SCREENING 2–MERCAPTOIMIDAZOLE DERIVATIVES FOR BREAST CANCER TREATMENT

SÀNG LỌC CÁC DẪN XUẤT 2–MERCAPTOIMIDAZOLE SỬ DỤNG LÀM THUỐC TRONG ĐIỀU TRỊ UNG THƯ VÚ

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Abstract - 2–Mecaptoimidazole (**2MC**), its tautomer (**2MI**), and derivatives were evaluated in silico for their antioxidant activity and potential for breast cancer drug development. In this investigation, 14 substituents were placed in various positions on ovothiol rings. **2MC**, **2MI**, and derivatives, including **5–NH_2–2MC**, **5–NMe_2–2MC**, **5–NH_2–2MI**, **5– NMe_2–2MI**, have BDE values that are lower than those of prominent antioxidants such as viniferifuran, resveratrol, and puerarin. These outcomes imply that the reaction between these substances and the radical in the gas phase may follow the FHT mechanism. All studied compounds have negative binding energies with ERα (1HVY) and Aromatase (1DNU), and all their ADME parameters meet the requirements of Lipinski's rule. Among them, **4–COOH–2MC**, **4–C_6H_5–2MC**, **5–COOH–2MC**, **5–C_6H_5–2MC**, **5–NH_2–2MC**, **1–C_6H_5–2MI, 5–COOH–2MI**, **5–CH≡C–2MI** and **5–C_6H_5–2MI** are potential compounds for drug development in breast cancer treatment, similar to the commercially available doxorubicin.

Key words - 2–Mecaptoimidazole; breast cancer; antioxidant; Erα; Aromatase

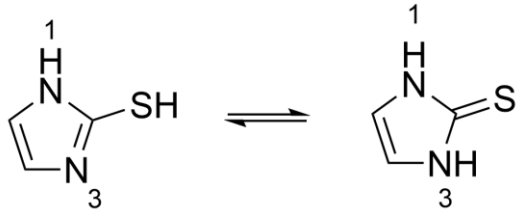
Tóm tắt - 2–Mecaptoimidazole **(2MC)**, hợp chất tautomer của nó (**2MI**) và các dẫn xuất được sàng lọc để đánh giá tiềm năng chống oxy hoá và điều trị ung thư vú. Khảo sát 14 nhóm thế trên vòng ovothiol cho thấy, **2MC**, **2MI** và các dẫn xuất **5–NH_2–2MC**, **5–NMe_2–2MC**, **5–NH_2–2MI** và **5–NMe_2–2MI** có giá trị BDE thấp hơn các hợp chất chống oxy hoá như viniferifuran, resveratrol và puerarin, dự đoán phản ứng bắt gốc tự do trong pha khí có thể xảy ra theo cơ chế FHT. Các hợp chất nghiên cứu đều có năng lượng tương tác âm với ERα (1HVY) và Aromatase (1DNU), các thông số dược động học ADME đều tuân thủ quy tắt Lipinsky, trong đó **4–COOH–2MC**, **4–C_6H_5–2MC**, **5–COOH–2MC**, **5–C_6H_5–2MC**, **5–NH_2–2MC**, **1–C_6H_5–2MI, 5–COOH–2MI**, **5–CH≡C–2MI** và **5–C_6H_5–2MI** là các dẫn xuất có tiềm năng để phát triển thuốc điều trị ung thư vú tương tự như doxorubicin.

Từ khóa – 2–Mecaptoimidazole; ung thư vú; chống oxy hoá; Erα; Aromatase

1. Introduction

Previous studies showed that the substances with the imidazole ring and sulfur demonstrated a lot of biological activities, including antioxidant, anticancer, antitubercular, antifungal, analgesic, and anti–HIV activities [1, 2]. Numerous imidazole derivatives have been used in the clinic to treat various types of diseases [3]. Mecaptoimidazole derivatives are formed from the substitution of thiol or thione onto the imidazole ring [4, 5]. These derivatives have been proven as promising antioxidant agents, with the rate constant of the hydroxyl radical scavenging reaction much higher than that of popular antioxidants such as Trolox, ascorbic acid, and trans-resveratrol [6, 7]. 2–Mecaptoimidazole (**2MC**), which is one of the natural ovothiols among them, was even proven to be a novel corrosion inhibitor for steel [8-10]. The tautomerization of **2MC** is thermodynamically favorable in both polar and non–polar environments (Figure 1).

