Interaction of benzenesulfonamide derivatives with Smyd3 using a theoretical model

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

[2] Faculty of Nutrition, University Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, Mexico

[3] National School of Biological Sciences of the National Polytechnic Institute. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, Mexico

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

Received: July 15, 2023 DOI: 10.14295/bjs.v3i1.455

Accepted: August 18, 2023 URL: https://doi.org/10.14295/bjs.v3i1.455

Abstract

Cancer is a serious public health problem worldwide. This clinical pathology is associated with the activation/release of several biomolecules, including the Smyd proteins family. In this way, some studies indicate that Smyd3 is associated with cancer cells growth. It is important to mention that some drugs act as Smyd3 inhibitors in the treat some cancers. However, their interaction is very confusing; for this reason, the aim of this research was to evaluate the theoretical interaction of benzenesulfonamide and their derivatives (compounds *2* to **28**) using 7o2c protein, novobiocin, BAY-6035, EPZ031686 and BCI-121 drugs as theoretical tools in DockingServer program. The results showed differences in the aminoacid residues involved in the interaction of benzenesulfonamide and their derivatives with 7o2c protein surface compared with novobiocin, BAY-6035, EPZ031686 and BCI-121 drugs. In additions, the inhibition constant (Ki) for benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 was very lower compared to benzenesulfonamide, novobiocin, BAY-6035, EPZ031686 and BCI-121. In conclusion, the benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 could be a good alternative as Smyd3 inhibitors to decrease cancer cells growth.

Keywords: cancer, smyd3, benzenesulfonamide, novobiocin.

Interação de derivados de benzenossulfonamida com Smyd3 usando um modelo teórico

Resumo

O câncer é um grave problema de saúde pública em todo o mundo. Esta patologia clínica está associada à ativação/liberação de várias biomoléculas, incluindo as proteínas da família Smyd. Desta forma, alguns estudos indicam que o Smyd3 está associado ao crescimento de células cancerígenas. É importante mencionar que algumas drogas atuam como inibidores de Smyd3 no tratamento de alguns tipos de câncer. No entanto, sua interação é muito confusa; por esta razão, o objetivo desta pesquisa foi avaliar a interação teórica de benzenossulfonamida e seus derivados (compostos 2 a 28) usando a proteína 7o2c, novobiocina, BAY-6035, EPZ031686 e drogas BCI-121 como ferramentas teóricas no programa DockingServer. Os resultados mostraram diferenças nos resíduos de aminoácidos envolvidos na interação da benzenossulfonamida e seus derivados com a superfície da proteína 7o2c em comparação com as drogas novobiocina, BAY-6035, EPZ031686 e BCI-121. Além disso, a constante de inibição (Ki) para os derivados de benzenossulfonamida 2, 7, 8, 13, 14, 17, 20, 21, 24 e 28 foi muito menor em comparação com benzenossulfonamida, novobiocina, BAY-6035, EPZ031686 e

BCI-121. Em conclusão, os derivados de benzenossulfonamida 2, 7, 8, 13, 14, 17, 20, 21, 24 e 28 podem ser uma boa alternativa como inibidores de Smyd3 para diminuir o crescimento de células cancerígenas.

Palavras-chave: câncer, smyd3, benzenesulfonamida, novobiocina.

1. Introduction

Cancer is a major health problem of health public in the world (Xia et al, 2022; Miller et al, 2022; Hanahan, 2022). This clinical pathology can be associated with several risk factors such as smoking (Hecht and Hatsukami, 2022), alcoholism (Yoo et al., 2022), ultra-processed food consumption (Wang et al., 2022) and some genetic factors (Deng et al., 2022; Stopsack et al., 2022; Shah and Bentrem, 2022; Hol et al., 2022; Jukarainen et al., 2022). Thus, some studies indicate that Smyd proteins family [Smyd1, Smyd2, Smyd3, Smyd4 and Smyd5] may play an important role in transcriptional activation involved in a several biological processes (Phan an et al., 2005; Leinhart and Brown, 2011), including the progression of many cancer types regulating cell growth (Song et al., 2019; Liu et al., 2023).

In this way, there are studies have shown that Smyd3 may be associated to some regulatory pathways in cancer cells growth (Giakountis et al., 2017); for example, a study showed that Smyd3 can promotes cell cycle progression by inducing cyclin D3 transcription and stabilizing the cyclin D1 protein in medulloblastoma (Asuthkar et al., 2022). Other data indicate that Smyd3 may associate with the NuRD (Nucleosome Remodeling Deacetylase) to regulate transcription and promote proliferation and invasiveness in hepatocellular carcinoma cells (Yang et al., 2022).

Besides, a report-displayed that Smyd3 promotes aerobic glycolysis in diffuse B-cell lymphoma via H3K4me3 (histone trimethylated at lysine 4 which is associated with active chromatin and gene expression) mediated PKM2 (pyruvate kinase) transcription (Tian et al., 2022). Another report shows that Smyd3 may promotes oral squamous cell carcinoma tumorigenesis via H3K4me3-mediated HMGA2 (High-mobility group AT-hook 2) transcription (Yang et al., 2023). In addition, a study indicate that Smyd3 may promotes TGFβ (transforming growth factor-β) dependent mesenchymal gene expression and cell migration in breast cancer (Fenizia et al., 2019).

On the other hand, to decrease the biological activity produced by Smyd3 in cancer cells have been used some drugs; for example, a study showed that compound BCI-121 (4-(aminocarbonyl)-N-(4-bromophenyl)-1-piperidineacetamide) significantly decreased the biological activity of Smyd3, resulting in decreased colorectal cancer cells growth (Peserico et al., 2015). Besides, a report indicate that novobiocin decreases Smyd3 expression and inhibits the migration of MDA-MB-231 human breast cancer cells (Luo et al., 2010). Other report showed that BAY-6035 act as Smyd3 inhibitor using high-throughput detection based on a heat exchange assay (Gradl et al., 2021). Besides, a study showed that compound EPZ031686 inhibith the biological activity of Smyd3 using a pharmacokinetic model (Mitchell et al., 2016).

All these data suggest that some drugs can act as Smyd3 inhibitors; however, the interaction of these compounds with Smyd3 surface is not clear. Analyzing these data, the aim of this research was to evaluate the possible interaction of benzenesulfonamide and their derivatives with Smyd3 using 7o2c protein, novobiocin, BAY-6035, EPZ031686 and BCI-121 drugs (Figure 1) as theoretical tools in DockingServer program (Figueroa-Valverde et al., 2021).

