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In vitro cytotoxicity and druglikeness of pyrazolines and pyridines bearing benzofuran moiety

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ABSTRACT

A series of pyrazolines and pyridines bearing benzofuran moiety (**M1–M10**) were synthesized for evaluation of their *in vitro* cytotoxicity against MCF-7 and HepG2 cell lines. Furthermore, *in silico* drug-likeness study was carried out. The result of the cytotoxicity of **M1–M10** showed that some compounds displayed cytotoxic activity against MCF-7 and HepG2 cells. An assessment of *in silico* drug-likeness study of **M1–M10** illustrates that some compounds showed an agreement to the Lipinski, Ghose, Veber, Egan, and Muegge rules with orally bioavailable.

INTRODUCTION

Pyrazolines were known to exhibit various biological activities (Havrylyuk *et al*., 2016; Ozgun *et al*., 2019; Pandey *et al*., 2016). For example, *N*-acetyl pyrazoline (**1**), 1-(5-(4-bromophenyl)-3-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone, was selective and cytotoxic for leukemic cells (Stefanes *et al*., 2019). *N*-benzenesulfonamide pyrazoline (**2**), 4-(5-(4-methoxyphenyl)-1′-phenyl-3′-(*p*-tolyl)-3,4-dihydro-1′*H*,2*H*-[3,4′-bipyrazol]-2-yl)benzenesulfonamide, acts as an antimalarial activity through the inhibition of β-hematin (Kumar *et al*., 2018). *N*-formyl-pyrazoline (**3**), 1-formyl-3-phenyl-5-(4-isopropylphenyl)-2-pyrazoline, showed a promising antimicrobial activity (Sid *et al*., 2016).

Pyridines are important *N*-heterocyclic compounds due to their biological activities (Abdel-Galil *et al*., 2006; Klimešová *et al*., 1999; Xu *et al*., 2017), such as compound (**4**), 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(6-(4-methoxyphenyl)-2-methylpyridin-3-yl)urea, which displayed anticancer activities against NCI-USA cell lines (El-Naggar *et al*., 2018a). Furthermore, compound (**5**), ethyl 4-methyl-1,7,8,9-tetrahydropyrano[2,3-*b*] pyrrolo[2,3-*d*]pyridine-3-carboxylate, showed antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* (Elkanzi *et al*., 2019).

Benzofuran moiety was very interesting *O*-heterocycle which was found in biologically active compounds (Atta *et al*., 2010; Wang *et al*., 2019; Zhu *et al*., 2013). Compound (**6**), 1-(7-allyl-6-hydroxy-4-methoxy-1-benzofuran-5-yl)-3-(4-chlorophenyl)prop-2-en-1-one, exhibited an antiproliferative activity (Ragab *et al*., 2014). Compound (**7**), (4-hydroxy-3-methylphenyl) (2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone, exhibited antibacterial activities (Jiang *et al*., 2011) (Figure 1).

In view of these above facts with the program for discovery biologically active compounds (Abd El-All *et al*., 2016; Elgemeie *et al*., 2008, 2009; Elgiushy *et al*., 2018; El-Naggar *et al*., 2018b; Hafez *et al*., 2013; Hassan and Hafez, 2018; Hassan *et al*., 2015a, 2015b, 2015c, 2016, 2017a, 2017b, 2017c, 2018a, 2018b,

