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An efficient synthesis of pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-one: a new ring system of pharmaceutical interest

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ABSTRACT

A series of pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-ones **4** was prepared in good yields by reacting enaminoketones with cyanomethylene active compounds such as phenylsulfonylacetonitrile, benzoylacetonitrile, and malononitrile. Derivatives of the title ring system were tested by the National Cancer Institute of Bethesda against a panel of about 60 human tumor cell lines, and one of them showed inhibitory activity against all cancer cell lines reaching on 48% of them GI_{50} values at submicromolar level and on the majority of the remaining ones in the low micromolar concentration.

1. Introduction

Quinolinones represent a class of heterocyclic compounds endowed with potent antitumor activity. In particular, small molecules such as substituted quinolin-2-ones of type **1** (Chart 1) are reported as inhibitors of tyrosine kinases and as activators of the quiescent caspase cascade, being crucial to trigger cancer cells to suicide.[1,2] In fact there is mounting evidence that cancer cells lack parts of the molecular machinery that activate the caspase cascade. This makes the cancer cells lose their capacity to suicide.[3]

Annelation of heterocyclic moieties on the positions 6-7 of the quinoline nucleus led to Angelicin heteroanalogues, which maintained remarkable antiproliferative activity either in the dark and under UVA light irradiation.[4–7] In this context, in our continuing studies aimed at the discovery and development of potential anticancer drug candidates, we have recently reported the synthesis of new classes of pyrroloquinolinones **2a**–**c**, some of which showed very promising photoantiproliferative properties, often higher than that of 8-methoxypsoralen (8-MOP) the most widely employed drug for photochemotherapy.[8–11]

Since replacement of the oxygen of the pyrone ring of Angelicin improved the interaction with DNA both in the dark and under irradiation with UV light[12,13] we synthesized derivatives of the new ring system thiopyrano[2,3-*e*]indole **3**, which showed potent phototoxic activity.[14]

This paper reports the synthesis of the new ring system pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-one **4** in which sulfur is introduced in the central ring of the tricyclic framework.

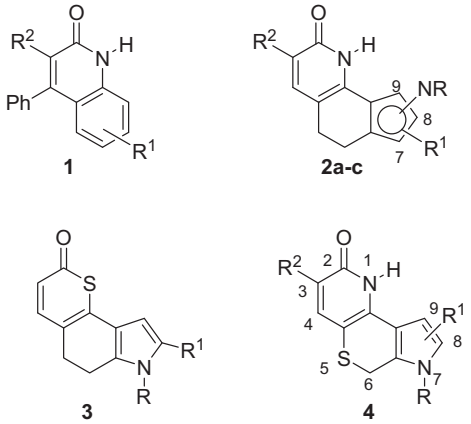

Chart 1. Structures of quinolin-2-ones (**1**), pyrrolo[2,3-*h*] quinolinones (**2a**, N-7), pyrrolo[3,4-*h*]quinolinones (**2b**, N-8), pyrrolo[3,2-*h*]quinolinones (**2c**, N-9), thiopyrano[2,3-*e*] benzopyrroles (**3**), and pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*] pyridin-2-ones (**4**).

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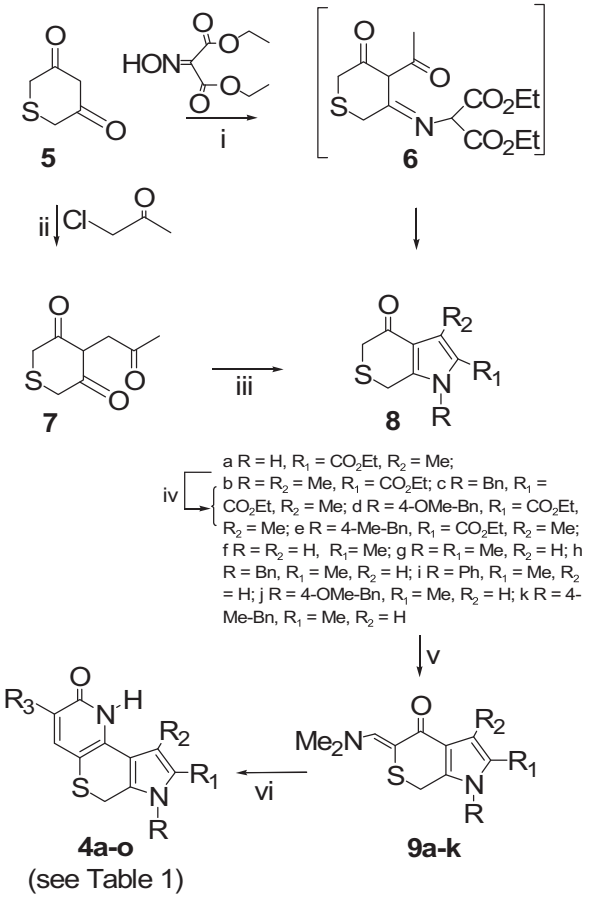
2. Results and discussion

One possible synthetic strategy for the target pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-ones **4** could have made use of enaminoketones **9** (Scheme 1, Table 1) as tool for the annelation of the pyridine ring. Such intermediates were obtained from thiopyranones of type **8**, about which not much is reported in literature. Only one patent in 1998 reported the synthesis in poor yield (15%) of the tetrahydrothiopyrano[3,4-*b*]pyrrole 2-pyridyl substituted as interleukin antagonists in treating cytokines mediated diseases.[15]



Scheme 1. Synthesis of pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-one **4**. Reagents and conditions: (i) AcONa, Zn, 90% AcOH, 100 °C, 1 h, 73%; (ii) KOH, MeOH, rt, 48 h, 90%; (iii) $AcONH_4$, AcOH, rt, 1 h or RNH_2, AcOH, reflux, 2 h, 66–77%; (iv) NaH, iodomethane or benzylchlorides, DMF, reflux, 2 h, 75–91%; (v) DMFDMA or TBDMAM, toluene, reflux, 2–24 h, 71–92%; (vi) R^3CH_2CN, EtOH, reflux, 24 h, 42–63%.

Table 1
Pyrrolo[3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-ones **4**

	R	R^1	R^2	R^3	Yield (%)
4a	H	CO_2Et	Me	SO_2Ph	55
4b	Me	CO_2Et	Me	SO_2Ph	48
4c	Bn	CO_2Et	Me	SO_2Ph	46
4d	4-OMe–Bn	CO_2Et	Me	SO_2Ph	42
4e	4-Me–Bn	CO_2Et	Me	SO_2Ph	62
4f	H	Me	H	SO_2Ph	43
4g	Me	Me	H	SO_2Ph	55
4h	Bn	Me	H	SO_2Ph	48
4i	Ph	Me	H	SO_2Ph	63
4j	4-OMe–Bn	Me	H	SO_2Ph	57
4k	4-Me–Bn	Me	H	SO_2Ph	60
4l	Me	CO_2Et	Me	CN	45
4m	Bn	CO_2Et	Me	CN	53
4n	Me	CO_2Et	Me	COPh	60
4o	Bn	CO_2Et	Me	COPh	57

We optimized a synthetic route for the preparation of the above mentioned ketones, starting from thiopyran-3,5-dione **5**, in turn conveniently prepared by condensation of methyl sulphanylacetate with chloroacetone, followed by intramolecular cyclization of the so obtained methyl[(2-oxopropyl)sulphanyl]acetate in basic media.[16]

Thiopyran-3,5-dione **5**, was then subjected to Knorr-type reductive condensation with freshly prepared diethyl hydroxyiminomalonate yielding, by way of the intermediate **6**, the 2,3-disubstituted compound **8a** (73%). This latter underwent alkylation at the pyrrole nitrogen with iodomethane or benzylchlorides, in the presence of NaH yielding the *N*-substituted derivatives **8b–e** (75–91%). Alternatively, compound **5**, formed by reaction with chloroacetone in the presence of potassium hydroxide in methanol at room temperature for 48 h was converted into derivative **7** (90%).

Condensation with ammonium acetate or with primary amines in acetic acid furnished 2-methyltetrahydrothiopyrano[3,4-*b*]pyrroles in good yields **8f–k** (66–77%).

Having in hand a good number of starting ketones of type **8**, the next step would be the functionalization of α position to the carbonyl to introduce in the molecule a second electrophilic center that, together with the carbonyl group, should allow the cyclization with dinucleofiles. Direct introduction of the enamine functionality has been studied.[17] Two of the most used amide acetals for this aim are *tert*-butoxybis(dimethylamino)methane (TBDMAM), also called Bredereck's reagent, which seemed to be the most efficient reagent and dimethylformamide dimethylacetal (DMFDMA) that is less reactive but far less expensive.

