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Eaton's reagent is an alternative of PPA: Solvent free synthesis, molecular docking and ADME studies of new angular and linear carbazole based naphtho naphthyridines

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ABSTRACT

An approach towards the preparation of novel angular and linear carbazole based naphtho naphthyridines are described in good yields. From schematic study on the condensation of 4-chloro-2-methylbenzo[*h*]quinoline and 3-amino-9-ethylcarbazole in presence of CuI as catalyst to *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-methylbenzo[*h*]quinolin-4-amine was stated as starting synthon. Thus, this carbazole based quinoline amine on treatment with Eaton's reagent catalyzed cyclisation reaction with Aromatic carboxylic acids to yield the linear and angular 8-substituted naphtho[*h*]carbazol [1,6] naphthyridines. This Eaton's reagent is a precise catalyst for the reaction of cyclizing *cum* aromatization agent followed by dehydration of the conversion of angular and linear naphthyridines in excellent yields compared with Polyphosphoric acid (PPA). Further, the molecular docking studies were conducted to offer binding mode into the binding sites of phosphoinositide-dependent protein kinase 1 (PDK-1) receptors. The synthesized compounds showed better docking scores and binding energies, when compared with reference drugs ARC-111 and Ellipticine. Pharmacokinetic (ADME) parameters of the potent derivatives have also been found to an acceptable range.

1. Introduction

In heterocyclic chemistry, the innovation of new potential functionalized molecules creates several advantages of synthetic methodologies to improve the existing drug-like chemical space and make more effective drug discovery of medicinal chemists [1]. Among all the heterocyclic compounds, nitrogen based quinolines and naphthyridines are the most favorable scaffolds in the medicinal chemistry [2]. The antimalarial drugs of aminoquinoline analogues [*i.e.* (Fig. 1), chloroquine (**I**), amodiaquine (**II**), and primaquine (**III**)] are the most significant role of several clinically used drugs [3].

The reaction with chloroquinoline derivatives have been broadly studied to derive biologically active substituted quinolones [4], and also in the synthesis of some naphthyridine analogues [5]. Among them, the quinoline derivatives, pyrido fused quinolines (Fig. 1, **IV**, *i.e.*, naphthyridines, benzonaphthyridines, and dibenzonaphthyridines) are plays a vital role in living cells and potent PDK-1 inhibitors (Fig. 1, **V** and **ARC-111**) [6,7]. Such naphthyridines are showed prominent biological activities such as CB2 selective

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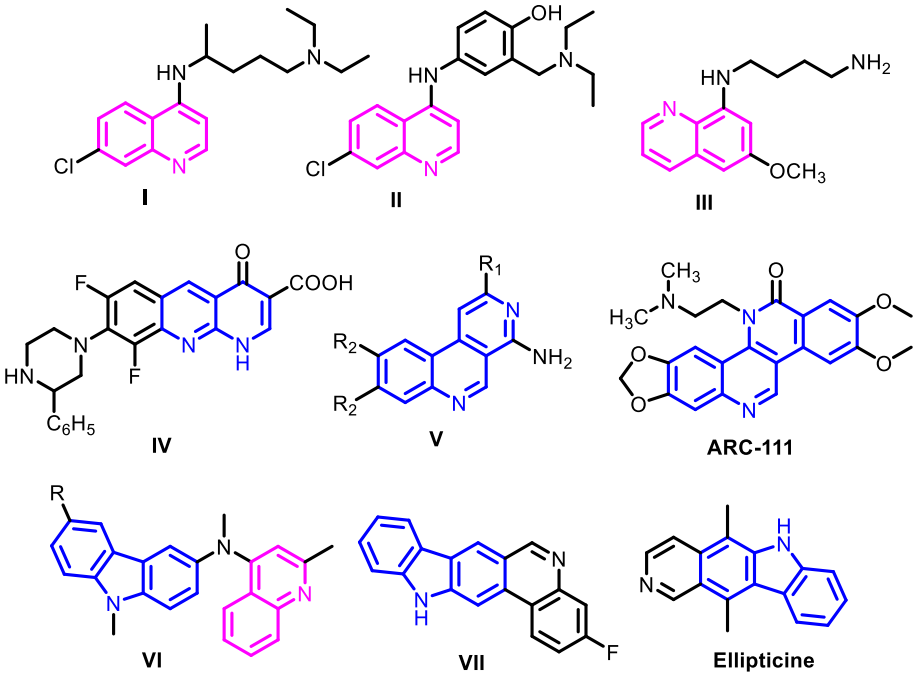


Fig. 1. Selected examples of quinoline, naphthyridine and carbazole based biological active molecules.

agonists [8], anti-HIV [9], anticancer [10], selective 3-phosphoinositide- dependent kinase-I inhibitors [11], and topoisomerase-I inhibitors [12]. The 3-phosphoinositide-dependent protein kinase 1 (PDK1) inhibitors perform a substantial function in cancer cell growth, survival, and tumor angiogenesis for drug discovery, also, PDK1 inhibitors represent a promising target for anticancer drugs in small molecules [13]. Carbazole and hetero annulated carbazole (Fig. 1, **VI**, **VII** and **Ellipticine**) analogues have elaborated wide array of biological activities such as antioxidant, antimicrobial, anticancer, antidiabetic, antitubercular and anti-convulsant activity [14].

An amine group inserted with an organic molecule to form C—N bond by using copper iodide as a catalyst, with a reduction of toxicity and more economical than other transition metal catalyst [15]. So, the amination reaction of aryl and heteroaryl halides have attained much consideration and gratitude using CuI catalyst [16]. Therefore, this combination *i.e.*, copper(I)iodide (CuI) and dimethyl sulfoxide (DMSO) has significant method to produce annulated compounds due to its more selectivity [17]. Further, the investigation of naphthyridines has extended to significantly active probe for biological properties in the recent decades [6,12,18]. In this context, the avenue through selective synthesis of naphthyridines with simply available catalysts, preferably solvent free synthesis of naphthyridines using PPA [19], Based on the above facts, we research on cyclizing *cum* dehydrating using acid catalyzed reactions using Eaton's reagent is an alternate acid catalyst for PPA [20] and various quinoline based heterocycles using Eaton's reagent catalyzed reactions [21–24].

We consider that, in the presence of Eaton's reagent is a precise catalyst for the reaction of cyclizing cum aromatization agent followed by dehydration of the conversion of angular and linear naphthyridines in good yields compared with polyphosphoric acid (phosphorus pentoxide in phosphoric acid) through quinoline carbazole amine intermediates using CuI/DMSO. Further, the molecular docking studies were achieved to examine the interactions between human protein kinase-1 receptors (PDK-1 inhibitors) and the synthesized compounds are docked with Autodock4.0 [25]. PDK-1 inhibitor is referred as “master kinase” due to it phosphorylates residues which is responsible for activation loop causes mutation in all tumor cells and results in high activation. So PDK -1 afford some important therapeutic agents in cancer treatment. Based on the information we choose such important inhibitor for docking [7]. The molecular docking studies were conducted to offer binding mode into the binding sites of phosphoinositide-dependent protein kinase 1 (PDK-1) inhibitors [7], which is compared with reference drugs ARC-111 and Ellipticine. Consequently, ADME (Absorption, Distribution, Metabolism and Excretion) [26] studies of the novel angular and linear carbazole based naphtho naphthyridine analogues are designed to investigate for chemical parameters of drug efficacy range.

2. Experimental and computational section

2.1. General

Melting points (M.p.) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). A Nicolet Avatar Model FT-IR spectrophotometer was used to record the FT-IR spectra (4000—400 cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 500 (500 MHz (^{1}H) and 125 MHz (^{13}C)) spectrometers using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Coupling constants (J) are reported in hertz (Hz). The terms J_o and J_m refer to ortho coupling constant and meta coupling constant. The terms s, d, t, dd refer to singlet, doublet, triplet and doublet of doublet, respectively, b s refers to a broad singlet. Mass spectra (MS) were recorded on Auto Spec EI + Shimadzu QP 2010 PLUS GC-MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. When known compounds had to be prepared according to literature procedures, pertinent references are given. When freshly preparing Eaton's reagent/PPA, the P_2O_5 should be taken in a dry box in our laboratory. The solvent and

reagents used for the preparations were of reagent grade and were purified by standard methods, petroleum ether used was of boiling range 60–80 °C. Anhydrous sodium sulphate was used to dry the solution of organic extracts. Thin layer chromatography (TLC) was performed using glass plates coated with silica gel-G containing 13% calcium sulphate as binder. Ethyl acetate and petroleum ether were used as developing solvents. A chamber containing iodine vapors was used to locate the spots. Separation and purification of the crude products was carried out using chromatographic columns packed with activated silica gel (60–120 mesh). In the case of mixture of solvents used for elution, the ratio of the mixture is given in brackets.

2.2. In silico analysis and ADME studies

Docking analysis was performed by Autodock4.0 tool [25]. Human phosphoinositide-dependent protein kinase 1 (PDK-1) receptor (PDB ID: 3H9O) [7a] was download from Protein Data Bank. Receptor and compounds were prepared for docking analysis with MGL Tool 1.5.6. Grid box values were given as X = 58, Y = 60, Z = 76, spacing angstrom as 0.753 Å, center of grid box value is X = 41.106, Y = −17.914, Z = 1.477 and total grid points per map of 277,123 was constructed by enveloping the entire receptor. The given input parameters were analyzed using a Lamarckian Genetic Algorithm (LGA). Each compound was performed for molecular docking of 100 runs, and it was chosen for best conformers. During the docking process, complex structure showing lowest binding energy, ligand efficiency, intermolecular energy with a greater number of hydrogen bonds were selected for competent results. ADME (absorption, distribution, metabolism, and excretion) study was carried out to identify the pharmacokinetics and drug-likeliness property for entire docked compounds namely 3, 5a-e, 6a-e, ARC111 and Ellipticine was done using SwissADME tool [29]. Studied compounds were fully optimized at B3LYP/6-31G(d) level in gas phase using Gaussian Software.

2.3. General procedure for the synthesis of N-(9-ethyl-9H-carbazol-3-yl)-2-methylbenzo[h] quinolin-4-amine (3)

An appropriate mixture of 4-chloro-2-methylbenzo[*h*]quinoline (**1**, 0.004 mol) was reacted with 3-amino-9-ethylcarbazole (**2**) (0.004 mol) using CuI and heated in DMSO at 120 °C for an hour. After the reaction completion was indication by the TLC, the reaction mixture was washed with water, dried, adsorbed and purified using silica gel column chromatography and eluted with ethyl acetate: methanol (94:6) mixture to get **3** which was then recrystallized using methanol.

