Indian Journal of Chemistry
Vol. 63, July 2024, pp. 701-708
DOI: 10.56042/ijc.v63i7.7677

Design and synthesis of some novel 1-chloro-6-(4-(sulfonyl) piperidin-4-yl) phenyl)-6,7-dihydro-5*H*-cyclopenta[c]pyridin-5-ones as *in vitro* anticancer agents

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Received 30 December 2023; accepted (revised) 28 June 2024

The multi-step synthesis and structural determination by ^{1}H and ^{13}C NMR, IR, and mass spectroscopic investigations of certain new piperidinyl-pyridines **10a-o** are described in this article. Compounds **10e**, **10g**, **10h**, **10i**, **10j**, and **10n** show greater efficacy with Doxorubicin, which is employed as a positive control, when tested for anti-cancer activity *in vitro* against two cancer cell lines, A549 and MCF-7. The compound **10g** shows promising action over A549 and MCF-7, with IC_{50} values of 16.3 and 12.3 M respectively. Other IC_{50} values indicate towards strong potential and were in the good promise range.

Keywords: Piperidinyl-pyridinones, Anti-cancer action, MCF-7 breast cancer cell lines, A549 lung cancer cell lines

Drug development and design have been going on for the last three decades in an effort to treat cancer disorders[1-6]. Because piperidine ring systems are fundamental components of a wide variety of naturally occurring goods as well as pharmacologically and medicinally active compounds, several efforts at their synthetic recreation have been performed. We describe the sequential synthesis of the designed target from Scheme 1 and Scheme 2 reductions, benzylicbromination, cyclization, and 4-chloro-2-(4-(1-(sulfonyl)piperidine-4-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-ones *via* NH activation cyclization of the system, which was reported exactly for the synthesis of the studied reaction[7-10].

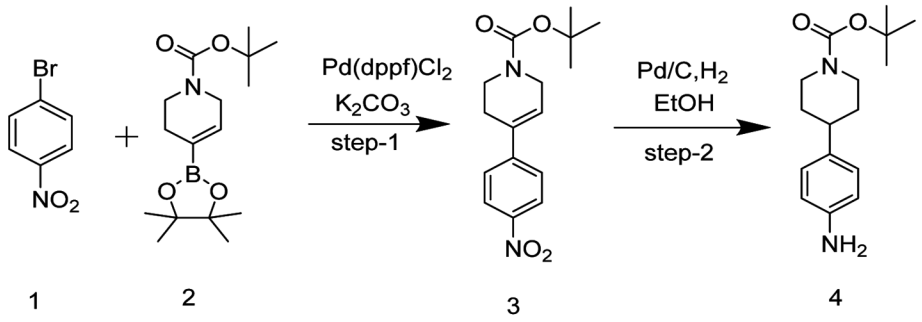
Results and Discussion

The synthetic procedure for the intended piperidinyl-pyridinones **10a–o** is shown in Scheme 1 and Scheme 2. In the beginning, 4-nitro 1-bromo benzene **1** and N-Boc-1,2,3,6-tetrahydro pyridine-4-boronic acid pinacol ester **2** were put into 1,4-dioxane. Next, K_2CO_3 was added and then 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) was incorporated in. The desired product, pure *tert*-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2*H*-carboxylate **3**, was obtained by heating the reaction mass to 100°C and stirring it while maintaining the same temperature for 6 h. After being treated with Pd/C in a par-shaker jar at RT while the reaction was carried out in the presence of hydrogen gas, the desired product, 1-Boc-4-(4-aminophenyl) piperidine **4**, was obtained.

