Tetrahedron 66 (2010) 7389–7398

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Heteroaromatic annulation studies on 2-[bis(methylthio)methylene]-1,3-indanedione: efficient routes to indenofused heterocycles

Rajiv K. Verma [a], Hiriyakkanavar Ila [b], Maya Shankar Singh [a,*]

[a] Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India
[b] New Chemistry Unit, Jawahar Lal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore 64, India

ARTICLE INFO

Article history:
Received 2 June 2010
Received in revised form 9 July 2010
Accepted 12 July 2010
Available online 21 July 2010

Keywords:
2-[Bis(methylthio)methylene]-1,3-indanedione
α-Oxoketene-*S*,*S* and *N*,*S*-acetals
Indenofused heterocycles
Polycyclic heteroaromatics
Heteroaromatic annulation

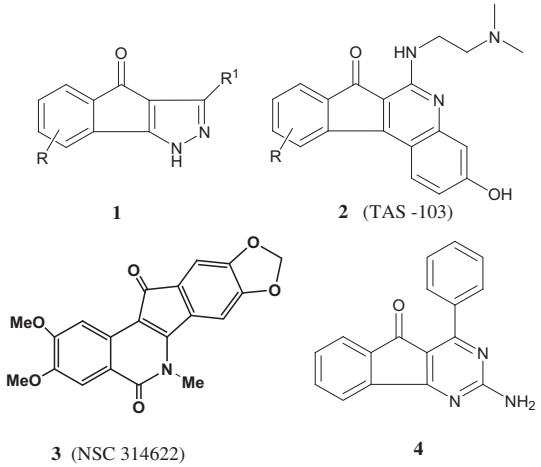
ABSTRACT

2-[Bis(methylthio)methylene]-1,3-indanedione has been shown to be a useful three carbon 1,3-dielectrophilic synthon for the highly efficient regiospecific synthesis of a variety of indenofused five- and six-membered heterocycles via heteroaromatic annulation. The methodology has been further elaborated to the corresponding *N*,*S*-acetals leading to amino substituted heterocycles, thus providing further point of diversity in the newly synthesized heterocyclic frameworks. Further, the facile access to cytotoxic indeno[2,1-*c*]quinolin-7-ones and the novel polycyclic heteroaromatics demonstrates the versatility of heteroaromatic annulation protocol via α-oxoketene-*S*,*S*-acetal in generating novel biologically important polycyclic heteroaromatics.

1. Introduction

Indenofused heterocycles have attracted considerable attention from both medicinal and synthetic chemists in recent years, because of the broad range of biological activity displayed by this class of compounds. Thus, indeno[1,2-*c*]pyrazol-4-ones **1** have recently been identified as potent and selective cyclin dependent kinase (CDK)[1] and check point kinase (CHK 1) inhibitors[2,3] showing excellent activity against various tumor cell linings and in vivo activity in human xenograph models. A few of these compounds exhibit antidepressive activity also.[4] Similarly, a number of indeno[2,1-*c*]quinolin-7-ones, such as **2** (TAS-103) and indeno[1,2-*c*]isoquinolin-5,11-dione **3** (NSC 314622) are reported to display marked cytotoxic activity and have been identified[5a,b] as potent DNA topoisomerase I and II inhibitors and in fact, indenoquinoline **2** has been advanced to phase I and II clinical trials (Chart 1).[5a] A number of indenofused pyrimidines, pyridazines, and 1,2,4-triazines are reported to show inhibitory potency toward monoamine oxidase (MAO) A and B,[6] whereas, an indenofused pyridone has been found to exhibit cardiotonic activity (PDE 3 inhibitor).[7a] Some indenofused pyrimidines are identified as a novel class of potent A_{2A} receptor antagonists[7b] (Chart 1, **4**).

Similarly, indenofused thiophene derivatives have been extensively explored in the field of organometallic chemistry because their transition metal complexes have been found to be promising catalysts for olefin polymerization.[8] However, despite their biological activities and other applications, synthesis of these indenofused heterocycles has not received much attention, ranging over diverse methods with many limitations and lacking generality. Therefore more general and



1 **2** (TAS -103)

3 (NSC 314622) **4**

Chart 1.

* Corresponding author. Fax: +91 542 2368127; e-mail address: mssinghbhu@Yahoo.co.in (M.S. Singh).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.031

efficient methods for these compounds are very much desirable in view of their broad range of biological activity.

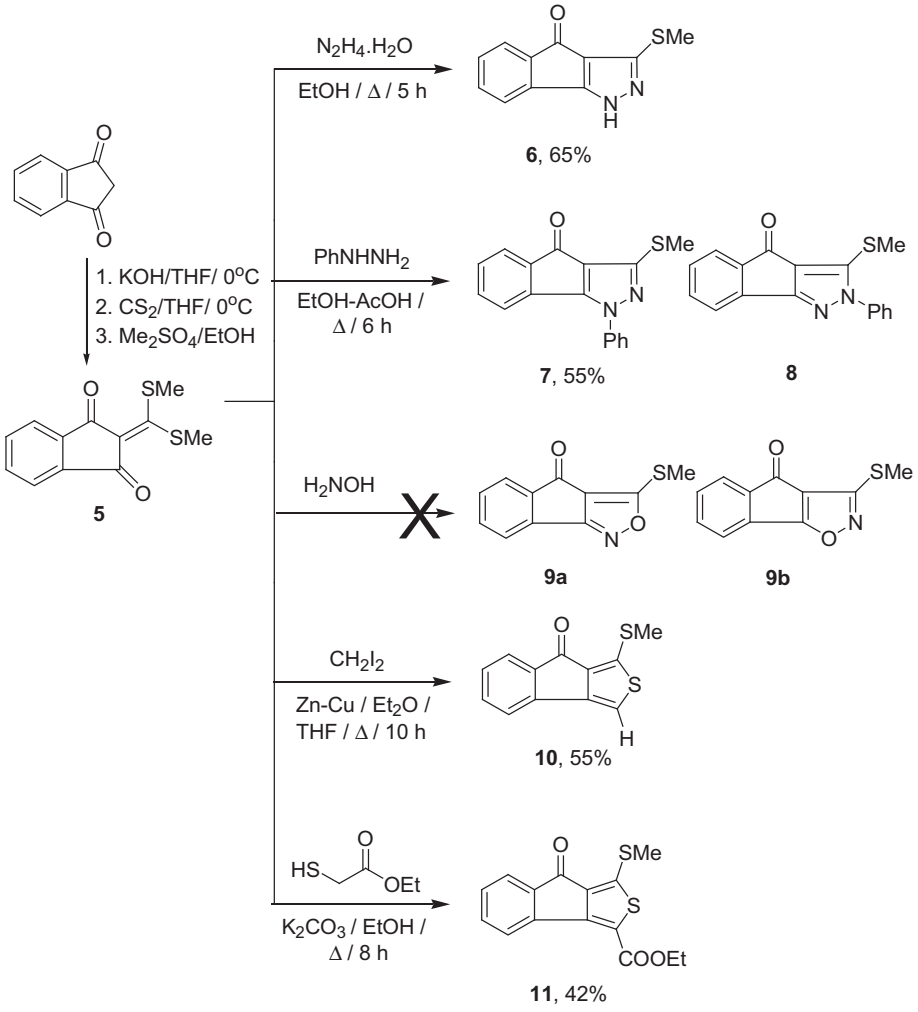
We therefore became interested in devising more general synthetic methods for indenofused five- and six-membered heterocycles via heteroaromatic annulation of 2-[bis(methylthio) methylene]-1,3-indanedione **5** (as 1,3-bielectrophile) with various 1,2- and 1,3-heterobinucleophiles in line with the extensive studies reported earlier by Junjappa-Ila (J-I) and co-workers.[9]

Our literature survey at this stage revealed that ketene dithioacetal **5** has been reported in the literature[10,11] and there are scattered reports of its reactions with anilines,[10a,11] active methylene compounds,[12a] ylides,[12b] *S*,*S*-dialkylsulfur diimides,[12d] and conversion to indenofused pyrimidines.[10a,12] Also, there is no report of synthesis of indenofused five-membered heterocycles from **5** thus, warranting a more elaborate investigation. We therefore undertook a systematic study toward utilizing ketene dithioacetal **5** and the derived *N*,*S*-acetals **20**, **21** as the versatile templates for the construction of indenofused five-, six-membered and condensed heterocycles. We herein, report the results of these studies in the present paper.

2. Results and discussion

The desired 2-[bis(methylthio)methylene]-1,3-indanedione **5** was prepared in 60% yield by modified procedure[10a] from 1,3-indanedione by treatment with carbon disulfide in the presence of KOH followed by alkylation with dimethylsulfate. The synthesis of indenofused five-membered heterocycles was first undertaken. Thus, when **5** was reacted with hydrazine hydrate in refluxing ethanol, the corresponding 3-(methylthio)indeno [1,2-*c*]pyrazol-4-one **6** was obtained in 65% yield (Scheme 1). Similarly, treatment of **5** with phenyl hydrazine in refluxing EtOH/AcOH (1:1) furnished 3-(methylthio)-1-*N*-phenyl-indeno [1,2-*c*]pyrazol-4-one **7** in 55% yield (Scheme 1). The structure and regiochemistry of **7** was established with the help of spectral, analytical data and also by X-ray crystallographic data[13] (Fig. 1). On the other hand, our attempts to obtain regioisomeric 2-*N*-phenyl-3-(methylthio)indeno[1,2-*c*]pyrazol-4-one **8** by reacting **5** with phenyl hydrazine in the presence of either NaH/DMF or in the presence of potassium *tert*-butoxide in refluxing *tert*-butanol under earlier described conditions[14a] gave only mixture of several products. Similarly, attempted cycloannulation of **5** with hydroxylamine under varying conditions ($Ba(OH)_2$/MeOH, MeONa/MeOH, Et_3N/MeOH, NaOAc/AcOH) led only to intractable product mixture from which no trace of the desired indenoisooxazoles **9a** or **9b** could be isolated.[14b]

The ketene dithioacetal **5** was next subjected to treatment with methylene iodide and Zn/Cu couple yielding the corresponding 7-(methylthio)-8*H*-indeno[1,2-*c*]thiophene-8-one **10** in 55% yield in line with the earlier observations on Simmon–Smith reaction on α-oxoketene dithioacetals (Scheme 1).[15] To further add diversity to indeno[1,2-*b*]thiophene framework, the ketene dithioacetal **5** was also subjected to cyclocondensation with ethyl thioglycolate in



Scheme 1.

