Cumhuriyet Sci. J., 45(2) (2024) 282-290
DOI: https://doi.org/10.17776/csj.1403956

Cumhuriyet Science Journal

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Theoretical Investigations on Phytochemicals: Physical Chemistry, FMO, MEP, Lipophilicity, Water Solubility, Drug-likeness, and Bioavailability

Nihat Karakuş [1,a,*]

[1] *Department of Chemistry, Faculty of Science, Sivas Cumhuriyet University, 58140, Sivas.*
**Corresponding author*

Research Article

History
Received: 12/12/2023
Accepted: 30/03/2024

ABSTRACT

Naturally-existing chemicals especially phytochemicals have been commonly used for medicinal purposes in terms of both traditional and contemporary respects. Allyl isothiocyanate structure exhibits antimicrobial and anticancer activity, whereas the allitridin, as one of the main components of the garlic, showed antifungal, antitumor, and antioxidant activity. Arabinose and galactose as monosaccharides also play a main role in drug-design research to facilitate drug delivery to target cells and regulate insulin resistance, respectively. Herein, the 3-isothiocyanatoprop-1-ene (Allyl isothiocyanate, AITC), 2,3,4,5-tetrahydroxypentanal (Ar, Arabinose), 1,3-diallyltrisulfane (Allitridin, DATS), 6-(hydroxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (Galactose, Gal), 6-methyltetrahydro-2H-pyran-2,3,4,5-tetraol (Rhamnose, Rh), and tetrahydro-2H-pyran-2,3,4,5-tetraol (cyclic-Arabinose, C-Ar) agents were investigated by using DFT. The B3LYP/6-311G** level computations were used to optimize the compounds' geometries and then to predict the reactivity indexes of the compounds. Also, lipophilicity and water-solubility features were determined to enlighten the physicochemical characteristics of the compounds. Then, the studied agents' pharmacokinetics were evaluated using the BOILED-Egg and radar graphs. Last, the bioavailability and drug-likeness behaviors were predicted. This trial work will be hoped to provide fundamental electronic and physicochemical insight into the relationship between drug-likeness and electronic structure.

Keywords: Phytochemicals, Arabinose, DFT study, Lipophilicity& water solubility, Drug-likeness.

[a] *nkarakus@cumhuriyet.edu.tr* *https://orcid.org/0000-0001-6223-7669*

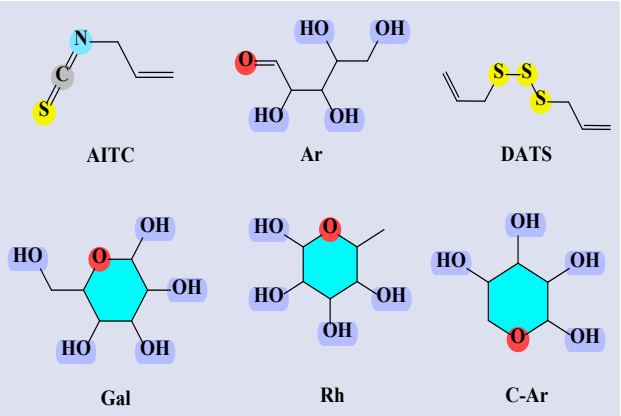
Introduction

Naturally occurring compounds have been important in the necessities of daily life, such as the clothing industry, nutritional needs, and medicinal purposes since ancient times. Nowadays, computational research is crucial in the basic science, engineering, and medical fields in terms of the controlled use of natural resources for greener chemistry. Although many compounds can be obtained from synthetic routes due to limited natural resources, computational tools provide very important information for preliminary predictions of the processes of interest due to their adverse effects on the economy, time, and, more importantly, humans and the environment.

Among the studied compounds, galactose and arabinose [1,2] as member of the monosaccharides known very well due to their biological importance and are commonly studied now. Also, the DATS derived from garlic has been reported to have a potential anticancer effect via binding the cysteine residues in β-tubulin to produce the sallylmercaptocystein [3]. Furthermore, the DATS obtained from allium vegetables as bioactive dietary agents can regulate the cancer hallmark pathways [4]. In this regard, organosulphur compounds obtained from allium vegetables were investigated to explore the prevention and therapy of human cancer using preclinical and limited clinical data [5]. In addition, the DATS has been reported regarding the possible antimetastatic agent by exploring the migration and invasion of human colon cancer cells [6]. In research on antimicrobial and cytotoxic activities of lepidium latifolium L. hydrodistillate, the pure allyl isothiocyanate exhibited the cytotoxic effect on bladder cancer UM-UC-3 and glioblastoma LN229 cell lines with the similar trend to hydrodistillate [7]. Rhamnose, as a naturally occurring deoxy sugar, has a crucial role in synthetic biology and biotechnology research [8,9]. In the past, the E. coli rhamnose-inducible rhaBAD promoter has been reported to explore the possible effects on freshwater cyanobacterium; the obtained results revealed that it is superior to cyanobacterial inducible promoter model with a non-toxicity, photostability, non-metabolizable inducer, etc [8]. Furthermore, the L-rhamnose and L-fucose have been observed in terms of the potential anticancer capabilities; the optimal L-rhamnose dose has been determined as 3.64 g/kg/day, and the tumour-inhibitory effect of L-rhamnose has been more promising than the L-Fucose [10]. However, the selected compounds are naturally occurring and applicable for medicinal purposes; the possible toxicity works on the living body and/or environment of these molecules have also been investigated [11,12].

Also, the quantum chemical computations at M062X−D3/6-311++G** level have been performed to explore the ciprofloxacin interactions with glucuronic acid, arabinose, glucosamine, and rhamnose; the results indicate that ciprofloxacin in the zwitterion form is preferable to complex carbohydrates and probably induce the proton exchange between these structures [13]. In a paper reported the molecular mechanism of diallyl trisulfide (DATS) on trans-crotonaldehyde (TCA), the Raman spectroscopic properties of DATS were estimated by using the DFT/B3LYP/6-31+g (d, p) level [14]. Recently, the phytochemicals extracted from mustard, including AITC, DATS, Gal, Ar, and Rh, have been explored for possible use in corrosion inhibition [15].