Tetrahydrothiopyrano[3,4-*b*]pyrrole-2-ones **8a–e** bearing the 2-ethoxycarbonyl functionality were converted into the corresponding enaminoketones **9a–e** (71–80%) in refluxing DMFDMA (Method A), whereas in the case of the thioketones of the 2-methyl series **8f–k** the use of an excess of Bredereck's reagent in refluxing toluene was required (Method B) to obtain enaminones **9g–k** (73–92%). Only in the case of **9f**, the compound was not isolated as pure sample and the crude was used directly in the next step. To achieve the tricyclic system **4**, namely the thiopyrano[3,2-*b*]pyridin-2-ones, we could react enaminoketones **9** with 1,3 dinucleophiles having a C–C–N structure, such as phenylsulfonylacetonitrile, benzoylacetonitrile, and malononitrile.

The substitution at position 3 of the pyridone ring was revealed to be of great importance in modulating the antiproliferative activity in the pyrroloquinolinone series.[8] In particular we previously reported that derivatives bearing the phenylsulphonyl group, showed the highest photoreactivity.

Thus, the reaction of **9a–k** with phenylsulfonylacetonitrile, afforded the corresponding pyrroloquinolinones **4a–k** in moderate to good yields (42–63%). Moreover the *N*-methyl and the *N*-benzyl enaminones **9b** and **9c** were reacted in the same reaction conditions with malononitrile to give **4l**, **m** (45, 53%) and with benzoylacetonitrile to achieve compounds **4n**, **o** (60, 57%).

Tetrahydrothiopyrano[3,4-*b*]pyrroles **4a–o** and dihydrothiopyran [3,4-*b*]pyrroles **8a–k** were submitted to the NCI of Bethesda for antiproliferative tests. Derivatives **8a–c**, **f–j**, and **4a–o** were selected for the one dose (10^{-5} M) screening on the full panel of about 60 human cancer cell lines derived from nine human cancer cell types, that have been grouped in disease sub-panels including leukemia, non-small cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumor cell lines. Only **8c** and **4a**, **b**, **f** among the tricyclic compounds were selected for further screenings at five concentrations at 10-fold dilution (10^{-4}–10^{-8} M) on the full panel. In particular **8c**, **4a**, and **4b** showed modest activity with growth inhibition reaching micromolar and submicromolar concentrations only against the HOP-92 cell line of the non-small cell lung cancer panel 1.21, 0.50, 1.11 μM, respectively (see Supplementary Data). Whereas derivative **4f** showed activity against all the tested cell lines (Table 2) at micromolar and submicromolar concentrations

(GI_{50} 0.14–40.3 μM) with a MID value of 1.86 μM reaching GI_{50} values at submicromolar level on 48% of the tested cell lines. The best selectivity was achieved for the breast cancer (0.36–2.38 μM), prostate cancer (0.38–0.83 μM), leukemia (0.37–4.88 μM), and melanoma (0.20–4.67 μM) sub-panels. Except for the SK-OV-3 and OVCAR-5 cell lines, of the ovarian cancer sub-panel and for SF-268 cell line of the CNS cancer sub-panel compound **4f** was active in the low micromolar range (0.25–3.12 μM and 0.39–2.44 μM, respectively) also against the ovarian and CNS cancer sub-panels.

Table 2
Inhibition of in vitro tumor cell growth by **4f**

Cell lines	(GI_{50} μM)[a,b]	Cell lines	(GI_{50} μM)[a,b]
Leukemia		M14	0.34
CCRF-CEM	0.41	MDA-MB-435	0.20
HL-60(TB)	0.37	SK-MEL-2	2.84
K-562	3.04	SK-MEL-28	4.67
MOLT-4	4.88	SK-MEL-5	0.66
RPMI-8226	0.66	UACC-62	0.30
Non-small cell lung cancer		*Ovarian cancer*	
A549/ATCC	40.3	IGROV1	0.91
EKVX	21.2	OVCAR-3	0.25
HOP-62	3.28	OVCAR-4	0.51
HOP-92	0.14	OVCAR-5	26.2
NCI-H226	17.2	OVCAR-8	3.12
NCI-H23	2.10	NCI/ADR-RES	0.45
NCI-H322M	27.8	SK-OV-3	30.1
NCI-H460	24.7	*Renal cancer*	
NCI-H522	5.23	786-0	20.4
Colon cancer		A498	22.1
COLO 205	16.8	ACHN	12.8
HCC-2998	2.76	CAKI-1	3.03
HCT-116	0.40	RXF 393	3.58
HCT-15	0.43	SN12C	0.72
HT29	0.31	TK-10	22.6
KM12	0.62	UO-31	16.2
SW-620	0.39	*Prostate cancer*	
CNS cancer		PC-3	0.38
SF-268	10.1	DU-145	0.83
SF-295	2.44	*Breast cancer*	
SF-539	0.39	MCF7	0.37
SNB-19	0.90	MDA-MB-231/ATCC	1.20
SNB-75	1.07	HS 578T	2.08
U251	0.39	BT-549	0.55
Melanoma		T-47D	0.36
LOX IMVI	0.83	MDA-MB-468	2.38
MALME-3M	0.42		

[a] Data obtained from NCI's in vitro disease-oriented tumor cells screen.
[b] GI_{50} is the molar concentration causing 50% growth inhibition of tumor cells.

3. Conclusions

In conclusion, we have reported an efficient method for the synthesis of derivatives of the new ring system tetrahydrothiopyrano[3,4-*b*]pyrroles in good yields. Versatile precursors were the thiopyranes **8**, which were converted into the key intermediate **9** by direct introduction of the enamino functionality. The 2-pyridone structure was obtained by reaction of these latter with cyanomethylene active compounds. Thiopyranes **8** and the tricyclic derivatives **4** were evaluated for the antiproliferative activity at the NCI of Bethesda, and **4f** showed an interesting broad spectrum of antiproliferative activity reaching the submicromolar level on 48% of the tested cell lines. The results obtained make this class of compounds interesting for further studies directed toward the synthesis of more potent antiproliferative agents.

4. Experimental section

4.1. General

All melting points were taken on a Buchi–Tottoli capillary apparatus and were uncorrected; IR spectra were determined, in $CHBr_3$, with a Jasco FT/IR 5300 spectrophotometer; ^1H and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions (TMS as internal reference) at 200 and 50.3 MHz, respectively, using a Bruker Avance II series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with a SEPACORE chromatography apparatus BÜCHI. Elemental analyses (C, H, and N) were within ±0.4% of the theoretical values.

4.2. Synthesis of 4-(2-oxopropyl)-2*H*-thiopyran-(4*H*,6*H*)-3,5-dione (7)

To a solution of 2*H*-thiopyran-3,5-dione **5** (1.40 g, 10.8 mmol) in methanol (10 mL), KOH (1.40 g, 25.0 mmol) dissolved in water (5 mL) was added. Chloroacetone (0.90 mL, 11.3 mmol) was added dropwise at 0 °C. The mixture was stirred at rt for 48 h, then acidified with 6 M HCl, and extracted with dichloromethane. The organic phase was dried and evaporated under reduced pressure to afford a crude, which was purified by chromatography column using DCM/EtOAc 8:2 as eluent. Brown oil; R_f=0.30 (CH_2Cl_2/CH_3OH 95:5); yield: 90%; IR (cm^{-1}) 1729 (CO), 1703 (CO), 1624 (CO). ^1H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 3.09 (2H, d, J=5.6 Hz, CH_2), 3.38–3.59 (4H, m, $CH_2\times2$), 4.13 (1H, t, J=5.6 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 29.9 (q), 37.0 (t), 39.2 (t×2), 62.2 (d), 195.2 (CO), 195.8 (CO), 206.2 (CO). Anal. Calcd for $C_8H_{10}O_3S$ (186.23): C, 51.60; H, 5.41. Found: C, 51.33; H, 5.32.