In this study, the **2MC** compound and its tautomer (**2MI**), as well as 70 derivatives were evaluated for their antioxidant activities and the potential of being used as a drug in breast cancer treatment. 14 popular substitutes in various positions on the imidazole ring, including the electron–withdrawing groups and the electron–donating groups were used such as NO_2, CN, CF_3, COOH, F, Cl, Br, CH≡C, C_6H_5, CH=CH, C_2H_5, OH, NH_2, and NMe_2. The target proteins used in this study were ERα (1HVY) and Aromatase (1DNU), one of the two main biomarkers in breast cancer [11].



2MC **2MI**

Figure 1. *Tautomerization of 2–Mercaptoimidazole*

2. Method

2.1. Computational method

The radical scavenging activity of the studied compounds was evaluated via three main mechanisms, including formal hydrogen transfer (FHT), sequential proton loss electron transfer (SPLET), single electron transfer followed by proton transfer (SETPT) [12-15]. The thermodynamic parameters corresponding to each mechanism were computed following the reactions:

FHT: $M–H \rightarrow M^{\bullet} + H^{\bullet}$ (BDE)

SETPT: M–H → $M–H^{\bullet+}$ + e^- (IE)

$M–H^{\bullet+}$ → $M^\bullet$ + H^+ (PDE)

SPLET: M–H → M^- + H^+ (PA)

M^-→ $M^\bullet$+ e^- (ETE)

With:

BDE = $H(M^\bullet) + H(H^\bullet) – H(M–H)$

IE = $H(M–H^{\bullet+}) + H(e^-) – H(M–H)$

PA = $H(M^-) + H(H^+) – H(M–H)$

All of the calculations in this study were carried out with Gaussian 16 programs [16-18], with the model chemistry of M062X/6–311++G(d,p). This model of calculation has been proven as a good method for predicting the thermodynamic parameters as well as the kinetics of antioxidant reactions [12, 17, 19, 20].

2.2. Docking method

All the docking work was carried out using Autodock Vina (v 1.1.2) [21]. The molecular geometries of studied substances were optimized using method M06–2X/6–311++G(d,p) before docking. The target proteins were taken from Protein Data Bank (https://www.rcsb.org/), including ERα (1HVY) and Aromatase (1DNU), one of the two main biomarkers in breast cancer [11]. Both proteins and ligands were prepared using AutoDockTools (v. 1.5.7). Search space was built as a cup of 40 Å, exhaustiveness was set at 8, the grid points separated 1 Å, which centered at x = 26.089, y = 0.172, z = 15.003 for 1DNU and x = 26.154, y = 19.548, z = 17.110 for 1HVY.

2.3. ADME method

The ADME properties of studied compounds, including the number of hydrogen bond acceptors (nHA), the sum of tabulated surface contributions of polar fragments (TPSA), the number of hydrogen bond donors (nHD), the logarithm of the n–octanol/water distribution coefficient (miLogP), the molecular weight (MW) were calculated by Molinspiration online property calculation (https://www.molinspiration.com), the human hepatotoxicity (H–HT), the Ames test for mutagenicity (AMES Toxicity) were predicted using the ADMETlab 2.0 tool [22]. The drug–likeness and drug–score values were computed using Osiris Property Explorer software (http://www.organic–chemistry.org/prog/peo/).

3. Results and discussion

3.1. Thermodynamic parameters and radical scavenging of 2MC, 2MI and derivatives

Recent studies have elucidated that the SPLET mechanism only plays an important role in the aqueous solution [12, 23]. Thus, in this study, we focused on the BDE and IE values of the FHT and SETPT mechanisms for evaluating the radical scavenging activity of **2MC**, **2MI,** and derivatives in the gas phase. The results are shown in Tables 1, 2, 3 and Figure 2, 3, 4, and 5.

From the calculated data, the BDE S–H bond of **2MC** is 73.6 kcal.mol^{-1} (Table 1), and that of derivatives ranged from 67.1 to 81.7 kcal.mol^{-1} (Table 2), lower than that of natural antioxidants such as viniferifuran (82.7 kcal.mol^{-1}) [24], resveratrol (83.9 kcal.mol^{-1}) [24], and puerarin (87.3 kcal.mol^{-1}) [25]. These results suggest that the reaction between **2MC** as well as derivatives and the radical may follow the FHT mechanism. The N–H BDE value is 87.4 kcal.mol^{-1}, higher than that of S–H bond (Table 1). The IE of **2MC** and derivatives ranged from 157.6 to 210.7 kcal.mol^{-1}, nearly 2.6 times higher than the BDE value of the N–H bond (Tables 1 and 2).

