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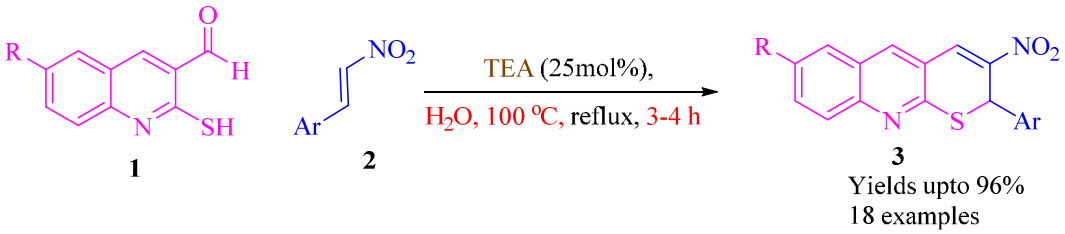

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ARTICLE TYPE

Facile "on water" domino reactions for the expedient synthesis of 2*H*-thiopyrano[2,3-*b*]quinolines

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A facile synthesis of novel 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines from the domino reactions of 2-mercaptoquinoline-3-carbaldehyde and substituted *β*-nitrostyrenes in the presence of triethylamine (TEA) in water is described. This "on water" protocol proceeds with high atom economy through the creation of one C-S and one C-C bond presumably *via* Michael addition-intramolecular aldol-dehydration domino sequence.

Introduction

Domino reactions involving two or more reactants lead to the expedient assembly of molecules of high structural complexity in a convergent and synthetically efficient manner. These processes occurring in one pot avoid the isolation and purification of intermediates, maximize the yield of the final product, minimize the wastage of solvent and chromatographic stationary phases and enhance the greenness of the transformations.[1] Consequently, domino reactions have become an attractive tool in combinatorial synthesis[2] and drug development programs.[3]

Another important facet of synthetic organic chemistry pertains to the efficient access of natural products, pharmaceuticals, agrochemicals etc in green solvents viz. water, ionic liquids etc. In particular, water as solvent for reactions offers unique advantages such as abundant availability, environment-friendliness and safety.[4] Further, the lipophilicity of water renders the facile segregation of the product. In addition, water facilitates many organic reactions, in particular, when the reactants are initially emulsionated in water and the transition states better solvated by hydrogen bonds with unsymmetrically H-bonded water molecules than the reactants. These reactions known as "on water" processes result in enhancements of rate and product yield compared to that in organic solvents which are usually toxic or unsafe. Moreover, water as a reaction medium facilitates unique solvation modes and assembly processes furnishing selectivities and reactivities that are often difficult to realize in organic solvents.[5]

Numerous natural and synthetic analogues comprising quinoline ring system display interesting biological activities such as antiviral,[6] antitumor,[7] antibacterial,[8] anti-inflammatory,[9] antiasthmatic,[10] antiproliferative,[11] antimalarial,[12] anti allergenic,[13] antifungal,[14] MCH1R antagonist[15] and potent HIV-integrase inhibition.[16] Among them, thiopyrano[2,3-*b*]quinoline exhibits remarkable biological activities such as antioxidant[17] and mGlu 1 receptor activity.[18] (Figure.1).

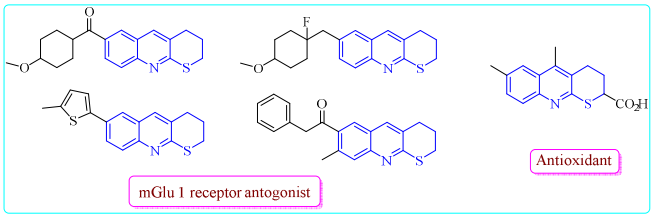
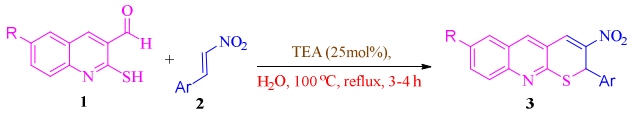


