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Research Article

ANTIPROLIFERATIVE AND *IN SILICO* ADMET STUDY OF NEW 4-(PIPERIDIN-1-YLMETHYL)-2-(THIOPHEN-2-YL) QUINOLINE ANALOGUES

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ABSTRACT

Objective: Synthesis and antiproliferative study of novel 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) derivatives.

Methods: 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinolines were synthesized by the addition of 4-(chloromethyl)-2-(thiophen-2-yl) quinoline (0.01 mol), piperidine (0.01 mol) in DMF (10 v) and K_2CO_3 (0.02 mol). The anticancer activity of the title compounds performed against T-47D, HeLa, HepG2, and MCF-7 human cancer cell lines growth was investigated by MTT assay.

Results: The compounds 7b and 7g exhibited 90% of the growth inhibitory effect on T-47D, HeLa, and MCF-7 and also 80% growth inhibition in HepG2 when compared with standard drug paclitaxel.

Conclusion: The synthesized compounds 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) exhibited a considerable degree of growth inhibition of human cancer cell lines. The synthesized molecules 7(a-j) are in acceptable range and are less toxic and can be considered as possible hits for drug discovery.

Keywords: MTT assay, *In silico*, T-47D, HeLa, HepG2, MCF-7, Molinspiration.

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INTRODUCTION

Cancer is a disease involving abnormal cell growth, leading to a tumor [1]. In poor countries, cancer kills more people than AIDS, malaria, and tuberculosis combined [2]. Cancer is one of the most serious problems to human life, which has drawn more attention all over the world [3]. Extensive scientific research has been devoted for developing effective anticancer therapeutics, involving an integrated employment of surgical techniques, radiation therapy, and chemotherapy [3]. Heterocyclic compounds are widely distributed in nature. Many are synthesized in laboratories and have been successfully used as clinical agents [4]. Among them, thiophene, a five-membered aromatic sulfur-containing heterocycle, has proven to be an attractive isostere, resulting in improved effectiveness of a drug [5]. Thiophene core has attracted the attention of the scientific community due to their anticancer and other therapeutic uses [6-18].

On the other hand, quinoline ring derivatives with anticancer potential have also shown excellent results through a different mechanism of action [19]. The anticancer potential of the derivatives on various cancer cells including those of leukemia and other cancer cells of breast, ovary, liver, lung, pancreas, and colon [20].

It is well known that the incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety merits [21]. Heterocyclic rings such as thiophene are important pharmacophores in search of molecules with antiproliferation activity [22-27].

In continuation of search on new compounds for antiproliferation treatment from our laboratory [28-32], we discovered that 2-(1-benzofuron-2-yl) quinoline-4-carboxylic acid and its esters [28] and 2-(benzofuran-2-yl)-4-(5-phenyl-4H-1,2,4-triazol-3-yl) quinoline and its derivatives [29] have possessed appreciable cytotoxic properties. Hence, the present work deals with the synthesis and antiproliferative potential of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline and its derivatives, along with detailed *in silico* pharmacokinetic and drug-likeness properties Scheme 1.

METHODS

Materials

Commercially available chemicals are used in the synthesis of compounds 7(a-j). The compounds were purified by column chromatography using silica gel 100–200 mesh with occasional monitoring by pre-coated aluminum thin layer chromatography (TLC) plates procured from Merck. Melting points were recorded by the open capillary method and are uncorrected by Raga Melting Point Apparatus. The ^{1}H-nuclear magnetic resonance (NMR) and ^{13}C-NMR spectra were recorded on a 400 MHz and 100 MHz, Bruker spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were recorded on the liquid chromatography-mass spectrometry Agilent mass spectrometer.

