3-Amino-8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno [2,3-d]pyrimidine: An Efficient Key Precursor for Novel Synthesis of Some Interesting Triazines and Triazepines as Potential Anti-Tumor Agents

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Abstract: A number of interesting heterocycles were prepared through interaction of the intermediate 3-amino-8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno-[2,3-d]pyrimidine (1) and reagents such as hydrazonyl halides 2 to furnish triazine derivatives 4a–l. Reaction of 1 with phenacyl bromide afforded compound 5. Moreover, the title compound 1 was subjected to condensation with active methylene compounds (ethyl acetoacetate and ethyl benzoylacetate) to give triazipinones 8a,b. The condensation with aromatic aldehydes afforded either the triazole derivatives 10a–d or Schiff base 11. In addition, the behaviour of compound 1 towards activated unsaturated compounds namely dimethyl acetylenedicarboxylate and ethoxymethylenemalonitrile was studied and it was found to furnish the triazine 13 and triazepine derivative 15, respectively. Combination of title compound 1 with chlorinated active methylene compounds delivered the triazine derivatives 18a–c. Reaction of 1 with chloroacetonitrile furnished compound 20. The structures of the products were elucidated based on their microanalyses and spectroscopic data. Finally, the antitumor activity of the new compounds 4a and 8a against human breast cell MCF-7 line and liver carcinoma cell line HepG2 were recorded.

Keywords: pyrimidotriazines; pyrimidotriazepinones; triazolopyrimidines; antitumor activity; hydrazonoyl halides
1. Introduction

The word tumor is commonly used as a synonym for a neoplasm [a solid or fluid-filled (cystic) lesion that may or may not be formed by an abnormal growth of neoplastic cells] that appears enlarged in size [1]. In modern medicine, the term tumor means a neoplasm that has formed a lump. While cancer is by definition malignant, a tumor can be benign, pre-malignant, or malignant, or can represent a lesion without any cancerous potential whatsoever. Development of novel drugs, and in particular new antitumour agents is a constantly growing need that concerns researchers throughout the World, consequently, as cancers continue to be an emerging problem. Numerous antitumor chemical drugs have been widely synthesized, including the chromenopyrimidines, which present interesting biological activities. The authors, who have contributed in the past to the exploration of this research topic, were interested in expanding their work by developing a facile synthesis of new derivatives and then test their antimicrobial, cytotoxicity activities [1–3], and in vitro antitubercular activity [4], in addition to antitumour activity. It was reported that pyrimidotriazines themselves posses biological activities with a wide range of applications [5–9]. The research done in this article could be regarded as an extension to our previous work [10] for constructing fused chromenopyrimidines heterocycles through reactions of the key compound 1 with a variety of reagents, especially hydrazonyl halides [11–14], which lead to interesting azoheterocyclic compounds.

2. Results and Discussion

2.1. Chemistry

The title compound 1 was prepared according to the procedure reported in literature [10], and it was proved to be highly reactive towards various reagents, resulting in the formation of a wide range of annulated chromenopyrimidine systems. With compound 1 in hand, a number of valuable heterocycles could be prepared. Firstly, the interaction between the aminopyrimidine 1 and hydrazonyl halides 2 in refluxing ethanol delivered the azotriazine derivatives 4a–l in good yields (Scheme 1). Structure assessment was based on their spectroscopic data. The IR spectra showed absorption bands at 3,470–3,410 (OH), 3,350–3,310 (NH) and at 1,593–1,573 cm$^{-1}$ (C=N), while the mass spectra revealed molecular ion peaks consistent with the proposed structures. The $^1$H-NMR spectra, for example for compound 4a, showed enrichment of the aromatic signals due to the additional aryl group, while two signals at 9.30 and 9.66 ppm for two D$_2$O exchangeable protons (NH, OH) also appeared. The spectral data presented here indicate collectively that such compounds 4a–l exist predominantly in the hydrazone tautomeric form 4A rather than 4B [15–20].

In order to prepare an authentic sample of compound 4a through an alternative route, the aminopyrimidine 1 was condensed with phenacyl bromide 6 in ethanol to afford the triazine derivative 5, whose structure was elucidated from its spectroscopic data. The mass spectrum showed a peak of m/z = 420 corresponding to the M.F. C$_{26}$H$_{20}$N$_4$O$_2$, while the $^1$H-NMR displayed a signal at 4.23 ppm attributable to a CH$_2$ group. When compound 5 was coupled to phenylidiazonium chloride, unfortunately, it failed to yield the desired compound 4a because the diazonium salt coupled preferentially to the more reactive phenolic ring to give compound 6 (Scheme 1). The structure
of compound 6 was established by its spectroscopic data compatible with the proposed structure (see Experimental).

Scheme 1. Synthesis of 5-arylatrazine derivatives 4a–l.

An even more convenient access for constructing triazepines based on the aminopyrimidine compound 1 was established using readily available active methylene reagents such as ethyl acetoacetate (7a) and ethyl benzyloacetate (7b) to convert the pyrimidin-8-ol 1 into the triazepinone derivatives 8a,b instead of 9a,b [18-25] (Scheme 2). The mass spectra of these compounds revealed peaks at characteristic m/z values corresponding to their molecular weights. In the 1H-NMR spectra, for example R= CH₃, a signal at 4.06 ppm integrating for two protons (CH₂), and only one downfield characteristic signal (D₂O exchangeable) corresponding to OH proton at 9.72 ppm, excluded the structures 9a,b as reaction products since they lack a CH₂ group and contain an NH function (no characteristic signal in 1H-NMR).
In continuation to our previous work on the title compound 1 and studying its behaviour towards aromatic aldehydes via condensation in basic medium (piperidine), the aromatic aldehydes were reacted in a different manner, all of which afforded the triazole derivatives 10, except salicyaldehyde that just gives the ordinary Schiff base 11 (Scheme 3).

