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

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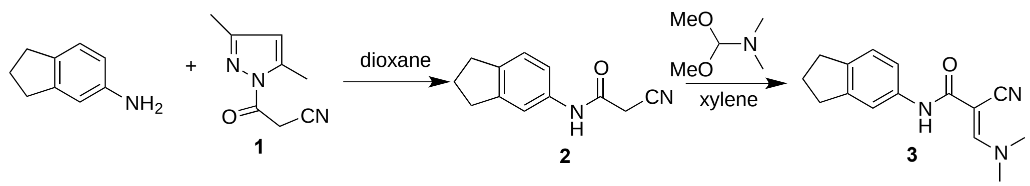
Abstract – 2-Cyano-*N*-(2,3-dihydro-1*H*-5-indenyl)-3-(dimethylamino)acrylamide (**3**) was used in synthetic paths to some novel indane-amide containing pyrazole, pyrimidine, fused pyrimidines, fused pyridines and 2-pyrone derivatives by reaction of **3** with various reagents. The newly synthesized 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 moietiy 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.

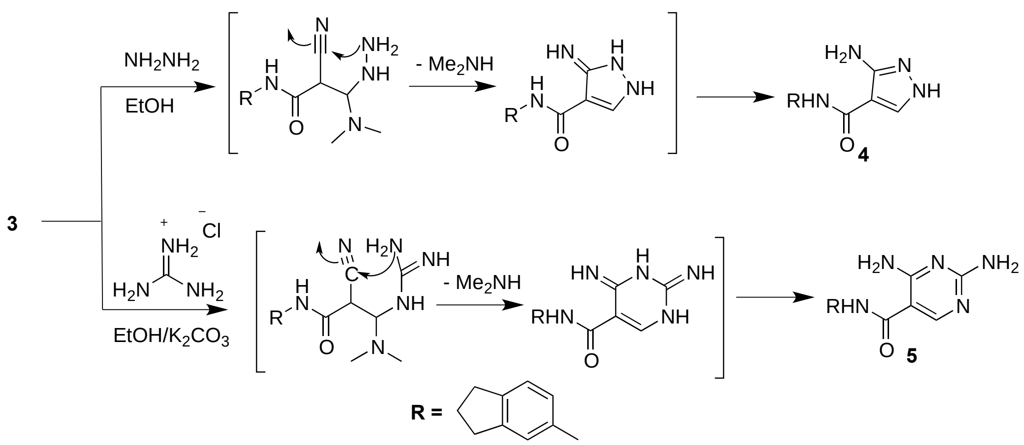
RESULTS AND DISCUSSION

Our starting point is to synthesis 2-cyano-*N*-(2,3-dihydro-1*H*-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-1*H*-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 δ 3.52, 7.38 and 7.68 ppm attributed to CH_2CN, CH-Ar and NH protons, respectively. On the other hand, ^{1}H-NMR spectrum of compound **3** revealed four singlet signals at δ 3.21, 3.36, 7.55 and 7.85 ppm owing to two methyl, vinylic CH and NH protons, respectively.