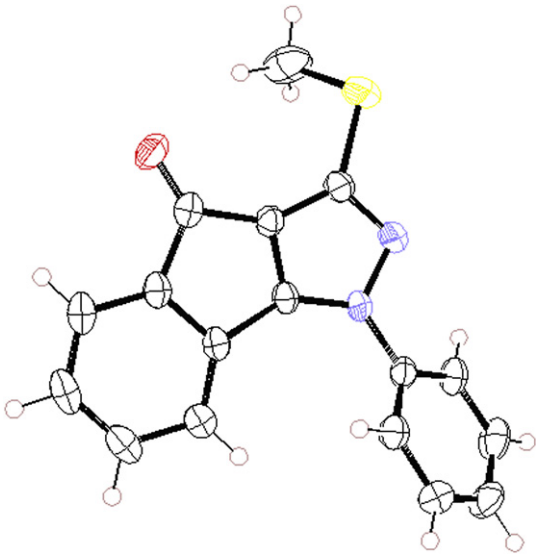
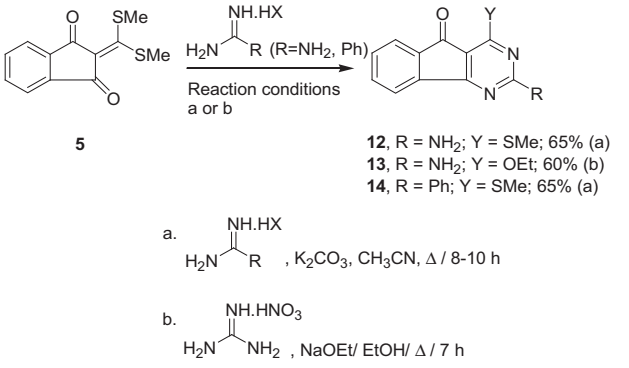


Figure 1. Ortep diagram of **7**.

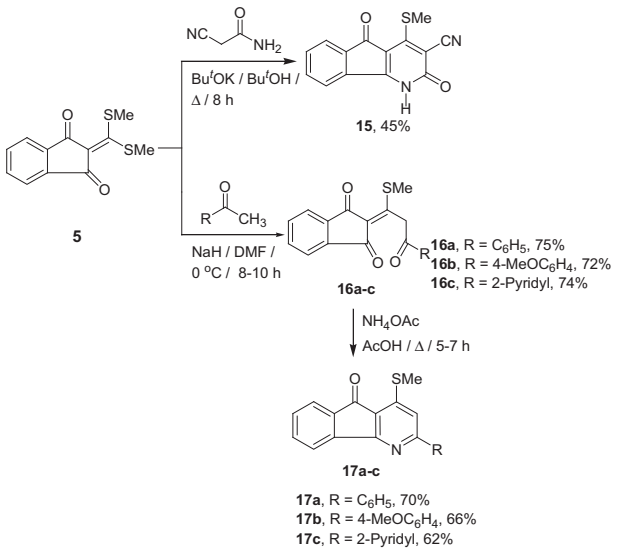
presence of potassium carbonate in ethanol to afford 7-(methylthio)-5-carboethoxy-8*H*-indeno[1,2-*c*] thiophene **11** in moderate yield (Scheme 1).

Cyclocondensation of **5** with 1,3-heterobinucleophiles was next examined with a view to synthesize indenofused six-membered heterocycles (Schemes 2 and 3). Thus, heterocyclization of **5** with guanidine nitrate in the presence of K_2CO_3 in refluxing acetonitrile furnished the 2-amino-4-(methylthio)-5*H*-indeno[1,2-*d*]pyrimidin-5-one **12** in 65% yield (Scheme 2). On the other hand, a similar reaction when conducted in the presence of sodium ethoxide in refluxing ethanol, afforded the corresponding 2-amino-4-ethoxy-5*H*-indeno[1,2-*d*]pyrimidine-5-one **13** in 60% yield in accordance with earlier reported alkoxypyrimidine synthesis from oxoketene dithioacetal by Junjappa and co-workers.[16] Similarly, the 2-(phenyl)-4-(methylthio)-5*H*-indeno[1,2-*d*]pyrimidin-5-one **14** could be obtained in 65% yield by treatment of **5** with 2-phenylamidine hydrochloride under identical conditions (K_2CO_3/MeCN) (Scheme 2).



Scheme 2.

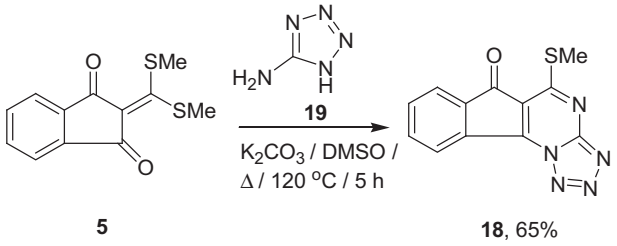
The versatility of heteroaromatic annulation was further demonstrated by synthesis of pyrido-fused indenones **15**, **17** as shown in the Scheme 3. Thus heteroannulation of **5** with cyanoacetamide in the presence of potassium *tert*-butoxide in *tert*-butanol yielded highly functionalized 4-(methylthio)-2,5-dioxo-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile **15** in moderate yield (45%) (Scheme 3).[17] In an another strategy for pyridine annulation, the ketene dithioacetal **5** was subjected to conjugate addition–elimination with acetophenone enolate to give conjugate adduct **16a**



Scheme 3.

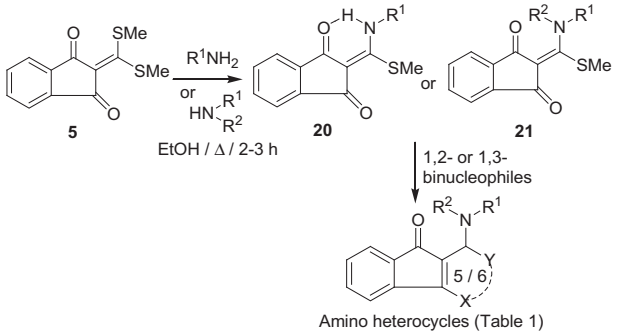
(75%), which on cyclization with ammonium acetate in refluxing acetic acid provided the corresponding 2-phenyl-5-oxo-4-(methylthio)-5*H*-indeno[1,2-*b*]pyridine **17a** in 70% yield (Scheme 3).[18] The corresponding 2-(4-methoxyphenyl) and 2-(2-pyridyl)-indenofused pyridines **17b**,**c** were similarly obtained in good yields following the same procedure (Scheme 3).

In one of the reactions, the ketene dithioacetal **5** was subjected to cyclocondensation with 5-aminotetrazole **19** in the presence of K_2CO_3 in DMSO at 120 °C, yielding a novel tetracyclic condensed polyaza heteroaromatic framework **18** in 65% yield (Scheme 4).



Scheme 4.

We further extended heteroaromatic annulation studies to the corresponding *N*,*S*-acetals **20** and **21** for the synthesis of amino substituted indenofused heterocycles with a view to add further point of diversity in these compounds (Scheme 5). Thus, the *N*,*S*-acetals **20** from primary amines and **21** from secondary cyclic amines could be smoothly obtained in high yields by direct



Scheme 5.

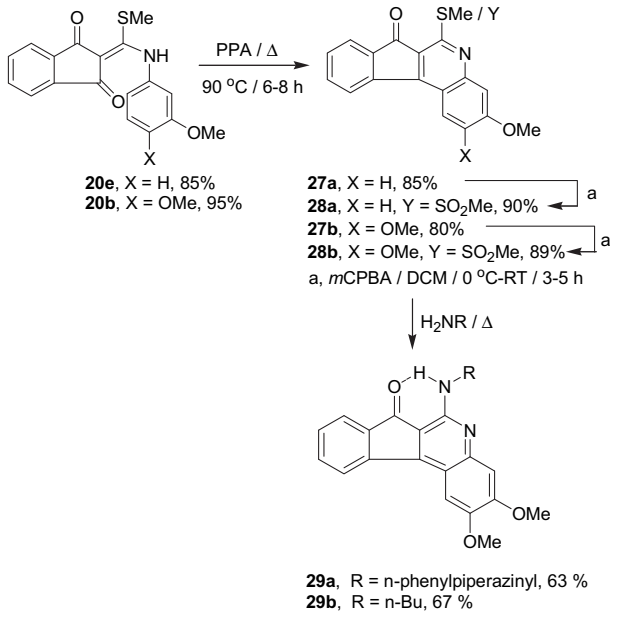
replacement of methylthio group in **5** by various amines (Scheme 5, Table 1). It should be noted that although synthesis of *N*,*S*-anilinoacetals have been reported in the literature,[19] no attempts were made to utilize them for further synthetic applications. Thus, the cycloannulation of *N*,*S*-acetals **20a**,**b** and **21a**,**b** with hydrazine hydrate under earlier described conditions afforded the corresponding 3-anilino/cycloamino indeno[1,2-*c*]pyrazol-4-ones **22a**,**b** (Table 1, entries 1 and 2) and **23a**,**b** (Table 1, entries 3 and 4) in 55–70% overall yields.[19] Similarly, treatment of *N*,*S*-acetals **20a**–**d** and **21b** with either guanidine nitrate or 2-phenylamidine hydrochloride in the presence of K_2CO_3 in refluxing acetonitrile afforded the respective 4-(anilino/benzylamino/*N*-phenylpiperazino)-2-amino (or 2-phenyl)indenopyrimidin-5-ones **24a**–**e** and **25** (Table 1, entries 5–9 and 10) in overall good yields.[20] Similarly, cyclization of **21b** with cyanoacetamide in the presence of potassium *tert*-butoxide in *tert*-butanol gave 2,5-dioxo-4-(4-phenyl-piperazin-1-yl)-2,5-dihydro-1*H*-indeno[1,2-*b*]pyridine- 3-carbonitrile **26** in 50% yield (Table 1, entry 11).[21] The structures of all the newly synthesized compounds were established with the help of spectral and analytical data.

In view of the potent DNA topoisomerase inhibitory activity reported for indenoquinolines,[4a,b] such as **2** (Chart 1), we planned to synthesize this tetracyclic planar heterocyclic scaffold as shown in the Scheme 6. Thus, the *N*,*S*-aminoacetals **20e** and **20b** from 3-methoxy and 3,4-dimethoxyanilines, respectively, were subjected to cyclization in the presence of polyphosphoric acid at 90 °C affording the desired 2-methoxy (or 2,3-dimethoxy)-6-(methylthio)indeno[2,1-*c*]quinolin-7-ones **27a**,**b** in excellent yields (Scheme 6).[22] The quinolines **27a**,**b** on oxidation with *m*-chloroperbenzoic acid yielded the corresponding 6-(methylsulfonyl) derivatives **28a**,**b** in high yields (Scheme 6). Subsequent replacement of methylsulfonyl group in **28b** by aliphatic amines gave the amino substituted indenofused quinolines **29a**,**b** in high yields (Scheme 6).

