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AI Prediction of the Physicochemical Structural Profile Required for Antitumor Drugs to Cross the Blood Brain Barrier

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Abstract

Effectiveness of chemotherapy treatment for brain-related disorders is primarily limited by the difficulty these drugs have, in crossing the Blood-Brain Barrier (BBB). With the help of artificial intelligence, it is possible to predict the ability of a molecule or drug to cross the BBB, in silico. By initially predicting the values of 17 physicochemical and topological structural descriptors of 136 drugs approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) recognized for their recreational or therapeutic effects on the central nervous system, it was possible to establish the structural profile of any drug or molecule that penetrates the BBB. This structural profile was settled using algorithms developed by the company Chemaxon and published in the Drug Data Bank. In a second step, the structural profile of 60 approved antitumor drugs, regardless of the type of cancer they target, was set up using their physicochemical and topological descriptors. Comparing the structural profile of these antitumor drugs with those of drugs known to act on the Central Nervous System (CNS) enabled us to select, those anticancer drugs, that cross the blood-brain barrier and could be suitable for treating brain tumors, like gliomas, and glioblastomas. To verify our approach, we established and compared the structural profile of the five main drugs clinically used and recommended for the treatment of glioblastoma to the reference structural profile of drugs that penetrate the blood-brain barrier. The results confirmed clinical observations, that only few anticancer drugs are effective in treating glioblastoma due to the limited or absent penetration of the BBB. Furthermore, developing the physicochemical and structural topological profile of molecules that penetrate the BBB can help to reorient drugs for a new therapeutic application related to the CNS and assist the medicinal chemist in the design of molecules targeting brain pathologies.

Keywords: CNS drugs; IA; Drug data bank; Blood brain barrier; Physicochemical and topological descriptors

Abbreviations: FDA: Federal drug administration; CNS: Central nervous system; BBB: Blood brain barrier; TKI: Tyrosine kinase inhibitors; EMA: European medicine agency

Introduction

The explosion of a supernova 5 billion years ago is responsible for the production of all the atoms that make up our solar system, and therefore those that constitute our planet earth and the living beings that inhabit it. The evolution of these atoms, from the formation of the simplest organic molecule, such as methane, to the most complex molecules such as nucleic acids and proteins could only have occurred through molecular transformations over time, which are now called chemical reactions by organic chemists [1].This simple historical overview, which could be described as atomic phylogeny, serves to remind us that the physicochemical properties of molecules, from

the simplest to the most complex, are closely linked to the structure of the primitive atoms that compose them. Consequently, when medicinal chemists design a new molecule for a targeted therapeutic application, they must consider all the physicochemical properties of the atoms that compose it. Today, the widespread application of Artificial Intelligence (AI) techniques considerably aids the design of new therapeutic drugs. Powerful software's help to predict the main physicochemical properties of any molecule even before its synthesis [2-4]. Medicinal chemists have access to online databases developed by drug data bank providers [5]. These databases record the physicochemical and topological descriptors predicted by AI for any drug listed in the International Pharmacopoeia. A key challenge in the treatment of CNS pathologies such as Alzheimer's disease, Parkinson's disease, glioma, glioblastoma, or other tauopathies, is that drugs must be able to cross the BBB and penetrate CNS [6]. BBB protects the brain from toxic substances and prevents excessive accumulation of drug; however, BBB also acts as a molecular filter, preventing drugs active on other biological targets from affecting CNS pathologies. In this respect, drug data bank [7], can provide substantial assistance to medicinal chemists by predicting the key structural, physicochemical and topological descriptors required for a given drug to cross the BBB. Predicting and identifying these descriptors offers significant advantages:

- Bypassing lengthy and costly chemical optimizations when developing drugs to treat CNS pathologies
- Selecting drugs that are already on the market and likely to cross the BBB, could be of particular interest. For instance, given the limited number of existing drugs to treat CNS tumors, and their ineffectiveness, selecting drugs that penetrate the CNS, could be highly productive
- Another advantage is repurposing drugs that have been approved internationally and have a physicochemical and topological profile likely to cross the BBB, for use in treating CNS pathologies

It should be underlined that this review only considers small FDA approved drugs listed in the international pharmacopeia. Monoclonal antibodies, which are widely used in the treatment of many cancers, are not considered [8].

