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Michael addition of active methylene compounds to (*Z*)-2-arylidenebenzo[*b*]thiophen-3(2*H*)-ones

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Abstract: A series of 2-amino-4-aryl-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylates and 2-amino-4-aryl-3-cyano-4H-1-benzothieno[3,2-*b*]pyrans has been synthesized through Michael addition of (*Z*)-2-arylidenebenzo[*b*]thiophen-3(2*H*)-ones with active methylene compounds, such as ethyl cyanoacetate and malononitrile. The reaction was carried out in ethanol, in the presence of piperidine as a basic catalyst. The structures of the prepared compounds were determined by spectroscopic methods: ^{1}H-NMR, ^{13}C-NMR and confirmed by single crystal X-Ray diffraction.

Keywords: Michael addition; benzothienopyrane; malononitrile; ethyl cyanoacetate; (Z)-2-arylidene-benzo[*b*]thiophen-3(2*H*)-ones; thioaurones.

Introduction

Substituted 2-amino-4-aryl-3-cyano-4*H*-pyran derivatives are very important heterocyclic compounds, which frequently exhibit a wide range of biological activities, such as antiproliferative[1,2], antibacterial[3,4], antitubercular[5], antioxidant[6], analgesic[7], antiparkinsonian[7], and anticancer[8,9] activities. In addition, they are useful starting materials for the synthesis of various fused heterocyclic compounds[10]. Due to the large spectrum of applications, 2-amino-4-aryl-3-cyano-4*H*-pyrans have attracted much attention from researchers in the last few years. Recently, a number of different methods have been reported for the synthesis of 2-amino-4-aryl-3-cyano-4*H*-pyrans, such as multi-component reactions[10].

In view of the fact that thioaurones have been known for a long time[11,12], a literature study shows that research has focused primarily on their synthesis[13-24]. The reactivity of these molecules has been the subject of only a few studies[25-29].

In our research[30-32], we aim at developing simple and efficient methods and techniques for the synthesis of heterocyclic compounds. Furthermore, the present study is based on the reactivity of (*Z*)-2-benzylidenebenzo[*b*]thiophene-3(2H)-ones (thioaurones) and derivatives such as α,β-unsaturated ketones with activated methylene compounds such as malononitrile and ethyl cyanoacetate.

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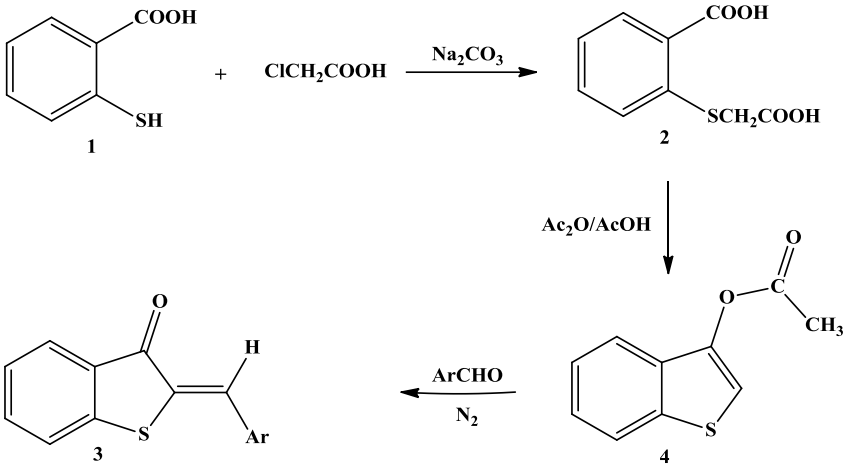
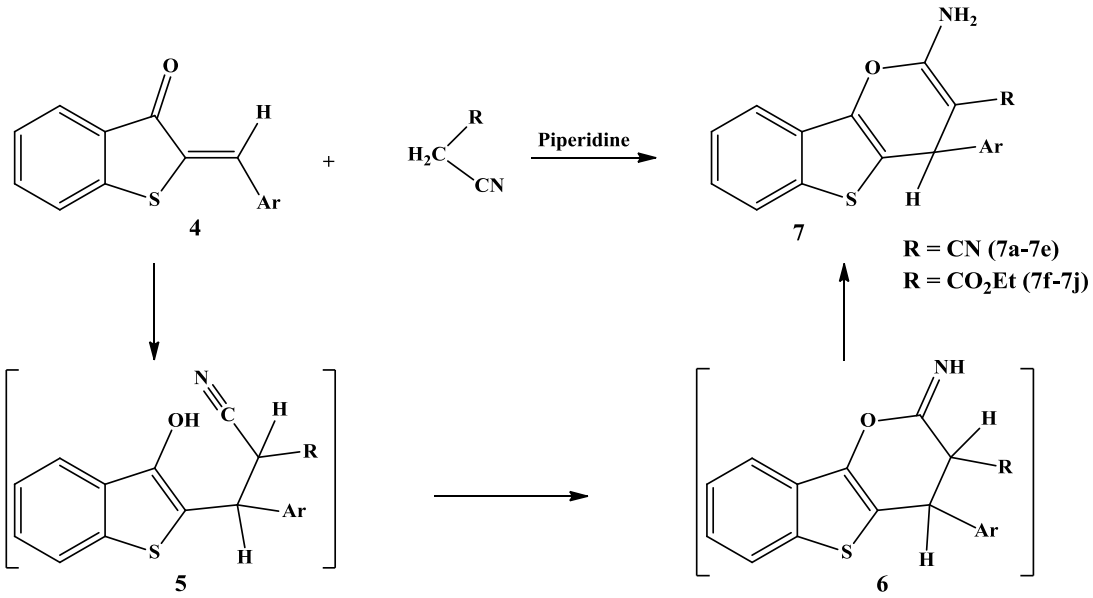
Results and Discussion