Table 1
Synthesis of amino substituted indenofused heterocycles

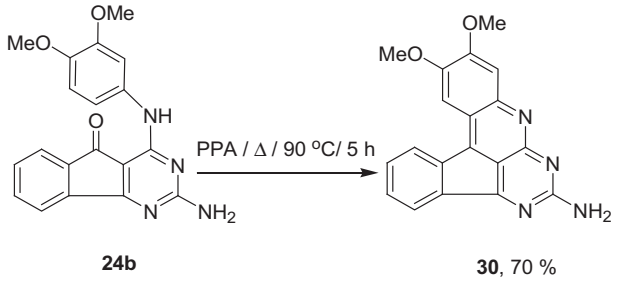
Entry	*N*,*S*-acetals **20**, **21**	Yield (%)	Reaction condition	Product (**22**–**26**)	Yield (%)
1	**20a**, Ar=4-MeOC$_6$H$_4$	90	[a]	**22a**, Ar=4-MeOC$_6$H$_4$	68
2	**20b**, Ar=3,4-(MeO)$_2$C$_6$H$_3$	95	[a]	**22b**, Ar=3,4-(MeO)$_2$C$_6$H$_3$	70
3	**21a**, X=CH$_2$,	80	[a]	**23a**, X=CH$_2$	60
4	**21b**, X=N–Ph,	75	[a]	**23b**, X=N–Ph	55
5	**20a**, Ar=4-MeOC$_6$H$_4$	90	[b]	**24a**, Ar=4-MeOC$_6$H$_4$, R^2=NH$_2$	75
6	**20b**, Ar=3,4-(MeO)$_2$C$_6$H$_3$	95	[b]	**24b**, Ar=3,4-(MeO)$_2$C$_6$H$_3$, R^2=NH$_2$	75
7	**20c**, Ar=C$_6$H$_5$	90	[b]	**24c**, Ar=C$_6$H$_5$, R^2=NH$_2$	78
8	**20b**, Ar=3,4-(MeO)$_2$C$_6$H$_3$	95	[c]	**24d**, Ar=3,4-(MeO)$_2$C$_6$H$_3$, R^2=Ph	50
9	**20d**, R^1=4-MeC$_6$H$_4$CH$_2$	85	[b]	**24e**, R^1=4-MeC$_6$H$_4$CH$_2$, R^2=NH$_2$	60
10	**21b**	75	[b]	**25**	75
11	**21b**	75	[d]	**26**	50

[a] Reaction Conditions: N_2H_4/EtOH/reflux/6–10 h.
[b] Guanidine nitrate/K_2CO_3/CH_3CN/reflux/8–10 h.
[c] Benzamidine hydrochloride/K_2CO_3/CH_3CN/reflux/8 h.
[d] Cyanoacetamide/KBu^{t}O/Bu^{t}OH/reflux/12 h.



Scheme 6.

In a further elaboration to construct novel indenofused polycyclic heteroaromatics, the 4-(3,4-dimethoxyanilino) indenopyrimidine **24b** was exposed to polyphosphoric acid at 90 °C for 5 h to afford an insoluble product, which was characterized as the novel pentacyclic planer heterocycle **30** on the basis of its spectral and analytical data (Scheme 7).



Scheme 7.

3. Conclusion

In summary, we have developed an efficient general protocol for indenofused five- and six-membered heterocycles via heteroaromatic annulation of 2-[bis(methylthio)methylene]-1,3-indanedione. The methodology has been further elaborated to the corresponding *N*,*S*-acetals leading to amino substituted heterocycles thus providing further point of diversity in the newly synthesized heterocyclic frameworks. Facile access to cytotoxic indeno[2,1-*c*]quinolin-7-ones **27** (Scheme 6) and the novel polycyclic heteroaromatics, such as **18** and **30** (Schemes 4 and 7) further demonstrates the versatility of heteroaromatic annulation protocol via α-oxoketene-*S*,*S*-acetal in generating novel biologically important polycyclic heteroaromatics, some of them cannot be synthesized easily by traditional classical methods. In view of the broad range of biological activities displayed by indenofused heterocycles, these newly synthesized compounds will prove useful for preliminary pharmacological screening. Our further efforts to improve the yields of indenofused five-membered heterocycles are in progress.

4. Experimental

4.1. General

All reagents were commercial and purchased from Merck, Aldrich and Fluka and were used as received. All ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 300 FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on Varian 3100 FT-IR spectrophotometer. Mass spectra were recorded at 70 eV ionizing voltage on a JEOL-D300 MS instrument. The C, H, and N analyses were performed from microanalytical laboratory, Department of Chemistry, Banaras Hindu University, Varanasi with an Exeter Analytical Inc. 'Model CE-400 CHN Analyzer'. X-ray diffraction was measured on Xcalibur Oxford CCD Diffractometer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck $60F_{254}$) using UV light (254 nm/365 nm) for visualization. Melting points were determined with Büchi B-540 melting point apparatus and are uncorrected.

4.2. Synthesis of 2-[bis(methylthio)methylene]-1,3-indanedione (5)

KOH (4 g, 68 mmol) in THF (20 mL) was suspended in round bottom flask fitted with a dropping funnel and $CaCl_2$ guard tube. CS_2 (3 mL, 41 mmol) was added to the reaction mixture at 0 °C with continuous stirring. After 45 min a solution of indane-1,3-dione (5 g, 34 mmol) in dry THF (20 mL) was added drop-wise at 0 °C and the reaction mixture was stirred overnight (8–10 h). The precipitated yellow colored dipotassium salt was filtered, washed with dry ether, and dried. The suspension of dipotassium salt in dry ethanol (100 mL) was methylated at 0 °C using neutral Me_2SO_4 (10 mL, 103 mmol) followed by stirring for further 5 h. Ethanol was distilled off and resulting slurry was poured over ice cold water and extracted with $CHCl_3$ (4×30 mL). The combined organic extract was washed with water (1×40 mL), brine (1×30 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude product, which was purified by column chromatography over silica gel using hexane/ethyl acetate (9:1) as eluent to give pure 2-[bis(methylthio)-methylene]-1,3-indanedione **5** as a yellow solid (5.1 g, 60%); mp 124–125 °C (reported mp 124–125 °C).[10a] R_f=0.57 (hexane/EtOAc, 80:20); IR (KBr): 3191, 2928, 1672, 1562 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–7.82 (m, 2H, ArH), 7.68–7.65 (m, 2H, ArH), 2.64 (s, 6H, 2×SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.8, 181.3, 140.3, 133.9, 122.5, 121.6, 21.6. ESIMS (*m*/*z*, %): 251 (M^{+}+1, 100). Anal. Calcd for $C_{12}H_{10}O_2S_2$: C, 57.57%; H, 4.03%. Found: C, 57.69; H, 4.15%.

*4.2.1. Synthesis of 3-methylthio-1H-indeno[1,2-c] pyrazol-4-one (**6**).* To a stirred solution of ketene dithioacetals **5** (0.5 mmol) in absolute ethanol (6 mL) was added a solution of hydrazine hydrate (0.073 mL, 0.5 mmol) in absolute ethanol (2 mL) drop-wise. The reaction mixture was stirred and refluxed for 5 h (monitored by TLC). Solvent was evaporated under vacuum and residue obtained was dissolved in dichloromethane (20 mL). Organic layer was washed with water (2×20 mL) followed by brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product, which was purified by column chromatography over silica gel to give white fibrous solid, mp 248 °C. Yield 0.070 g, 65%; R_f=0.35 (hexane/EtOAc, 80:20); IR (KBr): 3448, 2934, 1699, 1562, 1452, 1262 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (s, 1H, NH), 7.63 (d, *J*=7.2 Hz, 1H, ArH), 7.53–7.44 (m, 2H, ArH), 7.32 (d, *J*=7.5 Hz, 1H, ArH), 2.88 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.6, 163.9, 140.7, 140.6, 135.6, 133.9, 129.3,

123.7, 119.8, 15.5. ESIMS (m/z, %): 217 (M^++1, 100). Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09%; H, 3.73%; N, 12.95%. Found: C, 61.31%; H, 3.59%; N, 12.76%.

*4.2.2. Synthesis of 3-methylthio-1-phenyl-1H-indeno[1,2-c]pyrazol-4-one (**7**).* To a stirred solution of **5** (0.125 g, 0.5 mmol) in ethanol and glacial acetic acid (1:1, 6 mL), a solution of phenyl hydrazine (0.073 mL, 0.75 mmol) in glacial acetic acid (2 mL) was added dropwise. Reaction mixture was stirred and refluxed for 6 h (monitored by TLC). Solvent was evaporated under vacuum and residue was dissolved in dichloromethane (20 mL). Organic layer was washed with water (4×20 mL) followed by brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the product, which was purified by column chromatography over silica gel using hexane/ethyl acetate (19:1) to yield the desired compound **7** as yellow crystals. Yield 0.080 g, 55%; mp 159 °C; R_f=0.57 (hexane/EtOAc, 85:15); IR (KBr): 2932, 2845, 1689, 1592, 1507, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.48 (m, 6H, ArH), 7.31–7.28 (m, 2H, ArH), 7.17–7.14 (m, 1H, ArH), 2.73 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0, 157.8, 148.5, 140.7, 138.5, 132.7, 132.2, 130.2, 129.5, 128.9, 124.6, 123.4, 119.6, 14.5. ESIMS (*m*/*z*, %): 293 (M^++1, 100). Anal. Calcd for $C_{17}H_{12}N_2OS$: C, 69.84%; H, 4.14%; N, 9.58%. Found: C, 69.80%; H, 4.31%; N, 9.39%.