To illustrate the importance of the correlation between drugs physicochemical and topological molecular descriptors and their therapeutic effects, the following analyses were carried out:

a) Using AI-predicted molecular descriptors values common to any therapeutic drug recognized and approved for its effects on CNS, a structural profile of drugs that cross BBB is established, starting from a panel of 136 drugs active on the CNS. By comparing the predicted structural profile of any molecule or drug, with the reference structural profile established for BBB crossing molecules, allow to predict whether a drug or molecule is likely to cross the BBB.

b) Starting from the panel of FDA approved antitumoral drugs, three groups of drugs were selected:

- the group of 52 antitumor tyrosine kinase inhibitors [9]
- the group of 36 drugs used in neuro-oncology, alone or in combination [10]
- the group of 5 drugs specifically used for the brain tumors treatment, glioma and glioblastoma [11]

A typical profile for each group of drugs was established based on the physicochemical and topological descriptors of each constituent drug. Comparing the structural profiles of the three groups of drugs, with the reference structural profile established for drugs that cross the blood-brain barrier allow us:

- to predict, which anticancer drugs, in each of the three groups, can likely cross the BBB.
- to assist chemists in designing drugs that are likely to pass the BBB.
- to redirect drugs approved for a specific therapeutic indication towards a new indication relative to CNS pathologies.

Materials and Methods

Physicochemical and topological descriptors profile of drugs penetrating the BBB

Actually 4764 FDA approved drugs including: - antibiotics, - analgesics, - psychotropic drugs, - sleeping pills, - narcotics, - antitumor agents, - antihormonal agents, and other molecules with recognized therapeutic effects, are listed in the Drug Data Bank. Within this panel of 4764 drugs, 136 drugs which includes: -*anxiolytics*, -*sedatives*, -*sleeping pills*, - *painkillers*, -*psychic* or *psychological disorders drugs*, - *anesthetic derivatives*, -*anticonvulsants*, - *antiemetics*, - *neuro-stimulants*, - *analgesics*, - *psychotropics*, have all received FDA or EMA approved marketing authorization for the treatment of neurological disorders or are recognized for their deleterious or beneficial effects on the CNS [12].

The "branded names" of these 136 drugs are given below in alphabetical order [13].

Almotripan, Amantadine, Aminophenantren, Amitryptiline, Amitryline, Amobarbital, Amoxapine, Amphetamine, Apomorphine, Arimoclimol, Aripiprazole, Asenapine, Atropine, Barbital, Biperiden, Bradikine, Bufotenine, Buprenorphine, Buspirone, Butalbital, Caffeine, Capsaicin, Carbamazepine, Cardidopa, Cathinone, Celecoxib, Chlordiaepoxide, Chlorpromazine, Citalopram, Clonazepam, Clopiramine, Clozapine, Cocaine, Codeine, Dextroamphétamine, Diazepam, Diclofenac, Dietylpropion, Disulfiram, Donezepil, Doxepine Elepriptan, Ephedrine, Epinephrine Ergotamine, Escitalopram, Esketamine, Fenfluramine, Fentanyl, Fluophenazine, Fluoxamine, Fluoxetine, Fluvoxamine, Fiazepam, Forcabioca, Foslevodopa, Frovatripan, Gabapentin, Halopiridol, Heroin, Hydroxizine, Ibogaine, Ibuprophen, Imipramine, Ketamine, Ketorolac, Lamotrigine, Levitiracetam, Lorazepam Lozaripam, LSD, Lurasidone, Meloxicam, Mepiridi, Meprobramate, Mescaline, Metamphetamine, Methadone, Methphenidate, Methylphenidate, Midazolam, Morphine, Muscarine, Nalorphine, Naltrexone, Naproxen, Naratriptan, Nemantine, Nicotine, Niketamide, NMDA, N,N-dimethylpriptamine, Olanzepine, Oxazepam, Oxycodone, Paracetamol, Paroxetine, Perphenazine, Pentazorcine, Penthotal, Phenobarbital, Phenothiazine, Phentermine, Phenylcyclidine, Phenylethylamine, Phenytoin, Prednisolone, Pregabaline, Procaine, Psylocibin, Quetapine, Reserpine, Resveratrol, Rifinamide, Risperidone, Rivastigmine, Rizatriptan, Salicyclic acid, Salvinorine, Scopolamine, Serotonine, Sertraline, Sumatriptan, Temazepam, Tetrabenazine, Tetrahydrocannabinol, Theone, Thiothixene, Thioridazine, Triazolam, Trifluoroperazine, Valbenazine, Valproic acid, Zolmitriptan, Zolpidem, Zonisamide.