4.3. Synthesis of ethyl 3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-*b*]pyrrole-2-carboxylate (8a)

A solution of 2*H*-thiopyran-3,5-dione **5** (8.00 g, 61.4 mmol) and sodium acetate (15.8 g, 193 mmol) in acetic acid (90%, 80 mL) was heated at 70 °C. Zinc powder (13.5 g, 207 mmol) was added followed by dropwise addition of a freshly prepared solution of the hydroxyiminomalonate at a rate so as to maintain temperature at 90–100 °C. This latter was prepared by stirring at rt for 3 h a solution of ethylacetoacetate (8.50 g, 65.3 mmol) in acetic acid (50 mL) with a solution of sodium nitrite (4.60 g, 66.7 mmol) dissolved in water (20 mL). At the end of the addition of the hydroxyiminomalonate the reaction mixture was heated at 100 °C for 1 h. After 24 h stirring at rt the mixture was poured into crushed ice and the solid collected by filtration. Recrystallization with diethyl ether furnished derivative **8a**. White solid; R_f=0.11 (CH_2Cl_2); mp 218–219 °C; yield: 73%; IR (cm^{-1}): 3255 (NH), 1664 (CO), 1651 (CO). ^1H NMR (DMSO-d_6): δ 1.30 (3H, t, J=7.1 Hz, CH_3), 2.48 (3H, s, CH_3), 3.38 (2H, s, CH_2), 3.85 (2H, s, CH_2), 4.26 (2H, q, J=7.1 Hz, CH_2), 12.09 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.4 (q), 14.3 (q), 22.6 (t), 35.4 (t), 59.8 (t), 117.8 (s), 118.0 (s), 127.9 (s), 142.7 (s), 160.7 (CO), 190.1 (CO). Anal. Calcd for $C_{11}H_{13}NO_3S$ (239.29): C, 55.21; H, 5.48; N, 5.85. Found: C, 55.41; H, 5.34; N, 5.55.

4.4. General procedure for the preparation of ethyl 3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-*b*]pyrrole-2-carboxylate (8b–e)

To a solution of **8a** (2.50 mmol) dissolved in anhydrous DMF (10 mL), NaH (0.06 g, 2.50 mmol) was added at 0 °C and the reaction mixture was stirred at rt. After 1 h iodomethane or the proper benzylchloride (2.50 mmol) was added at 0 °C and the reaction mixture was heated under reflux for 2 h. Then, the reaction mixture was poured onto crushed ice and the precipitate was filtered off. The crude material was purified by column chromatography, using DCM/EtOAc 95:5 as eluent.

*4.4.1. Ethyl 1,3-dimethyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]-pyrrole-2-carboxylate (**8b**).* This product was obtained by reaction of **8a** with iodomethane. Yellow solid; R_f=0.30 (CH_2Cl_2); mp

126–128 °C; yield: 80%; IR (cm^{-1}): 1687 (CO), 1657 (CO). ^1H NMR ($CDCl_3$): δ 1.38 (3H, t, J=7.1 Hz, CH_3), 2.60 (3H, s, CH_3), 3.34 (2H, s, CH_2), 3.75 (2H, s, CH_2), 3.80 (3H, s, CH_3), 4.33 (2H, q, J=7.1 Hz, CH_2). ^{13}C NMR ($CDCl_3$): δ 12.3 (q), 14.4 (q), 22.7 (t), 33.5 (q), 35.9 (t), 60.3 (t), 117.8 (s), 121.1 (s), 131.0 (s), 142.8 (s), 162.1 (CO), 189.5 (CO). Anal. Calcd for $C_{12}H_{15}NO_3S$ (253.32): C, 56.90; H, 5.97; N, 5.53. Found: C, 56.77; H, 6.15; N, 5.35.

*4.4.2. Ethyl 1-benzyl-3-methy-4-oxo-1,4,5,7-tetrahydrothiopyrano-[3,4-b]pyrrole-2-carboxylate (**8c**).* This product was obtained by reaction of **8a** with benzyl chloride. White solid; R_f=0.43 (CH_2Cl_2); mp 102–103 °C; yield: 91%; IR (cm^{-1}): 1691 (CO), 1657 (CO). ^1H NMR (DMSO-d_6): δ 1.20 (3H, t, J=7.1 Hz, CH_3), 2.54 (3H, s, CH_3), 3.43 (2H, s, CH_2), 3.90 (2H, s, CH_2), 4.17 (2H, q, J=7.1 Hz, CH_2), 5.60 (2H, s, CH_2), 6.99 (2H, d, J=6.5 Hz, H-2′ and H-6′), 7.21–7.38 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (DMSO-d_6): δ 12.1 (q), 14.0 (q), 21.9 (t), 35.2 (t), 48.3 (t), 60.0 (t), 117.3 (s), 119.7 (s), 126.0 (d×2), 127.2 (d), 128.6 (d×2), 129.6 (s), 137.3 (s), 144.8 (s), 160.9 (CO), 190.0 (CO). Anal. Calcd for $C_{18}H_{19}NO_3S$ (329.41): C, 65.63; H, 5.81; N, 4.25. Found: C, 65.75; H, 5.99; N, 4.03.

*4.4.3. Ethyl 1-(4-methoxybenzyl)-3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**8d**).* This product was obtained by reaction of **8a** with 4-methoxybenzyl chloride. White solid; R_f=0.23 (CH_2Cl_2); mp 104–105 °C; yield: 85%; IR (cm^{-1}): 1693 (CO), 1660 (CO). ^1H NMR (DMSO-d_6): δ 1.23 (3H, t, J=7.1 Hz, CH_3), 2.52 (3H, s, CH_3), 3.41 (2H, s, CH_2), 3.71 (3H, s, CH_3), 3.91 (2H, s, CH_2), 4.20 (2H, q, J=7.1 Hz, CH_2), 5.52 (2H, s, CH_2), 6.88 (2H, d, J=8.8 Hz, H-3′ and H-5′), 6.97 (2H, d, J=8.8 Hz, H-2′ and H-6′). ^{13}C NMR (DMSO-d_6): δ 12.1 (q), 14.0 (q), 21.9 (t), 35.2 (t), 47.7 (t), 55.0 (q), 60.0 (t), 114.0 (d×2), 117.2 (s), 119.7 (s), 127.6 (d×2), 129.1 (s), 129.6 (s), 144.6 (s), 158.4 (s), 161.0 (CO), 190.0 (CO). Anal. Calcd for $C_{19}H_{21}NO_4S$ (359.44): C, 63.49; H, 5.89; N, 3.90. Found: C, 63.15; H, 6.01; N, 4.15.

*4.4.4. Ethyl 3-methyl-1-(4-methylbenzyl)-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**8e**).* This product was obtained by reaction of **8a** with 4-methylbenzyl chloride. White solid; R_f=0.20 (CH_2Cl_2); mp 127–129 °C; yield: 75%; IR (cm^{-1}): 1695 (CO), 1658 (CO). ^1H NMR (DMSO-d_6): δ 1.22 (3H, t, J=7.1 Hz, CH_3), 2.26 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.42 (2H, s, CH_2), 3.89 (2H, s, CH_2), 4.18 (2H, q, J=7.1 Hz, CH_2), 5.55 (2H, s, CH_2), 6.89 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.13 (2H, d, J=8.0 Hz, H-2′ and H-6′). ^{13}C NMR (DMSO-d_6): δ 12.1 (q), 14.0 (q), 20.6 (q), 21.9 (t), 35.2 (t), 48.0 (t), 60.0 (t), 117.2 (s), 119.7 (s), 126.0 (d×2), 129.2 (d×2), 129.6 (s), 134.2 (s), 136.4 (s), 144.7 (s), 161.0 (CO), 190.0 (CO). Anal. Calcd for $C_{19}H_{21}NO_3S$ (343.44): C, 66.45; H, 6.16; N, 4.08. Found: C, 66.22; H, 6.41; N, 3.85.

4.5. General procedure for the preparation of 2-methyl tetrahydrothiopyrano[3,4-*b*]pyrrol-4-ones (8f–k)

To a solution of 4-(2-oxopropyl)-2*H*-thiopyran-(4*H*,6*H*)-3,5-dione **7** (0.60 g, 3.20 mmol) in acetic acid (40 mL) ammonium acetate (1.00 g, 13.0 mmol) or the proper amine (3.2 mmol) was added. The mixture was stirred at rt or heated at the proper temperature for the suitable time then poured onto crushed ice. The desired compounds were separated as solids upon filtration or alternatively were extracted with dichloromethane, dried with sodium sulfate, and evaporated under reduced pressure. The crude material was purified by column chromatography, using DCM/EtOAc 98:2 as eluent.

*4.5.1. 2-Methyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)one (**8f**).* This product was obtained by reaction of **7** with ammonium acetate after 1 h at rt. Pale brown solid; R_f=0.10 (CH_2Cl_2); mp 225–227 °C; yield: 66%; IR (cm^{-1}): 3221 (NH), 1620 (CO). ^1H NMR (DMSO-d_6): δ 2.13 (3H, s, CH_3), 3.29 (2H, s, CH_2), 3.79 (2H, s, CH_2), 5.98 (1H, s, H-3), 11.28 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.8 (q), 22.5 (t), 34.7 (t), 103.5 (d), 119.0 (s), 128.1 (s), 139.5 (s), 188.8 (CO). Anal. Calcd for C_8H_9NOS (167.23): C, 57.46; H, 5.42; N, 8.38. Found: C, 57.22; H, 5.29; N, 8.53.

