 2.76-2.69 (q, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 8.3 Hz, 4H), 7.43 (s, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H) 7.82 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 29.6, 119.0, 122.0, 125.1, 126.3, 126.9, 128.0, 129.3, 129.9, 131.8, 134.0, 134.3, 137.6, 147.7, 149.2, 150.7, 155.6, 194.2; ; IR (KBr) υ_{max} 2967, 1669, 1552, 1563, 1259, 695 cm^{-1}; ESI-MS421 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{20}N_2OS$ $[M+H]^+$ 421.13691, found 421.13537. (Figures 3,4)

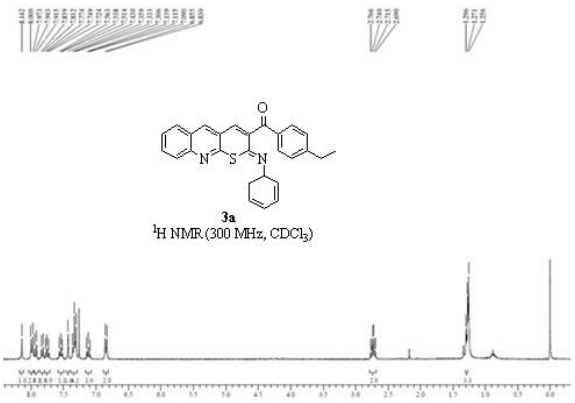


Figure 3: ^{1}H NMR of (Z)-(4-Ethylphenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3a).

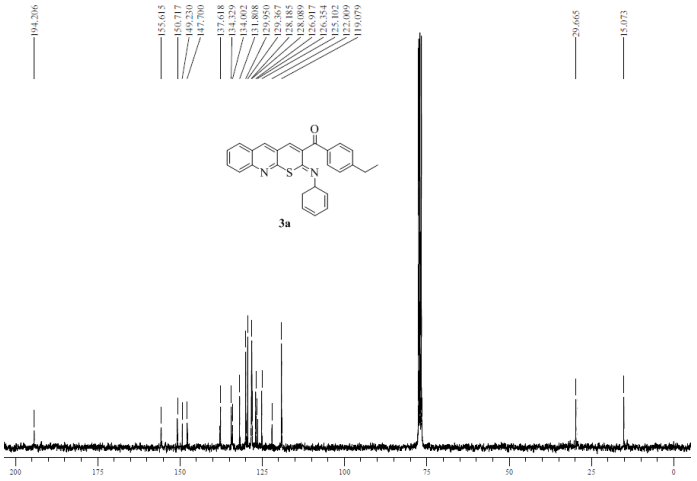


Figure 4: ^{13}C NMR of (Z)-(4-Ethylphenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3a).

(Z)-(4-Methoxyphenyl)(2-(phenylimino)-2*H*-thiopyrano [2,3-*b*]quinolin-3-yl)methanone (3b)

Yellow solid; Yield: 88%; R_f (30% EtOAc/hexane) 0.48; m.p. 191-192^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.85 (d, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.8, Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.4(s, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.74 (t, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.92 (d *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 2H),8.14(s, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ55.5. 113.8, 119.0, 121.9, 125.2,126.7, 126.9,128.1, 128.5, 129.2, 129.3, 129.5, 131.7, 132.1, 133.5, 134.1, 134.6, 137.5,137.7, 147.6, 149.2, 155.5, 155.7, 163.9, 193.1; IR (KBr) υ_{max} 1662, 1587, 1568, 1552, 1253, 758, 701 cm^{-1}; ESI-MS 423 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{18}O_2N_2S$ $[M+H]^+$423.11618, found 423.11645. (Figure 5,6)

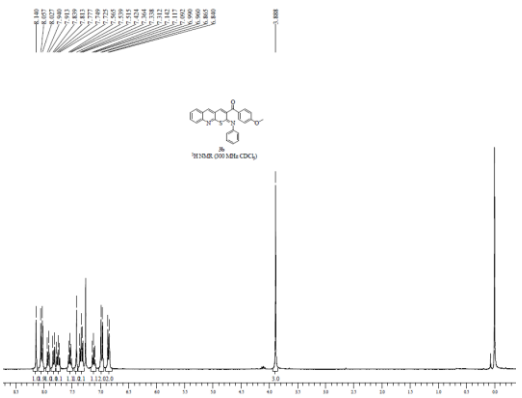


Figure 5: ^{1}H NMR of (Z)-(4-Methoxyphenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone(3b).

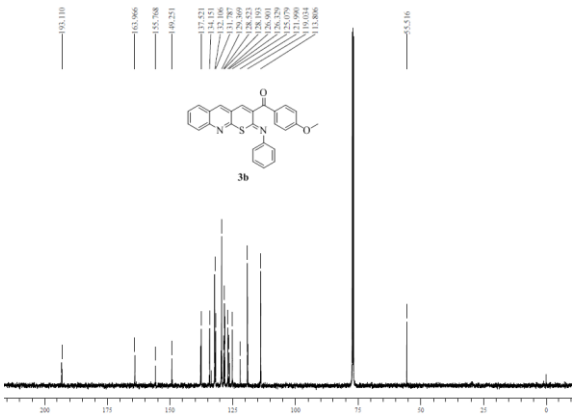


Figure 6: ^{13}C NMR of (Z)-(4-Methoxyphenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone(3b).

(Z)-Phenyl(2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)methanone (3c)

Yellow solid; Yield: 82%; R_f (30% EtOAc/hexane) 0.49;m.p. 190-191^{o}C; 1H NMR (300 MHz, CDCl3) δ 6.82 (d, J = 8.3 Hz, 2H), 7.11 (t, *J* =7.5 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.47 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.75 (t, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.1Hz, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.0, 121.9, 125.1, 126.3, 126.9, 128.2, 128.5, 129.3, 129.5, 131.9, 133.5, 134.6, 136.5, 137.5, 137.7, 147.7, 149.1, 155.6, 194.6; IR (KBr) υ_{max} 2925, 1668, 1557, 1263, 719, 698 cm-1; ESI-MS 393 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{16}ON_2S$ $[M+H]^+$393.10561, found 393.10574. (Figures 7,8)

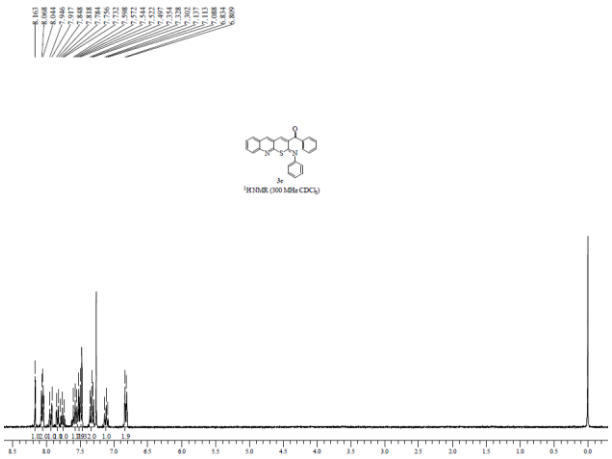


Figure 7: H NMR of (Z)-Phenyl(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3c).

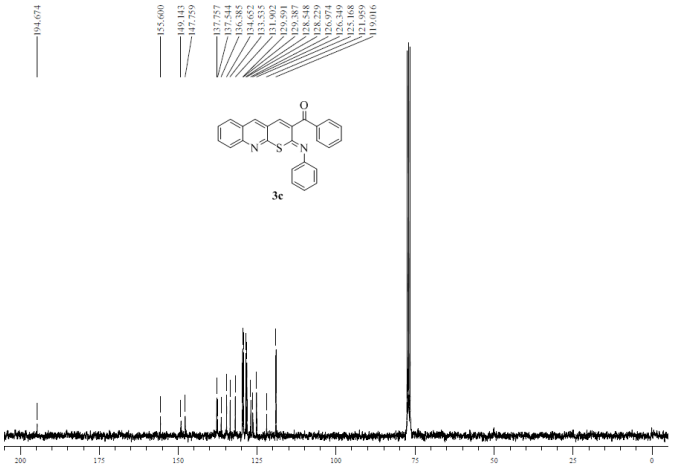


Figure 8: ^{13}C NMR of (Z)-Phenyl(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3c).

