Monatsh Chem (2012) 143:317–323
DOI 10.1007/s00706-011-0657-5

ORIGINAL PAPER

Expedient approach for the synthesis of novel indenothiophene derivatives

Shivaraj P. Patil · Muddassar A. Kazi · Shrikant B. Kanawade · Prashant S. Nikam · Madhukar N. Jachak · Raghunath B. Toche

Received: 6 May 2010 / Accepted: 7 September 2011 / Published online: 15 November 2011

Abstract Gewald reaction of 2-(2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-ylidene)malononitrile, elemental sulfur, and a catalytic amount of triethylamine furnished the new synthon 2-aminoindenothiophene-3-carbonitrile. Its reaction with conc. H_2SO_4 furnished the expected 2-amino-3-carboxamide derivative instead of the corresponding carboxylic acid. The key intermediates 2-aminoindenothiophene-3-carbonitrile and -3-carboxamide were used for the synthesis of tetracyclic indenothienopyrimidine derivatives by cyclocondensation reaction with acid chlorides, amides, formic acid, or hydrazine hydrate. Neat reactions of the carbonitrile with cyclic and aliphatic ketones in the presence of anhydrous $ZnCl_2$ furnished pentacyclic and tetracyclic indenothienopyridine derivatives, respectively, in good yields. All new compounds were characterized by spectroscopic and analytical data.

Keywords Indenothiophenes · Indenothienopyrimidines · Indenothienopyridines · 2-Aminoindenothiophene-3-carbonitrile · 2-Aminoindenothiophene-3-carboxamide · Gewald reaction

Introduction

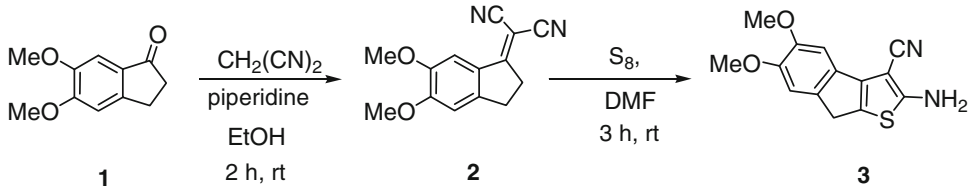
Significant attention has been given to the synthesis of thieno[2,3-*b*]pyridines owing to their broad range of biological activities. Thieno[2,3-*b*]pyridine and thieno[2,3-*b*]pyrimidine derivatives are lead molecules in drug design owing to their interesting biological activities displayed over a broad range of therapeutic classes. For example thieno[2,3-*b*]pyrimidines are inhibitors of cancer cell proliferation [1–3], antimicrobial agents [4–6], and anti-inflammatory agents particularly for treatment of arthritis and as bone resorption inhibiting agents [7–9]. They are also used as antihypertensive, vasodilator agents [10], anxiolytics [11], and selective cytotoxic agents for p21-deficient cells [12]. Thieno[2,3-*b*]pyridines are useful antagonists [13–23]. On the other hand, indenone derivatives are pharmaceutically useful compounds having a broad range of activities [24–27]. These properties of thienopyrimidines, thienopyridines, and indenones inspired us to develop the synthesis of new fused polycyclic heterocyclic molecules like indeno[2,1-*b*]thienopyridine and indeno[2,1-*b*]thienopyrimidine derivatives by cyclocondenstaion of 2-aminoindenothiophene-3-carbonitrile **3** and -3-carboxamide **4**.

Results and discussion

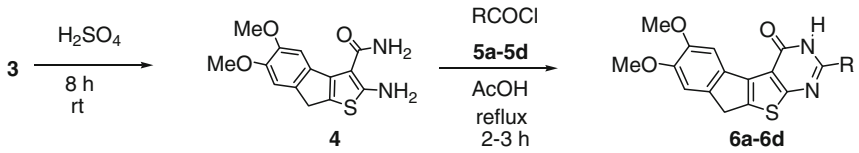
Indenomalononitrile **2** was obtained in excellent yield by reaction of indanone **1** and malononitrile in basic medium. Gewald reaction [28] of compound **2** with elemental sulfur and a catalytic amount of triethylamine gave 2-aminoindenothiophene-3-carbonitrile **3** in 75% yield (Scheme 1). The carbonitrile **3** on reaction with conc. H_2SO_4 [29, 30] furnished the expected 3-carboxamide **4** in excellent yield (Scheme 2). The reactive *o*-aminocarbonitrile group of compound **3** can react with an electrophilic-nucleophilic reagent to furnish new polycyclic pyridine derivatives. Compound **4**, having an *o*-aminocarboxamide functional

