ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 4, pp. 686–696. © Pleiades Publishing, Ltd., 2020.

Synthesis and Anti-Proliferative Activity of Novel Tricyclic Compounds Derived from 2-Substituted 1,3-Indandione

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Received July 16, 2019; revised February 8, 2020; accepted March 24, 2020

Abstract—A new series of fused 1,3-indandione derivatives has been synthesized and evaluated for anti-proliferative activity. 2-Alkene-1,3-indandione derivatives have been used as the precursors of a number of tricyclic compounds. The latter have been tested for anti-proliferative activity.

Keywords: 1,3-indandione, anti-proliferative, p38αMAPK and ERK1/2 protein kinases, molecular modeling

DOI: 10.1134/S1070363220040209

INTRODUCTION

Indenone scaffold fused with different heterocycles has been identified as a promising anticancer molecular system. Indenopyrazoles, indenopyrimidines and indeno[1,2-*c*]isoquinoline have received much attention as anti-cancer agents due to their broad spectrum of kinase inhibition such as platelet-derived growth factor receptor inhibitors (PDGFR), CDK inhibitors and tubulin polymerization inhibitors [1–4].

In the current study the newly synthesized indenone derivatives were tested for their *in vitro* antiproliferative activities, kinase inhibition activity. Molecular modeling was carried out for their molecular structures.

RESULTS AND DISCUSSION

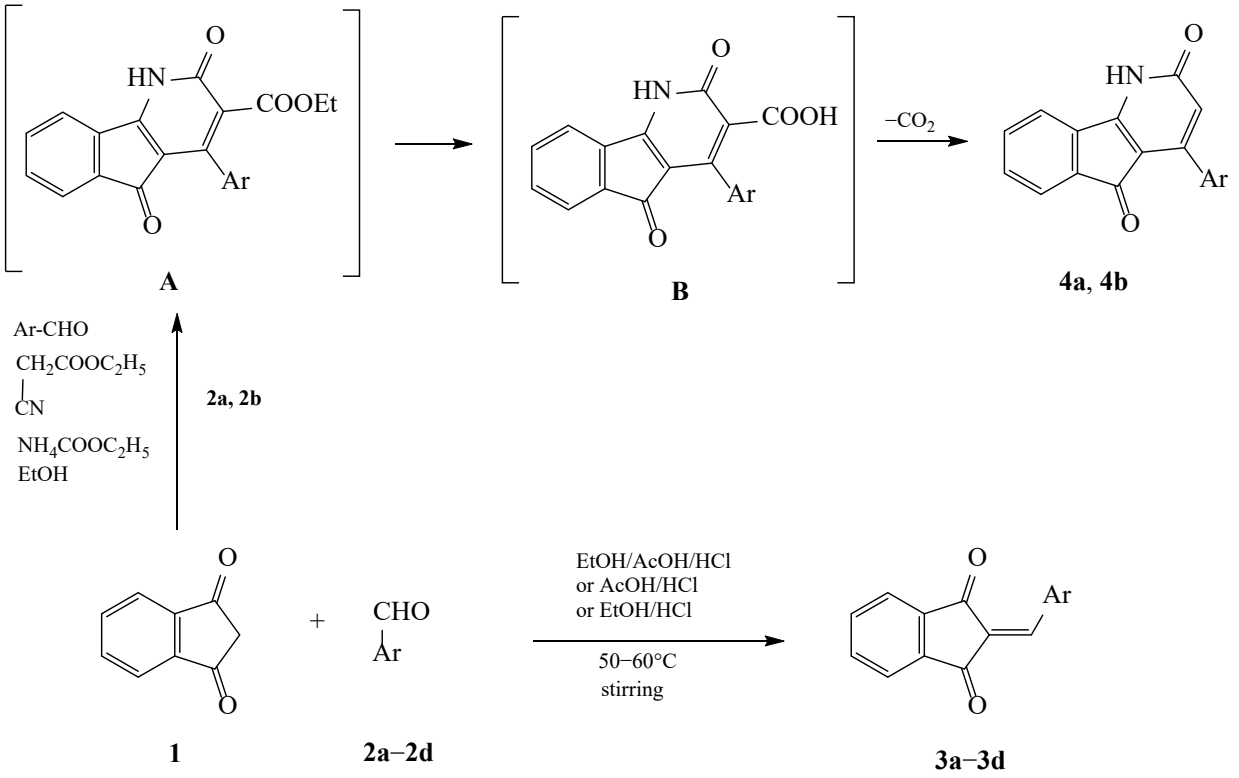
1,3-Indandione (**1**) reacted with aromatic aldehydes **2a**–**2d** at 50–60°C giving the corresponding 2-substituted derivatives **3a**–**3d**. One-pot reaction of 1,3-indandione **1** with ethylcyanoacetate and aromatic aldehydes **2a**, **2b** in the presence of anhydrous ammonium acetate proceeded via intermediates **A** and **B** affording 2-pyridinone derivatives **4a**, **4b** [5] (Scheme 1).

Reaction of arylidineindanedione **3a** and **3b** with hydrazine hydrate in ethanol [6] or in glacial acetic acid [7] gave indenopyrazole derivatives **5a**, **5b** and **6**. Also, compounds **3a**, **3b** reacted with 2,4-dinitrophenylhydrazine or phenyl hydrazine to give the corresponding arylindenopyrazole derivatives **7a**, **7b**. Reaction of compounds **3a**, **3b**, **3d** with semicarbazide or thiosemicarbazide [8] led to amide or thioamide derivatives **8a**–**8d**. The precursors **3a**–**3c** reacted with hydroxylamine hydrochloride to give the respective oxazole derivatives **9a**–**9c** (Scheme 2).

2-Substituted indene-1,3-diones **3a**, **3b** reacted with ethylcyanoacetate [7] to give indenocyanopyridone derivatives **10a**, **10b**, respectively. Reaction of the same precursors **3a**, **3b** with malononitrile [8–10] gave the corresponding derivatives **11a**–**11d**, **12a**, **12b** and **13a**, **13b** (Scheme 3).

Anti-proliferative activity. Anti-proliferative activity of compounds **4**–**13** was tested against breast, leukemia, lung, melanoma, and prostate carcinoma cell lines. Growth inhibitory activity of the screened compounds was evaluated using the MTT method [11] and sorafenib as a reference (Table 1). All compounds exhibited considerably potent anti-proliferative activity against breast (MCF-7 and T47D), leukemia (K-562), lung (A-549), melanoma (MDA-MB-435), and prostate carcinoma (PC-3) cell lines. The compounds **11a** and **11c** displayed the highest potency.

Scheme 1. Synthetic routes for compounds **3a**–**3d** and **4a, 4b**.



3: Ar = 2,5(MeO)$_2$C$_6$H$_3$ (**a**), 3-MeOC$_6$H$_4$ (**b**); 2-NO$_2$-4-Cl-C$_6$H$_3$ (**c**), 5-methylfuryl (**d**);
4: Ar = 2,5-(MeO)$_2$C$_6$H$_3$ (**a**), 3-MeOC$_6$H$_4$ (**b**).