*4.5.2. 1,2-Dimethyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)one (**8g**).* This product was obtained by reaction of **7** with methylamine after 2 h at reflux. Pale brown solid; R_f=0.11 (CH_2Cl_2); mp 147–148 °C; yield: 77%; IR (cm^{-1}): 1639 (CO). ^1H NMR (DMSO-d_6): δ 2.15 (3H, s, CH_3), 3.29 (2H, s, CH_2), 3.42 (3H, s, CH_3), 3.86 (2H, s, CH_2), 6.09 (1H, s, H-3). ^{13}C NMR (DMSO-d_6): δ 11.6 (q), 21.1 (t), 30.4 (q), 33.9 (t), 103.5 (d), 117.7 (s), 129.8 (s), 139.7 (s), 188.0 (CO). Anal. Calcd for $C_9H_{11}NOS$ (181.25): C, 59.64; H, 6.12; N, 7.73. Found: C, 59.44; H, 6.35; N, 7.99.

*4.5.3. 1-Benzyl-2-methyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**8h**).* This product was obtained by reaction of **7** with benzylamine after 2 h at reflux. Brown solid; R_f=0.14 (CH_2Cl_2); mp 89–90 °C; yield: 72%; IR (cm^{-1}): 1645 (CO). ^1H NMR (DMSO-d_6): δ 2.10 (3H, s, CH_3), 3.34 (2H, s, CH_2), 3.81 (2H, s, CH_2), 5.17 (2H, s, CH_2), 6.20 (1H, s, H-3), 7.00 (2H, d, J=6.5 Hz, H-2′ and H-6′), 7.24–7.40 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 21.4 (t), 34.1 (t), 46.6 (t), 104.3 (d), 118.2 (s), 126.1 (d×2), 127.4 (d), 128.8 (d×2), 129.8 (s), 137.1 (s), 140.9 (s), 188.3 (CO). Anal. Calcd for $C_{15}H_{15}NOS$ (257.35): C, 70.01; H, 5.87; N, 5.44. Found: C, 69.90; H, 5.99; N, 5.13.

*4.5.4. 2-Methyl-1-phenyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)one (**8i**).* This product was obtained by reaction of **7** with aniline after 2 h at reflux. Pale brown solid; R_f=0.52 (CH_2Cl_2); mp 162–163 °C; yield: 68%; IR (cm^{-1}): 1648 (CO). ^1H NMR (DMSO-d_6): δ 2.00 (3H, s, CH_3), 3.37 (2H, s, CH_2), 3.59 (2H, s, CH_2), 6.30 (1H, s, H-3), 7.39 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.52–7.59 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (DMSO-d_6): δ 12.2 (q), 22.0 (t), 34.3 (t), 104.4 (d), 118.6 (s), 127.5 (d×2), 128.9 (d), 129.7 (d×2), 130.2 (s), 135.9 (s), 140.0 (s), 188.6 (CO). Anal. Calcd for $C_{14}H_{13}NOS$ (243.32): C, 69.11; H, 5.39; N, 5.76. Found: C, 69.38; H, 5.08; N, 6.02.

*4.5.5. 1-(4-Methoxybenzyl)-2-methyl-1,7-dihydrothiopyrano[3,4-b]-pyrrol-4-(5H)one (**8j**).* This product was obtained by reaction of **7** with 4-methoxybenzylamine after 2 h at reflux. Brown solid; R_f=0.14 (CH_2Cl_2); mp 125–126 °C; yield: 70%; IR (cm^{-1}): 1647 (CO). ^1H NMR (DMSO-d_6): δ 2.11 (3H, s, CH_3), 3.34 (2H, s, CH_2), 3.72 (3H, s, CH_3), 3.82 (2H, s, CH_2), 5.08 (2H, s, CH_2), 6.17 (1H, s, H-3), 6.90 (2H, d, J=9.1 Hz, H-3′ and H-5′), 6.97 (2H, d, J=9.1 Hz, H-2′ and H-6′). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 21.4 (t), 34.0 (t), 46.1 (t), 55.0 (q), 104.2 (d), 114.2 (d×2), 118.1 (s), 127.5 (d×2), 128.9 (s), 129.7 (s), 139.9 (s), 158.5 (s), 188.2 (CO). Anal. Calcd for $C_{16}H_{17}NO_2S$ (287.38): C, 66.87; H, 5.96; N, 4.87. Found: C, 67.02; H, 5.80; N, 4.65.

*4.5.6. 2-Methyl-1-(4-methylbenzyl)-1,7-dihydrothiopyrano[3,4-b]-pyrrol-4-(5H)one (**8k**).* This product was obtained by reaction of **7** with 4-methylbenzylamine after 2 h at reflux. Pale brown solid; R_f=0.17 (CH_2Cl_2); mp 110–111 °C; yield: 75%; IR (cm^{-1}): 1647 (CO). ^1H NMR (DMSO-d_6): δ 2.09 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.36 (2H, s, CH_2), 3.80 (2H, s, CH_2), 5.11 (2H, s, CH_2), 6.18 (1H, s, H-3), 6.90 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.16 (2H, d, J=8.0 Hz, H-2′ and H-6′). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 20.6 (q), 21.4 (t), 34.0 (t), 46.4 (t), 104.2 (d), 118.1 (s), 126.1 (d×2), 129.3 (s), 129.8 (d×2), 134.0 (s), 136.6 (s), 139.9 (s), 188.3 (CO). Anal. Calcd for $C_{16}H_{17}NOS$ (271.38): C, 70.82; H, 6.31; N, 5.16. Found: C, 70.62; H, 6.19; N, 5.33.

4.6. General procedure for the preparation of enaminoketones 9a–k

Method A. A solution of the suitable **8a–e** (5.00 mmol) in DMFDMA (7 mL, 50.0 mmol) was heated under reflux for the

proper time 3–24 h. The reaction mixture was poured onto crushed ice, filtered, and dried. Recrystallization with diethyl ether afforded the desired enaminoketones.

Method B. To a solution of the proper **8f**–**k** (45.0 mmol) in anhydrous toluene (10 mL), TBDMAM (2.79 mL, 13.5 mmol) was added. The reaction was heated under reflux for 2 h. Upon cooling at rt, a solid separated from the reaction mixture, which was collected and dried.

*4.6.1. Ethyl 5-[(dimethylamino)methylidene]-3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**9a**).* This product was obtained by reaction of **8a** with method A after 3 h reflux. Yellow solid; R_f=0.31 (CH_2Cl_2/EtOAc 9:1); mp 196–197 °C; yield: 80%; IR (cm^{-1}): 3420 (NH), 1653 (CO), 1628 (CO). ^1H NMR (DMSO-d_6): δ 1.29 (3H, t, J=7.1 Hz, CH_3), 2.49 (3H, s, CH_3), 3.16 (6H, s, $CH_3\times2$), 3.74 (2H, s, CH_2), 4.24 (2H, q, J=7.1 Hz, CH_2), 7.59 (1H, s, CH), 11.79 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.4 (q), 14.4 (q), 24.1 (t), 43.1 (q×2), 59.5 (t), 90.9 (s), 117.4 (s), 118.9 (s), 128.3 (s), 139.4 (s), 147.7 (d), 160.9 (CO), 181.8 (CO). Anal. Calcd for $C_{14}H_{18}N_2O_3S$ (294.37): C, 57.12; H, 6.16; N, 9.52. Found: C, 57.25; H, 6.03; N, 9.33.

*4.6.2. Ethyl 5-[(dimethylamino)methylidene]-1,3-dimethyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**9b**).* This product was obtained by reaction of **8b** with method A after 4 h reflux. Brown solid; R_f=0.35 (CH_2Cl_2/EtOAc 9:1); mp 150–151 °C; yield: 74%; IR (cm^{-1}): 1684 (CO), 1628 (CO). ^1H NMR (DMSO-d_6): δ 1.29 (3H, t, J=7.1 Hz, CH_3), 2.51 (3H, s, CH_3), 3.17 (6H, s, $CH_3\times2$), 3.71 (3H, s, CH_3), 3.85 (2H, s, CH_2), 4.24 (2H, q, J=7.1 Hz, CH_2), 7.59 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 12.1 (q), 14.2 (q), 23.1 (t), 33.0 (q), 43.1 (q×2), 59.6 (t), 90.4 (s), 118.0 (s), 119.6 (s), 129.4 (s), 141.8 (s), 147.6 (d), 161.3 (CO), 181.5 (CO). Anal. Calcd for $C_{15}H_{20}N_2O_3S$ (308.40): C, 58.42; H, 6.54; N, 9.08. Found: C, 58.09; H, 6.67; N, 8.88.