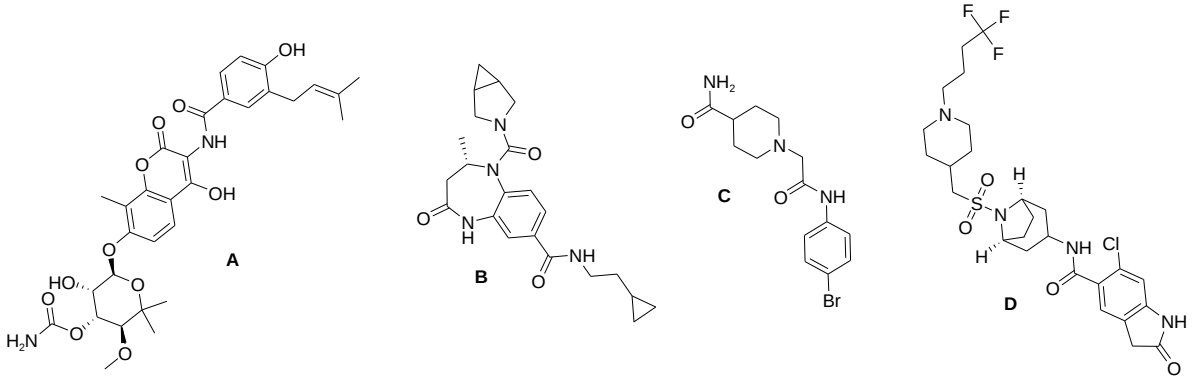


Figure 1. Chemical structure of novobiocin (**A**), BAY-6035 (**B**), EPZ031686 (**C**) and BCI-121 (**D**) drugs. Visualized on Pubchem in: https://pubchem.ncbi.nlm.nih.gov/.

2. Materials and Methods

2.1 General methodology

The chemical structure (Figure 2) of benzenesulfamide (**1**) and their derivatives (**2**-**28**) were visualized on Pubchem in: https://pubchem.ncbi.nlm.nih.gov/.

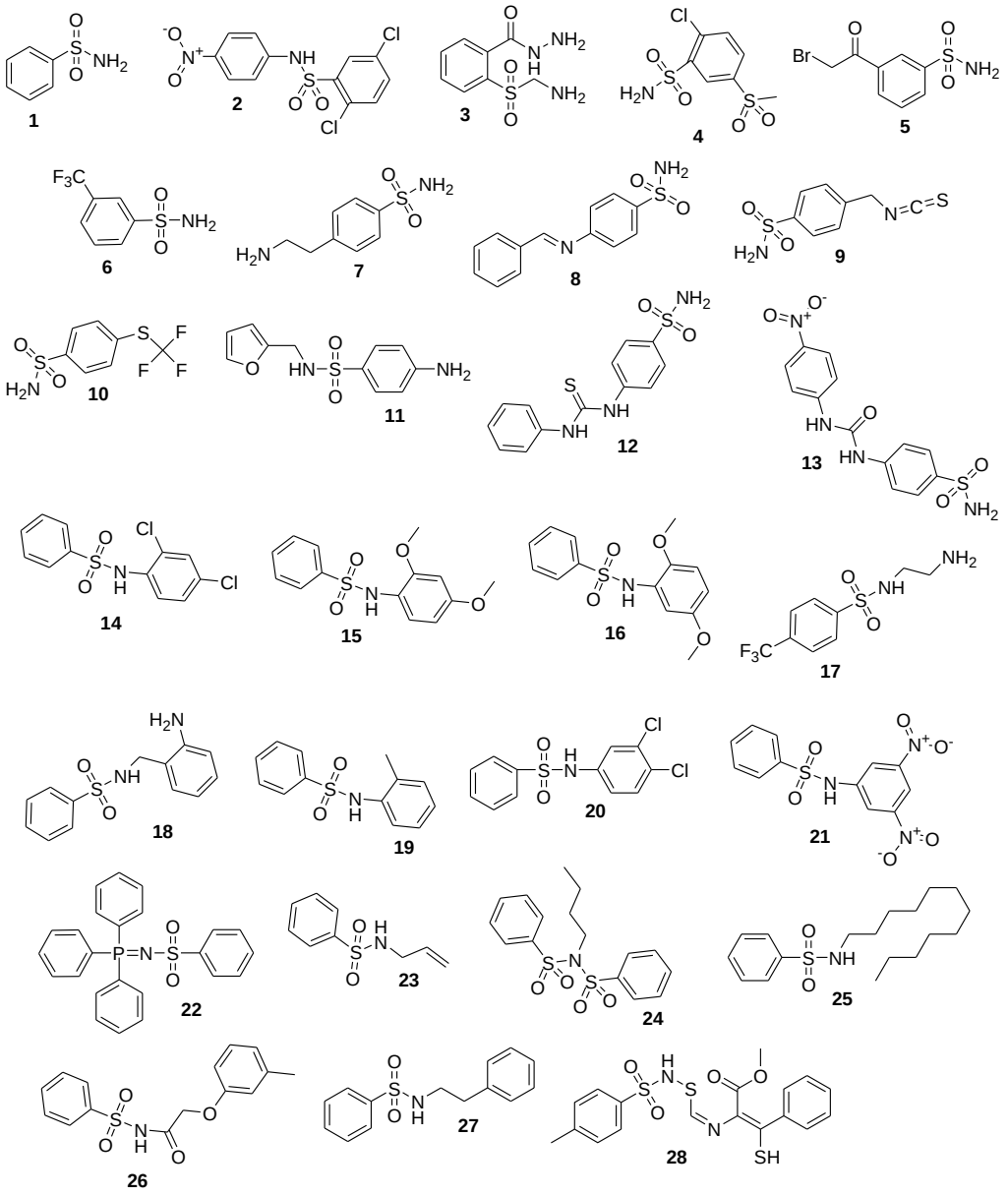


Figure 2. Structure chemical of benzenesulfonamide (**1**) and their derivatives (**2**-**28**).

1 = Benzenesulfonamide

2 = 2,5-Dichloro-N-(4-nitrophenyl)benzenesulfonamide

3 = 2-(Hydrazinocarbonyl)benzenesulfonamide

4 = 2-Chloro-5-(methylsulfonyl)benzenesulfonamide

15 = N-(2,4-dimethoxyphenyl)benzenesulfonamide

16= N-(2,5-dimethoxyphenyl)benzenesulfonamide

17 = N-(2-Aminoethyl)-4-(trifluoromethyl)benzenesulfonamide

18 = N- (2-aminophenyl)benzenesulfonamide

5 = 3-(Bromoacetyl)benzenesulfonamide

6 = 3-(Trifluoromethyl)benzenesulfonamide

7 = 4-(2-Aminoethyl)benzenesulfonamide

8 = 4-(benzylideneamino)benzenesulfonamide

9 = 4-(isothiocyanatomethyl)benzenesulfonamide

10 = 4-(tifluoromethylthio)benzenesulfonamide

11 = 4-Amino-N-(2-furylmethyl)benzenesulfo namide

12 = 4-[(Anilinocarbothioyl)amino]benzenesulfonamide

13 = 4-{[(4-Nitroanilino)carbonyl]amino}benzenesulfonamide

14 = N-(2,4-dichlorophenyl)benzenesulfonamide

19 = N-(2-methylphenyl)benzenesulfonamide

20 = N-(3,4-Dichlorophenyl)benzenesulfonamide

21 = N-(3,5-dinitrophenyl)benzenesulfonamide

22 = N-(triphenylphosphoranylidene)benzenesulfonamide

23 = N-allyl-benzenesulfonamide

24 = N-Butyl-N-(phenylsulfonyl)benzenesulfonamide

25 = N-dodecyl-benzenesulfonamide

26 = N-M-tolyloxyacetul-benzenesulfonamide

27 = N-phenethyl-benzenesulfonamide

28 = methyl (Z)-3-phenyl-2-[(Z)-[(p-tolylsulfonylamino)-sulfanyl- methylene]amino]- 3-sulfanyl-prop-2-enoate

2.2 Electronic parameters

The frontier molecular HOMO, LUMO were calculated using the Spartam´86 program (Spillane et al., 2003).

