Evaluation of coumarin and their derivatives as Janus Kinase-3 inhibitors using a theoretical model

Figueroa Valverde Lauro[1], López-Ramos Maria[1], Alvarez-Ramirez Magdalena[2], Rosas Nexticapa Marcela[2], Díaz-Cedillo Francisco[3], Mateu-Armad Maria Virginia[2] & Lopez-Gutierrez Tomas[1]

[1] Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México

[2] Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México

[3] Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México

Correspondence: Figueroa Valverde Lauro, Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp., México. E-mail: lfiguero@uacam.mx

Received: June 11, 2023 Accepted: June 30, 2023 Published: December 01, 2023

DOI: 10.14295/bjs.v2i12.423 URL: https://doi.org/10.14295/bjs.v2i12.423

Abstract

For several years, cancer has increased in the population, being one of the main causes of death worldwide. This clinical pathology is associated with the activation/release of various biomolecules, including the Janus kinase family (JAKs). It is important to mention that some studies indicate that some JAK inhibitors (ruxolitinib and tofacitinib) may have a significant effect on some autoimmune diseases and cancer; however, some of these drugs can produce secondary effects such as herpes zoster, infectious, acute respiratory distress and others. The aim of this study was to evaluate the interaction of coumarin and its derivatives (compounds 2 to 24) with the JAK-3 surface. In this way, the Interaction of coumarin and their derivatives with JAK-3 was determined using the 3pjc protein and either decernotinib or tofacitinib drugs as theoretical tools on DockinServer program. The results showed differences in the aminoacid residues involved in the interaction of coumarin and their derivatives with 3pjc protein surface compared with decernotinib and tofacitinib. Besides, the inhibition constant (Ki) for coumarin derivatives 7, 9 and 10 was lower compared with tofacitinib. However, Ki was lower for 2, 5, 7, 8, 9, 10, and 24 compared with decernotinib. In conclusion, the coumarin derivatives 2, 5, 7, 8, 9, 10, and 24 could be good alternatives as JAK-3 inhibitors to decrease cancer cells growth.

Keywords: cancer, Janus Kinase, JAK-3, coumarin.

Avaliação da cumarina e seus derivados como inibidores da Janus Quinase-3 usando modelo teórico

Resumo

Há vários anos, o câncer tem aumentado na população, sendo uma das principais causas de morte em todo o mundo. Esta patologia clínica está associada à ativação/liberação de várias biomoléculas, incluindo a família Janus quinase (JAKs). É importante mencionar que alguns estudos indicam que alguns inibidores de JAK (ruxolitinib e tofacitinib) podem ter um efeito significativo em algumas doenças autoimunes e no câncer; no entanto, algumas dessas drogas podem produzir efeitos secundários, como herpes zoster, infeccioso, desconforto respiratório agudo e outros. O objetivo deste estudo foi avaliar a interação da cumarina e seus derivados (compostos 2 a 24) com a superfície JAK-3. Desta forma, a interação da cumarina e seus derivados com JAK-3 foi determinada usando a proteína 3pjc e as drogas decernotinib ou tofacitinib como ferramentas teóricas no programa DockinServer. Os resultados mostraram diferenças nos resíduos de aminoácidos envolvidos na interação da cumarina e seus derivados com a superfície da proteína 3pjc em comparação com decernotinib e tofacitinib. Além disso, a constante de inibição (Ki) para os derivados cumarínicos 7, 9 e 10 foi menor em

comparação com o tofacitinibe. No entanto, Ki foi menor para 2, 5, 7, 8, 9, 10 e 24 em comparação com decernotinibe. Em conclusão, os derivados cumarínicos 2, 5, 7, 8, 9, 10 e 24 podem ser uma boa alternativa como inibidores de JAK-3 para diminuir o crescimento de células cancerígenas.

Palavras-chave: câncer, Janus Quinase, JAK-3, cumarina.

1. Introduction

Cancer is one of the leading causes of death worldwide (Xia et al., 2022; Siegel et al., 2022; Giaquinto et al., 2022; Miller et al., 2022). It is important to mention that several factors are involved in development this pathology clinic such as alcohol (Yoo et al., 2022; Im et al., 2022), obesity (Lazarus; Bays, 2022; Aminian et al., 2022), cigarette smoking (Hcht; Hatsukami, 2022; Phua et al., 2022), dietary fatty acid pattern (Wan et al., 2022; Tu et al., 2022).

Besides, there are some data indicating that some genetic factors may involving in cancer cells growth (De-Magalhães, 2022); for example, a study showed some mutations in KRAS gene (Kirten rat sarcoma viral) which were associated with colorectal cancer (Hayama et al., 2019). Other report indicate that BCR-ABL (transcript encodes a tyrosine kinase) gene mutations are associated with different forms of leukaemia (Zhang et al., 2016). In addition, some studies suggest that either androgen receptor or 5α-reductase enzyme are two factors associated to prostate cancer (Sowalsky et al., 2022; Lopez-Ramos et al., 2023).

Other data showed that HER2 (human epidermal growth factor receptor 2) overexpression could condition tumor growth in patients with breast cancer (Asgari-Karchekani et al., 2022; Grupta et al., 2022). Besides, some studies indicate that MYC (family of regulator genes and proto-oncogenes that code for transcription factors) may contribute to the progression of various human cancers (Dhanasekaran et al., 2022; Ala, 2022). Other study shows that EGFR (Epidermal growth factor receptor) gene is mutated and overactive in many cancers, including lung, breast, esophageal, head, and neck cancers (Seshacharyulu et al., 2012; Sigismund et al., 2018).