According to the accumulated data the compounds bearing 2,5-dimethoxyphenyl substituents demonstrated higher activity than those with 3-methoxyphenyl substituent.

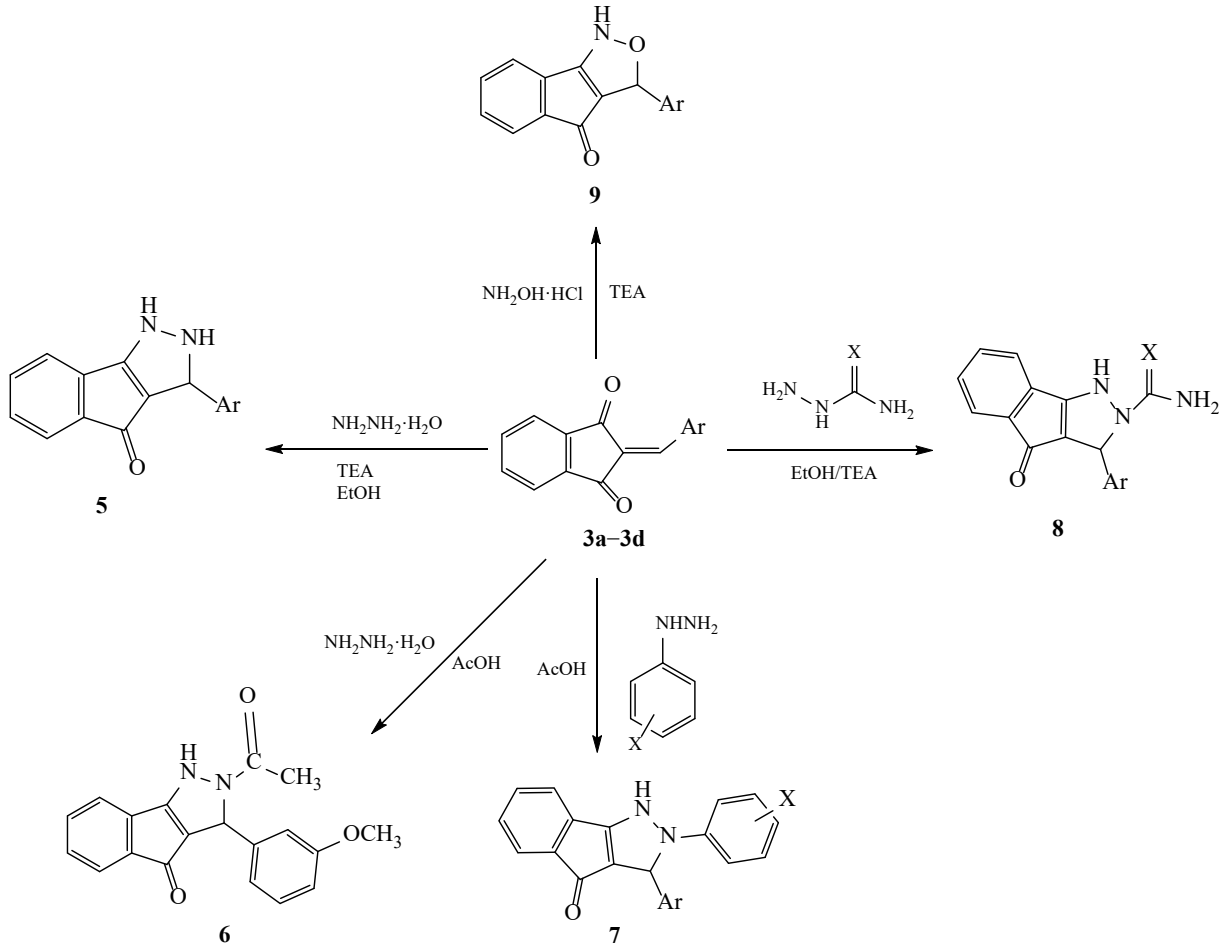
In vitro kinase inhibitory activity. The newly synthesized compounds **4**–**13** were tested against p38αMAPK and ERK1/2 protein kinases using Lantha Screen Kinase activity assay kits (Invitrogen), and sorafenib was used as a reference drug (Table 2). All tested compounds exhibited high inhibitory activity against ERK2 (IC_{50} range = 5.43–22.00 μM) in comparison with sorafenib (IC_{50} = 109.5 μM), while their activity against p38αMAPK and ERK1 kinases ranged from moderate to excellent.

It is evident that fusion of 1,3-indandione with five- or six-membered rings improved inhibitory activity of the compounds against p38αMAPK and ERK1/2 kinases.

Molecular modeling. Docking studies were performed to explore the potential binding modes of the top potent compounds **11a** and **11c** in the ATP-active sites of p38αMAPK, ERK1, and ERK2 kinases (PDB codes: 3ITZ, 4QTB and 5K4I, respectively) [12–14] using Molecular Operating Environment (MOE, 10.2008) software [15]. Water molecules were removed, and preparation of the receptor for docking study using Protonate 3D protocol was carried out. Self-docking of the original ligands P66, 38Z and 6QB with the corresponding p38αMAPK, ERK1 and ERK2 receptors was initially carried out to assess the performance of MOE in predicting the ligand–receptor binding modes. The self-docking calculations indicated excellent performance with RMSD values of 0.92, 0.80, and 0.85 Å, respectively (Fig. 1).

The docking approach indicated that 5-oxoindeno[1,2-*b*]-pyridine-3-carbonitrile skeleton was housed in the ATP regions of p38αMAPK, ERK1 and ERK2 via a favorable and effective mechanism, and was assisted by hydrogen bonding using its oxygen and cyano nitrogen atoms. Introduction of the 2,5-dimethoxyphenyl group resulted in improvement of the binding affinity to the target protein receptors via hydrogen bonding or hydrophobic interactions.

Scheme 2. Synthetic routes for compounds **5a**, **5b**, **6**, **7a**, **7b**, **8a**–**8d**, and **9a**–**9c.**



5: Ar = 3-MeOPh (**a**), 5-methylfuran-2-yl (**b**); **8**: Ar = 2,5-MeO_2Ph,X=O (**a**), 3-MeOPh,X =O (**b**), 4-Cl-3-NO_2Ph, X = O (**c**), 2,5-MeO_2Ph, X = S (**d**); **9**: Ar = 2,5-MeO_2Ph (**a**), 3-MeOPh (**b**), 5-methylfuran-2-yl (**c**); **7**: Ar = 2,5-MeO_2Ph, X = 2,4-di-NO_2 (**a**), 3-MeOPh; X = H (**b**).

