Hindawi
Journal of Chemistry
Volume 2019, Article ID 9403908, 10 pages
https://doi.org/10.1155/2019/9403908

*Research Article*

# Synthesis, X-Ray Crystal Structures, and Preliminary Antiproliferative Activities of New s-Triazine-hydroxybenzylidene Hydrazone Derivatives

**Assem Barakat**,[1,2] **Fardous F. El-Senduny**,[3] **Zainab Almarhoon**,[1] **Hessa H. Al-Rasheed**,[1] **Farid A. Badria**,[4] **Abdullah Mohammed Al-Majid**,[1] **Hazem A. Ghabbour**,[5] **and Ayman El-Faham**[1,2]

[1]*Chemistry Department, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[2]*Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Alexandria 21321, Egypt*
[3]*Department of Chemistry, Faculty of Science, Mansura University, Mansura 35516, Egypt*
[4]*Department of Pharmacognosy, Faculty of Pharmacy, Mansura University, Mansura 35516, Egypt*
[5]*Department of Medicinal Chemistry, Faculty of Pharmacy, Mansura University, Mansoura 35516, Egypt*

Correspondence should be addressed to Assem Barakat; ambarakat@ksu.edu.sa and Ayman El-Faham; aymanel_faham@hotmail.com

Received 10 February 2019; Accepted 11 April 2019; Published 30 April 2019

Academic Editor: Maria F. Carvalho



We herein report a new small library of Schiff-base compounds that encompasses s-triazine and (2 or 4)-hydroxylbenzylidene derivatives. These compounds were synthesized through a hydrazone linkage connecting both the s-triazine and hydroxybenzylidene derivatives. The synthetic strategy adopted allowed the synthesis of the target compounds with excellent yields and purities as observed from their NMR ($^1$H and $^{13}$C) and elemental analysis. Furthermore, **4f**, **5b**, and **5f** were further confirmed by X-ray single crystal diffraction technique. The preliminary antiproliferative activities for the synthesized compounds were tested against two different cancer cell lines including breast cancer (MCF-7) and colon cancer (HCT-116). From the eighteen compounds, which have been examined, only two derivatives having piperidine moiety showed more selectivity against the two cell lines MCF-7 and HCT-116, while the others showed very weak activity. The position of the hydroxyl group in the benzylidine ring and the substituent on the s-triazine moiety has great effect on the activity of the prepared compounds. The $IC_{50}$ values for the two derivatives **4a** and **5a** evaluated against breast cancer cells, very close to those for the chemotherapeutic drug cisplatin, are 27 $\mu$M (13.3 $\mu$g/mL), 17 $\mu$M (8.4 $\mu$g/mL), and 20 $\mu$M (6 $\mu$g/mL) for **4a**, **5a**, and cisplatin, respectively. These results propose the preliminary antiproliferative activity of these two derivatives may deserve further consideration for development of new derivatives as potent anticancer agents.

## 1. Introduction

Schiff bases have gained great importance in which these compounds have been found to exhibit antimicrobial [1–4], antiviral [1, 5], antioxidant [6], and antitumor [7, 8] activities. These activities are largely attributed due to the presence of the azomethine (R-NH-N=C-R) group which is important synthon for several transformations [9, 10]. In addition, the hydrazone linkage provides an appropriate system for pH-dependent of drugs release [11]. Several hydrazone derivatives have shown to exhibit antiproliferative activities with the ability to prevent cell progression in cancerous cells through different mechanisms [12]. Several hydrazone derivatives have been also shown antitumoral [13], antifungal, antiplatelet, antitubercular, antiviral, anticonvulsant, antimalarial, anti-inflammatory, and antipyretic activities [9, 14–19].

Similarly, s-triazine derivatives represent important class of compounds in medicinal chemistry [20–23]. Cyanuric chloride has been used as building blocks in the

synthesis of vast derivatives bearing the s-triazine moiety, due to the low-cost, commercial availability, and ease of displacement of the three chlorine atoms by various nucleophiles under controlled temperature [24]. These advantages allowed for the preparation of mono-, di- and trisubstituted s-triazines derivatives with a wide range of biological activities [25–27], such as adenosine receptor antagonist [28], antiamoebic [29], antileishmanial [31–33], anticancer [32], antimalarial [34], antimicrobial [35–37], antiviral [38], antitubercular [39], carbonic anhydrase inhibitor [40], and cathepsin B inhibitor [41], Previously, we reported new series of s-triazine Schiff-base derivatives [42–44]; among of the reported compounds, only three derivatives were able to inhibit the growth of lung (A549) and hepatocellular carcinoma (HepG2) cancer cell lines. The results showed that s-triazine with the two substituents methoxy and piperidine in the target product made the compound more selective to the hepatocyte carcinoma HepG2 ($IC_{50}$ value of 1.5 $\mu$g/mL). On the contrary, the combination between morpholine and piperdine motifs in the final target made the compound more selective to the lung carcinoma A549 ($IC_{50}$ value of 5.6 $\mu$g/ml) and with reasonable effect to the hepatocyte carcinoma HepG2 (IC50 value 6.5 $\mu$g/ml) [44], Recently, Bai et al. [45] identified a series of 1,3,5-triazine hydrazone derivatives as dual-effective inhibitors against both epidermal growth factor receptor (WTEGFR) and mutant epidermal growth factor receptor (EGFR). Moreover, some of them exhibited considerable antiproliferative activity against A549, A431, and NCIH1975 cell lines.

Menwear et al. [46] reported 1,3,5-triazine hydrazone based on 4-hydroxy-3,5-dimethoxyphenyl derivatives (Figure 1) as selective inhibitors of the mammalian target of rapamycin (mTOR). They claimed that the phenolic hydroxyl group in the series is critical in the activity because it acts as a hydrogen donor, where when it was substituted by a methoxy, a dramatic loss in the activity was observed.

These results encouraged us to develop small library (Figure 1) bearing of s-triazine derivatives with different substituents and (2 or 4)-hydroxybenzylidene derivatives through a hydrazone linkage. The antiproliferative activities of the target products will be discussed to fine-tune and get more information related to the effect of both substituent in the s-triazine moiety and the position of the hydroxyl group in the benzylidene core attached to the s-triazine through the hydrazone linkage.

## 2. Experimental Section

### 2.1. Chemistry

*2.1.1. General.* All reagents and solvents were purchased from commercial suppliers and were used without further purification; NMR spectra ($^1$H-NMR and $^{13}$C-NMR) were recorded on a JEOL 400 MHz spectrometer. $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) were run in either deuterated dimethylsulphoxide (DMSO-$d_6$) or deuterated chloroform ($CDCl_3$). Chemical shifts ($\delta$) are referred in terms of ppm and J-coupling constants are given in Hz. Mass spectra were recorded on a JEOL of JMS-600 H. Elemental analysis was carried out on an Elmer 2400 elemental analyzer. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer.

*2.1.2. 6-Chloro-4,6-disubstituted s-Triazine Derivatives* (**2a-i**). 6-Chloro-4,6-disubstituted s-triazine derivatives (**2a-i**) were synthesized following the strategies and methods already reported by our group and others [47–51], as shown in Scheme 1. 6-Hydrazine-4,6-disubstituted s-triazine derivatives were synthesized following the published and reported method by our group [47, 49]. All spectral data were in good agreement with the reported data.