It worth mention that when an EWG (Cl, NO₂) is in o-, m- or p-positions with respect to the aldehydic function, a condensation followed by cyclization occurred to give the triazoles 10, otherwise, the Schiff bases were produced, which is no doubt due to the + and –M effect of these substituents. The mass and ¹H-NMR spectra were sufficient to indicate the correct structures, for example the mass spectrum for the reaction product obtained from reaction with p-chlorobenzaldehyde.
showed a peak at $m/z = 440$ consistent with structure 10a (the Schiff base should give $m/z = 442$). The $^1$H-NMR spectrum revealed one downfield CH=N-signal at 9.67 ppm (the Schiff base should show two downfield signals for CH=N-protons). On the other hand, reaction of 1 with salicylaldehyde afforded the Schiff base 11, based on its spectroscopic data; the mass spectrum showed a molecular ion peak at 424 (triazole 10 should give 422). Also, the $^1$H-NMR displayed two downfield signals at 8.34, 8.36 ppm corresponding to CH=N and 2-H protons, in addition to two D$_2$O exchangeable signals (NH, OH) at 5.86 and 8.62 ppm.

Consequently, we aimed to investigate further the behaviour of the aminopyrimidine 1 towards activated unsaturated compounds such as dimethyl acetylenedicarboxylate and ethoxymethylene malonitrile. The reactions were performed without catalyst in ethanol. It was found that this reaction proceeds in a simple manner through addition to acetylenic function or the olefinic double bond followed by loss of methanol or ethanol to furnish the expected triazine derivative 13 or the triazepine derivative 15 respectively (Scheme 4).

**Scheme 4.** Reaction of title compound 1 with activated unsaturated compounds.

Confirmatory evidence for the structure assignment for compound 13 was provided by spectroscopic data. The IR spectrum revealed absorption bands at 1665, 1712 cm$^{-1}$ characteristic for C=O, and COOMe; in the $^1$H-NMR spectrum, two signals at 2.17, 3.48 ppm assignable to two CH$_3$ groups (CH$_3$, OCH$_3$) a more characteristic signal at 5.60 ppm integrating for one proton (=CHCOOMe).

The spectroscopic data for compound 15 were in a good agreement with this proposed structure, IR should show no great difference, while the electron ionization mass spectrum was consistent with the expected molecular mass for the proposed structure ($m/z = 326$). Furthermore, the $^1$H-NMR spectrum displayed a new signal at 8.57 ppm attributable to H5 in the trizepine ring.
Finally, an additional pathway for synthesis of substituted triazine derivatives 18a–c was achieved through reaction of the title compound 1 with α-halo compounds (namely ethyl α-chloroacetoacetate, α-chloroacetylacetone and α-chloroacetoacetanilide) in refluxing ethanol containing triethylamine (Scheme 5).

Scheme 5. Synthesis of triazine derivatives 18a–c and 20.

The reaction proceeds through nucleophilic substitution followed by cyclocondensation. The structural assignment of these compounds was based on spectral evidence and microanalyses. The mass spectra of these products 18a–c showed the molecular ion peaks at the expected m/z values. In their IR spectra, the appearance of absorption bands in the range 1712–1660 cm\(^{-1}\) confirmed the presence of a C=O group. The \(^1\)H-NMR spectrum, for example for compound 18a, revealed two signals at 2.21, 2.23 ppm each integrating for three protons (CH\(_3\)-phenolic ring, CH\(_3\)-triazine ring) in addition to the characteristic ethoxy triplet-quartet pattern; a new characteristic signal at 5.50 ppm assignable for H5 in triazine ring. In a similar manner, alkylation of the imino function of compound 1 with chloroacetonitrile followed by \textit{in situ} cyclization through the addition of the amino group to the cyano function delivered the aminotriazine derivative 20 (Scheme 5).

2.2. Antitumor Screening Test

The cytotoxicity of compounds 4a and 8a was evaluated against two cell lines representing two common forms of human cancer i.e. human hepatocellular carcinoma cell line (HepG2) and human breast adenocarcinoma cell line (MCF-7). For comparison purposes, the cytotoxicity of doxorubicin, a standard antitumor drug, was evaluated under the same conditions (IC\(_{50}\) value of doxorubicin = 0.59 ± 0.04 and 0.72 ± 0.08 µg/mL, respectively). The analysis of the data obtained indicated that the IC\(_{50}\) values (dose of the compound which causes a 50% reduction of survival values) for such compounds against human breast cell MCF-7 line are 5.36 ± 0.12 and 6.71 ± 0.09 µg/mL, respectively (Figure 1), but against
liver carcinoma cell line HepG2 they are 9.94 ± 0.15 and 6.93 ± 0.08 µg/mL, respectively (Figure 2). All values were calculated from dose-response curve done in triplicate for each compound. Values were given ± standard deviation. The value of IC50 indicated that:

(1) Generally, both the tested compounds tended to be more active cytotoxic agents against human breast cell MCF-7 line, than HepG2 cell line;
(2) Compound 4a is a more active cytotoxic agent against human breast cell MCF-7 line;
(3) Compound 8a is a more active cytotoxic agent against human hepatocellular carcinoma cell line HepG2.

**Figure 1.** Effect of concentration of compound 4a and 8a on MCF-7 cell.

**Figure 2.** Effect of concentration of compound 4a and 8a on HepG2 cell.
3. Experimental

3.1. Chemistry

3.1.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in a Pye-Unicam SP300 instrument in potassium bromide discs. 1H-NMR spectra were recorded in a Varian Mercury VXR-300 spectrometer at 300 MHz in DMSO-\textsubscript{d6} and the chemical shifts were related to TMS as standard solvent. Mass spectra were recorded in a GCMS-QP 1000 EX Shimadzu spectrometer, the ionizing voltage was 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt. Antitumor activity was evaluated by the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt.