Fig. 1 Selected examples of biologically active functionalized thiopyrano [2,3-*b*]quinolines

Synthetic methods for the construction thiapyrano[2,3-*b*]quinolines include the reactions of (i) 2-mercapto-4-methylquinoline and maleic anhydride in the presence of nanostructured-TiO_2,[17] (ii) 2-(3-methylbut-2-enylthio)quinoline-3-carbaldehyde and anilines in the presence of silica gel supported $InCl_3$ in CH_3CN,[19] (iii) 2-arylthioquinolin-3-carbaldehydes and activated olefins through intramolecular Friedel–Crafts reaction of Morita–Baylis–Hillman adducts in the presence of acid in dichloromethane,[20] (iv) 2-methylthio-3-(2-bromobenzoyl)quinoline in the presence of AIBN via radical cyclization in toluene,[21] (v) 7-substituted 2-allylsulfanyl-3-hydroximinomethylquinolines in the presence of aqueous NaOCl in $CHCl_3$,[22] (vi) 3-formyl-2-mercaptoquinoline with ethyl acetoacetate/ diethyl malonate/ethyl cyanoacetate in the presence of piperidine in CH_3CN,[23] (vii) 3-formyl-2-mercaptoquinoline with chloroacetyl chloride in DMF,[24] (viii) 3-formyl-2-mercaptoquinoline and phenoxyacetic acid in the presence of triethylamine and acetic anhydride,[25] (ix) 3-formyl-2-mercaptoquinoline with acetyl chloride in the presence of sodium methoxide,[26] (x) 3-formyl-2-mercaptoquinoline, malononitrile and 4-methylquinoline-2-thiol in the presence of anhydrous ammonium hydroxide,[27] (xi) 2-mercaptoquinoline-3-carbaldehyde and citral in the presence of EDDA in xylene,[28] (xii)

α,β-unsaturated aldehyde and 2-mercaptoquinoline-3-carbaldehyde in the presence of chiral organocatalysts in $CHCl_3$[29] and (xiii) acrylonitrile and 2-mercaptoquinoline-3-carbaldehyde in the presence of triethylamine in DMF.[30] These approaches, however, are associated with one or more drawbacks such as corrosive reagents, moderate yield, toxic solvents, expensive catalysts, lack of convergence and tedious work up.

These considerations in conjunction with the biological relevance of thiapyrano[2,3-*b*]quinoline ring system prompted us to develop an atom-efficient synthesis as a part of our ongoing research programme on the construction biologically significant novel heterocycles through domino[31] and/or green transformations[32] and report the results in this manuscript. In the present study, we have evolved an environmentally benign one-pot two-component domino synthesis of novel 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines from the reaction of 2-mercaptoquinoline-3-carbaldehyde **1** and substituted *β*-nitrostyrenes **2** in the presence of triethylamine (TEA) (25 mol%) in water (Scheme 1).



Scheme 1. Synthesis of 2*H*-thiopyrano[2,3-b]quinolines **3**

Results and Discussion

We began our study with the optimization of the model two-component reaction between equimolecular amounts of 2-mercaptoquinoline-3-carbaldehyde and *β*-nitrostyrene employing different solvents, bases and temperature and the results are summarized in Table 1. It was found that when water was used as the reaction medium in the presence of Na_2CO_3, the yield of the product was very low (Table 1, Entry 12). On the other hand, this reaction in water in the presence of TEA furnished a higher yield of the product in shorter reaction time than in other solvents (Table 1, Entries 1-5). Consequently, we have performed all subsequent reactions in water. A study of the effect of temperature on the reaction outcome shows that the yield of the product **3e** increases from 63 to 93% with an increase in temperature from 40 to 100°C (Table 1, Entries 1-4) respectively. The optimal catalyst load investigated with 25, 50, 75 and 100 mol% of TEA on the model reaction discloses that 25 mol% of TEA is sufficient to obtain an excellent yield of 94 % of **3e** (Table 1, Entry 4). Hence all reactions were performed in water at 100°C with 25 mol% of triethylamine. That this reaction proceeds via "on water" protocol is evident from the fact that (i) initially the mercaptoquinolinecarbaldehyde and *β*-nitrostyrenes are not soluble in water, (ii) upon addition of TEA, the former partially goes into solution during the progress of the reaction and (iii) the yield of the product is maximum in water as solvent. One great advantage associated with this protocol is that the isolation and purification of the product could be achieved by simply filtering the product and washing with cold ethanol. This protocol has an added advantage as column chromatographic purification has been avoided in workup.