(Z)-(4-Fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano [2,3-*b*]quinolin-3-yl)methanone (3d)

Yellow solid; Yield: 81%; R_f (30% EtOAc/hexane) 0.48; m.p. 166-167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 7.3 Hz, 2H), 7.19-7.09 (m, 3H), 7.33 (t, *J* = 7.9Hz, 2H), 7.46 (s, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 8.09-

8.05 (q, 2H), 8.16 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 115.8 (d, J = 21.79 Hz), 119.0, 121.8, 125.4, 126.3, 127.2, 127.8, 128.3, 129.4, 132.2 (d, J = 6.35 Hz), 132.7 (d, J = 2.72 Hz), 135.0, 136.9, 138.2, 147.4, 148.6, 155.4, 155.6, 165.9 (d, J = 256.12 Hz), 193.1; IR (KBr) υ_{max} 1667, 1595, 1548, 1257, 754 cm^{-1}; ESI-MS 411 [M+H]$^+$; HRMS (ESI) calcd for $C_{25}H_{15}ON_2FS$ [M+H]$^+$411.09619, found 411.09588.(Figure 9 and 10)

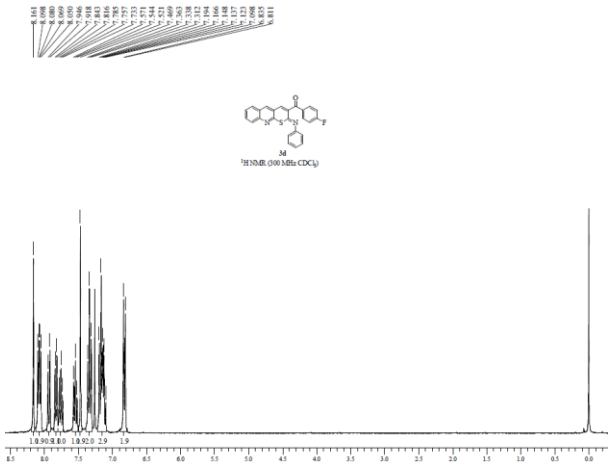


Figure 9: ^{1}H NMR of (Z)-(4-Fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3d).

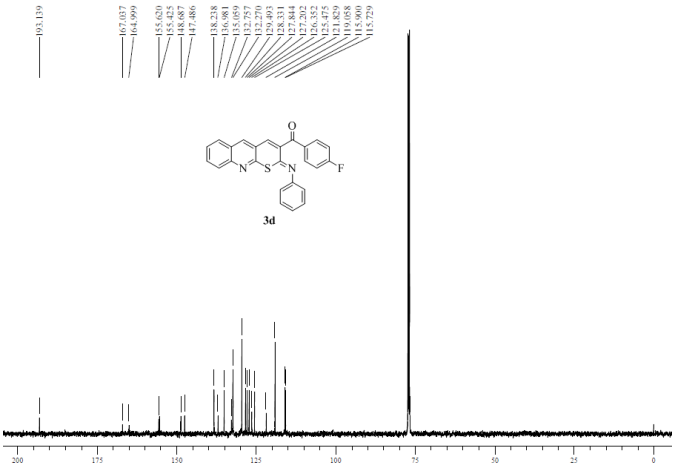


Figure 10: ^{13}C NMR of Z)-(4-Fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3d).

(Z)-(4-Chlorophenyl)(2-(phenylimino)-2*H*-thiopyrano [2,3-*b*]quinolin-3-yl)methanone (3e)

Yellow solid; Yield: 83%; R_f (30% EtOAc/hexane) 0.49; m.p. 202-203^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 7.5 Hz, 2H), 7.12 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 7.7 Hz, 2H), 7.46 (d, J = 8.8 Hz, 3H), 7.54 (t, J = 7.7 Hz, 1H)), 7.75 (t, J = 8.1, Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.9, 121.8, 125.2, 126.2, 127.0, 128.2, 128.8, 129.4, 130.8, 132.0, 134.7, 135.0, 137.0, 137.7, 139.9, 147.7, 148.9, 155.4, 193.5; IR (KBr) υ_{max} 3052, 1665, 1588, 1544, 1256, 1083, 756 cm^{-1}; ESI-MS 427 [M+H]$^+$; HRMS (ESI) calcd for $C_{25}H_{15}ON_2ClS$ [M+H]$^+$427.06664, found 427.06607. (Figure 11and 12)

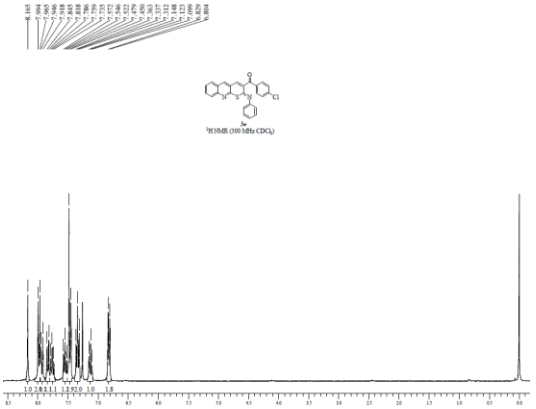


Figure 11: ^{1}H NMR of (Z)-(4-Chlorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3e).

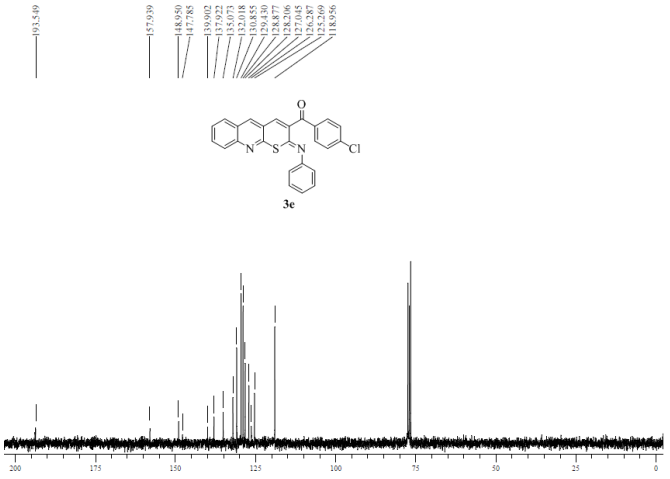


Figure 12: ^{13}C NMR of (Z)-(4-Chlorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3yl)methanone (3e).

