SYNTHETIC UTILITY OF 2-BENZYLIDENE-1,2,3,4-TETRAHYDRO-CARBAZOL-1-ONES. A FACILE SYNTHESES OF PYRANO[2,3-*a*]CARBAZOLES, PYRIDO[2,3-*a*]CARBAZOLES AND PYRIDAZINO[3,4-*a*]CARBAZOLES

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2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **1**, synthons easily accessible from the corresponding 1,2,3,4-tetrahydrocarbazol-1-ones, were utilized in the synthesis of fused carbazoles. In accordance, the reaction of **1** with malononitrile yielded pyrano[2,3-*a*]carbazoles **2a** and **2d** or pyrido[2,3-*a*]carbazoles **2b**, **2c** and **2e**. The reaction of **1** with thiocarbohydrazide or thiosemicarbazide under basic conditions afforded pyridazino[3,4-*a*]carbazoles **3** or thiol substituted pyridazino[3,4-*a*]carbazoles **4**, respectively, in good yields. The formation of the hitherto unknown compounds was well supported by plausible mechanisms. The products formed were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectral methods and by elemental analysis.

Keywords: 2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones; Aldol condensation; Malononitrile; Pyrano[2,3-*a*]carbazoles; Pyrido[2,3-*a*]carbazoles; Thiocarbohydrazide; Thiosemicarbazide; Pyridazino[3,4-*a*]carbazoles.

In recent years, carbazole alkaloids have gained more importance due to their varied and diverse biological activities[1–4]. Discovery of promising antineoplastic activity of ellipticine (5,11-dimethyl-6*H*-pyrido[3,4-*b*]carbazole), tetracyclic compounds of the pyridocarbazole type, have stimulated considerable interest in the field of similar fused systems[5]. In addition, pyrido[3,4-*b*]carbazoles were reported to elicit anti-HIV properties[6]. Earlier papers from our laboratory have explored 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **1** to construct various fused carbazoles of diverse pharmacological potentials[7–9]. At this context, there are more possibilities of utilizing this promising intermediate to construct newer fused carbazoles. It has been reported earlier that quaternization of the pyridine nitrogen of the pyrido[3,4-*b*]carbazole moiety, like in the case of the 9-hydroxy-2-methylellipticinium acetate, as well as introduction of a basic side chain into position 1 of the tetracyclic system, can enhance the desired

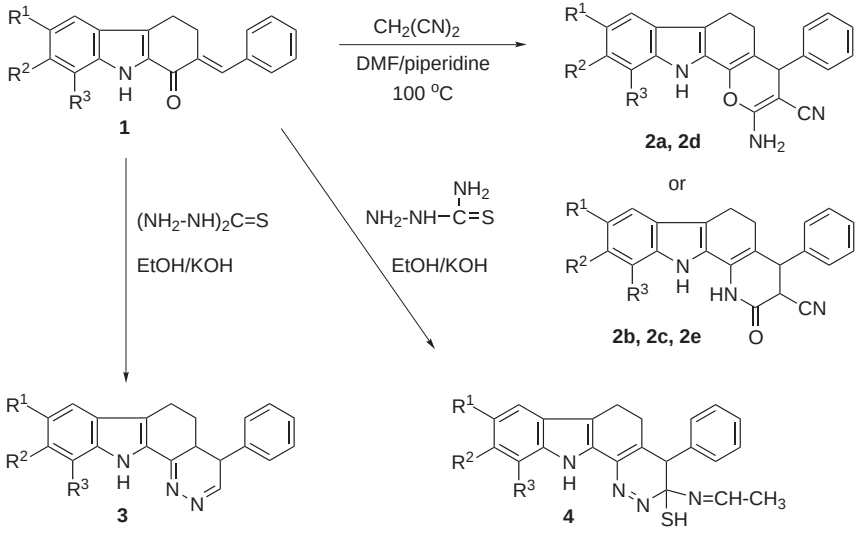
solubility. Moreover, it has been shown that such a (dialkylamino)-alkylamino substructure significantly enhances affinity to the phosphate backbone of DNA [10]. Some pyridazino carbazoles were also reported to be potent antitumor agents, but their synthesis was complicated[11,12]. Based on the above facts, we aimed to synthesize pyrimido- and pyridazino-fused carbazoles from 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **1**.

So far, [*b*]- and [*c*]-fused pyridocarbazoles have been reported[13]. The lack of reports on [*a*]-fused pyridocarbazoles and other carbazoles with heterocycles bearing a phenyl substitution at the position 4 have aroused our interest to devise an elegant synthetic route to pyrido[2,3-*a*]carbazoles, which could exhibit anticancer activity. As there are no reports on thio-substituted pyridazino[3,4-*a*]carbazoles, our present study also tries to devolope a short synthetic route to these compounds.

Starting 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one **1** was treated with malononitrile in *N*,*N*-dimethylformamide using piperidine as a catalyst. The reaction of 2-benzylidene-8-methyl-1,2,3,4-tetrahydrocarbazol-1-one (**1a**) afforded a single product, which was purified by column chromatography. The IR spectrum showed two absorption bands, one at 3295 and the other at 3210 cm^{-1}, which can be assigned to NH and NH_2 stretching vibrations, respectively. A strong band at 2206 cm^{-1} was due to the cyano group. The ^1H NMR spectrum recorded a three-proton singlet at δ 2.57 for 10-CH_3 protons, two multiplets appearing between δ 2.66–2.70 and 2.83–2.86 for the C-5 and C-6 methylene protons, respectively. A broad singlet at δ 5.16 was due to the amino group protons at the C-2 position. The 8-H proton appeared as a multiplet between δ 7.06 and 7.12. The aromatic protons at C-7 and C-9 appeared as doublets at δ 7.31 with J = 6.48 Hz and δ 7.43 with J = 7.12 Hz, respectively. The protons of the benzene ring appeared as an unresolved multiplet of five-proton intensity between δ 7.51 and 7.59. A sharp singlet in the downfield region of δ 7.63 was due to the 4-H [6,7]. The carbazole NH appeared as a broad singlet at δ 9.32. The mass spectrum showed the molecular ion peak at *m/z* 353 (23%). The elemental analysis (78.12% C, 5.42% H, 11.95% N) agreed well with the molecular formula $C_{23}H_{19}N_3O$. Based on the above spectral and analytical data, the structure of the product was assigned as 2-amino-10-methyl-4-phenyl-5,6-dihydro-4*H*-pyrano[2,3-*a*]carbazole-3-carbonitrile (**2a**). Extension of this reaction with **1d** afforded the corresponding 2-amino-4-phenyl-5,6-dihydro-4*H*-pyrano[2,3-*a*]carbazole-3-carbonitrile (**2d**).