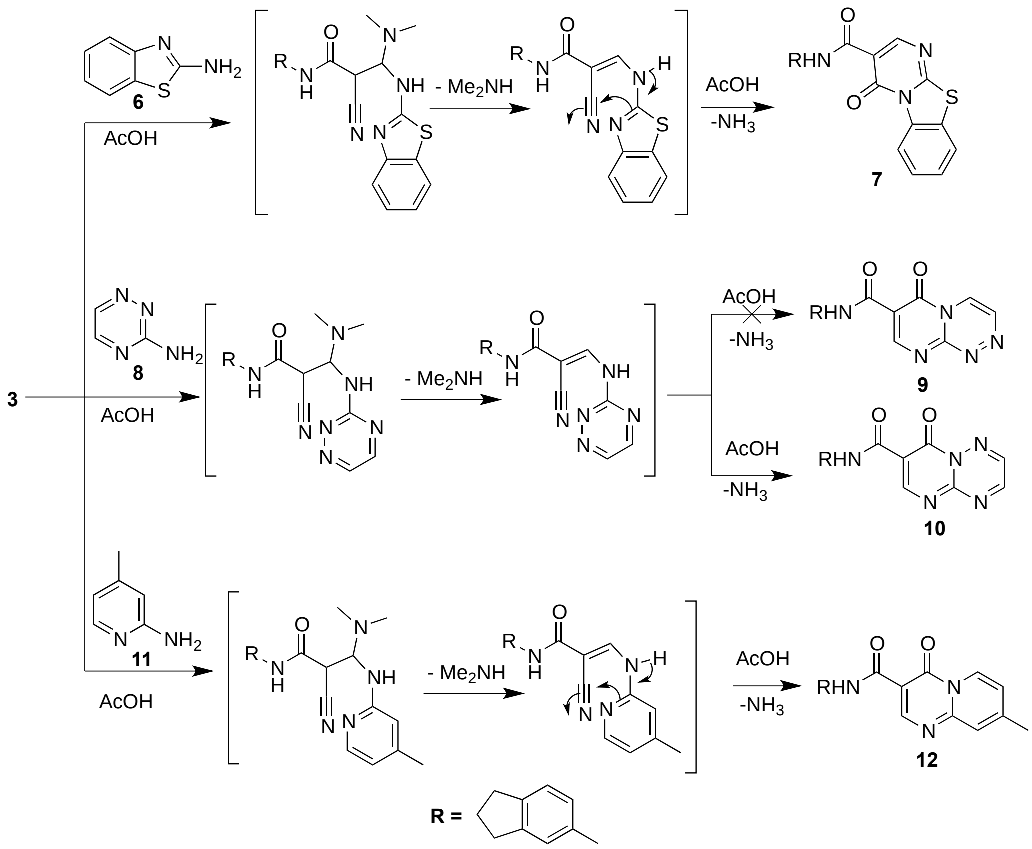
Scheme 1

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_2NH molecule and finally cycloaddition reaction to give products **4** and **5**.



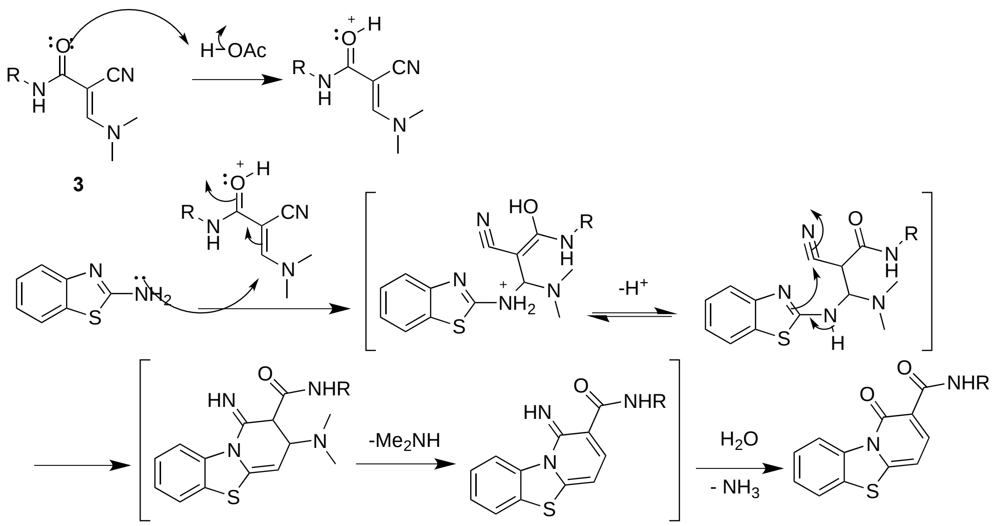
Scheme 2

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_2N 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_2O exchangeable) at δ 6.57 due to NH_2 in compound **4** and two singlet signals (D_2O exchangeable) at δ 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.