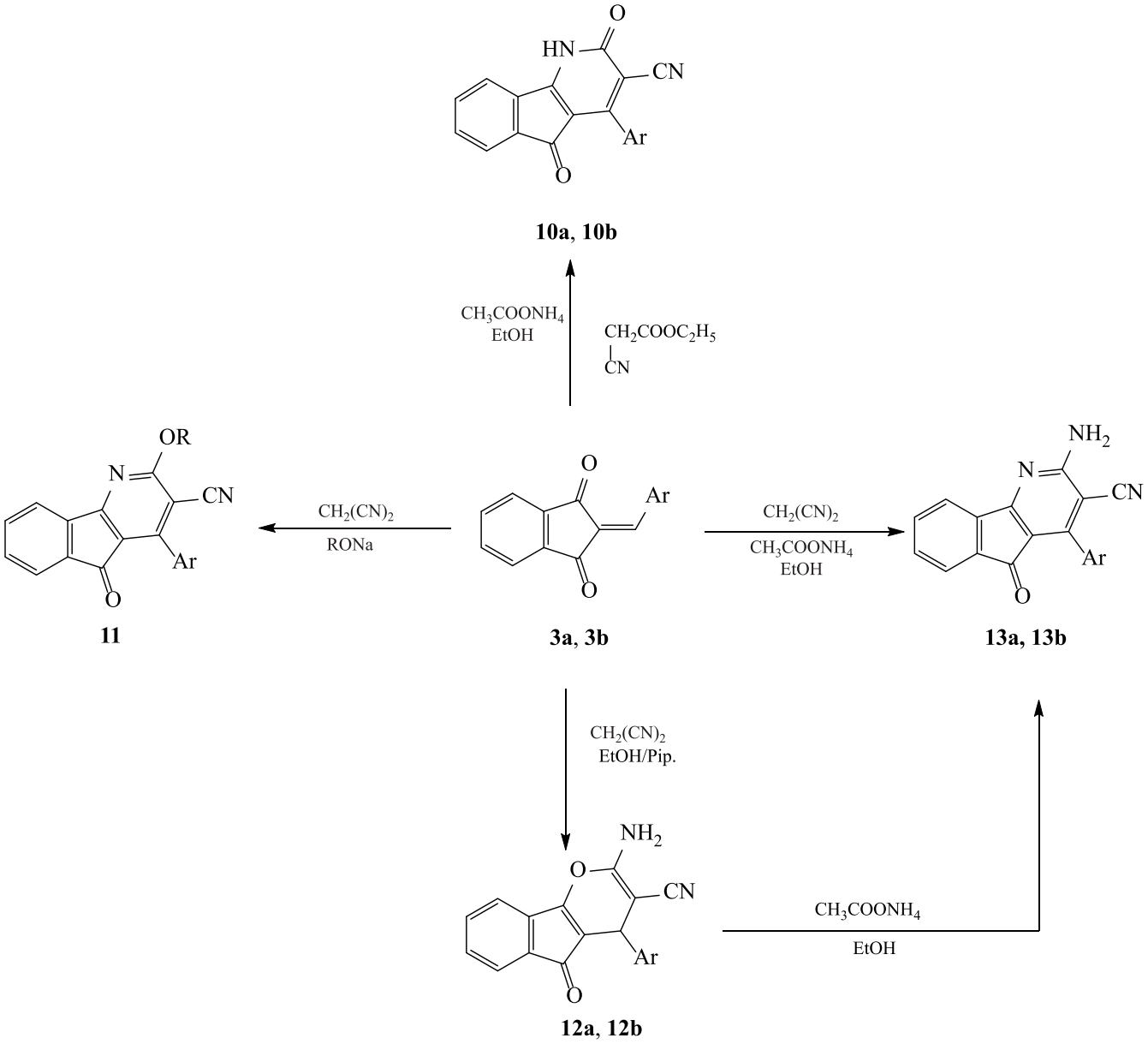
EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. IR spectra (KBr discs) were recorded on a Pye Unicam SP 3300 and Shimadzu FT-IR 8101 PCinfrared spectrophotometers. NMR spectra were measured on a Varian Mercury VX-300 NMR spectrometer using $CDCl_3$ or DMSO-d_6 as solvents Mass spectra were measured on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out on an Elementar-Vario EL at the Micro-Analytical Centre of Cairo University, Giza, Egypt. 2-Arylidine-2H-indene-1,3-diones were prepared according to the reported earlier method [5].

Synthesis of 2-substituted benzylidene-2*H*-indene-1,3-diones (3a–3d). A mixture of absolute ethanol with glacial acetic acid and concentrated hydrochloric acid (30 mL, 1 : 1 : 1), or glacial acetic acid with concentrated hydrochloric acid (20 mL, 1 : 1), or absolute ethanol with concentrated hydrochloric acid (20 mL, 1 : 1), 1,3-indandione (1 mmol) and appropriate aldehyde (1 mmol) was stirred at 50–60°C for 15, 20 or 30 min. The solid products formed were filtratered off, dried and recrystallized from ethanol to give the corresponding compounds **3a–3d**.

2-(2,5-Dimethoxybenzylidene)-2*H*-indene-1,3-dione (3a). Yields 99, 92, 84%; mp 127–129°C (EtOH). IR spectrum, ν, cm^{-1}: 1718 (C=O), 1676 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.92 s, 3.89 s (6H, $2OCH_3$), 7. 15–8.18 m (7H, Ar-H), 8.82 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 55.61, 56.15, 111.26, 114.54, 115.36, 115.70, 126.82, 128.86, 135.26, 141.10, 140.40, 151.44, 152.45,

Scheme 3. Synthetic routes for compounds **10a**, **10b**, **11a**–**11d**, **12a**, **12b**, and **13a**, **13b**.



Ar = 2,5-MeO_2Ph (**10a**, **11a**, **11c**, **12a**, **13a**), 3-MeOPh (**10b**, **11b**, **11d**, **12b**, **13b**); R = Me (**11a**, **11b**), Et (**11c**, **11d**).

190.80. MS: *m/z*: 294 $[M]^+$. Found, %: C 73.43; H 4.81. $C_{18}H_{14}O_4$ (294.31). Calculated, %: C 73.46; H 4.80.

2-(3-Methoxybenzylidene)-2*H*-indene-1,3-dione (3b). Yields 98, 93, 86%; mp 153–155°C (EtOH). IR spectrum, ν, cm^{-1}: 1720 (C=O), 1685 (C=O). ^1H NMR spectrum, δ, ppm: 3.76 s (3H, OCH_3), 7.04 s (1H, Ar-H), 7.65–8.00 m (7H, Ar-H), 8.56 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 55.61, 113.15, 113.50, 120.09, 126.88, 129.39, 135.22, 136.47, 140.38, 142.86, 147.06, 160.54, 190.85. MS: *m/z*: 264 $[M]^+$. Found, %: C 77.28; H 4.56; N 4.45. $C_{17}H_{12}O_3$ (264.29). Calculated, %: C 77.26; H 4.57; N 4.47.