On the other hand, there are some studies suggesting that Activation of JAKs (Janus kinase family; JAK-1, JAK-2 and JAK-3) is involved in cancer cells growth (Verma et al., 2003). For example, a study showed that The JAK3/ERK (Janus kinase-3/extra- cellular signal-regulated kinase) pathway might play an important role in EGFR-induced MMP-9 (matrix metallopeptidase 9) expression in breast cancer cells (Kim et al., 2009). Other study conducted in 932 clinical cases of non-small cell lung cancers (NSCLC) showed mutations in JAK2 and JAK3 using the Ion AmpliSeq Cancer Hotspot panel v2 assay (Li et al., 2017).

Besides, cell invasion of highly metastatic MTLn3 (a highly metastatic rat mammary adenocarcinoma cell line) cancer cells which is dependent of both phospholipase D2 (PLD2) and JAK-3 (Henkels et al., 2011). Another report suggests that JAK 3 may have a cytokine receptor-independent function; however, JAK-3 levels can increase in cutaneous T-cell lymphoma (Vadivel et al., 2021). All these data indicate that JAK-3 can produce changes in cancer cells growth. Here it is important to mention that some JAKs inhibitors have been used for treat some cancer cell lines; for example, a study showed that ruxolitinib (JAK1/2 inhibitor) synergistically enhances the anti-tumor activity of paclitaxel in human ovarian cancer (Han et al., 2018).

Other data indicate that lestaurtinib (JAK-2 inhibitor) can produce cytotoxicity to leukemia cells in a dose-response manner (Knapper et al., 2006). In addition, a report shows that treatment with itacitinib (JAK1 inhibitor) to patients with myelofibrosis can provide effective relief of symptoms related to this clinical pathology (Mascarenhas et al., 2017). Analyzing these data, the aim of this investigation was to evaluate theorethical activity of coumarin and their derivatives with JAK-3 using a 3pjc protein, decernotinib [selective JAK-3 inhibitor] (Genovese et al., 2016) and tofacitinib [JAK-1 and JAK-3 inhibitor (Shivanna et al., 2018) as theoretical tools (Figure 1) on DockingServer software.

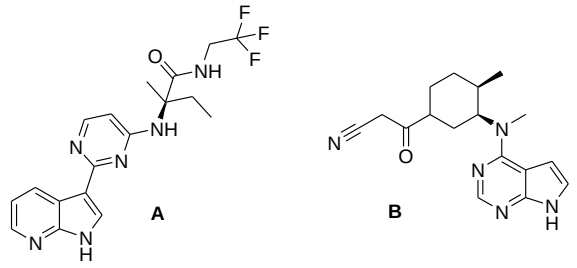

Figure 1. Chemical stucture of Decernotinib and Tofacitinib. Source: Pubchem, 2023.

2. Materials and Methods

2.1 Methodology general

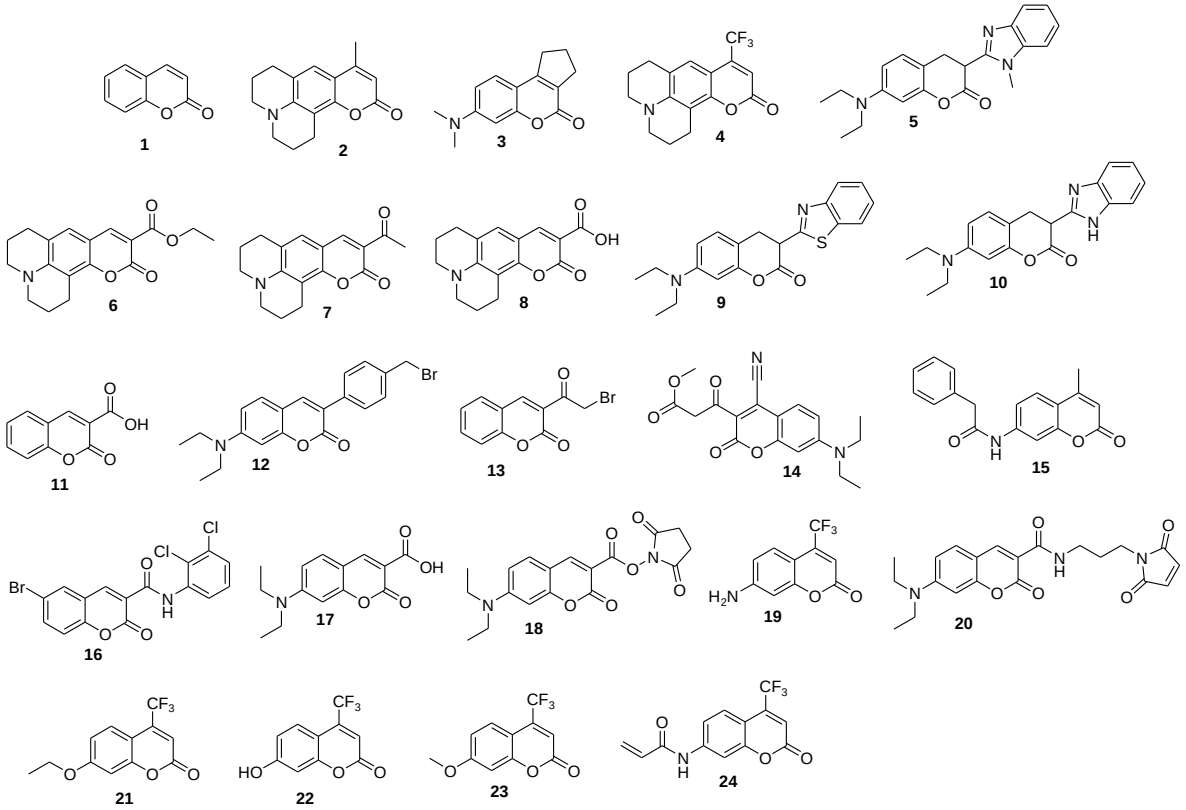

Figure 2. Structure chemical of coumarin and their derivatives. Source: Pubchem, 2023.

