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Synthesis and In Silico Drug-Likeness Modeling of 5-FU/ASA Hybrids

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Abstract: A series of 5-FU-ASA hybrids were synthesized with good yields using click chemistry as the key step. The structures of these compounds were elucidated by spectroscopic analysis. Finally, an optimal pharmacokinetic profile was also estimated for each synthetized hybrid. Taken together, hybrids **4a**–**h** could be used as starting points for further pharmacological studies concerning therapeutic cancer intervention.

Keywords: 5-FU; ASA; hybrid compounds; click chemistry; drug-likeness modeling

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1. Introduction

Molecular hybridization is the combination of two or more pharmacophores in one molecule. This has emerged as a promising strategy in medicinal chemistry in the search of new therapeutic alternatives to treat colorectal cancer [1,2], which is the second deadliest and widely diagnosed cancer in the world, accounting for 10% of all cancers [3]. Treatment used clinically for colorectal cancer (CRC) is based on 5-fluorouracil (5-FU), an antimetabolite of the pyrimidine analogue type. In addition, acetylsalicylic acid (ASA) an analgesic and anti-inflammatory agent [4] has shown chemopreventive potential over colon cancer [5]. On the other hand, click chemistry refers to a group of reactions that are fast, simple to use, easy to purify, versatile, regiospecific, and provide high product yields. An example of these reactions is the CuI-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes to form 1,2,3-triazoles. This methodology has been applied to the synthesis of diverse pharmaceutical agents suitable for medicinal chemistry, including hybrids molecules, and drugs discovery [6–10].

Based on the anticancer potential of both 5-FU and ASA and the need for new therapeutic alternatives for the treatment of CRC, we designed and synthesized several hydrolyzable conjugated hybrids 5-FU-ASA (Figure 1), which were obtained via click reaction between different ASA-alkylazides and propargyl-5-FU. Moreover, pharmacokinetic modelling studies were conducted aiming at investigating the potential of the synthetized hybrids as drug-like molecules.

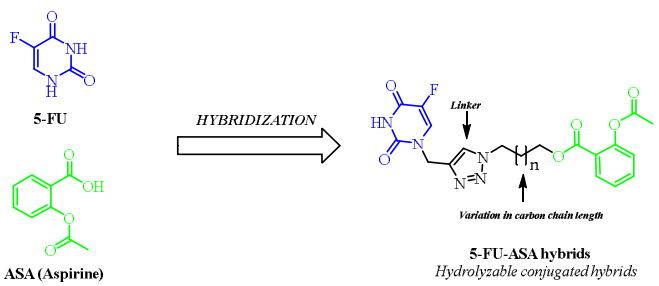
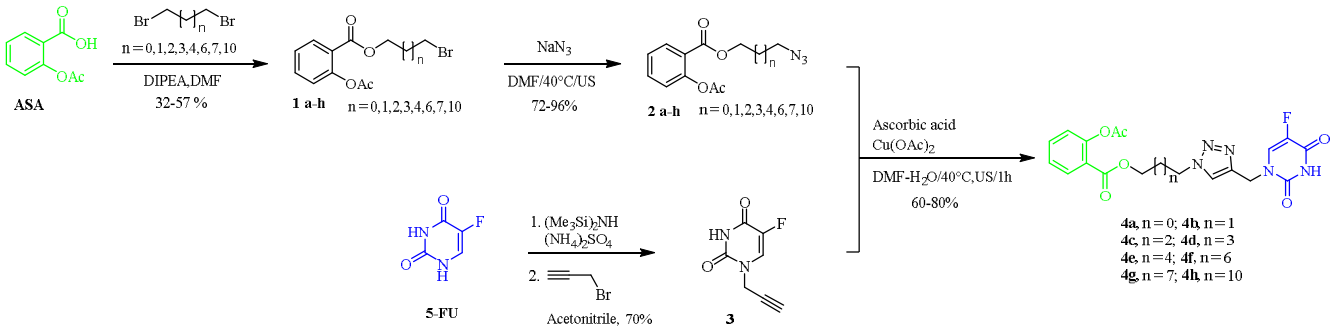


Figure 1. Design of 5-FU-ASA hybrids.

