Considering quinoxaline as a privileged structure for developing probes of impressive therapeutic potentials, some new azole and azine conjugates of quinoxaline were synthesized. Thus, ethyl 3-amino-1,4-dihydroquinoxaline-2-carboxylate (2) was prepared as one-pot three-component product and incorporated in a series of manipulations including cyclocondensation reactions to afford a series of pharmacophoric motif conjugates 8–12, 14, 15–17, 20–23, 24–29, 30–37, and 38–43 in fair yields. The newly synthesized were characterized by IR, 1H NMR, 13C NMR, and mass spectral data.


INTRODUCTION

Quinoxaline conjugates are important nitrogen containing heterocyclic conjugates of a wide variety of potential applications in biological, medicinal, and pharmacological fields. A large number of synthetic quinoxalines have been reported to exhibit anti-tubercular [1], anti-viral [2,3], anti-microbial [4,5], and neuroprotective [6,7] activity. Many quinoxaline derivatives have a wide application as dyes, electro luminescent materials, organic semiconductors, cavitands, chemically controllable switches, and DNA cleaving agents [8–13]. Also, some quinoxalines were used in the agricultural field as pesticides and used as chemical controllable switches, corrosion inhibitor [14,15], and insecticides [16].

Complexation of quinoxaline analogs, such as 2,3-bis(2-pyridyl)-quinoxaline (Fig. 1), with transition metals being of current interest in view of their binding to DNA, may suggest that conjugation of biologically active peptides with quinoxaline analogs can lead to new therapeutic agents possessing interesting anticancer properties [17].

Also, 2-(4-(7-chloroquinoxalin-2-yl)-phenoxy)propionic acid [18] and chloroquinoxaline sulfonamide [19] are the known antineoplastic quinoxaline topoisomerase II inhibitors (Fig. 1).

On the other hand, the synthesis and chemistry of quinoxalines have attracted considerable attention in the past 10 years, so quinoxalines are well known as privileged structure for easy construction of chemical scaffold [20,21]. Thus, quinoxaline derivatives have been reported to be prepared, but not limited, by intramolecular cyclisation of N-substituted aromatic o-diamines [22], ring transformation of benzofurazans [23], and condensation of benzofuran-1-oxide to form quinoxaline-N-oxides. [24] The most common method for the preparation of quinoxaline derivatives relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound, of which this type of reaction has limitations because of the use of pre-defined starting materials [25–28], which limit the number of substituents that can be added.

Thus, the aforesaid biological significance of quinoxaline analogs compelled us to continue working
[29–42] aiming at merging of chemical architectures of significant pharmacophoric activities for developing verifications of impressive therapeutic potentials, in particular against profound diseases; we initiated a program aiming at merging of quinoxaline, azole, and azine moieties in single architecture.

 RESULTS AND DISCUSSION

Previously, we launched a program that has proved to be a convenient route for the synthesis of azole and azine analogies [39–42]. Now, we have extended our synthetic program to the synthesis of otherwise inaccessible heterocyclic ring system, utilizing ethyl 3-amino-1,4-dihydroquinoxaline-2-carboxylate \( (2) \) as a key intermediate adorned with a reactive \( o \)-amino ester terminal system. It is known that a great variety of reactants bearing the \( o \)-amino ester fragment undergo cyclization via reaction with various one-carbon donors and some nucleophiles. Thus, \( o \)-amino ester tagged \( 2 \) was prepared as one-pot three-component condensation reaction through refluxing \( o \)-phenylenediamine with urea and ethylcyanoacetate in absolute EtOH, afforded a single product (as examined by thin-layer chromatography), for which five possible structures \( 3, 4, 5, 6, \) and \( 7 \) (Scheme 1). The reaction proceeded through initial elimination of \( \text{NH}_3 \) to afford the non-isolable intermediate \( 1 \), which subsequently cyclized via elimination of \( \text{HCN} \) molecule to afford \( 2 \) as shown in Scheme 1. Structure \( 2 \) was identified as the reaction product based on its elemental and spectral data, where, the \( m/z \) recorded at 219.0 (40%) corresponding to the formula \( \text{C}_{11}\text{H}_{13}\text{N}_{3}\text{O}_{2} \), beside the absence of \( \text{C}≡\text{N} \) (IR) absorption around \( (2220–2260 \text{ cm}^{-1}) \), in addition to the most characteristic signals of compound \( 2 \) in its \( ^1\text{H} \) NMR spectrum belong to the two quinoxaline exchangeable (N-H) protons at 12.35 and 12.62 ppm, the ethyl protons, were also, observed as a triplet and quartet at 1.21 and 4.15 ppm respectively, all favored formation of \( 2 \) and ruled out all other assumptions (Scheme 2).

The activation exerted by the carbonyl group towards the ethoxy group in \( 2 \) renders it available for the cyclocondensation addition with various amino compounds. Thus, when the compound \( 2 \) was reacted with an equimolar quantity of urea or thiourea, an initial

\[\begin{align*}
\text{Scheme 1. Synthesis of ethyl 3-amino-1,4-dihydroquinoxaline-2-carboxylate 2.}
\end{align*}\]
condensation of one amino group with the ethoxy group occurred releasing EtOH, followed by the releasing of NH₃ to afford 5,10-dihydrobenzo[g]pteridine-2,4(1H,3H)-dione (8) and 4-oxo-2-thioxo-2-thioxo-2,3,5,10-tetrahydro benzo[g]pteridin-4(1H)-one (9) respectively, (Scheme 3). The IR spectrum of 9 showed absorption bands centered around 1332, 1705, and 3170–3290 cm⁻¹ attributed to C=S str., C=O str., and four N–H str. groups, respectively. Its ¹H NMR spectrum revealed the disappearance of the amino and ethyl protons with a presence of five singlet signals at 11.25, 12.36, 12.71, and 13.01 for four endocyclic imino protons, respectively. The mass spectrum of 9 displayed an intense peak at m/z 232.0 (M⁺, 75%) corresponding to the expected molecular formula C₁₃H₈N₄OS. Further, cyclization of 2 was accomplished via refluxing with acetamidine hydrochloride in pyridine to afford 2-methyl-5,10-dihydrobenzo[g]pteridin-4(3H)-one (10). The methyl singlet (¹H NMR) at δ ≈ 2.25 ppm and its (IR) absorption band at 2987 cm⁻¹, beside the absence of absorption bands for the ethyl and NH₂ groups, with the recorded mass at m/z 214.0 corresponding to the formula C₁₁H₁₀N₄O, all supported the formation of compound 10. Moreover, compound 2, reacted with triethyl orthoformate to give the