3-Amino-8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3\textsubscript{H}-chromeno[2,3-d]pyrimidine (1) [10] and hydrazonoyl halides 2 [26,27] were prepared as reported in the literature.

3.1.2. Synthesis of 10-Hydroxy-3-substituted-12-methyl-13-phenyl-2-(2-substituted phenyl-hydrazono)-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazines 4a–l

**General procedure:** A mixture of 3-amino-8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3\textsubscript{H}-chromeno[2,3-d] pyrimidine (1, 0.32 g, 1 mmol) and the appropriate hydrazonoyl halide 2 (1 mmol) in ethanol (20 mL) was refluxed for 2 h (monitored by TLC), then allowed to cool and the solid formed was filtered off, washed with ethanol, dried and recrystallized from DMF to give 4a–l.

\textit{10-Hydroxy-3,12-dimethyl-13-phenyl-2-(2-phenylhydrazono)-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4a).} Yield 71%; reddish-brown solid; mp. 334 °C; IR (KBr): \(\nu\) 1630 (C=N), 3427 (br, OH, NH) cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): \(\delta\text{H}\) 2.14 (3H, s, 12-CH\textsubscript{3}), 2.16 (3H, s, 3-CH\textsubscript{3}), 5.40 (1H, s, 13-H), 6.45 (1H, s, 9-H), 6.52 (1H, s, 11-H), 6.75–7.45 (10H, m, Ar-H), 8.39 (1H, s, Ar-H), 9.30 (1H, br s, NH), 9.66 (1H, s, OH); MS \(m/z\) (%): 463 (M\textsuperscript{+} + 1, 38), 462 (M\textsuperscript{+}, 100), 385 (23), 192 (24), 77 (33). Anal. Calcd for C\textsubscript{27}H\textsubscript{22}N\textsubscript{6}O\textsubscript{2} (462.18): C, 70.12; H, 4.79; N, 18.17. Found C, 70.10; H, 4.65; N, 18.03%.

\textit{10-Hydroxy-3,12-dimethyl-13-phenyl-2-[2-(p-tolyl)hydrazono]-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4b).} Yield 74%; reddish-brown solid; mp. 345 °C; IR (KBr): \(\nu\) 1639 (C=N), 3421 (br, OH, NH) cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): \(\delta\text{H}\) 2.18 (3H, s, 12-CH\textsubscript{3}), 2.19 (3H, s, p-toly-CH\textsubscript{3}), 2.20 (3H, s, 3-CH\textsubscript{3}), 5.44 (1H, s, 13-H), 6.48 (1H, s, 9-H), 6.56 (1H, s, 11-H), 6.82–7.55 (9H, m, Ar-H), 8.42 (1H, s, 6-H), 9.37 (1H, br s, NH), 9.72 (1H, s, OH); MS \(m/z\) (%): 477 (M\textsuperscript{+} + 1, 34), 476 (M\textsuperscript{+}, 100), 399 (14), 253 (18), 200 (22), 77 (28). Anal. Calcd for C\textsubscript{28}H\textsubscript{24}N\textsubscript{6}O\textsubscript{2} (476.20): C, 70.57; H, 5.08; N, 17.64. Found C, 70.51; H, 5.11; N, 17.34%.

\textit{2-[2-(4-Chlorophenyl)hydrazono]-10-Hydroxy-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4c).} Yield 76%; reddish-brown solid; mp. 352 °C; IR (KBr): \(\nu\) 1639 (C=N), 3448 (br, OH,NH) cm\textsuperscript{-1}; \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): \(\delta\text{H}\) 2.19 (3H, s, 12-CH\textsubscript{3}), 2.21 (3H, s, p-toly-CH\textsubscript{3}), 2.20 (3H, s, 3-CH\textsubscript{3}), 5.42 (1H, s, 13-H), 6.49 (1H, s, 9-H), 6.58 (1H, s, 11-H), 6.88–7.63 (9H, m, Ar-H), 8.40 (1H, s, 6-H), 9.39 (1H, br s, NH), 9.75 (1H, s, OH); MS \(m/z\) (%): 498 (M\textsuperscript{+} + 2, 36), 497 (M\textsuperscript{+} + 1, 23), 496 (M\textsuperscript{+}, 100), 462 (M\textsuperscript{+} + 1, 38), 460 (M\textsuperscript{+}, 100), 385 (23), 192 (24), 77 (33). Anal. Calcd for C\textsubscript{28}H\textsubscript{24}N\textsubscript{6}O\textsubscript{2} (476.20): C, 70.57; H, 5.08; N, 17.64. Found C, 70.51; H, 5.11; N, 17.34%.
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428 (27), 253 (18), 209 (46), 77 (60), 55 (73). Anal. Calcd for C_{27}H_{21}ClN_6O_2 (496.14): C, 65.26; H, 4.26; N, 16.91. Found C, 65.10; H, 4.34; N, 16.69%.

10-Hydroxy-3,12-dimethyl-2-[2-(4-nitrophenyl)hydrazono]-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4d). Yield 76%; dark red solid; mp. 358 °C; IR (KBr): ν 1639 (C=N), 3440 (br, OH, NH) cm\(^{-1}\); \(^1\)H-NMR (DMSO-\(d_6\)): δH 2.20 (3H, s, 12-CH\(_3\)), 2.21 (3H, s, 3-CH\(_3\)), 5.48 (1H, s, 13-H), 6.48 (1H, s, 9-H), 6.60 (1H, s, 11-H), 6.89–7.77 (9H, m, Ar-H), 8.43 (1H, s, 6-H), 9.42 (1H, br s, NH), 9.77 (1H, s, OH); MS m/z (%): 508 (M\(^+\) + 1, 17), 507 (M\(^+\), 46), 429 (20), 294 (37), 253 (50), 77 (44), 55 (100). Anal. Calcd for C_{27}H_{21}N_7O_4 (507.17): C, 63.90; H, 4.17; N, 19.32. Found C, 63.76; H, 4.02; N, 19.12%.

