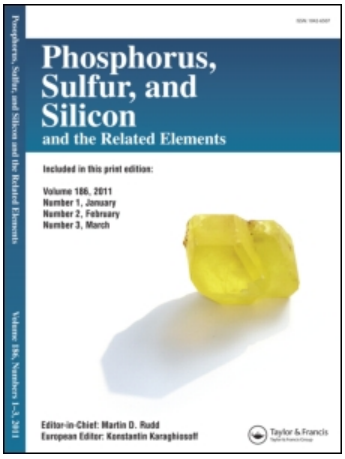

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Anti-Oxidant Activity of Novel Pyrimido[4,5-*b*]quinolin-4-one Derivatives With a New Ring System

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To cite this Article El-Gazzar, A. B. A. , Gaafar, A. M. , Youssef, M. M. , Abu-Hashem, A. A. and Badria, F. A.(2007) 'Synthesis and Anti-Oxidant Activity of Novel Pyrimido[4,5-*b*]quinolin-4-one Derivatives With a New Ring System', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 9, 2009 — 2037
To link to this Article: DOI: 10.1080/10426500701369864
URL: http://dx.doi.org/10.1080/10426500701369864

Phosphorus, Sulfur, and Silicon, 182:2009–2037, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701369864

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Reaction of 2-Hydrazino-derivative ***6b*** *with aliphatic acids yielded the triazolopyrido-pyrimidines* ***7a,b****. Also, reaction of* ***6b*** *with carbon disulfide or potassium thiocyanate afforded 10-mercapto/aminotriazolopyridopyrimidine (****9,10****), respectively. Compound* ***6b*** *reacted with nitrous acid gave tetrazolopyridopyrimidine* ***11****, the latter compound* ***11*** *reduced to 10-amino-derivative* ***12****. Pyridopyrimidine derivatives* ***4b*** *reacted with hydrazonoylchloride derivatives yielded triazolopyridopyrimidines* ***14a–c****. Also, the reaction of* ***6b*** *with aromatic aldehydes afforded the arylidines derivatives* ***16a–d,*** *which were cyclized to triazolopyridopyrimidines deivatives* ***17a–d****. Compound* ***6b*** *reacted with α-haloketones to give triazines derivatives* ***18*** *with new ring systems. On the other hand, reaction of* ***6b*** *with β-ketoesters afforded 10-pyrazolyl-pyridopyrimidines derivatives* ***19,20a–c,*** *and* ***22****. The latter compound was coupled with aldehydes and arylamine to give the derivatives* ***23,24,*** *respectively. The antioxidant activity using ABTS revealed that compound* ***9*** *exhibited an inhibitory effect (80%), compound* ***17c*** *protected the hemolysis of erythrocytes induced by AAPH.*

Keywords Antioxidant activity; a new ring system; ^{13}C-NMR spectra; pyrimido[4,5-b]quinoline; tetrazolo-; triazolo-; triazino-pyridopyrimidines

Received January 24, 2007; accepted March 16, 2007.

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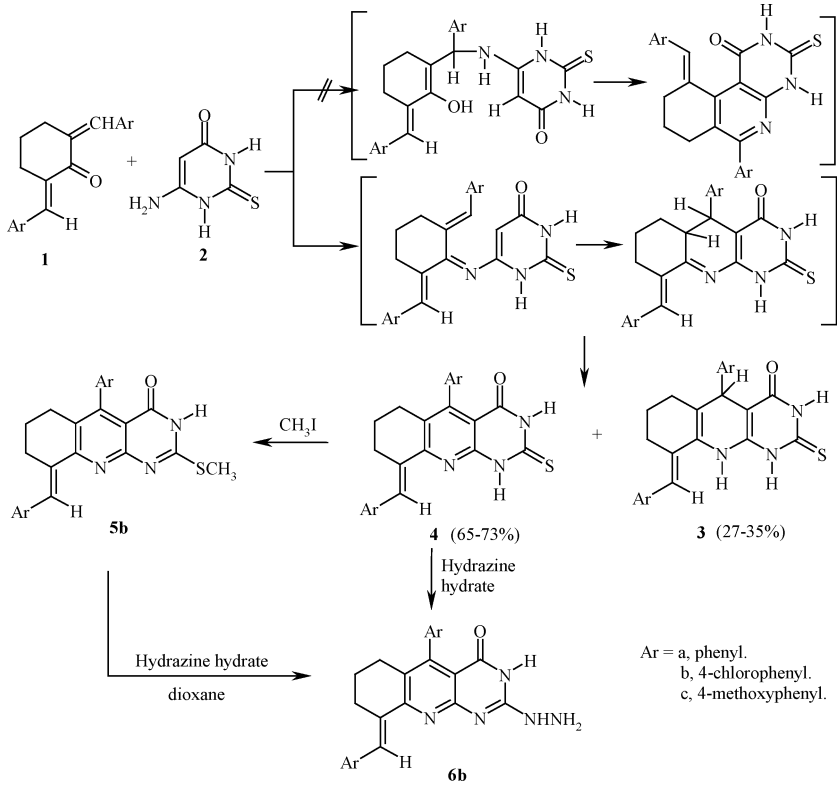
INTRODUCTION

Pyrido[2,3-*d*]pyrimidone derivatives attracted our attention due to the wide range of biological activities associated with this scaffold. Various related compounds of these pyridopyrimidine have biological activities ranging from kinase inhibitors (plated derived growth factor, PDGFr, fibroplast growth factor, FGFr, and epiderma growth factor, EGFr; inhibitor,[1] CSBP/P38 kinase inhibitor,[2] telomerase inhibitor[3]) for treatment of arthritis, adult respiratory distress syndrome, chronic obstractive pulmonary disease, or Alzheimer's disease.[4]

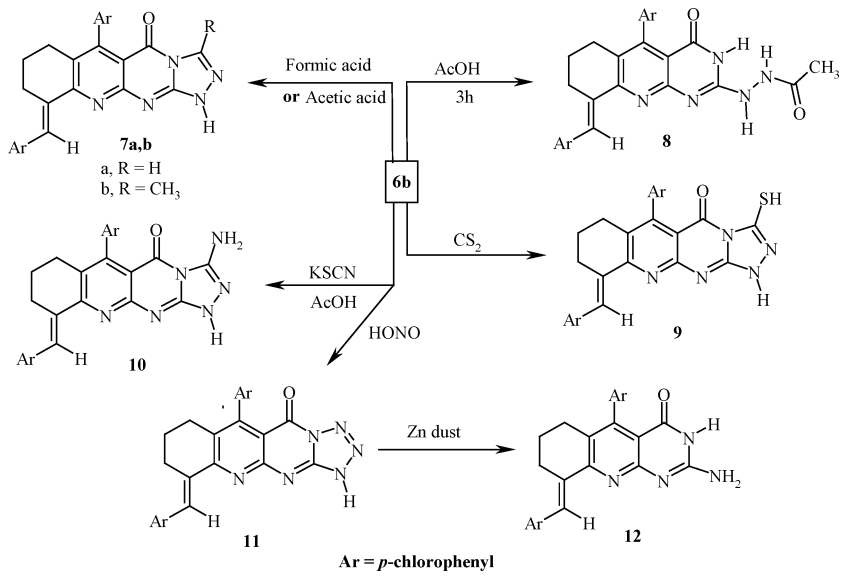
Our group has the interest in the development of synthetic strategy to synthetic polyfunctionalized heterocycles.[5–9] Also, this article describes our approach to the synthesis of polyfunctional heterocyclic compounds. We report here a convenient method for synthesis of triazolopyrido-pyrimidines, tetrazolopyridopyrimidines, and triazinopyridopyrimidines. Thus, heating under reflux 6-aminothiouracil with α,β-unsaturated ketones **1a–c** in boiling dimethylformamide for lengthy periods afforded a mixture of the oxidizing form of 9-arylidene-5-aryl-2-thioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]quinolin-4-one **4a–c** (60–70%) and non-oxidizes forms **3** (30–40%). Compounds **4a–c** reacted with methyl iodide afforded the corresponding 10-methylthio derivatives **5** (Scheme 1). The ^{1}H-NMR spectra of the resulting products are agreement with the assigned structures. The ^{1}H-NMR (DMSO-d_6) spectrum of 9-benzylidene-5-phenyl-2-thioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]quinolin-4-one (**4a**), as an example, showed signals at δ 1.64–1.67 (m, 2H, CH_2), 2.29–2.32 (t, 2H, CH_2), 2.75–2.97 (t, 2H, CH_2), 7.10–7.12 (m, 3H, phenyl), 7.16–7.17 (m, 4H, phenyl), 7.35–7.43 (m, 3H, phenyl), 8.21 (s, 1H, methylenic proton), and 11.50, 12.24 (two broad band, 2NH, D_2O exchangeable). Its mass spectrum showed the molecular [M^+] ion at [M^+] at m/z 397 (100%). The ^{13}C-NMR (DMSO-d_6) spectrum of **4b**, showed signals at 22.27, 26.73, 27.18 ppm (3C, $3CH_2$), 15 sp^2 carbon atoms with four symmetric carbon in two 4-chlorophenyl groups, 162.25 ppm (C=O) and absorption at 175.42 ppm (C=S). Its mass spectrum showed the molecular ion peak with 100% at m/z 465.

Mercapto groups may be removed in favor of hydrogen by desulfurization by boiling in hydrazine hydrate.[6,8] Therefore, the 9-(4-chlorobenzylidene)-5-(4-chlorophenyl)-2-hydrazino-2,-3,6,7,8,9-hexahydropyrimido[4,5-*b*] quinolin-4-one (**6b)** is a good source to enrich the synthesis of heterocyclic chemistry with several new azolopyridopyrimidines,pyrido-pyrimido-as-triazines, and pyrazolylpyridopyrimidines. Thus, heating under reflux 6b with aliphatic acids, namely, formic and acetic acids, for several hours yielded



