# Synthesis and Anticancer Evaluation of Some Novel 5-Amino[1,2,4]Triazole Derivatives

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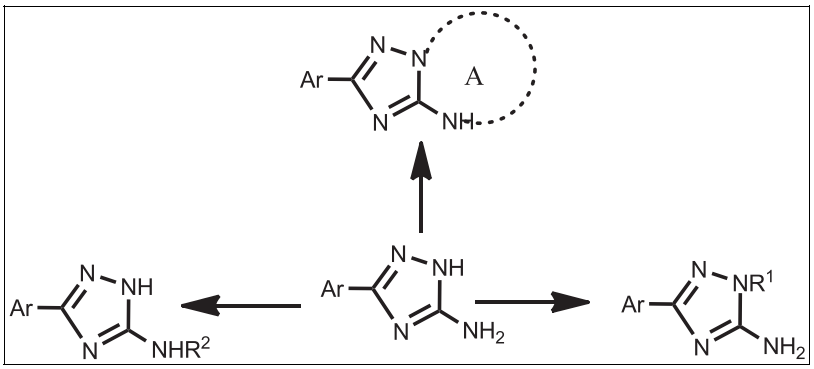


Novel [1,2,4]triazole derivatives were synthesized via various synthetic pathways. Among which were different substituted [1,2,4]triazole analogues that were synthesized, in addition to various fused [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives, [1,2,4]triazolo[1,5-*a*][1,3,5]triazines, and [1,2,4]triazolo[5,1-*c*][1,2,4]triazines. Besides, benzo[h][1,2,4]triazolo[5,1-*b*]quinazolines, [1,2,4]triazolo-[5,1-*b*]quinazoline, [1,2,4]triazolo[1,5-*a*]quinazoline and [1,2,4]triazolo[5,1-*d*][1,2,3,5]tetrazine derivatives were also synthesized. The newly synthesized compounds were evaluated for their *in vitro* anticancer activity against liver cancer HepG2 and breast cancer MCF7 cell lines compared with the reference drug doxorubicin. Compounds **4**, **7**, **15**, **17**, **28**, **34**, and **47** were found to exert promising anticancer activity against HepG2 cell line showing $IC_{50}$ values ranging from 17.69 to 25.4 μM/L, while compounds **7**, **14a**, **17**, **28**, and **34** showed significant activity against MCF7 cell line with $IC_{50}$ values ranging from 17.69 to 27.09 μM/L.

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## INTRODUCTION

[1,2,4]Triazole-derived heterocycles have attracted considerable interest as potential bioactive molecules owing to their versatile pharmacological activity profile embracing anticancer activity [1–8], antimicrobial activity [9–13], anti-inflammatory activity [14–17], antihypertensive activity [18,19], antiparasitic activity [20], antioxidant activity [21], antitubercular activity [22], antiviral activity [23,24], antimalarial activity [25], and thymidine phosphorylase inhibitory activity [3,4,26].

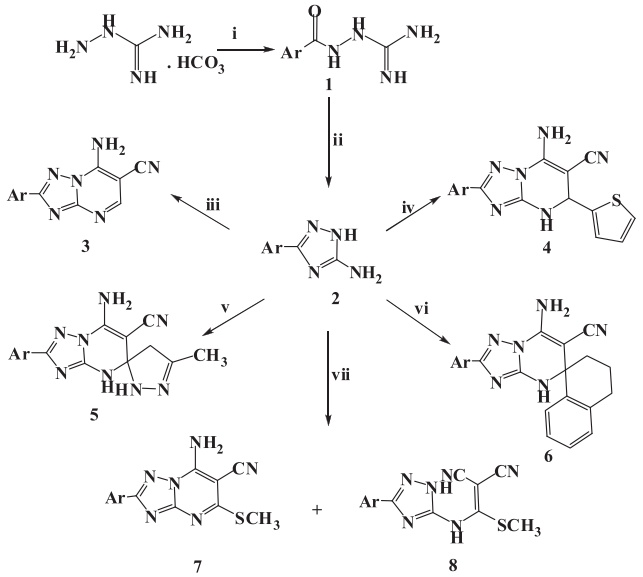
Therefore, it was aimed to synthesize various novel substituted [1,2,4]triazole derivatives, in addition to the synthesis of other novel triazole derivatives fused to different heterocyclic rings known to possess anticancer activity such as triazolopyrimidine [27–29], triazolotriazine [30], triazolotetrazine [31], and imidazotriazole [32].

## RESULTS AND DISCUSSION

**Chemistry.** 3-(4-Chlorophenyl)-4*H*-[1,2,4]triazole-5-amine **2** was prepared according to the reported procedure [33,34], which was utilized as a building unit for novel fused triazolopyrimidine compounds embracing the 2-aminonitrile functions as in derivatives **3**–**7** (Scheme 1). Compounds **3** and **4** were synthesized upon the reaction of compound **2** with the appropriate arylidenemalononitriles such as ethoxymethylenemalononitrile in refluxing glacial acetic acid and 2-(thiophen-2-ylmethylene)malononitrile in ethanol containing a catalytic amount of piperidine, respectively.

The spiro triazolopyrimidine derivatives **5** and **6** were prepared through a multicomponent reaction of 5-amino[1,2,4]triazole derivative **2**, malononitrile, and the appropriate ketone, namely, 3-methyl-5-pyrazolone and 1-tetralone, respectively, in refluxing ethanol containing catalytic amount of piperidine. Two possible mechanistic pathways [35,36] were expected involving either the formation of the ylidenenitrile as a first step followed by its reaction with compound **2** to yield the corresponding triazolopyrimidine product or the condensation of the aminotriazole with the appropriate ketone to yield the corresponding Schiff's base as a first step followed by

**Scheme 1.** Synthetic pathways for compounds **2**–**8**.



**Ar:** 4-Cl-$C_6H_5$

**Reagents and conditions**: **i)** 4-chlorobenzoyl chloride/ toluene, 70$^0$C.; **ii)** $NaOC_2H_5$ / $C_2H_5OH$/ reflux; **iii)** EMMN/ gl.AcOH/ reflux; **iv)** 2-(thiophen-2-ylmethylene)malononitrile/ $C_2H_5OH$/ piperidine/ reflux; **v)** 3-methyl-1H-pyrazol-5(4H)-one / malononitrile/ $C_2H_5OH$/ piperidine/ reflux; **vi)** 1-tetralone/ malononitrile/ $C_2H_5OH$, piperidine/ reflux; **vii)** [bis(methylthio)methylene]malononitrile/ $CH_3OH$/ reflux.

subsequent reaction with malononitrile. The formed intermediate further underwent intramolecular cyclization through addition of the triazole amino nitrogen on the cyano group yielding the final triazolopyrimidine derivative. However, in this study, the formation of compounds **5** and **6** was suggested to proceed through the ylidenemalononitrile intermediate as confirmed by spectral data.

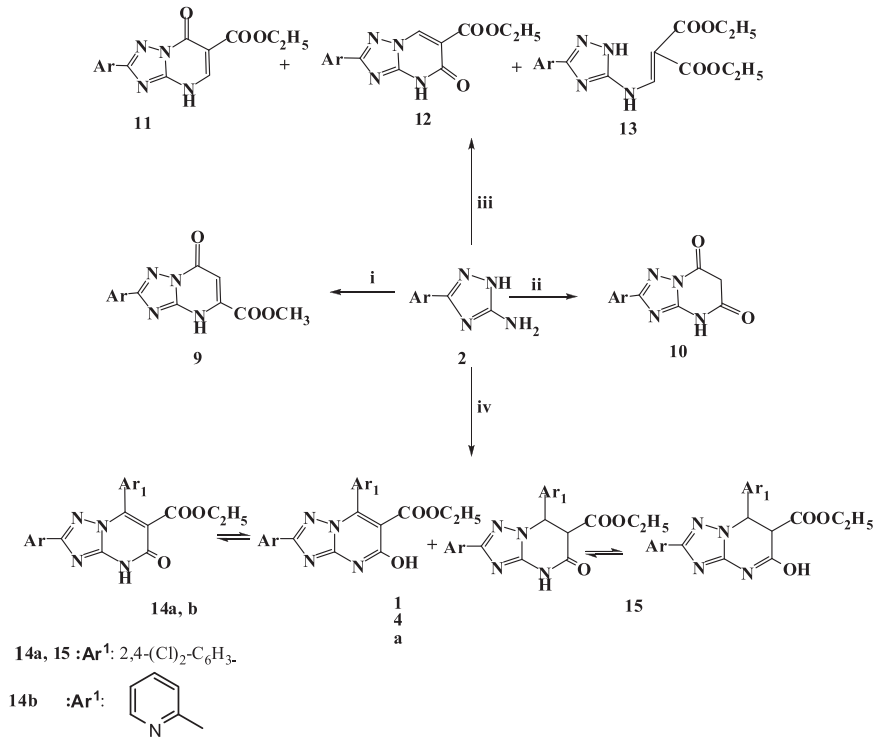
Furthermore, compound **2** was reacted with [bis(methylthio)methylene]malononitrile in refluxing methanol [37] to yield the open chain analogue **8**, which was isolated confirming the postulated mechanism for the synthesis of the target triazolopyrimidine derivative **7**. The reaction was proposed to proceed through the elimination of a methylmercaptan molecule to give compound **8** followed by subsequent intramolecular cyclization through addition of the secondary amino function on one of the cyano groups to yield the triazolopyrimidine analogue **7**.

Triazolopyrimidine compounds bearing oxo function were reported to exhibit important anticancer activity [5,7]. Therefore, compounds bearing oxo functions in 5 and/or 7 positions were designed to be synthesized (Scheme 2) through reacting compound **2** with dimethyl acetylenedicarboxylate (DMAD) in ethanol [38] and diethyl malonate in ethanolic sodium ethoxide [39] to yield compounds **9** and **10**, respectively. The $^1$H NMR spectrum of compound **9** displayed a singlet signal at $\delta$ 8.01 ppm corresponding to the triazolopyrimidine-$C_6$ proton, while $^1$H NMR spectrum of compound **10** displayed a singlet signal at $\delta$ 1.72 ppm due to methylene protons.

Furthermore, compound **2** was reacted with diethyl ethoxymethylenemalonate either by heating in water under reflux or by fusion. The reaction mechanism [40] was assumed to proceed via two mechanistic pathways (Route A and Route B, Fig. 1) involving the nucleophilic substitution of the ethoxy function either by the exocyclic amino group leading to the acyclic analogue **13**, followed by intramolecular cyclization via elimination of another ethanol moiety leading to the dihydrotriazolopyrimidinone **11** (Route A) or via the endocyclic secondary amino group followed by intramolecular cyclization (Route B) to yield the dihydrotriazolopyrimidinone **12**.

Our aim was extended to develop different synthetic methods for novel 5-oxo-[1,2,4]triazolo[1,5-*a*] pyrimidines. Therefore, compound **2** was reacted with the appropriate diethyl arylidenemalonate derivatives in absolute ethanol to give compounds **14a,b** and **15**. It is worth mentioning that such reactions were reported to yield a mixture of the corresponding dihydro and tetrahydrotriazolopyrimidine analogues [41]. The $^1$H NMR spectra of compounds **14a** and **15** displayed two deuterium oxide exchangeable singlet signals each integrated for half proton at $\delta$ 12.20 and 13.80 ppm and $\delta$ 12.22 and 13.82 ppm, respectively, corresponding to triazolopyrimidine NH and OH protons, respectively. However, the spectrum of compound **14b** displayed one

**Scheme 2.** Synthetic pathways for compounds **9**–**15**.




**Reagents and conditions**: **i)** DMAD/ $C_2H_5OH$/ reflux; **ii)** diethyl malonate/ $NaOC_2H_5$/ $C_2H_5OH$/ reflux; **iii)** diethyl ethoxymethylene malonate/ $H_2O$/ reflux or fusion; **iv)** appropriate arylidenemalonate/ $C_2H_5OH$/ reflux.

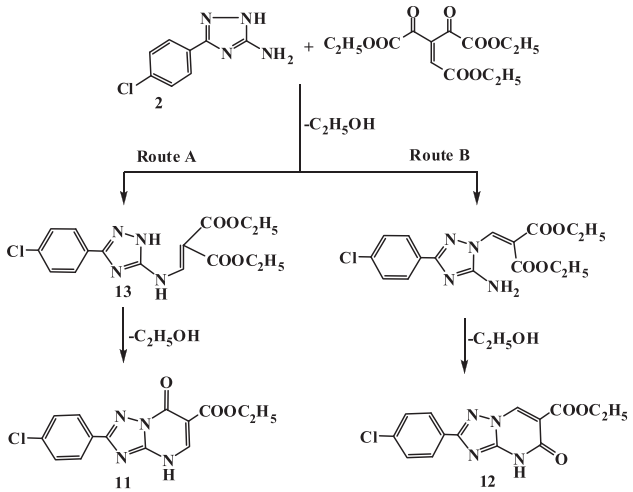
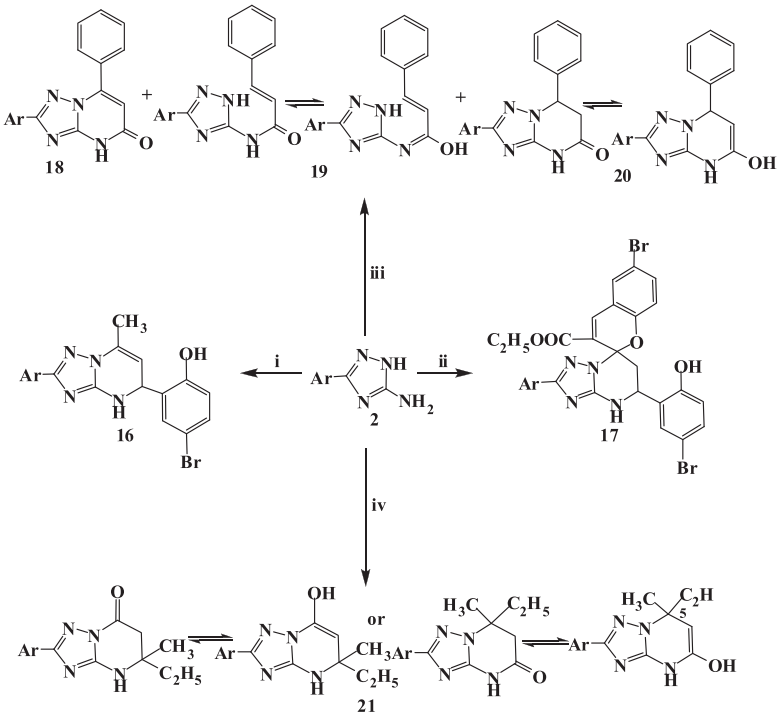



**Figure 1.** The postulated reaction mechanism for synthesis of compounds **11**, **12**, and **13**.

deuterium oxide exchangeable singlet signal integrated for one proton at $\delta$ 10.64 ppm attributed to the triazolopyrimidinone NH proton.

It is worth mentioning that attempts to synthesize compound **16** via stirring the multicomponent reaction mixture of 5-amino[1,2,4]triazole derivative **2**, 5-bromo salicylaldehyde, and acetone in methanol containing hydrochloric acid at 40°C according to the method developed by Gorobets and coworkers [42] and up to 70°C were unsuccessful. However, the target dihydrotriazolopyrimidine derivative **16** was obtained by heating under conventional reflux conditions (Scheme 3).

**Scheme 3.** Synthetic pathways for compounds **16**–**21**.



Ar: 4-Cl-C6H4
**Reagents and conditions:** i) acetone/ 5-bromosalicylaldehyde, $CH_3OH$/ HCl/dioxane, reflux; ii) ethyl acetoacetate/ 5-bromosalicylaldehyde/ $C_2H_5OH$/ HCl/dioxane, reflux; iii) cinnamoyl chloride/ $C_2H_5OH$/ reflux; iv) Meldrum,s acid / ethyl methyl ketone/ $C_2H_5OH$/ pyridine/ reflux.

The postulated mechanistic pathway is illustrated in Figure 2.

Furthermore, 5,6-dihydrospirobenzopyrantriazolopyrimidine derivatives were reported to be synthesized through the reaction of salicyaldehyde derivatives, aminotriazoles, and acetoacetate esters [43]. Therefore, the spiro[1,2,4] triazolo[1,5-*a*]pyrimidine-7,2′-chromene-3′-carboxylate derivative **17** was prepared by prolonged reflux of compound **2**, ethyl acetoacetate and 5-bromosalicyladehyde in ethanol/dioxane mixture

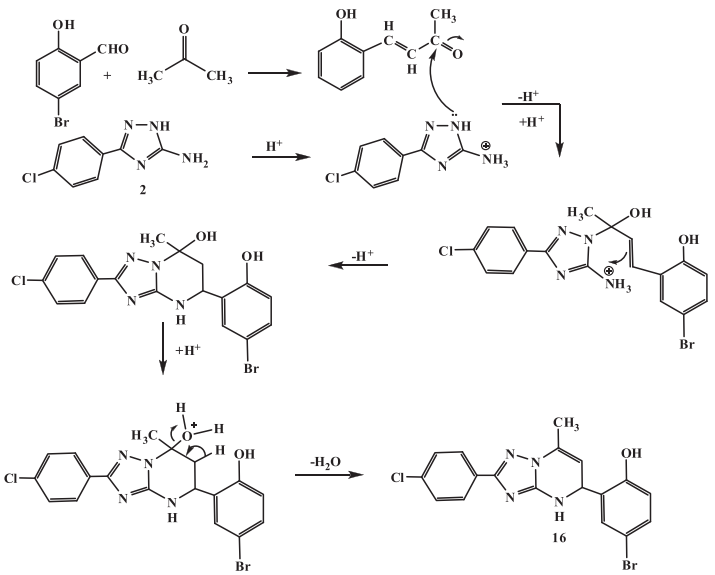


**Figure 2.** The postulated reaction mechanism for synthesis of compound **16**.

containing concentrated hydrochloric acid as a catalyst (Fig. 3).

Oxotriazolopyrimidine analogues **18**, **20**, and **21** were

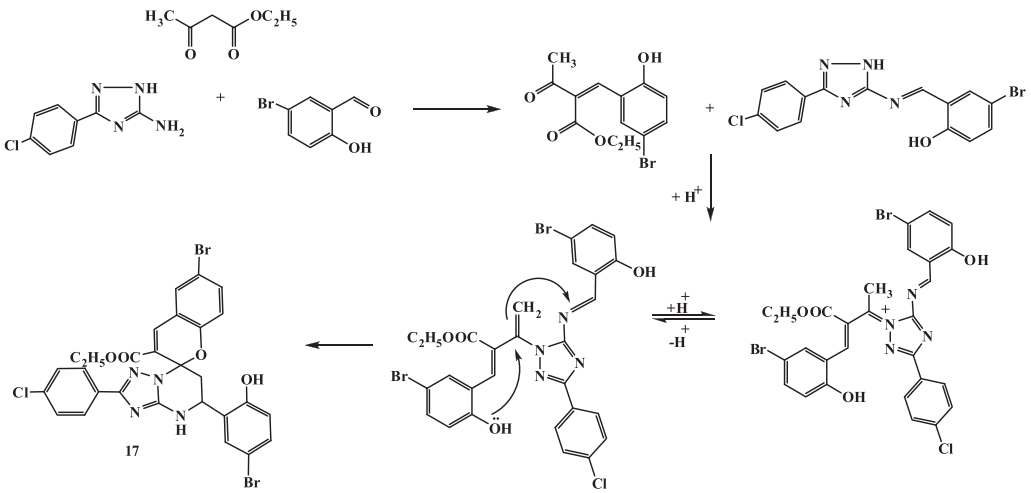


**Figure 3.** The postulated reaction mechanism for synthesis of compound **17**.

synthesized through heating equivalent amounts of 5-amino[1,2,4]triazole derivative **2** under reflux with eithercinnamoyl chloride in absolute ethanol to give compounds **18**, **19**, and **20**. The reaction was postulated to proceed through acylation of the exocyclic amino function with cinnamoyl chloride leading to the cinnamamide derivative **19**, which carried out intramolecular cyclization through the electrophilic addition of the endocyclic triazole NH function on the double bond leading to compound **20**, which underwent further dehydrogenation to furnish compound **18**. However, compound **21** was prepared through the reaction of an equimolar mixture of Meldrum's acid/ethylmethyl ketone in ethanol containing pyridine on the account that Lipson *et al*. [44] reported the cascade Knoevenagel–Michael reactions of Meldrum's acid, carbonyl compounds, and α-aminoazoles to yield 5- or 7-oxoazolopyrimidines.