2.3.1. N-(9-ethyl-9H-carbazol-3-yl)-2-methylbenzo[h]quinolin-4-amine (3)

Greenish yellow solid; mp: >300 °C; Yield: (93%); IR (KBr, cm^{-1}) ν_{max}: 3234(NH), 1596(C=N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.38 (t, 3H, N_9–CH_2**CH_3**, *J* = 7.00 Hz), 2.72 (s, 3H, C_2–CH_3), 4.52 (q, 2H, N_9–**CH_2**CH_3, *J* = 7.00 Hz), 6.64 (s, 1H, C_3–H), 7.23 (t, 1H, C_6'-H, *J* = 7.50 Hz), 7.50–7.55 (m, 2H, C_2'-, C_7'-H), 7.67 (d, 1H, C_1'-H, *J* = 8.50 Hz), 7.81 (d, 1H, C_8'-H, *J* = 8.50 Hz), 7.90 (m, 2H, C_7 & C_5'-H), 8.14 (d, 1H, C_6–H, *J* = 9.00 Hz), 8.20 (m, 2H, C_8 & C_9–H), 8.28 (d, 1H, C_4'-H, *J* = 2.00 Hz), 8.69 (d, 1H, C_5–H *J* = 9.00 Hz), 9.43 (d, 1H, C_{10}–H *J* = 7.50 Hz), 10.29 (bs, 1H, C_4–NH), 13.65 (bs, 1H, N_1–H); ^{13}C NMR (125 MHz, DMSO-d_6) (ppm) δ_C: 14.28(N_9–CH_2**C**H_3), 31.15 (C_2'-CH_3), 37.66 (N_9–**C**H_2CH_3), 102.73 (C_3), 107.28 (C_2'), 109.90 (C_4'), 110.31 (C_1'), 110.76 (C_8'), 113.79 (C_{4b}'), 118.68 (C_{4a}'), 119.52 (C_{4a}'), 120.11 (C_6') 121.28 (C_7'), 122.36(C_5), 123.47 (C_{8a}'), 124.47 (C_{9a}'), 125.48 (C_5'), 126.83 (C_{10}), 128.30 (C_6), 129.21 (C_8&C_7), 130.45(C_9), 134.68 (C_{10a}), 135.68 (C_{6a}), 138.90 (C_3'), 140.62 (C_{10b}) 152.36 (C_4), 154.52(C_2); MS (EI) *m/z* (%) 401 (M^+, 100), 386 (45); Anal. Calcd. for: $C_{28}H_{23}N_3$ (401): C, 83.76; H, 5.77; N, 10.47. Found: C, 83.81; H, 5.69; N, 10.50%.

2.4. General procedure for the synthesis of 12-ethyl-6-methyl-7-tolyl-12h-naphtho[h]carbazol [2,3-c]: [1,6]naphthyridine (5a) and 9-ethyl-6-methyl-7-tolyl-9H-naphtho[h]carbazol [2,3-b]: [1,6] naphthyridine (6a)

2.4.1. Method A

A mixture of an appropriate 3-(*N*-(2-methylquinolin-4-yl) amino)-9-ethyl-9*H*-carbazole (**3**, 1 mmol) and *p*-methylbenzoic acid (**4a**, 1.5 mmol) was added to freshly prepared polyphosphoric acid (1 g of P_2O_5 and 0.5 ml of H_3PO_4) and heated at 140 °C for 2 h. After the completion of the reaction, the mixture was poured into crushed ice and neutralized with saturated sodium bicarbonate solution to remove the excess of *p*-methylbenzoic acid. The crude product thus obtained was purified by column chromatography over silica gel using petroleum ether: ethyl acetate as an eluant to get yellow solid of the respective 12-ethyl-6-methyl-7-tolyl-12*H*-naphtho[*h*]carbazol[2,3-*c*] [1,6]naphthyridine (**5a**) and 9-ethyl-6-methyl-7-tolyl-9*H*-naphtho[*h*]carbazol[2,3-*b*] [1,6] naphthyridine (**6a**).

2.4.2. Method B

A mixture of an appropriate 3-(*N*-(2-methylquinolin-4-yl) amino)-9-ethyl-9*H*-carbazole (**3**, 1 mmol) and *p*-methylbenzoic acid (**4a**, 1.5 mmol) was added to freshly prepared Eaton's reagent (1 g of P_2O_5 and 0.5 ml of CH_3SO_3H) and heated at 120 °C for 1 h. After the completion of the reaction, the mixture was poured into crushed ice and neutralized with saturated sodium bicarbonate solution to remove the excess of *p*-methylbenzoic acid. The crude product thus obtained was purified by column chromatography over silica gel using petroleum ether: ethyl acetate as an eluant to get yellow solid of the respective 12-ethyl-6-methyl-7-tolyl-12*H*-naphtho[*h*]carbazol[2,3-*c*] [1,6]naphthyridine (**5a**) and 9-ethyl-6-methyl-7-tolyl-9*H*-naphtho[*h*]carbazol[2,3-*b*] [1,6] naphthyridine (**6a**). The same reaction condition was carried out with other aromatic (2-chlorobenzoic, 4-methoxybenzoic and 3-nitrobenzoic acids) and hetero (pyridine carboxylic acid) carboxylic acid to get their respective carbazolonaphthyridines (**5b-e** and **6b-e**).

2.4.3. 12-Ethyl-6-methyl-7-tolyl-12H-naphtho[h]carbazol [2,3-c]: [1,6]naphthyridine (5a)

Yellow solid; mp: 133–134 °C; Yield: (2%); IR (KBr, cm^{-1}) ν_{max}: 1584, 1530 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.45 (t, 3H, N_{12}–CH_2**CH_3**, *J* = 7.50 Hz), 2.30 (s, 3H, C_4'-CH_3), 2.48 (s, 3H, C_6–CH_3), 4.30 (q, 2H, N_{12}–**CH_2**CH_3, *J* = 7.00 Hz), 7.24–7.85 (m, 9H, C_2, C_3, C_8, C_9, C_{10}, C_2', C_3', C_5', C_6'-H), 8.00 (d, 1H, C_{11}–H *J* = 7.50Hz), 8.05 (d, 1H, C_{13}–H *J* = 8.00 Hz), 8.15 (d, 1H, C_{14}–H *J* = 8.50 Hz), 8.23 (d, 1H, C_1–H *J* = 8.00 Hz), 8.41 (d, 1H, C_{14}–H *J* = 8.00 Hz), 9.22 (d, 1H, C_4–H, *J* = 8.50 Hz), 9.33 (d, 1H, C_{16}–H *J* = 8.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 14.50, 21.65, 29.05, 38.18, 117.18, 118,35, 120.77, 121.54, 125,32, 126.53, 126.81, 127.28, 127.82, 128.17, 128.64 (2C), 129.18 (2C), 129.75, 130.06, 130.65 (2C), 131.99, 133.16, 134.39, 135.62, 137.84, 139.12, 139.57, 140.26, 140.61, 142.82, 144.88, 145.52, 147.78, 158.02; MS (EI) *m/z* (%) 501 (M^+, 100); Anal. Calcd. for: $C_{36}H_{27}N_3$ (501): C, 86.20; H, 5.43; N, 8.37%. Found: C, 86.17; H, 5.39; N, 8.44%.

2.4.4. 9-Ethyl-6-methyl-7-tolyl-9H-naphtho[h]carbazol[2,3-b] [1,6] naphthyridine (6a)

Yellow solid; mp: 243 °C; Yield: (68%); IR (KBr, cm^{-1}) ν_{max}: 1595, 1568 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.65 (t, 3H, N_9–CH_2**CH_3**, *J* = 7.50 Hz), 2.26 (s, 3H, C_4'-CH_3), 2.49 (s, 3H, C_6–CH_3), 4.63 (q, 2H, N_9–**CH_2**CH_3, *J* = 7.00 Hz), 6.75 (d, 1H, C_8–H,

J = 2.00 Hz), 7.27 (d, 1H, C_2'-H, J = 9.50 Hz), 7.34 (d, 1H, C_6'-H, J = 8.00 Hz), 7.54 (d, 1H, C13−H, J = 8.50 Hz), 7.60 (2d, 2H, C_3'& C_5'-H, J = 8.00 Hz), 7.69−7.76 (m, 2H, C_2-, C_3−H), 7.84 (dd, 1H, C_{10}−H J = 8.50 Hz, J = 1.50 Hz), 8.03−8.09 (m, 2H, C_{11} & C_{12}−H), 8.14 (d, 1H, C_1−H J = 9.00 Hz), 8.45 (d, 1H, C_{17}−H J = 9.00 Hz), 8.61 (s, 1H, C_{14}−H), 9.23 (d, 1H, C_4−H, J = 8.50 Hz), 9.31 (d, 1H, C_{16}−H J = 8.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 14.78, 22.01, 30.11, 39.22, 102.21, 109.13, 115.13, 117.11, 120.45, 123.56, 124.00, 125.23, 126.33, 127.16, 127.99, 128.48 (2C), 129.65 (2C), 129.56, 130.70 (2C), 130.64, 132.98, 134.40, 135.71, 137.90, 139.21, 139.66, 140.30, 140.57, 142.77, 144.98, 145.61, 147.78, 159.23; MS (EI) *m/z* (%) 501 (M^+, 100); Anal. Calcd. for: $C_{36}H_{27}N_3$ (501): C, 86.20; H, 5.43; N, 8.38%. Found: C, 86.24; H, 5.41; N, 8.35%.

