Nitrophenyl-group-containing Heterocycles. Part I. Synthesis, Characterization, Anticancer Activity and Antioxidant Properties of Some New 5,6,7,8-tetrahydroisoquinolines Bearing 3(4)-nitrophenyl Group

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Abstract

Regioselective cyclocondensation of 2,4-diacetyl-5-hydroxy-5-methyl-3-(3-nitrophenyl/4-nitrophenyl)cyclohexanones 1a,b with cyanothioacetamide afforded the corresponding 7-acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl/4-nitrophenyl)-5,6,7,8-tetrahydroisoquinoline-3(2H)-thiones 2a,b in 93-96%. Reaction of compounds 2a,b ethyl iodide, 2-chloroacetamide or N-(naphthalen-1-yl)-2-chloroacetamide (5) in the presence of sodium acetate gave the corresponding p(5,6,7,8-tetrahydroisoquinolin-3-yl)thio derivatives 3a,b, 4a,b and 6a,b. In a similar manner, reaction of a,b with other N-aryl-2-chloroacetamides 7a-d gave 2-[(7-acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl/4-nitrophenyl)-5,6,7,8-tetrahydroisoquinolin-3-yl)thio]-N-arylacetamides (8a-g). On heating of compounds 8a-e in ethanol containing anhydrous sodium carbonate, they converted into 7-acetyl-1-amino-N-aryl-5,8-dimethyl-8-hydroxy-6-(3-nitrophenyl/4-nitrophenyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamides 9a-e. Structural formulae of all synthesized compounds were characterized on the basis of their spectroscopic data. Also, the applications of most synthesized isoquinolines as anticancer and as antioxidant agents have been carried out and the obtained results are reported herein.

Introduction

5,6,7,8-Tetrahydroisoquinoline ring system is a structural fragment of many alkaloids that are next to indole alkaloids in their abundance [1–4]. Compounds containing a 5,6,7,8-tetrahydroisoquinoline fragment are used as intermediate products in the synthesis of alkaloids [5–7], precursors to enzyme inhibitors [8, 9], fungicides [10, 11], potassium receptor antagonists [12], and drugs for the treatment of cardiovascular diseases, bronchial asthma, tumors, and viral infections [4, 13]. 5,6,7,8-tetrahydroisoquinoline derivatives were also shown to exhibit anticonvulsant [14–16], antibacterial [17], neurotropic [18] and antimicrobial activities [19].

On the other hand, many nitro-group-containing compounds are reported to possess versatile applications in the fields of biochemistry and medicine [20–23].

In view of the above observations, the current work was planned to synthesize and characterize of some new 5,6,7,8-tetrahydroisoquinolines and related 6,7,8,9-tetrahyrothieno[2,3-c]isoquinolines bearing 3-nitrophenyl or 4-nitrophenyl moiety with the hope that these new compounds will find good applications in both biological and medicinal fields owing to their incorporation of various pharmacophores. Also, the applications of some synthesized compounds as anticancer and as antioxidant agents have been carried out and the obtained results are reported herein.

Results And Discussions

Synthesis
Treatment of 1,3-dicarbonyl compounds 1a,b with cyanothioacetamide in refluxing ethanol in the presence of piperidine as a basic catalyst resulted in regioselective cyclocondensation reaction affording the corresponding, 7-acetyl-8-(3-nitrophenyl or 4-nitrophenyl)-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline-3(2H)-thiones 3a,b in 93-96% yield (Scheme 1).

Reaction of compounds 2a,b with some halocompounds namely; ethyl iodide, 2-chloroacetamide or N-(naphthalen-1-yl)-2-chloroacetamide (5) by refluxing in ethanol, in the presence of slightly excess molar amounts of sodium acetate trihydrate, for one hour gave 3-ethylthio-5,6,7,8-tetrahydroisoquinoline 3, (5,6,7,8-tetrahydroisoquinolin-3-ylthio)acetamides 4a,b and N-(naphthalen-1-yl)-(5,6,7,8-tetrahydroisoquinolin-3-ylthio)acetamide 6 respectively (Scheme 2).

In a similar manner, reaction of compounds 2a,b with other N-aryl-2-chloroacetamides 7a-d gave 2-[(7-acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl/4-nitrophenyl)-5,6,7,8-tetrahydroisoquinolin-3-yl)thio]-N-arylacetamides 8a-g. On refluxing of compounds 8a-e with catalytic amounts of anhydrous sodium carbonate in abs. ethanol, they underwent intramolecular Thorpe-Ziegler cyclization affording 7-acetyl-1-amino-N-aryl-5,8-dimethyl-8-hydroxy-6-(3-nitrophenyl/4-nitrophenyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamides 9a-e. Compounds 9a-e were also synthesized via reaction of 2a,b with the respective N-aryl-2-chloroacetamides 7a-d in the presence of slightly excess molar amounts of anhydrous sodium carbonate (Scheme 3).

Cyclization of compounds 8a-e into the corresponding 6,7,8,9-tetrahydrothieno[2,3-c]isoquinolines 9a-e may obey intramolecular Thorpe-Ziegler cyclization which its mechanism is outlined in Scheme 4 [24].

