

# Coupling of Some Carbazole Analogs with 3pjc Protein Surface as JAK3 Inhibitors

## Abstract

Some studies indicate that Janus kinase 3 (JAK3) has been involved in several types of cancer. To treat this clinical pathology, some JAK3 inhibitors have been used, such as decernotinib, and facitinib; however, some of these drugs can produce increases in liver transaminase and lipid levels. It is noteworthy that novel medications have been created to inhibit the growth of cancer cells through various experimental and theoretical approaches. Accordingly, the purpose of this study was to ascertain whether carbazole analogs (1-25) could theoretically couple with JAK3, utilizing 3pjc protein, decernotinib, and facitinib as controls within DockingServer software. Data indicate that carbazole analogs could interact at different sites of 3pxb protein surface compared to decernotinib, and facitinib. Other results suggest that inhibition constant (Ki) related to carbazole-protein complexes formation for compounds 2, 5, 9, 17, 18, and 22 was lower compared to decernotinib and facitinib drugs. This phenomenon suggests that carbazole analogs 2, 5, 9, 17, 18, and 22 could act as JAK3 blockers agents resulting in a possible decrease of cancer cell growth.

**Keywords:** Cancer, Carbazole, Decernotinib, Facitinib, JAK 3

## Introduction

There are several data which indicate that cancer has increased in recent years worldwide,<sup>[1, 2]</sup> causing a decrease in life expectancy population.<sup>[3, 4]</sup> Several risk factors have been observed for cancer development such as alcoholism,<sup>[5]</sup> obesity,<sup>[6, 7]</sup> cigarette smoking,<sup>[8]</sup> and foods rich in fat.<sup>[9, 10]</sup> Furthermore, a study indicates that different genetic factors may be involved in different types of cancer cells,<sup>[11-16]</sup> for example, a report displayed that mutations in the KRAS gene (Kirsten rat sarcoma virus) are related to cancer cell growth.<sup>[17]</sup> Another study conducted in 436 French people with cancer indicates that 348 patients showed an established deleterious mutation in MSH2 (tumor suppressor gene).<sup>[18]</sup> Besides, a report suggests that BCR-ABL gene mutations (which encode for a tyrosine kinase) are linked to leukemia developed.<sup>[19]</sup> Another study indicates that mutations involved in HER2 (a membrane tyrosine kinase) are associated with breast cancer.<sup>[20, 21]</sup> Furthermore, a study indicates that overexpression of cMYC (regulator gene that codes for transcription factors) is associated with breast cancer.<sup>[22]</sup> Another report indicates that mutations in the EGFR gene are related to lung cancer cell growth

from 15 to 20% which 10% correspond to kinase domain insertions in exon 20.<sup>[23]</sup>

On the other hand, some data indicates that JAKs (Janus kinase family; cytoplasmic tyrosine kinases) may be associated with cancer cell growth,<sup>[24]</sup> in this way, JAK3 has been related to epithelial cancer cells.<sup>[25]</sup> Another study indicates that JAK3/STAT5 signaling system may contribute to gastric carcinoma development.<sup>[26]</sup> Furthermore, one report showed mutations of the JAK3 gene (p.V715I) which is expressed in both breast and gastric cancers.<sup>[27]</sup> Other data suggest that the JAK3/ERK pathway may induce MMP-9 expression related to breast cancer cell growth.<sup>[28]</sup> These studies suggest some JAK-3 gene mutations may be associated with different types of cancer. Take note that various medications are employed to regulate the growth of certain cancer cells; thus, a report was presented that the PRN371 drug can act as a JAK-3 inhibitor and induce T cell lymphoma apoptosis through abrogation JAK3-STAT pathway.<sup>[29]</sup> All these data suggest that some drugs can produce changes in the biological activity produced by JAK-3; however, its interaction with JAK-3 is