SCHEME 1

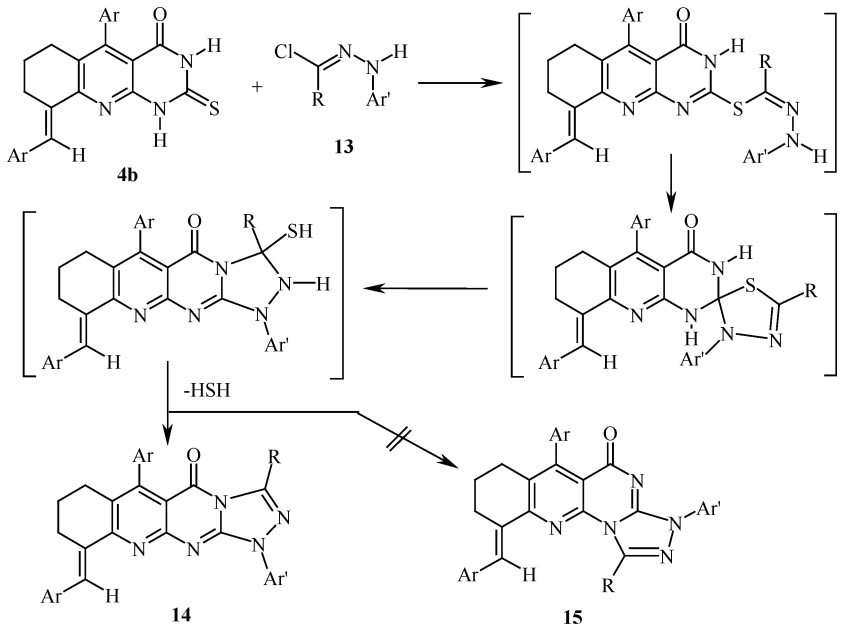
6-(4-chlorophenyl)-10-(4-chlorophenyl-methylene)-7,8,9-hexahydro[1,2,4]triazolo[4′, 3′:1,2]pyrimido[4,5-*b*]quinolin-5-one derivatives **7a**,**b**. Besides the correct values in elemental analyses, the ^{1}H-NMR spectrum of **7a**, as an example, showed signals at δ 1.69–1.74 (m, 2H, CH_2), 2.38–2.41 (t, 2H, CH_2), 2.79–2.82 (t, 2H, CH_2), 7.16–7.18 (d, 2H, phenyl), 7.42–7.45 (2d, 4H, phenyl), 7.53–7.56 (d, 2H, phenyl), 8.10 (s, 1H, methylenic proton), 8.23 (s, 1H, H triazole), and 9.27 (brs, 1H, NH, D_2O exchangable). The ^{13}C-NMR (DMSO-d_6) showed signals at 21.81, 26.46, 27.06 (3C, $3CH_2$) ppm, 108.60, 128.02, 128.15, 128.38, 129.32, 130.92, 131.34, 131.49, 132.43, 132.63, 134.26, 135.76, 136.43, 143.04, 152.65, 155.69, 158.75, (17 sp^2 carbon atoms) ppm, and the absorption at 162.16 (CO) ppm. On the other hand, heating under reflux compound **6b** with acetic acid for 3 hr. yielded the 2-acethydrazido derivative **8**. The IR spectrum of **8** displayed absorption bands at 3460 cm^{-1} (brs, NH), 1690 cm^{-1} (CO) and 1686 cm^{-1} (CO).



SCHEME 2

Compound **6b** reacted with carbon disulphide in ethanolic potassium hydroxide solution gave 6-(4-chlorophenyl)-10-(4-chlorophenylmethylene)-3-thioxo-7,8,9-hexahydro[1,2,4]tria-zolo[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (**9**) (Scheme 2). Similarly, heating **6b** with potassium thio-cyanate in boiling acetic acid afforded compound **10**. The IR spectrum of **9** displayed absorption bands at 3418 cm^{-1} (NH) and 1698 cm^{-1} (CO). Also**,** besides the correct values in elemental analysis and the spectra (^{1}H-NMR, ^{13}C-NMR) data of **9**,**10** are in agreement with the assigned structures.

Treatment of compound **6b** with nitrous acid at 0°C led to the formation of 6-(4-chloro-phenyl)-10-(4-chlorophenylmethylene)-3-amino-7,8,9-hexahydrotetrazolo[4′,3′:1,2]pyrimido-[4,5-*b*]quinolin-5-one (**11**). The ^{1}H-NMR spectrum (DMSO-d_6) of **11** showed signals at δ 1.66–1.70 (m, 2H, CH_2), 2.32–2.36 (t, 2H, CH_2), 2.79–2.96 (t, 2H, CH_2), 7.06–7.10 (d, 2H, phenyl), 7.34–7.36 (d, 2H, phenyl), 7.43–7.46 (2d, 4H, phenyl), 8.03 (s, 1H, methylenic proton), and 11.00 (brs, 1H, NH, D_2O exchangeable). Compound **11** was reduced to 2-amino-9-(4-chlorophenyl-methylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (**12**) by zinc dust in acetic acid. The ^{1}H-NMR spectrum (DMSO-d_6) of **12** showed signals at δ 1.70–1.73 (m, 2H, CH_2), 2.37–2.40 (t, 2H, CH_2), 2.81–2.96 (t, 2H, CH_2), 7.12–7.15 (d, 2H, phenyl), 7.39–7.43 (d, 2H, phenyl), 7.44–7.48



Ar = 4-Chlorophenyl

13, 14, a, R = Ar' = C_6H_5

13, 14, b R = $COCH_3$, Ar' = *p*-C_6H_4-Cl

13, 14, c, R = $COCH_3$, Ar' = *p*-C_6H_4-NO_2

13, 14, d , R = $COOC_2H_5$, Ar' = C_6H_5

SCHEME 3

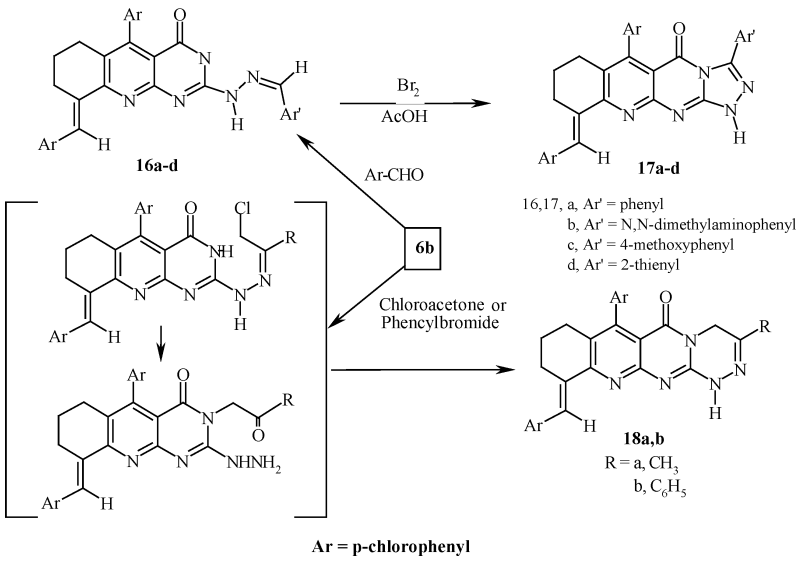
(2d, 4H, phenyl), 8.01 (s, 1H, methylenic proton), and 9.55 (brs, 1H, NH, D_2O exchangeable). Its ^{13}C-NMR (DMSO-d_6) showed signals at 21.80, 26.91, 26.95 (3C, $3CH_2$) ppm, 20 sp^2 carbon atoms, and the absorption at 160.19 (CO) ppm. The IR spectrum displayed absorption band at 3332 cm^{-1} (NH_2). The mass spectrum of **12** showed the molecular ion peak at m/z 449 (100%).

Thioxo pyridopyrimidone derivative **4b** reacted with hydrazonoyl chloride derivatives **13a–d** gave novel functionalized 6-(4-chlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro-1,3-subs tituted-triazolo[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (**14a–d**) (Scheme 3). The correct values in elemental analysis, the IR, ^{1}H-NMR, and mass spectra of the compounds **14a–d** are in agreement with the assigned structures. The N-3 nitrogen atom and not the N-1 nitrogen atom

was involved in the cyclization to form **14** rather than the isomeric compound **15**. The ^{13}C-NMR (DMSO-d_6) spectrum of **14a**, as an example, showed signals at δ 21.93, 26.81, 26.88 (3C, $3CH_2$) ppm, 27.09 (CH_3) ppm, (21 sp^2 carbon atoms), 160.19, 188.66 (2CO) ppm. Its Mass spectrum showed the molecular ion peak at m/z, 626 (100%).

According to El-Gazzar,[8,9] 2-hydrazino derivative (**6b**) gave the 2-(arylm ethylene-hydrazone-9-(4-chlorophenylmethylene)-5-(4-chloro phenyl)-6,7,8-hexahydropyrimido[4,5-*b*]-quinolin-4-ones **16a–d**, when treated with the appropriate aldehyde in boiling acetic acid for 20 min. Compounds **16a–d** gave compatible spectra and analytical data. The ^{13}C-NMR (DMSO-d_6) spectrum of compound **16c**, as an example, showed signals at 22.14, 26.64, 27.09, 55.33 (4C, $3CH_2$+CH_3) ppm, 21sp^2 carbon atoms, and the absorption at 160.84 (CO) ppm. Its mass spectrum showed the molecular ion for [M^+] at m/z 582 (17%). The arylhydrazones **16a–c** could be cyclized into the corresponding 3-aryl-6-(4-chlorophenyl)-10-(4-chlorophenyl-methylene)-7,8,9-hexahydro[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-ones (**17a–d**), when treated with excess bromine in acetic acid in presence of anhydrous sodium acetate. The ^{1}H-NMR (DMSO-d_6) spectrum of compound **17c**, as an example, showed the signals at δ 1.68–1.71 (t, 2H, CH_2), 2.32–2.34 (t, 2H, CH_2), 2.69–2.74 (t, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.96–7.12 (d, 2H, phenyl), 7.14–7.18 (d, 2H, phenyl), 7.39–7.46 (2d, 4H, phenyl), 7.76–7.81 (d, 4H, phenyl), 7.83–7.88 (d, 2H, phenyl), 8.08 (s, 1H, methylenic proton), and 11.50 (brs, NH, D_2O exchangeable). The ^{13}C-NMR (DMSO-d_6) showed the signals at 22.19, 26.56, 27.18, 55.56 (4C, $3CH_2$+CH_3) ppm, 21 sp^2 carbon atoms and the absorption at 161.84 (CO) ppm.