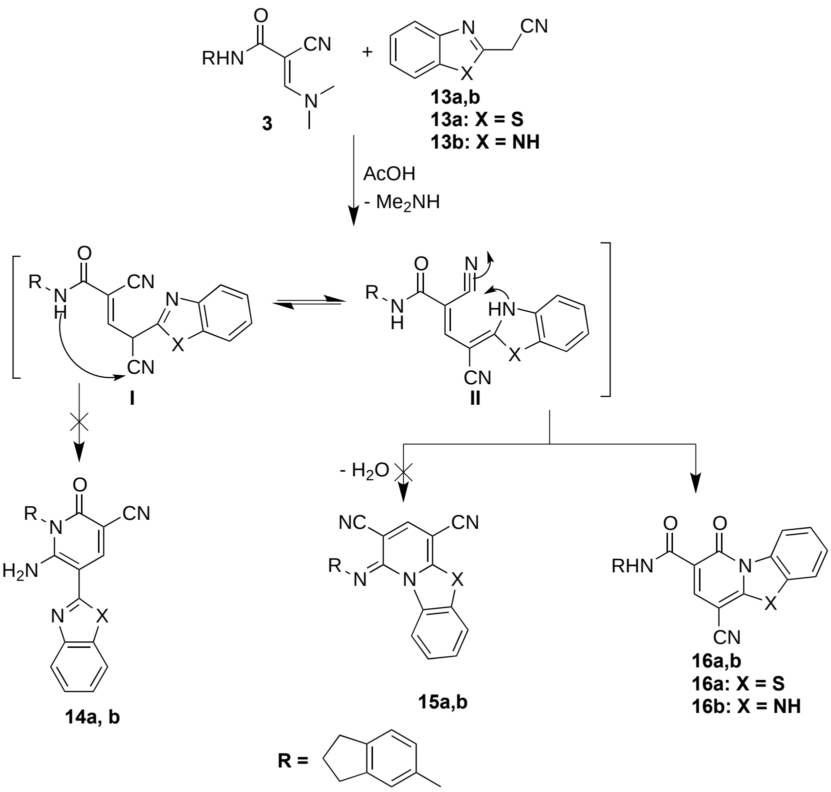
Scheme 3

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 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**[35] 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.



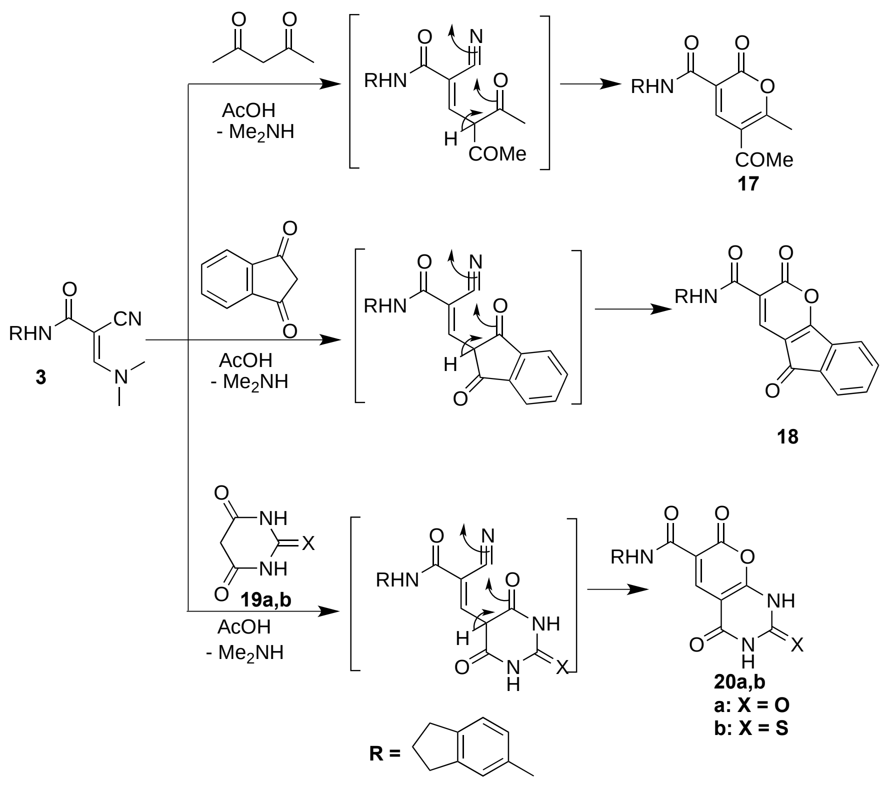
Scheme 4

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).