(Z)-(2-fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano [2,3-*b*]quinolin-3-yl)methanone (3f)

Yellow solid; Yield: 88%; R_f (30% EtOAc/hexane) 0.48;m.p. 152-153^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.3 Hz, 2H), 7.13 – 7.08 (m, 2H), 7.27 (s, 1H), 7.32 (t, *J*= 8.3 Hz, 2H), 7.53 (t, *J*= 7.0 Hz, 2H), 7.59 (s, 1H), 7.74 (t, *J*= 8.3 Hz,1H), 7.82 (d, *J*= 7.6 Hz, 1H), 7.91 (d, *J*= 9.0 Hz, 1H), 7.99 (t, *J*= 7.6 Hz, 1H), 8.19 (s 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.04 (d, *J*= 23.61 Hz), 118.9, 122.1, 124.53 (d, *J*= 2.72 Hz), 125.0, 126.13 (d, *J*= 10.89 Hz), 126.3, 126.9, 128.20 (d, *J*= 16.34 Hz), 129.4, 130.8, 131.9, 134.78 (d, *J*= 9.08 Hz), 135.2, 138.3, 138.6, 147.7, 149.1, 155.4, 155.9, 161.45 (d, *J*= 255.2 Hz), 190.7; IR (KBr) υ_{max} 2925, 1655, 1610, 1586, 1556, 1286, 753 cm^{-1}; ESI-MS 411 $[M+H]^+$; HRMS (ESI) calcd for $C_{25}H_{15}ON_2FS$ $[M+H]^+$411.09619, found 411.09595. (Figure 13 and 14)

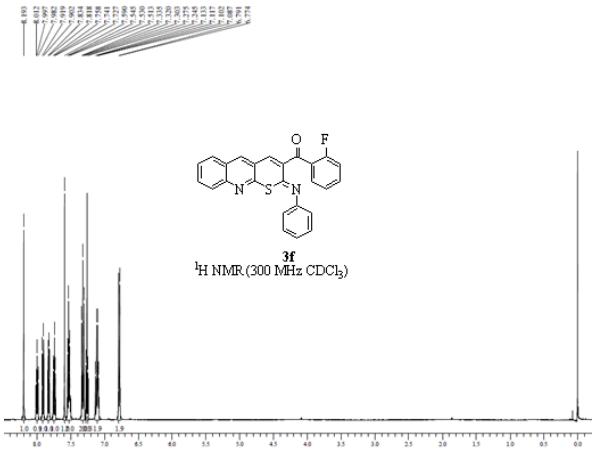


Figure 13: ^{1}H NMR (Z)-(2-fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3f).

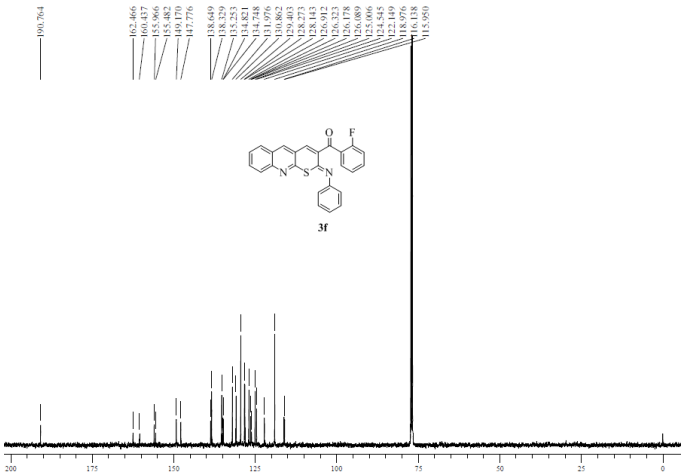


Figure 14: ^{13}C NMR (Z)-(2-fluorophenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3f).

(Z)-(7-Methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)(phenyl)methanone (3g)

Yellow solid; Yield: 90%; R_f (30% EtOAc/hexane) 0.50;m.p. 167-168 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 6.81 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 3.2 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 8.2 Hz, 2H),7.41-7.39 (q, 1H), 7.45 (d, J = 4.5 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 7.62-7.53 (m, 2H), 7.83 (d, J = 9.3 Hz, 1H), 8.05 (t, J = 3.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 104.1, 105.2, 119.0, 122.0, 124.8, 125.0, 125.7, 127.4, 128.4, 128.6, 128.9, 129.0, 129.3, 129.5, 129.6, 133.4, 134.6, 135.2, 136.4, 149.2, 158.0, 194.8; IR (KBr) υ_{max} 3423, 3057, 2926, 1666, 1619, 1552, 1221 cm^{-1}; ESI-MS 423 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{18}O_2N_2S$ $[M+H]^+$423.11618, found 423.11556. (Figure 15and16)

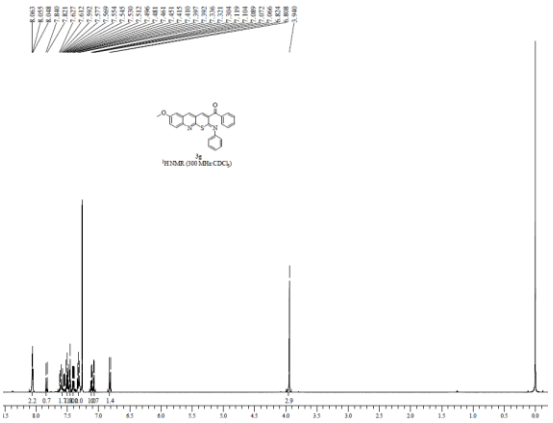


Figure 15: ^1H NMR of (Z)-(7-Methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3g).

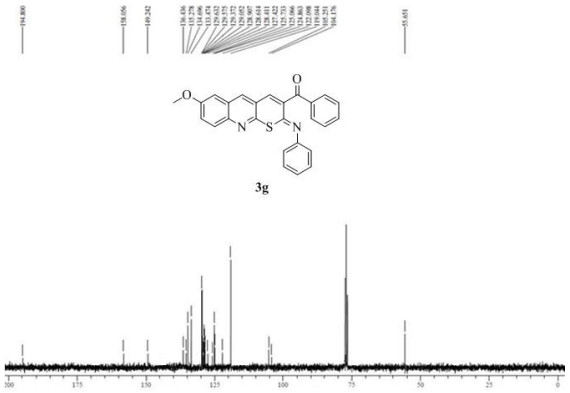


Figure 16: ^{13}C NMR of (Z)-(7-Methoxy-2-(phenylimino)-2H-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3g).

(Z)-(4-Fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl)methanone (3h)

Yellow solid; Yield: 89%; R_f (30% EtOAc/hexane) 0.48; m.p. 179-180 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 6.81 (d, J = 7.3 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 7.11 (t, J = 7.3 Hz, 2H), 7.16 (t, J = 8.5 Hz, 2H), 7.34 - 7.29 (m, 2H), 7.42 - 7.39 (m, 1H), 7.45 (s, 1H), 7.69 - 7.60 (m, 1H), 7.83 (d, J = 9.1 Hz, 1H), 8.09 -8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 105.2, 115.72 (d, J = 21.79 Hz), 118.9, 121.9, 124.9,125.1, 125.8, 126.3, 127.3, 128.4, 128.8, 129.4, 129.62 (d, J = 8.17 Hz), 132.20 (d, J = 9.99 Hz), 132.8, 134.8, 135.3, 136.5, 137.2, 140.3, 141.1, 149.1, 152.4, 155.9, 158.0, 165.92 (d, J = 255.21 Hz), 193.27; IR (KBr) υ_{max} 3055, 2928, 1665, 1621, 1596, 1552, 1224, 694 cm^{-1}; ESI-MS 441$[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{17}O_2FN_2S$ $[M+H]^+$ 441.10675,found441.10592. (Figure 17 and 18)

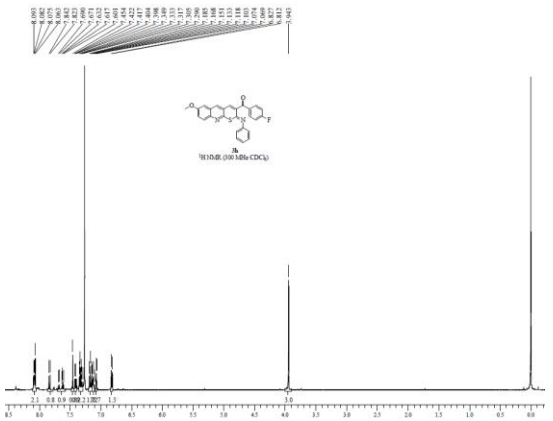


Figure 17: ^1H NMR of (Z)-(4-Fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3b]quinolin-3-yl)methanone (3h).