Scheme 2. The proposed mechanism for the formation of compound 2.
corresponding ethoxymethylene amino derivative 11, which used as precursor for the preparation of the key compound 12 via cyclization with hydrazide hydrate, as depicted in Scheme 3. On the other hand, reaction of 2 with triethyl orthoformate in Ac2O gave ethyl 3-formamido-1,4-dihydrooxinoaxaline-2-carboxylate (14) \(^\text{[43]}\), instead of ethyl 3-((ethoxymethylene)amino)-1,4-dihydrooxinoaxaline-2-carboxylate (11) (Scheme 3). The \(^1\)H NMR spectra of 12 revealed the presence of singlet at 4.57 ppm for NH2 protons, in addition to the two imino protons at 12.36 and 12.71 ppm. The mass spectrum of 12 displayed an ion peak at \(m/z\) 215.0 (M\(^+\), 25%) corresponding to the expected molecular formula C10H9N5O.

Chlorination of compound 10 with POCl3 affording 4-chloro-2-methyl-5,10-dihydrobenzo[\(g\)]pteridine (15) in good yield. The lack of absorption band of carbonyl group in the IR spectrum of 15, and its recorded \(m/z\) 232.0 (M\(^+\), 50%) corresponding to the expected molecular formula C11H9ClN4, supports the formation of 15 (Scheme 4). When compound 15 was converted to the hydrazide 16, new signals supported hydrazide structure appeared at 4.14 and 9.84 ppm (controlled by changing with D2O) integrating for two protons and one proton, in its \(^1\)H NMR spectrum, respectively. The IR spectra of 16 revealed an additional peak at 3212–3355 cm\(^{-1}\) because of hydrazide structure. MS of 16 showed the [M] \(^+\) ion at \(m/z\) 228.0 (35%). Compound 16 underwent further cyclization on treatment with HNO2 giving 4-azido-2-methyl-5,10-dihydrobenzo[\(g\)]pteridine (17) (Scheme 4). For further confirmation, compound 15 was treated with NaN\(_3\) in EtOH; this digestion afforded again compound 17 but in good yield. The signals of the hydrazide moiety protons originally observed in 16 (\(^1\)H NMR) at 4.14 and 9.84 ppm were vanished in 17 (\(^1\)H NMR), while the two endocyclic N–H signals were still observable at \(\delta\) 12.31 and 12.62 ppm, and their stretching bands (IR) were observed around 3212–3323 cm\(^{-1}\), in addition to a new absorption band at 2140 cm\(^{-1}\) attributed to azide moiety, was observed in the 17 (IR). The mass spectrum of 17 displayed an intense peak at \(m/z\) 239.0 (M\(^+\), 15%) corresponding to the expected molecular formula C11H9N7.

Next, we moved to the studying of the reaction of compound 2 with benzylisothiocyanate in 1,4-dioxane containing Et\(_3\)N, the reaction involved a nucleophilic attack by the amino function in 2 on the C=S terminal of the isocyanate reagent to produce the acyclic intermediates 18 and 19. The latter underwent 1,6-dipolar cyclization to afford 3-benzyl-2-mercapto-5,10-dihydrobenzo[\(g\)]pteridin-4(3\(H\))-one (20) in 70% yield (Scheme 5). The IR spectrum of compound 20 declared S-H\(_{\text{str}}\) band at 2450 cm\(^{-1}\), while the S-H proton (\(^1\)H NMR) appeared as singlet at 11.10 ppm. Subsequent methylation with dimethylsulfate and aqueous NaOH afforded 2-methylthio derivative 21 which upon nucleophilic displacement of the SMe group with hydrazine furnished the respective hydrazide derivative 22. The latter compound underwent further, cyclization via treating with benzoyl chloride as a one-carbon donor to afford the 1,2,4-triazolo[4,3-\(a\)]pyrimidine derivative 23 (Scheme 5).

In a similar manner, as depicted in Scheme 6, compound 24 was synthesized via treatment of compound 2 with 4-chlorophenyl isothiocyanate. The thiole moiety in 24 was easily replaced with chlorine via treatment with POCl3 to afford the corresponding chloro derivative 25 (Scheme 6). The chloro compound 25 is considered as a key intermediate to attain the hydrazino derivative 26. So subjection of 25 to hydrazine hydrate resulted in the formation of 26, which underwent further cyclization via treating with various one-carbon donors to afford the 1,2,4-triazolo[4,3-\(a\)]pyrimidine derivatives 27-29 (Scheme 6). The proposal structure of the synthesized compounds was derived from the spectral data (\(^1\)H NMR, \(^13\)C NMR, \(\text{IR, MS, etc.}\)).
MS, and IR) and satisfactory elemental analyses. Thus, the IR spectra of the product 27 showed the presence of absorption bands at 1705, and 3212–3323 cm⁻¹ because of C=Ostr., and two NHstr. groups, respectively. The signal of the hydrazide moiety protons originally observed in 26 (¹H NMR) at 4.14 and 9.84 ppm disappeared in 27 (¹H NMR), while the two endocyclic N—H signals were still observable at 12.31 and 12.62 ppm. The mass spectrum of 27 displayed an intense peak at m/z 426.0 (M⁺, 90%) corresponding to the expected molecular formula C₂₃H₁₅ClN₆O.