2.3 Ligand-protein

Binding of benzenesulfonamide and their derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) with Smyd3 was determined using 7o2c protein (https://doi.org/10.2210/pdb7O2C/pdb) as theoretical model (Graadi et al., 2021). In addition, to evaluate the thermodynamic parameters involved in benzenesulfonamide derivative-protein complex formation, the DockingServer program was used (Figueroa-Valverde et al., 2023).

2.4 Pharmacokinetic parameters

Pharmacokinetic factors of benzenesulfonamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) were determined using the SwissADME software (Figueroa-Valverde et al., 2023).

2.5 Toxicology evaluation

Theoretical toxicity for benzenesulfonamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) was determined using GUSAR software (Figueroa-Valverde et al., 2022).

3. Results and Discussion

3.1 Electronic parameters

In the Table 1 and Figure 3 nd 4 are showed some physicochemical parameters of benzenesulfonamide (**1**) and their derivatives (**2-28**).

Table 1. Physicochemical parameters for benzenesulfonamide (**1**) and their derivatives (**2**-**28**) involved in the chemical structure. The values were calculated using Spartan software.

Compound	HOMO	LUMO	HOMO-LUMO gap	μ	PSA	Pol	HBD	HBA
1	-9.81	2.72	12.53	3.95	61.31	49.99	1	4
2	-10.18	-0.06	10.12	9.34	84.52	61.56	1	7
3	-9.71	1.99	11.70	5.33	108.80	55.13	2	7
4	-10.48	1.91	12.39	3.16	94.42	55.41	1	7
5	-10.18	1.53	11.71	1.61	75.60	54.34	1	5
6	-10.51	1.99	12.50	4.18	61.31	52.64	1	4
7	-9.61	2.80	12.41	3.43	87.78	53.87	1	5
8	-8.87	2.11	10.98	6.56	68.19	59.22	1	5
9	-9.75	2.05	11.80	5.46	68.36	54.70	1	6
10	-10.30	1.68	11.98	4.42	61.32	54.30	1	5
11	-8.67	3.18	11.85	6.14	79.24	57.74	2	6
12	-8.46	1.84	10.30	2.30	78.69	61.82	3	7
13	-9.40	-0.11	9.51	1.84	133.28	63.05	3	10
14	-9.38	2.45	11.83	4.81	45.43	59.32	1	4
15	-8.60	2.90	11.50	6.25	58.42	61.64	1	6
16	-8.50	2.92	11.42	5.99	58.31	61.66	1	6
17	-10.43	1.66	12.09	4.25	71.82	56.81	1	5
18	-8.14	2.59	10.73	5.23	68.94	59.74	2	5
19	-8.93	2.67	11.60	6,44	44.89	58.65	1	4
20	-9.35	2.32	11.67	6.43	46.41	59.41	1	4
21	-10.28	-0.84	9.44	6.00	127.65	61.37	1	10
22	-9.23	2.54	11.77	7.99	38.82	72.64	0	4
23	-9.77	2.71	12.48	4.23	46.25	54.35	1	4
24	-9.76	2.44	12.20	7.62	65.26	65.80	0	7
25	-9.73	2.77	12.50	5.22	46.24	68.03	1	4
26	-8.62	2.60	11.22	4.95	64.87	62.67	1	6
27	-9.09	2.71	11.80	4.12	46.63	60.18	1	4
28	-8.32	2.28	10.60	2.95	68.89	70.42	2	8

μ = Dipole moment; PSA = Polar surface area ; Pol = Polarizability; HBD = Hidrogen bond donor; HBA = Hidrogem bond acceptor

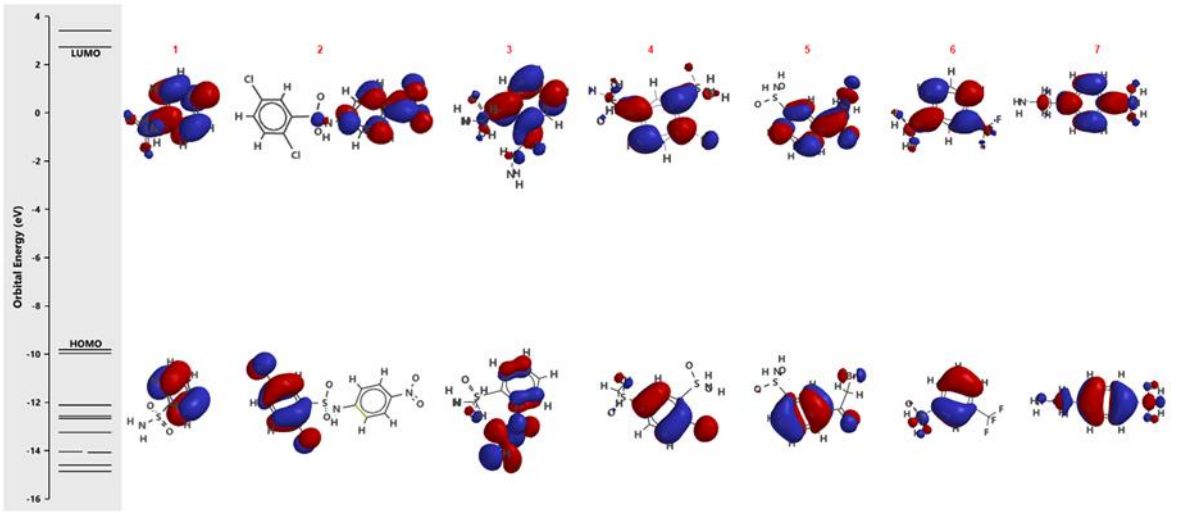
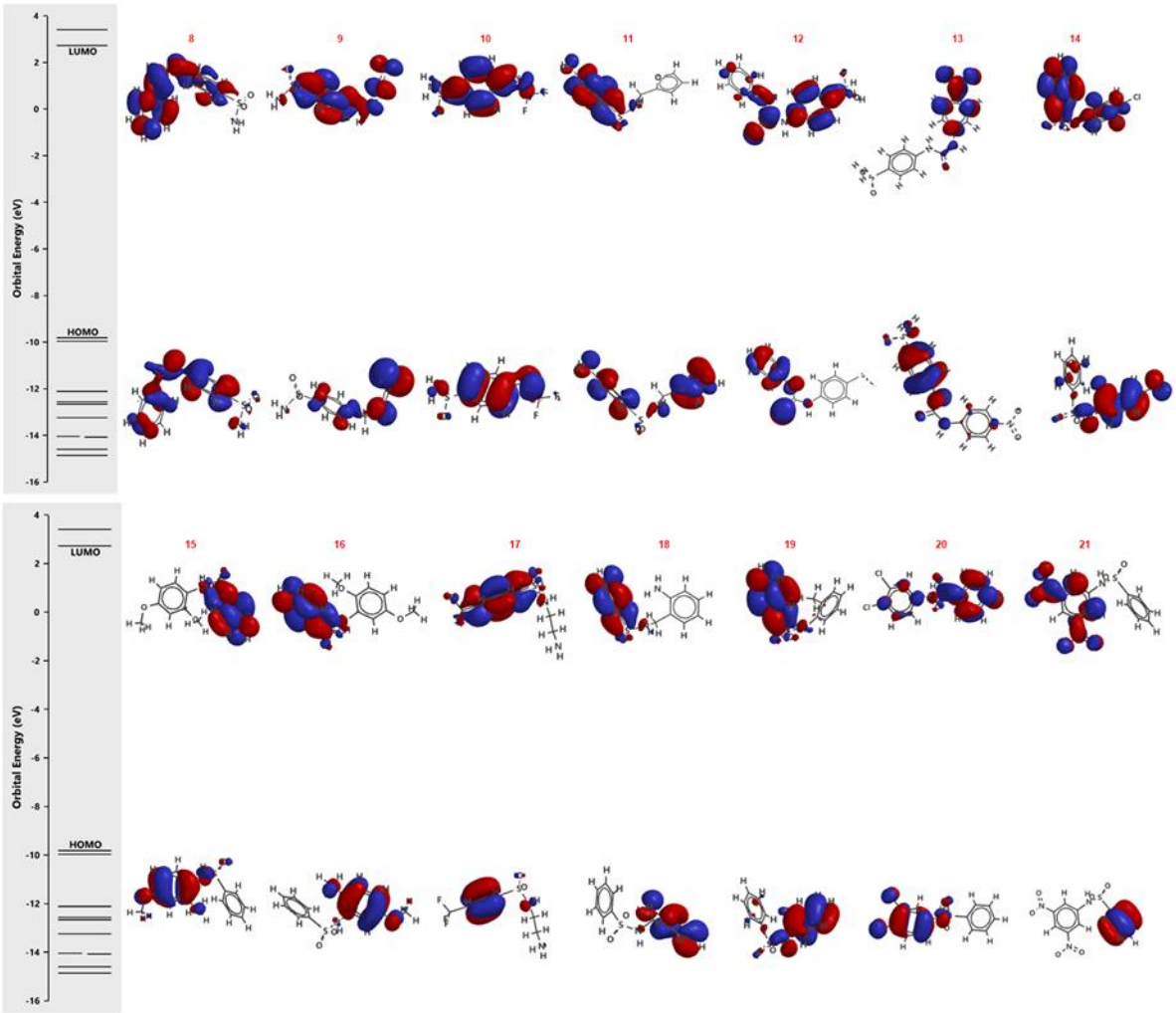