2-(4-Chloro-3-nitrobenzylidene)-2*H*-indene-1,3-dione (3c). Yields 97, 91, 88%; mp 222–224°C (EtOH). IR spectrum, ν, cm^{-1}: 1729 (C=O), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 7.91–8.64 m (7H, Ar-H), 9.27 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 124.70, 126.82, 128.36, 128.76, 132.54, 134.45, 135.26, 135.86, 140.40, 146.44, 150.10, 190.80. MS: *m/z*: 313 $[M]^+$. Found, %: C

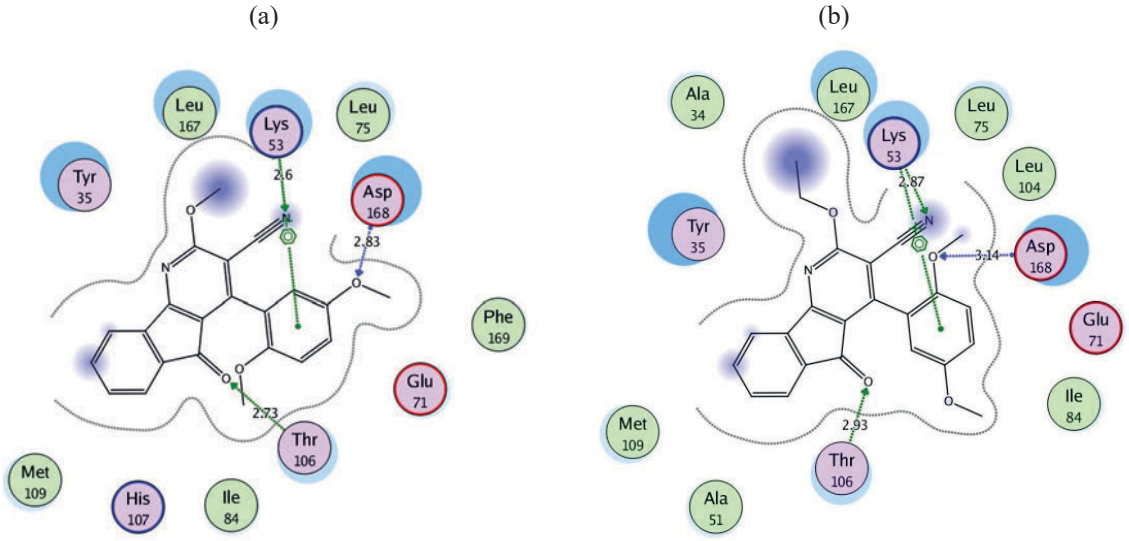


Fig. 1. 2D docking poses of compounds (a) **11a** and (b) **11c.**

61.28; H 2.56; Cl 11.33; N 4.48. $C_{16}H_8ClNO_4$ (313.69). Calculated, %: C 61.26; H 2.57; Cl 11.30; N 4.47.

2-[(5-Methylfuran-2-yl)methylene]-1*H*-indene-1,3(2*H*)-dione (3d). Yields 96, 90, 85%; mp 242–244°C (EtOH). IR spectrum, ν, cm^{-1}: 1729 (C=O), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 6.80–7.85 m (6H, Ar-H), 7.94 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 13.65, 109.34, 120.42, 126.85, 135.26, 140.46, 142.80, 147.52, 148.90, 157.54, 190.62. MS: *m/z:* 238 $[M]^+$. Found, %: C 75.55; H 4.16. $C_{15}H_{10}O_3$ (238.24). Calculated, %: C 75.62; H 4.23.

Synthesis of compounds 4a, 4b. A mixture of a compound **3a** or **3b** (1 mmol) with ethyl cyanoacetate (1 mmol) and ammonium acetate (2 mmol) in absolute ethanol (50 mL) was refluxed for 5 h. The obtained precipitate was filtered off, dried and recrystallized from ethanol to give the corresponding pure compounds **4a**, **4b**.

4-(2,5-Dimethoxyphenyl)-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (4a). Yield 83%, mp 124–126°C. IR spectrum, ν, cm^{-1}: 3386 (NH), 1715 (C=O), 1617 (C=O). ^1H NMR spectrum, δ, ppm: 3.78 s, 3.81 s (6H, $2OCH_3$), 7.12 s (1H, CH), 6.88–8.03 m (7H, Ar-H), 8.84 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.42, 56.12, 111.32, 114.00, 115.08, 115.90, 120.40, 123.14, 126.13, 127.46, 131.28, 132.10, 133.40, 135.24, 136.12, 138.55, 149.55, 152.16, 161.76, 190.40. MS: *m/z:* 333 $[M]^+$. Found, %: C 72.09; H 4.53; N 4.22. $C_{20}H_{15}NO_4$ (333.30). Calculated, %: C 72.06; H 4.54; N 4.20.

4-(3-Methoxyphenyl)-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (4b). Yield 88%, mp 85–87°C (EtOH). IR spectrum, ν, cm^{-1}: 3428 (NH), 1706 (C=O), 1619 (C=O). ^1H NMR spectrum, δ, ppm: 3.85 s (3H, OCH_3), 7.11 s (1H, CH), 7.41–7.89 m (8H, Ar-H), 8.73 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.61, 110.55, 114.39, 115.00, 121.32, 123.06, 126.10, 127.40, 129.16, 131.25, 132.15, 133.40, 133.45, 135.06, 136.04, 138.80, 158.90, 162.06, 190.43. MS: *m/z:* 303 $[M]^+$. Found, %: C 75.21; H 4.32; N 4.65. $C_{19}H_{13}NO_3$ (303.31). Calculated, %: C 75.24; H 4.32; N 4.62.

Synthesis of compounds 5a and 5b. To a mixture of a certain compound **3a**, **3b** (1 mmol) with hydrazine hydrate (1 mmol) in absolute ethanol (20 mL), few drops of TEA were added. The reaction mixture was refluxed for 2 h. The precipitate was cooled down to room temperature, acidified with few drops of dilute HCl, filtered off, washed with water, dried, and recrystallized from ethanol to give the corresponding pure compounds **5a**, **5b**.

3-(3-Methoxyphenyl)-2.3-dihydoindino[1,2-*c*]-pyrazol-4(1*H*)-one (5a). Yield 80%, mp 278–280°C. IR spectrum, ν, cm^{-1}: 3347 (NH), 3203 (NH), 1637 (C=O). ^1H NMR spectrum, δ, ppm: 3.48 s (3H, OCH_3), 4.36 s (1H, NH, D_2O exchangeable), 6.61 s (1H, NH, D_2O exchangeable), 7.39 s (1H, CH), 7.38–8.39 m (8H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 55.32, 65.60, 106.34, 110.76, 112.40, 118.54, 123.12, 126.45, 128.36, 129.34, 133.96, 135.08, 136.12, 145.00, 154.90, 160.15, 192.12. MS: *m/z:* 278 $[M]^+$. Found, %: C 73.38; H 5.09; N 10.06.