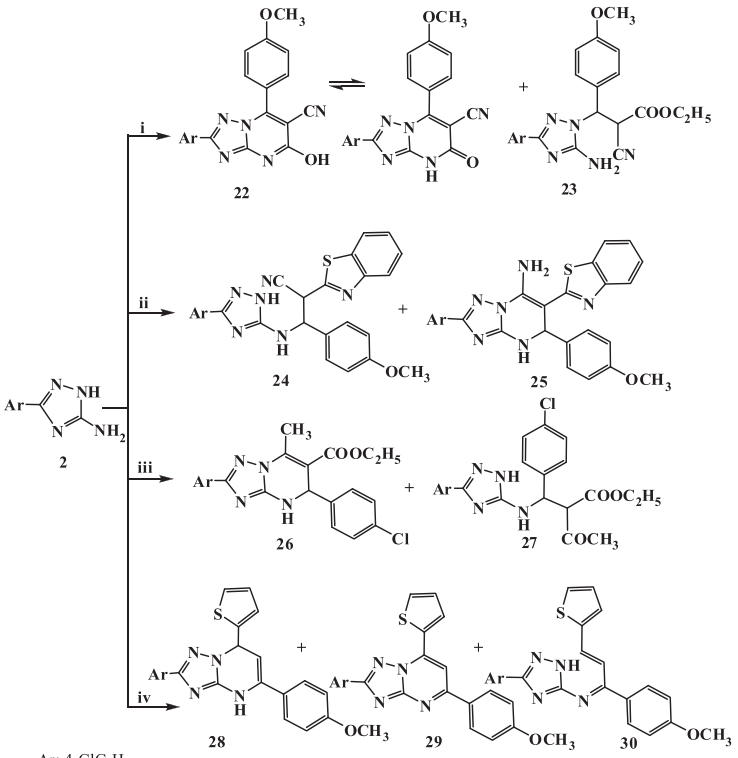
Our aim was extended to study various multicomponent reactions of 5-amino[1,2,4]triazole derivative **2**. Therefore, the triazolopyrimidine carbonitrile derivative **22** and the open chain derivative **23** were synthesized upon heating under reflux a mixture of compound **2**, 4-methoxybenzaldehyde, and ethyl cyanoacetate in absolute ethanol containing a catalytic amount of piperidine (Scheme 4). The infrared (IR) spectrum of compound **23** was characterized by the presence of an absorption band at 3395 $cm^{-1}$ attributed to the intramolecular hydrogen-bonded $NH_2$, in addition to absorption bands at 2215 and 1702 $cm^{-1}$ attributed to the cyano and carbonyl functions, respectively.

Moreover, the target 4,5-dihydro[1,2,4]triazolo[1,5-*a*] pyrimidine derivative **25** and the propanenitrile derivative **24** were obtained through a three-component one-pot reaction of 2-(benzo[d]thiazol-2-yl)acetonitrile, 4-methoxybenzaldehyde, and compound **2** in refluxing methanol containing a catalytic amount of ammonium acetate. IR spectrum of compound **24** showed an absorption band corresponding to cyano function at 2190 $cm^{-1}$, which was absent in the spectrum of compound **25**. $^1H$ NMR spectrum of compound **25** showed a singlet signal $\delta$ 7.23 ppm due to the triazolopyrimidine-$C_5$ proton.

The synthesis of compounds **26** and **27** was accomplished via conventional reflux of a one-pot reaction mixture of 5-amino[1,2,4]triazole derivative **2**, 4-chlorobenzaldehyde, and ethyl acetoacetate in dimethylformamide (DMF) [45]. The reaction was assumed to proceed through ylidene formation as a first step followed by Michael addition of triazole-$C_5$-$NH_2$ on the substituted benzylidene double bond yielding compound **27**, which carried out subsequent intramolecular condensation to yield compound **26**. $^1H$ NMR spectrum of compound **26** revealed only one deuterium oxide exchangeable singlet signal at $\delta$ 10.62 ppm integrated for one proton of the NH proton, in addition to a singlet signal at $\delta$ 7.38 ppm due to triazolopyrimidine-$C_5$ proton, whereas the spectrum of compound **27** revealed two deuterium oxide exchangeable singlet signals at $\delta$ 7.95 and 10.99 ppm corresponding to triazole-$C_5$-NH and endocyclic triazole NH protons, respectively.

Furthermore, the 5-amino[1,2,4]triazole derivative **2** was reacted with the chalcone; 1-(4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one in DMF to yield the

**Scheme 4.** Synthetic pathways for compounds **22**–**30**.



Ar: 4-$ClC_6H_4$
**Reagents and conditions:** i) ethyl cyanoacetate/ 4-methoxybenzaldehyde/ $C_2H_5OH$/ piperidine/ reflux; ii) 2-(benzo[d]thiazol-2-yl)acetonitrile/ 4-methoxybenzaldehyde/ $CH_3OH$/ $NH_4OAc$/ reflux; iii) ethyl acetoacetate/ 4-chlorobenzaldehyde/ DMF/ reflux; iv) 1-(4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one/ DMF/ reflux.

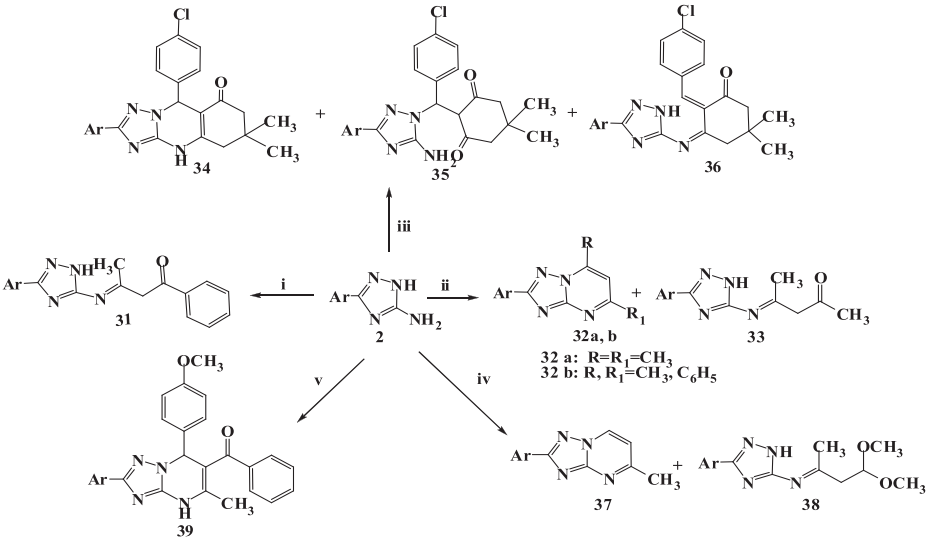
Schiff's base **30**, the dihydrotriazolopyrimidine **28**, and the triazolopyrimidine **29** derivatives. The reaction was assumed to proceed through initial Schiff's base formation followed by subsequent intramolecular cyclization through addition of the triazole endocyclic amino function on the double bond. The $^1$H NMR spectra of compounds **28** and **30** displayed deuterium oxide exchangeable singlet signals attributed to the triazolopyrimidine NH proton in compound **28** and the endocyclic triazole NH proton in compound **30** at $\delta$ 10.15 and 10.60 ppm, respectively. However, the $^1$H NMR spectrum of compound **29** was devoid of any deuterium oxide exchangeable signals.

5-Amino[1,2,4]triazole derivative **2** was heated under reflux with benzoylacetone in glacial acetic acid to yield the corresponding Schiff's analogue **31** (Scheme 5). It is worth mentioning that prolonged reflux of the reaction mixture up to 72 h did not yield the cyclic triazolopyrimidine. Furthermore, heating of compound **2** with excess of either acetylacetone or benzoylacetone at 250–270°C yielded the corresponding triazolopyrimidine derivatives **32a** and **32b**, respectively. However, the reaction with acetylacetone isolated also the acyclic Schiff's base **33**. The $^1$H NMR spectrum of **31** showed two singlet signals at $\delta$ 2.67 and 2.90 ppm corresponding to $CH_3$ and $CH_2$ protons, while $^1$H NMR spectra of compounds **32a,b** were devoid of any deuterium oxide exchangeable singlet signals of their precursors and displayed singlet signals $\delta$ 7.19 and $\delta$ 8.12 ppm due to the triazolopyrimidine-$C_6$ protons, respectively.

On the other hand, $^1$H NMR spectrum of compound **33** revealed two singlet signals at $\delta$ 2.78 and 6.65 ppm due to the keto–enol tautomeric protons, besides the two deuterium oxide exchangeable singlet signals at $\delta$ 10.60 and 13.13 ppm corresponding to the triazole endocyclic NH and the tautomeric NH protons, respectively.

Relying on the fact that multicomponent reactions represent an important pathway for building up different heterocyclic systems from simple precursors, therefore, equimolar amounts of 5-amino[1,2,4]triazole derivative **2**, dimedone, and 4-chlorobenzaldehyde were heated under reflux in DMF to yield the target triazoloquinazolinone derivative **34** in addition to compounds **35** and **36**. The reaction was proposed to proceed first through the reaction of dimedone with 4-chlorobenzaldehyde to yield the corresponding arylidene derivative followed by its reaction with the aminotriazole analogue **2** either through the electrophilic addition of the endocyclic NH on the arylidene double bond leading to the dimethylcyclohexanedione derivative

**Scheme 5.** Synthetic pathways for compounds **31**–**39**.



**Ar:** 4-Cl-$C_6H_4$
**Reagents and conditions**: **i)** benzoylacetone/ AcOH/ reflux; **ii)** acetylacetone or benzoylacetone/ fusion; **iii)** dimedone/ 4-chlorobenzaldehyde/ DMF/ reflux; **iv)** acetylacetaldehyde dimethyl acetal/ $NaOC_2H_5$/ $C_2H_5OH$/ R.T.; **v)** benzoylacetone/ 4-methoxybenzaldehyde/ gl.AcOH/ reflux.

**35** (Route A) analogous to the reported mechanism [46] or via condensation of the exocyclic amino function with the arylidene carbonyl to yield the iminocyclohexanone derivative **36** (Route B) followed by intramolecular cyclization to yield the target triazoloquinazolinone derivative **34**.

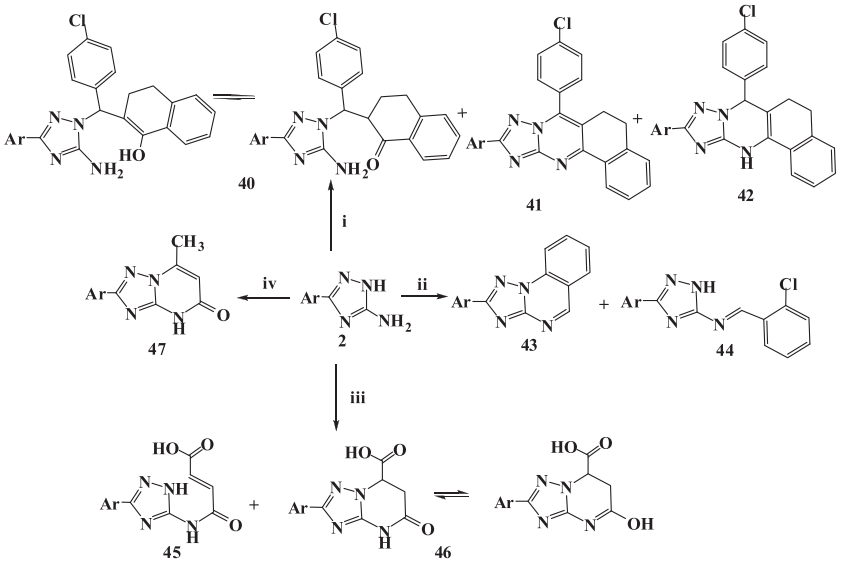
Furthermore, stirring of 5-amino[1,2,4]triazole derivative **2** with acetyl acetaldehyde dimethyl acetal in ethanolic sodium ethoxide at room temperature adopting the reported procedure [47] yielded both the fused triazolopyrimidine derivative **37** and the acyclic dimethoxybutylidene derivative **38**. The reaction was postulated to proceed via the initial formation of Schiff's base to yield the open chain analogue **38** followed by intramolecular nucleophilic substitution of methoxy function by the endocyclic NH with subsequent aromatization through elimination of a second methanol molecule. In continuation of our study for different synthetic pathways of various triazolopyrimidine derivatives, compound **39** was prepared via a Biginelli-like [48,49] multicomponent reaction of 5-amino[1,2,4] triazole derivative **2**, 4-methoxybenzaldehyde, and benzoylacetone in refluxing glacial acetic acid. The $^1$H NMR spectrum of **39** displayed a deuterium oxide exchangeable singlet signal at $\delta$ 12.10 ppm attributed to the triazolopyrimidine NH proton.

In attempts to study the anticancer activity of the fused benzo[h][1,2,4]triazolo[5,1-*b*]quinazolines, compounds **41** and **42** were prepared via the one-pot reaction of compound **2**, 1-tetralone, and 4-chlorobenzaldehyde in refluxing DMF (Scheme 6). However, the reaction also isolated the acyclic intermediate **40**. The $^1$H NMR spectrum of compound **40** displayed two deuterium oxide exchangeable singlet signals at $\delta$ 7.50 and 7.76 ppm attributed to OH tautomer and $NH_2$ protons, respectively, while the spectrum of compound **41** lacked any deuterium oxide exchangeable signals. However, the $^1$H NMR spectrum of compound **42** displayed only one deuterium oxide exchangeable singlet signal at $\delta$ 12.05 ppm attributed to triazoloquinazoline NH proton. Also, compound **2** and 2-chlorobenzaldehyde were heated under reflux in glacial acetic acid to yield the acyclic Schiff's base derivative **44** and the cyclic triazoloquinazoline analogue **43**.

Moreover, maleic anhydride was reported to react with amino-bearing compounds in different ways [50,51]. However, upon reaction of compound **2** with maleic anhydride in DMF, it gave both the open chain maleiamic acid derivative **45** and the cyclic tetrahydrotriazolopyrimidine carboxylic acid derivative **46**. The $^1$H NMR spectrum of compound **46** displayed two deuterium oxide exchangeable singlet signals at $\delta$ 6.05 and 12.10 ppm each integrated for one proton attributed to OH tautomeric proton and carboxylic proton, respectively.

Furthermore, triazolopyrimidinone derivative **47** was obtained via heating equimolar amounts of compound **2** and ethyl acetoacetate in glacial acetic acid under reflux conditions. The $^1$H NMR spectrum of compound **47** revealed a singlet signal at $\delta$ 5.85 ppm attributed to the triazolopyrimidine–$C_6$ proton, in addition to a deuterium oxide exchangeable singlet signal at $\delta$ 13.22 ppm due to the triazolopyrimidine NH proton.

**Scheme 6.** Synthetic pathways for compounds **40**–**47**.



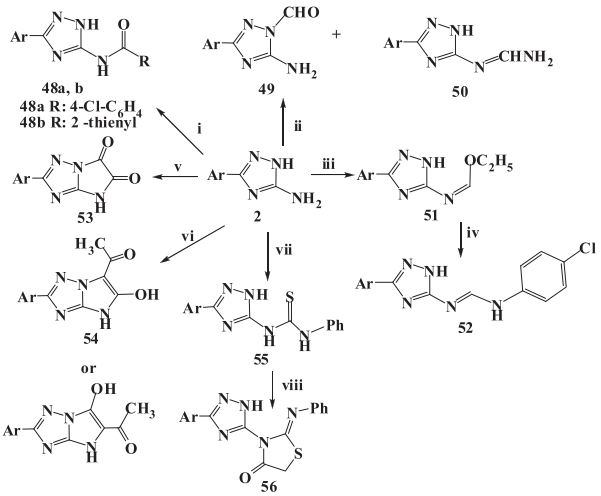
**Ar:** 4-Cl-$C_6H_4$
**Reagents and conditions**: **i)**1-tetralone/ 4-chlorobenzaldeyde/ DMF/ reflux.; **ii)** 2-chlorobenzaldehyde / gl. AcOH/ reflux; **iii)** maleic anhydride/ DMF/ reflux; **iv)** ethyl acetoacetate/ gl.AcOH/ reflux.

Acylation of compound **2** was carried out by stirring equimolar amounts of the appropriate acid chloride with 5-amino[1,2,4]triazole derivative **2** in dioxane/pyridine mixture at room temperature (Scheme 7). However, the sole products were found to be the exocyclic amino acylated triazole derivatives **48a,b** with no occurrence of the $N_1$ acylated products. The $^1$H NMR spectra of compounds **48a** and **48b** revealed two deuterium oxide exchangeable singlet signals at $\delta$ 8.14 and 10.62 ppm corresponding to the amide NH protons, respectively, in addition to two deuterium oxide exchangeable singlet signals at $\delta$ 13.15 and 12.20 ppm attributed to the intramolecular hydrogen-bonded triazole endocyclic NH protons, respectively.

In addition, compound **2** upon heating under reflux in excess formamide yielded both the endocyclic NH formylated product **49** and the condensation formimidamide derivative **50**.

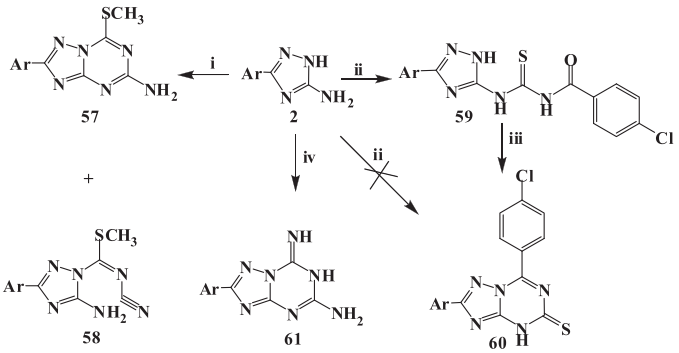
Utilizing the reactive triethyl orthoformate ester in the preparation of formimidate derivatives [52], compound **2**

**Scheme 7.** Synthetic pathways for compounds **48**–**56**.



**Ar:** 4-Cl-$C_6H_4$
**Reagents and conditions: i)** RCOCl/pyridine/ dioxan/ R.T.; **ii)** $HCONH_2$/ reflux; **iii)** $CH(OC_2H_5)_3$/ $Ac_2O$/ reflux; **iv)** 4-chloroaniline/$NaOC_2H_5$/ $C_2H_5OH$/ reflux; **v)** Oxalylchloride/ fusion; **vi)** ethyl 2-chloroacetoacetate/ $C_2H_5OH$/ piperidine/reflux; **vii)** PhNCS/ pyridine/ reflux; **viii)** ethyl chloroacetate/ $C_2H_5OH$/ pyridine/ reflux.

**Scheme 8.** Synthetic pathways for compounds **57**–**61**.



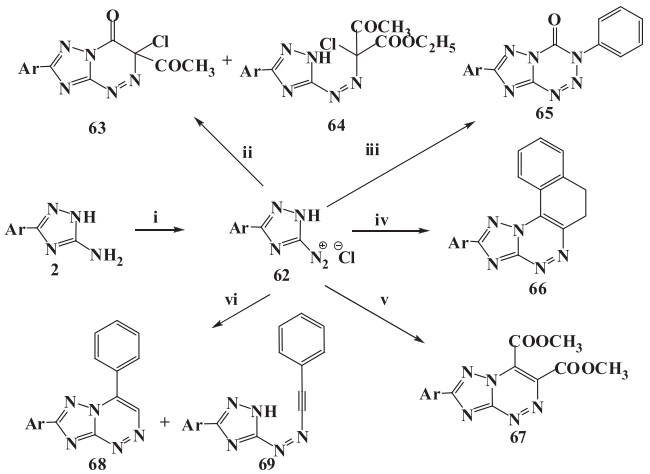
**Ar:** 4-Cl-C6H4
**Reagents and conditions: i)** dimethyl cyanocarbonimidodithioate/ $C_2H_5OH$/ piperidine/ reflux;
ii) 4-chlorobenzoylisothiocyanate/acetone/ reflux; iii) DMF/ reflux; iv) cyanogunidine/ $H_2O$/HCl/ reflux.

was heated with TEOF in acetic anhydride under reflux conditions to yield the formimidate analogue **51**, which was further refluxed with 4-chloroaniline in ethanolic sodium ethoxide to yield the target formimidamide derivative **52**.

Oxalyl chloride is one of the most important α,β-bifunctional electrophiles [53] that was utilized in building up an imidazole moiety on the [1,2,4]triazole backebone of compound **2** by fusion at 250°C to yield compound **53**. The IR spectrum of compound **53** revealed two absorption bands at 1705 and 1683 $cm^{-1}$ corresponding to two carbonyl functions. However, imidazotriazole derivative **54** was synthesized via heating equimolar amounts of 5-aminotriazole derivative **2** with ethyl 2-chloroacetoacetate ester in ethanol containing piperidine as a base. It is worth mentioning that upon carrying out the reaction in benzene or ethanolic sodium ethoxide, the reaction failed to proceed even with prolonged heating up to 72 h.

The intermediate phenylthiourea derivative **55** was obtained by refluxing equimolar amounts of compound **2** and phenyl isothiocyante in pyridine, which was further cyclized to the corresponding triazolyl thiazolidinone derivative **56** via heating under reflux with ethyl chloroacetate in ethanol/pyridine mixture. The $^1H$ NMR of compound **55** revealed three deuterium oxide exchangeable singlet signals at $\delta$ 8.70, 9.78, and 13.08 ppm attributed to the triazole-$C_5$-NH, endocyclic triazole NH, and SH tautomeric protons, respectively, while the $^1H$ NMR spectrum of compound **56** was characterized by the presence of a singlet signal at $\delta$ 4.30 ppm corresponding to thiazolidinone $CH_2$ protons, in addition to a deuterium oxide exchangeable singlet signal at $\delta$ 10.28 ppm attributed to the triazole endocyclic NH proton.

**Scheme 9.** Synthetic pathways for compounds **62**–**69**.



**Ar:** 4-Cl-$C_6H_4$
**Reagents and conditions**: **i)** $NaNO_2$/ conc. HCl/ 0-5 $^0$C; **ii)** ethyl 2-chloroacetoacetate/ NaOAc/ $C_2H_5OH$/ R.T.; **i**
**ii)** PhNCO/ $CH_2Cl_2$/ R.T.; **iv)** dimethylaminomethylene-1-tetralone/ pyridine/ 0-5 $^0$C; **v)** DMAD/ $C_2H_5OH$/ reflux;
**vi**) phenylacetylene/ fusion.