Interestingly, the same reaction of **1b**, **1c** and **1e**, resulted in the formation of a rearranged product, namely, 2-oxo-1,2,3,4,5,6-hexahydro-2-oxo-pyrido[2,3-*a*]carbazole-3-carbonitrile derivatives **2b**, **2c** and **2e**, re-

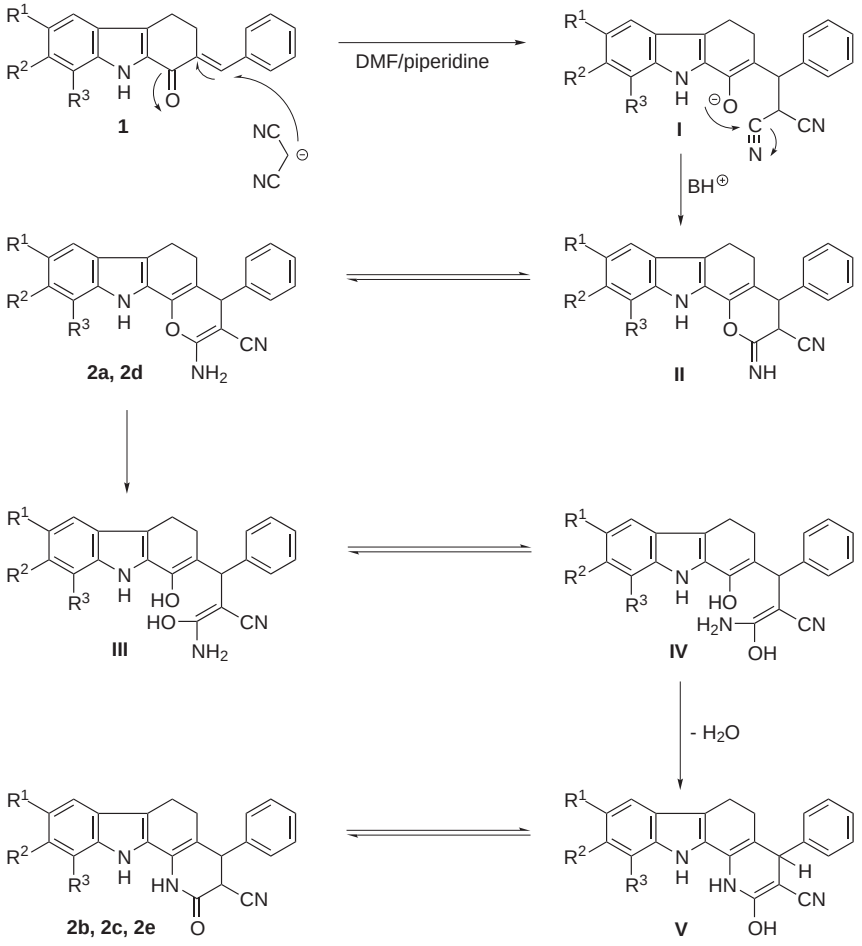
spectively (Scheme 1). The IR spectrum of **2b** showed broad bands at 3395 and 3261 cm^{-1} corresponding to two NH groups. The CN group stretching vibration was noted as a strong band at 2210 cm^{-1}. The intense band at 1643 cm^{-1} confirmed the presence of a carbonyl group. The ^1H NMR spectrum exhibited a three-proton singlet at δ 2.48 for 9-CH_3 protons, two multiplets, each for two protons between δ 2.64–3.07 and 3.24–3.32 for C-5 and C-6 protons, respectively. An unresolved multiplet appeared between δ 7.23 and 7.37, which was due to the five aromatic protons of the phenyl ring. Two doublets centered at δ 7.00 and 7.41 with J = 7.82 Hz correspond to the C-7 and C-8 protons, respectively. A singlet at δ 7.80 was due to the 10-H. The two protons at C-3 and C-4 positions resonated as a multiplet at δ 7.45–7.55. A singlet at δ 9.02 is due to the NH proton at C-1 and indicates the absence of the amino group at C-1 position. The carbazole-NH proton appeared as a broad singlet at δ 9.15. The elemental analysis and the mass spectrum data were in good agreement with the molecular formula $C_{23}H_{19}N_3O$. Similar products **2c** and **2e** were obtained from **1c** and **1e**, respectively (Scheme 1).



1–4	R^1	R^2	R^3
a	H	H	CH_3
b	H	CH_3	H
c	CH_3	H	H
d	H	H	H
e	Cl	H	H

SCHEME 1

The proposed mechanism is shown in Scheme 2. The 1,4-Michael addition of 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one **1** and the carbanion derived from malononitrile in the presence of piperidine resulted in the formation of the enolate intermediate **I**. This intermediate subsequently attacks the positive-induced carbon of one of the symmetric nitrile groups to afford **II**. Tautomerization of **II** gives **2a** or **2d**. The formation of **2b**, **2c** and