Table 1. Anti-proliferative activity of the synthesized compounds **4**–**13** against breast, leukemia, lung, melanoma, prostate cancerous cell lines

Compound	IC_{50}[a] (mean ± SEM), μM					
	Breast		Leukemia	Lung	Melanoma	Prostate
	MCF-7	T47D	K-562	A-549	MDA-MB-435	PC-3
Sorafenib	0.78±0.05	0.61±0.04	1.22±0.01	3.19±0.03	1.67±0.01	4.13±0.03
4a	4.12±0.06	4.00±0.04	4.67±0.03	8.78±0.08	8.32±0.09	9.45± 0.06
4b	4.22±0.05	4.01±0.05	4.88±0.03	8.23± 0.09	8.45± 0.09	9.89±0.06
5a	3.90±0.06	3.89±0.05	3.19±0.02	8.34±0.08	7.24±0.08	8.54±0.05
5b	3.98±0.07	3.90±0.06	4.45±0.03	8.56±0.08	7.56±0.08	9.32± 0.06
6	3.88±0.04	3.78±0.05	3.12±0.03	8.12±0.07	6.90±0.07	8.65±0.05
7a	3.55±0.06	3.55±0.04	2.67±0.03	7.12±0.07	5.89±0.06	8.43±0.05
7b	3.78±0.05	3.67± 0.05	2.89±0.02	7.32±0.08	6.24±0.07	8.46±0.05
8a	2.67±0.06	3.12±0.03	2.10±0.02	6.14±0.06	4.34±0.05	7.46±0.04
8b	3.12±0.06	3.22±0.03	2.10±0.03	6.35±0.07	4.56±0.05	8.21±0.05
8c	3.20±0.10	3.34±0.21	2.27±0.23	6.60±0.01	4.83±0.02	8.30±0.10
8d	3.46±0.05	3.45± 0.04	2.44±0.03	6.89±0.06	5.23±0.06	8.43±0.05
9a	3.83±0.12	3.54±0.21	3.21±0.15	7.94±0.20	6.83±0.10	8.74±0.13
9b	3.95±0.04	3.71±0.03	3.44±0.20	8.17±0.41	6.99±0.11	8.96±0.25
9c	4.15±0.02	3.88±0.10	3.97±0.04	8.32±0.01	7.25±0.20	9.22±0.01
10a	2.45±0.05	3.00±0.02	1.78±0.02	5.99±0.05	3.90±0.04	7.34±0.04
10b	2.34±0.04	2.99±0.02	1.77±0.02	5.77±0.04	3.67±0.00	7.12±0.04
11a	1.34±0.05	1.78±0.02	1.16±0.02	4.67±0.04	3.45±0.04	6.89±0.03
11b	1.76±0.01	2.36±0.01	1.47±0.41	4.96±0.08	3.95±0.12	7.11±0.15
11c	1.22±0.06	1.55±0.02	1.10±0.01	4.43±0.03	2.45±0.04	6.78±0.03
11d	1.48±0.22	1.60±0.10	1.26±0.15	4.77±0.13	2.87±0.02	6.90±0.24
12a	2.77±0.03	2.92±0.11	1.45±0.05	5.52±0.20	3.62±0.21	7.22±0.02
12b	3.20±0.16	3.16±0.15	1.82±0.03	5.77±0.31	3.90±0.05	7.65±0.13
13a	1.86±0.12	1.95±0.23	1.33±0.15	4.92±0.10	2.89±0.10	7.04±0.26
13b	2.05±0.20	2.30±0.06	1.39±0.20	5.18±0.42	3.22±0.52	7.50±0.15

[a] IC_{50} values were calculated as mean values of three separate experiments.

$C_{17}H_{14}N_2O_2$ (278.29). Calculated, %: C 73.37; H 5.07; N 10.07.

3-(5-Methylfuran-2-yl)-2.3-dihydoindino[1,2-*c*]-pyrazol-4(1*H*)-one (5b). Yield 82%, mp 116–118°C. IR spectrum, ν, cm^{-1}: 3423 (NH), 3206 (NH), 1633 (C=O). ^1H NMR spectrum, δ, ppm: 1.45 s (3H, CH_3), 5.31 s (1H, NH, D_2O exchangeable), 6.41 s (1H, NH, D_2O exchangeable), 7.16 s (1H, CH), 7.37–7.95 m (6H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 13.65, 63.75, 106.15, 106.42, 107.21, 123.15, 126.40, 128.38, 133.90, 135.12, 136.16, 150.48, 150.50, 154.85, 192.10. MS: *m/z:* 252 $[M]^+$. Found, %: C 71.43; H 4.81; N 11.11. $C_{15}H_{12}N_2O_2$ (252.27). Calculated, %: C 71.42; H 4.79; N 11.10.

2-Acetyl-3-(3-methoxyphenyl)-2.3-dihydoindino-[1,2-*c*]pyrazol-4(1*H*)-one (6). A mixture of compound **3b** (1 mmol) with hydrazine hydrate (1 mmol) in glacial acetic acid (20 mL) was refluxed for 3 h, then cooled down to room temperature and poured into ice water mixture. The precipitated solid was filtered off, washed with water, dried, and recrystallized from ethanol to give the pure compound **6**. Yield 82%, mp 107–109°C. IR spectrum, ν, cm^{-1}: 3222 (NH), 1693 (C=O), 1658 (C=O). ^1H NMR spectrum, δ, ppm: 1.83 s (3H, CH_3), 3.78 s (3H, OCH_3), 6.27 s (1H, CH), 6.78–8.27 m (8H, Ar-H), 9.65 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.32, 64.60, 106.04, 110.72, 112.30, 118.50, 123.10, 123.15, 126.40, 128.42, 129.38, 133.90, 134.80, 136.02, 144.86, 154.65, 161.00, 169.65, 191.85. MS: *m/z:* 320

Table 2. IC_{50}values (μM) of the compounds **4**–**13** tested against p38αMAPK and ERK1/2 kinases

Compound	IC_{50}[a]±SEM, μM		
	P38αMAPK	ERK1	ERK2
Sorafenib	37.40 ± 3.54	18.10 ± 1.64	109.50 ± 9.80
4a	50.11±0.47	26.78±0.56	21.00±0.81
4b	53.56±0.56	27.27±0.47	22.00±0.84
5a	43.56±0.47	24.39±0.59	19.09±0.71
5b	47.77±0.36	25.67±0.58	20.12±0.74
6	42.45±0.26	22.34±0.40	18.90±0.52
7a	37.89±0.28	19.94±0.38	16.78±0.32
7b	40.19±0.37	20.30±0.49	17.89±0.45
8a	30.11±0.38	13.56±0.26	9.67±0.60
8b	34.56±0.39	18.56±0.37	11.23±0.50
8c	37.23±0.23	19.02±0.14	13.48±0.061
8d	45.67±0.40	19.90±0.27	14.34±0.42
9a	40.27±0.2	21.43±0.02	16.52±0.31
9b	43.47±0.10	22.61±0.21	17.04±0.54
9c	44.28±0.14	24.01±0.32	19.23±0.20
10a	25.01±0.26	10.23±0.24	7.64±0.50
10b	27.00±0.27	11.45±0.25	8.76±0.41
11a	24.56±0.34	9.98±0.13	6.53±0.63
11b	25.33±0.02	10.72±0.05	7.22±0.30
11c	22.16±0.43	9.34±0.14	5.43±0.52
11d	22.81±0.30	9.77±0.16	5.98±0.20
12a	30.22±0.18	13.04±0.04	9.36±0.34
12b	32.26±0.04	14.98±0.30	11.71±0.03
13a	26.53±0.30	11.87±0.21	8.92±0.02
13b	28.12±0.26	12.06±0.03	9.06±0.21

[a] IC_{50} values were calculated as the mean values of three separate experiments.