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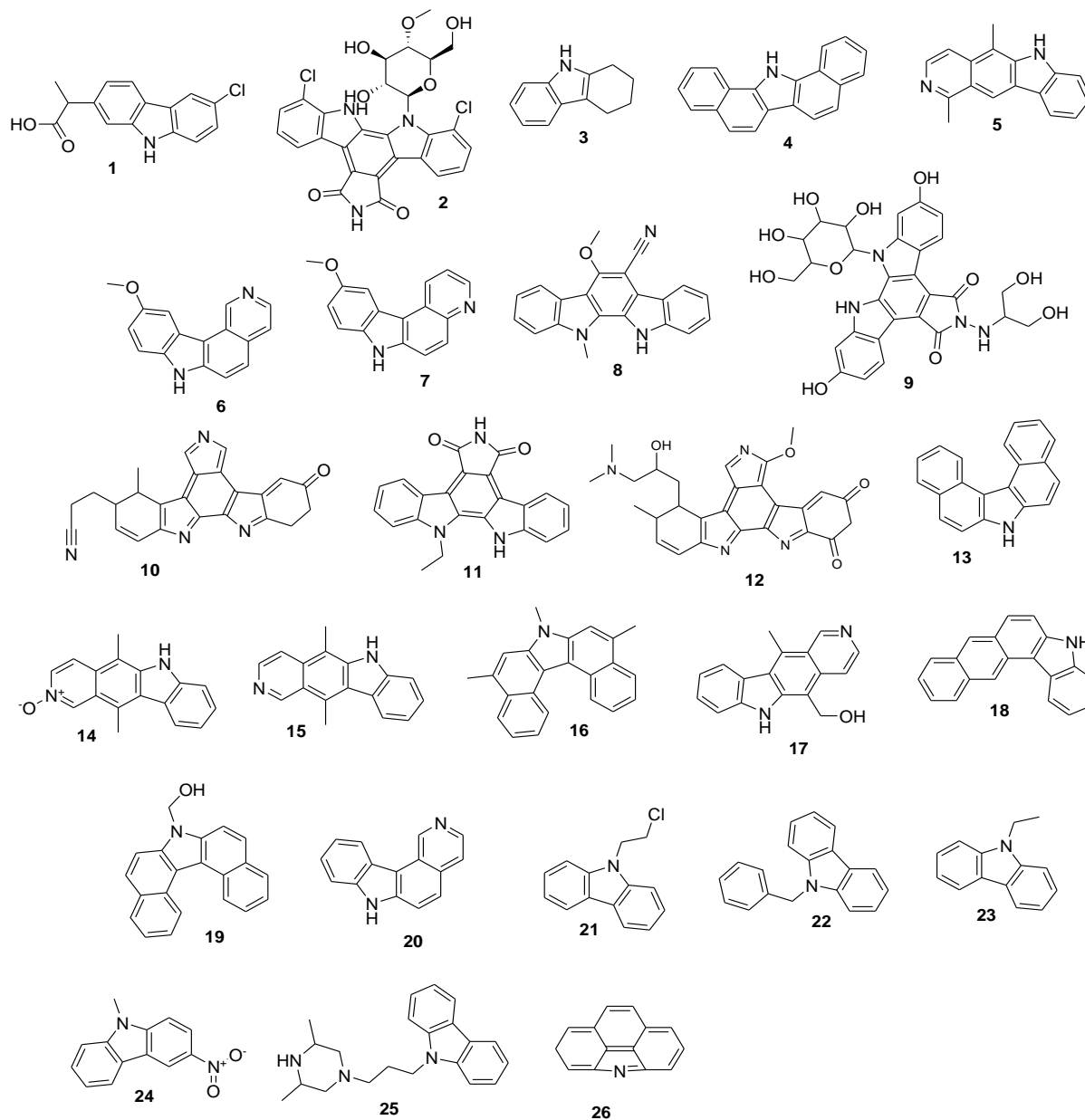
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confusing. Therefore, the objective of this study was to characterize the coupling of twenty-six carbazole (**Figure 1**) with Jak3 using the 3pic protein, decernotinib (JAK-3 antagonist),<sup>[30]</sup> and tofacitinib (non-selective JAK-1 and JAK-3 antagonist)<sup>[31]</sup> as theoretical tools in the DockingServer program.

## Materials and Methods

**Figure 1** depicts the structure of twenty-six carbazole derivatives, which were utilized to ascertain if they may interact in the following ways with the JAK3 surface:



**Figure 1.** Chemical structure of carbazole analogs (1-26). Source: <https://pubchem.ncbi.nlm.nih.gov>

1 = 2-(6-chloro-9H-carbazol-2-yl)propanoic acid

2 = 5,21-dichloro-3-[(2R,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-methoxyoxan-2-yl]-3,13,23-triazahexacyclo[14.7.0.0.10.4,9.0.11,15.0.17,22]tricoso-1,4(9),5,7,10,15,17 (22),18,20-nonaene-12,14-dione

3 = 1,2,3,4-Tetrahydrocarbazole

4 = 1,2,7,8-Dibenzcarbazole

5 = 1,5-Dimethyl-6H-pyrido(4,3-b)carbazole

6 = 10-methoxy-7H-pyrido[4,3-c]carbazole

7 = 10-Methoxy-7H-pyrido(2,3-c)carbazole

8 = 11,12-Dihydro-6-methoxy-11-methylindolo(2,3-a)carbazole-5-carbonitri-le

9 = 6,20-dihydroxy-13-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-3-[3,4, 5-trihydroxy-6-(hydroxymethyl)tetrahydropyran-2-yl]-3,13,23-triazahexacyclo[14.7.0.0.2,10.4,9.0.11,15.0.17,22]tricoso-1(16),2(10),4,6,8,11(15),17(22),18,20-nonaene-12,14-dione

10 = 12-(2-Cyanoethyl)-6,7,12,13-tetrahydro-13-methyl-5-oxo-5H-indolo-(2,3-a)pyrrolo(3,4-c)carbazole

11 = 3-ethyl-3,13,23-triazahexacyclo[14.7.0.0.10.4,9.0.11,15.0.17,22]trico-sa-1,4,6,8,10,15,17,19,21-nona-ene-12,14-dione

12 = 13-(3-dimethylamino-2-hydroxypropyl)-3-methoxy-12-methyl-6,7,12, 13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-dione