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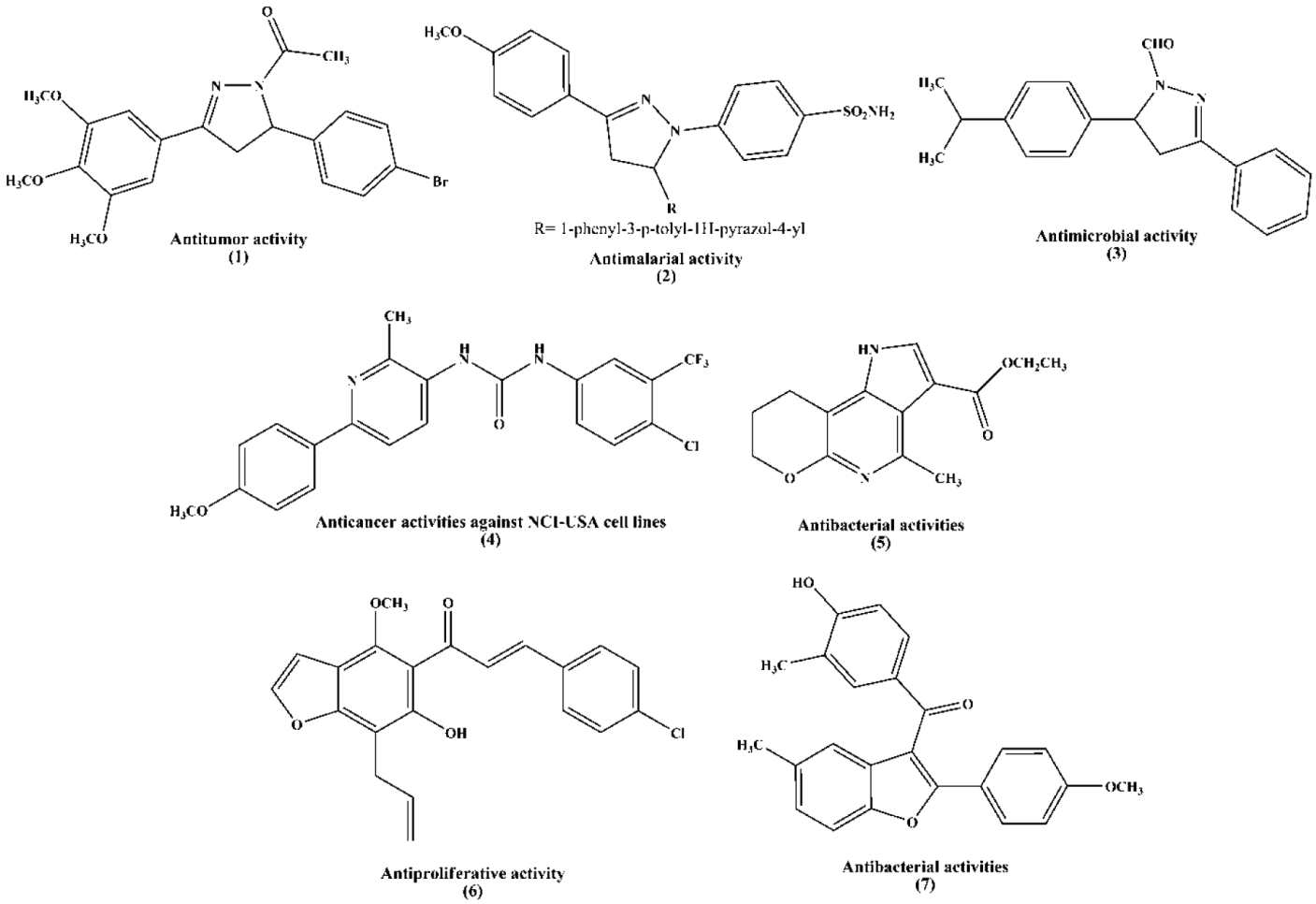


Figure 1. Examples of the bioactive compounds (pyrazolines, pyridines, and benzofurans).

2019; Khatab *et al*., 2019; Magd-El-Din *et al*., 2018; Osman *et al*., 2014), this research involves: (i) synthesization of pyrazolines and pyridines bearing benzofuran moiety (**M1–M10**), (ii) *in vitro* cytotoxicity evaluation of compounds **M1–M10** against MCF-7 and HepG2 cell lines, and (iii) we performed *in silico* druglikeness of compounds **M1–M10**.

MATERIALS AND METHODS

Chemistry

The target compounds [*1H*-pyrazolines (**M1–M3**), *N*-acetylpyrazolines (**M4–M6**), *N*-phenylpyrazolines (**M7** and **M8**), and pyridines (**M9** and **M10**)] were synthesized according to the reported procedure (Osman *et al*., 2012).

Cytotoxicity evaluation

An *in vitro* cytotoxic activity (IC_{50} µg/ml) of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**) against two cell lines (breast MCF-7 and liver HepG2) was measured by using the sulforhodamine B stain (SRB) assay (Skehan *et al*., 1990).

Physicochemical properties and druglikeness

The physicochemical properties and druglikeness of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**) were predicted by using the SwissADME website (http://swissadme.ch).