2. Results and Discussion

2.1. Chemistry

The synthesis of the hybrids is shown in Scheme 1. It began with the esterification of ASA with 1,ω-dibromoalkanes (ω = 3, 4, 5, 8, 9, and 12) producing ASA-bromoalkyls **1a**–**h** with yields ranging between 32% and 57%. Compounds **1a**–**h** were treated with sodium azide leading to the formation of the ASA-alkylazides **2a**–**h** with 72–96% yields. These compounds have already been reported [11]. Reaction of 5-FU with propargyl bromide led to the 5-FU-alkyne (**3**) with a 70% yield [12]. Finally, ultrasound assisted click reactions between azides **2a**–**h** and alkyne **3** led to the formation of hybrids **4a**–**h** with 60–80% yields [10]. The use of sonication in the Huisgen reaction reduces the reaction time, which is, on average, 24 h [13,14], and in our case, 1 h.



Scheme 1. Synthesis of 5-FU-ASA hybrids.

The structures of all compounds have been established by a combined study of HRMS-ESI (*m*/*z*), ^{1}H-NMR, and ^{13}C-NMR spectra. HRMS-ESI (*m*/*z*) spectra showed characteristic $[M + H]^+$ peaks corresponding to their molecular weights. The assignments of all signals to individual H or C-atoms were carried out based on typical δ-values and J-constants. The ^{1}H-NMR spectra of the hybrids dissolved in DMSO-d6 showed signals belonging to 5-FU (C**H**–C–F) around 8.10 ppm as a doublet. 5-FU-C**H**$_2$-triazolyl (4.87 ppm). The acetyl group of ASA was observed around 2.25 ppm. ^{13}C-NMR spectra of the hybrids showed signals corresponding to the carbonyl groups of the ASA around 169 and 163 ppm. The signal corresponding to the C-F of 5-FU appeared as a doublet around 141 and 139 ppm. The triazolyl ring exhibited signals around 142.2 and 124 ppm.

2.2. In Silico Pharmacokinetic Analysis of Conjugates **4a**–**h**

In silico calculations currently represent one of the most feasible and fast methodologies for accessing the pharmacokinetic and physicochemical properties of novel drug potential candidates. Particularly, a rigorous analysis of this data can be used as an efficient filter in the development of new oncolytic candidates. In this line, early predictions of biopharmaceutical profiling could enhance the probability of success in drug discovery settings followed by a significant reduction of time and money, thereby promoting further preclinical and clinical experiments for a lead compound [15,16]. Based on its chemical structures, the SwissADME web tool was used to evaluate seven key biopharmaceutical parameters for conjugates **4a**–**h** and then compared against those of 95% of approved drugs (Table 1) in order to investigate if novel hybrids can be regarded as valid development starting points for cancer drug discovery. Notably, favorable pharmacokinetics indices were found for conjugates compared to 95% of FDA-approved drugs. According to Lipinski's rule of five [16,17] (there should be no more than one violation), the synthetized hybrids could apparently be used as oral systemic drugs in humans. Thus, the degree of lipophilicity (calculated as logPo/w) was predicted to be in about 0.61–5.19, fitting well within the ideal range for lipid-based formulations [18] (−2.0 to 6.0).

Table 1. Lipinski's rule and pharmacokinetic score for the synthesized conjugates **4a**–**h**.

Comp. (n)	MW [a]	$LogP_{o/w}$ [b]	R.B. [c]	n-ON [d]	n-OHNH [e]	TPSA [f]	LRFV [g]	PAINS [h]
4a	417.35	0.61	9	10	1	138.19	0	0
4b	431.38	0.88	10	10	1	138.19	0	0
4c	445.41	1.15	11	10	1	138.19	0	0
4d	459.43	1.66	12	10	1	138.19	0	0
4e	473.46	2.16	13	10	1	138.19	0	0
4f	501.51	3.16	15	10	1	138.19	1	0
4g	515.54	3.68	16	10	1	138.19	1	0
4h	557.62	5.19	19	10	1	138.19	1	0

[a] Molecular weight of the hybrid (150–500). [b] Parameter calculated as consensus log P for octanol/water (−2 to 6.5). [c] Number of rotatable bonds (0–10). [d] Estimated n-ON number of hydrogen bond acceptors <10. [e] n-OHNH number of hydrogen bond donors ≤5. [f] Topological polar surface area (7.0–200 $Å^2$). [g] Lipinski's rule of five violations. [h] Identification of potentially problematic fragments for pan-assay interference compounds (PAINS).