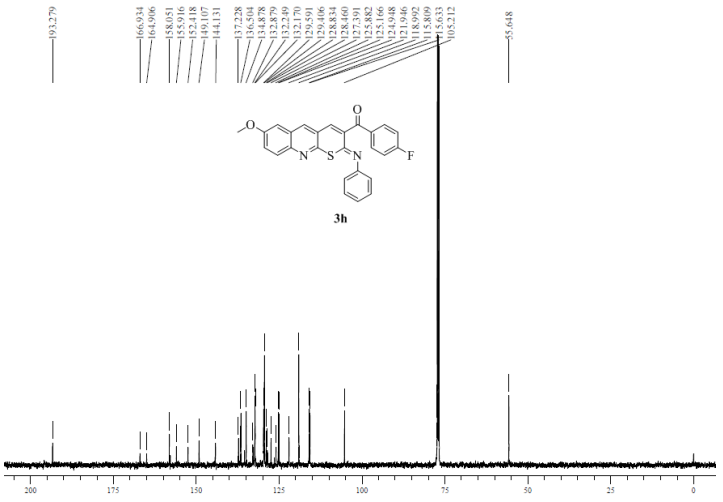


Figure 18: ^{13}C NMR of (Z)-(4-Fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3b]quinolin-3-yl)methanone (3h).

(Z)-Benzo[*d*][1,3]dioxol-5-yl(7-methoxy-2-(phenylimino) -2*H*-thiopyrano[2,3-*b*]quinolin-3-yl)methanone (3i)

Yellow solid; Yield: 81%; R_f (30% EtOAc/hexane) 0.46; m.p. 181-182ºC ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.05 (s, 2H), 6.85 (d, J = 7.4 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H),7.33 (t, J = 7.9 Hz, 2H), 7.40-7.32 (m, 2H), 7.53 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.81(d, J=9.1 Hz,1H), 8.01(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 101.9, 105.1, 107.9, 108.8, 119.0, 122.0, 124.7, 125.0, 126.8, 127.3, 129.3, 129.5, 131.1, 134.2, 136.2, 137.5, 144.0, 148.2, 149.3, 152.2, 152.4, 156.0, 157.9, 192.8; ; IR (KBr) υ_{max} 2912, 1658, 1622, 1558, 1490, 1440, 1259, 1215, 1034 cm^{-1}; ESI-MS 467 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{18}N_2O_4S$ $[M+H]^+$ 467.51100, found 467.51110.(Figure 19,20)

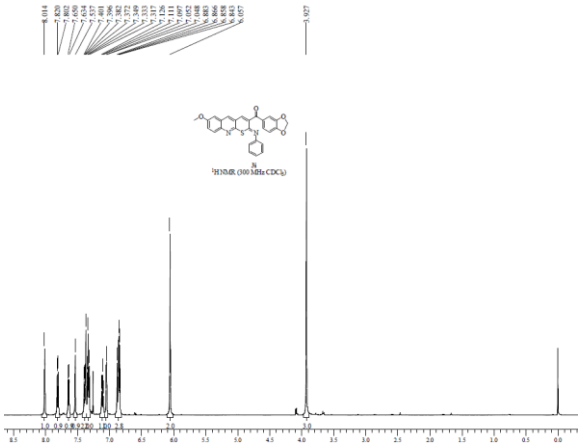


Figure 19: ^{1}H NMR of (Z)-Benzo[d][1,3]dioxol-5-yl(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3i).

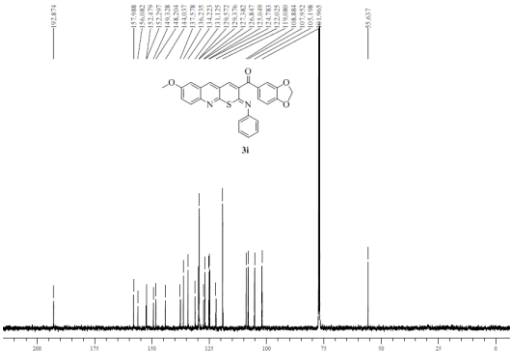


Figure 20: ^{13}C NMR of (Z)-Benzo[d][1,3]dioxol-5-yl(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3i).

(Z)-(4-ethylphenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl)methanone (3j)

Yellow solid; Yield: 87%; R_f (30% EtOAc/hexane) 0.52; m.p. 182-183 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.6 Hz, 3H), 2.74 –2.70 (q, 2H), 3.93 (s, 3H), 6.83 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 2.7 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.34 - 7.29 (m, 4H), 7.40 – 7.38 (m, 2H), 7.82 (d, J = 9.3 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 29.0, 55.6, 105.2, 119.0, 122.1, 124.7, 125.0, 127.4, 128.0,

128.9, 129.3, 129.6, 129.9, 133.9, 134.3, 136.2, 137.8, 144.0, 149.3, 150.7, 152.5, 156.0, 158.0, 194.3; IR (KBr) υ_{max} 2915, 1629, 1615, 1530, 1218, 1020 cm^{-1}; ESI-MS 451 $[M+H]^+$; HRMS (ESI) calcd for $C_{28}H_{22}N_2O_2S$ $[M+H]^+$ 451.14655, found 451.14655. (Figure 21 and 22)

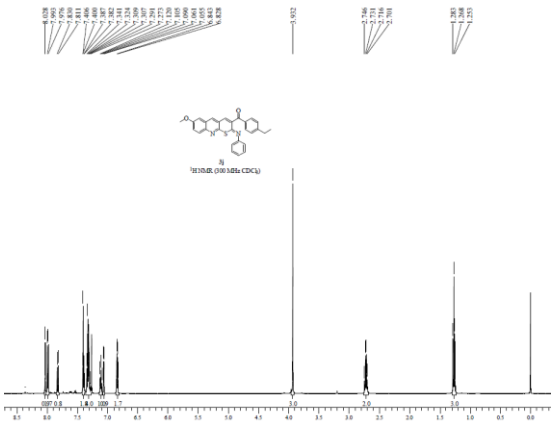


Figure 21: ^{1}H NMR of (Z)-(4-ethylphenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3j).

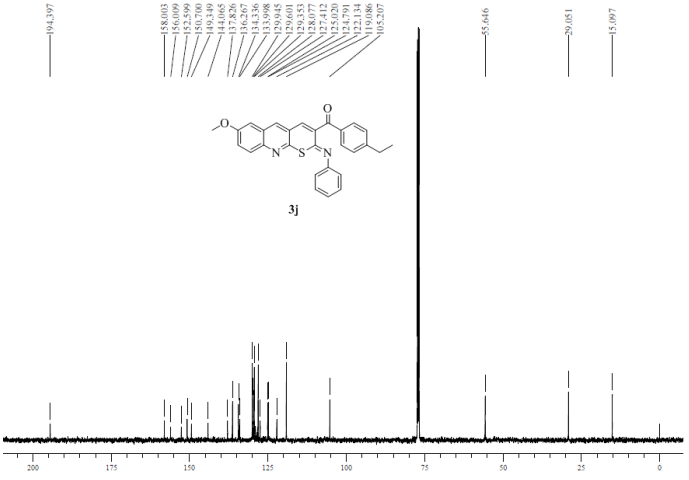


Figure 22: ^{13}C NMR of (Z)-(4-ethylphenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3j).