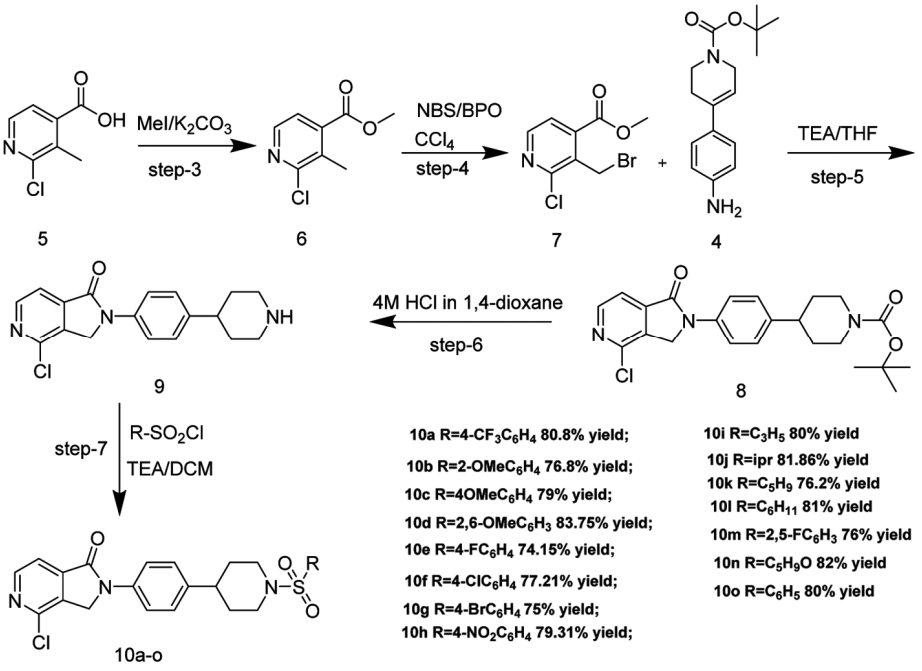
Methyl 2-chloro-3-methylisonicotinate **6** was obtained from providing 2-chloro-3-methylisonicotinic acid **5** with methyl iodide at RT with constant stirring for 16 h. Under decreased pressure, compound 6 treated with N-bromosuccinimide and benzoyl peroxide afforded methyl 3-(bromomethyl)-2-chloroisonicotinate **7**. Using a solution of methyl 3-(bromomethyl)-2-chloroisonicotinate **7** and 1-Boc-4-(4-aminophenyl) piperidine **4** in tetrahydrofuran and triethylamine at RT, the reaction mass was heated to a high temperature and kept there for 24 h to get **8**. To get compound **9**, add HCl to a solution of **8** in DCM while stirring the mixture at a temperature of less than 15°C. In order to get compound **10a** in Scheme 2, compound **9** was added to a mixture with DCM/Et_3N at RT and 4-(trifluoromethyl) benzene sulfonyl chloride at 0-5°C, and then the reaction mass was brought to RT and agitated for 2 h.

Biological Activity

The *in vitro* cytotoxic activity of the recently synthesized compounds **10a–o** was assessed using the MTT method[11,12] against the MCF-7 and A-549 cancer cell lines. As a positive control, the



Scheme 1 — Synthesis of 1-Boc-4-(4-aminophenyl) piperidine **4**



Scheme 2 — Synthesis of series of title compounds **10a-o**

chemotherapeutic drug target Doxorubicin was utilized. Table 1 reflects the addition of the aforementioned findings, which were acquired. When compared to the reference standard, six of the compounds that were subjected to the screening process (**10e**, **10g**, **10h**, **10i**, and **10j**) shown excellent potent activities. The measured IC_{50} values for **10g** were in excellent accordance with the calculated values of 16.3 and 12.3 M for A549 and MCF-7, respectively.

Anti-cancer activity (MTT assay)

The cytotoxic activity of all of the compounds **10a-o** was tested *in vitro* using MCF-7 and A-549 cancer cell lines. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was used to calculate the percentage of cells that survived after

Table 1 — *In vitro* cytotoxicity of targets **10a-o** with IC_{50} in μM

Compd	MCF-7	A549
10a	46.1	50.9
10b	40.1	60.4
10c	27	33.1
10d	30.7	39.3
10e	23.9	25.8
10f	ND	ND
10g	12.3	16.3
10h	24.4	27.1
10i	16.9	26.7
10j	15	21.3
10k	33.8	39.2
10l	ND	ND
10m	ND	ND
10n	19.4	22.2
10o	32.7	39.0
Doxorubicin	2.9	5.5

being exposed to test substances. The opted-for cell lines were acquired from NCCS Pune. Tissue culture flasks with a volume of 25 cm^2 were used to cultivate these cells in the appropriate medium. Humidified 5% CO_2 and 95% air was used to keep the cells alive in a 37°C 5% CO_2 incubator with 10% FBS and IX Penicillin/Streptomycin. At a density of 2×104 cells/well, both MCF-7 and A-549 cells were introduced onto a 96-well plate independently. The cells were cultured in the full medium for one day before being transferred to the reduced serum media. The control substance was DMSO. After 48 h of treatment with varied doses of test substances, the cells were treated with MTT (2.5 mg/mL) in the CO_2 incubator for 4 h. After removing the medium from each well, 100 L of DMSO was added to break down the formazan crystals. The optical density, which is directly proportional to cell number, was measured using an ELISA plate reader at 570 nm wavelength after full mixing. The data was presented as a ratio of cytotoxicity to viability. The trials were repeated three times for accuracy. The IC_{50} values were obtained from the percentage of cytotoxicity and compared with the reference medication Doxorubicin.

Experimental Section

Electro thermal apparatus was used to record the melting point of synthesized compounds and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and hromatography was performed by using SiO_2 gel. IR spectra (KBr) were recorded on a Perkin-Elmer BX series FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker AMX 100 MHz spectrometer. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument.