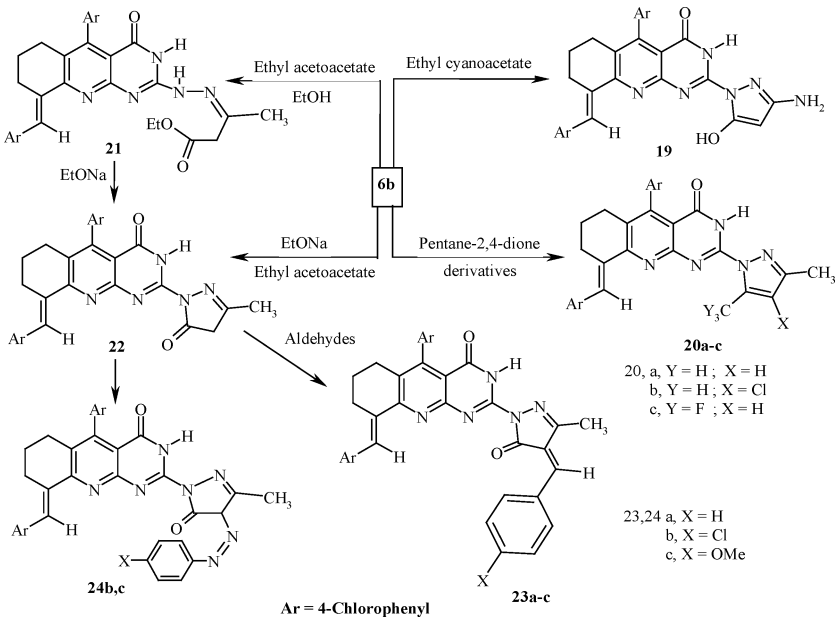
The 10-hydrazino derivative **6b** was used to prepare 11-(4-chlorophenyl-methylene)-7-(4-chlorophenyl)-3-(methyl/or phenyl)-8,9,10-hexahydro[1,2,4]triazino[4′,3′:1,2]-pyrimido[4,5-*b*]quinolin-6-ones (**18a**,**b**). Thus, heating under reflux **6b** with chloroacetone or phenacylbromide in dry xylene yielded directly the triazino- derivatives **18a**,**b**. The IR spectra of **18** displayed absorption bands around 3430 cm^{-1} (NH) and 1694 cm^{-1} (CO). The ^{1}H-NMR (DMSO-d_6) spectrum of compound **18a**, as an example, showed signals at δ 1.63–1.67 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.28–2.30 (t, 2H, CH_2) 2.79–2.80 (t, 2H, CH_2), 5.96 (s, 2H, CH_2), 7.11–7.15 (d, 2H, phenyl), 7.20–7.22 (d, 2H, phenyl), 7.29–7.33 (d, 2H, phenyl), 7.44–7.51 (d, 2H, phenyl), 8.11 (s, 1H, methylenic proton), and 11.54 (brs, NH D_2O exchangeable). Its ^{13}C-NMR (DMSO-d_6) showed signals at 15.10, 22.27, 26.73, 27.18, 64.86 (5C, $4CH_2$+CH_3) ppm, 21 sp^2 carbon atoms and the absorption at 160.05 (CO) ppm.



SCHEME 4

Moreover, when equimolar amounts of **6b** and pentane-2,4-dione derivatives were heated under reflux in ethanol, the 5-(4-chlorophenyl)-9-(4-chlorophenylmethylene)-2-(3-methyl-4-(un)substituted-5-pyrazol-1-yl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (**20a–c**) were obta ined in good yield. Besides, the correct values in elemental analysis and the spectral data of **20a–c** are in agreement with the assigned structure. The ^{1}H-NMR spectrum (DMSO-d_6) of **20a**, as an example, showed signals at δ 1.67–1.70 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.27–2.31 (t, 2H, CH_2), 2.74 (s, 3H, CH_3), 2.77–2.79 (t, 2H, CH_2), 6.20 (s, 1H, pyrazolyl proton), 7.16–7.18 (d, 2H, phenyl), 7.26–7.27 (d, 2H, phenyl), 7.40–7.46 (2d, 4H, phenyl), 8.09 (s, 1H, methylenic proton), and 10.90 (brs, NH D_2O exchangeable). Its ^{13}C-NMR (DMSO-d_6) showed the signals at 13,41, 19.02, 21.42, 25.67, 26.13 (5C, $3CH_2$+ $2CH_3$) ppm, 23 sp^2 carbon atoms, and the absorption at 165.31 (CO) ppm. Also, the IR spectrum displayed absorption bands at 3300 cm^{-1} (brs, NH), 1694 cm^{-1} (CO).

The 10-hydrazino derivative **6b** reacted with some β-ketooesters, β-cyanoesters, and β-diketones to form **19** and **22** derivatives. Compound **6b** and ethyl cyanoacetate were heated in ethanolic sodium ethoxide solution afforded the 10-(3-amino-5-hydroxy-4*H*-pyrazol-l-yl) derivative **19** (Scheme 5). The IR spectrum of **19** displayed absorption bands at 3340 cm^{-1} (NH) and 1690 cm^{-1} (CO). Its ^{13}C-NMR spectrum (DMSO-d_6) showed signals at δ 22.13, 26.69, 27.03 (3C, $3CH_2$) ppm, 23



SCHEME 5

sp^2 carbon atoms), and the absorption at 161.25 (CO) ppm. Compound **6b** condensed with ethyl acetoacetate upon heating in absolute ethanol, gave the hydrazone derivative **21**, while the 5-(4-chlorophenyl)-9-(4-chlorophenylmethylene)-2-(3-methyl-4*H*-pyrazol-5-one-1-yl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (**22**) was produced by heating **6b** with ethyl acetoacetate under reflux in ethanolic sodium ethoxide. Compound **21** could be converted to **22** upon heating in ethanolic sodium ethoxide solution. The ^{13}C-NMR spectrum (DMSO-d_6) of **21** showed the absorption bands at 13.98, 14.05, 22.06, 26.99, 43.92, 60.25 (6 sp^3) ppm, 21 sp^2 carbon atoms and the absorption bands 161.07, 169.58 (2CO) ppm. The ^{1}H-NMR spectrum of **22** showed no signals corresponding to ethyl group protons. Compound **22** was coupled with aromatic aldehydes to afford4-(4-arylmethylene)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-2-(3-methyl-pyrazol-5-one-1-yl)-6,7,8-hexahydro-pyrimido[4,5-*b*]quinolin-4-one(**23**). Also, compound **22** was coupled with phenyl diazonium salts to afford 2-(3-methyl-4-arylazo-pyrazol-5-one-1-yl)-9-(4-chlorophenyl-methylene)-5-(4-chlorophenyl)-6,7,8-hexahydro-pyrimido[4,5-*b*]quinolin-4-ones **(24)**. The IR spectrum of **23** showed absorption bands around 3420 cm^{-1} (OH), 3350 cm^{-1} (NH), and 1690, 1683 cm^{-1} (2CO). The ^{1}H-NMR spectrum (DMSO-d_6) of **23a**, as an example, showed signals at δ 1.66–1.69 (m, 2H, CH_2),

2.09 (s, 3H, CH_3), 2.26–2.29 (t, 2H, CH_2), 2.80–2.84 (t, 2H, CH_2), 7.12–7.15 (d, 2H, phenyl), 7.18–7.20 (m, 3H, phenyl), 7.32–7.34 (d, 2H, phenyl), 7.42–7.48 (2d, 4H, phenyl), 7.59–7.62 (m, 2H, phenyl), 8.09 (s, 1H, methylenic proton), 9.02 (s, 1H, methylenic proton), and 11.20 (brs, NH D_2O exchangeable). Moreover, The ^{1}H-NMR (DMSO-d_6) spectrum of compound **24c** showed signals at δ 1.65–1.70 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.27–2.31 (t, 2H, CH_2), 2.80–2.84 (t, 2H, CH_2), 3.96 (s, 3H, OCH_3), 7.19–7.21 (d, 2H, phenyl), 7.24–7.27 (d, 2H, phenyl), 7.34–7.39 (d, 2H, phenyl), 7.46–7.50 (2d, 4H, phenyl), 7.83–7.85 (d, 2H, phenyl), 8.17 (s, 1H, methylenic proton), and 11.40 (brs, NH D_2O exchangeable).

ASSAY FOR BLEOMYCIN DEPENDENT DNA GAMAGE

All compounds have been tested for Bleomycin, dependent DNA damage, may indicate that, glycosides may have some protective activity to DNA by certain mechanism, and their concentrations are small in total extract (Table II). Or, they may bind to DNA by certain mechanism leaving Bleomycin.

CONCLUSIONS

The prepared new ring systems seem to be interesting for biological activity studies. Furthermore, the present investigation offers rapid and effective new procedures for the synthesis of the polycondensed new heterocyclic ring systems.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL-ECA500 (National Research Center, Egypt) and JEOL JNM-LA-400 FT NMR Spectrometer (Universitat Konstanz, Germany), and chemical shifts were expressed as δ values against $SiMe_4$ as internal standards. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 spectrometer, (National Research Center and Chemstry Department, Cairo University). Mass spectra were recorded on GCMS-QP 1000 EX Shimadzu Japan (Gas Chromatography-Mass spectrometer). Microanalytical data were performed by the Microanalytical Center at Cairo University and National Research Center (Egypt) (Table I). The starting materials are prepared according to Quiroga[10,11] and El-gazzar.[5]

TABLE I Physical and Chemical Properties of Synthesized Compounds

No.	Yield (%)	m.p °C	Mol.From (Mol.Wt)	Microanalysis		
				C	H	N
4a	85	220–222 melted	$C_{24}H_{19}N_3OS$ (397.5)	72.52 72.54	4.82 4.81	10.57 10.55
4b	85	295–297 melted	$C_{24}H_{17}Cl_2N_3OS$ (466.4)	61.81 61.78	3.67 3.65	9.01 9.06
4c	83	280–282 melted	$C_{26}H_{23}N_3O_3S$ (457.5)	68.25 68.19	5.07 5.08	9.18 9.14
5b	77	327–330 melted	$C_{25}H_{19}Cl_2N_3SO$ (480.4)	62.51 62.50	3.98 3.96	8.74 8.72
6b	80	278–280 melted	$C_{24}H_{19}Cl_2N_5O$ (464.4)	62.08 62.11	4.12 4.09	15.08 15.03
7a	83	305–307 melted	$C_{25}H_{17}Cl_2N_5O$ (474.3)	63.30 63.27	3.61 3.62	14.76 14.69
7b	80	296–298 melted	$C_{26}H_{19}Cl_2N_5O$ (488.4)	63.94 63.91	3.92 3.95	14.34 14.26
8	82	320–322 melted	$C_{26}H_{21}Cl_2N_5O_2$ (506.4)	61.67 61.65	4.18 4.20	13.83 13.78
9	81	317–320 melted	$C_{25}H_{17}Cl_2N_5SO$ (506.4)	59.29 59.23	3.38 3.35	13.83 13.79
10	80	360–362 Melted	$C_{25}H_{18}Cl_2N_6O$ (489.3)	61.36 61.34	3.70 3.67	17.17 17.11
11	75	226–228 melted	$C_{24}H_{16}Cl_2N_6O$ (475.3)	60.65 60.63	3.39 3.36	17.68 17.28
12	78	266–268 melted	$C_{24}H_{18}Cl_2N_4O$ (449.3)	64.16 64.09	4.03 4.01	12.47 12.37
14a	70	362–364 melted	$C_{37}H_{25}Cl_2N_5O$ (626.5)	70.93 70.97	4.02 3.99	11.18 11.08
14b	80	215–217 melted	$C_{33}H_{22}Cl_3N_5O_2$ (626.9)	63.23 63.19	3.53 3.50	11.17 11.06
14c	85	240–243 melted	$C_{33}H_{22}Cl_2N_6O_4$ (637.4)	62.19 62.17	3.48 3.47	13.18 13.11
14d	79	285–287 melted	$C_{34}H_{25}Cl_2N_5O_3$ (622.5)	65.60 65.58	4.04 4.01	11.25 11.16
16a	85	342–345 melted	$C_{31}H_{23}Cl_2N_5O$ (552.4)	67.39 67.38	4.19 4.18	12.68 12.57
16b	82	335–337 melted	$C_{33}H_{28}Cl_2N_6O$ (595.5)	66.56 66.54	4.73 4.69	14.11 14.05
16c	85	338–340 melted	$C_{32}H_{25}Cl_2N_5O_2$ (582.5)	65.98 65.99	4.33 4.29	12.02 12.01
16d	83	250–352 melted	$C_{29}H_{21}Cl_2N_5OS$ (558.5)	62.37 62.39	3.79 3.80	12.54 12.48
17a	81	220–222 melted	$C_{31}H_{21}Cl_2N_5O$ (550.4)	67.65 67.68	3.84 3.85	12.72 12.67
17b	77	235–237 melted	$C_{33}H_{26}Cl_2N_6O$ (593.5)	66.79 66.75	4.41 4.43	14.16 14.09