In addition, we also calculated the PSA parameter, which together with the logPo/w value correlates passive molecular transport through membranes and drug-membrane interactions. [19] Based on our analysis, for all tested compounds, an estimated PSA value was found to be 138.19 $Å^2$, which fits well within the recommended range for oral drugs candidates (7.0 to 200 $Å^2$).

Finally, the pan-assay interference compounds (PAINS) filter which provides specific information on the potential toxicity of promiscuous compounds [20], showed that the novel hybrids could be used as safe starting prototypes for drug cancer development. In sum, our modelling showed that these novel molecules are projected to have the best pharmacokinetic qualities for further chemical biology projects.

3. Materials and Methods

3.1. Chemical Synthesis

5-FU (≥98.0%) and Aspirin (≥99.0%, Acetylsalicylic acid) were purchased from AK scientific and chemicals (Union City, CA, USA). Ultrasound equipment (BRANSON) was used to assist the reactions. NMR spectra were recorded on an AMX 300 instrument (Bruker, Billerica, MA, USA) operating at 300 MHz for ^1H and 75 MHz for ^{13}C. The signals of the deuterated solvents were used as references and the chemical shifts (δ) were displayed in ppm. TMS was used as an internal standard. Coupling constants (J) are given in Hertz (Hz). HRMS was obtained using a Bruker Impact II UHR-Q-TOF mass spectrometer (Bruker Daltonik GmbH, Bremen Germany) in positive mode. For column chromatography and thin layer chromatography (TLC), silica gel 60 (0.063–0.200 mesh, Merck, Whitehouse Station, NJ, USA) and precoated silica gel plates (Merck 60 F254 0.2 mm) were used.

General Procedure for the Synthesis of 5-FU-ASA Hybrids **4a**–**4h**

Hybrids **4a**–**h** were synthesized following a procedure described in the literature [11]. In a 10 mL flat-bottomed flask, ASA-alkylazides (**2a**–**h**) (1 mmol), propargyl-5-FU (**3**) (1 mmol), and DMF (5 mL) were placed, then the mixture was sonicated for 5 min to 40 °C. After this time, a mixture of ascorbic acid (0.5 mmol), copper acetate (0.5 mmol), DMF (1 mL), and water (1 mL) was added, and the reaction mixture sonicated for 1 h to 40 °C. Then, 10% HCl was added and extracted with ethyl acetate. The organic phase was dried on anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, and the residue was subjected to crystallization (MeOH:H_2O, 1:1 ratio). Finally, the solid obtained was purified by preparative chromatography on silica gel to obtain compounds **4a**–**h**. The ^1H, ^{13}C NMR, and MS spectra of all hybrids can be found in the Supplementary Materials.

2-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) ethyl 2-acetoxybenzoate (**4a**): Yield 71%, solid yellow, m.p. 136–139 °C; ^1H RMN (300 MHz, DMSO-d6): δ 8.19 (s, 1H; triazole-H), 8.14 (d, *J* = 6.7 Hz, 1H; 5-FU-H), 7.81 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.68 (td, *J* = 7.8, 1.7 Hz, 1H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.23 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.91 (s, 2H; triazole-CH2–), 4.75 (t, *J* = 7.0 Hz, 2H, –OCH_2–), 4.62 (t, *J* = 6.2 Hz,

2H, –NCH_2–), 2.20 (s, 3H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.55 (C=O), 163.80 (C=O), 158.30 and 157.97 (F–C–C=O), 150.61, 150.01, 142.85 (triazolyl), 141.68 y 138.59 (F–C), 135.03, 131.62, 130.48 and 130.04 (CH–C–F), 126.76, 124.60 (triazolyl), 124.54, 122.86, 63.60, 48.98, 43.18, 21.08. HRMS-ESI (*m*/*z*): calcd for $C_{18}H_{17}FN_5O_6$ [M + H]$^+$: 418.1118, found: 418.1157.