Scheme 5

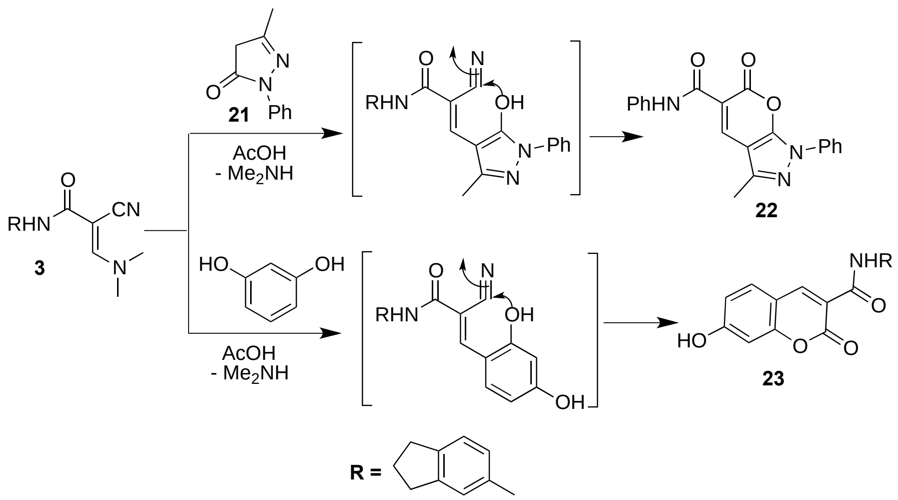
The reaction of **3** with compounds **13a**,**b** can lead to three possible structures **14a**,**b**, **15a**,**b** or **16a**,**b**. Compounds **14a**,**b** and **15a**,**b** could be formed if the geometry of double bond is *Z* in which NH in suitable situation for cycloaddition reaction on CN group 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 NH_2 in ^{1}H-NMR spectra of reaction products excluded structure **14a**,**b**. In addition, reaction product of **3** with **13b** displayed two singlet signals (D_2O 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

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:

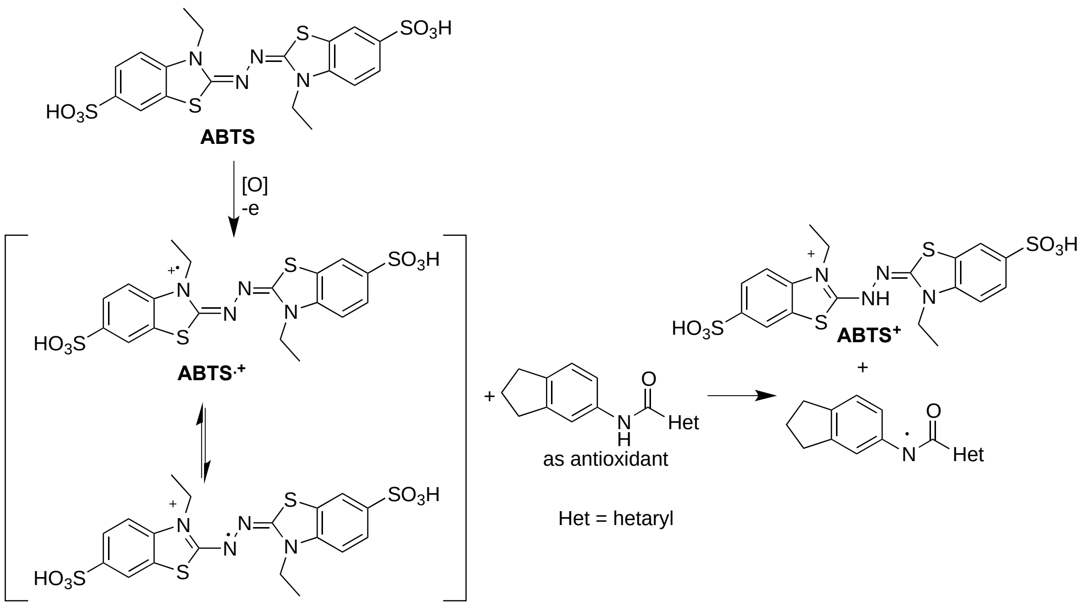
% Inhibition = (A_{control} - $A_{\mathrm{test}}/A_{\mathrm{control}}$) x 100

Table 1. Inhibition % values of the antioxidant activity of the tested compounds

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

% Inhibition = $(A_{\text{control}} - A_{\text{test}}/A_{\text{control}})$ x 100
Acontrol: Absorbance for ascorbic acid
Atest: Absorbance for the tested samples
Control: Ascorbic acid

The above data exhibited that the 7-hydroxychromene 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.



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-1*H*-inden-5-yl)acetamide (2)

A mixture of 2,3-dihydro-1*H*-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_2CN), 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 $C_{12}H_{12}N_2O$ (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-1*H*-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, $CHCl_3$-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 $C_{15}H_{17}N_3O$ (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-1*H*-inden-5-yl)-1*H*-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 $C_{13}H_{14}N_4O$ (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-1*H*-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):

m/z (%) 269 (M^+, 45.2); Anal. Calcd for $C_{14}H_{15}N_5O$ (269.31): C, 62.44; H, 5.61; N, 26.01%. Found: C, 62.36; H, 5.52; N, 25.97%.