TABLE I Physical and Chemical Properties of Synthesized Compounds (*Continued*)

No.	Yield (%)	m.p °C	Mol.From (Mol.Wt)	Microanalysis		
				C	H	N
17c	80	173–175 melted	$C_{32}H_{23}Cl_2N_5O_2$ (580.5)	66.21 66.19	3.99 4.00	12.07 12.00
17d	78	210–212 melted	$C_{29}H_{19}Cl_2N_5OS$ (556.4)	62.59 62.57	3.44 3.41	12.59 12.46
18a	80	286–288 melted	$C_{27}H_{21}Cl_2N_5O$ (502.4)	64.55 64.07	4.21 4.18	13.94 13.88
18b	85	190–192 melted	$C_{32}H_{23}Cl_2N_5O$ (564.5)	68.09 68.11	4.11 4.08	12.41 12.34
19	79	223–225 melted	$C_{27}H_{20}Cl_2N_6O_2$ (531.4)	61.03 61.01	3.79 3.80	15.82 15.75
20a	82	338–340 melted	$C_{29}H_{23}Cl_2N_5O$ (528.4)	65.91 65.87	4.39 4.37	13.25 13.27
20b	80	216–218 melted	$C_{29}H_{22}Cl_3N_5O$ (562.8)	61.88 61.79	3.94 3.93	12.44 12.39
20c	79	168–170 melted	$C_{29}H_{20}Cl_2F_3N_5O$ (582.4)	59.81 59.77	3.46 3.42	12.03 12.06
21	75	145–147 melted	$C_{30}H_{27}Cl_2N_5O_3$ (576.5)	62.51 62.48	4.72 4.71	12.19 12.16
22	80	370–372 dec.	$C_{28}H_{21}Cl_2N_5O_2$ (530.4)	63.41 63.39	3.99 3.98	13.20 13.12
23a	76	349–351 melted	$C_{35}H_{25}Cl_2N_5O_2$ (618.5)	67.97 67.95	4.07 4.08	11.32 11.30
23b	81	257–259 melted	$C_{35}H_{24}Cl_3N_5O_2$ (652.9)	64.38 64.29	3.70 3.66	10.72 10.67
23c	82	297–299 melted	$C_{36}H_{27}Cl_2N_5O_3$ (648.5)	66.67 66.70	4.19 4.20	10.80 10.72
24b	77	344–346 melted	$C_{34}H_{24}Cl_3N_7O_2$ (668.9)	61.05 61.03	3.61 3.59	14.66 14.65
24c	75	357–360 melted	$C_{35}H_{27}Cl_2N_7O_3$ (664.5)	63.26 63.21	4.09 4.07	14.75 14.73

9-Benzylidene-5-aryl-2-thioxo-2,3,6,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]quinolin-4-ones (4a–c)—General Procedure

A mixture from compound **1a–c** (10 mmol) and 6-aminothiouracil (**2**) (1.43 g, 10 mmol) was refluxed in 50 ml dimethylformamide for 20–30 h (under TLC control). The reaction mixture was cooled; the deposited precipitate was filtered off, washed with ethanol and dried, and crystallized from appropriate solvent to produce **4a–c** in good yield. The filtrate was concentrated and leave it overneight at 0°C, the precipitate

TABLE II Anti-Oxidant Assay for the Prepared New Compounds (Control (ABTS) 0.59, (AAPH) 0.824)

Methods	ABTS		Erythocyte hemolysis		Bleomycin-dependent DNA damage
Compounds	Absorbance	% Inhibition	Absorbance(A)	% Hemolysis	Absorbance
Ascorbic acid	0.05	91.50	0.007	0.85	0.881
4b	0.4	32.20	0.158	19.20	0.862
6b	0.34	42.40	0.042	5.10	0.858
7a	0.48	18.60	0.051	6.20	0.849
7b	0.39	33.90	0.02	2.40	0.843
8	0.59	0.00	0.037	4.50	0.872
9	0.12	80.00	0.024	2.90	0.866
10	0.42	28.80	0.012	1.40	0.883
11	0.45	23.70	0.059	7.20	0.886
12	0.47	20.30	0.03	3.60	0.868
16a	0.48	18.60	0.011	1.30	0.85
16b	0.49	16.90	0.012	1.40	0.868
16d	0.52	11.90	0.016	1.90	0.868
17b	0.49	16.90	0.038	4.60	0.883
17c	0.52	11.90	0.007	0.85	0.789
17d	0.5	15.20	0.016	1.90	0.885
18a	0.5	15.20	0.019	2.30	0.861
18b	0.44	25.40	0.021	2.50	0.876
19	0.41	30.50	0.011	1.30	0.885
20a	0.44	25.40	0.031	3.80	0.851
20b	0.48	19	0.014	1.70	0.881
21	0.4	32.20	0.052	6.30	0.871
22	0.39	33.90	0.015	1.80	0.848
23a	0.44	25	0.01	1.20	0.863
23b	0.52	11.90	0.014	1.70	0.875
24b	0.59	0.00	0.013	1.60	0.834

formed was filtered off, and crystallized from appropriate solvent to afford **3a–c** in low yield.

9-Benzylidene-5-phenyl-2-thioxo-2,3,6,7,8,9-hexahydro-1H-pyrimido[4,5-b]quinolin-4-one (4a)

The compound was obtained from the reaction of **1a** (2.74 g, 10 mmol), as a yellow powder, crystallized from dioxane; IR, cm^{-1}: 3350 (brs, NH), 3029 (CH aryl), 2913 (CH alkyl), 1686 (CO), 1632 (C=N). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.64–1.67 (m, 2H, CH_2), 2.29–2.32 (t, 2H, CH_2), 2.75–2.97 (t, 2H, CH_2), 7.10–7.12 (m, 3H, phenyl), 7.16–7.17 (m, 4H, phenyl), 7.35–7.43 (m, 3H, phenyl), 8.21 (s, 1H, methylenic proton), and 11.50, 12.24 (two broad band, 2NH). Its MS, [M^+], m/z 397 (100%).

9-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-2-thioxo-6,7,8-hexahydro-pyrimido[4,5-b]-quinolin-4-one (4b)

The compound was obtained from the reaction of **1b** (3.43 g, 10 mmol), as a yellow powder, crystallized from dioxane; IR, cm^{-1}: 3361 (brs, NH), 3025 (CH aryl), 2911 (CH alkyl), 1688 (CO), 1631 (C=N). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.64–1.67 (m, 2H, CH_2), 2.29–2.32 (t, 2H, CH_2) 2.75–2.97 (t, 2H, CH_2), 7.10–7.12 (d, 2H, p-sub-phenyl), 7.14–7.16 (d, 2H, p-sub-phenyl), 7.16–7.17 (doublet over doublet, 4H, p-sub-phenyl), 8.19 (s, 1H, methylenic proton), and 11.50 (brs, NH). ^{13}C-NMR (DMSO-d_6) ppm: δ 22.27, 26.73, 27.18 (3C, 3CH_2), 108.35, 127.95, 128.29, 128.52, 128.58, 129.44, 130.14, 131.17, 132.34, 132.43, 135.53, 135.70, 136.22, 149.71, 158.47 (15 sp^2 carbon atoms), 162.25 (CO), and 175.42 (CS). The MS, [M^+], m/z 465 (100%).

9-(4-Methoxybenzylidene)-5-(4-methoxyphenyl)-2-thioxo-6,7,8-hexahydro-1H-pyrimido[4,5-b]quinolin-4-one (4c)

The compound was obtained from the reaction of **1c** (3.34 g, 10 mmol), as a yellow powder, crystallized from dimethylformamide; IR, cm^{-1}: 3348 (brs, NH), 3029 (CH aryl), 2907 (CH alkyl), 1693 (CO), 1641 (C=N). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.68 (m, 2H, CH_2), 2.27–2.30 (t, 2H, CH_2), 2.74–2.95 (t, 2H, CH_2), 3.78 (s, 3H, OCH_3) 7.11–7.13 (d, 2H, p-sub-phenyl), 7.14–7.16 (d, 2H, p-sub-phenyl), 7.37–7.39 (d, 2H, p-sub-phenyl), 7.752–7.61 (d, 2H, p-sub-phenyl), 8.23 (s, 1H, methylenic proton), and 11.20, 12.32 (two broad band, 2NH). Its MS, [M^+], m/z 456 (100%).

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-methylthio-6,7,8-hexahydro-1H-pyrimido-[4,5-b] quinolin-4-one (5b)

To a warmed ethanolic potassium hydroxide solution (prepared by disolving 0.56 g, 10 mmol of potassium hydroxide in 50 ml ethanol) was added compound **4b** (4.66 g, 10 mmol) and heating was continued for 30 min. The mixture was allowed to cool to room temperature, and methyl iodide (20 mmol) was added. The mixture was stirred under reflux for 5 h and then allowed to cool to room temperature and finally poured into cold water (100 ml). The solid product precipitated was filtered off and washed with 100 ml water. The compound was obtained as pale white crystals, crystallized from dioxane; IR, cm^{-1}: 3445 (brs, NH), 3018 (CH alkyl), 1662 (CO), 1582 (C=N), 1542 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.62–1.67 (m, 2H, CH_2), 2.24–2.29 (t, 2H, CH_2), 2.52 (s, 3H, SCH_3), 2.72–2.74 (t, 2H, CH_2), 7.08–7.12 (d, 2H, phenyl), 7.34–7.39 (d, 2H,

phenyl), 7.40–7.44 (2d, 4H, phenyl), 8.45 (s, 1H, methylenic proton), and 11.20 (brs, 1H, NH, D_2O exchangable).

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-hydrazino-6,7,8-hexahydro-1H-pyrimido-[4,5-b]quinolin-4-one (6b)

Method A

A suspention of dry compound **4b** (4.66 g, 10 mmol) in hydrazine hydrate (80–90%) (25 ml) was stirred under gentle reflux. The insoluble solid dissolved within 10 min with copious evolution of methyl mercaptan to form a clear solution. After 30 min, when the solid product started separating out, heating was continued for 8 h. The reaction mixture was then allowed to cool to room temperature. The solid was filtered, washed with ethanol, dried, and crystallized from dimethylformamide.