2.4.5. 12-Ethyl-6-methyl-7-(4′-chlorophenyl)-12H-naphtho[h] carbazol [2,3-c]: [1,6]naphthyridine(5b)

Yellow solid; mp: 127 °C; Yield: 0.277 g (3%); IR (KBr, cm^{-1}) ν_{max}: 1609, 1567; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.57 (t, 3H, N_{12}−CH_2**CH_3**, J = 7.50 Hz), 2.42 (s, 3H, C_6−CH_3), 4.56 (q, 2H, N_{12}−**CH_2**CH_3, J = 7.00 Hz), 7.26−7.78 (m, 9H, C_2, C_3, C_8, C_9, C_{10}, C_2', C_3', C_5', C_6'-H), 8.03 (d, 1H, C_{11}−H J = 8.00Hz), 8.07−8.10 (2d, 2H, C_{13} & C_{14}−H J = 8.00 Hz), 8.18 (d, 1H, C_1−H J = 8.50 Hz), 8.46 (d, 1H, C_{17}−H J = 9.00 Hz), 9.27 (d, 1H, C_4−H, J = 9.00 Hz), 9.35 (d, 1H, C_{16}−H J = 8.00 Hz); MS (EI) *m/z* (%) 521 (M^+, 100); Anal. Calcd. for: $C_{35}H_{24}ClN_3$ (521): C, 80.53; H, 4.63; N, 8.05%. Found: C, 80.57; H, 4.59; N, 8.01%

2.4.5.1. 9-Ethyl-6-methyl-7-(4′-chlorophenyl)-9H-naphtho[h]carbazol [2,3-b]: [1,6]naphthyridine (6b).

Yellow solid; mp: 253−255 °C; Yield: (72%); IR (KBr, cm^{-1}) ν_{max}:, 1640, 1600; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.55 (t, 3H, N_9−CH_2**CH_3**, J = 7.50 Hz), 2.57 (s, 3H, C_6−CH_3), 4.56 (q, 2H, N_9−**CH_2**CH_3, J = 7.00 Hz), 6.79 (d, 1H, C_8−H, J = 1.50 Hz), 7.26−7.77 (m, 7H, C_2, C_3, C_{13}, C_2', C_3', C_5', C_6'-H), 7.85 (dd, 1H, C_{10}−H J = 8.50 Hz, J = 1.50 Hz), 8.03−8.10 (m, 2H, C_{11} & C_{12}−H), 8.18 (d, 1H, C_1−H J = 8.50 Hz), 8.44 (d, 1H, C_{17}−H J = 9.00 Hz), 8.66 (s, 1H, C_{14}−H), 9.25 (d, 1H, C_4−H, J = 8.00 Hz), 9.35 (d, 1H, C_{16}−H J = 8.00 Hz); MS (EI) *m/z* (%) 521 (M^+, 100); Anal. Calcd. for: $C_{35}H_{24}ClN_3$ (521): C, 80.53; H, 4.63; N, 8.05%. Found: C, 80.49; H, 4.67; N, 8.09%

2.4.6. 12-Ethyl-6-methyl-7-(4′-methoxyphenyl)-12H-naphtho[h] carbazol [2,3-c]: [1,6]naphthyridine (5c)

Yellow solid; mp: 119 °C; Yield: (3%); IR (KBr, cm^{-1}) ν_{max}:, 1644, 1587; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.57 (t, 3H, N_{12}−CH_2**CH_3**, J = 7.50 Hz), 2.55 (s, 3H, C_6−CH_3), 3.90 (s, 3H, C_4'-OCH_3), 4.49 (q, 2H, N_{12}−**CH_2**CH_3, J = 7.00 Hz), 7.25−7.90 (m, 9H, C_2, C_3, C_8, C_9, C_{10}, C_2', C_3', C_5', C_6'-H), 8.03 (d, 1H, C_{11}−H J = 7.50 Hz), 8.10 (2d, 2H, C_{13} & C_{14}−H J = 8.00 Hz), 8.20 (d, 1H, C_1−H J = 8.50 Hz), 8.39 (d, 1H, C_{17}−H J = 8.00 Hz), 9.24 (d, 1H, C_4−H, J = 8.50 Hz), 9.32 (d, 1H, C_{16}−H J = 8.00 Hz); MS (EI) *m/z* (%) 517 (M^+, 100); Anal. Calcd. for: $C_{36}H_{27}N_3O$ (517): C, 83.53; H, 5.26; N, 8.12; Found: C, 83.48; H, 5.29; N, 8.08%.

2.4.7. 9-Ethyl-6-methyl-7-(4′-methoxyphenyl)-9H-naphtho[h] carbazol [2,3-b]: [1,6]naphthyridine(6c)

Yellow solid; mp: 249−251 °C; Yield: (66%); IR (KBr, cm^{-1}) ν_{max}: 1599, 1554; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.50 (t, 3H, N_9−CH_2**CH_3**, J = 7.50 Hz), 2.51 (s, 3H, C_6−CH_3), 3.82 (s, 3H, C_4'-OCH_3), 4.41 (q, 2H, N_9−**CH_2**CH_3, J = 7.00 Hz), 6.87 (d, 1H, C_8−H, J = 1.50 Hz), 7.17 (2d, 2H, C_2' & C_6'-H J = 9.00 Hz), 7.44 (dd, 1H, C_{13}−H J = 7.50Hz, J = 2.00 Hz), 7.50−7.81 (m, 4H, C_2, C_3, C_3', & C_5'-H), 7.88 (d, 1H, C_{10}−H J = 8.50 Hz), 8.01−8.06 (m, 2H, C_{11} & C_{12}−H), 8.15 (d, 1H, C_1−H J = 8.50 Hz), 8.41 (d, 1H, C_{17}−H J = 8.50 Hz), 8.50 (s, 1H, C_{14}−H), 9.24 (d, 1H, C_4−H, J = 9.00 Hz), 9.36 (d, 1H, C_{16}−H J = 8.00 Hz MS (EI) *m/z* (%) 517 (M^+, 100); Anal. Calcd. for: $C_{36}H_{27}N_3O$ (517): C, 83.53; H, 5.26; N, 8.12; Found: C, 83.57; H, 5.20; N, 8.16%.

2.4.8. 12-Ethyl-6-methyl-7-(3′-nitrophenyl)-12H-naphtho[h] carbazol [2,3-c]: [1,6]naphthyridine (5d)

Yellow solid; mp: 127 °C; Yield: (3%); IR (KBr, cm^{-1}) ν_{max}: 1590, 1587, 1515, 1345; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.57 (t, 3H, N_{12}−CH_2**CH_3**, J = 7.50 Hz), 2.22 (s, 3H, C_6−CH_3), 4.38 (q, 2H, N_{12}−**CH_2**CH_3, J = 7.00 Hz), 7.20 (t, 1H, C5′-H, J = 8.00Hz)7.37−7.70 (m, 7H, C_2, C_3, C_8, C_9, C_{10}, C_4', C_6'-H), 7.94 (m, 3H, $C_{13,}$ C14,C11−H), 8.03 (s, 1H, C_2'-H), 8.21 (d, 1H, C_1−H J = 8.50 Hz), 8.42 (d, 1H, C_{17}−H J = 8.00 Hz), 9.23 (d, 1H, C_4−H, J = 8.50 Hz), 9.34 (d, 1H, C_{16}−H J = 8.00 Hz); MS (EI) *m/z* (%) 532 (M^+, 100); Anal. Calcd. for: $C_{35}H_{24}N_4O_2$ (532): C, 78.93; H, 4.54; N, 10.52; Found: C, 78.97; H, 4.49; N, 10.57%.

2.4.9. 9-Ethyl-6-methyl-7-(3′-nitrophenyl)-9H-naphtho[h]carbazol [2,3-b]: [1,6]naphthyridine(6d)

Yellow solid; mp: 266−268 °C; Yield: 0.277 g (62%); IR (KBr, cm^{-1}) ν_{max}: 1628, 1541, 1517, 1347; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.47 (t, 3H, N_9−CH_2**CH_3**, J = 6.50 Hz), 2.67 (s, 3H, C_6−CH_3), 4.37 (q, 2H, N_9−**CH_2**CH_3, J = 7.00 Hz), 6.51 (d, 1H, C_8−H, J = 2.00 Hz), 7.21 (t, 1H, C_5'-H J = 7.50Hz), 7.39−7.56 (m, 5H, C_2, C_3, C_{13}, C_3', C_6'-H), 7.67 (d, 1H, C_{10}−H, J = 7.50 Hz), 7.96 (m, 2H, C_{11} & C_{12}−H), 8.09 (s, 1H, C_2'-H), 8.20 (d, 1H, C_1−H J = 8.00 Hz), 8.50 (d, 1H, C_{17}−H J = 7.50 Hz), 8.65 (s, 1H, C_{14}−H), 9.26 (d, 1H, C_4−H, J = 8.50 Hz), 9.35 (d, 1H, C_{16}−H J = 8.00 Hz); MS (EI) *m/z* (%) 532 (M^+, 100); Anal. Calcd. for: $C_{35}H_{24}N_4O_2$ (532): C, 78.93; H, 4.54; N, 10.52; Found: C, 78.89; H, 4.57; N, 10.48%

2.4.10. 12-Ethyl-6-methyl-7-(pyridine-3-yl)-12H-naphtho[h] carbazol [2,3-c]: [1,6]naphthyridine (5e)

Yellow solid; mp: 101 °C; Yield: (2%); IR (KBr, cm^{-1}) ν_{max}: 1617, 1570, 1536 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.58 (t, 3H, N_{12}−CH_2**CH_3**, J = 7.00 Hz), 2.47 (s, 3H, C_6−CH_3), 4.59 (q, 2H, N_{12}−**CH_2**CH_3, J = 7.00 Hz), 7.31−7.73 (m, 9H, C_1, C_2, C_3, C_{10}, C_{11}, C_{12}, C_5'-H), 8.06 (d, 1H, C_{13}−H J = 7.00 Hz), 8.10 (2d, 2H, C_{14}−H J = 8.50 Hz), 8.35 (d, 1H, C_6'-H J = 8.50 Hz), 8.42 (d, 1H, C_4'-H J = 7.50 Hz), 8.51 (d, 1H, C_{17}−H J = 9.00 Hz), 8.80 (s, 1H, C_2″-H), 9.20 (d, 1H, C_4−H, J = 8.80 Hz), 9.30 (d, 1H, C_{16}−H J = 8.40 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 14.30, 21.71, 29.32, 38.41, 117.22, 118.40, 120.81, 121.60, 125.55, 126.71, 126.91, 127.33, 128.21, 128.46 (2C), 129.43 (2C), 129.65, 130.11, 130.72, 132.09, 133.65, 134.83, 136.02, 137.48, 139.22, 139.69, 140.64, 141.11, 142.94, 144.908, 146.02, 147.82, 158.05; MS (EI) *m/z* (%) 488 (M^+, 100); Anal. Calcd. for: $C_{34}H_{24}N_4$ (488): C, 83.58; H, 4.95; N, 11.47; Found: C, 83.62; H, 5.00; N, 11.38%.