3-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) propyl 2-acetoxybenzoate (**4b**): Yield 80%, solid yellow, m.p. 131–134 °C; ^{1}H RMN (300 MHz, DMSO-d6): δ 8.14 (s, 1H; triazole–H), 8.08 (d, *J* = 6.6 Hz, 1H; 5-FU-H), 7.94 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.69 (td, *J* = 7.4, 1.8 Hz, 1H), 7.42 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.88 (s, 2H; triazole-CH2–), 4.49 (t, *J* = 7.0 Hz, 2H, –OCH_2–), 4.23 (t, *J* = 6.2 Hz, 2H, –NCH_2–), 2.28 (s, 3H), 2.28–2.23 (m, 2H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.65 (C=O), 164.28 (C=O), 150.52, 142.93 (triazolyl), 141.01 and 138.23 (F–C), 134.85, 131.79, 130.17 and 129.72 (CH–C–F), 126.74, 124.48 (triazolyl), 124.14, 123.31, 62.53, 47.01, 43.18, 29.26, 21.23. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{19}FN_5O_6$ [M + H]$^+$: 432.1275, found: 432.1316.

4-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) butyl 2-acetoxybenzoate (**4c**): Yield 60%, solid yellow, m.p. 126–129 °C; ^{1}H RMN (300 MHz, DMSO-d6): 8.09 (s, 1H; triazole-H), 8.02 (d, *J* = 6.5 Hz, 1H; 5-FU-H), 7.94 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.68 (td, *J* = 7.3, 1.2 Hz, 1H), 7.42 (td, *J* = 7.5, 1.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.87 (s, 2H; triazole-CH2–), 4.40 (t, *J* = 7.0 Hz, 2H, –OCH_2–), 4.24 (t, *J* = 6.5 Hz, 2H, –NCH_2–), 2.25 (s, 3H), 1.94–1.89 (m, 2H), 1.67–1.63 (m, 2H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.60 (C=O), 164.49 (C=O), 157.44 and 157.06 (F–C–C=O), 150.39, 143.04 (triazolyl), 141.17 and 139.04 (F–C), 134.74, 131.67, 129.77 and 129.32 (CH–C–F), 126.78, 124.49 (triazolyl), 123.96, 123.59, 49.40, 43.19, 26.78, 24.43, 21.18. HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{21}FN_5O_6$ [M + H]$^+$: 446.1431, found: 446.1470.

5-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1H-1,2,3-triazol-1-yl) pentyl 2-acetoxybenzoate (**4d**): Yield 70%, solid yellow, m.p. 127–130 °C; ^{1}H RMN (300 MHz, DMSO-d6): δ 8.09 (d, 2H; FU-H, triazole-H), 7.92 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.68 (td, *J* = 7.3, 1.2 Hz, 1H), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.88 (s, 2H; triazole-CH_2–), 4.35 (t, *J* = 7.1 Hz, 2H, –OCH_2–), 4.21 (t, *J* = 6.5 Hz, 2H, –NCH_2–), 2.27 (s, 3H), 1.89–1.84 (m, 2H), 1.72–1.68 (m, 2H), 1.39–1.31 (m, 2H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.59 (C=O), 164.49 (C=O), 157.25 and 156.97 (F–C–C=O), 153.08, 152.20, 150.40, 142.78 (triazolyl), 141.09 and 138.04 (F–C), 134.71, 131.64, 130.20 and 130.04 (CH–C–F), 126.77, 124.49 (triazolyl), 123.89, 123.64, 65.06, 49.68, 43.20, 29.72, 27.91, 22.83, 21.22. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{23}FN_5O_6$ [M + H]$^+$: 460.1588, found: 460.1621