Synthesis of *tert*-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate, 3

Potassium carbonate was added to a solution containing 4-nitro-1-bromo benzene **1** and N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester in 1,4-dioxane and water. The solution was agitated and contained 15.0 g of 4-nitro-1-bromo benzene **1**, 74.25 mmol of N-Boc, and 30 mL of water. After 10 min of argon releasing, the reaction mass was added to 1,1′-Bis(diphenylphosphino) ferrocene]dichloropalladium (II). The reaction mass was stirred at 100°C for 6 h after heating it. The reaction mixture was filtered through a celite bed and washed with 200 mL of ethyl acetate once the reaction was finished. Two 300 mL portions of ethyl acetate were used for extraction after the filtrate was diluted with 300 mL of water. The combined organic layer was concentrated under decreased pressure after being washed with 200 mL of brine, dried over anhydrous sodium sulphate, and finally, obtained crude. With the use of column chromatography and elution with 12–18% ethyl acetate in petroleum ether, the beginning substances was refined. The recovered pure fractions were then concentrated under decreased pressure to yield pure 4-nitrophenyl *tert*-butyltrimethyl pyridine-1(2*H*)-carboxylate **3**, 87% yield as a yellow solid. R_f =0.6 (30% ethyl acetate in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 9.2Hz, 2H), 7.50 (d, J = 9.2Hz, 2H), 6.23 (bs, 1H), 4.13 (d, J = 2.8Hz, 2H), 3.66 (t, J = 5.6 Hz, 11.2Hz, 2H), 2.55 (bs, 2H), 1.50 (s, 9H); EI-MS: *m/z* (M+H) 290.31.

Synthesis of 1-Boc-4-(4-aminophenyl) piperidine, 4

At RT, 10% Pd/C (50% wet) (3.9 g, 20% weight/weight) was added to a stirred solution of *tert*-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate **3** (19.5 g, 64.56 mmol, 1.0 eq) in ethanol (390 mL, 20 vol) in a par-shaker jar. After bringing the mixture to RT, it was stirred for 16 h under pressure of H_2 (50 psi). Following the end of the reaction, 100 mL of ethanol was added and the liquid was filtered through celite. Reduced pressure was used to concentrate the filtrate in order to get 1-Boc-4-(4-aminophenyl) piperidine **4**. Yield 91.5% off-white solid, R_f =0.3 (30% ethyl acetate in *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 8.4Hz, 2H), 6.65-6.63 (m, 2H), 4.20 (bs, 2H), 3.57 (bs, 2H), 2.77 (t, J = 12Hz, 2H), 2.56-2.49 (m, 1H), 1.75 (d, J = 13.2Hz, 2H), 1.63-1.46 (m, 2H), 1.44 (s, 9H); EI-MS: *m/z* (M+H) 277.35.

Synthesis of methyl 2-chloro-3-methylisonicotinate, 6

In a 200 mL solution of 2-chloro-3-methylisonicotinic acid **5** (116.56 mmol) and potassium carbonate (233.12 mmol) in dimethyl formamide (DMF), 174.84 mmol of methyl iodide was added under stirring conditions at RT. Continued to stir the mixture for another 16 h at RT. Ice-cold water (1 L) was added to the reaction mixture after it was finished, and two 100 mm of ethyl acetate were used for extraction. Crude was gathered by washing

the combined organic layer with 400 mL of brine, drying it over anhydrous Na_2SO_4, and then concentrating it under reduced pressure. The raw material was refined by the use of column chromatography using a silica gel (100-200) mesh eluted with 10-15% ethyl acetate in *n*-hexane. The isolated molecule was then concentrated under decreased pressure to produce 3-Methylisonicotinate methyl 2-chloride **6**. Yield 93.38% as a colourless liquid. R_f =0.4 (10% ethyl acetate in *n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33-8.31 (dd, *J* = 0.4Hz, 5.2Hz, 1H), 7.53 (d, *J* = 4.8Hz, 1H), 3.96 (t, *J* = 2 Hz, 10.4H4Hz, 2H), 2.59 (s, 3H); EI-MS: *m/z* (M+H) 186.14.

Synthesis of methyl 3-(bromomethyl)-2-chloroisonicotinate, **7**

Benzoyl peroxide and N-bromosuccinimide were added to a carbon tetrachloride-stirred solution of methyl 2-chloro-3-methylisonicotinate at RT. Re-heated the mixture to reflux and stirred it continuously for 6 h. Filtering the solid and washing it with carbon tetrachloride were done when the reaction mixture was cooled to RT and the reaction was complete. Under decreased pressure, the filtrate was concentrated to obtain crude. To get methyl 3-(bromomethyl)-2-chloroisonicotinate **7**, the raw material was subjected to column chromatography with a silica (100-200) mesh, eluted with 0-5% EtOAc in *n*-hexane. The recovered pure fractions were then concentrated under reduced pressure. Yield 93.6% as an off-white solid. R_f =0.5 (10% ethyl acetate in *n*-hexane).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 5.2 Hz, 1H), 7.67 (d, *J* = 5.2 Hz, 1H), 5.02 (s, 2H), 3.99 (s, 3H); EI-MS: *m/z* (M+H) 264.0.