2.4.11. 9-Ethyl-6-methyl-7-(pyridin-3-yl)-9H-naphtho[h]carbazol [2,3-b]: [1,6]naphthyridine (6e)

Yellow solid; mp: 239 °C; Yield: (42%); IR (KBr, cm^{-1}) ν_{max}: 1640, 1612, 1588 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 1.55 (t, 3H, N_9−CH_2**CH_3**, J = 7.50 Hz), 2.56 (s, 3H, C_6−CH_3), 4.60 (q, 2H, N_9−**CH_2**CH_3, J = 7.00 Hz), 6.75 (d, 1H, C_8−H, J = 1.50 Hz), 7.30 (t, 1H, C_5'-H J = 9.00Hz), 7.46−7.51 (m, 4H, C_2, C_3, C_{10}, C_{13}−H), 8.03−8.21 (m, 3H, C_1, C_{11}, C_{12}−H), 8.32 (d, 1H, C_6'-H J = 5.20 Hz), 8.40 (d, 1H, C_4'-H J = 4.80 Hz), 8.46 (d, 1H, C_{17}−H J = 9.20 Hz), 8.64 (s, 1H, C_{14}−H), 8.86 (d, 1H, C_2'-H), 9.26 (d, 1H, C_4−H, J = 8.80 Hz), 9.32 (d, 1H, C_{16}−H J = 8.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 14.81, 22.22, 30.30, 39.56, 102.43, 109.24, 115.56, 117.41, 120.63, 124.19, 125.48, 126.81, 127.09, 127.79, 128.55 (2C), 129.72 (2C), 129.66, 130.59, 131.07, 133.21, 134.45, 135.61, 138.31, 139.04, 139.90, 140.67, 140.54, 143.67, 144.39, 145.38, 147.87, 158.64; MS (EI) *m/z* (%) 488 (M^+, 100); Anal. Calcd. for: $C_{34}H_{24}N_4$ (488): C, 83.58; H, 4.95; N, 11.47; Found: C, 83.60; H, 4.90; N, 11.50%.

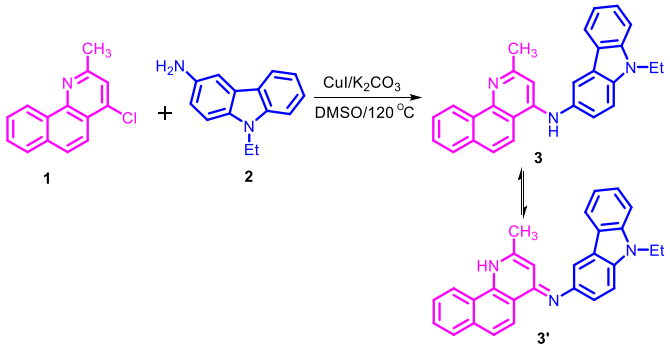
3. Results and discussion

3.1. Chemistry

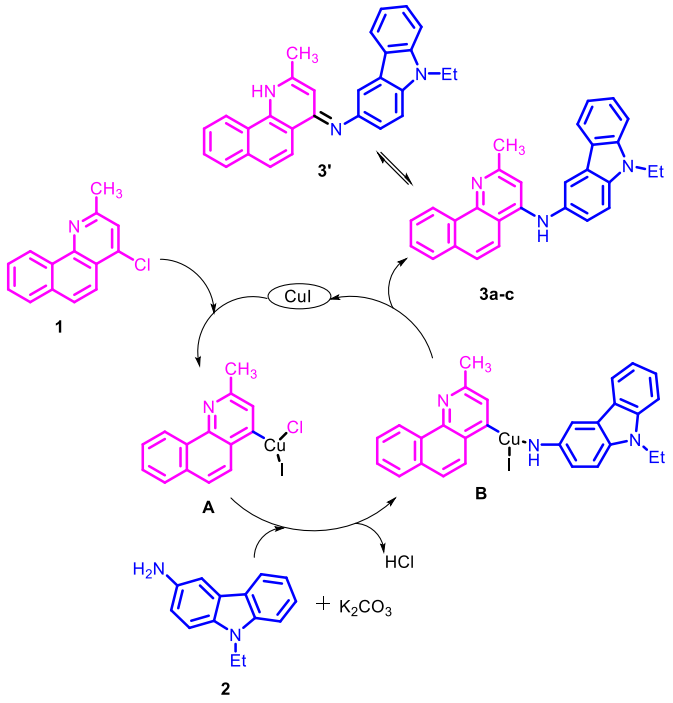
The approach to the preparation of various 8-substituted naphthocarbazol-naphthyridine, an equimolar mixture of 4-chloro-2-methylbenzo[*h*]quinoline (**1**) and 3-amino-9-ethylcarbazole (**2**) in DMSO using CuI and K_2CO_3 at 120 °C for 1 h afford a sole product (Scheme 1). Its FT-IR spectrum has shown stretching vibrations at 3234 $cm^{-1}$and 1596 cm^{-1}due to the presence of NH and C=N groups, respectively. Its ^{1}H NMR spectrum showed three proton triplet at δ 1.38 (J = 7.00 Hz) and a quartet at δ 4.52 (J = 7.00 Hz) due to methyl and methylene protons of the ethyl group. A three-proton sharp singlet displayed at δ 2.72 showed the presence of methyl proton of the benzoquionline moiety. A peculiar one proton singlet exhibited at δ 6.64 due to C_3–H of the benzoquinoline ring. The signals showed in a region between δ 7.23 and 9.43 were due to rest of the aromatic protons of both quinoline and carbazole ring. Two one proton broad singlets at δ 10.89 and δ 13.65 which were due to NH proton of the carbazole and its tautomeric form of quinoline NH (in 1:1 ratio). Its ^{13}C NMR spectrum revealed the presence of 28 carbons. The elemental analysis and the molecular ion peak at *m/z* 410 concurred well with the molecular formula, $C_{28}H_{23}N_3$. Hence the structure of the obtained product was assigned as *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-methylbenzo[*h*]quinolin-4-amine (**3**).

A plausible mechanism of the CuI catalyzed reaction between 4-chloro-2-methylbenzo[*h*]quinoline (**1**) and 3-amino-9-ethylcarbazole (**2**) is showed in Scheme 2. The first step is oxidative addition of 4-chloro-2-methylbenzo[*h*]quinoline (**1**) with CuI to form the intermediate **A** and compound **2** leads to the development of intermediate **B**. Finally, the intermediate **B** is subjected to a reductive elimination give to the compound **3** and regenerates the catalyst [16].

After getting potential intermediate **3**, we have focused our attention to react it with various aliphatic, aromatic, and hetero substituted carboxylic acids thereby anticipating getting the naphthyridine derivative (Scheme 3). Hence **3** were subjected to Bernthsen reaction of *p*-toluicacid (**4a**) in presence of PPA as catalyst at 140 °C afford the two products, which was confirmed by TLC. Here the possibility of getting two products because in carbazole ring there are two active sites for cyclisation to take place in C_2 position (linear) and C_4 position (angular). The first eluted product from column chromatography shown that the FT-IR spectrum stretching frequencies at 1584 cm^{-1} and 1530 cm^{-1} for two C=N groups. ^{1}H NMR spectrum showed two singlets at δ 2.30 and δ 2.48 was due to C_4' and C_6 methyl protons. Methylene and methyl protons of ethyl group in N_{12} have appeared at δ 1.45 (J = 7.50 Hz) as a triplet and δ 4.30 (J = 7.00 Hz) as a quartet, respectively. Other



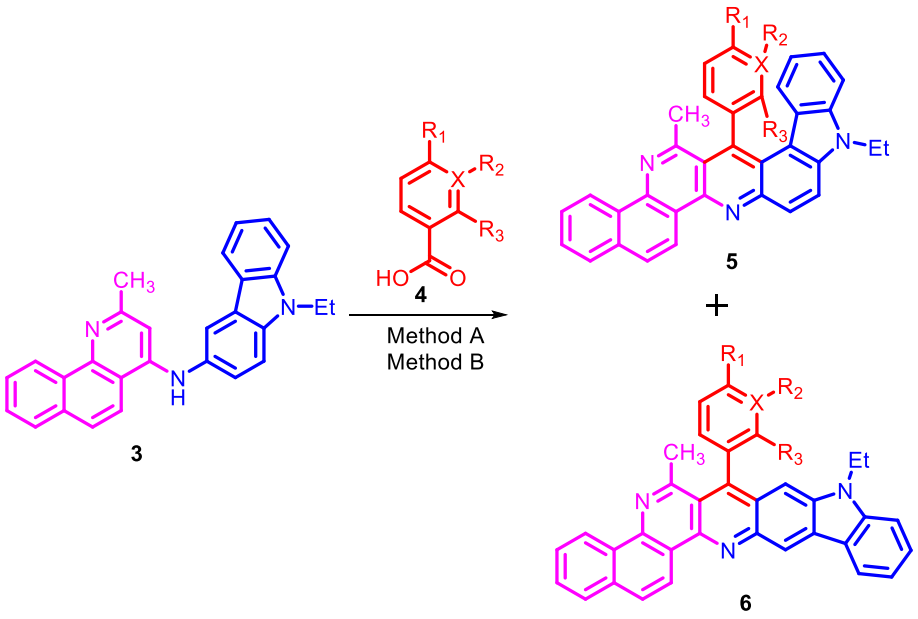
Scheme 1. Synthesis of carbazol-4-aminoquinoline (**3**).