**Table 1**

Six dose growth inhibition percent and $IC_{50}$ values of the tested compounds against HepG2 cell line.

| Sample concentration (μg/mL) Compound no. | Growth inhibition % | | | | | | $IC_{50}$ (μM/L) |
|---|---|---|---|---|---|---|---|
| | 100 | 50 | 25 | 12.5 | 6.25 | 3.125 | |
| **2** | 74.07 | 60.16 | 41.73 | 28.22 | 14.54 | 8.13 | 186.12 |
| **3** | 89.11 | 82.76 | 70.17 | 40.72 | 29.51 | 10.85 | 60.74 |
| **4** | 92.51 | 84.33 | 73.52 | 61.81 | 40.79 | 21.46 | 25.40 |
| **5** | 70.14 | 61.28 | 38.47 | 21.81 | 15.37 | 8.41 | 110.34 |
| **6** | 73.25 | 61.51 | 38.44 | 23.71 | 12.84 | 7.72 | 96.44 |
| **7** | 95.63 | 93.11 | 84.72 | 67.84 | 52.11 | 37.48 | 18.19 |
| **8** | 36.11 | 13.34 | 8.46 | 1.87 | 0 | 0 | – |
| **9** | 85.03 | 73.18 | 64.81 | 45.07 | 21.32 | 10.79 | 51.20 |
| **10** | 21.58 | 12.49 | 5.82 | 0.94 | 0.0 | 0.0 | – |
| **11** | 67.49 | 50.72 | 34.87 | 18.58 | 10.97 | 4.83 | 153.43 |
| **12** | 74.33 | 60.15 | 41.79 | 23.82 | 13.71 | 3.92 | 113.58 |
| **13** | 63.55 | 31.31 | 20.79 | 8.53 | 1.62 | 0.0 | – |
| **14a** | 86.15 | 75.28 | 63.03 | 47.16 | 25.87 | 14.08 | 31.70 |
| **14b** | 79.21 | 68.44 | 53.13 | 31.89 | 15.81 | 6.75 | 58.62 |
| **15** | 87.18 | 78.13 | 65.77 | 53.86 | 30.35 | 15.03 | 24.69 |
| **16** | 53.58 | 39.11 | 15.81 | 7.26 | 1.08 | 0.0 | 175.25 |
| **17** | 86.71 | 74.03 | 61.28 | 52.12 | 30.86 | 11.38 | 17.69 |
| **18** | 91.63 | 82.14 | 73.86 | 60.52 | 42.15 | 23.79 | 30.27 |
| **19** | 78.06 | 71.92 | 60.35 | 41.57 | 27.28 | 12.83 | 55.73 |
| **20** | 75.02 | 58.14 | 40.78 | 25.82 | 11.27 | 6.15 | 117.93 |
| **21** | 88.71 | 75.26 | 61.11 | 47.05 | 23.79 | 15.85 | 51.93 |
| **22** | 92.81 | 80.97 | 71.08 | 56.41 | 38.17 | 20.48 | 27.26 |
| **23** | 76.33 | 61.81 | 53.02 | 32.48 | 13.87 | 2.78 | 54.48 |
| **24** | 67.49 | 51.68 | 32.17 | 19.46 | 8.75 | 2.53 | 98.16 |
| **25** | 23.28 | 12.61 | 5.44 | 1.93 | 0.0 | 0.0 | – |
| **26** | 83.02 | 71.64 | 51.93 | 34.86 | 18.75 | 11.06 | 54.97 |
| **28** | 79.65 | 70.14 | 69.38 | 41.26 | 18.82 | 9.14 | 25.18 |
| **29** | 85.71 | 73.49 | 66.06 | 55.17 | 37.83 | 11.25 | 87.13 |
| **30** | 79.12 | 58.47 | 42.84 | 25.08 | 18.04 | 12.49 | 95.25 |
| **31** | 85.11 | 70.27 | 55.72 | 46.25 | 18.41 | 9.36 | 62.87 |
| **32a** | 84.71 | 71.83 | 53.48 | 28.72 | 15.15 | 9.77 | 89.68 |
| **32b** | 82.72 | 73.25 | 64.11 | 52.18 | 28.71 | 14.63 | 37.10 |
| **33** | 82.16 | 70.37 | 54.83 | 36.08 | 12.53 | 5.85 | 78.78 |
| **34** | 88.17 | 82.32 | 7.56 | 60.87 | 42.18 | 28.43 | 20.19 |
| **35** | 69.83 | 56.15 | 42.09 | 13.85 | 13.85 | 5.13 | 85.49 |
| **36** | 74.68 | 61.51 | 50.49 | 31.97 | 18.05 | 6.52 | 56.22 |
| **37** | 86.29 | 73.81 | 56.14 | 33.68 | 20.96 | 12.86 | 88.28 |
| **38** | 83.02 | 71.28 | 52.91 | 35.91 | 19.35 | 8.57 | 74.17 |
| **39** | 67.26 | 54.11 | 40.87 | 21.74 | 11.58 | 7.15 | 92.36 |
| **40** | 78.44 | 64.87 | 51.74 | 38.53 | 19.81 | 13.48 | 50.50 |
| **41** | 71.83 | 32.02 | 56.16 | 42.88 | 26.51 | 13.42 | 43.31 |
| **43** | 73.21 | 6.59 | 39.34 | 21.76 | 12.45 | 7.87 | 133.95 |
| **44** | 68.42 | 53.78 | 32.41 | 19.28 | 10.84 | 4.77 | 143.77 |
| **45** | 64.61 | 51.43 | 29.87 | 18.18 | 7.64 | 1.36 | 165.03 |
| **46** | 92.6 | 82.48 | 71.52 | 59.33 | 53.84 | 25.08 | 29.86 |
| **47** | 94.32 | 90.29 | 83.36 | 70.13 | 54.28 | 36.81 | 22.40 |
| **48b** | 78.11 | 77.35 | 68.63 | 61.38 | 40.77 | 21.84 | 31.89 |
| **49** | 60.38 | 32.41 | 18.75 | 9.53 | 1.38 | 0.0 | 365.63 |
| **50** | 76.15 | 69.36 | 52.44 | 35.88 | 21.46 | 8.22 | 104.67 |
| **51** | 89.74 | 75.08 | 63.75 | 51.12 | 32.49 | 17.86 | 48.27 |
| **52** | 85.33 | 72.41 | 40.38 | 21.54 | 8.13 | 1.68 | 97.84 |
| **53** | 78.74 | 64.33 | 47.62 | 25.84 | 16.75 | 9.59 | 115.03 |
| **54** | 47.33 | 24.04 | 10.83 | 3.75 | 0.57 | 0.0 | – |
| **55** | 85.54 | 72.49 | 59.96 | 23.41 | 10.37 | 4.51 | 65.49 |
| **56** | 51.78 | 29.13 | 13.46 | 7.55 | 2.82 | 0.0 | 259.85 |
| **57** | 79.52 | 32.77 | 43.71 | 25.28 | 11.44 | 3.73 | 113.75 |
| **58** | 87.16 | 78.37 | 67.81 | 50.32 | 28.08 | 12.46 | 42.36 |
| **59** | 73.81 | 62.16 | 47.08 | 30.27 | 17.44 | 5.83 | 75.97 |
| **60** | 87.36 | 63.41 | 52.19 | 37.55 | 25.17 | 12.78 | 61.72 |

(*Continues*)

**Table 1**

(*Continued*)

| Sample concentration (μg/mL) Compound no. | Growth inhibition % | | | | | | $IC_{50}$ (μM/L) |
|---|---|---|---|---|---|---|---|
| | 100 | 50 | 25 | 12.5 | 6.25 | 3.125 | |
| **61** | 83.59 | 67.13 | 52.71 | 34.86 | 18.28 | 9.34 | 88.28 |
| **63** | 81.56 | 68.21 | 54.08 | 41.73 | 24.38 | 10.86 | 64.48 |
| **64** | 78.18 | 62.41 | 51.06 | 36.88 | 19.07 | 6.52 | 65.10 |
| **65** | 80.28 | 67.14 | 39.19 | 32.77 | 15.85 | 6.22 | 80.38 |
| **66** | 83.28 | 67.14 | 54.09 | 37.13 | 24.38 | 10.56 | 65.91 |
| **67** | 69.02 | 55.81 | 30.48 | 15.27 | 8.53 | 2.82 | 127.41 |
| **68** | 82.41 | 69.36 | 56.14 | 38.57 | 20.43 | 12.94 | 66.94 |
| **69** | 63.18 | 8.57 | 12.28 | 12.28 | 5.91 | 0.58 | 237.86 |
| Doxorubicin | 100 | 89.05 | 85.7 | 83.10 | 78.97 | 69.68 | 8.56 |

However, at a certain stage of this study, it was desired to investigate the effect of fusion of different triazine rings to the triazole nucleus (Scheme 8) and encouraged by the findings that some triazolo[1,3,5]triazine derivatives exerted significant anticancer activity. Therefore, compound **2** was reacted with dimethyl cyanocarbonimidodithioate [54] in ethanol containing piperidine as a catalyst, which yielded both the cyclic triazolotriazine derivative **57** as well as the open chain carbimidothioate derivative **58**. The IR spectrum of compound **58** was characterized by the presence of an absorption band due to the cyano function at 2200 $cm^{-1}$.

Reaction of compound **2** with 4-chlorobenzoylisothiocyanate yielded the corresponding open chain thiourea analogue **59**, which was cyclized to the triazolotriazine derivative **60** upon heating under reflux in DMF. Furthermore, the synthesis of compound **61** was achieved via the reaction of compound **2** with cyanoguanidine in water containing a catalytic amount of concentrated hydrochloric acid [55]. The reaction mechanism is assumed to proceed through the nucleophilic addition of the triazole exocyclic amino function on the cyano group of cyanoguanidine followed by subsequent cyclization through elimination of one molecule of ammonia. The $^1H$ NMR spectrum of compound **61** was characterized by the presence of three deuterium oxide exchangeable singlet signals at $\delta$ 6.02, 6.67, and 10.41 ppm corresponding to $NH_2$ and triazolotriazine-$N_6$ and imine protons, respectively.

It was important to shed more light on the activity of some new triazolo[1,2,4]triazines; therefore, attempts to carry out a conversion of compound **2** into its corresponding triazolo[1,2,4]triazine analogues were achieved through initial diazotization of compound **2** to yield compound **62**, which was further coupled with different reagents (Scheme 9). Compound **62** was coupled with the β-dicarbonyl compound; ethyl 2-chloroacetoacetate in absolute ethanol containing a catalytic amount of sodium acetate at 0°C to yield both the cyclic triazolotriazine compound **63** and the open chain azo derivative **64**.

Furthermore, compound **62** was reacted with phenyl isocyanate to furnish the target [1,2,4]triazolo[5,1-*d*][1,2,3,5]tetrazinone derivative **65**. A well-known synthetic pathway for various fused azolotriazine derivatives is developed via coupling of enaminones with different diazoazoles [56–58]. Therefore, compound **62** was coupled with dimethylaminomethylene-1-tetralone in pyridine at 0–5°C to furnish the target compound **66**.

Moreover, DMAD was illustrated to react via the electrophilic addition on its triple bond with bifunctional compounds leading to their corresponding cyclized dicarboxylate derivatives [59,60]; thus, compound **62** was converted to the target triazolotriazinedicarboxylate derivative **67** through its reaction with DMAD under conventional reflux conditions because milder conditions as stirring at room temperature in dichloromethane did not allow the reaction to proceed. The $^1H$ NMR spectrum of compound **67** displayed a singlet signal at $\delta$ 4.10 ppm integrated for six protons due to the two methyl ester protons.

Finally, compound **62** was fused with phenylacetylene method to yield both the substitution product phenylethynyldiazenyl[1,2,4]triazole derivative **69** and the cyclic triazolotriazine derivative **68**.

It is worth mentioning that the reactions of phenylacetylene or other substituted terminal alkynes with diazo compounds or other N=N containing dipoles [58,61] involve first substitution reaction of the acetylenic proton followed by addition on the alkyne triple bond leading to different heterocyclic derivatives through a [3 + 2] dipolar cycloaddition of the diazo compound followed by [1,5] sigmatropic rearrangement and aromatization [62]. However, in this study, the reaction was postulated to proceed first through substitution of the acetylenic proton to yield the open chain compound **69**, which carried out intramolecular cyclization to give

**Table 2**

Six dose growth inhibition percent and $IC_{50}$ values of the tested compounds against MCF7 cell line.

| | Sample concentration | | | | | | |
|---|---|---|---|---|---|---|---|
| | Growth inhibition % | | | | | | |
| (μg/mL) Compound no. | 100 | 50 | 25 | 12.5 | 6.25 | 3.125 | $IC_{50}$ (μM/L) |
| **2** | 83.28 | 63.02 | 40.26 | 24.53 | 11.54 | 2.97 | 183.55 |
| **3** | 67.26 | 53.63 | 36.84 | 19.61 | 7.56 | 1.35 | 164.77 |
| **4** | 90.84 | 78.18 | 65.97 | 53.13 | 35.85 | 18.76 | 32.13 |
| **5** | 58.03 | 42.51 | 25.18 | 9.83 | 1.55 | 0.0 | 217.45 |
| **6** | 64.03 | 53.17 | 21.61 | 9.54 | 1.78 | 0.0 | 122.16 |
| **7** | 94.79 | 88.11 | 81.73 | 70.57 | 48.14 | 30.52 | 21.24 |
| **9** | 82.35 | 30.26 | 61.47 | 23.61 | 10.77 | 2.92 | 69.58 |
| **10** | 26.14 | 15.31 | 7.42 | 1.73 | 0.0 | 0.0 | – |
| **11** | 62.11 | 51.07 | 29.51 | 13.43 | 5.72 | 2.66 | 153.11 |
| **14a** | 83.76 | 74.32 | 67.89 | 56.33 | 21.09 | 10.86 | 24.58 |
| **14b** | 75.43 | 63.82 | 46.71 | 70.84 | 17.97 | 8.38 | 75.29 |
| **16** | 56.82 | 35.77 | 20.33 | 9.59 | 1.83 | 0.0 | 200.96 |
| **17** | 83.69 | 75.38 | 62.16 | 53.71 | 14.13 | 5.74 | 17.69 |
| **18** | 88.58 | 75.06 | 61.29 | 56.35 | 20.97 | 13.43 | 38.69 |
| **20** | 72.19 | 60.46 | 47.21 | 27.37 | 10.59 | 4.14 | 93.30 |
| **21** | 85.63 | 74.38 | 56.07 | 34.13 | 17.05 | 5.74 | 73.95 |
| **22** | 91.06 | 81.75 | 69.27 | 50.79 | 27.82 | 13.83 | 32.56 |
| **25** | 31.57 | 15.04 | 6.79 | 1.28 | 0.0 | 0.0 | – |
| **26** | 81.24 | 70.46 | 41.87 | 15.22 | 6.88 | 1.03 | 74.77 |
| **28** | 80.15 | 74.88 | 65.47 | 60.85 | 40.79 | 14.86 | 21.60 |
| **29** | 75.28 | 61.75 | 40.24 | 21.77 | 10.83 | 4.53 | 86.66 |
| **32a** | 78.32 | 60.59 | 32.42 | 16.83 | 8.58 | 1.94 | 156.94 |
| **32b** | 79.17 | 67.84 | 58.15 | 39.53 | 21.87 | 13.48 | 60.79 |
| **34** | 86.59 | 75.07 | 53.58 | 58.31 | 36.79 | 19.06 | 27.09 |
| **37** | 83.55 | 71.28 | 48.76 | 30.85 | 18.77 | 11.26 | 107.90 |
| **39** | 70.15 | 51.88 | 29.14 | 14.61 | 5.18 | 0.34 | 104.83 |
| **41** | 63.06 | 55.49 | 43.58 | 36.73 | 23.11 | 10.84 | 86.84 |
| **43** | 75.82 | 62.71 | 31.88 | 10.27 | 3.86 | 0.24 | 141.43 |
| **45** | 56.26 | 40.58 | 21.81 | 10.14 | 4.96 | 1.24 | 273.34 |
| **46** | 90.32 | 84.11 | 69.24 | 54.08 | 32.52 | 14.11 | 38.61 |
| **47** | 93.77 | 90.86 | 86.11 | 64.53 | 41.32 | 17.88 | 32.95 |
| **53** | 73.82 | 58.07 | 35.52 | 17.09 | 5.85 | 1.97 | 165.31 |
| **54** | 43.71 | 35.53 | 16.62 | 4.38 | 0.87 | 0.0 | – |
| **56** | 47.52 | 21.07 | 10.33 | 5.86 | 1.29 | 0.0 | – |
| **57** | 88.71 | 83.63 | 71.86 | 40.58 | 23.79 | 10.47 | 55.68 |
| **60** | 69.26 | 60.18 | 49.22 | 30.84 | 15.47 | 7.73 | 71.61 |
| **61** | 87.11 | 72.86 | 31.03 | 26.82 | 10.56 | 3.98 | 93.63 |
| **63** | 75.81 | 64.32 | 57.24 | 32.38 | 11.71 | 5.49 | 66.02 |
| **65** | 76.46 | 63.73 | 43.88 | 19.57 | 10.42 | 5.84 | 100.70 |
| **66** | 77.36 | 68.05 | 52.48 | 30.96 | 12.31 | 5.87 | 70.71 |
| **67** | 64.58 | 53.16 | 21.09 | 6.92 | 1.73 | 0 | 136.61 |
| **68** | 78.15 | 66.84 | 43.75 | 29.66 | 21.87 | 14.78 | 103.33 |
| Doxorubicin | 100 | 90.76 | 88.45 | 84.26 | 77.78 | 70.82 | 8.90 |

compound **68** via nucleophilic addition. The $^1$H NMR spectrum of compound **69** revealed a deuterium oxide exchangeable singlet signal at $\delta$ 12.20 ppm attributed to the triazole endocyclic NH proton.

**Anticancer screening.** The newly synthesized compounds were screened for their *in vitro* cytotoxic activity against human hepatocellular carcinoma HepG-2 and human breast cancer MCF-7 cell lines, in the Regional Center of Mycology and Biotechnology at Al-Azhar University using doxorubicin as a reference drug.

The six dose growth inhibition percent and the $IC_{50}$ values of the tested compounds against liver HepG2 and breast MCF7 cell lines are represented in Tables 1 and 2, respectively.

As revealed from the results presented in Tables 1 and 2; fusion of different substituted heterocycles to the [1,2,4] triazole ring led to variable anticancer activities. It is worth mentioning that fusion of different substituted pyrimidine rings to the triazole nucleus resulted in the most active compounds compared with the other screened heterocyclic compounds.

However, concerning the activities of different substituted triazolopyrimidine derivatives, it is observed that the 2-aminonitrile derivatives **4** and **7** bearing at C5

position either 2-thienyl or S-methyl moieties, respectively, exhibited highly potent anticancer activities against HepG2 and moderate activity against MCF-7 cell lines, in which compound **7** was nearly half potent to the reference drug doxorubicin against HepG2 cell line showing $IC_{50}$ value 18.19 μM/L, and it showed moderate activity against MCF-7 cell line with $IC_{50}$ value 21.24 μM/L. However, the spiro triazolopyrimidine derivative **17** exhibited strong anticancer activity against both cell lines nearly half potent compared with the reference drug doxorubicin showing $IC_{50}$ values 17.69 μM/L.

Also, the triazolopyrimidin-5-one analogues **18**, **46**, and **47** bearing at C7 position phenyl, carboxylic, or methyl groups exhibited moderate anticancer activities against both cell lines.

Besides, the triazolopyrimidin(5 or 7)one derivatives **14a**, **15**, **18**, and **22** bearing carboxylate functions at C6 positions as in compounds **14a** and **15**, or attached to a phenyl group at C7 position as in compound **18** or comprising nitrile and 4-methoxyphenyl groups at C6 and C7 positions, respectively, as in compound **22**, exerted moderate anticancer activity against both HepG2 and MCF-7 cell lines showing $IC_{50}$ values ranging from 24.69 to 31.70 μM/L and 24.58 to 38.69 μM/L, respectively. Also, the triazolopyrimidine compounds **28** and **32b** bearing at C5 position 4-methoxyphenyl, phenyl, or methyl groups while C7 position is occupied by 2-thienyl, phenyl, or methyl groups exerted moderate activity against HepG2 cell line with $IC_{50}$ values 25.18 and 37.10 μM/L, respectively. It is to be noted that only compound **28** showed appreciable anticancer activity against MCF-7 cell line with $IC_{50}$ value 21.60 μM/L.

Furthermore, the triazolotetrahydroquinolin-8-one analogue **34** exhibited promising anticancer activity against HepG2 and MCF-7 cell lines showing $IC_{50}$ values 20.19 and 27.09 μM/L, respectively. However, fusion of triazole ring to imidazole, [1,3,5]triazine, [1,2,5]triazine, and [1,2,3,5]tetrazine resulted in compounds possessing weak anticancer activity against both cell lines. In addition, the triazole derivative **48b** bearing thiophene-2-carboxamide moiety showed moderate activity against HepG2 cell line showing $IC_{50}$ value 31.89 μM/L.

## CONCLUSION

It could be concluded that among the tested compounds, fusion of the [1,2,4]triazole ring to different substituted pyrimidine rings resulted in the most active compounds compared with other heterocyclic rings; among which, 7-amino-2-(4-chlorophenyl)-5-(methylthio)[1,2,4] triazolo[1,5-*a*]pyrimidine-6-carbonitrile **7** and ethyl5′(5-bromo-2-hydroxyphenyl)-2′(4-chlorophenyl)-5′,6′-dihydro-4H-spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-a]pyrimidine)}-3-carboxylate **17** were the most active exhibiting nearly half potent activity against HepG2 cell line compared with the reference drug doxorubicin ($IC_{50}$ 8.56 μM/L) showing $IC_{50}$ values 18.19 and 17.69 μM/L, respectively, in addition to their moderate to strong activity against MCF7 cell line showing $IC_{50}$ values 21.24 and 17.69 μM/L, respectively (doxorubicin $IC_{50}$: 8.90 μM/L).