$[M]^+$. Found, %: C 71.26; H 5.05; N 8.71. $C_{19}H_{16}N_2O_3$ (320.34). Calculated, %: C 71.24; H 5.03; N 8.74.

Synthesis of compounds 7a and **7b.** A mixture of compound **3a** (1 mmol) with 2.4-dinitrophenylhydrazine (1 mmol) or **3b** (1 mmol) with phenylhydrazine (1 mmol) in glacial acetic acid (20 mL) was refluxed for 2 h. Thus obtained precipitate was filtered off, dried and recrystallized from dioxane to give the corresponding pure compounds **7a**, **7b**.

2,3-Dihydro-3-(2,5-dimethoxyphenyl)-1-(2,4-dinitrophenyl)indeno[1,2-*c*]pyrazol-4(1*H*)-one (7a). Yield 92%, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3287 (NH), 1685 (C=O). ^1H NMR spectrum, δ, ppm: 3.88 s, 3.91 s (6H, $2OCH_3$), 7.04 s (1H, CH), 7.14–8.96 m (10H, Ar-H), 11.77 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.42, 56.20, 66.64, 106.22, 111.85, 112.00, 113.42, 115.16, 120.02, 122.08, 123.25, 126.30, 128.36, 130.15, 133.80, 134.76, 134.78, 136.15, 139.50, 143.68, 148.45, 152.66, 154.64, 191.92. MS: *m/z:* 474 $[M]^+$. Found, %: C 60.75; H 383; N 11.82. $C_{24}H_{18}N_4O_7$ (474.42). Calculated, %: C 60.76; H 3.82; N 11.81.

2,3-Dihydro-3-(3-methoxyphenyl)-1-phenyl-indeno[1,2-*c*]pyrazol-4(1*H*)-one (7b). Yield 82%, mp 96–98°C. IR spectrum, ν, cm^{-1}: 3448 (NH), 1708 (C=O). ^1H NMR spectrum, δ, ppm: 3.79 s (3H, OCH_3), 5.93 s (1H, CH), 6.68–8.28 m (13H, Ar-H), 10.39 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.36, 73.60, 106.15, 110.78, 112.42, 113.52, 118.45, 122.56, 123.15, 126.36, 128.40, 129.02, 129.42, 133.84, 134.74, 136.14, 144.80, 151.65, 154.60, 161.08, 191.90. MS: *m/z:* 354 $[M]^+$. Found, %: C 77.96; H 5.14; N 7.92. $C_{23}H_{18}N_2O_2$ (354.40). Calculated, %: C 77.95; H 5.12; N 7.90.

Synthesis of compounds 8a–8d. A mixture of a compound **3a**–**3c** (1 mmol) with semicarbazide (1 mmol) or **3a** (1 mmol) with thiosemicarbazide (1 mmol) in absolute ethanol (30 mL) and TEA (10 mL) was refluxed for 3–5 h then poured into ice water mixture. Thus obtained solid was filtered off, washed with water, dried,

and recrystallized from ethanol to give the corresponding pure compounds **8a–8d**.

3-(2,5-Dimethoxyphenyl)-4-oxoindeno[1,2-*c*]-pyrazole-2(1*H*,3*H*,4*H*)carboxamide (8a). Yield 85%, mp 265–268°C. IR spectrum, ν, cm^{-1}: 3448 (NH), 3256 (NH_2), 1718 (C=O), 1679 (C=O). ^1H NMR spectrum, δ, ppm: 3.35 s, 3.40 s (6H, $2OCH_3$), 4.45 s (1H, CH), 6.64 s (2H, NH_2, D_2O exchangeable), 7.55–8.15 m (7H, Ar-H), 9.67 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.45, 56.08, 60.24, 106.36, 111.28, 112.52, 113.08, 122.15, 123.16, 126.34, 128.18, 133.85, 135.18, 136.10, 148.50, 152.80, 155.10, 159.13, 191.86. MS: *m/z:* 351 $[M]^+$. Found, %: C 64.97; H 4.89; N 11.97. $C_{19}H_{17}N_3O_4$ (351.36). Calculated, %: C 64.95; H 4.88; N 11.96.

3-(3-Methoxyphenyl)-4-oxoindeno[1,2-*c*]pyrazole-2(1*H*,3*H*,4*H*)-carboxamide (8b). Yield 88%, mp 280–283°C. IR spectrum, ν, cm^{-1}: 3392 (NH), 3181 (NH_2), 1710 (C=O), 1643 (C=O). ^1H NMR spectrum, δ, ppm: 3.36 s (3H, OCH_3), 3.82 s (1H, CH), 6.62 s (2H, NH_2, D_2O exchangeable), 7.55–8.13 m (8H, Ar-H), 9.67 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.30, 65.62, 106.30, 111.56, 112.32, 119.25, 123.02, 126.40, 128.16, 129.80, 133.90, 135.12, 136.18, 144.10, 155.12, 159.00, 160.18, 191.80. MS: *m/z:* 321 $[M]^+$. Found, %: C 67.29; H 71.01; N 13.10. $C_{18}H_{15}N_3O_3$ (321.33). Calculated, %: C 67.28; H 71.00; N 13.08.

3-(4-Chloro-3-nitrophenyl)-4-oxoindeno[1,2-*c*]-pyrazole-2(1*H*,3*H*,4*H*)carboxamide (8c). Yield 94%, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3461 (NH), 3168 (NH_2), 1710 (C=O), 1681 (C=O). ^1H NMR spectrum, δ, ppm: 4.36 s (1H, CH), 6.67 s (2H, NH_2, D_2O exchangeable), 7.58–8.52 m (7H, Ar-H), 10.52 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 65.10, 106.32, 123.08, 124.56, 125.32, 126.40, 128.16, 132.12, 132.80, 133.90, 135.14, 136.10, 142.10, 147.18, 155.15, 159.00, 191.84. MS: *m/z:* 370 $[M]^+$. Found, %: C 55.06; H 3.00; Cl 9.58; N 15.13. $C_{17}H_{11}ClN_4O_4$ (370.75). Calculated, %: C 55.07; H 2.99; Cl 9.56; N 15.11.

3-(2,5-Dimethoxyphenyl)-4-oxoindeno[1,2-*c*]-pyrazole-2(1*H*,3*H*,4*H*)-carbothioamide (8d). Yield 77%, mp 181–183°C. IR spectrum, ν, cm^{-1}: 3433 (NH), 3316 (NH_2), 1716 (C=O), 1684 (C=O). ^1H NMR spectrum, δ, ppm: 3.51 s (1H, CH), 3.78 s, 3.76 s (6H, $2OCH_3$), 6.94 s (2H, NH_2, D_2O exchangeable), 7.01–8.34 m (7H, Ar-H), 11.41 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.46, 56.08, 65.24, 106.32, 111.34, 112.50, 113.08, 122.16, 123.10, 126.30, 128.22, 133.80, 135.12, 136.15, 148.44, 153.00, 155.12, 159.16, 191.74. MS: *m/z:* 367 $[M]^+$. Found, %: C 62.12; H 4.68; N 11.45; S, 874. $C_{19}H_{17}N_3O_3S$ (367.42). Calculated, %: C 62.11; H 4.66; N 11.44; S, 873.