1, 2, I–V	R^1	R^2	R^3
a	H	H	CH_3
b	H	CH_3	H
c	CH_3	H	H
d	H	H	H
e	Cl	H	H

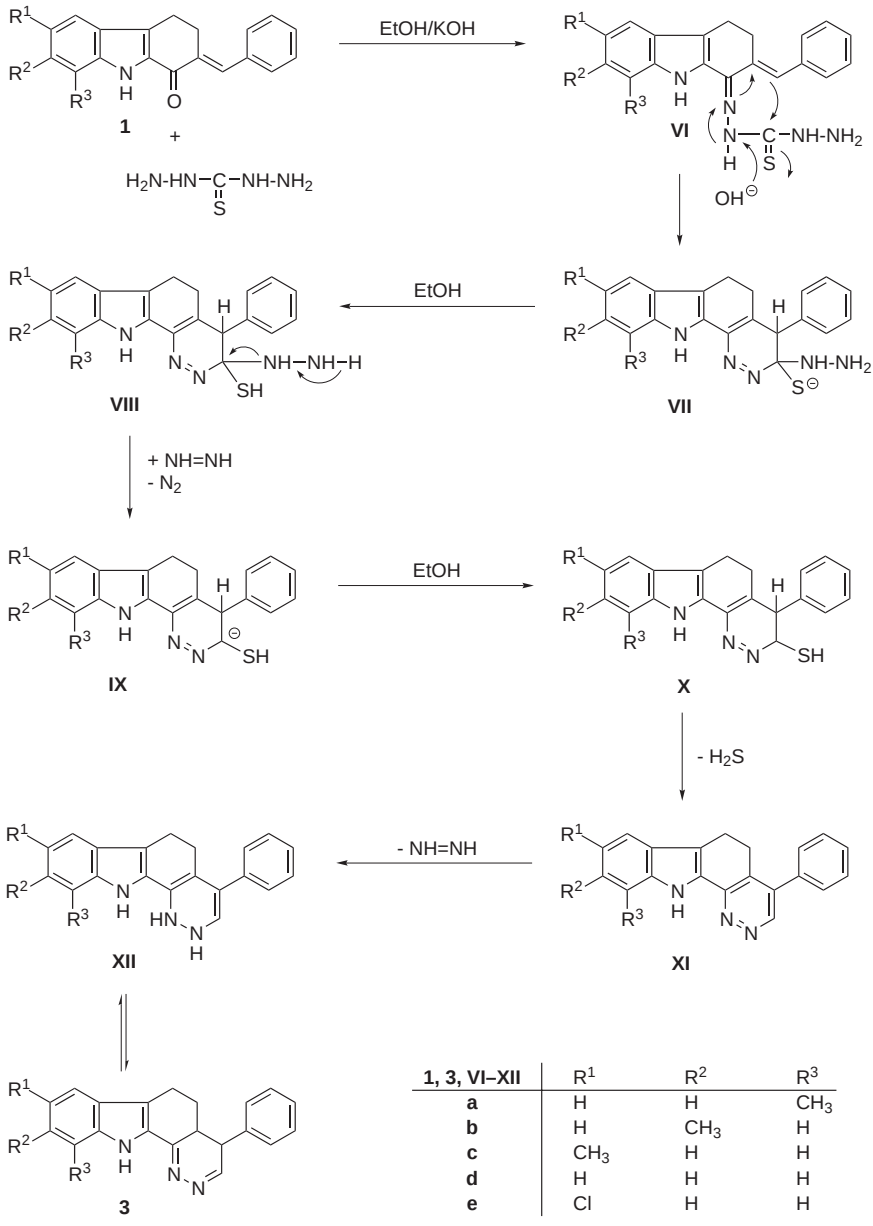
SCHEME 2

2e might be viewed as follows. The tautomer of **II** under basic conditions cleaved the pyran ring to give the intermediate **IV** through **III**, which on cyclization affords the tricyclic intermediate **V**, a tautomer of the 2-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-*a*]carbazole-3-carbonitrile **2**.

In another experiment, the reaction of 2-benzylidene-8-methyl-1,2,3,4-tetrahydrocarbazol-1-one (**1a**) with thiocarbohydrazide in alcoholic KOH yielded a yellow crystalline product. The IR spectra of the compound showed a prominent band at 3290 cm^{-1} corresponding to the NH group. The C=N group stretching vibration was noted as a band with low intensity at 1583 cm^{-1}. The ^1H NMR spectrum recorded the following resonances. A three-proton singlet appeared at δ 2.49 corresponding to the 10-CH_3. Two multiplets of two-proton intensity at δ 2.20–2.73 and 2.99–3.09 are due to the C-5 and C-6 methylene protons, respectively. A multiplet appeared in the region δ 3.25–3.28 due to the 4a-H. The benzylic proton[6,7] at C-4 resonated as a multilplet between δ 7.06 and 7.10. A doublet centered at δ 7.15 with J = 7.28 Hz was due to 3-H. A six-proton unresolved multiplet appeared between δ 7.31 and 7.43 which accounts for the protons between C-2′ to C-6′ and the C-8 aromatic proton. Two doublets at δ 7.45 with J = 7.44 Hz and δ 7.51 with J = 7.60 Hz appeared due to the H-7 and H-9, respectively. The carbazole NH appeared as a broad singlet at δ 8.95. The mass spectrum also recorded the molecular ion peak at *m/z* 313 (25%) and the elemental analysis (80.49% C, 6.03% H, 13.48% N) agreed well with the molecular formula $C_{21}H_{19}N_3$. Based on these data, the structure of 10-methyl-4-phenyl-4,4a,5,6-tetrahydropyridazino[3,4-*a*]carbazole (**3a**) was assigned. Similar compounds, **3b**, **3c**, **3d** and **3e**, were prepared from **1b**, **1c**, **1d** and **1e**, respectively (Scheme 1).

The proposed mechanism is shown in Scheme 3. 2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-one **1** under basic conditions in ethanol with thiocarbohydrazide forms a thiocarbonohydrazone intermediate **VI**. In the presence of a base, the benzylic carbon attacks the thioamide carbon atom to afford the cyclized intermediate **VII**. In the presence of ethanol, the S^- gets protonated to form intermediate **VIII**, which loses diimide to afford **X** via **IX**. The thiol intermediate **X** loses sulfur as H_2S and subsequently diimide donates hydrogen[14–16] to the intermediate to form **XII**, which tautomerizes to afford the compound **3**.

The reaction of 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **1** with thiocarbohydrazide has yielded pyridazinocarbazoles and not the thiol-substituted pyridazinocarbazoles as expected. Also, the elimination of dimide in the plausible mechanism, has also inspired our thoughts to use a reactant which has one amino group less than that of the thiocarbo-



