SYNTHESIS AND ANTIOXIDANT ACTIVITIES OF SOME NOVEL INDANE-AMIDE SUBSTITUTED PYRAZOLE, PYRIMIDINE, PYRIDINE AND 2-PYRONE DERIVATIVES

Khaled S. Mohamed1* and Elsherbiny H. El-Sayed2

1Engineering Chemistry Department, Higher Institute for Engineering and Technology, New Damietta, Egypt. E-mail: Khaled_samirm@yahoo.com
2Department of Chemistry, Faculty of Science, Port Said University, 42526 Port Said, Egypt. E-mail: Saeed201691@yahoo.com

Abstract – 2-Cyano-N-(2,3-dihydro-1H-5-indenyl)-3-(dimethylamino)acrylamide (3) was used in synthetic paths to some novel indane-amide containing pyrazole, pyrimidine, fused pyrimidines, fused pyridines and 2-pyrones by reaction of 3 with various reagents. The newly synthesized compounds were investigated for their antioxidant activity. Some of the tested compounds exposed auspicious activities.

INTRODUCTION
Neuroprotective activity of aminoindane has a great attention because of its biological activity towards Alzheimer's disease or stroke.1 Also, acrylamide are privileged structures, which attracted significant attention in the designing of biologically active molecules.2-8 It's investigated and exhibited the various biological and pharmaceutical activities like antitumor,9 antimicrobial,10,11 analgesic, and anti-inflammatory drugs.12 On the other hand, chromene derivatives has a great interest in the field of synthetic and medicinal chemistry, and displayed a lot of bioactivity such as bactericides,13-16 fungicides,17 anti-inflammatory,18-19 anticoagulant,20 anti-HIV therapy,21 dyes,22 and antitumor agents.23 In this context, join the fused heterocyclic compound and indane moiety through a carboxamide linkage has been investigated. In view of the aforementioned findings, and as a continuation of our effort to identify new candidates that may be valuable in designing new, potent, selective, and antioxidant agents,24-32 we report herein a facile synthesis of novel fused heterocyclic compounds and the evaluation of their antioxidant agents. This combination was considered to study the biological significance to the target molecules. Based on the reported antioxidant activities of amides,33,34 we report here synthesis and
antioxidant activities of some novel indane-amide with the expectation to develop a novel antioxidant compounds.

RESULTS AND DISCUSSION
Our starting point is to synthesis 2-cyano-N-(2,3-dihydro-1H-inden-5-yl)-3-(dimethylamino)acrylamide (3) as starting compound for the synthesis of novel fused heterocyclic compounds that can possess awaited biological activity. So, treatment of 2,3-dihydro-1H-inden-5-amine with pyrazole derivative 1 in dioxane afforded the cyanoacetyl derivative 2, which gave the desired acrylamide derivative 3 on its reaction with DMF-DMA in dry xylene (Scheme 1). The structures of 2 and 3 were confirmed based on its analytical and spectral data. Thus, $^1$H-NMR spectrum of compound 2 revealed three singlet signals at $\delta$ 3.52, 7.38 and 7.68 ppm attributed to CH$_2$CN, CH-Ar and NH protons, respectively. On the other hand, $^1$H-NMR spectrum of compound 3 revealed four singlet signals at $\delta$ 3.21, 3.36, 7.55 and 7.85 ppm owing to two methyl, vinylic CH and NH protons, respectively.

![Scheme 1](image)

Treatment of acrylamide 3 with bidentate nucleophiles such as hydrazine hydrate and guanidine hydrochloride afforded the pyrazole and pyrimidine derivatives 4 and 5, respectively (Scheme 2). The reaction was proceeded initially by aza-Michael reaction followed by loss of Me$_2$NH molecule and finally cycloaddition reaction to give products 4 and 5.

![Scheme 2](image)
The IR spectra of compounds 4 and 5 showed absence of any absorption peaks due to nitrile group, in addition $^1$H-NMR spectra of compounds 4 and 5 devoid two singlet signals of Me$_2$N present in compound 3, which authorize that CN and NMe$_2$ groups were involved in the cyclization reaction. Moreover, $^1$H-NMR spectra of compounds 4 and 5 supported their structures by providing a singlet signal (D$_2$O exchangeable) at $\delta$ 6.57 due to NH$_2$ in compound 4 and two singlet signals (D$_2$O exchangeable) at $\delta$ 6.48, 6.86 ppm corresponding to two NH$_2$ groups in structure 5. Treatment of compound 3 with heterocyclic amines 6, 8 and 11 in refluxing acetic acid furnished fused pyrimidine derivatives 7, 10 and 12, respectively (Scheme 3). The role of acidic medium of formation of compounds 7, 10 and 12 is protonation of oxygen of carbonyl group in compound 3, which increase electrophilic character of double bond towards aza-Michael addition of amines.