A typical profile of a molecule crossing the BBB was established based on the average values of 17 physicochemical and topological descriptors predicted by AI for these 136 drugs approved for their various effects on the CNS. This profile was developed in version (5.1.13) of DrugBank Online (2025), which is created and maintained by the University of Alberta (Canada) [14].

For each of the 136 drugs listed in the Drug Data Bank which was developed by ChemAxon (https://www.chemxon.com) [15], the values of the following 17 physicochemical and topological descriptors are predicted : Molecular formula, density, boiling point, molar mass, partition coefficient, solubility in water, charged partial surface area (topological), polarizability (topological), acid and basic pKa, molecular weight, number of hydrogen donors bonds, number of hydrogen acceptor bonds, number of free rotated bonds, bioavailability, and number of cycles. Moreover, the compliance of these descriptors values with the so-called "drug likeness rules," (Lipinsky's rule, Ghose's rule, Veber's rule, and Molecular Detection of Drug Resistance rule (MDDR rule) which are also predicted by AI, are also reported in the Drugbank data [16,17]. As recently published [18], QSAR (Quantitative Srtucture Activity Relationship), these 17 physicochemical and topological descriptors are commonly used in rational drug design. Moreover, it should be underlined that the AI values of the descriptors: log P, log S, pkA acid and basic predicted for each approved drug included in this study, align with the experimental data and are available in the drug ChemAxon data bank.

Table 1 shows the average value of each physicochemical descriptor, calculated from the values of the 136 drugs, as well as the standard deviation for each considered descriptor.

Table 1 also shows the average compliance of the 136 drugs with the "drug likeness rules'' expressed as the "number of drugs that meet these rules and the number of drugs that do not.''

- Lipinsky's rule also known as rule of five, states: - no more than 5 hydrogen bond donors; - no more than 10 hydrogen bond acceptors, - a molecular mass less than 500 Da [19].

- Ghose 's Filter rule, states: - a partition coefficient (Log P) between −0.4 to +5.6; -a molecular refractivity between 40 and 130; -a molecular weight between 180 and 480; - a number of atoms between 20 to70, which includes H-bond donors and H-bond acceptors [20].

Table 1: CNS drugs structural profile.
Average of predicted physicochemical descriptors values and compliance with likeness rules, based on 136 drugs known to cross the BBB.

CNS: physicochemical descriptors values		CNS Compliance with the drug likeness rules
Molecular Weigh	282 ± 54	109 drugs out of 136 respect the Lipinsky's rule*
Solubility mg/ml	0.43 ± 0.05	92 drugs out of 136 respect the Ghose's rule**
Log P	1.88 ± 0.12	38 drugs out of 136 respect the Veber's rule ***
Log S	- 2.87 ± 0.81	11 drugs out of 136 respect the MDDR-like rule ****
pK_A (acid)	11.28 ± 0.98	
pK_A (basic)	6.4 ± 0.56	
Hydrogen bonds donnors	2± 1	
Hydrogen bonds acceptors	3 ± 1	
Rotational bonds	4 ± 1	
Polar surface area ($A^{\circ 2}$)	49.36 ±7.1	
Polarizability ($A^{\circ 3}$)	34.58 ± 6	
Bioavailability	1	
Number of rings	2 ± 1	

- Veber's rule states: 10 or fewer rotatable bonds; - polar surface area of or less 140 A°, no more than 12 H-bond donors and acceptors [21].

- MDDR-like rule: The descriptors used for the MDDR-like rule are: -the number of rings, -the number of rigid bonds, and the number of rotatable bonds. The probability of finding a "druglike" compound is higher within the following ranges: number of rings ≥ 3, number of rigid bonds ≥ 18, number of rotatable bonds ≥ 6. The probability of finding a 'nondrug-like' compound is higher in the ranges: -number of rings ≤ 2; number of rigid bonds ≤ 17, number of rotatable bonds ≤ 5 [22,23].