The compounds of **4f**, **5b**, and **5f** obtained as single crystals by slow evaporation from ethanol solution to afford the pure compounds at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic Mo *Kα* radiation, $\lambda = 0.71073$ Å at 293 (2) and 296 (2) K. Cell refinement and data reduction were carried out by Bruker SAINT. SHELXT was used to solve structures [52, 53]. The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on *F*. CCDC No. 1567719 (**4f**), 1567728 (**5b**), and 1567725 (**5f**) containng the supplementary crystallographic data for these compounds wwhich can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

*2.1.3. General Procedure for the Synthesis of Schiff Bases* **4a-i** *and* **5a-h**. A solution of hydroxybenzaldehyde derivatives **3a-b** (6 mmol), drop of acetic acid, and s-triazine derivatives **2a-i** (6 mmol) in EtOH (10 ml) were mixed and heated under reflux for 3 h (TLC 20% EtOAc/n-hexane). The solvent was evaporated slowly, to provide the corresponding product **4a-i** and **5a-h**.

*(1) (E)-2,6-Di-tert-butyl-4-((2-(4,6-di(piperidin-1-yl)-1,3,5-triazin 2-yl)hydrazono)methyl)phenol (**4a**).* Yellow powder in yield 93%; m.p: >250°C; IR (KBr, $cm^{-1}$): 3637, 3423, 3197, 2960, 2935, 1583, 1570, 1510, 1462;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.34 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.46 (s, 1H, Ph), 7.19 (s, 1H, Ph), 3.73 (brs, 8H, $4CH_2$), 1.55 (m, 8H, $4CH_2$), 1.38 (s, 18H, $6CH_3$), 1.34 (m, 4H, $2CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 206.9, 156.6, 136.0, 128.9,124.4, 44.7, 34.3, 30.9, 30.1, 25.8, 24.6; LC/MS (ESI): 494.70 $[M + 1]^+$; Anal. for $C_{28}H_{43}N_7O$; Calcd: C, 68.12; H, 8.78; N, 19.86; Found: C, 68.13; H, 8.79; N, 19.89.

*(2) (E)-2,6-Di-tert-butyl-4-((2-(4,6-dimorpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4b**).* Yellow powder in yield 91%; m.p: 180°C; IR (KBr, $cm^{-1}$): 3086, 3053, 2953, 2885,1598, 1560, 1516, 1463, 1371;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.25 (s, 1H, CH =), 8.10 (brs, 1H, NH), 7.38 (s, 1H, Ph), 7.12 (s, 1H, Ph), 3.70 (brs, 8H, $4CH_2$), 1.50 (m, 8H,

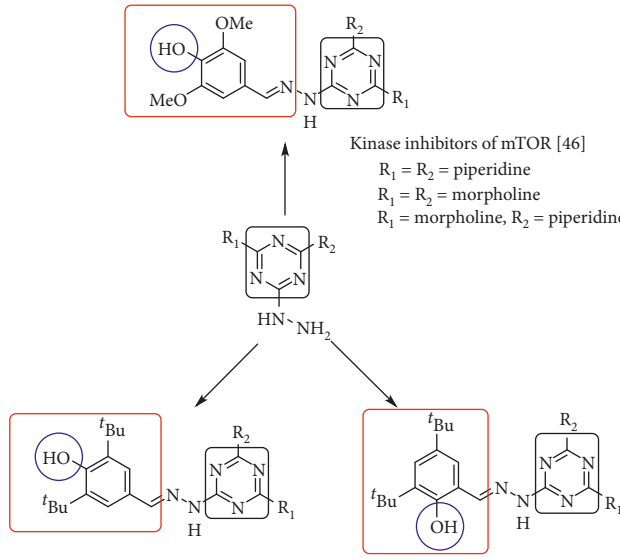
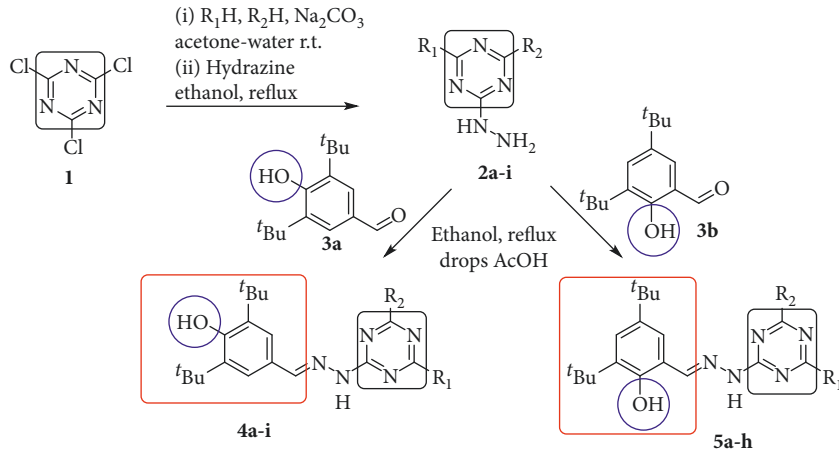



Figure 1: Rational design for the target products.




Scheme 1: Synthetic route for preparation of s-triazine Schiff-base derivatives.

$4CH_2$), 1.35 (s, 18H, $6CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.9, 155.3, 135.1, 129.0, 125.1, 65.9, 44.6, 34.2, 30.9, 30.1LC/MS (ESI): 498.31 $[M+1]^+$; Anal. for $C_{26}H_{39}N_7O_3$; Calcd: C, 62.75; H, 7.90; N, 19.70; Found: C, 62.71; H, 7.91 N, 19.72.

*(3) (E)-2,6-Di-tert-butyl-4-((2-(4-(diethylamino)-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol* (**4c**). Yellow powder in yield 89%; m.p: 195°C; IR (KBr, $cm^{-1}$): 3420, 2999, 2960, 2908, 2870, 1624, 1591, 1456;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.60 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.66 (s, 1H, Ph), 7.50 (s, 1H, Ph), 3.82 (brs, 4H, $2CH_2$), 3.72 (t, 4H, $J$ = 22.3 Hz, $2CH_2$), 3.60 (brs, 4H, $2CH_2$), 1.49 (s, 9H, $3CH_3$), 1.44 (s, 9H, $3CH_3$), 1.18 (m, 6H, $2CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.4, 176.5 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 47.9, 44.7, 34.3, 31.1, 12.3; LC/MS (ESI): 484.33 $[M+1]^+$; Anal. for $C_{26}H_{41}N_7O_2$; Calcd: C, 64.57; H, 8.54; N, 20.27; Found: C, 64.57; H, 8.53; N, 20.25.

*(4) (E)-2,6-Di-tert-butyl-4-((2-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4d**).* Yellow powder in yield 80%; m.p: 114°C; IR (KBr, $cm^{-1}$): 3215, 3045, 2958, 2908, 2866, 1614, 1598, 1544,1463;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.94 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.70 (s, 1H, Ph), 7.52 (s, 1H, Ph), 3.93 (s, 3H, $OCH_3$), 3.83 (brs, 4H, $2CH_2$), 3.70 (brs, 4H, $2CH_2$), 1.45 (s, 9H, $3CH_3$), 1.43 (s, 9H, $3CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 194.6, 173.5, 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 53.9, 47.9, 34.3, 31.0; LC/MS (ESI): 443.27 $[M + 1]^+$; Anal. for $C_{23}H_{34}N_6O_3$; Calcd: C, 62.42; H, 7.74; N, 18.99; Found: C, 62.43; H, 7.75; N, 19.01.