The (*Z*)-2-arylidenebenzo[*b*]thiophen-3(2*H*)-ones (**4**) are synthesized by condensation of *p*-substituted benzaldehydes with 3-acetoxybenzothiophene (**3**), which itself is obtained in good yield by the Rössing decarboxylative condensation[33] of 2-[(carboxymethyl) sulfanyl]benzoic acid (**2**). The latter was synthesized from thiosalicylic acid (**1**) and monochloroacetic acid (Scheme 1).



Scheme 1. Synthetic pathway for the preparation of compounds (**4**).

The activated methylene compounds, containing electron-withdrawing groups, such as malononitrile, ethyl cyanoacetate and ethyl malonate react with α,β-unsaturated ketones by Michael addition reaction[34-36]. In this study, we have investigated the behavior of ethyl cyanoacetate and malononitrile with respect to the (*Z*)-2-benzylidenebenzo[*b*]thiophen-3(2*H*)-ones and derivatives (**4**) in ethanol in the presence of piperidine as a basic catalyst.



Scheme 2. Synthetic pathway for the preparation of compounds (**7**).

We have shown that cyclocondensation starts with a Michael 1,4-addition, followed by intramolecular cyclization via nucleophilic addition of the hydroxyl group to the cyano group,

and not onto the carboxylate in the compound **5**, to afford the tricyclic heterocycles 2-amino-4-aryl-3-cyano-4*H*-1-benzothieno[3,2-*b*]pyrans **7a**-**7e** and 2-amino-4-aryl-4*H*-1-benzothieno [3,2-*b*]pyran-3-carboxylates **7f**-**7j**, respectively, in good yield (Scheme 2, Table 1).

Table 1. Physical properties data of compounds **7a-j**.

Product 7	Ar	R	m.p (°C)	Molecular Formula	Time (h)	Yield[a] (%)
a	C_6H_5	CN	220-222	$C_{18}H_{12}N_2OS$	2h	45
b	$p(CH_3O)C_6H_4$	CN	242-244	$C_{19}H_{14}N_2O_2S$	2h	30
c	$p(CH_3)C_6H_4$	CN	240-242	$C_{19}H_{14}N_2OS$	2h	33
d	$p(Cl)C_6H_4$	CN	250-252	$C_{18}H_{11}ClN_2OS$	2h	48
e	$m(NO_2)C_6H_4$	CN	260-262	$C_{18}H_{11}N_3O_3S$	2h	64
f	C_6H_5	CO_2Et	156-158	$C_{20}H_{12}N_2OS$	4h	43
g	$p(CH_3O)C_6H_4$	CO_2Et	120-122	$C_{21}H_{19}NO_4S$	3h	28
h	$p(CH_3)C_6H_4$	CO_2Et	122-124	$C_{21}H_{19}NO_3S$	3h	31
i	$p(Cl)C_6H_4$	CO_2Et	132-134	$C_{18}H_{16}ClNO_3S$	3h	67
j	$m(NO_2)C_6H_4$	CO_2Et	190-192	$C_{20}H_{16}N_2O_5S$	6h	68

[a]Yields refer to pure isolated products.