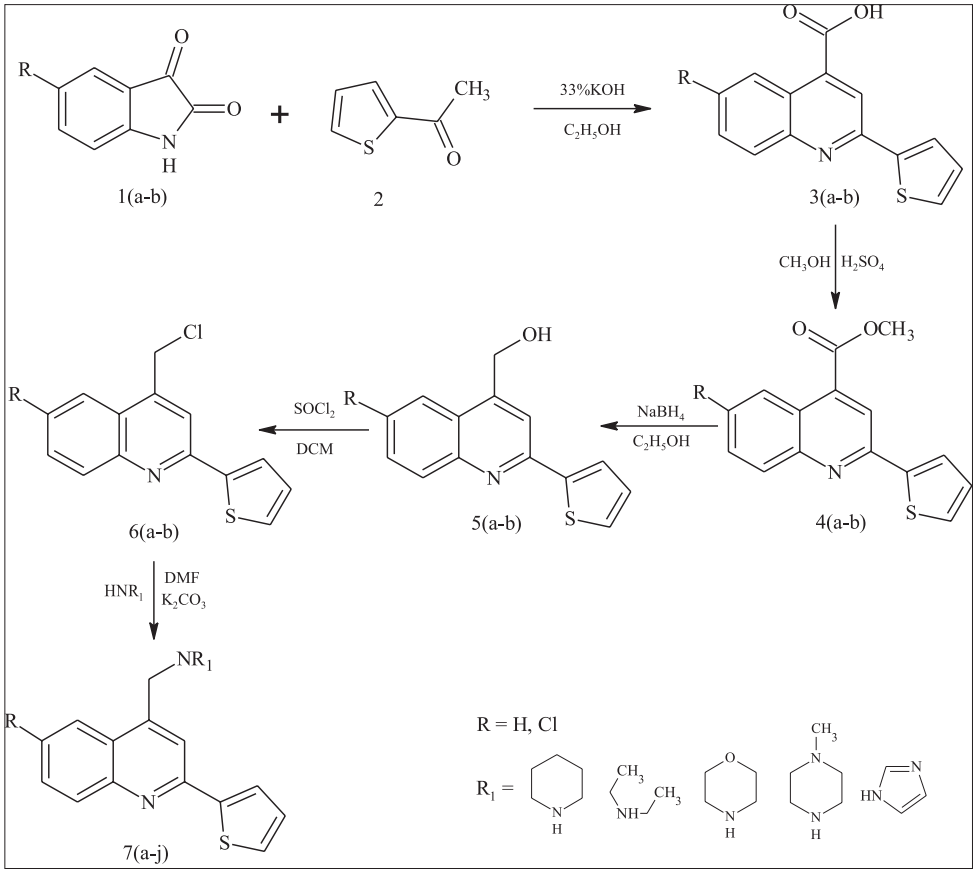
Method

2-(1-thiophene-2-yl)quinoline-4-carboxylic acid 3(a-b)

Isatin 1(a-b) (0.01 mol) and ethanol (10 v) were taken in a round bottom flask, to this 33% aq. KOH was added dropwise at 0–5°C followed by addition of 2-acetylthiophene 2 (0.01 mol). The reaction was refluxed at 75°C for 8 h. After completion, the reaction mixture was neutralized with dilute HCl. The precipitate, thus, formed was filtered, washed with ethyl acetate to remove impurities and dried to get compound 3(a-b).

Methyl 2-(1-thiophene-2-yl) quinolone-4-carboxylates 4(a-b)

2-(1-thiophene-2-yl) quinoline-4-carboxylic acid 3(a-b) (0.01 mol) was taken in methanol (10 v) in a round bottom flask, to this two drops of Conc. H_2SO_4 was added. The reaction was refluxed at 75°C for 8 h. After completion, the reaction mixture was poured into ice-cold water. The precipitate formed was, thus, filtered and dried to yield 4(a-b).



Scheme 1: Synthesis of compounds 7(a-b)

2-(thiophen-2-yl) quinolin-4-yl]methanol 5(a-b)

Methyl 2-(1-thiophene-2-yl) quinolone-4-carboxylates 4(a-b) (0.01 mol), methanol (10 v) was taken in a round bottom flask, to this sodium borohydrate (0.04 mol) was added at 0–5°C and kept at ambient temperature for stirring at 25–30°C for about 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice-cold water; a precipitate formed was filtered and dried to get compounds 5(a-b).

4-(chloromethyl)-2-(thiophen-2-yl) quinoline 6(a-b)

The compound [2-(thiophen-2-yl)quinolin-4-yl]methanol 5(a-b) (0.01 mol) was taken in dichloromethane (DCM) (10 v) in a round bottom flask, to this thionyl chloride (0.04 mol) was added at 0°C and kept for stirring at 25–30°C for 3 h. After completion of the reaction, the reaction mixture was neutralized with sodium bicarbonate solution and extracted with DCM; the DCM was evaporated to get a solid mass to yield 6(a-b).

4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl)quinoline 7(a-j)

The compound 4-(chloromethyl)-2-(thiophen-2-yl)quinoline 6(a-b) (0.01 mol) was taken in DMF (10 v) in a round bottom flask, to this K_2CO_3 (0.02 mol) was added followed by addition of substituted amine (0.01 mol). The reaction was kept for stirring at 25–30°C for 2 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate; the organic layer was concentrated and dried. Purification of the synthesized compounds was achieved by column chromatography using n-hexane: Ethyl acetate (v/v) gradient as the mobile phase.

Spectral data

4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a). Yield (72%): White amorphous, mp 165-168°C. Infrared (IR) (KBr) $cm^{-1:}$ 3327 (Ar C-H), 2922 (CH_2-str), 1647 (C=C), 1295 (C-N), 734 (C-S). ^{1}H NMR (400 MHz, dimethyl sulfoxide [DMSO]-d_6) (ppm): 1.386 (d, 2H, J=4.4Hz), 1.478(d, 4H, J=5.6Hz), 2.42(d, 4H, J=4.8Hz), 4.384(s, 2H), 7.202(t, 1H, J=8.8Hz), 7.533(t, 1H, J=1.2Hz), 7.674–7.729(m, 2H), 7.970–7.971(m, 3H), 8.223(d, 1H, J=9.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 24.149, 25.846(2), 54.526(2), 59.748, 117.927, 124.941, 126.253, 126.693, 127.166, 128.897, 129.083, 129.786, 130.139, 144.981, 145.605, 147.872, 151.691. Calculated mass: 308.44 g/mol. MS (ESI-m/z): 309.75 (M+1).