S. P. Patil · M. A. Kazi · S. B. Kanawade · P. S. Nikam · M. N. Jachak · R. B. Toche (✉)
Department of Chemistry, Organic Chemistry Research Center, K.T.H.M. College, University of Pune, Gangapur Road, Nashik, Maharashtra 422002, India
e-mail: raghunath_toche@rediffmail.com

Scheme 1

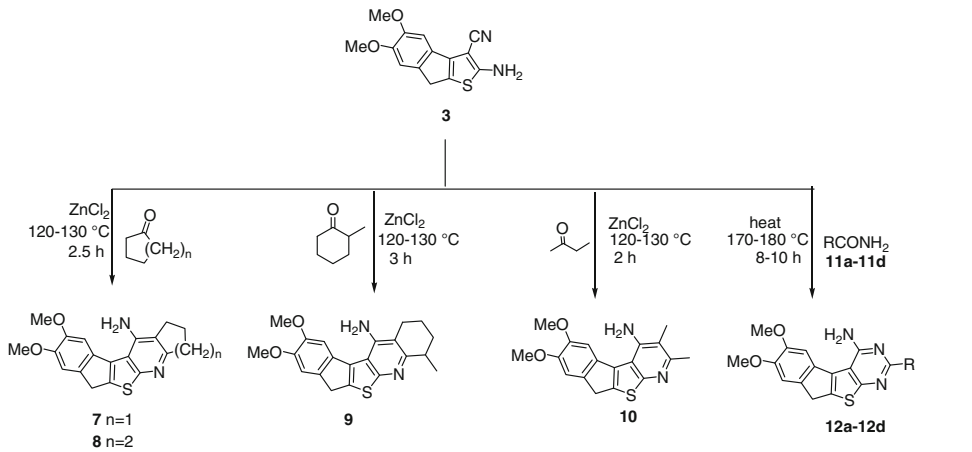


Scheme 2



6	Entry Acid chloride 5a-5d	R
a	CH_3COCl	CH_3
b	Ph COCl	Ph
c	$ClCOCH_2Cl$	CH_2Cl
d	$ClCO(CH_2)_3Cl$	$(CH_2)_3Cl$

Scheme 3



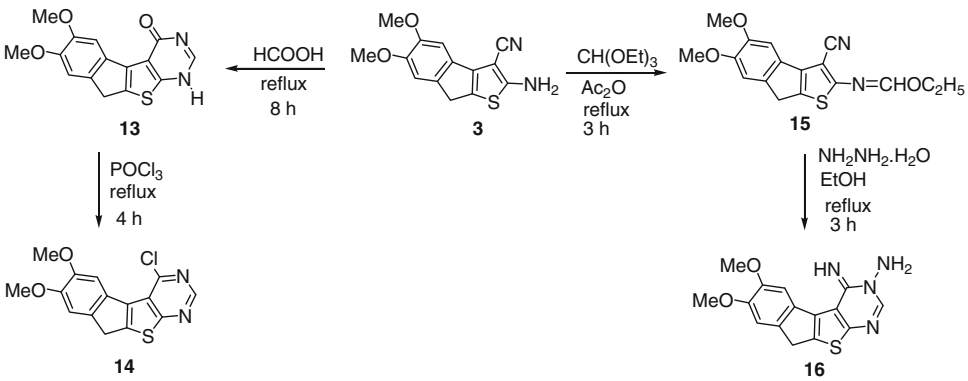
12	Entry Amide 11a-11d	R
a	$HCONH_2$	H
b	H_3CCONH_2	CH_3
c	$PhCONH_2$	Ph
d	$NCCH_2CONH_2$	$NCCH_2$

group, can also react with electrophilic reagents to give new polycyclic pyrimidine derivatives.

Structures of compounds **2**–**4** were assigned by spectroscopic and analytical characterizations as shown in the "Experimental" section.

Acid-catalyzed bis-nucleophilic cyclocondensation of *o*-aminocarboxamide **4** with acid chloride in acetic acid furnished pyrimidone derivatives **6a**–**6d** in 70–80% yields (Scheme 2). Acid chlorides having an electron-withdrawing group α to the carbonyl reacted slowly and gave low yields, whereas those with an electron-donating group at the same position reacted faster and furnished high yields of pure product. Compounds **6a**–**6d** were purified by column chromatography eluting with chloroform–methanol (8:2) and were characterized by analytical and spectral data. Reaction of 2-amino-3-carbonitrile **3** with cyclic ketones in the presence of anhydrous $ZnCl_2$ at 120–130 °C yielded pentacyclic amines **7**–**9**, and with ethyl methyl ketone it furnished tetracyclic 6,7-dimethoxy-2,3-dimethyl-9*H*-indeno[1′,2′:4,5]thieno[3,2-*e*]pyridin-4-amine (**10**) in good yield. Anhydrous $ZnCl_2$ as a Lewis acid catalyst activates the C=O group and the high temperature

Scheme 4



(120–130 °C) facilitates carbanion formation α to the carbonyl group. Unsymmetrical ketones react via the more acidic α-methylene group yielding compounds **9** and **10** as sole products (Scheme 3). It was observed that cyclohexanone gave a clean reaction product with higher yield compared with other ketones.