RESULTS AND DISCUSSION

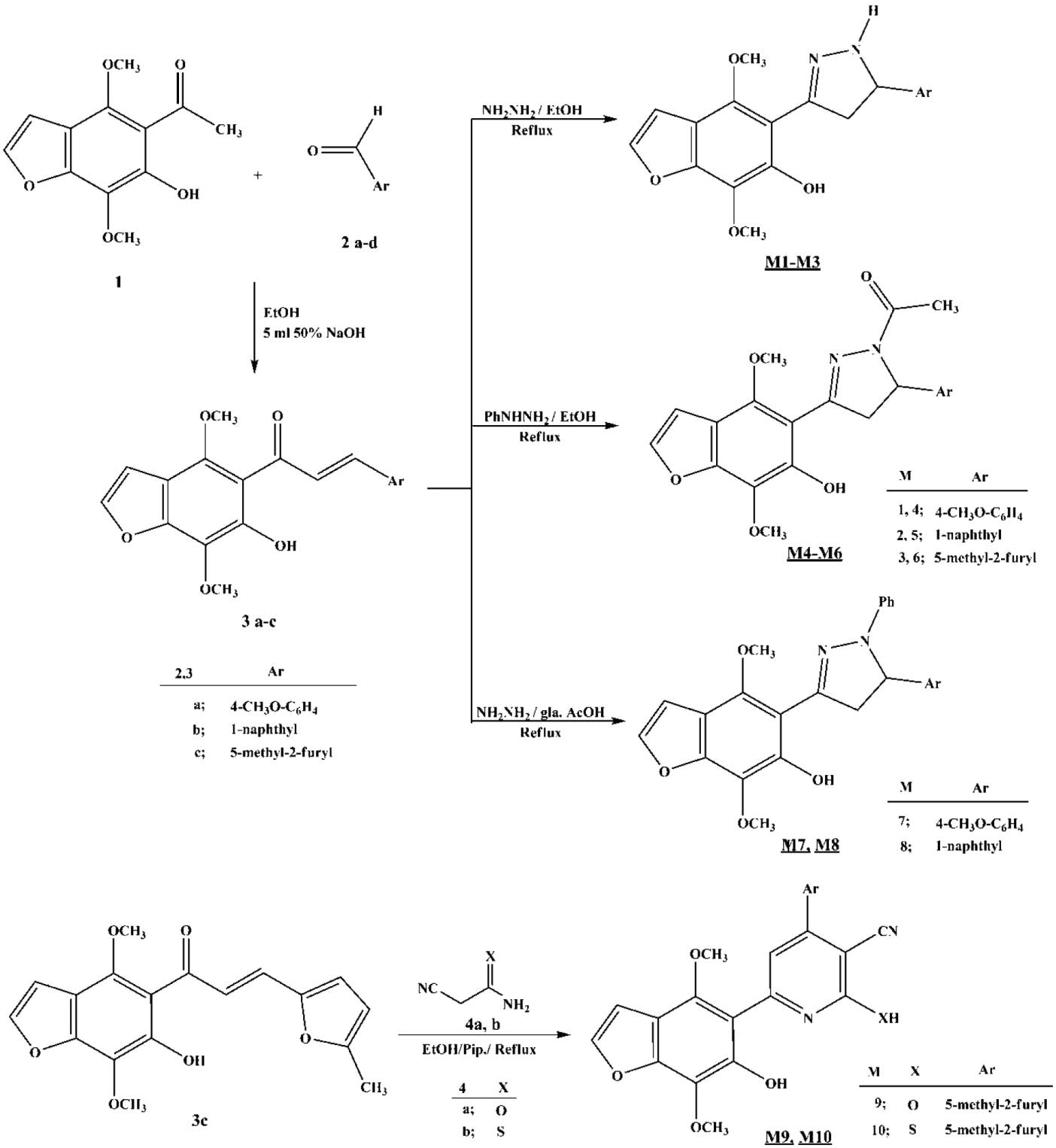
The chemistry

The synthetic route is outlined in Scheme 1. The target compounds [*1H*-pyrazolines (**M1–M3**), *N*-acetylpyrazolines (**M4–M6**), or *N*-phenylpyrazolines (**M7** and **M8**)] were synthesized by the condensation of chalcones with hydrazine hydrate in ethanol, hydrazine hydrate in glacial acetic acid, or phenylhydrazine in ethanol, respectively. Furthermore, pyridines **M9** and **M10** were synthesized by the reaction of **3c** with 2-cyano(thio)acetamide **4a**, **b** (Osman *et al*., 2012).