Note:

1 = chromen-2-one

2 = 6-methyl-3-oxa-13-azatetracyclo[7.7.1.$0^{2,7}$.$0^{13,17}$] heptadeca-1 (17),2(7),5,8-tetraen-4-one

3 = 7-(dimethylamino)-2,3-dihydro-1*H*-cyclopenta[c] chromen-4- one

4 = 6-(trifluoromethyl)-3-oxa-13-azatetracyclo[7.7.1.$0^{2,7}$. $0^{13,17}$]- heptadeca-1(17),2(7),5,8-tetraen-4-one

5 = 7-(diethylamino)-3-(1-methylbenzimidazol-2-yl) chromen-2- one

6 = ethyl

13 = 3-(2-Bromo-acetyl)-chromen-2-one

14 = 3-(4-Cyano-7-diethylamino-2-oxo-2H-chromen-3-yl) -3-oxo- propionic acid methyl ester

15 = *N*-(4-Methyl-2-oxo-2H-chromen-7-yl)-2-phenyl-acet amide

16 = 6-Bromo-2-oxo-2H-chromene-3-carboxylic acid (2,3-dichloro- phenyl)-amide

17 = 7-Diethylamino-2-oxo-2H-chromene-3-carboxylic acid

4-oxo-3-oxa-13-azatetracyclo[7.7.1.$0^{2,7}$.$0^{13,17}$] heptadeca-1,5,7,9(17)-tetraene-5-carboxylate

7 = 5-acetyl-3-oxa-13-azatetracyclo[7.7.1.$0^{2,7}$.$0^{13,17}$]heptadeca-1, 5,7,9(17)-tetraen-4-one

8 = 4-oxo-3-oxa-13-azatetracyclo[7.7.1.$0^{2,7}$.$0^{13,17}$]heptadeca- 1,5,7, 9(17)-tetraene-5-carboxylic acid

9 = 3-(1,3-benzothiazol-2-yl)-7-(diethylamino)chromen-2-one

10 = 3-(1*H*-benzimidazol-2-yl)-7-(diethylamino)chromen-2-one

11 = 2-oxochromene-3-carboxylic acid

12 = 3-(4-Bromomethyl-phenyl)-7-diethylamino-chromen-2-one

18 = 7-Diethylamino-2-oxo-2H-chromene-3-carboxylic acid 2,5- dioxo-pyrrolidin-1-yl ester

19 = 7-Amino-4-trifluoromethyl-chromen-2-one

20 = 7-Diethylamino-2-oxo-2H-chromene-3-carboxylic acid [3-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-propyl]-amide

21 = 7-Ethoxy-4-trifluoromethyl-chromen-2-one

22 = 7-Hydroxy-4-trifluoromethyl-chromen-2-one

23 = 7-Methoxy-4-trifluoromethyl-chromen-2-one

24 = 7-Diethylamino-2-oxo-2H-chromene-3-carboxylic acid 2,5- dioxo-pyrrolidin-1-yl ester

2.2 Ligand-protein

Binding of coumarin and their derivatives with JAK-3 was determined using 3pjc (PDB doi: https://doi.org/10.2210/ pdb3PJC/pdb) protein (Thoma et al., 2011) as theoretical model. In addition, to evaluate the thermodynamic parameters involved in coumarin derivative-protein complex formation, the DockingServer program was used (Figuero-Valverde et al., 2023).

2.3 Pharmacokinetic parameters

Theoretical pharmacokinetic involved in the chemical structure of coumarin derivatives (2, 5, 7, 8, 9, 10 and 24) were determined using the SwissADME software (Rudik et al., 2022).

2.4 Toxicology evaluation

Toxicity evaluation for coumarin derivatives 2, 5, 7, 8, 9, 10 and 24 was determined using GUSAR software (Rudik et al., 2022).

3. Results

3.1 Ligand-protein complex

In the table 1 showing different aminoacid residues involved in the coupling of coumarin and their derivatives (compounds 2-24) with 3pj protein surface.

Table 1. Aminoacid residues involved in the coupling of coumarin and their derivatives (compounds 2-24) with 3pjc protein surface.