**Characterizaton**

The structures of newly synthesized compounds were characterized and confirmed on the basis of their spectroscopic data (cf. Experimental part). Thus, IR spectra of 2a,b showed characteristic absorption bands in the regions 3482-3429 cm⁻¹ for (O-H), 3235- 3106 cm⁻¹ for (NH), 2221- 2220 cm⁻¹ for (C≡N), and 1710-1708 cm⁻¹ for (C=O, acetyl). ¹H NMR spectra of 2a,b are in agreement with those of their analogues which reported before [25]. IR spectrum of 3 revealed the disappearance of NH whereas its NMR spectra showed the presence of ethyl group. IR spectra of 4a,b, 6 and 8a-e showed absorption bands in the regions 3556 - 3427 cm⁻¹ for (OH), 3351- 3260 cm⁻¹ for (NH), 2221- 2215 cm⁻¹ for (C≡N), 1712-1694 cm⁻¹ for (C=O, acetyl) and 1682- 1666 cm⁻¹ (C=O, amide). ¹H NMR spectra of 4a,b, 6 and 8a-g showed the presence of a double doublet signal [33] corresponds to SCH₂ group at δ value around 4.0 and a singlet signal at δ value ranged from 8.99 to 10.95 corresponds to NH group. IR spectra of 9a-e revealed the disappearance of the carbonitrile band and presence of four absorption bands in the region 3517 - 3314 cm⁻¹ characteristic for (OH, NH₂ and NH) group beside other two bands in the regions 1705 -1698 cm⁻¹ and 1651-1624 cm⁻¹ corresponds to acetyl group and amidic carbonyl group, respectively. ¹H NMR spectra of 9a-e showed the presence of a broad singlet signal referred to the amino group at δ value ranged from 6.90 to 7.14 instead of the signal of SCH₂ group which exists in the spectra of 8a-e. The presence of tertiary alcoholic group in all compounds was ascertained from their ¹H NMR spectra which
possess a singlet signal at δ value ranged from 4.56 to 4.89 equivalent to one proton of (OH) group. $^1$H NMR spectra of all compounds displayed characteristic signals at certain δ values which are equivalent to the protons of cyclohexene ring and in accordance with those reported before for their analogues [25]. $^{13}$C NMR spectra of compounds 4a, 8b-d, 8f and 9a-e displayed characteristic peaks at certain δ values which are in agreement with their structures.

Cytotoxic activity

The cytotoxic activity of compounds coded with 2a, 3, 4a, 6, 8b, 8c, 8e, 8f, 8g against PACA2 (Pancreatic cancer cell line) and that of compounds coded with 4b, 8d, 8e, 9a, 9c, 9d, 9e against A549 (Lung carcinoma cell line) has evaluated in vitro at different concentrations ranged from 0.78 to 100 μM using the MTT assay method. In this work, doxorubicin was used as a positive control drug for comparison purposes with the drug candidates 2a, 3, 4a, 4b, 6, 8b, 8c, 8d, 8e, 8f, 8g, 9a, 9c, 9d and 9e under the same experimental conditions. Different concentrations of these compounds were tested to reach the concentration which could cause death for 50 % of the cancer cells; IC$_{50}$ (see tables in supporting information) and the IC$_{50}$ value of each compound was estimated in the figures given below. After the cells were exposed to the solutions of the compounds under test for an incubation time of 72 h, cytotoxic activity was determined and expressed as IC$_{50}$ and IC$_{90}$ values.

The results obtained (Tables 1 and 2) revealed that among all tested compounds: (i) five compounds 3, 8b, 8f and 8g showed mild to strong cytotoxic activity against PACA2 (Pancreatic cancer cell line) with IC$_{50}$ of 63.1, 24.6, 69.9, 32.6 and 81.9 μM respectively, (ii) only three compounds 9a, 9c and 9e which showed considerable cytotoxic activity against A549 (Lung carcinoma cell line) with IC$_{50}$ of 49.3, 67.7 and 59.7 μM respectively, (iii) compounds 8f and 9c exhibit the highest activity and (iv) rest of the tested compounds being inactive against the two cell lines under investigation.

Table 1: Cytotoxic activity of compounds 2a, 3, 4a, 6, 8b, 8c, 8e, 8f and 8g against PACA2 (Pancreatic cancer cell line) at concentration of 100 μM and their IC$_{50}$, IC$_{90}$ values.
### Table 2: Cytotoxic activity of compounds 4b, 8d, 8e, 9a, 9c, 9d and 9e against A549 (Lung carcinoma cell line) at concentration of 100 µM and their IC<sub>50</sub>, IC<sub>90</sub> values.

| Remarks                | IC<sub>90</sub> (µM) | IC<sub>50</sub> (µM) | Compound No. |
|------------------------|-----------------------|-----------------------|--------------|
| 2.3% at 100 µM         | —                     | —                     | 4b           |
| 3.2% at 100 µM         | —                     | —                     | 8d           |
| 45.3% at 100 µM        | —                     | —                     | 8e           |
| 88.8% at 100 µM        | 85.7                  | 49.3                  | 9a           |
| 77.0% at 100 µM        | 112.5                 | 67.7                  | 9c           |
| 47.2% at 100 µM        | —                     | —                     | 9d           |
| 76.6% at 100 µM        | 108.3                 | 59.7                  | 9e           |
| 5% at 100 µM           | —                     | —                     | DMSO         |
| 0%                     | —                     | —                     | Negative control |

#### Antioxidant activity

Fourteen compounds were evaluated for DPPH scavenging activity as a measurement of their antioxidant activity. Data are represented by Mean±SD of 3 replicates. DPPH scavenging activity are represented as %. Table 3 declared variable percentage of inhibition of DPPH scavenging activity of the tested compounds in a dose-dependent relationship compared with vitamin C as a standard. The highest dose of synthesized compounds that is 0.10 µg/mL represents the highest antioxidant activity.
of all compounds relative to vitamin C. The synthesized compounds 2a, 2b, 4a and 9a showed the highest antioxidant activity at concentration of 0.1µg/mL (dose–dependent manner).

