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ORIGINAL PAPER

One-pot synthesis of 2-aminotetrahydrothiopyrano[4,3-*b*]-pyran-3-carbonitrile derivatives using mesoporous NH_2-MCM-41

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Abstract A facile and general procedure is presented for the one-pot synthesis of 2-aminotetrahydrothiopyrano[4,3-*b*]pyran-3-carbonitrile derivatives. It is based on the three-component condensation of aliphatic, aromatic, or heterocyclic aldehydes, malononitrile, and thiopyran in the presence of mesoporous amino-functionalized MCM-41 silica in ethanol. This efficient technique has the advantage of giving 2-aminotetrahydrothiopyrano[4,3-*b*]pyran-3-carbonitrile derivatives using a heterogeneous mesoporous reagent in high yields, in short reaction times, and offers a simple product isolation procedure.

Keywords 2-Aminotetrahydrothiopyrano[4,3-*b*]-pyran-3-carbonitrile · Thiopyran · Amino-functionalized MCM-41 · One-pot synthesis

Introduction

4*H*-Chromene derivatives are important heterocyclic compounds with a number of biological and pharmacological properties including spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities [1]. 4*H*-Chromene derivatives are generally synthesized using a three-component reaction of cyclic 1,3-diketones, aryl aldehydes, and malononitrile under various reaction conditions. The conventional reported syntheses of 4*H*-chromene derivatives employ piperidine and triethylamine as catalytic or stoichiometric reagents in organic solvents [2–5]. In recent years, interest in this reaction has increased rapidly and several modified procedures have been reported [6–8]. Alternative and more efficient strategies for the synthesis of 4*H*-chromene derivatives involving different catalysts and conditions including alkylammonium salts [9, 10], $(NH_4)_2HPO_4$ [11], (*S*)-proline [12], $Re(PFO)_3$ [13], and KF-Al_2O_3 [14] have been described. Moreover, in view of the diverse therapeutic activity, this reaction was enlarged by the variation of the aldehyde, malononitrile derivatives [15], 1,3-dicarbonyl compound building blocks, including the use of cyclic ketones [16] and cyclic diketones [9, 17], and the use of 1- or 2-naphthol [18, 19] instead of ketones or diketones.

This work reports an efficient protocol for the synthesis of 4*H*-chromene derivatives using heterocyclic ketones instead of conventional ketones in the presence of mesoporous NH_2-MCM-41 silica. This is mainly motivated by recent reports highlighting the design of sulfur-containing drugs with interesting activities [20–23].

It should be noted that using heterocyclic ketones for the synthesis of 4*H*-chromene derivatives has been reported only in a few examples [24]. Nakib et al. [24] synthesized 2-amino-4-aryl-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran-3-carbonitriles by the reaction of 3-benzylidenethiochroman-4-one with malononitrile in the presence of piperidine in moderate yields. These derivatives displayed antifungal activity in vitro against the pathogenic fungi *Cryptococcus neoformans*, *Torulopsis glabrata*, *Trichosporon cutaneum*, *Candida albicans*, *C. paropsilosis*, and *C. tropicalis*.

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Results and discussion

In the framework of our studies on multicomponent reactions for the synthesis of 2-amino-5,6-dihydropyrimidin-4(3*H*)-one, 2-aminotetrahydro-4*H*-chromene, and 2-amino-4*H*-benzo[*h*]chromene derivatives using amino-functionalized MCM-41 as catalyst [25, 26] and in continuation of our interest in the application of mesoporous MCM-41, we report herein an efficient protocol for the synthesis of 2-aminothiopyran derivatives using heterocyclic ketones instead of conventional ketones. One-pot condensation of various aldehydes **1a**–**1k** with malononitrile (**2**) and thiopyran (**3**) in the presence of mesoporous amino-functionalized MCM-41 (NH_2-MCM-41) in refluxing ethanol was investigated for the synthesis of novel 2-aminotetrahydrothiopyrano[4,3-*b*]pyran-3-carbonitrile derivatives (Scheme 1).

Mesoporous MCM-41 silica utilized in this work was synthesized according to a previously reported procedure and functionalized with 3-aminopropyltriethoxysilane (APTES) [27–29]. Elemental analyses supported that the amine was immobilized on the surface. Brunauer–Emmett–Teller (BET) surface area measurement revealed that the MCM-41 surface area (1,018 m^2/g) decreased to 638 m^2/g after grafting APTES molecules. The amount of grafted amine on MCM-41 is estimated to be 3.24 mmol of amine per gram of silica [30].