Compounds	
Decernotinib	Leu_{828}; Gly_{829}; Phe_{833}; Val_{836}; Lys_{855}; $Met_{902;}$ $Cys_{909;}$ $Asp_{912;}$ $Arg_{953;}$ $Asn_{954;}$ $Leu_{956;}$ Asp_{967}
Tofacitinib	Leu_{828}; Phe_{833}; Val_{836}; Ala_{853}; $Lys_{855;}$ $Glu_{871;}$ $Leu_{875;}$ $Leu_{900;}$ $Met_{902;}$ $Tyr_{904;}$ Leu_{956}
1	Phe_{833}; Val_{836}; Lys_{855}; $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Met_{902;}$ Asp_{967}
2	Phe_{833}; Val_{836}; Ala_{853}; Lys_{855}; $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Leu_{900;}$ $Met_{902;}$ $Leu_{956;}$ $Asp_{967;}$
3	Leu_{828}; Lys_{855}; $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Met_{902;}$ $Leu_{956;}$ Asp_{967}
4	Leu_{828}; Phe_{833}; Val_{836}; Ala_{853}; Val_{884}; Met_{902}
5	Leu_{828}; Phe_{833}; Val_{836}; Lys_{855}; $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Leu_{900;}$ $Tyr_{904;}$ $Leu_{956;}$ Asp_{967}
6	Leu_{828}; Phe_{833}; $Val_{836;}$ $Lys_{855;}$ $Glu_{871;}$ $Val_{884;}$ $Met_{902;}$ $Arg_{953;}$ $Asn_{954;}$ $Ala_{966;}$ Asp_{967}
7	Leu_{828}; Phe_{833}; Val_{836}; Ala_{853}; Lys_{855}; $Glu_{871;}$ $Val_{884;}$ $Leu_{900;}$ $Met_{902;}$ $Tyr_{904;}$ $Leu_{956;}$ Asp_{967}
8	Leu_{828}; Phe_{833}; Val_{836}; Ala_{853}; $Lys_{855;}$ $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Leu_{900;}$ $Met_{902;}$ $Tyr_{904;}$ $Leu_{956;}$ Asp_{967}
9	Phe_{833}; Val_{836}; $Glu_{871;}$ $Leu_{875;}$ $Val_{884;}$ $Leu_{900;}$ $Met_{902;}$ $Cys_{909;}$ $Asp_{912;}$ $Ala_{966;}$ $Asp_{966;}$ Asp_{967}
10	Leu_{828}; Phe_{833}; Val_{836}; Lys_{855}; Leu_{875}; $Leu_{900;}$ $Met_{902;}$ $Tyr_{904;}$ $Leu_{956;}$ Asp_{967}
11	Phe_{833}; Lys_{855}; Met_{902}; Arg_{953}; Asn_{954}; Ala_{966}; Asp_{967}
12	Leu_{828}; Lys_{855}; Glu_{871}; Leu_{875}; Val_{884}; Met_{902}; Tyr_{904}; Leu_{956}; Phe_{968}
13	Phe_{833}; Lys_{855}; Glu_{871}; Leu_{875}; Arg_{953}; Asn_{954}; Leu_{956}; Ala_{966}; Asp_{967}
14	Leu_{828}; Phe_{833}; Val_{836}; Lys_{855}; Glu_{871}; Leu_{875}; Val_{884}; Met_{902}; Cys_{909}; Arg_{953}; Leu_{956}; Asp_{967}
15	Leu_{828}; Phe_{833}; Val_{836}; Glu_{871}; Leu_{875}; Val_{884}; Met_{902}; Asp_{967}
16	Leu_{828}; Val_{836}; Ala_{853}; Glu_{871}; Leu_{875}; Val_{884}; Tyr_{904}; Leu_{956}; Ala_{966}; Asp_{967}
17	Leu_{828}; Ala_{853}; Val_{884}; Met_{902}; Met_{902}; Tyr_{904}; Leu_{956}
18	Phe_{833}; Val_{836}; Lys_{855}; Glu_{871}; Val_{884}; Met_{902}; Cys_{909}; Arg_{953}; Leu_{956}; Ala_{966}; Asp_{967}
19	Phe_{833}; Val_{836}; Ala_{853}; Lys_{855}; Glu_{871}; Leu_{875}; Val_{884}; Met_{902}; Glu_{903}; Leu_{956}; Asp_{967}; Phe_{968}
20	Phe_{833}; Val_{836}; Ala_{853}; Lys_{855}; Tyr_{904}; Asp_{912}; Leu_{956}; Ala_{966}; Asp_{967}
21	Leu_{828}; Val_{836}; Ala_{853}; Leu_{875}; Val_{884}; Met_{902}; Glu_{903}; Tyr_{904}; Leu_{905}; Leu_{956}
22	Phe_{833}; Val_{836}; Ala_{853}; Glu_{871}; Leu_{875}; Val_{884}; Leu_{900}; Met_{902}; Leu_{956}; Ala_{966}; Phe_{968}
23	Leu_{828}; Val_{836}; Ala_{853}; Val_{884}; Met_{902}; Glu_{903}; Tyr_{904}; Leu_{905}; Leu_{956}
24	Leu_{828}; Val_{836}; Ala_{853}; Lys_{855}; Glu_{871}; Leu_{875}; Leu_{900}; Met_{902}; Glu_{903}; Tyr_{904}; Leu_{905}; Leu_{956}

Source: Authors, 2023.

3.2 Thermodynamic parameters

The theoretical results indicate differences in the energy levels involved in the interaction of coumarin and its derivatives with JAK-3 (3pjc protein) compared with both decernotinib and tofacitinib drugs (Table 2).

Table 2. Thermodynamic parameters involved in the interaction of coumarin derivatives with 3pjc protein surface using DockingServer software.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Decernotinib	-7.49	3.22	-8.24	0.03	-8.22	
Tofacitinib	-7.69	2.30	-8.60	-0.09	-8.69	721.73
1	-4.78	314.72	-4.75	-0.03	-4.78	407.53
2	-7.57	2.82	-7.59	0.02	-7.57	600.46
3	-6.55	15.84	-6.83	-0.02	-6.85	588.15
4	-8.63	471.84	-8.92	-0.01	-8.93	612.52
5	-7.58	2.78	-8.77	-0.01	-8.78	809.13
6	-7.34	4.15	-8.11	0.00	-8.10	715.80
7	-7.89	1.64	-8.20	0.01	-8.19	656.04
8	-7.59	2.74	-7.97	0.08	-7.89	623.98
9	-8.11	1.13	-8.95	0.00	-8.94	822.28
10	-7.90	1.61	-8.26	-0.02	-8.28	778.34
11	-4.78	311.65	-5.16	0.08	-5.08	497.59
12	-7.25	4.85	-8.61	-0.03	-8.63	785.45
13	-5.79	56.73	-6.15	-0.06	-6.21	518.98
14	-6.29	24.69	-8.09	-0.05	-8.14	824.56
15	-7.04	6.91	-7.86	0.01	-7.85	734.52
16	-9.27	159.78	-9.22	0.00	-9.22	740.29
17	-5.80	55.82	-6.82	0.15	-6.97	612.56
18	-6.62	14.13	-8.25	0.00	-8.26	746.72
19	-6.15	31.21	-6.69	-0.05	-6.74	480.62
20	-7.23	5.04	-8.31	-0.06	-8.37	849.25
21	-6.59	14.74	-7.56	0.01	-7.54	575.39
22	-6.20	28.57	-6.76	-0.04	-6.80	485.37
23	-6.49	17.64	-7.08	-0.02	-7.10	534.03
24	-7.59	2.72	-8.48	-0.02	-8.50	607.16

Note: **A** = Est: Free Energy of Binding (kcal/mol); **B** = Inhibition Constant, Ki (mM); **C** = vdW + Hbond + desolv Energy (kcal/mol); **D** = Electrostatic Energy (kcal/mol); **E** = Total Intermolec. Energy (kcal/mol); **F** = Interact. Surface. Source: Authors, 2023.