13 = 3,4,5,6-Dibenzcarbazole

14 = 5,11-Dimethyl-6H-pyrido(4,3-b)carbazole 2-oxide

- 15 = 5,11-Dimethyl-6H-pyrido(4,3-b)carbazole
- 16 = 5,7,9-Trimethyl-7H-dibenzo(c,g)carbazole
- 17 = 5-(Hydroxymethyl)-11-methyl-6H-pyrido(4,3-b)carbazole
- 18 = 5H-Naphtho[2,3-c]carbazole
- 19 = 7-Hydroxymethyldibenzo(c,g)carbazole
- 20. 7H-Pyrido(4,3-c)carbazole
- 21 = 9-(.beta.-Chloroethyl)carbazole
- 22 = 9-Benzyl-9H-carbazole
- 23 = 9-Ethyl-9H-carbazole
- 24 = 9-Methyl-3-nitro-9H-carbazole
- 25 = 9-[3-(3,5-Dimethyl-piperazin-1-yl)-propyl]-9H-carbazole
- 26 = 4H-Benzo(def)carbazole

### Ligand-protein complex

Interaction of twenty-six carbazole derivatives with JAK3 was evaluated using 3pjc protein,<sup>[32]</sup> decernotinib and facitinib as controls in DockingServer program.<sup>[33]</sup>

### Pharmacokinetic parameters

Different pharmacokinetic factors for carbazole analogs (2, 5, 9, 17, 18, and 22) were determined with the use of the SwissADME software.<sup>[34]</sup>

### Toxicity analysis

The GUSAR software was utilized to assess the potential toxicity of carbazole analogs (2, 5, 9, 17, 18, and 22) as well as decernotinib and facitinib when administered through various routes.<sup>[35]</sup>

### Results and Discussion

Certain observations in the literature suggest that analogs of carbazoles may cause changes in the development of cancer cells; for example, alectinib drug has been used as monotherapy to treat lung cancer.<sup>[36]</sup> Another study showed that compound 3,6-di(2-furyl)-9H-carbazole can act as a carcinogenic agent through topoisomerase II inhibition using MCF-7 (breast cancer) cell lines.<sup>[37]</sup> Furthermore, a report displayed that some N-acylated carbazole derivatives can decrease breast cancer cell growth using MDA-MB-231 cell lines.<sup>[38]</sup> Another report showed that a tetrahydrocarbazole derivative exerts anticancer activity against lung cancer using a Calu-1 cell line.<sup>[39]</sup> Besides, a study indicates that the compound MHY407 can produce biological activity in breast cancer using an MCF-7 cell line.<sup>[40]</sup> All of these studies suggest that some drugs are used to control the growth of

cancer cells; however, their interaction with JAK3 in cancer cell growth is unclear. Thus, this study aimed to characterize the interaction of twenty-six carbazole analogs with JAK3 using 3pjc protein, decernotinib, and facitinib as theoretical tools in the DockingServer program.

### Protein-ligand

There are several protocols to characterize the protein-ligand complex formation; for example, a study displays the interaction of a carbazole-acetate derivative with tyrosinase and human glutathione receptors using the Autodock program.<sup>[41]</sup> Other studies suggest that some carbazole analogs can interact with peroxisome proliferator-activated receptor gamma using GROMAC software.<sup>[42]</sup> Besides, a report indicates that a carbazole-chrome-carboxamide analog can interact with cyclin-dependent kinase 2 using the Biovia Discovery Studio program.<sup>[43]</sup> These theoretical data suggest that some carbazoles interact with different biomolecules; therefore, the objective of this research was to characterize the coupling of twenty-six carbazoles with JAK3 using DockingServer software.<sup>[33]</sup> **Table 1** and **Figure 2** displayed the possible interaction of carbazole derivatives with 3pjc protein through coupling with different amino acid residues. In this way, the results indicate that Leu<sub>828</sub> could interact with carbazole analogs 1, 3-21, and 24 in a similar manner to decernotinib and facitinib; these data suggest that possible biological activity produced by carbazole analogs could be conditioned by the interaction with different types of amino acids involved in carbazole-JAK3 complex formation. However, it is crucial to note that the formation of carbazole-protein complexes may be influenced by certain thermodynamic parameters.

**Table 1. Coupling of carbazole derivatives (1-26), decernotinib, and facitinib with amino acid residues of 3pjc protein surface.**

Compound	Aminoacid residues
Decernotinib	Leu <sub>828</sub> ; Gly <sub>829</sub> ; Phe <sub>833</sub> ; Lys <sub>855</sub> ; Met <sub>902</sub> ; Cys <sub>909</sub> ; Asp <sub>912</sub> ; Arg <sub>953</sub> ; Asn <sub>954</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
Facitinib	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub>
1	Leu <sub>828</sub> ; Ala <sub>853</sub> ; Tyr <sub>904</sub> ; Leu <sub>905</sub> ; Leu <sub>956</sub>
2	Phe <sub>833</sub> ; Tyr <sub>904</sub> ; Leu <sub>905</sub> ; Arg <sub>911</sub> ; Asp <sub>912</sub> ; Leu <sub>956</sub>
3	Leu <sub>828</sub> ; Ala <sub>853</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub>
4	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
5	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
6	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
7	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
8	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>