Furthermore, o-amino-ester 2 reacted with hydrazine hydrate to afford 3-amino-1,4-dihydroquinoxaline-2-carbohydrazide (30), which cyclized to 2-mercapto-pyrimidine derivative 31, via treating with carbon disulfide, the latter compound easily methylated with dimethylsulfate and aqueous NaOH afforded 2-methylthio derivative 32, which upon nucleophilic displacement of the SME group with hydrazine yielded the respective hydrazino derivative 33. Compound 33 underwent further cyclization via curing with some of laboratory available one-carbon donors to afford the 1,2,4-triazolo[1,5-a]pyrimidine derivatives 34–36 (Scheme 7). The structures of isolated products 34–36 were evidenced by spectral data together with elemental analyses. For instance, the IR spectra of isolated products displayed in each case the absorption bands in the regions 1695–1726, and 3212–3323 cm⁻¹ because of C=Ostr., NHstr., and NH₂str., groups, respectively. The mass spectrum of 34 displayed an ion peak at m/z 255.0 (M⁺, 35%) corresponding to the expected molecular formula C₁₁H₉N₇O. On the other hand, the synthesis of the new 1,3,4-oxadiazole incorporated quinoxaline moiety 37 is achieved as shown in Scheme 7, via cyclization of the acid hydrazide intermediate 30 with benzoic acid in POCl₃ under reflux.

Finally, the o-amino-ester 2 undergoes further, classical cyclocondensation reaction via heating with excess of formamide to afford 5,10-dihydrobenzo[g]pteridin-4(3H)-one (38), which easily chlorinated through treating with POCl₃, which afforded the corresponding chloro derivative 39. Heating 39 with hydrazine hydrate under reflux afforded the target.
compounds 41–43 (Scheme 8). The IR spectrum of 41 showed absorption bands at 3100–3280 cm\(^{-1}\) attributed to two NH\(_{str}\) groups. Its \(^1\)H NMR spectrum showed the disappearance of the signals of the hydrazinyl protons originally observed in 40 at 5.36 and 8.64 ppm. The mass spectrum of 41 displayed an intense peak at \(m/z\) 224.0 (M\(^+\), 55%) corresponding to the expected molecular formula C\(_{11}\)H\(_8\)N\(_6\).

**EXPERIMENTAL**

Reagents were purchased from Sigma Aldrich (Bayouni Trading Co. Ltd., Al-Khobar, Saudi Arabia) and used without further purification. Reaction progress was monitored by thin-layer chromatography on silica gel pre-coated F254 Merck plates (Darmstadt, Germany). Spots were visualized by ultraviolet irradiation. Melting points were determined on a Gallenkamp electrothermal apparatus (Weiss-Gallenkamp, Loughborough, UK) and are uncorrected. IR spectra were recorded as potassium bromide disks using Bruker-Vector 22 Fourier transform infrared spectrophotometer (Billerica, MA). The NMR spectra were recorded with a Varian Mercury VX-R-300 NMR spectrometer (Palo Alto, CA) at 300 and 75 MHz for \(^1\)H and \(^{13}\)C NMR spectra, respectively, is using DMSO-\(d_6\) as solvents. Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer (Palo Alto, CA) at 70 eV. Elemental analyses were carried out at the Micro-analytical Center of Cairo University, Giza, Egypt.

**Ethyl 3-amino-1,4-dihydroquinoxaline-2-carboxylate** (2). To a solution of \(\alpha\)-phenylenediamine (1.08 g, 10 mmol) in absolute EtOH (30 mL) containing few drops of Et\(_3\)N as a catalyst, urea (0.60 g, 10 mmol), and ethylenecyanocetate (1.13 mL, 10 mmol) was refluxed for 6 h. The formed pale yellow precipitate was filtered off and finally purified by recrystallization from EtOH to
afford 2 as pale yellow crystals in 86% yield; mp 200–202°C; IR (KBr): v (cm⁻¹), 1730 (CO ester), 3100–3400 (NH₄⁺, NH₂⁻); ¹H NMR (δ, DMSO-d₆): 1.21 (t, J = 7.51 Hz, 3H, CH₃); 4.15 (q, J = 7.51 Hz, 2H, CH₂CH₃); 5.51 (s, 2H, NH₂; D₂O exchangeable); 7.10–8.01 (m, 4H, Ar-H, 12.35 (s, 1H, N=Hquinox.; D₂O exchangeable); and 12.62 (s, 1H, N=Hquinox.; D₂O exchangeable). ¹³C NMR (DMSO-d₆): 14.2 (CH), 61.5 (CH₂), 87.1, 119.4, 119.8, 120.3, 131.4, 137.6 (C=C) and 165.4 (CO); MS (m/z, %): 219.0 (M⁺, 40). Anal. Calcd for C₁₁H₁₂N₂O₂ (219.24): C, 60.26; H, 5.98; N, 19.17%. Found: C, 60.12; H, 5.78; N, 19.01%.

5,10-Dihydrobenzo[g]pteridine-2,4(1H,3H)-dione (8). A mixture of compound 6 (2.19 g, 10 mmol) and urea (0.6 g, 10 mmol) was heated at 200°C for 6 h, the reaction mixture was cooled and poured into NaOH solution, and any insoluble material was removed by filtration. The filtrate was then acidified with 2 N HCl to give a red precipitate, which was collected by filtration, washed with H₂O, and dried on a funnel to afford compound 8 in 70% yield; mp 250–252°C; MS (m/z, %): 216.0 (M⁺, 30). Anal. Calcd for C₇H₇N₂O₂ (216.20): C, 55.55; H, 3.73; N, 25.91%. Found: C, 55.42; H, 3.64; N, 25.75%.