**Table 3**: DPPH Scavenging activity of isoquinioline derivatives.*
| Compd. No. | Conc. | R1     | R2     | R1 Inhibition | R1 Inhibition | Mean  | St.De (%) |
|------------|-------|--------|--------|---------------|---------------|-------|-----------|
| 2a         | 0.10  | 0.016  | 0.019  | 96.72         | 96.10         | 96.41 | 0.44a     |
| 2a         | 0.05  | 0.264  | 0.269  | 45.82         | 44.80         | 45.31 | 0.73b     |
| 2a         | 0.01  | 0.342  | 0.344  | 29.82         | 29.41         | 29.61 | 0.29c     |
| 2b         | 0.10  | 0.018  | 0.017  | 96.31         | 96.51         | 96.41 | 0.15a     |
| 2b         | 0.05  | 0.019  | 0.020  | 96.10         | 95.90         | 96.00 | 0.15a     |
| 2b         | 0.01  | 0.028  | 0.027  | 94.25         | 94.46         | 94.36 | 0.15a     |
| 3b         | 0.10  | 0.163  | 0.166  | 66.55         | 65.93         | 66.24 | 0.44d     |
| 3b         | 0.05  | 0.198  | 0.202  | 59.37         | 58.55         | 58.96 | 0.58e     |
| 3b         | 0.01  | 0.249  | 0.253  | 48.90         | 48.08         | 48.49 | 0.58b     |
| 4a         | 0.10  | 0.021  | 0.024  | 95.69         | 95.07         | 95.38 | 0.44a     |
| 4a         | 0.05  | 0.023  | 0.021  | 95.28         | 95.69         | 95.49 | 0.29a     |
| 4a         | 0.01  | 0.052  | 0.055  | 89.33         | 88.71         | 89.02 | 0.44f     |
| 4b         | 0.10  | 0.078  | 0.080  | 83.99         | 83.58         | 83.79 | 0.29f     |
| 4b         | 0.05  | 0.170  | 0.176  | 65.11         | 63.88         | 64.50 | 0.87d     |
| 4b         | 0.01  | 0.266  | 0.269  | 45.41         | 44.80         | 45.11 | 0.44b     |
| 6a         | 0.10  | 0.065  | 0.069  | 86.66         | 85.84         | 86.25 | 0.58f     |
| 6a         | 0.05  | 0.082  | 0.081  | 83.17         | 83.38         | 83.28 | 0.15f     |
| 6a         | 0.01  | 0.255  | 0.259  | 47.67         | 46.85         | 47.26 | 0.58b     |
| 8b         | 0.10  | 0.127  | 0.130  | 73.94         | 73.32         | 73.63 | 0.44g     |
| 8b         | 0.05  | 0.210  | 0.216  | 56.91         | 55.67         | 56.29 | 0.87e     |
| 8b         | 0.01  | 0.280  | 0.297  | 42.54         | 39.05         | 40.80 | 2.47b     |
| 8c         | 0.10  | 0.178  | 0.175  | 63.47         | 64.09         | 63.78 | 0.44d     |
| 8c         | 0.05  | 0.269  | 0.272  | 44.80         | 44.18         | 44.49 | 0.44b     |
..Table 3: Continued.

| Compd. No. | Conc. | R1 | R2 | R1 Inhibation | R1 Inhibation | Mean | St. De (%) |
|-------------|-------|----|----|---------------|---------------|------|------------|
| 8d          | 0.05  | 0.200 | 0.205 | 58.96          | 57.93          | 58.44 | 0.73<sup>e</sup> |
| 8d          | 0.01  | 0.241 | 0.245 | 50.54          | 49.72          | 50.13 | 0.58<sup>b</sup> |
| 8e          | 0.10  | 0.101 | 0.106 | 79.27          | 78.25          | 78.76 | 0.73<sup>g</sup> |
| 8e          | 0.05  | 0.173 | 0.177 | 64.50          | 63.68          | 64.09 | 0.58<sup>d</sup> |
| 8e          | 0.01  | 0.288 | 0.293 | 40.90          | 39.87          | 40.39 | 0.73<sup>b</sup> |
| 8f          | 0.10  | 0.187 | 0.191 | 61.63          | 60.80          | 61.21 | 0.58<sup>d</sup> |
| 8f          | 0.05  | 0.212 | 0.215 | 56.49          | 55.88          | 56.19 | 0.44<sup>e</sup> |
| 8f          | 0.01  | 0.226 | 0.229 | 53.62          | 53.01          | 53.31 | 0.44<sup>e</sup> |
| 9a          | 0.10  | 0.037 | 0.039 | 92.41          | 92.00          | 92.20 | 0.29<sup>a</sup> |
| 9a          | 0.05  | 0.042 | 0.045 | 91.38          | 90.77          | 91.07 | 0.44<sup>a</sup> |
| 9a          | 0.01  | 0.175 | 0.179 | 64.09          | 63.27          | 63.68 | 0.58<sup>d</sup> |
| 9d          | 0.10  | 0.172 | 0.174 | 64.70          | 64.29          | 64.50 | 0.29<sup>d</sup> |
| 9d          | 0.05  | 0.257 | 0.251 | 47.26          | 48.49          | 47.88 | 0.87<sup>b</sup> |
| 9d          | 0.01  | 0.298 | 0.292 | 38.85          | 40.08          | 39.46 | 0.87<sup>b</sup> |
| 9e          | 0.10  | 0.152 | 0.155 | 68.81          | 68.19          | 68.50 | 0.44<sup>d</sup> |
| 9e          | 0.05  | 0.188 | 0.191 | 61.42          | 60.80          | 61.11 | 0.44<sup>d</sup> |
| 9e          | 0.01  | 0.233 | 0.236 | 52.19          | 51.57          | 51.88 | 0.44<sup>b</sup> |

* Data are represented by Mean±SD of 3 replicats. DPPH scavenging activity represented as %.

Statistical analysis is carried out using two way ANOVA coupled with CO-state computer program where similar letters are insignificant and different letters are significant at \(P \leq 0.05\). Vitamin C standard,
was used as positive control. DPPH scavenging activity was calculated as following: % Inhibition = 100 - [Absorbance of the test compound/Absorbance of the control] × 100

The DPPH scavenging activity of the most potent compounds 2a, 2b, 4a, 9a compared with that of Vitamine C in a dose dependent manner are given in Table 4. The DPPH scavenging activity of the latter compounds obeys the order 2b > 4a > 9a > 2a (Figure 3).