*4.2.3. Synthesis of 1-methylthio-2-thia-cyclopenta-[a]inden-8-one (**10**).* A solution of CH_2I_2 (0.2 mL, 2.5 mmol) in dry ether (5 mL) was added drop-wise to a stirred suspension of Zn/Cu couple (activated by heating in oven at 100 °C for 10 h) (0.4 g, 3.0 mmol) in dry ether (20 mL) at reflux temperature under nitrogen atmosphere. After 1 h, a solution of **5** (0.187 g, 0.75 mmol) in dry THF (10 mL) was added drop-wise and refluxing was continued for 10 h (monitored by TLC). The reaction mixture was cooled to room temperature and the organic layer was decanted. The residue was extracted with chloroform (3×20 mL) and the combined extract was washed with water (1×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the crude product obtained was purified by column chromatography over silica gel using hexane/ethyl acetate (20:1) as eluent to give **10** as creamish fibers, mp 187 °C. Yield 0.095 g, 55%; R_f=0.45 (hexane/EtOAc, 80:20); IR (KBr): 2925, 2855, 1683, 1561, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H, ArH), 7.91–7.88 (m, 2H, ArH), 7.75–7.72 (m, 2H, ArH), 2.66 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 186.8, 156.0, 141.5, 140.3, 134.7, 134.6, 126.4, 123.3, 122.7, 20.1. ESIMS (*m*/*z*, %): 233 (M^++1, 100). Anal. Calcd for $C_{12}H_8OS_2$: C, 62.04%; H, 3.47%. Found: C, 62.16%; H, 3.32%.

*4.2.4. Synthesis of 1-methylthio-8-oxo-8H-2-thia-cyclopenta[a]indene-3-carboxylic acid ethyl ester (**11**).* Ethyl thioglycolate (0.045 mL, 0.5 mmol) dissolved in EtOH (2 mL) was added dropwise to the stirred suspension of K_2CO_3 (0.069 g, 0.5 mmol) and **5** (0.125 g, 0.5 mmol) in EtOH (5 mL). The solution was refluxed for 8 h (monitored by TLC). Solvent was evaporated under vacuum and the residue obtained was dissolved in dichloromethane (20 mL). Organic layer was washed with water (1×20 mL) followed by brine (1×20 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under vacuum and the residue obtained was purified by column chromatography over silica gel using hexane/ethyl acetate (15:1) as eluent to afford **11** as yellow solid, mp 151 °C. Yield 0.064 g, 42%; R_f=0.61 (hexane/EtOAc, 80:20); IR (KBr): 2991, 2851, 1698, 1597, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, *J*=7.5 Hz, 1H, ArH), 7.68 (d, *J*=7.5 Hz, 1H, ArH), 7.53 (dd, *J*=7.5, 7.2 Hz, 1H, ArH), 7.36 (dd, *J*=7.5, 7.2 Hz, 1H, ArH), 4.40 (q, *J*=7.2 Hz, 2H, CH_2), 2.70 (s, 3H, SCH_3), 1.43 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.8, 160.9, 151.1, 151.0, 141.5, 139.0, 136.1, 134.3, 129.9, 125.9, 124.2, 121.3, 94.5, 61.6, 17.8, 14.3. ESIMS (*m*/*z*, %): 305 (M^++1, 100). Anal. Calcd for $C_{15}H_{12}O_3S_2$: C, 59.19%; H, 3.97%. Found: C, 58.94%; H, 4.18%.

*4.2.5. Synthesis of aminopyrimidines **12** and **14**.* Guanidine nitrate or benzamidine hydrochloride (0.52 mmol) was added to a stirred suspension of K_2CO_3 (0.138 g, 1 mmol) in acetonitrile (10 mL). After 30 min, ketene dithioacetal **5** (0.125 g, 0.5 mmol) was added and the reaction mixture was refluxed for 8–10 h (monitored by TLC). Solvent was evaporated under vacuum. The residue obtained was treated with cold water and extracted with ethyl acetate (3×20 mL). The combined organic extract was washed with water (2×20 mL) followed by brine (1×20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue obtained was purified by column chromatography over silica gel using hexane/ethyl acetate (6:1) as eluent to give **12** and **14**.

*4.2.6. 2-Amino-4-methylthio-indeno[1,2-d] pyrimidin-5-one (**12**).* Yellow solid, mp 261–263 °C; yield 0.085 g, 65%; R_f=0.18 (hexane/EtOAc, 80:20); IR (KBr): 3311, 3199, 2915, 2826, 1689, 1617, 1524, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.69 (m, 2H, ArH), 7.55–7.53 (m, 2H, ArH), 5.58 (s, 2H, NH_2), 2.56 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 187.2, 173.0, 167.5, 163.3, 138.6, 135.5, 132.4, 131.3, 121.7, 120.2, 10.0. ESIMS (*m*/*z*, %): 244 (M^++1, 100). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24%; H, 3.73%; N, 17.27%. Found: C, 59.39%; H, 3.59%; N, 17.15%.

*4.2.7. 4-Methylthio-2-phenyl-indeno[1,2-d] pyrimidin-5-one (**14**).* Yellow solid, mp 210–211 °C; yield 0.083 g, 55%; R_f=0.66 (hexane/EtOAc, 80:20); IR (KBr): 3161, 1585, 1487, 1394, 1265, 1194, 1157, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (dd, *J*=7.8, 1.5 Hz, 2H, ArH), 7.99 (d, *J*=7.2 Hz, 1H, ArH), 7.76 (d, *J*=6.9 Hz, 1H, ArH), 7.64–7.53 (m, 5H, ArH), 2.79 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 172.2, 167.1, 166.5, 140.7, 139.2, 136.9, 135.2, 134.4, 132.6, 131.9, 129.3, 128.5, 123.7, 122.0, 118.9, 114.0, 11.5. ESIMS (*m*/*z*, %): 304 (M^++1, 20). Anal. Calcd for $C_{18}H_{12}N_2OS$: C, 71.03%; H, 3.97%; N, 9.20%. Found: C, 70.95%; H, 4.05%; N, 9.39%.

*4.2.8. Synthesis of 2-amino-4-ethoxy-indeno[1,2-d] pyrimidin-5-one (**13**).* Guanidine nitrate (0.064 g, 0.52 mmol) was added to a stirred solution of sodium ethoxide (1.1 mmol, prepared in situ form 0.028 g Na and 1 mL dry ethanol) in ethanol (8 mL). After 15 min, ketene dithioacetal **5** (0.125 g, 0.5 mmol) was added and reaction mixture was refluxed for 7 h. After the completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. The residue obtained was triturated with water (5 mL). The solid obtained was filtered and recrystallized from ethanol to give **13** as yellow solid, mp 210–211 °C. Yield 0.072 g, 60%; IR (KBr): 3454, 3305, 3124, 1707, 1641, 1572, 1491, 1082 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.34–8.24 (m, 2H, ArH), 8.17–8.07 (m, 2H, ArH), 6.78 (s, 2H, NH_2), 4.46 (q, *J*=7.2 Hz, 2H, CH_2), 1.47 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ: 186.4, 169.4, 166.8, 165.9, 165.5, 139.5, 136.7, 133.7, 132.6, 122.9, 122.7, 61.2, 14.3. ESIMS (*m*/*z*, %): 242 (M^++1, 20). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72%; H, 4.60%; N, 17.42%. Found: C, 64.60%; H, 4.75%; N, 17.39%.

*4.2.9. Syntheis of 4-methylthio-2,5-dioxo-2,5-dihydro-1H-indeno [1,2-b]pyridine-3-carbonitrile (**15**).* To a stirred suspension of Bu^tOK (0.168 g, 1.5 mmol) in Bu^tOH (10 mL) at room temperature, cyanoacetamide (0.067 g, 0.5 mmol) was added. After 10 min, ketene dithioacetal **5** (0.125 g, 0.5 mmol) was added and the reaction mixture was refluxed for 8 h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure to give the salt of pyridine **15**, which was dissolved in water (10 mL) followed by acidification with dilute HCl (5 mL, 5%). The solid obtained was filtered, washed with water, and recrystallized from ethanol to give the desired compound **15** as yellow

solid, mp 320 °C (decompose). Yield 0.060 g, 45%; IR (KBr): 3449, 2921, 2859, 2357, 1635, 1556, 1459 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.0 (s, 1H, OH), 8.00–7.63 (m, 4H, ArH), 2.82 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 186.2, 161.2, 160.6, 159.2, 134.6, 134.2, 134.1, 133.7, 123.1, 122.9, 116.1, 17.0. ESIMS (*m*/*z*, %): 269 (M^++1, 100). Anal. Calcd for $C_{14}H_8N_2O_2S$: C, 62.67%; H, 3.01%; N, 10.44%. Found: C, 62.55%; H, 2.87%; N, 10.67%.

4.2.10. General procedure for synthesis of ***17a–c****.* A solution of acetophenone/4-methoxyacetophenone or 2-acetyl pyridine (0.52 mmol) in dry DMF (2 mL) was added drop-wise to a stirred suspension of NaH (60%, 0.032 g, 0.8 mmol) in dry DMF (3 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was further stirred for 1 h. A solution of **5** (0.125 g, 0.5 mmol) in dry DMF (5 mL) was added drop-wise at 0 °C and the content was stirred at room temperature for 10 h (monitored by TLC). The reaction mixture was poured into saturated aqueous ammonium chloride solution (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extract was washed with water (4×25 mL) followed by brine (1×25 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to yield adduct **16a** (75%), **16b** (72%) or **16c** (74%).

*4.2.11. 2-(1-Methylthio-3-oxo-3-phenyl-propylidene)-1,3-indanedione (****16a****).* Yellow solid, yield 0.120 g, 75%; R_f=0.31 (hexane/EtOAc, 50:50); IR (KBr): 3062, 2919, 1702, 1687, 1606, 1561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–8.04 (m, 1H, ArH), 7.87 (d, *J*=6.3 Hz, 1H, ArH), 7.78 (d, *J*=5.7 Hz, 2H, ArH), 7.68–7.66 (m, 3H, ArH), 7.55 (d, *J*=7.5 Hz, 2H, ArH), 5.27 (s, 2H, CH_2), 2.42 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 190.2, 188.6, 170.5, 140.7, 140.2, 136.0, 134.6, 134.3, 133.8, 128.9, 128.2, 124.9, 122.9, 122.5, 40.6, 14.3.

Anhydrous ammonium acetate (0.115 g, 1.5 mmol) was added to a solution of adduct **16a–c** in glacial acetic acid (10 mL) and the reaction mixture was refluxed for 6 h (monitored by TLC). It was then cooled, poured into ice cold water and extracted with ethyl acetate (3×30 mL). The combined organic extract was washed with water (3×30 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography over silica gel using hexane/ethyl acetate (10:1) as eluent to afford the yellow solid **17**.