*4.6.3. Ethyl 1-benzyl-5-[(dimethylamino)methylidene]-3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**9c**).* This product was obtained by reaction of **8c** with method A after 5 h reflux. White solid; R_f=0.38 (CH_2Cl_2/EtOAc 9:1); mp 134–135 °C; yield: 71%; IR (cm^{-1}): 1685 (CO), 1628 (CO). ^1H NMR (DMSO-d_6): δ 1.19 (3H, t, J=7.1 Hz, CH_3), 2.54 (3H, s, CH_3), 3.16 (6H, s, $CH_3\times2$), 3.79 (2H, s, CH_2), 4.16 (2H, q, J=7.1 Hz, CH_2), 5.58 (2H, s, CH_2), 6.94 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.19–7.36 (3H, m, H-3′, H-4′, and H-5′), 7.62 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 12.3 (q), 14.0 (q), 23.0 (t), 43.1 (q×2), 47.8 (t), 59.7 (t), 90.4 (s), 118.5 (s), 119.1 (s), 125.9 (d×2), 127.1 (d), 128.6 (d×2), 130.2 (s), 137.8 (s), 142.0 (s), 147.9 (d), 161.1 (CO), 181.5 (CO). Anal. Calcd for $C_{21}H_{24}N_2O_3S$ (384.49): C, 65.60; H, 6.29; N, 7.29. Found: C, 65.79; H, 6.14; N, 7.44.

*4.6.4. Ethyl 5-[(dimethylamino)methylidene]-1-(4-methoxybenzyl)-3-methyl-4-oxo-1,4,5,7-tetrahydrothiopyrano [3,4-b]pyrrole-2-carboxylate (**9d**).* This product was obtained by reaction of **8d** with method A after 24 h reflux. Yellow solid; R_f=0.56 (CH_2Cl_2/EtOAc 9:1); mp 130–131 °C; yield: 72%; IR (cm^{-1}): 1684 (CO), 1630 (CO). ^1H NMR (DMSO-d_6): δ 1.23 (3H, t, J=7.1 Hz, CH_3), 2.53 (3H, s, CH_3), 3.16 (6H, s, $CH_3\times2$), 3.70 (3H, s, CH_3), 3.80 (2H, s, CH_2), 4.18 (2H, q, J=7.1 Hz, CH_2), 5.50 (2H, s, CH_2), 6.86 (2H, d, J=9.0 Hz, H-3′ and H-5′), 6.93 (2H, d, J=9.0 Hz, H-2′ and H-6′), 7.61 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 12.2 (q), 14.1 (q), 23.4 (t), 43.1 (q×2), 47.2 (t), 55.0 (q), 59.7 (t), 90.4 (s), 114.0 (d×2), 118.5 (s), 119.0 (s), 127.4 (d×2), 129.7 (s), 130.1 (s), 141.9 (s), 147.9 (d), 158.3 (s), 161.2 (CO), 181.5 (CO). Anal. Calcd for $C_{22}H_{26}N_2O_4S$ (414.52): C, 63.75; H, 6.32; N, 6.76. Found: C, 64.02; H, 6.55; N, 6.44.

*4.6.5. Ethyl 5-[(dimethylamino)methylidene]-3-methyl-1-(4-methylbenzyl)-4-oxo-1,4,5,7-tetrahydrothiopyrano[3,4-b]pyrrole-2-carboxylate (**9e**).* This product was obtained by reaction of **8e** with method A after 24 h reflux. Orange solid; R_f=0.54 (CH_2Cl_2/EtOAc 9:1); mp 150–151 °C; yield: 77%; IR (cm^{-1}): 1685 (CO), 1628 (CO). ^1H NMR (DMSO-d_6): δ 1.21 (3H, t, J=7.1 Hz, CH_3), 2.24 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.16 (6H, s, $CH_3\times2$), 3.78 (2H, s, CH_2), 4.16 (2H, q, J=7.1 Hz, CH_2), 5.52 (2H, s, CH_2), 6.84 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.11 (2H, d, J=8.0 Hz, H-2′ and H-6′), 7.62 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 12.2 (q), 14.1 (q), 20.6 (q), 23.4 (t), 43.1 (q×2), 47.6 (t), 59.7 (t), 90.4 (s), 118.5 (s), 119.1 (s), 125.9 (d×2), 129.1 (d×2), 130.1 (s), 134.8 (s), 136.3 (s), 142.0 (s), 147.9 (d), 161.1 (CO), 181.5 (CO). Anal. Calcd for $C_{22}H_{26}N_2O_3S$ (398.52): C, 66.31; H, 6.58; N, 7.03. Found: C, 66.46; H, 6.77; N, 6.85.

*4.6.6. 5-[(Dimethylamino)methylidene]-2-methyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9f**).* This product was obtained by reaction of **8f** with method B. Purification by recrystallization or chromatography column was not possible as compound **9f** was unstable with respect to hydrolysis of the enamine so it was used for the next step without purification.

*4.6.7. 5-[(Dimethylamino)methylidene]-1,2-dimethyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9g**).* This product was obtained by reaction of **8g** with method B. Yellow solid; R_f=0.28 (CH_2Cl_2/EtOAc 9:1); mp 150–151 °C; yield: 92%; IR (cm^{-1}): 1658 (CO). ^1H NMR (DMSO-d_6): δ 2.14 (3H, s, CH_3), 3.14 (6H, s, $CH_3\times2$), 3.38 (3H, s, CH_3), 3.81 (2H, s, CH_2), 6.05 (1H, s, H-3), 7.48 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 23.1 (t), 30.0 (q), 43.0 (q×2), 90.1 (s), 104.5 (d), 119.0 (s), 128.8 (s), 135.8 (s), 146.3 (d), 180.4 (CO). Anal. Calcd for $C_{12}H_{16}N_2OS$ (236.33): C, 60.99; H, 6.82; N, 11.85. Found: C, 61.18; H, 6.69; N, 11.54.

*4.6.8. 1-Benzyl-5-[(dimethylamino)methylidene]-2-methyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9h**).* This product was obtained by reaction of **8h** with method B. Brown solid; R_f=0.30 (CH_2Cl_2/EtOAc 9:1); mp 146–147 °C; yield: 80%; IR (cm^{-1}): 1624 (CO). ^1H NMR (DMSO-d_6): δ 2.08 (3H, s, CH_3), 3.13 (6H, s, $CH_3\times2$), 3.75 (2H, s, CH_2), 5.13 (2H, s, CH_2), 6.15 (1H, s, H-3), 6.96 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.26–7.38 (3H, m, H-3′, H-4′ and H-5′), 7.52 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 23.3 (t), 43.0 (q×2), 46.2 (t), 90.0 (s), 105.4 (d), 119.6 (s), 126.0 (d×2), 127.2 (d), 128.7 (d×2), 136.0 (s), 137.6 (s), 146.6 (d), 150.1 (s), 180.5 (CO). Anal. Calcd for $C_{18}H_{20}N_2OS$ (312.43): C, 69.20; H, 6.45; N, 8.97. Found: C, 69.55; H, 6.10; N, 9.12.

*4.6.9. 5-[(Dimethylamino)methylidene]-2-methyl-1-phenyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9i**).* This product was obtained by reaction of **8i** with method B. Brown solid; R_f=0.31 (CH_2Cl_2/EtOAc 9:1); mp 144–145 °C; yield: 74%; IR (cm^{-1}): 1642 (CO). ^1H NMR (DMSO-d_6): δ 2.01 (3H, s, CH_3), 3.14 (6H, s, $CH_3\times2$), 3.54 (2H, s, CH_2), 6.25 (1H, s, H-3), 7.36 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.49–7.59 (4H, m, H-3′, H-4′, H-5′, and CH). ^{13}C NMR (DMSO-d_6): δ 12.3 (q), 23.8 (t), 43.0 (q×2), 90.1 (s), 105.6 (d), 120.0 (s), 127.5 (d×2), 128.5 (d), 129.1 (s), 129.5 (d×2), 135.8 (s), 136.1 (s), 146.7 (d), 180.6 (CO). Anal. Calcd for $C_{17}H_{18}N_2OS$ (298.40): C, 68.43; H, 6.08; N, 9.39. Found: C, 68.59; H, 6.31; N, 9.01.

