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Original Article

Antiproliferative Activity of Novel Imatinib Analogue as Potential Anticancer Agents, Synthesis and *in vitro* Screening

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ABSTRACT

Background: A series of N-(2,5-dimethylphenyl)-4-pyridin-3-ylpyrimidin-2-amine derivatives were synthesized as Imatinib derivatives, bearing 2-chloroquinoline as a heteroaryl motif. **Materials and Methods:** The compounds were synthesized by reducing *in situ* prepared azomethine intermediate using NaBH4 as a reducing agent in methanol as a solvent. Fourier transformation-IR, proton-NMR along with mass spectrometry were used to determine the structures of the compounds. The antiproliferative activity of the compounds against cell lines A549 and MCF7 was evaluated in vitro using the MTT assay protocol. **Results:** The compounds showed moderate cell growth inhibition at a concentration of 10 µM. Among the test compounds, the compound with a dimethoxy group at the 6 and 8 positions of the 2-chloroquinoline ring displayed the highest antiproliferative activity. **Conclusion:** The synthesized Imatinib derivatives exhibited moderate antiproliferative activity against A549 and MCF7 cell lines, and the compound with a dimethoxy group at the 6 and 8 positions of the 2-chloroquinoline ring showed the highest activity. These findings suggest that further studies can be performed to optimize the antiproliferative activity of these compounds.

Keywords: Imatinib derivatives, Quinoline, Reducing amination, Antiproliferative activity.

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INTRODUCTION

There are about 90s enzymes named as Protein Tyrosine Kinases (PTKs) and which have been identified as having crucial roles in cells, including controlling cell proliferation, differentiation, and morphogenesis.[1] Protein Tyrosine Kinases (PTKs) come in a variety of forms, with RTKs (Receptor Tyrosine Kinases) and NRTKs (Non-receptor Tyrosine Kinases) being two of the more well-known examples (NRTKs). Examples of RTKs and NRTKs include insulin receptors and Growth Factor Receptors (GFRs) such as Epidermal Growth Factor Receptor (EGFR) and A Basic kinase Ligand 1 (ABL1).[2] As their activity becomes disorganised, these PTKs are linked to the emergence of certain cancers.[3]

It has been shown that the oncogene BCR-ABL1 (a Protein Tyrosine Kinase, or PTK) is expressed in 95% of individuals with Chronic Myeloid Leukaemia (CML),[4] but is not expressed in normal organisms since it is the result of cellular dysregulation.

The exploration of the fact that TK was involved in CML, this has led to the studies on several small molecules which results in identification and optimization leading to imatinib (1). Imatinib, is marketed as Gleevec or Glivec (by Novartis), is an effective oral chemotherapeutic medication for cancer treatment, and earliest drug effective in PTK BCR-ABL1 mediated cancers. It has completely changed the way in which CML is being treated.[5] This medication inhibits BCR-ABL1 enzyme activity by blocking ATP binding, thus preventing substrate phosphorylation and activity, and avoiding transduction of signals required for normal cellular metabolism. The evolution of resistance to this therapy, however, has highlighted the need for the creation of new 2nd and 3rd -generation inhibitors. Unfortunately, many patients have developed resistance to the newer Tyrosine Kinase Inhibitors (TKIs), highlighting the ongoing need to find alternative treatments for these tumours.[6-8] In present study, a series of Imatinib derivatives were designed and synthesized as an plausible effective treatment for CML or resistant CML.