Table 1. *The calculated BDE and IE values (kcal.mol^{-1}) in the gas phase of **2MC** and **2MI***

Compounds	Position	BDE	IE
2MC	N–H	87.4	189.3
	S–H	73.6	
2MI	N–H	81.9	178.3
	C–H	115.4	

Table 2. *The calculated BDE and IE values (kcal.mol^{-1}) in the gas phase of **2MC** derivatives*

Substitutions/ Positions	BDE			IE		
	1	4	5	1	4	5
NO_2	81.7	76.7	78.3	204.5	208.4	210.7
CN	76.9	76.4	76.7	206.0	203.8	203.6
CF_3	76.5	76.1	76.9	199.1	202.3	202.9
COOH	81.2	76.0	77.0	193.5	196.7	197.5
F	76.0	72.7	72.7	199.0	192.2	191.3
Cl	75.9	73.4	73.1	194.4	190.5	189.1
Br	75.1	73.5	73.9	191.6	189.8	189.0
CH≡C	76.1	74.3	73.7	192.5	187.0	185.6
C_6H_5	75.0	72.5	72.0	181.6	174.8	174.1
CH=CH	73.8	73.2	72.9	186.8	179.4	179.9
C_2H_5	73.6	72.7	72.1	182.3	181.5	180.0
OH	70.7	71.5	70.3	191.1	180.8	178.7
NH_2	77.7	68.8	68.7	186.0	166.4	167.3
NMe_2	77.4	68.4	67.1	182.4	157.6	158.2
2MC	73.6 (S–H)			189.3		

According to the data presented in Tables 1 and 3, the BDE (N–H) of **2MI** is less than that of the C–H bond but greater than that of the S-H bond of **2MC**. Similarly, the IE value is marginally lower than the **2MC** value. The BDE (N–H) ranged from 74.5 to 85.4 kcal/mol for derivatives, which was greater than the BDE (S–H) for **2MC** derivatives.

The differences in the BDE (S–H) values between **2MC** and studied derivatives are calculated and shown in Figure 2. In position 1, the presence of substitutes increases the BDE (S–H) values, except for C_2H_5 (ΔBDE ~0.0 kcal.mol^{-1}) and OH (ΔBDE = –2.9 kcal.mol^{-1}). The most significant changes were observed at NO_2 and COOH, with ΔBDE at 8.1 kcal.mol^{-1} and 7.6 kcal.mol^{-1}, respectively. In positions 4 and 5, the presence of electron–withdrawing groups (ie., NO_2, CN, CF_3, and COOH) increase the BDE (S–H) with the ΔBDE ranged from 2.4 to 4.7 kcal.mol^{-1}, and the electron–donating group (ie., C_2H_5, OH, NH_2–2MC and NMe_2) decrease the BDE (S–H) with the ΔBDE ranged from –0.9 to –6.5 kcal.mol^{-1}. On the contrary, the change in BDE (S–H) caused by F, Cl, Br, and CH≡C are relatively small (0.1 to 0.9 kcal.mol^{-1} in absolute). It was remarkable that the BDE (S–H) of **4–NMe_2–2MC** and **4–NMe_2–2MC** are lower than that of any other derivatives.

Table 3. *The calculated BDE and IE values (kcal.mol^{-1}) in the gas phase of* ***2MI*** *derivatives*

Substitution/ Position	BDE		IE	
	1	5	1	5
NO_2	84.8	81.9	192.6	195.6
CN	83.5	81.4	194.2	191.5
CF_3	82.9	80.6	187.2	188.9
COOH	84.2	85.4	183.3	184.0
F	80.9	75.3	184.8	182.4
Cl	81.6	78.4	181.5	180.7
Br	81.6	78.9	179.6	179.9
CH≡C	82.4	82.4	180.7	178.1
C_6H_5	82.0	80.0	171.0	169.8
CH=CH	82.6	81.5	176.6	174.2
C_2H_5	82.4	81.4	172.0	172.0
OH	82.3	78.3	182.2	173.3
NH_2	81.4	75.0	173.7	165.3
NMe_2	81.5	74.5	170.5	159.0
2MI	81.9 (N–H)		178.3	