## EXPERIMENTAL

**Chemistry.** All melting points were measured on Electrothermal LA 9000 SERIES, digital melting point apparatus and were uncorrected. IR spectra (KBr) were recorded on Nikolet IR 200 FT IR Spectrophotometer ($\upsilon$, $cm^{-1}$), Pharmaceutical Analytical Unit, Faculty of Pharmacy, Cairo University. The $^1H$ NMR and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ at 300 MHz on Varian Gemini EM NMR Spectrometer (δ ppm) using tetramethylsilane as internal standard, laboratories of the nuclear magnetic resonance, Chemical Warfare Department, Ministry of Defense. Mass spectra were recorded on DI-50 unit of Schimadzu GC/MS-QP5050A Spectrometer at 70 ev, Regional Center for Mycology and Biotechnology, Al-Azhar University. Microanalytical data were performed on Elementar Vario EI III CHN analyzer, Regional Center for Mycology and Biotechnology, Al-Azhar University. Thin-layer chromatography was performed on pre-coated (0.25 mm) silica gel GF 254 plates (E. Merk, Germany). Compounds were visualized under 254 nm UV lamp.

***7-Amino-2-(4-chlorophenyl)-[1,2,4]triazolo[1,5-a] pyrimidine-6-carbo nitrile (3).*** An equimolar mixture of [1,2,4]triazole-5-amine derivative **2** [10,20] (0.19 g, 1 mmol) and 2-(ethyoxymethylene)malononitrile (0.12 g, 1 mmol) in glacial acetic acid (5 mL) was refluxed for 24 h. The reaction mixture was filtered while hot, and the solid obtained was washed with hot acetic acid, dried, and recrystallized from glacial acetic acid to give compound **3**.

Pale yellow crystals, 0.08 g (30%), mp > 300°C. IR (KBr, $cm^{-1}$): 3356, 3169 ($NH_2$), 3070 (CH-aromatic), 2230 (C≡N), 1635 (C≡N), 1595 (C≡C), 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 7.65 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H), 8.22 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H), 8.63 (s, 1H, triazolopyrimidine-$C_5$-H), 9.23 (s, 2H, $NH_2$, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 272 ($M^+$ + H, 36), 271 ($M^+$, 53), 270 (100). *Anal*. Calcd (%) for $C_{12}H_7ClN_6$ (270.68): C, 53.25; H, 2.61; N, 31.05. Found (%): C, 53.41; H, 2.59; N, 31.32.

***7-Amino-2-(4-chlorophenyl)-5-(thiophen-2-yl)-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (4).*** A solution of [1,2,4]triazole-5-amine derivative **2** (0.19 g,

1 mmol) in absolute ethanol (5 mL) containing a catalytic amount of piperidine (0.02 mL) was treated with 2-(thiophen-2-ylmethylene)malononitrile (0.16 g, 1 mmol). The reaction mixture was then heated under reflux for 48 h, then cooled, and concentrated under reduced pressure, and the residue was treated with *n*-hexane to precipitate a solid product that was filtered, washed with hexane, dried, and crystallized from ethanol/hexane mixture (1:9) to give compound **4**.

Dark brown powder, 0.25 g (72%); mp 145–146°C. IR (KBr, $cm^{-1}$): 3323, 3215, 3146 (NH, $NH_2$), 2957 (CH-aromatic), 2203 (C≡N), 1646 (C=N), 1568 (C=C), 1088 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 6.04 (s, 2H, $NH_2$, $D_2O$ exchangeable), 7.31 (t, 1H, $J$ = 5.1 Hz, thiophene-$C_4$-H), 7.37 (s, 1H, thiophene-$C_3$-H), 7.45 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H), 7.88 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H), 8.08 (d, 1H, $J$ = 5.1 Hz, thiophene-$C_5$-H), 8.39 (s, 1H, triazolopyrimidine-$C_5$-H), 12.10 (s, 1H, triazolopyrimidine-NH, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, δ ppm): 43.70 (triazolopyrimidine-$C_5$), 102.02 (triazolopyrimidine-$C_6$), 116.61 (C≡N), 126.89 (thiophene-$C_4$), 126.98 (thiophene-$C_3$), 128.53 (thiophene-$C_5$), 128.57 (thiophene-$C_2$), 134.88 (4-Cl-$C_6H_4$-$C_{2,6}$), 135.76 (4-Cl-$C_6H_4$-$C_{3,5}$), 137.60 (4-Cl-$C_6H_4$-$C_1$), 137.71 (4-Cl-$C_6H_4$-$C_4$), 143.47 (triazolopyrimidine-$C_7$), 161.00 (triazolopyrimidine-$C_{3a}$), 162.53 (triazolopyrimidine-$C_2$). Mass spectrum, *m/z* (%): 353 ($M^+$ −2, 1), 194 (100). *Anal*. Calcd (%) for $C_{16}H_{11}ClN_6S$ (354.82): C, 54.16; H, 3.12; N, 23.69. Found (%): C, 54.71; H, 2.54; N, 24.06.

**General procedure for synthesis of compounds 5** and **6**. An equimolar mixture of compound **2** (0.2 g, 1 mmol), malononitrile (0.06 g, 1 mmol), and the appropriate ketone, namely, 1-tetralone or 3-methyl-1*H*-pyrazol-5(4*H*)-one (1 mmol) in absolute ethanol (5 mL) in the presence of a catalytic amount of piperidine (1 drop) was heated under reflux for 24 h. The reaction mixture was filtered while hot, and the obtained precipitate was washed with ethanol, dried, and crystallized from ethanol to yield compounds **5** and **6**, respectively.

***7-Amino-2-(4-chlorophenyl)-3′-methyl-4′,5′-dihydro-1′H-spiro{[5′]pyrazole-5′,5-[1,2,4]triazolo[1,5-a]pyrimidine}-6-carbonitrile (5).*** Grayish white powder, 0.23 g (67.5%); mp 262–264°C. IR (KBr, $cm^{-1}$): 3405, 3330, 3228, 3173 (NH, $NH_2$), 2990 (CH-aromatic), 2840 (CH-aliphatic), 2211 (C≡N), 1610 (C=N), 1568 (C=C), 1091 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 1.05 (s, 3H, $CH_3$), 4.11 (s, 2H, $NH_2$, $D_2O$ exchangeable), 5.57 (s, 2H, $CH_2$), 7.31 (s,1H, pyrazole NH, $D_2O$ exchangeable), 7.63 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H), 8.10 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H), 12.20 (s,1H, triazolopyrimidine NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 341 ($M^+$, 0.21); 67 (100). *Anal*. Calcd (%) for $C_{15}H_{13}ClN_8$ (340.77): C, 52.87; H, 3.85; N, 32.88. Found (%): C, 53.04; H, 3.89; N, 33.12.

***7-Amino-2-(4-chlorophenyl)-1′,2′,3′,4′-tetrahydro-4H-spiro{[1′]naphthalene-1′,5-[1,2,4]triazolo[1,5-a]pyrimidine}-6-carbonitrile (6).*** Dark brown powder, 0.31 g (80%); mp > 300°C. IR (KBr, $cm^{-1}$): 3369, 3327, 3199, 3178 (NH, $NH_2$), 3095 (CH-aromatic), 2950 (CH-aliphatic), 2204 (C≡N), 1602 (C=N), 1590 (C=C), 1093 (*p*-Cl-phenyl). Mass spectrum, *m/z* (%): 390 ($M^+$ +1, 0.22), 43 (100). *Anal*. Calcd (%) for $C_{21}H_{17}ClN_6$ (388.85): C, 64.86; H, 4.41; N, 21.61. Found (%): C, 64.98; H, 4.46; N, 21.78.

**General procedure for synthesis of compounds 7** and **8**. An equimolar mixture of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) and [bis(methylthio)methylene] malononitrile (0.17 g, 1 mmol) in methanol (5 mL) was heated under reflux for 12 h. The reaction mixture was filtered while hot, and the obtained precipitate was washed with ethanol, dried, and crystallized from ethanol/hexane mixture (9:1) to yield compound **7**. The filtrate of the reaction mixture was allowed to cool, and the formed precipitate was filtered, washed with cold ethanol, dried, and recrystallized from ethanol/hexane mixture (6:4) to yield compound **8**.

***7-Amino-2-(4-chlorophenyl)-5-(methylthio)-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (7).*** Pale yellow powder, 0.016 g (5%); mp 278–279°C. IR (KBr, $cm^{-1}$): 3313, 3273, 3215 (NH, $NH_2$), 3064 (CH-aromatic), 2926 (CH-aliphatic), 2277 (C≡N), 1593 (C=N), 1575 (C=C), 1317 (S-$CH_3$), 1261, 1064 (C–S–C), 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 3.26 (s, 3H, S-$CH_3$), 3.43 (s, 2H, $NH_2$, $D_2O$ exchangeable), 7.52 (s, 1H, triazolopyrimidine-$C_5$-H), 7.56 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H), 7.99 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H), 12.21 (s, 1H, triazolopyrimidine-NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 317 ($M^+$ −2, 1), 110 (100). *Anal*. Calcd (%) for $C_{13}H_{11}ClN_6S$ (318.78): C, 48.98; H, 3.48; N, 26.36. Found (%): C, 49.29; H, 3.16; N, 26.68.

***2-[(3-(4-Chlorophenyl)-2H-[1,2,4]triazol-5-ylamino)(methylthio)methyl]malononitrile (8).*** Pale yellow crystals, 0.13 g (40%); mp 248–250°C. IR (KBr, $cm^{-1}$): 3313, 3190 (NH); 3057 (CH-aromatic); 2922 (CH-aliphatic); 2210 (C≡N); 1635 (C=N); 1560 (C=C); 1265, 1064 (C-S-C); 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 2.79 (s, 3H, S-$CH_3$); 3.39 (s, 1H, NH, $D_2O$ exchangeable); 7.54 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.97 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.62 (s, 1H, triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{13}H_8ClN_6S$ (316.77): C, 49.29; H, 2.86; N, 26.53. Found (%): C, 49.67; H, 2.51; N, 26.89.

***Methyl 2-(4-chlorophenyl)-7-oxo-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylate (9).*** To a solution of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) in absolute ethanol (5 mL), DMAD (0.21 g, 0.2 mL, 1.5 mmol) was added dropwise while stirring. The

reaction mixture was heated under reflux for 14 h, then allowed to cool, and the precipitated solid was filtered, washed with ethanol, dried, and finally recrystallized from ethanol to yield compound **9**.

Yellow crystals, 0.15 g (50%); mp 297–298°C. IR (KBr, $cm^{-1}$): 3236 (NH); 3045 (CH-aromatic); 2958, 2922 (CH-aliphatic); 1738, 1683 (two C=O); 1641 (C=N); 1573 (C=C); 1274, 1058 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.37 (s, 3H, $OCH_3$); 7.60 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.01 (s, 1H, triazolopyrimidine-$C_6$-H); 10.61 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 305 ($M^+$, 4); 304 ($M^+$ −1, 12); 303 ($M^+$ −2, 1); 111 (100). *Anal*. Calcd (%) for $C_{13}H_9ClN_4O_3$ (304.69): C, 51.25; H, 2.98; N, 18.39. Found (%): C, 51.43; H, 2.96; N, 18.58.

***2-(4-Chlorophenyl)[1,2,4]triazolo[1,5-a]pyrimidine-5,7(4H,6H)-dione (10).*** To a well-stirred solution, [1,2,4] triazole-5-amine derivative **2** (0.19 g, 1 mmol) in ethanolic sodium ethoxide [prepared by dissolving (0.05 g, 2 mmol) of sodium metal in 5 mL ethanol] was added with diethyl malonate (0.16 g, 0.15 mL, 1 mmol). The reaction mixture was heated under reflux for 30 h, then allowed to cool. The formed solid was filtered and dissolved in water, and the aqueous solution was acidified with diluted hydrochloric acid. The separated solid was collected by filtration, washed with water, dried, and crystallized from benzene/ethanol mixture (6:4) to yield compound **10**.

Brown powder, 0.12 g (47%); mp > 300°C. IR (KBr, $cm^{-1}$): 3421 (broad OH, NH); 3040 (CH-aromatic); 1734, 1680 (two C=O); 1647 (C=N); 1575 (C=C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm):1.72 (s, 2H, $CH_2$); 6.00 (s, 1H, NH, $D_2O$ exchangeable); 7.52 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.90 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). Mass spectrum, *m/z* (%): 263 ($M^+$, 3); 261 ($M^+$ −2, 6); 50 (100). *Anal*. Calcd (%) for $C_{11}H_7ClN_4O_2$ (262.65): C, 50.30; H, 2.69; N, 21.33. Found (%): C, 50.43; H, 2.67; N, 21.46.

***General procedure for synthesis of compounds 11, 12, and 13.***

Method A

An equimolar mixture of compound **2** (0.19 g, 1 mmol) and diethyl ethoxymethylenemalonate (0.22 g, 0.19 mL, 1 mmol) was fused in an oil bath at 250°C for 4 h. The fused mass was allowed to cool and triturated with ethanol, and the obtained solid was washed with ethanol, filtered off, dried, and boiled in absolute ethanol to yield compound **11**. However, upon concentration of the collected ethanolic portions, a solid was obtained that was filtered off, washed with ethanol and dried to yield compound **12**. The ethanolic filtrate remaining after crystallization of compound **12** upon cooling and standing overnight separated a solid that was filtered, washed with ethanol, and dried to yield compound **13**.

Method B

An equimolar mixture of compound **2** (0.2 g, 1 mmol) and diethyl ethoxymethylenemalonate (0.22 g, 0.19 mL, 1 mmol) was heated under reflux in $H_2O$ (8 mL) for 40 h. The aqueous reaction mixture was filtered while hot, and the obtained solid was filtered off, washed with $H_2O$, dried, and crystallized from ethanol to yield compound **13**. The aqueous filtrate was triturated with ethanol (5 mL), and the formed precipitate was filtered, washed with aqueous ethanol, dried, and recrystallized from ethanol to yield compound **11** that was filtered while hot. Compound **12** was isolated upon cooling and standing overnight.

***Ethyl 2-(4-chlorophenyl)-7-oxo-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (11).*** Yellow crystals, 0.04 g (12.5%); mp 260–262°C. IR (KBr, $cm^{-1}$): 3138 (NH); 3059 (CH-aromatic); 2905 (CH-aliphatic); 1699 (C=O); 1628 (C=N); 1580 (C=C); 1281, 1088 (C–O–C); 1088 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.28 (t, 3H, $J$ = 7.2 Hz, $CH_2$-$\underline{CH_3}$); 4.25 (q, 2H, $J$ = 7.2 Hz, $\underline{CH_2}$-$CH_3$); 7.60 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.12 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.64 (s, 1H, triazolopyrimidine-$C_5$-H); 8.90 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 320 ($M^+$ +1, 4); 319 ($M^+$, 6); 139 (100). *Anal*. Calcd (%) for $C_{14}H_{11}ClN_4O_3$ (318.72): C, 52.76; H, 3.48; N, 17.58. Found (%): C, 52.93; H, 3.51; N, 17.81.

***Ethyl 2-(4-chlorophenyl)-5-oxo-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (12).*** Reddish brown crystals, 0.06 g (18%); mp 132–133°C. IR (KBr, $cm^{-1}$): 3225, 3199 (NH); 3061 (CH-aromatic); 2929, 2880 (CH-aliphatic); 1705, 1683 (C=O); 1591 (C=N); 1568 (C=C); 1265, 1091 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.05 (t, 3H, $J$ = 6.9 Hz, $CH_2$-$\underline{CH_3}$); 4.26 (q, 2H, $J$ = 6.9 Hz, $\underline{CH_2}$-$CH_3$); 7.61 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.64 (s, 1H, triazolopyrimidine-$C_7$-H);10.62 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{14}H_{11}ClN_4O_3$ (318.72): C, 52.76; H, 3.48. Found (%): C, 52.90; H, 4.79.

***Diethyl 2-[(3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-ylamino) methylene]malonate (13).*** Deep brown powder, 0.16 g (45%); mp > 300°C. IR (KBr, $cm^{-1}$): 3381, 3188 (NH); 3032 (CH-aromatic); 2937 (CH-aliphatic); 1697 (C=O); 1645 (C=N); 1568 (C=C); 1271, 1093 (C–O–C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.25 (t, 6H, $J$ = 6.9 Hz,two $CH_2$-$\underline{CH_3}$); 3.98–4.17 (m, 4H, two $\underline{CH_2}$-$CH_3$); 6.00 (s, 1H, triazole-$C_5$-NH, $D_2O$ exchangeable); 7.45 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.75 (s, 1H, –$\underline{CH}$=C($COOC_2H_5$)$_2$); 7.87 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 9.89 (s, 1H, triazole-NH, $D_2O$

exchangeable). Mass spectrum, *m/z* (%): 365 ($M^+$, 2); 98 (100). *Anal*. Calcd (%) for $C_{16}H_{17}ClN_4O_4$ (364.78): C, 52.68; H, 4.70; N, 15.36. Found (%): C, 52.77; H, 4.78; N, 15.49.

**General procedure for synthesis of compounds 14a,b** and **15**. An equimolar mixture of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) and the appropriate diethyl arylidenemalonate (1 mmol), namely, diethyl 2-(2,4-dichlorobenzylidene)malonate or diethyl 2-(pyridine-2-yl) methylene)malonate in absolute ethanol (5 mL) was heated under reflux for 24 h. The reaction mixture was filtered while hot, and the obtained solid was washed with ethanol, dried, and recrystallized from ethyl acetate/hexane mixture (4:6) to yield compounds **14a,b**. However, upon cooling the filtrate of the reaction mixture, a solid was separated, filtered off, washed with ethanol, dried, and finally recrystallized from ethanol to yield compound **15**.

***Ethyl 2-(4-chlorophenyl)-7-(2,4-dichlorophenyl)-5-oxo-4,5-dihydro [1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (14a)***. Pale yellow powder, 0.09 g (20%); mp 256–257°C. IR (KBr, $cm^{-1}$): 3420 (OH); 3188 (NH); 3066, 3012 (CH-aromatic); 2841 (CH-aliphatic); 1700, 1676 (two C=O); 1593 (C=N); 1560 (C=C); 1265, 1070 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.10–1.15 (m, 3H, $CH_2\underline{CH_3}$); 3.48–3.52 (m, 2H, $\underline{CH_2}CH_3$); 7.52–7.65 (m, 1H, 2,4-$(Cl)_2$-$C_6H_3$-C$_6$-H); 7.93 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.99 (d, 1H, $J$ = 8.7 Hz, 2,4-$(Cl)_2$-$C_6H_3$-$C_5$-H); 8.10 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.15 (s, 1H, 2,4-$(Cl)_2$-$C_6H_3$-$C_3$-H); 12.20 (s, ½ H, NH, $D_2O$ exchangeable); 13.80 (s, ½ H, OH tautomer, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{20}H_{13}Cl_3N_4O_3$ (463.70): C, 51.58, H, 2.83; N, 12.08. Found (%): C, 51.89; H, 2.87; N, 12.24.

***Ethyl 2-(4-chlorophenyl)-5-oxo-7-(pyridin-2-yl)-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (14b)***. Brown powder, 0.07 g (17%); mp 253–254°C. IR (KBr, $cm^{-1}$): 3192 (NH); 3064 (CH-aromatic); 2926, 2852 (CH-aliphatic); 1720, 1676 (two C=O); 1591 (C=N); 1560 (C=C); 1265, 1064 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.23–1.25 (m, 3H, $CH_2\underline{CH_3}$); 4.20–4.26 (m, 2H, $\underline{CH_2}CH_3$); 7.50–7.55 (m, 1H, pyridyl-$C_4$-H); 7.59–7.64 (m, 1H, pyridyl-$C_3$-H); 7.90–7.95 (m, 1H, pyridyl-$C_5$-H); 7.98 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.10 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.59–8.64 (m, 1H, pyridyl-$C_6$-H); 10.64 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 396 ($M^+$, 1); 137 (100). *Anal*. Calcd (%) for $C_{19}H_{14}ClN_5O_3$ (395.80): C, 57.66; H, 3.57; N, 17.69. Found (%): C, 57.85; H; 3.66; N, 17.82.

***Ethyl 2-(4-chlorophenyl)-7-(2,4-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (15).*** White crystals, 0.02 g (5%); mp 270–272°C. IR (KBr, $cm^{-1}$): 3311, 3267 (NH); 3066 (CH-aromatic); 2840 (CH-aliphatic); 1700, 1676 (two C=O); 1593 (C=N); 1560 (C=C); 1261, 1064 (C–O–C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.20–1.24 (m, 3H, $CH_2\text{-}\underline{CH_3}$); 4.09 (s, 2H, $\underline{CH_2}\text{-}CH_3$); 7.52–7.56 (m, 2H, triazolopyrimidine-$C_{6,7}$-H); 7.62 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 1H, $J$ = 8.4 Hz, 2,4-$(Cl)_2$-$C_6H_3$-C$_6$-H); 7.99 (d, 1H, $J$ = 8.4 Hz, 2,4-$(Cl)_2$-$C_6H_3$-$C_5$-H); 8.10 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.15 (s, 1H, 2,4-$(Cl)_2$-$C_6H_3$-$C_3$-H); 12.22 (s, ½ H, NH, $D_2O$ exchangeable); 13.82 (s, ½ H, OH tautomer, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{20}H_{15}Cl_3N_4O_3$ (465.72): C, 51.65; H, 2.83; N, 12.08. Found (%): C, 51.94; H, 2.87; N, 12.19.