9	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Tyr <sub>904</sub> ; Arg <sub>911</sub> ; Asp <sub>912</sub> ; Arg <sub>953</sub> ; Asn <sub>954</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub>
10	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>905</sub> ; Arg <sub>953</sub> ; Asn <sub>954</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
11	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>905</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
12	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>905</sub> ; Cys <sub>909</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub> ; Phe <sub>968</sub>
13	Leu <sub>828</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub>
14	Leu <sub>828</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
15	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
16	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
17	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
18	Leu <sub>828</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
19	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Met <sub>902</sub> ; Glu <sub>903</sub> ; Asp <sub>967</sub>
20	Leu <sub>828</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>900</sub> ; Arg <sub>953</sub> ; Asn <sub>954</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub>
21	Leu <sub>828</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Val <sub>884</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub>
22	Phe <sub>833</sub> ; Ala <sub>853</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Leu <sub>900</sub> ; Met <sub>902</sub> ; Asn <sub>954</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub>
23	Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Leu <sub>956</sub> ; Asp <sub>967</sub> ; Phe <sub>968</sub>
24	Leu <sub>828</sub> ; Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Tyr <sub>904</sub> ; Leu <sub>956</sub>
25	Phe <sub>833</sub> ; Val <sub>836</sub> ; Ala <sub>853</sub> ; Val <sub>884</sub> ; Met <sub>902</sub> ; Cys <sub>909</sub> ; Arg <sub>953</sub> ; Asn <sub>954</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub>
26	Phe <sub>833</sub> ; Val <sub>836</sub> ; Lys <sub>855</sub> ; Glu <sub>871</sub> ; Leu <sub>875</sub> ; Val <sub>884</sub> ; Leu <sub>900</sub> ; Leu <sub>956</sub> ; Ala <sub>966</sub> ; Asp <sub>967</sub>

### Thermodynamic parameters

In the literature, there are some protocols to predict Protein-ligand complex formation.<sup>[33]</sup> This research used the DockingServer program to characterize some thermodynamic parameters that can influence the formation of the carbazole-protein complex. **Table 2** shows variations in energy levels for

carbazole analogs compared to both decernotinib and facitinib drugs. Furthermore, the inhibition constant (Ki) was lower for carbazole analogs 2, 5, 9, 17, 18, and 22 compared with either decernotinib or facitinib drugs. These data suggest that carbazole derivatives 2, 5, 9, 17, 18, and 22 may be good JAK3 inhibitor agents. However, to confirm these findings, more research needs to be carried out using some biological models.

**Table 2. Various energies at which carbazole analogs (1-26), decernotinib, and facitinib bind to the 3pic protein surface.**

Compound	A	B	C	D	E	F
Decernotinib	-7.49	3.22	-8.24	0.03	-8.22	
Facitinib	-7.69	2.30	-8.60	-0.09	-8.69	721.73
1	-6.85	13.41	-7.40	0.16	-7.24	605.29
2	-8.14	1.09	-8.17	-0.09	-8.26	920.84
3	-5.88	48.59	-5.87	-0.02	-5.88	517.31
4	-8.90	298.71	-8.90	-0.01	-8.90	655.44
5	-8.12	1.12	-8.17	0.05	-8.12	619.48
6	-6.81	10.21	-7.10	-0.01	-7.11	610.86
7	-6.96	7.87	-7.29	0.02	-7.26	618.32
8	-8.29	840.37	-8.64	-0.03	-8.68	757.91
9	-8.12	1.12	-7.07	-0.06	-7.13	978.78
10	-10.0	40.29	-10.8	-0.10	-10.9	832.21
11	-9.24	167.36	-9.49	-0.05	-9.54	750.89
12	-11.2	5.66	-11.0	-0.16	-11.2	917.10
13	-9.04	236.64	-9.02	-0.02	-9.04	663.47
14	-7.52	4.84	-7.35	0.09	-7.25	644.57
15	-9.62	88.48	-9.60	-0.02	-9.62	789.57
16	-9.62	88.48	-9.60	-0.02	-9.62	769.57
17	-7.99	1.38	-7.97	-0.04	-8.02	635.47
18	-8.17	1.02	-8.17	0.00	-8.17	681.72
19	-8.72	405.22	-9.27	-0.05	-9.32	694.50

20	-6.81	10.21	-6.73	-0.08	-6.81	585.75
21	-6.59	14.76	-7.13	-0.02	-7.15	603.83
22	-7.85	1.75	-8.40	-0.01	-8.41	659.47
23	-5.97	41.95	-6.25	-0.02	-6.27	536.45
24	-6.91	8.59	-7.21	0.00	-7.21	563.12
25	-8.82	341.24	-9.30	-0.24	-9.54	770.48
26	-6.42	19.63	-6.41	-0.01	-6.42	516.33

A = Est: Free Energy of Binding (kcal/mol); B = Est. 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.