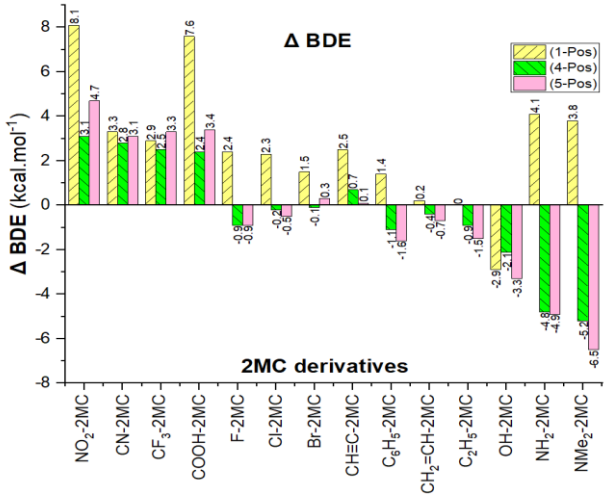


Figure 2. *The calculated ΔBDEs (in kcal.mol^{-1}), compared with* ***2MC****) of monosubstituted* ***2MC****s in the gas phase*

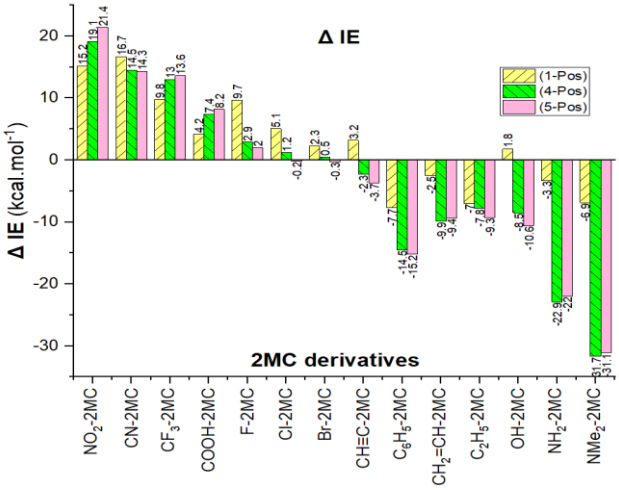


Figure 3. *The calculated ΔIEs (in kcal.mol^{-1}, compared with* ***2MC****) of monosubstituted* ***2MC****s in the gas phase*

From the data in Figure 3, apart from Cl, Br, CH≡C and OH, the electron-withdrawing groups (ie., NO_2, CN, CF_3, COOH, and F) increase the IE values, whereas the electron–donating groups (ie., C_6H_5, CH=CH, C_2H_5, NH_2–2MC and NMe_2) decrease the IE value at all positions. The strongest effective substituent at 4 and 5 positions is NMe_2 with ΔIE ranging from –31.1 kcal.mol^{-1} to 31.7 kcal.mol^{-1}.

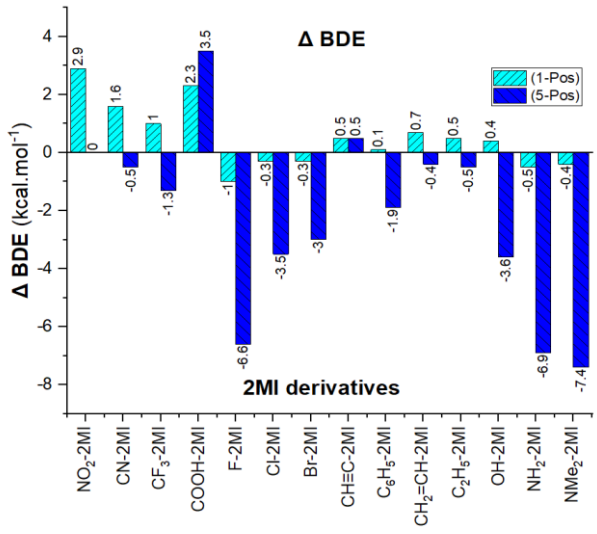


Figure 4. *The calculated ΔBDEs (in kcal.mol^{-1}, compared with* ***2MI****) of monosubstituted* ***2MI****s in the gas phase*

According to Figure 4, the effect of substituents at the 1 position is negligible, with ΔBDE ranging between –1.0 and 2.9 kcal.mol^{-1}. Whereas almost all substituents diminish the BDE (N–H), with the lowest ΔBDE at –7.4 kcal/mol^{-1}. ΔBDE values are positive only for COOH and CH≡C (3.5 and 0.5 kcal.mol^{-1}, respectively).