Reaction of 3 with 3-amino-1,2,4-triazine (8) can occur in two pathways to afford possibly isomeric structures 9 and 10. If double bond character in amine 8 present between C$_3$-N$_4$, the formed product will be compound 9, while if double bond character in amine 8 present between N$_2$-C$_3$, the formed product will be compound 10. X-Ray study of compound 8$^{15}$ showed the existence of double bond character between N$_2$-C$_3$ in compound 8 that support formation of isomeric structure 10 and not 9. The analytical and
spectral data for the compounds 7, 10 and 12 were in covenant with the suggested structures. A detailed mechanism of formation of compound 7 was shown in Scheme 4.

On the other hand, when the acrylamide 3 was reacted with 2-benzothiazolylacetonitrile (13a) or 2-benzoimidazolylacetonitrile (13b) in refluxing glacial ethanoic acid yielded pyrido[2,1-b]benzothiazole (16a) and pyrido[1,2-a]benzimidazole (16b) derivatives, respectively (Scheme 5).
The reaction of 3 with compounds 13a,b can lead to three possible structures 14a,b, 15a,b or 16a,b. Compounds 14a,b and 15a,b could be formed if the geometry of double bond is Z in which NH in suitable situation for cycloaddition reaction on CN group in 14a,b or cyclocondensation reaction of NH with carbonyl group to form 15a,b. The Z configuration of double in intermediate I or II is not favored due to highly steric effect. Formation of 16a,b confirm that configuration of double bond in intermediate II should be E configuration. IR spectra of reaction products confirmed structure 16a,b and ruled out structures 14a,b and 15a,b by providing two absorption peaks for two amidic carbonyl groups. Also, absence of any singlet signal for NH2 in 1H-NMR spectra of reaction products excluded structure 14a,b. In addition, reaction product of 3 with 13b displayed two singlet signals (D2O exchangeable) for two NH groups to confirm structure 16b and reject structure 15a,b. Interaction of 3 with 1,3-dicarbonyl compounds namely; acetylacetone, 1,3-indanedione, barbituric acid and thiobarbituric acid in glacial acetic acid offered the 2-pyrone derivatives 17, 18 and 20a,b, respectively (Scheme 6).

Scheme 6

The formation of compounds 17, 18, 20a,b was assumed via Michael addition of enolic form of 1,3-dicarbonyl compounds to the activated double bond in compound 3 followed by intramolecular nucleophilic cycloaddition reaction of enolic OH to CN function to form the imino intermediate that converted into finally 2-pyrone by loss of dimethylamine and hydrolysis of imino to carbonyl group.
Formation of δ-lactone in structures 17, 18 and 20a,b was supported from their IR spectra, which provided stretching frequencies of lactone carbonyl in the region of 1713-1720 cm\(^{-1}\). Moreover, \(^1\)H-NMR spectra of compounds 17, 18 and 20a,b gave more substantiation of their structures by offering singlet signal in the region of δ 8.41-8.64 ppm attributed to C\(_4\)-H of 2-pyrone ring. The mass spectra of compounds 17, 18 and 20a,b provided molecular ion peaks coincide with their anticipated structures. Similarly, pyrano[2,3-c]pyrazole derivative 22 and coumarin derivative 23 were synthesized by reaction of 3 with pyrazolone derivative 21 and resorcinol in refluxing glacial acetic acid, respectively (Scheme 7).

![Scheme 7](image)

The formation of compounds 22 and 23 was proceeded via similar mechanism of compounds 17, 18 and 20a,b. Spectroscopic data of compounds 22 and 23 were obtained in covenant with their proposed structures.

