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Synthesis of novel complex conjugated imines containing a fragment of the anticancer drug Imatinib†

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Abstract: A new series of complex conjugated imine **10a-r** analogs of anticancer drug Imatinib were synthesized in moderate to good yields, under ecofriendly conditions. Some of these molecules containing fluorine atoms and privileged scaffolds such as, pyridine and pyrrole. These molecules could have potential applications in medicinal chemistry

Keywords: Conjugated Imines, Ecofriendly, Imatinib, Phenylaminopyrimide (PAP).

1. Introduction

The synthesis of library of complex nitrogen heterocycles under eco-friendly conditions, good yields and with a wide variety of biological activities presents a challenge to synthetic chemists [1]. One way to achieve this, is by employing the combinatorial chemistry approach that allows synthesize compounds via rapid and efficient methodologies, with a variety of substituents simple and complex as heterocyclic scaffolds of interest in medicinal chemistry [2]. Condensation of a primary amine with an aldehyde or ketone to obtain imines compounds is an example of such reactions and was first reported by Hugo Schiff in 1864. Schiff bases are of great importance in medicinal chemistry, considered as "privileged ligands ", due their derivatives or analogues have been shown to exhibit a plethora of biological activities, including anti-cancer, antiviral, antibacterial, antifungal, antioxidant, anticonvulsant, anti-inflammatory, antitubercular, antidepressant and antimalarial properties [3-5]. The biological activity of these molecules is mainly due to the hydrogen bond formation between the target and the lone pair of electrons in a sp^2 hybridized orbital of nitrogen atom of the imine functional group (-C=N-) [6].

On the other hand, phenylaminopyrimidines (PAP, blue color figure 1) are regarded as privileged scaffolds in medicinal chemistry, resulting of their well documented anticancer properties. [7-9]. Imatinib **1**, is an anticancer drug approved by FDA in 2001 for the treatment of chronic myeloid leukemia (CML) and in 2003 for treatment of gastrointestinal stromal tumor (GIST). The interest in the synthesis of new derivatives or analogues of Imatinib is due to the

resistance showed of some patients under Imatinib treatment (examples are shown in Figure 1). [10, 11].