Synthesis of compounds 9a–9c. A mixture of a compound **3a**–**3c** (1 mmol) with hydroxylamine hydrochloride (1 mmol) in absolute ethanol (30 mL) and TEA (10 mL) was refluxed for 5 h, then poured into acidified ice water. The solid formed was filtered off, washed with water, dried, and recrystallized from ethanol to give the corresponding pure products **9a**–**9c**.

3-(2,5-Dimethoxyphenyl)-1,3-dihydro-4*H*-indeno-[1,2-*c*]isoxazol-4-one (9a). Yield 77%, mp 244–246°C. IR spectrum, ν, cm^{-1}: 3425 (NH), 1715 (C=O). ^1H NMR spectrum, δ, ppm: 3.78 s, 3.90 s (6H, $2OCH_3$), 6.75 s (1H, CH), 6.80–8.40 m (7H, Ar-H), 9.01 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.48, 56.00, 78.68, 109.14, 112.00, 112.34, 114.14, 123.13, 126.42, 128.32, 129.00, 133.93, 135.13, 136.10, 148.86, 153.54, 154.80, 192.22. MS: *m/z:* 309 $[M]^+$. Found, %: C 69.91; H 4.90; N 4.52. $C_{18}H_{15}NO_4$ (309.32). Calculated, %: C 69.89; H 4.89; N 4.53.

3-(3-Methoxyphenyl)-1,3-dihydro-4*H*-indeno-[1,2-*c*]isoxazol-4-one (9b). Yield 78%, mp 263–264°C. IR spectrum, ν, cm^{-1}: 3407 (NH), 1720 (C=O). ^1H NMR spectrum, δ, ppm: 3.78 s (3H, OCH_3), 6.99 s (1H, CH), 7.01–8.69 m (8H, Ar-H), 12.77 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.45, 84.68, 109.14, 111.00, 113.14, 119.42, 123.10, 126.40, 128.30, 129.54, 133.90, 135.10, 136.16, 142.25, 154.86, 160.34, 192.24. MS: *m/z:* 279 $[M]^+$. Found, %: C 73.13; H 4.70; N 5.03. $C_{17}H_{13}NO_3$ (279.29). Calculated, %: C 73.11; H 4.69; N 5.02.

3-(5-Methylfuran-2-yl)-1,3-dihydro-4*H*-indeno-[1,2-*c*]isoxazol-4-one (9c). Yield 81%, mp 112–114°C. IR spectrum, ν, cm^{-1}: 3259 (NH), 1685 (C=O). ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 6.50 s (1H, CH), 7.37–8.61 m (6H, Ar-H), 12.49 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 13.60, 83.98, 106.22, 109.33, 109.52, 123.17, 126.45, 128.42, 133.96, 135.18, 136.18, 152.24, 152.34, 154.80, 192.15. MS: *m/z:* 253 $[M]^+$. Found, %: C 71.13; H 4.40; N 5.54. $C_{15}H_{11}NO_3$ (253.25). Calculated, %: C 71.14; H 4.38; N 5.53.

Synthesis of compounds 10a, 10b. A mixture of a compound **3a** or **3b** (1 mmol) with ethyl cyanoacetate (1 mmol) and anhydrous ammonium acetate (2 g) in absolute ethanol (40 mL) was refluxed for 2 h. Thus formed precipitate was filtered off, dried and

recrystallized from ethanol to give the corresponding pure compounds **10a**, **10b**.

2,5-Dihydro-2,5-dioxo-4-(2,5-dimethoxyphenyl)-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (10a). Yield 86%, mp 124–126°C. IR spectrum, ν, cm^{-1}: 3351 (NH), 2224 (CN), 1716 (C=O), 1642 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.86 s, 3.88 s (6H, $2OCH_3$), 6.85–8.55 m (7H, Ar-H), 14.45 br. s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.79, 56.89, 110.98, 111.00, 114.20, 115.00, 115.48, 115.95, 120.90, 123.46, 126.27, 128.40, 134.06, 135.94, 136.76, 138.04, 149.83, 152.54, 159.42, 169.10, 190.94. MS: *m/z:* 358 $[M]^+$. Found, %: C 70.40; H 4.96; N 7.83. $C_{21}H_{14}N_2O_4$ (358.35). Calculated, %: C 70.39; H 3.94; N 7.82.

2,5-Dihydro-2,5-dioxo-4-(3-methoxyphenyl)-1*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (10b). Yield 81%, mp 183-185°C.IR spectrum, ν, cm^{-1}: 3448 (NH), 2223 (CN), 1704 (C=O), 1646 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 7.07–8.05 m (8H, Ar-H), 9.25 s (1H, NH, D_2O exchangeable). ^{13}C NMR spectrum, δ, ppm: 55.66, 110.72, 110.90, 113.44, 115.05, 115.78, 121.12, 123.46, 126.27, 128.44, 129.50, 133.75, 134.14, 135.90, 136.70, 138.00, 159.42, 160.48, 169.17, 190.86. MS: *m/z:* 328 $[M]^+$. Found, %: C 73.17; H 3.70; N 7.51. $C_{20}H_{12}N_2O_3$ (328.32). Calculated, %: C 73.16; H 3.68; N 8.53.

Synthesis of compounds 11a–11d. A mixture of a compound **3a** or **3b** (1 mmol) with malononitrile (1 mmol) and sodium methoxide or sodium ethoxide was refluxed for 3 h. Thus formed precipitate was filtered off, dried and recrystallized from dioxane to give the corresponding pure compounds **11a**–**11d**.

4-(2,5-Dimethoxyphenyl)-2-methoxy-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (11a). Yield 78%, mp > 300°C. IR spectrum, ν, cm^{-1}: 2252 (CN), 1646 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.71 s, 3.72 s (6H, $2OCH_3$), 3.79 s (3H, OCH_3), 6.63–8.47 m (7H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 53.50, 55.45, 56.00, 92.20, 112.10, 112.48, 114.16, 115.75, 116.46, 121.24, 123.86, 127.26, 128.00, 133.08, 134.12, 142.90, 149.46, 153.04, 157.10, 166.42, 168.16, 192.45. MS: *m/z:* 372 $[M]^+$. Found, %: C 70.94; H 4.35; N 7.49. $C_{22}H_{16}N_2O_4$ (372.11). Calculated, %: C 70.96; H 4.33; N 7.52.

2-Methoxy-4-(3-methoxyphenyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (11b). Yield 79%, mp 293–295°C. IR spectrum, ν, cm^{-1}: 2237 (CN), 1649 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.36 s (3H, OCH_3), 3.78 s (3H, OCH_3), 6.64–8.42 m (8H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 53.56, 55.46, 92.26, 113.36, 114.12, 114.45, 116.45, 119.60, 121.25, 123.85, 127.25, 130.00, 133.12, 134.18, 138.96, 142.86, 157.10, 160.88, 166.40, 168.10, 192.40. MS: *m/z:* 342 $[M]^+$. Found, %: C 73.65; H 4.11; N 8.19. $C_{21}H_{14}N_2O_3$ (342.10). Calculated, %: C 73.68; H 4.12; N 8.18.