Table 1.Optimization of the reaction conditions for the synthesis of **3e**

Entry	Base (100 mol%)	Solvent	Time (h)	Temp (°C)	Yield of 3e[e] (%)
1	TEA	water	8.0	rt	63
2	TEA	water	4.0	40	72
3	TEA	water	3.5	70	89
4	TEA	water	2.0	-[d]	93
5	TEA[a]	water	2.1	-[d]	92
6	TEA[b]	water	2.4	-[d]	93
7	TEA[c]	water	3.0	-[d]	94
9	TEA	EtOH	4.0	-[d]	84
10	TEA	MeOH	3.0	-[d]	75
11	TEA	DCM	4.3	-[d]	70
12	TEA	THF	3.5	-[d]	62
13	TEA	CH_3CN	4.5	-[d]	59
14	TEA	DMF	3.0	-[d]	57
15	K_2CO_3	water	5.0	-[d]	64
16	Na_2CO_3	water	6.5	-[d]	34
17	DABCO	water	6.0	-[d]	49
18	DBU	water	4.0	-[d]	55
19	DMAP	water	4.5	-[d]	61
20	Pyridine	water	4.0	-[d]	58

[a]75 mol%, [b]50 mol% and [c]25 mol% used; [d]These reactions performed at reflux conditions; [e]Isolated yield after washing with cold ethanol.

Table 2. Synthesis of 2*H*-thiopyrano[2,3-*b*]quinolines **3**

Entry	Comp.	R	Ar	Time (h)	Yield of 3 (%)[a]
1	**3a**	H	4-FC_6H_4	4.0	87
2	**3b**	H	4-ClC_6H_4	3.3	89
3	**3c**	H	4-BrC_6H_4	3.5	92
4	**3d**	H	4-$CF_3C_6H_4$	4.0	85
5	**3e**	H	C_6H_5	3.0	94
6	**3f**	H	4-MeC_6H_4	3.0	95
7	**3g**	H	4-EtC_6H_4	3.0	93
8	**3h**	H	4-$Bu^tC_6H_4$	3.0	92
9	**3i**	H	4-$MeOC_6H_4$	3.0	96
10	**3j**	H	2-FC_6H_4	4.0	90
11	**3k**	H	2-$MeOC_6H_4$	3.0	94
12	**3l**	H	3-FC_6H_4	3.0	92
13	**3m**	H	3-$MeOC_6H_4$	3.0	95
14	**3n**	H	1-Naphthyl	3.0	91
15	**3o**	H	2-Thienyl	3.0	94
16	**3p**	Me	4-ClC_6H_4	3.0	90
17	**3q**	Me	4-MeC_6H_4	3.0	93
18	**3r**	OMe	4-MeC_6H_4	3.0	91

[a]Isolated yield after washing with cold ethanol.

Typically, the reaction was performed with a mixture of 2-mercaptoquinoline-3-carbaldehyde **1** (1.0 mmol) and substituted *β*-nitrostyrene **2** (1.0 mmol) in the presence of TEA (0.25 mol) in water (10 ml) under heating to reflux at 100°C for 3-4 h. After completion of the reaction (TLC), the resulting crude product was purified by washing with cold ethanol, which afforded a library of 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines **3** in 85-96% yields (Table 2). This domino reaction proceeded well with electron-

releasing as well as electron-withdrawing group, sterically hindered aryl rings and heteroaromatic nitro olefins as well. Moreover, the reaction proceeds well with quinoline part bearing electron releasing groups such as -Me and -OMe, while the presence of substituents like -Cl and –Br led to a mixture of products.