2-[2-(4-Bromophenyl)hydrazono]-10-Hydroxy-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4e). Yield 71%; dark reddish-brown solid; mp. 358 °C; IR (KBr): ν 1633 (C=N), 3452 (br, OH, NH) cm\(^{-1}\); 1H-NMR (DMSO-\(d_6\)): δH 2.18 (3H, s, 12-CH\(_3\)), 2.20 (3H, s, 3-CH\(_3\)), 5.43 (1H, s, 13-H), 6.51 (1H, s, 9-H), 6.60 (1H, s, 11-H), 6.90–7.69 (9H, m, Ar-H), 8.41 (1H, s, 6-H), 9.38 (1H, br s, NH), 9.69 (1H, s, OH); MS m/z (%): 542 (M\(^+\) + 2, 93), 541 (M\(^+\) + 1, 71), 540 (M\(^+\)), 100), 463 (13), 253 (25), 90 (40), 77 (9). Anal. Calcd for C_{27}H_{21}BrN_6O_2 (540.09): C, 59.90; H, 3.91; N, 15.52. Found C, 59.70; H, 3.86; N, 15.37%.

10-Hydroxy-2-[2-(4-methoxyphenyl)hydrazono]-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4f). Yield 74%; dark red solid; mp. 320 °C; IR (KBr): ν 1638 (C=N), 3412 (br, OH and NH) cm\(^{-1}\); \(^1\)H-NMR (DMSO-\(d_6\)): δH 2.12 (3H, s, 12-CH\(_3\)), 2.15 (3H, s, 3-CH\(_3\)), 3.71 (3H, s, OCH\(_3\)), 5.37 (1H, s, 13-H), 6.45 (1H, s, 9-H), 6.51 (1H, s, 11-H), 6.86–7.44 (9H, m, Ar-H), 8.35 (1H, s, 6-H), 9.14 (1H, br s, NH), 9.65 (1H, s, OH); MS m/z (%): 493 (M\(^+\) + 1, 33), 492 (M\(^+\)), 100), 415 (10), 253 (15), 122 (31), 77 (22). Anal. Calcd for C_{28}H_{24}N_6O_3 (492.19): C, 68.28; H, 4.91; N, 17.06. Found C, 68.11; H, 4.78; N, 16.89%.

10-Hydroxy-12-methyl-3,13-diphenyl-2-(2-phenylhydrazono)-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4g). Yield 70%; orange solid; mp. 316 °C; IR (KBr): ν 1637 (C=N), 3438 (br, OH, NH) cm\(^{-1}\); \(^1\)H-NMR (DMSO-\(d_6\)): δH 2.19 (3H, s, 12-CH\(_3\)), 2.15 (3H, s, 3-CH\(_3\)), 2.57 (3H, s, p-tolyl-CH\(_3\)), 6.54 (1H, s, 13-H), 6.47 (1H, s, 9-H), 6.51 (1H, s, 11-H), 6.73–7.88 (16H, m, Ar-H), 8.47 (1H, s, 6-H), 9.48 (1H, br s, NH), 9.74 (1H, s, OH); MS m/z (%): 524 (M\(^+\) + 16), 384 (12), 228 (100), 77 (20). Anal. Calcd for C_{32}H_{24}N_6O_2 (524.20): C, 73.27; H, 4.61; N, 16.02. Found C, 73.12; H, 4.45; N, 15.22%.

10-Hydroxy-12-methyl-3,13-diphenyl-2-[2(p-tolyl)hydrazono]-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4h). Yield 74%; dark brown solid; mp. 312 °C; IR (KBr): ν 1628 (C=N), 3427 (br, OH and NH) cm\(^{-1}\); \(^1\)H-NMR (DMSO-\(d_6\)): δH 2.18 (3H, s, 12-CH\(_3\)), 2.50 (3H, s, p-tolyl-CH\(_3\)), 5.44 (1H, s, 13-H), 6.47 (1H, s, 9-H), 6.54 (1H, s, 11-H), 6.76–7.87 (14H, m, Ar-H), 8.42 (1H, s, 6-H), 9.44 (1H, br s, NH), 9.64 (1H, s, OH); MS m/z (%): 540 (M\(^+\) + 2, 9), 539 (M\(^+\) + 1, 42), 538 (M\(^+\)), 100), 316 (10), 238 (17), 77 (27). Anal. Calcd for C_{33}H_{26}N_6O_2 (538.21): C, 73.59; H, 4.87; N, 15.60. Found C, 73.59; H, 4.87; N, 15.60%.
2-[2-(4-Chlorophenyl)hydrazono]-10-Hydroxy-12-methyl-3,13-diphenyl-2H,13H-chromeno-[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4i). Yield 72%; dark brown solid; mp. 330 °C; IR (KBr): ν 1643 (C=N), 3444 (br, OH and NH) cm$^{-1}$; $^{1}H$-NMR (DMSO-$d_{6}$): δ$_{H}$ 2.15 (3H, s, 12-CH$_{3}$), 5.43 (1H, s, 13-H), 6.40 (1H, s, 9-H), 6.51 (1H, s, 11-H), 6.72–7.98 (14H, m, Ar-H), 8.43 (1H, s, 6-H), 9.45 (1H, br s, NH), 9.70 (1H, s, OH); MS m/z (%): 559 (M$^{+}$ + 1, 9), 558 (M$^{+}$, 21), 391 (12), 201 (21), 105 (47), 77 (47), 55 (100). Anal. Calcd for C$_{32}$H$_{23}$ClN$_{6}$O$_{2}$ (558.16): C, 68.75; H, 4.15; N, 15.03. Found C, 68.73; H, 4.10; N, 15.00%.