**ANTIOXIDANT ACTIVITY**

The newly synthesized compounds were evaluated for antioxidant activity by ABTS method\(^{36}\) using ascorbic acid as the standard drug. The results described in Table 1 exhibited that compounds 7, 16a and 23 provided high antioxidant activities compared with the control (ascorbic acid), the antioxidant potency otherwise, compounds 4, 5, 12, 17, 18, 20b and 22 disclosed moderate inhibition range of 54.88–78.71%, while other compounds displayed low antioxidant activity with percentage inhibition 19.33–42.18%. The inhibition ratio (%) was calculated using the following formula:

\[
\% \text{ Inhibition} = \left( \frac{A_{\text{control}} - A_{\text{test}}}{A_{\text{control}}} \right) \times 100
\]
Table 1. Inhibition % values of the antioxidant activity of the tested compounds

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Absorbance of samples</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of ABTS</td>
<td>0.512</td>
<td>0.0</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>0.059</td>
<td>88.47</td>
</tr>
<tr>
<td>4</td>
<td>0.118</td>
<td>76.95</td>
</tr>
<tr>
<td>5</td>
<td>0.109</td>
<td>78.71</td>
</tr>
<tr>
<td>7</td>
<td>0.079</td>
<td>84.57</td>
</tr>
<tr>
<td>10</td>
<td>0.396</td>
<td>22.65</td>
</tr>
<tr>
<td>12</td>
<td>0.187</td>
<td>63.47</td>
</tr>
<tr>
<td>16a</td>
<td>0.081</td>
<td>84.17</td>
</tr>
<tr>
<td>16b</td>
<td>0.296</td>
<td>42.18</td>
</tr>
<tr>
<td>17</td>
<td>0.135</td>
<td>73.63</td>
</tr>
<tr>
<td>18</td>
<td>0.126</td>
<td>75.39</td>
</tr>
<tr>
<td>20a</td>
<td>0.394</td>
<td>23.04</td>
</tr>
<tr>
<td>20b</td>
<td>0.210</td>
<td>58.98</td>
</tr>
<tr>
<td>22</td>
<td>0.231</td>
<td>54.88</td>
</tr>
<tr>
<td>23</td>
<td>0.068</td>
<td>86.71</td>
</tr>
</tbody>
</table>

% Inhibition = \( \frac{A_{\text{control}} - A_{\text{test}}}{A_{\text{control}}} \times 100 \)

Acontrol: Absorbance for ascorbic acid
Atest: Absorbance for the tested samples
Control: Ascorbic acid

The above data exhibited that the 7-hydroxychromone derivative 23 has the highest antioxidant activity which in agreement of reported literatures.\(^{37,38}\) The highly activity of compound 23 is due to easily hydrogen transfer from OH towards free radical. The other highly active compounds are 7 and 16a may be attributed to comprising benzothiazole moiety.\(^{39,40}\) The mechanism of action of novel synthesized compounds as antioxidants on ABTS was showed in Scheme 8.
CONCLUSION

The objective of the present study was to synthesize and investigate the antioxidant activity of some novel heterocycles containing indane-amide moiety with the expectation of ascertaining new structures lead to serving as antioxidant activity. The results revealed that compounds 7, 16a and 23 displayed the comparable antioxidant activity compared to the activity of ascorbic acid.

EXPERIMENTAL

Melting points Melting points were measured with a Gallenkamp apparatus are uncorrected. IR spectra were recorded KBr discs on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science, Mansoura University. The $^1$H-NMR and $^{13}$C-NMR spectra were measured on Bruker WP AC 500 MHz (125 MHz) in CDCl$_3$ and DMSO-$d_6$ as solvents, using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as δ ppm. Mass spectra were determined on Finnigan Incos 500 (70 eV). Elemental analyses were carried out at the Microanalytical Centre, Faculty of Science, Cairo University, Egypt. The results were found to be in good agreement with the calculated values.

Synthesis of 2-cyano-N-(2,3-dihydro-1H-inden-5-yl)acetamide (2)

A mixture of 2,3-dihydro-1H-inden-5-amine (1.33 g, 10 mmol) and pyrazole derivative 1 (1.63 g, 10 mmol) was boiled in dioxane (20 mL) for 4 h, allowed to stand at room temperature. The solid product was obtained by filtration, dried and recrystallized from EtOH to afford compound 2 in 95% yield; White crystals; mp 150-152 °C (EtOH); IR (KBr): ν/cm$^{-1}$ = 3281 (NH), 2256 (CN), 1672 (C=O); $^1$H-NMR (500 MHz, CDCl$_3$) δ (ppm): 2.08 (pentet, 2H, $J = 7.5$ Hz, CH$_2$), 2.85-2.90 (m, 4H, 2CH$_2$), 3.52 (s, 2H,
CH$_2$CN), 7.13-7.18 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 7.68 (s, 1H, NH); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ (ppm): 25.61, 27.84, 33.49, 33.52, 117.45, 118.88, 121.16, 124.63, 138.72, 140.15, 143.35, 171.26; MS (EI, 70 eV): m/z (%) 200 (M$^+$, 25); Anal. Calcd for C$_{12}$H$_{12}$N$_2$O (200.24): C, 71.98; H, 6.04; N, 13.99%. Found: C, 71.91; H, 6.01; N, 13.94%.

