Synthesis and *in-vitro* screening of Imatinib Schiff's base as potential anticancer agents.

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Abstract

A series of azomethine compounds (Schiff's bases) of Imatinib key intermediate N-(2,5-dimethylphenyl)-4-pyridin-3-ylpyrimidin-2-amine bearing2-chloroquinoline as heteroaryl motif was synthesised as Imatinibanalogues. The compounds were prepared by refluxing Imatinib key intermediate with 2-chloroquinoline aldehyde in ethanol as solvent. Spectraltechniques such as Fouriertransformation-IR, Proton-NMRalong with mass spectrometrywas applied for structure elucidation. *In-vitro*screening for antiproliferative activity of compounds verses cell lines A549 and MCF7 were performed using MTT assay protocol. The results of antiproliferative activity revealed the compounds disclosedgood to moderate cell growth inhibition at conc. of 10 μM. All the compound exhibited percentage cell viability of 50% or less than 50% at concentration of 10μM.

Keywords: Imatinib derivatives, quinoline, Schiff's base, antiproliferative activity.

Introduction

There are about 90s enzymes namedas 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 (nonreceptor 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 abasic 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].Further, Schiff's bases and their metal complexes have shown promising *in-vitro* anticancer activity. There are several literatureswhich emphasis the potential of Schiff's bases as promising anticancer agents[9-12]. In present study, a series of Imatinib key intermediate Schiff's base with 2-chloroquinoline were designed and synthesized as plausible effective treatment for CML or resistant CML.

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>Figure 1. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Material and Methods:

Chemistry

The melting points were measured in an oil bath fitted with thermometer in anopen glass capillary method. Perkin Elmer and Bruker NMR instrument Model No, DPX 400 MHz spectrophotometer were used to record respective IR and PNMR spectra using with deuterated DMSOor $CHCl_3$ 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[13, 14].

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>Figure 2. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Preparation of 2-chloroquinoline-3-carbaldehyde (IIIa-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 g) were added dropwise, while stirring. After 10 minutes, acetanilide (0.05 mol, 6.75 g) was introduced and then mixture was warmed to 75-80 °C for 16-18 hours. When reaction completes, about 300 mL of ice water was mixed to the reaction mass and stirred for 30 minutes at temperatures between 0 -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 N^1-((2-chloro-substituted-quinolin-3-yl)methyl)-4-methyl-N^3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVa-g)

To a solution of substituted 2-chloroquinoline-3-carbaldehydes (0.001 M) in methanol (10 mL), 0.0012 mole of intermediate **(1)**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 withstirring 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 (**IVa-g**) [15,16]. TLC was used to examine the reaction's development and the compound's purity. In the form of a mobile phase, ethylacetate and formic acid (5:4:1)

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>> Table 1. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>> Table 2. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

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[17–20]. 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 **IVa-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.

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

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>> Table 3. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

RESULTS AND DISCUSSION

Chemistry

Imatinib derivatives (**IVa-g**) were prepared inaccordance with the synthetic route depicted in scheme **1 (Figure 2)**.The intermediates compounds (**IIIa–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 (**IVa-g**) were prepared by reacting substituted 2-chloroquinoline aldehyde in absolute ethanol as solvent and few drops of acetic acid as catalyst. The physical properties of final compounds (**IVa-g**) are presented in Table I. The purity was checked by TLC and elemental analyses. Structure interpretationwas confirmed by FT-IR, proton-NMR, as well as MS data.

The successfulformation azomethine compounds (Schiff's bases) of Imatinib intermediate (1) with substituted quinoline aldehyde (**IIIa-g**) was confirmed by various method. In NMR the appearance of azomethine proton (-CH=N-) function was observed at delta value 9.23 for compound **IVa**and subsequent disappearance of aldehydic proton peak, indicate formation of desired azomethine compounds. Further, the it was confirmed by mass spectra of synthesized compound using (HRMS) ESI-MS which recorded at 450.1432 $[M^+]$ and 452.1435for $[M+2]^+$ due presence of halogen atom. The spectral details FT-IR, H^1-NMR and CHN analysis of all compounds were reported and presented in Table 2.

Anticancer activity

In accordance with standard methods reported in literature, all synthesised imatinib derivatives (**IVa-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.