*(5) (E)-2,6-Di-tert-butyl-4-((2-(4-morpholino-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4e**).* Yellow powder in yield 90%, m.p: >250°C; IR (KBr, $cm^{-1}$): 3215,3157, 3045, 2958, 2908, 2866, 1614, 1598, 1544, 1463; $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.34 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.46 (s, 1H, Ph), 7.19 (s, 1H, Ph), 3.73 (brs, 8H, $4CH_2$), 1.50 (m, 4H, $2CH_2$), 1.45 (m, 4H, $2CH_2$), 1.38 (s, 18H, $6CH_3$), 1.34 (m, 2H, $CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.7, 156.6, 136.0, 128.9, 124.4, 44.7, 34.3, 30.9, 30.1, 25.8, 24.6; LC/MS (ESI): 496.33 $[M + 1]^+$; Anal. for $C_{27}H_{41}N_7O_2$; Calcd: C, 65.43; H, 8.34; N, 19.78; Found: C, 65.43; H, 8.35; N, 19.76.

*(6) (E)-4-((2-(4-(Benzylamino)-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)-2,6-di-tert-butylphenol (**4f**).* Yellow powder in yield 88%, m.p: 169°C; IR (KBr, $cm^{-1}$): 3421, 3116, 2958, 2860, 1618, 1591, 1508, 1440;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.22 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.55 (s, 1H, Ph), 7.37-7.28 (m, 5H, Ph), 7.19 (s, 1H, Ph), 4.23 (s, 2H, $CH_2$Ph), 3.73 (brs, 4H, $2CH_2$), 1.50 (m, 4H, $2CH_2$), 1.40 (s, 18H, $6CH_3$);$^{13}$C-NMR (100 MHz, DMSO-$d_6$):$\delta$ = 198.7, 156.6, 136.0, 129.5, 128.9, 124.4, 123.2, 65.9, 44.7, 31.2, 30.0, 25.6, 24.5; LC/MS (ESI): 518.32 $[M + 1]^+$; Anal. for $C_{27}H_{41}N_7O_2$; Calcd: C, 67.28; H, 7.59; N, 18.94; Found: C, 67.30; H, 7.60; N, 18.95.

*(7) (E)-2,6-Di-tert-butyl-4-((2-(4-morpholino-6-(phenylamino)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4g**).* Yellow powder in yield 87%; m.p: 151°C; IR (KBr, $cm^{-1}$): 3448, 3215, 3169, 2953, 2866, 1595, 1570, 1554, 1476, 1435, 1440;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.35 (s, 1H, CH =), 8.02 (brs, 1H, NH), 7.50 (s, 1H, Ph), 7.30-7.26 (m, 5H, Ph), 7.20 (s, 1H, Ph), 3.70 (brs, 4H, $2CH_2$), 1.56 (m, 4H, $2CH_2$), 1.35 (s, 18H, $6CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.7, 156.6, 136.0, 129.5, 128.9, 124.4, 123.2, 66.0, 31.2, 30.0, 25.6, 24.5; LC/MS (ESI): 504.30 $[M + 1]^+$; Anal. for $C_{28}H_{37}N_7O_2$; Calcd: C, 66.77; H, 7.41; N, 19.47; Found: C, 66.76; H, 7.40; N, 19.49.

*(8) (E)-2,6-Di-tert-butyl-4-((2-(4-methoxy-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4h**).* Yellow powder in yield 93%; m.p: 124°C; IR (KBr, $cm^{-1}$): 3302, 2958, 2908, 2866, 1614, 1587, 1545, 1504, 1438, 1409;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.94 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.70 (s, 1H, Ph), 7.52 (s, 1H, Ph), 3.93 (s, 3H, $OCH_3$), 3.83 (brs, 4H, $2CH_2$), 3.70 (brs, 4H, $2CH_2$), 1.45 (s, 9H, $3CH_3$), 1.43 (s, 9H, $3CH_3$), 1.35 (m, 2H, $CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 194.6, 173.5, 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 53.9, 47.9, 34.3, 31.0; LC/MS (ESI): 441.29 $[M + 1]^+$; Anal. for $C_{24}H_{36}N_6O_2$; Calcd: C, 65.43; H, 8.24; N, 19.07; Found: C, 65.44; H, 8.23; N, 19.10.

*(9) (E)-2,6-Di-tert-butyl-4-((2-(4-(diethylamino)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**4i**).* Yellow powder in yield 94%; m.p: 169°C; IR (KBr, $cm^{-1}$): 3423, 3197, 2960, 2908, 2858, 1583, 1570, 1510, 1435;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.44 (s, 1H, CH =), 7.95 (brs, 1H, NH), 7.55 (s, 1H, Ph), 7.47 (s, 1H, Ph), 3.76 (brs, 4H, $2CH_2$), 3.72 (t, 4H, $J$ = 22.3 Hz, $2CH_2$), 3.60 (brs, 4H, $2CH_2$), 1.49 (s, 9H, $3CH_3$), 1.44 (s, 9H, $3CH_3$), 128 (m, 2H, $CH_2$), 1.22 (m, 6H, $2CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 199.3, 176.1, 156.2, 142.8, 136.0, 125.3, 124.4, 67.5, 47.9, 44.7, 34.3, 31.0, 12.2; LC/MS (ESI): 482.35 $[M + 1]^+$; Anal. for $C_{27}H_{43}N_7O$; Calcd: C, 67.32; H, 9.00; N, 20.36; Found: C, 67.31; H, 9.00; N, 20.35.

*(10) (E)-2,4-Di-tert-butyl-6-((2-(4,6-di(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**5a**).* Yellow powder in yield 90%; m.p: 217°C; IR (KBr, $cm^{-1}$): 3637, 3423, 3197, 2960, 2935, 1583, 1570, 1510, 1462;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.03 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.32 (s, 1H, Ph), 7.01 (s, 1H, Ph), 3.79 (brs, 8H, $4CH_2$), 1.51 (m, 8H, $4CH_2$), 1.38 (s, 18H, $6CH_3$), 1.27 (m, 4H, $2CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 206.9, 156.6, 136.0, 128.9, 124.4, 44.7, 34.3, 30.9, 30.1, 25.8, 24.6; LC/MS (ESI): 494.35 $[M + 1]^+$; Anal. for $C_{28}H_{43}N_7O$; Calcd: C, 68.12; H, 8.78; N, 19.86; Found: C, 68.11; H, 8.78; N, 19.83.

*(11) (E)-2,4-Di-tert-butyl-6-((2-(4,6-dimorpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**5b**).* Yellow powder in yield 95%; m.p: 188°C; IR (KBr, $cm^{-1}$): 3086, 3053, 2953, 2885,1598, 1560, 1516, 1463, 1371;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.25 (s, 1H, CH =), 8.10 (brs, 1H, NH), 7.38 (s, 1H, Ph), 7.12 (s, 1H, Ph), 3.70 (brs, 8H, $4CH_2$), 1.50 (m, 8H, $4CH_2$), 1.35 (s, 18H, $6CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.9, 155.3, 135.1, 129.0, 125.1, 65.9, 44.6, 34.2, 30.9, 30.1; LC/MS (ESI): 498.31 $[M + 1]^+$; Anal. for $C_{26}H_{39}N_7O_3$; Calcd: C, 62.75; H, 7.90; N, 19.70; Found: C, 62.75; H, 7.89; N, 19.72.

