

# Aldehyde Phenylamino-Pyrimidine as Key Precursor for the Synthesis of Imatinib Analogs and In Silico Studies of Their Intermediates †

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† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: <https://ecsoc-27.sciforum.net/>.

**Abstract:** The synthesis of aldehyde-PAP as a key precursor through a triple reaction sequence: diazotization-addition/CuAAC/oxidation by using 4-methyl-*N*<sup>3</sup>-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine as the starting material is described. Furthermore, a molecular docking study was conducted to assess the potential of these compounds as possible ABL kinase inhibitors. Finally, leveraging our in-silico investigations, we introduce a small virtual library of compounds Imatinib analogs, which will aid in identifying the optimal candidates for further in vitro experimentation.

**Keywords:** Imatinib analogs; phenylamino-pyrimidine; molecular docking; 1,2,3,-triazoles

## 1. Introduction

One of the current challenges in medicinal chemistry is the quest for novel molecules with high biological potential [1–3]. An approach to achieve this is through the synthesis of analogs of a lead compound or drug, following the concept pioneered by Sir James Whyte Black, Nobel Prize laureate in Medicine, who famously stated: “The most valuable foundation for discovering a new drug is to start with one already known” [4–7].

On the other hand, Imatinib (Gleevec) **1** is a tyrosine kinase inhibitor that has proven to be highly effective in treating certain types of cancer, such as chronic myeloid leukemia and gastrointestinal stromal tumors [8,9]. It contains the phenylaminopyrimidine (PAP) scaffold [10,11]. A pressing concern with such pharmaceuticals is the development of pharmacoresistance, underscoring the significant interest among synthetic and medicinal chemists in synthesizing structural analogs [12–14]. This endeavor seeks to usher in a new generation of active pharmaceutical ingredients.

Herein, we report the synthesis of aldehyde-PAP **3** as a key precursor through a triple reaction sequence: diazotization-addition/CuAAC/oxidation by using 4-methyl-*N*<sup>3</sup>-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine as the starting material. In addition, a molecular docking study was conducted to assess the potential of these compounds as possible ABL kinase inhibitors as well as a small series of virtual compounds bearing imine fragment.

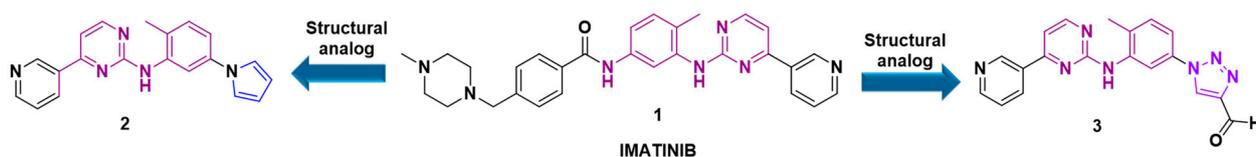
**Citation:** Tierrablanca-Arias, L.E.; Cervantes-Valencia, H.; Piña-Gordillo, M.N.; Chacón-García, L.; Suárez-Castro, A.; Cortes-García, C.J. Aldehyde Phenylamino-Pyrimidine as Key Precursor for the Synthesis of Imatinib Analogs and In Silico Studies of Their Intermediates. *Chem. Proc.* **2023**, *14*, x. <https://doi.org/10.3390/xxxxx>

Academic Editor(s): Name

Published: 15 November 2023



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**Figure 1.** Imatinib structure and our target molecules.

## 2. Materials and Methods

### 2.1. Experimental Section

All reagents, reactants, and solvents were purchased from Merck (before Sigma-Aldrich Co) without further purification. Melting points were determined on a Fischer apparatus and were not corrected. NMR spectra were recorded at 400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$  on a Varian Mercury 400 spectrometer, using  $\text{CDCl}_3$  as the solvent and TMS as the internal standard. The chemical shift ( $\delta$ ) is reported in ppm, and the  $J$  values are given in Hertz. HRMS spectra were acquired on a Bruker MicroTOF-II spectrometer.