The structure of the resultant product was assigned by FT-IR and ^{1}H NMR, ^{13}C NMR spectral analysis and confirmed by single crystal X-ray diffraction analysis of **7j** (Fig. 1).

The IR spectra of the synthesized products manifest absorption bands of deformation and stretching vibrations of the amino group (NH_2) at 1631-1656 and 3302-3489 cm^{-1}, respectively. The absorption band of the cyano group (CN) at 2121-2193 cm^{-1} confirms the presence of the cyano group conjugated with the amino group in pyran rings. The absorption bands of the carbonyl groups are observed at 1650-1673 cm^{-1}.

The ^{1}H NMR spectra of compounds **7** show a slightly broadened signal for the primary amino group at δ 6.53-7.31 ppm, and a singlet for the methane group adjacent to the aryl group is observed at δ 4.98-5.28 ppm. The usual signals due to the benzothiophene and aryl fragments appear at δ 6.77-8.45 ppm.

In addition to the signals corresponding to the aliphatic group, the ^{13}C NMR spectra present a signal at 169 ppm, attributed to the carbon of the carbonyl group. The other signal is attributed to the carbon of the cyano group (CN), which appears at 119 ppm. The problem of the structural assignment was solved by means of an X-ray crystal structural determination (Fig. 1), thus confirming the structure of ethyl 2-amino-4-(3-nitrophenyl)-4H-1-benzothieno [3,2-b]pyran-3-carboxylate (**7f**)[37].

Yields, molecular formulae, and some physical properties of compounds **7a-j** are summarized in Table 1.

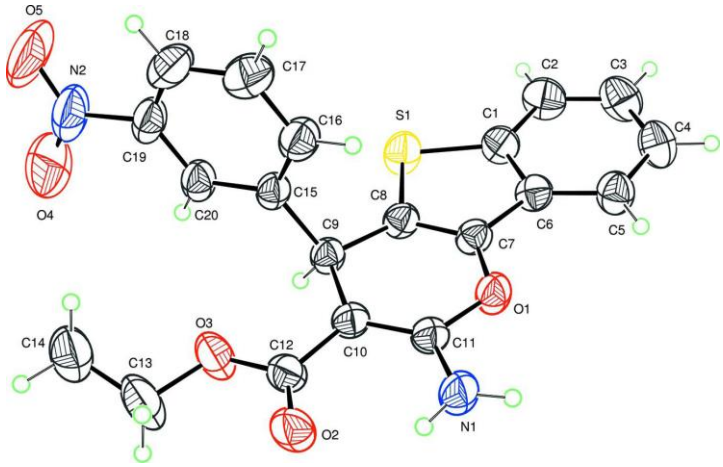


Figure 1. Ortep view of the compound **(7j)** with displacement ellipsoids drawn at the 50% probability level.

Conclusion

In summary, we have developed a simple and regioselective method for the preparation of 2-amino-4-aryl-3-cyano-4*H*-1-benzothieno[3,2-*b*]pyrans and 2-amino-4-aryl-4*H*-1-benzo thieno[3,2-*b*]pyran-3-carboxylates, by condensation of active methylene (ethyl cyanoacetate, malononitrile) to thioaurones in an alcoholic solvent medium, using piperidine as a basic catalyst. The products were obtained in excellent yields. The study of the biological activity of the synthesized products will be the subject of a future report.

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Experimental Section

All melting points were determined using a KOFLER Bench apparatus and are uncorrected. IR spectra were recorded using a FT-IR VERTEX 70 spectrophotometer. The NMR spectra were recorded at ambient temperature on an AVANCE 300 BRUKER spectrometer working at 300 MHz and 75 MHz for the proton and ^{13}C, respectively, with $CDCl_3$ and DMSO as solvent. The chemical shifts (δ) and coupling constants (*J*) are given in parts per million (ppm) and Hertz (Hz), respectively. Multiplicities were recorded as s (singlet), br.s (broad signal), d (doublet), dd (double doublet), t (triplet), q (quartet) or m (multiplet). All the reactions were monitored by TLC, which was performed on Merck aluminum-backed plates pre-coated with silica (0.2 mm, 60 F_{254}). For column chromatography, Merck silica gel (70-230 mesh) was used. Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. The numbering of the hydrogen and carbon atoms applied in scheme 2 is in accordance with the IUPAC nomenclature.