The model reaction was carried out simply by mixing an equimolar quantity of *p*-nitrobenzaldehyde (**1e**), malononitrile, and thiopyran in ethanol. The resulting mixture was heated to reflux for the time indicated in Table 1. The progress of the reaction was monitored by TLC. Then the mixture was poured into hot ethanol and filtered through a sintered funnel. The filtrate was evaporated in vacuo. The crude product was purified by recrystallization in ethanol. When the reaction was carried out in refluxing ethanol as solvent in catalyst-free conditions, the reaction was relatively slow and no product was formed after 24 h (Table 1, entry 1). Increasing the reaction time did not show a significant effect on the yield.

We then examined the influence of $AlPW_{12}O_{40}{\cdot}XH_2O$ heteropolyacid (3 mol%) catalyst on this reaction (Table 1, entry 2). The catalyst was found to be inefficient for this reaction and no product was formed after 24 h in refluxing ethanol even with 6 mol% of catalyst (Table 1, entry 3).

Scheme 1

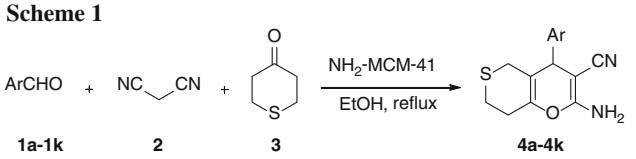


Table 1 Different conditions for the synthesis of 2-amino-4-(4-nitrophenyl)-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile (**4e**)

Entry	Catalyst/mol%	Time/h	Yield/%[a]
1	0	24	0
2	$AlPW_{12}O_{40}{\cdot}XH_2O$ (3)	24	0
3	$AlPW_{12}O_{40}{\cdot}XH_2O$ (6)	24	0
4	NH_2-MCM-41 (10)	8	53
5	NH_2-MCM-41 (20)	5	60
6	NH_2-MCM-41 (40)	2.5	85
7	NH_2-MCM-41 (100)	2.5	87

Reaction conditions: 4-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and thiopyran (1 mmol) in refluxing ethanol

[a] Isolated yield

Table 2 Synthesis of 2-amino-4-aryl-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile building blocks **4a**–**4k**

Entry	R	Product	Time/h	Yield/%[a]	M.p./°C
1	C_6H_5	**4a**	8	70	254.3
2	*p*-CH_3-C_6H_4	**4b**	5	75	231.3
3	*p*-OH-C_6H_4	**4c**	5.45	79	235.2
4	*m*-OH-C_6H_4	**4d**	8	65	237
5	*p*-NO_2-C_6H_4	**4e**	2.30	85	229.2
6	*m*-NO_2-C_6H_4	**4f**	4.30	97	237.2
7	*o*-NO_2-C_6H_4	**4g**	8	55	220.5
8	*p*-Cl-C_6H_4	**4h**	7	90	254.4
9	*p*-Br-C_6H_4	**4i**	3.30	90	257.2
10	*p*-CH_3O-C_6H_4	**4j**	2	80	245
11	2-Furanyl	**4k**	8	60	223.4

Reaction conditions: aldehyde (1 mmol), malononitrile (1.1 mmol), thiopyran (1 mmol), NH_2-MCM-41 (40 mol%) in refluxing ethanol

[a] Isolated yield

When the reaction was carried out in the presence of mesoporous NH_2-MCM-41 (10 mol%), the product **4e** was isolated in 53 % yield after 8 h in refluxing ethanol (Table 1, entry 4). The results suggest that amino-functionalized MCM-41 in ethanol can be used as an efficient and alternative reagent for this reaction. The results are summarized in Table 1.

The influence of the NH_2-MCM-41 concentration on the reaction yield was investigated. 2-Amino-4-(4-nitrophenyl)-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile (**4e**) was obtained in 60, 85, and 87 % yield by increasing NH_2-MCM-41 concentration to 20, 40, and 100 mol%, respectively (Table 1, entries 5–7). Increasing the NH_2-MCM-41 concentration over 40 mol% shows no significant effect on the yield, suggesting that 40 mol% of NH_2-MCM-41 is sufficient for this reaction.