(Z)-(7-methoxy-2-((4-methoxyphenyl)imino)-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl) (phenyl)methanone (3k)

Yellow solid; Yield: 79%; R_f (30% EtOAc/hexane) 0.50; m.p. 191-192 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.93 (s, 3H), 6.87 – 6.80 (m, 4H), 7.06 (d, J = 2.6 Hz, 1H), 7.40 - 7.38 (m, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 55.6, 105.2, 114.4, 120.9, 124.8, 128.5, 129.6, 133.4, 134.1, 136.2, 136.4, 137.9, 142.2, 154.9, 158.0, 195.4; IR (KBr) υ_{max} 3414, 2928, 1674, 1626, 1546, 1493, 1218, 1163 cm^{-1}; ESI-MS 453 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{20}N_2O_3S$ $[M+H]^+$ 453.12674, found 453.12556. (Figure 23,24)

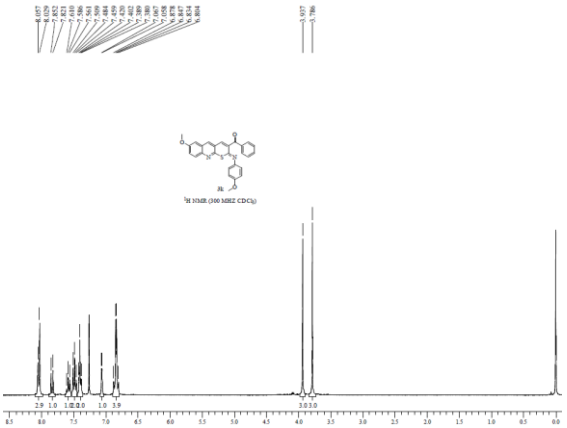


Figure 23: ^{1}H NMR of (Z)-(7-methoxy-2-((4-methoxyphenyl)imino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3k).

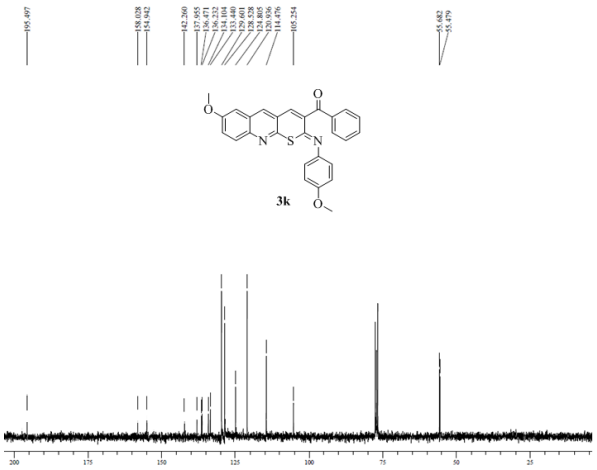


Figure 24: ^{13}C NMR of (Z)-(7-methoxy-2-((4-methoxyphenyl)imino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3k).

(Z)-(2-chlorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl) methanone (3l)

Yellow solid; Yield: 88%; R_f (30% EtOAc/hexane) 0.51; m.p. 176-177 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 6.71 (d, J = 7.4 Hz, 1H), 7.12 - 7.07 (m, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.40 – 7.31 (m, 6H), 7.76 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 9.4 Hz, 1H), 8.129 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 105.3, 118.8, 125.0, 126.9, 129.3, 129.5, 130.0, 130.5, 130.9, 132.2, 136.0, 137.1, 137.4, 137.6, 137.9, 144.2, 149.1, 153.2, 154.9, 157.9, 160.0, 193.5; IR (KBr) υ_{max} 2930, 1652, 1625, 1520, 1215, 1034, 742 cm^{-1}; ESI-MS 457 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{17}N_2O_2ClS$ $[M+H]^+$ 457.06993, found 457.06988. (Figure 25 and 26)

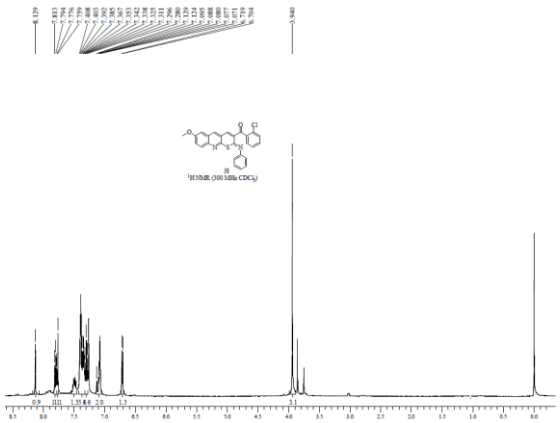


Figure 25: ^{1}H NMR of (Z)-(2-chlorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3l).

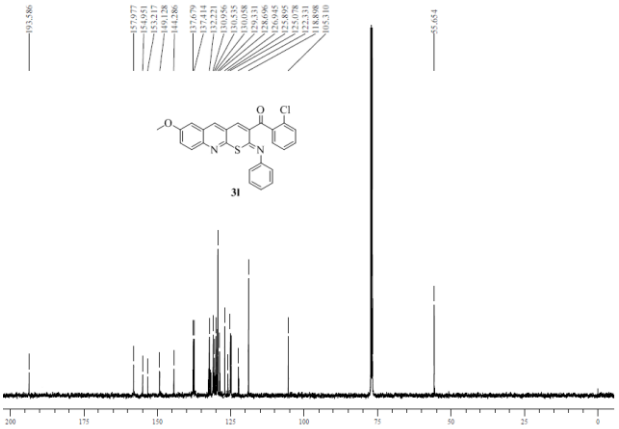


Figure 26: ^{13}C NMR of (Z)-(2-chlorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3l).

(Z)-(2-fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl)methanone (3m)

Yellow solid; Yield: 84%; R_f (30% EtOAc/hexane) 0.48; m.p. 185-186 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 3H), 7.05 – 7.01 (m, 1H), 7.12 (d, J = 2.6 Hz, 1H), 7.28 (t, J = 7.7 Hz, 3H), 7.39 - 7.36 (m, 1H), 7.52 (t, J = 7.4 Hz, 2H), 7.60 (t, J = 7.7 Hz, 2H), 7.67 (d, J = 9.3 Hz, 1H), 7.78 (s, 1H), 8.09 (t, J = 7.7 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 105.3, 118.8, 124.8, 125.0, 126.9, 129.3, 129.5, 130.0, 130.5, 130.9,

131.7, 131.9, 132.33 (d, *J* = 27.10 Hz), 137.27 (d, *J* = 30.1 Hz), 137.6, 137.9, 144.2, 149.1, 156.4 (d, *J* = 255.26 Hz), 193.5; IR (KBr) υ_{max} 3414, 2925, 1651, 1607, 1222 cm^{-1}; ESI-MS 441 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{17}N_2O_2SF$ $[M+H]^+$ 441.11933, found 441.10743. (Figure 27 and 28)

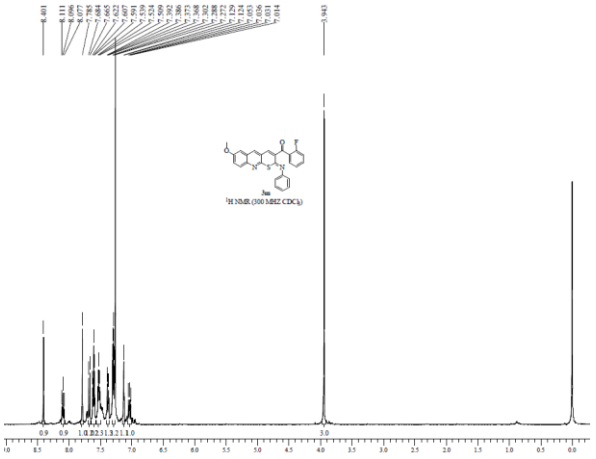


Figure 27: ^{1}H NMR of (Z)-(2-fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3m).

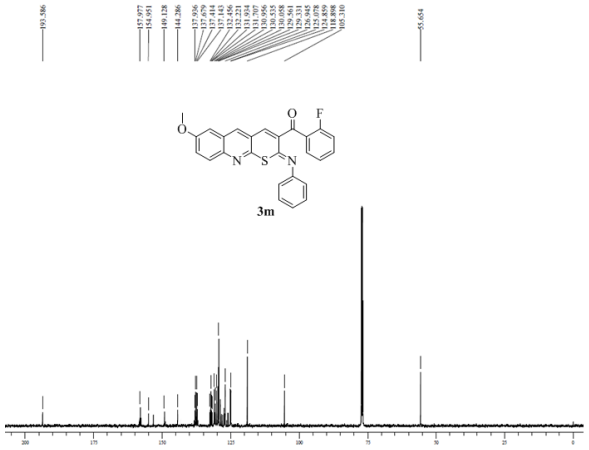


Figure 28: ^{13}CNMR of (Z)-(2-fluorophenyl)(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)methanone (3m).