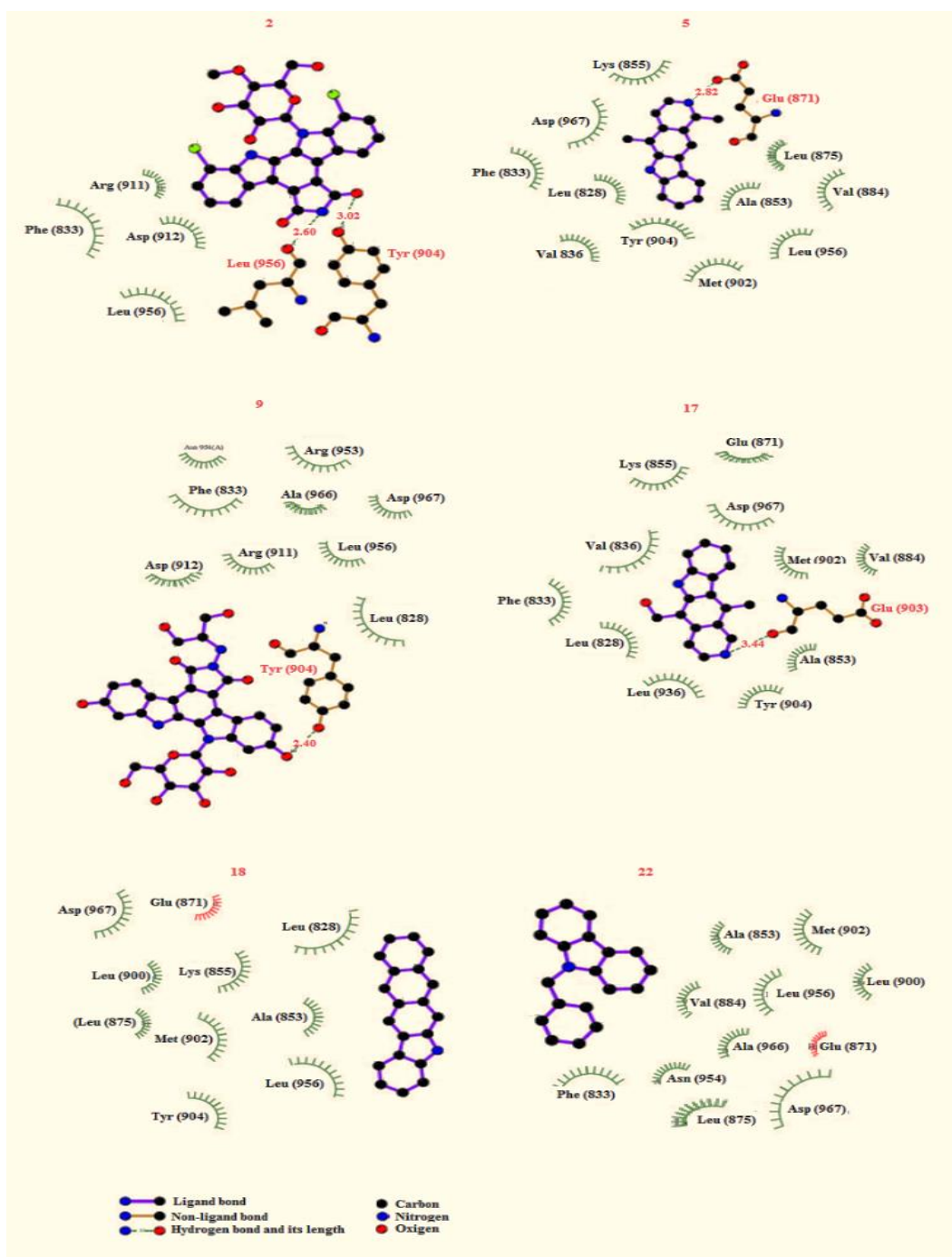


Figure 2. Coupling carbazole derivatives (2, 5, 9, 17, 18, and 22) with the 3pic protein surface.



### Pharmacokinetic evaluation

Various substances with anticancer action can have their pharmacokinetic parameters predicted and analyzed using a variety of techniques; in this way, a report displayed the pharmacokinetic properties of several carbazoles using some theoretical programs to evaluate the possibility of some of these could have biological activity orally in humans.<sup>[44]</sup> For example, the pharmacokinetic properties of compound SR13668 were determined using the system version of the data from software 10.2.<sup>[45]</sup> This data suggests that some theoretical programs can be used to predict different pharmacokinetic parameters; in this way, this study aimed to characterize

several pharmacokinetic factors for carbazole analogs 2, 5, 9, 17, 18, and 22 using the SwissADME program (**Table 3**). The determined data showed the possibility of variations in the metabolism of carbazole analogs, involving different types of cytochrome P450 isoenzymes. In this way, compound 2 shows low absorption compared with carbazole analogs 5, 9, 17, 18, and 22. Furthermore, the compound could act as an inhibitor of CYP2C9, which could cause changes in the biological activity of other drugs that are substrates of this isoenzyme such as celecoxib and flurbiprofen (nonsteroidal anti-inflammatory drugs),<sup>[46]</sup> glibenclamide and gliclazide (antidiabetic agents).<sup>[47]</sup>

**Table 3. Pharmacokinetic factors for carbazole analogs 2, 5, 9, 17, 18, and 22**

Parameter	2	5	9	17	18	22
GI absorption	Low	High	Low	High	High	High
BBB permeant	No	Yes	No	Yes	No	Yes
P-GP substrate	No	Yes	No	Yes	Yes	Yes
CYP1A2 inhibitor	No	Yes	No	Yes	Yes	Yes
CYP2C19 inhibitor	No	Yes	No	Yes	No	Yes
CYP2C9 inhibitor	Yes	No	No	No	No	No
CYP2D6 inhibitor	No	Yes	No	Yes	No	Yes
CYP3A4 inhibitor	No	Yes	No	Yes	No	Yes
Consensus LogP <sub>o/w</sub>	2.75	3.84	-0.77	3.14	4.82	4.48

### Toxicity analysis

Some data suggest that several carbazole analogs may produce toxicity in different biological models;<sup>[48, 49]</sup> for example, a report showed that carbazol-oxadiazol-one analog can produce a higher toxicity degree compared with a carbazol-acetyl derivative.<sup>[42]</sup> Analyzing these data, in this

investigation the toxicity degree of carbazole derivatives 2, 5, 9, 17, 18, and 22 was determined using the Gussar program. The results indicate that compound 9 requires a higher dose through the intraperitoneal route compared to carbazole analogs 2, 5, 17, 18, and 22. These data suggest that the level of toxicity is associated with both dose and administration routes.