6-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) hexyl 2-acetoxybenzoate (**4e**): Yield 75%, solid yellow, m.p. 109–111 °C; ^{1}H RMN (300 MHz, DMSO-d6): δ 8.11 (d, *J* = 6.6 Hz, 1H; 5-FU-H), 8.09 (s, 1H; triazole-H), 7.93 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.68 (td, *J* = 7.8, 1.7 Hz, 1H), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.88 (s, 2H; triazole-CH_2–), 4.33 (t, *J* = 7.1 Hz, 2H, –OCH_2–), 4.21 (t, *J* = 6.6 Hz, 2H, –NCH_2–), 2.27 (s, 3H), 1.84–1.79 (m, 2H), 1.68–1.62 (m, 2H), 1.41–1.36 (m, 2H), 1.31–1.26 (m, 2H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.59 (C=O), 164.54 (C=O), 158.53 and 158.38 (F–C–C=O), 150.39, 142.72 (triazolyl), 141.80 and 138.74 (F–C), 134.69, 131.65, 130.35 and 129.90 (CH–C–F), 126.78, 124.49 (triazolyl), 123.85, 123.68, 65.21, 49.76, 49.05, 43.23, 30.00, 28.36, 25.94, 25.22, 21.22. HRMS-ESI (*m*/*z*): calcd for $C_{22}H_{25}FN_5O_6$ [M + H]$^+$: 474.1744, found: 474.1783

8-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) octyl 2-acetoxybenzoate (**4f**): Yield 70%, solid yellow, m.p. 90–94 °C; ^{1}H RMN (300 MHz, DMSO-d6): δ 8.12 (d, *J* = 6.6 Hz, 1H; 5-FU-H), 8.08 (s, 1H; triazole-H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.68 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.88 (s, 2H; triazole-CH_2–), 4.32 (t, *J* = 7.1 Hz, 2H, –OCH_2–), 4.21 (t, *J* = 6.6 Hz, 2H, –NCH_2–), 2.27 (s, 3H), 1.82–1.76 (m, 2H), 1.68–1.63 (m, 2H), 1.35–1.22 (m, 8H). ^{13}C RMN (75 MHz, DMSO-d_6): δ 169.58 (C=O), 164.55 (C=O), 158.71 and 157.62 (F–C–C=O), 150.39, 142.69 (triazolyl), 141.79 and 138.73 (F–C), 134.68, 131.62, 129.91 and 129.85 (CH–C–F), 126.78, 124.50 (triazolyl), 123.84, 123.71, 65.32, 49.81, 43.22, 30.07, 28.92, 28.71, 28.50, 26.22, 25.73, 21.23. HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{29}FN_5O_6$ [M + H]$^+$: 502.2057, found: 502.2092.

9-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) nonyl 2-acetoxybenzoate (**4g**): Yield 68%, solid yellow, m.p. 93–95 °C; ^{1}H RMN (300 MHz, DMSO-d6): δ 8.15 (d, *J* = 6.7 Hz, 1H; 5-FU-H), 8.09 (s, 1H; triazole-H), 7.93 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.68 (td, *J* = 7.7, 1.6 Hz, 1H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.89 (s, 2H; triazole-CH_2–), 4.31 (t, *J* = 7.2 Hz, 2H, –OCH_2–), 4.22 (t, *J* = 6.6 Hz, 2H, –NCH_2–), 2.27 (s, 3H), 1.81–1.76 (m, 2H), 1.68–1.63 (m, 2H), 1.37–1.20 (m, 10H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.57 (C=O), 164.56 (C=O), 158.28 and 157.92 (F–C–C=O), 150.39, 149.97, 142.59 triazolyl), 141.68 and 138.64 (F–C), 134.68, 131.62, 130.57 and 130.12 (CH–C–F), 126.77, 124.50 (triazolyl), 123.85, 123.71, 65.34, 49.83, 43.22, 30.08, 29.18, 28.98, 28.72, 28.52, 26.24, 25.77, 21.22. HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{31}FN_5O_6$ [M + H]$^+$: 516.2214, found: 516.2242.