3.3 Pharmacokinetic evaluation

Table 3 shows that gastrointestinal (GI) absorption rate was high for either decernotinib or facitinib drugs and the coumarin derivatives 2, 5, 7, 8-10 and 24. In addition, The CYPs involved in the pharmacokinetic process were different.

Table 3. Theorethical Pharmacokinetic parameters involved in decernotinib (I), tofacitinib (II), coumarin derivatives 2, 5, 7, 8-10 and 24.

Parameter	*I*	*II*	*2*	*5*	*7*	*8*	*9*	*10*	*24*
GI absorption	High	High	High	High	High	High	High	High	High
BBB permeant	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P-gp sustrate	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
CYP1A2 inhibitor	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
CYP2C9 inhibitor	No	No	No	Yes	No	No	Yes	Yes	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP3A4 inhibitor	Yes	No	No	Yes	No	No	Yes	Yes	No
Consensus Log$P_{O/W}$	2.97	2.10	2.96	3.45	2.67	2.37	4.18	3.37	2.80

Note: GI = Gastrointestinal; BBB = Blood-Brain-Barrier; P-gp = P-glycoprotein; CYP = Cytochrome P450; $LogP_O/_W$ = Octanol-water partition coefficient. Source: Authors, 2023.

3.4 Toxicology analysis

Table 4 showed differences in the possible dose administered for either decernotinib or tofacitinib drugs and the coumarin derivatives 2, 5, 7, 8-10 and 24 through the different routes of administration.

Table 4. Theoretical toxicity analysis produced by decernotinib (I), tofacitinib (II), coumarin derivatives 2, 5, 7, 8-10 and 24.

Compound	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
I	661.30	128.50	1060.00	568.30
II	98.70	37.27	954.80	268.20
2	200.80	19.23	382.00	342.20
5	187.50	55.23	628.20	298.00
7	182.20	29.05	538.90	587.90
8	406.70	102.80	552.20	560.00
9	266.00	90.20	594.30	597.30
10	168.70	58.54	503.60	514.10
24	342.80	134.50	391.20	1488.00

Note: IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration. Source:Authors, 2023.

4. Discussion

In the literature there are some studies indicating that JAK-3 may be associated with cancer cells growth (Verma et al., 2003; Kim et al., 2009; Li et al., 2017; Henkels et al., 2011; Vadivedel et al., 2021). For this reason, a theoretical study was conducted in this investigation to evaluate the possibility that coumarin and their derivatives could interact with JAK-3 surface using the DockingServer software.

4.1 Ligand-protein analysis.

Computer modeling has been developed and widely applied in studying molecules to evaluate their possible biological activity (Crampon et al., 2022; Ota et al., 2022; Zhang; Chen, 2022). Analyzing this data, the interaction of coumarin and their derivatives (compounds 2 to 24) with the JAK-3 surface was determined using the 3pjc protein (crystal Structure of JAK-3) as control. In addition, some JAK-3 inhibitors such as decernotinib

and tofacitinib served as theoretical tools on DockingServer software. The results display different amino acid residues involved in the interaction of coumarin and their derivatives with 3pjc protein surface compared with decernotinib and tofacitinib; this phenomenon could be due to differences in their chemical structure.

4.2 Bond energies analysis

There are some studies which suggest that protein-ligand complex formation could depend of several thermodynamic factors such as free energy of binding, inhibition constant, van der Waals + hidrogen bond + desolv energy (vdW + Hbond + desolv Energy), electrostatic energy and total intermolecular energy (Figueroa-Valverde et al., 2021). For this reason, in this research some thermodynamic parameters involved in the interaction of coumarin and its derivatives with the 3pjc surface protein were evaluated using the DockingServer model. The results (Table 2) showed differences in the energies levels for coumarin and their derivatives compared with decernotinib and tofacitinib.

Besides, inhibition constant (Ki) for coumarin derivatives 7, 9 and 10 was lower compared with tofacitinib. However, Ki was lower for 2, 5, 7, 8, 9, 10 and 24 compared with decernotinib. These data indicate that coumarin derivatives 2, 5, 7, 8, 9, 10 and 24 could inhibit the biological activity of JAK-3 and this phenomenon could be translated as decrease in cancer cells growth. However, it is important to mention that some pharmacokinetic parameters involved in the chemical structure of coumarin derivatives need to be evaluated in some cancer model.

4.3 Pharmacokinetic evaluation.

In the literature, some methods to predict several pharmacokinetic parameters of different drugs have been used to determinate their biological activity (Nguyen et al., 2022; Valluri et al., 2022; Goutelle et al., 2022). For this reason, in this research, some pharmacokinetic factors for coumarin derivatives such as 2, 5, 7, 8, 9, 10 and 24 were determined using SwissADME software (Table 3).

The results indicate differences in gastrointestinal absorption and metabolism which involving several cytochrome P450 systems. This phenomenon could be to differences in the chemical structure of each coumarin derivatives and their degree of lipophilicity ($LogP_{O/W}$).

4.4 Theoretical toxicity

Several methods such as ProTox-II (Baren and Ulker, 2022), STopTox (Pokharkar et al., 2022), ToxAlert (Perez et al., 2001), q-Tox (Urios et al., 2006) for predict toxicity degree have been used. Analyzing these data, in this investigation the possible theoretical toxicity produced by coumarin derivatives 2, 5, 7, 8-10 and 24 was determined using the GUSAR software (Da-Rocha et al., 2022).