***4-Bromo-2-(2-(4-chlorophenyl)-7-methyl-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-5-yl)phenol (16)***. To an equimolar mixture of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) and 5-bromosalicyladehyde (0.2 g, 1 mmol) in methanol (5 mL), a mixture of acetone (0.15 g, 0.22 mL, 3 mmol) and dioxane (1 mL) containing a catalytic amount of concentrated hydrochloric acid (2 drops) was added. The reaction mixture was then heated under reflux for 36 h. The reaction mixture was allowed to cool, and the obtained solid product was filtered off, washed with methanol, dried, and recrystallized from methanol to yield compound **16**.

Brown crystals, 0.15 g (36%); mp 129–132°C. IR (KBr, $cm^{-1}$): 3419, 3404, 3292, 3124 (br.OH & NH); 3072, 2974 (CH-aromatic); 2926, 2870 (CH-aliphatic); 1616 (C=N); 1475 (C=C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.23 (s, 3H, $CH_3$); 4.30 (d, 1H, $J$ = 6.9 Hz, dihydro-triazolopyrimidine-$C_5$-H); 6.81 (s, 1H, dihydrotriazolopyrimidine-$C_6$-H); 6.97 (d, 2H, $J$ = 8.4 Hz, 5-Br-2-OH-$C_6H_3$-$C_3$-H); 7.18–7.40 (m, 1H, 5-Br-2-OH-$C_6H_3$-$C_4$-H); 7.53–7.68 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.71 (s, 1H, 5-Br-2-OH-$C_6H_3$-C$_6$-H); 7.95 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.90 (s, 1H, OH, $D_2O$ exchangeable); 11.10 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, δ ppm): 40.31 ($CH_3$, under DMSO); 110.65 (triazolopyrimidine-$C_5$); 119.77 (triazolopyrimidine-$C_6$); 119.95 (5-Br-2-OH-$C_6H_3$-$C_3$); 123.98 (5-Br-2-OH-$C_6H_3$-$C_4$); 128.59 (5-Br-2-OH-$C_6H_3$-$C_1$); 128.78 (4-Cl-$C_6H_4$-$C_{2,6}$); 129.95 (triazolopyrimidine-$C_7$); 130.34 (5-Br-2-OH-$C_6H_3$-C$_6$); 130.51 (4-Cl-$C_6H_4$-$C_{3,5}$); 131.13 (5-Br-2-OH-$C_6H_3$-$C_2$); 137.71 (4-Cl-$C_6H_4$-$C_1$); 138.34 (5-Br-2-OH-$C_6H_3$-$C_5$); 138.50 (4-Cl-$C_6H_4$-$C_4$); 159.79 (triazolopyrimidine-$C_{3a}$); 166.40 (triazolopyrimidine-$C_2$). Mass spectrum, *m/z* (%): 419 ($M^+$ +1, 1); 63 (100). *Anal*. Calcd (%) for $C_{18}H_{16}BrClN_4O$ (417.69): C, 51.76; H, 3.38; N, 13.41. Found: C, 51.76; H, 3.75; N, 13.04.

***Ethyl 5′(5-bromo-2-hydroxyphenyl)-2′(4-chlorophenyl)-5′,6′-dihydro-4H-spiro{[1]benzopyran-2,7′-[1,2,4]triazolo[1,5-a]pyrimidine)}-3-carboxylate (17)***. To a solution of compound **2** (0.2 g, 1 mmol) in absolute ethanol (5 mL),

5-bromosalicyaldehyde (0.2 g, 1 mmol) and ethyl acetoacetate (0.13 g, 0.13 mL, 1 mmol) were added; then, 1 mL of dioxane containing concentrated hydrochloric acid (1 drop) was added, and the mixture was heated under reflux for 40 h. The reaction mixture was allowed to cool and poured onto ice-cold water, and the precipitated solid was filtered, washed with water, dried, and crystallized from ethanol/hexane mixture (8:2) to yield compound **17**.

Reddish brown powder, 0.35 g (52%); mp 120–122°C. IR (KBr, $cm^{-1}$): 3404, 3387 (br. OH); 3267, 3246 (NH); 2978, 2951 (CH-aromatic); 2850 (CH- aliphatic); 1712 (C=O); 1629 (C=N); 1560 (C=C); 1274, 1086 (C–O–C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.21–1.33 (m, 3H, $CH_2$-$\underline{CH_3}$); 4.13–4.37 (m, 2H, $\underline{CH_2}$-$CH_3$); 5.80–5.90 (m, 2H, triazolopyrimidine-$C_6$-H); 6.28–6.30 (m, 1H, triazolopyrimidine-$C_5$-H); 6.79 (d, 1H, $J$ = 8.1 Hz, 5-Br-2-OH-$C_6H_3$-$C_3$-H); 6.85–6.95 (m, 1H, benzopyrane-$C_8$-H); 7.10 (s, 1H, NH, $D_2O$ exchangeable); 7.41–7.55 (m, 1H, benzopyrane-$C_7$-H); 7.59 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.1 Hz, 5-Br-2-OH-$C_6H_3$-$C_4$-H); 8.01 (s, 2H, benzopyrane-$C_{4,5}$-H); 8.10 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.20 (s, 1H, 5-Br-2-OH-$C_6H_3$-$C_6$-H); 8.92 (s, 1H, OH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 673 ($M^+$, 1); 226 (100). *Anal*. Calcd (%) for $C_{28}H_{21}Br_2ClN_4O_4$ (672.75): C, 49.99; H, 3.15; N, 8.33 Found (%): C, 49.99; H, 3.21; N, 8.33.

**General procedure for synthesis of compounds 18**, **19**, and **20**. An equimolar mixture of cinnamoyl chloride (0.16 g, 1 mmol) and [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) was heated under reflux in absolute ethanol (5 mL)for 24 h. The precipitated solid was filtered while hot, washed with ethanol, dried, and recrystallized from benzene/ethanol mixture (8:2) to give compound **18**. The filtrate of the reaction mixture was allowed to cool to precipitate a solid that was filtered off, washed with benzene, dried, and recrystallized from ethanol to yield compound **19**. The residual crystallization solvent of **19** was concentrated and triturated with *n*-hexane to isolate compound **20** that was filtered, washed with *n*-hexane, dried, and crystallized from *n*-hexane.

***2-(4-Chlorophenyl)-7-phenyl[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (18).*** Colorless crystals, 0.044 g (15%); mp > 300°C. IR (KBr, $cm^{-1}$): 3280, 3213 (NH); 2982 (CH-aromatic); 1656 (C=O); 1593 (C=N); 1513 (C=C); 1089 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.52 (d, 2H, $J$ = 8.5 Hz, $C_6H_5$-$C_{3,5}$-H); 7.59 (d, 2H, $J$ = 8.5 Hz, $C_6H_5$-$C_{2,6}$-H); 7.60–7.65 (m, 2H, $C_6H_5$-$C_4$-H & triazolopyrimidine-$C_6$-H); 7.90 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.03 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.18 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{17}H_{11}ClN_4O$ (294.65): C, 63.26; H, 3.44; N, 17.36. Found (%): C, 63.41; H, 3.52; N, 17.47.

***N-[3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-yl]cinnamamide (19).*** White crystals, 0.002 g (7.5%); mp 186–188°C. IR (KBr, $cm^{-1}$): 3365, 3296; 3221 (broad OH & NH); 3026, 2981 (CH-aromatic); 2835 (CH-aliphatic); 1668 (C=O); 1629 (C=N); 1571 (C=C); 1095 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 6.50 (s, 1H, O=C–$\underline{CH}$=CH); 6.55 (s, 1H, CH=$\underline{CH}$–$C_6H_5$); 7.40–7.42 (m, 3H, $C_6H_5$-$C_{3,4,5}$-H); 7.60–7.63 (m, 2H, $C_6H_5$-$C_{2,6}$-H); 7.66–7.69 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 9.60 (s, ½ H, $\underline{NH}$–C=O, $D_2O$ exchangeable); 10.70 (s, 1H, triazole-NH, $D_2O$ exchangeable); 12.38 (s, ½ H, OH tautomer, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 325 ($M^+$, 1); 324 ($M^+$ −1, 1); 77 (100). *Anal*. Calcd (%) for $C_{17}H_{13}ClN_4O$ (324.76): C, 62.81. H, 4.03; N, 17.25. Found (%): C, 62.99; H, 4.09; N, 17.48.

***2-(4-Chlorophenyl)-7-phenyl-6,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (20).*** Pale brown powder, 0.05 g (15%); mp 186–188°C. IR (KBr, $cm^{-1}$): 3440 (br.OH); 3385, 3369 (NH); 3086, 3064 (CH-aromatic); 2883, 2831 (CH-aliphatic); 1683 (C=O); 1629 (C=N); 1558 (C=C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 6.50 (s, 1H, triazolopyrimidine-$C_6$-H); 6.55 (s, 1H, triazolopyrimidine-$C_7$-H); 7.32–7.38 (m, 1H, $C_6H_5$-$C_4$-H); 7.41 (d, 2H, $J$ = 7.5 Hz, $C_6H_5$-$C_{3,5}$-H); 7.44–7.51 (m, 2H, $C_6H_5$-$C_{2,6}$-H); 7.61 (s, 1H, OH tautomer, $D_2O$ exchangeable); 7.65–7.73 (m, 4H, 4-Cl-$\underline{C_6H_4}$); 12.38 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, δ ppm): 40.32 (triazolopyrimidine-$C_6$, under DMSO); 119.12 (triazolopyrimidine-$C_7$); 127.20 ($C_6H_5$-$C_4$); 128.04 ($C_6H_5$-$C_{2,6}$); 128.22 ($C_6H_5$-$C_{3,5}$); 128.75 ($C_6H_5$-$C_1$); 128.94 (4-Cl-$C_6H_4$-$C_{2,6}$); 130.12 (4-Cl-$C_6H_4$-$C_1$); 130.20 (4-Cl-$C_6H_4$-$C_{3,5}$); 134.17 (4-Cl-$C_6H_4$-$C_4$); 143.77 (triazolopyrimidine-$C_{3a}$); 143.93 (triazolopyrimidine-$C_2$); 167.48 (C=O). Mass spectrum, *m/z* (%): 325 ($M^+$, 6); 324 ($M^+$ −1, 14); 147 (100). *Anal*. Calcd (%) for $C_{17}H_3ClN_4O$ (324.76): C, 62.87; H, 4.03; N, 17.25. Found (%): C, 63.04; H, 4.07; N, 17.32.

***2-(4-Chlorophenyl)-5-ethyl-5-methyl-5,6-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one or 2-(4-chlorophenyl)-7-ethyl-7-methyl-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (21).*** An equimolar mixture of compound **2** (0.19 g, 1 mmol), Meldrum's acid (0.14 g, 1 mmol), and ethyl methyl ketone (0.07 g, 0.06 mL, 1 mmol) was heated under reflux for 36 h in ethanol/pyridine mixture (1:1, 10 mL). The reaction mixture was then allowed to cool, and the precipitated solid was filtered, washed with ethanol, dried, and recrystallized from ethanol to yield compound **21**.

Colorless needle crystals, 0.078 g (27%); mp 137–138°C. IR (KBr, $cm^{-1}$): 3435 (OH tautomer); 3280 (NH); 3064, 2991 (CH-aromatic); 2916 (CH-aliphatic); 1722, 1685 (C=O); 1649 (C=N); 1558 (C=C); 1095 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.06–1.26 (m, 8H, $CH_3$ & $\underline{CH_2CH_3}$); 2.00 (s, 1H, dihydrotriazolopyrimidine-

$C_6$-H); 4.11 (s, ½ H, dihydrotriazolopyrimidin-7-ol-tautomer-$C_6$-H); 6.00 (s, ½ H, OH tautomer, $D_2O$ exchangeable); 7.45 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.88 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.45 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (DMSO-$d_6$, δ ppm): 13.82 (triazolopyrimidine-$C_7$-$CH_2\underline{C}H_3$); 13.97 (triazolopyrimidine isomer-$C_5$-$CH_2\underline{C}H_3$); 41.52 ($\underline{C}H_2CH_3$); 41.63 ($CH_3$); 41.68 (triazolopyrimidine-$C_6$); 60.56 (triazolopyrimidine-$C_5$ or $C_7$); 126.89 (4-Cl-$C_6H_4$-$C_6$); 127.00 (4-Cl-$C_6H_4$-$C_2$); 128.34 (4-Cl-$C_6H_4$-$C_5$); 128.54 (4-Cl-$C_6H_4$-$C_3$); 130.80 (4-Cl-$C_6H_4$-$C_1$); 132.68 (4-Cl-$C_6H_4$-$C_4$); 156.93 (triazolopyrimidine-$C_{3a}$); 157.85 (triazolopyrimidine-$C_2$); 166.81 (7-oxotriazolopyrimidine-$C_7$); 167.91(5-oxotriazolopyrimidine isomer-$C_5$). *Anal*. Calcd (%) for $C_{14}H_{15}ClN_4O$ (290.75): C, 57.83; H, 5.20; N, 19.27. Found (%): C, 58.04; H, 5.26; N, 19.44.

**General procedure for synthesis of compounds 22** and **23**. An equimolar mixture of compound **2** (0.19 g, 1 mmol), 4-methoxybenzaldehyde (0.14 g, 0.13 mL, 1 mmol), and ethyl cyanoacetate (0.12 g, 0.11 mL, 1 mmol) in absolute ethanol (5 mL) containing a catalytic amount of piperidine (1 drop) was heated under reflux for 30 h. The formed precipitate was filtered while hot, washed with hot ethanol, dried, and finally crystallized from ethanol/hexane mixture (1:1) to give compound **22**. The filtrate of the reaction mixture upon standing overnight separated a solid product that was collected, washed with ethanol, dried, and crystallized from ethanol to yield compound **23**.

***2-(4-Chlorophenyl)-7-(4-methoxyphenyl)-5-oxo-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (22).*** Pale yellow crystals, 0.23 g (60%); mp 270–272°C. IR (KBr, $cm^{-1}$): 3403 (OH); 3275 (NH); 3059 (CH-aromatic); 2835 (CH-aliphatic); 2213 (C≡N); 1674 (C=O); 1629 (C=N); 1572 (C=C); 1253, 1029 (C–O–C); 1085 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.88 (s, 3H, $OCH_3$); 7.52–7.60 (m, 2H, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.64 (d, 2H, $J$ = 7.2 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.08–8.15 (m, 2H, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.20 (s, ½ H, triazolopyrimidine-NH, $D_2O$ exchangeable); 13.81 (s, 1/2H, OH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 378 ($M^{+\cdot}$, 8); 140 (100). *Anal*. Calcd (%) for $C_{19}H_{12}ClN_5O_2$ (377.78): C, 60.41; H, 3.20; N, 18.54. Found (%): C, 60.67; H, 3.18; N, 18.72.

***Ethyl 3-[5-amino-3-(4-chlorophenyl)-1H-[1,2,4]triazol-1-yl]-2-cyano-3-(4-methoxyphenyl)acrylate (23).*** Pale yellow powder, 0.13 g (30%); mp 243–245°C. IR (KBr, $cm^{-1}$): 3395 (intramolecular hydrogen-bonded $NH_2$); 3093, 2999 (CH-aromatic); 2921, 2844 (CH-aliphatic); 2215 (C≡N); 1702 (C=O); 1595 (C=N); 1508 (C=C); 1257; 1026 (C–O–C); 1086 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.30 (t, 3H, $J$ = 7.2 Hz, $CH_2$-$\underline{C}H_3$); 3.30 (s, 2H, $NH_2$, $D_2O$ exchangeable); 3.75 (d, 1H, $J$ = 11.1 Hz, –$\underline{C}H$(CN)-$COOC_2H_5$); 3.88 (s, 3H, $OCH_3$); 3.98–4.10 (m, 1H, $\underline{C}H$-4-$OCH_3$-$C_6H_4$); 4.30 (q, 2H, $J$ = 7.2 Hz, $\underline{C}H_2$-$CH_3$); 7.04 (d, 2H, $J$ = 6.6 Hz, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.15 (d, 2H, $J$ = 6.6 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.87 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.09 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). Mass spectrum, *m/z* (%): 427 ($M^+$ +1, 1); 139 (100). *Anal*. Calcd (%) for $C_{21}H_{20}ClN_5O_3$ (425.85): C, 59.23; H, 4.73; N, 16.44. Found: C, 59.40; H, 4.80; N, 16.69.

**General procedure for synthesis of compounds 24** and **25**. An equimolar mixture of compound **2** (0.19 g, 1 mmol), 2-(benzo[d]thiazol-2-yl)acetonitrile [63] (0.17 g, 1 mmol), and 4-methoxybenzaldehyde (0.14 g, 0.13 mL, 1 mmol) in methanol (5 mL) was heated under reflux for 36 h in the presence of a catalytic amount of ammonium acetate (0.025 g, 0.3 mmol). The reaction mixture was allowed to cool and concentrated, and the obtained solid product was filtered, washed with methanol dried, and recrystallized from ethanol to yield compound **24**, which was isolated as a first crop. However, the residual ethanolic portion upon standing overnight separated compound **25**, which was filtered, washed with ethanol, and dried.

***2-(Benzo[d]thiazol-2-yl)-3-(5-(4-chlorophenyl)-2H-[1,2,4]triazol-3-ylamino)-3-(4-methoxyphenyl)propanenitrile (24).*** Faint green crystals; 0.2 g (41%); mp 116–118 °C. IR (KBr, $cm^{-1}$): 3375, 3317, 3147 (NH); 3057 (CH-aromatic); 2935, 2912 (CH-aliphatic); 2190 (C≡N); 1604 (C=N); 1591(C=C); 1286, 1091 (C–S–C); 1261, 1028 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.70 (d, 2H, $J$ = 6.6 Hz, two CH); 3.92 (s, 3H, $OCH_3$); 6.99 (s, 1H, triazole-$C_3$-NH, $D_2O$ exchangeable); 7.10–7.16 (m, 2H,benzothiazole-$C_{5,6}$-H); 7.44 (d, 2H, $J$ = 9.3 Hz, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.51(d, 2H, $J$ = 9.3 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.88–7.98 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.99–8.05 (m, 2H, benzothiazole-$C_{4,7}$-H); 8.10 (d, 2H, $J$ = 8.1 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.60 (s, 1H, triazole NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 489 ($M^+$ +2, 2); 487 ($M^+$, 2); 55 (100). *Anal*. Calcd (%) for $C_{25}H_{19}ClN_6OS$ (486.98): C, 61.66; H, 3.93; N, 17.26. Found (%): C, 61.86; H, 3.98; N, 17.51.

***6-(Benzo[d]thiazol-2-yl)-2-(4-chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimidin-7-amine (25).*** Pale yellow crystals, 0.18 g (37%); mp 160–162°C. IR (KBr, $cm^{-1}$): 3369, 3142 ($NH_2$, NH); 3049 (CH-aromatic); 2935, 2835 (CH-aliphatic); 1604 (C=N); 1560 (C=C); 1309, 1091 (C–S–C); 1261, 1028 (C–O–C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.91 (s, 3H, O-$CH_3$); 7.06 (s, 2H, $NH_2$, $D_2O$ exchangeable); 7.12 (d, 2H, $J$ = 8.7 Hz, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.23 (s, 1H, triazolopyrimidine-$C_5$-H); 7.40–7.45 (m, 2H, 4–$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.49–7.54 (m, 2H, benzothiazole-$C_{5,6}$-H); 7.61 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.89–7.97 (m, 2H, benzothiazole-$C_{4,7}$-H); 8.10 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.63 (s,

1H, triazolopyrimidine-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{25}H_{19}ClN_6OS$ (486.98): C, 61.66; H, 3.93; N, 17.26. Found (%): C, 61.93; H, 4.01; N, 17.42.

**General procedure for synthesis of compounds 26** and **27**. Equimolar amounts of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol), 4-chlorobenzaldehyde (0.14 g, 1 mmol), and ethyl acetoacetate (0.13 g, 0.12 mL, 1 mmol) were heated under reflux in DMF (5 mL) for 24 h. The reaction mixture was allowed to cool then poured onto crushed ice. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol/*n*-hexane mixture (7:3) to yield compound **26** that was filtered while hot, washed with hot ethanol, and dried. However, the crystallization solvent mixture upon cooling precipitated a solid, which was filtered, washed with hot ethanol, and dried to yield compound **27**.

***Ethyl 2,5-bis(4-chlorophenyl)-7-methyl-4,5-dihydro[1,2,4]triazolo[1,5-a]pyrimid- ine-6-carboxylate (26)***. Light brown powder, 0.02 g (5%); mp 250–251°C. IR (KBr, $cm^{-1}$): 3259 (NH); 3063 (CH-aromatic); 2853 (CH-aliphatic); 1676 (C=O); 1638 (C=N); 1589 (C=C); 1268, 1087 (C–O–C); 1087 (*p*-Cl-phenyl).$^1$H NMR (DMSO-$d_6$, δ ppm): 1.02–1.10 (m, 3H, $CH_2$-$\underline{CH_3}$); 2.44 (s, 3H, $CH_3$); 3.95–4.00 (m, 2H, $\underline{CH_2}$–$CH_3$); 7.38 (s, 1H, triazolopyrimdine-$C_5$-H); 7.45–7.49 (m, 2H, triazolopyrimdine-$C_5$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.62 (d, 2H, $J$ = 8.3 Hz, triazolopyrimdine-$C_2$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.85 (d, 2H, $J$ = 6.9 Hz, triazolopyrimdine-$C_5$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 7.94 (d, 2H, $J$ = 8.3 Hz, triazolopyrimdine-$C_2$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.62 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 429 ($M^+$, 5); 428 ($M^{+\cdot}-1$, 1); 43 (100). *Anal*. Calcd (%) for $C_{21}H_{18}Cl_2N_4O_2$ (429.30): C, 58.75; H, 4.23; N, 13.05. Found (%): C, 58.91; H, 4.32; N, 13.27.