We tested a variety of aldehydes **1a**–**1k** under the optimized reaction conditions. It should be noted that for an

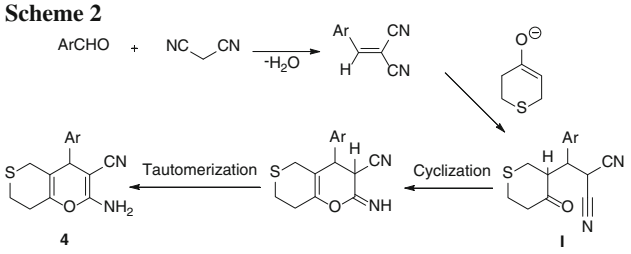
easy purification (facile elimination of the unreacted aldehyde), we used 1.1 equivalents of malononitrile for 1 equivalent of aldehyde. The results in Table 2 show that NH_2-MCM-41 can be used in the synthesis of 2-amino-4-aryl-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile building blocks **4a**–**4k** with various aromatic and heterocyclic aldehydes in high yields and short reaction times. The presence of electron-donating, electron-withdrawing, and heterocyclic groups on the aldehyde afforded the corresponding products in good to excellent yields. All compounds were characterized on the basis of their spectroscopic data such as ^{1}H and ^{13}C NMR, mass spectroscopy, infrared spectra, and elemental analysis.

We also investigated the reusability of the NH_2-MCM-41. After completion of the reaction, hot ethanol was added to the reaction mixture while stirring and the mixture was filtered through a sintered funnel to separate the insoluble catalyst. Then the mesoporous NH_2-MCM-41 was dried and re-used in another reaction. The recycled NH_2-MCM-41 was used for three consecutive reactions without any significant loss in its activity and the product **4e** was obtained in 85, 84, and 82 % yield, respectively.

A reasonable mechanism for this reaction is outlined in Scheme 2 [9]. The reaction may proceed through the arylidenemalononitrile intermediate (formed in situ by the reaction of an aldehyde with malononitrile), and the subsequent addition of enolate of thiopyran to the arylidenemalononitrile to generate the intermediate **I**. The cyclization of the intermediate **I** followed by tautomerization affords the corresponding 2-amino-4-aryl-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile building blocks **4a**–**4k** (Scheme 2). It should be noted that the presence of arylidenemalononitrile intermediate is made based on GCMS analysis. Furthermore, we obtained the same final product by performing the reaction in two steps: the first step consists in the synthesis of arylidenemalononitrile by the reaction of an aldehyde with malononitrile, and the second step is the reaction of the arylidenemalononitrile with thiopyran.

In conclusion, we have developed an efficient procedure for the synthesis of 2-amino-4-aryl-7,8-dihydro-4*H*,5*H*-thiopyrano[4,3-*b*]pyran-3-carbonitrile building blocks, which are often encountered in biologically active compounds. Formation of products using amino-functionalized MCM-41 as a highly promising environmentally friendly base reagent, in good to high yields within relatively short time periods, and ease of operation and purification make this protocol attractive. Reusability of amino-functionalized MCM-41 is an additional advantage. The reaction system can be successfully applied to a variety of aryl and heterocyclic aldehydes to synthesize a wide variety of novel heterocycles in good to high yields. Further investigations are needed to estimate the biological activity of these novel 2-aminothiopyran derivatives.

Scheme 2



Experimental

Melting points were determined in evacuated capillaries with a Büchi B-545 apparatus. ^{1}H NMR spectra were recorded on Bruker spectrometer at 80 or 500 MHz in DMSO-d_6 using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 100 or 125 MHz in DMSO-d_6. Mass spectra were obtained on a Fisons GC 8000/TRIO 1000 at 70 eV. Infrared (IR) spectra were recorded from KBr disks with a Bruker Vector 22 Fourier transform infrared (FTIR) spectrophotometer. Elemental analyses were performed on a ThermoFinigan Flash EA 1112 series elemental analyzer.

Synthesis of amino-functionalized MCM-41 (NH_2-MCM-41)

In a typical reaction, 1 g of MCM-41 was suspended in 50 cm^3 of toluene and the mixture was stirred for 1 h. To this mixture, 1.5 g of APTES was added and refluxed overnight. The white solid was filtered through a sintered funnel and was extracted using a Soxhlet extractor with toluene and dried overnight under reduced pressure at 70 °C [30].