Synthesis of 2-[(Carboxymethyl)sulfanyl]benzoic acid 2

To a solution of sodium hydroxide (0.25 mol) in water (250 ml) was added thiosalicylic acid (0.065 mol) and monochloroacetic acid (0.065 mol). The reaction mixture was refluxed for 4 hours then on active carbon (1g) for 10 min. The mixture was filtered, and acidified with concentrated hydrochloric acid. The precipitate that formed was collected by filtration, washed with water, and recrystallized from ethanol. Yield: (77 %) as a white solid, mp. 210 °C.

Synthesis of 3-Acetoxybenzothiophene 3

A mixture of acetic acid (20 ml), acetic anhydride (80 ml) and **1** (0.05 mol) was heated for one hour. The excess of acetic anhydride was removed under reduced pressure. Then, the reaction residue was washed with water and extracted using hot ethyl ether. The organic layer was dried over Na_2SO_4. The solvent was removed, and the crude product was purified by column chromatography on silica gel (4:1 hexane/ether) to give **3** in liquid form.
Yield (70 %), red oil. IR (film): 1764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (δ/ppm): 7.41-7.86 (m, 4H, H aromatic), 7.46 (s, 1H, H ethylenic), 2.41 (s, 3H, $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 21.0, 111.9, 120.5, 122.9, 124.4, 125.2, 132.2, 136.9, 140.8, 168.3.

Synthesis of (Z)-2-Benzylidenebenzo[*b*]thiophen-3(2*H*)-one and derivatives 4

An aqueous solution of sodium hydroxide (2N) was placed in a three-necked flask equipped with a condenser, a dropping funnel and a nitrogen bubbler. A stream of nitrogen was bubbled through the solution with stirring for 2 to 3 minutes. Then, 3-acetoxy-benzothiophene **3 (**20 mmol) was added. Arylaldehyde (20 mmol) dissolved in ethanol (4 ml) was then added dropwise. The reaction mixture was stirred and heated for 20 - 30 min., until the formation of a solid, which was filtered, washed with water and recrystallized from ethanol.

(*Z*)-2-Benzylidenebenzo[*b*]thiophen-3(2*H*)-one (4a)

Yield (80 %) as a yellow solid; mp 134 °C. IR (KBr) ν(C=O): 1681 cm^{-1}, ν(C=C): 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (δ/ppm): 7.95 (s, 1H, H ethylenic), 7.94 (dd, 1H), 7.75 (dd, 2H), 7.34-7.62 (m, 5H), 7.28-7.31 (m, 1H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 123.9, 125.6, 127.1, 129.1, 130.0, 130.3, 130.5, 131.0, 133.6, 134.3, 135.3, 146.1, 188.7.

(*Z*)-2-(4-Methoxybenzylidene)benzo[*b*]thiophen-3(2*H*)-one (4b):

Yield (78 %) as a yellow solid; m.p 142 °C. IR (KBr) ν(C=O): 1679 cm^{-1}, ν(C=C): 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (δ/ppm): 7.95 (dd, 1H), 7.94 (dd, 2H), 7.94 (s, 1H, s, ethylenic-H), 7.69-7.93 (m, 2H, H aromatic), 7.27-7.67 (m, 1H), 7.01 (dd, 2H), 3.78 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 55.2, 124.3, 126.1, 127.5, 129.2, 130.6, 131.1, 132.7, 133.5, 133.0, 136.5, 152.4, 159.9, 188.7.

(*Z*)-2-(4-Methylbenzylidene)benzo[*b*]thiophen-3(2*H*)-one (4c)

Yield (83 %) as a yellow solid; mp 144 °C. IR (KBr) ν(C=O): 1670 cm^{-1}, ν(C=C): 1587 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (δ/ppm): 7.98 (s, 1H, ethylenic-H), 7.93 (dd, 2H), 7.75 (dd, 1H), 7.61 (dd, 2H), 7.34-7.62 (m, 5H, H aromatic), 7.28-7.31 (m, 1H), 2.14 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 21.6, 123.8, 125.5, 126.9, 129.2, 130.3, 130.6, 131.0, 131.5, 133.1, 133.7, 135.1, 146.1, 188.65.