BBB drug crossing profile, applied to anticancer drugs

Three groups of anticancer drugs were considered:

First group: Approved Tyrosine Kinase Inhibitors

Discovered in the 2000s tyrosine kinase enzymes [24,25], have emerged as potential targets for the treatment of different types of cancers, including lung, kidney, melanoma, colorectal, liver, ovarian, prostate, and leukemia. Unfortunately, their use in treating brain tumors remains limited or even completely ineffective, despite the fact that tyrosine kinase enzymes are widely present in the central nervous system [26]. This failure is primarily due to their inability to cross the blood-brain barrier [27]. Actually 52 Tyrosine kinase Inhibitors (TKI) listed below have been developed and approved for the treatment of specific cancers [28,29].

Afatinib, *Alectinib*, *Asciminib*, *Axitinib*, *Binimetinib*, *Bosutinib*, *Brigatinib*, *Carbozantinib*, *Cediranib*, *Ceritinib*, *Cobimetinib*, *Crizotinib*, *Dabrafenib*, *Dacomitinib*, *Dasatinib*, *Dovitinib*, *Encorafinib*, *Entrectinib*, *Erlotinib*, *Gefitinib*, *Imatinib*, *Infigratinib*, *Lapatinib*, *Larotrectinib*, *Lenvatinib*, *Lorlatinib*, *Mobocertinib*, *Necatinib*, *Nintedanib*, *Niraparib*, *Nolotinib*, *Osimertinib*, *Pazopanib*, *Pemigatenib*, *Pexidartinib*, *Pralsetinib*, *Regorafenib*, *Ripretinib*, *Ruxalotinib*, *Savolitinib*, *Selpercatinib*, *Selumetinib*, *Sorafinib*, *Sunitinib*, *Talazoparib*, *Tepotinib*, *Trametinib*, *Tucatinib*, *Vandetanib*, *Vatalanib*, *Vemurafenib*, *Zasocitinib*.

For each of these drugs, the predicted physicochemical and topological descriptors values, and their compliances with the predicted "drug likeness rules", are shown in Table 2.

Based on the reference profile established from the physicochemical and topological descriptors of drugs that penetrate the BBB (Table 1), regardless their class (alkylating agents or antimetabolites) and their biological target, we select antitumor drugs, whose profile most closely matched the reference profile of BBB penetrating drugs from the whole set of FDA approved drugs [30].

Table 2: Structural profile of anticancer tyrosine kinase inhibitors. Average of predicted physicochemical descriptors values and likeness rules compliance of Tyrosine Kinase Inhibitors.

TKI Descriptors values		TKI Drug likeness rules compliance	
Molecular Weigh	477.46 ± 66	Lipinsky rule	38 yes/ 24no
Water Solubility mg/ml	0.0363 ± 0.0004	Ghose filter	27 yes /35 no
Log P values	3.863 ± 1.11	Veber rule	0 yes/ 62 no
Log S	- 4.56 ± 0.94	MDDR rule	40 yes/ 22no
pK_A (acid)	12.36 ± 2.68		
pK_A (basic)	6.46 ± 2.13		
Hydrogen bonds donnors	2 ± 1		
Hydrogen bonds acceptors	5 .7 ± 1.5		
Rotational bonds	6 ± 1.58		
Polar surface area ($A°^2$)	90.83 ± 17.60		
Polarizability ($A°^3$)	48.331 ± 8.84		
Number of rings	4.35 ± 0.87		
Bioavailability	1		

The predicted structural profile of TKI's group presented in Table 2 confirms that these drugs are ineffective in treating brain tumors when used alone. TKI'S profile shows that only four out of seventeen considered descriptors, are consistent with the predicted values for BBB crossing drugs, presented in Table 1.

This lack or very weak antitumor activity of TKI inhibitors against brain tumors can be explained, by their physicochemical and topological structures not allowing them to cross BBB or by them to penetrate BBB very poorly. Due to their weak activity on brain tumors, to-day TKI's are no longer used in monotherapy but rather in combination with other anticancer agents and in co-administration with efflux transporter inhibitors such as drugs that's readily cross the BBB [31] or in association with psychiatric and non-psychiatric drugs that penetrate the BBB [32].