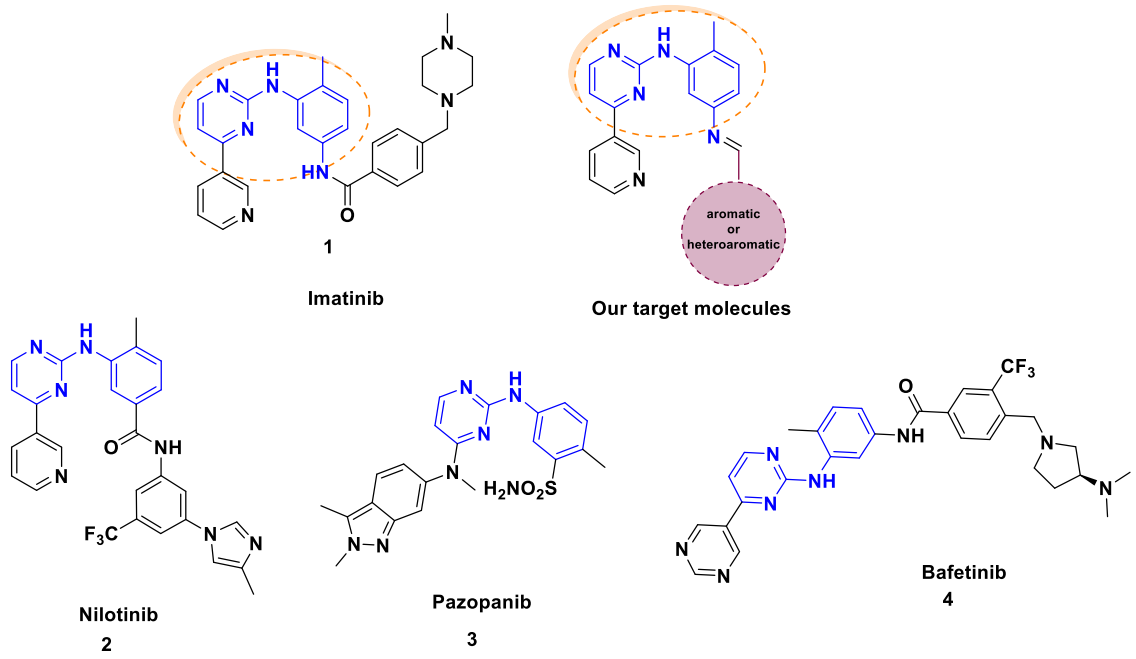


Figure 1. Imatinib structure **1**, target molecules and their analogues drugs with PAP scaffold.

The condensation of aldehydes and amines for synthesized imines is well known methodology. However, the synthesis of Schiff bases from complex anilines and aromatic (fluorinated) or nitrogenated heteroaromatic (five and six members) aldehydes is practically unexplored [12-16].

Herein we report the synthesis of a new series of complex conjugated imines containing the fragment PAP present in the anticancer drug Imatinib (Imines-PAP) using the conditions reported by Mohana in 2010 [17,18]. Besides the conjugated imines-PAP reported here contain nitrogenated heteroaromatic scaffolds of interest in medicinal chemistry such as, pyridine or pyrrole. The aldehydes used contain as substituents fluorine atoms and hydroxyl groups.

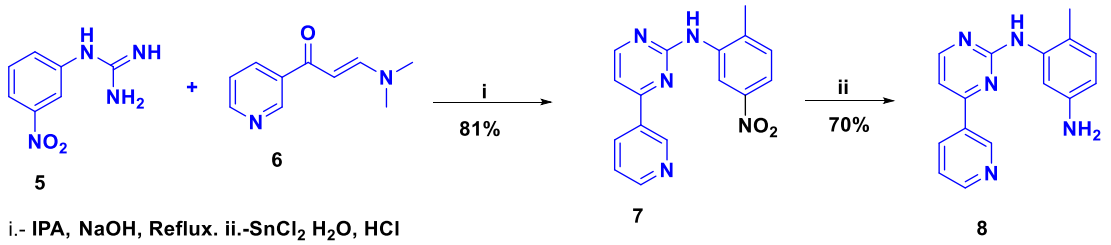
2. Materials and Methods

2.1. Experimental Section

All chemical reagents and solvents were purchased from Sigma-Aldrich Co. without further purification. Thin-layer chromatography (TLC) was performed with silica gel plates from Merck (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light and by using as eluent a mixture of heptane and ethyl acetate. NMR spectra were recorded on Bruker spectrometer Avance 400 MHz and Fourier 300 MHz using TMS as an internal reference. Chemical Shift (δ) are reported in ppm, and *J* values are given in Hertz, and deuterated DMSO-d_6 was used as solvent. High-resolution mass spectrometry (HRMS) was performed using a Micro TOF-II spectrometer and the samples were ionized by electrospray ionization on positive mode (ESI^+). FT-IR spectra were recorded on a Perkin Elmer 100 FT-IR spectrometer by ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters (ν/cm^{-1}). Melting points were determined on a Mettler Toledo apparatus.

2.2. Preparation of amino compound (amino-PAP)

The component amino-PAP was synthesized via the methodology reported by Zimmerman. (Scheme 1) [19].



Scheme 1. Synthesis of amino-PAP.

2.3. General procedure for complex conjugated imines-PAP **10a-r**

The complex conjugated imines-PAP were synthesized according to the reported methodology [17,18]: To Ethanol (0.4M) was added to a mixture of amino-PAP **8** (0.7 mmol, 1 eq) and aldehyde (0.7 mmol, 1eq). The reaction mixture was stirred at room temperature until reaction complete by solid formation and then the suspension was filtered and washed with 3 mL of Ethanol and dried under vacuum to afford the imine-PAP **10a-r**.