*4.2.12. 4-Methylthio-2-phenyl-indeno[1,2-b] pyridine-5-one (****17a****).* Yellow solid, mp 174–176 °C; yield 0.106 g, 70%; R_f=0.65 (hexane/EtOAc, 80:20); IR (KBr): 3062, 2919, 1699, 1606, 1561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.11–8.09 (m, 2H, ArH), 7.93 (d, *J*=7.5 Hz, 1H, ArH), 7.71 (d, *J*=7.2 Hz, 1H, ArH), 7.61–7.41 (m, 5H, ArH), 7.37 (s, 1H, ArH), 2.62 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 165.4, 160.8, 151.1, 142.6, 138.5, 134.5, 130.9, 130.0, 128.8, 127.4, 123.4, 122.1, 121.1, 113.9, 13.1. ESIMS (*m*/*z*, %): 304 (M^++1, 100). Anal. Calcd for $C_{19}H_{13}NOS$: C, 75.22%; H, 4.32%; N, 4.62%. Found: C, 75.10%; H, 4.15%; N, 4.79%.

*4.2.13. 2-(4-Methoxyphenyl)-4-methylthio-indeno [1,2-b]pyridine-5-one (****17b****).* Yellow solid, mp 193–196 °C; yield 0.108 g, 65%; R_f=0.63 (hexane/EtOAc, 80:20); IR (KBr): 2921, 1697, 1547, 1459 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J*=8.7 Hz, 2H, ArH), 7.91 (d, *J*=7.5 Hz, 1H, ArH), 7.69 (d, *J*=7.5 Hz, 1H, ArH), 7.55 (dd, *J*=8.1, 7.8 Hz, 1H, ArH), 7.42 (dd, *J*=8.1, 7.8 Hz, 1H, ArH), 7.30 (s, 1H, ArH), 7.03 (d, *J*=8.7 Hz, 2H, ArH), 3.90 (s, 3H, OCH_3), 2.61 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, CD_3COCD_3+DMSO-d_6): δ 191.8, 164.9, 161.6, 159.8, 151.5, 142.3, 138.3, 135.1, 131.18, 130.4, 129.2, 122.9, 120.8, 114.1, 113.1, 55.0, 12.2. ESIMS (*m*/*z*, %): 334 (M^++1, 100). Anal. Calcd for $C_{20}H_{15}NO_2S$: C, 72.05%; H, 4.53%; N, 4.20%. Found: C, 72.10%; H, 4.35%; N, 4.09%.

*4.2.14. 4-Methylthio-2-pyridin-2-yl-indeno[1,2-b] pyridine-5-one (****17c****).* Yellow solid, mp 219–221 °C; yield 0.094 g, 62%; R_f=0.55 (hexane/EtOAc, 80:20); IR (KBr): 2927, 2850, 1694, 1668, 1531, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, *J*=4.2 Hz, 1H, ArH), 8.63 (d, *J*=7.8 Hz, 1H, ArH), 8.25 (s, 1H, ArH), 7.94–7.86 (m, 2H, ArH), 7.72 (d, *J*=7.2 Hz, 1H, ArH), 7.59 (t, *J*=7.2 Hz, 1H, ArH), 7.47–7.36 (m, 2H, ArH), 2.69 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 165.0, 158.6, 155.0, 151.8, 149.2, 142.5, 137.0, 135.3, 134.5, 130.9, 124.5, 123.5, 123.4, 122.3, 121.0, 114.7, 13.3. ESIMS (*m*/*z*, %): 305 (M^++1, 100). Anal. Calcd for $C_{18}H_{12}N_2OS$: C, 71.03%; H, 3.97%; N, 9.20%. Found: C, 71.10%; H, 3.85%; N, 9.02%.

*4.2.15. Synthesis of 5-methylthio-1,2,3,4,10c-pentaazacyclopenta[c] fluoren-6-one (****18****).* To a stirred solution of ketene dithioacetal **5** (0.125 g, 0.5 mmol) in DMSO (4 mL), a solution of 5-aminotetrazole **19** (0.043 g, 0.5 mmol) in DMSO (4 mL) was added. Reaction mixture was heated at 120 °C with stirring for 5 h (monitored by TLC). The reaction mixture was cooled to room temperature and poured over crushed ice followed by acidification with 10% HCl solution. Resulting yellow colored solid was recrystallized in ethanol to yield **18** as yellow solid, mp 198 °C. Yield 0.087 g, 65%; IR (KBr): 2911, 1709, 1572, 1463, 1288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J*=6.6 Hz, 1H, ArH), 7.73 (d, *J*=6.9 Hz, 1H, ArH), 7.59 (dd, *J*=8.1 Hz, 2H, ArH), 2.64 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 188.6, 174.2, 169.1, 164.3, 139.2, 135.2, 134.4, 133.0, 123.5, 122.2, 117.0, 11.4. ESIMS (*m*/*z*, %): 270 (M^++1, 100). Anal. Calcd for $C_{12}H_7N_5OS$: C, 53.52%; H, 2.62%; N, 26.01 Found: C, 53.39%; H, 2.70%; N, 25.85.

4.3. Synthesis of arylamino or cycloamino *N,S*-acetals (20, 21)

A solution of respective amines (1 mmol) in dry ethanol (4 mL) was added to a stirred solution of **5** (0.250 g, 1 mmol) in dry ethanol (5 mL) at room temperature. Reaction mixture was refluxed for 2 h (monitored by TLC). The resulting arylamino-/cycloamino *N,S*-acetals were purified by crystallization in ethanol or by column chromatography over silica gel using hexane/ethyl acetate as eluent to give pure **20** and **21**.

*4.3.1. 2-[(4-Methoxyphenylamino)methylthio-methylene]-1,3-indanedione (****20a****).* Yellow crystals, mp 137–138 °C (reported mp 138–140 °C);[10a] yield 0.292 g, 90%; R_f=0.49 (hexane/EtOAc, 80:20); IR (KBr): 3448, 3043, 1634, 1547, 1398, 1334 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.23 (s, 1H, NH), 7.72–7.57 (m, 4H, ArH), 7.24 (d, *J*=8.7 Hz, 2H, ArH), 6.94 (d, *J*=8.7 Hz, 2H, ArH), 3.84 (s, 3H, OCH_3), 2.32 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 158.7, 148.3, 133.1, 130.3, 128.0, 126.4, 121.4, 117.4, 114.5, 105.5, 55.5, 18.0. ESIMS (*m*/*z*, %): 326 (M^++1, 100). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44%; H, 4.65%; N, 4.30%. Found: C, 66.59%; H, 4.39%; N, 4.52%.

*4.3.2. 2-[(3,4-Dimethoxyphenylamino)methylthio-methylene]-1,3-indanedione (****20b****).* Yellow crystals, mp 137 °C; yield 0.337 g, 95%; R_f=0.32 (hexane/EtOAc, 80:20); IR (KBr): 3448, 3029, 2923, 1637, 1592, 1498, 1341 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.26 (s, 1H, NH), 7.74–7.73 (m, 2H, ArH), 7.78–7.76 (m, 2H, ArH), 6.90–6.85 (m, 3H, ArH), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.35 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 149.3, 148.3, 133.1, 130.4, 128.0, 127.7, 127.4, 121.4, 117.4, 111.0, 108.5, 105.6, 56.1, 56.0, 18.0. ESIMS (*m*/*z*, %): 356 (M^++1, 100). Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21%; H, 4.82%; N, 3.94%. Found: C, 64.43%; H, 3.59%; N, 3.76%.

*4.3.3. 2-(Methylthio-phenylamino-methylene)-1,3-indanedione (****20c****).* Yellow crystals, mp 147–149 °C (reported mp 149–152 °C);[10a] Yield 0.265 g, 90%; IR (KBr): 3459, 3038, 2945, 1619, 1587, 1479, 1332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.31 (s, 1H, NH), 7.73–7.72 (m, 2H, ArH), 7.61–7.58 (m, 2H, ArH), 7.44–7.33 (m, 5H, ArH), 2.29 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 169.0, 162.9, 161.6, 137.7, 137.1, 133.4, 133.2, 129.4, 127.2, 124.8, 121.5, 106.1, 105.7, 101.1, 18.0. ESIMS (*m*/*z*, %): 296 (M^++1, 100). Anal. Calcd

for $C_{17}H_{13}NO_2S$: C, 69.13%; H, 4.44%; N, 4.74%. Found: C, 69.36%; H, 4.58%; N, 4.53%.

*4.3.4. 2-[(4-Methylbenzylamino)methylthio-methylene]-1,3-indanedione (**20d**).* Yellow crystals, mp 148–149 °C; yield 0.292 g, 85%; IR (KBr): 3435, 2925, 2857, 1686, 1631, 1547, 1415 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.93 (s, 1H, NH), 7.68–7.65 (m, 2H, ArH), 7.56–7.53 (m, 2H, ArH), 7.25–7.19 (m, 4H, ArH), 4.81 (d, J=5.7 Hz, 2H, NCH_2), 2.73 (s, 3H, SCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 139.0, 137.9, 132.8, 132.9, 129.7, 127.3, 121.2, 103.8, 48.8, 21.1, 18.8. ESIMS (m/z, %): 324 (M^++1, 100). Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56%; H, 5.30%; N, 4.33%. Found: C, 70.79%; H, 5.49%; N, 4.59%.

*4.3.5. 2-[(3-Methoxyphenylamino)methylthio-methylene]-1,3-indanedione (**20e**).* Yellow crystals, mp 134–136 °C; yield 0.276 g, 85%; R_f=0.33 (hexane/EtOAc, 80:20); IR (KBr): 3449, 2925, 1639, 1536, 1397, 1326 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.27 (s, 1H, NH), 7.73 (d, J=3.0 Hz, 2H, ArH), 7.61–7.58 (m, 2H, ArH), 7.33 (dd, J=8.5, 7.8 Hz, 1H, ArH), 6.94 (d, J=8.1 Hz, 2H, ArH), 6.86 (d, J=8.4 Hz, 1H, ArH), 3.83 (s, 3H, OCH_3), 2.32 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 160.3, 138.8, 133.2, 130.1, 121.5, 117.0, 113.0, 110.3, 106.2, 55.4, 18.0. ESIMS (m/z, %): 326 (M^++1, 100). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44%; H, 4.65%; N, 4.30%. Found: C, 66.57%; H, 4.42%; N, 4.49%.

*4.3.6. 2-(Methylthio-piperidin-1-yl-methylene)-1,3-indanedione (**21a**).* Yellow thick viscous oil; yield 0.229 g, 80%; R_f=0.10 (hexane/EtOAc, 80:20); IR (KBr): 3439, 3023, 2945, 1644, 1583, 1477, 1359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.65 (m, 2H, ArH), 7.51–7.46 (m, 2H, ArH), 3.86 (br s, 4H, 2×NCH_2), 2.50 (s, 3H, SCH_3), 1.76–1.64 (m, 6H, 3×CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.4, 174.1, 150.9, 140.6, 131.2, 129.1, 121.2, 120.9, 102.5, 18.7, 21.4, 14.5. ESIMS (m/z, %): 288 (M^++1, 100). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87%; H, 5.96%; N, 4.87%. Found: C, 66.63%; H, 5.69%; N, 4.63%.