N-ethyl-*N*-{[2-(thiophen-2-yl)quinolin-4-yl]methyl}ethanamine 7(b). Yield (70%): White amorphous, mp 176-180°C. IR (KBr) $cm^{-1:}$ 3307 (Ar C-H), 2922 (CH_2-str), 1650 (C=C), 1247 (C-N), 736 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.104(t, 6H, J=7.2Hz), 2.639(d, 4H, J=7.2Hz), 4.048(s, 2H), 7.456(t, 1H, J=1.2Hz), 7.491–7.546(m, 3H), 7.696(t, 1H, J=8.4Hz), 8.025(s,1H), 8.183(d, 2H, J=8.4Hz), 8.23(d, 1H, J=8.4Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 11.824(2), 47.465(2), 54.950, 123.635, 125.824, 127.558(2), 128.748(2), 129.134(2), 130.183, 139.924, 146.570, 148.375, 157.031. Calculated mass: 296.42 g/mol. MS (ESI-m/z): 297.45 (M+1).

4-(morpholin-4-ylmethyl)-2-(thiophen-2-yl)quinoline 7(c). Yield (69%): White amorphous, mp 158-162°C. IR (KBr) $cm^{-1:}$ 3301 (Ar C-H), 2922 (CH_2-str), 1649 (C=C), 1245 (C-N), 1012 (C-O), 736 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.12(d, 4H, J=7.2Hz), 2.638(d,4H, J=7.2Hz), 4.001(s, 2H), 7.466(t, 1H, J=8.4Hz), 7.528(t, 2H, J=10Hz), 7.632(d, 1H, J=9.2Hz), 8.033(s, 1H), 8.105(d, 1H, J=9.2Hz), 8.163(d, 1H, J=6.8Hz), 8.252(d, 1H, J=2.4Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 53.123, 56.909(2), 67.950(2), 115.277, 120.058, 120.094, 127.627(2), 128.877(2), 129.904, 148.833, 148.850, 157.260, 157.334, 159.385. Calculated mass: 310.41 g/mol. MS (ESI-m/z): 311.45 (M+1).

4-[(4-methylpiperazin-1-yl)methyl]-2-(thiophen-2-yl)quinoline 7(d). Yield (68%): Yellow amorphous, mp 180–183°C. IR (KBr) $cm^{-1:}$ 3354(Ar C-H), 2931(CH_2-str), 1649(C=C), 1297(C-N), 762(C-S).^{1}H NMR (400

MHz, $CDCl_3$) (ppm): 2.303(s, 3H), 2.483–2.617(m, 8H), 3.984(s, 2H), 7.476(t, 1H, J=6.4Hz), 7.530(t, 2H, J=9.2Hz), 7.712(t, 1H, J=7.2Hz), 7.914(s, 1H), 8.159-8.193(m, 2H), 8.235(d, 1H, J=8Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 43.172, 53.872(2), 57.506(2), 60.970, 113.587, 119.663, 119.698, 119.953, 125.636, 125.700, 127.622(2), 128.857(2), 129.635, 156.895, 157.513, 159.552. Calculated mass: 323.45 g/mol. MS (ESI-m/z): 324.4 (M+1).

4-(1*H*-imidazol-1-ylmethyl)-2-(thiophen-2-yl)quinoline 7(e). Yield (71%): Yellow amorphous, mp 205–208°C. IR (KBr) $cm^{-1:}$ 3302 (Ar C-H), 3114 (CH_2-str), 1677 (C=C), 1273 (C-N), 768 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 4.936(s, 2H), 7.020(t, 1H, J=2.4Hz), 7.233(t, 1H, J=2Hz), 7.436–7.515(m, 3H), 7.671(s, 1H), 7.718(d, 1H, J=9.2Hz), 7.879(d, 1H, J=2.4Hz), 8.014(d, 2H, *J*=8Hz), 8.175(d, 1H, *J*=8.8Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 53.964, 125.293(2), 127.061, 127.745(2), 128.301, 128.574, 131.718(2), 136.795(2), 143.151(2), 148.091, 153.718, 158.952, 166.663. Calculated mass: 291.37 g/mol. MS (ESI-m/z): 292.40 (M+1).

6-chloro-4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl)quinoline 7(f). Yield (73%): White amorphous, mp 182–185°C. IR (KBr) $cm^{-1:}$ 3225 (Ar C-H), 2927 (CH_2-str), 1641 (C=C), 1249 (C-N), 746 (C-S), 659 (C-Cl).^{1}H NMR (400 MHz, DMSO-d_6) (ppm): 1.133(t, 2H, J=8.4Hz), 1.990(t, 4H, J=3.2Hz), 2.392(d, 4H, J=1.6Hz), 4.01(s, 2H), 7.117(t, 1H, J=8Hz), 7.259(d, 1H, J=8.4Hz), 7.354–7.435 (m, 1H), 7.483-7.682(m, 2H), 8.254(d, 1H, J=1Hz). ^{13}C NMR (100 MHz, DMSO-d_6 ppm): 23.949, 26.049, 54.576, 59.948, 118.027, 125.041, 126.353, 126.693, 127.166, 128.897, 129.083, 129.786, 130.139, 144.981, 145.605, 148.072, 152.091. Calculated mass: 342.88 g/mol. MS (ESI-m/z): 343.85 (M+1).