(E)-N-(5-((2-fluorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10a**):

yellow solid, mp = 215.8 °C; R_f = 0.50 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3241, 2940, 1585, 1529, 1453, 122, 1091; ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.29 (s, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.36-7.32 (m, 2H), 7.53 (dd, *J* = 7.7, 4.9 Hz, 1H), 8.10 (t, *J* = 7.3Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.70 (d, *J* = 3.8 Hz, 1H), 8.81 (s, 1H), 9.01 (s, 1H), 9.27(d, *J* = 1.0 Hz, 1H),^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 108.3, 116.6,116.7, 117.5, 117.8, 124.0, 124.2, 125.3, 128.2, 130.8, 131.4, 132.7, 133.8, 133.9, 134.6, 139.0, 148.6, 149.6, 151.9, 152.7, 160.0, 162.1, 163.5; HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{19}FN_5$ $[M+H]^+$ 384.1619; found 384.1697.

(E)-N-(5-((2,3-difluorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10b**):

yellow solid, mp = 216°C; R_f = 0.50 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3445, 3050, 1600, 1585, 1536, 1449, 1198, 1008.; ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.29 (s, 3H), 7.08 (d, *J* = 6.4 Hz, 1H), 7.29 (od, *J* = 8.0 Hz, 1H), 7.35-7.32 (m, 1H), 7.44 (d, *J* = 5.1 Hz, 1H), 7.59-7-50 (m, 2H), 7.63 (s, 1H), 7.88 (t, *J* = 6.9 Hz, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.70 (d, *J* = 3.7 Hz, 1H), 8.79 (s, 1H), 9.04 (s, 1H), 9.27(d, *J* = 1.0 Hz, 1H),^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.4, 108.2, 117.7, 117.9, 120.4, 123.5, 124.3, 125.6, 126.1, 126.2, 131.2, 131.4, 132.6, 134.7, 139.0, 148.6, 149.2, 151.9, 159.9, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{17}F_2N_5Na$ $[M+Na]^+$ 424.1344; found 424.1506.

(E)-N-(5-((2,4-difluorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10c**):

yellow solid,; R_f = 0.35 (Hep-AcOEt 3:7 *v*/*v*); ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.29 (s, 3H), 7.05 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.29-7.18 (m, 2H), 7.45-7.34 (m, 2H), 7.51 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 8.18-8.10 (m, 1H), 8.43-8.39 (m, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.73 (s, 1H), 9.00 (s, 1H), 9.27 (d, *J* = 1.7 Hz, 1H). ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 108.2, 113.1,

117.4, 117.6, 120.9, 124.2, 129.9, 130.7, 131.4, 132.6, 134.6, 139.0, 148.6, 149.5, 151.9, 159.9, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{17}F_2N_5Na$ $[M+Na]^+$ 424.1344; found 424.1485.

(E)-N-(5-((2,5-difluorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10d**):

yellow solid, mp = 135°C; R_f = 0.34 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3438, 3037, 1571, 1534, 1448, 1149, 1007.; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.29 (s, 3H), 7.08 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.45-7.35 (m, 2H), 7.44 (od, *J* = 5.3 Hz, 1H), 7.51 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.80-7.75 (m, 1H), 8.41 (ad, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.69 (ad, *J* = 4.6 Hz, 1H), 8.75 (d *J* = 1.9 Hz, 1H), 9.04 (s, 1H), 9.27(ad, *J* = 1.4 Hz, 1H),^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.3, 108.3, 113.3, 113.6, 117.7, 117.9, 118.5, 118.5, 118.8, 120.3, 124.2, 125.5, 131.2, 132.6, 134.6, 139.0, 148.6, 149.0, 151.6, 151.9, 157.2, 159.9, 160.4, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{17}F_2N_5Na$ $[M+Na]^+$ 424.1344; found 424.1442.