Typical procedure for the synthesis of 2-aminothiopyran derivatives

A solution of aldehyde **1a**–**1k** (1 mmol), malononitrile (**2**, 1.1 mmol), and thiopyran (**3**, 1 mmol) in 2 cm^3 of ethanol was stirred mechanically in the presence of 40 mol% of mesoporous amino-functionalized MCM-41. The reaction mixture was refluxed for the time indicated in Table 2 and the progress of the reaction was monitored by TLC. Then the mixture was poured into hot ethanol and stirred for 30 min. The mixture was filtered through a sintered funnel and the solvent was evaporated in vacuo. For further purification the crude product was recrystallized from ethanol.

2-Amino-4-phenyl-7,8-dihydro-4H,5H-thiopyrano[4,3-b]-pyran-3-carbonitrile (**4a**, $C_{15}H_{14}N_2OS$)
M.p.: 254.3 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.21–2.31 (m, 2H, CH_2), 2.85–3.52 (m, 3H, CH_2), 3.65 (d, J = 14.4 Hz, 1H, CH_2), 5.80–6.05 (m, 1H, CH), 7.48 (br s, 7H, NH_2 and CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.45, 28.15, 35.57, 43.30, 49.92, 81.95, 112.46, 112.73, 116.46, 118.03, 129.37, 129.73, 130.07, 134.30, 144.61 ppm; MS (EI, 70 eV): *m/z* (%) = 270 (5, M^+), 228 (5), 193 (6), 77 (7); IR (KBr): $\bar{\nu}$ = 3,424, 3,343, 3,254, 2,923, 2,210, 1,646, 1,600, 1,455, 1,421, 1,391, 1,283 cm^{-1}; Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36 %. Found: C, 67.80; H, 5.30; N, 10.11 %.

2-Amino-4-(4-methylphenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4b**, $C_{16}H_{16}N_2OS$)
M.p.: 231.1 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.15–2.30 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.80–3.45 (m, 3H, CH_2), 3.58 (d, J = 12.0 Hz, 1H, CH_2), 5.80–6.00 (m, 1H, CH), 7.20–7.40 (m, 4H, CH arom), 7.45 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 21.18, 25.43, 28.14, 35.62, 43.41, 49.66, 81.92, 112.51, 112.81, 116.45, 117.94, 127.45, 129.95, 131.24, 139.18, 144.61 ppm; MS (EI, 70 eV): *m/z* (%) = 285 (1, $[M + 1]^+$), 242 (2), 115 (13), 91 (20), 75 (5), 45 (100); IR (KBr): $\bar{\nu}$ = 3,555, 3,426, 3,332, 3,222, 2,969, 2,874, 2,210, 1,644, 1,600, 1,515, 1,418, 1,388, 1,315, 1,281, 1,046 cm^{-1}; Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85 %. Found: C, 67.99; H, 5.64; N, 9.81 %.

2-Amino-4-(4-hydroxyphenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4c**, $C_{15}H_{14}N_2O_2S$)
M.p.: 235.2 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.10–2.40 (m, 2H, CH_2), 2.60–3.35 (m, 3H, CH_2), 3.49 (d, J = 14.4 Hz, 1H, CH_2), 5.85–6.10 (m, 1H, CH), 6.79 (d, J = 8.8 Hz, 2H, CH arom), 7.27 (d, J = 7.8 Hz, 2H, CH arom), 7.42 (br s, 2H, NH_2), 9.64 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.48, 28.22, 35.80, 43.69, 49.61, 81.96, 112.64, 112.84, 116.10, 116.50, 117.85, 124.21, 130.26, 144.67, 158.50 ppm; MS (EI, 70 eV): *m/z* (%) = 287 (1, $[M + 1]^+$), 261 (4), 244 (1), 115 (1), 75 (2), 29 (100); IR (KBr): $\bar{\nu}$ = 3,514, 3,419, 3,336, 3,231, 2,874, 2,209, 1,654, 1,613, 1,598, 1,516, 1,446, 1,417, 1,387, 1,342, 1,263, 1,213, 1,198, 1,177 cm^{-1}; Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78 %. Found: C, 63.37; H, 4.96; N, 9.63 %.