In this study, well-known compounds extracted from natural sources were selected to explore the relationships between electronic structure and possible chemical direction. The compounds were optimized and confirmed by the B3LYP/6-311G** level computations. The FMO "Frontier Molecular Orbitals" investigations were performed to determine the reactivity tendencies and directions of the compounds. Also, *in silico* works were performed to estimate the compounds' physicochemical characteristics and structure relationships. For this purpose, the lipophilicity and water solubility properties were assessed and evaluated. The pharmacokinetics and bioavailability properties of the compounds were determined by using *in silico* analyses as well. From the results obtained, this work will hopefully provide the main information on the structural requirements for evaluating chemical and biological reactivity tendencies and directions.



Scheme 1. Chemical Structures of the studied compounds

Computational Methods

DFT Computational Study

All quantum mechanical computations of AITC, Ar, DATS, Gal, Rh, and C-Ar agents were conducted by the G09W [16] package, at B3LYP [17,18] / 6-311G(d,p) level [19]. GaussView 6.0.16 [20] package was used for visualizations of the optimized geometries, and FMO plots as well as to perform the FMO and MEP analyses.

The thermochemical functions of the compounds were evaluated on the basis of statistical mechanics [21,22]. Accordingly, the total partition and vibrational partition functions are given below

$$Q = Q_{trans.}\, x\, Q_{rot.}\, x\, Q_{vib.}\, Q_{elec.}$$

$$Q_{vib.} = \prod_{j=1}^{3N-6} \frac{e^{-\Theta_{v,j}/2T}}{\left(1-e^{-\frac{\Theta v,j}{T}}\right)}$$

Here, the terms are defined as follows: Q→ "total partition function", $Q_{trans.}$→ "translational partition function", $Q_{rot.}$→ "rotational partition function", $Q_{vib.}$→ vibrational partition function", and $Q_{elec.}$→ "electronic partition function". Hence, the thermodynamic quantities, $E_{vib.}$ "vibrational thermal energy", $S_{vib.}$ "vibrational entropy", and $Cv_{vib.}$ "vibrational heat capacity". Here, the notations are expressed as $\Theta_{vj} = \frac{h\nu_j}{k}$ "the vibrational temperature", h→ "Planck constant", k→ "Boltzmann constant", and ν_j→" j^{th} fundamental frequency".

$$E_{vib.} = Nk \sum_{j=1}^{3N-6} \left(\frac{\Theta_{v,j}}{2} + \frac{\Theta_{vj}\, e^{-\Theta_{v,j}/T}}{\left(1 - e^{-\frac{\Theta v,j}{T}}\right)} \right)$$

$$S_{vib} = Nk \sum_{j=1}^{3N-6} \left[\frac{\Theta_{v,j}/T}{\left(e^{\Theta_{v,j}/T} - 1\right)} - ln\left(1 - e^{-\Theta_{v,j}/T}\right) \right]$$

$$Cv_{vib.} = Nk \sum_{j=1}^{3N-6} \left[\left(\frac{\Theta_{vj}}{T}\right)^2 \frac{e^{\Theta_{vj/T}}}{\left(e^{\Theta_{v,j}/T} - 1\right)^2} \right]$$

The *I* "ionization energy" and *A* "electron affinity" [23] were calculated according to the Koopmans Theorem through the energies HOMO and LUMO. Then, the possible reactivity indexes of the compounds were calculated by using the following equations

$$I = -E_{HOMO}$$

$$A = -E_{LUMO}$$

$$\chi = -\left(\frac{I+A}{2}\right)$$

$$\eta = \frac{I-A}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$\Delta N_{max} = \frac{I+A}{2(I-A)}$$

$$\omega^{+} \approx (I+3A)^2/(16(I-A))$$

$$\omega^{-} \approx (3I+A)^2/(16(I-A))$$

$$\Delta\varepsilon_{back-donation} = -\frac{\eta}{4}$$

Here, the terms are described as χ → "electronic chemical potential" η → "global hardness", ω → "electrophilicity", ΔN_{max} → "the maximum charge transfer capability index" [24,25], ω- "the electrodonating power" and ω+ "the electroaccepting power" [26], and $\Delta E_{back\text{-}donat.}$ "back-donation energy" [27].

Lipophilicity and water solubility features

The lipophilicity indexes of the studied agents were estimated using five approaches: the ILOGP [28], XLOGP3 [29], WLOGP [30], MLOGP [31], and SILICOS-IT [32], by performed SwissADME [33]. The lipophilicity index (Log P) is described depending on the concentrations of a specific system in octanol (C_o) and water (C_w) as follows

$$Log\ P_{o/w} = Log\ \frac{C_o}{C_w}$$

In addition, the water-soluble features were estimated by using ALI described by Ali et al [34] and ESOL [35] provided by Delaney. The relevant equations for both of them are defined as follows

$$\log S = -1.0239\ \log P - 0.0148\ TPSA - 0.0058\ (m.p.(C) - 25) + 0.3295\ aroOHdel + 0.5337\ (ALI)$$

$$\log Sw = 0.16 - 0.63\ clogP - 0.0062\ MWT + 0.066\ RB - 0.74\ AP\ (ESOL)$$

In the ALI method, the terms are described as the aroOHdel → "the number of the aromatic –OH group(s)", the TPSA → "topological surface area", and m.p → "melting point". On the other hand, the Delaney method depends on the "Molecular weight, MWT", "Rotatable bonds, RB", and "Aromatic proportion, AP".