(E)-N-(5-((3,5-difluorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10e**):

Beige solid, R_f = 0.37 (Hep-AcOEt 3:7 *v*/*v*); ^{1}H-RMN (400 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.07 (d, *J* = 8.0, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.45-7.41 (m, 2H), 7.54-7.51 (m, 1H), 7.61 (d, *J* = 6.8 Hz, 1H), 7.65 (s, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.70 (s, 2H), 9.00 (s, 1H), 9.29 (s, 1H). DEPTQ-RMN (100 MHz, DMSO-d_6): δ 18.3, 106.7, 107.0, 107.2, 108.3, 111.5, 111.6, 111.7, 111.8, 117.7, 117.8, 124.3, 131.1, 131.3, 131.1, 131.4, 132.6, 134.7, 139.1, 140.1,140.2, 140.3, 148.6, 148.8, 151.9, 157.8, 159.9, 161.5, 161.8, 161.9, 162.1, 164.2, 164.4. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{17}F_2N_5Na$ $[M+Na]^+$ 424.1344; found 424.1361.

(E)-N-(2-methyl-5-(((perfluorophenyl)methylene)amino)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10f**):

Beige solid. ^{1}H-RMN (400 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.52-7.49 (m, 1H), 7.67 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.63 (s, 1H), 8.68 (d, *J* = 4.4 Hz, 1H), 8.99 (s, 1H), 9.26 (s, 1H). DEPTQ-RMN (100 MHz, DMSO-d_6): δ 18.3, 108.3, 111.6, 1117.7, 111.8, 117.1, 117.6, 124.2, 131.4, 132.6, 134.6, 136.3, 136.5, 136.6, 138.8, 139.0, 139.1, 140.8, 143.4, 144.7, 147.2, 148.3, 148.5, 149.1, 151.9, 159.9, 161.4, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{15}F_2N_5$ $[M+H]^+$ 456.1242; found 456.1368.

(E)-N-(5-(((1H-pyrrol-2-yl)methylene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10g**):

yellow solid, mp = 179°C; R_f = 0.25 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3400, 3050, 1610, 1523, 1477, 1004.; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.26 (s, 3H), 6.94 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.21-6.19 (m, 1H), 6.69 (m, 1H), 7.01 (ad, *J* = 1.0 Hz, 1H), 7.23 (ad, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.53 (ddd, *J* = 8.1, 4.8, 0.6 Hz, 1H), 8.34 (s, 1H), 8.43 (adt, *J* = 8.2, 1.9 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H), 8.71 (dd *J* = 4.8, 1.6 Hz, 1H), 8.98 (s, 1H), 9.29(d, *J* = 1.6 Hz, 1H), 11.77 (bs, 1H). ^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.2, 108.2, 110.1, 112.6, 116.8, 117.3, 124.3, 129.0, 131.1, 131.3, 132.7, 134.7, 138.9, 148.6, 150.3, 150.6, 151.9, 159.9, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{21}H_{17}N_6$ $[M+H]^+$ 353.1520; found 353.2453.

(E)-N-(2-methyl-5-((4-(pyridin-2-yl)benzylidene)amino)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10i**):

yellow solid. ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.35 (s, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.50-7.421 (m, 2H), 7.60-7.56 (m, 1H), 7.77 (s, 1H), 7.99-7.94 (m, 1H), 8.10 (d, *J* = 8.1 Hz, 2H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), 8.75 (d, *J* = 5.6 Hz, 2H), 8.78 (s, 1H), 9.03 (s, 1H), 9.34 (s, 1H). ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 108.3, 117.7, 117.8, 121.2, 123.6, 124.3, 127.4, 129.5, 130.4, 131.4, 132.7, 134.7, 137.1, 137.9, 139.0, 141.6, 148.6, 149.8, 150.2, 152.0, 155.7, 159.6, 160.0, 161.6, 162.1. HRMS (ESI+) *m*/*z* calcd. for $C_{28}H_{23}N_6$ $[M+H]^+$ 443.1979; found 443.2083.