**Table 4. Toxicity degree for carbazole analogs 2, 5, 9, 17, 18, and 20.**

Compound	IP LD50 (mg/kg)	IV LD50 (mg/kg)	Oral LD50 (mg/kg)	SC LD50 (mg/kg)
2	552.70	558.60	5621.00	3130.00
5	429.10	67.01	649.30	190.20
9	871.00	719.20	3459.00	2179.00
17	800.10	76.74	1278.00	208.70
18	305.20	72.81	1328.00	217.60
22	355.80	45.41	2194.00	723.50

IP - Intraperitoneal route of administration  
 IV - Intravenous route of administration  
 Oral - Oral route of administration  
 SC - Subcutaneous route of administration

### Conclusion

This research has reported the interaction of carbazole derivatives to the JAK3 surface using 3pjc protein as a theoretical tool. The results suggest that carbazole derivatives 2, 5, 9, 17, 18, and 22 could have a higher affinity for 3pjc protein surface compared with the compounds 1, 3, 4-6, 6-8, 10-16, 19, 20, and 23-26. These data suggest that carbazole analogs 2, 5, 9, 17, 18, and 22 can act as JAK3 antagonists;

this phenomenon could reduce cancer cell growth, which translates as a therapeutic alternative to treat some cancers.

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### Conflict of interest

None.

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None.

## Ethics statement

All procedures in this study were performed in accordance with protocols for the Pharmacochimistry Laboratory of the University Autonomous of Campeche.