MATERIALS AND METHODS

Chemistry

The melting points were measured in an oil bath fitted with thermometer in an open glass capillary method. Perkin Elmer and Bruker NMR instrument Model No, DPX 400 MHz

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spectrophotometer were used to record respective IR and PNMR spectra using with deuterated DMSO or $CHCl_3$ as the NMR vehicle. The JEOL SX102/DA-6000 machine/ instrument was used to record mass spectra. The reaction progress and purity were monitored using TLC with silica gel of G grade. A literature-based procedure for preparing 2-chloroquinoline-3-carbaldehyde was followed.[9,10]

Preparation of 2-chloroquinoline-3-carbaldehyde (3a-g)

Dimethylformamide (0.125 mol, 9.13 g) in a drying-tube-equipped flask, chilled to 0 °C and then and phosphoryl chloride (0.35 mol, 57.3 gm) were added dropwise, while stirring. After 10 min, acetanilide (0.05 mol, 6.75 g) was introduced and then mixture was warmed to 75-80°C for 16-18 hr. When reaction completes, about 300 mL of ice water was mixed to the reaction mass and stirred for 30 min at temperatures between 0 and 10 degrees Celsius. A solid at this stage separates out, which was separated by filtration, washed and air dried. The solid product is then dissolved in ethyl acetate, recrystalized as creamy-yellow, glossy needle-shaped crystals. According to the results of the Schiff test, the obtained solid appears to have a carbonyl group. To ensure the compound was pure, it was analysed using TLC with TEF (5:4:1) as the mobile phase.

(Yield: 69%; melting point: 148-149°C).

Similarly, methoxy and methyl substituted 2-chloroquinoline-3-carbaldehydes were also synthesized.

Process for preparations of N1-((2-chlor o-substituted-quinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (4a-g)

To a solution of substituted 2-chloroquinoline-3-carbaldehydes (0.001 M) in methanol (10 mL), 0.0012 mole of intermediate (I) was added, while the mixture was stirred at r. t. To this reaction mixture, iodine (50 mg) was introduced, while continue stirring at r. t. until iodine was completely dissolved. Later, (0.002 M) of solid sodium borohydride was added with stirring it at r. t. until the reaction was completed. A solid precipitate obtained, it was worked up to obtained a solid compound, which was crystallized with EtOH to yield the final products (4a-g).[11,12] TLC was used to examine the reaction's development and the compound's purity. In the form of a mobile phase, ethyl acetate and formic acid (5:4:1).

Evaluation of Anticancer Activity

MTT Assay

In vitro anticancer efficacy

The effectiveness of novel imatinib derivatives against human cancer cell lines was measured by following a MTT assay.[13-16] Human breast adenocarcinoma cells (MCF7; ATCC HTB-22) and Human alveolar adenocarcinoma epithelial cells (A549; ATCC CCL-185) were used to check the cytotoxic efficacy. DME (Dulbecco's Modified Eagle Medium) supplemented with 10% Foetal Bovine Serum (FBS) was used for the cell culture. The cells were grown in a T25 flask in a humidified environment containing 5% carbon dioxide at 37 degrees Celsius. The studies were done on passage 3 cells, which were passaged every other day at roughly 70-80% confluence during their growth phase.

Cytotoxicity assay

Cell lines A549 and MCF7 (Human) were inoculated at a volume of $1x10^3$ cells / well into 96 well plates. The plates then allowed to grow and attach for an additional night before the antiproliferative activity of the compounds 4a-g was evaluated. The cells were then mixed with test compounds at conc 10 µM along with vehicle treatment (control) in triplicate wells and kept for forty-eight hrs incubation. Then 10 µL of MTT (5 mg/mL stock in 1xPBS) was introduced to each well and incubated again for 3 hr for which results in formazan crystals. The crystals were examined under the microscope, and then 100 L of DMSO was added to each well, which was then placed in an orbital shaker to dissolve the formazan. The ELISA plate reader was used to measure the absorbance of each well at 570 nm (650 nm reference). The following formula was used to determine the percentage of cells that survived.

$$\% \text{ Cell survival} = \{(\text{Control} - \text{Treated})/\text{Control}\} \times 100$$

RESULTS AND DISCUSSION

Chemistry

Imatinib derivatives (4a-g) were prepared in accordance with the synthetic route depicted in scheme 1 (Figure 1), following one-pot method. The intermediates compounds (3a–g) were obtained by acetylation of substituted aniline to yield anilides. These anilides were then treated with Vilsmeir-Haack reagent to obtained quinoline aldehyde. Imatinib derivatives (4a-g) were prepared by one-pot reductive amination using $NaBH_4/I_2$ as catalyst in methanol as solvent. The physical properties of final compounds (4a-g) are presented in Table 1. The purity was checked by TLC and elemental analyses. Structure interpretation was confirmed by FT-IR, proton-NMR, as well as MS data.