Compounds **7**–**10** were purified by column chromatography using chloroform–methanol (9:1) as an eluent to afford 50–60% yields. A facile reaction occurred when *o*-aminocarbonitrile **3** was heated with neat aromatic/aliphatic amides to afford aminothienopyrimidine derivatives **12a**–**12e** in good yields. Here steric hindrance of the group α to the carbonyl affects the yield, e.g., formamide gave 60% yield, whereas the yield decreases with the introduction of a bulky group. Cyanoacetamide gave a low yield and required a longer reaction time.

In order to build a fused tricyclic pyrimidine ring, compound **3** was reacted with triethyl orthoformate to introduce a replaceable ethoxy group, which underwent a nucleophilic substitution reaction in the presence of acetic anhydride furnishing intermediate **15** in excellent yield. Compound **15** on Knoevenagel reaction with hydrazine hydrate in ethanol yielded novel 4,9-dihydro-4-imino-6,7-dimethoxy-3*H*-indeno[1′,2′:4,5]thieno[2,3-*d*]pyrimidin-3-amine (**16**) in 75% yield. Similarly, compound **3** on refluxing in formic acid furnished compound **13** in 65% yield, which on further refluxing in $POCl_3$ gave chloropyrimidine derivative **14** in 78% yield (Scheme 4).

The formation of compound **13** was rationalized by acid hydrolysis of the nitrile moiety of **3** to an amide in formic acid followed by condensation of the amine and amide with the carbonyl group of formic acid, i.e., here formic acid acts as reagent, catalyst, and solvent.

Conclusion

2-Aminoindenothiophene-3-carbonitrile and -3-carboxamide are new synthons for bis-electrophilic and bis-nucleophilic reactions to yield novel fused polycyclic indenothienopyridine and indenothienopyrimidine derivatives. The new compounds may have biological activity. All reactions reported here are clean with simple workup, yield single products, and require inexpensive chemicals and reagents.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) and multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The solvents for NMR spectra were dimethyl sulfoxide (DMSO)-d_6 and $CDCl_3$ unless otherwise stated. Infrared spectra were recorded as KBr disks on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu GC–MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analyses were performed on a Thermo Quest Flash 1112 Series EA analyzer. The reactions were monitored by thin-layer chromatography (TLC), carried out on 0.2-mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

2-(2,3-Dihydro-5,6-dimethoxy-1H-inden-1-ylidene)-malononitrile (**2**, $C_{14}H_{12}N_2O_2$)

The reaction mixture of 19.20 g 5,6-dimethoxyindan-1-one (0.1 mol), 6.6 g malononitrile (0.1 mol), and 2 cm^3 piperidine in 100 cm^3 ethanol was stirred at room temperature for 2 h (TLC monitoring, chloroform–methanol 9:1). The solvent was distilled off under vacuum and the residue was stirred in cold ethanol. The product was filtered, washed with cold ethanol, dried, and recrystallized from *N*,*N*-dimethylformamide (DMF)–ethanol 1:4 to afford a yellow

amorphous solid **2**. Yield 19.22 g (80%); m.p.: 215–217 °C; $R_f = 0.57$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,240, 1,620, 1,595, 1,160 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.47 (t, J = 6.5 Hz, 2H, CH_2), 3.54 (t, J = 6.5 Hz, 2H, CH_2), 3.61 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 7.14 (s, 1H, ArH), 7.17 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.4, 38.6, 62.2, 80.9, 111.2, 120.3, 121.8, 142.3, 146.7, 149.0, 152.1, 172.5 ppm; MS (ESI): m/z = 240 (M^+).

2-Amino-5,6-dimethoxy-8H-indeno[2,1-b]thiophene-3-carbonitrile (**3**, $C_{14}H_{12}N_2O_2S$)

To the stirred solution of 24.02 g 2-(2,3-dihydro-5,6-dimethoxy-1*H*-inden-1-ylidene)malononitrile **2** (0.1 mol) and 3.2 g elemental sulfur (0.1 mol) in 50 cm^3 DMF 5 cm^3 triethylamine was added dropwise over a period of 5 min and the resulting reaction mixture was stirred for 3 h at room temperature (TLC monitoring, chloroform–methanol 9:1). The solvent was removed under reduce pressure and the residue was stirred in 500 cm^3 ice-cold water. The separated solid was filtered, washed with water, dried, and recrystallized from 1,4-dioxane to afford a faint brown amorphous solid. Yield 20.4 g (75%); m.p.: 231–233 °C; R_f = 0.51 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,400, 3,325, 2,880, 2,210, 1,595, 1,095 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.61 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.06 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.30 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 32.6, 55.5, 55.6, 101.6, 108.5, 109.7, 116.1, 122.7, 127.7, 130.6, 138.1, 140.4, 146.7, 147.8 ppm; MS (ESI): m/z = 272 (M^+).