In Table 2, it can be also observed that of the 52 TKI'S, two drugs (*Entrectinib* and *Osimertinib*) whose physicochemical and topological structural descriptors do not meet criteria required for sufficient penetration into the cerebrospinal fluid, nevertheless exhibit clinical activity against brain tumors.

Second group: Drugs used specifically in neuro-oncology, alone or in combination.

Since the 1960s, approximately 94 molecules have been approved for use in cancer chemotherapy. Among these

94 molecules, 36 are more specifically recommended and used alone or in combination by neuro-oncologists for the treatment of brain tumors [33,34].

AEE788, *Azulfidine*, *Banoxantrone*, *Bortezomid*, *Carboplatin*, *Carbozentinib*, *Carmustine*, *Celecoxib*, *Cilengentinide*, *Cis-Platin*, *Cyclophosphamide*, *Dasatinib*, *Erlotinib*, *Etoposide*, *Evorolimus*, *Fluocytosine*, *Gefitinib*, *Imatinib*, *Irinotecan*, *Lapatinb*, *Lefunomide*, *Lomustine*, *Methotrexate*, *Ornasertib*, *Placlitaxel*, *Procarbazine*, *Rosiglitazone*, *Simvastatin*, *Sirolimus*, *Sorafinib*, *Sunifinib*, *Temozolomide*, *Temsirolimus*, *Tipifarnib*, *Varinostat*, *Vincristine*.

The structural profile of the 36 drugs mostly used alone or in combination in cancer chemotherapy by neuro-oncologists, is given in Table 3.

Third group: Drugs specifically used for the treatment of glioblastomas.

Four drugs: *Hydroxyurea*, *Procarbazine*, *Carmustine*, *Temozolomide*, alone or in combination, are commonly used, for the treatment of Glioblastomas, mainly because of their alkylating properties [35]. Monoclonal antibodies, such as *Bevacizumab*, widely used for the treatment of Glioblastoma, are not considered in this study since they cannot be considered as small molecules [36]. Based on the average values of 17 physicochemical and topological descriptors predicted by AI, the structural profile for each of these 4 alkylating drugs, and their compliance with the drug -likeness rules, were established and reported in Table 4 [37,38].

Table 3: Structural profile of brain tumors drugs used in treatment trials. Average predicted physicochemical descriptors values and compliance with likeness rules, based on 36 used for glioblastoma treatment

Physicochemical descriptors values		Compliance with the drug likeness rules
Molecular Weigh	478 ± 212	23 drugs out of 37 respect the Lipinsky's rule*
Water Solubility mg/ml	0.2 ± 0.63	18 drugs out of 37 respect the Ghose's rule**
Log P	2.63 ± 1.57	0 drugs out of 37 respect the Veber's rule ***
Log S	- 3.9 ± 1.32	18 drugs out of 37 respect the MDDR-like rule ****
pK_A (acid)	11.13 ± 3.4	
pK_A (basic)	2.98 ±3. 84	
Hydrogen bonds donnors	2.3 ± 1.6	
Hydrogen bonds acceptors	5.9 ±2.26	
Rotational bonds	3.5 ± 1.96	
Polar surface area ($A^{\circ 2}$)	110.9 ± 55.7	
Polarizability ($A^{\circ 3}$)	46.64 ± 25.5	
Bioavailability	1	
Number of rings	3.4 ± 1.8	

Discussion

Table 4: Structural profile of the four drugs mostly used for Glioblastoma treatment.
Predicted physicochemical and topological descriptors values of the 4 most commonly used alkylating drugs for glioblastoma chemotherapy.