The results shown in Table 4 suggest that tofacitinib require low doses via either intravenous or intraperitoneal or subcutaneous routes to produce toxicity compared to coumarin derivatives. Besides, decernotinib require higher dose to produce toxicity compared with coumarin derivatives 2, 5, 7 and 8-10; however, compound 24 require higher dose to produce toxicity compared with decernotinib. These results could be due to differences in their lipophilicity degree of each coumarin.

5. Conclusions

This study reports the interaction of coumarin derivatives, decernotinib and tofacitinib with JAK-3. The results showed that the coumarin derivatives 2, 5, 7, 8, 9, 10 and 24 could be a good alternative as JAK-3 inhibitors and this phenomenon could translate into a decrease in cancer cell growth.

6. Auhors' Contributions

Figueroa-Valverde Lauro: substantial contribution to research design, acquisition, analysis and interpretation of data. *Diaz-Cedillo Francisco*: substantial contribution to research design. *Diaz-Cedillo Francisco*: acquisition, analysis and interpretation of data. *Alvarez-Ramirez Magdalena*: acquisition, analysis and interpretation of data. *Rosas-Nexticapa Marcela*: acquisition, analysis and interpretation of data. *Lopez-Ramos Maria*: acquisition, analysis and interpretation of data. *Mateu-Armand Virginia*: acquisition, analysis and interpretation of data. Approval of the submitted and final versions: all authors.

7. Funding
This research received no external funding.

8. Conflict of interest
The authors declare that this research has no conflict of interest with any public or private association.

9. Ethics Approval

Not applicable.

10. References

Ala, M. (2022). Target c-Myc to treat pancreatic cancer. *Cancer Biology & Therapy*, 23(1), 34-50. https://doi.org/10.1080/15384047.2021.2017223

Aminian, A., Wilson, R., Al-Kurd, A., Tu, C., Milinovich, A., & Kroh, M. (2022). Association of bariatric surgery with cancer risk and mortality in adults with obesity. *Journal of American Medical Association*, 327(24), 2423-33. https://doi.org/10.1001/jama.2022.9009

Asgari-Karchekani, S., Aryannejad, A., Mousavi, S., Shahsavarhaghighi, S., & Tavangar, S. (2022). The role of HER2 alterations in clinicopathological and molecular characteristics of breast cancer and HER2-targeted therapies: a comprehensive review. *Medical Oncology*, 39(12), 210. https://doi.org/10.1007/s12032-022-01817-6

Banerjee, P., & Ulker, O. (2022). Combinative ex vivo studies and in silico models ProTox-II for investigating the toxicity of chemicals used mainly in cosmetic products. *Toxicology Mechanisms and Methods*, 32(7), 542-548. https://doi.org/10.1080/15376516.2022.2053623

Crampon, K., Giorkallos, A., Deldossi, M., Baud, S., & Steffenel, L. (2022). Machine-learning methods for ligand–protein molecular docking. *Drug Discovery Today*, 27(1), 151-164. https://doi.org/10.1016/j.drudis.2021.09.007

Da-Rocha, M., Marinho, E., Marinho, M., & dos-Santos, H. (2022). Virtual screening in pharmacokinetics, bioactivity, and toxicity of the amburana cearensis secondary metabolites. *Biointerface Research in Applied Chemistry*, 12(6), 8471-8491. doi.org/10.33263/BRIAC126.84718491

De-Magalhães, J. (2022). Every gene can (and possibly will) be associated with cancer. *Trends in Genetics*, 38(3), 216-217. https://doi.org/10.1016/j.tig.2021.09.005

Dhanasekaran, R., Deutzmann, A., Mahauad-Fernandez, W., Hansen, A., Gouw, A., Felsher, D. (2022). The MYC oncogene – the grand orchestrator of cancer growth and immune evasion. *Nature Reviews Clinical Oncology*, 19(1), 23-26. https://doi.org/10.1038/s41571-021-00549-2

Figueroa-Valverde, L., Alvarez-Ramirez, M., Rosas-Nexticapa, M., Cedillo, F., López-Ramos, M., Mateu-Armad, M. (2021). Synthesis of two testosterone derivatives and their theoretical evaluation as serotonin reuptake transporter inhibitors. *Biointerface Research in Applied Chemistry*, 11, 12462-12470. https://doi.org/10.33263/BRIAC115.1246212470

Figueroa-Valverde, L., Rosas-Nexticapa, M., Montserrat, M., Díaz-Cedillo, F., López-Ramos, M., & Alvarez-Ramirez, M. (2022). Synthesis and theoretical interaction of 3-(2-oxabicyclo [7.4. 0] trideca-1 (13), 9, 11-trien-7-yn-12-yloxy)-steroid deriva-tive with 17β-hydroxysteroid dehydrogenase enzyme surface. *Biointerface Research in Applied Chemistry*, 13(6), 266. https://doi.org/10.33263/BRIAC133.266

Genovese, M., Van-Vollenhoven, R., Pacheco-Tena, C., Zhang, Y., & Kinnman, N. (2016). VX-509 (Decernotinib), an oral selective JAK-3 inhibitor, in combination with methotrexate in patients with rheumatoid arthritis. *Arthritis & Rheumatology*, 68(1), 46-55. https://doi.org/10.1002/art.39473

Giaquinto, A., Miller, K., Tossas, K., Winn, R., Jemal, A., & Siegel, R. (2022). Cancer statistics for African American/black people 2022. *Cancer Journal for Clinicians*, 72(3): 202-29. https://doi.org/10.3322/caac.21718

Goutelle, S., Woillard, J., Neely, M., Yamada, W., & Bourguignon, L. (2022). Nonparametric methods in population pharmacokinetics. *The Journal of Clinical Pharmacology*, 62(2), 142-57. https://doi.org/10.1002/jcph.1650