2-Amino-5,6-dimethoxy-8H-indeno[2,1-b]thiophene-3-carboxamide (**4**, $C_{14}H_{14}N_2O_3S$)

2-Amino-5,6-dimethoxy-8*H*-indeno[2,1-*b*]thiophene-3-carbonitrile **3** (27.23 g, 0.1 mol) was stirred in 50 cm^3 conc. H_2SO_4 for 8 h at room temperature (TLC monitoring, chloroform–methanol 9:1). The reaction mixture was poured over 500 cm^3 crushed ice and neutralized with saturated aqueous Na_2CO_3 solution. The solid product was filtered, dried, and recrystallized from DMF–methanol 1:4 to afford a colorless solid. Yield 24.6 g (85%); m.p.: 243–245 °C; R_f = 0.49 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,440, 3,310, 3,210, 1,666, 1,612, 1,110 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.40 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.90 (br s, 2H, $CONH_2$), 6.86 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.30 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 32.5, 55.4, 55.5, 109.1, 116.4, 122.4, 127.6, 138.1, 139.8, 141.4, 146.9, 147.7, 156.3, 169.9 ppm; MS (ESI): m/z = 290 (M^+).

General procedure for the synthesis of **6a–6d**

A mixture of 2.72 g compound **4** (0.01 mol) and acid chlorides **5a–5d** (0.01 mol) was refluxed in 10 cm^3 acetic acid for 2 h (TLC monitoring, chloroform–methanol 9:1). After cooling the reaction mixture was poured into 100 cm^3 ice-cold water. The separated solid was filtered, washed with water, dried, and recrystallized from a suitable solvent. The product was purified by column chromatography eluting with chloroform.

3,9-Dihydro-6,7-dimethoxy-2-methyl-4H-indeno-[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-one
(**6a**, $C_{16}H_{14}N_2O_3S$)

Recrystallized from DMF–methanol 1:4; brown amorphous solid. Yield 2.51 g (80%); m.p.: 298–300 °C; R_f = 0.54 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,350, 1,670, 1,620, 1,120 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.23 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 7.18 (s, 1H, ArH), 7.26 (s, 1H, ArH), 11.80 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 22.4, 34.5, 55.6, 55.7, 83.7, 102.0, 109.8, 114.3, 129.4, 134.0, 138.5, 139.7, 147.4, 148.0, 152.2, 168.3 ppm; MS (ESI): m/z = 314 (M^+).

3,9-Dihydro-6,7-dimethoxy-2-phenyl-4H-indeno-[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-one
(**6b**, $C_{21}H_{16}N_2O_3S$)

Recrystallized from DMF–methanol 1:4; brown amorphous solid. Yield 3.01 g (80%); m.p.: 308–310 °C; R_f = 0.52 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,355, 1,672, 1,618, 1,595, 1,118 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.70 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.20 (s, 1H, ArH), 7.25 (s,1H, ArH), 7.30–7.52 (m, 5H, ArH), 11.70 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.5, 64.3, 116.2, 118.1, 122.3, 125.9, 126.1, 127.4, 127.6, 132.6, 135.4, 137.0, 139.2, 139.4, 141.6, 152.1, 160.4, 172.4 ppm; MS (ESI): m/z = 376 (M^+).

2-(Chloromethyl)-3,9-dihydro-6,7-dimethoxy-4H-indeno-[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-one
(**6c**, $C_{16}H_{13}ClN_2O_3S$)

Purified by column chromatography (silica gel) eluting with chloroform; faint brown amorphous solid. Yield 2.64 g (76%); m.p.: 256–260 °C; R_f = 0.57 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,345, 1,665, 1,621, 1,126 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.71 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 7.17 (s, 1H, ArH), 7.24 (s, 1H, ArH), 11.78 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.7, 52.1, 63.5, 115.8, 117.4, 126.1, 131.6, 137.4, 137.7, 142.5, 149.9, 148.2, 155.3, 165.2, 171.9 ppm; MS (ESI): m/z = 348 (M^+), 350 ($[M + 2]^+$).