In vitro cytotoxic activity

The cytotoxicity (IC_{50} µg/ml) of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**) was measured by using the sulforhodamine B stain (SRB) assay (Skehan *et al*., 1990) against two cell lines (breast MCF-7 and liver HepG2). The result of the cytotoxicity values is shown in Table 1, and we could see that:

- The compounds, **M1** (IC_{50} = 12.08 ± 1.20 µg/ml), **M2** (IC_{50} = 12.22 ± 2.80 µg/ml), **M3** (IC_{50} = 10.43 ± 1.12 µg/ml), **M4** (IC_{50} = 10.65 ± 4.61 µg/ml), and **M6** (IC_{50} = 10.50 ± 0.60 µg/ml), show cytotoxic activity against MCF-7 cancer cells, but this activity is less than the positive control [doxorubicin (IC_{50} = 4.70 ± 0.55 µg/ml)].



Scheme 1. Synthesis of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).

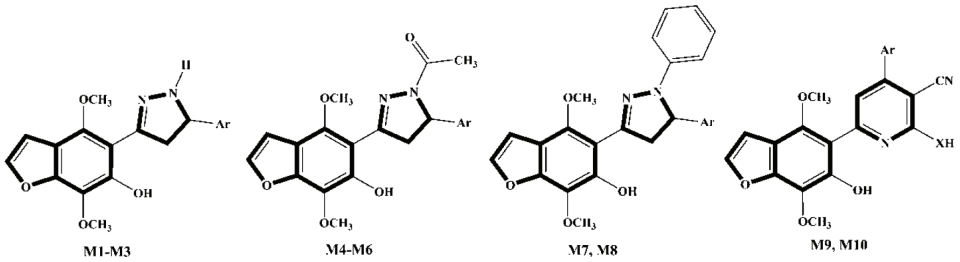
- For HepG-2 cancer cells, the compounds **M1–M4** and **M6** show IC_{50} values in the range from 10.41 ± 2.71 to 12.75 ± 0.60 µg/ml.
- The results revealed that the compounds **M5** and **M7–M10** did not exert any activity against MCF-7 and HepG-2 cancer cell lines.

Physicochemical properties and druglikeness

We predicted the physicochemical properties and druglikeness of the compounds (**M1–M10**) by using the SwissADME website (http://swissadme.ch).

The physicochemical properties give a global description of the structures of compounds (**M1–M10**) including molecular

Table 1. *In vitro* cytotoxicity (IC_{50} µg/ml) of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).



Compounds	Ar	X	Human cancer cell lines	
			MCF-7	HepG2
M1	4-CH_3O-C_6H_4	–	12.08 ± 1.20	11.05 ± 3.52
M2	1-naphthyl	–	12.22 ± 2.80	12.73 ± 1.50
M3	5-methyl-2-furyl	–	10.43 ± 1.12	10.41 ± 2.71
M4	4-CH_3O-C_6H_4	–	10.65 ± 4.61	12.75 ± 0.60
M5	1-naphthyl	–	NA	NA
M6	5-methyl-2-furyl	–	10.50 ± 0.60	11.25 ± 5.65
M7	4-CH_3O-C_6H_4	–	NA	NA
M8	1-naphthyl	–	NA	NA
M9	5-methyl-2-furyl	O	NA	NA
M10	5-methyl-2-furyl	S	NA	NA
Doxorubicin	–	–	4.70 ± 0.55	4.20 ± 0.40

N.A. is no activity

Table 2. Physicochemical properties and lipophilicity of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).

Properties		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Molecular weight		368.38	388.42	342.35	410.42	430.45	384.38	444.48	464.51	392.36	408.43
# Heavy atoms		27	29	25	30	32	28	33	35	29	29
# Arom. heavy atoms		15	19	14	15	19	14	21	25	20	20
Fraction Csp3		0.25	0.17	0.28	0.27	0.20	0.30	0.19	0.14	0.14	0.14
# Rotatable bonds		5	4	4	6	5	5	6	5	4	4
# H-Bond acceptors		6	5	6	7	6	7	6	5	8	7
# H-Bond donors		2	2	2	1	1	1	1	1	2	1
Molar Refractivity		108.39	119.41	99.13	108.30	129.32	109.04	133.53	144.55	103.86	109.09
Total polar surface area Å²		85.45	76.22	89.36	93.73	84.50	97.64	76.66	67.43	121.88	140.45
Lipophilicity	**MLOGP**	1.21	2.22	0.52	1.20	2.17	0.53	2.54	3.50	0.06	0.44
	WLOGP	2.52	3.66	2.41	2.78	3.92	2.67	4.43	5.58	4.36	4.95
	XLOGP3	3.29	4.57	2.82	2.66	3.94	2.19	4.98	6.26	3.88	3.83

weight, molecular refractivity, topological polar surface area, number of rotatable bonds, heavy atoms, and hydrogen bond acceptors and donors (Table 2).