**Table 4:** DPPH scavenging activity of the Potent isoquinioline compounds compared with ascorbic acid.*

| Compound No. | % of inhibition at dose 10 micro of 0.1gm | % of inhibition at dose 10 micro of 0.05gm | % of inhibition at dose 10 micro of 0.01gm |
|--------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Ascorbic acid| 99.20±4.22a                              | 66.70±5.32d                             | 48.78±2.22b                             |
| 2a           | 96.41±0.44a                              | 45.31±0.73b                             | 29.31±0.29c                             |
| 2b           | 96.41±0.15a                              | 96.00±0.15a                             | 94.36±0.15a                             |
| 4a           | 95.38±0.44a                              | 95.49±0.29a                             | 89.02±0.44a                             |
| 9a           | 92.20±0.29a %                            | 91.07±0.44a %                           | 63.68±0.58d %                           |

* Data are represented by Mean±SD of 3 replicats. DPPH scavenging activity represented as %. Statistical analysis is carried out using two way ANOVA coupled with CO-state computer program where similar letters are insignificant and different letters are significant at \( P \leq 0.05 \). Vitamin C standard, was used as positive control. DPPH scavenging activity was calculated as following: % Inhibition = 100 - [Absorbance of the test compound/Absorbance of the control] × 100

**Conclusions**

In this paper, we have successfully synthesized 7-acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl/4-nitrophenyl)-5,6,7,8-tetrahydrosoquinoline-3(2H)-thiones 2a,b in excellent yields via cyclocondensation reaction of 2,4-diacetyl-5-hydroxy-5-methyl-3-(3-nitrophenyl/4-nitrophenyl)cyclohexanones 1a,b with cyanothioacetamide. Compounds 2a,b were used as starting materials for synthesizing two new series of isoquinoline derivatives; 3-substituted thio-5,6,7,8-tetrahydroisoquinoline-4-carbonitriles 3,4a,b, 6 and 8a-g, and related 1-amino-2-substituted-6,7,8,9-tetrahydrothieno [2,3-c] isoquinolines 9a-e. Structural formulae of all new compounds were characterized on the basis of their spectroscopic data. Most of the synthesized compounds showed good activity as anticancer agents and excellent activity as antioxidants.

**Experimental Section**

**General**
Melting points were determined on a Gallan-Kamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr, $\nu_{\text{max}}$ in cm$^{-1}$). The $^1$H and $^{13}$C NMR spectra were recorded on a Varian A5 500 MHz spectrometer using DMSO-$d_6$ (except for compounds 3 and 4a in CDCl$_3$) as a solvent and tetramethylsilane (TMS) as internal reference. Coupling constants ($J$ values) are given in Hertz (Hz). The purity of the obtained products is checked by TLC.

**Reaction of 2-acetyl-cyclohexanones 1a,b with cyanothioacetamide; Synthesis compounds 2a,b**

A mixture of compound 1a,b (10 mmol), cyanothioacetamide (10 mmol) and piperidine (0.8 mL, 10 mmol) in ethanol (100 mL) was refluxed for 2 h. The yellow crystals that formed on hot were collected, washed with methanol, dried in air to give compounds 2a,b. The purity of these products is 100% and needs no any purification.

7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydroisoquinoline-3(2H)-thione (2a). Yield: 96%; m. p: 279-280 °C. IR: 3429 (O-H), 3235 (N-H); 3139 (C-H, sp$^2$); 2971 (C-H, sp$^3$); 2221 (C≡N); 1710 (C=O). $^1$H NMR: $\delta$ 13.68 (s, 1H, NH); 7.95-8.05 (m, 2H, ArH); 7.51-7.58 (m, 2H, ArH); 5.05 (s, 1H, OH); 4.61-4.63 (d, $J$ =10, 1H, C$^8$H); 3.23-3.26 (d, $J$ =15, 1H, C$^5$H), 2.88-2.90 (d, $J$ =10, 1H, C$^7$H), 2.83-2.87 (d, $J$ =20, 1H, C$^5$H); 2.12 (s, 3H, COCH$_3$); 1.86 (s, 3H, CH$_3$); 1.23 (s, 3H, CH$_3$).

7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(4-nitrophenyl)-5,6,7,8-tetrahydroisoquinoline-3(2H)-thione (2b). Yield: 93%; m. p 290-291°C. IR: 3482 (O-H); 3235 (NH); 3106 (C-H, sp$^2$); 2971, 2872 (C-H, sp$^3$); 2220 (C≡N); 1708 (C=O). $^1$H NMR: $\delta$ 7.84-7.86 (d, $J$ =10, 2H, ArH); 7.62-7.64 (d, $J$ =10, 2H, ArH); 7.51-7.53 (d, $J$ =10, 2H, ArH); 7.33-7.34 (d, $J$ =5, 2H, ArH); 5.04 (s, 1H, OH); 4.97-4.99 (d, $J$ =10, 1H, C$^8$H); 3.13-3.16 (d, $J$ =20, 2H, C$^5$H), 3.10-3.11 (d, $J$ =5, 2H, C$^7$H), 2.86-2.90 (d, $J$ =20, 1H, C$^5$H); 2.02 (s, 3H, COCH$_3$); 1.93 (s, 3H, CH$_3$); 1.29 (s, 3H, CH$_3$).