2-(3-Chloropropyl)-3,9-dihydro-6,7-dimethoxy-4H-indeno-[1′,2′:4,5]thieno[2,3-d]pyrimidin-4-one
(**6d**, $C_{18}H_{17}ClN_2O_3S$)

Faint brown amorphous solid; purified by column chromatography (silica gel) eluting with chloroform–methanol 9:1.

Yield 2.63 g (70%); m.p.: 243–245 °C; R_f = 0.55 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,320, 1,666, 1,618, 1,120 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.01 (m, 2H, CH_2), 2.48 (t, 2H, J = 6.5 Hz, CH_2), 3.62 (t, 2H, J = 6.9 Hz, CH_2), 3.71 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 7.21 (s, 1H, ArH), 7.23 (s,1H, ArH), 11.42 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.8, 24.1, 33.4, 49.5, 63.2, 112.8, 116.7, 126.1, 132.4, 137.4, 138.1, 138.5, 141.2, 148.3, 148.7, 154.2, 162.3, 169.9 ppm; MS (ESI): m/z = 376 (M^+), 378 ([M + 2]$^+$).

General procedure for the synthesis of **7–10**

A mixture of 2.72 g **3** (0.01 mol), cyclic/alicyclic ketone (0.01 mol), and anhydrous $ZnCl_2$ (0.005 mol) was heated at 120–130 °C for 2–3 h (TLC monitoring, chloroform–methanol 9:1). After cooling, the reaction mixture was stirred in 100 cm^3 ice-cold water and neutralized with aqueous NaOH solution. The separated solid was collected by filtration, washed with water, and recrystallized from a suitable solvent.

1,2,3,6-Tetrahydro-8,9-dimethoxy-cyclopenta[b]indeno-[1′,2′:4,5]thieno[3,2-e]pyridin-11-amine
(**7**, $C_{19}H_{18}N_2O_2S$)
Purified by column chromatography (silica gel) eluting from chloroform–methanol 9:1; brown amorphous solid. Yield 2.18 g (58%); m.p.: 227–229 °C; R_f = 0.34 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,345, 3,305, 1,616, 1,110 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.25 (t, J = 7.5 Hz, 2H, CH_2), 2.88 (t, J = 7.5 Hz, 2H, CH_2), 3.09 (t, J = 7.5 Hz, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.58 (br s, 2H, NH_2), 7.51 (s, 1H, ArH), 7.00 (s, 1H, ArH) ppm; ^{13}C NMR (DMSO-d_6): δ = 22.4, 27.1, 33.6, 35.1, 55.4, 55.8, 106.3, 109.5, 114.4, 117.8, 131.9, 137.1, 137.3, 137.9, 146.3, 146.4, 147.4, 162.1, 164.7 ppm; MS (ESI): m/z = 338 (M^+).

2,3,4,7-Tetrahydro-9,10-dimethoxy-1H-indeno-[1′,2′:4,5]thieno[2,3-b]quinolin-12-amine
(**8**, $C_{20}H_{20}N_2O_2S$)
Purified by column chromatography (silica gel) eluting from chloroform–methanol 9:1; faint brown solid. Yield 2.11 g (60%); m.p.: 240–243 °C; R_f = 0.31 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,315, 3,285, 1,666, 1,110 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.94 (t, J = 6.5 Hz, 4H, 2 × CH_2), 2.63 (t, J = 6.5 Hz, 2H, CH_2), 2.97 (t, J = 6.5 Hz, 2H, CH_2), 3.82 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.62 (br s, 2H, NH_2), 7.13 (s, 1H, ArH), 7.49 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.4, 23.9, 24.1, 32.4, 61.5, 114.8, 116.4, 120.5, 122.1, 126.2, 131.1, 132.6, 136.8, 147.3, 148.4, 150.4, 154.3, 157.4 ppm; MS (ESI): m/z = 352 (M^+).

2,3,4,7-Tetrahydro-9,10-dimethoxy-4-methyl-1H-indeno-[1′,2′:4,5]thieno[2,3-b]quinolin-12-amine
(**9**, $C_{21}H_{22}N_2O_2S$)
Purified by colomn chromatography (silica gel) eluting from chloroform–methanol 9:1); brown amorphous solid. Yield 1.83 g (50%); m.p. 197–199 °C; IR (KBr): $\bar{\nu}$ = 3,335, 3,295, 1,610, 1,105 cm^{-1}; R_f = 0.27 (chloroform–methanol 9:1); ^1H NMR (DMSO-d_6): δ = 1.30 (d, J = 6.9 Hz, 3H, CH_3), 1.70–1.80 (m, 2H, CH_2), 1.92–195 (m, 2H, CH_2), 2.54 (t, J = 5.4 Hz, 2H, CH_2), 2.86–2.92 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2), 5.77 (br s, 2H, NH_2), 7.25 (s, 1H, ArH), 7.60 (s,1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.7, 22.7, 22.9, 25.4, 31.8, 62.5, 114.4, 116.2, 121.0, 121.8, 126.7, 130.4, 133.4, 134.7, 146.3, 149.0, 151.2, 153.1, 158.2 ppm; MS (ESI): m/z = 366 (M^+).