### 2.2. Synthesis of *N*-(2-methyl-5-(1H-pyrrol-1-yl)phenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (2)

In a 50 mL round-bottom flask, the compound amino-PAP 4 (200 mg, 1 equiv.) was dissolved in acetic acid (7 mL, 0.2 M) at room temperature, followed by the addition of 2,5-dimethoxytetrahydrofuran 5 (93.43  $\mu\text{L}$ , 1 equiv.). The reaction mixture was stirred for 2 h at 70  $^\circ\text{C}$ . Subsequently, the reaction mixture was evaporated under reduced pressure with methanol washes. The reaction crude was treated with 15 mL of  $\text{H}_2\text{O}$  and 15 mL of DCM (dichloromethane); the phases were separated, and the aqueous phase was washed again with 15 mL of DCM. The organic phases were combined, washed with  $\text{H}_2\text{O}$  (2x20 mL), dried with sodium sulfate, and evaporated under reduced pressure. The reaction crude was purified via column chromatography with ethyl acetate (AcOEt), isolating the compound pyrrole-PAP 2 as a yellow solid.

Yellow solid; mp = 120–122  $^\circ\text{C}$ ;  $R_f$  = 0.44 (EtOAc:MeOH 9.5:0.5 v/v);  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.24 (s, 1H), 8.73 (d,  $J$  = 3.3 Hz, 1), 8.51 (d,  $J$  = 5.2 Hz, 1 H), 8.47 (d,  $J$  = 2.4 Hz, 1H), 8.38 (dt,  $J$  = 8.0, 2.0 Hz, 1 H), 7.41 (dd,  $J$  = 8.0, 4.8 Hz, 1H), 7.26–7.13 (m, 6H), 7.05 (dd,  $J$  = 0.8, 2.4 Hz, 1H), 6.35 (t,  $J$  = 2.2 Hz, 2H), 2.37 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.6, 160.4, 159.1, 151.6, 148.4, 139.4, 138.3, 134.5, 132.6, 131.1, 124.5, 123.6, 119.3, 114.9, 113.1, 110.0, 108.5, 17.5. HRMS (ESI $^+$ ): m/z: Calcd. for  $\text{C}_{20}\text{H}_{18}\text{N}_5$  [ $\text{M} + \text{H}$ ] $^+$ : 328.1557; Found: 328.1550.

### 2.3. Synthesis of *N*-(5-azido-2-methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (7)

In a 50 mL round-bottom flask, the compound amino-PAP 4 (500 mg, 1 equiv.) was dissolved in HCl 6 M (1.8 mL, 1 M). Then, a solution of  $\text{NaNO}_2$  (186.5 mg, 1.5 equiv.) in 4.5 mL of  $\text{H}_2\text{O}$  (0.6 M) was slowly added dropwise at 0  $^\circ\text{C}$ , and the mixture was stirred for 20 min. Subsequently, a solution of  $\text{NaN}_3$  (468.5 mg, 4 equiv.) in 9.01 mL of  $\text{H}_2\text{O}$  (0.8 M) was added dropwise at 0  $^\circ\text{C}$ . The reaction mixture was stirred at room temperature for 1 h. Afterward, 15 mL of  $\text{H}_2\text{O}$  and 15 mL of AcOEt were added. The phases were separated, and the aqueous phase was washed again with 15 mL of AcOEt. The organic phases were combined, washed with  $\text{H}_2\text{O}$  (2  $\times$  20 mL), and dried with sodium sulfate. Then, the dried product was evaporated under reduced pressure, resulting in the isolation of the compound azide-PAP 7 as a yellow solid.

Yellow solid; mp = 109–112  $^\circ\text{C}$ ;  $R_f$  = 0.73 (EtOAc:Hex 7:3 v/v);  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.25 (d,  $J$  = 2.3 Hz, 1H), 8.73 (dd,  $J$  = 4.9, 1.6 Hz, 1H), 8.52 (d,  $J$  = 5.2 Hz, 1H), 8.40 (d,  $J$  = 7.9 Hz, 1H), 8.21 (d,  $J$  = 2.3 Hz, 1H), 7.44 (dd,  $J$  = 8.1, 4.9 Hz, 1H), 7.21 (d,  $J$  = 5.2 Hz, 1H), 7.18–7.14 (m, 2H), 6.67 (dd,  $J$  = 8.1, 2.4 Hz, 1H), 2.34 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.9, 160.5, 159.3, 151.8, 148.6, 138.9, 138.6, 134.9, 132.8, 131.6, 124.0, 123.7, 113.8, 111.0, 108.9, 17.8. HRMS (ESI $^+$ ): m/z: Calcd. for  $\text{C}_{16}\text{H}_{13}\text{N}_7$  [ $\text{M} + \text{H}$ ] $^+$ : 304.1305; Found: 304.1306.