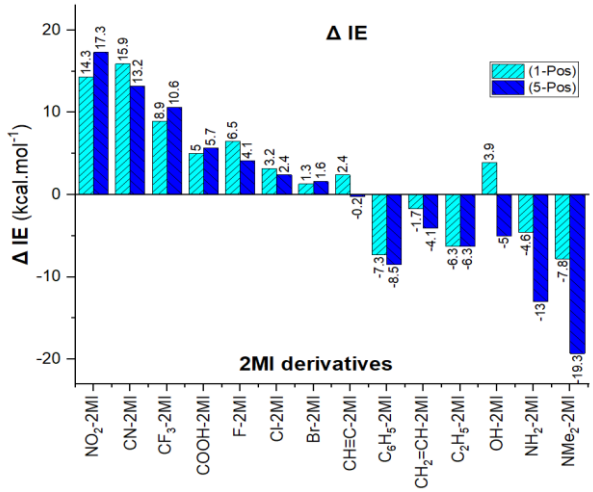


Figure 5. *The calculated ΔIEs (in kcal.mol^{-1}, compared with* ***2MI****) of monosubstituted* ***2MI****s in the gas phase*

Figure 5 displays the disparities between the IE values of derivatives and 2MI. According to the calculated data, almost all electron-withdrawing groups at the 1 and 5 positions increase the IE value, with the largest change occurring at the 5 position of CN (ΔIE = 17.3 kcal/mol^{-1}). In contrast, the electron-donating groups decrease the IE value of 2MI at both positions, excluding the OH at position 1. The lowest IE value belongs to NMe_2–2MI at position 5.

3.2. Inhibitory activity of Derivatives of 2MC and 2MI

The predicted docking energies of the derivatives of

2MC and **2MI** at the active site of ERα (1HVY) and Aromatase (1DNU) are presented in Table 7.

Analysis of the obtained data from Table 7, all biding affinity of **2MC** and derivatives are negative. Among them, the calculated binding affinities of **2MC** are –3.6 kcal.mol^{-1} for Aromatase and –3.1 kcal.mol^{-1} for ERα. The calculated binding energies of derivatives ranged from –3.1 to –6.2 kcal.mol^{-1}. These results suggest that the interaction of these compounds with Aromatase and ERα is thermodynamically favorable. Almost all derivatives have binding energies lower than that of **2MC**, with the negative ΔG. The most promising derivative for Aromatas is **5–COOH–2MC** (ΔG = –2.4 kcal.mol^{-1}), and ERα is 4–C_6H_5 (ΔG = –1.9 kcal.mol^{-1}). **2MC** and other derivatives have significant low binding affinities, including **1–NO_2–2MC, 1–CF_3–2MC, 1–COOH–2MC, 1–Br–2MC, 1–C_6H_5–2MC, 4–NO_2–2MC, 4–CF_3–2MC, 4–COOH–2MC, 4–C_6H_5–2MC, 5–NO_2–2MC, 5–CF_3–2MC, 5–C_6H_5–2MC** and **5–NH_2–2MC** (ΔG < –1.0 kcal. mol^{-1}) should also be selected for further considerations.