Method B

A suspension of compound **5** (4.80, 10 mmol) and hydrazine hydrate (99–100%, 25 ml) was stirred under reflux in dioxane (20 ml) for 12 h. The reaction mixture was allowed to cool to room temperature and poured into cold water. The precipitate was filtered off, washed with water and ethanol, and then was dried and crystallized; IR, cm^{-1}: 3198 (brs, NH), 3036 (CH aryl), 2934 (CH alkyl), 1676 (CO). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.64–1.69 (m, 2H, CH_2), 2.29–2.32 (t, 2H, CH_2), 2.76–2.78 (t, 2H, CH_2), 7.06–7.12 (d, 2H, phenyl), 7.39–7.41 (d, 2H, phenyl), 7.43–7.47 (2d, 4H, phenyl), 8.02 (s, 1H, methylenic proton), and 9.50 (brs, 1H, NH, D_2O exchangable). ^{13}C-NMR (DMSO-d_6) ppm: δ 22.27, 22.73, 27.19 (3C, $3CH_2$), 109.14, 127.73, 127.79, 128.34, 129.35, 129.43, 131.15, 131.64, 136.13, 136.35, 137.93, 150.06, 155.15 (16C SP^2 carbon atoms), 160.19 (CO). Its MS, [M^+], m/z 464 (100%).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro[1,2,4]triazolo[4′,3′-:1,2]pyrimido[4,5-*b*]quinolin-5-one (7a)

A mixture of compound **6b** (4.64 g, 10 mmol) and formic acid (10 ml) was heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature and poured into water (100 ml). The formed solid was collected by filtration, washed with ethanol (20 ml), dried and crystallized from ethanol; IR, cm^{-1}: 3430 (brs, NH), 3024 (CH aryl), 2951 (CH alkyl), 1727 (CO), 1617 (C=N), 1562 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.69–1.74 (m, 2H, CH_2), 2.38–2.41 (t, 2H, CH_2), 2.79–2.82 (t, 2H, CH_2), 7.16–7.18 (d, 2H, phenyl), 7.42–7.45 (2d, 4H, phenyl), 7.53–7.56 (d, 2H, phenyl), 8.10 (s, 1H, methylenic proton), 8.23 (s, 1H, H

triazole), and 9.27 (brs, 1H, NH, D_2O exchangable). ^{13}C-NMR (DMSO-d_6) ppm: δ 21.81, 26.46, 27.06 (3C, $3CH_2$), 108.60, 128.02, 128.15, 128.38, 129.32, 130.92, 131.34, 131.49, 132.43, 132.63, 134.26, 135.76, 136.43, 143.04, 152.65, 155.69, 158.75, (17 sp^2 carbon atoms), 162.16 (CO).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-methyl-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (7b)

A mixture of **6b** (4.64 g, 10 mmol), glacial acetic acid (30 ml) was stirred under reflux for 12 h. (under TLC analysis). The reaction mixture was allowed to cool to room temperature and poured into water (100 ml). The solid so-formed was collected by filtration, washed with ethanol (20 ml), dried, and crystallized from dioxane; IR,cm^{-1}: 3377 (brs, NH), 3038 (CH aryl), 2972 (CH alkyl), 1698 (CO), 1636 (C=N), 1565 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.61–1.64 (m, 2H, CH_2), 2.26–2.30 (t, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.75–2.77 (t, 2H, CH_2), 7.08–7.13 (d, 2H, phenyl), 7.42–7.45 (d, 2H, phenyl), 7.47–7.51 (2d, 4H, phenyl), 8.02 (s, 1H, methylenic proton), and 9.52 (brs, 1H, NH, D_2O exchangable).

2-Acethydrazido-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydro-pyrimido[4,5-*b*]quinolin-4-one (8)

A solution of compound **6b** (4.64 g, 10 mmol) in glacial acetic acid, was refluxed for 3 h. The reaction mixture was then allowed to cool to room temperature, poured into cold water (100 ml), the solid so-formed was collected by filtration, dried and crystallized from dioxane; IR, cm^{-1}: 3460 (brs, NH), 3089 (CH, aryl), 2949 (CH alkyl), 1690, 1686 (2CO), 1615 (C=N), 1560 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.63–1.67 (m, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.76–2.79 (t, 2H, CH_2), 7.11–7.15 (d, 2H, phenyl), 7.38–7.43 (d, 2H, phenyl), 7.48–7.54 (2d, 4H, phenyl), 8.12 (s, 1H, methylenic proton), and 9.52, 10.50 (brs, 2NH, D_2O exchangable).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-thioxo-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido [4,5-*b*]quinolin-5-one (9)

To a warmed ethanolic sodium hydroxide solution (prepared by dissolving (0.40 g, 10 mmol) of sodium hydroxide in ethanol (50 ml) was added (4.64 g, 10 mmol) of compound **6b** and excess carbon disulphide

(10 ml). The mixture was heated on a waterbath at 80°C under reflux for 12 h, then allowed to cool to room temprature, poured into water (100 ml), neutralized by dilute acetic acid, and the formed precipitate was filtered off and dried. The product was crystallized from ethanol; IR, cm^{-1}: 3418 (brs, NH), 3023 (CH aryl), 2953 (CH alkyl), 1698 (CO), 1652 (C=N), 1557 (C=C). ^{1}H-NMR (DMSO-d_6): δ 1.70–1.71 (m, 2H, CH_2), 2.34–2.37 (t, 2H, CH_2), 2.56 (s, 1H, SH), 2.81–3.07 (t, 2H, CH_2), 7.09–7.14 (d, 2H, phenyl), 7.36–7.39 (d, 2H, phenyl), 7.44–7.45 (2d, 4H, phenyl), 8.00 (s, 1H, methylenic proton), and 9.24 (brs, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6): δ 22.16, 26.98, 27.04 (3C, $3CH_2$), 110.51, 127.50, 128.39, 129.43, 129.78, 130.34, 131.09, 131.14, 131.20, 131.40, 131.93, 135.32, 136.62, 143.04, 152.55, 155.64, 158.85, (17 sp^2 carbon atoms), 163.12 (CO).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-amino-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (10)

A mixture of compound **6b** (4.64 g, 10 mmol) and potassium thiocyanate (0.97 g, 10 mmol) was heated under reflux in acetic acid for 8 h. The reaction mixture was allowed to cool to room temperature and poured into water. The precipitate so-formed was collected by filtration, dried and crystallized from dioxane as yellow powder; IR, cm^{-1}: 3395 (brs, NH), 3060 (CH aryl), 2935 (CH alkyl), 1703 (CO), 1637 (C=N), 1556 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.71–1.74 (m, 2H, CH_2), 2.38–2.41 (t, 2H, CH_2), 2.82–2.97 (t, 2H, CH_2), 7.14–7.16 (d, 2H, phenyl), 7.43–7.44 (d, 2H, phenyl), 7.45–7.49 (2d, 4H, phenyl), 8.00 (s, 1H, methylenic proton), and 9.28 (brs, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 21.82, 26.92, 26.97 (3C, $3CH_2$), 109.41, 127.90, 127.96, 128.51, 129.26, 130.07, 130.99, 131.34, 132.26, 135.60, 135.80, 136.76, 144.71, 144.73, 147.95, 152.65, 155.07 (17 sp^2 carbon atoms), 159.15 (CO).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-amino-7,8,9-hexahydro-tetrazolo-[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (11)

To an ice-cold solution of compound **6b** (4.64 g, 10 mmol) in acetic acid (10 ml), a solution of sodium nitrite (1.04 g, 15 mmol) was added dropwise in the least amount of water in an ice bath at −5°C. The reaction mixture was allowed to stand overnight at room temperature, then it was poured into water (100 ml). The solid so-precipitated was filtered off and crystallized from ethanol to produce pale yellow powder; IR, cm^{-1}: 3420 (brs, NH), 3027 (CH aryl), 2940 (CH alkyl), 1678 (CO), 1634

(N=N), 1612 (C=N), 1554 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.66–1.70 (m, 2H, CH_2), 2.32–2.36 (t, 2H, CH_2), 2.79–2.96 (t, 2H, CH_2), 7.06–7.10 (d, 2H, phenyl), 7.34–7.36 (d, 2H, phenyl), 7.43–7.46 (2d, 4H, phenyl), 8.03 (s, 1H, methylenic proton), and 11.00 (brs, 1H, NH, D_2O exchangeable).

2-Amino-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]-quinolin-4-one (12)

To a well stirred solution, the appropriate tetrazolothienopyrimidine **11** (4.75 g, 10 mmol) in glacial acetic acid (50 ml) was added protion wise activated zinc dust (10.00 g) at room temperature over a period of 1 h. Stirring was continued for an additional 3 h. Thereafter, the reaction mixture was heated on a waterbath (80–90°C) for 3 h. The progress of reduction was monitored by TLC. After allowing the reaction mixture to cool to room temperature, it was poured into cold water (100 ml). The insoluble solid which separated was filtered, washed with water, and dried. The crude solid was extracted with hot benzene, and the solid obtained after the removel of benzene under reduced pressure was crystallized from dioxane; IR, cm^{-1}: 3332 (brs, NH_2), 3019 (CH aryl), 2937 (CH alkyl), 1693 (CO), 1621 (C=N), 1559 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.70–1.73 (m, 2H, CH_2), 2.37–2.40 (t, 2H, CH_2), 2.81–2.96 (t, 2H, CH_2), 7.12–7.15 (d, 2H, phenyl), 7.39–7.43 (d, 2H, phenyl), 7.44–7.48 (2d, 4H, phenyl), 8.01 (s, 1H, methylenic proton), and 9.55 (brs, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 21.80, 26.91, 26.95 (3C, 3CH_2), 109.58, 127.87, 127.91, 128.54, 129.27, 130.13, 130.89, 131.31, 132.35, 135.52, 135.78, 136.63, 144.68, 144.76, 147.93, 152.66, 155.09 (17 sp^2 carbon atoms), 160.19 (CO).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro-1,3-(substituted)-tria-zolo[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (14a–d)—General Procedure

A mixture from compound **4b** (4.66 g, 10 mmol) and the appropriate hydrazonoyl chlorides **13a–c** (10 mmol) was stirred under reflux in dry chloroform (30 ml) and 4 drops of triethylamine for 5 h. The solvent was evaporated under reduced pressure. The solid produced was washed three time with 30 ml methanol and crystallized from an appropriate solvent to produce **14a–c** in high yields.

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro-1,3-diphenyl-triazolo-[4′,3′:1,2]pyrimido[4,5-b]quinolin-5-one(14a)

The compound was obtained from **4b** and N-phenylbenzene-carbohydrazonoyl chloride **13a** (2.31 g, 10 mmol), as white crystals and crystallized from dioxane; IR, cm^{-1}: 3057 (CH aryl), 2927 (CH alkyl), 1707 (CO), 1672 (C=N), 1543 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.67–1.70 (m, 2H, CH_2), 2.36–2.39 (t, 2H, CH_2), 2.83–2.90 (t, 2H, CH_2), 7.08–7.11 (d, 2H, phenyl), 7.23–7.25 (m, 5H, phenyl), 7.38–7.43 (m, 7H, phenyl), 7.40–7.43 (2d, 4H, phenyl), and 8.05 (s, 1H, methylenic proton).