*(12) (E)-2,4-Di-tert-butyl-6-((2-(4-(diethylamino)-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**5c**).* Yellow powder in yield 87%; m.p: 203°C; IR (KBr, $cm^{-1}$): 3421, 3116, 2966, 2980, 1647, 1618, 1591, 1508,1499, 1440;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.82 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.53 (s, 1H, Ph), 7.54 (s, 1H, Ph), 3.82 (brs, 4H, $2CH_2$), 3.72 (t, 4H, $J$ = 22.3 Hz, $2CH_2$), 3.60 (brs, 4H, $2CH_2$), 1.57 (s, 9H, $3CH_3$), 1.40 (s, 9H, $3CH_3$), 1.18 (m, 6H, $2CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.4, 176.5, 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 47.9, 44.7, 34.3, 31.1, 12.3; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = ; LC/MS (ESI): 484.33 $[M + 1]^+$; Anal. for $C_{26}H_{41}N_7O_2$; Calcd: C, 64.57; H, 8.54; N, 20.27; Found: C, 64.56; H, 8.53; N, 20.24.

*(13) (E)-2,4-Di-tert-butyl-6-((2-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (**5d**).* Yellow powder in yield 83%; m.p: 195°C; IR (KBr, $cm^{-1}$): 3215, 3045, 2958, 2908, 2866, 1614, 1598, 1544,1463;$^1$H-NMR (400 MHz,

DMSO-$d_6$): $\delta$ 7.95 (s, 1H, CH =), 7.78 (brs, 1H, NH), 7.65 (s, 1H, Ph), 7.50 (s, 1H, Ph), 3.92 (s, 3H, $OCH_3$), 3.83 (brs, 4H, $2CH_2$), 3.70 (brs, 4H, $2CH_2$), 1.45 (s, 9H, $3CH_3$), 1.43 (s, 9H, $3CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 194.6, 173.5 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 53.9, 47.9, 34.3, 31.0; LC/MS (ESI): 443.27 $[M + 1]^+$; Anal. for $C_{23}H_{34}N_6O_3$; Calcd: C, 62.42; H, 7.74; N, 18.99; Found: C, 62.42; H, 7.75; N, 19.22.

*(14) (E)-2,4-Di-tert-butyl-6-((2-(4-morpholino-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (***5e***).* Yellow powder in yield 86%; m.p: 171°C; IR (KBr, $cm^{-1}$) 3134, 3045, 2958, 2908, 2866, 1614, 1598, 1544, 1463; $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.34 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.46 (s, 1H, Ph), 7.19 (s, 1H, Ph), 3.73 (brs, 8H, $4CH_2$), 1.50 (m, 4H, $2CH_2$), 1.45 (m, 4H, $2CH_2$), 1.38 (s, 18H, $6CH_3$), 1.34 (m, 2H, $CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.7, 156.6, 136.0, 128.9, 124.4, 44.7, 34.3, 30.9, 30.1, 25.8, 24.6; LC/MS (ESI): 496.33 $[M + 1]^+$; Anal. for $C_{27}H_{41}N_7O_2$; Calcd: C, 65.43; H, 8.34; N, 19.78; Found: C, 65.44; H, 8.35; N, 19.97.

*(15) (E)-2-((2-(4-(Benzylamino)-6-morpholino-1,3,5-triazin-2-yl)hydrazono)methyl)-4,6-di-tert-butylphenol (***5f***).* Yellow powder in yield 85%; m.p: 152°C; IR (KBr, $cm^{-1}$): 3421, 3116, 2958, 2860, 1618, 1591, 1508, 1440;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.22 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.55 (s, 1H, Ph), 7.37-7.28 (m, 5H, Ph), 7.19 (s, 1H, Ph), 4.23 (s, 2H, $CH_2$Ph), 3.73 (brs, 4H, $2CH_2$), 1.50 (m, 4H, $2CH_2$), 1.40 (s, 18H, $6CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.7, 156.6, 136.0, 129.5, 128.9, 124.4, 123.2, 65.9, 44.7, 31.2, 30.0, 25.6, 24.5; $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = ; LC/MS (ESI): 518.32 $[M + 1]^+$; Anal. For $C_{27}H_{41}N_7O_2$; Calcd: C, 67.28; H, 7.59; N, 18.94; Found: C, 67.29; H, 7.60; N, 19.06.

*(16) (E)-2,4-di-tert-butyl-6-((2-(4-morpholino-6-(phenylamino)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (***5g***).* Yellow powder in yield 88%; m.p: 242°C; IR (KBr, $cm^{-1}$): 3448, 3215, 3169, 2953, 2866, 1595, 1570, 1554, 1476, 1435, 1440;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.35 (s, 1H, CH =), 8.02 (brs, 1H, NH), 7.50 (s, 1H, Ph), 7.30-7.26 (m, 5H, Ph), 7.20 (s, 1H, Ph), 3.70 (brs, 4H, $2CH_2$), 1.56 (m, 4H, $2CH_2$), 1.35 (s, 18H, $6CH_3$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 198.7, 156.6, 136.0, 129.5, 128.9, 124.4, 123.2, 66.0, 31.2, 30.0, 25.6, 24.5; LC/MS (ESI): 504.30 $[M + 1]^+$; Anal. for $C_{28}H_{37}N_7O_2$; Calcd: C, 66.77; H, 7.41; N, 19.47; Found: C, 66.77; H, 7.41; N, 19.48.

*(17) (E)-2,4-Di-tert-butyl-4-((2-(4-methoxy-6-(piperidin-1-yl)-1,3,5-triazin-2-yl)hydrazono)methyl)phenol (***5h***).* Yellow powder in yield 81%; m.p: 155°C; IR (KBr, $cm^{-1}$): 3302, 2958, 2908, 2866, 1614, 1587, 1545, 1504, 1438, 1409;$^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.94 (s, 1H, CH =), 7.80 (brs, 1H, NH), 7.70 (s, 1H, Ph), 7.52 (s, 1H, Ph), 3.93 (s, 3H, $OCH_3$), 3.83 (brs, 4H, $2CH_2$), 3.70 (brs, 4H, $2CH_2$), 1.45 (s, 9H, $3CH_3$), 1.43 (s, 9H, $3CH_3$), 1.35 (m, 2H, $CH_2$); $^{13}$C-NMR (100 MHz, DMSO-$d_6$): $\delta$ = 194.6, 173.5 156.6, 143.9, 136.0, 125.3, 124.4, 67.5, 53.9, 47.9, 34.3, 31.0; LC/MS (ESI): 441.29 $[M + 1]^+$; Anal. for $C_{24}H_{36}N_6O_2$; Calcd: C, 65.43; H, 8.24; N, 19.07; Found: C, 65.42; H, 8.25; N, 19.20.

*2.2. Anticancer Activity.* The cytotoxic activity of 18 newly synthesized compounds was tested against two mammalian cancer cell lines, colon cancer cells (HCT-116), and breast cancer cells (MCF-7). The cell lines were obtained from VACSERA, holding company for biological products and vaccines, Cairo, Egypt. The cells were grown at 37°C and 10% $CO_2$ in DMEM (Lonza, 12-604F) medium supplemented with 10% fetal bovine serum (FBS, Lonza, Cat. No.14-801E), 100 IU/mL penicillin, and 100 $\mu$g/mL streptomycin (Lonza, 17-602E). The viability of the cells were quantified by using MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), which measures the activity of mitochondrial dehydrogenase in the viable cells [54].