2-[2-(3-Bromophenyl)hydrazono]-10-Hydroxy-12-methyl-3,13-diphenyl-2H,13H-chromeno-[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4j). Yield 70%; dark brown solid; mp. 180 °C; IR (KBr): ν 1643 (C=N), 3413 (br, OH and NH) cm$^{-1}$; $^{1}H$-NMR (DMSO-$d_{6}$): δ$_{H}$ 2.17 (3H, s, 12-CH$_{3}$), 5.46 (1H, s, 13-H), 6.48 (1H, s, 9-H), 6.56 (1H, s, 11-H), 6.69–7.90 (14H, m, Ar-H), 8.47 (1H, br s, NH), 9.50 (1H, s, OH); MS m/z (%): 604 (M$^{+}$ + 2, 3), 603 (M$^{+}$ + 1, 4), 602 (M$^{+}$, 3), 503 (4), 471 (5), 305 (15), 228 (88), 105 (100), 77 (79). Anal. Calcd for C$_{32}$H$_{23}$BrN$_{6}$O$_{2}$ (602.11): C, 63.69; H, 3.84; N, 13.93. Found C, 63.57; H, 3.75; N, 13.68%.

Ethyl4-[10-hydroxy-12-methyl-3,13-diphenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazin-2-ylidene)hydrazinyl]benzoate (4k). Yield 70%; dark brown solid; mp. 352 °C; IR (KBr): ν 1639 (C=N), 1715 (C=O), 3420 (br, OH and NH) cm$^{-1}$; $^{1}H$-NMR (DMSO-$d_{6}$): δ$_{H}$ 1.34 (3H, t, CH$_{3}$), 2.21 (3H, s, 12-CH$_{3}$), 4.51 (2H, q, CH$_{2}$), 5.51 (1H, s, 13-H), 6.52 (1H, s, 9-H), 6.58 (1H, s, 11-H), 6.70–7.92 (14H, m, Ar-H), 8.40 (1H, s, 6-H), 9.51 (1H, br s, NH), 9.70 (1H, s, OH); MS m/z (%): 597 (M$^{+}$ + 1, 13), 596 (M$^{+}$, 24), 567 (100), 524 (39), 432 (18), 228 (49), 105 (100), 77 (79). Anal. Calcd for C$_{35}$H$_{28}$N$_{6}$O$_{4}$ (596.22): C, 70.46; H, 4.73; N, 14.09. Found C, 70.34; H, 4.45; N, 13.97%.

10-Hydroxy-12-methyl-13-phenyl-3-[2-(2-phenylhydrazono)-(thiophen-2-yl)]-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (4l). Yield 76%; dark red solid; mp. 228 °C; IR (KBr): ν 1647 (C=N), 3387 (br, OH, NH) cm$^{-1}$; $^{1}H$-NMR (DMSO-$d_{6}$): δ$_{H}$ 2.19 (3H, s, 12-CH$_{3}$), 5.46 (1H, s, 13-H), 6.48 (1H, s, 9-H), 6.56 (1H, s, 11-H), 6.68–7.96 (13H, m, Ar-H), 8.49 (1H, s, 6-H), 9.50 (1H, br s, NH), 9.71 (1H, s, OH); MS m/z (%): 597 (M$^{+}$ + 1, 13), 596 (M$^{+}$, 24), 567 (100), 524 (39), 432 (18), 228 (49), 103 (78), 77 (79). Anal. Calcd for C$_{30}$H$_{22}$N$_{6}$O$_{2}$S (530.15): C, 67.91; H, 4.18; N, 15.84. Found C, 67.91; H, 4.18; N, 15.84%.

3.1.3. Synthesis of 10-hydroxy-12-methyl-9-phenylazo-2,13-diphenyl-13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine 6

Synthesis of 10-hydroxy-12-methyl-2,13-diphenyl-13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (5). A mixture of 1 (0.320 g, 1 mmol) and phenacyl bromide (0.198 g, 1 mmol) in absolute ethanol (30 mL) was refluxed for 2 h (monitored by TLC). The product started to separate out during the course of reaction. The crystalline solid was filtered, washed with water, dried and recrystallized from dioxane to give compound 5 in 76% yield as yellow solid; mp. 230 °C; IR (KBr): ν 1632 (C=N), 3425 (OH) cm$^{-1}$; $^{1}H$-NMR (DMSO-$d_{6}$): δ$_{H}$ 2.14 (3H, s, 12-CH$_{3}$), 4.23 (2H, s, CH$_{2}$), 5.55 (1H, s, 13-H), 6.52 (1H, s, 9-H), 6.54 (1H, s, 11-H), 7.18–7.38 (10H, m, Ar-H), 8.63 (1H, s, 6-H), 9.82 (1H, s, OH); MS m/z (%): 421 (M$^{+}$ + 1, 1), 420 (M$^{+}$, 2), 329 (14), 305 (16), 253 (21), 228 (100), 201 (23), 105 (15), 77 (79). Anal. Calcd for C$_{30}$H$_{22}$N$_{6}$O$_{2}$S (530.15): C, 67.91; H, 4.18; N, 15.84. Found C, 67.91; H, 4.18; N, 15.84%.
77 (26); Anal. Calcd for C_{26}H_{20}N_{4}O_{2} (420.47): C, 74.27; H, 4.79; N, 13.32. Found C, 74.14; H, 4.87; N, 13.35%.