Synthesis of compound 8

Triethylamine was added at RT to a stirred solution of methyl 3-(bromomethyl)-2-chloroisonicotinate **7** (60.60 mmol) and 1-Boc-4-(4-aminophenyl) piperidine 4 (60.60 mmol) in tetrahydrofuran (640 mL, 40 vol). Reheated the mixture to reflux and stirred it continuously for 24 h. Crude was obtained by concentrating the reaction mixture under decreased pressure after the reaction had finished. The solid compound was obtained by titrating the crude compound with 150 mL of diethyl ether. Sodium sulfate was used for drying, and 8 was obtained after dissolving the solid chemical in 500 mL of dichloromethane and washing it with 250 mL of water and 200 mL of brine. Yield 82.91% as an off-white solid. R_f =0.5 (30% ethyl acetate in *n*-hexane).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.8Hz, 1H), 7.78-7.75 (m,3H), 7.31-7.29 (m, 2H), 4.89 (s, 2H), 4.26 (bs, 2H), 2.82 (t, *J* = 11.6Hz, 2H), 2.69-2.65 (m, 1H), 1.83 (d, *J* = 12.8H, 2H), 1.65-1.61 (dd, *J* = 3.6Hz, 12.4Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 154.8, 150.2, 146.4, 143.8, 143.5, 136.5, 134.0, 127.7, 120.3, 117.2, 79.5, 49.7, 44.3, 42.2, 33.1, 28.5; IR (KBr): 3392, 3061, 2976, 2921, 2851, 1912, 1716, 1677, 1582, 1516,1455, 1414, 1372, 1275, 1233, 1167, 1115, 1073, 1028, 986, 910, 846, 767, 708, 544 cm^{-1}; EI-MS: *m/z* (M+H) 428.36.

Synthesis of compound 9

Add 4.0M HCl in 1,4-dioxane (200 mL, 10 vol) to a stirred solution of compound **8** (49.29 mmol) in dichloromethane (105 mL, 5 vol) at a temperature below 15 0C. Stirred the reaction mixture at RT for 6 h after letting it cool to RT. In order to get crude, the reaction mixture was concentrated at low pressure. After dissolving the chemical in 200 mL of water, we used 2M NaOH to get the *p*H down to 9, and then we extracted the residue using 3×300 mL of 10% methanol in dichloromethane. A 200 mL brine wash, drying over sodium sulphate, and subsequent concentration under decreased pressure yielded crude from the mixed organic layer. Using 200 mL of diethyl ether, the crude chemical was titrated to give **9**. Yield 90.2% as an off-white solid.R_f = 0.3 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.0Hz, 1H), 7.77-7.74 (m, 3H), 7.31 (d, *J* = 9.0Hz, 2H), 4.89 (s, 2H), 3.21 (d, *J* = 12Hz, 2H), 2.79-2.74 (td, *J* = 2.0Hz, 12.0Hz, 2H), 2.69-2.63(m, 1H), 2.01 (bs, 1H), 1.84 (d, *J* = 12.5Hz, 2H), 1.70-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 150.1, 146.3, 144.4, 143.8, 136.2, 134.0, 127.7, 120.2, 117.1, 49.7, 47.0, 42.5, 34.3; IR (KBr): 3291,3299, 3077, 3011, 2935, 2800, 2731, 1917, 1815, 1700, 1581, 1511, 1421, 1377, 1277, 1233, 1187, 1146, 1066, 1018, 972, 913, 876, 835, 763, 702, 646, 608, 549, 420 cm^{-1}; EI-MS: *m/z* (M+H) 328.30.

Synthesis of 4-chloro-2-(4-(1-((4-(trifluoromethyl) phenyl)sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, **10a**

To a stirred solution of compound **9** (0.917 mmol) in dichloromethane (6 mL, 20 vol) was added triethylamine (2.75 mmol) at RT and cooled the reaction mass to 0°C. Added substituted benzene sulfonyl chloride (1.376 mmol) at 0-5°C. Allowed the reaction mass to RT and stirred the reaction mass at