N-{[6-chloro-2-(thiophen-2-yl)quinolin-4-yl]methyl}-*N*-ethylethanamine 7(g). Yield (78%): White amorphous, mp 162-164°C. IR (KBr) $cm^{-1:}$ 3413 (Ar C-H), 2923 (CH_2-str), 1643 (C=C), 1254 (C-N), 760 (C-*S*), 669 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 1.104(t, 6H, J=14.4Hz), 2.439(d, 4H, J=7.2Hz), 4.208(s, 2H), 7.456(t, 1H, J=14.4Hz), 7.491–7.546(m, 2H), 7.696(s, 1H), 8.025(s, 1H), 8.183(d, 1H, J=8Hz), 8.231(d, 1H, J=8Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 13.824(2), 49.465(2), 59.950, 123.635, 125.824, 127.558(2), 128.748(2), 129.134(2), 130.183, 139.924, 146.570, 148.375, 157.031. Calculated mass: 330.8 g/mol. MS (ESI-m/z): 331.8 (M+1).

6-chloro-4-(morpholin-4-ylmethyl)-2-(thiophen-2-yl)quinoline 7(h). Yield (86%): Pale yellow amorphous, mp 155-157°C. IR (KBr) $cm^{-1:}$ 3302 (Ar C-H), 2927 (CH_2-str), 1634 (C=C), 1240 (C-N), 769 (C-S), 663 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) d NMR (400 MHz, CDClel*J*=8Hz), 2.961(d,4H, J=8.8Hz), 4.000(s, 2H), 7.466(t, 1H, J=8.4Hz), 7.528(t, 2H, J=8.4Hz), 7.632(d, 1H, J=9.2Hz), 8.033(s, 1H), 8.105(d, 1H, J=9.2Hz), 8.163(d, 1H, J=6.8Hz), ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 51.909(2), 59.923, 66.950(2), 115.277, 120.058, 120.094, 127.627(2), 128.877(2), 129.904, 148.833, 148.850, 157.260, 157.334, 159.385. Calculated mass: 344.85 g/mol. MS (ESI-m/z): 345.8 (M+1).

6-chloro-4-[(4-methylpiperazin-1-yl)methyl]-2-(thiophen-2-yl) quinoline 7(i). Yield (81%): Yellow amorphous, mp 171-174°C. IR (KBr) $cm^{-1:}$ 3201 (Ar C-H), 2920 (CH_2-str), 1650 (C=C), 1231 (C-N), 742 (C-S), 669 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 2.112(s, 3H), 2.483–2.617(m, 8H), 4.000(s, 2H), 7.476(t, 1H, J=6.4Hz), 7.530(t, 2H, J=9.2Hz), 7.712(t, 1H, J=7.2Hz), 7.914(s, 1H), 8.159-8.193(m, 2H), 8.224(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 43.100, 52.072(2), 55.906(2), 59.970, 119.663, 119.698, 119.953, 125.636, 125.700, 127.622(2), 128.857(2), 129.635, 156.895, 157.513, 159.552. Calculated mass: 357.9 g/mol. MS (ESI-m/z): 358.7 (M+1).

6-chloro-4-(1*H*-imidazol-1-ylmethyl)-2-(thiophen-2-yl)quinoline 7(j). Yield (75%): Yellow amorphous, mp 195-199°C. IR (KBr) $cm^{-1:}$ 3194 (Ar C-H), 2918 (CH_2-str), 1660 (C=C), 1282 (C-N), 757 (C-S), 658 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) (ppm): 4.437(s, 2H), 7.436–7.515(m, 3H), 7.671(s, 1H), 7.718(dd, 1H, J=2Hz, 2.4Hz), 7.879(d, 2H, J=2.4Hz), 8.014(d, 2H, J=8Hz), 8.175(d, 1H, J=8.8Hz). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): 51.864, 125.293(2), 127.061, 127.745(2), 128.301, 128.574, 131.718(2), 136.795(2), 143.151(2), 148.091, 153.718, 158.952, 166.663. Calculated mass: 325.8 g/mol. MS (ESI-m/z): 326.75 (M+1).

Biological activity

Absorption, distribution, metabolism, excretion, and toxicity prediction

The molecular descriptors of compounds 7(a-j) are predicted by pharmacokinetic parameters such as ADMET. The evaluation of biologically active molecules and to eliminate the poor once can be known by ADMET/SAR studies [33] wherein the active lead molecule which contains undesirable functional groups can be removed based on Lipinski rule. The molecular descriptors of synthesized compounds 7(a-j) are optimized using quantitative structure-activity relationship properties. Aqueous solubility (PlogS), blood-brain barrier penetration (QPlogBB), intestinal absorption (logHIA) [34], hepatotoxicity, and Caco-2 cell permeability (QPPCaco) helps to understand drug metabolism for the synthesized molecules.