Pharmacokinetics, Druglikeness, and Bioavailability Study

Herein, the GI "Gastrointestinal" absorption (white) and BBB "blood–brain barrier" permeation (yolk) have been illustrated and evaluated depending on the BOILED-Egg model. The selected Cytochrome P450 characteristics, which are CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, and gp (glycoprotein) substrate potency have also been estimated by SwissADME [33] via the SVM "support vector machine" model.

Also, the Lipinski [31], Ghose [36], Veber [37], Egan [38], and Muegge [39] approaches have been used to predict the drug-likeness characteristics of the compounds and the Abbott score [40] for bioavailabilities has been computed by using the SwissADME [33] tools.

Result and Discussion

Molecular Geometry and Thermochemistry

In computational research, the elucidation of the thermochemistry and physical characteristics of the relevant molecular systems is the main first step for further investigation and analysis.d In this work, the computed thermodynamic parameters and physical characteristics of the studied ligands are presented in Table 1.

Depending on the structural isomerism, the ΔE (au) of the C-Ar molecule would have been lower than the corresponding open-chain form (Ar): the ΔE (au) values of Ar and C-Ar were determined as -572.640688 au and -572.645566 au, respectively. Like being in ΔE (au), the other thermochemical and physical values of these molecules were also close to each other. Namely, the ΔH quantity of Ar and C-Ar were determined in -572.628692 and -572.634697 au, respectively, whereas the ΔG of them was predicted as -572.677490 and -572.679951 au. On the other hand, the lowest thermodynamic quantities among the studied molecules were estimated for the DATS molecule due to the existence of three sulfur atoms, as expected from the quantum statistics or statistical mechanics [21]. Namely, the ΔE, ΔH, and ΔG values of DATS were calculated as -1429.185987, -1429.172523, and -1429.228069 au, respectively. In addition, the ΔG value of the AITC, Gal, and Rh molecules was computed as -608.374666, -687.209130, and -611.978951 au, respectively. Also, the $E_{therm.}$ values of the compounds were determined as 55.451 (AITC), 108.178 (Ar), 99.238 (DATS), 131.531 (Gal), 127.579 (Rh), and 109.162 au (C-Ar). The Cv and S values of the Gal were determined as 47.346 and 106.823 cal/molK, respectively, whereas these quantities of DATS were estimated as 41.393 and 116.906 cal/molK. On the other hand, the Cv and S values of the Ar molecule were determined as 40.183 and 102.704 cal/mol, respectively, while these values for the closed-ring Ar were determined as 38.464 and 95.245 cal/molK. The dipole moment order of the compounds was determined as DATS (1.542)< C-Ar (1.571)< Ar (2.943)< Gal (3.636)< AITC (3.735)< Rh (3.802), whereas the α (au) order of the molecules was computed as AITC (69.143)< C-Ar (71.352)< Ar (73.194)< Rh (82.541)< Gal (85.993)< DATS (139.315).

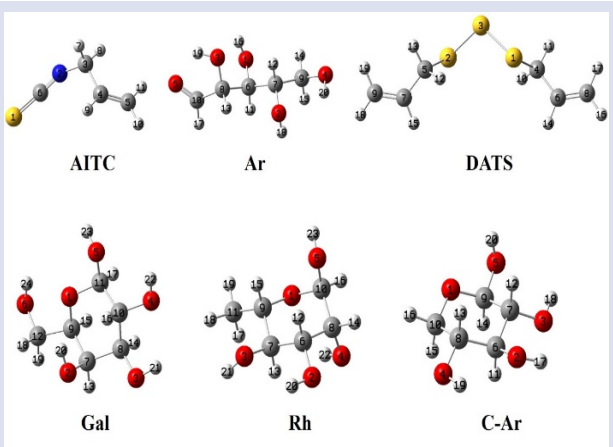


Figure 1. The optimized geometries

Table 1. The thermochemical and physical parameters of the studied compounds

	AITC	Ar	DATS	Gal	Rh	C-Ar
ΔE (au)	-608.341498	-572.640688	-1429.185987	-687.171634	-611.943046	-572.645566
ΔH (au)	-608.333658	-572.628692	-1429.172523	-687.158375	-611.930723	-572.634697
ΔG (au)	-608.374666	-572.677490	-1429.228069	-687.209130	-611.978951	-572.679951
$E_{therm.}$(kcal/mol)	55.451	108.178	99.238	131.531	127.579	109.162
Cv (cal/molK)	22.083	40.183	41.393	47.346	44.203	38.464
S (cal/molK)	86.308	102.704	116.906	106.823	101.503	95.245
μ (D)	3.735	2.943	1.542	3.636	3.802	1.571
α (au)	69.143	73.194	139.315	85.993	82.541	71.352

Lipophilicity and Water Solubility Features

The lipophilicity and water-soluble characteristics of the molecular systems have an essential role in investigating the physicochemical properties that help predict, evaluate, and provide a deep understanding of the chemical processes. In addition to the basic information of the molecular systems, especially, they are critical properties in drug-design research. In this respect, the determined lipophilic and water-soluble scores of the studied compounds were summarized in Table 2.