12-(4-((5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl)-1*H*-1,2,3-triazol-1-yl) dodecyl 2-acetoxybenzoate (**4h**): Yield 70%, solid yellow, m.p. 99–102 °C. 1H RMN (300 MHz, DMSO-d6): δ 8.13 (d, *J* = 6.6 Hz, 1H; 5-FU-H), 8.08 (s, 1H; triazole-H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.68 (td, *J* = 7.8, 1.7 Hz, 1H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.24 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.89 (s, 2H; triazole-CH_2–), 4.31 (t, *J* = 7.1 Hz, 2H, –OCH_2–), 4.22 (t, *J* = 6.6 Hz, 2H, –NCH_2–), 2.27 (s, 3H), 1.80–1.75 (m, 2H), 1.68–1.64 (m, 2H), 1.36–1.21 (m, 16H). ^{13}C RMN (75 MHz, DMSO-d6): δ 169.56 (C=O), 164.56 (C=O), 158.44 and 157.80 (F–C–C=O), 150.39, 142.62 (triazolyl), 141.72 and 138.06 (F–C), 134.68, 131.61, 130.03 and 129.84 (CH–C–F), 126.77, 124.51 (triazolyl), 123.86, 123.72, 65.35, 49.84, 43.21, 30.08, 29.35, 29.30, 29.08, 28.80, 28.53, 26.27, 25.80, 21.22. HRMS-ESI (*m*/*z*): calcd for $C_{28}H_{37}FN_5O_6$ [M + H]$^+$: 558.2683, found: 558.2716.

3.2. Drug-Likeness Modelling

To investigate the drug-likeness characteristics, the SWISSADME online software was employed aiming at estimating seven crucial physicochemical and pharmacokinetic descriptors related to drug development and medicinal chemistry friendliness [21]. The properties analyzed include the number of rotatable bonds, donor–acceptor groups, topological polar surface area (TPSA), Lipinski's rule of five, the lipophilicity index logPo/w (octanol/water participation coefficient) value, and the pan-assay interference compounds (PAINS) alerts.

4. Conclusions

In this work, the authors synthesized eight new 5-FU-ASA hybrids using, as a key step, Huisgen 1,3-dipolar cycloaddition, an example of click chemistry, with good yields. These compounds were characterized by NMR and high-resolution masses. Cytotoxicity studies of these compounds are underway. Concerning pharmacokinetic modelling, we have seen that the novel hybrids possess good drug-like attributes with similar values to those of the majority of marketed drugs, such as "a balanced" hydrophilic-lipophilic character, and do not inflict more than one violation of LRFV, making these compounds valid candidates in future anti-cancer drug-development projects.

Supplementary Materials: Supplementary data (^{1}H, ^{13}C NMR and MS spectra of compounds **4a**–**4h**) associated with this article can be found, in the online version. Figure S1a: ^{1}H NMR of compound **4a**, Figure S1b: ^{13}C NMR of compound **4a** and Figure S1c: MS spectra of compound **4a**; Figure S2a: ^{1}H NMR of compound **4b**, Figure S2b: ^{13}C NMR of compound **4b** and Figure S2c: MS spectra of compound **4b**; Figure S3a: ^{1}H NMR of compound **4c**, Figure S3b: ^{13}C NMR of compound **4c** and Figure S3c: MS spectra of compound **4c**; Figure S4a: ^{1}H NMR of compound **4d**, Figure S4b: ^{13}C NMR of compound **4d** and Figure S4c: MS spectra of compound **4d**; Figure S5a: ^{1}H NMR of compound **4e**, Figure S5b: ^{13}C NMR of compound **4e** and Figure S5c: MS spectra of compound **4e**; Figure S6a: ^{1}H NMR of compound **4f**, Figure S6b: ^{13}C NMR of compound **4f** and Figure S6c: MS spectra of compound **4f**; Figure S7a: ^{1}H NMR of compound **4g**, Figure S7b: ^{13}C NMR of compound **4g** and Figure S7c: MS spectra of compound **4g**; Figure S8a: ^{1}H NMR of compound **4h**, Figure S8b: ^{13}C NMR of compound **4h** and Figure S8c: MS spectra of compound **4h**.

Author Contributions: W.C.-L.: Synthesis and characterization of hybrid molecules. A.F.Y.: in silico studies, analysis, writing—original Draft. W.C.-G.: resources, supervision, project administration, funding acquisition, writing—original draft, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study is available in this article and Supporting Information.

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