2-Thioxo-3,5,10-tetrahydrobenzo[g]pteridine-4(1H)-one (9). To a mixture of 2 (2.19 g, 10 mmol) and thiourea (0.72 g, 10 mmol) in absolute EtOH (30 mL), sodium ethoxide (0.23 g of Na in 10 mL EtOH) was added. The reaction mixture was refluxed for 8 h, concentrated, and cooled. The separated solid was filtered off, washed with H₂O several times, and recrystallized from the EtOH to afford compound 9, as brown crystals in 60% yield; mp 260–262°C. IR (KBr): v (cm⁻¹): 3132 (C=S ar.), 1705 (C=O ar.), 3170–3290 (4NH); ¹H NMR (δ, DMSO-d₆): 7.10–8.01 (m, 4H, Ar-H), 11.25 (s, 1H, N=Hpyrimid.; D₂O exchangeable), 12.36 (s, 1H, N=Hquinox.; D₂O exchangeable), 12.71 (s, 1H, N=Hquinox.; D₂O exchangeable), and 13.01 (s, 1H, N=Hpyrimid.; D₂O exchangeable); MS (m/z, %): 232.0 (M⁺, 75). Anal. Calcd for C₇H₇N₂O₂S (232.26): C, 51.71; H, 3.47; N, 24.12; S, 13.81%. Found: C, 51.56; H, 3.28; N, 24.01; S, 13.69%.

2-Methyl-5,10-dihydrobenzo[g]pteridine-4(1H)-one (10). To a solution of the compound 2 (0.21 g, 1 mmol) in pyridine mixture (15 mL), aceticamidine hydrochloride (0.94 g, 1 mmol) was added; the reaction mixture was heated under reflux for 4 h, left to cool, and poured on ice/HCl; the obtained precipitate was filtered, washed with H₂O, dried, and recrystallized from EtOH afforded 10 in 72% yields as deep brown; mp 180–181°C; IR (KBr): v (cm⁻¹): 1695 (amidic C=O ar.), 2987 (Me), 3170–3290 (3NH₄⁺); ¹H NMR (δ, DMSO-d₆): 2.15 (s, 3H, Me), 6.78–6.98 (m, 4H, Ar-H), 12.36 (s, 1H, N=Hquinox.; D₂O exchangeable), 12.71 (s, 1H, N=Hquinox.; D₂O exchangeable), and 13.01 (s, 1H, N=Hpyrimid.; D₂O exchangeable); MS (m/z, %): 214.0 (M⁺, 50). Anal. Calcd for C₁₁H₁₀N₂O (214.22): C, 61.67; H, 4.71; N, 26.15%. Found: 61.52; H, 4.64; N, 26.07%.

Ethyl 3-(ethoxymethylene)amino)-1,4-dihydroquinazoline-2-carboxylate (11). A solution of compound 2 (0.21 g, 1 mmol) and triethyl orthoformate (15 mL) was heated on reflux for 8 h. After cooling, the precipitate was filtered, washed with MeOH, and recrystallized from EtOH to give 11 in 80% yield as pale yellow crystals; mp 270–272°C; IR (KBr): v (cm⁻¹), 1725–1735 (2CO ester), 1620 (C=N ar., NH₂), 1300–3400 (NH; NH₂); ¹H NMR (δ, DMSO-d₆): 1.11 (t, J = 7.51 Hz, 3H, CH₂CH₃), 1.21 (t, J = 7.51 Hz, 3H, CH₂CH₃), 3.95 (q, J = 7.51 Hz, 2H, CH₂CH₃), 4.15 (q, 2H, CH₂CH₃), 7.10–8.01 (m, 5H, Ar-H & –N=CH), 12.35 (s, 1H, N=Hquinox.; D₂O exchangeable), and 12.62 (s, 1H, N=Hquinox.; D₂O exchangeable); MS (m/z, %): 275.0 (M⁺, 25). Anal. Calcd for C₁₁H₁₂N₂O₃ (275.30): C, 61.08; H, 6.22; N, 15.26%. Found: C, 61.01; H, 6.11; N, 15.14%.

3-Amino-5,10-dihydrobenzo[4]-steroid-4(1H)-one (12). A mixture of compound 7 (0.27 g, 1 mmol) with hydrazine hydrate (5 mL) in EtOH (30 mL) was refluxed for 4 h, then left overnight at room temperature. The solid product so formed was filtered off, washed with MeOH, dried well, and recrystallized from EtOH to afford 12 in 73% yield as yellowish crystals; mp 255–257°C; ¹H NMR (δ, DMSO-d₆): 4.57 (s, 2H, NH₂; D₂O exchangeable), 7.18–7.38 (m, 5H, Ar-H & Pyrim.; H-2), 12.36 (s, 1H, N=Hquinox.; D₂O exchangeable), and 12.71 (s, 1H, N=Hquinox.; D₂O exchangeable); MS (m/z, %): 215.0 (M⁺, 25). Anal. Calcd for C₁₀H₁₀N₄O (215.21): C, 55.81; H, 4.22; N, 32.54%. Found: C, 55.72; H, 4.14; N, 32.38%.

Ethyl 3-formamido-1,4-dihydroquinazoline-2-carboxylate (14). A mixture of compound 2 (0.21 g, 1 mmol) with triethyl orthoformate (0.30 mL, 2 mmol) and Ac₂O (30 mL) was refluxed for 2 h. The solvent was removed under reduced pressure, and the resulting solid was washed with MeOH and recrystallized from MeOH to yield 14 as yellow powder in 50% yield; mp 256–258°C; IR (KBr): v (cm⁻¹), 1731 (CO ester), 3100–3354 (2NH₂); ¹H NMR (δ, DMSO-d₆): 1.21 (t, J = 7.51 Hz, 3H, CH₂CH₃), 4.15 (q, J = 7.51 Hz, 2H, CH₂CH₃), 7.10–8.01 (m, 4H, Ar-H), 10.45 (s, 1H, CHO), 11.27 (s, 1H, COH–N=H, D₂O exchangeable), 12.35 (s, 1H, N=Hquinox.; D₂O exchangeable), and 12.62 (s, 1H, N=Hquinox.; D₂O exchangeable); MS (m/z, %): 247.0 (M⁺, 15). Anal. Calcd for C₁₂H₁₁N₃O₃ (247.25): C, 58.29; H, 5.30; N, 16.99%. Found: C, 58.12; H, 5.23; N, 16.79%.