(Z)-(2-((2,4-dichlorophenyl)imino)-7-methoxy-2*H*-thiopyrano[2,3-*b*]quinolin-3-yl)(phenyl)methanone (3n)

Yellow solid; Yield: 75%; R_f (30% EtOAc/hexane) 0.49; m.p. 179-180 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 7.55 - 7.39 (m, 6H), 7.65 – 7.60 (m, 2H), 7.82 (d, *J* = 9.2 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 113.8, 119.30, 121.9, 125.0, 126.3, 126.9, 128.5, 129.3, 131.7, 132.1, 134.1, 137.5, 137.7, 147.6, 149.2, 155.5, 155.7, 163.9, 193.1; IR (KBr) υ_{max} 2923, 1667, 1626, 1552, 1232, 1220, 831 cm^{-1}; ESI-MS 491 $[M+H]^+$; HRMS (ESI) calcd for $C_{26}H_{16}N_2O_2SCl_2$ $[M+H]^+$ 491.03823, found 491.03842.(Figure 29 and 30)

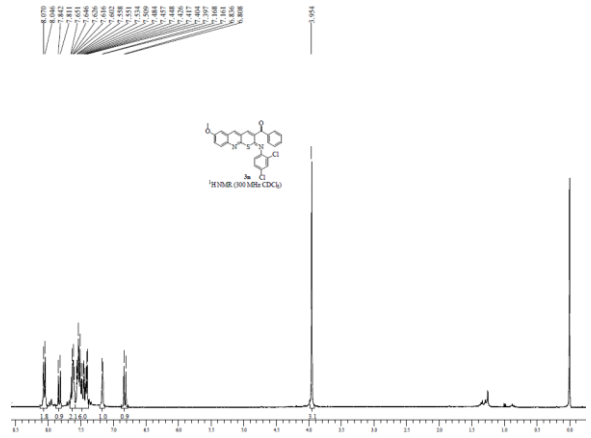


Figure 29: ^{1}H NMR of (Z)-(2-((2,4-dichlorophenyl)imino)-7-methoxy-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3n).

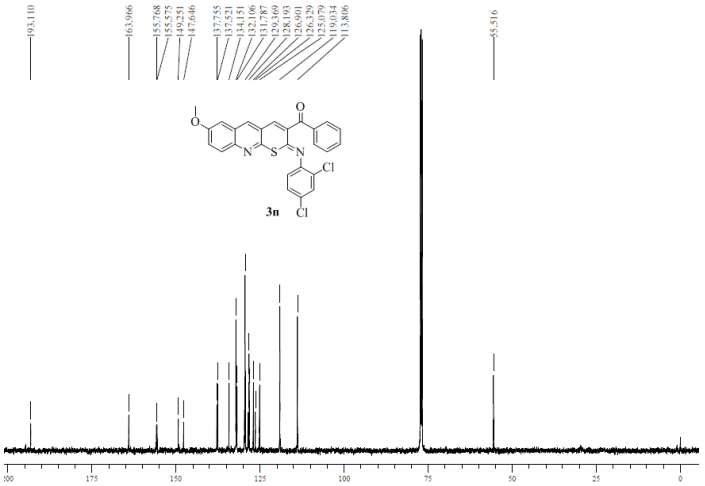


Figure 30: ^{13}C NMR of (Z)-(2-((2,4-dichlorophenyl)imino)-7-methoxy-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(phenyl)methanone (3n).

(Z)-(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)(4-methoxyphenyl) methanone (3o)

Yellow solid; Yield: 84%; R_f (30% EtOAc/hexane) 0.47; m.p. 195-196 $^{\circ}$C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (d, J = 5.4 Hz, 3H), 3.98 (s, 3H), 6.84 (d, J = 7.31 Hz, 1H), 6.97 (d, J = 9.1 Hz, 2H), 7.13 - 7.05 (m, 2H), 7.41 - 7.29 (m, 4H), 7.69 - 7.53 (m, 1H), 7.82 (d, J = 9.1 Hz, 1H), 8.05 – 7.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 55.6, 105.1, 113.8, 113.9, 119.0, 122.1, 124.7, 125.0, 125.6, 127.4, 128.8, 129.3, 129.5, 132.1, 134.2, 136.2, 144.0, 149.3, 156.0,157.9, 163.9, 193.2; IR (KBr) υ_{max}2931, 1601, 1546, 1255, 1218, 1029 cm^{-1}; ESI-MS 453 [M+H]$^+$; HRMS (ESI) calcd for $C_{27}H_{20}N_2O_3S$ [M+H]$^+$ 453.12674, found 453.12567. (Figure 31 and 32)

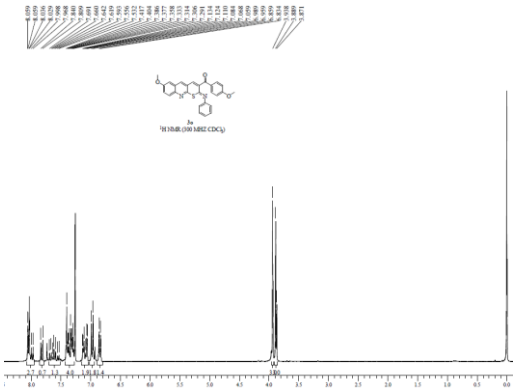


Figure 31: ^{1}H NMR of (Z)-(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(4-methoxyphenyl)methanone (3o).

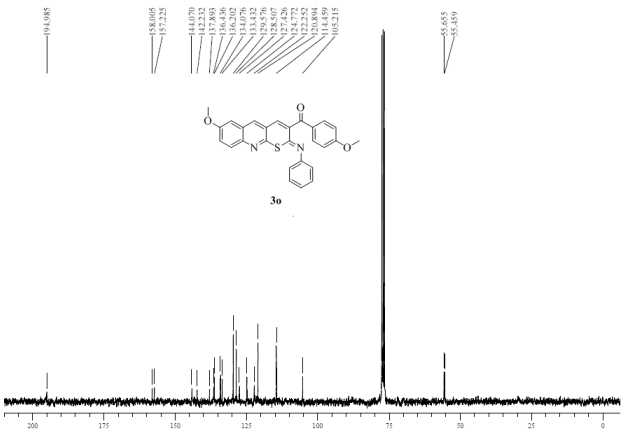


Figure 32: ^{13}C NMR of (Z)-(7-methoxy-2-(phenylimino)-2*H*-thiopyrano[2,3-b]quinolin-3-yl)(4-methoxyphenyl)methanone (3o).