Synthesis of 2-cyano-N-(2,3-dihydro-1H-inden-5-yl)-3-(dimethylamino)acrylamide (3). Boiling of compound 2 (2.00 g, 0.01 mol) and dimethylformamide dimethyl acetal (1.32 mL, 0.01 mol) in dry xylene (25 mL) for 6 h. The orange yellow precipitate product was filtered off and recrystallized from EtOH to give compound 2 in 88%; Orange yellow crystals; mp 244-245°C (EtOH); IR (KBr): ν/cm$^{-1}$ = 3325 (NH), 2186 (CN), 1666 (C=O); $^1$H-NMR (500 MHz, CDCl$_3$) δ (ppm): 2.02 (pentet, 2H, J = 7.5 Hz, CH$_2$), 2.83-2.89 (m, 4H, 2CH$_2$), 3.21 (s, 3H, CH$_3$), 3.36 (s, 3H, CH$_3$), 7.13-7.18 (m, 2H, Ar-H), 7.43 (s, 1H, Ar-H), 7.55 (s, 1H, CH), 7.85 (s, 1H, NH); $^{13}$C-NMR (125 MHz, CDCl$_3$-d$_6$) δ (ppm): 25.07, 33.45, 33.68, 43.98, 45.31, 87.86, 114.26, 118.73, 121.33, 124.96, 138.17, 140.04, 143.58, 148.62, 163.96; MS (EI, 70 eV): m/z (%) 255 (M$^+$, 46); Anal. Calcd for C$_{15}$H$_{17}$N$_3$O (255.32): C, 70.56; H, 6.71; N, 16.46%. Found: C, 70.48; H, 6.66; N, 16.39%.

Synthesis of 3-amino-N-(2,3-dihydro-1H-inden-5-yl)-1H-pyrazole-4-carboxamide (4). To a solution of acrylamide 3 (2.55 g, 0.01 mol) in EtOH (20 mL), hydrazine hydrate (0.2 mL) was added. The reaction mixture was refluxed for 6 h, then left to cool. The solid product was filtered off and recrystallized from EtOH to give compound 4 in 86% yield; buff crystals; mp 156-157°C (EtOH); IR (KBr): ν/cm$^{-1}$ = 3387, 3299 (NH$_2$), 3209, 3142 (2NH), 1671 (C=O); $^1$H-NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.06 (pentet, 2H, J = 7.5 Hz, CH$_2$), 2.81-2.87 (m, 4H, 2CH$_2$), 6.57 (s, 2H, NH$_2$), 7.13-7.19 (m, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 8.45 (s, 1H, C$_5$-H pyrazole), 10.23 (s, 1H, NH), 10.43 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-d$_6$) δ (ppm): 25.64, 33.39, 33.56, 102.23, 118.96, 121.35, 124.78, 134.14, 138.66, 140.60, 143.93, 155.24, 163.97; MS (EI, 70 eV): m/z (%) 242 (M$^+$, 22.6); Anal. Calcd for C$_{15}$H$_{14}$N$_4$O (242.28): C, 64.45; H, 5.82; N, 23.13%. Found: C, 64.38; H, 5.77; N, 23.10%.

Synthesis of 2,4-diamino-N-(2,3-dihydro-1H-inden-5-yl)pyrimidine-5-carboxamide (5). Refluxing a mixture of acrylamide 3 (2.55 g, 0.01 mol) and guanidine hydrochloride (0.95 g, 0.01 mol) in EtOH (20 mL) comprising anhydrous potassium carbonate (1.38 g, 0.01 mol) for 8 h, then left to cool. The solid product was filtered off, washed with water and recrystallized from EtOH to give compound 4 in 82% yield; Buff crystals; mp 270-271°C (EtOH); IR (KBr): ν/cm$^{-1}$ = 3858, 3644, 3367, 3311 (2NH$_2$), 3168 (NH), 1669 (C=O); $^1$H-NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.05 (pentet, 2H, J = 7.5 Hz, CH$_2$), 2.83-2.89 (m, 4H, 2CH$_2$), 6.48 (s, 2H, NH$_2$), 6.86 (s, 2H, NH$_2$), 7.14-7.18 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 7.88 (s, 1H, C$_6$-H pyrimidine), 10.48 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-d$_6$) δ (ppm): 25.52, 33.19, 33.75, 102.48, 118.62, 121.03, 124.75, 138.14, 140.34, 143.66, 149.85, 158.7, 160.68, 163.19; MS (EI, 70 eV):
General method for the preparation of some fused pyrimidine heterocyclic derivatives. An equimolar amount of acrylamide 3 (2.55 g, 0.01 mol) and the appropriate heterocyclic amines (2-aminobenzothiazole, 3-amino-1,2,4-triazine and 2-amino-4-methylpyridine) in glacial acetic acid (15 mL) was refluxed for 10-12 h (TLC controlled), then left to cool. The solid product that formed on pouring reaction mixture on ice cold water was filtered off and recrystallized from EtOH to give compounds 7, 10 and 12.