(*Z*)-2-(4-Chlorobenzylidene)benzo[*b*]thiophen-3(2*H*)-one (4d)

Yield (85 %) as a yellow solid; mp 162 °C. IR (KBr) ν(C=O): 1678 cm^{-1}, ν(C=C): 1580 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 7.95 (dd, 1H), 7.89 (s, 1H, ethylenic-H), 7.64–7.56 (m, 3H), 7.51-7.43 (m, 3H), 7.33 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 124.3, 126.1, 127.5, 129.2, 130.6, 131.1, 132.4, 133.1, 133.3, 135.8, 136.5, 146.1, 188.8.

(*Z*)-2-(3-Nitrobenzylidene)benzo[*b*]thiophen-3(2*H*)-one (4e)

Yield (80 %) as a yellow solid; mp 229 °C. IR (KBr) ν(C=O): 1681 cm^{-1}, ν(C=C): 1591 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm) : 7.95 (1H, dd), 7.89 (1H,s), 7.64-7.56 (3H, m), 7.51-7.43 (3H,m), 7.33 (1H, dd). ^{13}C NMR (75 MHz, DMSO) (δ/ppm): 124.5, 126.3, 128.5, 129.4, 131.6, 132.2, 132.8, 133.2, 133.6, 135.8, 136.5, 146.1, 188.7.

General procedure for the synthesis of benzothienopyran and derivatives (7)

In a 100 ml flask equipped with a condenser, arylidenes **4** (4 mmol) and ethyl cyanoacetate (5 mmol) or malononitrile (5 mmol) were dissolved in ethanol (30 mL). Then, piperidine (1 mL) was added, and the reaction mixture was refluxed. Thin layer chromatography revealed the formation of a single product. The organic phase was evaporated under reduced pressure. The resulting residue was recrystallized from ethanol.

2-Amino-3-cyano-4-phenyl-4*H*-1-benzothieno[3,2-*b*]pyran (7a)

Yield: (77 %) as red needles; mp: 220-222 °C. IR (neat) ν(NH_2): 3457, 3320, 3318 cm^{-1}, δ(NH_2) : 1656 cm^{-1}, ν(CN): 2188 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm): 5.04 (s, 1H, H(4)), benzylic-H), 7.14 (br.s, 2H, NH_2), 7.28 (d, 2H, *J* = 7.2 Hz), 7.35 (d, 2H, *J* = 6.3 Hz), 7.37-7.43 (m, 2H), 7.48 (t, 1H, *J* = 7.8 Hz), 7.69 (d, 1H, H(6) aromatic, *J* = 7.5 Hz), 7.88 (d, 1H, H(9), aromatic, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, DMSO) (δ/ppm): 39.9 (C_4), 56.6, 118.6, 119.8 (CN), 120.6, 123.8, 125.5, 126.0, 127.9, 127.9, 129.1(5), 129.2, 136.3, 138.6, 144.5, 160.9.

2-Amino-3-cyano-4-(4-methoxyphenyl)-4*H*-1-benzothieno[3,2-*b*]pyran (7b)

Yield: (77 %) as white crystals; mp: 242-244 °C. IR (neat) ν(NH_2): 3489, 3430, 3354 cm^{-1}, δ(NH_2) : 1618 cm^{-1}, ν(CN): 2121 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm): 3.74 (s, 3H, OCH_3), 4.98 (s, 1H, H(4), benzylic), 7.05 (dd, 4H, H aromatic, *J* = 8.6 Hz), 7.07 (br.s, 2H, NH_2), 7.39 (t, 1H, H(7), aromatic, *J* = 8.1 Hz), 7.47 (t, 1H, H(8), aromatic, *J*= 8.5 Hz), 7.59 (d, 1H, H(6), *J* = 7.7 Hz), 7.87 (d, 1H, H(9), *J* = 7.9 Hz). ^{13}C NMR (75 MHz, DMSO) (δ/ppm): 39.1 (C_4), 55.6 (CH_3), 57.0, 114.6, 119.0, 119.8 (CN), 120.6, 123.8, 125.4, 126.0, 129.0, 129.3, 136.2, 136.6, 138.4, 159.1, 160.7.