(4-Ethylphenyl)(1-phenyl-2-thioxo-1,2-dihydrobenzo[*b*][1,8]naphthyridin-3-yl) methanone (4a)

Brick red solid; Yield (10%); R_f (30% EtOAc/hexane) 0.47; m.p. 245-246^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3H), 2.74-2.67 (q, J = 7.5 Hz, 2H), 7.29 (d, J = 8.3 Hz, 3H), 7.32 (s, 1H), 7.57-7.50 (m, 2H), 7.62 (t, J= 8.3 Hz, 2H), 7.71 (t, J= 10.0 Hz, 1H), 7.77 (d, J= 10.0, 2H), 7.91 (t, J= 8.3 Hz, 3H), 8.49 (s 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 29.0, 117.7, 125.3, 126.3, 127.8, 128.2, 128.4, 128.8, 129.1, 129.6, 129.9, 131.9, 134.0, 137.1, 140.4, 142.2, 148.0, 149.9, 150.6, 186.4,192.4; IR (KBr) υ_{max} 2926, 1660, 1610, 1287, 730 cm^{-1}; ESI-MS 421[M+H]$^+$; HRMS (ESI)

calcd for $C_{27}H_{20}ON_2S$ $[M+H]^+$ 421.13691, found 421.13553. (Figure 33 and 34)

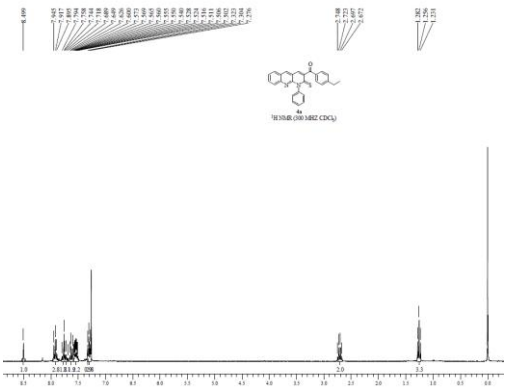


Figure 33: ^{1}H NMR of (4-Ethylphenyl)(1-phenyl-2-thioxo-1,2-dihydrobenzo [b][1,8] naphthyridin-3- yl)methanone (4a).

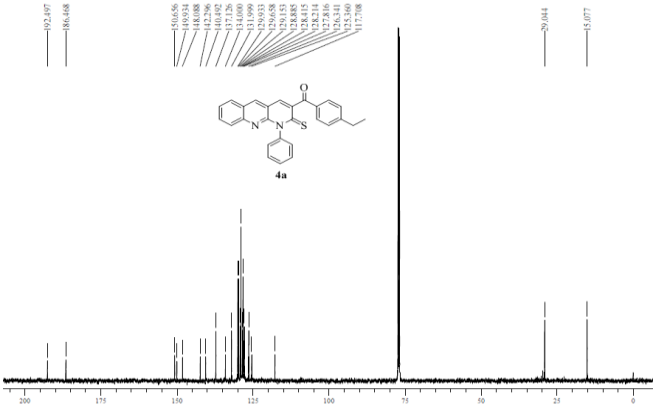
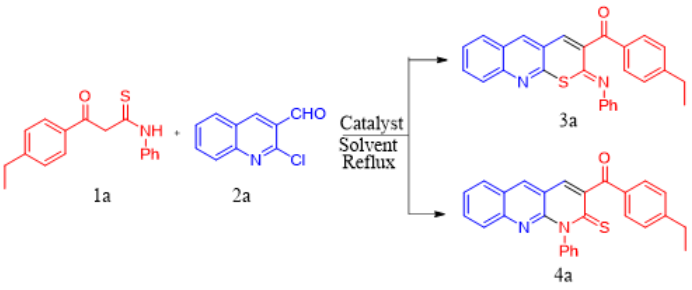


Figure 34: ^{13}C NMR of (4-Ethylphenyl)(1-phenyl-2-thioxo-1,2-dihydro benzo [b] [1,8] naphthyridin-3- yl)methanone (4a).

RESULT AND DISCUSION

In a typical reaction, 3-(4-ethylphenyl)-3-oxo-N-phenyl propanethioamide (**1a**) and 2-chloroquinoline-3-carbaldehyde (**2a**) were reacted in ethanol using DMAP (10 mol%) as catalyst under different set of conditions. Initially, the reaction was conducted at room temperature for 24 hours and found to be no reaction (Table 1, entry 2). However, the same reaction was conducted under reflux condition for 4 hours (Table 1, entry 3) resulted two isomers such as (*Z*)-(4-Ethyl phenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)methanone **3a** (90%, S-cyclization product) and trace amount of (4-Ethylphenyl)(1-phenyl-2-thioxo-1,2-dihydrobenzo[*b*][1,8 naphthyridin-3-yl)methanone **4a** (*N*-cyclization product). Encouraging by this result, we extensively screened the effect of solvents on the formation of products. The reaction is conducted in different solvents such as toluene, THF, DMF, H2O and Dioxane with DMAP (10 mol%) as a catalyst under reflux conditions and observed the less yields when compared to initial hit solvent ethanol (Table 1, entry 4-9). (Scheme 1).



Scheme 1: Synthesis of compound 3a and compound 4a

Table1: Optimization studies for the synthesis of compound 3a and compound 4a.

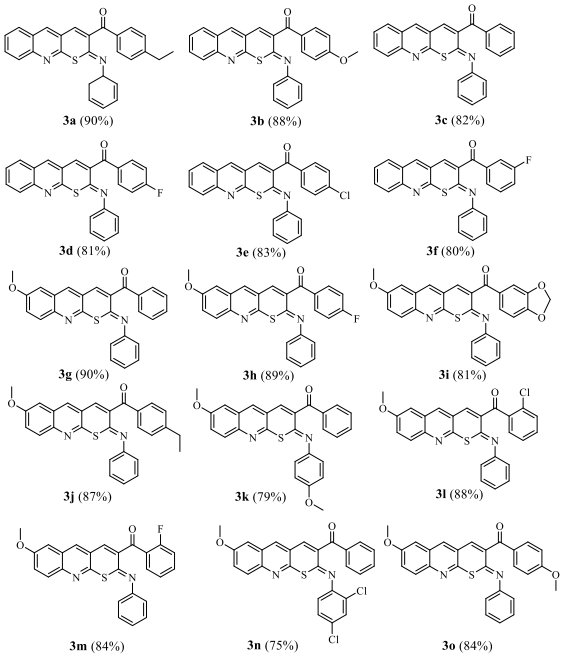
S no	Catalyst (mol%)	Solvent	Time(h)	Temp(C)	Yield(3a)	Yield(4a)
1		EtOH	24	rt	NR	NR
2	DMAP(10)	EtOH	24	rt	NR	NR
3	DMAP(10)	EtOH	4	reflux	90	trace
4	DMAP(10)	Toluene	4	reflux	85	trace

5	DMAP(10)	THF	4	reflux	82	trace
6	DMAP(10)	DMF	4	reflux	80	trace
7	DMAP(10)	Dioxane	4	reflux	78	trace
8	DMAP(10)	CH3CN	4	reflux	81	trace
9	DMAP(10)	water	4	reflux	NR	NR
10	DMAP(20)	EtOH	4	reflux	86	trace
11	DMAP(5)	EtOH	4	reflux	70	trace
12	Piparazine(10)	EtOH	4	reflux	72	10
13	DABCO(10)	EtOH	4	reflux	65	8
14	Et3N(10)	EtOH	4	reflux	78	8
15	ALCL3(10)	EtOH	4	reflux	NR	NR
16	InCL3(10)	EtOH	4	reflux	NR	NR
17	K2CO3(10)	EtOH	4	reflux	NR	NR
18	KOH(10)	EtOH	4	reflux	NR	NR
19	BF3ET2O(10)	EtOH	4	reflux	NR	NR

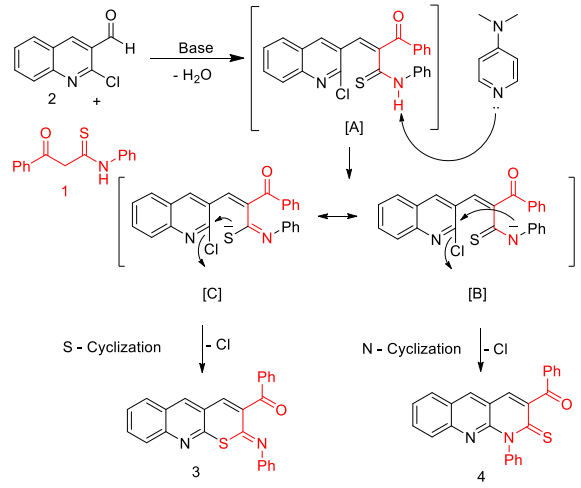
To study the feasibility, we examined the reaction in ethanol with a different kind of catalysts such as piperazine, DABCO, pyrrolidine, triethylamine, Aluminium(III) chloride, Indium(III) chloride, potassium carbonate, potassium hydroxide, and Boron trifluoride diethyl etherate 10 mol% each under reflux conditions (Table 1, entry 12-19). In the case of piperazine, we found title compound 3a in 72% yield along with the compound dihydrobenzo[b][1,8] naphthyridin **(4a)** in 10% yield and both these structures are confirmed by a single X-ray crystallography technique. DMAP is the preferred catalyst in ethanol solvent facilitated a higher product yield (**Table 1, entry 3**). The detailed screening of solvents and catalysts are tabulated in Table 1.