The cells were seeded in 96-well plates as $5 \times 10^4$ cells/mL (100 $\mu$l/well). Six serial dilutions of tested compounds were added after overnight incubation of the cells at 37°C and 5% $CO_2$. DMSO was used as a negative control (0.5 %). The cells were incubated for 48 hrs. After that, 10 $\mu$l of MTT (5 mg/ml PBS) was added to each well and incubated for another 4 hours. The formazan crystals were solubilized by 100 $\mu$l acidified SDS solution (10% SDS/0.01 M HCl). Biotek® plate reader measured the absorbance after 14 hours of incubation at 37°C and 5% $CO_2$ at 570 nm. Each experiment was repeated three times, and standard deviation was calculated (±). $IC_{50}$ was calculated as the concentrations that cause 50% inhibition for cell growth.

## 3. Results and Discussion

*3.1. Chemistry.* The s-triazine Schiff-base derivatives **4a-i** and **5a-h** were synthesized in three steps: (i) one pot-reaction of cyanuric chloride with the first amine in acetone-water media and in the presence of $Na_2CO_3$ at 0–5°C for 2 h. The second amine was added to the reaction mixture followed by addition of equivalent amount of $Na_2CO_3$ at 5°C and then let the reaction mixture reach the room temperature under stirring for 18 h to afford 6-chloro-2,4-disubstituted-s-triazine derivatives in good yields and purities; the spectral data were in good agreement with the reported in the literature [44]. (ii) 6-chloro-2,4-disubstituted-s-triazine derivatives reacted with hydrazine hydrate in ethanol according to the reported method [47, 49], to afford the hydrazino derivatives **2a-i** as white solid in good yields and purities which have been used directly in the next step without further purification. (iii) 6-hydrazino-2,4-disubstituted-s-triazine **2a-i** were reacted with substituted aldehydes **3a,b** in ethanol under reflux in the presence of catalytic amount of AcOH to give the target products **4a-i** and **5a-i** in high yields (Scheme 1).

The final products were separated by simple filtration after the precipitation. The molecular structure were deduced by different set of physical spectrophotometric tools including H-NMR, C-NMR, LC-MS, IR, and CHN elemental analysis. Of these, the molecular structure of three compounds, namely, **4f, 5b**, and **5f**, has been further confirmed by X-ray single crystal diffraction technique (Figure 2).

In the title compounds, the crystallographic data and refinement information are summarized in Figures S1–S6 and Tables S1–S9 (Supplementary Materials). The asymmetric

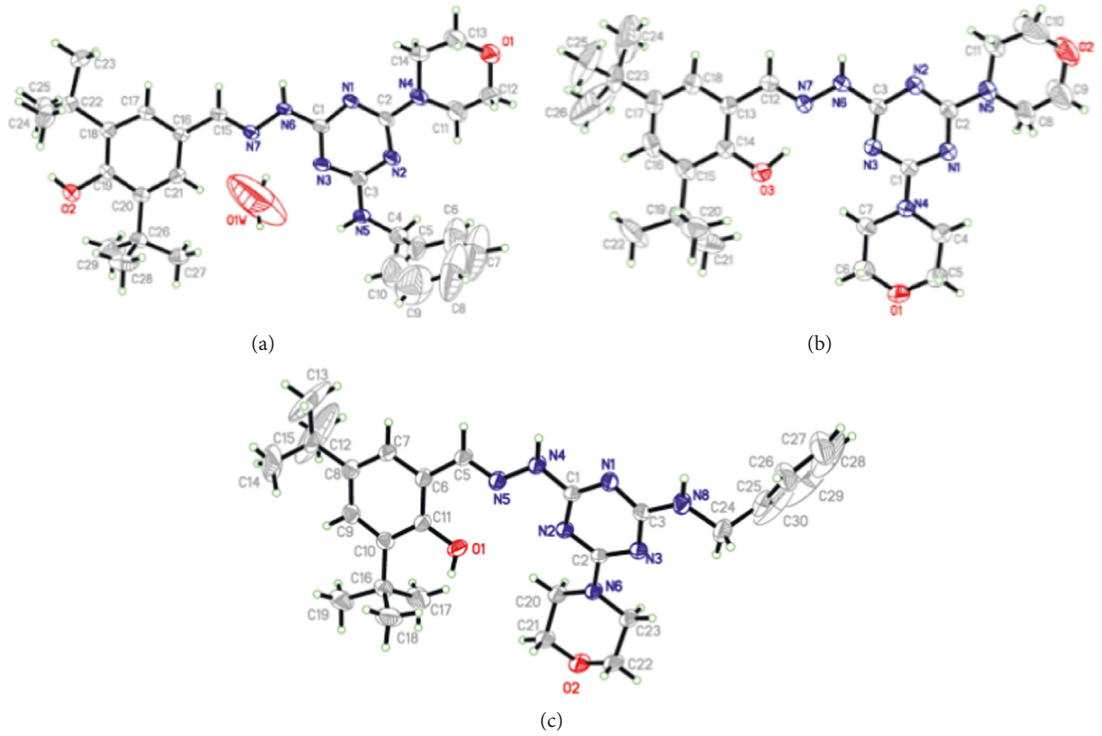



Figure 2: ORTEP diagram of the titled compounds **4f** (a), **5b** (b), and **5f** (c). Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

unit of the three containing is shown in Figure 2, where compound **4f** contains an additional lattice water molecule. All the bond lengths and angles are in normal ranges [55].

In the crystal packing, the molecules of compound **5b** are linked together by one hydrogen bond between N6—H1N6···O1. Compound **5f** molecules are connected with each other via three hydrogen bonds O2—H2A···O1, N5—H5A···N3, and N6—H6C···N1. Finally, molecules of structure **5f** arranged in the crystal structure using only one hydrogen bond between N4—H1N4···O2.

*3.2. Biological Activity.* Antiproliferative activity for the new synthesized s-triazine Schiff-base derivatives was tested against two cancer cell lines for breast cancer (MCF-7) and colon cancer (HCT-116). An initial screening for the possible antiproliferative activity was carried out at 10 $\mu$M for 48 hours, and then the viability was determined by MTT assay. Among 18 tested compounds, only compounds **4a** and **5a** showed cytotoxic activity against breast cancer cells at 10 $\mu$M (Figure 3). On the contrary, very weak activity was observed for the tested compounds against colon cancer cells (Figure 4).

Based on the results obtained and showed in Figures 3 and 4, we can concluded that 2-hydroxybenzylidene derivatives showed better activity than the analogous 4-hydroxybenzylidene **5a-h** derivatives vs. **4a-h** derivatives even in the weak activity. This might be due to in the 4-position the hydroxyl group is more sterically hindered, while when the hydroxyl group in the 3- position, it become less sterically hindered and more available for hydrogen donor, also has more inductive on the benzylidene ring, which usually preferred in most of the cases as previously reported [46, 49]. In the meantime, the substituents in the s-triazine ring have affected the activity of the prepared compounds. The substituent with two piperidine ring always showed higher reactivity than the same with two morpholine ring as shown in cases **4a** and **5a** vs. **4b** and **5b**. The same effect of piperidine was noticed in the cases of **5e** vs. **5b** and **4c** vs. **4i** (which they have weak activity). On the contrary, the presence of two morpholine rings showed better activity than derivatives with only one as in the cases **4b** vs. **5c**, **5d**, **5f**, **5g**, and **5h**. These observations agreed with our previously reported data [44].

As noticed from Figure 5, the concentration that kills 50% of breast cancer cells was evaluated for the two most active compounds **4a** and **5a**. Compound **4a** showed $IC_{50}$ of 27 $\mu$M (13.3 $\mu$g/mL), while **5a** was more active at $IC_{50}$ of 17 $\mu$M (8.4 $\mu$g/mL) which was very close to the chemotherapeutic drug cisplatin which killed 50% of the cells at concentration of 20 $\mu$M (6 $\mu$g/mL).