**Reaction of compounds 2a,b with ethyl iodide, 2-chloroacetamide, N-(naphthalen-1-yl)-2-chloroacetamide (5) or N-aryl-2-chloroacetamides 7a-d; Synthesis of compounds 3, 4a,b, 6 and 8a-g**

A mixture of 2a,b (10 mmol), ethyl iodide, 2-chloroacetamide, N-(naphthalen-1-yl)-2-chloroacetamide (5) or N-aryl-2-chloroacetamides 7a-d (10 mmol) and sodium acetate trihydrate (1.5 g, 11 mmol) in ethanol (100 mL) was refluxed for one hour. The solid that formed on dilution with water (50 mL) was collected and then crystallized from ethanol to give white crystals of compounds 3, 4a,b, 6 and 8a-g respectively.

7-Acetyl-4-cyano-1,6-dimethyl-3-ethylthio-6-hydroxy-8-(4-nitrophenyl)-5,6,7,8-tetrahydroisoquinoline (3): Yield: 83%; m.p.: 144-145 °C. IR: 3509 (O-H); 3098 (C-H, sp$^2$); 2974, 2919 (C-H, sp$^3$); 2213 (C≡N); 1698 (C=O), 1603(C=N). $^1$H NMR: $\delta$ 8.13-8.15 (d, $J$ = 10, 2H ArH), 7.35-7.37 (d, $J$ = 10, 2H, ArH), 4.99 (s, 1H, OH), 4.75-4.78 (d, $J$ = 15, 1H, C$^8$H), 3.15-3.31 (m, 3H: C$^5$H and SCH$_2$), 2.87-2.95 (m, 2H: C$^7$H and C$^5$H), 2.18 (s, 2H, COCH$_3$), 1.98 (s, 3H, CH$_3$), 1.31 (s, 3H, CH$_3$), 1.29 (t, 3H, CH$_3$).
2-[(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]acetamide (4a): Yield: 91%; m.p.: 174-175°C. IR: 3481, 3373 (O-H, NH2); 2991, 2930 (C-H, sp3); 2215 (C≡N); 1701 (C=O, acetyl); 1660 (C=O, amide). 1H NMR: δ 7.37-8.18 (m, 6H: NH2 and ArH), 4.53-4.55 (d, J = 10.0, 1H, C8-H), 3.82-3.97 (dd, J = 15.0, 2H, SCH2), 3.02-3.21 (m, 3H: C7-H and C5-H2), 1.96 (s, 3H, COCH3), 1.87 (s, 3H, CH3), 1.42 (s, 3H, CH3). 13C NMR: δ 214.79, 175.43, 161.92, 160.77, 160.44, 160.11, 159.78, 158.14, 149.88, 149.66, 145.64, 134.84, 131.34, 129.23, 123.41, 122.78, 118.74, 116.47, 114.65, 114.20, 111.93, 106.45, 69.90, 64.12, 45.89, 42.55, 35.59, 33.60, 28.30, 25.83.

2-[(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(4-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]acetamide (4b): Yield: 88%; m.p.: 178-179 °C. IR: 3466, 3355 (O-H, NH2); 2968, 2919 (C-H, sp3); 2222 (C≡N); 1709 (C=O, acetyl); 1662 (C=O, amide). 1H NMR: δ 8.09-8.11 (d, J = 10.0, 2H, ArH), 7.54 (s, 1H, NH), 7.30-7.32 (dd, J = 5.0, 2H, ArH), 7.09 (s, 1H, NH), 5.00 (s, 1H, OH), 4.70-4.72 (d, J = 10.0, 1H, C8-H), 3.81-3.89 (dd, J = 15.0, 2H, SCH2), 3.25-3.28 (d, J = 15.0, 1H, C5-H), 2.88-2.90 (d, J = 10.0, 1H, C7-H), 2.83-2.87 (d, J = 20.0, 1H, C5-H), 2.23 (s, 3H, COCH3), 1.91 (s, 3H, CH3), 1.24 (s, 3H, CH3).

2-[(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]-N-(naphthalen-1-y1)acetamide (6)

Yield: 86 %; m.p.: 237-238 °C. IR: 3527 (O-H); 3401 (N-H); 3063 (C-H, sp2); 2970, 2928 (C-H, sp3); 2214 (C≡N); 1702 (2 C=O); 1597 (C≡N). 1H NMR: δ 10.19 (s, 1H, NH), 7.30-8.01 (m, 11H, ArH); 5.01 (s, 1H, OH), 4.76-4.78 (d, J =10, 1H, C8-H); 4.22-4.30 (dd, J=15, 2H, SCH2); 3.25-3.27 (d, J=10, 1H, C5-H), 2.87-2.95 (m, 2H: C7-H and C5-H), 2.15 (s, 3H, COCH3), 1.97 (s, 3H, CH3), 1.27 (s, 3H, CH3).

2-[(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]-N-phenylacetamide (8a). Yield: 93%; m.p.: 191-192 °C. IR: 3500 (O-H); 3353(N-H); 3082 (C-H, sp2); 2971, 2923 (C-H, sp3); 2214 (C≡N); 1698 (C=O, acetyl); 1666 (C=O, amide). 1H NMR: δ 10.25 (s, 1H, NH), 8.06-8.08 (d, 1H, ArH), 7.94-7.95 (d, 1H, ArH), 7.51-7.56 (m, 4H, ArH), 7.24-7.28 (m, 2H, ArH), 7.00-7.04 (m, 1H, ArH), 5.00 (s, 1H, OH), 4.76-4.79 (d, J = 15, 1H, C8-H), 4.08-4.18 (dd, J = 15, 2H, SCH2), 3.45 (m, 1H, C5-H), 2.93-2.97 (m, 2H: C7-H and C5-H), 2.19 (s, 3H, COCH3), 1.91 (s, 3H, CH3), 1.28 (s, 3H, CH3).