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>> Figure 3. <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

The results of anticancer evaluation studies for synthesized compounds (**IVa–g**)is illustrated in Table 3 and the same is also represented as bar diagram in figure 3. A preliminary analysis of table reveals that all the (**IVa-g**) compounds exhibited good to moderate antiproliferatory activity against the test cell lines. All the compound exhibited % cell viability of 50% or less then 50% at concentration of 10μM. The compound **IVa**and**IVc** exhibited % cell viability of about 25.32 and 28.36 against A549 cell lines respectively, likewise these compounds exhibit similar antiproliferative activity against the MCF7 cell linesconcentration of 10μM. While remaining compounds displayed % cell viability in between 30 to 50 % at concentration of 10μM.

Conclusion

In conclusion, a series of seven imatinib derivatives were synthesized by refluxing imatinib key intermediate**1** with 2-chloroquinoline-3-carbaldehydes(**IIIa-g**)in ethanol as a vehicle and few drops of acetic acid as catalyst.

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

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. All the compounds exhibited % cell viability of 50 or less than 50 % at concentration of 10μM. Only two compound **IVa**and**IVc** showed highest anticancer activity at conc. 10μM. Since, all

seven compounds share a common scaffold except the substitution in the quinoline ring, the scaffold appears to be a promising structural framework for further increasing the anticancer activity.

Declaration of Competing Interest

The authors declareno conflict of interest.

Acknowledgement

The work is self-funded;however, the authors acknowledge their institutions for providing necessary facility and support to carry out this research work.Authors also thankful to Dr. Deepak Kumar of (Shoolini University, Solan 173229, India) for helping and providing anticancer activity.

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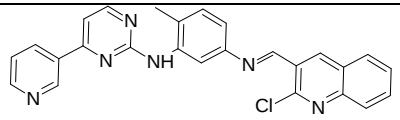
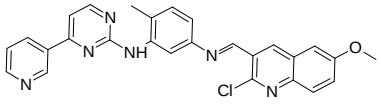
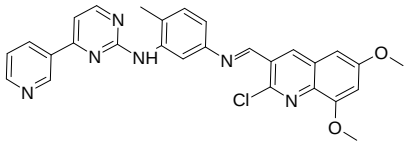
Table 1: Physiochemical data of synthesized Imatinib derivatives (IVa-g).

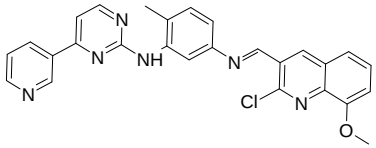
S. No.	Compd. No	R1	Yield (%)	m.p. (C)	M. F	Mol. Wt.	Rf
1	**IVa**	H	63	131	$C_{26}H_{19}ClN_6$	450.1360	0.48
2	**IVb**	6-OCH_3	58	193-194	$C_{27}H_{21}ClN_6O$	480.1465	0.43
3	**IVc**	6,8-OCH_3	60	123	$C_{28}H_{23}ClN_6O_2$	510.1571	0.42
4	**IVd**	8-OCH_3	70	149	$C_{27}H_{21}ClN_6O$	480.1465	0.45
5	**IVe**	6-CH_3	52	181-182	$C_{27}H_{21}ClN_6$	464.1516	0.46
6	**IVf**	8-CH_3	55	163-165	$C_{27}H_{21}ClN_6$	464.1516	0.41
7	**IVg**	6,8-CH_3	63	129-132	$C_{28}H_{23}ClN_6$	478.1673	0.43

Table 2: Spectral data of synthesized Imatinib derivatives (IVa-g)