## 4. Conclusions

The new series of s-triazine Schiff-base derivatives were synthesized using the mild and conventional method. The chemical structures of the prepared compounds have been confirmed by different sets of spectroscopic techniques. The newly compounds examined against antiproliferative activity showed that two derivatives have piperidine moiety more selective against the two cell lines (MCF-7) and (HCT-116).

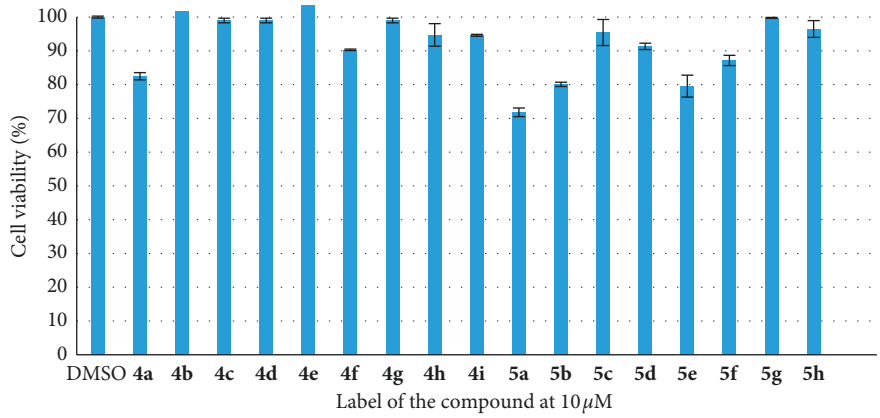



Figure 3: Cytotoxic activity for **4a-i** and **5a-h** against breast cancer cells (MCF-7).

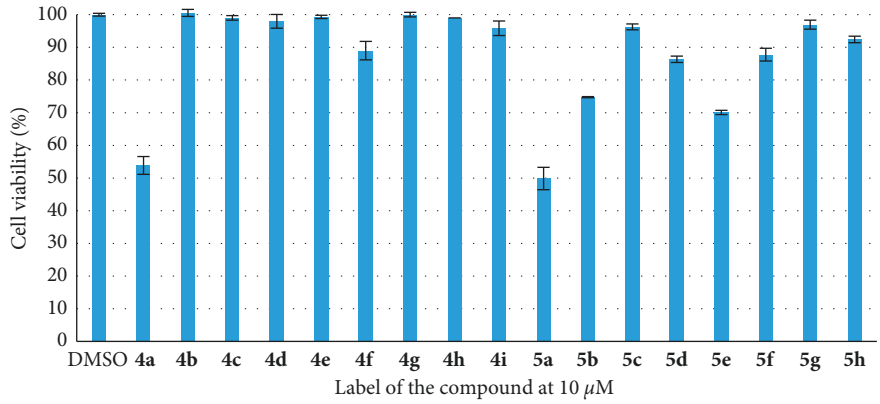



Figure 4: Anticancer activity **4a-i** and **5a-h** against colon cancer cells (HCT-116).

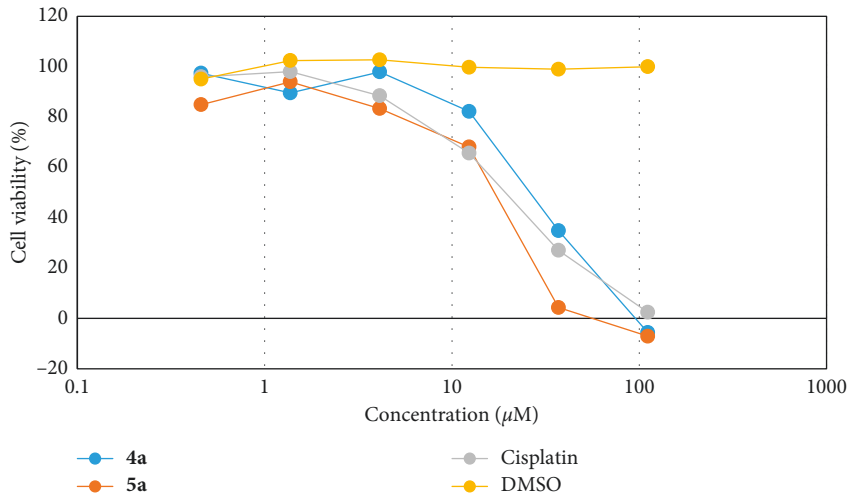



Figure 5: Cytotoxicity of **4a** and **5a** against MCF-7 cells. Cells were treated with DMSO, **4a**, and **5a** or cisplatin for 48 hours and then the viability was determined by MTT assay.

Based on the results obtained, we can conclude that both the substituent on the triazine ring and the position of the hydroxy group in the benzylidene moiety have critical effect on the biological activity of the prepared compounds, where 2-hydroxybenzylidene derivatives showed better activity than the analogous 4-hydroxybenzylidene **5a-h** derivatives vs. **4a-h** derivatives even in the weak activity cases. The substituents in the s-triazine ring have affected the activity

where s-triazine with two piperidine ring always showed higher reactivity than analogous one two morpholine ring as shown in case **4a** and **5a** vs. **4b** and **5b**. The concentration that kills 50% of breast cancer cells was evaluated for the two most active compounds **4a** and **5a**. Compound **5a** showed higher activity ($IC_{50} = 17\,\mu M$ ($8.4\,\mu g/mL$)) than **4a** ($IC_{50} = 27\,\mu M$ ($13.3\,\mu g/mL$)). These values, especially those of **5a,** are very close to that of the chemotherapeutic drug cisplatin, having $IC_{50}$ of $20\,\mu M$ ($6\,\mu g/mL$). Finally, we propose that the antiproliferative activity of these two compounds (**4a** and **5a**) deserves further attention for additional development as potent anticancer agents.

## Data Availability

Crystallographic data for the structures reported in this manuscript have been deposited in the Cambridge Crystallographic Data Centre under the following CCDC numbers: 1567719 (**4b**), 1567728 (**5b**), and 1567725 (**5f**). Copies of these data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Acknowledgments

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University, Saudi Arabia, for providing funding (no. RGP-234).

## Supplementary Materials

Figures S1–S6: ORTEP diagram and molecular packing of compounds **4b**, **5b**, and **5f**; Tables S1–S9: summary of the crystallographic data and refinement information of compounds **4b**, **5b**, and **5f**. (*Supplementary Materials*)

## References

[1] A. Jarrahpour, D. Khalili, E. De Clercq, C. Salmi, and J. Brunel, "Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of Isatin and their derivatives," *Molecules*, vol. 12, no. 8, pp. 1720–1730, 2007.

[2] P. Perumal, A. R. Bilal, R. S. R. Dontireddy, and R. K. Natesh, "Synthesis and anti-microbial screening of some Schiff bases of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3*H*)-ones," *European Journal of Medicinal Chemistry*, vol. 44, pp. 2328–2333, 2009.

[3] C. Kui, Z. Qing, Q. Yong, S. Lei, Z. Jing, and Z. Hai, "Synthesis, antibacterial activities and molecular docking studies of peptide and Schiff bases as targeted antibiotics," *Bioorganic and Medicinal Chemistry*, vol. 17, pp. 7861–7871, 2009.

[4] A. Hameed, M. al-Rashida, M. Uroos, S. Abid Ali, and K. M. Khan, "Schiff bases in medicinal chemistry: a patent review (2010-2015)," *Expert Opinion on Therapeutic Patents*, vol. 27, no. 1, pp. 63–79, 2017.