Table 7. *Binding energies (Gs, kcal.mol^{-1}) of **2MC, 2MI and** derivatives*

Pos/ Subs	Gs	NO_2	CN	CF_3	COOH	F	Cl	Br	CH≡C	C_6H_5	CH_2=CH	C_2H_5	OH	NH_2	NMe_2
1-2MC	Gs[a]	–4.8	–4.5	–4.4	–4.8	–3.9	–3.8	–4.8	–4.4	–6.2	–3.8	–3.8	–4.3	–4.3	–4.1
	ΔG*[a]	**–1.2**	–0.9	–0.8	**–1.2**	–0.3	–0.2	**–1.2**	–0.8	**–2.6**	–0.2	–0.2	–0.7	–0.7	–0.5
	Gs[b]	–3.8	–3.7	–4.3	–4.4	–3.2	–3.2	–3.1	–3.5	–4.6	–3.5	–3.4	–3.4	–3.5	–3.4
	ΔG*[b]	–0.7	–0.6	**–1.2**	**–1.3**	–0.1	–0.1	0.0	–0.4	**–1.5**	–0.4	–0.3	–0.3	–0.4	–0.3
4-2MC	Gs[a]	–4.8	–4.4	–5.0	–5.0	–4.1	–4.0	–3.9	–4.4	–5.5	–4.2	–4.3	–4.1	–4.1	–4.4
	ΔG*[a]	**–1.2**	–0.8	**–1.4**	**–1.4**	–0.5	–0.4	–0.3	–0.8	**–1.9**	–0.6	–0.7	–0.5	–0.5	–0.8
	Gs[b]	–4.5	–4.0	–4.3	–4.3	–3.5	–3.3	–3.2	–3.6	–5.0	–3.6	–3.6	–3.7	–3.8	–3.8
	ΔG*[b]	**–1.4**	–0.9	**–1.2**	**–1.2**	–0.4	–0.2	–0.1	–0.5	**–1.9**	–0.5	–0.5	–0.6	–0.7	–0.7
5-2MC	Gs[a]	–4.8	–4.5	–5.0	–6.0	–4.0	–4.1	–3.9	–4.4	–5.5	–4.2	–4.2	–4.4	–4.8	–4.3
	ΔG*[a]	**–1.2**	–0.9	**–1.4**	**–2.4**	–0.4	–0.5	–0.3	–0.8	**–1.9**	–0.6	–0.6	–0.8	**–1.2**	–0.7
	Gs[b]	–4.3	–4.0	–4.6	–4.5	–3.6	–3.5	–3.3	–3.7	–4.8	–3.7	–3.6	–3.9	–3.9	–3.7
	ΔG*[b]	**–1.2**	–0.9	**–1.5**	**–1.4**	–0.5	–0.4	–0.2	–0.6	**–1.7**	–0.6	–0.5	–0.8	**–0.8**	–0.6
1-2MI	Gs[a]	–4.7	–4.3	–4.5	–4.7	–3.9	–3.7	–3.7	–4.0	–5.2	–3.9	–3.8	–4.3	–4.4	–4.1
	ΔG*[a]	–0.8	–0.4	–0.6	–0.8	0.0	0.2	0.2	–0.1	**–1.3**	0.0	0.1	–0.4	–0.5	–0.2
	Gs[b]	–4.3	–3.9	–4.6	–4.6	–3.7	–3.5	–3.4	–3.6	–5.3	–3.9	–3.9	–3.8	–3.9	–3.8
	ΔG*[b]	**–1.1**	–0.7	**–1.4**	**–1.4**	–0.5	–0.3	–0.2	–0.4	**–2.1**	–0.7	–0.7	–0.6	–0.7	–0.6
5-2MI	Gs[a]	–4.9	–4.6	–5.2	–4.9	–4.0	–4.1	–4.0	–5.5	–5.6	–5.7	–4.3	–4.6	–4.5	–4.5
	ΔG*[a]	**–1.0**	–0.7	**–1.3**	**–1.0**	–0.1	–0.2	–0.1	**–1.6**	**–1.7**	**–1.8**	–0.4	–0.7	–0.6	–0.6
	Gs[b]	–4.6	–4.1	–4.8	–4.6	–3.8	–3.6	–3.4	–3.9	–5.1	–3.8	–3.7	–3.9	–4.1	–4.1
	ΔG*[b]	**–1.4**	–0.9	**–1.6**	**–1.4**	–0.6	–0.4	–0.2	**–0.7**	**–1.9**	**–0.6**	–0.5	–0.7	–0.9	–0.9

[a]: 1DNU, [b]: 1HVY
(*) The calculated ΔG* in kcal.mol–1, compared with 2MC/ 2MI
Gs (1DNU-2MC) = –3.6 kcal.mol^{-1}, Gs (1HVY-2MC) = –3.1 kcal.mol^{-1}
Gs (1DNU-2MI) = –3.9 kcal.mol^{-1}, Gs (1HVY-2MI) = –3.2 kcal.mol^{-1}

Table 7 also revealed that, with the exception of F, Cl, Br, CH_2=CH, and C_2H_5 at position 1, all substitutions at positions 1 and 5 of **2MI** appear to have a positive influence on binding energy. CH_2=CH at position 5 has the greatest effect on the binding affinity of **2MI** with Aromatase (1DNU), with –1.8 kcal.mol^{-1}, while C_6H_5 at position 5 has the greatest effect on the binding affinity of **2MI** with ERα (1HVY), with ΔG = –1.9 kcal.mol^{-1}. In addition, the ΔG* values of the following derivatives were substantially lower: **1–NO_2–2MI**, **1–CF_3–2MI, 1–COOH–2MI**, **1–C_6H_5–2MI**, **5–NO_2–2MI**, **5–CF_3–2MI**, **5–COOH–2MI**, **5–CH≡C–2MI**. Based on calculated data, these substances displayed good inhibitory potential against the target protein and should be considered for the ADME study.