## References

- Siegel R, Giaquinto A, Jemal A. Cancer statistics, 2024. *Cancer J Clin*. 2024;74(1):12-49. doi:10.3322/caac.21820
- Bray F, Laversanne M, Sung H, Ferlay J, Siegel R, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin*. 2024;74(3):229-63. doi:10.3322/caac.21834
- Micheli A, Baili P, Quinn M, Mugno E, Capocaccia R, Grosclaude P, et al. Life expectancy and cancer survival in the EUROcare-3 cancer registry areas. *Ann Oncol*. 2023;14:v28-40. doi:10.1093/annonc/mdg752
- Yourman L, Bergstrom J, Bryant E, Pollner A, Moore A, Schoenborn N, et al. Variation in receipt of cancer screening and immunizations by 10-year life expectancy among US adults aged 65 or older in 2019. *J Gen Int Med*. 2024;39(3):440-9.
- Brown R, Bigelow P, Dubin J, Neiterman E. Breast cancer, alcohol, and phosphate toxicity. *J Appl Toxicol*. 2024;44(1):17-27. doi:10.1002/jat.4504
- Oze I, Ito H, Koyanagi Y, Abe S, Rahman M, Islam M, et al. Obesity is associated with biliary tract cancer mortality and incidence: A pooled analysis of 21 cohort studies in the Asia Cohort Consortium. *Int J Cancer*. 2024;154(7):1174-90. doi:10.1002/ijc.34794
- Jones A, Scheurlen K, Macleod A, Simon H, Galandiuk S. Obesity and inflammatory factors in the progression of early-onset colorectal cancer. *Cancers*. 2024;16(7):1403. doi:10.3390/cancers16071403
- Trivilin L, Mendes S, Borçoi A, Cassiano D, Archanjo A, De-Oliveira M, et al. In vivo model of colorectal cancer: Impact to cigarette smoke exposition on neoplasm development. *Peer Rev*. 2024;6(8):70-86. doi:10.53660/PRW-2071-3812
- Mei J, Qian M, Hou Y, Liang M, Chen Y, Wang C, et al. Association of saturated fatty acids with cancer risk: A systematic review and meta-analysis. *Lipids Health Dis*. 2024;23(1):32.
- Dao TL, Hilf R. Dietary fat and breast cancer: A search for mechanisms. *Exer Calor Fat Cancer*. 2024;223-37.
- Wan Y, Wu K, Wang L, Yin K, Song M. Dietary fat and fatty acids in relation to risk of colorectal cancer. *Eur J Nut*. 2022;61(4):1863-73. doi:10.1007/s00394-021-02777-9
- Usui Y, Taniyama Y, Endo M, Koyanagi Y, Kasugai Y, Oze I, et al. *Helicobacter pylori*, homologous-recombination genes, and gastric cancer. *New Eng J Med*. 2023;388(13):1181-90.
- Horackova K, Janatova M, Kleiblova P, Kleibl Z, Soukupova J. Early-onset ovarian cancer < 30 years: What do we know about its genetic predisposition? *Int J Mol Sci*. 2023;24(23):17020.
- Breast Cancer Association Consortium. Breast cancer risk genes-association analysis in more than 113,000 women. *New Engl J Med*. 2021;384(5):428-39.
- Kasi P, Lee J, Pasquina L, Decker B, Vanden P, Pavlick D, et al. Circulating tumor DNA enables sensitive detection of actionable gene fusions and rearrangements across cancer types. *Clin Cancer Res*. 2024;30(4):836-48. doi:10.1158/1078-0432.CCR-23-2693
- Shitara K, Muro K, Watanabe J, Yamazaki K, Ohori H, Shiozawa M, et al. Baseline ctDNA gene alterations as a biomarker of survival after panitumumab and chemotherapy in metastatic colorectal cancer. *Nat Med*. 2024;30(3):730-9.
- Sosinsky A, Ambrose J, Cross W, Turnbull C, Henderson S, Jones L, et al. Insights for precision oncology from the integration of genomic and clinical data of 13,880 tumors from the 100,000 Genomes Cancer Programme. *Nat Med*. 2024;30(1):279-89.
- Pineda-Lancheros L, Gálvez-Navas J, Rojo-Tolosa S, Membrive-Jiménez C, Valverde-Merino M, Martínez-Martínez F, et al. Polymorphisms in VDR, CYP27B1, CYP2R1, GC and CYP24A1 genes as biomarkers of survival in non-small cell lung cancer: A systematic review. *Nutrients*. 2023;15(6):1525.
- Hayama T, Hashiguchi Y, Okamoto K, Okada Y, Ono K, Shimada R. G12V and G12C mutations in the gene KRAS are associated with a poorer prognosis in primary colorectal cancer. *Int J Colorectal Dis*. 2019;34:1491-6. doi:10.1007/s00384-019-03344-9
- Marra A, Chandralapaty S, Modi S. Management of patients with advanced-stage HER2-positive breast cancer: Current evidence and future perspectives. *Nat Rev Clin Oncol*. 2024;21(3):1-18.
- Gutierrez C, Schiff R. HER2: Biology, detection, and clinical implications. *Arch Pathol Lab Med*. 2011;135(1):55-62. doi:10.5858/2010-0454-RAR.1
- Duffy M, O'Grady S, Tang M, Crown J. MYC as a target for cancer treatment. *Cancer Treat Rev*. 2021;94:102154. doi:10.1016/j.ctrv.2021.102154
- Dhiwar P, Purawarga G, Pal R, Singh E, Ghara A, Maji L, et al. An assessment of EGFR and HER2 inhibitors with structure-activity relationship of fused pyrimidine derivatives for breast cancer: A brief review. *J Biomol Struct Dyn*. 2024;42(3):1564-81. doi:10.1080/07391102.2023.2204351
- Jia J, Zhou X, Chu Q. Mechanisms and therapeutic prospect of the JAK-STAT signaling pathway in liver cancer. *Mol Cell Biochem*. 2024:1-17.
- Lai K, Jin Y, Graham D, Witthuhn B, Ihle J, Liu E. A kinase-deficient splice variant of the human JAK3 is expressed in hematopoietic and epithelial cancer cells (\*). *J Biol Chem*. 1995;270(42):25028-36. doi:10.1074/jbc.270.42.25028
- Hu Q, Dou N, Wu Q, Gao Y, Li Y, Chen J. JAK3/STAT5 signaling-triggered upregulation of PIK3CD contributes to gastric carcinoma development. *J Cell Comm Signal*. 2024;18(1):e12017. doi:10.1002/ccs3.12017
- Li S, Ma M, Li H, Waluszko A, Sidorenko T, Schadt E, et al. Cancer gene profiling in non-small cell lung cancers reveals activating mutations in JAK2 and JAK3 with therapeutic implications. *Genome Med*. 2017;9:1-11.
- Vadivel C, Glud M, Torres-Rusillo S, Boding L, Willerslev-Olsen A, Buus T, et al. JAK3 is expressed in the nucleus of malignant T cells in cutaneous T cell lymphoma (CTCL). *Cancers*. 2021;13(2):280. doi:10.3390/cancers13020280
- Jeong E, Kim M, Nam H, Min C, Lee S, Chung Y, et al. Somatic mutations of JAK1 and JAK3 in acute leukemias and solid cancers. *Clin Cancer Res*. 2008;14(12):3716-21. doi:10.1158/1078-0432.CCR-07-4839
- Lv Y, Mi P, Babon J, Fan G, Qi J, Cao L, et al. Small molecule drug discovery targeting the JAK-STAT pathway. *Pharmacol Res*. 2024;107217. doi:10.1016/j.phrs.2024.107217
- Taylor P, Choy E, Baraliakos X, Szekanecz Z, Xavier R, Isaacs J, et al. Differential properties of Janus kinase inhibitors in the treatment of immune-mediated inflammatory diseases. *Rheumatology*. 2024;63(2):298-308. doi:10.1093/rheumatology/kead448
- Thoma G, Nuninger F, Falchetto R, Hermes E, Tavares G, Vangrevelinghe E, et al. Identification of a potent Janus kinase 3 inhibitor with high selectivity within the Janus kinase family. *J Med Chem*. 2011;54(1):284-8. doi:10.1021/jm101157
- Lopez-Ramos M, Figuroa-Valverde L, Alvarez-Ramirez M, Rosas-Nexicapa M, Mateu-Armand M, Cauch-Carrillo R. Interaction of eight steroid derivatives with VEGFR-1 using a theoretical model. *Braz J Sci*. 2024;3(3):11-24. doi:10.14295/bjs.v3i3.523
- Figuroa-Valverde L, Rosas-Nexicapa M, Alvarez-Ramirez M, López-Ramos M, Díaz-Cedillo F, Mateu-Armand M. Evaluation of biological activity exerted by Dibenzo [b, e] Thiophene-11 (6H)-One on left ventricular pressure using an isolated rat heart model. *Drug Res*. 2023;73(05):263-70. doi:10.1055/a-1995-6351
- Figuroa-Valverde L, Díaz-Cedillo F, Rosas-Nexicapa M, Alvarez-Ramirez M, Mateu-Armand M, López-Ramos M. Interaction of some amino-nitrile derivatives with vascular endothelial growth factor receptor 1 (VEGFR1) using a theoretical model. *Drug Res*. 2023;73(06):355-64. doi:10.1055/a-2062-3571
- Wu Y, Dziadziuszko R, Ahn J, Barlesi F, Nishio M, Lee D, et al. Alectinib in resected ALK-positive non-small-cell lung cancer. *New Engl J Med*. 2024;390(14):1265-76. doi:10.1056/NEJMoa2310532
- Olszewski M, Maciejewska N, Kallingal A, Chylewska A, Dąbrowska A, Biedulska M, et al. Palindromic carbazole derivatives: Unveiling