***Ethyl 2-[(4-chlorophenyl)(3-(4-chlorophenyl)-1H-[1,2,4]triazol-5-yl-amino) methyl]-3-oxobutanoate (27)***. Light brown crystals, 0.22 g (50%); mp 114–116°C. IR (KBr, $cm^{-1}$): 3365, 3246, 3184 (NH); 3066 (CH-aromatic); 2870, 2854 (CH-aliphatic); 1701, 1683 (C=O); 1637 (C=N); 1585 (C=C); 1282, 1091 (C–O–C); 1091 (*p*-Cl-phenyl).$^1$H NMR (DMSO-$d_6$, δ ppm): 1.06 (t, 3H, $J$ = 6.9 Hz, $CH_2$-$\underline{CH_3}$); 1.40 (s, 3H, $\underline{CH_3}$CO); 2.89 (s, 1H, CO$\underline{CH}$CO); 3.97 (q, 2H, $J$ = 6.9 Hz, $\underline{CH_2}$-$CH_3$); 6.34 (s, 1H, $\underline{CH}$-4-Cl-$C_6H_4$); 7.31 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.39 (d, 2H, $J$ = 8.7 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.46 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 7.84 (d, 2H, $J$ = 8.7 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 7.95 (s, 1H, triazole-$C_5$-NH, $D_2O$ exchangeable); 10.99 (s, 1H, triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{21}H_{20}Cl_2N_4O_3$ (447.31): C, 56.39; H; 4.51; N, 12.53. Found (%): C, 56.53; H, 4.33; N, 12.53.

**General procedure for synthesis of compounds 28**, **29**, and **30**. To a solution of compound **2** (0.19 g, 1 mmol) in DMF (2 mL), a solution of 1-(4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one [64] (0.24 g, 1 mmol) in DMF (2 mL) was added dropwise. The reaction mixture was then heated under reflux for 24 h, and the formed precipitate was filtered while hot, washed with DMF, dried, and recrystallized from DMF/ethyl acetate mixture (1:1) to yield compound **28**. The filtrate of the reaction mixture was allowed to cool and then poured onto crushed ice. The obtained solid product was collected, washed with water, dried, and crystallized from ethanol. The insoluble part in ethanol was found to be compound **29** that was isolated while hot, washed with ethanol, and dried. However, ethanolic filtrate upon cooling a solid precipitate was obtained, filtered, washed with ethanol, and dried to yield compound **30**.

***2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-7-(thiophen-2-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (28)***. Dark brown crystals, 0.13 g (30%); mp > 300°C. IR (KBr, $cm^{-1}$): 3390, 3334, 3296 (NH); 3072 (CH-aromatic); 2904 (CH-aliphatic); 1597 (C=N); 1548 (C=C); 1282, 1089 (C–S–C); 1244, 1070 (C–O–C); 1089 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.88 (s, 3H, $OCH_3$); 6.97 (d, 1H, $J$ = 9 Hz, thiophene-$C_3$-H); 7.14 (d, 1H, $J$ = 9 Hz, thiophene-$C_5$-H); 7.40–7.50 (m, 1H, thiophene-$C_4$-H); 7.66 (d, 2H, $J$ = 8.1 Hz, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 8.21 (s, 1H, triazolopyrimidine-$C_7$-H); 8.31 (d, 4H, $J$ = 8.1 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H & 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.40 (d, 2H, $J$ = 7.8 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.79 (s, 1H, triazolopyrimidine-$C_6$-H); 10.15 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{22}H_{17}ClN_4OS$ (420.91): C, 62.78; H, 4.07; N, 13.31. Found (%) C, 62.94; H, 4.11; N, 13.53.

***2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-7-(thiophen-2-yl)-6,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine (29)***. Brown crystals, 0.04 g (10%); mp 85–86°C. IR (KBr, $cm^{-1}$): 3012 (CH-aromatic); 2924(CH-aliphatic); 1646 (C=N); 1581 (C=C); 1248, 1088 (C–S–C & C–O–C); 1088 (*p*-Cl-phenyl). $^1$HNMR (DMSO-$d_6$, δ ppm): 3.87 (s, 3H, $OCH_3$); 7.08 (d, 1H, $J$ = 8.7 Hz, thiophene-$C_3$-H); 7.19–7.20 (m, 2H, thiophene-$C_{4,5}$-H); 7.53–7.62 (m, 2H, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.66–7.68 (m, 2H, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.75–7.77 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.89 (s, 1H, triazolopyrimidine-$C_6$-H); 8.10 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). *Anal*. Calcd (%) for $C_{22}H_{15}ClN_4OS$ (418.90): C, 63.08; H, 3.61; N, 13.73. Found (%): C, 63.26; H, 3.59; N, 13.52.

***3-(4-Chlorophenyl)-N-[1-(4-methoxyphenyl)-3-(thiophen-2-yl)allylidene]-1H-[1,2,4]triazol-5-amine (30)***. Light brown crystals, 0.08 (20%); mp 178–180°C. IR (KBr, $cm^{-1}$): 3292, 3213 (NH); 3066, 3051 (CH-aromatic); 2837 (CH-aliphatic); 1602 (C=N); 1571 (C=C); 1292, 1097 (C–S–C); 1280, 1029 (C–O–C); 1097 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 3.28 (s, 3H, $OCH_3$); 7.02 (d, 2H, $J$ = 8.6 Hz, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.08 (d, 1H, $J$ = 9 Hz,

CH=CH-2-thienyl); 7.19 (t, 1H, $J$ = 5.1 Hz, thiophene-$C_4$-H); 7.53 (s, 1H, CH=CH-2-thienyl); 7.58–7.67 (m, 1H, thiophene-$C_3$-H); 7.76 (d, 1H, $J$ = 5.1 Hz, thiophene-$C_5$-H); 7.80 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.6 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 8.09 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.60 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 421 ($M^+$, 0.1); 420 ($M^+$ −1, 2); 419 ($M^+$ −2, 18); 73 (100). *Anal*. Calcd (%) for $C_{22}H_{17}ClN_4OS$ (420.91): C, 62.78; H, 4.07; N, 13.31. Found (%): C, 62.89; H, 4.13; N, 13.48.

***3-(3-(4-Chlorophenyl)-1H-[1,2,4]triazol-5-ylimino)-1-phenylbutan-1-one (31).*** An equimolar mixture of compound **2** (0.19 g, 1 mmol) and benzoylacetone (0.16 g, 1 mmol) was heated under reflux in glacial acetic acid (5 mL) for 36 h. The reaction mixture was allowed to cool, and the formed precipitate was filtered, washed with acetic acid, dried, and recrystallized from ethanol to yield compound 31.

Deep brown powder, 0.2 g (60%); mp 199–201°C. IR (KBr, $cm^{-1}$): 3305, 3271 (NH); 3064 (CH-aromatic); 2924, 2852 (CH-aliphatic); 1674 (C=O); 1593 (C=N); 1573 (C=C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.67 (s, 3H, $CH_3$); 2.90 (s, 2H, $CH_2$); 7.60–7.69 (m, 3H, $C_6H_5$-$C_{3,4,5}$-H); 7.93 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.20 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.23–8.27 (m, 2H, $C_6H_5$-$C_{2,6}$-H); 10.60 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 339 ($M^+$, 2); 338 ($M^+$ −1, 1); 337 ($M^+$ −2, 1); 105 (100). *Anal*. Calcd (%) for $C_{18}H_{15}ClN_4O$ (338.79): C, 63.81; H, 4.46; N, 16.54. Found (%): C, 63.94; H, 4.54; N, 16.97.

**General procedure for synthesis of compounds 32a,b** and **33**. Equimolar amounts of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) and the appropriate ketone, namely, acetylacetone or benzoylacetone (1 mmol), were fused in an oil bath at 250°C for 2 h. The reaction mixture was allowed to cool then triturated with ethanol. The separated solid was filtered off, washed with ethanol, dried, and recrystallized from ethanol to yield compounds **32a,b**. However, concentration of the crystallization filtrate of compound **32a** led to isolation of crystals, which were filtered and dried to yield compound **33**.

***2-(4-Chlorophenyl)-5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidine (32a).*** White powder, 0.05 g (20%); mp 260–261°C. IR (KBr, $cm^{-1}$): 3043 (CH-aromatic); 2917, 2847 (CH-aliphatic); 1627 (C=N); 1541 (C=C); 1083 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.60 (s, 3H, triazolopyrimidine-$C_5$-$CH_3$); 2.78 (s, 3H, triazolopyrimidine-$C_7$-$CH_3$); 7.19 (s, 1H, triazolopyrimidine-$C_6$-H); 7.61 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.22 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). Mass spectrum, *m/z* (%): 259 ($M^+$, 2); 258 ($M^+$ −1, 9); 257($M^+$ −2, 2); 139 (100). *Anal*. Cacld (%) for $C_{13}H_{11}ClN_4$ (258.7): C, 60.35; H, 4.29, N, 21.66. Found (%): C, 60.51; H, 4.31; N, 21.85.

***2-(4-Chlorophenyl)-(5 or 7)-methyl-(7 or 5)-phenyl-[1,2,4]triazolo [1,5-a]pyrimidine (32b).*** Dark brown crystals, 0.13 g (40%); mp > 300°C. IR (KBr, $cm^{-1}$): 3093, 3049 (CH-aromatic); 2924, 2852 (CH-aliphatic); 1591 (C=N); 1573 (C=C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.24 (s, 3H, $CH_3$); 7.55–7.65 (m, 5H, $C_6H_5$); 7.93 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H), 8.00 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.12 (s, 1H, triazolopyrimidine-$C_6$-H). Mass spectrum, *m/z* (%): 322 ($M^+$ +1, 2); 321 ($M^+$, 2); 320 ($M^+$ −1, 6); 156 (100). *Anal*. Calcd (%) for $C_{18}H_{13}ClN_4$ (320.78): C, 67.40; H, 4.08; N, 17.47. Found (%): C, 67.62; H, 4.11; N, 17.62.

***4-[3-(4-Chlorophenyl)-1H-[1,2,4]triazol-5-ylimino]pentan-2-one (33).*** Pale yellow crystals, 0.046 g (17%); mp 185–186°C. IR (KBr, $cm^{-1}$): 3431, 3385 (broad OH); 3280, 3210 (NH); 3095, 3068 (CH-aromatic); 2926, 2852 (CH-aliphatic); 1591(C=N), 1550 (C=C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.10 (s, 3H, –C=C(OH) $CH_3$); 2.33 (s, 3H, N=C–$CH_3$); 2.78 (s, 1H, $CH_2$–C=O); 6.65 (s, 1/2H, CH=C(OH) tautomer); 7.56 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.60 (s, 1H, NH, $D_2O$ exchangeable); 13.13 (s, ½ H, OH tautomer, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{13}H_{13}ClN_4O$ (276.72): C, 56.42; H, 4.74; N, 20.25. Found (%): C, 56.59; H, 4.88; N, 20.47.

**General procedure for synthesis of compounds 34**, **35**, and **36**. Equimolar amounts of compound **2** (0.19 g, 1 mmol), 4-chlorobenzaldehyde (0.14 g, 1 mmol), and dimedone (0.14 g, 1 mmol) were heated under reflux in DMF (5 mL) for 8 h. The reaction mixture was allowed to cool, and the separated solid was filtered, washed with DMF, dried, and crystallized from DMF/ethanol mixture (8:2) to yield compound **34**. The filtrate of the reaction mixture was concentrated, then triturated with cold ethanol to yield a precipitate that was filtered, washed with ethanol, dried, and recrystallized from ethanol to yield compound **35**. However, treatment of the collected ethanolic portions with ice-cold water led to separation of a precipitate that was collected, washed with water, dried, and recrystallized from ethanol to yield compound **36**.

***2,9-Bis(4-chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydro[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (34).*** Yellow crystals, 0.07 g (15%); mp > 300°C. IR (KBr, $cm^{-1}$): 3200, 3151 (NH); 3055, 3030 (CH-aromatic); 2981, 2885 (CH-aliphatic); 1662 (C=O); 1643 (C=N); 1566 (C=C); 1087 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 0.90 (s, 6H, two $CH_3$); 2.73 (s, 2H, triazoloquinazoline-$C_5$-H); 2.89 (s, 1H, triazoloquinazoline-$C_7$-H); 4.50 (s, ½ H, triazoloquinazoline-$C_7$-CH=C(OH) tautomer); 6.28 (s, 1H, triazoloquinazoline-$C_9$-H); 7.18 (d, 2H, $J$ = 8.4 Hz, triazoloquinazoline-$C_9$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.28 (d, 2H, $J$ = 8.7 Hz, triazoloquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.47 (d, 2H, $J$ = 8.4 Hz, triazoloquinazoline-$C_9$-4-Cl-$C_6H_4$-

$C_{3,5}$-H); 7.90 (d, 2H, $J$ = 8.7 Hz, triazoloquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.07 (s, ½ H, OH tautomer, $D_2O$ exchangeable); 11.28 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{23}H_{20}Cl_2N_4O$ (439.34): C, 62.88; H, 4.59; N, 12.75. Found (%): C, 63.04; H, 4.66; N, 12.97.

***2-[(5-Amino-3-(4-chlorophenyl)-1H-[1,2,4]triazol-1-yl)(4-chlorophenyl)methyl]-5,5-dimethylcyclohexane-1,3-dione (35).*** Pale yellow solid, 0.08 g (17%); mp 272–273°C. IR (KBr, $cm^{-1}$): 3309, 3271 ($NH_2$); 3095, 3064 (CH-aromatic); 2960 (CH-aliphatic); 1674 (C=O); 1593 (C=N); 1558 (C=C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.12 (s, 6H, two $CH_3$); 2.59 (s, 4H, cyclohexanedione-$C_{3,5}$-H); 2.90 (s, 1H, cyclohexanedione-$C_1$-H); 3.18 (s, 2H, $NH_2$, $D_2O$ exchangeable); 4.50 (s, 1H, CH-4-Cl-$C_6H_4$); 7.53–7.58 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.63 (d, 2H, $J$ = 8.4 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.10 (d, 2H, $J$ = 8.4 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{3,5}$-H). *Anal*. Calcd (%) for $C_{23}H_{22}Cl_2N_4O_2$ (457.35): C, 60.40; H, 4.85; N, 12.25. Found (%): C, 60.58; H, 4.92; N, 12.25.

***2-(4-Chlorobenzylidene)-3-[3-(4-chlorophenyl)-1H-[1,2,4]triazol-5-ylimino]-5,5-dimethylcyclohexan-3-one (36).*** Brown solid, 0.02 g (5%); mp 152–153°C. IR (KBr, $cm^{-1}$): 3211, 3172 (NH); 3085, 3064 (CH-aromatic); 2875 (CH-aliphatic); 1657 (C=O); 1589 (C=N); 1550 (C=C); 1087 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 0.97 (s, 6H, two $CH_3$); 1.03 (s, 2H, cyclohexanone-$C_6$-H); 2.50 (s, 1H, cyclohexanone-$C_4$-H); 4.50 (s, ½ H, cyclohexenol tautomer-$C_4$-H); 7.13 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.19 (s, 1H, C=CH-4-Cl-$C_6H_4$); 7.30 (d, 2H, $J$ = 8.4 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.56 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 7.93 (d, 2H, $J$ = 8.4 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.61(s, 1H, NH, $D_2O$ exchangeable); 13.09 (s, ½ H, OH tautomer, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 439 ($M^+$, 1); 100 (100). *Anal*. Calcd (%) for $C_{23}H_{20}Cl_2N_4O$ (439.34): C, 62.88; H, 4.59; N, 12.75. Found (%): C, 63.14; H, 4.66; N, 12.92.

**General procedure for synthesis of compounds 37** and **38**. To a well-stirred solution of compound **2** (0.19 g, 1 mmol) in ethanolic sodium ethoxide [prepared by dissolving sodium metal (0.01 g, 0.5 mmol) in 5 mL absolute ethanol], a solution of acetylacetaldehyde dimethyl acetal (0.13 g, 0.12 mL, 1 mmol) inabsolute ethanol (2 mL) was added dropwise while stirring over a period of 10 min. The reaction mixture was stirred at room temperature for 24 h, then poured onto ice-cold water and triturated with few drops of dilute hydrochloric acid. The precipitated solid was filtered, washed with water, dried, and crystallized from benzene/ethanol mixture (9:1) to yield compounds **37** and **38**.

***2-(4-Chlorophenyl)-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine (37).*** Pale yellow powder, 0.05 g (20%); mp > 300°C. IR (KBr, $cm^{-1}$): 3060 (CH-aromatic); 2900 (CH-aliphatic); 1595 (C=N); 1565 (C=C); 1083 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.23 (s, 3H, $CH_3$); 7.64–7.70 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.00 (d, 1H, J = 8.1 Hz, triazolopyrimidine-$C_6$-H); 8.05–8.15 (m, 1H, triazolopyrimidine-$C_7$-H). *Anal*. Calcd (%) for $C_{12}H_9ClN_4$ (244.68): C, 58.90; H, 3.71; N, 22.90. Found (%): C, 59.08; H, 3.78; N, 23.19.

***3-(4-Chlorophenyl)-N-(3,3-dimethoxy-1-methylpropylidene-1H-[1,2,4]triazol-5-amine (38).*** Pale yellow crystals, 0.06 g (20%); mp 199–200°C. IR (KBr, $cm^{-1}$): 3180 (NH); 3020 (CH-aromatic); 2926, 2850 (CH-aliphatic); 1593 (C=N); 1570 (C=C); 1282, 1090 (C–O–C); 1090 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.23 (s, 3H, $CH_3$); 2.30–2.39 (m, 2H, $CH_2$); 2.60–2.70 (m, 1H, CH); 3.30 (s, 6H, two $COCH_3$, under DMSO); 7.61(d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.60 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{14}H_{17}ClN_4O_2$ (308.76); C, 54.46; H, 5.55; N, 18.15. Found (%): C, 54.62; H, 5.63; N, 18.41.

***2-[(4-Chlorophenyl)-7-(4-methoxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo [1,5-a]pyrimidin-6-yl]phenylmethanone (39).*** The [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) was heated under reflux with equimolar amounts ofbenzoylacetone (0.16 g, 1 mmol) and 4-methoxybenzaldehyde (0.13 gm, 0.12 mL, 1 mmol) in glacial acetic acid (5 mL) for 36 h. The reaction mixture was allowed to cool, and the solvent was evaporated under reduced pressure. The obtained residue was then triturated with cold ethanol, and the formed precipitate was filtered, washed with ethanol, dried, and recrystallized from ethanol/hexane mixture (3:7) to yield compound **39**.

Yellow crystals, 0.12 g (27%); mp 200–203°C. IR (KBr, $cm^{-1}$):3446, 3419, 3392 (broad OH tautomer); 3321, 3311(NH); 3060, 3050 (CH-aromatic); 2926, 2840 (CH-aliphatic); 1680 (C=O); 1595 (C=N); 1539 (C=C); 1253, 1029 (C–O–C); 1087 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 1.90 (s, 3H, $CH_3$); 3.88 (s, 3H, $OCH_3$); 6.78–6.80 (m, 2H, 4-$OCH_3$-$C_6H_4$-$C_{3,5}$-H); 7.05 (d, 2H, $J$ = 9 Hz, 4-$OCH_3$-$C_6H_4$-$C_{2,6}$-H); 7.30–7.36 (m, 2H, $C_6H_5$-$C_{3,5}$-H); 7.60–7.76 (m, 1H, $C_6H_5$-$C_4$-H); 7.83 (s, 1H, triazolopyrimidine-$C_7$-H); 7.93 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.03–8.09 (m, 2H, $C_6H_5$-$C_{2,6}$-H); 8.22 (d, 2H, J = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.10 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 459 ($M^+$ +2, 0.1); 457 ($M^+$, 2); 55 (100). *Anal*. Calcd (%) for $C_{26}H_{21}ClN_4O_2$ (456.92): C, 68.34; H, 4.63; N, 12.26. Found (%): C, 68.52; H, 4.72; N, 12.43.

**General procedure for synthesis of compounds 40**, **41**, and **42**. A mixture of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol), 4-chlorobenzaldehyde (0.14 g, 1 mmol), and 1-tetralone (0.14 g, 0.11 mL, 1 mmol) in

DMF (5 mL) was heated under reflux for 40 h. The reaction mixture was allowed to cool, and the separated solid was filtered, washed with DMF, dried, and recrystallized from ethanol to yield compound **40**. The filtrate of the reaction mixture was concentrated and triturated with ethanol, and the formed solid was filtered, washed with ethanol, dried, and recrystallized from ethanol to yield compound **41**, while the collected ethanolic portions from compound **41** were poured onto crushed ice, and the obtained solid was filtered, washed with water, dried, and recrystallized from hexane to yield compound **42**.