1, 3, VI–XII	R^1	R^2	R^3
a	H	H	CH_3
b	H	CH_3	H
c	CH_3	H	H
d	H	H	H
e	Cl	H	H

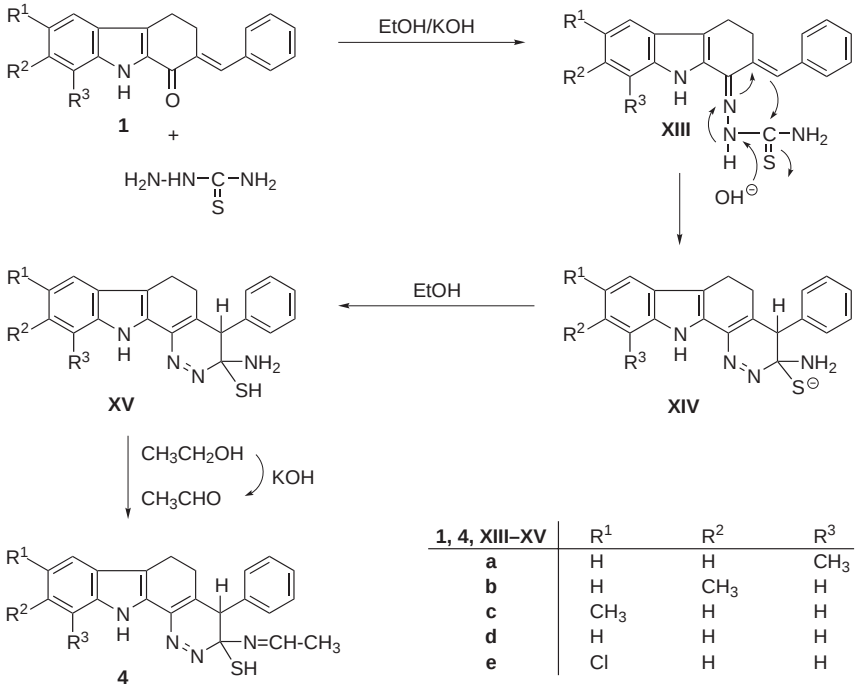
SCHEME 3

hydrazide. Based on this aim thiosemicarbazide was chosen as the reactant. 2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-one **1** was reacted with thiosemicarbazide in alcoholic KOH. Interestingly, the reaction afforded a thiol-substituted compound, 3-(ethylideneamino)-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-*a*]carbazole-3-thiol **4**. The reaction of 2-benzylidene-7-methyl-1,2,3,4-tetrahydrocarbazol-1-one (**1b**) with thiosemicarbazide in alcoholic KOH afforded a product which melted at 140 °C. The product in its IR spectrum showed strong bands at 3246 cm^{-1} corresponding to the NH stretching vibration. The less intense band at 1624 cm^{-1} was due to the C=N stretching vibrations. The ^1H NMR spectrum showed a multiplet between δ 1.24 and 1.28 corresponding to the imino methyl protons at C-3. Two multiplets of two-proton intensity at δ 2.22–2.69 and 2.97–3.10 are due to the methylene protons at C-5 and C-6, respectively. A singlet at δ 2.47 corresponds to the methyl protons at C-9. The SH proton at C-3 appeared as a multiplet in the region δ 3.23–3.32. The –C**H**=CH_3 proton at C-3 appeared as a multiplet in the region δ 6.97–7.00. A multiplet of five-proton intensity in the region δ 7.19–7.40 was due to the aromatic protons C-2′ to C-6′ of the phenyl ring. The 4-H resonated as a singlet at δ 7.42. Two doublets with single proton intensity each appeared at δ 7.53 and 7.66 with J = 6.76 Hz for the C-7 and C-8 protons, respectively. A singlet at δ 7.79 was due to the 10-H. A broad singlet at δ 8.96 corresponds to the carbazole NH proton. The appearance of the molecular ion peak at m/z = 386 (2%) also agreed well with the proposed structure. The elemental analysis (71.55% C, 5.65% H, 14.58% N) provided the molecular formula $C_{23}H_{22}N_4S$ for **4b**, as 3-(ethylideneamino)-9-methyl-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-*a*]-carbazole-3-thiol. The repeatability of the experiment was successfully tested on **1a** and **1c**–**1e** to afford the respective, 3-ethylidene-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-*a*]carbazole-3-thiols as **4a**, **4c**, **4d** and **4e** (Scheme 1).

The proposed mechanism is shown in Scheme 4. The formation of 3-(ethylideneamino)-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-*a*]carbazole-3-thiol **4** might be explained mechanistically as follows. The reaction of 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one **1** reacts with thiosemicarbazide in the presence of ethanol and KOH forming the thiosemicarbazone **XIII**, which cyclizes in the presence of the base to yield **XV** via **XIV**. The intermediate **XV** on condensation with acetaldehyde formed in situ[17,18] under this condition from ethanol affords the ethylideneamino compound **4**.

In conclusion, in this report we have presented a facile and elegant method to prepare pyrido[2,3-*a*]carbazoles, pyrano[2,3-*a*]carbazoles,

pyridazino[3,4-*a*]carbazoles by utilizing 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one. The synthetic route proposed is short and the yields of the compounds are good. All the compounds have been characterized by spectral and elemental analyses. The formation of the hitherto unknown compounds has been explained by plausible mechanisms.



1, 4, XIII–XV	R^1	R^2	R^3
a	H	H	CH_3
b	H	CH_3	H
c	CH_3	H	H
d	H	H	H
e	Cl	H	H

SCHEME 4

EXPERIMENTAL

Melting points were determined using a Mettler FP 51 apparatus and are uncorrected. UV spectra were recorded in ethanol using a Perkin–Elmer UV-VIS spectrophotometer. IR spectra (in cm^{-1}) were recorded on a Shimadzu FTIR-8201 PC spectrophotometer using potassium bromide. ^1H NMR and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were recorded on a Varian AMX 400 FT-NMR spectrometer using tetramethylsilane as internal reference in $CDCl_3$. Mass spectra were recorded on a Jeol-JMS-D-300 mass spectrometer (70 eV). Microanalyses were done on a Perkin–Elmer Model 240 CHN analyzer. The purity of the products was tested by TLC using glass plates coated with silica gel G (HiMedia Laboratories, India). Peteroleum ether and ethyl acetate were used as developing solvents.

Reaction of 2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-ones **1** with malononitrile. General Procedure

A solution of the respective 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one (**1**; 1 mmol) in *N*,*N*-dimethylformamide (15 ml) was prepared and piperidine (2 ml) was added. Malononitrile (0.66 g, 5 mmol) was added and the mixture was heated on a water bath for 5 h. Then the mixture was poured onto crushed ice, the mixture was neutralized with ice-cold HCl (1:1) and extracted with ethyl acetate (3 × 50 ml). The organic layer was thoroughly washed with water and dried over anhydrous sodium sulfate. On removal of the solvent, the brown crude mixture obtained was purified by column chromatography on silica using a petroleum ether–ethyl acetate (98:2) mixture as eluant to afford a yellow crystalline product.

2-Amino-10-methyl-4-phenyl-5,6-dihydropyrano[2,3-a]carbazol-3-carbonitrile (**2a**). Yield 70%, m.p. 211 °C (petroleum ether–ethyl acetate). For $C_{23}H_{19}N_3O$ (353.4) calculated: 78.16% C, 5.42% H, 11.89% N; found: 78.12% C, 05.42% H, 11.95% N. UV, λ_{max} (log ε): 226 (4.49), 248 (4.89), 282 (3.85), 294 (4.05), 310 (3.97), 326 (3.94), 339 (3.92). IR: 3295, 3210, 2923, 2825, 2206 (CN), 1647, 1624, 1541, 1489, 1458, 1319. ^{1}H NMR: 2.57 s, 3 H (CH_3-10); 2.66–2.70 m, 2 H (H-5); 2.83–2.86 m, 2 H (H-6); 5.16 s, 2 H (NH_2-2); 7.06–7.12 m, 1 H (H-8); 7.31 d, 1 H, *J* = 6.48 (H-7); 7.43 d, 1 H, *J* = 7.12 (H-9); 7.51–7.59 m, 5 H (H-2′ to H-6′); 7.63 s, 1 H (H-4); 9.32 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.78 (C_{10}-CH_3), 21.47 (C_5), 27.75 (C_6), 36.49 (C_4), 52.97 (C_2), 107.91 (CN), 112.19 (C_{6a}), 112.78 (C_7), 115.98 (C_3), 118.39 (C_9), 119.87 (C_8), 120.94 (C_{10}), 121.07 (C_{6b}), 121.47 (C_{10a}), 125.51 (C_{11a}), 127.09 (C_{4a}), 127.29 ($C_{1'}$), 127.81 ($C_{3'}$), 128.39 ($C_{2'}$), 128.96 ($C_{4'}$), 129.29 ($C_{5'}$), 130.05 ($C_{6'}$), 135.21 (C_{11b}). MS (EI, *m/z* (rel.%)): 353 (23) [M^+], 335 (8), 314 (20), 303 (10), 292 (26), 256 (16), 241 (10), 227 (80).