**N-(2,3-Dihydro-1H-inden-5-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (7)**

Brown crystals; yield 68%; mp 280-282 °C (EtOH); IR (KBr): ν/cm⁻¹ = 3363 (NH), 1674, 1667 (2C=O); ¹H-NMR (DMSO-d₆) δ (ppm): 2.06 (pentet, 2H, J = 7.5 Hz, CH₂), 2.83-2.88 (m, 4H, 2CH₂), 7.13-7.18 (m, 2H, Ar-H), 7.31-7.67 (m, 5H, Ar-H), 8.51 (s, 1H, C-H pyrimidine), 10.46 (s, 1H, NH); ¹³C-NMR (125 MHz, DMSO-d₆) δ (ppm): 25.7, 33.5, 33.8, 118.6, 120.2, 122.6, 124.2, 125.1, 125.6, 126.3, 129.3, 130.8, 136.5, 138.2, 140.7, 143.6, 150.1, 158.4, 160.8, 163.3; MS (EI, 70 eV): m/z (%) 361 (M⁺, 38); Anal. Calcd for C₂₀H₁₅N₃O₂S (361.42): C, 66.47; H, 4.18; N, 11.63%. Found: C, 66.43; H, 4.13; N, 11.69%.

**N-(2,3-Dihydro-1H-inden-5-yl)-8-oxo-8H-pyrimido[1,2-b][1,2,4]triazine-7-carboxamide (10)**

Brown powder; yield 76%; mp > 300 °C (EtOH); IR (KBr): ν/cm⁻¹ = 3437 (NH), 1669, 1665 (2C=O); ¹H-NMR (500 MHz, DMSO-d₆) δ (ppm): 2.05 (pentet, 2H, J = 7.5 Hz, CH₂), 2.82-2.89 (m, 4H, 2CH₂), 7.13-7.18 (m, 2H, Ar-H), 7.43 (s, 1H, C-H pyrimidine), 8.66 (d, 1H, J = 2 Hz, triazine H-5), 8.82 (d, 1H, J = 2 Hz, triazine H-6), 8.94 (s, 1H, C-H pyrimidine), 10.45 (s, 1H, NH); ¹³C-NMR (125 MHz, DMSO-d₆) δ (ppm): 25.51, 33.29, 33.64, 118.22, 121.04, 124.75, 129.16, 136.34, 138.77, 140.08, 143.96, 146.53, 151.81, 154.26, 160.47, 163.96; MS (EI, 70 eV): m/z (%) 307 (M⁺, 42); Anal. Calcd for C₁₆H₁₃N₅O₂ (307.31): C, 62.53; H, 4.26; N, 22.79%. Found: C, 62.47; H, 4.19; N, 22.72%.

**N-(2,3-Dihydro-1H-inden-5-yl)-8-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (12)**

Brown powder; yield 71%; mp 275-277 °C (EtOH); IR (KBr): ν/cm⁻¹ = 3385 (NH), 1666, 1660 (2C=O); ¹H-NMR (500 MHz, DMSO-d₆) δ (ppm): 2.06 (pentet, 2H, J = 7.5 Hz, CH₂), 2.35 (s, 3H, CH₃), 2.84-2.90 (m, 4H, 2CH₂), 7.14-7.19 (m, 3H, Ar-H), 7.31 (s, 1H, C₉-H pyridopyrimidine), 8.26 (d, 1H, J = 12 Hz, C₆-H pyridopyrimidine), 8.96 (s, 1H, C-H pyrimidine), 10.43 (s, 1H, NH); ¹³C-NMR (125 MHz, DMSO-d₆) δ (ppm): 21.05, 25.66, 33.24, 33.76, 115.16, 118.72, 121.53, 122.45, 124.86, 126.14, 129.32, 138.41, 140.81, 143.98, 145.07, 151.63, 153.14, 160.38, 163.74; MS (EI, 70 eV): m/z (%) 319 (M⁺, 46); Anal. Calcd for C₁₉H₁₇N₃O₂ (319.36): C, 71.46; H, 5.37; N, 13.16%. Found: C, 71.38; H, 5.31; N, 13.19%.