Finally, the TEA in the aqueous filtrate after the reaction was over could also be removed by our previously reported procedure by passing the solution through polymer-bound acid resin, Indion 790 to ensure the purity of water ultimately let into the environment thereby obviating pollution.[32b] Further, this transformation is characterized by remarkable synthetic efficiency affording the product with innocuous by-product, water.

The structure of 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines **3** was deduced from one- and two-dimensional NMR spectroscopic data as detailed for **3f** as a representative example (vide Supporting Information). Finally, the structure of the product was also confirmed by an X-ray crystallographic study[34] of a single crystal of **3c** (Figure 3).

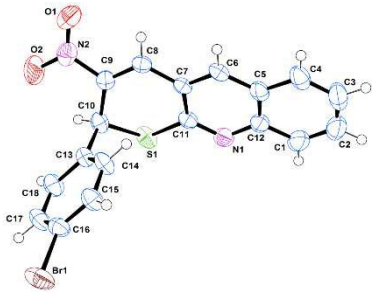
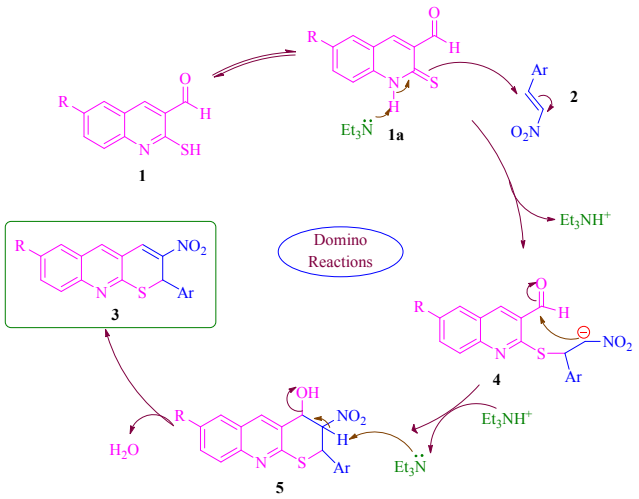


Fig. 3 ORTEP diagram for **3c**.

A plausible mechanism for the formation of 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines is depicted in Scheme 2.



Scheme 2. Probable domino mechanistic pathway leading to the formation of **3**.

Presumably, this transformation is presumably triggered by the Michael addition of the thiolate anion of 2-mercaptoquinoline-3-carbaldehyde, generated from the reaction of 2-mercaptoquinoline-3-carbaldehyde **1** with base, to β-nitrostyrenes **2** affording intermediate **4**. Subsequent intramolecular aldol reaction of **4** and concomitant elimination of water molecule furnishes 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines **3**. Overall, this is a two-component domino transformation via the formation of one C-S and one C-C bond.

Conclusion

In conclusion, we have developed an eco-friendly two-component "on water" domino protocol for the facile synthesis of novel 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines in good yields from simple, readily available starting materials. This protocol, following group-assisted-purification chemistry (GAP Chemistry)[33] obviating traditional column chromatographic and recrystallization steps, occurs with the formation of a C-S and a C-C bond in a one pot operation.

Experimental Section

General information

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H-NMR, ^{13}C-NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Mass spectra were recorded in LCQ Fleet mass spectrometer, Thermo Fisher Instruments Limited, US. Electrospray ionisation mass spectrometry (ESI-MS) analysis was performed in the positive ion mode on a liquid chromatography ion trap.

General procedure for the Synthesis of 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines (3a-r)

A mixture of 2-mercaptoquinoline-3-carbaldehyde (1.0 mmol) and substituted *β*-nitrostyrenes (1.0 mmol) in the presence of triethylamine (TEA) (0.25 mmol) in water (10 ml) was heated to reflux at 100°C for 3-4 h. After completion of the reaction (TLC), the resulting crude product was purified by washing with cold ethanol, which afforded a library of 3-nitro-2-aryl-2*H*-thiopyrano[2,3-*b*]quinolines **3** in excellent yields.