2-Amino-4-(3-hydroxyphenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4d**, $C_{15}H_{14}N_2O_2S$)
M.p.: 237.0 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.20–2.40 (m, 2H, CH_2), 2.90–3.70 (m, 4H, CH_2), 5.80–6.00 (m, 1H, CH), 6.70–7.40 (m, 5H, CH arom), 7.45 (br s, 2H, NH_2), 9.62 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.47, 28.01, 35.98, 43.14, 49.77, 81.89, 112.43, 112.83, 116.45, 117.86, 130.07, 130.43, 135.72, 144.78, 158.08 ppm; MS (EI, 70 eV): *m/z* (%) = 287 (3, $[M + 1]^+$), 261 (5), 244 (1), 195 (6), 75 (45), 45 (46), 31 (100); IR (KBr): $\bar{\nu}$ = 4,313, 3,330, 3,225, 2,872, 2,212, 1,649, 1,588, 1,492, 1,456, 1,418, 1,386, 1,341, 1,315, 1,283, 1,219, 1,165, 1,102 cm^{-1}; Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78 %. Found: C, 63.21; H, 4.95; N, 9.75 %.

2-Amino-4-(4-nitrophenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4e**, $C_{15}H_{13}N_3O_3S$)
M.p.: 229.2 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.15–2.40 (m, 2H, CH_2), 2.88–3.70 (m, 3H, CH_2), 3.95 (d, J = 14.4 Hz, 1H, CH_2), 5.90–6.05 (m, 1H, CH), 7.53 (br s, 2H, NH_2), 7.82 (d, J = 8.4 Hz, 2H, CH arom), 8.33 (d, J = 8.9 Hz, 2H, CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.44, 27.96, 35.29, 42.65, 49.16, 82.05, 112.15, 112.36, 116.34, 118.47, 124.21, 129.60, 141.56, 144.14, 148.50 ppm; MS (EI, 70 eV): *m/z* (%) = 316 (3, $[M + 1]^+$), 269 (3), 227 (3), 199 (70), 141 (100), 115 (78), 75 (80), 45 (83); IR (KBr): $\bar{\nu}$ = 3,451, 3,358, 2,881, 2,208, 1,635, 1,593, 1,530, 1,390, 1,348, 1,284, 1,110 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33 %. Found: C, 58.26; H, 4.15; N, 13.30 %.

2-Amino-4-(3-nitrophenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4f**, $C_{15}H_{13}N_3O_3S$)
M.p.: 237.2 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.10–2.40 (m, 2H, CH_2), 2.90–3.70 (m, 3H, CH_2), 4.03 (d, J = 13.6 Hz, 1H, CH_2), 5.85–6.10 (m, 1H, CH), 7.55 (br s, 2H, NH_2), 7.65–8.50 (m, 4H, CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.43, 28.01, 35.25, 42.90, 49.10, 82.10, 112.23, 112.41, 116.36, 118.51, 124.76, 129.56, 131.02, 136.92, 144.09 ppm; MS (EI, 70 eV): *m/z* (%) = 316 (1, $[M + 1]^+$), 244 (3), 115 (2), 75 (3), 45 (85), 30 (100); IR (KBr): $\bar{\nu}$ = 3,331, 3,152, 2,201, 1,651, 1,536, 1,602, 1,417, 1,353, 1,047 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33 %. Found: C, 58.62; H, 4.26; N, 13.04 %.

2-Amino-4-(2-nitrophenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4g**, $C_{15}H_{13}N_3O_3S$)
M.p.: 220.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.30–2.50 (m, 2H, CH_2), 3.12–3.25 (m, 2H, CH_2), 3.50 (d, J = 12.0 Hz, 1H, CH_2), 4.16 (d, J = 12.0 Hz, 1H, CH_2), 5.99 (br s, 1H, CH), 7.58 (br s, 2H, NH_2), 7.76 (t, J = 8.0 Hz, 1H, CH arom), 7.92 (t, J = 8.0 Hz, 1H, CH arom), 8.05–8.11 (m, 2H, CH arom) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 25.44, 28.01, 35.27, 42.90, 49.10, 82.09, 112.26, 112.43, 116.40, 117.61, 125.77,

129.40, 131.00, 136.95, 144.05 ppm; MS (EI, 70 eV): *m/z* (%) = 316 (8, $[M + 1]^+$), 244 (5), 115 (2), 76 (8), 45 (85), 30 (98); IR (KBr): $\bar{\nu}$ = 3,447, 3,320, 3,218, 2,967, 2,212, 1,642, 1,599, 1,525, 1,344 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33 %. Found: C, 58.43; H, 4.09; N, 13.12 %.