The successful reductive amination of penultimate intermediate with substituted quinoline aldehyde (3a-g) was confirmed by various method. In NMR the appearance of $-CH_2NH-$ function was observed at delta value 4.07 and 4.56 for NH and $-CH_2$ respectively. Further, the it was confirmed by mass spectra of synthesized compound using (HRMS) ESI-MS which recorded at 452.1923. The spectral details FT-IR, H-NMR and CHN analysis of all compounds were reported and presented in Table 2.

Table 1: Physiochemical data of synthesized Imatinib derivatives (4a-g).

Sl. No.	Compd. No	R^1	Yield (%)	m.p. (C)	M. F	Mol. Wt.	R_f
1	4a	H	43	160-162	$C_{26}H_{21}ClN_6$	452.9381	0.38
2	4b	6-OCH_3	52	176-179	$C_{27}H_{23}ClN_6O$	482.9641	0.39
3	Vc	6,8-OCH_3	40	192-193	$C_{28}H_{25}ClN_6O_2$	512.9901	0.37
4	Vd	8-OCH_3	33	150-152	$C_{27}H_{23}ClN_6O$	482.9641	0.40
5	Ve	6-CH_3	42	149-151	$C_{27}H_{23}ClN_6$	466.9647	0.41
6	Vf	8-CH_3	50	190-193	$C_{27}H_{23}ClN_6$	466.9647	0.39
7	Vg	6,8-CH_3	48	158-160	$C_{28}H_{25}ClN_6$	480.9913	0.36

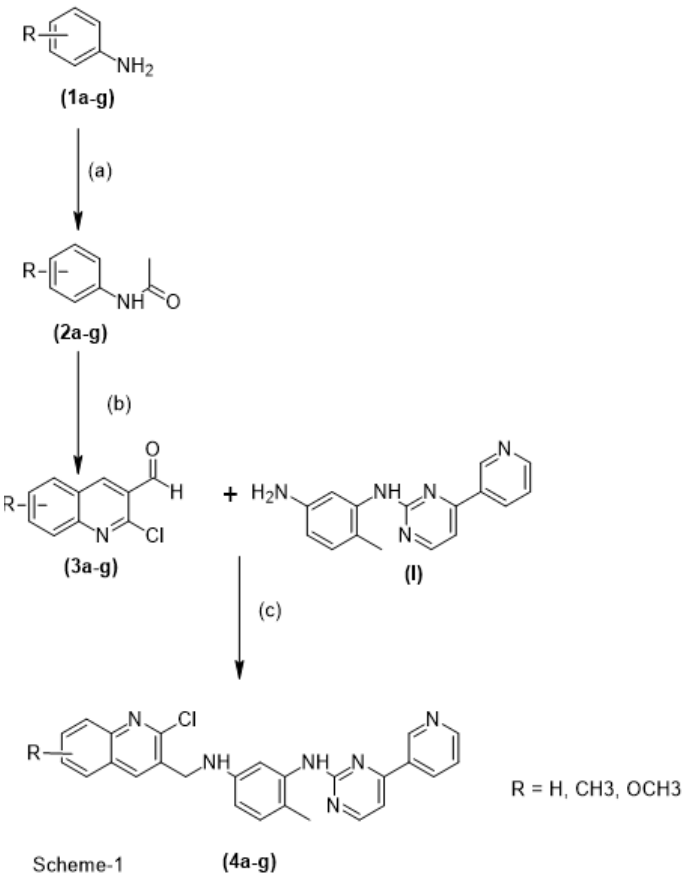

Figure 1: Route of synthesis (Scheme-1) of imatinib derivatives. a) Ac_2O/AcOH, b) DMF/$POCl_3$ c) $NaBH_4/I_2$.