The lipophilicity indexes of the compounds were estimated by using five different approaches, and the average lipophilicity was given in Table 2 as well. Depending on the approach used, the lipophilicity indexes changed in the following orders:

iLOGP: DATS (2.65)> AITC (1.93)> Rh (0.85)> Gal (-0.12)> C-Ar (-0.39)> Ar (-0.65)

XLOGP3: DATS (2.64)> AITC (2.41)> Rh (-2.09)> Ar (-2.32)> C-Ar (-3.02)> Gal (-3.24)

WLOGP: DATS (3.39)> AITC (1.28)> Rh (-2.19)> C-Ar (-2.58)> Ar (-2.74)> Gal (-3.22)

MLOGP: DATS (2.35)> AITC (1.98)> Rh (-1.94)> C-Ar (-2.32)> Ar (-2.48)> Gal (-2.75)

SILICOS-IT: DATS (2.38)> AITC (2.37)> Ar (-1.29)> C-Ar (-1.70)> Rh (-1.72)> Gal (-2.30)

Avg.: DATS (2.68)> AITC (1.99)> Rh (-1.42)> Ar (-1.90)> C-Ar (-2.00)>Gal (-2.33)

Table 2. Lipophilicity and water solubility of the studied compounds

	AITC	Ar	DATS	Gal	Rh	C-Ar
Formula	C4H5NS	C5H10O5	C6H10S3	C6H12O6	C6H12O5	C5H10O5
Molecular weight(g/mol)	99.15	150.13	178.34	180.16	164.16	150.13
Num. heavy atoms	6	10	9	12	11	10
Num. arom. heavy atoms	0	0	0	0	0	0
Fraction Csp3	0.25	0.80	0.33	1.00	1.00	1.00
Num. rotatable bonds	2	4	6	1	0	0
Num. H-bond acceptors	1	5	0	6	5	5
Num. H-bond donors	0	4	0	5	4	4
Molar Refractivity	30.03	31.00	52.78	35.74	34.57	29.77
TPSA (Å²)	44.45	97.99	75.90	110.38	90.15	90.15
Lipophilicity						
iLOGP	1.93	-0.65	2.65	-0.12	0.85	-0.39
XLOGP3	2.41	-2.32	2.64	-3.24	-2.09	-3.02
WLOGP	1.28	-2.74	3.39	-3.22	-2.19	-2.58
MLOGP	1.98	-2.48	2.35	-2.75	-1.94	-2.32
SILICOS-IT	2.37	-1.29	2.38	-2.30	-1.72	-1.70
Avg. LogPo/w	1.99	-1.90	2.68	-2.33	-1.42	-2.00
Water Solubility						
Log S (ESOL)	-1.84	0.95	-2.21	1.15	0.46	1.13
Solubility (mg/mL)	1.43	1350	109	2550	4.72	2030
Class	VS	HS	S	HS	HS	HS
Log S (Ali)	-2.99	0.80	-3.88	1.49	0.72	1.69
Solubility (mg/mL)	0.103	944	0.0233	5610	870	7340
Class	S	HS	S	HS	HS	HS
Log S (SILICOS-IT)	-0.85	1.94	-1.91	2.62	2.06	2.23
Solubility (mg/mL)	14.1	13000	2.18	74200	19100	25600
Class	S	S	S	S	S	S

*The abbreviations are defined as S, Soluable; VS, very soluable. HS; Highly soluble

As known well, the water-solubility classification of the relevant molecule is as Insoluble< -10 < poorly< -6 < moderately < -4< soluble < -2< very < 0 < highly. Accordingly, all compounds were determined water soluble depending on all approaches used, but the most soluble one would be Gal while the less soluble was found to be DATS, as implied by the lipophilicity indexes. Considering the importance of both the lipophilicity and water solubility properties of the compounds due to their role in the ADMET characteristics of the molecular systems, the computed results will be hoped to help further early-stage drug-design research.

Accordingly, the DATS, including the -S-S-S bridge between the two allyl terminals was determined the most lipophilic compound, as expected by the structural nature of the aliphatic chain and the presence of the sulfurs. Due to the presence of the hydrophilic -OH groups, Gal, C-Ar, Ar, and Rh compounds were determined to be less lipophilic among the compounds, as expected. Although the Ar was determined to be less lipophilic according to the iLOGP scores, the Gal molecule was found to be less lipophilic based on the other approaches and the average scores.

Furthermore, the water solubility scores of the compounds were calculated in the following orders:

Log S (ESOL): Gal (1.15)> C-Ar (1.13)> Ar (0.95)> Rh (0.46)> AITC (-1.84)> DATS (-2.21)

Log S (Ali): C-Ar (1.69)> Gal (1.49)> Ar (0.80)> Rh (0.72)> AITC (-2.99)> DATS (-3.88)

Log S (SILICOS-IT): Gal (2.62)> C-Ar (2.23)> Rh (2.06)> Ar (1.94)> AITC (-0.85)> DATS (-1.91)

Druglikeness and Bioavailability Study

Also, computational tools have been efficiently applied to explore potential agents by predicting the structural necessities of drug-design research in terms of pharmacokinetics. Herein, the BOILED-Egg model and pharmacokinetic radar graphs of the compounds were visualized in Fig. 2; the calculated bioavailability and drug-likeness characteristics were presented in Table 3.

The five approaches like Lipinski, Ghose, Veber, Egan, and Muegge were used to determine the drug-likeness properties of the compounds. According to the Lipinski, Veber, and Egan formulae, all compounds could be bioavailable since there were not determined a violations in terms of structural and physical views. Moreover, the DATS molecule could not be a bioavailable agent because of the atom number<20 depending on the Ghose rules and MW<200 depending on the Muegge rules. On the other hand, AITC, Ar, and C-Ar molecules would have 3 violations depending on the Ghose scales, and thus their bioavailability could be in danger. According to Ghose, the limitations for the bioavailability of AITC were related to the structural properties that were MW<160, MR<40, and Natoms<20, while the possible contravening for Ar and C-Ar molecules were also related to the physicochemical properties (WLOGP<-0.4). According to Muegge, the C atom number of the AITC could be a problem in possibly being used for biological purposes due to it being calculated lower than 5. In summary, the bioavailability values of all compounds were determined to be 0.55, which implied that the studied compounds could be promising bioavailable agents, depending on the Abbott scores.