*4.6.10. 5-[(Dimethylamino)methylidene]-1-(4-methoxybenzyl)-2-methyl-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9j**).* This product was obtained by reaction of **8j** with method B. Brown solid; R_f=0.35 (CH_2Cl_2/EtOAc 9:1); mp 130–131 °C; yield: 78%; IR (cm^{-1}): 1624 (CO). ^1H NMR (DMSO-d_6): δ 2.09 (3H, s, CH_3), 3.13 (6H, s, $CH_3\times2$), 3.71 (3H, s, CH_3), 3.75 (2H, s, CH_2), 5.04 (2H, s, CH_2), 6.13 (1H, s, H-3), 6.88 (2H, d, J=9.6 Hz, H-3′ and H-5′), 6.93 (2H, d, J=9.6 Hz, H-2′ and H-6′), 7.51 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 23.4 (t), 43.0 (q×2), 45.7 (t), 55.0 (q), 90.1 (s), 105.3 (d), 114.1 (d×2), 119.5 (s), 127.4 (d×2), 128.7 (s), 129.4 (s), 135.9 (s), 146.5 (d),

158.4 (s), 180.5 (CO). Anal. Calcd for $C_{19}H_{22}N_2O_2S$ (342.46): C, 66.64; H, 6.48; N, 8.18. Found: C, 66.33; H, 6.69; N, 7.95.

*4.6.11. 5-[(Dimethylamino)methylidene]-2-methyl-1-(4-methylbenzyl)-1,7-dihydrothiopyrano[3,4-b]pyrrol-4-(5H)-one (**9k**).* This product was obtained by reaction of **8k** with method B. Red solid; R_f=0.26 (CH_2Cl_2/EtOAc 9:1); mp 148–149 °C; yield: 73%; IR (cm^{-1}): 1624 (CO). ^1H NMR (DMSO-d_6): δ 2.08 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.13 (6H, s, $CH_3\times2$), 3.73 (2H, s, CH_2), 5.07 (2H, s, CH_2), 6.14 (1H, s, H-3), 6.86 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.14 (2H, d, J=8.0 Hz, H-2′ and H-6′), 7.51 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ 11.7 (q), 20.6 (q), 23.4 (t), 43.0 (q×2), 46.0 (t), 90.1 (s), 105.3 (d), 119.5 (s), 126.0 (d×2), 128.7 (s), 129.3 (d×2), 134.5 (s), 135.9 (s), 136.4 (s), 146.5 (d), 180.5 (CO). Anal. Calcd for $C_{19}H_{22}N_2OS$ (326.46): C, 69.90; H, 6.79; N, 8.58. Found: C, 69.71; H, 6.55; N, 8.85.

4.7. General procedure for the preparation of pyrrolo [3′,2′:4,5]thiopyrano[3,2-*b*]pyridin-2-ones (4a–o)

To a solution of the enaminones **9** (20.0 mmol) in anhydrous ethanol (10 mL), the suitable cyanomethylene compound (22.0 mmol) was added and heated under reflux for 24 h. The solid material, which separated from the solution was filtered off, washed with fresh ethanol, and dried. Recrystallization from methanol gave the desired compounds as yellow solids.

*4.7.1. Ethyl 9-methyl-2-oxo-3-(phenylsulfonyl)-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4a**).* This product was obtained by reaction of **9a** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.12 (CH_2Cl_2/EtOAc 8:2); mp 214–dec °C; yield: 55%; IR (cm^{-1}): 3251 (NH), 3226 (NH), 1666 (CO), 1635 (CO). ^1H NMR (DMSO-d_6): δ 1.30 (3H, t, J=7.1 Hz, CH_3), 2.55 (3H, s, CH_3), 3.99 (2H, s, CH_2), 4.26 (2H, q, J=7.1 Hz, CH_2), 7.59–7.69 (3H, m, H-3″, H-4″ and H-5″), 7.97 (2H, d, J=8.2 Hz, H-2″ and H-6″), 8.16 (1H, s, H-4), 11.78 (1H, s, NH), 12.19 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.3 (q), 14.3 (q), 22.7 (t), 59.7 (t), 118.8 (s), 126.1 (s), 127.9 (d), 128.0 (d×2), 128.8 (d×2), 133.3 (d), 135.1 (s), 140.4 (s), 144.2 (s), 149.1 (s), 151.3 (s), 153.3 (s), 157.1 (CO), 160.6 (CO). Anal. Calcd for $C_{20}H_{18}N_2O_5S_2$ (430.49): C, 55.80; H, 4.21; N, 6.51. Found: C, 56.15; H, 4.06; N, 6.23.

*4.7.2. Ethyl 7,9-dimethyl-2-oxo-3-(phenylsulfonyl)-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4b**).* This product was obtained by reaction of **9b** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.31(CH_2Cl_2/EtOAc 8:2); mp 185–186 °C; yield: 48%; IR (cm^{-1}): 3390 (NH), 1689 (CO), 1643 (CO). ^1H NMR (DMSO-d_6): δ 1.30 (3H, t, J=7.1 Hz, CH_3), 2.52 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.12 (2H, s, CH_2), 4.26 (2H, q, J=7.1 Hz, CH_2), 7.56–7.69 (3H, m, H-3″, H-4″, and H-5″), 7.98 (2H, d, J=7.1 Hz, H-2″ and H-6″), 8.17 (1H, s, H-4), 11.83 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.2 (q), 14.2 (q), 21.7 (t), 33.4 (q), 59.9 (t), 121.2 (s), 126.8 (s), 127.9 (d), 128.0 (d×2), 128.9 (d×2), 132.8 (s), 133.4 (d), 137.9 (s), 140.4 (s), 144.3 (s), 148.6 (s), 150.6 (s), 157.1 (CO), 161.0 (CO). Anal. Calcd for $C_{21}H_{20}N_2O_5S_2$ (444.52): C, 56.74; H, 4.53; N, 6.30. Found: C, 56.81; H, 4.43; N, 6.01.

*4.7.3. Ethyl 7-benzyl-9-methyl-2-oxo-3-(phenylsulfonyl)-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4c**).* This product was obtained by reaction of **9c** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.46 (CH_2Cl_2/EtOAc 8:2); mp 270–272 °C; yield: 46%; IR (cm^{-1}): 3351 (NH), 1705 (CO), 1674 (CO). ^1H NMR (DMSO-d_6): δ 1.20 (3H, t, J=7.1 Hz, CH_3), 2.57 (3H, s, CH_3), 4.05 (2H, s, CH_2), 4.18 (2H, q, J=7.1 Hz, CH_2), 5.65 (2H, s, CH_2), 6.98 (2H, d, J=6.4 Hz, H-2′ and H-6′), 7.23–7.36 (3H, m, H-3′, H-4′, and H-5′), 7.56–7.73 (3H, m, H-3″, H-4″, and H-5″), 7.98 (2H, d, J=6.8 Hz, H-2″ and H-6″), 8.19 (1H, s, H-4), 11.88 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.4 (q), 14.0 (q), 21.8 (t), 48.1 (t), 60.0 (t), 120.5 (s), 125.9 (d×2), 127.2 (d), 128.0 (d×2), 128.5 (d), 128.6 (d×2), 128.9 (d×2), 129.7 (s), 132.6 (s), 133.3 (d), 136.9 (s), 137.7 (s), 138.0 (s), 140.4 (s), 141.3 (s), 142.4 (s), 157.4 (CO), 160.8 (CO). Anal. Calcd for $C_{27}H_{24}N_2O_5S_2$ (520.62): C, 62.29; H, 4.65; N, 5.38. Found: C, 62.41; H, 4.47; N, 5.52.

*4.7.4. Ethyl 7-(4-methoxybenzyl)-9-methyl-2-oxo-3-(phenylsulfonyl)-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano [3,2-b]pyridine-8-carboxylate (**4d**).* This product was obtained by reaction of **9d** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.47 (CH_2Cl_2/EtOAc 8:2); mp 252–dec °C; yield: 42%; IR (cm^{-1}): 3392 (NH), 1689 (CO), 1641 (CO). ^1H NMR (DMSO-d_6): δ 1.23 (3H, t, J=7.1 Hz, CH_3), 2.54 (3H, s, CH_3), 3.70 (3H, s, CH_3), 4.11 (2H, s, CH_2), 4.21 (2H, q, J=7.1 Hz, CH_2), 5.56 (2H, s, CH_2), 6.86 (2H, d, J=8.7 Hz, H-3′ and H-5′), 6.96 (2H, d, J=8.7 Hz, H-2′ and H-6′), 7.55–7.73 (3H, m, H-3″, H-4″, and H-5″), 7.98 (2H, d, J=6.8 Hz, H-2″ and H-6″), 8.19 (1H, s, H-4), 11.87 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.3 (q), 14.1 (q), 21.9 (t), 47.7 (t), 55.0 (q), 60.0 (t), 114.0 (d×2), 116.8 (s), 120.5 (s), 124.6 (s), 127.5 (d), 127.6 (d×2), 128.0 (d×2), 128.9 (d×2), 129.5 (s), 133.4 (d), 134.0 (s), 137.5 (s), 137.9 (s), 140.4 (s), 151.9 (s), 157.2 (s), 158.4 (CO), 160.9 (CO). Anal. Calcd for $C_{28}H_{26}N_2O_6S_2$ (550.64): C, 61.08; H, 4.76; N, 5.09. Found: C, 60.95; H, 4.61; N, 5.39.