(E)-N-(2-methyl-5-((pyridin-3-ylmethylene)amino)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10j**):

White solid, ^{1}H-RMN (400 MHz, DMSO-d$_6$): δ 2.30 (s, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.55-7.51 (m,2H), 7.65 (s, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.70 (d, *J* = 4.0 Hz, 1H), 8.76 (s, 1H), 9.01 (s, 1H), 9.06 (s, 1H), 9.29 (s, 1H). DEPTQ-RMN (100 MHz, DMSO-d$_6$): δ 18.3, 108.3, 117.6, 117.8, 124.3, 124.5, 130.8, 131.3, 132.1, 132.6, 134.7, 135.3, 139.0, 148.6, 149.4, 150.8, 151.9, 152.3, 157.9, 160.0, 161.5, 162.1. HRMS (ESI+) *m*/*z* calcd. for $C_{22}H_{19}N_6$ $[M+H]^+$ 367.1666; found 367.1694.

(E)-4-(((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)imino)methyl)phenol (**10k**):

beige solid, mp = 219°C; R_f = 0.32 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3375, 2940, 1620, 1580, 1509, 1454, 1223, 1005; ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.28 (s, 3H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.97 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.51 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 8.41 (ad, *J* = 8.1 Hz, 1H), 8.51-8.50 (m, 1H), 8.53 (s, 1H), 8.70 (add, *J* = 4.6, 1.3 Hz, 1H), 8.96 (s, 1H), 9.29 (d *J* = 1.5 Hz, 1H), 10.12 (bs, 1H); ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 108.1, 115.8, 116.1, 117.5, 124.3, 128.1, 129.5, 131.0, 132.7, 134.7, 138.9, 148.6, 150.4, 151.9, 159.5, 159.9, 161.0, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{20}N_5O$[M+H]$^+$ 382.1662; found 382.1746.

(E)-4-(((4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)imino)methyl)benzene-1,2-diol (**10l**):

yellow solid, mp = 232°C; R_f = 0.10 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3420, 2971, 1560, 1540, 1452, 1287, 1046. ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.27 (s, 3H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.96 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.27-7.18 (m, 2H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.54-7.50 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 8.43-8.40 (m, 2H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.96 (s, 1H), 9.12 (s, 1H), 9.29 (d, *J* = 1.7 Hz, 1H), 9.35 (s, 1H). ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.2, 108.2, 114.5, 116.0, 117.4, 117.5, 123.1, 124.3, 128.5, 129.5, 131.2, 132.7, 134.7, 138.8, 146.2, 148.5, 149.7, 150.3, 151.9, 159.7, 159.9, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{20}N_5O_2$[M+H]$^+$ 398.1612; found 398.1664.

(E)-N-(5-((4-(benzyloxy)benzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10m**):

white solid, mp = 101°C; R_f = 0.36 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3446, 3034, 1629, 1579, 1509, 1452, 1016. ^{1}H-RMN (300 MHz, DMSO-d$_6$): δ 2.28 (s, 3H), 5.18 (s, 2H), 7.00 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.56-7.34 (m, 8H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.42 (ad, *J* = 8.0 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.57 (s, 1H), 8.7 (dd, *J* = 4.8, 1.5 Hz, 1H), 9.00 (s, 1H), 9.30 (d, *J* = 1.4 Hz, 1H). ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 69.9, 108.2, 115.5, 117.5, 124.3, 127.6, 128.3,

128.9, 129.7, 129.8, 130.8, 131.2, 132.7, 134.7, 137.1, 138.9, 148.6, 150.1, 151.9, 159.3, 160.0, 161.3, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{30}H_{25}N_5NaO$ $[M+Na]^+$ 494.1951; found 494.2016.