3-Acetyl-1,6-(4-dichlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro-triazolo[4′,3′-:1,2]pyrimido[4,5-b]quinolin-5-one (14b)

The compound was obtained from **4b** and 2-oxo-N-(4-chloro-phenyl) propane hydrazonoyl chloride **13b** (1.96 g, 10 mmol), as a white powder and crystallized from dimethlformamide; IR, cm^{-1}: 3079 (CH aryl), 2928 (CH alkyl), 1701 (CO), 1645 (C=N), 1586 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.71–1.73 (m, 2H, CH_2), 2.38–2.41 (t, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.80–2.88 (t, 2H, CH_2), 7.10–7.13 (d, 2H, phenyl), 7.21–7.24 (d, 2H, phenyl), 7.36–7.40 (m, 7H, phenyl), 7.42–7.45 (2d, 4H, phenyl), and 8.02 (s, 1H, methylenic proton). ^{13}C-NMR (DMSO-d_6) ppm: δ 21.93, 26.81, 26.88 (3C, $3CH_2$), 27.09 (CH_3), 107.58, 121.51, 122.03, 127.80, 127.88, 127.92, 127.97, 128.02, 128.19, 128.35, 128.59, 129.06, 129.19, 129.33, 131.35, 135.78, 136.63, 144.68, 152.66, 154.67, 155.09 (21 sp^2 carbon atoms), 160.19, 188.66 (2CO).

3-Acetyl-6-(4-chlorophenyl)-10-(4-chlorophenylmethylene)-1-(4-nitrophenyl)-7,8,9-hexa-hydrotriazolo[4′,3′:1,2] pyrimido[4,5-b]quinolin-5-one (14c)

The compound was obtained from **4b** and 2-oxo-N-(4-nitrophenyl) propane hydrazonoyl chloride **13c** (2.06 g, 10 mmol), as a white powder and crystallized from ethanol; IR, cm^{-1}: 3079 (CH aryl), 2928 (CH alkyl), 1701, 1687 (2CO), 1586 (C=N), 1542 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.70–1.73 (m, 2H, CH_2), 2.37–2.40 (t, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.81–2.87 (t, 2H, CH_2), 7.11–7.13 (d, 2H, phenyl), 7.22–7.25 (d, 2H, phenyl), 7.37–7.40 (m, 5H, phenyl), 7.41–7.44 (2d, 4H, phenyl), 7.56–7.59 (d, 2H, phenyl), and 8.11 (s, 1H, methylenic proton).

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-ethylcaboxylate-7,8,9-hexahydro-1-phenyl-triazolo[4′,3′:1,2]pyrimido[4,5-b]quinolin-5-one (14d)

The compound was obtained from **4b** and chloro-(phenyl hydrazono)ethylacetate **13d** (2.27 g, 10 mmol), as a white powder and crystallized from ethanol; IR, cm^{-1}: 3056 (CH aryl), 2951 (CH alkyl), 1755, 1667 (2CO), 1613 (C=N), 1568 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.31–1.34 (t, 3H, CH_3), 1.72–1.75 (t, 2H, CH_2), 2.39–2.44 (t, 2H, CH_2), 2.81–2.83 (t, 2H, CH_2), 4.52–4.58 (q, 2H, CH_2), 7.14–7.16 (d, 2H, phenyl), 7.18–7.38 (m, 3H, phenyl), 7.40–7.42 (d, 2H, phenyl), 7.45–7.48 (2d, 4H, phenyl), 7.52–7.54 (m, 2H, phenyl), and 8.27 (s, 1H, methylenic proton). ^{13}C-NMR (DMSO-d_6) ppm: δ 13.38, 21.93, 26.86, 27.88, 63.66 (4C, $3CH_2$+CH_3), 110.67, 121.45, 127.59, 127.86, 127.96, 128.70, 129.19, 129.39, 130.16, 131.02, 132.24, 132.73, 132.86, 135.61, 135.63, 135.97, 136.46, 136.96, 142.86, 151.92, 154.83, (21 sp^2 carbon atoms), 157.25, 165.34 (2CO).

2-(Arylmethylenehydrazone-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexa-hydropyrimido[4,5-*b*]quinolin-4-one (16a–d)—General Procedure

A mixture from compound **6b** (4.64 g, 10 mmol), the appropriate aromatic aldehyde (10 mmol) was stirred under reflux in glacial acetic acid (30 ml) for 20 min. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml), whereby a solid was filtered off and crystallized from appropriate solvent to produces **16a–d** in high yields.

2-(Phenylmethylenehydrazone-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexa-hydropyrimido[4,5-b]quinolin-4-one (16a)

The compound was obtained from the reaction of **6b** and benzaldehyde (1.06 g, 10 mmol), as yellow crystals and crystallized from dioxane; IR, cm^{-1}: 3366 (brs, NH), 3076 (CH aryl), 2935 (CH alkyl), 1694 (CO), 1653 (C=N), 1580 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.70 (t, 2H, CH_2), 2.29–2.33 (t, 2H, CH_2), 2.80–2.83 (t, 2H, CH_2), 7.17–7.20 (d, 2H, phenyl), 7.34–7.38 (m, 3H, phenyl), 7.40–7.43 (d, 4H, phenyl), 7.45–7.48 (2d, 4H, phenyl), 7.91–7.93 (m, 2H, phenyl), 8.09 (s, 1H, methylenic proton), 8.20 (s, 1H, methylenic proton), and 11.20 (brs, NH, D_2O exchangeable). The MS, [M^+], m/z 552 (11%).

2-(4-N,N-Dimethylaminophenylmethylenehydrazone)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (16b)

The compound was obtained from the reaction of **6b** and 4-chlorobenzaldehyde (1.40 g, 10 mmol), as pale yellow crystals and crystallized from ethanol; IR, cm^{-1}: 3410 (brs, NH), 3038 (CH aryl), 2968 (CH alkyl), 1696 (CO), 1619 (C=N), 1557 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.66–1.71 (t, 2H, CH_2), 2.30–2.33 (t, 2H, CH_2), 2.82–2.84 (t, 2H, CH_2), 3.00 (s, 6H, $2CH_3$), 7.19–7.22 (d, 2H, phenyl), 7.33–7.37 (d, 2H, phenyl), 7.41–7.45 (d, 4H, phenyl), 7.47–7.49 (d, 2H, phenyl), 7.91–7.93 (d, 2H, phenyl), 8.06 (s, 1H, methylenic proton), 8.23 (s, 1H, methylenic proton), and 11.25 (brs, NH, D_2O exchangeable)

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-(4-methoxyphenylmethylenehydrazone-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (16c)

The compound was obtained from the reaction of **6b** and 4-methoxybenzaldehyde (1.36 g, 10 m mol), as yellow powder, crystallized from ethanol; IR, cm^{-1}: 3379 (brs, NH), 3020 (CH aryl), 2939 (CH alkyl), 1697 (CO), 1636 (C=N), 1576 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.68 (t, 2H, CH_2), 2.30–2.32 (t, 2H, CH_2), 2.76–2.79 (t, 2H, CH_2), 3.80 (s, 3H, OCH_3), 6.94–7.15 (d, 2H, phenyl), 7.16–7.19 (d, 2H, phenyl), 7.42–7.46 (2d, 4H, phenyl), 7.77–7.80 (d, 4H, phenyl), 7.84–7.7.89 (d, 2H, phenyl), 8.10 (s, 1H, methylenic proton), 8.22 (s, 1H, methylenic proton), and 11.00 (brs, NH, D_2O exchangeable).^{13}C-NMR (DMSO-d_6) ppm: δ 22.14, 26.64, 27.09, 55.33 (4C, $3CH_2$+CH_3), 108.58, 114.19, 126.28, 127.28, 127.31, 127.67, 127.79, 128.31, 128.65, 128.95, 129.26, 129.36, 131.19, 131.76, 135.91, 135.93, 136.15, 145.99, 149.79, 150.09, 156.38, (21 sp^2 carbon atoms), 160.84 (CO). The MS, [M^+], m/z 582 (17%).

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-(2-thienylmethylenehydrazone-6,7,8-hexa-hydropyrimido[4,5-b]quinolin-4-one (16d)

The compound was obtained from the reaction of **6b** and 2-thiophene carboxaldehyde (1.12 g, 10 mmol), as brown powder, crystallized from ethanol; IR, cm^{-1}: 3345 (brs, NH), 3112 (CH aryl), 2976 (CH alkyl), 1689 (CO), 1624 (C=N), 1568 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.67–1.69 (t, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2), 2.80–2.82 (t, 2H, CH_2), 6.96–7.15 (d, 2H, phenyl), 7.19–7.22 (t, 1H, thienyl), 7.41–7.45 (2d, 4H, phenyl), 7.75–7.78 (d, 1H, thienyl), 7.98–7.8.01 (d, 1H, thienyl), 8.15 (s, 1H, methylenic proton), 8.27 (s, 1H, methylenic proton), and 11.25 (brs, NH, D_2O exchangeable).

3-Aryl-6-(4-chlorophenyl)-10-(4-chlorophenylmethylene)-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-*b*]quinolin-5-one (17a–d)—General Procedure

A mixture of compound (**16a–d**) (10 mmol), anhydrous sodium acetate (1.64 g, 20 mmol) and bromine (1.60 g, 10 mmol) was stirred under reflux in glacial acetic acid (30 ml) in a wasterbath at 80°C for long time (under TLC control). The reaction mixture was allowed to cool to room temperature, poured into water (100 ml), and the solid so-formed was collected by filtration and crystallized from appropriate solvent, to produced **17a–d**.

6-(4-Chlorophenyl)-10-(4-chlorophenylmethylene)-3-phenyl-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido [4,5-b]quinolin-5-one (17a)

The compound was obtained from the reaction of **16a**, as a yellow powder and crystallized from ethanol; IR, cm^{-1}: 3418 (brs, NH), 3046 (CH aryl), 2950 (CH alkyl), 1678 (CO), 1614 (C=N), 1557 (C=C).^{1}H-NMR (DMSO-d_6) ppm: δ 1.69–1.72 (t, 2H, CH_2), 2.30–2.34 (t, 2H, CH_2), 2.79–2.82 (t, 2H, CH_2), 7.18–7.21 (d, 2H, phenyl), 7.33–7.39 (m, 3H, phenyl), 7.41–7.45 (d, 4H, phenyl), 7.44–7.49 (d, 2H, phenyl), 7.63–7.7.67 (m, 2H, phenyl), 8.06 (s, 1H, methylenic proton), and 10.60 (brs, NH, D_2O exchangeable).