General method for the reaction of acrylamide 3 with activated nitrile. An equimolar amount of acrylamide 3 (2.55 g, 0.01 mol) and 2-benzothiazolylacetonitrile or 2-benzoimidazolylacetonitrile in glacial acetic acid (15 mL) was refluxed for 10 h, then left to cool. The solid product was filtered off and
recrystallized from EtOH to give compounds 16a,b.

4-Cyano-N-(2,3-dihydro-1H-inden-5-yl)-1-oxo-1H-benzo[4,5]thiazolo[3,2-a]pyridine-2-carboxamide (16a)

Brown powder; yield 65%; mp 286-288 °C (EtOH); IR (KBr): v/cm\(^{-1}\) = 3361 (NH), 2218 (CN), 1669, 1664 (2C=O); \(^1\)H-NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.08 (pentet, 2H, \(J = 7.5\) Hz, CH\(_2\)), 2.84-2.90 (m, 4H, 2CH\(_2\)), 7.13-7.18 (m, 2H, Ar-H), 7.36 (s, 1H, Ar-H), 7.63-8.03 (m, 4H, Ar-H), 8.76 (s, 1H, C-H pyridine), 10.54 (s, 1H, NH); \(^{13}\)C-NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 25.52, 33.24, 33.58, 78.98, 111.54, 115.02, 116.96, 118.73, 121.22, 122.40, 124.59, 125.27, 126.71, 129.26, 133.21, 136.54, 138.66, 140.72, 143.55, 158.63, 160.86, 163.72; MS (EI, 70 eV): m/z (%) 385 (M\(^+\), 37); Anal. Calcd for C\(_{22}\)H\(_{15}\)N\(_3\)O\(_2\)S (385.44): C, 68.56; H, 3.92; N, 10.90%. Found: C, 68.51; H, 3.89; N, 10.85%.

4-Cyano-N-(2,3-dihydro-1H-inden-5-yl)-1-oxo-1,5-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-2-carboxamide (16b)

Reddish brown powder; yield 67%; mp 292-294 °C (EtOH); IR (KBr): \(\nu/cm\(^{-1}\) = 3368, 3309 (2NH), 2216 (CN), 7.04-7.48 (m, 7H, Ar-H), 8.73 (s, 1H, C-H pyridine), 10.43 (s, 1H, CONH), 10.76 (s, 1H, NH); \(^{13}\)C-NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 25.51, 33.24, 33.55, 66.97, 111.49, 113.88, 115.37, 116.62, 118.57, 120.19, 121.24, 124.86, 125.71, 131.04, 133.52, 136.34, 138.47, 140.35, 143.56, 153.18, 160.24, 163.47; MS (EI, 70 eV): m/z (%) 368 (M\(^+\), 46); Anal. Calcd for C\(_{22}\)H\(_{16}\)N\(_4\)O\(_2\) (368.40): C, 71.73; H, 4.38; N, 15.21%. Found: C, 71.69; H, 4.36; N, 15.12%.

General method for the preparation of 2H-pyran-2-one derivatives. An equimolar amount of acrylamide 3 (2.55 g, 0.01 mol) and keto active methylene compounds (acetylacetone, 1,3-indanedione, barbituric acid, thiobarbituric acid and pyrazolone derivative) or resorcinol in glacial acetic acid (15 mL) was refluxed for 8-12 h (TLC controlled). The reaction mixture was poured in crushed ice; the formed precipitate was filtered off, washed with water for several times followed by washing with cold EtOH. The solid product was recrystallized from EtOH to give compounds 17, 18, 20a,b, 22 and 23.