According to the BOILED-Egg model, the AITC and DATS molecules would have the capability of BBB permeation (yolk region of the BOILED-Egg), while the other molecules would have no ability in terms of the BBB permeation due to their location out of the yolk of the egg. Among the studied compounds, the Rh molecule could have a potency of P-gp substrate because it was positioned in the range of the white of the BOILED-Egg, while the other compounds could have no potential for P-gp substrate. Here, it could be said that the -CH3 substitution makes the Rh gain P-gp substrate potency because the C-Ar molecule included the -H substitution in the same position as -CH3 of Rh. On the other hand, the hydroxymethyl substitution on the pyran ring of Gal could be responsible for being far away from the possible power in terms of pharmacokinetics. Also, the red frame on the radar plots of the compounds showed the optimal physicochemical space for oral bioavailability.

Table 3. Druglikeness and bioavailability scores

	AITC	*Ar*	*DATS*	*Gal*	*Rh*	*C-Ar*
Lipinski	Yes	Yes	Yes	Yes	Yes	Yes
Ghose	No 3 violations: MW<160, MR<40, #atoms<20	No 3 violations: MW<160, WLOGP<-0.4, MR<40	No 1 violation: #atoms<20	No 2 violations: WLOGP<-0.4, MR<40	No 2 violations: WLOGP<-0.4, MR<40	No 3 violations: MW<160, WLOGP<-0.4, MR<40
Veber	Yes	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes	Yes
Muegge	No 2 violations: MW<200, #C<5	No 2 violations: MW<200, XLOGP3<-2	No 1 violation: MW<200	No 2 violations: MW<200, XLOGP3<-2	No 2 violations: MW<200, XLOGP3<-2	No 2 violations: MW<200, XLOGP3<-2
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55

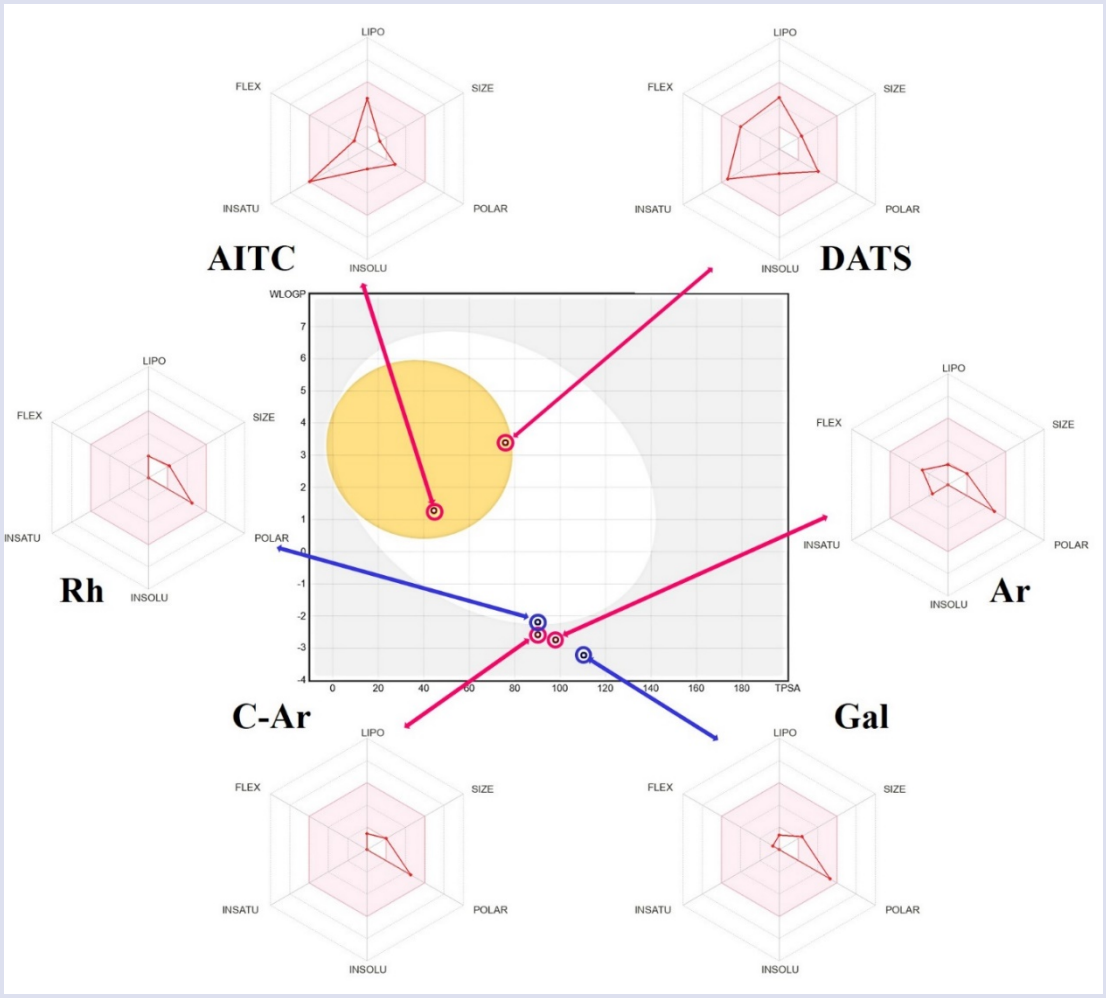


Fig. 2. BOILED-Egg model and pharmacokinetic radar graphs

FMO (Frontier Molecular Orbital) Analysis and MEP (Molecular Electrostatic Potential)

The energies and shapes of the FMOs of the molecular systems have provided helpful information by pointing out the possible reactivity directions and region(s) and applying them to different types of molecular systems, from simple organics to complex structures. Herein, the calculated reactivity values of the compounds were presented in Table 4; the surfaces of the HOMO, LUMO, and MEP of them were displayed in Fig. 3.