2-(4-fluorophenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3a: Yellow solid. Yield: 87%; mp. 167–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.77 (s, 1H), 6.89–6.96 (m, 2H), 7.20–7.26 (m, 2H), 7.52–7.57 (m, 1H), 7.77 (td, J = 8.4, 1.2 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 41.5, 116.0 ($^{2}J_{C,F}$ = 21.7 Hz), 121.9, 126.1, 127.0, 128.1 ($^{3}J_{C,F}$ = 8.4 Hz), 128.4, 128.5, 130.9, 132.5, 136.0 ($^{4}J_{C,F}$ = 3.3 Hz), 139.4, 145.2, 149.4, 155.1, 162.6 ($^{1}J_{C,F}$ = 246.6 Hz); ESI-MS: m/z. Calcd: 338.05; Found: 339.14 (M^{+}).

2-(4-chlorophenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3b: Pale Yellow solid. Yield: 89%; mp. 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.75 (s, 1H), 7.17–7.23 (m, 4H), 7.53–7.58 (m, 1H), 7.77 (td, *J* = 8.4, 1.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 8.21 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 41.6, 121.9, 126.1, 127.1, 127.3, 127.7, 128.5, 129.3, 131.1, 132.6, 134.5, 138.6, 139.5, 145.0, 149.4, 155.0; ESI-MS: m/z. Calcd: 354.02; Found: 355.19 (M^+).

2-(4-bromophenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3c: Pale Yellow solid. Yield: 92%; mp. 198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.74 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.35–7.38 (m, 2H), 7.53–7.58 (m, 1H), 7.76 (td, *J* = 7.8, 1.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.21 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 41.7, 121.9, 122.7, 126.1, 127.1, 128.0, 128.5, 128.5, 131.1, 132.3, 132.6, 139.1, 139.5, 144.9, 149.4, 154.9; ESI-MS: m/z. Calcd: 397.97; Found: 399.06 (M^+), 401.12 (M+3).

3-nitro-2-(4-(trifluoromethyl)phenyl)-2*H*-thiopyrano[2,3-*b*]quinoline 3d: Yellow solid. Yield: 85%; mp. 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.82 (s, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.50–7.57 (m, 3H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.29 (s, 1H), 8.35 (s, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 41.8, 121.8, 126.1, 126.2, 126.7, 127.2, 128.5, 128.6, 130.7 ($^2J_{C,F}$ = 32.9 Hz), 131.5, 132.7, 139.7, 143.8, 144.5, 149.4, 154.7; ESI-MS: m/z. Calcd: 388.05; Found: 389.20 (M^+).

3-nitro-2-phenyl-2*H*-thiopyrano[2,3-*b*]quinoline 3e: Pale Yellow solid. Yield: 94%; mp. 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.78 (s,1H), 7.21–7.24 (m, 5H), 7.50–7.56 (m,1H), 7.75 (td, *J* = 8.4, 1.2 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 42.2, 122.2, 126.4, 126.3, 126.9, 128.4, 128.5, 128.6, 129.1, 130.9, 132.4, 139.3, 140.0, 145.3, 149.3, 155.5; ESI-MS: m/z. Calcd: 320.06; Found: 321.21 (M^+).

3-nitro-2-(*p*-tolyl)-2*H*-thiopyrano[2,3-*b*]quinoline 3f: Yellow solid. Yield: 95%; mp. 214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.26 (s, 3H), 5.76 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.75 (td, *J* = 7.8, 1.5 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 8.18 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.0, 42.1, 122.2, 126.2, 126.3, 126.8, 128.4, 128.5, 129.8, 130.5, 132.2, 137.2, 138.5, 139.0, 145.7, 149.4, 155.7; ESI-MS: m/z. Calcd: 334.08; Found: 335.18 (M^+).