[5] V. S. Koneni, N. R. Jammikuntla, B. Gitika, and J. K. Saxena, "Novel keto-enamine Schiffs bases from 7-hydroxy-4-methyl-2-oxo-2H-benzo[h] chromene-8,10-dicarbaldehyde as potential antidyslipidemic and antioxidant agents," *European Journal of Medicinal Chemistry*, vol. 43, no. 11, pp. 2592–2596, 2008.

[6] J. Vanco, O. Svajlenova, E. Racanska, J. Muselik, and J. J. Valentova, "Antiradical activity of different copper (II) Schiff base complexes and their effect on alloxan induced diabetes," *Journal of Trace Element in Medicine Biololgy*, vol. 18, pp. 155–161, 2004.

[7] D. Sinha, A. K. Tiwari, S. Singh et al., "Synthesis, characterization and biological activity of Schiff base analogues of indole-3-carboxaldehyde," *European Journal of Medicinal Chemistry*, vol. 43, no. 1, pp. 160–165, 2008.

[8] J. Xie, S. Shen, R. Chen et al., "Synthesis, characterization and antitumor activity of Ln(III) complexes with hydrazone Schiff base derived from 2-acetylpyridine and isonicotinohydrazone," *Oncology Letters*, vol. 13, no. 6, pp. 4413–4419, 2017.

[9] S. Rollas and S. Küçükgüzel, "Biological activities of hydrazone derivatives," *Molecules*, vol. 12, no. 8, pp. 1910–1939, 2007.

[10] B. Narasimhan, P. Kumar, and D. Sharma, "Biological activities of hydrazide derivatives in the new millennium," *Acta Pharmaceutica Sciencia*, vol. 52, pp. 169–180, 2010.

[11] K. Ulbrich and V. Subr, "Polymeric anticancer drugs with pH-controlled activation," *Advanced Drug Delivery Reviews*, vol. 56, no. 7, pp. 1023–1050, 2004.

[12] V. Onnis, M. T. Cocco, R. Fadda, and C. Congiu, "Synthesis and evaluation of anticancer activity of 2-arylamino-6-trifluoromethyl-3-(hydrazonocarbonyl)pyridines," *Bioorganic and Medicinal Chemistry*, vol. 17, no. 17, pp. 6158–6165, 2009.

[13] S. A. M. El-Hawash, A. E. Abdel Wahab, and M. A. El-Demellawy, "Cyanoacetic acid hydrazones of 3-(and 4-) Acetylpyridine and some derived ring systems as potential antitumor and anti-HCV agents," *Archiv der Pharmazie*, vol. 339, no. 1, pp. 14–23, 2006.

[14] C. M. da Silva, D. L. da Silva, L. V. Modolo et al., "Schiff bases: a short review of their antimicrobial activities," *Journal of Advanced Research*, vol. 2, no. 1, pp. 1–8, 2011.

[15] P. Przybylski, A. Huczynski, K. Pyta, B. Brzezinski, and F. Bartl, "Biological properties of Schiff bases and azo derivatives of phenols," *Current Organic Chemistry*, vol. 13, no. 2, pp. 124–148, 2009.

[16] M. Singh and N. Raghav, "Biological activities of hydrazones: a review," *International Journal Pharmacy and Pharmaceutical Science*, vol. 3, pp. 26–32, 2011.

[17] B. Kaya, Y. Özkay, H. E. Temel, and Z. A. Kaplancıkl, "Synthesis and biological evaluation of novel piperazine containing hydrazone derivatives," *Journal of Chemistry*, vol. 2016, Article ID 5878410, 7 pages, 2016.

[18] M. C. Mandewale, B. Thorat, D. Shelke, and R. Yamgar, "Synthesis and biological evaluation of new hydrazone derivatives of Quinoline and their Cu(II) and Zn(II) complexes against *Mycobacterium tuberculosi*," *Bioinorganic Chemistry and Applications*, vol. 2015, Article ID 153015, 14 pages, 2015.

[19] G. Verma, A. Marella, M. Shaquiquzzaman, M. Akhtar, M. R. Ali, and M. M. Alam, "A review exploring biological activities of hydrazones," *Journal Pharmacy and Bioallied Science*, vol. 6, no. 2, pp. 69–80, 2014.

[20] B. Viira, A. Selyutina, A. T. García-Sosa et al., "Design, discovery, modelling, synthesis, and biological evaluation of novel and small, low toxicity s-triazine derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors," *Bioorganic and Medicinal Chemistry*, vol. 24, no. 11, pp. 2519–2529, 2016.

[21] B. Żołnowska, J. Sławiński, K. Szafrańskia et al., "Novel 2-(2-arylmethylthio-4-chloro-5-methylbenzenesulfonyl)-1-(1,3,5-triazin-2-ylamino)guanidine derivatives: inhibition of human

carbonic anhydrase cytosolic isozymes I and II and the transmembrane tumor-associated isozymes IX and XII, anticancer activity, and molecular modeling studies," *European Journal of Medicinal Chemistry*, vol. 143, pp. 1931–1941, 2018.

[22] T. Linder, M. Schnürch, and M. D. Mihovilovic, "One-pot synthesis of triazines as potential agents affecting cell differentiation," *Monatshefte für Chemie-Chemical Monthly*, vol. 149, no. 7, pp. 1257–1284, 2018.

[23] L. Zhang, T. Li, L. Huang et al., "Preparation and application of melamine cross-linked poly ammonium as shale inhibitor," *Chemistry Central Journal*, vol. 12, no. 1, 2018.

[24] G. Blotny, "Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis," *Tetrahedron*, vol. 62, no. 41, pp. 9507–9522, 2006.

[25] D. Bartholomew, *Comprehensive Heterocyclic Chemistry II*, A. J. Boulton, Ed., vol. 6, pp. 575–636, Pergamon, Oxford, UK, 1996.

[26] D. L. Comins and S. O'Connor, *Advances in Heterocyclic Chemistry*, A. R. Katritzky, Ed., vol. 44, p. 243, Academic Press, New York, NY, USA, 1988.

[27] B. Kolesinska and Z. J. Kaminski, "The umpolung of substituent effect in nucleophilic aromatic substitution. A new approach to the synthesis of N,N-disubstituted melamines (triazine triskelions) under mild reaction conditions," *Tetrahedron*, vol. 65, no. 18, pp. 3573–3576, 2009.

[28] G. Pastorin, S. Federico, S. Paoletta et al., "Synthesis and pharmacological characterization of a new series of 5,7-disubstituted-[1,2,4]triazolo[1,5-a][1,3,5]triazine derivatives as adenosine receptor antagonists: a preliminary inspection of ligand-receptor recognition process," *Bioorganic and Medicinal Chemistry*, vol. 18, no. 7, pp. 2524–2536, 2010.

[29] M. Y. Wani, A. R. Bhat, A. Azam, I. Choi, and F. Athar, "Probing the antiamoebic and cytotoxicity potency of novel tetrazole and triazine derivatives," *European Journal of Medicinal Chemistry*, vol. 48, pp. 313–320, 2012.

[30] F. Popowycz, C. Schneider, S. DeBonis et al., "Synthesis and antiproliferative evaluation of pyrazolo[1,5-a]-1,3,5-triazine myoseverin derivatives," *Bioorganic and Medicinal Chemistry*, vol. 17, no. 9, pp. 3471–3478, 2009.