2-Ethoxy-4-(2,5-dimethoxyphenyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (11c). Yield 76%, mp 271–273°C. IR spectrum, ν, cm^{-1}: 2238 (CN), 1646 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, CH_3, J = 16 Hz), 3.72 s, 3.74 s (6H, $2OCH_3$), 4.44 q (2H, CH_2, J = 16 Hz), 6.66–8.49 m (7H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 14.76, 55.48, 56.04, 63.56, 92.20, 112.10, 112.45, 114.18, 115.70, 116.40, 121.20, 123.80, 127.28, 128.00, 133.10, 134.16, 142.79, 149.40, 153.12, 157.15, 166.42, 168.18, 192.32. MS: *m/z:* 386 $[M]^+$. Found, %: C 71.48; H 4.68; N 7.26. $C_{23}H_{18}N_2O_4$ (386.41). Calculated, %: C 71.49; H 4.70; N 7.25.

2-Ethoxy-4-(3-methoxyphenyl)-5-oxo-5*H*-indeno-[1,2-*b*]pyridine-3-carbonitrile (11d). Yield 80%, mp 264–266°C. IR spectrum, ν, cm^{-1}: 2364 (CN), 1656 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, CH_3), 3.66 s (3H, OCH_3), 4.45 q (2H, CH_2), 6.42–8.44 m (8H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 14.70, 55.58, 64.00, 92.20, 113.42, 114.18, 114.30, 116.40, 119.50, 121.22, 123.81, 127.24, 130.05, 133.12, 134.25, 138.56, 142.68, 157.17, 161.00, 166.48, 168.08, 192.18. MS: *m/z:* 356 (M^+), 354 $[M-2]^+$. Found, %: C 74.18; H 4.54; N 7.83. $C_{22}H_{16}N_2O_3$ (356.37). Calculated, %: C 74.15; H 4.53; N 7.86.

Synthesis of compounds 12a and 12b. A mixture of a compound **3a** or **3b** (1 mmol) with malononitrile (1 mmol), absolute ethanol (20 mL) and few drops of piperidine was stirred for 4 h and poured into ice water mixture. The precipitate was filtered off, dried and recrystallized from ethanol to give the corresponding pure compounds **12a**, **12b**.

2-Amino-4,5-dihydro-4-(2,5-dimethoxyphenyl)-5-oxo-indeno[1,2-*b*]pyran-3-carbonitrile (12a). Yield 78%, mp 114–115°C. IR spectrum, ν, cm^{-1}: 3343, 3210 (NH_2), 2206 (CN), 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.50 s (1H, CH), 3.80 s, 3.82 s (6H, $2OCH_3$), 5.38 s (2H, NH_2, D_2O exchangeable), 6.68–7.93 m (7H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 32.86, 55.18, 56.34, 58.15, 102.86, 112.00, 112.15, 114.32, 119.12, 122.14, 123.12, 126.04, 128.10, 134.15, 136.10, 137.56, 150.80, 152.60, 159.65, 170.80, 191.86. MS: *m/z:* 360 $[M]^+$. Found, %: C 70.01; H 4.50; N 7.76. $C_{21}H_{16}N_2O_4$ (360.36). Calculated, %: C 69.99; H 4.48; N 7.77.

2-Amino-4,5-dihydro-4-(3-methoxyphenyl)-5-oxoindeno[1,2-*b*]pyran-3-carbonitrile (12b). Yield 76%, mp 93–95°C. IR spectrum, ν, cm^{-1}: 3432 (NH_2), 2205 (CN), 1743 (C=O). ^1H NMR spectrum, δ, ppm: 3.70 s (1H, CH), 3.88 s (3H, OCH_3), 4.44 s (2H, NH_2, D_2O exchangeable), 6.68–8.01 m (8H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 42.80, 55.38, 57.92, 102.50, 111.15, 113.80, 119.12, 120.30, 123.16, 126.08, 128.00, 129.00, 134.12, 136.00, 137.52, 142.22, 159.60, 160.00, 170.45, 191.80. MS: *m/z:* 330 $[M]^+$. Found, %: C 72.73; H 4.29; N 8.50. $C_{20}H_{14}N_2O_3$ (330.34). Calculated, %: C 72.72; H 4.27; N 8.48.

Synthesis of compounds 13a and 13b. *a.* A mixture of a compound **3a** or **3b** (1 mmol) with malononitrile (1 mmol) and anhydrous ammonium acetate (1 g) in absolute ethanol (30 mL) was refluxed for 3 h. The precipitate was filtered off, dried and recrystallized from the proper solvent to give the corresponding pure compounds **13a**, **13b**.

b. A mixture of a compound **12a** or **12b** (1 mmol) with anhydrous ammonium acetate (1 g) in absolute ethanol (30 mL) was refluxed for 2 h, the precipitate was filtered off, dried and recrystallized from the proper solvent to give the corresponding pure compounds **13a**, **13b**.

2-Amino-4-(2,5-dimethoxyphenyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile (13a). Yield 79%, mp > 300°C (dioxane). IR spectrum, ν, cm^{-1}: 3397, 3342 (NH_2), 2215 (CN), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 3.73 s, 3.67 s (6H, $2OCH_3$), 6.91 s (2H, NH_2, D_2O exchangeable), 7.12–8.19 m (7H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 55.34, 56.18, 85.15, 111.86, 112.45, 113.15, 114.15, 117.56, 121.12, 123.16, 127.12, 128.04, 133.10, 134.08, 142.75, 148.14, 152.80, 156.90, 164.65, 167.98, 191.34. MS: *m/z:* 357 $[M]^+$. Found, %: C 70.59; H 4.25; N 11.77. $C_{21}H_{15}N_3O_3$ (357.36). Calculated, %: C 70.58; H 4.23; N 11.76.

2-Amino-4-(3-methoxyphenyl)-5-oxo-5*H*-indeno-[1,2-*b*]pyridine-3-carbonitrile (13b). Yield 83%, mp 284–286°C (EtOH). IR spectrum, ν, cm^{-1}: 3440, 3399, 3338, 3237 (NH_2), 2215 (CN), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 3.81 s (3H, OCH_3), 7.35 s (2H, NH_2, D_2O exchangeable), 7.56–8.39 m (8H, Ar-H). ^{13}C NMR spectrum, δ, ppm: 55.62, 85.00, 113.23, 113.35, 114.34, 117.50, 119.80, 121.16, 123.15, 127.16, 130.80, 133.24, 134.12, 138.43, 142.79, 156.74, 160.65, 164.60, 167.84, 192.00. MS: *m/z:* 327 $[M]^+$. Found, %: C 73.40; H 4.01; N 12.85. $C_{20}H_{13}N_3O_2$ (327.34). Calculated, %: C 73.38; H 4.00; N 12.84.

ACKNOWLEDGMENTS

Authors are grateful to King Saud University for funding the work through Researchers Supporting Project (project no. RSP-2019/66).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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