10-(4-Chlorophenylmethylene)-3-(N,N-dimethylaminophenyl)-6-(4-dichlorophenyl)-7,8,9-hexahydro[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-b]quinolin-5-one (17b)

The compound was obtained from the reaction of **16b**, as a yellow powder and crystallized from dioxane; IR, cm^{-1}: 3420 (brs, NH), 3036 (CH aryl), 2967 (CH alkyl), 1686 (CO), 1590 (C=N), 1564 (C=C).^{1}H-NMR (DMSO-d_6) ppm: δ 1.68–1.72 (t, 2H, CH_2), 2.31–2.33 (t, 2H, CH_2), 2.74–2.78 (t, 2H, CH_2), 6.98–7.16 (d, 2H, phenyl), 3.04 (s, 6H, $2CH_3$), 7.16–7.19 (d, 2H, phenyl), 7.43–7.47 (2d, 4H, phenyl), 7.74–7.78 (d, 4H, phenyl), 7.89–7.7.92 (d, 2H, phenyl), 8.09 (s, 1H, methylenic proton), and 10.40 (brs, NH, D_2O exchangeable).

10-(4-chlorophenylmethylene)-6-(4-chlorophenyl)-3-(4-methoxyphenyl)-7,8,9-hexahydro-[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-b]quinolin-5-one (17c)

The compound was obtained from the reaction of **16c**, as a yellow powder and crystallized from dimethylformamide; IR, cm^{-1}: 3400 (brs, NH), 3066 (CH aryl), 3925 (CH alkyl), 1711 (CO), 1655 (C=N), 1580 (C=C).^{1}H-NMR (DMSO-d_6) ppm: δ 1.68–1.71 (t, 2H, CH_2), 2.32–2.34

(t, 2H, CH_2), 2.69–2.74 (t, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.96–7.12 (d, 2H, phenyl), 7.14–7.18 (d, 2H, phenyl), 7.39–7.46 (2d, 4H, phenyl), 7.76–7.81 (d, 4H, phenyl), 7.83–7.7.88 (d, 2H, phenyl), 8.08 (s, 1H, methylenic proton), and 11.50 (brs, NH, D_2O exchangeable).^{13}C-NMR (DMSO-d_6) ppm: δ 22.19, 26.56, 27.18, 55.56 (4C, $3CH_2$+CH_3), 109.58, 126.08, 126.29, 127.18, 127.29, 127.59, 127.68, 128.30, 128.63, 128.87, 129.21, 129.54, 131.21, 131.56, 135.76, 135.83, 136.25, 145.56, 149.69, 150.19, 156.36, (21 sp^2 carbon atoms), 161.84 (CO).

10-(4-Chlorophenylmethylene)-6-(4-chlorophenyl)-3-(2-thienyl)-7,8,9-hexahydro[1,2,4]-triazolo[4′,3′:1,2]pyrimido[4,5-b]quinolin-5-one (17d)

The compound was obtained from the reaction of **16d**, as a brownish powder and crystallized from dioxane; IR, cm^{-1}: 3360 (brs, NH), 3087 (CH aryl), 2950 (CH alkyl), 1687 (CO), 1643 (C=N), 1576 (C=C).^{1}H-NMR (DMSO-d_6) ppm: δ 1.68–1.70 (t, 2H, CH_2), 2.30–2.33 (t, 2H, CH_2), 2.81–2.83 (t, 2H, CH_2), 6.94–7.10 (d, 2H, phenyl), 7.18–7.21 (t, 1H, thienyl), 7.42–7.45 (2d, 4H, phenyl), 7.76–7.78 (d, 1H, thienyl), 7.97–7.8.01 (d, 1H, thienyl), 8.12 (s, 1H, methylenic proton), and 11.10 (brs, NH, D_2O exchangeable).

11-(4-Chlorophenylmethylene)-7-(4-chlorophenyl)-3-(methyl/or phenyl)-8,9,10-hexa-hydro[1,2,4]triazino[4′,3′:1,2] pyrimido[4,5-*b*]quinolin-6-one (18a,b)—General Procedure

A mixture of compound **6b** (4.64 g, 10 mmol) with chloroacetone or phenacylbromide (10 mmol) was heated under reflux 5 h in 30 ml of dry xylene. The solid precipitated that separated upon cooling was filtered off and crystallized from appropriate solvent to produce **18a**,**b** in high yields.

11-(4-Chlorophenylmethylene)-7-(4-chlorophenyl)-3-methyl-8,9,10-hexahydro-[1,2,4]-triazino[4′,3′:1,2]pyrimido[4,5-b]quinolin-6-one (18a)

The compound was obtained from the reaction of **6b** and chloroacetone (0.93 g, 10 mmol), as a pale yellow powder and crystallized from dimethylform-amide; IR, cm^{-1}: 3430 (brs, NH), 3045 (CH aryl), 2985 (CH alkyl), 1694 (CO), 1657 (C=N), 1585 (C=C); ^{1}H-NMR (DMSO-d_6) ppm: δ 1.63–1.67 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.28–2.30 (t, 2H, CH_2) 2.79–2.80 (t, 2H, CH_2), 5.96 (s, 2H, CH_2), 7.11–7.15 (d, 2H, phenyl), 7.20–7.22 (d, 2H, phenyl), 7.29–7.33 (d, 2H, phenyl), 7.44–7.51 (d, 2H, phenyl), 8.11 (s, 1H, methylenic proton), and 11.54 (brs,

NH D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 15.10, 22.27, 26.73, 27.18, 64.86 (5C, $4CH_2$+ CH_3), 109.13, 126.81, 127.98, 128.12, 128.33, 129.04, 129.12, 129.42, 131.33, 131.80, 135.69, 136.02, 143.66, 146.09, 150.41, 156.46, 157.56 (21 sp^2 carbon atoms) and 160.05 (CO).

11-(4-Chlorophenylmethylene)-7-(4-chlorophenyl)-3-phenyl-8,9,10-hexahydro[1,2,4]triazino-[4′,3′:1,2]pyrimido[4,5-b]quinolin-6-one (18b)

The compound was obtained from the reaction of **6b** and phenacylbromide (1.99 g, 10 mmol), as brown powder and crystallized from dioxane; IR, cm^{-1}: 3410 (brs, NH), 3012 (CH aryl), 2930 (CH alkyl), 1687 (CO), 1632 (C=N), 1532 (C=C), ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.67 (m, 2H, CH_2), 2.27–2.30 (t, 2H, CH_2), 2.80–2.83 (t, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.11–7.14 (d, 2H, phenyl), 7.19–7.21 (m, 3H, phenyl), 7.31–7.34 (d, 2H, phenyl), 7.43–7.50 (2d, 4H, phenyl), 7.65–7.72 (m, 2H, phenyl), 8.13 (s, 1H, methylenic proton), and 11.34 (brs, NH D_2O exchangeable).

2-(3-Amino-5-hydroxy-4*H*-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chloro-phenyl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (19)

To a warmed ethanolic sodium ethoxide solution [prepared by dissolving (0.23 g, 10 m mol) sodium metal in absolute ethanol (30 ml)] was added each of compound **6b** (4.64 g, 10 mmol) and ethylcyanoacetate (1.13 g, 10 mmol). The mixture was stirred under reflux for 8 h, the reaction mixture was allowed to cool to room temperature, then poured into cold water (100 ml) and neutralized with acetic acid. The solid product so-precipitated was filtered off, washed with water, ethanol, dried and crystallized from dioxane as yellow powder; IR, cm^{-1}: 3340 (brs, NH), 3040 (CH aryl) 2934 (CH alkyl), 1690 (CO), 1620 (C=N), 1549 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.63–1.65 (m, 2H, CH_2), 2.28–2.30 (t, 2H, CH_2), 2.76–2.80 (t, 2H, CH_2), 3.52 (brs, OH), 6.02 (s, 1H, pyrazolyl proton), 7.10–7.13 (d, 2H, phenyl), 7.31–7.35 (d, 2H, phenyl), 7.43–7.46 (2d, 4H, phenyl), 8.04 (s, 1H, methylenic proton) and 10.31 (brs, NH D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 22.13, 26.69, 27.03 (3C, $3CH_2$), 106.41, 108.95, 127.86, 127.73, 128.09, 128.30, 128.36, 128.44, 129.17, 129.31, 129.42, 131.22, 131.32, 131.45, 135.85, 137.86, 149.88, 149.99, 155.56 (23 sp^2 carbon atoms) and 161.25 (CO).

5-(4-Chlorophenyl)-9-(4-chlorophenylmethylene)-2-(3-methyl-4-(un)substituted-5-pyrazol-1-yl)-6,7,8-hexahydropyrimido [4,5-*b*]quinolin-4-one (20a–c)—General Procedure

A mixture of compound **6b** (4.64 g, 10 mmol), (10 mmol) of either β-diketone in absolute ethanol (30 ml) was stirred under reflux for 5 h. The reaction mixture was allowed to cool to 0°C for 3 h, the deposited so-precipitate was filtered off, dried and crystallized from appropriate solvent to produce **20a–c** in high yields.

2-(3-Methyl-4-(un)substituted-5-substituted pyrazol-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (20a)

The compound was obtained from the reaction of **6b** and pentan-2,4-dione (1.00 g, 10 mmol), as a pale light crystals, crystallized from dioxane; IR, cm^{-1}: 3300 (brs, NH), 3042 (CH aryl), 2937 (CH alkyl), 1694 (CO), 1629 (C=N), 1548 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ ^{1}H-NMR (DMSO-d_6) ppm: δ 1.67–1.70 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.27–2.31 (t, 2H, CH_2), 2.74 (s, 3H, CH_3), 2.77–2.79 (t, 2H, CH_2), 6.20 (s, 1H, pyrazolyl proton), 7.16–7.18 (d, 2H, phenyl), 7.26–7.27 (d, 2H, phenyl), 7.40–7.46 (2d, 4H, phenyl), 8.09 (s, 1H, methylenic proton), and 10.90 (brs, NH D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 13,41, 19.02, 21.42, 25.67, 26.13 (5C, $3CH_2 + 2CH_3$), 110.41, 110.91, 111.00, 127.44, 127.51, 127.55, 128.56, 128.69, 130.09, 130.19, 131.38, 136.52, 138.88, 142.60, 146.02, 149.00, 149.46, 150.53, 156.80, (23 sp^2 carbon atoms) and 165.31 (CO).

2-(3-Methyl-4-(un)substituted-5-substituted pyrazol-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (20b)

The compound was obtained from the reaction of **6b** and 3-chloropentan-2,4-dione (1.34 g, 10 mmol), as a light white powder and crystallized from ethanol; IR, cm^{-1}: 3286 (brs, NH), 3080 (CH aryl), 2939 (CH alkyl), 1678 (CO), 1605 (C=N), 1543 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ ^{1}H-NMR (DMSO-d_6) ppm: δ 1.66–1.70 (m, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.26–2.31 (t, 2H, CH_2), 2.76 (s, 3H, CH_3), 2.79–2.82 (t, 2H, CH_2), 7.13–7.17 (d, 2H, phenyl), 7.28–7.32 (d, 2H, phenyl), 7.41–7.46 (2d, 4H, phenyl), 8.07 (s, 1H, methylenic proton), and 10.35 (brs, NH D_2O exchangeable).