9-Methyl-2-oxo-4-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-a]carbazole-3-carbonitrile (**2b**). Yield 75%, m.p. 190 °C (petroleum ether–ethyl acetate). For $C_{23}H_{19}N_3O$ (353.4) calculated: 78.16% C, 5.42% H, 11.89% N; found: 78.14% C, 05.45% H, 11.83% N. UV, λ_{max} (log ε): 238 (4.64), 250 (4.85), 282 (3.87), 296 (4.05), 307 (3.98), 328 (3.59), 339 (3.54). IR: 3395, 3261, 2924, 2825, 2210 (CN), 1643, 1624, 1578, 1541, 1489, 1437, 1263. ^{1}H NMR: 2.48 s, 3 H (CH_3-9); 2.64–3.07 m, 2 H (H-5); 3.24–3.32 m, 2 H (H-6); 7.00 d, 1 H, *J* = 7.82 (H-7); 7.23–7.37 d m, 5 H (H-2′ to H-6′); 7.41 d, 1 H, *J* = 7.82 (H-8); 7.45–7.55 m, 2 H (H-3, H-4); 7.80 s, 1 H (H-10); 9.02 s, 1 H (NH-1); 9.15 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.51 (C_9-CH_3), 21.49 (C_5), 27.81 (C_6), 25.42 (C_4), 41.77 (C_3), 109.11 (CN), 112.41 (C_{6a}), 119.51 (C_7), 120.77 (C_{10}), 126.24 (C_9), 127.95 (C_{11a}), 128.44 (C_8), 128.73 (C_{10a}), 129.02 (C_{6b}), 129.25 ($C_{1'}$), 129.83 ($C_{3'}$), 132.51 (C_{11b}), 135.22 ($C_{2'}$), 136.37 ($C_{4'}$), 136.61 ($C_{5'}$), 137.21 ($C_{6'}$), 190.58 (C=O).

8-Methyl-2-oxo-4-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-a]carbazole-3-carbonitrile (**2c**). Yield 77%, m.p. 175 °C (petroleum ether–ethyl acetate). For $C_{23}H_{19}N_3O$ (353.4) calculated: 78.16% C, 5.42% H, 11.89% N; found: 78.27% C, 05.31% H, 11.82% N. UV, λ_{max} (log ε): 226 (4.61), 248 (4.68), 285 (3.93), 295 (4.16), 310 (3.97), 333 (3.71), 346 (3.67). IR: 3355, 3277, 2925, 2854, 2232 (CN), 1638, 1587, 1541, 1489, 1437, 1263. ^{1}H NMR: 2.46 s, 3 H (CH_3-8); 2.96–3.06 m, 2 H (H-5); 3.24–3.32 m, 2 H (H-6); 7.22 d, 1 H, *J* = 8.34 (H-9); 7.42 d, 1 H, *J* = 8.84 (H-10); 7.45 s, 1 H (H-7); 7.47–7.63 m, 7 H (H-3, H-4, H-2′ to H-6′); 8.72 s, 1 H (NH-1); 9.03 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.95 (C_8-CH_3), 21.42 (C_5), 27.67 (C_6), 25.38 (C_4), 41.81 (C_3), 111.39 (CN), 112.27 (C_{6a}), 119.37 (C_7), 120.65 (C_9), 121.81 (C_{4a}), 126.21 (C_{10}), 127.98 (C_{11a}), 128.26 (C_8), 128.46 (C_{6b}), 128.64 (C_{10a}), 129.27 ($C_{1'}$), 129.78 ($C_{3'}$), 132.57 (C_{11b}), 135.20 ($C_{2'}$), 136.31 ($C_{4'}$), 136.54 ($C_{5'}$), 137.14 ($C_{6'}$), 191.23 (C=O).

2-Amino-4-phenyl-5,6-dihydropyrano[2,3-a]carbazol-3-carbonitrile (**2d**) Yield 78%, m.p. 105 °C (petroleum ether–ethyl acetate). For $C_{22}H_{17}N_3O$ (339.4) calculated: 77.86% C, 5.05% H, 12.38% N; found: 77.80% C, 5.09% H, 12.33% N. UV, λ_{max} (log ε): 229 (4.44), 243 (4.62), 250 (4.46), 261 (4.34), 295 (4.21), 306 (3.96), 322 (3.94), 335 (3.92). IR: 3390, 3285, 2924, 2855, 2210 (CN), 1645, 1545, 1435, 1332, 1016. ^{1}H NMR: 2.26–2.78 m, 2 H (H-5); 2.83–3.10 m, 2 H (H-6); 5.16 s, 2 H (NH_2-2); 7.16 d, 1 H, *J* = 7.68 (H-7); 7.29–7.48 m, 5 H (H-2′ to H-6′); 7.51 d, 1 H, *J* = 7.24 (H-10); 7.56–7.71 m, 2 H (H-8, H-9); 7.80 s, 1 H (H-4); 9.34 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 25.02 (C_5), 23.21 (C_6), 36.47 (C_4), 52.19 (C_2), 107.55 (CN), 112.07 (C_{6a}), 112.63 (C_7), 115.94 (C_3), 118.23 (C_9), 119.82 (C_8), 120.55 (C_{10}), 120.72 (C_{6b}), 121.40 (C_{10a}), 125.45 (C_{11a}), 127.05 (C_{4a}), 127.26 ($C_{1'}$), 127.76 ($C_{3'}$), 128.31 ($C_{2'}$), 128.86 ($C_{4'}$), 129.21 ($C_{5'}$), 129.79 ($C_{6'}$), 135.38 (C_{11b}).

9-Chloro-2-oxo-4-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-a]carbazole-3-carbonitrile (**2e**) Yield 69%, m.p. 155 °C (petroleum ether–ethyl acetate). For $C_{22}H_{16}N_3OCl$ (373.8) calculated: 70.68% C, 4.31% H, 11.24% N; found: 70.78% C, 4.22% H, 11.31% N. UV, λ_{max} (log ε): 229 (4.65), 251 (4.69), 288 (3.96), 298 (4.18), 318 (3.99), 338 (3.74), 354 (3.70). IR: 3325, 3250, 2923, 2825, 2206 (CN), 1637, 1624, 1541, 1489, 1458, 1319. ^{1}H NMR: 2.64–2.80 m, 2 H (H-5); 2.86–2.98 m, 2 H (H-6); 7.16–7.22 m, 5 H (H-2′ to H-6′); 7.32–7.37 m, 3 H (H-7, H-9, H-10); 7.47–7.58 m, 2 H (H-3, H-4); 8.81 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 21.55 (C_5), 27.69 (C_6), 25.49 (C_4), 42.09 (C_3), 107.88 (CN), 113.01 (C_{6a}), 119.59 (C_7), 120.69 (C_9), 121.95 (C_{4a}), 126.32 (C_{10}), 128.05 (C_{11a}), 128.16 (C_8), 128.46 (C_{6b}), 128.65 (C_{10a}), 129.29 ($C_{1'}$), 129.71 ($C_{3'}$), 132.59 (C_{11b}), 135.23 ($C_{2'}$), 136.39 ($C_{4'}$), 136.67 ($C_{5'}$), 137.25 ($C_{6'}$), 190.95 (C=O).