2-[(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]-N(4-tolyl)acetamide (8b). Yield: 95%; m.p.: 187-188 °C. IR: 3559 (O-H); 3317 (N-H); 3034 (C-H, sp2); 2973, 2924 (C-H, sp3); 2213 (C≡N); 1701 (C=O, acetyl); 1675 (C=O, amide). 1H NMR: δ 10.12 (s, 1H, NH), 8.06-8.08 (d, 1H, ArH), 7.94-7.95 (m, 1H, ArH), 7.53-7.55 (m, 2H, ArH), 7.38-7.40 (d, 2H, ArH), 7.04-7.06 (d, 2H, ArH), 4.99 (s, 1H, OH), 4.76-4.78 (d, J = 10.0, 1H, C8-H), 4.06-4.15 (dd, J = 15, 2H, SCH2), 2.89-2.97 (m, 3H: C7-H and C5-H2), 2.21 (s, 3H, CH3 of 4-tolyl residue), 2.17 (s, 3H, COCH3), 1.99 (s, 3H, CH3), 1.28 (s, 3H, CH3). 13C NMR: δ 208.74, 200.27, 181.20, 165.58, 160.36, 157.54, 150.02, 147.75, 145.84, 136.23, 134.97, 132.03, 130.00, 128.88, 128.47, 122.54, 121.56, 118.87, 114.90, 103.87, 67.23, 65.74, 55.86, 43.11, 42.28, 34.55, 30.84, 27.33, 24.51, 20.21, 18.36.
2-(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(3-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]-N(4-chlorophenyl)acetamide (8c)

Yield: 84%; m.p.: 205-206 °C. IR: 3536 (O-H); 3289 (N-H); 3074 (C-H, sp^2); 2973, 2924 (C-H, sp^3); 2216 (C≡N); 1694 (C=O, acetyl); 1666 (C=O, amide). ^1H NMR: δ 10.37 (s, 1H, NH), 8.06 (d, 1H, ArH), 7.94 (s, 1H, ArH), 7.54-7.56 (m, 4H, ArH), 7.29-7.31 (d, J = 10, 2H, ArH), 4.99 (s, 1H, OH), 4.76-4.78 (d, J = 10, 1H C^5H), 4.14-4.17 (dd, 2H, SCH^2), 3.30-3.32 (d, J =10, 1H, C^5H), 2.93-2.95 (m, 2H: C^7H and C^5H), 2.17 (s, 3H, COCH^3), 1.89 (s, 3H, CH^3), 1.28 (s, 3H, CH^3). ^13C NMR: δ 204.15, 161.49, 155.77, 152.85, 145.47, 143.16, 141.23, 133.10, 130.38, 125.41, 123.94, 123.18, 122.10, 117.96, 116.97, 115.78, 110.30, 99.30, 62.66, 61.15, 38.53, 37.70, 30.01, 26.27, 22.75, 19.90.

2-(7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-(4-nitrophenyl)-5,6,7,8-tetrahydro-isoquinolin-3-yl)thio]-N-(4-chlorophenyl)acetamide (8f)

Yield: 94%; m.p.: 205-206 °C. IR: 3536 (O-H); 3289 (N-H); 3074 (C-H, sp^2); 2973, 2924 (C-H, sp^3); 2216 (C≡N); 1694 (C=O, acetyl); 1666 (C=O, amide). ^1H NMR: δ 10.37 (s, 1H, NH), 8.06 (d, 1H, ArH), 7.94 (s, 1H, ArH), 7.54-7.56 (m, 4H, ArH), 7.29-7.31 (d, J = 10, 2H, ArH), 4.99 (s, 1H, OH), 4.76-4.78 (d, J = 10, 1H C^5H), 4.14-4.17 (dd, 2H, SCH^2), 3.30-3.32 (d, J =10, 1H, C^5H), 2.93-2.95 (m, 2H: C^7H and C^5H), 2.17 (s, 3H, COCH^3), 1.89 (s, 3H, CH^3), 1.28 (s, 3H, CH^3). ^13C NMR: δ 204.15, 161.49, 155.77, 152.85, 145.47, 143.16, 141.23, 133.10, 130.38, 125.41, 123.94, 123.18, 122.10, 117.96, 116.97, 115.78, 110.30, 99.30, 62.66, 61.15, 38.53, 37.70, 30.01, 26.27, 22.75, 19.90.
Yield: 86%; m.p.: 193-194 °C. IR: 3540 (O-H); 3337 (N-H); 3109 (C-H, sp²); 2968 (C-H, sp³); 2220 (C≡N); 1683 (3 C=O); 1595 (C=N). ¹H NMR: δ 10.57 (s, 1H, NH), 8.06-8.11 (d, 2H, ArH), 7.84-7.86 (d, 2H, ArH), 7.62-7.65 (d, 2H, ArH), 7.28-7.31 (d, 2H, ArH), 5.02 (s, 1H, OH), 4.76-4.78 (d, 1H, C⁸H), 4.36-4.38 (d, 1H, C⁵H), 4.11-4.13 (dd, 2H, SCH₂), 2.88-2.91 (m, 2H: C⁷H and C⁵H), 2.12 (s, 3H, COCH₃), 1.80 (s, 3H, COCH₃), 1.23 (s, 3H, CH₃ attached to pyridine ring), 1.03 (s, 3H, CH₃).

7-Acetyl-1-amino-2-(N-aryl carbamoyl)-5,8-dimethyl-8-hydroxy-6-(3-nitro-phenyl or 4-nitrophenyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolines 9a-e; general procedures.

Method A)

To a suspension of 8a-e (10 mmol) in abs. ethanol (60 mL), anhydrous sodium carbonate (0.30 g) was added. The reaction mixture was refluxed for 3 hours. The yellow crystals that formed while hot were collected, washed with water, dried in air and then crystallized from dioxane to give 9a-e.