Figure 3. HOMO-LUMO gap for benzenesulfonamide (**1**) and their derivatives (**2**-**7**). Visualized with Spartan´86 program.



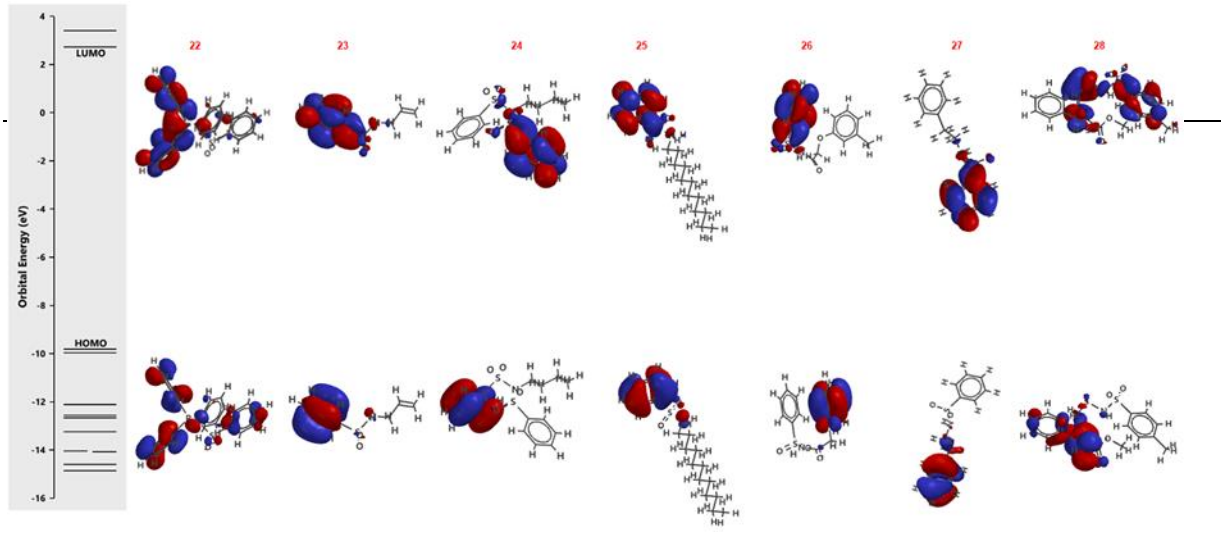


Figure 4. HOMO-LUMO gap for benzenesulfonamide derivatives (**8**-**28**). Visualized with Spartan´86 program.

3.2 Ligand-protein complex

Table 2 shows the different aminoacid residues involved in the interaction of benzenesulfonamide and its derivatives (compounds **2-28**) with 7o2c protein surface. Other data suggest that some aminoacid residues of 7o2c protein surface can interact with novobiocin, BAY-6035, EPZ031686 and BCI-121 drugs.

Table 2. Aminoacid residues involved in theoretical interaction of Novobiocin, BAY-6035, BCI-121, benzenesulfonamide (BS) and benzenesulfonamide derivative (1-27) with 7o2c protein surface.

Compound	Aminoacid Residues
Novobiocin	Thr_{184}; Cys_{186}; Glu_{192}; Ile_{214}; Ile_{237}; Cys_{238}; Asp_{241}; Tyr_{257}; Glu_{294}; Lys_{297}
BAY-6035	Phe_{183}; Ser_{213}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{239}; Met_{242}; Phe_{362}; His_{366}; Pro_{367}; Val_{368}
BCI-121	Asn_{181}; Ser_{182}; Phe_{183}; Thr_{184}; Ser_{202}; Leu_{204}; Tyr_{239}; Met_{242}; Phe_{362}; His_{366}; pro_{367}; Val_{368}
EPZ031686	Phe_{183}; Thr_{184}; Ile_{214}; Ile_{237}; Tyr_{239}; Asp_{241}; Gln_{252}; Gln_{256}; Tyr_{257}; His_{366}; Val_{368}
1	Phe_{183}; Ile_{237}; Tyr_{239}; Tyr_{257}
2	Ser_{182}; Thr_{184}; Met_{190}; Ile_{214}; Phe_{216}; Ile_{237}; Cys_{238}; Tyr_{239}; Tyr_{257}; Pro_{367}
3	Cys_{186}; Ser_{213}; Ile_{214}; Phe_{216}; Cys_{238}; Tyr_{239}; His_{366}
4	Phe_{183}; Thr_{184}; Ser_{213}; Ile_{214}; Ile_{237}; Cys_{238}; Leu_{240}; His_{366}
5	Thr_{184}; Ser_{213}; Ile_{214}; Ile_{237}; His_{366}; Pro_{367}
6	Phe_{183}; Thr_{184}; Ser_{213}; Ile_{214}; Phe_{216}; Tyr_{239}; His_{366};Pro_{367}
7	Phe_{183}; Thr_{184}; Ser_{202}; Leu_{204}; Ile_{214}; Ile_{237}; Tyr_{239}; Tyr_{257}
8	Phe_{183}; Thr_{184}; Cys_{186}; Ser_{213}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{239}; Tyr_{257}
9	Asn_{181}; Thr_{184}; Tyr_{239}; Tyr_{257}
10	Thr_{184}; Cys_{186}; Pro_{210}; Cys_{212}; Ser_{213}; Ile_{214}; Phe_{216}; Ile_{237}; Cys_{238}; His_{366}
11	Phe_{183}; Thr_{184}; Pro_{210}; Cys_{212}; Ser_{213}; Ile_{214}; Ile_{237}; Cys_{238}; His_{366}
12	Ser_{182}, Phe_{183}; Thr_{184}; Cys_{186}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{239}; Tyr_{257}
13	Asn_{181}; Phe_{183}; Thr_{184}; Cys_{186}; Met_{190}; Ser_{202}; Ile_{214}; Ile_{237}; Tyr_{239}; Tyr_{257}; Val_{368}
14	Phe_{183}; Thr_{184}; Cys_{186}; Pro_{210}; Ser_{213}; Ile_{214}; Phe_{216}; Cys_{238}; His_{366}; Pro_{367}
15	Met_{190}; Ser_{213}; Ile_{214}; Cys_{238}; His_{366}; Pro_{367}; Val_{368}
16	Phe_{183}; Thr_{184}; Ser_{213}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{239}; Pro_{367}
17	Cys_{186}; Met_{190}; Pro_{210}; Cys_{212}; Ser_{213}; Ile_{214}; Val_{215}; Phe_{216}; Ile_{237}; Cys_{238}; His_{366}
18	Ile_{214}; Ile_{237}; Cys_{238}; Tyr_{239}; Tyr_{257}; Pro_{367}
19	Cys_{186}; Met_{190}; Ser_{213}; Ile_{214}; Phe_{216}; His_{366}; Pro_{367}; Val_{368}
20	Ser_{182}, Phe_{183}; Thr_{184}; Cys_{186}; Ile_{214}; Phe_{216}; Tyr_{239}; Tyr_{257}