Scheme 2. CuI catalyzed proposed mechanism of **3**.

aromatic protons are popped up between the regions δ 7.24–9.33. Two doublets at δ 8.05 (J = 8.00 Hz) and 8.15 (J = 8.50 Hz) due to C_{13} and C_{14} protons, respectively, which is clearly showed the formed product was angular. Its ^{13}C NMR spectrum revealed the existence of 36 carbons. Based on the spectral and analytical details confirmed the obtained product as angular product namely, 12-ethyl-6-methyl-7-tolyl-12*H*-naphtho[*h*]carbazol[2,3-*c*] [1,6]naphthyridine (**5a**). The second eluted product from column chromatography of the FT-IR spectrum displayed stretching frequencies at 1595 cm^{-1} and 1568 cm^{-1} and for two C=N groups, respectively. In its ^{1}H NMR spectrum of compound has two singlets at δ 2.26 and δ 2.49 were assigned for C_4'- and C_6–CH_3 groups, respectively. The methylene and methyl protons of ethyl group in N_9 have occurred as two multiplets in the region δ 4.61–4.65 and δ 1.60–1.62, respectively. All the aromatic protons are demonstrated between the regions δ 6.75–9.31. Presence of two singlets at δ 6.75 and 8.61 are clearly confirms the formation of linear product. Its ^{13}C NMR spectrum were explained the occurrence of 36 carbons and its mass spectrum indicated the molecular ion peak at *m/z* 501. All the aforesaid data revealed the product as linear product namely, 9-ethyl-6-methyl-7-tolyl-9*H*-naphtho[*h*]carbazol[2,3-*b*] [1,6]naphthyridine (**6a**). The same reaction was extended with other substituted aromatic carboxylic acids (*p*-chlorobenzoic acid (**4b**), *p*-methoxy benzoic acid (**4c**), 3-nitrobenzoic acid (**4d**), and pyridine-3-carboxylic acid (**4e**)) to get corresponding linear and angular 8-substituted naphtho[*h*]carbazol [1,6]naphthyridines (**5b-e** and **6b-e**) (Scheme 3).

In all the cases the yield of the angular product was low and for linear product moderate by using PPA catalyst (**Method A**). Hence, with the intention of increasing the yield of the products, freshly prepared Eaton's reagent (CH_3SO_3H/P_2O_5 with 10:1 ratio) was considered as a suitable alternative to polyphosphoric acid. By using Eaton's reagent (**Method B**) the yield of the linear product was increased whereas the angular product remains in low yield. Comparisons of the yield of both products are given in Table 1.



Scheme 3. Synthesis of angular and linear naphtho[*h*]carbazolo naphthyridines (**5** and **6**). **Reaction conditions**: (i) Method A = PPA as catalyst at 140 °C. (ii) Method B = Eaton's reagent as catalyst at 120 °C.

Table 1
Synthesis of compounds **5** and **6** with yield comparison.

S.No	Compounds	R_1	R_2	R_3	X	Yield(%)[a]	
						Method A	Method B
1.	**5a**	CH_3	H	H	C	2	2
2.	**6a**	CH_3	H	H	C	45	68
3.	**5b**	H	H	Cl	C	2	3
4.	**6b**	H	H	Cl	C	40	72
5.	**5c**	OCH_3	H	H	C	3	3
6.	**6c**	OCH_3	H	H	C	47	66
7.	**5d**	H	NO_2	H	C	2	3
8.	**6d**	H	NO_2	H	C	41	62
9.	**5e**	H	–	H	N	2	2
10.	**6e**	H	–	H	N	21	42

[a] Isolated yield after purification by the column chromatography.

(i) **Method A** = PPA as catalyst at 140 °C. (ii) **Method B** = Eaton's reagent as catalyst at 120 °C.

The detailed mechanism of the Eaton's reagent catalyzed cyclisation of the compound **5** and **6** is represented in Scheme 4. The plausible mechanism for the formation of angular and linear naphthyridine, which may take place firstly by the conversion of **3** under Eaton's reagent, which is subsequently on electrophilic substitution under the influence of H^+ donated by Eaton's reagent afforded the intermediates **II** and **V** through the intermediates **I** and **IV**. Which on further aromatization and prototrophic shift with the elimination of H_2O molecule through the intermediates **III** and **VI** ended up in the formation of final products **5** and **6** (Scheme 4). Initially, benzoylation takes place in a more viable C4-position of the carbazole moiety and then with an excess of benzoic acid, the reaction proceeds at the C2-position because of electrophilic substitution *cum* aromatization of carbazole moiety forming linear product is more yield compared to angular product [27]. This Eaton's reagent is a precise catalyst for the reaction of cyclizing *cum* aromatization agent followed by dehydration of the conversion of angular and linear naphthyridines in excellent yields compared with PPA.

3.2. In silico molecular docking

Molecular docking study was achieved to examine the interactions between phosphoinositide-dependent protein kinase 1 (PDK-1) receptors and prepared synthesized compounds using Autodock4.0 [25]. The molecular docking studies were conducted to offer binding mode into the binding sites of phosphoinositide-dependent protein (PDB ID: 3H9O) kinase 1 (PDK-1) receptors [7], which is compared with reference drugs ARC-111 and Ellipticine. The synthesized compounds were docked appropriately into PDK-1 receptor with the following respective parameters: (i) lowest binding energy (ii) lowest ligand efficiency (iii) lowest intermolecular energy and (iv) a greater number of hydrogen bonds. Table 2 demonstrates the binding energies of the synthesized docked compounds (**3**, **5a-e** and **6a-e**) with the PDK-1 inhibitors, which is compared with reference drugs ARC-111 and Ellipticine. According to Table 2 has shown the lowest binding energy value range between −9.68 kcal/mol to −4.6 kcal/mol and important interactions can be found between atoms and residues namely SER94, LYS111, LYS123, GLU130, TYR146, LYS207, ASP223, THR245, SER258, ALA259, GLU328, TRP347.

The screened compounds have high binding affinity to the target as their binding energy values range from −9.68 kcal/mol to −4.6 kcal/mol, which are higher than the reference drugs ARC-111 and Ellipticine. We envisioned the binding energy of the standards, Ellipticine forms a hydrogen bond by interaction of the NH group of the carbazole moiety with the nitrogen atom of TRP347:O (2.6A°) with a binding energy is −6.9 kcal/mol with −6.9 kcal/mol intermolecular binding energy, and ligand efficiency −0.36 kcal/mol (Fig. S1). ARC-111 drug forms two hydrogen bonding interaction of nitrogen atoms of LYS123:NZ (3.1A°), LYS123:NZ (3.5A°), respectively with binding energy is −4.81 kcal/mol, ligand efficiency −0.16 kcal/mol, and −6.3 kcal/mol intermolecular binding energy (Fig. S2).

N-(9-ethyl-9*H*-carbazol-3-yl)-2-methylbenzo[*h*]quinolin-4-amine (**3**) indicated the binding energy −8.72 kcal/mol and −9.62 kcal/mol, intermolecular energy, ligand efficiency

Table 2
The energy value of phosphoinositide-dependent protein kinase 1 (PDK-1) receptors interaction with compounds.

compounds	Binding energy (kcal/mol)	Ligand efficiency (kcal/mol)	Intermolecular energy (kcal/mol)	Hydrogen bond residues		
				Receptor atom	Ligand atom	Distance (A°)
3	−8.72	−0.28	−9.62	SER94:OG	H	2.1
5a	−9.26	−0.24	−9.86	LYS207:NZ	N	3.1
6a	−7.54	−0.19	−8.14	TYR146:OH	N	2.8
5b	−4.6	−0.12	−5.19	LYS123:NZ	N	3.1
6b	−8.44	−0.22	−9.04	LYS207:NZ	N	2.1
5c	−4.67	−0.12	−5.56	LYS207:NZ	N	3.2
6c	−8.65	−0.22	−9.55	LYS207:NZ	N	3.1
				THR245:OG1	N	3.0
5d	**−9.68**	**−0.24**	**−10.57**	**LYS111:NZ**	**O**	**3.5**
				GLU130:OE2	**O**	**3.0**
				LYS207:NZ	**N**	**3.4**
6d	**−9.53**	**−0.23**	**−10.42**	**SER258:OG**	**N**	**2.5**
				ALA259:N	**N**	**3.4**
				GLU328:OE1	**N**	**2.9**
5e	−9.06	−0.24	−9.65	LYS123:NZ	N	3.5
6e	−8.43	−0.22	−9.03	LYS207:NZ	N	2.5
ARC-111	−4.81	−0.16	−6.3	LYS123:NZ	N	3.5
				ASP223:OD2	N	3.1
Ellipticine	−6.9	−0.36	−6.9	TRP347:O	H	2.6

(−0.28 kcal/mol) and it formed a hydrogen bond interaction of SER94:OG (2.1A°) with carbazole ring nitrogen atom NH group. It was shown in Fig. 2. The compound (**3**), in comparison with standard drugs ARC-111 and Ellipticine, almost the synthesized compound (**3**) exhibited better binding efficiency.

12-Ethyl-6-methyl-7-aryl-12*H*-naphtho[*h*]carbazol[2,3-*c*] [1,6] naphthyridine (**5a-e**) compounds displayed the docking scores ranging from −9.68 kcal/mol to −4.6 kcal/mol. Among them, the compound (**5d**) exposed the best lowest binding energy (−9.68 kcal/mol), ligand efficiency (−0.24 kcal/mol), lowest intermolecular energy (−10.57 kcal/mol) and it forms three hydrogen bonds by the interactions of LYS111:NZ, GLU130:OE2 with phenyl ring nitro group both oxygen atoms with respective bond residues are 3.5A° and 3.0A°. The third hydrogen bond interaction of naphthyridine ring nitrogen atom with LYS207:NZ with bond residue is 3.4A°. It was shown in Fig. 3. Among all the compounds (**5a-e**), in comparison with standard drugs ARC-111 and Ellipticine, almost all the synthesized compounds showed improved binding energy, but compound **5d** displayed as the most potent binding affinity with PDK-1 inhibitors.

9-Ethyl-6-methyl-7-aryl-9*H*-naphtho[*h*]carbazol[2,3-*b*] [1,6] naphthyridine (**6a-e**) compounds disclosed to the docking scores

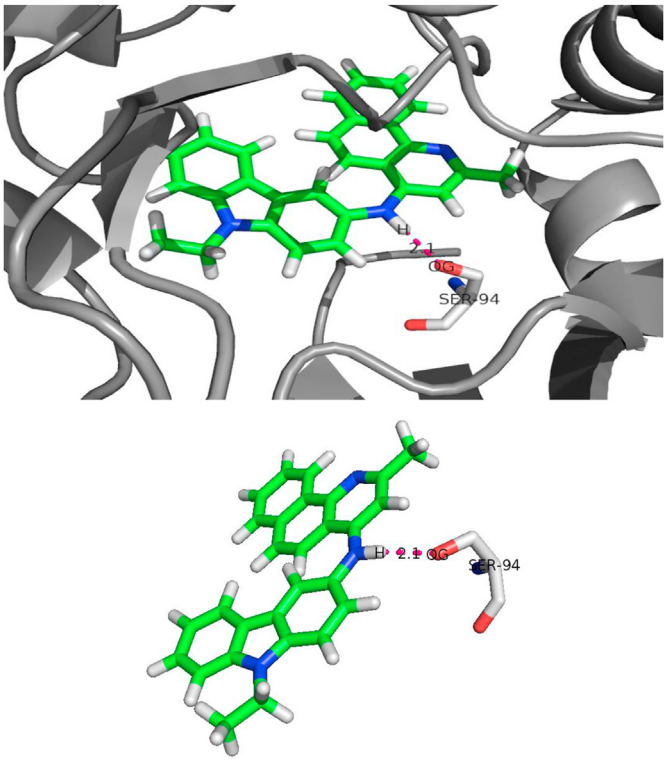


Fig. 2. Graphical representation of PDK-1 receptor docked with compound **3**.