7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-6-(3-nitrophenyl)-N-phenyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (9a). Yield: 87%; m.p.: 287-288 °C. IR: 3415, 3388, 3314 (O-H, NH₂, N-H); 2914 (C-H, sp³); 1703 (C=O, acetyl); 1622 (C=O, amide). ¹H NMR: δ 9.43 (s, 1H, NH); 7.31-7.84 (m, 9H, ArH); 7.09 (s, 2H, NH₂); 4.86-4.88 (d, J = 10, 1H, C⁶H); 4.84 (s, 1H, OH); 3.64-3.67 (d, J = 15, 1H, C⁹H); 3.41-3.44 (d, J = 20, 1H, C⁷H); 2.93-2.95 (d, J = 10, 1H, C⁹H); 2.28 (s, 3H, CH₃ of 4-tolyl residue); 2.21 (s, 3H, COCH₃); 2.03 (s, 3H, CH₃); 1.33 (s, 3H, CH₃). ¹³C NMR: δ 209.44, 164.31, 158.22, 156.58, 149.38, 147.92, 147.07, 142.88, 138.83, 135.08, 130.11, 128.36, 128.24, 123.45, 123.02, 122.40, 121.51, 121.26, 97.03, 67.14, 65.90, 42.90, 41.98, 31.17, 27.94, 24.74.

7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-6-(3-nitrophenyl)-N-(4-tolyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (9b). Yield: 92%; m.p.: 291-292 °C. IR: 3415, 3388, 3314 (O-H, NH₂, N-H); 2914 (C-H, sp³); 1703 (C=O, acetyl); 1622 (C=O, amide). ¹H NMR: δ 9.35 (s, 1H, NH); 7.06-8.08 (d, J = 10, 1H, ArH); 7.84 (s, 1H, ArH); 7.53-7.58 (m, 4H, ArH); 7.12-7.14 (d, 2H, J = 10, ArH); 7.07 (s, 2H, NH₂); 4.86-4.88 (d, J = 10, 1H, C⁶H); 4.84 (s, 1H, OH); 3.64-3.67 (d, J = 15, 1H, C⁹H); 3.41-3.45 (d, J = 20, 1H, C⁷H); 2.93-2.95 (d, J = 10, 1H, C⁹H); 2.28 (s, 3H, CH₃ of 4-tolyl residue); 2.21 (s, 3H, COCH₃); 2.03 (s, 3H, CH₃); 1.33 (s, 3H, CH₃). ¹³C NMR: δ 209.44, 164.19, 158.12, 156.53, 149.19, 147.92, 147.08, 142.38, 136.25, 135.07, 132.42, 130.11, 128.77, 128.21, 123.08, 122.40, 121.51, 121.31, 97.20, 67.15, 65.90, 42.91, 41.97, 31.18, 27.95, 24.73, 20.46.

7-Acetyl-1-amino-N-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-6-(3-nitrophenyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (9c). It was obtained by cyclization of compound 8c. Yield: 94%; m.p.: 293-294 °C. IR: 3417, 3383, 3314 (O-H, NH₂, N-H); 3075 (C-H, sp²); 2914 (C-H, sp³); 1706 (C=O, amide). ¹H NMR: δ 9.35 (s, 1H, NH); 7.06-8.08 (d, J = 10, 1H, ArH); 7.84 (s, 1H, ArH); 7.53-7.58 (m, 4H, ArH); 7.12-7.14 (d, 2H, J = 10, ArH); 7.07 (s, 2H, NH₂); 4.86-4.88 (d, J = 10, 1H, C⁶H); 4.84 (s, 1H, OH); 3.64-3.67 (d, J = 15, 1H, C⁹H); 3.41-3.45 (d, J = 20, 1H, C⁷H); 2.93-2.95 (d, J = 10, 1H, C⁹H); 2.28 (s, 3H, CH₃ of 4-tolyl residue); 2.21 (s, 3H, COCH₃); 2.03 (s, 3H, CH₃); 1.33 (s, 3H, CH₃). ¹³C NMR: δ 209.44, 164.19, 158.12, 156.53, 149.19, 147.92, 147.08, 142.38, 136.25, 135.07, 132.42, 130.11, 128.77, 128.21, 123.08, 122.40, 121.51, 121.31, 97.20, 67.15, 65.90, 42.91, 41.97, 31.18, 27.95, 24.73, 20.46.
acetyl); 1622 (C=O, amide). $^1$H NMR: $^\delta$ 9.56 (s, 1H, NH); 7.36-8.08 (m, 8H, ArH); 7.13 (s, 2H, NH$_2$); 4.86-4.88 (d, $J = 10$, 1H, C$_6$H); 4.85 (s, 1H, OH); 3.64-3.67(d, $J = 15$, 1H, C$_9$H), 3.40-3.44 (d, $J = 20$, 1H, C$_7$H); 2.93-2.95 (d, $J = 10$, 1H, C$_9$H); 2.21 (s, 3H, COCH$_3$); 2.04 (s, 3H, CH$_3$); 1.33 (s, 3H, CH$_3$). $^{13}$C NMR: $^\delta$ 209.42, 164.35, 158.33, 156.65, 149.62, 147.92, 147.04, 142.94, 135.07, 130.10, 128.27, 128.23, 126.96, 122.95, 122.65, 122.41, 121.51, 96.81, 67.14, 65.88, 42.8, 41.99, 31.17, 27.94, 24.74.