21	Thr_{184}; Ser_{213}; Ile_{214}; Ile_{237}; Cys_{238}; Tyr_{239}; Met_{242}; Tyr_{257}; Phe_{362}; His_{366}
22	Thr_{184}; Met_{190} Ile_{214}; Phe_{216}; Ile_{237}; Cys_{238}; Met_{242}; Phe_{362}; His_{366}; Val_{368}
23	Phe_{183}; Ile_{214}; Ile_{237}; Tyr_{239}; Tyr_{257}
24	Cys_{186}; Met_{190}; Pro_{210}; Ser_{213}; Ile_{214}; Ile_{237}; His_{366}; Pro_{367}; Val_{368}
25	Phe_{183}; Cys_{186}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{257}; Pro_{267}
26	Phe_{183}; Thr_{184}; Ile_{214}; Phe_{216}; Ile_{237}; Tyr_{239}; Tyr_{257}
27	Phe_{183}; Thr_{184}; Pro_{210}; Ser_{213}; Ile_{214}; Ile_{237}; Cys_{238}; Tyr_{257}; His_{366}
28	Cys_{186}; Ser_{213}; Ile_{214}; Phe_{216}; Ile_{237}; Asp_{241}; His_{366}; Pro_{367}; Val_{368}

3.2 Thermodynamic parameters

The theoretical results displayed differences in the energy levels involved in the interaction of bencenesulfonamide (**1**) and its derivatives (**2**-**28**) with Smy3 (7o2c protein) compared with Novobiocin, BAY-6035, BCI-121, and EPZ031686 drugs (Table 3). In addition, inhibition constant for benzenesulfonamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) was lower compared with Novobiocin, EPZ031686, BAY-6035, BCI-121 and benzenesulfonamide.

Table 3. Thermodynamic parameters involved in the interaction of Novobiocin, BAY-6035, BCI-121, EPZ031686, benzenesulfonamide (**1**) and their derivative (**2**-**28**) with 7o2c protein surface.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
Novobiocin	-6.55	85.63	-7.78	0.00	-7.78	1265.70
BAY-6035	-9.08	221.13	-10.20	-0.02	-10.22	981.15
BCI-121	-8.66	445.25	-8.93	-0.54	-9.47	716.99
EPZ031686	-9.78	67.67	-11.42	-0.41	-11.83	1080.45
1	-5.85	51.54	-6.36	-0.08	-6.44	421.07
2	-7.86	1.75	-8.99	0.27	-8.71	699.77
3	-6.77	10.88	-5.21	-0.05	-5.26	556.22
4	-6.27	25.35	-7.03	-0.10	-7.12	580.23
5	-5.53	88.18	-6.60	-0.10	-6.70	526.10
6	-5.90	47.09	-6.73	-0.07	-6.80	513.18
7	-7.00	7.33	-7.61	-0.88	-8-49	527.15
8	-7.36	4.06	-8.51	-0.04	-8.55	663.63
9	-6.05	36.75	-7.45	-0.06	-7.51	560.74
10	-8.60	14.57	-7.75	-0.07	-7.82	526.78
11	-6.28	24.72	-6.79	-0.01	-6.80	648.21
12	-8.45	635.71	-9.06	-0.04	-9.90	730.18
13	-7.85	1.77	-9.47	0.00	-9.47	784.05
14	-7.39	3.84	-8.09	0.00	-8.09	713.07
15	-6.41	19.99	-6.77	-0.03	-6.80	705.40
16	-5.64	73.29	-7.26	0.29	-6.98	728.48
17	-7.02	7.18	-6.95	-0.31	-7.26	579.21
18	-6.77	10.88	-7.00	-0.05	-7.05	687.37
19	-6.37	21.30	-6.66	-0.04	-6.70	602.66

20	-7.33	4.22	-7.91	-0.02	-7.92	734.84
21	-7.79	1.94	-9.11	-0.12	-9.23	713.35
22	-8.38	714.36	-10.53	0.04	-10.49	888.43
23	-5.75	60.88	-6.86	-0.05	-6.91	516.45
24	-7.16	5.69	-8.63	0.01	-8.63	754.69
25	-6.59	80.54	-8.05	0.00	-8.04	809.77
26	-6.43	19.28	-7.81	0.34	-7.47	748.99
27	-6.75	11.24	-7.99	-0.03	-8.02	671.64
28	-6.97	7.75	-7.72	-0.01	-7.73	860.06

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.*

3.3 Pharmacokinetic evaluation

The results (Table 4) show differences in gastrointestinal (GI) absorption rate for either bencenesulfonamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28). In addition, The CYPs (Cytochrome P450) involved in the pharmacokinetic process were different.

Table 4. Theorethical Pharmacokinetic parameters involved in decernotinib (I), tofacitinib (II), benzenesulfamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28).

Parameter	**2**	**7**	**8**	**13**	**14**	**17**	**20**	**21**	**24**	**28**
GI absorption	High	High	High	Low	High	High	High	Low	High	High
BBB permeant	No	No	No	No	Yes	No	Yes	No	No	No
P-gp sustrate	No	No	No	No	No	No	No	Yes	No	No
CYP1A2 inhibitor	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No
CYP2C9 inhibitor	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	Yes	Yes
CYP3A4 inhibitor	Yes	No	No	No	Yes	No	Yes	No	Yes	No
Consensus $LogP_{O/W}$	2.67	0.28	1.88	0.63	3.28	1.51	3.22	0.94	2.94	4.50

Note: GI = Gastrointestinal; BBB = Blood-Brain-Barrier; P-gp = P-glycoprotein; CYP = Cytochrome P450; $LogP_{O}/_{W}$ = Octanol-water partition coefficient.