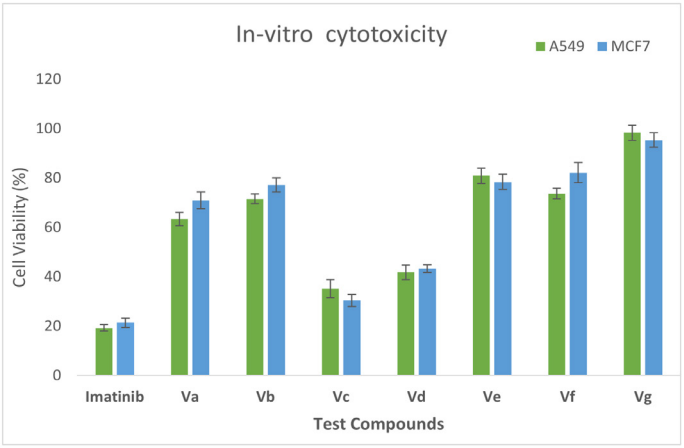

Figure 2: Screening of imatinib derivatives 3a–g at 10 μM concentration, against human cell lines A549 (in green) and MCF7 (blue). Bars represent the mean ± standard deviation.

Anticancer activity

In accordance with standard methods reported in literature,[41–44] all synthesized imatinib derivatives (4a-g) were tested for *in vitro* anticancer activity against two human cancer cell lines, A549 (human alveolar adenocarcinoma) and MCF7 (human breast adenocarcinoma) using MTT assay]. As a standard medication, imatinib was used to compare the *in vitro* activity tested compound. Solution of test compounds were prepared in triplicates and results reported as % cell survival at 10μM.

The results of anticancer evaluation studies for synthesized compounds (4a–g) is illustrated in Table 3 and the same is also represented as bar diagram in Figure 2. A preliminary analysis of table reveals that all the (4a-g) compounds exhibited moderate anti-proliferatory activity against the test cell lines. Among the imatinib derivatives, compound having dimethoxy group in the 2-chloroquinoline ring showed highest anticancer activity at conc. of 10μM as shown by the least cell viability in Table . The compound 4c exhibited % cell viability of 35.21±3.67 and 30.36±2.40 for A549 and MCF7 cell lines respectively. Another compound Vd displayed similar kind of growth inhibitory effects. While rest of the compounds exhibited less cytotoxicity.

CONCLUSION

In conclusion, a series of seven imatinib derivatives were synthesized by one-pot reductive amination of imatinib key intermediate I with 2-chloroquinoline-3-carbaldehyde (3a-g) using $NaBH_4/I_2$ as reducing agent in methanol as a vehicle for reduction.

The *in vitro* anticancer effects of the newly synthesised imatinib analogues (4a-g), against two human cancer cell lines A549 and MCF7 was studied using MTT assay following Imatinib serving as the gold standard.

Table 2: Spectral data of synthesized Imatinib derivatives (4a-g).