(E)-N-(2-methyl-5-((3,4,5-trimethoxybenzylidene)amino)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10n**):

white solid, mp = 128°C; R_f = 0.20 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3200, 3050, 1600, 1557, 1445, 1001. ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.29 (s, 3H), 3.73 (s, 3H), 3.86 (s, 3H), 7.06 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.28-7.26 (m, 3H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.54 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 8.43 (adt, *J* = 8.2, 1.9 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 8.58 (s, 1H), 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.98 (s, 1H), 9.32 (d, *J* = 1.6 Hz, 1H). ^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.2, 49.1, 56.3, 60.6, 106.1, 108.3, 117.1, 117.6, 124.3, 129.8, 131.3, 132.1, 132.6, 134.7, 138.9, 140.6, 148.6, 149.7, 151.9, 153.6, 159.8, 160.0, 161.4, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{26}H_{25}N_5NaO_3$ $[M+Na]^+$ 478.1850; found 478.2009.

(E)-N-(5-((2-bromobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10o**):

yellow solid, mp = 126 °C; R_f = 0.36 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3252, 3052, 1582, 1557, 1454, 1024; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.05 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), .53-7.42 (m, 4H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 8.13 (dd, *J* = 7.6, 1.8 Hz, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.53 (d, *J* = 5.1 Hz, 1H), 8.69 (dd, *J* = 4.6, 1.2 Hz, 1H), 8.83 (s, 1H), 9.05 (s,1H), 9.27(d, *J* = 1.5 Hz, 1H). ^{13}C-RMN (75 MHz, DMSO-d_6): δ ^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.3, 108.3, 117.6, 124.3, 125.7, 128.6, 129.2, 131.0, 131.5, 132.6, 133.5, 133.7, 134.5, 134.7, 139.1, 148.6, 149.4, 151.9, 158.2, 159.9, 161.5, 162.1. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{18}BrN_5Na$ $[M+Na]^+$ 466.0638; found 466.0721.

(E)-N-(5-((4-bromobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10p**):

yellow solid, mp = 146 °C; R_f = 0.40 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3400, 3050, 1610, 1572, 1510, 1441, 1010; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.29 (s, 3H), 7.05 (d, *J* = 6.8 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.45 (m, 1H), 7.88-7.52 (m, 6H), 8.42 (d, *J* = 6.6 Hz, 1H), 8.69-8.66 (m, 2 H), 9.03 (s, 1H), 9.29 (s, 1H). ^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.3, 108.3, 117.8, 124.3, 125.3, 130.5, 130.8, 131.3, 132.3, 132.6, 134.7, 135.8, 139.0, 148.6, 149.4, 151.9, 159.0, 161.5, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{18}BrN_5Na$ $[M+Na]^+$ 466.0638; found 466.0658.

(E)-N-(5-((4-chlorobenzylidene)amino)-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10q**):

yellow solid, mp = 131 °C; R_f = 0.44 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3431, 3083, 1587, 1565, 1530, 1449, 1082,1011; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.29 (s, 3H), 7.06 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 7.54 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.61-7.58 (m, 3H), 7.95 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 7.9 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 8.71-8.69 (m, 2H), 9.00 (s, 1H), 9.29 (s, 1H). ^{13}C-RMN (75 MHz, DMSO-d_6): δ 18.2, 108.3, 117.6, 117.8, 124.3, 129.4, 130.5, 130.6, 131.3, 132.7, 134.7, 135.5, 136.3, 139.0, 148.6, 149.4, 151.9, 158.9, 159.9, 161.5, 162.1. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{19}ClN_5$ $[M+H]^+$ 400.1323; found 400.1395.