3.4 Toxicology analysis

The results of theorethical evaluation of toxicity for bencenesulfonamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) are showed in the Table 5. These data indicate that toxicity could depend of dose administered for bencenesulfonamide derivatives through of different routes of administration.

Table 5. Theoretical toxicity analysis produced by bencenesulfonamide derivatives.

Compound	Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
2	26.83.00	686.70	1896.00	1031.00
7	303.70	586.80	2100.00	321.70
8	730.80	830.80	2068.00	1669.00
13	1395.00	890.30	2371.00	1167.00
14	1453.00	782.60	2677.00	1727.00
17	607.30	1203.00	805.00	857.20
20	1148.00	942.30	2415.00	1263.00
21	1788.00	1421.00	2391.00	515.80
24	411.20	223.90	2949.00	1707.00
28	954.70	463.90	1549.00	1660.00

Note: IP - Intraperitoneal route of administration; IV - Intravenous route of administration; Oral - Oral route of administration; SC - Subcutaneous route of administration

4. Discussion

There are several studies which indicate that some Smy3 inhibitors can be used to try slow cancer cells growth (Mitchell et al., 2016; Gradl et al., 2021); however, the interaction of these compounds with Smy3 is not clear. For this reason, a theoretical study was conducted to evaluate the possibility that benzenesulfamide and their derivatives could interact with Smy3 surface as follows:

4.1 Electronic parameters.

Some data indicate that frontier electron density can been used for predicting the most reactive position in π-electron systems and several types of reactions in conjugated system. It is important to mention that highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) values and their energy gap can reflect the chemical activity of a molecule (Prasad et al., 2008). In this way, some methods such as density functional teory (matunova et al., 2019), Multiwfn software (Manoj et al., 2022) and Gaussian software (Rijal et al., 2022) have been used to evaluate frontier molecular orbitals (HOMO-LUMO gap) of some compounds (Srivastava et al., 2005; Ferro et al., 2006).

In Figure 3 shows the energy levels for benzenesulfonamide (1) and their derivatives (2-28). Besides, other data displayed that the HOMO-LUMO gap values were > 12 for bencenesulfonamide and their derivatives (2, 4, 6, 7, 23 and 25) comparade with 3, 5, 8-22, 24 and 26-28; this phenomenon is translated as higher stability of molecules.

4.1 Ligand-protein complex.

In the literature, there are some computer modeling such as DOCK (Mosquera-yuqui et al., 2022), GROMAS (Qu et al., 2022), SFs (Shen et al., 2020), Swarm Dock (Torchata et al., 2020 to evaluate the formation of the ligand-protein complex. The aim of this research was to evaluate the interaction of benznesulfonamide and their derivatives (compounds **1** to **28**) with the Smyd3 protein surface using the 7o2c protein, novobiocin, BAY-6035, BCI-121 and EPZ031686 as theoretical tools in DockingServer software.

The results display different aminoacid residues involved in the interaction of benzenesulfonamide and their derivatives with 7o2c protein surface compared with novobiocin, BAY-6035, BCI-121 and EPZ031686. For example, for compound **2** (Met_{190}); for **7** (Ser_{202}); for **13** (Met_{190} and Ser_{202}); for **17** (Met_{190}, Pro_{210}, Cys_{212}; Val_{215} and Cys_{238}); for **20** (Ser_{182}); for **21** (Ser_{213}); for **24** (Met_{190}, Pro_{210} and Ser_{202}) and **28** (Ser_{213} and Asp_{241}). This phenomenon could be due to differences in their chemical structure.

4.2 Bond energies evaluation

Several reports have showed that protein-ligand complex formation could depend of several thermodynamic parameters (Figueroa-Valverde et al., 2023). For this reason, in this study some 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 were determined using the DockingServer model. The results shows differences in energies values for benzenesulfonamide (**1**) and their derivatives (**2**-**28**), novobiocin, BAY-6035, BCI-121 and EPZ031686.

In addition, inhibition constant (Ki) for benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 was very lower compared with novobiocin, BAY-6035, BCI-121 and EPZ031686. This results suggest that benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 could act as Smyd3 inhibitors and this phenomenon could be translated as decrease in cancer cells growth. Nevertheless, it is noteworthy that some pharmacokinetic factors could determinate the biological activity of this benzenesulfonamide derivatives on Smyd3.

4.3 Pharmacokinetic evaluation.

In the literature, there are some methods to predict different pharmacokinetic processes involved in the administration of several drugs such as Phoenix WinNonlin (Zhao et al., 2022), PKMP (Shah, 2022), CertaraPhonix (Li et al., 2020) and SwissADME (Mekki et al., 2022). For this reason, in this research, some pharmacokinetic factors for benzenesulfamide derivatives (2, 7, 8, 13, 14, 17, 20, 21, 24 and 28) were evaluated using SwissADME software. The results suggest differences in gastrointestinal absorption and metabolism, which involve several cytochrome P450 systems. This phenomenon could be to differences in the chemical structure of each benzenesulfonamide derivative and their degree of lipophilicity ($LogP_{O/W}$).

4.4 Theoretical toxicity

Several methods such as ProTox-II (Banerjee and Ulker, 2022), STopTox (Abishad et al., 2021), ToxAlert (Perez et al., 2001), TEST (He et al., 2022) have been used to evaluate the toxicity degree. Analyzing these data, in this investigation the possible theoretical toxicity produced by benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 was determined using the GUSAR software (Karpenko et al., 2022). The results suggest that benzenesulfonamide 21 requires higher doses via intraperitoneal and intravenous to produce toxicity compared to benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 24 and 28. However, the compound 24 requires higher doses to exert toxicity via oral and subcutaneous compared with 2, 7, 8, 13, 14, 17, 20, 21 and 28. These results could be due to the different administration routes or to differences in lipophilicity degree of each benzenesulfonamide derivative.

5. Conclusions

This research reports the interaction of benzenesulfonamide and their derivatives with Smyd3. The results showed that the benzenesulfonamide derivatives 2, 7, 8, 13, 14, 17, 20, 21, 24 and 28 could be a good alternative as Smyd3inhibitors and this phenomenon could translate into a decrease in cancer cell growth. However, it is worth mentioning that experimental data is required to support this hypothesis.

6. Authors' Contributions

Substantial contribution to research design: Figueroa-Valverde Lauro and Diaz-Cedillo Francisco; Acquisition, analysis and interpretation of data: Figueroa-Valverde Lauro L, Diaz-Cedillo Francisco, Alvarez-Ramirez Magdalena, Rosas-Nexticapa Marcela, Lopez-Ramos Maria and Mateu-Armand Virginia. 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

Abishad, P., Niveditha, P., Unni, V., Vergi, J., Kurkure, N., Chaudhari, S., Rawool, D. B., & Barduddhe, S. (2021). In silico molecular docking and *in vitro* antimicrobial efficacy of phytochemicals against multi-drug-resistant enteroaggregative *Escherichia coli* and non-typhoidal *Salmonella* spp. *Gut Pathogens*, 13(1), 1-11. https://doi.org/10.1186/s13099-021-00443-3

Asuthkar, S., Venkataraman, S., Avilala, J., Shishido, K., Vibhakar, R., & Veo, B. (2022). SMYD3 promotes cell cycle progression by inducing cyclin D3 transcription and stabilizing the cyclin D1 protein in medulloblastoma. *Cancers*, 14(7), 1673. https://doi.org/10.3390/cancers14071673

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 Mechanism and Methods*, 32(7), 542-548. https://doi.org/10.1080/15376516.2022.2053623

Deng, X., Li, M., Deng, S., & Wang, L. (2022). Hybrid gene, selection approach using XGBoost and multi-objective genetic algorithm for cancer classification. *Medical & Biological Engenineering & Computing*, 60(3), 663-681.