The global reactivity parameters of the compounds changed as the following orders:

H (-I): DATS (-6.681)> AITC (-6.788)> Rh (-7.180)> Gal (-7.233)> C-Ar -7.284)> Ar (-7.371)

L (-A): C-Ar (0.645)> Rh (0.488)> Gal (0.359)> AITC (-0.823)> C-Ar (-1.547)> DATS (-1.635)

ΔE (L-H): C-Ar (7.930)> Rh (7.668)> Gal (7.592)> AITC (5.965)> Ar (5.824)> DATS (5.046)

χ: C-Ar (-3.319)> Rh (-3.346)> Gal (-3.437)> AITC (-3.805)> DATS (-4.158)> Ar (-4.459)

η: C-Ar (3.965)> Rh (3.834)> Gal (3.796)> AITC (2.983)> Ar (2.912)> DATS (2.523)

ω: DATS (0.126)> Ar (0.125)> AITC (0.089)> Gal (0.057)> Rh (0.054)> C-Ar (0.051)

ω^+: DATS (0.061)> Ar (0.057)> AITC (0.033)> Gal (0.011)> Rh (0.010)> C-Ar (0.008)

ω^-: Ar (0.221)> DATS (0.214)> AITC (0.173)> Gal (0.138)> Rh (0.133)> C-Ar (0.130)

ΔN_{max}: DATS (1.648)> Ar (1.531)> AITC (1.276)> Gal (0.905)> Rh (0.873)> C-Ar (0.837)

ΔE_{back}: DATS (-0.631)> Ar (-0.728)> AITC (-0.746)> Gal (-0.949)> Rh (-0.958)> C-Ar (-0.991)

According to the HOMO energy order, the DATS could be the best nucleophile, while the Ar could be the less nucleophilic character. Also, the C-Ar would prefer to interact with the external system, whereas the intramolecular charge transfer for the DATS would be possible. In terms of the electronic chemical stability, the χ orders implied that the Ar would be more stable than the others. Also, C-Ar could be the hardest agent, whereas the DATS was determined to be the softer agent among the compounds. The DATS compound would have the most electrophilic character and electron-accepting power, whereas the C-Ar could have the lowest electrophilic character and less electroaccepting potency. Also, the electron-donating capability of all compounds could be domineering in comparison to the electron acceptance

potency. Last, the C-Ar agent could gain more stability via back-donation than the other compounds.

Furthermore, the FMO graphs are used as a popular tool for studying the electronic properties of molecular structure in drug discovery, design, and pharmacokinetic profiling, as they help to understand the reactivity of a molecule, i.e., how it can behave in chemical reactions. In this regard, the HOMO density of the compounds Ar, Gal, Rh, and C-Ar expanded on the whole surface, while the HOMO of both AITC and DATS molecules separated on the surface except for the allyl group(s). Except for the Ar compound, the LUMO of the other agents was also distributed on the whole surface. The LUMO for the Ar agent was half expanded on the surface. Moreover, Molecular Electrostatic Potential (MEP) diagrams are visual representations of the electron density on the surface of molecules of interest, where the positive and negative charge densities in various regions of the molecule are expressed in colors. Generally, red represents electron-rich regions, and blue represents electron-poor regions. Other colors, such as yellow and green, indicate neutral or intermediate potential values. From Fig. 3, the red color (V<0) as a marker of the electron-abundance site appeared on the allyl group(s) for both the AITC and DATS molecules, whereas the blue color (V>0) as a sign of the electron-poor field appeared on the sulfur (s) of these compounds. Also, the tri-sulfur bridge of the DATS and sulfur atom of the AITC molecules would seem blue. For the compounds, the H atom of the -OH group could wear blue, while the oxygens of these compounds appeared by orange color as a marker of the electron-rich region at a moderate-level.

Table 4. The chemical reactivity indices

	AITC	Ar	DATS	Gal	Rh	C-Ar
H (-I)	-6.788	-7.371	-6.681	-7.233	-7.180	-7.284
L (-A)	-0.823	-1.547	-1.635	0.359	0.488	0.645
ΔE (L-H)	5.965	5.824	5.046	7.592	7.668	7.930
χ	-3.805	-4.459	-4.158	-3.437	-3.346	-3.319
η	2.983	2.912	2.523	3.796	3.834	3.965
ω	0.089	0.125	0.126	0.057	0.054	0.051
ω^+	0.033	0.057	0.061	0.011	0.010	0.008
ω^-	0.173	0.221	0.214	0.138	0.133	0.130
$\Delta N_{max.}$	1.276	1.531	1.648	0.905	0.873	0.837
$\Delta E_{back.}$	-0.746	-0.728	-0.631	-0.949	-0.958	-0.991