#### 2.4. Synthesis of (1-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazol-4-yl)methanol (9)

In a 25 mL round-bottom flask, the compound azide-PAP 7 (390.9 mg, 1 equiv.) was dissolved in a mixture of DMF/H<sub>2</sub>O (0.1 M, 13 mL 1:1 v/v), and propargyl alcohol 8 (93.7 mg, 1.3 equiv.) was added. Then, CuSO<sub>4</sub>·5H<sub>2</sub>O (16.0 mg, 0.05 equiv.) and sodium ascorbate (25.5 mg, 0.10 equiv.) were added to the reaction mixture, which was stirred at room temperature for 24 h. After this period, the reaction mixture was evaporated under reduced pressure with toluene washes. Finally, the product was vacuum-filtered with 15 mL of H<sub>2</sub>O and 15 mL of AcOEt, resulting in triazole-PAP 9 isolation as a light brown solid.

Light Brown solid; mp = 190–195 °C; *R*<sub>F</sub> = 0.55 (EtOAc:MeOH 8:2 v/v); <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 9.11 (s, 1H), 8.62–8.53 (m, 3H), 8.35 (s, 1H), 7.74–7.40 (m, 6H), 4.59 (s, 2H), 2.33 (s, 3H). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 162.5, 161.4, 160.3, 152.1, 149.7, 148.9, 139.7, 135.5, 134.8, 132.2, 132.0, 121.5, 116.1, 115.8, 109.0, 55.7, 18.5. HRMS (ESI<sup>+</sup>): *m/z*: Calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>7</sub>O [M + H]<sup>+</sup>: 360.1567; Found: 360.1579.

#### 2.5. Synthesis of 1-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-1H-1,2,3-triazole-4-carbaldehyde (3)

In a 1 mL round-bottom flask, the compound triazole-PAP 9 (50 mg, 1 equiv.) was dissolved in (DCM) (0.2 mL, 0.5 M), and IBX (77.9 mg, 2 equiv.) was added. The reaction mixture was stirred for 48 h at room temperature. After this time, it was evaporated under reduced pressure. Subsequently, the crude product was purified by column chromatography with ethyl acetate (AcOEt), resulting in the isolation of aldehyde-PAP 3 as a beige solid.

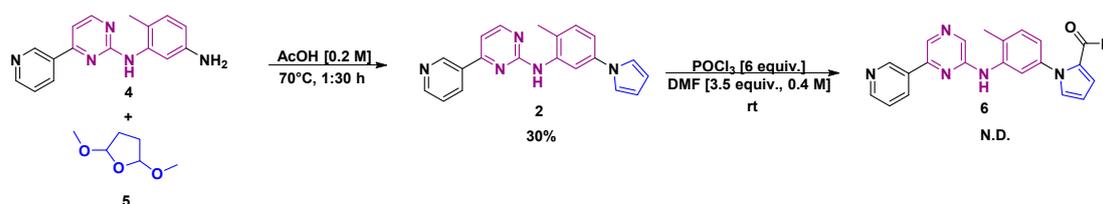
Beige solid; mp = 179–191 °C; *R*<sub>F</sub> = 0.44 (EtOAc); <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.10 (s 1H), 9.53 (s, 1H), 9.28 (s, 1H), 8.57 (d, *J* = 5.0 Hz, 1H), 8.01–7.93 (m, 3H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.71–7.67 (m, 2H), 7.54–7.50 (m, 2H), 5.35 (s, 3H). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 185.7, 168.5, 161.3, 160.3, 152.2, 148.2, 139.8, 135.2, 135.1, 133.2, 132.2, 131.8, 131.1, 127.0, 126.6, 121.1, 116.6, 109.1, 18.5. HRMS (ESI<sup>+</sup>): *m/z*: Calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>7</sub>O [M + H]<sup>+</sup>: 358.1416; Found: 358.1429.

#### 2.6. Computational Details

See supporting information for computational details.