The bioavailability radar of the compounds, pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**), displayed a rapid evaluation of druglikeness.

The bioavailability radar includes the following six physicochemical properties:

(1) Lipophilicity (XLOGP3 between −0.7 and +5.0).
(2) Size (molecular weight between 150 and 500 g/mol).
(3) Polarity (the total polar surface area between 20 and 130 Å²).
(4) Solubility (log S not higher than 6).
(5) Saturation (fraction Csp3 not less than 0.25).
(6) Flexibility (the number of rotatable bonds not more than 9).

The bioavailability radar of the compounds for six physicochemical properties is shown in Figure 2**.** The pink area represents the optimal range of these properties (Lovering *et al*., 2009; Ritchie *et al*., 2011), and the red line represents the properties of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).

In Figure 2, the red lines of four compounds (**M1**, **M3**, **M4**, and **M6**) are in the range of the pink area. Therefore, we can conclude that these compounds are predicted orally bioavailable.

Furthermore, druglikeness was established based on the physicochemical properties to find oral drug candidates (Daina *et al*., 2017). There are five different rule-based filters which are defined as follows:

1) Lipinski's filter includes molecular weight ≤ 500, MLOGP (lipophilicity) ≤ 4.15, hydrogen bond acceptors

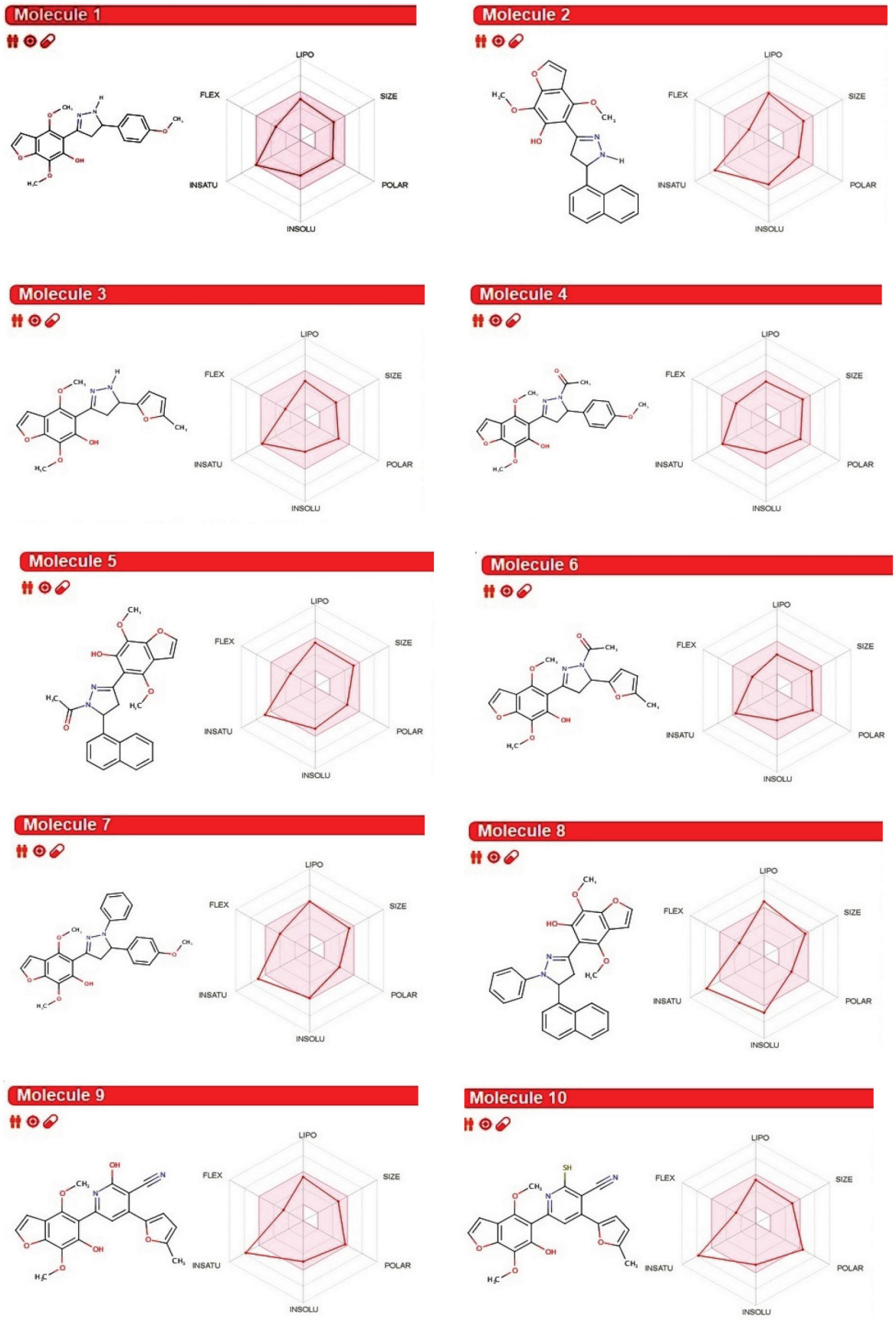


Figure 2. The bioavailability radar of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).

Table 3. Drug-likeness evaluation of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**).

Rule-based filters	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Lipinski violations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ghose violations	Yes	Yes	Yes	Yes	Yes	Yes	No; 1 violation: MR > 130	No; 1 violation: MR > 130	Yes	Yes
Veber violations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No; 1 violation: TPSA > 140
Egan violations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No; 1 violation: TPSA > 131.6
Muegge violations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No; 1 violation: XLOGP3 > 5	Yes	Yes

≤ 10, and hydrogen bond donors ≤ 5 (Lipinski *et al*., 2001).