Synthesis of 4-Phenyl-4,4a,5,6-tetrahydropyridazino[3,4-*a*]carbazoles **3a**–**3e**. General Procedure

The respective 2-benzylidene-1,2,3,4-tetrahydrocarbazol-1-one (**1**; 1 mmol) was dissolved in 5% alcoholic solution of KOH and thiocarbohydrazide (0.159 g, 1.5 mmol) was added. The reaction mixture was refluxed on a water bath for 6 h and then the excess of solvent was removed. The mixture was then poured onto ice neutralized with ice-cold HCl (1:1) and extracted with ethyl acetate (3 × 50 ml). The organic layer was thoroughly washed with water and dried over anhydrous sodium sulfate. The obtained brown crude mixture was purified by column chromatography on silica using a petroleum ether–ethyl acetate (95:5) mixture as eluent to afford a yellow crystalline product.

10-Methyl-4-phenyl-4,4a,5,6-tetrahydropyridazino[3,4-a]carbazole (**3a**). Yield 65%, m.p. 142 °C (petroleum ether–ethyl acetate). For $C_{21}H_{19}N_3$ (313.4) calculated: 80.48% C, 6.11% H, 13.41% N; found: 80.49% C, 6.03% H, 13.48% N. UV, λ_{max} (log ε): 229 (4.51), 245 (4.84), 280 (3.83), 298 (4.09), 315 (4.12), 325 (3.91), 339 (3.92). IR: 3290, 2921, 2850, 1647, 1583, 1549, 1445, 1327, 1227, 1171, 743, 689. ^{1}H NMR: 2.20–2.73 m, 2 H (H-5); 2.49 s, 3 H (10-CH_3); 2.99–3.09 m, 2 H (H-6); 3.25–3.28 m, 1 H (H-4a); 7.06–7.10 m, 1 H (H-4); 7.15 d, 1 H, *J* = 7.28 (H-3); 7.31–7.43 m, 6 H (H-2′ to H-6′, H-8); 7.45 d, 1 H, *J* = 7.44 (H-7); 7.51 d, 1 H, *J* = 7.60 (H-9); 8.95 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.02 (C_{10}-CH_3), 25.08 (C_5), 27.86 (C_6), 37.47 (C_{4a}), 38.09 (C_4), 110.14 (C_3), 113.17 (C_{11b}), 121.23 (C_{6a}), 121.98 (C_7), 122.43 (C_8), 123.18 (C_9), 125.91 (C_{10}), 126.87 (C_{6b}), 127.51 (C_{10a}), 128.76 (C_{11a}), 129.07 ($C_{1'}$), 129.81 ($C_{3'}$), 132.23 ($C_{2'}$), 133.80 ($C_{4'}$), 135.10 ($C_{5'}$), 136.51 ($C_{6'}$). MS (EI, *m/z* (rel.%)): 313 (25) [M^+], 286 (78), 272 (10), 258 (22), 242 (10), 231 (10), 210 (5), 198 (3).

9-Methyl-4-phenyl-4,4a,5,6-tetrahydropyridazino[3,4-a]carbazole (**3b**). Yield 68%, m.p. 175 °C (petroleum ether–ethyl acetate). For $C_{21}H_{19}N_3$ (313.4) calculated: 80.48% C, 6.11% H, 13.41% N; found: 80.45% C, 6.01% H, 13.54% N. UV, λ_{max} (log ε): 236 (4.62), 254 (4.87), 287 (3.89), 298 (4.07), 310 (3.99), 325 (3.55), 337 (3.57). IR: 3242, 2924, 2857, 1641, 1578, 1536, 1475, 1333, 1262, 1168. ^{1}H NMR: 2.22–2.68 m, 2 H (H-5); 2.46 s, 3 H (9-CH_3); 2.83–3.07 m, 2 H (H-6); 3.24–3.33 m, 1 H (H-4a); 6.85–7.00 m, 1 H (H-4); 7.22 d, 1 H, *J* = 8.68 (H-3); 7.28 d, 1 H, *J* = 8.16 (H-7); 7.31–7.48 m, 5 H (H-2′ to H-6′); 7.53 d, 1 H, *J* = 8.16 (H-8); 7.82 s, 1 H (H-10); 9.33 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 19.99 (C_9-CH_3), 25.03 (C_5), 27.62 (C_6), 37.79 (C_{4a}), 38.20 (C_4), 110.49 (C_3), 112.39 (C_{11b}), 120.98 (C_{6a}), 121.54 (C_7), 122.69 (C_8), 123.96 (C_{10}), 125.38 (C_9), 127.24 (C_{6b}), 128.20 (C_{10a}), 128.44 (C_{11a}), 128.85 ($C_{1'}$), 129.75 ($C_{3'}$), 132.17 ($C_{2'}$), 133.82 ($C_{4'}$), 135.08 ($C_{5'}$), 136.41 ($C_{6'}$).

8-Methyl-4-phenyl-4,4a,5,6-tetrahydropyridazino[3,4-a]carbazole (**3c**). Yield 60%, m.p. 135 °C (petroleum ether–ethyl acetate). For $C_{21}H_{19}N_3$ (313.4) calculated: 80.48% C, 6.11% H, 13.41% N; found: 80.56% C, 6.12% H, 13.32% N. UV, λ_{max} (log ε): 224 (4.60), 248 (4.69), 288 (3.96), 299 (4.18), 317 (3.99), 338 (3.75), 348 (3.68). IR: 3278, 2924, 2851, 1639, 1583, 1541, 1485, 1387, 1325, 1168, 795. ^{1}H NMR: 2.22–2.66 m, 2 H (H-5); 2.45 s, 3 H (8-CH_3); 2.97–3.10 m, 2 H (H-6); 3.24–3.27 m, 1 H (H-4a); 7.18–7.22 m, 1 H (H-4); 7.30 d, 1 H, *J* = 8.24 (H-9); 7.33–7.37 m, 5 H (H-2′ to H-6′); 7.41 d, 1 H, *J* = 8.24 (H-10); 7.45 d, 1 H, *J* = 7.52 (H-3); 7.80 s, 1 H (H-7); 9.00 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 19.56 (C_8-CH_3), 25.18 (C_5), 27.91 (C_6), 37.81 (C_{4a}), 38.43 (C_4), 110.27 (C_3), 113.17 (C_{11b}), 121.05 (C_{6a}), 121.61 (C_7), 123.23 (C_{10}), 123.89 (C_9), 125.49 (C_8), 127.71 (C_{6b}), 128.11 (C_{10a}), 128.78 (C_{11a}), 128.99 ($C_{1'}$), 129.51 ($C_{3'}$), 132.28 ($C_{2'}$), 133.69 ($C_{4'}$), 135.21 ($C_{5'}$), 136.57 ($C_{6'}$).