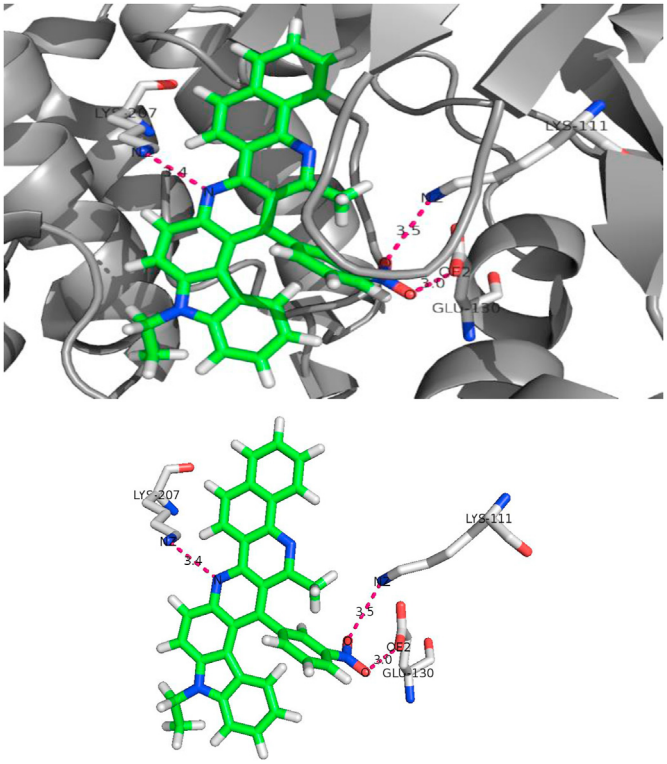


Fig. 3. Graphical representation of PDK-1 receptor docked with compound **5d**.

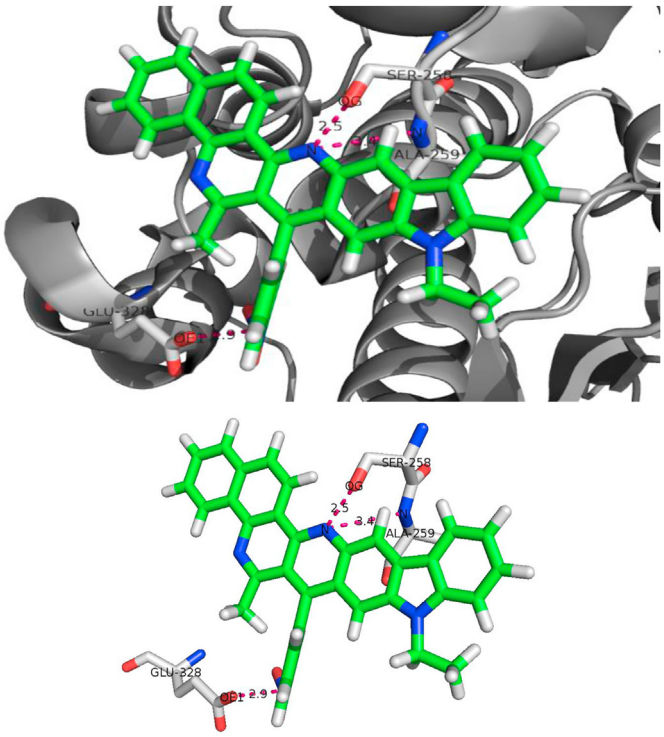


Fig. 4. Graphical representation of PDK-1 receptor docked with compound **6d**.

ranging from −9.53 kcal/mol to −7.54 kcal/mol. Among them, the compound (**6d**) demonstrated the best lowest binding energy (−9.53 kcal/mol), ligand efficiency (−0.23 kcal/mol), lowest intermolecular energy (−10.42 kcal/mol) and it formed three hydrogen bonds by the interactions of SER258:OG and ALA259:N with naphthyridine ring nitrogen atom respective bond residues are 2.5A^o and 3.4A^o and the other hydrogen interaction of nitrophenyl ring nitrogen atom with GLU328:OE1 with bond residue is 2.9A^o. It was stated in Fig. 4. Among all the compounds (**6a-e**), in comparison with standard drugs ARC-111 and Ellipticine, all the other synthesized compounds indicated adequate binding energy, in compound **6d** displayed as the most potent binding affinity with PDK-1 inhibitors.

The anticipated binding mode can help us to excellent knowledge of the nature of interactions of these (**3**, **5a-e**, and **6a-e**) synthesized compounds. In evaluation of the standard ARC-111 and ellipticine, nearly all the synthesized compounds seemed potent binding efficacy. The compounds **5d** and **6d** showed more potent binding interaction compared with all other compounds and standard drugs. In general, it was noticed that all the synthesized compounds (**3**, **5a-e** and **6a-e**, Figs. S3−S10) were docked with phosphoinositide-dependent kinase 1 (PDK-1) inhibitors, and it revealed that all compounds have more potent binding affinity when compared to the standard drugs ARC-111 (Fig. S2) and Ellipticine (Fig. S1). Cartoon representation of the docking images (Figs. 2−4) are shown the receptor in grey and stick model shows the residue interaction in grey and compounds in green. Hydrogen bond interactions are represented in dotted magenta line.

Furthermore, studied compounds are optimized at B3LYP/6-31G(d) level and no imaginary frequency is observed. Thermodynamic parameters which are total energy (E_{Total}), enthalpy (H) and Gibbs free energy (G) are given in Table 3.

According to Table 3, the energy difference between compound 5 and 6 groups is nearly zero. All energy is almost similar to each other. However, it can be said that group 6 is slightly more stable than group 5. It can be seen from Scheme 3, steric repulsions are expected to be greater in group 5 compounds.

3.3. ADME analysis

ADME (absorption, distribution, metabolism, and excretion) study was carried out to identify the pharmacokinetics and drug-likeness properties of the all docked compounds (**3**, **5a-e**, **6a-e**, **ARC111** and **Ellipticine**) using SwissADME tool [28]. The criteria include molecular weight ≤500; hydrogen bond donor (HBD) ≤5, hydrogen bond acceptor (HBA) ≤10, iLogP ≤5, rotatable bonds (RB) ≤9 [26]. HBA (H-bond acceptors) and HBD (donors) in compounds satisfy with Lipinski's rule [29] of five and were found to be in the acceptable range except **5a-d** and **6a-d** compounds (Table 4). In addition to these parameters, some ADME parameters are given in supplemental material. According to these parameters, all values are within the confidence interval. According to this stage of compounds (**3**, **5e** and **6e**) has obeyed and hence can be considered as good lead compounds in drug discovery. In general, we can decide that the investigated compounds exhibited good absorption, distribution, and oral bioavailability within the body by not having more than one violation of Lipinski's rule of five (Table 4). These results are validated for the effective design of the focus on compounds.

4. Conclusion

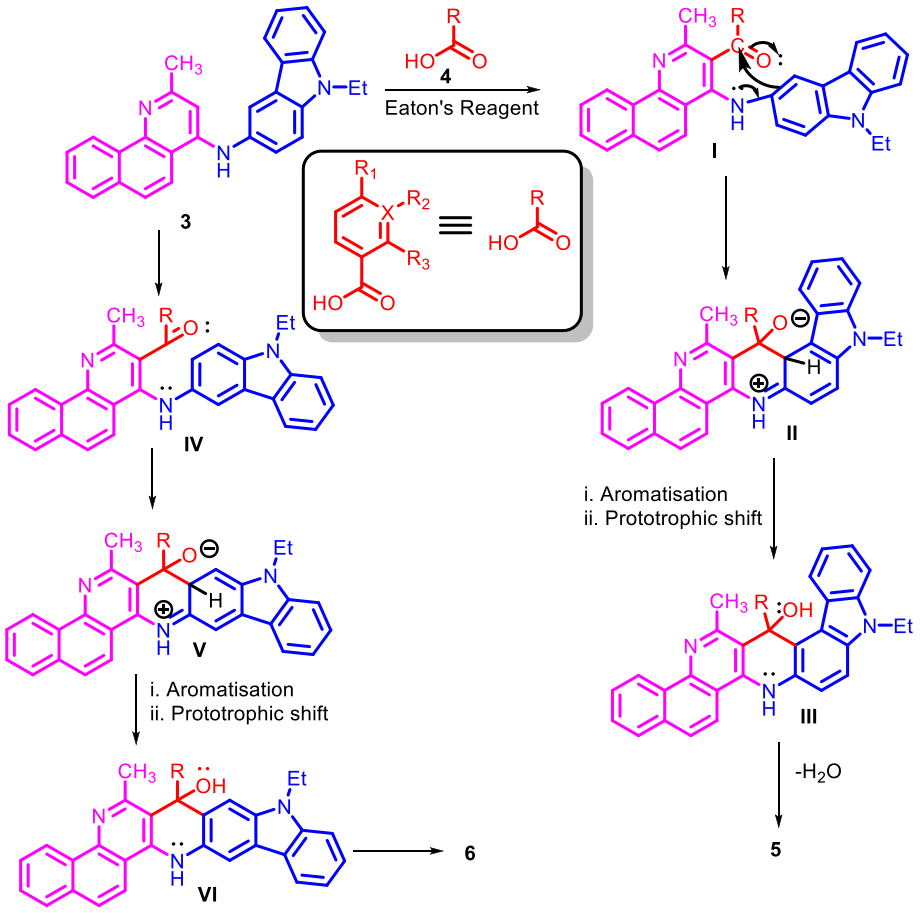
Current work towards the solvent free synthesis of novel angular and linear carbazole based naphtho naphthyridines are depicted in good yields using Eaton's reagent as a catalyst. This Eaton's reagent is a precise catalyst for the reaction of cyclizing *cum* aromatization agent followed by dehydration of the conversion of angular and linear naphthyridines in excellent yields compared with PPA. Further, the molecular docking studies were revealed that all the synthesized compounds displayed good binding energy

Table 3
Thermodynamic parameters of studied compounds.