Compd. No	Structure of Compound	FT-IR, H^1-NMR, & Mass spectral Data
IVa		**(E)-N1-((2-chloroquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine(IVa)** **FT-IR** (KBr) cm $^{-1}$: 3196 (N-H), 1635 (C=N), 1613 (C=C). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ^1H NMR: δ 2.12 (3H, s, CH_3), 6.65-6.81 (2H, m, Ar-H), 7.15-7.38 (5H, m, Ar-H). 7.61-7.75 (m, 2H, Ar-H). 8.08-8.18 (3H, m, Ar-H) 8.11 (s, 1H, Ar-H), 8.61-8.64 (1H, m, Ar-H), 9.09 (1H, bs, Ar-H), 9.23 (1H, CH=N). **ESI-MS:** m/z: 450.1432 [M^+], 452.1435 [M+2]$^+$. Anal. Calcd for $C_{26}H_{19}ClN_6$; C, 69.25; H, 4.25; N, 18.64. Found; C, 69.52; H, 4.29; N, 18.72.
IVb		**(E)-N1-((2-chloro-6-methoxyquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVb)** **FT-IR** (KBr) cm $^{-1}$: 3129 (N-H), 1641 (C=N), 1625 (C=C). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 2.12 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.55-6.77 (2H, m, Ar-H), 7.25-7.40 (6H, m, Ar-H). 7.54 (s, 1H, Ar-H), 8.12-8.20 (3H, m, Ar-H) 8.12 (s, 1H, Ar-H), 8.62-8.65 (1H, m, Ar-H), 9.07 (1H, bs, Ar-H), 9.21 (1H, CH=N). **ESI-MS:**m/z: 480.1501 [M+] 482.1509 [M+2], Anal. Calcd for $C_{27}H_{21}ClN_6O$; C, 67.43; H, 4.40; N, 17.47. Found; C, 67.59; H, 4.44; N, 17.52.
Vc		**(E)-N1-((2-chloro-6,8-dimethoxyquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVc).** **FT-IR** (KBr) cm $^{-1}$: 3135 (N-H), 1645 (C=N), 1621 (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), 6.59-6.73 (2H,

m, Ar-H,), 7.19-7.32 (6H, m, Ar-H). 7.68 (s, 1H, Ar-H), 8.09-8.18 (2H, m, Ar-H) 8.15 (s, 1H, Ar-H), 8.51-8.55 (1H, m, Ar-H), 9.06 (1H, bs, Ar-H), 9.25 (1H, CH=N).

Anal. Calcd for $C_{28}H_{23}ClN_6O_2$; C, 65.82; H, 4.54; N, 16.45. Found. C, 65.95; H, 4.94; N, 16.51.

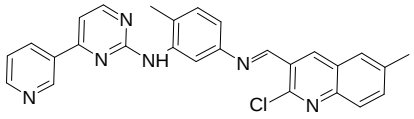
Vd 

(E)-N1-((2-chloro-8-methoxyquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVd)

FT-IR (KBr) cm $^{-1}$: 3145 (N-H), 1632 (C=N), 1620 (C=C).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.12 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.52-6.63 (2H, m, Ar-H), 7.22-7.39 (5H, m, Ar-H), 7.58-7.67 (m, 2H, Ar-H), 8.13-8.22 (3H, m, Ar-H), 8.17 (s, 1H, Ar-H), 8.59-8.62 (1H, m, Ar-H), 9.08 (1H, bs, Ar-H), 9.20 (1H, CH=N).

Anal. Calcd for $C_{27}H_{21}ClN_6O$; C, 67.43; H, 4.40; N, 17.47. Found. C, 67.58; H, 4.45; N, 17.55 %.

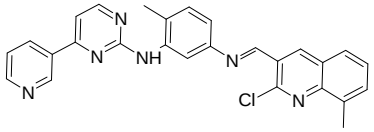
Ve 

(E)-N1-((2-chloro-6-methylquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVe).

FT-IR (KBr) cm $^{-1}$: 3135 (N-H), 16469 (C=N), 1635 (C=C).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (3H, s, CH_3), 2.26 (3H, s, CH_3), 6.60-6.73 (2H, m, Ar-H), 7.14-7.36 (6H, m, Ar-H), 7.66 (s, 1H, Ar-H), 8.10-8.24 (3H, m, Ar-H) 8.66-8.69 (1H, m, Ar-H), 9.06 (1H, bs, Ar-H), 9.24 (1H, CH=N).

Anal. Calcd for $C_{27}H_{21}ClN_6$; C, 69.75; H, 4.55; N, 18.08. Found. C, 69.82; H, 4.58; N, 18.15

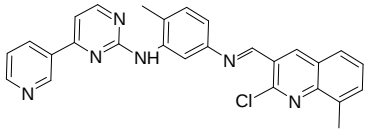
Vf 

(E)-N1-((2-chloro-8-methylquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVf)

FT-IR (KBr) cm $^{-1}$: 3125 (N-H), 1647 (C=N), 1625 (C=C).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.13 (3H, s, CH_3), 2.27 (3H, s, CH_3), 6.60-6.71 (2H, m, Ar-H,), 7.22-7.35 (5H, m, Ar-H), 7.65-7.72 (m, 2H, Ar-H), 8.12-8.27 (4H, m, Ar-H) 8.62-8.67 (1H, m, Ar-H), 9.09 (1H, bs, Ar-H), 9.25 (1H, CH=N).