	Hydroxy urea	Temozolomide	Carmustine	Procarbazine
Molecular Weigh	62	194	214	221
Solubility mg/ml	269	5.09	1.53	0.228
Log P	1.8	−0.28	1.02	0.99
Log S	−0.58	-	−2.2	−3
pK_A (acid)	10.14	10.46	13.36	15.03
pK_A (basic)	−4.9	−3.6	−5.3	5.56
Hydrogen bonds acceptors	2	5	2	3
Hydrogen bonds Donnors	3	12	1	3
Polar Surface Area $A^{\circ 2}$:	75.35	105.94	61.77	53.16
Rotational bonds	0	1	5	5
Polarizability $A^{\circ 3}$	5.94	16.68	18.8	25.88
Number of rings	0	2	0	1
Bioavailability	1	1	1	1
Lipinsky rule	Yes	Yes	Yes	Yes
Ghose filter	No	Yes	Yes	Yes
Veber rule	No	No	No	No
MDDR rule	No	No	No	No

Profile of CNS penetrating drugs

Qualitatively speaking, Table I shows that drugs which penetrate across the BBB are generally lipophilic, with a median partition coefficient median around 1.88 ± 0.12 and a molecular mass between 228 and 336 Da. Furthermore, it can be seen that BBB penetration is not only related to molecular mass or lipophilicity; others descriptors, such as hydrogen donor and acceptor, molecular electrostatic potential, surface area, size, hydrogen bonding interactions, ionization properties, and molecular flexibility, also correlate with BBB penetration. The values of these descriptors for drugs CNS pathologies generally have a smaller range than those for general drugs therapeutics [39].

Comparison between the reference profile established for drugs BBB penetrating drugs and the profile of the tyrosine kinase inhibitor group profile

Table 2, reveals that only four of the 17 descriptors values are consistent with the corresponding values of the BBB crossing drugs descriptors shown in Table 1. This result

is consistent with the observed clinical lack or very weak clinical activity of these drugs on patient brain tumors. Two explanations can be put forward: first, their physicochemical and topological descriptors of TKI's do not allow them to cross the BBB or to penetrate the very well CNS; second, TKI's that can cross the BBB, have no antitumor effects on brain tumors. Nevertheless, two TKI's drugs are used clinically for the treatment of brain tumors:

Entrectinib, a TKI inhibitor, differs from other RTKIs, in that it interacts weakly with P-glycoproteins, allowing better BBB penetration. *Entrectinib* is used in combination with other treatments or as a monotherapy, for the treatment of glioblastomas, particularly in patients who have developed metastases in the CNS [40].

Osimertinib. (Tagrisso) is a RTKI that is currently used clinically, because of its weak interaction with glycoproteins which facilitates BBB penetration [41].

Moreover, the physicochemical and topological descriptors values of these two drugs (*Entrectinib* and *Osimertinib*) are closer to those of molecules that cross the BBB, particularly with regard to the number of rotational bonds and donor and acceptor hydrogen bonds [42]. Today, a new generation of RTKIs has been designed to overcome efflux pumps and facilitate penetration into the brain. Promising RTKI's are undergoing clinical evaluation for brain tumors [43-45].

Comparison of BBB drugs crossing reference profile with the profile of the 36 anti-tumor drugs used by neuro-oncologists at UCLA for the treatment of glioblastoma

These 36 small drugs are used in monotherapy or in combination by specialized neuro oncologists. They target key signaling pathways involved in the formation and development of glioblastoma [46]. Comparing the average values of the 17 physicochemical and topological descriptors of these 36 compounds (Table 3), with the average values of these same descriptors for CNS-active drugs that cross the BBB (Table 1), confirms the previous observation that these drugs have limited BBB penetration and are not very effective in treating glioblastoma when used as monotherapy. Several procedures have been proposed to facilitate and improve the crossing of the BBB by antitumor molecules (microbubbles, ultrasound, or administration by infusion) [47].

One interesting procedure is the combination of anti-tumor drugs with drugs used to treat CNS diseases. Promising clinical trials have been obtained with combinations involving temozolomide (which belongs to this third group of drugs), with compounds known for their psychological and psychiatric effects on the CNS such as carbamazepine, ethosuximide, gabapentin, lamotrigine, levetiracetam, magnesium sulfate, oxcarbazepine, phenytoin, primidone, tiagabine, topiramate, valproic acid and vigabatrin [48]. One of the hypotheses proposed to explain temozolomide's potentiated effect on glioblastoma, when combined with CNS-active compounds, is that CNS-active drugs facilitate temozolomide's passage, across the BBB, thereby increasing its concentration in the brain and consequently potentiating its effect on brain tumors [49-51].