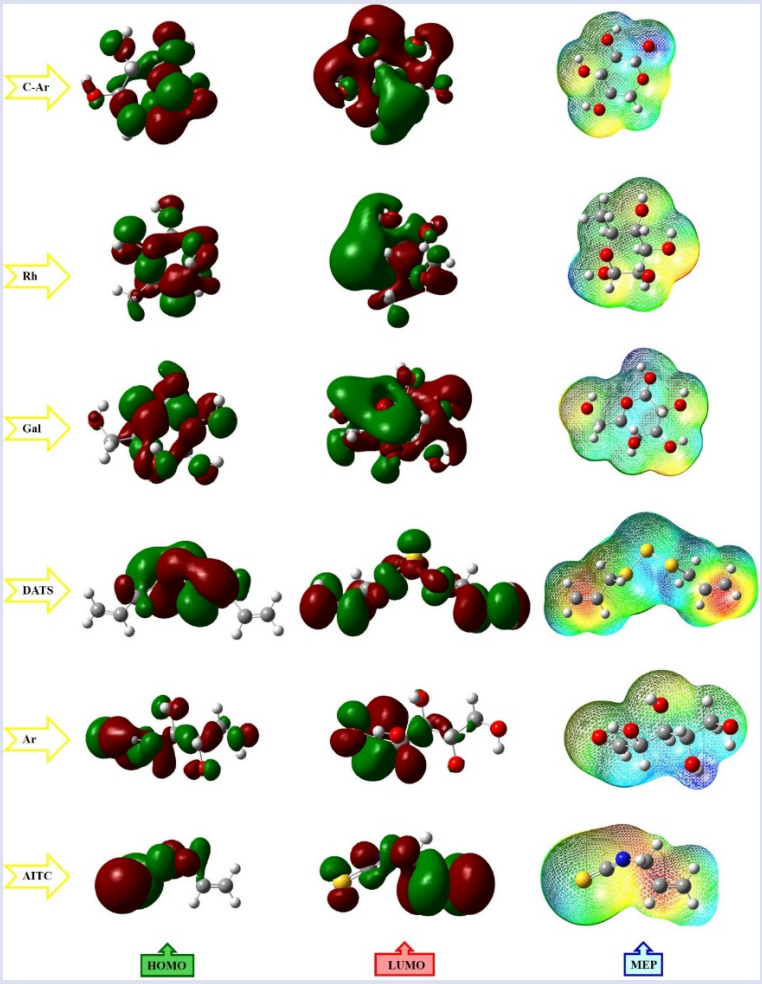


Fig. 3. HOMO& LUMO (isoval:0.02), and MEP (isoval:0.0004) plots

Conclusions

Herein, the phytochemical agents AITC, Ar, DATS, Gal, Rh, and C-Ar have been explored in relation to the electronic structure and drug-likeness relationship. In this regard, the optimized and confirmed structures were used for future analyses of the compounds. According to the average lipophilicity indices, the DATS agent was predicted as the most lipophilic compound, with the order of Avg.: DATS (2.68)> AITC (1.99)> Rh (-1.42)> Ar (-1.90)> C-Ar (-2.00)>Gal (-2.33). Depending on the Log S (SILICOS-IT) approach, Gal (2.62)> C-Ar (2.23)> Rh (2.06)> Ar (1.94)> AITC (-0.85)> DATS (-1.91), the DATS was predicted the less water-soluble agent whereas the Gal was estimated to have the most water solubility. The FMO analyses revealed the possible reactivity features of the compounds. Namely, the hardness order of the compounds displayed that the C-Ar C-Ar (3.965 eV) would be the hardest, whereas the DATS (2.523 eV) would be the softest one among the compounds. Furthermore, the C-Ar (-0.991) could gain the most stability via back-donation, whereas the DATS (-0.631 eV) could gain less stability via back-donation. From the results obtained, this work is hoped to help the deep understanding of the relationship between the electronic structure and bioavailability & drug-likeness.

Conflicts of interest

The authors declare that, there are no conflicts of interest in this work.

Acknowledgments

All calculations have been carried out at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid e-Infrastructure).

References

[1] Whittaker M. M., Whittaker J. W., The active site of galactose oxidase, *Journal of Biological Chemistry*, 263 (13) (1988) 6074-6080.

[2] Jansen L. M., van Rijbroe, K. W. M., den Bakker P. C., Klaassen-Heshof D. J., Kolkman W. J. B., Venbrux N., Migchielsen V., Hutzezon J., Lenferink W. B., Lücker S., Ranoux A., Raaijmakers H. W. C., Boltje T. J., Synthesis and Performance of Biobased Surfactants Prepared by the One-Pot Reductive Amination of l-Arabinose and d-Galacturonic Acid, *ACS Sustainable Chemistry & Engineering*, 11 (45) (2023) 16117-16123.

[3] Seki T., Hosono T., Hosono-Fukao T., Inada K., Tanaka R., Ogihara J., Ariga T., Anticancer effects of diallyl trisulfide derived from garlic, *Asia Pac. J. Clin. Nutr.*, 17 (1) (2008) 249-252.

[4] Puccinelli M. T., Stan S. D., Dietary Bioactive Diallyl Trisulfide in Cancer Prevention and Treatment, *International Journal of Molecular Sciences*, 18(8) (2017) 1645.

[5] Powolny A. A., Singh S. V., Multitargeted prevention and therapy of cancer by diallyl trisulfide and related Allium vegetable-derived organosulfur compounds, *Cancer Letters*, 269(2) (2008) 305-314.

[6] Lai K. C., Hs S. C., Kuo, C. L., Yang J. S., Ma C. Y., Lu H. F., Tang N., Hsia T., Ho H., Chung J. G., Diallyl sulfide, diallyl disulfide, and diallyl trisulfide inhibit migration and invasion in human colon cancer colo 205 cells through the inhibition of matrix metalloproteinase-2,-7, and-9 expressions, *Environmental Toxicology*, 28(9) (2013) 479-488.

[7] Blažević I., Đulović A., Maravić A., Čikeš Čulić V., Montaut S., Rollin P., Antimicrobial and cytotoxic activities of Lepidium latifolium L. Hydrodistillate, extract and its major sulfur volatile allyl isothiocyanate, *Chemistry & Biodiversity*, 16(4) (2019) e1800661.

[8] Kelly C. L., Taylor G. M., Hitchcock A., Torres-Méndez, A., Heap, J. T., A Rhamnose-Inducible System for Precise and Temporal Control of Gene Expression in Cyanobacteria, *ACS Synthetic Biology,* 7(4) (2018) 1056-1066.

[9] Kelly C. L., Liu Z., Yoshihara A., Jenkinson S. F., Wormald M. R., Otero J., Estévez A., Kato A., Marqvorsen M. H. S., Fleet G. W. J., Estévez R. J., Izumori K., Heap J. T., Synthetic Chemical Inducers and Genetic Decoupling Enable Orthogonal Control of the rhaBAD Promoter, *ACS Synthetic Biology*, 5(10) (2016) 1136-1145.

[10] Tomsik P., Soukup T., Cermakova E., Micuda S., Niang M., Sucha L., Rezacova M., L-rhamnose and L-fucose suppress cancer growth in mice, *Central European Journal of Biology*, 6 (2011) 1-9.