4-Phenyl-4,4a,5,6-tetrahydropyridazino[3,4-a]carbazole (**3d**). Yield 70%, m.p. 170 °C (petroleum ether–ethyl acetate). For $C_{20}H_{17}N_3$ (299.4) calculated: 80.24% C, 5.72% H, 14.04% N; found: 80.32% C, 5.61% H, 14.07% N. UV, λ_{max} (log ε): 224 (4.45), 248 (4.66), 252 (4.49), 265 (4.34), 296 (4.27), 315 (3.98), 329 (3.97), 338 (3.95). IR: 3267, 2920, 2855, 1647, 1591, 1541, 1477, 1335, 1165, 731. ^{1}H NMR: 2.24–2.68 m, 2 H (H-5); 3.00–3.17 m, 2 H (H-6); 3.25–3.28 m, 1 H (H-4a); 7.31–7.37 m, 7 H (H-2′ to H-6′, H-8, H-9); 7.39 d, 1 H, *J* = 7.00 (H-3); 7.45 d, 1 H, *J* = 7.28 (H-7); 7.55 d, 1 H, *J* = 7.44 (H-10); 9.16 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 25.71 (C_5), 27.59 (C_6), 37.76 (C_{4a}), 38.47 (C_4), 110.61 (C_3), 113.29 (C_{11b}), 121.31 (C_{6a}), 121.95 (C_7), 123.67 (C_{10}), 124.09 (C_9), 124.98 (C_8), 127.63 (C_{6b}), 128.41 (C_{10a}), 128.66 (C_{11a}), 129.01 ($C_{1'}$), 129.43 ($C_{3'}$), 132.47 ($C_{2'}$), 133.70 ($C_{4'}$), 135.43 ($C_{5'}$), 136.81 ($C_{6'}$).

8-Chloro-4-phenyl-4,4a,5,6-tetrahydropyridazino[3,4-a]carbazole (**3e**). Yield 70%, m.p. 135 °C (petroleum ether–ethyl acetate). For $C_{20}H_{16}ClN_3$ (333.8) calculated: 71.96% C, 4.83% H, 12.59% N; found: 71.95% C, 4.78% H, 12.54% N. UV, λ_{max} (log ε): 228 (4.65), 255 (4.72), 283 (3.95), 292 (4.17), 319 (3.98), 342 (3.78), 354 (3.70). IR: 3265, 2920, 2855, 1643, 1587, 1566, 1541, 1469, 1381, 1132, 769. ^{1}H NMR: 2.24–2.68 m, 2 H (H-5); 2.96–3.05 m, 2 H (H-6); 3.24–3.28 m, 1 H (H-4a); 7.31–7.39 m, 6 H (H-4, H-2′ to H-6′); 7.42 d, 1 H, *J* = 8.60 (H-3); 7.45–7.53 m, 2 H (H-9, H-10); 7.81 s, 1 H (H-7); 9.16 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 25.41 (C_5), 27.77 (C_6), 37.49 (C_{4a}), 38.81 (C_4), 111.09 (C_3), 113.21 (C_{11b}), 121.17 (C_{6a}), 122.40 (C_7), 123.54 (C_{10}), 123.90 (C_8), 126.98 (C_6), 127.85 (C_{6b}), 128.27 (C_{10a}), 128.81 (C_{11a}), 129.05 ($C_{1'}$), 129.57 ($C_{3'}$), 132.37 ($C_{2'}$), 133.74 ($C_{4'}$), 135.42 ($C_{5'}$), 136.51 ($C_{6'}$).

Synthesis of 3-(Ethylideneamino)-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-*a*]carbazol-3-thiols **4a**–**4e**. General Procedure

2-Benzylidene-1,2,3,4-tetrahydrocarbazol-1-one (**1**; 1 mmol) was dissolved in 5% alcoholic KOH solution and thiosemicarbazide (0.182 g, 2 mmol) was added. The reaction mixture was refluxed on a water bath for 5 h. Then the excess solvent was removed by distillation and poured onto crushed ice. The mixture was then neutralized with HCl (1:1) and extracted with ethyl acetate to yield a crude product, which was purified by column chromatography on silica. Petroleum ether–ethyl acetate (97:3) was used as eluent to afford yellow crystalline product.

3-(Ethylideneamino)-10-methyl-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-a]carbazol-3-thiol (**4a**). Yield 69%, m.p. 165 °C (petroleum ether–ethyl acetate). For $C_{23}H_{22}N_4S$ (386.5) calculated: 71.46% C, 5.74% H, 14.50% N, 8.30% S; found: 71.45% C, 5.78% H, 14.43% N, 8.24% S. UV, λ_{max} (log ε): 225 (4.50), 247 (4.84), 285 (3.85), 296 (4.10), 313 (3.97), 328 (3.93), 338 (3.94). IR: 3293, 2921, 2851, 1650, 1570, 1544, 1477, 1445, 1326, 1172, 1138, 746, 648. ^{1}H NMR: 1.25–1.27 m, 3 H (imino CH_3); 2.24–2.41 m, 2 H (H-5); 2.49 s, 3 H (10-CH_3); 2.60–3.16 m, 2 H (H-6); 3.25–3.28 m, 1 H (3-SH); 7.06–7.16 m, 6 H (imino CH, H-2′ to H-6′); 7.31–7.40 m, 1 H (H-8); 7.43 d, 1 H, *J* = 7.96 (H-7); 7.51 d, 1 H, *J* = 8.00 (H-9); 7.81 s, 1 H (H-4); 8.80 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.54 (C_{10}-CH_3), 21.71 (N=CH-CH_3), 25.12 (C_5), 27.81 (C_6), 29.18 (C_4), 38.44 (N=CH-CH_3), 59.76 (C_3), 113.05 (C_{4a}), 120.41 (C_{6a}), 123.78 (C_{11a}), 126.12 (C_{11b}), 125.17 (C_7), 128.07 (C_9), 128.81 (C_8), 129.42 (C_{10}), 129.54 (C_{10a}), 130.01 (C_{6b}), 131.54 ($C_{1'}$), 131.79 ($C_{3'}$), 132.31 ($C_{2'}$), 133.81 ($C_{4'}$), 135.10 ($C_{5'}$), 136.52 ($C_{6'}$).

3-(Ethylideneamino)-9-methyl-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-a]carbazol-3-thiol (**4b**). Yield 72%, m.p. 140 °C (petroleum ether–ethyl acetate). For $C_{23}H_{22}N_4S$ (386.5) calculated: 71.46% C, 5.74% H, 14.50% N, 8.30% S; found: 71.55% C, 5.65% H, 14.58% N, 8.22% S. UV, λ_{max} (log ε): 238 (4.64), 250 (4.85), 282 (3.87), 296 (4.05), 307 (3.98), 328 (3.59), 339 (3.54). IR: 3246, 2924, 2854, 1650, 1624, 1577, 1535, 1473, 1445, 1333, 1226, 1168, 769. ^{1}H NMR: 1.24–1.28 m, 3 H (imino CH_3); 2.22–2.69 m, 2 H (H-5); 2.47 s, 3 H (9-CH_3); 2.97–3.06 m, 2 H (H-6); 3.23–3.32 m, 1 H (3-SH); 6.97–7.00 m, 1 H (imino CH); 7.19–7.40 m, 5 H (H-2′ to H-6′); 7.42 s, 1 H (H-4); 7.53 d, 1 H, *J* = 6.76 (H-7); 7.66 d, 1 H, *J* = 6.76 (H-8); 7.79 s, 1 H (H-10); 8.96 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.71 (C_9-CH_3), 21.95 (N=CH-CH_3), 25.30 (C_5), 27.77 (C_6), 29.21 (C_4), 38.57 (N=CH-CH_3), 58.09 (C_3), 112.45 (C_{4a}), 121.27 (C_{6a}), 123.35 (C_{11a}), 125.57 (C_{11b}), 127.28 (C_7), 128.41 (C_{10}), 128.61 (C_8), 129.05 (C_9), 129.30 (C_{10a}), 129.67 (C_{6b}), 131.51 ($C_{1'}$), 131.97 ($C_{3'}$), 132.54 ($C_{2'}$), 133.37 ($C_{4'}$), 135.21 ($C_{5'}$), 136.57 ($C_{6'}$). MS (EI, *m/z* (rel.%)): 386 (2) [M^+], 313 (8), 286 (41), 270 (10), 258 (10), 243 (6), 236 (2), 199 (5).