*4.3.7. 2-[Methylthio-(4-phenyl-piperazin-1-yl)-methylene]-1,3-indanedione (**21b**).* Yellow crystals, mp 120–121 °C; yield 0.273 g, 75%; R_f=0.09 (hexane/EtOAc, 70:30); IR (KBr): 3448, 3029, 2923, 2853, 1637, 1592, 1498, 1408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.68 (m, 2H, ArH), 7.56–7.55 (m, 2H, ArH), 7.31–7.29 (m, 2H, ArH), 6.92–6.89 (m, 3H, ArH), 4.08 (t, J=4.2 Hz, 4H, 2×NCH_2), 3.41 (t, J=4.5 Hz, 4H, 2×CH_2), 2.54 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.1, 177.2, 149.9, 139.5, 132.4, 129.3, 120.9, 120.7, 116.3, 103.5, 49.2, 18.7. ESIMS (m/z, %): 365 (M^++1, 100). Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.20%; H, 5.53%; N, 7.69%. Found: C, 69.42%; H, 5.63%; N, 7.36%.

*4.3.8. Synthesis of aminopyrazoles (**22**, **23**).* To a stirred solution of *N*,*S*-acetals **20** or **21** (0.5 mmol) in absolute ethanol (6 mL), a solution of hydrazine hydrate (0.073 mL, 0.5 mmol) in absolute ethanol (2 mL) was added drop-wise. Resulting solution was refluxed for 6–10 h with continuous stirring. After the completion of the reaction (monitored by TLC), solvent was evaporated under vacuum and the residue obtained was dissolved in DCM (20 mL). Organic layer was washed with water (4×30 mL) and brine (1×30 mL) followed by drying over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the crude product, which was purified by column chromatography over silica gel.

*4.3.9. 3-(4-Methoxyphenylamino)-1H-indeno[1,2-c] pyrazol-4-one (**22a**).* Yellow solid, mp 173–175 °C; yield 0.099 g, 68%; R_f=0.61 (DCM); IR (KBr): 3327, 3219, 3061, 2959, 1624, 1589, 1510, 1435, 1296, 1236, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H, NH), 9.85 (s, 1H, NH), 7.61–7.58 (m, 2H, ArH), 7.51–7.48 (m, 2H, ArH), 7.18 (d, J=8.7 Hz, 2H, ArH), 6.91 (d, J=8.7 Hz, 2H, ArH), 3.82 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 159.9, 158.1, 138.8, 132.3, 130.9, 126.0, 120.6, 114.4, 92.6, 55.4. ESIMS (m/z, %): 292 (M^++1, 100). Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09%; H, 4.50%; N, 14.42%. Found: C, 70.24%; H, 4.69%; N, 14.64%.

*4.3.10. 3-(3,4-Dimethoxyphenylamino)-1H-indeno [1,2-c]pyrazol-4-one (**22b**).* Yellow solid, mp 167–169 °C; yield 0.112 g, 70%; R_f=0.53 (DCM); IR (KBr): 3448, 2933, 1627, 1585, 1511, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.83 (s, 1H, NH), 10.48 (s, 1H, NH), 7.62–7.51 (m, 4H, ArH), 6.77–6.75 (m, 3H, ArH), 3.89 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.1, 148.44, 138.3, 132.2, 119.9, 116.1, 111.2, 108.1, 55.6, 55.4. ESIMS (m/z, %): 322 (M^++1, 100). Anal. Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28%; H, 4.71%; N, 13.08%. Found: C, 67.12%; H, 4.99%; N, 12.94%.

*4.3.11. 3-Piperidin-1-yl-1H-indeno[1,2-c]pyrazol-4-one (**23a**).* Yellow solid, mp 246 °C; yield 0.076 g, 60%; R_f=0.21 (hexane/EtOAc, 80:20); IR (KBr): 3457, 2927, 1688, 1583, 1477, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J=6.9 Hz, 1H, ArH), 7.45 (d, J=6.9 Hz, 1H, ArH), 7.41–7.36 (m, 2H, ArH), 3.58–3.56 (m, 4H, NCH_2), 1.66–1.65 (m, 6H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.1, 163.9, 148.7, 142.9, 135.2, 132.0, 129.1, 123.4, 119.5, 102.2, 49.3, 25.0, 23.6. ESIMS (m/z, %): 354 (M^++1, 100). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13%; H, 5.97%; N, 16.59%. Found: C, 71.35%; H, 5.17%; N, 13.13%.

*4.3.12. 3-(4-Phenylpiperazin-1-yl)-1H-indeno[1,2-c]pyrazol-4-one (**23b**).* Yellow solid, mp 257–258 °C; yield 0.090 g; 55%; R_f=0.20 (DCM/MeOH, 99:1); IR (KBr): 3421, 2934, 1699, 1562, 1452, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J=7.2 Hz, 1H, ArH), 7.50 (d, J=7.2 Hz, 1H, ArH), 7.41 (dd, J=7.5, 7.2 Hz, 1H, ArH), 7.32–7.29 (m, 3H, ArH), 6.97 (m, 3H, ArH), 3.81 (t, J=4.5 Hz, 4H, 2×CH_2), 3.34 (t, J=4.8 Hz, 4H, 2×CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.2, 162.1, 150.7, 148.6, 142.2, 135.2, 132.5, 128.9, 122.9, 119.5, 119.4, 116.0, 102.3, 47.7, 48.4. ESIMS (m/z, %): 331 (M^++1, 100). Anal. Calcd for $C_{20}H_{18}N_4O$: C, 72.71%; H, 5.49%; N, 16.96%. Found: C, 72.61%; H, 5.52%; N, 16.80%.

*4.3.13. Synthesis of aminopyrimidines (**24**, **25**).* Guanidine nitrate or benzamidine hydrochloride (0.52 mmol) was added to a stirred suspension of K_2CO_3 (0.138 g, 1 mmol) in acetonitrile (10 mL). After 30 min, arylamino or cycloamino *N*,*S*-acetals **20** or **21** (0.5 mmol) was added and reaction mixture was refluxed for 8–10 h (monitored by TLC). Solvent was evaporated under vacuum; residue was treated with cold water and extracted with ethyl acetate (3×20 mL). Combined organic extract was washed with water (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel using dichloromethane: methanol (99:1) as eluent to yield **24**, **25**.

*4.3.14. Synthesis of 2-amino-4-(4-methoxyphenyl-amino)-indeno [1,2-d]pyrimidin-5-one (**24a**).* Yellow solid, mp 221–222 °C; yield 0.119 g, 75%; R_f=0.45 (DCM/MeOH, 99:2); IR (KBr): 3478, 3351, 3199, 2929, 2927, 1673, 1629, 1561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1H, NH), 7.70–7.48 (m, 6H, ArH), 6.90 (d, J=9.0 Hz, 2H, ArH), 5.51 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.3, 174.1, 165.5, 156.6, 155.6, 136.3, 132.2, 131.2, 130.4, 122.4, 121.8, 121.7, 120.2, 113.4, 98.3, 54.8. ESIMS (m/z, %): 319 (M^++1, 100). Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91%; H, 4.43%; N, 17.60%. Found: C, 67.71%; H, 4.28%; N, 17.81%.

*4.3.15. 2-Amino-4-(3,4-dimethoxyphenylamino)-indeno[1,2-d]pyrimidin-5-one (**24b**).* Dark red solid, mp 248–250 °C; yield 0.130 g, 75%; R_f=0.24 (DCM/MeOH, 99:2); IR (KBr): 3475, 3356, 3201, 2931, 2931, 1678, 1634, 1569, 1069 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.54 (s, 1H, ArH), 7.79 (s, 2H, NH_2), 7.67–7.60 (m, 4H, ArH), 7.49 (s, 1H, NH), 7.24 (d, J=8.1 Hz, 1H, ArH), 6.89 (d, J=8.4 Hz, 1H, ArH), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 188.1, 174.5, 165.8, 156.7, 148.6, 139.6, 136.6, 133.2, 132.2, 131.6,

122.1, 120.7, 113.2, 111.9, 106.6, 55.7, 55.6. ESIMS (*m*/*z*, %): 349 (M^++1, 100). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51%; H, 4.63%; N, 16.08%. Found: C, 65.63%; H, 4.79%; N, 15.91%.

*4.3.16. 2-Amino-4-phenylamino-indeno[1,2-d] pyrimidin-5-one (**24c**).* Yellow crystal, mp 214–215 °C; yield 0.112 g, 78%; R_f=0.49 (DCM/MeOH, 99:1); IR (KBr): 3473, 3297, 3135, 2925, 1690, 1623, 1572, 1436, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H, NH), 7.71–7.66 (m, 4H, ArH), 7.55–7.47 (m, 2H, ArH), 7.39–7.36 (m, 2H, ArH), 7.15–7.10 (m, 1H, ArH), 5.59 (s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.3, 174.8, 165.9, 156.8, 148.6, 139.6, 138.4, 136.6, 133.2, 132.2, 128.7, 123.3, 122.2, 120.9, 120.7, 98.2. ESIMS (*m*/*z*, %): 389 (M^++1, 100). Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82%; H, 4.20%; N, 19.43%. Found: C, 70.65%; H, 4.01%; N, 19.29%.

*4.3.17. 4-(3,4-Dimethoxyphenylamino)-2-phenyl-indeno[1,2-d]pyrimidin-5-one (**24d**).* Violet solid, mp 186–187 °C; yield 0.103 g; 50%; R_f=0.32 (hexane/EtOAc, 80:20); IR (KBr): 2911, 2863, 1699, 1621, 1549 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.59–8.57 (m, 3H, ArH), 7.94 (d, *J*=6.9 Hz, 1H, ArH), 7.73–7.50 (m, 7H, ArH), 6.92 (d, *J*=8.7 Hz, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 173.7, 169.0, 155.4, 148.9, 145.8, 141.3, 137.5, 135.3, 134.0, 132.0, 131.7, 131.4, 130.8, 129.2, 128.8, 128.3, 123.1, 121.7, 112.8, 111.3, 105.8, 104.4, 55.1, 55.9. ESIMS (*m*/*z*, %): 410 (M^++1, 100). Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34%; H, 4.68%; N, 10.26%. Found: C, 73.47%; H, 4.51%; N, 9.97%.