Compounds	Total Energy (Hertree)	Enthalpy (Hertree)	Gibbs Free Energy (Hertree)
3	−1244.377075	−1244.376131	−1244.458047
5a	−1535.440108	−1535.439164	−1535.533775
6a	−1535.440109	−1535.439164	−1535.533775
5b	−1955.742726	−1955.741782	−1955.834127
6b	−1955.742812	−1955.741868	−1955.834253
5c	−1610.609494	−1610.608550	−1610.704372
6c	−1610.609500	−1610.608556	−1610.704418
5d	−1700.575276	−1700.574332	−1700.670543
6d	−1700.575348	−1700.574404	−1700.670551
5e	−1512.190727	−1512.189783	−1512.279275
6e	−1512.190727	−1512.189783	−1512.279275

Table 4
ADMET profile and drug-likeness properties of reference drugs and synthesized compounds (**3**, **5a-e** and **6a-e**).

Compounds	Property and recommended values					
	Mol. Weight (≤500 g/mol)	HB Donor (≤5)	HB Acceptor (≤10)	Rotatable Bonds (≤9)	iLOGP (≤5)	Lipinski violation
3	**401.50**	**1**	**1**	**3**	**4.01**	**0**
5a	501.62	0	2	2	4.79	1
6a	501.62	0	2	2	5.03	1
5b	522.04	0	2	2	4.58	1
6b	522.04	0	2	2	4.78	1
5c	517.62	0	3	3	4.81	1
6c	517.62	0	3	3	4.99	1
5d	533.60	1	4	3	−1.92	1
6d	534.61	2	5	3	−1.76	1
5e	**488.58**	**0**	**3**	**2**	**4.30**	**0**
6e	**488.58**	**0**	**3**	**2**	**4.43**	**0**
ARC-111	423.46	0	7	5	3.93	0
Ellipticine	246.31	1	1	0	2.30	0



Scheme 4. Plausible mechanism for the formation of products **5** and **6**.

towards of phosphoinositide-dependent protein kinase 1 (PDK-1) inhibitors ranging from −9.68 kcal/mol to −4.60 kcal/mol, which are more potent than the reference drugs ARC-111 (−4.81 kcal/mol) and Ellipticine (−6.9 kcal/mol). The compounds **5d** and **6d** showed more potent binding interaction compared with all other compounds and standard drugs ARC111 and Ellipticine. Pharmacokinetic (ADME) parameters of the potent derivatives have also been found to an acceptable range. Lipinski's rule of compounds (**3**, **5e** and **6e**) has obeyed and hence may be considered good lead compounds for the future drug discovery.

Credit author statement

Kolandaivel Prabha: Conceptualization, Methodology, Writing-Original draft preparation., Rajendran Satheeshkumar.: Data curation, original draft preparation., Muthu Sankar Aathi: Software, Validation., Chinnarasu Chandrasekar: Reviewing and Editing., Tiruchengode Arumugam Sukantha: Reviewing and Editing., Balasubramanian Mythili Gnanamangai: Reviewing and Editing., Roberto Acevedo: Reviewing and Editing., Koray Sayin: Data curation, Reviewing and Editing., Karnam Jayarampillai Rajendra Prasad: Reviewing and Editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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References

[1] (a) M.J. Cook, A.R. Katritzky, P. Linda, A.R., in: Katritzky (Ed.), Aromaticity of Heterocycles, Adv. Heterocycl. Chem. Vol, vol. 17, Wiley-Interscience, New York, 1974, p. 255;
(b) , in: C.W. Bird, G.W.H. Cheeseman, A.R. in Katritzky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, vol. 4, Pergamon Press, Oxford, 1984, p. 1;
(c) A.P. Taylor, R.P. Robinson, Y.M. Fobian, D.C. Blakemore, L.H. Jones, O. Fadeyi, Modern advances in heterocyclic chemistry in drug discovery, Org. Biomol. Chem. 14 (2016) 6611–6637.

[2] (a) K. Ramandeep, K. Kapil, Synthetic and medicinal perspective of quinolines as antiviral agents, Eur. J. Med. Chem. 215 (2021), 113220;
(b) L.M. Nainwal, S. Tasneem, W. Akhtar, G. Verma, M.F. Khan, S. Parvez, M. Shaquiquzzaman, M. Akhter, M.M. Alam, Green recipes to quinoline: a review, Eur. J. Med. Chem. 164 (2019) 121–170;
(c) V.P. Litvinov, Advances in the chemistry of naphthyridines, Adv. Heterocycl. Chem. 91 (2006) 189–300;
(d) G. Chabowska, E. Barg, A. Wójcicka, Biological activity of naturally derived naphthyridines, Molecules 26 (14) (2021) 4324.

[3] (a) S.M. Basavarajaiah, P. Raviraj, G.Y. Nagesh, A comprehensive review on the biological interest of quinoline and its derivatives, Bioorg. Med. Chem. 32 (2021), 115973;
(c) A.H. Abadi, G.H. Hegazy, A.A. El-Zaher, Synthesis of novel 4-substituted-7-trifluoromethylquinoline derivatives with nitric oxide releasing properties and their evaluation as analgesic and anti-inflammatory agents, Bioorg. Med. Chem. 13 (2005) 5759–5765.

[4] (a) C.C. Price, E.W. Maynert, V. Boekelheide, Some 4,8-diaminoquinolines, J. Org. Chem. 14 (3) (1949) 484–487;
(b) S. Rossiter, J.M. Peron, P.J. Whitfield, K. Jones, Synthesis, and anthelmintic properties of arylquinolines with activity against drug-resistant nematodes, Bioorg. Med. Chem. Lett. 15 (2005) 4806–4808;
(c) K. Prabhaa, R. Satheeshkumar, K.J. Rajendra Prasad, Synthesis, and cytotoxicity of novel indoloquinolines and benzonaphthyridines from 4-chloro-2,8-dimethylquinoline and variety of hetero amines, ChemistrySelect 6 (28) (2021) 7136–7142.

[5] (a) A. Chandra, B. Singh, S. Upadhyay, R.M. Singh, Copper-free Sonogashira coupling of 2-chloroquinolines with phenyl acetylene and quick annulation to benzo[b][1,6]-naphthyridine derivatives in aqueous ammonia, Tetrahedron 64 (2008), 11680;
(b) K. Prabhaa, R. Satheeshkumar, K.J. Rajendra Prasad, Synthesis, and cytotoxicity of novel indoloquinolines and benzonaphthyridines from 4-chloro-2,8-dimethylquinoline and variety of hetero amines, ChemistrySelect 6 (28) (2021) 7136–7142.

[6] (a) M. Manoj, K.J. Rajendra Prasad, Facile synthesis of alkyl and aryl substituted dibenzo[b,g][1,8]naphthyridin-5-ones, Synth. Commun. 40 (2010) 3290;
(b) K. Prabha, K.J. Rajendra Prasad, Synthesis of alkyl and aryl substituted benzo[h]Naphtho[1,2-b][1,6]naphthyridines, syn, Comm 42 (2012) 2277–2289;
(c) C. Masdeu, M. Fuertes, M.E. Endika, A. Selas, G. Rubiales, F. Palacios, C. Alonso, Fused 1,5-naphthyridines: synthetic tools and applications, Molecules 25 (2020) 3508;
(d) K. Prabha, K.J. Rajendra Prasad, Synthesis, and spectroscopic distinction of benzonaphthonaphthyridine and its isomer, Syn, Commun. Now. 44 (2014) 1441–1452;
(e) E.F. Elslager, F.H. Tendict, Synthetic Amebicides. VI. Benzo[b][1,8]phenanthrolines, Benzo[b][l,10]phenanthrolines, Dibenzo[b,h][1,6]-naphthyridines, and Benzoth[h]quino[4,3-b]quinolines, J. Med. Chem. 5 (1962) 546;
(f) M.S. Hutton, S.P. Mackay, O. Meth-Cohn, Synthesis of Dibenzo[c,h][1,6] naphthyridine, [2]Benzopyrano[4,3-c]quinoline and Benzo[i]-phenanthridine analogues of the Quaternary Benzo[c]phenanthridines, Synthesis (2000) 1121.

[7] (a) K.H. Kim, A. Wissner, M.B. Floyd Jr., H.L. Fraser, Y.D. Wang, R.G. Dushin, Y. Hu, A. Olland, B. Guo, K. Arndt, Benzo[c][2,7]-naphthyridines as inhibitors of PDK-1, Bioorg. Med. Chem. Lett 19 (2009) 5225–5228.

[8] C. Manera, M.G. Cascio, V. Benetti, M. Allarà, T. Tuccinardi, A. Martinelli, G. Saccomanni, E. Vivoli, C. Ghelardini, V. Di Marzo, P.L. Ferrarini, New 1,8-naphthyridine and quinoline derivatives as CB2 selective agonists, Bioorg. Med. Chem. Lett 17 (2007) 6505–6510.

[9] L. Zhuang, J.S. Wai, M.W. Embrey, T.E. Fisher, M.S. Egbertson, L.S. Payne, J.P. Guare, J.P. Vacca, D. J Hazuda, P.J. Felock, A.L. Wolfe, K.A. Stillmock, M.V. Witmer, G. Moyer, W.A. Schleif, L.J. Gabryelski, Y.M. Leonard, J.J. Lynch, S.R. Michelson, S.D. Young, Design and synthesis of 8-hydroxy[1,6]naphthyridines as novel inhibitors of HIV-1 integrase in vitro and in infected cells, J. Med. Chem. 46 (2003) 453–456.

[10] (a) M. Atanasova, S. Ilieva, B. Galabov, QSAR analysis of 1,4-dihydro-4-oxo-1-(2-thiazolyl)-1,8-naphthyridines with anticancer activity, Eur. J. Med. Chem. 42 (2007) 1184–1192;
(b) N. Desbois, P. David, M. Johnny, C. Claire, C. Bruno, F. Bouyer, Cis-dichloroplatinum(II) complexes tethered to dibenzo[c,h][1,6]naphthyridin-6-ones: synthesis and cytotoxicity in human cancer cell lines in vitro, Eur. J. Med. Chem. 69 (2013) 719–727.