Gupta, R., Gupta, S., Antonios, B., Ghimire, B., & Jindal, V. (2022). Therapeutic landscape of advanced HER2-positive breast cancer in 2022. *Medical Oncology*, 9(12), 258. https://doi.org/10.1007/s12032-022-01849-y

Han, E., Wen, W., Dellinger, T., Wu, J., Lu, S., & Jove, R. (2018). Ruxolitinib synergistically enhances the anti-tumor activity of paclitaxel in human ovarian cancer. *Oncotarget*, 9(36), 24304-24319. https://doi.org/10.18632%2Foncotarget.24368

Hayama, T., Hashiguchi, Y., Okamoto, K., Okada, Y., Ono, K., & Shimada, R. (2019). G12V and G12C mutations in the gene KRAS are associated with a poorer prognosis in primary colorectal cancer. *International Journal of Colorectal Disease*, 34, 1491-1496. https://doi.org/10.1007/s00384-019-03344-9

Hecht, S., & Hatsukami, D. (2022). Smokeless tobacco and cigarette smoking: chemical mechanisms and cancer prevention. *Nature Reviews Cancer*, 22(3), 143-155. https://doi.org/10.1038/s41568-021-00423-4

Henkels, K., Farkaly, T., Mahankali, M., Segall, J., & Gomez-Cambronero, J. (2011). Cell invasion of highly metastatic MTLn3 cancer cells is dependent on phospholipase D2 (PLD2) and Janus kinase 3 (JAK3). *Journal of Molecular Biology*, 408(5), 850-862. https://doi.org/10.1016/j.jmb.2011.03.01

Im, P., Yang, L., Kartsonaki, C., Chen, Y., Guo, Y., & Du, H. (2022). Alcohol metabolism genes and risks of site-specific cancers in Chinese adults: An 11-year prospective study. *International Journal of Cancer*, 150(10), 1627-1639. https://doi.org/10.1002/ijc.33917

Kim, S., Choi, J., Lim, H., Lee, S., Kim, W., Cho, S., Kim, J. S., Kim, J-H., Choe, J-H., Nam, S. J., Lee, J. E., & Yang, J-H. (2009). EGF-induced MMP-9 expression is mediated by the JAK3/ERK pathway, but not by the JAK3/STAT-3 pathway in a SKBR3 breast cancer cell line. *Cell Signnallig*, 21(6), 892-898. https://doi.org/10.1016/j.cellsig.2009.01.034

Knapper, S., Mills, K., Gilkes, A., Austin, S., Walsh, V., & Burnett, A. (2006). The effects of lestaurtinib (CEP701) and PKC412 on primary AML blasts: the induction of cytotoxicity varies with dependence on FLT3 signaling in both FLT3-mutated and wild-type cases. *Blood*, 108(10), 3494-3503. https://doi.org/10.1182/blood-2006-04-015487

Lazarus, E., & Bays, H. (2022). Cancer and obesity: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. *Obesity Pillars*, 3, 100026. https://doi.org/10.1016/j.obpill.2022.100026

Li, S., Ma, M., Li, H., Waluszko, A., Sidorenko, T., & Schadt, E. (2017). Cancer gene profiling in non-small cell lung cancers reveals activating mutations in JAK2 and JAK3 with therapeutic implications. *Genome Medicine*, 9, 1-11. https://doi.org/10.1186/s13073-017-0478-1

Lopez-Ramos, M., Figueroa-Valverde, L., Diaz-Cedillo, F., Rosas-Nexticapa, M., & Alvarez-Ramirez, M. (2023). Theoretical evaluation of twenty-cannabinoid derivatives on either androgen receptor or 5α-reductase enzyme. *Clinical Cancer Investigation Journal*, 12(2), 27-32. https://doi.org/10.51847/5MYimTzeXf

Mascarenhas, J., Talpaz, M., Gupta, V., Foltz, L., Savona, M., & Paquette, R. (2017). Primary analysis of a phase II open-label trial of INCB039110, a selective JAK1 inhibitor, in patients with myelofibrosis. *Haematologica*, 102(2), 327-335. https://doi.org/10.3324%2Fhaematol.2016.151126

Mekky, A., Sanad, S., Abdelfattah, A. (2022). Tandem synthesis, antibacterial evaluation and SwissADME prediction study of new bis (1, 3, 4-oxadiazoles) linked to arene units. *Mendeleev Communications*, 32(5), 612-614. https://doi.org/10.1016/j.mencom. 2022.09.014

Miller, K., Nogueira, L., Devasia, T., Mariotto, A., Yabroff, K., & Jemal, A. (2022). Cancer treatment and survivorship statistics, 2022. *Cancer Journal of Clinicians*, 72(5), 409-436. https://doi.org/10.3322/caac.21731

Nguyen, T., Kim, J., Choi, H., Maeng, H., Koo, T. (2022). Development of an LC-MS/MS method for ARV-110, a PROTAC molecule, and applications to pharmacokinetic studies. *Molecules*, 27(6), 1977. https://doi.org/10.3390/molecules27061977

Ota, C., Suzuki, H., Tanaka, S., & Takano, K. (2022). Dispersion effect of molecular crowding on ligand-protein surface binding sites of *Escherichia coli* RNase HI. *Langmuir*, 38(47), 14497-14507. https://doi.org/10.1021/acs.langmuir.2c02625

Pérez, S., La-Farré, M., García, M., & Barceló, D. (2001). Occurrence of polycyclic aromatic hydrocarbons in sewage sludge and their contribution to its toxicity in the ToxAlert® 100 bioassay. *Chemosphere*, 45(6-7),

705-712. https://doi.org/10.1016/S0045-6535(01)00152-7

Phua, Z., MacInnis, R., & Jayasekara, H. (2022). Cigarette smoking and risk of second primary cancer: a systematic review and meta-analysis. *Cancer Epidemiology*, 78, 102160. https://doi.org/10.1016/j.canep.2022.102160