6,7-Dimethoxy-2,3-dimethyl-9H-indeno[1′,2′:4,5]-thieno[3,2-e]pyridin-4-amine (**10**, $C_{18}H_{18}N_2O_2S$)
Purified by column chromatography (silica gel) eluting from chloroform–methanol 9:1; brown amorphous solid. Yield 1.66 g (51%); m.p.: 298–300 °C; R_f = 0.29 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,360, 3,305, 1,618, 1,122 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.24 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.82 (s, 2H, CH_2), 5.20 (br s, 2H, NH_2), 7.21 (s, 1H, ArH), 7.33 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.1, 22.9, 30.1, 60.7, 115.4, 117.4, 120.8, 122.0, 127.4, 132.4, 133.8, 135.1, 145.3, 147.0, 150.4, 157.1 ppm; MS (ESI): m/z = 326 (M^+).

General procedure for the synthesis of **12a–12d**

A mixture of 2.72 g compound **3** (0.01 mol) and formamide (**11a**)/acetamide (**11b**)/benzamide (**11c**)/cyanoacetamide (**11d**) (0.01 mol) was heated in an oil bath for 8–10 h at 170–180 °C with constant stirring (TLC check, toluene–acetone 9:1). After cooling, the reaction mixture was poured into 10 cm^3 ice-cold methanol and stirred at room temperature for 30 min. The precipitated solid was collected by suction filtration, washed with cold ethanol, and dried to afford analytical grade **12a–12d** in good yields. These compounds did not require purification.

6,7-Dimethoxy-9H-indeno[1′,2′:4,5]thieno[2,3-d]-pyrimidin-4-amine (**12a**, $C_{15}H_{13}N_3O_2S$)
Brown amorphous solid; yield 1.79 g (60%). M.p.: 188–190 °C; R_f = 0.40 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,340, 3,310, 1,610, 1,105 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.81 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.94 (s, 2H, CH_2), 7.02 (br s, 2H, NH_2), 7.26 (s, 1H, ArH), 7.48 (s, 1H, ArH), 8.32 (s, 1H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 34.6, 55.6, 55.7, 102.1, 109.3, 110.8, 130.5, 131.8, 136.3,

138.2, 146.5, 147.7, 151.1, 157.4, 159.2 ppm; MS (ESI): m/z = 299 (M^+).

6,7-Dimethoxy-2-methyl-9H-indeno[1′,2′:4,5]thieno-[2,3-d]pyrimidin-4-amine (**12b**, $C_{16}H_{15}N_3O_2S$)
Brown amorphous solid; yield 1.75 g (56%). M.p.: 280–282 °C; R_f = 0.37 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,325, 3,290, 1,610, 1,110 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2), 4.80 (br s, 2H, NH_2), 3.22 (s, 3H, CH_3), 7.28 (s, 1H, ArH), 7.36 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.4, 30.6, 62.6, 115.0, 117.4, 120.9, 127.7, 132.4, 133.8, 138.1, 146.8, 148.1, 149.1, 159.3, 164.0 ppm; MS (ESI): m/z = 313 (M^+).

6,7-Dimethoxy-2-phenyl-9H-indeno[1′,2′:4,5]thieno-[2,3-d]pyrimidin-4-amine (**12c**, $C_{21}H_{17}N_3O_2S$)
Brown amorphous solid; yield 2.06 g (55%). M.p.: 250 °C; R_f = 0.43 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,320, 3,200, 1,618, 1,122 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2), 4.65 (br s, 2H, NH_2), 7.01–7.30 (m, 5H, ArH), 7.36 (s, 1H, ArH), 7.40 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.2, 60.2, 113.5, 116.8, 122.9, 127.9, 128.4, 129.4, 130.1, 132.9, 134.7, 139.1, 141.5, 147.2, 148.5, 149.7, 160.0, 162.3 ppm; MS (ESI): m/z = 375 (M^+).