Antiproliferative activity by MTT assay

The synthesized compounds 7(a-j) were screened for their *in vitro* antiproliferation activity against human cancer cell lines (HeLa, HepG2, MCF-7, and T-47D cell lines) by MTT assay (Table 1). The cell lines were obtained from the National Centre of Cell Sciences, Pune, India, and were cultured at a seeding density of 0.2×106 in DMEM/RPMI medium supplemented with 100 U/ml penicillin, 10% FBS, and 100 µg/l streptomycin, respectively, and maintained in a humidified atmosphere with 5% CO_2 at 37°C. The samples were dissolved in DMSO and further diluted in cell culture medium. The antiproliferative response of different molecules was assessed by MTT assay [35]. Cells (.10,000) were plated in 200 µl growth medium in the presence or absence of the molecule (25, 50, and 100 µg/ml) in 96-well culture plates for 24 h. Then, the culture plates were centrifuged at 2000 rpm for 10 min at room temperature. About 100 µl of the supernatant was discarded, and 20 µl of MTT (5 mg/ml in PBS) was added to each well and incubated for 4 h at 37°C. The viability of the cells was determined using a spectrophotometer at 570 nm. The (50%) inhibitory concentration, that is, the concentration of the compound required to inhibit cell growth by 50%, was determined.

RESULTS AND DISCUSSION

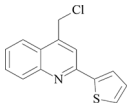
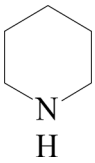
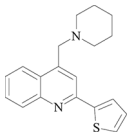
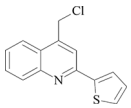
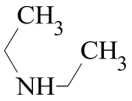
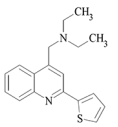
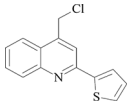
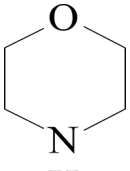
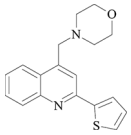
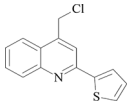
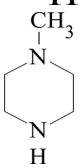
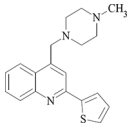
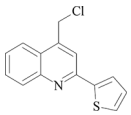
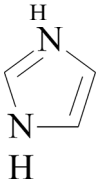
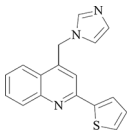
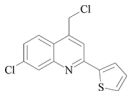
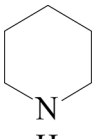
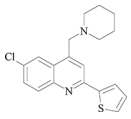
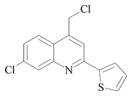
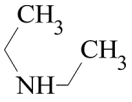
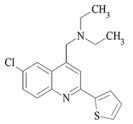
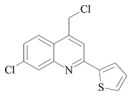
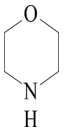
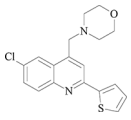
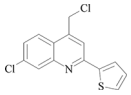
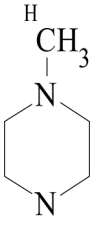
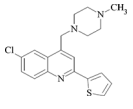
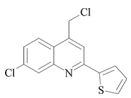
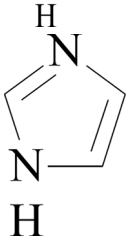
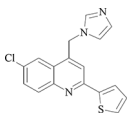
Chemistry

Synthesized 2-(1-thiophene-2-yl) quinoline-4-carboxylic acid 3(a-b) by reacting substituted isatin 1(a-b) with 2-acetyl thiophene 2 in the presence of 33% aqueous KOH and ethanol under reflux condition. Obtained acid 3(a-b) was further esterified using methanol using the catalytic amount of concentration H_2SO_4. The ester 4(a-b) was reduced to alcohol using $NaBH_4$ in the presence of methanol. The obtained alcohols 5(a-b) was further reacted with $SOCl_2$ to yield 4-(chloromethyl)-2-(thiophen-2-yl) quinoline 6(a-b). Nucleophilic substitution at C4 with secondary amines was achieved in the presence of DMF and K_2CO_3 to yield title compounds 7(a-j). The structures of all the newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, Fourier-transform IR and mass spectral analysis.

The IR spectra of synthesized compounds 7(a-j) showed absorption band between 3194 and 3413 cm^{-1} due to the C-H aromatic stretching. 2913–2918 cm^{-1} for -CH_2 stretching, 1231–1297 cm^{-1} for C-N stretching, 736–769 cm^{-1} for C-S stretching, and 659–669 cm^{-1} for C-Cl stretching of 7f, 7g, 7h, 7i, and 7j.