2-Amino-3-cyano-4-(4-methylphenyl)-4*H*-1-benzothieno[3,2-*b*]pyran (7c)

Yield: (77 %) as a whitish solid; mp: 240-242 °C. IR (neat): ν(NH_2): 3457, 3316, 3195 cm^{-1}, ν(CN): 2194 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm): 2.28 (s, 3H, CH_3), 4.99 (s, 1H, H(4), benzylic), 7.13 (br.s, 2H, NH_2), 7.27 (s, 4H, H aromatic), 7.27 (t, 1H, H(7), *J* = 8.2 Hz), 7.41 (t, 1H, H(8), *J* = 8.1 Hz), 7.67 (d, 1H, H(6), *J* = 7.5 Hz), 7.87 (d, 1H, H(9), *J* = 7.8 Hz). ^{13}C NMR (75 MHz, DMSO) (δ/ppm): 21.1 (CH_3), 39.5 (C_4), 56.7, 118.8, 119.8 (CN), 120.6, 123.8, 125.5, 126.0, 129.2, 136.2, 137.1, 138.5, 141.6, 160.9.

2-Amino-3-cyano-4-(4-chlorphenyl)-4*H*-1-benzothieno[3,2-*b*]pyran (7d)

Yield: (73 %) as colorless needles; mp: 250-252 °C. IR (neat): ν(NH_2): 3464, 3316, 3195 cm^{-1}, δ(NH_2): 1652 cm^{-1}, ν(CN): 2190 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm): 5.09 (s, 1H, H(4), benzylic), 7.20 (br.s, 2H, NH_2), 7.32 (t, 1H, H(7), aromatic, *J* = 7.1 Hz), 7.37 (dd, 4H, aromatic, *J* = 7.9 Hz), 7.48 (t, 1H, H(8), aromatic, *J* = 8.0 Hz), 7.69 (d, 1H, H(6)), aromatic, *J* = 7.5 Hz), 7.89 (d, 1H, H(9), aromatic, *J* = 7.8 Hz). ^{13}C NMR (75 MHz,

DMSO) (δ/ppm): 39.2 (C_4), 56.2, 117.9, 119.9 (CN), 120.4, 129.1, 129.2, 129.8, 132.5, 136.3, 138.7, 143.5, 160.9.

2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*-1-benzothieno[3,2-*b*]pyran (7e)

Yield: (73 %) as colorless needles; mp: 260-262 °C. IR (neat): ν(NH_2): 3442, 3319, 3211 cm^{-1}, δ(NH_2): 1642 cm^{-1}, ν(CN): 2186 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) (δ/ppm): 5.34 (s, 1H, H(4), benzylic), 7.31 (br.s, 2H, NH_2), 7.43 (t, 1H, H(7), aromatic, *J* = 7.4 Hz), 7.51 (t, 1H, H(8), aromatic, *J* = 7.6 Hz), 7.69 (m, 2H, aromatic), 7.80 (d, 1H, H(6), aromatic, *J* = 7.5 Hz), 7.91 (d, 1H, H(9), aromatic, *J* = 7.9 Hz), 8.45 (s, 2H, aromatic).
^{13}C NMR (75 MHz, DMSO) (δ/ppm): 21.2 (C_4), 55.6, 117.1, 120.0 (CN), 120.3, 122.3, 123.1, 123.9, 125.7, 126.3, 129.0, 129.2, 131.0, 134.8, 136.4, 139.1, 146.7, 148.5, 161.1.

Ethyl 2-amino-4-phenyl-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylate (7f)

Yield: (42.6%) as colorless crystals; mp: 156-158°C. IR (neat): ν(NH_2): 3424, 3306 cm^{-1}, δ(NH_2): 1615 cm^{-1}, ν(C=O): 1666 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 1.09 (t, 3H, CH_3), 4.06 (q, 2H, CH_2), 5.17 (s, 1H, H(4), benzylic), 6.54 (br.s, 2H, NH_2), 7.16-7.38 (m, 6H, aromatic), 7.41 (t, 1H, H(8), aromatic, *J* = 7.8 Hz), 7.67 (d, 1H, H(6), aromatic, *J* = 8.0 Hz), 7.75 (d, 1H, H(9), aromatic, *J* = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 14.2, 39.4, 59.6, 119.7, 121.3, 122.9, 124.4, 124.9, 126.6 127.4, 128.2, 129.5, 136.7, 137.8, 146.6, 160.5, 169.6.