2-(4-ethylphenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3g: Pale Yellow solid. Yield: 93%; mp. 217–218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.14 (t, *J* = 7.5 Hz, 3H), 2.55 (q, *J* = 7.6 Hz, 2H), 5.76 (s, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.50–7.55 (m, 1H), 7.75 (td, *J* = 7.7, 1.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 15.3, 28.4, 42.0, 122.2, 126.1, 126.2, 126.9, 128.4, 128.5, 128.6, 130.6, 132.3, 137.3, 139.2, 144.8, 145.5, 149.3, 155.6; ESI-MS: m/z. Calcd: 348.09; Found: 349.22 (M^+).

2-(4-*(tert*-butyl)phenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3h: Pale Yellow solid. Yield: 92%; mp. 252–253 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (s, 9H), 5.77 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.73–7.78 (m, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 31.1, 34.5, 41.9, 122.3, 125.9, 126.0, 126.1, 126.9, 128.4, 128.5, 130.6, 132.3, 136.9, 139.1, 145.6, 149.3, 151.6, 155.6; ESI-MS: m/z. Calcd: 376.12; Found: 377.21 (M^+).

2-(4-methoxyphenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3i: Yellow solid. Yield: 96%; mp. 208–209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.72 (s, 3H), 5.75 (s, 1H), 6.73–6.76 (m, 2H), 7.15–7.18 (m, 2H), 7.51–7.56 (m, 1H), 7.76(td, *J* = 7.7, 1.4 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 41.8, 55.2, 114.4, 122.2, 126.1, 126.9, 127.6, 128.4, 128.5, 130.4, 132.2, 132.3, 145.6, 149.3, 155.6, 159.7; ESI-MS: m/z. Calcd: 350.07; Found: 351.21 (M^+).

2-(2-fluorophenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3j: Pale Yellow solid. Yield: 90%; mp. 216–217 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.10 (s, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 7.01–7.11 (m, 2H), 7.19–7.24 (m, 1H) 7.54 (t, *J* = 7.5 Hz, 1H), 7.73–7.78 (m, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.21 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 35.9 ($^3J_{C,F}$ = 3.7 Hz), 116.3 ($^2J_{C,F}$ = 21.2 Hz), 122.0, 124.5 ($^3J_{C,F}$ = 3.5 Hz), 126.2, 127.0, 127.1 ($^4J_{C,F}$ = 2.7 Hz), 127.3, 128.5, 130.3 ($^3J_{C,F}$ = 8.3 Hz), 132.0, 132.4, 139.4, 143.8, 149.4, 155.4, 159.2 ($^1J_{C,F}$ = 248.2 Hz); ESI-MS: m/z. Calcd: 338.05; Found: 339.18 (M^+).

2-(2-methoxyphenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3k: Yellow solid. Yield: 94%; mp. 199–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H:3.86, (s, 3H), 6.19 (s, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.17–7.23 (m, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 36.4, 55.6, 111.3, 120.5, 122.5, 126.0, 126.1, 126.7, 127.4, 128.3, 128.4, 129.7, 132.0, 132.1, 139.0, 144.4, 149.2, 155.7, 156.7; ESI-MS: m/z. Calcd: 350.07; Found: 351.18 (M^+).

2-(3-fluorophenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3l: Yellow solid. Yield: 92%; mp. 210–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.77 (s, 1H), 6.94 (d, *J* = 9.3 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.19–7.23 (m, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.75 (m, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 8.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 39.3, 111.5 ($^2J_{C,F}$ = 22.3 Hz), 113.4 ($^2J_{C,F}$ = 20.8 Hz), 120.3 ($^4J_{C,F}$ = 2.8 Hz), 120.4, 124.4, 125.1, 126.1, 127.3, 129.2 ($^3J_{C,F}$ = 8.1 Hz), 130.6, 130.7, 138.9, 141.6 ($^3J_{C,F}$ = 6.7 Hz), 142.4, 147.1, 153.0, 160.7 ($^1J_{C,F}$ = 241.0 Hz); ESI-MS: m/z. Calcd: 338.05; Found: 339.2 (M^+).