3.3. Pharmacokinetic properties of derivatives of 2MC and 2MI

In the area of drug discovery, pharmacokinetics studies (including absorption, distribution, metabolism, and excretion – ADME) always played an important role in supporting to optimize the new medicine properties via their success rate [26]. A successive design of drug–like molecules must agree with Lipinski's rule [27], including the limitation of the number of hydrogen bond acceptors (nHA ≤ 10), number of hydrogen bond donors (nHD ≤ 5), the logarithm of the n–octanol/water distribution coefficient (miLogP ≤ 5) and molecular weight (MW ≤ 500 daltons).

The results of calculated ADME parameters and Ames toxicity of selected compounds are presented in Table 8. The drug–likeness and drug–score are shown in Figures 6 and 7.

As per data in Table 8, both **2MC**, **2MI,** and all selected derivatives obeyed Lipinski's rule. The results recommend a great oral bioavailability for studied compounds. Almost all of the toxicity of **2MC** derivatives are higher than that of the parent compound, whereas, **1–COOH–2MI, 1–C_6H_5–2MI,** and **5–C_6H_5–2MI** are less hepatotoxic than **2MI**. Besides, the drug–likeness, and drug–score of **2MC** are –2.83 and 0.52, respectively, and that of **2MI** are –1.11 and 0.61. These results are comparable with the drug–score of the common drug approved for breast cancer treatment–doxorubicin (drug–score 0.55) [28]. Additionally, **4–COOH–2MC**, **4–C_6H_5–2MC**, **5–COOH–2MC**,

5–C_6H_5–2MC, **5–NH_2–2MC**, **1–C_6H_5–2MI, 5–COOH–2MI**, **5–CH≡C–2MI, 5–C_6H_5–2MI** are better than that of their parent compounds. Especially, **1–C_6H_5–2MI, 5–COOH–2MI**, and **5–C_6H_5–2MI** have positive drug-likeness, revealing its potential use as a safe drug. Thus, these compounds are candidates for drug development in breast cancer treatment.

Table 8. *ADME parameters of **2MC** and **2MI** derivatives*

Com pounds	n HA	TPSA	n HD	logP	MW	H–HT	Ames Toxicity
2MC	**2**	**28.68**	**1**	**0.64**	**100.15**	**0.401**	**0.008**
1–NO_2–2MC	5	63.65	0	0.47	145.14	0.809	0.994
1–CF_3–2MC	2	17.83	0	1.62	168.14	0.679	0.787
1–COOH–2MC	4	55.12	1	–0.06	144.16	0.221	0.010
1–Br–2MC	2	17.83	0	1.42	179.04	0.842	0.476
1–C_6H_5–2MC	2	17.83	0	1.98	176.24	0.455	0.019
4–NO_2–2MC	5	74.51	1	0.72	145.14	0.828	0.967
4–CF_3–2MC	2	28.68	1	1.77	168.14	0.618	0.013
4–COOH–2MC	4	65.98	2	0.45	144.16	0.755	0.008
4–C_6H_5–2MC	2	28.68	1	2.31	176.24	0.288	0.019
5–NO_2–2MC	5	74.51	1	0.72	145.14	0.838	0.977
5–CF_3–2MC	2	28.68	1	1.77	168.14	0.613	0.018
5–COOH–2MC	4	65.98	2	0.45	144.16	0.686	0.012
5–C_6H_5–2MC	2	28.68	1	2.31	176.24	0.464	0.018
5–NH_2–2MC	3	54.71	3	0.25	115.16	0.463	0.034
2MI	**2**	**31.58**	**2**	**–0.09**	**100.15**	**0.938**	**0.224**
1–NO_2–2MI	5	66.55	1	–0.26	145.14	0.951	0.992
1–CF_3–2MI	2	20.73	1	0.89	168.14	0.938	0.802
1–COOH–2MI	4	58.02	2	–0.79	144.16	0.787	0.020
1–C_6H_5–2MI	2	20.73	1	1.25	176.24	0.875	0.111
5–NO_2–2MI	5	77.41	2	0.00	145.14	0.96	0.974
5–CF_3–2MI	2	31.58	2	1.05	168.14	0.945	0.118
5–COOH–2MI	4	68.88	3	–0.28	144.16	0.954	0.054
5–CH≡C–2MI	2	31.58	2	–0.09	124.17	0.961	0.352
5–C_6H_5–2MI	2	31.58	2	1.69	176.24	0.922	0.127
5–CH_2=CH–2MI	2	31.58	2	0.82	126.18	0.949	0.193