In the ^{1}H NMR, the presence of singlet peak within the range of 3.984–4.936 ppm corresponds to N–CH_2 protons of 7(a-j). The peaks resonated between 7.117 and 8.254 ppm corresponding to the aromatic protons of 7(a-j). The doublet peak appeared between 1.133 and 1.386 ppm, the triplet between 1.478 and 1.990 ppm and another doublet peaks between 2.39 and 2.42 ppm corresponds to piperidine protons of 7a

Table 1: Characterization data of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) derivatives

Entry	Methyl chlorides	2° amines	Product	% of yield	M. Pt.°C
7a				72	165–168
7b				70	176–180
7c				69	158–162
7d				68	180–183
7e				71	205–208
7f				73	182–185
7g				78	162–164
7h				86	155–157
7i				81	171–174
7j				75	195–199

and 7f. The triplet peaks which appeared at 1.104 ppm and the doublet peaks which appeared within the range of 2.439–2.639 ppm correspond to the H_3C-H_2C-N-CH_2-CH_3 protons of 7b and 7g. The ^1H NMR spectra of morpholine protons in 7c and 7h shows two doublet peaks at 1.12–

1.78 ppm and 2.638–2.961 ppm. The singlet peak at 2.112–2.303 ppm corresponds to N-CH_3, whereas multiplet appeared at 2.483–2.617 ppm corresponds to piperazine protons of 7d and 7i. The ^{13}C NMR spectra showed a peak ranging between 51.864 and 60.970 ppm corresponds to CH_2-N carbon of 7(a-j). The peaks appeared at 113.587–166.663 ppm corresponding to aromatic carbons of 7(a-j). The peaks appeared at 23.949–24.149, 26.049–25.816, and 54.526–54.576 ppm corresponding to piperidine carbons of 7a and 7f. The peaks appeared at 11.824–13.824 and 47.465–49.465 ppm corresponding to the H_3C-H_2C-N-CH_2-CH_3 carbons of 7b and 7g. The peaks appeared at 51.909–56.91 and 66.95–67.95 ppm corresponding to the morpholine carbons of 7c and 7h. The peaks at 43.100–43.172 ppm corresponding to –N-CH_3 of 7d and 7i, and also the peaks at 52.072–53.872 and 57.506–55.506 ppm corresponding to piperazine carbons of 7d and 7i. The mass analysis of 7(a-j) displayed the molecular ion peak conforming their molecular weight (MW).

Pharmacokinetic properties

Before 10 years ago, about 50% of potential therapeutic compounds failed in clinical trials or were removed from the market due to unacceptable side effects and poor ADME properties. In fact, it is now far less (about 8%) compounds that fail due to poor ADME properties, because of advancement in the science of drug discovery/design. Filtering and optimization of ADME properties in the early stage of the drug discovery are intensively investigated [36]. However, the experimental evaluation of ADME profiles is expensive, and the workload cannot meet the demands of drug screening and lead optimization. In conjunction with high throughput *in vitro* screening, computational techniques that can filter/predict ADME profiles have become an alternative approach [33]. Hence, using computer-based methods such as ADME and SAR tools the molecular descriptors and drug likeness properties were studied.

The pharmacokinetic properties are represented in Table 2. The coefficient of blood/brain barrier penetration (logB/B) was computed and access with the central nervous system (CNS). The CNS activity was computed on −2 (inactive) to +2 (active) scales which show all the molecules have displayed within an acceptable range. The interpretation of test compounds with references show that compounds were in acceptable range and hence, can be used to make an oral dosage for better absorption, transport, metabolism, and maintain homeostatic condition. The synthesized molecules 7(a-j) showed significant activity with human intestinal absorption and metabolism. It is noticed that the reference molecules enhance the bioavailability properties that lead to less toxic effects against the target protein. The functional groups of compounds such as F, Cl, and CH_3 had enhanced logP values and have the greatest retention within human intestine The logPGI (substrate), and non-inhibitors have drug-drug interaction within tissue that transforms xenobiotics of vigorous reduction of drug absorption and released more bile (liver) and urine (kidney). The reference range of −5 (poor) to +1 (good) and substrate inhibitor from 0 to 1 in which the reference and test compounds (7a-j) shows good activity with human intestinal absorption and metabolism. The aqueous solubility of compounds lies with a range of 0 (poor) to 2 (good), showed that all the molecules (7a-j) had good solubility and logPapp, and the overall results predicted that test compounds have good drug-like, lead-like, and fragment-like properties.

Drug likeness score and bioactivity score of entitled compounds

Lipinski's rule of five is commonly used by pharmaceutical chemists in drug design and development to predict oral bioavailability of potential lead or drug molecules. According to Lipinski's rule of five, a candidate molecule will likely to be orally active, if: (i) The MW is under 500, (ii) the calculated octanol/water partition coefficient (Log P) <5, (iii) there should be

Table 2: ADME and pharmacological parameters prediction for the ligands 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) using admet SAR toolbox