3-(Ethylideneamino)-8-methyl-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-a]carbazol-3-thiol (**4c**). Yield 65%, m.p. 145 °C (petroleum ether–ethyl acetate). For $C_{23}H_{22}N_4S$ (386.5) calculated: 71.46% C, 5.74% H, 14.50% N, 8.30% S; found: 71.60% C, 5.75% H, 14.44% N, 8.31% S. UV (ethanol), λ_{max} (log ε): 229 (4.68), 254 (4.70), 288 (3.94), 299 (4.18), 318 (3.99), 338 (3.74), 349 (3.69). IR: 3245, 2921, 2855, 1641, 1583, 1541, 1489, 1325, 804, 769. ^{1}H NMR: 1.24–1.27 m, 3 H (imino CH_3); 2.45 s, 3 H (8-CH_3); 2.62–2.69 m, 2 H (H-5); 2.97–3.06 m, 2 H (H-6); 3.23–3.26 m, 1 H (3-SH); 7.19–7.29 m, 6 H (imino CH, H-2′ to H-6′); 7.32 d, 1 H, *J* = 8.62 (H-9); 7.42 s, 1 H (H-4); 7.53 d, 1 H, *J* = 8.62 (H-10); 7.80 s, 1 H (H-7); 8.75 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 20.96 (C_8-CH_3), 21.44 (N=CH-CH_3), 25.05 (C_5), 27.67 (C_6), 29.27 (C_4), 38.29 (N=CH-CH_3), 58.91 (C_3), 112.23 (C_{4a}), 120.62 (C_{6a}), 123.49 (C_{11a}),

125.87 (C_{11b}), 126.21 (C_7), 128.25 (C_9), 128.45 (C_{10}), 129.03 (C_8), 129.26 (C_{10a}), 129.78 (C_{6b}), 131.50 ($C_{1'}$), 131.98 ($C_{3'}$), 132.58 ($C_{2'}$), 133.41 ($C_{4'}$), 135.20 ($C_{5'}$), 136.43 ($C_{6'}$).

3-(Ethylideneamino)-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-a]carbazol-3-thiol (**4d**). Yield 75%, m.p. 150 °C (petroleum ether–ethyl acetate). For $C_{22}H_{20}N_4S$ (372.5) calculated: 70.94% C, 5.41% H, 15.04% N, 8.61% S; found: 70.90% C, 5.42% H, 15.10% N, 8.68% S. UV, λ_{max} (log ε): 222 (4.43), 246 (4.65), 250 (4.48), 261 (4.32), 298 (4.26), 318 (3.99), 325 (3.96), 336 (3.92). IR: 3273, 2926, 2851, 1647, 1593, 1541, 1473, 1436, 1330, 934, 733. ^{1}H NMR: 1.23–1.28 m, 3 H (imino CH_3); 2.65–2.69 m, 2 H (H-5); 3.00–3.10 m, 2 H (H-6); 3.25–3.29 m, 1 H (3-SH); 7.05–7.18 m, 6 H (imino CH, H-2′ to H-6′); 7.29–7.66 m, 4 H (H-7, H-8, H-9, H-10); 7.82 s, 1 H (H-4); 8.89 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 21.51 (N=CH-CH_3), 25.12 (C_5), 27.48 (C_6), 29.32 (C_4), 38.35 (N=CH-CH_3), 58.79 (C_3), 113.15 (C_{4a}), 120.71 (C_{6a}), 122.79 (C_{11a}), 125.57 (C_{11b}), 126.32 (C_7), 128.27 (C_9), 128.59 (C_{10}), 129.01 (C_8), 129.17 (C_{10a}), 129.69 (C_{6b}), 131.52 ($C_{1'}$), 131.95 ($C_{3'}$), 132.54 ($C_{2'}$), 133.28 ($C_{4'}$), 135.28 ($C_{5'}$), 136.47 ($C_{6'}$).

8-Chloro-3-(ethylideneamino)-4-phenyl-3,4,5,6-tetrahydropyridazino[3,4-a]carbazol-3-thiol (**4e**). Yield 65%, m.p. 180 °C (petroleum ether–ethyl acetate). For $C_{22}H_{19}ClN_4S$ (406.9) calculated: 64.93% C, 4.70% H, 13.76% N 7.89% S; found: 64.87% C, 4.80% H, 13.65% N, 7.80% S. UV, λ_{max} (log ε): 231 (4.69), 258 (4.72), 290 (3.96), 299 (4.18), 320 (4.01), 339 (3.75), 358 (3.72). IR: 3263, 2925, 2857, 1643, 1587, 1541, 1468, 1323, 804, 769. ^{1}H NMR: 1.24–1.27 m, 3 H (imino CH_3); 2.05–2.69 m, 2 H (H-5); 2.95–3.05 m, 2 H (H-6); 3.24–3.29 m, 1 H (3-SH); 7.06–7.24 m, 1 H (imino CH); 7.29–7.43 m, 2 H (H-9, H-10); 7.44–7.55 m, 5 H (H-2′ to H-6′); 7.63 s, 1 H (H-7); 7.82 s, 1 H (H-4); 8.96 b s, 1 H (carbazole NH). ^{13}C NMR ($CDCl_3$): 21.51 (N=CH-CH_3), 25.09 (C_5), 27.67 (C_6), 29.35 (C_4), 38.41 (N=CH-CH_3), 57.81 (C_3), 113.05 (C_{4a}), 121.57 (C_{6a}), 123.41 (C_{11a}), 125.62 (C_{11b}), 126.23 (C_7), 128.28 (C_9), 128.57 (C_{10}), 129.13 (C_8), 129.29 (C_{10a}), 129.85 (C_{6b}), 131.48 ($C_{1'}$), 131.89 ($C_{3'}$), 132.58 ($C_{2'}$), 133.49 ($C_{4'}$), 135.37 ($C_{5'}$), 136.69 ($C_{6'}$).

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