By using the above-optimized conditions, we have synthesized several thiopyrano quinoline compounds and found that it is tolerated in different electron-withdrawing and releasing groups. Compound **1** having electron-donating groups (ethyl or methoxy) proceeded the reaction smoothly to afford the corresponding products **3a** (92%), **3b** (92%), **3j** (87%), and **3o** (84%) in excellent yields. The halogen group (fluorine and chlorine on aryl group R1) substituted β-aroyl-thioacetanilides have easily tolerated the reaction and furnished the corresponding products **3d, 3e, 3f, 3h, 3m** and **3l** respectively in excellent yields (81%, 83%, 80%, 89%, 92% and 95%). Further, we examined the para-methoxy and ortho, para-dichloro substituted β-aroyl-thioacetanilide (on aryl group R_2) and observed the product **3k** (79%) and **3n** (75%) in good yields.

A plausible mechanism for the product formation is indicated in **Scheme 3**, the first step consists of DMAP catalyzed Knovenagel condensation between the quinoline aldehyde [**2**] and active methylene group of 3-oxo-N,3-diarylpropanethioamide [**1**] leading to the formation of intermediate [**A**] (Z)-2-benzoyl-3-(2-chloroquinolin-3-yl)-N-phenylprop-2-enethioamide next, the (DMAP) base abstract the proton from [**A**] generated anion on –NH- gives intermediate [**B**], which undergoes rapid keto-enol tautomerization forms intermediate [**C**] further chemo-selective intramolecular S-cyclization to yielded the product **3** and a trace amount of N- cyclization to forms the product **4** outlined in **Scheme 2**.



Scheme 2: Scope of β-aroyl-thioacetanilides (1) and 2-chloro quinoline-3-carbaldehyde (2).



Scheme 3: Mechanism for the formation of compound 3 and 4.

The newly synthesized polysubstituted thiopyrano[2,3-*b*]quinolines (**3a-3o**) and benzo[*b*][1,8] naphthyridine derivative (**4a**) were thoroughly characterized by IR, HRMS, ^{1}H- and ^{13}C-NMR spectral data. The individual structures of (Z)-(4-Ethylphenyl)(2-(phenylimino)-2*H*-thiopyrano[2,3-*b*] quinolin-3-yl)methanone (**3a**) and (4-Ethylphenyl)(1-phenyl-2-thioxo-1,2-dihydrobenzo[b][1,8] naphthyridin-3-yl)methanone (**4a**) were further established by the X-ray diffraction analysis (Figure 35) of their single crystals obtained from ethanol.

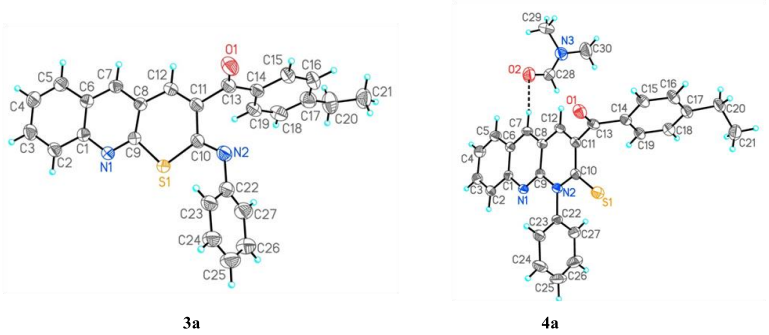


Figure 35: Representative X-ray crystallography structures of **3a** and **4a**. CCDC number of **3a** is **1561445** and CCDC number of **4a** is **1561446**.

CONCLUSION

In summary, we have successfully developed a simple, efficient DMAP catalyzed cascade protocol for the synthesis of variously substituted functionalized thiopyrano [2,3-*b*]quinoline derivatives (**3a-3o**) accessible β-aroyl-acetanilides and 2-chloro quinoline-3-carbaldehydes , This protocol is effective along with well functional group tolerance which demonstrate its synthetic importance.

ACKNOWLEDGMENT

The authors acknowledge the financial support from the Council of Scientific and Industrial Research (CSIR-IICT), India.

REFERENCES

[1] Raveendra D, Laith Al-Mawsawi Q, Zahrah Z et al., J Med Chem. **2008**, 51: p. 1136.
[2] Roma G, Braccio MD, Grossi G et al., Eur. J. Med. Chem. **2000**, 11: p. 1021.
[3] Masanao S. J Infect Chemother. **1995**, 1: p. 16-29.
[4] Richard MB, Frans JS, Richard KH et al., Malaria Journal. **2014**, 1: p. 339.
[5] Rolf WW, Jane XK, Martin JS et al., Exp Parasitol. **2008**, 118: p. 487–497.
[6] Stocks PA, Raynes KJ and Ward SA. Novel Quinoline Antimalarials.
[7] Chauhan PMS and Srivastava SK. Curr Med Chem. **2001**, 8: p.1535
[8] Kaur K, Jain M, Reddy RP et al., Eur J Med Chem. **2010**, 45: p.3245.
[9] Musiol R, Serda M and Hensel-Bielowka PJS. Curr Med Chem. **2010**, 17: p. 1960.
[10] Chen YL, Fang KC, Sheu JY et al., J Med Chem. **2001**, 44: p. 2374.
[11] Ferrarini PL, Mori C and Badawneh M. Eur J Chem. **2000**, 35: p. 815.
[12] Fatemeh T, Tayebeh B, Zinatossadat H et al., Mehdi nucle aicds therapeutics. **2012**, 22: p. 265.
[13] Solomon VR and Lee H. Curr Med Chem. **2011**, 18: p. 1488.
[14] Schneller SW. Adv Heterocycl Chem. **1975**, 18: p. 59
[15] Chen QP, Leslie WD, Bruce CB et al., J Med Chem. **1994**, 37: p. 593
[16] Wissner A, Hamann PR and Yamashita A. WO0066583, 2000, CAN 133, 350203.
[17] Mabire D, Coupa S, Adelinet C et al., J Med Chem. **2005**, 48: p. 2134.
[18] Naik HRP, Naik HSB, Naik TRR et al., Med Chem. **2009**, 5: p. 148.

[19] Wang XS, Li Q, Wu JR et al., J Comb Chem. **2009**, 11: p. 433.
[20] Singh B, Chandra A, Asthana M et al., Tetrahedron Lett. **2012**, 53: p. 3242.
[21] Kanani MB and Patel MP. RSC Adv. **2014**, 4: p. 28798.
[22] Srikanthreddy N, Sreenivas A, Ranthankarreddy K et al., Tetrahedron. **2017**, 73: p. 4730.
[23] Srikanth Reddy N, Ravi Kumar N, Krishna Swaroop D et al., Eur J Org Chem. **2019**, 13: p. 2409
[24] Sreenivas A, Satish K, Reddy KJ et al., RSC Advances. **2013**, 3: p. 20990.
[25] Sreenivas A, JagadeeshBabu N and Rambabu Y. Tetrahedron. **2014**, 70: p. 5768.