***2-[(5-Amino-3-(4-chlorophenyl)-1H-[1,2,4]triazol-1-yl)(4-chlorophenyl)methyl]-3,4-dihydronaphthalen-1(2H)-one (40).*** Yellow crystals, 0.15 g (33%); mp 255–257°C. IR (KBr, $cm^{-1}$): 3417 (broad OH tautomer); 3323, 3224 ($NH_2$); 3066, 3026 (CH-aromatic); 2912, 2850 (CH-aliphatic); 1668 (C=O); 1593 (C=N); 1558 (C=C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.74–2.98 (m, 2 ½H, dihydronaphthalene-$C_2$-CH & $C_3$-$CH_2$); 3.07 (t, 2H, *J* = 6.5 Hz, dihydronaphthalene-$C_4$-$CH_2$); 5.00 (s, 1H, CH-4-Cl-$C_6H_4$); 7.39 (t, 2H, *J* = 7.5 Hz, dihydronaphthalene-$C_{6,7}$-H); 7.50 (s, ½ H, OH tautomer, $D_2O$ exchangeable); 7.53–7.63 (m, 6H, dihydronaphthalene-$C_{5,8}$-H & two 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.76 (s, 2H, $NH_2$, $D_2O$ exchangeable); 7.97 (d, 2H, *J* = 7.8 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.33 (d, 2H, *J* = 8.7 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{3,5}$-H). *Anal*. Calcd (%) for $C_{25}H_{20}Cl_2N_4O$ (463.36): C, 64.80; H, 4.35; N, 12.09. Found (%): C, 65.03; H, 4.42; N, 12.35.

***7,10-Bis(4-chlorophenyl)-5,6-dihydrobenzo[h][1,2,4]triazolo[5,1-b]quinazoline (41).*** Brown crystals, 0.06 g (13%); mp 140–141°C. IR (KBr, $cm^{-1}$): 3050 (CH-aromatic); 2945, 2880 (CH-aliphatic); 1593 (C=N); 1560 (C=C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.95 (t, 2H, *J* = 6 Hz, triazolobenzoquinazoline-$C_9$-H); 3.07 (t, 2H, *J* = 6 Hz, triazolobenzoquinazoline-$C_{10}$-H); 7.40 (t, 2H, *J* = 7.5 Hz, triazolobenzoquinazoline-$C_{6,7}$-H); 7.51–7.72 (m, 4H, triazolobenzoquinazoline-$C_{5,8}$-H & $C_{11}$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.96 (d, 2H, *J* = 8.4 Hz, triazolobenzoquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.23 (d, 2H, *J* = 8.4 Hz, triazolobenzoquinazoline-$C_{11}$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.33 (d, 2H, *J* = 8.4 Hz, triazolobenzoquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{3,5}$-H). *Anal*. Calcd (%) for $C_{25}H_{16}Cl_2N_4$ (443.33): C, 67.73; H, 3.64; N, 12.64. Found (%): C, 67.85; H, 3.70; N, 12.88.

***7,10-Bis(4-chlorophenyl)-5,6,7,12-tetrahydrobenzo[h][1,2,4]triazolo[5,1-b]quinazoline (42).*** Pale brown powder, 0.02 g (4.5%); mp 104–106°C. IR (KBr, $cm^{-1}$): 3189 (NH); 3067 (CH-aromatic); 2931, 2840 (CH-aliphatic); 1594 (C=N); 1486 (C=C); 1087 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.93–2.95 (m, 2H, triazolobenzoquinazoline-$C_9$-H); 3.05–3.10 (m, 2H, triazolobenzoquinazoline-$C_{10}$-H); 5.71 (s, 1H, triazolobenzoquinazoline-$C_{11}$-H); 7.30–7.49 (m, 2H, triazolobenzoquinazoline-$C_{6,7}$-H); 7.50–7.72 (m, 2H, triazolobenzoquinazoline-$C_{5,8}$-H); 7.85–7.95 (m, 2H, triazolobenzoquinazoline-$C_{11}$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.05 (d, 2H, *J* = 8.4 Hz, triazolobenzoquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.23 (d, 2H, *J* = 7.5 Hz, triazolobenzoquinazoline-$C_{11}$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.33 (d, 2H, *J* = 8.4 Hz, triazolo-benzoquinazoline-$C_2$-4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.05 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 445 ($M^+$, 1); 444 ($M^+$ −1, 275 (100). *Anal*. Calcd (%) for $C_{25}H_{18}Cl_2N_4$ (445.34): C, 67.42; H, 4.07; N, 12.58. Found (%): C, 67.42; H, 4.37; N, 12.34.

**General procedure for synthesis of compounds 43** and **44**. An equimolar mixture of [1,2,4]triazole-5-amine derivative **2**(0.19 g, 1 mmol) and 2-chlorobenzaldehyde (0.14 g, 0.11 mL, 1 mmol) in glacial acetic acid (5 mL) was refluxed for 36 h. The reaction mixture was filtered while hot, and the solid obtained was washed with acetic acid, dried, and recrystallized from ethyl acetate/hexane mixture (7:3) to yield compound **43**. The filtrate of the reaction mixture was allowed to cool, and the separated solid was filtered, washed with acetic acid, dried, and recrystallized from ethanol to yield compound **44**.

***2-(4-Chlorophenyl)[1,2,4]triazolo[1,5-a]quinazoline (43).*** Brown crystals, 0.1 g (35%); mp > 300°C IR (KBr, $cm^{-1}$): 3042 (CH-aromatic); 1646 (C=N); 1466 (C=C); 1092 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.38–7.78 (m, 8H, triazoloquinazoline-$C_{6,7,8,9}$-H & 4-Cl-$C_6H_4$); 8.15 (s, 1H, triazoloquinazoline-$C_5$-H). Mass spectrum, *m/z* (%): 281 ($M^+$, 1); 139 (100). *Anal*. Calcd (%) for $C_{15}H_9ClN_4$ (280.71): C, 64.18; H, 3.23; N, 19.96. Found (%): C, 64.3; H, 3.29; N, 20.17.

***N-(2-chlorobenzylidene)-3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-amine (44).*** Pale brown crystals, 0.11 g (33%), mp 248–250°C. IR (KBr, $cm^{-1}$): 3215, 3197 (NH); 3066, 3010 (CH-aromatic); 2927, 2852 (CH-aliphatic); 1591 (C=N); 1560 (C=C); 1091 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.38–7.48 (m, 1H, 2-Cl-$C_6H_4$-$C_5$-H); 7.51 (d, 2H, *J* = 8 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.58–7.63 (m, 1H, 2-Cl-$C_6H_4$-$C_4$-H); 7.74 (d, 2H, *J* = 8.1 Hz, 2-Cl-$C_6H_4$-$C_6$-H); 7.82–7.85 (m, 1H, 2-Cl-$C_6H_4$-$C_3$-H); 7.94 (d, 2H, *J* = 8 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.15 (s, 1H, N=CH); 10.61 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 319 ($M^+$ +2, 1); 317 ($M^+$, 6); 316 ($M^+$ −1, 13); 315 ($M^+$ −2, 5); 281 (100). *Anal*. Calcd (%) for $C_{15}H_{10}Cl_2N_4$ (317.17): C, 56.80; H, 3.18; N, 17.66. Found (%), C, 56.97; H, 3.22; N, 17.84.

**General procedure for synthesis of compounds 45** and **46**. To a solution of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) in DMF (5 mL), a solution of maleic anhydride (0.01 g, 1 mmol) in DMF (2 mL) was added, and the reaction mixture was heated under reflux for 36 h. The reaction was then concentrated and allowed to cool, and the obtained solid was filtered, washed with DMF, dried, and

boiled in ethanol; in which the insoluble solid was found to be compound **45**, while compound **46** was isolated upon cooling of ethanol.

***4-[3-(4-Chlorophenyl)-1H-[1,2,4]triazol-5-ylamino]-4-oxobut-2-enoic acid (45).*** Dark brown crystals, 0.035 g (12%); mp > 300°C. IR (KBr, $cm^{-1}$): 3371 (broad OH); 3269, 3215 (NH); 3059, 3026 (CH-aromatic); 2873 (CH-aliphatic); 1701 (C=O); 1602 (C=N); 1570 (C=C); 1089 (*p*-Cl-phenyl). Mass spectrum, *m/z* (%): 293 ($M^+$, 1); 113 (100). *Anal*. Calcd (%) for $C_{12}H_9ClN_4O_3$ (292.68): C, 49.24; H, 3.10; N, 19.14. Found (%): C, 49.41; H, 3.15; N, 19.32.

***2-(4-Chlorophenyl)-5-oxo-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (46).*** Dark brown crystals; 0.055 g (19%); mp 117–118°C. IR (KBr, $cm^{-1}$): 3387 (broad OH); 3244, 3209, 3186 (NH); 3080, 3068 (CH-aromatic); 2877, 2841 (CH-aliphatic); 1701, 1685 (C=O); 1635 (C=N); 1570 (C=C); 1089 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.70–3.03 (m, 2H, triazolopyrimidine-$C_6$-H); 6.05 (s, 1H, OH tautomer, $D_2O$ exchangeable); 6.78–6.80 (m, 2H, triazolopyrimidine-$C_7$-H); 7.44–7.70 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.86–8.16 (m, 2H, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.10 (s, 1H, COOH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{12}H_9ClN_4O_3$ (292.68): C, 49.24; H, 3.10; N, 19.14. Found (%): C, 49.51; H, 3.17; N, 19.29.

***2-(4-Chlorophenyl)-7-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-one (47).*** An equimolar mixture of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) and ethyl acetoacetate (0.13 g, 0.12 mL, 1 mmol) in glacial acetic acid (5 mL) was heated under reflux for 24 hr. The reaction mixture was allowed to cool, and the precipitated solid was filtered, washed with acetic acid, dried, and recrystallized from acetic acid to yield compound **47**.

Pale brown crystals, 0.097 g (37%); mp > 300°C. IR (KBr, $cm^{-1}$): 3188 (NH); 3055 (CH-aromatic); 2905 (CH-aliphatic); 1674 (C=O); 1604 (C=N); 1556 (C=C); 1089 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 2.34 (s, 3H, $CH_3$); 5.85 (s, 1H, triazolopyrimidine-$C_6$-H); 7.59 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 8.11 (d, 2H, *J* = 8.4 Hz; 4-Cl-$C_6H_4$-$C_{3,5}$-H); 13.22 (s, 1H, NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 261 ($M^+$, 12); 260 ($M^+$ −1, 76); 68 (100). *Anal*. Calcd (%) for $C_{12}H_9ClN_4O$ (260.68): C, 55.29; H, 3.48; N, 21.49. Found (%): C, 55.42; H, 3.51; N, 21.64.

**General procedure for synthesis of compounds 48a and 48b.** A solution of the appropriate acid chloride (1 mmol), namely, 4-chlorobenzoylchloride or thiophene-2-carbonylchloride in dioxane (2 mL), was added dropwise to a solution of compound **2** (0.19 g, 1 mmol) in dioxane/pyridine mixture (10:1, 5 mL), with continuous stirring at 0–5°C. The reaction mixture was left to be stirred for additional 30 min at this temperature; then, stirring was continued at room temperature for 24 h. The reaction mixture was then poured onto ice-cold water (15 mL), and the formed precipitate was filtered, washed with water, dried, and recrystallized from ethanol to yield compounds **48a** and **48b**, respectively.

***N-4-Chloro-[3-(4-chlorophenyl)-1H-[1,2,4]triazol-5-yl]benzamide (48a).*** Colorless crystals, 0.22 g (67%); mp 192–193°C. IR (KBr, $cm^{-1}$): 3412, 3392 (intramolecular hydrogen-bonded NH); 3095 (CH-aromatic); 1720 (C=O); 1591 (C=N); 1485 (C=C); 1080 (*p*-Cl-phenyl). $^1$H NMR(DMSO-$d_6$, δ ppm): 7.57 (d, 2H, *J* = 8.7 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.71 (d, 2H, *J* = 8.6 Hz, CO-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 4H, *J* = 8.6 Hz, triazole-$C_3$-4-Cl-$C_6H_4$-$C_{3,5}$-H & CO-4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.14 (s, 1H, NH-CO, $D_2O$ exchangeable); 13.15 (s, 1H, intramolecular hydrogen-bonded triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{15}H_{10}Cl_2N_4O$ (333.17): C, 54.07, H, 3.03; N, 16.82. Found (%): C, 54.29; H, 3.11; N, 16.98.

***N-[3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-yl]thiophene-2-carboxamide (48b).*** White crystals, 0.11 g (37%); mp 269–270°C. IR (KBr, $cm^{-1}$): 3250, 3184 (NH); 3017 (CH-aromatic); 1672 (C=O); 1594 (C=N); 1563 (C=C); 1259, 1088 (C–S–C); 1088 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.15–7.22 (m, 1H, thiophene-$C_4$-H); 7.54 (d, 1H, *J* = 6.6 Hz, thiophene-$C_3$-H); 7.61 (d, 2H, *J* = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.71–7.75 (m, 1H, thiophene-$C_5$-H); 7.94 (d, 2H, *J* = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.62 (s, 1H, NH-CO, $D_2O$ exchangeable); 12.20 (s, 1H, intramolecular hydrogen-bonded triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{13}H_9ClN_4O_5$ (304.75): C, 51.23; H, 2.98; N, 18.38. Found (%): C, 51.47; H, 3.05; N, 18.62.

**General procedure for synthesis of compounds 49 and 50.** [1,2,4]Triazole-5-amine derivative **2** (0.19 g, 1 mmol) was heated under reflux in excess formamide (5 mL) for 8 h. The reaction mixture was filtered while hot, and the obtained solid was boiled in ethanol, filtered, and dried to yield compound **49**. The collected ethanolic portion was allowed to cool and stand overnight to yield a gummy residue that was triturated with ethanol/*n*-hexane mixture (1:1) to separate a precipitate that was filtered, washed with ethanol, dried, and crystallized from ethanol/*n*-hexane mixture (8:2) to yield compound **50**.

***5-Amino-3-(4-chlorophenyl)-1H-[1,2,4]triazole-1-carboxaldehyde (49).*** Deep brown crystals, 0.13 g (60%); mp > 300°C. IR (KBr, $cm^{-1}$): 3296, 3169 ($NH_2$); 3078 (CH-aromatic); 1690 (C=O); 1593 (C=N); 1556 (C=C); 1085 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.40–7.57 (m, 2H, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94–7.99 (m, 2H, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.15 (s, 2H, $NH_2$, $D_2O$ exchangeable); 9.10 (s, 1H, CHO). Mass spectrum, *m/z* (%): 223 ($M^+$, 2); 139 (100). *Anal*. Calcd (%) for $C_9H_7ClN_4O$ (222.63): C, 48.55; H, 3.17, N, 25.17. Found (%): C, 48.68; H, 3.13; N, 25.29.

***N′-[5-(4-chlorophenyl)-1H-[1,2,4]triazol-3-yl]imidoformamide (50).*** Reddish brown powder, 0.015 g

(6.5%); mp 180–182°C. IR (KBr, $cm^{-1}$): 3369, 3259, 3176 (NH, $NH_2$); 3050 (CH-aromatic); 2840 (CH-aliphatic); 1618 (C=N); 1568 (C=C); 1089 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 7.44 (s, 1H, N=CH); 7.47 (s, 2H, $NH_2$, $D_2O$ exchangeable); 7.52 (d, 2H, *J* = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.88 (d, 2H, *J* = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.20 (s, 1H, triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_9H_8ClN_5$ (221.65): C, 48.77; H, 3.64; N, 31.60. Found (%): C, 49.01; H, 3.69; N, 31.877.

***Ethyl* N-*[3-(4-chlorophenyl)-1*H-*[1,2,4]triazol-5-yl] imidoformate (51).*** An equimolar mixture of [1,2,4] triazole-5-amine derivative **2** (0.19 g, 1 mmol) and triethyl orthoformate (0.15 g, 0.13 mL, 1 mmol) in acetic anhydride (5 mL) was refluxed for 24 h. The reaction mixture was concentrated, then allowed to cool. The residue was triturated with ethanol, and the precipitated solid was filtered, washed with ethanol, dried, and crystallized from ethanol to yield compound **51**.

Brown powder, 0.1 g (40%); mp 170–172°C. IR (KBr, $cm^{-1}$): 3232 (NH); 3055, 3020 (CH-aromatic); 2929, 2850 (CH-aliphatic); 1608 (C=N); 1593 (C=C); 1265, 1082 (C–O–C); 1093 (*p*-Cl-phenyl). Mass spectrum, *m/z* (%): 252 ($M^+$ +1, 16); 251 ($M^+$, 36); 149 (100). *Anal*. Calcd (%) for $C_{11}H_{11}ClN_4O$ (250.68): C, 52.70; H, 4.42; N, 22.35. Found (%): C, 52.47; H, 4.36; N, 22.16.

**N-*(4-chlorophenyl)*-N′-*[3-(4-chlorophenyl)-1*H-*[1,2,4] triazol-5-yl]imido formamide (52).*** To a well-stirred solution of compound **51** (0.25 g, 1 mmol) in ethanolic sodium ethoxide [prepared by dissolving (0.02 g, 1 mmol) of sodium metal in 5 mL absolute ethanol], a solution of 4-chloroaniline (0.13 g, 1 mmol) in absolute ethanol (2 mL) was added, and the mixture was refluxed for 10 h. The reaction mixture was allowed to cool, then poured onto ice-cold water. The separated solid was filtered off, washed with water, dried, and recrystallized from ethanol to yield compound **52**.

Pale yellow powder, 0.17 g (52%); mp > 300°C. IR (KBr, $cm^{-1}$): 3280, 3200(NH); 3090 (CH-aromatic); 1650 (C=N); 1590 (C=C); 1076 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 5.05 (s, 1H, CH); 7.40–7.60 (m, 4H, two 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.80–8.00 (m, 4H, two 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.60 (s, 1H, NH-4-Cl-$C_6H_4$, $D_2O$ exchangeable); 12.23 (s, 1H, triazole-NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 332 ($M^+$, 1); 45 (100). *Anal*. Calcd (%) for $C_{15}H_{11}Cl_2N_5$ (332.19): C, 54.23; H, 3.34; N, 21.08. Found (%): C, 54.47; H, 3.36; N, 21.16.

***2-(4-Chlorophenyl)-4*H-*imidazo[1,2-*b*][1,2,4]triazole-5,6-dione (53).*** An equimolar mixture of compound **2** (0.19 g, 1 mmol) and oxalyl chloride (0.12 mL, 1 mmol) was fused at 220–230°C for 5 h. The reaction mixture was allowed to cool and triturated with etanol. The obtained solid product was filtered, dried, and crystallized from ethanol to yield compound **53**.

Light brown powder, 0.19 g (76%); mp 260–262°C. IR (KBr, $cm^{-1}$): 3178 (NH); 3035 (CH-aromatic); 1705, 1683 (C=O); 1589 (C=N); 1541 (C=C); 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 7.51 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 11.59 (s, ½ H, NH, $D_2O$ exchangeable); 13.43 (s, ½ H, OH tautomer, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{10}H_5ClN_4O_2$ (248.63): C, 48.31; H, 2.03; N, 22.53. Found (%): C, 46.71; H, 2.38; N, 22.53.

***1-[2-(4-Chlorophenyl)-5-hydroxy-4*H-*imidazo[1,2-*b*][1,2,4] triazol-6-yl]ethanone or 1-[2-(4-chlorophenyl)-6-hydroxy-4*H-*imidazo[1,2-*b*][1,2,4]triazol-5-yl]ethanone (54).*** A solution of compound **2** (0.19 g, 1 mmol) in absolute ethanol (5 mL) was treated with ethyl 2-chloroacetoacetate (0.16 g, 0.13 mL, 1 mmol) in presence of a catalytic amount of piperidine (1 drop). The reaction mixture was heated under reflux for 28 h, then filtered while hot, and the separated solid was washed with ethanol, dried, and crystallized from ethanol/*n*-hexane mixture (1:1) to yield compound **54**.

Pale yellow powder, 0.027 g (10%); mp > 300°C. IR (KBr, $cm^{-1}$): 3414 (br. OH); 3311, 3197 (NH); 3060 (CH-aromatic); 2910 (CH-aliphatic); 1734, 1680 (C=O); 1593 (C=N); 1560 (C=C); 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 2.99 (s, 3H, $CH_3$); 7.56 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.62 (s, ½ H, 5-hydroxyimidazotriazole-NH, $D_2O$ exchangeable); 10.61 (s, ½ H, 6-hydroxyimidazotriazole-NH, $D_2O$ exchangeable); 13.09 (s, 1H, OH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 277 ($M^+$, 1); 272 ($M^+$ −1, 2); 44 (100). *Anal*. Calcd (%) for $C_{12}H_9ClN_4O_2$ (276.68): C, 52.09; H; 3.28; N, 20.25. Found (%): C, 52.21; H, 3.33; N, 20.43.

**N-*[3-(4-chlorophenyl)-1*H-*[1,2,4]triazol-5-yl]*-N′-*phenylthiourea (55).*** To a solution of [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) in pyridine (5 mL), phenyl isothiocyanate (0.13 g, 0.12 mL, 1 mmol) was added while stirring. The reaction mixture was heated under reflux for 10 h; then, it was allowed to cool and concentrated under reduced pressure. The gummy residue was triturated with diethyl ether to yield a solid that was filtered off, washed with diethyl ether, dried, and crystallized from ethanol to give compound **55**.