- their antiproliferative effect via topoisomerase II catalytic inhibition and apoptosis induction. *J Enzyme Inh Med Chem.* 2024;39(1):2302920. doi:10.1080/14756366.2024.2302920
38. Kolli S, Prasad B, Babu P. TFAA/H<sub>3</sub>PO<sub>4</sub> mediated unprecedented N-acylation of carbazoles leading to small molecules possessing anti-proliferative activities against cancer cells. *Org Biomol Chem.* 2014;12(32):6080-4. doi:10.1039/C4OB00686K
  39. Kumar T, Mahadevan K, Kumara M. Synthesis and cytotoxic studies of 2, 3-dimethylindoles and tetrahydrocarbazoles. *Int J Pharm Pharm Sci.* 2014;6(2):137-40.
  40. Yoon S, Kim J-H, Lee Y. A novel carbazole derivative, MHY407, sensitizes cancer cells to doxorubicin-, etoposide-, and radiation treatment via DNA damage. *Eur J Pharmacol.* 2012;697(1-3):24-31.
  41. Serdaroğlu G, Uludağ N, Ercag E, Sugumar, Rajkumar P. Carbazole derivatives: Synthesis, spectroscopic characterization, antioxidant activity, molecular docking study, and the quantum chemical calculations. *J Mol Liquids.* 2021;330:115651. doi:10.1016/j.molliq.2021.115651
  42. Çapan İ, Hawash M, Jaradat N, Sert Y, Servi R, Koca İ. Design, synthesis, molecular docking, and biological evaluation of new carbazole derivatives as anticancer, and antioxidant agents. *BMC Chem.* 2023;17(1):60. doi:10.1186/s13065-023-00961-y
  43. Patel M, Pandey N, Timaniya J, Parikh P, Chauhan A, Jain N, et al. Coumarin-carbazole based functionalized pyrazolines: Synthesis, characterization, anticancer investigation and molecular docking. *RSC Adv.* 2021;11(44):27627-44. doi:10.1039/D1RA03970A
  44. Sungthong B, Sithon K, Panyatip P, Tadtong S, Nunthaboot N, Puthongking P. Quantitative analysis and in silico molecular docking screening for acetylcholinesterase inhibitor and ADME prediction of coumarins and carbazole alkaloids from *Clausena harmandiana*. *Nat Prod.* 2022;16(4):358-69.
  45. Kapetanovic I, Muzzio M, Hu S, Crowell J, Rajewski R, Haslam J, et al. Pharmacokinetics and enhanced bioavailability of candidate cancer preventative agent, SR13668 in dogs and monkeys. *Cancer Chemother Pharmacol.* 2010;65:1109-16.
  46. Ahlström M, Ridderström M, Zamora I. CYP2C9 structure-metabolism relationships: Substrates, inhibitors, and metabolites. *J Med Chem.* 2007;50(22):5382-91. doi:10.1021/jm070745g
  47. Daly A, Rettie A, Fowler D, Miners J. Pharmacogenomics of CYP2C9: Functional and clinical considerations. *J Pers Med.* 2017;8(1):1. doi:10.3390/jpm8010001
  48. Liu Y, Jin X, Ye Y, Xu Z, Du Z, Hong H, et al. Emerging disinfection byproducts 3-bromine carbazole induces cardiac developmental toxicity via aryl hydrocarbon receptor activation in zebrafish larvae. *Environm Poll.* 2024;346:123609. doi:10.1016/j.envpol.2024.123609
  49. Gabelova A. 7H-Dibenzo [c, g] carbazole: Metabolic pathways and toxicity. *Chem Biol Interact.* 2020;323:109077. doi:10.1016/j.cbi.2020.109077