RT for 2 h. After completion of the reaction; the reaction mixture was diluted with dichloromethane (20 mL) and washed with water (20 mL), brine (20 mL). Dried the organic layer over sodium sulphate and concentrated under reduced pressure to get crude. The crude compound was purified by column chromatography using silica gel (100-200) mesh eluted with 2-4% Methanol in dichloromethane and collected pure fractions were concentrated under reduced pressure to afford compound **10a** in 80.8% yield as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.0Hz, 1H), 7.93 (d, *J* = 8.0Hz, 2H), 7.83 (d, *J* = 8.0Hz, 2H), 7.76 (t, *J* = 9.0 Hz, 14.5Hz, 3H), 7.23 (d, *J* = 11.5Hz, 2H), 4.89 (s, 2H), 3.98 (d, *J* = 11.5Hz, 2H), 2.53-2.47 (m, 1H), 2.45-2.40 (td, *J* = 2.5Hz, 12.0Hz, 2H), 1.94-1.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.2, 146.4, 143.7, 142.1, 140.0, 136.8, 134.6, 134.3, 134.0, 128.1, 127.6, 126.3, 126.2, 124.3, 122.1, 120.3, 117.1, 49.6, 46.7, 41.2, 32.5; IR (KBr): 3456, 3050, 2925, 2850, 2745, 2678, 1932, 1818, 1693, 1618, 1579, 1518, 1463, 1390, 1333, 1279, 1166, 1061, 1013, 944, 904, 841, 772, 724, 601, 543, 476, 431 cm^{-1}; EI-MS: *m/z* (M+H) 536.27.

Synthesis of 4-chloro-2-(4-(1-((2-methoxyphenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10b

Yield 76.8% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.0Hz, 1H), 7.94-7.91 (m, 1H), 7.76 (t, *J* = 8.5Hz, 13.5Hz, 3H), 7.56-7.52 (m, 1H), 7.27 (d, *J* = 6.0Hz, 2H), 7.07-7.04 (m, 2H), 4.89 (s, 2H), 4.02 (d, *J* = 12.5Hz, 2H), 3.95 (d, *J* = 5.0Hz, 3H), 2.77-2.71 (td, *J* = 2.0Hz, 12.5Hz, 2H), 2.61-2.56 (m, 1H), 1.88 (d, *J* = 11.0Hz, 2H), 1.84-1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 156.9, 150.1, 146.4, 143.4, 142.8, 136.6, 134.4, 134.0, 131.7, 127.6, 126.7, 120.4, 120.3, 117.1, 112.3, 56.0, 49.6, 46.5, 41.7, 33.1; IR (KBr): 3515, 3392, 3078, 3013, 2935, 2842, 2677, 2039, 1929, 1814, 1704, 1583, 1518, 1478, 1380, 1321, 1283, 1245, 1189, 1142, 1067, 1017, 950, 908, 848, 804, 764, 720, 672, 618, 578, 540, 479, 441 cm^{-1}; EI-MS: *m/z* (M+H) 498.24.

Synthesis of 4-chloro-2-(4-(1-((4-methoxyphenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10c

Yield 79% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.2Hz, 1H), 7.77-7.72 (m, 5H), 7.26-7.23 (m, 2H), 7.04-7.01 (m, 2H), 4.88 (s, 2H), 3.92 (d, *J* = 11.6Hz, 2H), 3.90 (s, 3H), 2.50-2.42 (m, 1H), 2.40-2.33 (td, *J* = 3.2Hz, 11.6Hz, 2H), 1.92-1.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 162.3, 150.1, 146.4, 143.7, 142.5, 136.7, 134.0, 129.8, 127.8, 127.6, 120.3, 117.1, 114.2, 55.6, 49.6, 46.7, 41.3, 32.5; IR (KBr): 3455, 2921, 2844, 2677, 1905, 1818, 1694, 1586, 1511, 1457, 1387, 1335, 1258, 1154, 1097, 1018, 941, 902, 836, 769, 724, 657, 617, 560 cm^{-1}; EI-MS: *m/z* (M+H) 498.28.

Synthesis of 4-chloro-2-(4-(1-((2,6-dimethoxyphenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10d

Yield 83.74% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 5.0Hz, 1H), 7.76 (t, *J* = 9.0Hz, 3H), 7.41 (t, *J* = 8.5Hz, 3H), 7.29 (s, 1H), 6.64 (d, *J* = 8.5Hz, 2H), 4.89 (s, 2H), 4.07 (d, *J* = 12.5Hz, 2H), 3.90 (s, 6H), 2.81-2.75 (td, *J* = 2.5Hz, 12.5Hz, 2H), 2.64-2.57 (m, 1H), 1.90-1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 159.3, 150.1, 146.3, 143.7, 143.0, 136.6, 134.0, 133.7, 127.6, 120.3, 117.1, 116.9, 105.3, 56.7, 49.6, 46.2, 41.9, 33.2; IR (KBr): 3454, 3088, 2929, 2846, 1819, 1703, 1581, 1517, 1474, 1428, 1388, 1342, 1251, 1159, 1104, 1055, 1016, 940, 837, 791, 755, 711, 650, 611, 561, 501, 437 cm^{-1}. EI-MS: *m/z* (M+H) 528.27.