### 3. Results and Discussion

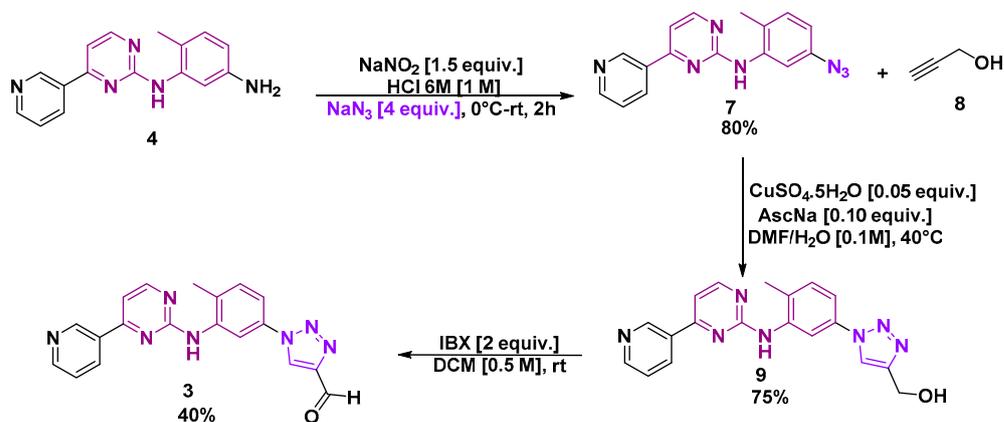
Our study began with synthesizing the aldehyde pyrrole-PAP 6 from amino-PAP 4 through a two-step synthesis. In the initial step, a Clauson-Kaas reaction was carried out using the conditions previously reported by Dallemagne's research group [15], forming pyrrole-PAP 6 with a 30% yield. Subsequently, multiple formylation experiments were conducted under classical Vilsmeier-Haack conditions using POCl<sub>3</sub> [16,17]; however, no formylated product was obtained (Scheme 1).



**Scheme 1.** General synthetic scheme for the synthesis of aldehyde pyrrole-PAP 6.

Consequently, we modified our approach, synthesizing the aldehyde triazole-PAP 3 through a three-step reaction sequence (Scheme 2). This compound is a critical precursor for developing a new series of Imatinib analogs, incorporating pharmacophoric fragments such as 1,4-disubstituted-1,2,3-triazoles. In the first step, an amino-PAP 4

diazotization/addition reaction was performed, resulting in an 80% yield of azide-PAP 7. The second step involved a copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) between propargylic alcohol 8 and azide-PAP 7, using reaction conditions recently described by our research group [18], yielding the primary alcohol triazole-PAP 9 with a 75% yield. Finally, oxidation of the primary alcohol with IBX produced the aldehyde triazole-PAP 3 with a 40% yield.



**Scheme 2.** General synthetic scheme for the synthesis of aldehyde triazole-PAP 3.

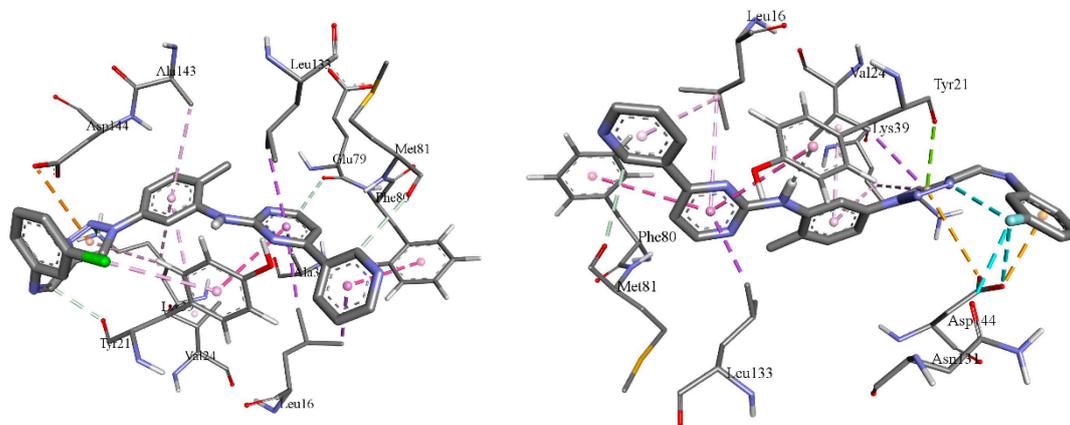
In addition, molecular docking studies were conducted to assess the potential inhibitory effects of molecules 2 and 9 on Tyrosine kinase enzymes. Furthermore, a virtual library of imine-PAP compounds denoted as 10a–i, was subjected to in silico molecular docking to identify promising candidates for synthesis through Schiff condensation reactions between aldehyde 3 and various aniline derivatives of differing stereoelectronic characteristics (for details, please refer to the supplementary information). The results of this analysis are presented in Table 1. Notably, compounds 10c and 10f exhibited superior selectivity for the active site of the ABL kinase enzyme, particularly in its mutated form.