Anal. Calcd for $C_{27}H_{21}ClN_6$; C, 69.75; H, 4.55; N, 18.08. Found. C, 69.86; H, 4.58; N, 18.14. %

Vg 

(E)-N1-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)-4-methyl-N3-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (IVg)

FT-IR (KBr) cm $^{-1}$: 3162 (N-H), 1642 (C=N), 1612 (C=C).

	^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.12 (3H, s, CH_3), 2.24 (6H, s, 2xCH_3), 6.60-6.71 (2H, m, Ar-H), 7.24-7.39 (5H, m, Ar-H), 7.62-7.66 (m, 1H, Ar-H), 8.10-8.22 (4H, m, Ar-H) 8.55-8.62 (1H, m, Ar-H), 9.07 (1H, bs, Ar-H), 9.22 (1H, CH=N). Anal. Calcd for $C_{28}H_{23}ClN_6$; C, 70.21; H, 4.84; N, 17.55. Found. C, 70.48; H, 4.89; N, 17.64.

Table 3: In-vitro antiproliferative activity data of synthesized Imatinib Schiff's bases.

S. No.	Compd. No	R1	Cell Viability (%) at 10µM (% ± S.D.)	
			A549	**MCF7**
1	**IVa**	H	25.32±2.25	30.12±3.19
2	**IVb**	6-OCH_3	35.14±1.46	40.36±2.68
3	**IVc**	6,8-OCH_3	28.36±3.09	33.66±2.39
4	**IVd**	8-OCH_3	40.22±2.90	42.31±1.58
5	**IVe**	6-CH_3	36.21±3.16	29.87±3.16
6	**IVf**	8-CH_3	38.19±2.21	42.36±4.01
7	**IVg**	6,8-CH_3	50.25±3.19	52.14±2.59
8	**Imatinib**	------	15.23±1.19	21.05±1.89

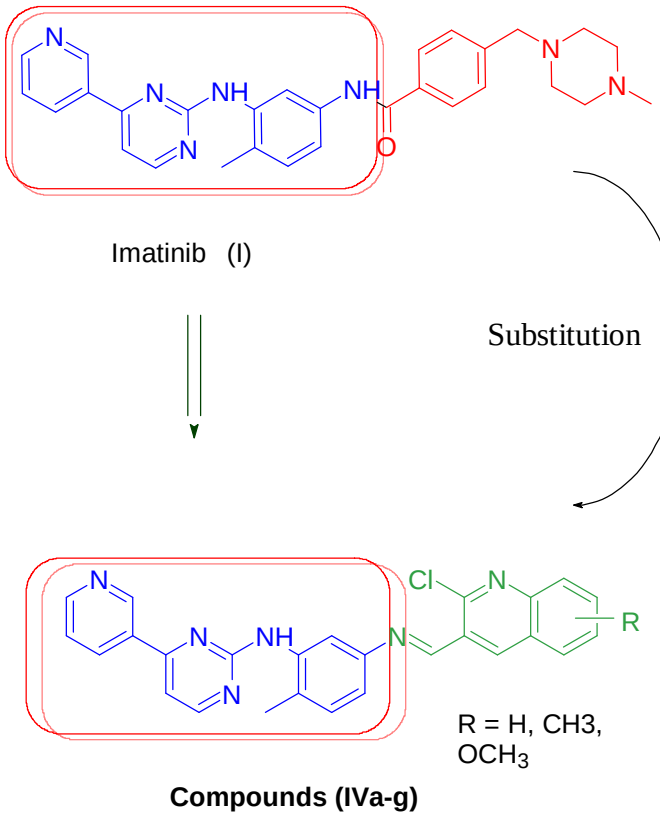


Figure 1. Design of proposed imatinib intermediates Schiff's bases as target compounds.