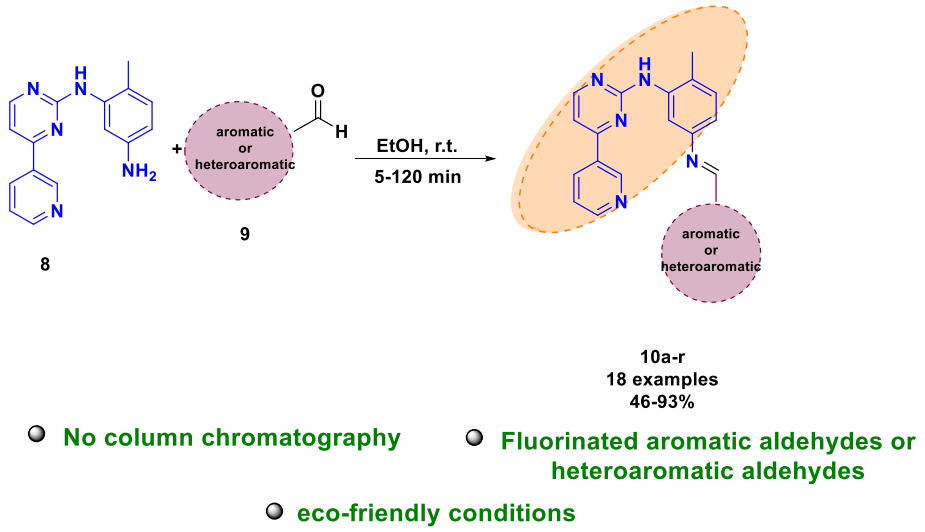
(E)-N-(2-methyl-5-((3-nitrobenzylidene)amino)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (**10r**):

yellow solid, mp = 184 °C; R_f = 0.30 (Hep-AcOEt 3:7 *v*/*v*); FT-IR (ATR)ν_{max}/cm^{-1} 3250, 3078, 1630, 1583, 1524, 1447, 1088; ^{1}H-RMN (300 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.10 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.30 (d, *J*

= 8.2 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 8.35-8.32 (m, 2H), 8.43 (dt, *J* = 8.1, 1.9 Hz, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.72 (t, *J* = 1.8 Hz, 1H), 8.84 (s, 1H), 9.05 (s, 1H), 9.29 (d, *J* = 1.7 Hz, 1H). ^{13}C-RMN (75 MHz, DMSO-d$_6$): δ 18.3, 108.3, 117.8, 117.9, 123.2, 124.3, 126.0, 130.9, 131.0, 131.4, 132.6, 134.7, 134.9, 138.1, 139.0, 148.6, 148.8, 151.9, 158.2, 160.0, 161.4, 162.0. HRMS (ESI+) *m*/*z* calcd. for $C_{23}H_{18}N_6O_2Na$ $[M+Na]^+$ 433.1383; found 400.1446.

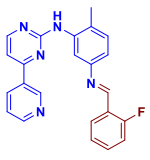
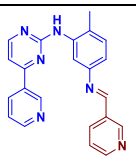
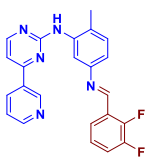
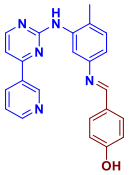
3. Results and Discussion