**Table 1.** Free energy and  $k_i$  predicted results of the synthesized ligands 2 and 9, as well as imines-PAP 10a–i with two ABL kinase receptors.

Compounds	Receptor			
	4WTP		2HZI	
	$\Delta G$ (kcal/mol)	$k_i$ (nM)	$\Delta G$ (kcal/mol)	$k_i$ (nM)
2	−9.32	147.95	−9.51	107.06
9	−9.7	77.39	−8.89	304.09
10a	−10.69	14.51	−10.82	11.78
10b	−9.39	131.87	−8.55	536.54
10c	−10.54	18.67	−11.39	4.46
10d	−10.5	20.27	−8.88	309.21
10e	−9.82	63.43	−9.75	71.42
10f	−12.04	1.49	−9.09	215.89
10g	−9.62	89.23	−10.78	12.51
10h	−10.41	23.34	−10.45	21.89
10i	−11.56	3.38	−9.54	101.34

Based on the obtained results, it is evident that derivatives 10c and 10f exhibited free energies of −10.54 and −12.04 kcal/mol, respectively. The most noteworthy interactions observed in both ligands included a hydrogen bond interaction between the triazole moiety of 10f and Lys39. Additionally, predominant pi-sigma type interactions were noted between the pyridine fragment of both compounds and Leu16 and Leu133, as well as the

toluene fragment with Val24. Furthermore, pi-type interactions were observed, including stacking interactions between the triazole fragment and Tyr21, and between the pyridine portion and Phe80. Finally, a pi-anion type interaction was identified between the triazole fragment and Asp144 in both compounds (Figure 2).



**Figure 2.** Depiction of the receptor ligand interactions between compounds **10c** (left) and **10f** (right) with the 4WTP ABL kinase receptor.

#### 4. Conclusions

In summary, aldehyde-PAP **3** was synthesized under mild reaction conditions in three-step reactions. This aldehyde could be a powerful synthetic platform to obtain a new family of Imatinib analogs bearing pharmacophoric fragments such as 1,2,3-triazoles and pyridine. As a result, we have tentatively proposed a virtual library of imino-PAP **10a-i**-type compounds through Schiff condensation reactions to identify potential candidates for further synthesis. Molecular docking studies on these imines suggest their potential utility in developing tyrosine kinase inhibitors, a hypothesis that warrants verification through subsequent *in vitro* investigations.

**Author Contributions:** Conceptualization, C.J.C.-G. and A.S.-C.; methodology, L.E.T.-A. and M.N.P.-G.; software, L.C.-G. and H.C.-V.; validation, A.S.-C. and M.N.P.-G.; formal analysis, L.C.-G. and A.S.-C.; investigation, C.J.C.-G. and H.C.-V.; resources, C.J.C.-G. and L.C.-G.; data curation, L.E.T.-A. and M.N.P.-G.; writing—original draft preparation, C.J.C.-G. and L.E.T.-A.; writing—review and editing C.J.C.-G., and A.S.-C.; visualization, H.C.-V. and A.S.-C.; supervision, C.J.C.-G.; project administration, C.J.C.-G. and L.C.-G.; and funding acquisition, C.J.C.-G. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors gratefully acknowledged the financial support from Programa para el Desarrollo Profesional Docente, para el Tipo Superior (PRODEP PTC-404), and CIC-UMSNH (14766).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** Carlos C.-G. is grateful for financial support from Programa para el Desarrollo Profesional Docente, para el Tipo Superior (PRODEP PTC-404), and CIC-UMSNH (14766). Abel S.-C. is also grateful to CONAHCYT for scholarship 765046.

**Conflicts of Interest:** The authors declare no conflict of interest or state.

#### References

- Nicolaou, C.A.; Humblet, C.; Hu, H.; Martin, E.M.; Dorsey, F.C.; Castle, T.M.; Burton, K.I.; Hu, H.; Hendle, J.; Hickey, M.J.; et al. Idea2Data: Toward a new paradigm for drug discovery. *ACS Med. Chem. Lett.* **2019**, *10*, 279–286.
- Hughes, J.P.; Rees, S.; Kalindjian, S.B.; Philpott, K.L. Principles of early drug discovery. *Br. J. Pharmacol.* **2011**, *162*, 1239–1249.