Sl. No.	Compd. No	FT-IR, H^1-NMR, and Mass spectral Data
1	4a	N1-((2-chloroquinolin-3-yl)methyl)-4-methyl-N3-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine (4a) FT-IR (KBr) cm^{-1}: 3109 (N-H), 1597 (C=N), 1613 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ ^{1}H NMR: δ 2.10 (3H, s, CH_3), 4.07 (bs, 1H, NH), 4.56 (d, 2H, -CH_2), 6.63-6.80 (2H, m, Ar-H, J = 6.5), 7.18-7.39 (5H, m, Ar-H). 7.60-7.72 (m, 2H, Ar-H) 8.10-8.23 (3H, m, Ar-H) 8.09 (s, 1H, Ar-H), 8.60-8.64 (1H, m, Ar-H), 9.17 (1H, bs, Ar-H). ESI-MS: m/z: 452.1923 [M^+], 454.1980 [M+2]$^+$. Anal. Calcd for $C_{26}H_{21}ClN_6$; C, 68.94; H, 4.67; N, 18.55. Found; C, 68.82; H, 4.69; N, 18.50.
2	4b	N1-((2-chloro-6-methoxyquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4b) FT-IR (KBr) cm^{-1}: 3122 (N-H), 1590 (C=N), 1620 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 4.08 (bs, 1H, NH), 4.59 (d, 2H, -CH_2), 6.59-6.78 (2H, m, Ar-H, J = 6.5), 7.23-7.42 (6H, m, Ar-H). 7.59 (s, 1H, Ar-H), 8.12-8.21 (3H, m, Ar-H) 8.08 (s, 1H, Ar-H), 8.60-8.64 (1H, m, Ar-H), 9.20 (1H, bs, Ar-H). ESI-MS: m/z: 482.1803 [M+] 484.1992 [M+2], Anal. Calcd. for $C_{27}H_{23}ClN_6O$; C, 67.15; H, 4.80; N, 17.40. Found. C, 67.32; H, 4.87; N, 17.48.
3	Vc	N1-((2-chloro-6,8-dimethoxyquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4c). FT-IR (KBr) cm^{-1}: 3130 (N-H), 1601 (C=N), 1626 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.11 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.12 (bs, 1H, NH), 4.55 (d, 2H, -CH_2), 6.56-6.72 (2H, m, Ar-H,), 7.22-7.37 (6H, m, Ar-H). 7.67 (s, 1H, Ar-H), 8.05-8.17 (2H, m, Ar-H) 8.12 (s, 1H, Ar-H), 8.58-8.62 (1H, m, Ar-H), 9.19 (1H, bs, Ar-H). Anal. Calcd for $C_{28}H_{25}ClN_6O_2$; C, 65.56; H, 4.91; N, 16.38. Found. C, 65.68; H, 4.94; N, 16.42.
4	Vd	N1-((2-chloro-8-methoxyquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4d). FT-IR (KBr) cm^{-1}: 3120 (N-H), 1593 (C=N), 1629 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 4.13 (bs, 1H, NH), 4.61 (d, 2H, -CH_2), 6.50-6.64 (2H, m, Ar-H), 7.21-7.38 (5H, m, Ar-H), 7.60-7.69 (m, 2H, Ar-H), 8.15-8.24 (3H, m, Ar-H) 8.14 (s, 1H, Ar-H), 8.57-8.61 (1H, m, Ar-H), 9.17 (1H, bs, Ar-H). Anal. Calcd for $C_{27}H_{23}ClN_6O$; C, 67.15; H, 4.80; N, 17.40. Found. C, 67.31; H, 4.86; N, 17.49%.
5	Ve	N1-((2-chloro-6-methylquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4e). FT-IR (KBr) cm^{-1}: 3122 (N-H), 1599 (C=N), 1630 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.14 (bs, 1H, NH), 4.57 (d, 2H, -CH_2), 6.62-6.75 (2H, m, Ar-H), 7.18-7.39 (6H, m, Ar-H), 7.62 (s, 1H, Ar-H), 8.16-8.22 (3H, m, Ar-H) 8.13 (s, 1H, Ar-H), 8.63-8.67 (1H, m, Ar-H), 9.23 (1H, bs, Ar-H). Anal. Calcd for $C_{27}H_{23}ClN_6$; C, 69.45; H, 4.96; N, 18.00. Found. C, 69.61; H, 4.91; N, 18.06.
6	Vf	N1-((2-chloro-8-methylquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4f). FT-IR (KBr) cm^{-1}: 3124 (N-H), 1597 (C=N), 1618 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.13 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.18 (bs, 1H, NH), 4.52 (d, 2H, -CH_2), 6.60-6.73 (2H, m, Ar-H,), 7.22-7.37 (5H, m, Ar-H), 7.62-7.70 (m, 2H, Ar-H), 8.13-8.26 (3H, m, Ar-H) 8.10 (s, 1H, Ar-H), 8.61-8.66 (1H, m, Ar-H), 9.18 (1H, bs, Ar-H). Anal. Calcd for $C_{27}H_{23}ClN_6$; C, 69.45; H, 4.96; N, 18.00. Found. C, 69.58; H, 4.92; N, 18.08%.
7	Vg	N1-((2-chloro-6,8-dimethylquinolin-3-yl)methyl)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl) benzene-1,3-diamine (4g). FT-IR (KBr) cm^{-1}: 3111 (N-H), 1594 (C=N), 1612 (C=C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.10 (3H, s, CH_3), 2.26 (6H, s, 2xCH_3), 4.10 (bs, 1H, NH), 4.60 (d, 2H, -CH_2), 6.63-6.72 (2H, m, Ar-H), 7.23-7.38 (5H, m, Ar-H), 7.60-7.66 (m, 1H, Ar-H), 8.10-8.23 (3H, m, Ar-H) 8.13 (s, 1H, Ar-H), 8.58-8.63 (1H, m, Ar-H), 9.21 (1H, bs, Ar-H). Anal. Calcd for $C_{28}H_{25}ClN_6$; C, 69.92; H, 5.24; N, 17.47. Found. C, 69.84; H, 5.28; N, 17.51.