General procedure for preparation of compounds 15, 25, and 39. To a stirred mixture of compound 10, 24, or 38 (10 mmol), in anhydrous DMF (20 mL), POCl₃ (10 mL) was added dropwise at −10 to −5°C. The reaction mixture was stirred for further 1 h at RT; then, the
reaction mixture was heated with stirring for 2 h at 60°C. After the reaction was completed, the mixture was poured onto crushed ice (200 g) under vigorous stirring. After storing the mixture overnight at 0°C, the pale yellow solid was collected by filtration and washed successively with aqueous Na₂CO₃ (5%) and water and then was air dried and recrystallized from proper solvent to afford the chloro derivatives 15, 25, and 39, respectively. The physical data of these compounds are as follows.

4-Chloro-2-methyl-5,10-dihydrobenzo[γ]pteridine (15). Yellow powder from EtOH in 65% yield; mp 192–194°C; IR (KBr): ν (cm⁻¹), 1620–1625 (2C=N₆), 3120–3354 (2NH₂₋₋, D₂O exchangeable), 2.15 (s, 3H, Me), 6.78–6.98 (m, 4H, Ar-H), 12.36 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.71 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 240.0 (M⁺+2, 15), 238.0 (M⁺, 45). Anal. Calcd for C₁₀H₇ClN₄ (218.64): C, 55.93; H, 2.69; Cl, 16.10; N, 25.47%. Found: C, 55.76; H, 2.62; Cl, 16.53; N, 25.74%.

3-Chloro-2-ethyl-2,4-dihydrobenz[γ]pteridine (16). Yellow powder from EtOH in 80% yield; mp 230–232°C; IR (KBr): ν (cm⁻¹), 1620–1625 (2C=N₆), 3212–3355 (3NH₂₋₋, NH₂₋₋, D₂O exchangeable); 1H NMR (δ, DMSO-d₆): 1.05 (s, 3H, Me), 4.14 (s, 2H, NH₂-draz., D₂O exchangeable), 6.78–6.98 (m, 4H, Ar-H), 9.84 (s, 1H, NH₂-draz., D₂O exchangeable), 12.21 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.57 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 228.0 (M⁺, 35). Anal. Calcd for C₁₁H₁₂N₆ (228.25): C, 57.88; H, 5.30; N, 36.82%. Found: C, 57.65; H, 5.19; N, 36.63%.

3-(4-Chlorophenyl)-2-hydrazinyl-5,10-dihydrobenzo[γ]pteridine-4(3H)-one (26). Yellowish crystals in 76% yield, from dioxane; mp 159–161°C; IR (KBr): ν (cm⁻¹), 1621 (C=N₆), 3212–3355 (3NH₂₋₋, NH₂₋₋, D₂O exchangeable); 1H NMR (δ, DMSO-d₆): 4.14 (s, 2H, NH₂-draz., D₂O exchangeable), 6.78–6.98 (m, 4H, Ar-H), 9.84 (s, 1H, NH₂-draz., D₂O exchangeable), 12.21 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.57 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 342.0 (M⁺+2, 15), 340.0 (M⁺, 45). Anal. Calcd for C₁₆H₁₁Cl₂N₄O (414.23): C, 56.20; H, 3.58; Cl, 10.24; N, 24.66%. Found: C, 56.20; H, 3.58; Cl, 10.24; N, 24.28%.

6.98 (m, 4H, Ar-H), 9.84 (s, 1H, NH₂-draz., D₂O exchangeable), and 12.37 (s, 1H, N-Hquinoc., D₂O exchangeable); MS (m/z, %): 214.0 (M⁺, 25). Anal. Calcd for C₁₆H₁₁Cl₂N₄O (414.23): C, 56.07; H, 4.71; N, 39.23%. Found: C, 55.87; H, 4.52; N, 39.14%.

4-Azido-2-methyl-5,10-dihydrobenzo[γ]pteridine (17). Method A. To an ice-cold solution of compound 16 (0.22 g, 1 mmol) in AcOH acid (15 mL), a solution of NaNO₂ (0.15 mol) in a least amount of H₂O was added dropwise in an ice bath at −5°C. The reaction mixture was allowed to stand overnight at RT, then poured onto water (100 mL). The solid precipitated was filtered off and recrystallized from EtOH to yield 17 as yellow powder in a 55% yield.

Method B. A mixture of 15 (0.23 g, 1 mmol) and sodium azide (3.25 g, 5 mmol) in 15 mL of EtOH was stirred at 80°C for 24 h. Then, the reaction mixture was poured into 150 mL of crushed ice; the obtained solid was collected by filtration and recrystallized from EtOH to afford 17 as yellow powder in a 55% yield.

General procedure for preparation of compounds 16, 26, and 40. A mixture of choloro compound 15, 25, or 39 (5 mmol) and hydrazide hydrate (0.5 mL) in EtOH (30 mL) was heated under reflux for 6 h; the solid product so obtained after cooling was collected by filtration and recrystallized from proper solvent to afford the hydrazino derivatives 16, 26, and 40, respectively. The physical data of these compounds are as follows.

4-Hydrazinyl-2-methyl-5,10-dihydrobenzo[γ]pteridine (16). Yellow powder from EtOH in 80% yield; mp 230–232°C; IR (KBr): ν (cm⁻¹), 1620–1625 (2C=N₆), 3212–3355 (3 NH₂₋₋, NH₂₋₋, D₂O exchangeable); 1H NMR (δ, DMSO-d₆): 1.05 (s, 3H, Me), 4.14 (s, 2H, NH₂-draz., D₂O exchangeable), 6.78–6.98 (m, 4H, Ar-H), 9.84 (s, 1H, NH₂-draz., D₂O exchangeable), 12.21 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.57 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 228.0 (M⁺, 35). Anal. Calcd for C₁₁H₁₂N₆ (228.25): C, 57.88; H, 5.30; N, 36.82%. Found: C, 57.65; H, 5.19; N, 36.63%.