Synthesis of 4-chloro-2-(4-(1-((4-fluorophenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10e

Yield 74.15% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 5.0Hz, 1H), 7.84-7.80 (m, 2H), 7.78-7.75 (m, 3H), 7.26-7.23 (m, 3H), 4.88 (s, 2H), 3.97-3.95 (dd, *J* = 1.5Hz, 9.5Hz, 2H), 2.48-2.46 (td, *J* = 8.0Hz, 11.5Hz, 1H), 2.42-2.37 (td, *J* = 2.5Hz, 11.5Hz, 2H), 1.94-1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ166.2, 164.5, 164.2, 150.2, 146.4, 143.8, 142.3, 136.8, 134.0, 132.4, 132.3, 130.4, 130.3, 127.6, 120.4, 117.2, 116.4, 116.2, 49.7, 46.7, 41.3, 32.5; IR (KBr): 3454, 3055, 2932, 2836,2745, 2677, 1923, 1820, 1693, 1585, 1519, 1453, 1388, 1337, 1285, 1236, 1152, 1088, 1044, 1011, 937, 837, 768, 724, 652, 613, 578, 541, 436 cm^{-1}; EI-MS: *m/z* (M+H) 486.25.

Synthesis of 4-chloro-2-(4-(1-((4-chlorophenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10f

Yield 77.21% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ

8.61 (d, J = 5.0Hz, 1H), 7.77-7.73 (m, 2H), 7.55-7.53 (m, 5H), 7.25 (d, J = 8.5Hz, 2H), 4.88 (s, 2H), 3.94 (d, J = 11.5Hz, 2H), 2.51-2.45 (m, 1.0H), 2.42-2.37 (td, J = 2.5Hz, 12.0Hz, 2H), 1.93-1.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.5, 150.1, 146.4, 143.7, 142.2, 139.3, 136.8, 134.7,134.0, 129.3, 129.0, 127.6, 120.3, 117.2, 117.1, 49.6, 46.7, 41.2, 32.4; IR (KBr): 3441, 2920, 2843, 1911, 1819, 1694, 1619, 1577, 1516, 1466, 1386, 1337, 1278, 1157, 1092, 1014, 940, 902, 827, 761, 712, 611, 575, 540, 479, 435 cm^{-1}; EI-MS: *m/z* (M+H) 502.20.

Synthesis of 2-(4-(1-((4-bromophenyl)sulfonyl) piperidin-4-yl)phenyl)-4-chloro-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10g

Yield 75% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 5.0Hz, 1H), 7.77-7.65 (m, 7H), 7.25 (d, J = 8.5Hz, 2H), 4.88 (s, 2H), 3.94 (d, J = 11.5Hz, 2H), 2.51-2.37 (m, 3H), 1.93-1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.1, 146.4, 143.7, 142.2, 136.8, 135.3, 134.0, 132.3, 129.2, 127.8, 127.6, 120.3, 117.1, 49.6, 46.7, 41.2, 32.4; IR (KBr): 3449, 3303, 3050, 2922, 2851, 2732, 1907, 1818, 1696, 1617, 1575, 1515, 1464, 1422, 1384, 1338, 1271, 1160, 1096, 1058, 1011, 943, 904, 826, 751, 706, 649, 604, 543, 483, 422 cm^{-1}; EI-MS: *m/z* (M+H) 546.17.

Synthesis of 4-chloro-2-(4-(1-((4-nitrophenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10h

Yield 79.31% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 5.0 Hz, 1H), 8.42-8.40 (dd, J = 2.0Hz, 7.0Hz, 2H), 8.00-7.99 (dd, J = 1.5Hz, 6.5Hz, 2H),7.78-7.75 (t, J = 8.5Hz, 3H), 7.26 (d, J = 8.5Hz, 2H), 4.88 (s, 2H), 4.01 (d, J = 11.5Hz, 2H), 2.53-2.44 (m, 3H), 1.94 (d, J = 11Hz, 2H), 1.91-1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.6, 150.2, 146.4, 143.7, 142.5, 141.9, 136.9, 134.0, 128.8, 127.6, 124.3, 120.4, 117.2, 49.6, 46.7, 41.1, 32.5; IR (KBr): 3458, 3109, 2924, 2854, 2679, 1814, 1697, 1582, 1523, 1459, 1417, 1379, 1345, 1308, 1262, 1167, 1091, 1013, 929, 849, 799, 746, 699, 604, 539, 462, 417 cm^{-1}; EI-MS: *m/z* (M+H) 513.26.