[31] N. Sunduru, A. Agarwal, S. B. Katiyar et al., "Synthesis of 2,4,6-trisubstituted pyrimidine and triazine heterocycles as antileishmanial agents," *Bioorganic and Medicinal Chemistry*, vol. 14, no. 23, pp. 7706–7715, 2006.

[32] P. Baréa, V. A. Barbosa, D. L. Bidóia et al., "Synthesis, antileishmanial activity and mechanism of action studies of novel $\beta$-carboline-1,3,5-triazine hybrids," *European Journal of Medicinal Chemistry*, vol. 150, pp. 579–590, 2018.

[33] S. N. Khattab, H. H. Khalil, A. A. Bekhit et al., "1,3,5-Triazino peptide derivatives: synthesis, characterization, and preliminary antileishmanial activity," *ChemMedChem*, vol. 13, no. 7, pp. 725–735, 2018.

[34] C. Zhou, J. Min, Z. Liu et al., "Synthesis and biological evaluation of novel 1,3,5-triazine derivatives as antimicrobial agents," *Bioorganic and Medicinal Chemistry Letters*, vol. 18, no. 4, pp. 1308–1311, 2008.

[35] T. Vilaivan, N. Saesaengseerung, D. Jarprung, S. Kamchonwongpaisan, W. Sirawaraporn, and Y. Yuthavong, "Synthesis of solution-phase combinatorial library of 4,6-Diamino-1,2-dihydro-1,3,5-triazine and identification of new leads against A16V+S108T mutant dihydrofolate reductase of plasmodium falciparum," *Bioorganic and Medicinal Chemistry*, vol. 11, no. 2, pp. 217–224, 2003.

[36] M. Dinari, F. Gharahi, and P. Asadi, "Synthesis, spectroscopic characterization, antimicrobial evaluation and molecular docking study of novel triazine-quinazolinone based hybrids," *Journal of Molecular Structure*, vol. 1156, pp. 43–50, 2018.

[37] D. R. Ramadan, A. A. Elbardan, A. A. Bekhit, A. El-Faham, and S. N. Khattab, "Synthesis and characterization of novel dimeric s-triazine derivatives as potential anti-bacterial agents against MDR clinical isolates," *New Journal of Chemistry*, vol. 42, no. 13, pp. 10676–10688, 2018.

[38] M. Krecmerova, M. Masojidkova, and A. Holy, "Acyclic nucleoside phosphonates with 5-azacytosine base moiety substituted in C-6 position," *Bioorganic and Medicinal Chemistry*, vol. 18, pp. 387–395, 2010.

[39] N. Sunduru, L. Gupta, V. Chaturvedi, R. Dwivedi, S. Sinha, and P. M. S. Chauhan, "Discovery of new 1,3,5-triazine scaffolds with potent activity against *Mycobacterium tuberculosis* H37Rv," *European Journal of Medicinal Chemistry*, vol. 45, no. 8, pp. 3335–3345, 2010.

[40] V. Garaj, L. Puccetti, G. Fasolis et al., "Carbonic anhydrase inhibitors: novel sulfonamides incorporating 1,3,5-triazine moieties as inhibitors of the cytosolic and tumour-associated carbonic anhydrase isozymes I, II and IX," *Bioorganic and Medicinal Chemistry Letters*, vol. 15, no. 12, pp. 3102–3108, 2005.

[41] I. Sosic, B. Mirkovi, S. Turk, B. Stefane, J. Kos, and S. Gobec, "Discovery and kinetic evaluation of 6-substituted 4-benzylthio-1,3,5-triazin-2(1H)-ones as inhibitors of cathepsin B," *European Journal of Medicinal Chemistry*, vol. 46, no. 9, pp. 4648–4656, 2011.

[42] H. H. Al-Rasheed, M. Al Alshaikh, J. M. Khaled, N. S. Alharbi, and A. El-Faham, "Ultrasonic irradiation: synthesis, characterization, and preliminary antimicrobial activity of novel series of 4,6-disubstituted-1,3,5-triazine containing hydrazone derivatives," *Journal of Chemistry*, vol. 2016, Article ID 3464758, 9 pages, 2016.

[43] H. H. Al-Rasheed, E. N. Sholkamy, M. Al Alshaikh, M. R. H. Siddiqui, A. S. Al-Obaidi, and A. El-Faham, "Synthesis, characterization, and antimicrobial studies of novel series of 2,4-*bis*(hydrazino)-6-substituted-1,3,5-triazine and their Schiff base derivatives," *Journal of Chemistry*, vol. 2018, Article ID 8507567, 13 pages, 2018.

[44] A. El-Faham, S. M. Soliman, H. A. Ghabbour et al., "Ultrasonic promoted synthesis of novel s -triazine-Schiff base derivatives; molecular structure, spectroscopic studies and their preliminary anti-proliferative activities," *Journal of Molecular Structure*, vol. 1125, pp. 121–135, 2016.

[45] F. Bai, H. Liu, L. Tong et al., "Discovery of novel selective inhibitors for EGFR-T790M/L858R," *Bioorganic and Medicinal Chemistry Letters*, vol. 22, no. 3, pp. 1365–1370, 2012.

[46] K. A. Menear, S. Gomez, K. Malagu et al., "Identification and optimisation of novel and selective small molecular weight kinase inhibitors of mTOR," *Bioorganic and Medicinal Chemistry Letters*, vol. 19, no. 20, pp. 5898–5901, 2009.

[47] A. Sharma, H. Ghabbour, S. T. Khan, B. G. de la Torre, F. Albericio, and A. El-Faham, "Novel pyrazolyl-s-triazine derivatives, molecular structure and antimicrobial activity," *Journal of Molecular Structure*, vol. 1145, pp. 244–253, 2017.

[48] M. Venkatraj, K. K. Ariën, H. Heeres et al., "From human immunodeficiency virus non-nucleoside reverse transcriptase inhibitors to potent and selective antitrypanosomal compounds," *Bioorganic and Medicinal Chemistry*, vol. 22, no. 19, pp. 5241–5248, 2014.

[49] A. El-Faham and Y. Elnakady, "Synthesis, characterization of novel morpholino-1, 3, 5-triazinyl amino acid Ester derivatives and their anti-proliferation activities," *Letters in Organic Chemistry*, vol. 12, no. 10, pp. 753–758, 2015.

[50] W. Zhu, Y. Liu, Y. Zhao et al., "Synthesis and biological evaluation of novel 6-Hydrazinyl-2,4-bismorpholino pyrimidine and 1,3,5-triazine derivatives as potential antitumor agents," *Archiv der Pharmazie*, vol. 345, no. 10, pp. 812–821, 2012.

[51] J. K. Srivastava, G. G. Pillai, H. R. Bhat, A. Verma, and U. P. Singh, "Design and discovery of novel monastrol-1,3,5-triazines as potent anti-breast cancer agent *via* attenuating Epidermal Growth Factor Receptor tyrosine kinase," *Scientific Reports*, vol. 7, no. 1, 2017.

[52] G. M. Sheldrick, "A short history ofSHELX," *Acta Crystallographica Section A Foundations of Crystallography*, vol. 64, no. 1, pp. 112–122, 2008.

[53] G. M. Sheldrick, *SHELXTL-PC (Version 5.1)*, Siemens Analytical Instruments, Inc., Madison, WI, USA, 1997.

[54] T. Mosmann, "Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays," *Journal of Immunological Methods*, vol. 65, no. 1-2, pp. 55–63, 1983.

[55] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, "Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds," *Journal of the Chemical Society, Perkin Transactions II*, vol. 2, pp. S1–S19, 1987.