Ligand	PlogBB[a]	logHIA[c]	PCaco[b]	logpGI (substrate)[d]	logPGI (non-inhibitor)[e]	PlogS[f]	logpapp[g]
7a	0.9739	0.9933	0.5960	0.6022	0.7155	−4.5213	1.2429
7b	0.9766	1.0000	0.6048	0.6105	0.7204	−3.6755	1.3600
7c	0.9917	1.0000	0.5411	0.5298	0.5275	−3.0107	0.9967
7d	0.9823	1.0000	0.6345	0.7945	0.5000	−3.1751	1.1469
7e	0.9794	0.9921	0.5614	0.5914	0.7223	−3.6995	1.2795
7f	0.9859	0.9972	0.5448	0.5567	0.7417	−4.1212	0.7263
7g	0.9695	1.0000	0.6181	0.5999	0.7426	−4.4258	1.2817
7h	0.9895	1.0000	0.5000	0.5244	0.6247	−3.8148	0.8203
7i	0.9745	1.0000	0.6300	0.7901	0.5671	−3.7563	0.9495
7j	0.9739	0.9933	0.5960	0.6022	0.7155	−4.5213	1.2429
Paclitaxel	0.9748	0.9140	0.8957	0.8345	0.5509	−3.8728	0.4145

[a]Predicted blood/brain barrier partition coefficient (1-high penetration, 2-medium penetration, and 3-low penetration). [b]Predicted Caco-2 cell permeability in nm/s (acceptable range: −1 is poor, 1 is great). [c]Predicted human intestinal absorption in nm/s (acceptable range: 0 poor, >1 great). [d]Predicted P-glycoprotein substrate in nm/s (acceptable range of−5 is poor, 1 is great). [e]Predicted P-glycoprotein inhibitor in nm/s (accepted range: 0–1). [f]Predicted aqueous solubility, (concern value is 0–2 highly soluble). [g]Predicted probability of Caco-2 cell permeability in cm/s (concern value is−1–1)

Table 3: Drug likeness score for the synthesized 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j)

Compounds	MW[a]	miLog P[b]	TPSA[c]	n-Atoms	n-ON[d]	n-OHNH[e]	n-Violation	n-rotb[f]
7a	308.75	4.56	16.13	22	2	0	0	3
7b	296.44	4.40	16.13	21	2	0	0	5
7c	310.42	3.50	25.36	22	3	0	0	3
7d	323.46	3.54	19.37	23	3	0	0	3
7e	291.38	3.50	30.72	21	3	0	0	3
7f	342.89	5.21	16.13	23	2	0	1	3
7g	330.88	5.06	16.13	22	2	0	1	5
7h	344.87	4.15	25.36	23	3	0	0	3
7i	357.91	4.20	19.37	24	3	0	0	3
7j	325.82	4.15	30.72	22	3	0	0	3
Paclitaxel	853.92	4.95	221.31	62	15	4	2	14

[a]MW. [b]Logarithm of partition coefficient between n-octanol and water (miLogP). [c]TPSA. dNumber of hydrogen bond acceptors (n-ON). [e]Number of hydrogen bond donors (n-OHNH). [f]Number of rotatable bonds (n-rotb). MW: Molecular weight, TPSA: Topological polar surface area

<5 hydrogen bond donors (OH and NH groups), and (iv) with <10 hydrogen bond acceptors (notably N and O) [37]. The molecular properties of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) derivatives were calculated using molinspiration cheminformatics software and are presented in Table 3. As all the analogs of title compounds obey Lipinski's rule of five, hence, they are considered as orally active.

The bioactivity scores of the title compounds for drug targets were also predicted by molinspiration cheminformatics and are presented in Table 4. A molecule having bioactivity score more than 0.00 is most likely to exhibit considerable biological activities, while values −0.50–0.00 are expected to be moderately active, and if the score is <0.50 it is presumed to be inactive. The results clearly reveal that the physiological actions of synthesized analogs might involve multiple mechanisms of action and could be due to the interactions with G protein–coupled receptors ligands, nuclear receptor ligands, and inhibit protease, and other enzymes. The bioactivity score of compounds is suggestive of significant interaction with all drug targets. The identified compounds showed a better bioactivity score than standard drugs.

Evaluation of antiproliferative activity

The synthesized compounds 7(a-j) were screened for their *in vitro* antiproliferative activity against human cancer cell lines, namely, HeLa (human cervical cancer cell line), HepG2 (human liver cancer line), T-47D

Table 4: Bioactive score of the synthesized 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j) according to Molinspiration cheminformatics software

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
7a	0.04	−0.10	0.19	−0.20	−0.14	0.07
7b	−0.06	−0.17	0.14	−0.28	−0.28	0.01
7c	−0.06	−0.21	0.22	−0.24	−0.19	0.01
7d	0.05	−0.07	0.27	−0.23	−0.15	0.05
7e	0.02	−0.18	0.18	−0.33	−0.22	0.35
7f	0.04	−0.10	0.17	−0.19	−0.14	0.03
7g	−0.04	−0.17	0.14	−0.26	−0.27	−0.02
7h	−0.05	−0.21	0.20	−0.23	−0.19	−0.03
7i	0.05	−0.08	0.24	−0.24	−0.16	0.01
7j	0.03	−0.18	0.18	−0.30	−0.21	0.30
Paclitaxel	−2.67	−3.43	−3.51	−3.12	−2.0	−2.87