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-1*H*-inden-5-yl)-4-oxo-4*H*-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); ^{1}H-NMR (DMSO-*d*$_6$) δ (ppm): 2.06 (pentet, 2H, *J* = 7.5 Hz, CH_2), 2.83-2.88 (m, 4H, 2CH_2), 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); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) *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 $C_{20}H_{15}N_3O_2S$ (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-1*H*-inden-5-yl)-8-oxo-8*H*-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); ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 2.05 (pentet, 2H, *J* = 7.5 Hz, CH_2), 2.82-2.89 (m, 4H, 2CH_2), 7.13-7.18 (m, 2H, Ar-H), 7.43 (s, 1H, Ar-H), 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); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) *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 $C_{16}H_{13}N_5O_2$ (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-1*H*-inden-5-yl)-8-methyl-4-oxo-4*H*-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); ^{1}H-NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 2.06 (pentet, 2H, *J* = 7.5 Hz, CH_2), 2.35 (s, 3H, CH_3), 2.84-2.90 (m, 4H, 2CH_2), 7.14-7.19 (m, 3H, Ar-H), 7.31 (s, 1H, C_9-H pyridopyrimidine), 7.45 (s, 1H, Ar-H), 8.26 (d, 1H, *J* = 12 Hz, C_6-H pyridopyrimidine), 8.96 (s, 1H, C-H pyrimidine), 10.43 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-*d*$_6$) *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 $C_{19}H_{17}N_3O_2$ (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-1*H*-inden-5-yl)-1-oxo-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2-carboxamide (16a)

Brown powder; yield 65%; mp 286-288 °C (EtOH); IR (KBr): ν/cm^{-1}= 3361 (NH), 2218 (CN), 1669, 1664 (2C=O); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (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) δ (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 $C_{22}H_{15}N_3O_2S$ (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-1*H*-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): ν/cm^{-1}= 3368, 3309 (2NH), 2216 (CN), 1669, 1661 (2C=O); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.06 (pentet, 2H, J = 7.5 Hz, CH_2), 2.82-2.89 (m, 4H, $2CH_2$), 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) δ (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 $C_{22}H_{16}N_4O_2$ (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 2*H*-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-1*H*-inden-5-yl)-6-methyl-2-oxo-2*H*-pyran-3-carboxamide (17)

Pale yellow crystals; yield 73%; mp 260-262 °C; IR (KBr): ν/cm^{-1}= 3230 (NH), 1718, 1689, 1667 (3C=O); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (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) δ (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-1*H*-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): ν/cm^{-1}= 3411 (NH), 1713, 1678, 1659 (3C=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%.

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

Buff powder; yield 79%; mp > 300 °C; IR (KBr): ν/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), 10.87 (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 $C_{17}H_{13}N_3O_5$ (339.31): C, 60.18; H, 3.86; N, 12.38%. Found: C, 60.14; H, 3.78; N, 12.32%.

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

Orange yellow crystals; yield 76%; mp > 300 °C; IR (KBr): ν/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), 7.13-7.18 (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): 25.55, 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 $C_{17}H_{13}N_3O_4S$ (355.37): C, 57.46; H, 3.69; N, 11.82%. Found: C, 57.43; H, 3.62; N, 11.84%.

***N*-(2,3-Dihydro-1*H*-inden-5-yl)-7-hydroxy-2-oxo-2*H*-chromene-3-carboxamide (22)**

Brown powder; yield 57%; mp 290-292 °C; IR (KBr): ν/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), 2.83-2.88 (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): 25.62, 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-1*H*-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): ν/cm^{-1}= 3368 (NH), 1720, 1665 (2C=O); ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 2.04 (pentet, 2H, J = 7.5 Hz, CH_2), 2.25 (s, 3H, CH_3), 2.84-2.89 (m, 4H, $2CH_2$), 7.13-7.17 (m, 2H, Ar-H), 7.38 (s, 1H, Ar-H), 7.49-7.85 (m, 5H, Ar-H), 8.36 (s, 1H, C_4-H pyran), 10.31 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ (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 $C_{23}H_{19}N_3O_3$ (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 ($A_{control}$) of the resulting green-blue solution (ABTS radical solution) was recorded at λ_{max}734 nm. The absorbance (A_{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.

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