Brown powder, 0.09 g (27%); mp 110–112°C. IR (KBr, $cm^{-1}$): 3250, 3125 (NH); 3040 (CH-aromatic); 1627 (C=N); 1537 (C=C); 1589, 1487, 1288, 1007 (I, II, III, IV bands of N–C=S); 1087 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 6.48–6.56 (m, 1H, $C_6H_5$-$C_4$-H); 7.07–7.12 (m, 2H, $C_6H_5$-$C_{3,5}$-H); 7.36 (d, 2H, *J* = 7.8 Hz, $C_6H_5$-$C_{2,6}$-H); 7.43 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.97 (d, 2H, *J* = 8.4 Hz, 4-Cl-$C_6H_5$-$C_{3,5}$-H); 8.70 (s, 1H, triazole-$C_5$-NH, $D_2O$ exchangeable);

9.78 (s, 1H, triazole NH, $D_2O$ exchangeable); 13.09 (s, 1H, SH tautomer, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{15}H_{12}ClN_5S$ (329.81): C, 54.63; H, 3.67; N, 21.23. Found (%): C, 54.78; H, 3.72; N, 21.49.

***3-[3-(4-Chlorophenyl)-1H-[1,2,4]triazol-5-yl]-2-(phenylimino)1,3-thiazolidin-4-one (56).*** An equimolar mixture of compound **55** (0.32 g, 1 mmol) and ethyl chloroaceto-acetate (0.12 g, 0.11 mL, 1 mmol) in ethanol/pyridine mixture (1:1) (6 mL) was refluxed for 12 h. The reaction mixture was allowed to cool, then poured onto ice-cold water, and the obtained solid was filtered off, washed with water, dried, and crystallized from ethanol to yield compound **56**.

Pale yellow powder, 0.18 g (48%); mp 175–177°C. IR (KBr, $cm^{-1}$): 3352 (NH); 3057 (CH-aromatic); 2900 (CH-aliphatic); 1653 (C=O); 1598 (C=N); 1531 (C=C); 1261, 1060 (C–S–C); 1090 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 4.30 (s, 2H, thiazolidine-$C_5$-H); 7.11 (t, 1H, $J$ = 7.8 Hz, $C_6H_5$-$C_4$-H); 7.34 (t, 2H, $J$ = 7.8 Hz, $C_6H_5$-$C_{3,5}$-H); 7.60 (d, 2H, $J$ = 7.8 Hz, $C_6H_5$-$C_{2,6}$-H); 7.75 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.98 (d, 2H, $J$ = 8.7 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.28 (s, 1H, triazole NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{17}H_{12}ClN_5OS$ (369.83): C, 55.21; H, 3.27; N, 18.94. Found (%): C, 55.42; H, 3.31; N, 19.18.

**General procedure for synthesis of compounds 57** and **58**. A suspension of dimethyl cyanocarbonimidodithioate (0.14 g, 1 mmol), [1,2,4] triazole-5-amine derivative **2** (0.19 g, 1 mmol), and a catalytic amount of piperidine (1 drop) in absolute ethanol (5 mL) was heated under reflux for 36 h. The reaction mixture was filtered while hot, and the obtained solid was washed with ethanol, dried, and crystallized from ethanol/*n*-hexane mixture (2:8) to yield compound **57**. However, concentration of the filtrate of the reaction mixture yielded an oily residue that was extracted with diethyl ether/dichloromethane mixture (1:1) to precipitate a solid, which was collected by filtration, washed with diethyl ether/dichloromethane mixture, and dried to yield compound **58**.

***2-(4-Chlorophenyl)-7-methylthio[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-amine (57).*** Light brown crystals, 0.02 g (8%); mp 244–246°C. IR (KBr, $cm^{-1}$): 3375, 3334 ($NH_2$); 2960 (CH-aromatic); 2900 (CH-aliphatic); 2880 (S-$CH_3$); 1620, 1589 (C=N); 1558 (C=C); 1284, 1072 (C–S–C); 1089 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 3.18 (s, 3H, S-$CH_3$); 4.08 (s, 2H, $NH_2$, $D_2O$ exchangeable); 7.45–7.70 (m, 4H, 4-Cl-$C_6H_4$). *Anal*. Calcd (%) for $C_{11}H_9ClN_6S$ (292.75): C, 45.13; H, 3.10; N, 28.71. Found (%): C, 45.30; H, 3.16; N, 28.98.

***Methyl 5-amino-3-(4-chlorophenyl)-N-cyano-1H-[1,2,4]triazole-1-carbimido-thioate (58).*** Pale yellow crystals, 0.1 g (33%); mp > 300°C. IR (KBr, $cm^{-1}$): 3327, 3292 ($NH_2$); 3012 (CH-aromatic); 2927 (CH-aliphatic); 2854 (S-$CH_3$); 2200 (C≡N); 1604 (C=N); 1560 (C=C); 1282, 1089 (C–S–C); 1089 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 3.13 (s, 3H, $SCH_3$); 4.09 (s, 2H, $NH_2$, $D_2O$ exchangeable); 7.49–7.79 (m, 4H, 4-Cl-$C_6H_4$). Mass spectrum, *m/z* (%): 293 ($M^+$, 3); 138 (100). *Anal*. Calcd (%) for $C_{11}H_9ClN_6S$ (292.75): C, 45.13; H, 3.10; N, 28.71. Found (%): C, 45.41; H, 3.07; N, 28.96.

***4-Chloro-N-[(3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-yl) carbamothioyl]benzamide (59).*** A solution of compound **2** (0.19 g, 1 mmol) in acetone (5 mL) was added to a suspension of 4-chlorobenzoyl isothiocyanate (0.19 g, 1 mmol) [prepared by refluxing equimolar amounts of ammonium thiocyante (0.76 g, 1 mmol) and 4-chlorobenzoyl chloride (0.17 g, 0.13 mL, 1 mmol) in acetone (10 mL) till a white precipitate of 4-chlorobenzoyl isothiocyante is formed], and reflux was then continued for 24 h. The reaction mixture was allowed to cool and concentrated under reduced pressure, and the precipitated solid was filtered, washed with acetone, dried, and crystallized from acetone to yield compound **59**.

Light brown powder, 0.11 g (27%); mp 187–188°C. IR (KBr, $cm^{-1}$): 3363, 3172 (NH); 3093, 3064 (CH-aromatic); 1699 (C=O); 1649 (C=N); 1591, 1489, 1273, 1014 (I, II, III, IV bands of N–C=S); 1571 (C=C); 1089 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 7.44 (s, 1H, NH–C=O, $D_2O$ exchangeable); 7.51 (d, 2H, $J$ = 8.4 Hz, triazole-4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.57 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.89 (d, 2H, $J$ = 8.4 Hz, triazole-4-Cl-$C_6H_4$-$C_{3,5}$-H); 7.94 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 8.01 (s, 1H, triazole-$C_5$-NH, $D_2O$ exchangeable), 13.13 (s, 1H, intramolecular hydrogen-bonded triazole-NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{16}H_{11}Cl_2N_5OS$ (392.26): C, 48.99; H, 2.83; N, 17.85. Found (%): C, 49.17; H, 2.81; N, 18.02.

***2,7-Bis(4-chlorophenyl)[1,2,4]triazolo[1,5-a][1,3,5]triazine-5(4H)-thione (60).*** The carbamothioyl benzamide derivative **59** (0.39 g, 1 mmol) was heated under reflux for 14 h in dry DMF (5 mL). After cooling, the mixture was diluted with ice-cold water to separate a solid precipitate, which was filtered off, washed with water, dried, and crystallized from ethanol to yield compound **60**.

Light brown powder, yield: 0.3 g (80%); mp 217–219°C. IR (KBr, $cm^{-1}$): 3327, 3288 (NH); 3084, 3064 (CH-aromatic); 1647 (C=N); 1595 (C=C); 1556, 1496, 1232, 1026 (I, II, III, IV bands of N–C=S); 1082 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 7.56 (d, 4H, $J$ = 8.4 Hz, two 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 4H, $J$ = 8.4 Hz, two 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.61 (s, ½ H, NH, $D_2O$ exchangeable); 13.13 (s, ½ H, SH tautomer, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 374 ($M^+$, 5); 179 (100). *Anal*. Calcd (%) For $C_{16}H_9Cl_2N_5S$ (374.25): C, 51.35; H, 2.42; N, 18.71. Found (%): C, 51.35; H, 2.42; N, 18.71.

***2-(4-Chlorophenyl)[1,2,4]triazolo[1,5-a][1,3,5]triazine-5,7-diamine (61).*** An equimolar mixture of cyanoguanidine (0.08 g, 1 mmol) and [1,2,4]triazole-5-amine derivative **2** (0.19 g, 1 mmol) was refluxed in water (5 mL) containing concentrated hydrochloric acid (0.3 mL) for 48 h. The reaction mixture was filtered while hot, and the obtained solid product was washed with water, dried, and crystallized from ethanol to yield compound **61**.

Yellow powder, 0.19 g (75%), mp > 300°C. IR (KBr, $cm^{-1}$): 3325, 3188, 3126, 3109 (NH, $NH_2$); 3040 (CH-aromatic); 1645 (C=N); 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 6.02 (s, 2H, $NH_2$, $D_2O$ exchangeable); 6.67 (s, 1H, triazolotriazine-$N_6$-H, $D_2O$ exchangeable); 7.56 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.93 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 10.41 (s, 1H, imine NH, $D_2O$ exchangeable). Mass spectrum, *m/z* (%): 262 ($M^+$, 10); 261 ($M^+ -1$, 38); 260 ($M^{+\cdot} -2$, 16); 221 (100). *Anal*. Calcd (%) for $C_{10}H_8ClN_7$ (261.67): C, 45.90; H, 3.08; N, 37.47. Found (%): C, 46.08; H, 3.14; N, 37.69.

***3-(4-Chlorophenyl)-2H-[1,2,4]triazol-5-diazonium chloride (62).*** A mixture of compound **2** (0.2 g, 1 mmol) and concentrated hydrochloric acid (2 mL) in absolute ethanol (5 mL) was cooled to 0–5°C. While stirring and cooling, an ice-cold solution of sodium nitrite (0.08 g, 1 mmol in 1 mL water) was added dropwise over a period of 10 min to the aforementioned mixture. The reaction mixture was stirred at the same temperature for additional 2 h. The cold diazonium solution was used as such in the next coupling steps or left to stand overnight to isolate solid crystals that were used as such in the following steps.

**General procedure for synthesis of compounds 63** and **64**. To an ice-cold mixture of the triazole diazonium chloride derivative **62** (0.2 g, 1 mmol) and anhydrous sodium acetate (0.03 g, 0.4 mmol) in absolute ethanol (5 mL), an ice-cold solution of ethyl 2-chloroacetoacetate (0.16 g, 0.14 mL, 1 mmol) in absolute ethanol (2 mL) was added dropwise over a period of 5 min while stirring and cooling in an ice bath. Stirring was then continued for 24 h at room temperature. The reaction mixture was then poured onto an ice-cold water, and the precipitated solid was filtered, washed with water, dried, and crystallized from ethanol/*n*-hexane mixture (6:4) to yield compound **63** that was isolated upon filtration of the hot crystallization solvent mixture and dried. The filtrate of crystallization was allowed to cool to precipitate a solid that was filtered and dried to yield compound **64**.

***3-Chloro-7-(4-chlorophenyl)[1,2,4]triazolo[5,1-c][1,2,4]triazin-4(1H)-one (63).*** Pale yellow powder, 0.02 g (6%); mp 250–252°C. IR (KBr, $cm^{-1}$): 3068, 3051 (CH-aromatic); 2937, 2889 (CH-aliphatic); 1700, 1681 (C=O); 1593 (C=N); 1560 (C=C); 1425 (N=N); 1093 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 2.70 (s, 3H, CO$\underline{CH_3}$); 7.57 (d, 2H, $J$ = 8.8 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.8 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). Mass spectrum, *m/z* (%): 326 ($M^+$ +2, 2); 325 ($M^+$ +1, 1); 324 ($M^+$, 2); 139 (100). *Anal*. Calcd (%) for $C_{12}H_7Cl_2N_5O_2$ (324.12): C, 44.47; H, 2.18; N, 21.61. Found (%): C, 44.47; H, 2.18; N, 21.61.

***Ethyl 2-chloro-2-[2-(3-(4-chlorophenyl)-2H-[1,2,4]triazol-5-yl)hydrazono]acetate (64).*** Pale yellow powder, 0.062 g (19%); mp 238–240°C. IR (KBr, $cm^{-1}$): 3412, 3275 (NH); 3049 (CH-aromatic); 2927, 2852 (CH-aliphatic); 1735, 1683 (C=O); 1618 (C=N); 1560 (C=C); 1419 (N=N); 1238, 1016 (C–O–C); 1091 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 1.01–1.11 (m, 3H, $CH_2\underline{CH_3}$); 2.70 (s, 3H, CO$\underline{CH_3}$); 3.18–3.22 (m, 2H, $\underline{CH_2}CH_3$); 7.57 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.94 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 13.15 (s, 1H, intramolecular hydrogen-bonded triazole NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{12}H_{11}Cl_2N_5O_2$ (370.19): C, 45.42; H, 3.54; N, 18.92. Found (%): C, 45.36; H, 3.38; N, 18.98.

***7-(4-Chlorophenyl)-3-phenyl[1,2,4]triazolo[5,1-d][1,2,3,5]tetrazin-4(3H)-one (65).*** Equimolar amounts of phenylisocyanate (0.12 g, 0.1 mL, 1 mmol) and compound **62** (0.2 g, 1 mmol) in methylene chloride (5 mL) were stirred at room temperature for 36 h. The reaction mixture was then filtered, and the obtained precipitate was washed with methylene chloride, dried, and crystallized from ethanol to yield compound **65**.

Pale yellow crystals, 0.11 g (34%); mp 245–247°C. IR (KBr, $cm^{-1}$): 3030 (CH-aromatic); 1695 (C=O); 1630 (C=N); 1591 (C=C); 1409 (N=N); 1101 (*p*-Cl-phenyl). $^1H$ NMR (DMSO-$d_6$, δ ppm): 6.53 (d, 2H, $J$ = 8.1 Hz, $C_6H_5$-$C_{2,6}$-H); 6.90–6.98 (m, 3H, $C_6H_5$-$C_{3,4,5}$-H); 7.32 (d, 2H, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.88 (d, 2, $J$ = 8.4 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). *Anal*. Calcd (%) for $C_{15}H_9ClN_6O$ (324.72): C, 55.48; H, 2.79; N, 25.88. Found (%): C, 55.56; H, 2.83; N, 26.17.

***10-[4-Chlorophenyl]-5,6-dihydronaphtho[1′,2′-e][1′,2′-e][1,2,4]triazolo[3,2-c][1,2,4]triazine (66).*** A solution of dimethylaminomethylene-1-tetralone (0.2 g, 1 mmol) in pyridine (5 mL) was cooled in an ice bath at 0–5°C. While stirring and cooling, a cold solution of the triazol-5-diazonium chloride derivative **62** (0.2 g, 1 mmol) in pyridine (5 mL) was added portion wise. After complete addition of the diazonium compound **62**, the mixture was stirred for further 30 min while cooling in an ice bath. The reaction mixture was then left in a refrigerator for 5 days, and the precipitated solid was filtered, washed with water, dried, and finally crystallized from dioxane/ethanol mixture (1:1) to yield compound **66**.

Reddish brown crystals, 0.19 g (56%); mp > 300°C. IR (KBr, $cm^{-1}$): 3040 (CH-aromatic); 2927 (CH-aliphatic); 1591 (C=N); 1546 (C=C); 1419 (N=N); 1099 (*p*-Cl-phenyl). Mass spectrum, *m/z* (%): 334 ($M^+$, 2); 332 ($M^+ -2$, 3); 139 (100). *Anal*. Calcd (%) for $C_{18}H_{12}ClN_5$

(333.77): C, 64.77; H, 3.62; N, 20.98. Found (%): C, 64.92; H, 3.69; N, 21.17.

***Dimethyl 7-(4-chlorophenyl)[1,2,4]triazolo[5,1-c][1,2,4] triazine-3,4-dicarboxylate (67).*** An equimolar mixture of the triazol-5-diazonium chloride derivative **62** (0.2 g, 1 mmol) and dimethyl acetylene dicarboxylate (0.14 g, 0.12 ml, 1 mmol) in absolute ethanol (5 mL) was heated under reflux for 16 h. The reaction mixture was allowed to cool, and the obtained solid was filtered, washed with ethanol, dried, and recrystallized from ethanol to yield compound **67**.

Pale yellow crystals, 0.086 g (25%); mp > 300°C. IR (KBr, $cm^{-1}$): 3068, 3051 (CH-aromatic); 2937, 2908 (CH-aliphatic); 1718 (C=O); 1637 (C=N); 1597 (C=C); 1408 (N=N); 1232, 1093 (C–O–C); 1093 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 4.10 (s, 6H, two $CH_3$); 7.27 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.82 (d, 2H, $J$ = 8.6 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H). Mass spectrum, *m/z* (%): 348 ($M^+$, 2); 69 (100). *Anal*. Calcd (%) for $C_{14}H_{10}ClN_5O_4$ (347.71): C, 48.36; H, 2.90; N, 20.14. Found (%); C, 48.49; H, 2.88; N, 20.37.

**General procedure for synthesis of compounds 68** and **69**. Equimolar amounts of the triazol-5-diazonium chloride derivative **62** (0.2 g, 1 mmol) and phenylacetylene (0.1 g, 0.09 mL, 1 mmol) were fused together in an oil bath at 250°C for 8 h. The reaction mixture was allowed to cool, then triturated with ethanol. The obtained solid was filtered off, washed with ethanol, dried, and crystallized from ethanol to yield compounds **68** that was filtered while hot and dried. The crystallization filtrate was concentrated and allowed to cool to give a solid product, which was dried to yield compound **69**.

***7-(4-Chlorophenyl)-4-phenyl[1,2,4]triazolo[5,1-c][1,2,4] triazine (68).*** Dark brown crystals, 0.1 g (33%); mp > 300°C. IR (KBr, $cm^{-1}$): 3040 (CH-aromatic); 1639 (C=N); 1593 (C=C); 1417 (N=N); 1097 (*p*-Cl-phenyl). Mass spectrum, *m/z* (%): 308 ($M^+$, 2); 44 (100). *Anal*. Calcd (%) for $C_{16}H_{10}ClN_5$ (307.74): C, 62.45; H, 3.28; N, 22.76. Found (%): C, 62.64; H, 3.32; N, 22.95.

***3-(4-Chlorophenyl)-5-[(phenylethynyl)diazenyl]-1H-[1,2,4] triazole (69).*** Reddish brown crystals, 0.058 g (19%); mp 107–108°C. IR (KBr, $cm^{-1}$): 3370, 3274 (NH); 3057, 3026 (CH-aromatic); 2270 (C≡C) 1595 (C=N); 1550 (C=C); 1410 (N=N); 1095 (*p*-Cl-phenyl). $^1$H NMR (DMSO-$d_6$, δ ppm): 7.29 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{2,6}$-H); 7.32–7.63 (m, 5H, $\underline{C_6H_5}$); 7.80 (d, 2H, $J$ = 8.3 Hz, 4-Cl-$C_6H_4$-$C_{3,5}$-H); 12.20 (s, 1H, NH, $D_2O$ exchangeable). *Anal*. Calcd (%) for $C_{10}H_{10}ClN_5$ (307.74): C, 62.45; H, 3.28; N, 22.76. Found (%): C, 62.58; H, 3.32; N, 22.89.

**Anticancer screening.** The synthesized compounds were screened for their *in vitro* cytotoxic activity against human hepatocellular liver carcinoma (HepG2) and human breast cancer cell line (MCF7). Doxorubicin was used as the reference drug.

**Mammalian cell lines.** MCF7 cells (human breast cancer cell line) were obtained from VACSERA Tissue culture unit (Cairo, Egypt). HepG2 cells (human cell line of a well-differentiated hepatocellular carcinoma isolated from a liver biopsy of a male Caucasian aged 15 years) were obtained from the American type culture collection.

## CELL LINE PROPAGATION

The cells were propagated in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer, and 50 μg/mL gentamycin. All cells were maintained at 37°C in a humidified atmosphere with 5% $CO_2$ and were subcultured two times a week.

## CYTOTOXICITY EVALUATION USING VIABILITY ASSAY

For cytotoxicity assay, the cells were seeded in 96-well plate at a cell concentration of 104 cells per well in 100 μL of growth medium. Fresh medium containing different concentrations of the test sample was added after 24 h of seeding. Serial twofold dilutions of the tested chemical compound were added to confluent cell monolayers dispensed into 96-well, flat-bottomed microtiter plates (Falcon, NJ, USA) using a multichannel pipette. The microtiter plates were incubated at 37°C in a humidified incubator with 5% $CO_2$ for a period of 48 h. Three wells were used for each concentration of the test sample. Control cells were incubated without test sample and with or without DMSO. The little percentage of DMSO present in the wells (maximal 0.1%) was found not to affect the experiment. After incubation of the cells for 24 h at 37°C, various concentrations of sample (100, 50, 25, 12.5, 6.25, and 3.125 μg/L) were added, and the incubation was continued for 48 h, and viable cell yield was determined by a colorimetric method. After the end of the incubation period, media were aspirated, and the crystal violet solution (1%) was added to each well for at least 30 min. The stain was removed, and the plates were rinsed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, and then, the absorbance of the plates were measured after gently shaken on Microplate reader (TECAN Inc., Switzerland), using a test wavelength of 490 nm. All results were corrected for background absorbance detected in wells without added stain. Treated samples were compared with the cell control in the absence of the tested compounds. All experiments were carried out in triplicate. The cell cytotoxic effect of each tested compound was

calculated [65,66]. The cytotoxicity of the tested compounds was estimated in terms of percent growth inhibition compared with untreated control cells and their $IC_{50}$ in μM/L, which is the concentration of the compound that inhibits the tumor cell growth by 50%.

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