*4.7.5. Ethyl 9-methyl-7-(4-methylbenzyl)-2-oxo-3-(phenylsulfonyl)-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano [3,2-b]pyridine-8-carboxylate (**4e**).* This product was obtained by reaction of **9e** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.28 (CH_2Cl_2/EtOAc 8:2); mp 225–226 °C; yield: 62%; IR (cm^{-1}): 3357 (NH), 1689 (CO), 1639 (CO). ^1H NMR (DMSO-d_6): δ 1.22 (3H, t, J=7.1 Hz, CH_3), 2.24 (3H, s, CH_3), 2.55 (3H, s, CH_3), 4.09 (2H, s, CH_2), 4.19 (2H, q, J=7.1 Hz, CH_2), 5.59 (2H, s, CH_2), 6.88 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.11 (2H, d, J=8.0 Hz, H-2′ and H-6′), 7.55–7.96 (3H, m, H-3″, H-4″, and H-5″), 7.98 (2H, d, J=6.7 Hz, H-2″ and H-6″), 8.19 (1H, s, H-4), 11.88 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.3 (q), 14.0 (q), 20.6 (q), 21.8 (t), 47.9 (t), 60.0 (t), 115.0 (s), 120.5 (s), 120.7 (s), 126.0 (d×2), 127.5 (s), 127.6 (s), 127.7 (s), 128.0 (d×2), 128.9 (d×2), 129.1 (d), 129.2 (d×2), 133.4 (d), 134.6 (s), 136.4 (s), 137.3 (s), 140.0 (s), 157.2 (CO), 160.8 (CO). Anal. Calcd for $C_{28}H_{26}N_2O_5S_2$ (534.64): C, 62.90; H, 4.90; N, 5.24. Found: C, 62.54; H, 4.76; N, 5.51.

*4.7.6. 8-Methyl-3-(phenylsulfonyl)-6,7-dihydropyrrolo [3′,2′:4,5]thiopyrano[3,2-b]pyridin-2-(1H)-one (**4f**).* This product was obtained by reaction of **9f** with phenylsulfonylacetonitrile. Dark brown solid; R_f=0.10 (CH_2Cl_2/EtOAc 8:2); mp >410 °C; yield: 43%; IR (cm^{-1}): 3382 (NH), 3259 (NH), 1645 (CO). ^1H NMR (DMSO-d_6): δ 2.15 (3H, s, CH_3), 4.00 (2H, s, CH_2), 6.44 (1H, s, H-9), 7.56–7.66 (3H, m, H-3″, H-4″, and H-5″), 7.96 (2H, d, J=6.8 Hz, H-2″ and H-6″), 8.01 (1H, s, H-4), 11.49 (1H, s, NH), 12.24 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.5 (q), 22.8 (t), 103.3 (d), 110.2 (s), 119.9 (s), 120.3 (s), 127.8 (d×2), 128.6 (d), 128.7 (d×2), 131.0 (s), 133.3 (d), 140.8 (s), 148.5 (s), 154.3 (s), 162.4 (CO). Anal. Calcd for $C_{17}H_{14}N_2O_3S_2$ (358.43): C, 56.97; H, 3.94; N, 7.82. Found: C, 57.14; H, 4.22; N, 7.65.

*4.7.7. 7,8-Dimethyl-3-(phenylsulfonyl)-6,7-dihydropyrrolo[3′,2′:4,5]-thiopyrano[3,2-b]pyridin-2-(1H)-one (**4g**).* This product was obtained by reaction of **9g** with phenylsulfonylacetonitrile. Brown solid; R_f=0.19 (CH_2Cl_2/EtOAc 8:2); mp 263–264 °C; yield: 55%; IR (cm^{-1}): 3417 (NH), 1626 (CO). ^1H NMR (DMSO-d_6): δ 2.17 (3H, s, CH_3), 3.45 (3H, s, CH_3), 4.11 (2H, s, CH_2), 6.54 (1H, s, H-9), 7.52–7.69 (3H, m, H-3″, H-4″, and H-5″), 7.97 (2H, d, J=6.7 Hz, H-2″ and H-6″), 8.02 (1H, s, H-4), 12.23 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.8 (q), 22.0 (t), 30.5 (q), 103.5 (d), 111.0 (s), 120.2 (s), 127.8 (d×2), 128.6 (d), 128.7 (d×2), 131.1 (s), 132.4 (s), 133.0 (d), 140.8 (s), 141.2 (s), 157.0 (s), 160.3 (CO). Anal. Calcd for $C_{18}H_{16}N_2O_3S_2$ (372.46): C, 58.05; H, 4.33; N, 7.52. Found: C, 58.18; H, 4.17; N, 7.32.

*4.7.8. 7-Benzyl-8-methyl-3-(phenylsulfonyl)-6,7-dihydropyrrolo -[3′,2′:4,5]thiopyrano[3,2-b]pyridin-2-(1H)-one (**4h**).* This product

was obtained by reaction of **9h** with phenylsulfonylacetonitrile. Yellow solid; R_f=0.31 (CH_2Cl_2/EtOAc 8:2); mp 290–292 °C; yield: 48%; IR (cm^{-1}): 3411 (NH), 1635 (CO). ^1H NMR (DMSO-d_6): δ 2.10 (3H, s, CH_3), 4.07 (2H, s, CH_2), 5.21 (2H, s, CH_2), 6.62 (1H, s, H-9), 6.99 (2H, d, J=6.4 Hz, H-2′ and H-6′), 7.26–7.39 (3H, m, H-3′, H-4′, and H-5′), 7.52–7.70 (3H, m, H-3″, H-4″, and H-5″), 7.97 (2H, d, J=6.7 Hz, H-2″ and H-6″), 8.04 (1H, s, H-4), 12.33 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.9 (q), 22.2 (t), 46.6 (t), 104.4 (d), 126.0 (d×2), 127.4 (d), 127.8 (d×2), 128.7 (d×2), 128.7 (d), 128.8 (d×2), 130.9 (s), 132.4 (s), 133.0 (d), 137.1 (s), 138.6 (s), 140.7 (s), 144.3 (s), 146.1 (s), 157.0 (s), 163.1 (CO). Anal. Calcd for $C_{24}H_{20}N_2O_3S_2$ (448.55): C, 64.27; H, 4.49; N, 6.25. Found: C, 64.59; H, 4.12; N, 6.57.

*4.7.9. 8-Methyl-7-phenyl-3-(phenylsulfonyl)-6,7-dihydropyrrolo-[3′,2′:4,5]thiopyrano[3,2-b]pyridin-2-(1H)-one (**4i**).* This product was obtained by reaction of **9i** with phenylsulfonylacetonitrile. Dark green solid; R_f=0.25 (CH_2Cl_2/EtOAc 8:2); mp 295–296 °C; yield: 63%; IR (cm^{-1}): 3386 (NH), 1633 (CO). ^1H NMR (DMSO-d_6): δ 2.03 (3H, s, CH_3), 3.81 (2H, s, CH_2), 6.70 (1H, s, H-9), 7.38 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.55–7.67 (6H, m, Ar), 7.98 (2H, d, J=6.7 Hz, H-2″ and H-6″), 8.05 (1H, s, H-4), 12.38 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.4 (q), 22.6 (t), 104.4 (d), 107.7 (s), 112.2 (s), 121.2 (s), 127.4 (d×2), 127.8 (d), 127.9 (d×2), 128.7 (d×2), 129.0 (d), 129.6 (d×2), 131.1 (s), 131.9 (s), 133.1 (d), 135.5 (s), 140.6 (s), 157.0 (s), 162.3 (CO). Anal. Calcd for $C_{23}H_{18}N_2O_3S_2$ (434.53): C, 63.58; H, 4.18; N, 6.45. Found: C, 63.30; H, 4.47; N, 6.71.