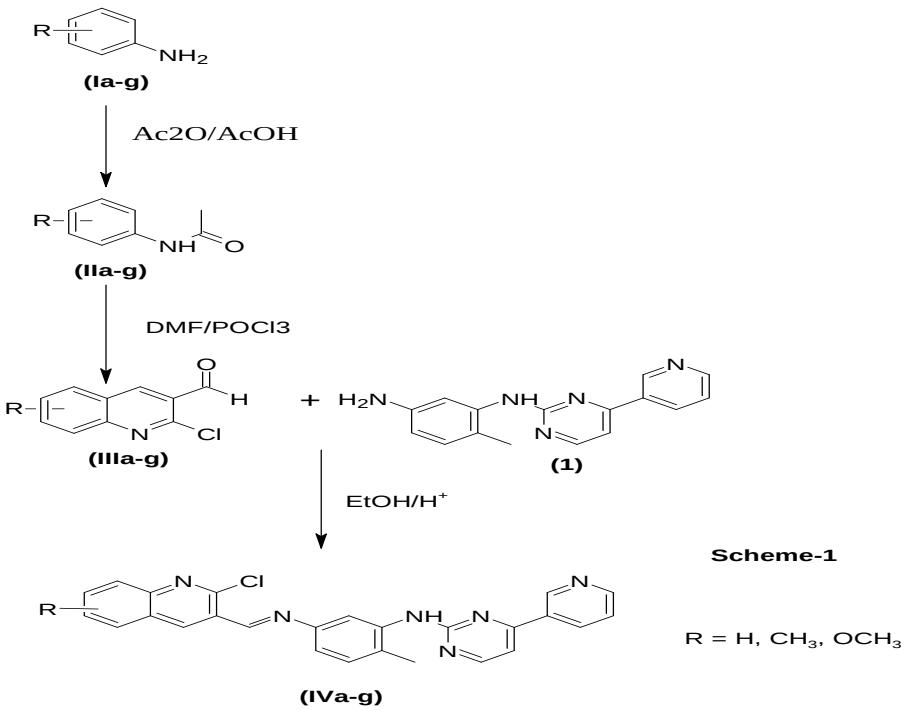


Figure 2. Route of synthesis of Imatinib intermediates Schiff's bases

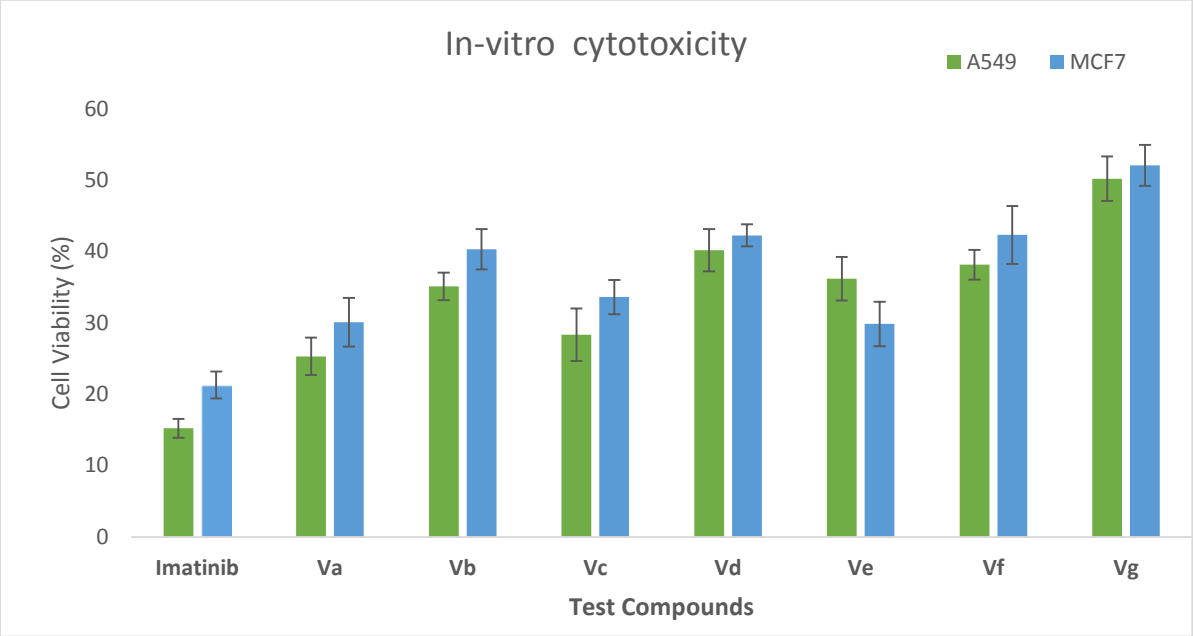


Figure 3. Screening of Schiff's bases (**IVa–g)** at 10 μM concentration, against human cell lines A549 (in green) and MCF7 (blue). Bars represent the mean ± standard deviation.