5-Acetyl-N-(2,3-dihydro-1H-inden-5-yl)-6-methyl-2-oxo-2H-pyran-3-carboxamide (17)

Pale yellow crystals; yield 73%; mp 260-262 °C; IR (KBr): v/cm\(^{-1}\) = 3230 (NH), 1718, 1689, 1667 (3C=O); \(^1\)H-NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.05 (pentet, 2H, \(J = 7.5\) Hz, CH\(_2\)), 2.35 (s, 3H, COCH\(_3\)), 2.51 (s, 3H, CH\(_3\)), 2.84-2.90 (m, 4H, 2CH\(_2\)), 7.13-7.19 (m, 2H, Ar-H), 7.36 (s, 1H, Ar-H), 8.41 (s, 1H, C\(_4\)-H pyran), 10.44 (s, 1H, NH); \(^{13}\)C-NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 19.93, 25.67, 29.25, 33.41, 33.68, 116.29, 118.34, 121.42, 122.69, 124.63, 138.50, 140.39, 143.26, 148.40, 160.82, 163.27, 165.46, 195.68; MS (EI, 70 eV): m/z (%) 311 (M\(^+\), 36); Anal. Calcd for C\(_{18}\)H\(_{17}\)NO\(_4\) (311.34): C, 69.44; H, 5.50; N, 4.50%. Found: C, 69.36; H, 5.46; N, 4.47%.

N-(2,3-Dihydro-1H-inden-5-yl)-2,5-dioxo-2,5-dihydroindeno[1,2-b]pyran-3-carboxamide (18)
Gray powder; yield 61%; mp > 300 °C; IR (KBr): v/cm$^{-1}$ = 3411 (NH), 1713, 1678, 1659 (C=O); $^1$H-NMR (500 MHz, DMSO-$d_6$) δ (ppm): 2.05 (pentet, 2H, $J = 7.5$ Hz, CH$_2$), 2.84-2.90 (m, 4H, 2CH$_2$), 7.13-7.18 (m, 2H, Ar-H), 7.31-7.77 (m, 5H, Ar-H), 8.47 (s, 1H, C$_4$-H pyran), 10.44 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$) δ (ppm): 25.54, 33.31, 33.66, 116.25, 118.69, 121.21, 122.48, 123.50, 124.84, 126.78, 127.62, 129.84, 136.59, 137.53, 138.38, 140.23, 143.64, 148.56, 154.60, 160.80, 163.59, 194.57; MS (EI, 70 eV): m/z (%) 357 (M$^+$, 21); Anal. Calcd for C$_{22}$H$_{15}$NO$_4$ (357.37): C, 73.94; H, 4.23; N, 3.92%. Found: C, 73.90; H, 4.20; N, 4.11%.

$\text{N-(2,3-Dihydro-1H-inden-5-yl)-2,4,7-trioxo-1,3,4,7-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxamide (20a)}$

Buff powder; yield 79%; mp > 300 °C; IR (KBr): v/cm$^{-1}$ = 3429, 3359, 3288 (3NH), 1719, 1682, 1673, 1654 (4C=O); $^1$H-NMR (500 MHz, DMSO-$d_6$) δ (ppm): 2.04 (pentet, 2H, $J = 7.5$ Hz, CH$_2$), 2.84-2.90 (m, 4H, 2CH$_2$), 7.13-7.17 (m, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 8.64 (s, 1H, C$_4$-H pyran), 10.25 (s, 1H, NH), 10.68 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$) δ (ppm): 25.62, 33.36, 33.68, 116.41, 118.65, 121.35, 122.17, 124.86, 138.57, 140.31, 143.62, 148.49, 152.10, 154.37, 158.45, 160.24, 163.39; MS (EI, 70 eV): m/z (%) 339 (M$^+$, 17); Anal. Calcd for C$_{17}$H$_{13}$N$_3$O$_5$ (339.31): C, 60.18; H, 3.86; N, 12.38%. Found: C, 60.14; H, 3.78; N, 12.32%.

$\text{N-(2,3-Dihydro-1H-inden-5-yl)-4,7-dioxo-2-thioxo-1,3,4,7-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carboxamide (20b)}$

Orange yellow crystals; yield 76%; mp > 300 °C; IR (KBr): v/cm$^{-1}$ = 3408, 3368, 3305 (3NH), 1717, 1683, 1677, 1638 (4C=O); $^1$H-NMR (500 MHz, DMSO-$d_6$) δ (ppm): 2.05 (pentet, 2H, $J = 7.5$ Hz, CH$_2$), 2.84-2.90 (m, 4H, 2CH$_2$), 7.13-7.17 (m, 2H, Ar-H), 7.34 (s, 1H, Ar-H), 8.61 (s, 1H, C$_4$-H pyran), 10.21 (s, 1H, NH), 10.86 (s, 1H, NH), 11.23 (s, 1H, NH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$) δ (ppm): 25.5 5, 33.24, 33.68, 116.27, 118.51, 121.36, 122.80, 124.62, 138.71, 140.27, 143.56, 148.91, 158.67, 160.42, 163.35, 165.39, 178.24; MS (EI, 70 eV): m/z (%) 355 (M$^+$, 25); Anal. Calcd for C$_{17}$H$_{13}$N$_3$O$_4$S (355.37): C, 57.46; H, 3.69; N, 11.82%. Found: C, 57.43; H, 3.62; N, 11.84%.