General procedure for preparation of compounds 20 and 24. Equimolar amounts of 2 (1 mmol) and benzyloxothiocyanate or 4-chlorophenylsulfonothioate (1 mmol) in 1,4-dioxane (20 mL) containing Et₃N (1.0 mL) were heated under reflux for 5 h. After cooking, the reaction mixture was acidified by HCl acid, and the crude product was precipitated, collected by filtration, and recrystallized...
from proper solvent to afford 20 and 24, respectively. The physical data of these compounds are as follows.

3-Benzyl-2-mercapto-5,10-dihydrobenzo[g]pteridin-4(3H)-one (20). As reddish brown crystals (DMF) in 70% yield; mp > 300°C; IR (KBr): ν (cm⁻¹), 1622 (C=Oaryl), 1707 (C(=O)aryl), 2215 (C≡Oaryl), 2450 (S-Haryl), 3212–3323 (2NHaryl); ¹H NMR (δ, DMSO-d₆): 4.37 (s, 2H, CH₂), 6.78–7.38 (m, 9H, Ar-H), 11.10 (s, 1H, S-H), 12.30 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.64 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 322.0 (M⁺, 25%); Anal. Caled for C₁₇H₁₄N₄OS (322.38): C, 63.33; H, 4.38; N, 17.38; S, 9.95%; Found: C, 63.11; H, 4.18; N, 17.20; S, 9.73%.

3-(4-Chlorophenyl)-2-mercapto-5,10-dihydrobenzo[g]pteridin-4(3H)-one (24). Brown powder from [EtOH/DMF(3:1)] in 70% yield; mp 257–259°C; IR (KBr): ν (cm⁻¹), 1620 (C=Oaryl), 1710 (C(=O)aryl), 3120–3354 (2 NHaryl); MS (m/z, %): 344.0 (M⁺+2, 10), 342.0 (30); Anal. Caled for C₁₀H₁₅ClN₃O₅ (369.83): C, 56.06; H, 3.23; Cl, 10.34; N, 16.34; O, 0%; Found: C, 55.89; H, 3.12; Cl, 10.21; N, 16.19%.

General procedure for preparation of compounds 21 and 32. A solution of compound 20 or 31 (1 mmol) in 150 mL of 0.1M NaOH and 15 mL Me₂SO₄ was stirred for 5 min, and the mixture was heated at 70°C for 30 min. After cooling, the solution was filtered and neutralized by 2M HCl acid. The precipitate was collected by filtration and recrystallized from proper solvent to afford the methylthio derivatives 21 and 32, respectively. The physical data of these compounds are as follows.

3-Benzyl-2-(methylthio)-5,10-dihydrobenzo[g]pteridin-4(3H)-one (21). Brown crystals (EtOH) in 60% yield; mp 278–280°C; ¹H NMR (δ, DMSO-d₆): 2.57 (s, 3H, Me), 4.32 (s, 2H, CH₂), 6.78–7.38 (m, 9H, Ar-H), 11.10 (s, 1H, S-H), 12.30 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.64 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 336.0 (M⁺, 40%); Anal. Caled for C₁₈H₁₆N₄OS (336.41): C, 64.26; H, 4.79; N, 16.65; S, 9.53%; Found: C, 64.12; H, 4.51; N, 16.49; S, 9.36%.

Amino-2-(methylthio)-5,10-dihydrobenzo[g]pteridin-4(3H)-one (32). As yellow crystals [EtOH/ DMF (3:1)] in 56% yield; mp 293–295°C; IR (KBr): ν (cm⁻¹), 1622 (C=Oaryl), 1708 (C(=O)aryl), 3142–3361 (2 NHaryl, NH₂aryl); ¹H NMR (δ, DMSO-d₆): 2.57 (s, 3H, Me), 4.65 (s, 2H, NH₂, D₂O exchangeable), 6.78–7.02 (m, 4H, Ar-H), 12.32 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.71 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 261.0 (M⁺, 35%); Anal. Caled for C₁₁H₁₂N₂O₂S (261.30): C, 50.56; H, 4.24; N, 26.80%; Found: C, 50.31; H, 4.10; N, 26.53%.

General procedure for preparation of compounds 22 and 33. A mixture of compound 21 or 32 (1 mmol) and hydrazine hydrate (3 mL) in 30 mL EtOH was refluxed for 5 h. Then, the reaction mixture was concentrated under reduced pressure, and the residue washed with acidified cold H₂O and then triturated with MeOH. The formed yellow product was filtered off, washed well with MeOH, and recrystallized from proper solvent to afford the hydrazinyl derivatives 22 and 33, respectively. The physical data of these compounds are as follows.

3-Benzyl-2-hydrazinyl-5,10-dihydrobenzo[g]pteridin-4(3H)-one (22). As yellow crystals (EtOH) in 70% yield; mp 243–245°C; IR (KBr): ν (cm⁻¹), 1622 (C=Oaryl), 1698 (C(=O)aryl), 3218–3428 (3NHaryl, NH₂aryl); MS (m/z, %): 320.0 (M⁺, 40%); Anal. Caled for C₁₃H₁₁N₅O₂ (320.35): C, 63.74; H, 5.03; N, 26.23%; Found: C, 63.58; H, 4.85; N, 26.12%.