[11] A. Gopalsamy, M. Shi, D.H. Boschelli, R. Williamson, A. Olland, Y. Hu, G. Krishnamurthy, X. Han, K. Arndt, B. Guo, Discovery of dibenzo[c,f][2,7]-naphthyridines as potent and selective 3-phosphoinositide-dependent kinase-1 inhibitors, J. Med. Chem. 50 (2007) 5547–5549.

[12] (a) A.L. Ruchelman, S.K. Singh, A. Ray, X.H. Wu, J.M. Yang, T.K. Li, A. Liu, L.F. Liu, E.J. LaVoie, 5H-dibenzo[c,h]1,6-naphthyridin-6-ones: novel topoisomerase I-targeting anticancer agents with potent cytotoxic activity, Bioorg. Med. Chem. 11 (2003) 2061–2073;
(b) E. Martín-Encinas, A. Selas, C. Tesauro, G. Rubiales, B.R. Knudsen, F. Palancios, C. Alonso, Synthesis of novel hybrid quinolino[4,3-b][1,5]naphthyridines and quinolino[4,3-b][1,5]naphthyridin-6(5H)-one derivatives and biological evaluation as topoisomerase I inhibitors and antiproliferatives, Eur. J. Med. Chem. 195 (2020), 112292.

[13] (a) K. Prabha, R. Satheeshkumar, V. Nasif, J. Saranya, K. Sayin, J. Natarajan, C. Chandrasekar, K.J. Rajendra Prasad, Synthesis, in vitro cytotoxicity, and DFT studies of novel 2-amino substituted benzonaphthyridines as PDK1 inhibitors, ChemistrySelect 7 (13) (2022), e202200288;
(b) O.M. Soltan, M.E. Shoman, S.A. Abdel-Aziz, A. Narumi, H. Konno, M. Abdel-Aziz, Molecular hybrids: a five-year survey on structures of multiple targeted hybrids of protein kinase inhibitors for cancer therapy, Eur. J. Med. Chem. 225 (2021), 113768;
(c) R. Satheeshkumar, S. Kalaiselvi, K.J. Rajendra Prasad, W.L. Wang, C. Salas, Friedländer's synthesis of quinolines as a pivotal step in the development of bioactive heterocyclic derivatives in the current era of medicinal chemistry, Chem. Biol. Drug Des. 100 (6) (2022) 1042–1085.

[14] (a) K. Murali, H.A. Sparkes, K.J. Rajendra Prasad, Synthesis of hetero annulated isoxazolo-, pyrido- and pyrimido carbazoles: screened for in vitro antitumor activity and structure activity relationships, a novel 2-amino-4-(3'-bromo-4'-methoxyphenyl)-8-chloro-11H-pyrimido[4,5-a]carbazole as an antitumor agent, Eur. J. Med. Chem. 128 (2017) 319–331;
(b) G. Wang, S. Sun, H. Guo, Current status of carbazole hybrids as anticancer agents, Eur. J. Med. Chem. 229 (2022), 113999;
(c) T. Indumathi, V.S. Jamal Ahamed, S.S. Moon, F.R. Fronczek, K.J. Rajendra Prasad, l-Proline anchored multicomponent synthesis of novel pyrido[2,3-a] carbazoles, investigation of in vitro antimicrobial, antioxidant, cytotoxicity and structure activity relationship studies, Eur. J. Med. Chem. 46 (2011) 5580–5590;
(d) I. Khelifi, T. Naret, A. Hamze, J. Bignon, H. Levaique M.C. Garcia Alvarez, J. Dubois, O. Provot, M. Alami, N, N-bis-heteroaryl methylamines: potent antimitotic and highly cytotoxic agents, Eur. J. Med. Chem. 168 (2019) 176–188;
(e) B.M. Ramalingam, D.N. Moorthy, S.R. Chowdhury, T. Mageshwaran, E. Vellaichamy, S. Saha, K. Ganesan, B.N. Rajesh, S. Iqbal, H.K. Majumder, K. Gunasekaran, R. Siva, A.K. Mohanakrishnan, Synthesis and biological evaluation of calothrixins B and their deoxygenated analogues, J. Med. Chem. 61 (2018) 1285–1315.

[15] (a) M. Neetha, S. Saranya, N.A. Harry, G. Anilkumar, Recent advances and perspectives in the copper-catalysed amination of aryl and heteroaryl halides, ChemistrySelect 5 (2020) 736–753;
(b) A. Cai, W. Yan, X. Zeng, S.B. Zacate, T.H. Chao, J.A. Krause, M.-J. Cheng, W. Liu, Copper-catalyzed carbo-difluoromethylation of alkenes via radical relay, Nat. Commun. 12 (2021) 3272.

[16] (a) K. Prabha, K.J. Rajendra Prasad, Benzoquinoline amines – key intermediates for the synthesis of angular and linear dinaphthonaphthyridines, J. Adv. Res. 6 (2015) 631–641;
(b) K. Prabha, K.J. Rajendra Prasad, Dinaphthonaphthyridines—a class of novel molecules with potent antioxidant and anticancer activity, Med. Chem. Commun. 4 (2013) 340–346;

(c) K. Prabha, R. Satheeshkumar, K.J. Rajendra Prasad, Synthesis of novel benzo naphtho naphthyridines from 2, 4-dicloroquinolines, J. Heterocycl. Chem. 58 (9) (2021) 1809–1854.
[17] M.Y. Chang, Y.S. Wu, H.Y. Chen, CuI-mediated synthesis of sulfonyl benzofuran-3-ones and chroman-4-ones, Org. Lett. 20 (2018) 1824–1827.
[18] K.N. Vennila, K. Prabha, D. Sunny, S. Madhuri, K.P. Elango, Preparation and biological evaluation of quinoline amines as anticancer agents and its molecular docking, Med. Chem. Res. 28 (2019) 1298–1307.
[19] (a) M. Manoj, K.J. Rajendra Prasad, Effect of substituents in the syntheses of phenyl-substituted dibenzonaphthyridines, J. Heterocycl. Chem. 50 (2013) 1049;
(b) M. Manoj, K.J. Rajendra Prasad, An efficient synthesis of phenyl substituted dibenzonaphthyridines, J. Chem. Res. (2009) 485–488;
(c) M. Manoj, K.J. Rajendra Prasad, Synthesis of novel phenyl substituted dibenzonaphthyridines, J. Chem. Res. (2009) 713–718.
[20] P.E. Eaton, G.R. Carlson, J.T. Lee, Phosphorus pentoxide-methanesulfonic acid. Convenient alternative to polyphosphoric acid, J. Org. Chem. 38 (1973) 4071–4073.
[21] C. Pal, K. Milan Kumar, B. Uday, A. Susanta, Synthesis of novel heme-interacting acridone derivatives to prevent free heme-mediated protein oxidation and degradation, Bioorg. Chem.Lett. 21 (12) (2011) 3563–3567.
[22] C.B. Melzer, B. Franz, A novel approach to oxoisoaporphine alkaloids via regioselective metalation of alkoxy isoquinolines, Beilstein J. Org. Chem. 13 (2017) 1564–1571.
[23] G. Senthil Kumar, M. Zeller, R.G. Gonnade, K.J. Rajendra Prasad, Highly regioselective C4-hydrazinylation of 2, 4-dichloroquinolines: expedient synthesis of aminoquinoline substituted pyrrolidin-2, 5-diones via hydrazinylquinolines, Tetrahedron Lett. 55 (2014) 4240–4244.
[24] (a) R. Satheeshkumar, K.J. Rajendra Prasad, Solvent-free synthesis of dibenzo [b,j][1,10]-phenanthroline derivatives using Eaton's reagent as catalyst, Synth. Commun. 47 (2017) 990–998;
(b) R. Satheeshkumar, W. Kaminsky, H.A. Sparkes, K.J. Rajendra Prasad, Efficient protocol for synthesis of pyrazolo[3,4-a]acridines, Synth. Commun. 45 (2015) 2203–2215;
(c) R. Satheeshkumar, K.J. Rajendra Prasad, W.L. Wang, C.B. Espinosa, C.O. Salas, Solvent-free synthesis of new quinoline derivatives via Eaton's reagent catalysed friedländer synthesis, ChemistrySelect 7 (7) (2022), e202104416.
[25] G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility, J. Comput. Chem. 30 (2009) 2785–2791.
[26] (a) Cícera Datiane de Morais, Oliveira-Tintino, Saulo Relison Tintino, Débora Feitosa Muniz, Cristina Rodrigues dos Santos Barbosa, Raimundo Luiz Silva Pereira, Iêda Maria Begnini, Ricardo Andrade Rebelo, Luiz Eversonda Silva, Sandro Lucio Mireski, Michele Caroline Nasato, Maria Isabel Lacowicz Krautler, Pedro Silvino Pereira, Tereza Cristina Leal Balbino, José Galberto Martins da Costa, Fabiola Fernandes Galvão Rodrigues, Alexandre Magno Rodrigues Teixeira, Humberto Medeiros Barreto, Irwin Rose Alencarde Menezes, Henrique Douglas Melo Coutinho, Teresinha Gonçalves da Silva, Chemical synthesis, molecular docking and MepA efflux pump inhibitory effect by 1,8-naphthyridines sulfonamides, Eur. J. Pharmaceut. Sci. 160 (2021), 105753;
(b) R.A. Kardile, A.P. Sarkate, A.S. Borude, R.S. Mane, D.K. Lokwani, S.V. Tiwari, R. Azad, P.V.L.S. Burra, S.R. Thopate, Design and synthesis of novel conformationally constrained 7,12-dihydrodibenzo[b,h][1,6] naphthyridine and 7H-Chromeno[3,2-c] quinoline derivatives as topoisomerase I inhibitors: in vitro screening, molecular docking and ADME predictions, Bioorg. Chem. 115 (2021), 105174.
[27] (a) Y. Ezhumalai, P. Kumaresan, Z. Matthias, K.J. Rajendra Prasad, Efficient synthesis of benzo[h]carbazol[3,2-b][1,6]naphthyridines, J. Heterocycl. Chem. 59 (2022) 1191–1197;
(b) Y. Ezhumalai, Z. Matthias, K.J. Rajendra Prasad, Microwave assisted synthesis of indolo[2,3-b]dibenzo[b,g][1,8]naphthyridines, Tetrahedron Lett. 53 (2012) 1514–1517.
[28] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules, Sci. Rep. 7 (2017), 42717.
[29] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliv. Rev. 23 (1–3) (1997) 3–25.