**Coupling of 5 with benzenediazonium chloride.** To a solution of 5 (0.421 g, 1 mmol) in ethanol (20 mL) was added sodium acetate trihydrate (0.138 g, 1 mmol), and the mixture was cooled to 0–5 °C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride (1 mmol) [prepared by diazotizing aniline] dissolved in hydrochloric acid (6 M, 1 mL) with a solution of sodium nitrite (0.07 g, 1 mmol) in water (2 mL). After complete addition of the diazonium salt, the reaction mixture was stirred for a further 30 min in an ice bath. The solid that separated was filtered off, washed with water and finally recrystallized from ethanol to give product 6. Yield 78%; orange solid; mp. 298 °C; IR (KBr): ν 1634 (C=N), 3466 (br, OH and NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ H 2.16 (3H, s, 12-CH₃), 4.24 (2H, s, CH₂), 5.56 (1H, s, 13-H), 6.54 (1H, s, 11-H), 7.03–7.41 (15H, m, Ar-H), 8.63 (1H, s, 6-H), 9.88 (1H, s, OH); MS m/z (%): 524 (M⁺, 23), 305 (100), 228 (87), 77 (64). Anal. Calcd for C_{32}H_{24}N_{6}O_{2} (524.20): C, 73.27; H, 4.61; N, 16.02. Found C, 73.10; H, 4.65; N, 15.12%.

### 3.1.4. Synthesis of 4-substituted-11-hydroxy-13-methyl-14-phenyl-3H,14H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazepin-2(3H)-ones 8a,b.

A mixture of compound 1 (0.32 g, 1 mmol) and ethyl acetoacetate or ethyl benzoyleacetate (1.5 mmol) was heated under reflux for 2 h. After cooling, the solid precipitated was collected and crystallized from dioxane to give 8a,b, respectively.

**11-Hydroxy-4,13-dimethyl-14-phenyl-3H,14H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazepin-2(3H)-one (8a).** Yield 74%; yellow solid; mp. 189 °C; IR (KBr): ν 1635 (C=N), 1720 (CO), 3251 (NH), 3406 (OH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ H 2.07 (3H, s, 13-CH₃), 2.17 (3H, s, 12-CH₃), 4.06 (2H, s, CH₂), 5.57 (1H, s, 14-H), 6.50 (1H, s, 10-H), 6.60 (1H, s, 12-H), 7.14–7.29 (5H, m, Ar-H), 9.50 (1H, s, 7-H), 9.72 (1H, s, OH); MS m/z (%): 388 (M⁺ + 2, 1), 387 (M⁺ + 1, 5), 386 (M⁺, 16), 309 (100), 266 (19) 77 (11), 55. Anal. Calcd for C_{22}H_{18}N_{4}O_{3} (386.14): C, 68.38; H, 4.70; N, 14.50. Found C, 68.32; H, 4.65; N, 14.36%.

**11-Hydroxy-13-methyl-4,14-diphenyl-3H,14H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazepin-2(3H)-one (8b).** Yield 74%; yellow solid; mp. 214 °C; IR (KBr): ν 1632 (C=N), 1702 (CO), 3416 (OH) cm⁻¹; ¹H-NMR (DMSO-d₆): δ H 2.10 (3H, s, 13-CH₃), 4.15 (2H, s, CH₂), 5.62 (1H, s, 14-H), 6.55 (1H, s, 10-H), 6.68 (1H, s, 12-H), 7.06–7.67 (10H, m, Ar-H), 9.52 (1H, s, 7-H), 9.82 (1H, s, OH); MS m/z (%): 449 (M⁺ + 1, 8), 448 (M⁺, 20), 371 (100), 266 (24), 105 (76), 77 (75). Anal. Calcd for C_{27}H_{20}N_{4}O_{3} (448.15): C, 72.31; H, 4.49; N, 12.49. Found C, 72.18; H, 4.34; N, 12.29%.

### 3.1.5. Reaction of N-aminopyrimidine 1 with Aromatic Aldehydes

**General procedure:** An appropriate aromatic aldehyde (1 mmol.) was added to a solution of the N-aminopyrimidine 1 (0.32 g, 1 mmol) in absolute ethanol (15 mL) containing a few drops of piperidine, the resulting mixture refluxed for 3 h. The solids formed after cooling were collected by filtration, washed with ether and crystallized from DMF.
9-Hydroxy-11-methyl-12-phenyl-2-(4-chlorophenyl)-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (10a). Yield 76%; yellow solid; mp. 270 °C; IR (KBr): ν 1639 (C=N), 3441 (br, OH) cm⁻¹; ¹H-NMR (DMSO-d₆): δH 2.20 (3H, s, 11-CH₃), 6.01 (1H, s, 12-CH), 5.86 (1H, s, NH), 6.47 (1H, s, 8-H), 6.55 (1H, s, 10-H), 7.08–8.40 (9H, m, Ar-H), 9.67 (1H, s, 5-H), 11.36 (1H, s, OH); MS m/z (%): 440 (M⁺, 2), 366 (12), 305 (100), 228 (69), 201 (33), 138(73), 77(52). Anal. Calcd for C₂₅H₁₇ClN₄O₂S (440.10): C, 68.11; H, 3.89; N, 12.71. Found C, 68.01; H, 3.67; N, 12.56%.

2-(2-Chlorophenyl)-9-hydroxy-11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (10b). Yield 74%; yellow solid; mp. 252 °C; IR (KBr): ν 1636 (C=N), 3438 (OH) cm⁻¹; ¹H-NMR (DMSO-d₆): δH 2.21 (3H, s, 11-CH₃), 6.02 (1H, s, 12-CH), 6.48 (1H, s, 8-H), 6.52 (1H, s, 10-H), 7.05–8.33 (9H, m, Ar-H), 9.60 (1H, s, 5-H), 11.03 (1H, s, OH); MS m/z (%): 440 (M⁺, 12), 305 (66), 228 (100), 138(58), 77(47). Anal. Calcd for C₂₅H₁₇ClN₄O₂S (440.10): C, 68.11; H, 3.89; N, 12.71.