Table 3: *In vitro* antiproliferative activity data of synthesized Imatinib derivatives.

Sl. No.	Compd. No	R^1	Cell Viability (%) at 10μM (% ± S.D.)	
			A549	MCF7
1	4a	H	63.36±2.63	70.87±3.41
2	4b	6-OCH_3	71.55±1.92	77.26±2.84
3	Vc	6,8-OCH_3	35.21±3.67	30.36±2.40
4	Vd	8-OCH_3	41.77±2.95	43.31±1.54
5	Ve	6-CH_3	80.88±3.05	78.36±3.11
6	Vf	8-CH_3	73.65±2.09	82.14±4.05
7	Vg	6,8-CH_3	98.32±3.10	95.36±2.88
8	Imatinib	------	19.21±1.32	21.32±1.88

The *in vitro* examination of imatinib derivatives against the test cell lines showed that substitution of phenyl methylene piperazine with 2-chloroquinoline results in retention of the anticancer activity but a slight decrease in comparison to the standard drug imatinib. Only one compound 4c showed highest anticancer activity at conc. 10μM. Since, all seven compounds share a common scaffold except the substitution in the quinoline ring. The presence of dimethoxy group at 6 and 8 position of quinoline ring could be the reason for slightly better anticancer activity among the group. This observation may serve as a starting point for further exploitation of the scaffold as promising anticancer drug molecules.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATP: Adenosine triphosphate; **CML:** Chronic myeloid leukemia; **DMSO:** Dimethyl sulfoxide; **GFRs:** Growth factor receptors; **NMR:** Nuclear magnetic resonance; **PNMR:** Proton nuclear magnetic resonance; **PKKs:** Protein tyrosine kinases; **RTKs:** Receptor tyrosine kinases; **NRTKs:** Nonreceptor tyrosine kinases; **TLC:** Thin layer chromatography; **TEF;** Toluene: Ethyl acetate: Formic acid.

SUMMARY

N-(2,5-dimethylphenyl)-4-pyridin-3-ylpyrimidin-2-amine derivatives bearing 2-chloroquinoline compounds were prepared as Imatinib derivatives. Analogues were screened for antiproliferative activity verses cell lines A549 and MCF7 using MTT assay protocol. The results of antiproliferative activity provides a moderate cell growth inhibition at conc. of 10 μM by the test compounds. Among the test compounds compound having dimethoxy group at 6 and 8 position of 2-chloroquinoline ring displayed highest antiproliferative activity.

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