Amino-1,4-dihydrazinylquinolin-2-carboxylic acid (33). As yellow crystals in 75% yield; mp 231–233°C; IR (KBr): ν (cm⁻¹), 1654 (CO amide), 3100–3500 (NHaryl, NH₂aryl); ¹H NMR (δ, DMSO-d₆): 4.38 (s, 2H, NH₂hydraz, D₂O exchangeable), 5.52 (s, 2H, NH₂, D₂O exchangeable), 7.10–8.01 (m, 4H, Ar-H), 9.31 (s, 1H, NH₂hydraz, D₂O exchangeable), 12.35 (s, 1H, N-Hquinox., D₂O exchangeable) and 12.62 (s, 1H, N-Hquinox., D₂O exchangeable); ¹C NMR (DMSO-d₆): 89.1, 119.4, 119.8, 120.3, 131.4, 136.5 (C=C) and 165.9 (CO); MS (m/z, %): 205.0 (M⁺, 30%). Anal. Caled for C₁₁H₁₁N₂O₂ (205.22): C, 52.67; H, 5.40; N, 34.13%; Found: C, 52.48; H, 5.26; N, 34.02%.

General procedure for preparation of compounds 23 and 27. To solution of compound 22 or 26 (1 mmol) and anhydrous K₂CO₃ (1.38 g) in acetonitrile (30 mL), benzoyl chloride (1.4 mL, 10 mmol) was added dropwise. The mixture was stirred at RT for about 6 h. The mixture was then poured onto H₂O, and the resulted solid was filtered off, washed with MeOH, dried, and recrystallized from proper solvent to afford the triazolopyrimidines 23 and 27, respectively. The physical data of these compounds are as follows.

4-Benzyl-1-phenyl-6,11-dihydrobenzo[g]j1,2,4-triazolo[4,3-a]pteridin-5(4H)-one (23). As reddish crystals (EtOH) in 75% yield; mp 271–273°C; ¹H NMR (δ, DMSO-d₆): 4.47 (s, 2H, CH₂), 6.78–8.28 (m, 14H, Ar-H), 12.35 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.74 (s, 1H, N-Hquinox., D₂O exchangeable); MS (m/z, %): 406.0 (M⁺, 30); Anal. Caled for C₂₄H₁₈N₄O₂ (406.44): C, 70.92; H, 4.46; N, 20.68%; Found: C, 70.81; H, 4.42; N, 20.47%.

4-(4-Chlorophenyl)-1-phenyl-6,11-dihydrobenzo[g]j1,2,4-triazolo[4,3-a]pteridin-5(4H)-one (27). A brown powder from EtOH in 70% yield; mp 198–200°C; IR (KBr): ν (cm⁻¹), 1620–1628 (C=Oaryl), 1705 (C(=O)aryl), 3212–3323 (2NHaryl, NH₂aryl); ¹H NMR (δ, DMSO-d₆): 6.78–7.48 (m, 8H, Ar-H), 12.31 (s, 1H, N-Hquinox., D₂O exchangeable), and 12.62 (s, 1H, N-Hquinox., D₂O exchangeable), respectively. The physical data of these compounds are as follows.

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Anal and then poured into ice-cold H2O. The solid product was filtered, washed with H2O, dried, and crystallized from EtOH as pale yellow crystals in 60% yield; mp 239–241°C; MS (m/z, %): 443.0 (M+2, 10), 441.0 (M+, 30); Anal. Calcd for C23H16ClN5O (441.87): C, 62.52; H, 3.65; Cl, 8.14; N, 22.19%. Found: C, 62.34; H, 3.51; Cl, 7.89; N, 22.07%.

**General procedure for preparation of compounds 29, 36, and 43.** A mixture of compound 26, 33, or 40 (1 mmol) and potassium thiocyanate (0.48 g, 5 mmol) was heated at reflux for 10 h in glacial AcOH (20 mL); the reaction mixture was cooled to RT and then poured into H2O. The precipitate formed was collected by filtration, dried, and recrystallized from proper solvent to afford the triazolo-pyrimidines 29, 36, and 43, respectively. The physical data of these compounds are as follows.

**1-Amino-4-(4-chlorophenyl)-6,11-dihydrobenzo[g][1,2,4]triazolo[4,3-a]pteridin-11(3H)-one (29).** Brown crystals from [EtOH/dioxane (2:1)] in 76% yield; mp 245–247°C; IR (KBr): ν (cm−1): 1619–1625 (2C=O); 1709 (C=O); 3181–3419 (2 NH2, NH2str); 1'H NMR (δ, DMSO-d6): 6.38 (s, 1H, NH2, D2O exchangeable); 7.18–7.68 (m, 8H, Ar-H); 12.33 (s, 1H, NH, D2O exchangeable), and 12.73 (s, 1H, N-H, D2O exchangeable); 13°C NMR (75 MHz, DMSO-d6): 76.4 (C2-Quinox), 78.1 (C-2-Quinox), 115.3, 117.8, 129.1, 131.7, 133.2, 136.7, 137.6 (12 C=C), 157.6, 160.6 (2 C=N), 169.2 (C=O); MS (m/z, %): 367.0 (M+2, 9), 365.0 (28); Anal. Calcd for C17H12N2ClO2 (365.78): C, 55.82; H, 3.31; Cl, 9.69; N, 26.61%; Found: C, 55.63; H, 3.19; Cl, 9.52; N, 26.67%.

**2,3-Diamino-5,10-dihydrobenzo[g][1,2,4]triazolo[5,1-b]pteridin-11(3H)-one (36).** Yellowish brown crystals from [DMF/EtOH (1:3)] in 70% yield; mp 271–273°C; IR (KBr): ν (cm−1): 1617–1625 (2 C=O); 1715 (C=O); 3212–3323 (2 NH2, NH2str); MS (m/z, %): 270.0 (M+); Anal. Calcd for C11H10N6O (270.25): C, 48.89; H, 3.73; N, 41.46%; Found: C, 48.71; H, 3.60; N, 41.25%.

**7,12-Dihydrobenzo[g][1,2,4]triazolo[4,3-c]pteridin-3-amine (43).** Brown solid from EtOH in 65% yield; mp 225–227°C; IR (KBr): ν (cm−1): 1616–1625 (3C=O); 3109–3281 (2NH2, 2NHstr); MS (m/z, %): 239.0 (M+, 42); Anal. Calcd for C11H10N6 (239.24): C, 55.22; H, 3.79; N, 40.98%; Found: C, 55.14; H, 3.58; N, 40.76%.