2-(3-methoxyphenyl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3m: Pale Yellow solid. Yield: 95%; mp. 152–153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.71 (s, 3H), 5.75 (s, 1H), 6.74–6.83 (m, 3H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.72–7.78 (m, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 8.18 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 42.1, 55.2, 112.5, 113.5,118.5, 122.1, 126.1, 126.9, 128.4, 128.5, 130.2, 131.0, 132.3, 139.3, 141.4, 145.1, 149.3, 155.4, 159.9; ESI-MS: m/z. Calcd: 350.07; Found: 351.20 (M^+).

2-(naphthalen-1-yl)-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3n: Yellow solid. Yield: 91%; mp. 287–288 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.62 (s, 1H), 7.14–7.22 (m, 2H), 7.49–7.59 (m, 2H), 7.66–7.75 (m, 3H), 7.86 (t, J = 7.9 Hz, 3H), 8.20 (d, J = 8.7 Hz, 1H), 8.26 (s, 1H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 37.9, 122.2, 122.7, 123.2, 125.0, 126.1, 126.2, 127.0, 127.1, 128.5, 129.1, 129.2, 129.4, 132.3, 132.4, 134.2, 134.5, 139.5, 144.7, 149.3, 155.5; ESI-MS: m/z. Calcd: 370.08; Found: 371.19 (M^+).

3-nitro-2-(thiophen-2-yl)-2*H*-thiopyrano[2,3-*b*]quinoline 3o: Green solid. Yield: 94%; mp. 201–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.06 (s, 1H), 6.82 (dd, J = 5.1, 3.6 Hz, 1H), 6.95 (dt, J = 3.6, 1.0 Hz, 1H), 7.11 (dd, J = 5.1, 1.2 Hz, 1H), 7.55 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 8.22 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 37.6, 122.1, 125.5, 125.9, 126.2, 127.0, 127.1, 128.5, 130.4, 132.5, 139.5, 143.0, 145.5, 149.4, 155.0, 166.1; ESI-MS: m/z. Calcd: 326.02; Found: 327.14 (M^+).

2-(4-chlorophenyl)-7-methyl-3-nitro-2*H*-thiopyrano[2,3-*b*]quinoline 3p: Yellow solid. Yield: 90% mp. 251-252; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.54 (s, 3H), 5.73 (s, 1H), 7.16–7.22 (m, 4H), 7.59–7.61 (m, 2H), 7.84 (d, J = 9.3 Hz, 1H), 8.11 (s, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.4, 41.5, 121.8, 126.2, 127.3, 127.7, 128.1, 129.2, 131.3, 134.4, 134.8, 137.2, 138.6, 138.9, 144.8, 148.0, 153.7; ESI-MS: m/z. Calcd: 368.04; Found: 369.06 (M^+).

7-methyl-3-nitro-2-(*p*-tolyl)-2*H*-thiopyrano[2,3-*b*]quinoline 3q: Light yellow solid. Yield: 93% mp. 238-239; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.25 (s, 3H), 2.53 (s, 3H), 5.74 (s, 1H), 7.02 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.56–7.58 (m, 2H), 7.83 (d, J = 9.0 Hz, 1H), 8.09 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.0, 21.4, 41.9, 122.1, 126.2, 127.3, 128.1, 129.7, 130.9, 134.6, 137.0, 137.1, 138.4, 138.6, 145.3, 148.0, 154.3; ESI-MS: m/z. Calcd: 348.09; Found: 349.12 (M^+).

7-methoxy-3-nitro-2-(*p*-tolyl)-2*H*-thiopyrano[2,3-*b*]quinoline 3r: orange solid. Yield: 91% mp. 197-198; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.25 (s, 3H), 3.94 (s, 3H), 5.72 (s, 1H), 7.00–7.13 (m, 5H), 7.39 (dd, J = 9.1, 2.8 Hz, 1H), 7.83 (d, J = 9.3 Hz, 1H), 8.01 (s, 1H), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.0, 41.8, 55.6, 105.8, 122.4, 124.8, 126.1, 127.1, 129.7, 129.8, 130.8, 137.0, 137.9, 138.4, 145.5, 152.2, 157.9; ESI-MS: m/z. Calcd: 364.09; Found: 365.08 (M^+).

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application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].