4-Amino-6,7-dimethoxy-9H-indeno[1′,2′:4,5]thieno-[2,3-d]pyrimidin-2-acetonitrile (**12d**, $C_{17}H_{14}N_4O_2S$)
Brown amorphous solid; yield 1.52 g (45%). M.p.: 277–279 °C; R_f = 0.37 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,320, 3,200, 2,255, 1,610, 1,120 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.71 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2), 4.60 (br s, 2H, NH_2), 7.32 (s, 1H, ArH), 7.36 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 26.1, 30.2, 63.1, 110.2, 114.1, 116.2, 123.8, 129.9, 131.5, 135.9, 141.2, 146.2, 147.7, 149.3, 157.2, 164.2 ppm; MS (ESI): m/z = 338 (M^+).

1,9-Dihydro-6,7-dimethoxy-4H-indeno[1′,2′:4,5]-thieno[2,3-d]pyrimidin-4-one (**13**, $C_{15}H_{12}N_2O_3S$)
A mixture of 2.72 g **3** (0.1 mol) and 10 cm^3 formic acid was refluxed for 8 h. The solvent was removed under reduced pressure and the separated solid was filtered and recrystallized from ethanol to give **13** as a brown crystalline solid. Yield 2.05 g (65%); m.p.: 284–286 °C; R_f = 0.44 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,338, 1,671, 1,616, 1,110 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.77 (s, 3H, OCH_3), 3.78 (s, 2H, OCH_3), 3.79 (s, 2H, CH_2), 7.15 (s, 1H, ArH), 7.25 (s, 1H, ArH), 8.42 (s, 1H, ArH), 12.15 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 35.1, 55.6, 55.7, 106.1, 109.4, 110.8, 130.6, 136.8, 138.2, 138.4, 146.8, 147.5, 152.8, 158.8, 171.2 ppm; MS (ESI): m/z = 300 (M^+).

4-Chloro-6,7-dimethoxy-9H-indeno[1′,2′:4,5]thieno-[2,3-d]pyrimidine (**14,** $C_{15}H_{11}ClN_2O_2S$)
Compound **13** (3.00 g, 0.01 mol) was refluxed in 10 cm^3 $POCl_3$ for 4 h. The excess solvent was removed under reduced pressure and the reaction mixture was stirred in 1 kg crushed ice. The separated solid was filtered, washed with water, dried, and recrystallized from ethanol–DMF to give compound **14** as brown crystalline solid. Yield 2.48 g (78%); m.p.: 290–293 °C; R_f = 0.56 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 1,620, 1,590, 1,120 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.90 (s, 2H, CH_2), 7.12 (s, 1H, ArH), 7.28 (s, 1H, ArH), 8.60 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.2, 60.4, 113.4, 115.5, 124.8, 130.2, 134.3, 136.6, 141.2, 147.9, 148.6, 149.5, 151.5, 160.2 ppm; MS (ESI): m/z = 318 (M^+), 320 ($[M + 2]^+$).

2-(Ethoxymethyleneamino)-5,6-dimethoxy-8H-indeno-[2,1-b]thiophene-3-carbonitrile (**15**, $C_{17}H_{16}N_2O_3S$)
A mixture of 2.72 g compound **3** (0.01 mol) and 1.64 cm^3 triethyl orthoformate (0.01 mol) was refluxed in 15 cm^3 acetic anhydride for 3 h. After cooling the reaction mixture was poured into 200 cm^3 cold water. The precipitated solid was collected by filtration, washed with water, dried, and recrystallized from methanol to afford a brown crystalline solid. Yield 2.52 g (80%); m.p.: 175–177 °C; R_f = 0.58 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,245, 1,610, 1,630, 1,115 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.40 (t, J = 7.2 Hz, CH_3), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.92 (s, 2H, CH_2), 4.37 (q, J = 7.2 Hz, 2H, OCH_2), 7.28 (s, 1H, ArH), 7.30 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.4, 30.4, 58.4, 60.4, 113.5, 117.5, 119.3, 129.9, 136.5, 140.2, 144.3, 146.1, 149.6, 157.1, 165.2 ppm; MS (ESI): m/z = 328 (M^+).

4,9-Dihydro-4-imino-6,7-dimethoxy-3H-indeno-[1′,2′:4,5]thieno[2,3-d]pyrimidin-3-amine
(**16**, $C_{15}H_{14}N_4O_2S$)
Hydrazine hydrate (0.98 cm^3, 0.01 mol) was added to a stirred solution of 3.16 g **15** (0.01 mol) in 12 cm^3 ethanol. The reaction was refluxed for 3 h. After cooling the reaction mixture was poured into 100 cm^3 ice-cold water under stirring. The precipitated solid was filtered, dried, and recrystallized from benzene to yield compound **16** as an off-white amorphous solid. Yield 2.35 g (75%); m.p.: 195–197 °C; R_f = 0.47 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,350, 3,325, 3,240, 1,616, 1,112 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2), 5.69 (br s, 2H, NH_2), 7.19 (s, 1H, ArH), 7.26 (s, 1H, ArH), 7.97 (s, 1H, ArH), 8.84 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.4, 57.2, 57.4, 110.1, 114.4, 129.6, 134.3, 138.1, 138.8, 139.1, 144.6, 146.7, 150.8, 154.9, 165.7 ppm; MS (ESI): m/z = 314 (M^+).