*4.3.18. 2-Amino-4-(4-methylbenzylamino)indeno [1,2-d]pyrimidin-5-one (**24e**).* Yellow solid, mp 238–239 °C; yield 0.094 g, 60%; R_f=0.64 (DCM/MeOH, 99:2); IR (KBr): 3467, 3347, 3303, 3185, 2915, 2925, 2856, 1674, 1635, 1451, 1069 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.60–7.54 (m, 7H, ArH, NH_2, NH), 7.24 (d, *J*=7.8 Hz, 2H, ArH), 7.12 (d, *J*=7.8 Hz, 2H, ArH), 4.62 (d, *J*=6.0 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 188.2, 174.7, 165.9, 158.36, 139.6, 136.7, 136.4, 135.8, 132.8, 131.9, 128.8, 127.4, 121.9, 120.5, 97.7, 42.2, 20.69. ESIMS (*m*/*z*, %): 317 (M^++1, 100). Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13%; H, 5.10%; N, 17.71%. Found: C, 72.27%; H, 5.01%; N, 17.97%.

*4.3.19. 2-Amino-4-(4-phenylpiperazin-1-yl)-indeno[1,2-d]pyrimidin-5-one (**25**).* Yellow solid, mp 180–182 °C; yield 0.133 g, 75%; R_f=0.56 (DCM/MeOH, 99:5); IR (KBr): 3291, 3178, 2921, 2850, 1680, 1628, 1524, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J*=6.3 Hz, 1H, ArH), 7.63 (d, *J*=6.0 Hz, 1H, ArH), 7.49 (dd, *J*=5.7, 5.4 Hz, 2H, ArH), 7.31–7.28 (m, 1H, ArH), 6.96 (d, *J*=8.1 Hz, 2H, ArH), 6.91–6.89 (m, 2H, ArH), 5.33 (s, 2H, NH_2), 4.20 (t, *J*=4.8 Hz, 4H, 2×CH_2), 3.31 (t, *J*=4.8 Hz, 4H, 2×CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 178.1, 164.1, 159.3, 151.0, 139.6, 136.2, 132.9, 132.0, 129.2, 122.5, 120.5, 120.1, 116.3, 100.8, 49.6, 48.1. ESIMS (*m*/*z*, %): 358 (M^++1, 100). Anal. Calcd for $C_{21}H_{19}N_5O$: C, 70.57%; H, 5.36%; N, 19.59%. Found: C, 70.69%; H, 5.11%; N, 19.41%.

*4.3.20. Synthesis of 2,5-dioxo-4-(4-phenyl-piperazin-1-yl)-2,5-dihydro-1H-indeno[1,2-b] pyridine-3-carbonitrile (**26**).* To a stirred suspension of Bu^{t}OK (0.168 g, 1.5 mmol) in Bu^{t}OH (10 mL) at room temperature, cyanoacetamide (0.067 g, 0.5 mmol) was added. After 10 min, *N*,*S*-acetal **21b** (0.182 g, 0.5 mmol) was added and the reaction mixture was refluxed for 12 h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure to give the salt of pyridine **26**, which was dissolved in water (10 mL) followed by acidification with dilute HCl (5 mL, 5%). The solid obtained was filtered, washed with water, and recrystallized from ethanol to give the desired compound **26** as yellow solid, mp >300 °C (decompose). Yield 0.095 g, 50%; IR (KBr): 3451, 2923, 2849, 2343, 1629, 1542, 1431 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 13.31 (s, 1H, OH), 7.91 (d, *J*=6.6 Hz, 1H, ArH), 7.54–7.44 (m, 3H, ArH), 7.18 (dd, *J*=7.5, 7.2 Hz, 2H, ArH), 6.95 (d, *J*=7.8 Hz, 2H, ArH), 6.78–6.73 (m, 1H, ArH), 3.71 (t, *J*=4.2 Hz, 4H, 2×CH_2), 3.30 (t, *J*=4.2 Hz, 4H, 2×CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 185.4, 163.7, 162.5, 158.6, 150.6, 134.4, 134.1, 133.6, 133.3, 129.0, 122.7, 122.1, 119.3, 118.1, 115.7, 103.8, 51.4, 49.0. ESIMS (*m*/*z*, %): 383(M^++1, 100). Anal. Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24%; H, 4.74%; N, 14.65%. Found: C, 72.01%; H, 4.52%; N, 14.80%.

*4.3.21. Synthesis of indenoquinolines (**27a**,**b**).* A mixture of arylamino N,*S*-acetal **20e** or **20b** (0.5 mmol) and PPA (5 g) was heated at 90 °C for 5-6 h (monitored by TLC). The reaction mixture was cooled, neutralized with saturated $NaHCO_3$ solution and extracted with DCM (3×20 mL). The organic layer was washed with water (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. The crude product was purified by crystallization from ethanol to give **27a** and **27b**.

*4.3.22. 3-Methoxy-6-methylthio-indeno[2,1-c] quinolin-7-one (**27a**).* Orange solid, mp 210–211 °C; yield 0.130 g, 85%; R_f=0.36 (hexane/EtOAc, 80:20); IR (KBr): 2915, 2865, 1687, 1625, 1557, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J*=9.3 Hz, 1H, ArH), 8.05 (d, *J*=8.1 Hz, 1H, ArH), 7.74 (d, *J*=6.9 Hz, 1H, ArH), 7.69 (d, *J*=8.4 Hz, 1H, ArH), 7.48–7.46 (m, 1H, ArH), 7.34–7.26 (m, 2H, ArH), 7.22–7.18 (m, 1H, ArH), 4.01 (s, 3H, OCH_3), 2.73 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 163.2, 154.4, 151.3, 149.8, 141.4, 134.3, 133.8, 130.8, 124.4, 123.9, 119.7, 116.2, 107.6, 56.6, 11.8. ESIMS (*m*/*z*, %): 308 (M^++1, 100). Anal. Calcd for $C_{18}H_{13}NO_2S$: C, 70.34%; H, 4.26%; N, 4.56%. Found: C, 70.19%; H, 4.41%; N, 4.39%.

*4.3.23. 2,3-Dimethoxy-6-methylthio-indeno[2,1-c] quinolin-7-one (**27b**).* Orange solid, mp 239–240 °C; yield 0.135 g, 80%; R_f=0.23 (hexane/EtOAc, 80:20); IR (KBr): 2921, 2851, 1697, 1619, 1561, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (dd, *J*=7.5 Hz, 1H, ArH), 7.74 (d, *J*=7.2 Hz, 1H, ArH), 7.59 (d, *J*=7.2 Hz, 1H, ArH), 7.54 (s, 1H, ArH), 7.45 (dd, *J*=7.2 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 4.11 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 2.72 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 163.2, 154.91, 150.4, 149.8, 141.6, 134.5, 133.7, 130.5, 123.9, 123.8, 116.2, 108.1, 102.1, 56.2, 56.0, 11.8. ESIMS (*m*/*z*, %): 338 (M^++1, 100). Anal. Calcd for $C_{19}H_{15}NO_3S$: C, 67.64%; H, 4.48%; N, 4.15%. Found: C, 67.77%; H, 4.55%; N, 4.02%.

*4.3.24. Synthesis of 6-methanesulfonyl derivative of indenoquinolines (**28**).* To a stirred solution of indenoquinoline **27** (0.5 mmol) in dry DCM (10 mL) was added a solution of *m*-CPBA (0.258 g, 1.5 mmol) in dry DCM (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h (monitored by TLC). The reaction was hydrolyzed by adding 5% sodium thiosulfate solution (15 mL). The organic layer was washed with $NaHCO_3$ solution (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product, which was purified by recrystallization from ethanol.

*4.3.25. 6-Methanesulfonyl-3-methoxy-indeno[2,1-c] quinolin-7-one (**28a**).* Yellow solid, mp 223–225 °C (decompose); yield 0.159 g, 94%; IR (KBr): 2910, 2869, 1687, 1598, 1557, 1313 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, *J*=9.3 Hz, 1H, ArH), 8.13 (d, *J*=7.5 Hz, 1H, ArH), 7.82 (d, *J*=7.2 Hz, 1H, ArH), 7.68–7.45 (m, 4H, ArH), 4.03 (s, 3H, OCH_3), 3.54 (s, 3H, SO_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 163.9, 152.2, 151.4, 140.9, 134.7, 132.0, 125.9, 125.0, 124.7, 124.1, 119.7, 113.9, 109.5, 56.0, 40.5. ESIMS (*m*/*z*, %): 340 (M^++1, 100). Anal. Calcd for $C_{18}H_{13}NO_4S$: C, 63.71%; H, 3.86%; N, 4.13%. Found: C, 63.59%; H, 3.61%; N, 4.29%.

*4.3.26. 6-Methanesulfonyl-2,3-dimethoxy-indeno [2,1-c]quinolin-7-one (**28b**).* Yellow solid, mp 320 °C (decompose); yield 0.173 g, 94%; IR (KBr): 2910, 2845, 1692, 1601, 1542, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J*=7.5 Hz, 1H, ArH), 7.79 (d, *J*=7.2 Hz, 1H, ArH), 7.66 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.54–7.50 (m, 2H, ArH),

4.18 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3), 3.53 (s, 3H, SO_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7, 164.0, 152.1, 150.7, 140.8, 134.5, 132.1, 125.9, 125.1, 124.7, 124.2, 119.9, 113.4, 109.7, 56.1, 56.0, 40.4. ESIMS (m/z, %): 370 (M^++1, 100). Anal. Calcd for $C_{19}H_{15}NO_5S$: C, 61.78%; H, 4.09%; N, 3.79%. Found: C, 61.56%; H, 4.21%; N, 3.91%.

*4.3.27. Synthesis of amino substituted indenoquinolines (**29**).* A mixture of 6-(methylsulfonyl)quinolines **28** (0.5 mmol) and the corresponding aliphatic/sec amine (2.0 mmol) was heated at 140–150 °C in a sealed tube for 3–4 h with constant stirring. After the completion of the reaction (monitored by TLC), reaction mixture was then cooled, diluted with DCM (20 mL), and washed with water (2×25 mL) followed by brine (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the crude products **29**, which were purified by column chromatography over silica gel using DCM as eluent.