Pokharkar, O., Lakshmanan, H., Zyryanov, G., & Tsurkan, M. (2022). *In silico* evaluation of antifungal compounds from marine sponges against COVID-19-associated mucormycosis. *Marine Drugs*, 20(3), 215. https://doi.org/10.3390/md20030215

Rudik, A., Dmitriev, A., Lagunin, A., Filimonov, D., & Poroikov, V. (2022). Computational prediction of inhibitors and inducers of the major isoforms of cytochrome P450. *Molecules*, 7(18), 5875. https://doi.org/10.3390/molecules27185875

Seshacharyulu, P., Ponnusamy, M., Haridas, D., Jain, M., Ganti, A., & Batra, S. (2012). Targeting the EGFR signaling pathway in cancer therapy. *Expert Opinion on Therapeutic Targets*, 16(1), 15-31. https://doi.org/10.1517/14728222.2011.648617

Shivanna, C., Shenoy, C., & Priya, R. (2018). Tofacitinib (selective Janus kinase inhibitor 1 and 3): a promising therapy for the treatment of alopecia areata: a case report of six patients. *International Journal of Trichology*, 10(3), 103-107. https://doi.org/10.4103%2Fijt.ijt_21_18

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *Cancer Journal of Clinicians*, 72(1), 7-33. https://doi.org/10.3322/caac.21708

Sigismund, S., Avanzato, D., & Lanzetti, L. (2018). Emerging functions of the EGFR in cancer. *Molecular Oncology*, 12(1), 3-20. https://doi.org/10.1002/1878-0261.12155

Sowalsky, A. G., Figueiredo, L. R., Coleman, I., Gurel, B., & Bogdan, D. (2022). Assessment of androgen receptor splice variant-7 as a biomarker of clinical response in castration-sensitive prostate cancer. *Clinical Cancer Research*, 28(16), 3509-3525. https://doi.org/10.1158/1078-0432.CCR-22-0851

Thoma, G., Nuninger, F., Falchetto, R., Hermes, E., Tavares, G., Vangrevelinghe, E., & Zerwes, H-G. (2011). Identification of a potent Janus kinase 3 inhibitor with high selectivity within the Janus kinase family. *Journal of Medicinal Chemistry*, 54(1), 284-288. https://doi.org/10.1021/jm101157q

Tu, K., Ma, T., Zhou, R., Xu, L., Fang, Y., & Zhang, C. (2022). Association between dietary fatty acid patterns and colorectal cancer risk: A large-scale case-control study in China. *Nutrients*, 14(20), 4375. doi.org/10.3389/fnut.2022.864098.

Urios, A., Largeron, M., Fleury, M., & Blanco, M. (2006). A convenient approach for evaluating the toxicity profiles of *in vitro* neuroprotective alkylaminophenol derivatives. *Free Radical Biology and Medicine*, 40(5), 791-800. https://doi.org/10.1016/j.freeradbiomed.2005.10.001

Vadivel, C., Gluud, M., Torres-Rusillo, S., Boding, L., Willerslev-Olsen, A., Buus, T., Nielsen, T. K., Persson, J. L., Bonefeld, C. M., Geisler, C., Krejsgaard, T., Fuglsang, A. T., Odum, N., & Woetmann, A. (2021). JAK3 is expressed in the nucleus of malignant T cells in cutaneous T cell lymphoma (CTCL). *Cancers*, 13(2), 280. https://doi.org/10.3390/cancers13020280

Valluri, V., Katari, N., Khatri, C., Kasar, P., Polagani, S., Jonnalagadda, S. (2022). A novel LC-MS/MS method for simultaneous estimation of acalabrutinib and its active metabolite acalabrutinib M 27 in human plasma and application to a human pharmacokinetic study. *RSC Advances*, 12(11), 6631-6639. https://doi.org/10.1039/D1RA09026G

Verma, A., Kambhampati, S., Parmar, S., & Platanias, L. (2003). Jak family of kinases in cancer. *Cancer and Metastasis Reviews*, 22, 423-434. https://doi.org/10.1023/A:1023805715476

Wan, Y., Wu, K., Wang, L., Yin, K., Song, M. (2022). Dietary fat and fatty acids in relation to risk of colorectal cancer. *European Journal of Nutrition*, 61(4), 1863-1873. https://doi.org/10.1007/s00394-021-02777-9

Xia, C., Dong, X., Li, H., Cao, M., Sun, D., He, S., Yang, F., Yan, X., Zhang, S., Li, N., & Chen, W. (2022). Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chinese Medical Journal*, 135(05), 584-590. https://mednexus.org/doi/full/10.1097/CM9.0000000000002108

Yoo, J. E., Han, K., Shin, D. W, Kim, D., Kim, D., Kim, B-S., Chun, S., Jeon, K. H., Jung, W., Park, J., Park, J. H., Choi, K. S., & Kim, J. S. (2022). Association between changes in alcohol consumption and cancer risk. *JAMA Network Open*, 5(8), e2228544. https://doi.org/10.1001/jamanetworkopen.2022.28544

Zhang, H-M., Li, Q., Zhu, X., Liu, W., Hu, H., Liu, T., Cheng, F., You, Y., Zhong, Z., Zou, P., Li, Q., Chen, Z., & Guo, A-Y. (2016). miR-146b-5p within BCR-ABL1–positive microvesicles promotes leukemic transformation of hematopoietic cells. *Cancer Research*, 76(10), 2901-2911. https://doi.org/10.1158/0008-5472.CAN-15-2120

Zhang, J., & Chen, H. (2022). De novo molecule design using molecular generative models constrained by ligand–protein interactions. *Journal of Chemical Information and Modeling*, 62(14), 3291-306. https://doi.org/10.1021/acs.jcim.2c00177