[11] Lin H., Ramesh S., Chang Y., Tsai C., Tsai C., Shibu M. A., Tamilselvi S., Mahalakshmi B., Kuo W., Huang C., D-galactose-induced toxicity associated senescence mitigated by alpinate oxyphyllae fructus fortified adipose-derived mesenchymal stem cells, *Environmental Toxicology*, 36(1) (2021) 86-94.

[12] Liu G., Hale G. E., Hughes C. L., Galactose metabolism and ovarian toxicity, *Reproductive Toxicology*, 14(5) (2000) 377-384.

[13] Coba-Jiménez L., Maza J., Guerra M., Deluque-Gómez J., Cubillán N., Interaction of Ciprofloxacin with Arabinose, Glucosamine, Glucuronic Acid and Rhamnose: Insights from Genetic Algorithm and Quantum Chemistry, *Chemistry Select*, 7(2) (2022) e202103836.

[14] Su Y., Chen L., Cheng Y., Zhang F., Su Y., Li Z., Raman spectroscopic characteristics of diallyl trisulfide acting on trans-crotonaldehyde, *Journal of Raman Spectroscopy*, 46(11) (2015) 1067-1072.

[15] Dehghani A., Mostafatabar A. H., Ramezanzadeh B., Synergistic anticorrosion effect of Brassica Hirta phytoconstituents and cerium ions on mild steel in saline media: Surface and electrochemical evaluations, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 656 (2023) 130503.

[16] Frisch M. J., Gaussian 09W, Revision D.01, Gaussian, Inc, Wallingford CT, (2013).

[17] Becke A. D., A new mixing of Hartree–Fock and local density-functional theories, *J. Chem. Phys.,* 98 (1993) 1372-1377.

[18] Lee C., Yang W., Parr R. G., Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev.,* B37 (1988) 785-789.

[19] Raghavachari K., Binkley J. S., Seeger R., Pople J. A., Self-Consistent Molecular Orbital Methods. 20. Basis set for correlated wave-functions, *J. Chem. Phys*., 72 (1980) 650-654.

[20] GaussView 6.0.16, Gaussian, Inc, Wallingford CT, 2016.
[21] Herzberg G., Molecular Spectra and Molecular Structure III, 1st Edition, D. Van Nostrand Company, Inc., New York, (1964).
[22] Serdaroglu G., Durmaz S., DFT and statistical mechanics entropy calculations of diatomic and polyatomic molecules, *Indian J. Chem*., 49 (2010) 861-866.
[23] Koopmans T., Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den Einzelnen Elektronen Eines Atoms, *Physica*, 1 (1934) 104-113.
[24] Perdew J. P., Parr R. G., Levy M., Balduz J. L., Density-Functional Theory for Fractional Particle Number: Derivative Discontinuities of the Energy, *Phys. Rev. Lett*., 49(23) (1982) 1691-1694.
[25] Parr R. G., Pearson R. G., Absolute hardness: companion parameter to absolute electronegativity, *J. Am. Chem. Soc.*, 105 (1983) 7512-7516.
[26] Gazquez J. L., Cedillo A., Vela A., Electrodonating and Electroaccepting Powers, *J. Phys. Chem. A*, 111 (10) (2007) 1966-1970.
[27] Gomez B., Likhanova N. V., Domínguez-Aguilar M. A., Martínez-Palou R., Vela A., Gazquez J. L., Quantum Chemical Study of the Inhibitive Properties of 2-Pyridyl-Azoles, *J. Phys. Chem. B*, 110(18) (2006) 8928-8934.
[28] Daina A., Michielin O., Zoete V., iLOGP: a simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach, *J. Chem. Inf. Model.*, 54(12) (2014) 3284-3301.
[29] Cheng T., Zhao Y., Li X., Lin F., X Y., Zhang, X., Lai L., Computation of octanol–water partition coefficients by guiding an additive model with knowledge, *J. Chem. Inf. Model.*, 47(6) (2007) 2140-2148.
[30] Wildman S. A., Crippen G. M., Prediction of physicochemical parameters by atomic contributions, *J. Chem. Inf. Comp. Sci.,* 39(5) (1999) 868-873.
[31] Lipinski C. A., Lombardo F., Dominy B. W., Feeney P. J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug Deliv. Rev.,* 64 (2012) 4-17.
[32] Computational approaches streamlining drug discovery. Available at: https://www.silicos-it.be. Retrieved April 28, (2023).
[33] Daina A., Michielin O., Zoete V., SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules, *Sci. Rep.-UK*, 7(1) (2017) 1-13.
[34] Ali J., Camilleri P., Brown M. B., Hutt A. J., Kirton S. B., In silico prediction of aqueous solubility using simple QSPR models: the importance of phenol and phenol-like moieties, *J. Chem. Inf. Model*., 52(11) (2012) 2950-2957.
[35] Delaney J. S., ESOL: estimating aqueous solubility directly from molecular structure, *J. Chem. Inf. Comp. Sci*., 44(3) (2004) 1000-1005.
[36] Ghose A. K., Viswanadhan V. N., Wendoloski J. J., A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases, *J. Comb. Chem*., 1(1) (1999) 55-68.
[37] Veber D. F., Johnson S. R., Cheng H. Y., Smith B. R., Ward K. W., Kopple K. D., Molecular properties that influence the oral bioavailability of drug candidates, *J. Med. Chem*., 45(12) (2002) 2615-2623.
[38] Egan W. J., Merz K. M., Baldwin J. J., Prediction of drug absorption using multivariate statistics, *J. Med. Chem*., 43(21) (2000) 3867-3877.
[39] Muegge I., Heald S. L., Brittelli D., Simple selection criteria for drug-like chemical matter, *J. Med. Chem*., 44(12) (2001) 1841-1846.
[40] Martin Y. C., A bioavailability score, *J. Med. Chem*., 48(9) (2005) 3164-3170.