2-(2,4-Dichlorophenyl)-9-hydroxy-11-methyl-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (10c). Yield 74%; yellow solid; mp. 298 °C; IR (KBr): ν 1639 (C=N), 3444 (OH) cm⁻¹; ¹H-NMR (DMSO-d₆): δH 2.25 (3H, s, 11-CH₃), 6.12 (1H, s, 12-CH), 5.88 (1H, s, NH), 6.49 (1H, s, 8-H), 6.61 (1H, s, 10-H), 7.08–8.46 (8H, m, Ar-H), 9.74 (1H, s, 5-H), 11.36 (1H, s, OH); MS m/z (%): 476 (M⁺ + 2, 7), 474 (M⁺, 6), 397 (26), 305 (24), 228 (75), 145 (100), 77 (38). Anal. Calcd for C₂₅H₁₆Cl₂N₄O₂ (474.07): C, 63.17; H, 3.39; N, 11.79. Found C, 63.10; H, 3.21; N, 11.53%.

9-Hydroxy-11-methyl-2-(3-nitrophenyl)-12-phenyl-12H-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (10d). Yield 72%; yellow solid; mp. 240 °C; IR (KBr): ν 1632 (C=N), 3412 (OH) cm⁻¹; ¹H-NMR (DMSO-d₆): 2.09 (3H, s, CH₃), 5.58 (1H, s, 11-H), 6.42 (1H, s, 9-H), 6.57 (1H, s, 7-H), 6.89–7.56 (9H, m, Ar-H), 8.27 (1H, s, CH=N-N), 8.37 (1H, s, 2-H), 8.53 (1H, s, NH), 8.57 (1H, s, OH); MS m/z (%): 452 (M⁺ + 1, 6), 451 (M⁺, 17), 374 (100), 172 (13), 77 (18). Anal. Calcd for C₂₅H₁₇N₅O₄ (451.13): C, 66.51; H, 3.80; N, 15.51. Found C, 66.34; H, 3.65; N, 15.41%.

3-(2-Hydroxybenzylideneamino)-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-ol (11). Yield 78%; canary yellow solid; mp. 192 °C; IR (KBr): ν 1616 (C=N), 3433 (very br, 2OH, NH) cm⁻¹; ¹H-NMR (DMSO-d₆): δH 2.19 (3H, s, 6-CH₃), 5.58 (1H, s, 11-H), 6.42 (1H, s, 8-H), 6.57 (1H, s, 10-H), 7.10–8.46 (9H, m, Ar-H), 9.50 (1H, s, 5-H), 9.72 (1H, br s, OH); MS m/z (%): 424 (M⁺ + 1, 6), 451 (M⁺, 17), 374 (100), 172 (13), 77 (18). Anal. Calcd for C₂₅H₂₀N₄O₃ (424.15): C, 70.74; H, 4.75; N, 13.20. Found C, 70.31; H, 4.56; N, 13.02%.

3.1.6. Reaction of 1 with Activated Unsaturated Compounds

Synthesis of 10-hydroxy-12-methyl-2-oxo-13-phenyl-13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazin-3(4H)-ylidene)acetate (13). An equimolar mixture of 1 (0.32 g, 1 mmol) and dimethylacetelylene dicarboxylate (0.142 g, 1 mmol) in methanol (20 mL) was refluxed for 2 h (monitored by TLC). The formed solid was collected by filtration and recrystallized from DMF to give compound 13. Yield 78%; canary yellow solid; mp. 184 °C; IR (KBr): ν = 1633 (C=N), 1665, 1712 (C=O), 3466 (br, OH
and NH) cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): $\delta_H$ 2.17 (3H, s, 12-CH$_3$), 3.48 (3H, s, OCH$_3$), 5.42 (1H, s, 13-H), 6.60 (1H, s, CH=CO$_2$Me), 6.52 (1H, s, 9-H), 6.62 (1H, s, 11-H), 7.11–7.34 (5H, m, Ar-H), 9.12 (1H, s, 6-H), 9.95 (1H, s, NH), 10.15 (1H, s, OH); MS m/z (%): 432 (M$^+$ + 2, 2), 431 (M$^+$ + 1, 2), 430 (M$^+$, 5), 305 (22), 253 (25), 228 (100), 105 (69), 77 (62). Anal. Calcd for C$_{23}$H$_{18}$N$_4$O$_5$ (430.13): C, 64.18; H, 4.22; N, 13.02. Found C, 64.12; H, 4.13; N, 12.82%.

Synthesis of 4-Amino-11-hydroxy-13-methyl-14-phenyl-3H,14H-chromeno[2,3-d]pyrimido[1,6-b]1,2,4 triazepine-3-carbonitrile (15). A mixture of 1 (0.32 g, 1 mmol) and ethoxymethylene malononitrile (0.122 g, 1 mmol) in methanol (20 mL) was refluxed for 1 h (monitored by TLC). The reaction mixture was cooled and the resulting precipitate was filtered off and recrystallized from DMF/EtOH to give 15. Yield 76%; yellow solid; mp. 330 °C; IR (KBr): $v$ 1628 (C=N), 2197 (CN), 3214, 3180 (NH$_2$), 3466 (OH) cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): $\delta_H$ 2.07 (3H, s, 13-CH$_3$), 5.61 (1H, s, 14-H), 6.50 (1H, s, 10-H), 6.60 (1H, s, 12-H), 7.12–7.33 (7H, m, Ar-H + NH$_2$), 8.57 (1H, s, 2-H), 9.57 (1H, s, 7-H), 9.72 (1H, s, OH); MS m/z (%): 396 (M$^+$, 3), 330 (13), 253 (100), 77 (11). Anal. Calcd for C$_{22}$H$_{16}$N$_6$O$_2$ (396.13): C, 66.66; H, 4.07; N, 21.20. Found C, 66.38; H, 4.01; N, 21.03%.

3.1.7. Reaction of 1 with Active Chloromethylene Compounds 16a–c and Chloroacetonitrile

**General procedure**: To a solution of 1 (0.32 g, 1 mmol) and triethylamine (0.7 mL) in ethanol was added active chloromethylene compounds 16a–c and chloroacetonitrile (1 mmol) dropwise while stirring the reaction mixture. After complete addition, the reaction mixture was refluxed for 2 h (monitored by TLC). The solid that precipitated was filtered off, washed with H$_2$O, dried and finally crystallized from ethanol to give the respective 18a–c and 20.