Fenizia, C., Bottino, C., Corbetta, S., Fittipaldi, R., Floris, P., & Gaudenzi, G. (2019). SMYD3 promotes the epithelial–mesenchymal transition in breast cancer. *Nucleic Acids Resesearch*, 47(3), 1278-1293. https://doi.org/10.1093/nar/gky1221

Ferro, N., Tacoronte J, Reinard, T., Bultinck, P., Montero, L. (2006). Structure–activity analysis on ecdysteroids: A structural and quantum chemical approach based on two biological systems. *Journal of Molecular Structure: THEOCHEM*, 758(2-3), 263-274. https://doi.org/10.1016/j.theochem.2005.10.027

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., Alvarez-Ramirez, M., Lopez-Ramos, M., & Mateu-Armand V. (2022). Theoretical evaluation of interaction of some dibenzo derivatives on both androgen receptor and 5a-reductase enzyme. Clinical *Cancer Investigation Journal*, 11(5), 11-16. https://doi.org/10.51847/fIVMfELA7I

Figueroa-Valverde, L., Rosas-Nexticapa, M., Alvarez-Ramirez, M., López-Ramos, M., Díaz-Cedillo, F., & Mateu-Armad, M. (2023). Evaluation of Biological Activity Exerted by Dibenzo [b, e] Thiophene-11 (6H)-One on Left Ventricular Pressure Using an Isolated Rat Heart Model. *Drug Research*, 263-270. https://doi.org/10.1055/a-1995-6351

Figueroa-Valverde, L., Rosas-Nexticapa, M., Montserrat, M., Díaz-Cedillo, F., López-Ramos, M. & Alvarez-Ramirez, M. (2023). 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, 266. https://doi.org/10.33263/BRIAC133.266

Giakountis, A., Moulos, P., Sarris, M., Hatzis, P., & Talianidis, I. (2017). Smyd3-associated regulatory pathways in cancer. *Seminars in Cancer Biology*, 42, 70-80. https://doi.org/10.1016/j.semcancer.2016.08.008

Gradl, S., Steuber, H., Weiske, J., Szewczyk, M., Schmees, N., & Siegel, S. (2021). Discovery of the SMYD3 inhibitor BAY-6035 using thermal shift assay (TSA)-based high-throughput screening. *SLAS DISCOVERY: Advancing the Science of Drug Discovery*, 26(8), 947-960. https://doi.org/10.1177/24725552211019

Hanahan, D. (2022). Hallmarks of cancer: new dimensions. *Cancer Discovery*, 12(1), 31-46. https://doi.org/10.1158/2159-8290.CD-21-1059

He, Y., Ca, Y., Fan, S., Meng, T., Zhang, Y., & Li, X. (2022) Hydroxyl radicals can significantly influence the toxicity of ofloxacin transformation products during ozonation. *Journal of Hazardous Materials*, 438, 129503. https://doi.org/10.1016/j.jhazmat.2022.129503

Hecht, S., & Hatsukami, D. (2022). Smokeless tobacco and cigarette smoking: chemical mechanisms and cancer prevention. *Nature Review Cancer*, 22(3), 143-155.

Hol, J., Kuiper, R., Van-Dijk, F., Waanders, E., Van-Peer S. E., Koudijs, M. J., Bladergroen, R., van Reijmersdal, S. V., Morgado, L. M., Bliek, J., Lombardi, M. P., Hopman, S., Drost, J., Krijger, R. R., van den Heuvel-Eibrink, M. M., & Jongmans, M. C. J. (2022). Prevalence of (Epi) genetic predisposing factors in A 5-year unselected national Wilms tumor cohort: a comprehensive clinical and genomic characterization. *Journal of Clinical Oncology*, 40(17), 1892-1902. https://doi.org/10.1200%2FJCO.21.02510

Jukarainen, S., Kiiskinen, T., Kuitunen, S., Havulinna, A., Karjalainen, J., & Cordioli M. (2022). Genetic risk factors have a substantial impact on healthy life years. *Nature Medicine*, 28(9), 1893-1901.

Karpenko, Y., Hunchak, Y., Gutyj, B., Hunchak, A., Parchenko, M., & Parchenko, V. (2022). Advanced research for physico-chemical properties and parameters of toxicity piperazinium 2-((5-(furan-2-YL)-4-phenyl-4H-1, 2, 4-triazol-3-YL) THIO) acetate. *ScienceRise:Pharmaceutical Science*, 2(36): 18-25.

Leinhart, K., & Brown, M. (2011). SET/MYND lysine methyltransferases regulate gene transcription and protein activity. *Genes*, 2(1), 210-218. https://doi.org/10.3390/ genes2010210

Li, X., Wang, L., Wang, L., Yu, J., Lu, G., & Zhao W. (2020). Overcoming therapeutic failure in osteosarcoma via Apatinib-encapulated hydrophobic poly (ester amide) nanoparticles. *Biomaterials Science*, 2020; 8(21), 5888-5899.

Liu, D., Liu, M., Wang, W., Li, X., Shi, E., & Zhang, C. (2023). SMYD Family Members Serve as Potential Prognostic Markers and Correlate with Immune Infiltrates in Gastric Cancer. *Journal of Oncology*, 1-16. https://doi.org/10.1155/2023/6032864

Luo, X., Zou, J., Wang, S,, Zhang, T., & Xi, T. (2010). Novobiocin decreases SMYD3 expression and inhibits the migration of MDA-MB-231 human breast cancer cells. *IUBMB Life*, 62(3), 194-199. https://doi.org/10.1002/iub.288

Manoj, K., Elangovan, N., & Chandrasekar, S. (2022). Synthesis, XRD, hirshfeld surface analysis, ESP, HOMO-LUMO, quantum chemical modeling and anticancer activity of di (p-methyl benzyl)(dibromo)(1, 10-phenanthroline) tin (IV) complex. *Inorganic Chemistry Communications*, 139, 109324. https://doi.org/10.1016/j.inoche.2022.109324

Matunová, V., & Rezek, B. (2019). DFT calculations reveal pronounced HOMO–LUMO spatial separation in polypyrrole–nanodiamond systems. *Physical Chemistry Chemical Physics*, 21(21), 11033-11042. https://doi.org/10.1039/C8CP07622G

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.