**3-Amino-2-mercapto-5,10-dihydrobenzo[g]pteridin-4(3H)-one (31).** A solution of compound 2 (0.21 g, 1 mmol) in pyridine (30 mL) was reacted with carbon disulphide (1 mmol), and the reaction mixture was refluxed for 5 h. The mixture was poured into ice water, filtered, and recrystallized from EtOH to afford 31 in 80% yield as brown powder mp 270–272°C; IR (KBr): ν (cm−1): 1622 (C=O), 1711 (C=O), 2450 (S-H2), 3142–3361 (2 NH2, NH2str); 1'H NMR (δ, DMSO-d6): 4.65 (s, 2H, NH2, D2O exchangeable), 6.78–7.02 (m, 4H, Ar-H), 11.12 (b, s, 1H, NH, D2O exchangeable); 12.32 (s, 1H, N–Hquinox, D2O exchangeable) and 12.71 (s, 1H, N–Hquinox, D2O exchangeable); MS (m/z, %): 247.0 (M+, 55); Anal. Calcd for C10H8N2O (247.28): C, 48.57; H, 3.67; N, 28.32; S, 12.97%; Found: C, 48.37; H, 3.51; N, 28.14; S, 12.71%.

**General procedure for preparation of compounds 34 and 41.** A mixture of compound 33 or 40 (1 mmol), formic acid (5 mL), and catalytic amount of HCl conc. acid was heated under reflux for 10 h; the reaction mixture was cooled to RT and poured onto H2O (150 mL); the resulted solid was filtered off, washed with MeOH, dried, and recrystallized using proper solvent to afford the triazolo-pyrimidines 34 and 41, respectively. The physical data of these compounds are as follows.

**3-Amino-5,10-dihydrobenzo[g][1,2,4]triazolo[5,1-b]pteridin-11(3H)-one (34).** Orange powder from EtOH in 55% yield; mp 125–127°C; IR (KBr): ν (cm−1): 1617–1623 (2C=N); 1702 (C=O); 3212–3323 (2NH2, NH2str); 1'H NMR (300 MHz, DMSO-d6): 4.28 (s, 1H, NH2, D2O exchangeable), 7.18–7.52 (m, 4H, Ar-H), 8.76 (s, 1H, Triaz-C=N-H), 12.41 (s, 1H, N–Hquinox, D2O exchangeable), and 12.53 (s, 1H, N–Hquinox, D2O exchangeable); MS (m/z, %): 255.0 (M+, 35); Anal. Calcd for C11H9N6O (255.24): C, 51.76; H, 3.55; N, 38.41%; Found: C, 51.51; H, 3.28; N, 38.27%.

**7,12-Dihydrobenzo[g][1,2,4]triazolo[4,3-c]pteridine (41).** Yellow crystals from MeOH in 67% yield; mp 175–177°C; IR (KBr): ν (cm−1): 1612–1625 (3C=N); 3100–3280 (2NH2, 2NHstr); 1'H NMR (300 MHz, DMSO-d6): 7.18–7.52 (m, 5H, Ar-H & Pyrimm-C=N-H), 8.51 (s, 1H, Triaz-C=N-H), 12.31 (s, 1H, N–Hquinox, D2O exchangeable), and 12.47 (s, 1H, N–Hquinox, D2O exchangeable); MS (m/z, %): 224.0 (M, 55); Anal. Calcd for C11H8N6 (242.22): C, 58.92; H, 3.60; N, 37.48%; Found: C, 58.74; H, 3.41; N, 37.28%.

**General procedure for preparation of compounds 35 and 42.** The compound 33 or 40 (10 mmol) was dissolved in glacial AcOH acid (25 mL) and stirred under reflux for 10 h; the reaction mixture was allowed to cool to RT and poured onto H2O (50 mL). The solid thus formed was collected by filtration. The crude solid was washed with cold EtOH (20 mL), and recrystallized from proper solvent to afford the triazolo-pyrimidine derivatives 35 and 42, respectively. The physical data of these compounds are as follows.

**3-Amino-2-methyl-5,10-dihydrobenzo[g][1,2,4]triazolo[5,1-b]pteridin-11(3H)-one (35).** Buff color solid from EtOH in
72% yield; mp 214–216°C; IR (KBr): v (cm⁻¹) 1617–1623 (2C=NHstr.), 1705 (C=Ostr.), 2987 (Me), 3212–3232 (2NH₂str., NH₂str.); ¹H NMR (300 MHz, DMSO-d₆): 2.02 (s, 3H, Me), 4.31 (s, 1H, NH₂, D₂O exchangeable), 6.98–7.52 (m, 4H, Ar-H), 11.97 (s, 1H, N–Hquinox., D₂O exchangeable), and 12.21 (s, 1H, N–Hquinox., D₂O exchangeable); MS (m/z, %): 291.0 (M⁺, 45); Anal. Calcd for C₁₂H₁₀N₆ (238.25): C, 60.50; H, 4.23; N, 24.04%. Found: C, 60.71; H, 4.38; N, 23.84%.

5,10-Dihydrobenzo[g]pteridin-4(3H)-one (38). A mixture of compound 30 (0.20 g, 1 mmol) in 20 mL POC₁₃, 1.2 g of PhCO₂H was added. To a mixture of compound 37, %: 200.0 (M⁺, 15); Anal. Calcd for C₁₀H₁₁N₄O (291.31): C, 65.71; H, 4.38; N, 23.84%.

CONCLUSION

In the present work, ethyl 3-amino-1,4-dihydroquinazoline-2-carboxylate (2) was prepared as a precursor in good yield. The reactivity of the terminal o-amino-ester as well as hydrazide moieties was exploited in a series of manipulations encompassing cyclodepsilation for the synthesis of new two and/or three pharmacophoric – motif probes. A panel of pharmacological investigations on these new probes is going in due course.

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