3. Bleicher, K.H.; Bohm, H.J.; Muller, K.; Alanine, A.I. Hit and lead generation: Beyond high-throughput screening. *Nature* **2003**, *2*, 369–378. <https://doi.org/10.1038/nrd1086>.
4. Brown, N. *Scaffold Hopping in Medicinal Chemistry*, 1st ed.; Editorial Wiley-VCH: Weinheim, Germany, 2014.
5. Dörwald, F.Z. *Lead Optimization for Medicinal Chemist*, 1st ed.; Editorial Wiley-VCH: Weinheim, Germany, 2012.
6. Fischer, J.; Ganellin, C.R. *Analogue-Based Drug Discovery II*, 2nd ed.; Editorial Wiley-VCH: Weinheim, Germany, 2010.
7. Raju, T.N.K. The Nobel Chronicles. *Lancet* **2000**, *355*, 1022.
8. Wishart, D.S.; Feunang, Y.D.; Guo, A.C.; Lo, E.J.; Marcu, A.; Grant, J.R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; et al. DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic. Acids. Res.* **2018**, *46*, D1074–D1082.
9. Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anti-cancer drug. *Nat. Rev.* **2002**, *1*, 493.
10. Santos, C.; Pimentel, L.; Canzian, H.; Oliveira, A.; Junior, F.; Dantas, R.; Hoelz, L.; Marinho, D.; Cunha, A.; Bastos, M.; et al. Hybrids of Imatinib with Quinoline: Synthesis, Antimyeloproliferative Activity Evaluation, and Molecular Docking. *Pharmaceuticals* **2022**, *15*, 309–332.
11. LL Oliveira, A.; Moura, S.; Pimentel, L.; Neto, J.; Dantas, R.; Silva, F., Jr.; Bastos, M.; Boechat, N. New Imatinib Derivatives with Antiproliferative Activity against A549 and K562 Cancer Cells. *Molecules* **2022**, *27*, 750–763.
12. Zhang, Q.; Wang, J.; Wang, F.; Chen, X.; He, Y.; You, Q.; Zhou, H. Identification of Type II Inhibitors Targeting BRAF Using Privileged Pharmacophores. *Chem. Biol. Drug. Des.* **2014**, *83*, 27–36.
13. Desogus, A.; Schenone, S.; Brullo, C.; Tintori, C.; Musumeci, F. Bcr-Abl tyrosine kinase inhibitors: A patent review. *Expert Opin. Ther. Pat.* **2015**, *25*, 397–412.
14. Zhao, H.; Guo, Z. Medicinal chemistry strategies in follow-on drug discovery. *Drug Discov. Today* **2009**, *14*, 516–522.
15. Jourdan, J.P.; Since, M.; Kihel, L.E.; Lecoutey, C.; Corvaisier, S.; Legay, R.; de Oliveira Santos, J.S.; Cresteil, T.; Malzert-Fréon, A.; Rochais, C.; et al. Novel benzylidenephénylpyrrolizinones with pleiotropic activities potentially useful in Alzheimer's disease treatment. *J. Med. Chem.* **2016**, *114*, 365–379.
16. Servín-García, G.; Chacon-García, L.; Islas-Jacome, A.; Gomez-Hurtado, M.A.; Rodríguez-García, G.; del Río, R.E.; Cortés-García, C.J. Late-stage functionalization of Vouacapane derivatives from *Caesalpinia platyloba* by a Groebke-Blackburn-Bienaymé reaction. *J. Heterocycl. Chem.* **2023**, 1–8. <https://doi.org/10.1002/jhet.4710>.
17. Iranpoor, N.; Panahi, F.; Erfan, S.; Roozbin, F. Selective and Efficient Formylation of Indoles (C3) and Pyrroles (C2) Using 2,4,6-Trichloro-1,3,5-Triazine/Dimethylformamide (TCT/DMF) Mixed Reagent. *J. Heterocycl. Chem.* **2017**, *54*, 904–910.
18. Aguilar-Morales, C.M.; Araujo-Huitrudo, J.G.; López-Hernández, Y.; Contreras-Celedón, C.; Islas-Jacome, A.; Granados-López, A.J.; Solorio-Alvarado, C.R.; López, J.A.; Chacón-García, L.; Cortés-García, C.J. A One-Pot Six-Component Reaction for the Synthesis of 1,5-Disubstituted Tetrazol-1,2,3-Triazole Hybrids and Their Cytotoxic Activity against the MCF-7 Cell Line. *Molecules* **2021**, *26*, 6104–6117.

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