Synthesis of 4-chloro-2-(4-(1-(cyclopropylsulfonyl) piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo [3,4-c]pyridin-1-one, 10i

Yield 80% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 5.0Hz, 1H), 7.80-7.78 (dd, J = 2.0Hz, 7.0Hz, 2H), 7.62 (d, J = 5.0Hz, 1H), 7.31 (d, J = 8.5Hz, 2H), 4.90 (s, 2H), 3.97-3.95 (dd, J = 2.0Hz, 10.0Hz, 2H), 2.97-2.91 (td, J = 2.5Hz, 12.0Hz, 2H), 2.68-2.66 (m, 1H), 2.33-2.30 (m, 1H), 1.98-1.95 (m, 2H), 1.86-1.83 (m, 2H), 1.21-1.20 (dd, J = 2.0Hz, 4.5Hz, 2H), 1.02-1.00 (dd, J = 2.0Hz, 8.0Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 150.2, 146.4, 143.8, 142.5, 136.8,134.0, 127.6, 120.3, 117.1, 49.7, 46.8, 41.6, 32.9, 25.9, 4.3; IR (KBr): 3465, 3369, 3042, 2918, 2838, 2741, 2676, 1943, 1821, 1692, 1579, 1515, 1458, 1423, 1385, 1331, 1284, 1190, 1146, 1065, 1020, 980, 935, 888, 829, 738, 675, 613, 539, 473, 433 cm^{-1}**;** EI-MS: *m/z* (M+H) 432.32.

Synthesis of 4-chloro-2-(4-(1-(isopropylsulfonyl) piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10j

Yield 81.86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (m, 3H), 7.29 (d, J = 8.5Hz, 2H), 4.90 (s, 2H), 3.99-3.96 (dd, J = 2.0Hz, 11.0Hz, 2H), 3.25-3.20 (m, 1H), 3.03-2.98 (td, J = 2.0Hz, 12.5Hz, 2H), 2.71-2.66 (m, 1H), 1.91 (d, J = 11.5Hz, 2H), 1.83-1.76 (m, 2H), 1.38 (d, J = 7.0Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.1, 146.4, 143.8, 142.7, 136.7, 134.0, 127.6, 120.3, 117.1, 53.3, 49.7, 46.9, 41.8, 33.5, 16.8; IR (KBr): 3449, 3367, 3048, 2990, 2916, 2847, 2741, 2681, 1942, 1824, 1692, 1618, 1579, 1515, 1458, 1384, 1322, 1279, 1239, 1186, 1140, 1058, 1016, 982, 934, 840, 771, 730, 665, 613, 580, 540, 477, 434 cm^{-1}; EI-MS: *m/z* (M+H) 434.30.

Synthesis of 4-chloro-2-(4-(1-(cyclopentylsulfonyl) piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10k

Yield 76.2% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 4.8Hz, 1H), 7.79-7.75 (m, 3H), 7.29 (d, J = 8.4Hz, 2H), 4.90 (s, 2H), 3.99-3.96 (dd, J = 2.0Hz, 10.4Hz, 2H), 3.48 (t, J = 10.0Hz, 1H), 2.97-2.90 (td, 2.4Hz, 12.4Hz, 2H), 2.69-2.63 (m, 1H), 2.05-2.00 (m, 4H), 1.92 (d, J = 10.8Hz, 2H) 1.86-1.75 (m, 4H), 1.69-1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.2, 146.4, 143.8, 142.6, 136.7, 134.0, 127.6, 120.3, 117.1, 60.4, 49.6, 46.8, 41.7, 33.3, 33.2, 28.0, 25.6; IR (KBr): 3368, 3050, 2960, 2858, 1946, 1824, 1693, 1618, 1579, 1515, 1454, 1384, 1322, 1280, 1242, 1189, 1143, 1064, 1018, 938, 834, 770, 715, 617, 584, 545, 432 cm^{-1}; EI-MS: *m/z* (M+H) 460.33.

Synthesis of 4-chloro-2-(4-(1-(cyclohexylsulfonyl) piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10l

Yield 81% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.8Hz, 1H), 7.79-7.75 (m, 3H), 7.30 (d, *J* = 7.2Hz, 2H), 4.90 (s, 2H), 3.98-3.95 (m, 2H), 3.03-2.91 (m, 3H), 2.69-2.67 (m, 1H), 2.13 (d, *J* = 11.6Hz, 2H), 1.92-1.89 (m, 4H), 1.83-1.70 (m, 3H), 1.55-1.52 (dd, *J* = 2.8Hz, 12.4Hz, 2H), 1.32-1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.1, 146.4, 143.8, 142.7, 136.7, 134.0, 127.7, 120.3, 117.1, 61.4, 49.7, 46.8, 41.8, 33.5, 26.6, 25.2, 25.1; IR (KBr): 3381, 3081, 3045, 2936, 2853, 2670, 1944, 1894, 1824, 1705, 1617, 1578, 1513, 1452, 1381, 1320, 1271, 1181, 1139, 1064, 1013, 947, 904, 868, 825, 767, 704, 588, 545, 485, 438 cm^{-1}; EI-MS: *m/z* (M+H) 474.16.