*4.7.10. 7-(4-Methoxybenzyl)-8-methyl-3-(phenylsulfonyl)-6,7-dihydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridin-2-(1H)-one (**4j**).* This product was obtained by reaction of **9j** with phenylsulfonylacetonitrile. Green solid; R_f=0.19 (CH_2Cl_2/EtOAc 8:2); mp 272–274 °C; yield: 57%; IR (cm^{-1}): 3430 (NH), 1641 (CO). ^1H NMR (DMSO-d_6): δ 2.11 (3H, s, CH_3), 3.71 (3H, s, CH_3), 4.07 (2H, s, CH_2), 5.12 (2H, s, CH_2), 6.57 (1H, s, H-9), 6.88 (2H, d, J=8.9 Hz, H-3′ and H-5′), 6.95 (2H, d, J=8.9 Hz, H-2′ and H-6′), 7.53–7.65 (3H, m, H-3″, H-4″, and H-5″), 7.96 (2H, d, J=7.0 Hz, H-2″ and H-6″), 8.01 (1H, s, H-4), 12.34 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.8 (q), 22.4 (t), 46.8 (t), 55.1 (q), 104.5 (d), 110.5 (s), 114.3 (d×2), 117.8 (s), 123.5 (s), 126.0 (d), 127.6 (d×2), 127.8 (d×2), 128.7 (d×2), 130.9 (s), 133.3 (d), 140.7 (s), 142.0 (s), 145.7 (s), 147.1 (s), 154.0 (s), 161.2 (CO). Anal. Calcd for $C_{25}H_{22}N_2O_4S_2$ (478.58): C, 62.74; H, 4.63; N, 5.85. Found: C, 62.49; H, 4.31; N, 5.97.

*4.7.11. 8-Methyl-7-(4-methylbenzyl)-3-(phenylsulfonyl)-6,7-dihydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridin-2-(1H)-one (**4k**).* This product was obtained by reaction of **9k** with phenylsulfonylacetonitrile. Brown solid; R_f=0.34 (CH_2Cl_2/EtOAc 8:2); mp 276–278 °C; yield: 60%; IR (cm^{-1}): 3425 (NH), 1631 (CO). ^1H NMR (DMSO-d_6): δ 2.09 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.07 (2H, s, CH_2), 5.15 (2H, s, CH_2), 6.61 (1H, s, H-9), 6.88 (2H, d, J=8.0 Hz, H-3′ and H-5′), 7.14 (2H, d, J=8.0 Hz, H-2′ and H-6′), 7.52–7.70 (3H, m, H-3″, H-4″, and H-5″), 7.97 (2H, d, J=6.7 Hz, H-2″ and H-6″), 8.04 (1H, s, H-4), 12.30 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 11.9 (q), 20.6 (q), 22.2 (t), 46.3 (t), 104.3 (d), 120.8 (s), 125.9 (d), 126.0 (d×2), 127.8 (d×2), 128.7 (d×2), 129.3 (d×2), 130.8 (s), 132.4 (s), 133.1 (d), 134.1 (s), 134.9 (s), 136.6 (s), 140.7 (s), 146.1 (s), 157.1 (s), 163.3 (CO). Anal. Calcd for $C_{25}H_{22}N_2O_3S_2$ (462.58): C, 64.91; H, 4.79; N, 6.06. Found: C, 65.09; H, 4.58; N, 5.87.

*4.7.12. Ethyl 3-cyano-7,9-dimethyl-2-oxo-1,2,6,7-tetrahydropyrrolo-[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4l**).* This product was obtained by reaction of **9b** with malononitrile. Orange solid; R_f=0.22 (CH_2Cl_2/EtOAc 8:2); mp 336–dec °C; yield: 45%; IR (cm^{-1}): 3346 (NH), 2222 (CN), 1685 (CO), 1645 (CO). ^1H NMR (DMSO-d_6): δ 1.32 (3H, t, J=7.1 Hz, CH_3), 2.60 (3H, s, CH_3), 3.78 (3H, s, CH_3), 4.10 (2H, s, CH_2), 4.28 (2H, q, J=7.1 Hz, CH_2), 8.08 (1H, s, H-4), 12.02 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.3 (q), 14.2 (q), 21.5 (t), 33.4 (q), 59.9 (t), 111.3 (s), 114.9 (s), 116.3 (s), 121.2 (s), 127.0 (s), 132.5 (s), 137.7 (s), 143.0 (d), 149.3 (s), 161.0 (CO), 161.3 (CO). Anal. Calcd for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.35; H, 4.59; N, 12.76. Found: C, 58.05; H, 4.77; N, 12.99.

*4.7.13. Ethyl 7-benzyl-3-cyano-9-methyl-2-oxo-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4m**).* This product was obtained by reaction of **9c** with malononitrile. Yellow solid; R_f=0.18 (CH_2Cl_2/EtOAc 8:2); mp 273–275 °C; yield: 53%; IR (cm^{-1}): 3405 (NH), 2221 (CN), 1663 (CO), 1639 (CO). ^1H NMR (DMSO-d_6): δ 1.21 (3H, t, J=7.1 Hz, CH_3), 2.64 (3H, s, CH_3), 4.08 (2H, s, CH_2), 4.19 (2H, q, J=7.1 Hz, CH_2), 5.21 (2H, s, CH_2), 6.99 (2H, d, J=6.5 Hz, H-2′ and H-6′), 7.20–7.36 (3H, m, H-3′, H-4′, and H-5′), 8.11 (1H, s, H-4), 12.10 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.5 (q), 13.9 (q), 21.7 (t), 48.3 (t), 60.1 (t), 116.3 (s), 120.6 (s), 120.8 (s), 125.9 (d×2), 126.0 (s), 127.1 (d), 127.2 (s), 128.4 (d×2), 128.6 (d), 132.6 (s), 137.7 (s), 137.8 (s), 137.9 (s), 160.8 (CO), 160.9 (CO). Anal. Calcd for $C_{22}H_{19}N_3O_3S$ (405.47): C, 65.17; H, 4.72; N, 10.36. Found: C, 65.45; H, 4.67; N, 10.08.

*4.7.14. Ethyl 3-(benzoyl)-7,9-dimethyl-2-oxo-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4n**).* This product was obtained by reaction of **9b** with benzoylacetonitrile. Yellow solid; R_f=0.58 (CH_2Cl_2/EtOAc 9:1); mp 232–233 °C; yield: 60%; IR (cm^{-1}): 3401 (NH), 1699 (CO), 1695 (CO), 1662 (CO). ^1H NMR (DMSO-d_6): δ 1.33 (3H, t, J=7.1 Hz, CH_3), 2.66 (3H, s, CH_3), 3.80 (3H, s, CH_3), 4.13 (2H, s, CH_2), 4.28 (2H, q, J=7.1 Hz, CH_2), 7.47–7.78 (6H, m, Ph and H-4), 11.33 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.4 (q), 14.2 (q), 21.6 (t), 33.3 (q), 59.8 (t), 90.1 (s), 120.9 (s), 126.9 (s), 128.4 (d×2), 129.0 (d), 129.1 (d×2), 132.8 (d), 137.0 (s), 137.4 (s), 159.6 (s), 161.2 (s), 170.4 (s), 172.3 (CO), 179.9 (CO), 194.2 (CO). Anal. Calcd for $C_{22}H_{20}N_2O_4S$ (408.47): C, 64.69; H, 4.94; N, 6.86. Found: C, 64.40; H, 5.08; N, 6.98.

*4.7.15. Ethyl 3-(benzoyl)-7-benzyl-9-methyl-2-oxo-1,2,6,7-tetrahydropyrrolo[3′,2′:4,5]thiopyrano[3,2-b]pyridine-8-carboxylate (**4o**).* This product was obtained by reaction of **9c** with benzoylacetonitrile. Yellow solid; R_f=0.56 (CH_2Cl_2/EtOAc 9:1); mp 183–184 °C; yield: 57%; IR (cm^{-1}): 3393 (NH), 1684 (CO), 1683 (CO), 1608 (CO). ^1H NMR (DMSO-d_6): δ 1.22 (3H, t, J=7.1 Hz, CH_3), 2.71 (3H, s, CH_3), 4.09 (2H, s, CH_2), 4.20 (2H, q, J=7.1 Hz, CH_2), 5.67 (2H, s, CH_2), 7.00 (2H, d, J=6.6 Hz, H-2′ and H-6′), 7.20–7.37 (3H, m, H-3′, H-4′, and H-5′), 7.47–7.68 (3H, m, H-3″, H-4″, and H-5″), 7.75 (1H, s, H-4), 7.76 (2H, d, J=6.6 Hz, H-2″ and H-6″), 11.38 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.6 (q), 14.0 (q), 21.8 (t), 48.0 (t), 60.0 (t), 116.5 (s), 120.3 (s), 120.5 (s), 125.9 (d×2), 127.0 (s), 127.2 (d), 127.8 (d), 128.4 (d×2), 128.6 (d×2), 129.2 (d×2), 132.9 (d), 133.0 (s), 137.1 (s), 137.3 (s), 137.9 (s), 159.1 (s), 159.5 (CO), 161.0 (CO), 161.1 (CO). Anal. Calcd for $C_{28}H_{24}N_2O_4S$ (484.57): C, 69.40; H, 4.99; N, 5.78. Found: C, 69.22; H, 5.16; N, 5.54.

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Supplementary data

Inhibition of in vitro tumor cell growth of compounds **8c**, **4a**, and **4b**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.04.041.

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