GPCR: G protein-coupled receptors

Table 5: Antiproliferative activity of 4-(piperidin-1-ylmethyl)-2-(thiophen-2-yl) quinoline 7(a-j)

Percentage growth inhibition in different cell lines					
Compound	**Concentration (µm)**	**Hela**	**Hepg$_2$**	**MCF-7**	**T-47D**
7a	25	20.87721	25.73231	31.89912	21.17284
	50	23.29711	22.45831	33.31121	20.46914
	100	30.13156	29.13386	35.72314	−9.56913
7b	25	52.76516	45.81726	49.77011	39.32581
	50	53.18087	45.91121	46.27713	34.15842
	100	52.65265	44.41213	48.12171	33.15023
7c	25	39.33827	35.79639	34.51121	−8.13421
	50	39.50112	29.68751	34.72131	−3.26211
	100	32.43745	32.87938	36.31274	15.76251
7d	25	41.63125	45.12614	37.82514	28.72461
	50	44.24764	38.15654	33.12164	33.61411
	100	49.12156	42.34789	35.76156	34.78854
7e	25	38.0531	36.78161	38.39513	29.75461
	50	32.20339	35.41667	30.01181	33.89321
	100	34.21043	39.68872	34.79153	−2.76356
7f	25	32.56131	26.98972	27.45631	18.56789
	50	35.61231	30.45886	29.44325	20.17191
	100	38.71241	36.10015	32.53151	19.20234
7g	25	56.38132	46.68309	45.12321	35.25131
	50	57.49688	47.25964	48.73544	38.45816
	100	58.91233	49.54812	49.96324	39.12312
7h	25	32.11546	28.50015	31.65865	25.97842
	50	39.23467	31.52415	32.12865	20.87126
	100	37.46793	30.56913	34.58426	28.87412
7i	25	52.98459	39.58741	36.58142	33.58447
	50	48.69455	40.98471	43.84155	31.97584
	100	53.48645	44.98845	46.54155	36.78451
7j	25	41.66591	21.04568	31.56327	19.54782
	50	39.58452	23.54314	34.87542	21.85641
	100	45.69824	25.67215	39.58712	30.96412
Paclitaxel	25	59.36544	49.64155	44.96321	35.63211
	50	62.78245	55.69784	49.21478	40.64165
	100	64.36695	58.97541	53.94595	42.68458

Values are expressed as mean (n=3). HeLa-human cervical cancer cell line, HepG2-human liver cancer line, T-47D-human breast ductal carcinoma cell line, MCF-7-human breast carcinoma cancer cell line

(human breast ductal carcinoma cell line), and MCF-7 (human breast carcinoma cancer cell line). Paclitaxel is used as reference standard. The antiproliferative activity results were represented in Table 5. The data represent that some of the compounds exhibited good inhibitory activity toward the growth of HeLa, HePG2, MCF-7, and T-47D cell lines.

In particular, compounds 7b, 7g, and 7i showed good antiproliferative activities against HeLa, HepG2, and MCF-7 cells also shows moderate antiproliferative activity against T-47D cell line. Furthermore, 7c, 7d, 7e, 7f, 7h, and 7j showed moderate antiproliferative activity against HeLa and MCF-7 cell lines, and remaining compound 7a showed moderate inhibition of growth of MCF-7 cell lines. Overall, the compounds 7b and 7g are exhibited good antiproliferative activity nearer to the standard anticancer drug paclitaxel in Hela, HepG2, and MCF-7 cell lines.

Previously, in our laboratory, the quinoline C-2 coupled furan and benzofuran moieties shows appreciable antiproliferative activity. Likewise, in the present study, the quinoline C-2 coupled thiophene moieties exhibited potent antiproliferative activity. Due to this, the introduction of thiophene at the 2nd position of quinoline enhances the antiproliferative activity. From the results, 7b and 7g were found as good antiproliferative agents due to the presence of diethylamino functional group at the 4th position of quinoline ring. The diethylamino alkyl chain is a key structure for binding and also increasing the lipophilicity due to this the molecules might be exhibited good antiproliferative activity.

CONCLUSION

The compounds 7b, 7g, and 7i showed good antiproliferative activities against HeLa, HepG2, and MCF-7 cells, show moderate antiproliferative activity against T-47D cell line. Furthermore, 7a, 7c, 7d, 7e, 7f, 7h, and 7j showed moderate antiproliferative activity against HeLa and MCF-7 cell lines. The ADMET studies of title compounds are found to be obeying the ADME properties and are non-toxic. From the above discussion, we conclude that all the molecules are found to be active and obey Lipinski's rules of five and demonstrated good drug-likeness values. Hence, they can be taken as possible hits, which on further modification can reveal compounds with good activity for future development, either as lead molecules or as drugs.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Dr. N D Satyanarayan, idea generator and direction of the investigation and overall responsible of the work. Mr. Harishkumar S, researcher working for Ph.D. involved in the synthesis, characterization, Mr. Santhosha S M, researcher, involved in spectral characterization and *in silico* studies.

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