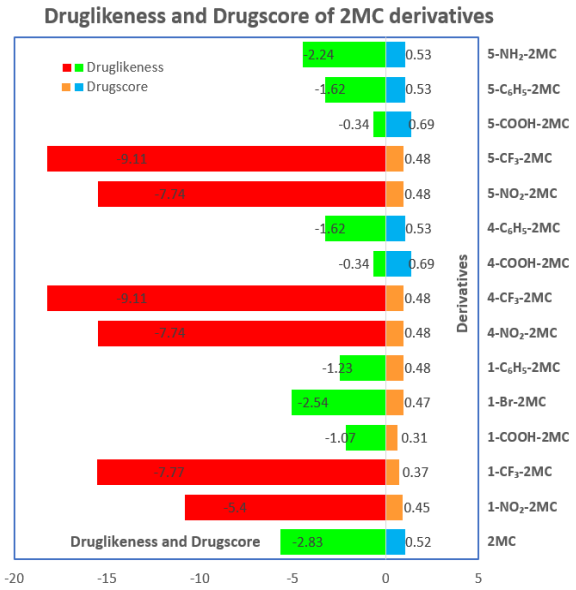


Figure 6. *Druglikeness and drugscore of **2MC** derivatives*

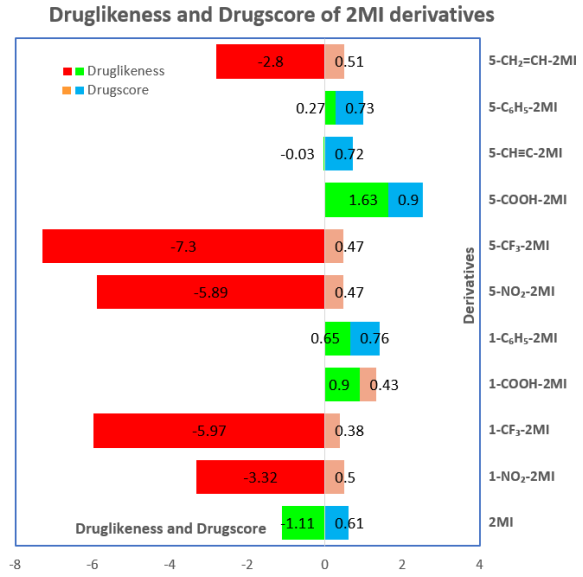


Figure 7. *Druglikeness and drugscore of **2MI** derivatives*

4. Conclusion

In this study**, 2MC**, **2MI,** and 70 derivatives were *in silico* screened for evaluating their antioxidant activity in the gas phase, inhibitory activity, and pharmacokinetic properties as potential candidates. The results showed that **2MC**, **2MI,** and their derivatives, including **5– NH_2–2MC**, **5– NMe_2–2MC**, **5– NH_2–2MI**, **5– NMe_2–2MI** have BDE values lower than those of popular antioxidants such as viniferifuran, resveratrol, puerarin. The results suggest that the radical scavenging activity of those substances may be better than that of the reference antioxidants. All studied compounds, including **2MC** and **2MI,** possess a good inhibitory potential against the target proteins with negative binding energies with ERα (ranging from –5.3 kcal.mol^{-1} to –3.1 kcal.mol^{-1}) and Aromatase (ranging from –6.2 kcal.mol^{-1} to –3.6 kcal.mol^{-1}). All ADME parameters of **2MC**, **2MI,** and selected derivatives agree with Lipinski's rule. Among them, **4–COOH–2MC**, **4–C_6H_5–2MC**, **5–COOH–2MC**, **5–C_6H_5–2MC**, **5–NH_2–2MC**, **1–C_6H_5–2MI, 5–COOH–2MI**, **5–CH≡C–2MI** and **5–C_6H_5–2MI** are potential compounds for drug development in breast cancer treatment, like commercialized doxorubicin.

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