Structural profile of drugs clinically used for treatment of glioblastoma

Hydroxyurea, *Carmustine*, *Lomustine*, *Nimustine*, *Temozolomide*, and *Procarbazine* are alkylating compounds frequently used in chemotherapy for brain tumors [52]. Despite their short half-life and limited ability to cross the blood-brain barrier, these derivatives have proven beneficial in terms of patient survival [53]. Table 4 presents the predicted physicochemical and topological descriptor values of these four drugs approved for the treatment of gliomas and glioblastomas, in monotherapy or in combination. Clinical trials of various combinations of the aforementioned drugs show that these combinations significantly increase the survival of patients with brain tumors compared to their use as monotherapy [54]. These compounds are small alkylating molecules that induce effective antitumor activity by producing alkylating species that target various signaling pathways involved in brain tumor development. Their antitumor activities will be even more effective if these molecules cross the blood-brain barrier to reach the tumor at sufficient concentrations [55]. In general, these alkylating drugs are compounds that bind covalently with biomolecules under physiological conditions by the production of alkylating species [56]. Hydroxyurea releases nitroxide-type free radicals, Procarbazine releases peroxide species (H_2O_2), Carmustine releases electrophilic species, such as chloroethyl carbonium ions, and Temozolomide generates methyl diazonium ions. If we examine the values of the predicted physicochemical and topological descriptors of these compounds, we note: -These drugs, at a physiological pH of approximately 7, have acidic pKa values between 10 and 15 and basic pKa values between -3 and -5. It is established that for acidic compounds, when the pH is less than the pKa by 2 units, 99% of the acid is in a non-ionized form; and that for basic compounds, when the pH is greater than the pKa, by 2 units, 99% of the compound is in a non-ionized form. The AI-predicted acidic and basic pKa values for each of these four drugs at a physiological pH of 7, show that these derivatives are preferentially in a non-ionized form, which favor their penetration through the BBB [57].

Moreover, the predicted values of the molecular descriptors of these drugs (MW, Log P, hydrogen bonds, bioavailability, compliance rules (Lipinsky, Ghose, Veber, and MDDR)) are of the same order of magnitude as predicted values of these same descriptors for drugs active on the CNS.

Conclusion

Algorithms developed by AI specialists (Chemaxon) currently allow in silico prediction of the values of the physicochemical and topological descriptors of any molecule whether natural, synthetic or hypothetical prior to synthesis. Predicted values of descriptors such as molecular weight, solubility, partition coefficient, acid-base properties, surface polarity, polarizability, the number and nature of donor and acceptor hydrogen bonds, the number of rotationally free bonds, and bioavailability are listed in databases such as PubChem and Drug Bank [17,58,59]. This Drug Databank reports the predicted structural values of the physicochemical and topological descriptors listed above for 4764 molecules or drugs approved or authorized by the FDA. Of these 4764 drugs, 136 have pharmacological effects on the central nervous system. A reference structural profile for drugs to cross the BBB was first established from the predicted values of the structural descriptors for this group of 136 drugs acting on the CNS. This CNS drug reference profile was then used to select from the 92 approved antitumor drugs (TKI'S or alkylating agents) reported in the Drug Data Bank, those whose physicochemical and topological descriptor predicted values were consistent with those of the reference CNS drugs profile. Consequently, drugs that can cross the BBB, could be suitable for trials to treat brain tumors, glioma and glioblastoma. Our reported results show that, of the 92 antitumor drugs included in our study, only four have a structural profile compatible with the CNS drug profile. First this finding is consistent with clinical trials which have showing that most anticancer drugs prescribed, have little or no activity in treating brain tumors. Second this reference profile is a useful tool for medicinal chemists seeking to create molecules for treating tumor. Third, this CNS drugs crossing reference profile enables the selection of currently available approved drugs, that could be repurposed for therapeutic applications related to the treatment of brain tumors.

Fundamental physiochemical features of CNS drugs are related to their ability to penetrate the Blood Brain Barrier affinity and exibit CNS activity. The AI driven predictions presented in this study represent important workflows which could be integrated in the search for drugs which have a chance to enter into monotherapy or in combination for the treatment of brain tumors.

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Compliance with Ethical Standards

This article does not contain any studies involving animals.

Conflict of Interest

The author declares that he has no conflict of Interest with any national or international agencies.

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