Acknowledgments We gratefully acknowledge financial support for this research by CSIR New Delhi, the University of Pune for spectral analysis, and the Principal, KTHM College, Nashik-02 for facilities.

References

1. Torrance C, Agarwal V, Vogelstein B, Kinzler K (2001) Nat Biotechnol 19:940
2. Hanahan D, Weinberg R (2000) Cell 100:57
3. Levine A (1997) Cell 88:323
4. Patil C, Sadana G (1991) J Ind Chem Soc 68:169
5. Sharaideh Z, Sallal A (1997) Bioorg Med Chem Lett 54:233
6. Bompart J, Giral L, Malicorne G, Puygreneir M (1987) Eur J Med Chem 22:139
7. Sohda T, Makino H, Baba A (1996) PCT Int Appl WO 96,14,319
8. Sohda T, Makino H, Baba A (1996) Chem Abstr 125:114583x
9. Manhas M, Sharma S, Amin S (1972) J Med Chem 15:106
10. Adachi I, Yamomori T, Hiramatsu Y, Sakai K, Mihara S, Kawakami M, Masui M, Uno O, Ueda M (1988) Chem Pharm Bull 36:4389
11. Blackburn T, Davies D, Forbes I, Hayward C, Johnson C, Martin R, Piper D, Thomas D, Thompson M, Upton N, Ward R (1995) Bioorg Med Chem Lett 5:2589
12. Jennings L, Kincaid L, Wang D, Krishnamurti G, Beyer C, McGinnis J, Miranda M, Discafani C, Rabindran S (2005) Bioorg Med Chem Lett 15:4731
13. Furuya S, Choh N, Kato K, Hinuma S (1995) PCT Int Appl WO 95,28,405
14. Furuya S, Choh N, Kato K, Hinuma S (1996) Chem Abstr 124:202226t
15. Cho N, Harada M, Imeada T, Matsumoto H, Hayase Y, Sasaki S, Furuya S, Suzuki N, Okubo S, Ogi K, Endo S, Onda H, Fujino M (1998) J Med Chem 41:4190
16. Miki S, Fukuoka K, Akita M, Kawakami J, Furuya S, Isshimaru Y (1999) PCT Int Appl WO 99,09,033
17. Miki S, Fukuoka K, Akita M, Kawakami J, Furuya S, Isshimaru Y (1999) Chem Abstr 130:196644h
18. Suzuki N, Matsumoto H, Furuya S (1997) Eur Pat Appl 781,774
19. Suzuki N, Matsumoto H, Furuya S (1997) Chem Abstr 127:135807e
20. Furuya S, Choh N, Suzuk N, Imada T (2000) PCT Int Appl WO 00,00,493
21. Furuya S, Choh N, Suzuk N, Imada T (2000) Chem Abstr 132:64179s
22. Furuya S, Matsumoto H, Hayase Y, Suzuki N, Imada T (1997) PCT Int Appl WO 97,41,26
23. Furuya S, Matsumoto H, Hayase Y, Suzuki N, Imada T (1998) Chem Abstr 128:13211f
24. Haadsma-Svensson S, Cleek K, Dinh D, Duncan J, Haber C, Huff R, Lajiness M, Nichols N, Smith M, Svensson K, Zaya M (2001) J Med Chem 44:4716
25. Ladduwahetty T, MacLeod A, Merchant K, Sternfeld F (2004) US Patent 2004/6226
26. Chordia M, Murphree L, Macdonald T, Linden J, Olsson R (2002) Bioorg Med Chem Lett 12:1563
27. Ho C, Ludovici D, Maharoof U, Mei J, Sechler J, Tuman R, Strobel E, Andraka L, Yen H, Leo G, Li J (2005) J Med Chem 48:8163
28. Sabnis R (1994) J Sulfur Chem 16:1
29. Morwick T, Berry A, Brichwood J, Carodoza M, Catron K, Deturi M, Emeigh J, Homon C, Hrapchak M, Jacober S, Jakes S, Kaplita P, Kelly T, Ksiazek J, Liuzzi M, Magolda R, Mao C, Marshall D, McNeil D, Prokopowicz A, Sarko C, Scouten E, Sledziona C, Sun S, Watrous J, Wu J, Cywin C (2006) J Med Chem 49:2898
30. Tsai L, Miwa T, Newman M (1957) J Am Chem Soc 79:2530