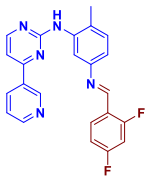
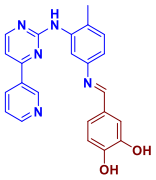
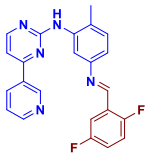
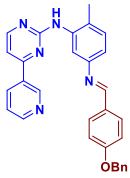
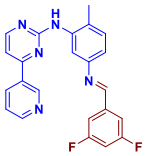
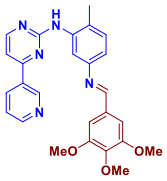
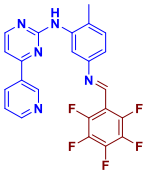
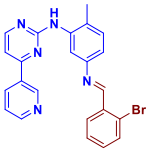
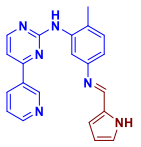
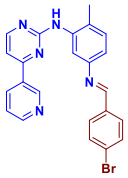
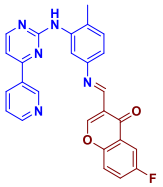
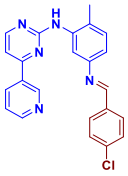
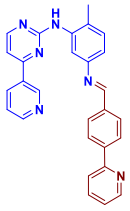
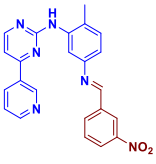
the complex conjugated imines-PAP analogs of Imatinib were synthesized in moderate to good yields, using Schiff condensation under ecofriendly conditions by varying different aromatic and heteroaromatic aldehydes and amine component was maintained constant. (Table 1) Different aldehydes with different electronic and structural nature were used to study the reaction scope.



Scheme 2. General synthetic route for the synthesis of complex conjugated imines-PAP **10a-r**

Table 1. Scope of reaction in the synthesis of complex conjugated imines PAP **10a-r**.

Imine-PAP	Yield	Imine-PAP	yield
 **10a**	80%	 **10j**	46%
 **10b**	89%	 **10k**	75%

 **10c**	60%	 **10l**	92%
 **10d**	57%	 **10m**	71%
 **10e**	90%	 **10n**	67%
 **10f**	85%	 **10o**	76%
 **10g**	55%	 **10p**	63%
 **10h**	n.d.[1]	 **10q**	75%
 **10i**	50%	 **10r**	73%

[1] not detected.

Firstly, a series of fluorinated conjugated imines-PAP **10a-f** were synthesized. The synthesis of target-molecule containing fluorine atoms is a common strategy in the drug discovery process, as it can improve their binding affinity, metabolic stability, lipophilicity and basicity [20-22]. Besides approximately 30% of new approved drugs contain at least one fluorine atom [20]. Fluorinated imines-PAP **10a-f** possibly have activity as inhibitors to *pan*-PIM kinase as the fluorinated analogues reported by Nishiguchi et al. [23].

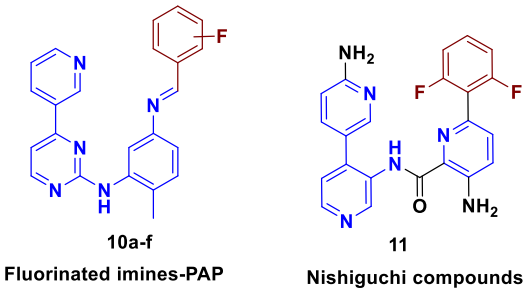


Figure 2. Fluorinated conjugated imines-PAP **10a-f** and analogues reported by Nishiguchi et al.

Moreover, the synthesis of at least two biologically active molecules in the same molecule to design a new hybrid compounds is a powerful strategy on drug design and analogues drugs. This strategy is known as molecular hybridization [24,25]. Accordingly, the novel hybrid imines containing heterocycles considered as privileged scaffolds such as pyrrol (pyrrol-PAP **10g**) [26], and pyridine [27] (Pyridine-PAP **10i** and **10j**) were synthesized. These complex conjugated imines-PAP, therefore, represent a contribution to the synthesis of Schiff bases containing nitrogenated heterocycles.

4. Conclusions

Complex conjugated imines-PAP analogs of Imatinib **10a-r** were obtained under eco-friendly conditions in moderate to good yields with good substrate scope. These new analogues imines-PAP containing nitrogenated heterocycles and fluorine atoms, can serve as promising anticancer compounds.

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Author Contributions: All authors contribute equally to the work

Conflicts of Interest: The authors declare no conflicts of interest or state

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