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

Mitchell, L., Boriack-Sjodin, P., Smith, S., Thomenius, M., Rioux, N., & Munchhof. (2016). Novel oxindole sulfonamides and sulfamides: EPZ031686, the first orally bioavailable small molecule SMYD3 inhibitor. *Medicinal Chemistry Letters*, 7(2), 134-138. https://doi.org/10.1021/acsmedchemlett.5b00272

Mosquera-Yuqui, F., Lopez-Guerra, N., & Moncayo-Palacio, E. A. (2022). Targeting the 3CLpro and RdRp of SARS-CoV-2 with phytochemicals from medicinal plants of the Andean Region: molecular docking and molecular dynamics simulations. *Journal of Biomolecular Structure and Dynamics*, 40(5), 2010-2023. https://doi.org/10.1080/07391102.2020.1835716

Pasha, F., Srivastava, H., & Singh, P. (2005). Comparative QSAR study of phenol derivatives with the help of density functional theory. *Bioorganic Medicinal Chemistry*, 13(24), 6823-6829. https://doi.org/10.1016/j.bmc. 2005.07.064

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

Peserico, A., Germani, A., Sanese, P., Barbosa, A., Di-Virgilio, V., & Fittipaldi, R. (2015). A SMYD3

Small-Molecule Inhibitor Impairing Cancer Cell Growth. *Journal of Cellular Physiology*, 230, 2447–2460. https://doi.org/10.1002/jcp.24975.

Phan, D., Rasmussen, T., Nakagawa, O., McAnally, J., Gottlieb, P., & Tucker, P. (2005). BOP, a regulator of right ventricular heart development, is a direct transcriptional target of MEF2C in the developing heart. *Development and Dissease*, 132(11), 2669-2678. https://doi.org/10.1242/dev.01849

Prasad, Y., Kumar, P., Smiles, D., & Babu, P. (2008). QSAR studies on chalcone derivatives as antibacterial agents against Bacillus pumilis. *Arkivoc*, 11: 266-276.

Rijal, R., Lamichhane, H., & Pudasainee, K. (2022). Molecular structure, homo-lumo analysis and vibrational spectroscopy of the cancer healing pro-drug temozolomide based on dft calculations. *AIMS Biophysics*, 9, 208-220.

Qu, X., Dong, L., Zhang, J., Si, Y., & Wang, B. (2022). Systematic Improvement of the Performance of Machine Learning Scoring Functions by Incorporating Features of Protein-Bound Water Molecules. *Journal of Chemical Information and Modeling*, 62(18), 4369-4379. https://doi.org/10.1021/acs.jcim.2c00916

Shah, A. (2022). Pharmacokinetic Modeling Program (PKMP): A Software for PK/PD Data Analysis. In *Pharmacokinetics and Pharmacodynamics of Nanoparticulate Drug Delivery Systems*, pp. 101-139. Cham: Springer International Publishing.

Shah, D., & Bentrem, D. (2022). Environmental and genetic risk factors for gastric cancer. *Journal of Surgical Oncology*, 125(7), 1096-1103. https://doi.org/10.1002/jso.26869

Shen, C., Ding, J., Wang, Z., Cao, D., Ding, X, & Hou, T. (2020). From machine learning to deep learning: Advances in scoring functions for protein–ligand docking. *Wires Computational Molecular Science*, 10(1), 1-23. https://doi.org/10.1002/wcms.1429

Song, J., Liu, Y., Chen, Q., Yang, J., Jiang, Z, Zhang, H., Liu, Z., & Jin, B. (2019). Expression patterns and the prognostic value of the SMYD family members in human breast carcinoma using integrative bioinformatics analysis. *Oncology Letters*, 17(4), 3851-3861. https://doi.org/10.3892/ol.2019.10054

Spillane, W., Kelly, L., Feeney, B., Drew, M., & Hattotuwagama, C. (2003). Synthesis of heterosulfamates. Search for structure-taste relationships. *Arkivoc*, 7, 297-309. https://www.arkat-usa.org/get-file.php?fileid=19751

Stopsack, K., Nandakumar, S., Arora, K., Nguyen, B., Vasselman, S., Nweji, B., mCbride, S. M., Morris, M. J., Rathkof, D. E., Slovin, S. F., Danila, D. C., Autio, K. A., Scher, H. I., Mucci, L. A., Solit, D. B., Gönen, M., Chen, Y., Berger, M. F., Schultz, N., Abida, W., & Kantoff, P. W. (2022). Differences in prostate cancer genomes by self-reported race: contributions of genetic ancestry, modifiable cancer risk factors, and clinical factors. *Clinical Cancer Research*, 28(2), 318-326. https://doi.org/10.1158/1078-0432.CCR-21-2577

Tian, T., Li, J., Shi, D., Zen, Y., Yu, B., & Li, X. (2022). SMYD3 promotes aerobic glycolysis in diffuse large B-cell lymphoma via H3K4me3-mediated PKM2 transcription. *Cell Death & Disease*, 13(9), 763. https://doi.org/10.1038/s41419-022-05208-7

Torchala, M., Gerguri, T., Chaleil, R. A., Gordon, P., Russell, F., Keshani, M., & Bates, P. A. (2020). Enhanced sampling of protein conformational states for dynamic cross-docking within the protein-protein docking server SwarmDock. *Proteins: Structure, Function, and Bioinformatics*, 88(8), 962-972. https://publons.com/publon/10.1002/prot.25851.

Wang, L., Du, M., Wang, K., Khandpur, N., Rossato, S. L., Drouin-Chartier., j-p., Steele, E. M., Giovannucci, E., Song, M., Zhang, F. F. (2022). Association of ultra-processed food consumption with colorectal cancer risk among men and women: results from three prospective US cohort studies. *The BMJ*, 378. https://doi.org/10.1136/bmj-2021-068921

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

Yang, Y., Qiu, R., Zhao, S., Shen, L., Tang, B., Weng, Q., Xu, Z., Zheng, L., Chen, W., Shu, G., Wang, Y., Zhao, Z., Chen, M., & Ji, J. (2022). SMYD3 associates with the NuRD (MTA1/2) complex to regulate transcription and promote proliferation and invasiveness in hepatocellular carcinoma cells. *BMC Biology*, 20(1), 20-22294. https://doi.org/10.1186/s12915-022-01499-6

Yang, Z., Liu, F., Li, Z., Liu, N., Yao, X., Zhou, Y., Zhang, L., Jiang, P., Liu, H., Kong, L., Lang, C., Xu, X., Jia,

J., Nakajima, T., Gu, W., Zheng, L., & Zhang, Z. (2023). Histone lysine methyltransferase SMYD3 promotes oral squamous cell carcinoma tumorigenesis via H3K4me3-mediated HMGA2 transcription. *Clinical Epigigenetics*, 15(1), 1-21. https://doi.org/10.1186/s13148-023-01506-9

Ye, W., Shen, C., Xiong, G. L., Ding, J., Lu, A., Hou, T., & Cao, D. (2020). Improving docking-based virtual screening ability by integrating multiple energy auxiliary terms from molecular docking scoring. *Journal of Chemical Information and Modeling*, 60(9), 4216-4230. https://doi.org/10.1021/acs.jcim.9b00977

Yoo, J. E., Han, K., Shin, D. W., Kim, D. W., 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. *Journal American Medical Association*, 5(8), 1-14. doi:10.1001/jamanetworkopen.2022.28544

Zhao, Y., Chen, P., Dou, L., Li, F., L., M., Xu, L., Chen, J., Jia, M., Huang, S., Wang, N., Luan, S., Yang, J., Bai, N., & Liu, D. (2022). Co-administration with voriconazole doubles the exposure of ruxolitinib in patients with hematological malignancies. *Drug Design, Development and Therapy*, 16, 817-825. https://www.tandfonline.com/doi/full/10.2147/DDDT.S354270

Funding

Not applicable.

Intitutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.