7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-6-(4-nitrophenyl)-N-phenyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (9d). Yield: 91%; m.p.: 285-286 °C. IR: 3406, 3320 (O-H, NH$_2$, N-H); 2921(C-H, sp$^3$); 1703 (C=O, acetyl); 1622 (C=O, amide). $^1$H NMR: $^\delta$ 9.41 (s, 1H, NH); 8.11-8.13 (d, $J = 10$, 2H, ArH); 7.67-7.69 (d, $J = 10$, 2H, ArH); 7.28-7.33 (m, 5H, ArH); 7.08 (s, 2H, NH$_2$); 4.84 (s, 1H, OH); 4.82-4.84 (d, $J = 10$, 1H, C$_6$H); 3.59-3.63(d, $J = 15$, 1H, C$_9$H), 3.40-3.43 (d, $J = 20$, 1H, C$_7$H); 2.87-2.89 (d, $J = 10$, 1H, C$_9$H); 2.19 (s, 3H, COCH$_3$); 2.00 (s, 3H, CH$_3$); 1.32 (s, 3H, CH$_3$). $^{13}$C NMR: $^\delta$ 209.25, 164.33, 158.17, 156.61, 152.92, 149.35, 145.94, 142.71, 138.84, 129.40, 128.37, 128.22, 123.80, 123.46, 123.02, 121.26, 97.03, 67.14, 65.73, 43.19, 41.96, 31.19, 27.92, 24.61. Anal. Calcd. for C$_{28}$H$_{26}$N$_4$O$_5$S (530.16): C, 63.38; H, 4.94; N, 10.56%. Found: C, 62.98; H, 5.01; N, 10.62%.

7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-6-(4-nitrophenyl)-N-(4-tolyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (9e). Yield: 92%; m.p.: 292-293 °C. IR: 3400, 3322 (O-H, NH$_2$, N-H); 2919 (C-H, sp$^3$); 1701 (C=O, acetyl); 1623 (C=O, amide). $^1$H NMR: $^\delta$ 9.33 (s, 1H, NH); 8.11-8.13 (d, $J = 10$, 2H, ArH); 7.55-7.57 (d, $J = 10$, 2H, ArH); 7.27-7.29 (d, $J = 10$, 2H, ArH); 7.11-7.13 (d, $J = 10$, 2H, ArH); 7.05 (s, 2H, NH$_2$); 4.84 (br s, 1H, OH); 4.82-4.84 (d, $J = 10$, 1H, C$_6$H); 3.59-3.62 (d, $J = 15$, 1H, C$_9$H), 3.40-3.44 (d, $J = 20$, 1H, C$_7$H); 2.86-2.89 (d, $J = 10$, 1H, C$_9$H); 2.27 (s, 3H, CH$_3$ of 4-tolyl residue); 2.19 (s, 3H, COCH$_3$); 2.01 (s, 3H, CH$_3$); 1.32 (s, 3H, CH$_3$).

Method B).

To mixture of 2a,b (10 mmol) and respective N-aryl-2-chloroacetamide 7a-d (10 mmol) in ethanol (60 mL), anhydrous sodium carbonate (1.30 g) was added. The resulting mixture was refluxed for 3 hours. The solid that formed while hot was collected, washed with water, dried in air and then crystallized from dioxane to give compounds 9a-e; yield: 80-86%.

Cytotoxic activity

The cytotoxicity activity of the some synthesized compounds was determined according to the MTT method [26-28].

The pancreatic (PACA2) and human cancer lung (A549) cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and 1% GlutaMAX. Then the cells were seeded into sterile 96-well plates at a density of 10 $\times$ 10$^3$ cells/well and maintained at 37°C for 24 h.
Cancerous cells were exposed to compounds at concentrations of 0.75, 1.75, 3.125, 6.250, 12.500, 25, 50, and 100 μM for 72 h. The media was removing and add 40µl MTT stock solution to each well. The resulting solutions were incubated for more than 4 h. Subsequently, then add 120 µL of 10% SDS as solubilising reagent. GraphPad Prism software program was used to calculate the IC50 and IC90 values.

**Antioxidant activity**

DPPH has been used for measurement of free radical scavenging ability of antioxidants. Reduction of an alcoholic DPPH solution [29-31] in the presence of a hydrogen-donating antioxidant is the mainly step of this method. Hydrogen atom or electron-donation ability of the tested compounds were measured spectrophotometrically from the bleaching of the purple-colored ethanol solution of 2,2-diphenyl-1-picylhydrazyl (DPPH). In this study, antioxidant activity of the tested compounds was measured using the stable radical 2,2- diphenyl-1-picylhydrazyl (DPPH). The free radical scavenging capacity of the tested compounds was determined using DPPH. A solution 1: prepared by dissolving DPPH (0.002 gm) in ethanol (50 mL ethanol ). Solution 2: prepared by dissolving different weights 0.1, 0.05, 0.01 grams of each sample in 1mL of DMSO then take 10 µL of each sample solution with 1mL ethanol. Then mix 1mL of solution 1 with 1mL of solution 2 and the resulting mixture was vortexed thoroughly and left in the dark for about 30 min. The absorbance of the mixture was spectrophotometrically measured at $\lambda_{\text{max}} = 517$ nm against blank 1mL absolute ethanol and compared to the ascorbic acid (Vitamin C). DPPH radical scavenging activity (% RSA) of compounds was calculated from the absorbance at the start (0) and after some reaction time (T) according to the equation (1).

$$\text{(% RSA)} = \frac{(\text{ABS}-\text{ATS})}{\text{ABS}} \times 100 \quad (1)$$

Where ABS is the absorbance of blank sample (DPPH) solution without the compound to be tested and ATS is the absorbance of tested sample.

**Declarations**

**Supporting Information**

The Supporting Information is available free of charge at.......... It contains IR, $^1$H NMR and $^{13}$C NMR spectra of all newly synthesized compounds.

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**Schemes**

Scheme 1 to 4 are only available as downloads in the Supplementary Files section.

**Figures**
Cytotoxic activity of different concentrations of compounds 3, 8b, 8f and 8g against PACA2.

Figure 1
Figure 2

Cytotoxic activity of different concentrations of compounds 9a, 9c and 9e against A549.
Figure 3

Antioxidant activity of compounds 2a, 2b, 4a, 9a and ascorbic acid as a standard.

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