2-Acetyl-10-hydroxy-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4] triazine (18a). Yield 74%; yellow solid; mp. 212 °C; IR (KBr): $v$ 1639 (C=N), 1698 (C=O), 3410 (OH) cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): $\delta_H$ 2.17 (3H, s, 12-CH$_3$), 2.19 (3H, s, 3-CH$_3$), 2.25 (3H, s, CH$_3$CO), 5.48 (1H, s, 2-H), 5.6 (1H, s, 13-H), 6.46 (1H, s, 9-H), 6.58 (1H, s, 11-H), 7.14–7.54 (5H, m, Ar-H), 8.20 (1H, s, 6-H), 9.69 (1H, br s, OH); MS m/z (%): 400 (M$^+$, 8), 305 (12), 276 (100), 253 (11), 228 (92), 105 (18), 77 (15). Anal. Calcd for C$_{23}$H$_{20}$N$_4$O$_3$ (400.15): C, 68.99; H, 5.03; N, 13.99. Found C, 68.78; H, 4.83; N, 13.86%.

Ethyl-10-hydroxy-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4] triazine-2-carboxylate (18b). Yield 74%; yellow solid; mp. 160 °C; IR (KBr): $v$ 1634 (C=N), 1712 (C=O), 3422 (OH) cm$^{-1}$; $^1$H-NMR (DMSO-$d_6$): $\delta_H$ 1.30 (3H, t, CH$_3$), 2.21 (3H, s, 12-CH$_3$), 2.23 (3H, s, 3-CH$_3$), 4.22 (2H, q, CH$_2$), 5.50 (1H, s, 2-H), 5.58 (1H, s, 13-H), 6.40 (1H, s, 9-H), 6.49 (1H, s, 11-H), 7.11–7.36 (5H, m, Ar-H), 8.17 (1H, s, 6-H), 9.61 (1H, br s, OH); MS m/z (%): 430 (M$^+$, 12), 354 (16), 305 (59), 268 (43), 228 (100), 105 (18), 76 (52). Anal. Calcd for C$_{24}$H$_{22}$N$_4$O$_3$ (430.16): C, 66.97; H, 5.15; N, 13.02. Found C, 66.76; H, 5.01; N, 12.92%.

10-Hydroxy-3,12-dimethyl-N,13-diphenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4] triazine-2-carboxamide (18c). Yield 76%; yellow solid; mp. 198 °C; IR (KBr): $v$ 1636 (C=N), 1660 (C=O), 3433
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(1H, s, 2-H), 5.59 (1H, s, 13-H), 6.40 (1H, s, 9-H), 6.52 (1H, s, 11-H), 7.19–7.84 (10H, m, Ar-H), 8.18 (1H, s, 6-H), 9.45 (1H, s, NH), 9.79 (1H, br s, OH); MS m/z (%): 477 (M+, 16), 305 (100), 268 (43), 228 (94), 105 (46), 77 (68). Anal. Calcd for C_{28}H_{23}N_{5}O_{3} (477.18): C, 70.43; H, 4.85; N, 14.67. Found C, 70.33; H, 4.74; N, 14.62%.

3-Amino-10-hydroxy-3,12-dimethyl-13-phenyl-2H,13H-chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazine (20). Yield 73%; yellow solid; mp. 165 °C; IR (KBr): v 1639 (C=N), 3356, 3198 (NH 2), 3406 (OH) cm\(^{-1}\). \(^1\)H-NMR (DMSO-d\(_6\)): \(\delta_{H}\) 2.11 (3H, s, 12-CH\(_3\)), 3.88 (2H, s, CH\(_2\)), 5.57 (1H, s, 13-H), 6.35 (2H, br s, NH\(_2\)), 6.52 (1H, s, 9-H), 6.50 (1H, s, 11-H), 7.11–7.42 (5H, m, Ar-H), 8.67 (1H, s, 6-H), 9.84 (1H, s, OH); MS m/z (%): 359 (M\(^+\), 3), 253 (25), 228 (100), 77 (23). Anal. Calcd for C\(_{20}\)H\(_{17}\)N\(_5\)O\(_2\) (359.14): C, 66.84; H, 4.77; N, 19.49. Found C, 66.67; H, 4.54; N, 19.36%.

3.2. Cytotoxic Activity

Potential cytotoxicity of the compounds was tested using the method of Skehan et al. [28], using Sulfo-Rhodamine-B stain (SRB). Cells were plated in 96-multiwell plates (10\(^{4}\) cells/well) for 24 h before treatment with the tested compound to allow attachment of cell to the wall of the plate. Different concentrations of the compound under test (0, 1.56, 3.125, 6.25, 12.5, 25, and 50 µg/mL) were added to the cell monolayer in triplicate wells individual dose, monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO\(_2\). After 48 h, cells were fixed, washed and stained with SRB stain, excess stain was washed with acetic acid and attached stain was recovered with \(\text{tris}\)-EDTA buffer, color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound and the IC\(_{50}\) was calculated (Figures 1 and 2).

4. Conclusions

In this report, a simple method for the synthesis of new chromeno[2,3-d]pyrimido[1,6-b][1,2,4]triazines, chromeno[2,3-d]pyrimido[1,6-b][1,2,4] triazepinones and chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines by the reactions of 3-amino-8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydro-3H-chromeno[2,3-d]pyrimidine and hydrazonoyl halides, ethyl acetoacetate, ethyl benzoylacetate, and aromatic aldehydes are demonstrated. The new compounds 4\(_a\) and 8\(_a\) have been evaluated for the antitumor activity against human breast cell MCF-7 line and liver carcinoma cell line HepG2.

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Sample Availability: Samples of the synthesized compounds are available from the authors.

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