2) Ghose's filter includes 160 ≤ molecular weight ≤ 480, −0.4 ≤ WLOGP (lipophilicity) ≤ 5.6, 40 ≤ the molar refractivity ≤ 130, and 20 ≤ number of atoms ≤ 70 (Ghose *et al*., 1999).
3) Veber's filter includes the number of rotatable bonds ≤ 10 and the total polar surface area ≤ 140 (Veber *et al*., 2002).
4) Egan's filter includes WLOGP (Lipophilicity) ≤ 5.88 and the total polar surface area ≤ 131.6 (Egan *et al*., 2000).
5) Muegge's filter includes 200 ≤ molecular weight ≤ 600, −2 ≤ XLOGP3 (lipophilicity) ≤ 5, the total polar surface area ≤ 150, the number of rings ≤ 7, the number of carbon > 4, the number of heteroatoms > 1, the number of rotatable bonds ≤15, the hydrogen bond acceptors ≤ 10, and the hydrogen bond donors ≤ 5 (Muegge *et al*., 2001).

The result of drug-likeness evaluation of pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**) is shown in Table 3, and we can conclude that:

- All the compounds, pyrazolines (**M1–M8**) and pyridines (**M9** and **M10**), are in agreement with the Lipinski's rule.
- According to Ghose's rule, all the compounds pass this rule excluding the two pyrazoline compounds (**M7** and **M8**) due to the molar refractivity more than 130.
- In the cases of Veber's rule and Egan's rule, all the compounds are in agreement with the two rules excluding one compound, pyridine **M10**, due to the total polar surface area more than 140 and 131.6, respectively.
- According to Muegge's rule, all the compounds are in agreement with this rule excluding pyrazoline **M8** due to its lipophilicity (XLOGP3) more than 5.

CONCLUSION

In this work, a series of pyrazolines **M1–M8** and pyridines **M9** and **M10** were synthesized for the evaluation of their *in vitro* cytotoxic activities against two cell lines such as MCF-7 and HepG2. In general, some of pyrazolines and pyridines displayed cytotoxicity. Furthermore, the drug-likeness study revealed that most of the compounds fulfill the requirements of Lipinski, Ghose, Veber, Egan, and Muegge rules, and four compounds (**M1**, **M3**, **M4**, and **M6**) are predicted orally bioavailable. These preliminary results provide the lead for the design of more potent and selective anticancer drugs.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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