*4.3.28. 2,3-Dimethoxy-6-(4-phenyl-piperidin-1-yl)-benzo[c]fluoren-7-one (**29a**).* Deep red solid; yield 0.142 g, 63%; R_f=0.51 (DCM); IR (KBr): 3010, 2945, 1699, 1623, 1541, 1342 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J=7.2 Hz, 1H, ArH), 7.71–6.94 (m, 2H, ArH), 7.54 (s, 1H, ArH), 7.46–7.41 (m, 1H, ArH), 7.17 (s, 1H, ArH), 7.03 (d, J=8.4 Hz, 2H, ArH), 6.90–6.87 (m, 2H, ArH), 4.08 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.81 (t, J=4.8 Hz, 4H, 2×NCH_2), 3.46 (t, J=4.6 Hz, 4H, 2×NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.5, 170.2, 155.7, 149.5, 147.3, 143.6, 139.7, 133.2, 131.9, 129.6, 128.2, 126.7, 119.1, 117.3, 113.5, 109.3, 57.3, 56.4, 56.3, 53.2. ESIMS (m/z, %): 452 (M^++1, 100). Anal. Calcd for $C_{28}H_{25}N_3O_3$: C, 74.48%; H, 5.58%; N, 9.31%. Found: C, 74.51%; H, 5.39%; N, 9.09%.

*4.3.29. 6-Butylamino-2,3-dimethoxy benzo[c]fluoren-7-one (**29b**).* Deep red solid; yield 0.121 g, 67%; R_f=0.54 (DCM); IR (KBr): 2930, 2865, 1687, 1612, 1555, 1345 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.56 (s, 1H, NH), 7.97 (d, J=7.5 Hz, 1H, ArH), 7.75 (d, J=7.2 Hz, 1H, ArH), 7.56 (s, 1H, ArH), 7.44–7.40 (m, 2H, ArH), 7.14 (s, 1H, ArH), 4.09 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 3.42 (q, J=7.08 Hz, 2H, CH_2), 1.52–1.59 (m, 2H, CH_2), 1.29–1.38 (m, 2H, CH_2), 0.86 (t, J=7.32 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.4, 164.1, 155.3, 148.3, 146.8, 143.7, 139.0, 132.2, 131.0, 129.1, 116.3, 106.3, 56.4, 56.5, 49.5, 34.5, 20.0, 13.6. ESIMS (m/z, %): 363 (M^++1, 100). Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91%; H, 6.12%; N, 7.73%. Found: C, 72.81%; H, 6.31%; N, 7.58%.

*4.3.30. Synthesis of 10,11-dimethoxy-5,7,8-triaza-benzo[a]aceanthrylen-6-ylamine (**30**).* A mixture of 4-arylaminopyrimidine **24b** (0.174 g, 0.5 mmol) and PPA (5 g) was heated at 90 °C for 5 h (monitored by TLC). The reaction mixture was cooled, neutralized with saturated $NaHCO_3$ solution, and extracted using DCM (3×20 mL). The organic layer was washed with water (2×20 mL), brine (1×20 mL), and dried over anhydrous Na_2SO_4. The crude product was purified by recrystallization from ethanol to give **30** as dark red solid. Yield 0.115 g, 70%; IR (KBr): 3341, 3244, 2980, 2945, 1542, 1433, 1078 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.39 (d, J=7.5 Hz, 1H, ArH), 7.95 (d, J=7.2 Hz, 1H, ArH), 7.67–7.54 (m, 5H, ArH+NH_2), 7.34 (s, 1H, ArH), 4.07 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.5, 155.7, 153.9, 151.2, 148.3, 145.9, 135.3, 133.2, 129.7, 128.3, 127.8, 127.3, 125.6, 110.4, 108.4, 58.5, 58.3. ESIMS (m/z, %): 331 (M^++1, 100). Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08%; H, 4.27%; N, 16.96%. Found: C, 69.23%; H, 4.42%; N, 16.79%.

Acknowledgements

This work was carried out under financial support from Council of Scientific and Industrial Research (Grant 01(2260)/08/EMR-II) and Department of Science and Technology (Grant SR/S1/OC-66/2009), New Delhi. R.K.V. is grateful to Council of Scientific and Industrial Research (CSIR), New Delhi for senior research fellowship.

Supplementary data

Supplementary data associated with this article can be found online version at doi:10.1016/j.tet.2010.07.031.

References and notes

1. (a) Nugiel, D. A.; Vidwans, A.; Etzkorn, A. M.; Rossi, K. A.; Benfield, P. A.; Burton, C. R.; Cox, S.; Doleniak, D.; Seitz, S. P. *J. Med. Chem.* **2002**, *45*, 5224–5232; (b) Yue, E. W.; Higley, C. A.; DiMeo, S. V.; Carini, D. J.; Nugiel, D. A.; Benware, C.; Benfield, P. A.; Burton, C. R.; Cox, S.; Grafstrom, R. H.; Sharp, D. M.; Sisk, L. M.; Boylan, J. F.; Muckelbauer, J. K.; Smallwood, A. M.; Chen, H.; Chang, C.-H.; Seitz, S. P.; Trainor, G. L. *J. Med. Chem.* **2002**, *45*, 5233–5248; (c) Nugiel, D. A.; Etzkorn, A.-M.; Vidwans, A.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Cox, S.; Czerniak, P. M.; Doleniak, D.; Seitz, S. P. *J. Med. Chem.* **2001**, *44*, 1334–1336; (d) Usui, T.; Ban, H. S.; Kawada, J.; Hirokawa, T.; Nakamura, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 285–288; (e) Yue, E. W.; DiMeo, S. V.; Higley, C. A.; Markwalder, J. A.; Burton, C. R.; Benfield, P. A.; Grafstrom, R. H.; Cox, S.; Muckelbauer, J. K.; Smallwood, A. M.; Chen, H.; Cheng, C.-H.; Trainor, G. L.; Seitz, S. P. *Biorg. Med. Chem. Lett.* **2004**, *14*, 343–346.
2. Tao, Z.-F.; Li, G.; Tong, Y.; Stewart, K. D.; Chen, Z.; Bui, M.-H.; Merta, P.; Park, C.; Kover, P.; Zhang, H.; Sham, H. L.; Rosenberg, S. H.; Sowin, T. J.; Lin, N.-H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5944–5951.
3. Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett.* **2005**, *46*, 7615–7618 and references there.
4. (a) Flores, M.C.; Loev, B. U.S. Patent 2,989,538, 1961; (b) Loev, B.; Mosher, Wm. A. U.S. Patent 2,969,374, 1961.
5. (a) Ryckebusch, A.; Garcin, D.; Lansiaux, A.; Goossens, J.-F.; Baldeyrou, B.; Houssin, R.; Bailly, C.; Henichart, J.-P. *J. Med. Chem.* **2008**, *51*, 3617–3629 and references there; (b) Tseng, C.-H.; Chen, Y.-L.; Lu, P.-J.; Yang, C.-N.; Tzeng, C.-C. *Bioorg. Med. Chem.* **2008**, *16*, 3153–3162 and references there.
6. Carotti, A.; Catto, M.; Leonetti, F.; Campagna, F.; Soto-Otero, R.; Mendez-Alvarez, E.; Thull, U.; Tesla, B.; Altomare, C. *J. Med. Chem.* **2007**, *50*, 5364–5371.
7. (a) Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M.; Mosti, L. *Bioorg. Med. Chem.* **2003**, *11*, 4749–4759; (b) Matasi, J. J.; Caldwell, J. P.; Hao, J.; Neustadt, B.; Arik, L.; Foster, C. J.; Lachowicz, J.; Tuishian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1333–1336.
8. (a) Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. *Tetrahedron Lett.* **2005**, *46*, 1233–1236; (b) Ewen, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 4763–4773.
9. (a) Review: Ila, H.; Jujappa, H.; Mohanta, P. K. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 2001; Chapter 1, pp 1–24 (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506; Recent Papers; (c) Kumar, S.; Ila, H.; Junjappa, H. *Tetrahedron* **2007**, *63*, 10067–10076 and references there; (d) Mishra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246–1251 and references there; (e) Yadav, A. K.; Yadav, S. K. S.; Siddiqui, I.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Synlett* **2008**, 2674–2680; (f) Singh, P. P.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 5496–5501.
10. (a) Augustin, M.; Grath, C.; Kristen, H.; Peseke, K.; Wiechmann, C. *J. Prakt. Chem.* **1979**, *321*, 205–214; (b) Mashraqui, S. H.; Hariharasubramaniam, H. *J. Chem. Res. Synop.* **1999**, 492–493.
11. Tominaga, Y.; Fujito, H.; Norisue, H.; Ushirogochi, A.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1980**, *100*, 699–705.
12. (a) Tominaga, Y.; Norisue, H.; Matsuda, Y.; Kobayashi, G. *Yakugaku Zasshi* **1984**, *104*, 127–133; (b) Tominaga, Y.; Norisue, H.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 2910–2914; (c) Tominaga, Y.; Sakai, S.; Kohra, S.; Tsuka, J.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1985**, *33*, 962–970; (d) Ried, W.; Jacobi, M. A. *Chem. Ber.* **1988**, *121*, 805–808.
13. Crystal data for **7**: $C_{17}H_{12}N_2OS$, yellow, M=292.36, monoclinic, space group P 21/n, a=7.2869(2), b=19.8570(5), c=19.5674(5) Å, V=2828.89(13) Å^3, μ=0.228 mm^{-1}, Z=8, T=293 K, F_{000}=1216.0, R=0.0471, wR^2=0.1127. The CCDC deposition number: CCDC 777778.
14. (a) Peruncheralathan, S.; Khan, T. A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 10030–10035; (b) Purkayastha, M. L.; Ila, H.; Junjappa, H. *Synthesis* **1989**, 20–24.
15. (a) Bhat, L. N.; Thomas, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1992**, *48*, 10377–10388; (b) Thomas, A.; Singh, G.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1989**, *30*, 3093–3096.
16. (a) Chauhan, S. M. S.; Junjappa, H. *Synthesis* **1974**, 880–882; (b) Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779–1787.
17. (a) Rastogi, R. R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 549–553; (b) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. *J. Am. Chem. Soc.* **1981**, *103*, 3585–3586.
18. Barun, O.; Patra, P. K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1999**, *40*, 3797–3800.
19. (a) Chauhan, S. M. S.; Junjappa, H. *Synthesis* **1975**, 798–801; (b) Vishwakarma, J. N.; Chowdhury, B. K. R.; Ila, H.; Junjappa, H. *Ind. J. Chem.* **1985**, *24B*, 472–476; (c) Peruncheralathan, S.; Yadav, A. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2005**, *70*, 9644–9647.
20. (a) Kumar, A.; Aggarawal, V.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 748–751; (b) Vishwakarma, J. N.; Apparao, S.; Ila, H.; Junjappa, H. *Ind. J. Chem.* **1985**, *24B*, 466–471.
21. Aggarwal, V.; Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 214–216.
22. For quinoline synthesis from ketene dithioacetal and *N,S*-acetal, see: (a) Panda, K.; Siddiqui, I.; Mahata, P. K.; Ila, H.; Junjappa, H. *Synlett* **2004**, 449–452; (b) Mahata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966–3975.