2-Amino-4-(4-chlorophenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4h**, $C_{15}H_{13}ClN_2OS$)
M.p.: 231.1 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.15–2.40 (m, 2H, CH_2), 2.91–3.60 (m, 3H, CH_2), 3.73 (d, J = 13.6 Hz, 1H, CH_2), 5.85–6.05 (m, 1H, CH), 7.30–7.70 (m, 6H, NH_2 and CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.43, 28.09, 35.43, 43.13, 49.18, 82.05, 112.37, 112.58, 116.39, 118.22, 129.45, 129.90, 133.29, 134.57, 144.38 ppm; MS (EI, 70 eV): *m/z* (%) = 305 (3, $[M + 1]^+$), 278 (1), 244 (5), 115 (30), 75 (45), 45 (100); IR (KBr): $\bar{\nu}$ = 3,432, 3,345, 3,212, 2,210, 1,640, 1,598, 1,494, 1,413, 1,387, 1,342, 1,278, 1,227, 1,094, 1,047, 1,016 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 11.63 %. Found: C, 60.75; H, 4.36; N, 11.32 %.

2-Amino-4-(4-bromophenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4i**, $C_{15}H_{13}BrN_2OS$)
M.p.: 257.2 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.10–2.35 (m, 2H, CH_2), 2.90–3.55 (m, 3H, CH_2), 3.76 (d, J = 14.4 Hz, 1H, CH_2), 5.85–6.00 (m, 1H, CH), 7.35–7.80 (m, 6H, NH_2 and CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.48, 28.12, 35.35, 43.05, 49.30, 82.05, 112.37, 112.55, 116.42, 118.23, 123.29, 129.87, 132.37, 133.65, 144.33 ppm; MS (EI, 70 eV): *m/z* (%) = 351 (2, $[M + 2]^+$), 349 (2) $(M)^+$, 227 (13), 125 (15), 75 (6), 45 (100); IR (KBr): $\bar{\nu}$ = 3,434, 3,345, 3,212, 2,209, 1,640, 1,597, 1,489, 1,411, 1,389, 1,278, 1,227, 1,076, 1,011 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}BrN_2OS$: C, 51.59; H, 3.75; N, 8.02 %. Found: C, 52.34; H, 3.73; N, 8.35 %.

2-Amino-4-(4-methoxyphenyl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4j**, $C_{16}H_{16}N_2O_2S$)
M.p.: 245.0 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.10–2.42 (m, 2H, CH_2), 2.72–3.47 (m, 3H, CH_2), 3.60 (d, J = 14.4 Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 5.83–6.10 (m, 1H, CH), 7.00–7.45 (m, 4H, CH arom and 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.45, 28.19, 35.74, 43.58, 49.37, 55.60, 81.91, 112.60, 112.82, 114.18, 116.49, 117.89, 125.99, 130.19, 144.65, 160.18 ppm; MS (EI, 70 eV): *m/z* (%) = 301 (1, $[M + 1]^+$), 244 (1), 227 (4), 115 (5), 45 (100); IR (KBr): $\bar{\nu}$ = 3,429, 3,344, 3,244, 2,213, 1,641, 1,612, 1,596, 1,516, 1,420, 1,388, 1,289, 1,183, 1,027 cm^{-1}; Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33 %. Found: C, 65.01; H, 5.37; N, 9.56 %.

2-Amino-4-(furan-2-yl)-7,8-dihydro-4H,5H-thiopyrano[4,3-b]pyran-3-carbonitrile
(**4k**, $C_{13}H_{12}N_2O_2S$)
M.p.: 231.1 °C; ^{1}H NMR (DMSO-d_6, 80 MHz): δ = 2.00–2.40 (m, 2H, CH_2), 2.60–3.65 (m, 3H, CH_2), 3.97 (d, J = 12.0 Hz, 1H, CH_2), 5.80–6.00 (m, 1H, CH), 6.50–6.70 (m, 2H, CH arom), 7.50 (br s, 2H, NH_2), 7.83 (br s, 1H, CH arom) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 25.38, 27.58, 35.86, 41.59, 44.86, 81.82, 111.32, 112.51, 112.58, 117.82, 129.49, 145.16, 147.94 ppm; MS (EI, 70 eV): *m/z* (%) = 235 (1), 193 (2), 115 (2), 45 (100); IR (KBr): $\bar{\nu}$ = 3,424, 3,340, 3,222, 2,211, 1,644, 1,602, 1,497, 1,424, 1,391, 1,148, 1,016 cm^{-1}; Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76 %. Found: C, 58.78; H, 4.67; N, 10.65 %.

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