Ethyl 2-amino-4-(4-methoxyphenyl)-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylate (7g)

Yield: (28 %) as yellow needles; mp: 120-122 °C. IR (neat): ν(NH_2): 3476, 3308 cm^{-1}, δ(NH_2): 1631 cm^{-1}, ν(C=O): 1673 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 1.10 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.06 (q, 2H, CH_2), 5.07 (s, 1H, H(4), benzylic), 6.50 (br.s, 2H, NH_2), 6.98 (dd, 4H, aromatic, *J* = 8.6 Hz), 6.99 (t, 2H, H(7), H(8), aromatic, *J* = 8.8 Hz), 7.54 (d, 1H, H(9), aromatic, *J* = 8.0 Hz), 7.92 (d, 1H, H(6), *J* = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 14.2, 22.6, 38.5, 59.5, 121.6, 122.8, 124.4, 124.8, 126.7, 127.8, 128.8, 129.6, 136.7, 138.2, 143.1, 146.0, 160.4, 169.5.

Ethyl 2-amino-4-(4-methylphenyl)-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylate (7h)

Yield: (30 %) as a yellow solid; mp: 122-124 °C. IR (neat): ν(NH_2): 3476, 3308 cm^{-1}, δ(NH_2): 1631 cm^{-1}, ν(C=O): 1673 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 1.10 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.06 (q, 2H, CH_2), 5.13 (s, 1H, H(4), benzylic), 6.53 (br.s, 2H, NH_2), 7.28 (s, 4H, H aromatic), 7.32 (t, 1H, H(7), aromatic, *J* = 7.8 Hz), 7.38 (t, 1H, H(8), aromatic, *J* = 7.2 Hz), 7.72 (d, 1H, H(6), aromatic, *J* = 7.5 Hz), 7.96 (d, 1H, H(9), aromatic, *J* = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 14.2, 21.0, 38.9, 59.6, 121.5, 122.9, 124.4, 124.8, 126.7, 127.5, 128.8, 129.7, 136.0, 136.7, 140.9, 143.7, 160.5, 169.6.

Ethyl 2-amino-4-(4-chlorophenyl)-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylate (7i)

Yield: (67%) as colorless crystals; mp: 132-134°C. IR (neat): ν(NH_2): 3476, 3308 cm^{-1}, δ(NH_2): 1631 cm^{-1}, ν(C=O): 1673 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 1.11 (t, 3H, CH_3), 4.06 (q, 2H, CH_2), 5.14 (s, 1H, H(4), benzylic), 6.55 (br.s, 2H, NH_2), 7.24 (s, 4H, H aromatic), 7.33 (t, 1H, H(7), aromatic, *J* = 8.1 Hz), 7.40 (t, 1H, H(8), aromatic, *J* = 8.1 Hz), 7.67 (d, 1H, H(6), *J* = 8.1 Hz), 7.74 (d, 1H, H(9), aromatic, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 14.2, 38.9, 59.7, 120.5, 120.5, 121.3, 123.9, 125.2, 128.6, 128.9, 129.2, 129.5, 130.1, 131.2, 136.7, 138.0, 145.1, 160.5, 169.4.

Ethyl 2-amino-4-(3-nitrophenyl)-4*H*-1-benzothieno[3,2-*b*]pyran-3-carboxylate (7j)

Yield: (68%) as yellowish crystals; mp 190-192°C. IR (neat): ν(NH_2): 3433, 3302 cm^{-1}, δ(NH_2): 1635 cm^{-1}, ν(C=O): 1667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (δ/ppm): 1.12 (t, 3H, CH_3), 4.07 (q, 2H, CH_2), 5.28 (s, 1H, H(4), benzylic), 6.65 (s, 2H, NH_2), 7.28-7.49 (m, 3H, H aromatic), 7.61-7.69 (m, 2H, H(7), H(8) aromatic), 7.77 (d, 1H, H(6), aromatic, *J* = 7.5 Hz), 8.06 (d, 1H, H(9), *J* = 8.1 Hz), 8.20 (s, 1H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$) (δ/ppm): 14.2, 39.3, 59.8, 119.2, 119.9, 121.8, 122.6, 122.9, 124.7, 125.4, 129.2, 133.8, 136.7, 138.4, 148.2, 148.7, 160.6, 169.0.

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