Synthesis of 4-chloro-2-(4-(1-((2,5-difluorophenyl) sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10m

Yield 76% as an off-white solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.4Hz, 1H), 7.78-7.74 (m, 3H), 7.60-7.58 (m, 1H), 7.30-7.21 (m, 4H), 4.89 (s, 2H), 4.03 (d, *J* = 12.4Hz, 2H), 2.72 (t, *J* = 12.4Hz, 2H), 2.62-2.56 (m, 1H), 1.96-1.92 (m, 2H), 1.88-1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 159.1, 156.6, 156.1, 153.6, 150.2, 150.0, 149.2, 146.4, 143.7, 142.2, 136.8, 134.0, 127.6, 121.6, 120.3, 118.8, 118.0, 49.6, 46.8, 41.31, 32.7; IR (KBr): 3464, 3378, 3059, 2931, 2857, 2674, 1924, 1819, 1698, 1619, 1580, 1522, 1484, 1419, 1386, 1344, 1296, 1253, 1196, 1155, 1069, 1018, 940, 885, 838, 769, 725, 597, 537, 477, 439 cm^{-1}; EI-MSm/z (M+H) 504.26.

Synthesis of 4-chloro-2-(4-(1-((tetrahydro-2*H*-pyran-4-yl)sulfonyl)piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1-one, 10n

Yield 82% as an off-white solid. R_f = 0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 5.2Hz, 1H), 7.79-7.75 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.90 (s, 2H), 4.12-4.08 (dd, *J* = 3.6Hz, 12.0Hz, 14.8Hz, 2H), 3.99-3.96 (dd, *J* = 2.0Hz, 10.8Hz, 2H), 3.43-3.39 (td, *J* = 2.4Hz, 12.0Hz, 2H), 3.18-3.15 (m, 1H), 3.06-2.99 (td, *J* = 2.4Hz, 12.8Hz, 2H), 2.70-2.50 (m, 1H), 2.01-1.89 (m, 6H), 1.84-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.2, 146.4, 143.7, 142.5, 136.7, 134.0, 127.6,119.9, 117.1, 66.5, 58.6, 49.6, 46.8, 41.7, 33.4, 26.7; IR (KBr): 3495, 3372, 3052, 2964, 2918, 2845, 2754, 2684, 1822, 1694, 1617, 1576, 1515, 1453, 1385, 1317, 1238, 1185, 1138, 1079, 1016, 946, 902, 837, 767, 709, 608, 540, 477, 438 cm^{-1}; EI-MS: *m/z* (M+H) 476.32.

Synthesis of 4-chloro-2-(4-(1-(phenylsulfonyl) piperidin-4-yl)phenyl)-2,3-dihydro-1*H*-pyrrolo [3,4-c]pyridin-1-one, 10o

Yield 80% as a yellow solid. R_f =0.7 (10% methanol in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (bs, 1H), 7.82-7.75 (dd, *J* = 6.0Hz, 5H), 7.63-7.57 (dd, *J* = 6.0Hz, 3H), 7.23(s, 1H), 4.88 (s, 2H), 3.96 (d, *J* = 10.0Hz, 2H), 2.47-2.37 (m, 3H), 1.89-1.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.5, 150.2, 146.4, 143.8, 142.5, 136.8, 136.3, 134.0, 132.7, 129.0, 127.7, 127.6, 120.4, 117.2, 49.7, 46.8, 41.3, 32.5; IR (KBr): 3439, 3058, 2922, 2837, 1959, 1899, 1821, 1694, 1617, 1577, 1516, 1454, 1386, 1334, 1282, 1239, 1163, 1092, 1018, 938, 842, 802, 737, 691, 616, 579, 539, 478, 438 cm^{-1}; EI-MS: *m/z* (M+H) 468.29.

Conclusion

We have depicted the novel piperidinyl-pyridinones **10a–o** in good to high yields. *In vitro* anti-cancer activity of the compounds **10a–o** counter to two cancer cell lines like A549 and MCF-7 revealed that the **10e**, **10g**, **10h**, **10i**, **10j**, and **10n** have shown better activity against all the cells by using reference doxorubicin. Predominantly, the compound **10g** has IC_{50} values concluded for A549 and MCF-7, with IC_{50} values of 16.3 and 12.3 μM.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Acknowledgment

The authors are thankful to the Department of Chemistry, Chaitanya Deemed to be University, Hanumakonda for providing research facilities and to Aragen Life Sciences Pvt. Ltd., Medicinal Chemistry Division, Hyderabad.

Conflict of Interests

Authors declare no conflict of interest of any kind – academic or financial for publication of this piece of work.

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