2-(3-Methyl-4-(un)substituted-5-substituted pyrazol-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (20c)

The compound was obtained from the reaction of **6b** and 1,1,1-trifluro-2,4-pentandione (1.54 g, 10 mmol), as a pale light colorless crystals, crystallized from ethanol; IR, cm^{-1}: 3396 (brs, NH), 3060 (CH aryl), 2933 (CH alkyl), 1705 (CO), 1636 (C=N), 1556 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.70 (m, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.76–2.79 (t, 2H, CH_2), 6.43 (s, 1H, pyrazolyl proton), 7.17–7.19 (d, 2H, phenyl), 7.28–7.31 (d, 2H, phenyl), 7.39–7.44 (2d, 4H, phenyl), 8.15 (s, 1H, methylenic proton), and 11.50 (brs, NH D_2O exchangeable).

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-(ethylacetoacetatehydrazone)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (21)

A mixture of compound **6b** (4.64 g, 10 mmol) and ethylacetoacetate (1.30 g, 10 mmol) was refluxed in absolute ethanol (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature and the solid precipitate so-produced was filtered off and crystallized from ethanol as white powder; IR (KBr) cm^{-1}: 3371 (brs, NH), 3032 (CH aryl), 2922 (CH alkyl), 1735, 1688 (2CO), 1632 (C=N), 1565 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.22–1.29 (t, 3H, CH_3), 1.63–1.66 (m, 2H, CH_2), 2.03 (s, 3H, CH_3), 2.25–2.30 (t, 2H, CH_2) 2.76–2.80 (t, 2H, CH_2), 3.40 (s, 2H, CH_2), 4.09–4.14 (q, 2H, CH_2), 7.12–7.14 (d, 2H, phenyl), 7.18–7.22 (d, 2H, phenyl), 7.29–7.32 (d, 2H, phenyl), 7.41–7.46 (d, 2H, phenyl), 8.10 (s, 1H, methylenic proton), and 10.55 (brs, NH D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 13.98, 14.05, 22.06, 26.99, 43.92, 60.25 (6 sp3 carbon atoms), 111.20, 127.87, 127.89, 127.94, 128.17, 128.35, 128.39, 128.46, 129.18, 129.20, 129.27, 129.31, 129.36, 130.85, 153.19, 155.90, 157.71 (21 sp^2 carbon atoms) and 161.07, 169.58 (2CO).

5-(4-Chlorophenyl)-9-(4-chlorophenylmethylene)-2-(3-methyl-4*H*-pyrazol-5-one-1-yl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (22)

Method A

A solution of compound **6b** (4.64 g, 10 mmol) and ethylacetoacetate (1.30 g, 10 mmol) in sodium ethoxide solution (prepared by dissolving 0.23 g of sodium metal in 30 ml ethanol) was heated under reflux with stirring for 6 h. The reaction mixture was allowed to cool and poured

into cold water (100 ml) and neutralized by acetic acid, whereby a solid was precipitated, which was filtered off and crystallized from ethanol.

Method B

A solution of compound **21** (5.76 g, 10 mmol) was heated under reflux with sodium ethoxide solution 0.23g of sodium metal in 30 ml ethanol, for 3h. The reaction mixture was allowed to cool, poured into water (100 ml) and neutralized by acetic acid, the precipitate formed was filtered off and crystallized from ethanol; IR, cm^{-1}: 3380 (brs, NH), 3067 (CH aryl), 2938 (CH alkyl), 1693 (CO), 1623 (C=N), 1580 (C=C). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.65–1.67 (m, 2H, CH_2), 1.99 (s, 3H, CH_3), 2.24–2.30 (t, 2H, CH_2), 2.77–2.80 (t, 2H, CH_2), 4.53 (s, 2H, CH_2), 7.11–7.13 (d, 2H, phenyl), 7.19–7.23 (d, 2H, phenyl), 7.28–7.32 (d, 2H, phenyl), 7.42–7.48 (d, 2H, phenyl), 8.12 (s, 1H, methylenic proton), and 10.30 (brs, NH D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: δ 14.96, 22.20, 26.84, 27.21, 82.92 (5C, $4CH_2$+ CH_3), 110.90, 126.91, 127.64, 128.24, 128.58, 129.50, 131.16, 131.48, 131.83, 135.93, 136.14, 138.07, 149.55, 151.62, 153.59, 155.90, 157.71 (21 sp^2 carbon atoms) and 163.06, 167.49 (2CO).

4-(4-Arylmethylene)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-2-(3-methylpyrazol-5-one-1-yl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (23a–c)—General Procedure

A mixture from compound **22** (5.30 g, 10 mmol) and the appropriate aromatic aldehydes (10 mmol) was stirred under reflux in dioxane (30 ml) and 4 drops of pipridine for 5 h. The reaction mixture was allowed to cool and poured into water (100 ml). The solid produced was washed with 30 ml ethanol and crystallized form an appropriate solvent to produce **23a–c** in high yields.

2-(3-methyl-4-(4-phenylmethylene)-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (23a)

The compound was obtained from the reaction of **22** and benzaldehyde (1.06 g, 10 mmol), as a yellow powder, crystallized from dimethylformamide; IR, cm^{-1}: 3350 (brs, NH), 3038 (CH aryl), 2927 (CH alkyl), 1690, 1683 (2CO), 1620 (C=N), 1545 (C=C), ^{1}H-NMR (DMSO-d_6): δ 1.66–1.69 (m, 2H, CH_2), 2.09 (s, 3H, CH_3), 2.26–2.29 (t, 2H, CH_2), 2.80–2.84 (t, 2H, CH_2), 7.12–7.15 (d, 2H, phenyl), 7.18–7.20 (m, 3H, phenyl), 7.32–7.34 (d, 2H, phenyl), 7.42–7.48 (2d, 4H, phenyl), 7.59–7.62 (m, 2H,

phenyl), 8.09 (s, 1H, methylenic proton), 9.02 (s, 1H, methylenic proton), and 11.20 (brs, NH D_2O exchangeable).

2-(3-Methyl-4-(4-chlorophenylmethylene)-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (23b)

The compound was obtained from the reaction of **22** and 4-chlorobenzaldehyde (1.40 g, 10 mmol), as a yellow powder, crystallized from dimethylformamide; IR, cm^{-1}: 3380 (brs, NH), 3065 (CH aryl), 2939 (CH alkyl), 1688, 1682 (2CO), 1643 (C=N), 1550 (C=C), ^{1}H-NMR (DMSO-d_6): δ 1.65–1.68 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.28–2.32 (t, 2H, CH_2), 2.79–2.83 (t, 2H, CH_2), 7.13–7.15 (d, 2H, phenyl), 7.21–7.24 (d, 2H, phenyl), 7.31–7.34 (d, 2H, phenyl), 7.44–7.49 (2d, 4H, phenyl), 7.82–7.84 (d, 2H, phenyl), 8.11 (s, 1H, methylenic proton), 8.86 (s, 1H, methylenic proton), and 10.60 (brs, NH D_2O exchangeable).

2-(3-Methyl-4-(4-methoxyphenylmethylene)-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (23c)

The compound was obtained from the reaction of **22** and 4-methoxybenzaldehyde (1.36 g, 10 mmol), as a pale red powder, crystallized from dimethylformamide; IR, cm^{-1}: 3405 (brs, NH), 3029 (CH aryl), 2943 (CH alkyl), 1695, 1687 (2CO), 1654 (C=N), 1565 (C=C), ^{1}H-NMR (DMSO-d_6): δ 1.68–1.71 (m, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.28–2.31 (t, 2H, CH_2), 2.82–2.85 (t, 2H, CH_2), 3.98 (s, 3H, OCH_3), 7.09–7.14 (d, 2H, phenyl), 7.21–7.25 (d, 2H, phenyl), 7.33–7.36 (d, 2H, phenyl), 7.45–7.50 (2d, 4H, phenyl), 7.87–7.90 (d, 2H, phenyl), 8.07 (s, 1H, methylenic proton), 8.72 (s, 1H, methylenic proton), and 11.40 (brs, NH D_2O exchangeable).

9-(4-Chlorophenylmethylene)-5-(4-chlorophenyl)-2-(3-methyl-4-arylazo-pyrazol-5-one-1-yl)-6,7,8-hexahydropyrimido[4,5-*b*]quinolin-4-one (24b,c)—General Procedure

To an ice-cold solution of the appropriate aromatic amine (10 mmol) in concentrated hydrochloric acid (3 ml), was added dropwise a solution of sodium nitrite (1.03 g, 0.01 mole) dissolved in the least amount of water, in an ice bath at –5°C. This previously prepared diazonium salt was added dropwise to a mixture of **22** (5.30 g, 10 mmol) and anhydrous sodium acetate in ethanol. The reaction mixture was allowed to stand overnight at room temperature, then it was poured into water. The

formed solid was filtered off and washed with water. The product was recrystallized from dioxane to produce as **24b**,**c**.

2-(3-Methyl-4-(4-chlorophenylazo-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (24b)

The compound was obtained from the reaction of **22** and 4-chloroaniline (1.27 g, 10 mmol), as a brown powder, crystallized from dimethylformamide; IR, cm^{-1}: 3330 (brs, NH), 3019 (CH aryl), 2927 (CH alkyl), 1691, 1686 (2CO), 1643 (N=N), 1550 (C=C), ^{1}H-NMR (DMSO-d_6): δ 1.67–1.73 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.29–2.32 (t, 2H, CH_2), 2.82–2.85 (t, 2H, CH_2), 7.11–7.14 (d, 2H, phenyl), 7.23–7.27 (d, 2H, phenyl), 7.34–7.38 (d, 2H, phenyl), 7.42–7.46 (2d, 4H, phenyl), 7.81–7.84 (d, 2H, phenyl), 8.18 (s, 1H, methylenic proton), and 11.30 (brs, NH D_2O exchangeable).

2-(3-methyl-4-(4-Methoxyphenylazo-pyrazol-5-one-1-yl)-9-(4-chlorophenylmethylene)-5-(4-chlorophenyl)-6,7,8-hexahydropyrimido[4,5-b]quinolin-4-one (24c)

The compound was obtained from the reaction of **22** and 4-methoxyaniline (1.23 g, 10 mmol), as a brown powder, crystallized from dimethylformamide; IR, cm^{-1}: 3410 (brs, NH), 3047 (CH aryl), 2936 (CH alkyl), 1692, 1688 (2CO), 1655 (N=N), 1535 (C=C), ^{1}H-NMR (DMSO-d_6): δ 1.65–1.70 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.27–2.31 (t, 2H, CH_2), 2.80–2.84 (t, 2H, CH_2), 3.96 (s, 3H, OCH_3), 7.19–7.21 (d, 2H, phenyl), 7.24–7.27 (d, 2H, phenyl), 7.34–7.39 (d, 2H, phenyl), 7.46–7.50 (2d, 4H, phenyl), 7.83–7.85 (d, 2H, phenyl), 8.17 (s, 1H, methylenic proton), and 11.40 (brs, NH D_2O exchangeable).

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