$\text{N-(2,3-Dihydro-1H-inden-5-yl)-7-hydroxy-2-oxo-2H-chromene-3-carboxamide (22)}$

Brown powder; yield 57%; mp 290-292 °C; IR (KBr): v/cm$^{-1}$ = 3421 (OH), 3353 (NH), 1719, 1668 (2C=O); $^1$H-NMR (500 MHz, DMSO-$d_6$) δ (ppm): 2.03 (pentet, 2H, $J = 7.5$ Hz, CH$_2$), 2.84-2.88 (m, 4H, 2CH$_2$), 6.64 (s, 1H, H-8), 6.82 (d, 1H, $J = 9$ Hz, C$_6$-H coumarin), 6.98 (d, 1H, $J = 9$ Hz, C$_5$-H coumarin), 7.12-7.16 (m, 2H, Ar-H), 7.35 (s, 1H, Ar-H), 8.42 (s, 1H, C$_4$-H coumarin), 10.42 (s, 1H, NH), 12.31 (s, 1H, OH); $^{13}$C-NMR (125 MHz, DMSO-$d_6$) δ (ppm): 25.55, 33.20, 33.58, 102.13, 110.37, 116.22, 118.49, 121.52, 122.36, 124.78, 128.64, 138.50, 140.15, 143.47, 148.26, 154.63, 158.37, 160.66, 163.28; MS (EI, 70 eV): m/z (%) 321 (M$^+$, 18); Anal. Calcd for C$_{19}$H$_{15}$NO$_4$ (321.33): C, 71.02; H, 4.71; N, 4.36%. Found: C, 70.96; H, 4.63; N, 4.27%. 
**N-(2,3-Dihydro-1H-inden-5-yl)-3-methyl-6-oxo-1-phenyl-1,6-dihydropyrano[2,3-c]pyrazole-5-carboxamide (23)**

Yellow crystals; yield 64%; mp 275-277 °C; IR (KBr): \(\nu/\text{cm}^{-1} = 3368 \text{ (NH)}, 1720, 1665 \text{ (2C=O)}\); \(^1\text{H-NMR}(500 \text{ MHz, DMSO-d}_6) \delta \text{ (ppm): } 2.04 \text{ (pentet, 2H, } J = 7.5 \text{ Hz, CH}_2\text{), } 2.25 \text{ (s, 3H, CH}_3\text{), } 2.84-2.89 \text{ (m, 4H, 2CH}_2\text{), } 7.13-7.17 \text{ (m, 2H, Ar-H), } 7.38 \text{ (s, 1H, Ar-H), } 7.49-7.85 \text{ (m, 5H, Ar-H), } 8.36 \text{ (s, 1H, C}_4\text{-H pyran), 10.31 \text{ (s, 1H, NH)}}\); \(^{13}\text{C-NMR}(125 \text{ MHz, DMSO-d}_6) \delta \text{ (ppm): } 13.64, 25.61, 33.40, 33.76, 116.41, 118.29, 121.32, 122.57, 123.63, 124.55, 126.38, 129.21, 136.46, 138.57, 140.28, 143.31, 145.29, 148.60, 154.68, 160.39, 163.27; MS (EI, 70 eV): \(m/z\) (%) 385 (M\(^+\), 34); Anal. Calcd for C\(_{23}\)H\(_{19}\)N\(_3\)O\(_3\) (385.42): C, 71.68; H, 4.97; N, 10.90%. Found: C, 71.66; H, 4.90; N, 10.81%.

**ANTIOXIDANT SCREENING**

Antioxidant activity determinations were evaluated from the bleaching of ABTS derived radical cations. The radical cation derived from ABTS was prepared by reaction of ABTS (60 µL) with MnO\(_2\) (3 mL, 25 mg/mL) in (5 mL) aqueous buffer solution (pH 7). After shaking the solution for a few minutes, it was centrifuged and filtered. The absorbance (A\(_{\text{control}}\)) of the resulting green-blue solution (ABTS radical solution) was recorded at \(\lambda_{\text{max}}\) 734 nm. The absorbance (A\(_{\text{test}}\)) was measured upon the addition of (20 µL of 1 mg/mL) solution of the tested sample in spectroscopic grade MeOH/buffer (1:1 v/v) to the ABTS solution.

**REFERENCES**


