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Design, Synthesis and in Silico Studies of New 2-MethylQuinazolin-4(3*H*)-Ones Derivatives

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Abstract: The concept of the green chemistry consists in the development of an environmentally friendly approach for organic synthesis using ecological and efficient protocols. In order to develop a methodology that could fit into the green chemistry field, for the synthesis of new quinazolin-4(3*H*)-ones derivatives via benzoxazinone, the choice was made on the use of both as catalysts, known for their efficiency, and microwave irradiations for time saving.The quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities. They generally display useful therapeutic and pharmacological properties such as anti-inflammatory, anti-convulsant, antihypertensive and antimalarial activity.The derivatives of the 2-metylquinazolin-4(3*H*)-ones **3a-d** series was synthesized from 2-methyl benzoxazin-4(3*H*)-one **1** and aniline in the presence of $H_3PW_{12}O_{40}$ (PW_{12}) under microwave irradiation and solvent free conditions. The compound structures were established using IR, 1H-NMR, 13C-NMR and mass spectroscopy. The toxicity of the hydrazone derivatives was studied through ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) simulations using ADMET Lab 2.0 server.

Keywords: Keggin-type heteropolyacids, Quinazolin-4(3*H*)-ones, Benzoxazin-4(3*H*)-one

Introduction

Quinazolin-4(3*H*)-ones are versatile nitrogen heterocyclic compounds, displaying a broad spectrum of biological and pharmalogical activities such as anti-fungal (El-Hashash et al., 2015), anti-tumoral (Kumar et al., 2003), hypotensive (EI-Brollosy et al., 2003), anti-cancer (Khili et al., 1994), anti-HIV(Alagarsamy et al., 2003), analgesic (Alagarsamy et al., 2002), anti-inflammatory (Kumar et al., 2007) etc. Moreover, the quinazolin-4(3*H*)-one moiety is found in several bioactive natural products (Saleh et al., 2004). For these reasons their synthesis has received considerable attention (Rad- Moghadam & Khajavi, 2006). In this work, we have synthesized quinazoline-4(3*H*)-ones and we have studies in silico properties prediction.

In our previous work (Ighilahriz et al., 2017), we have shown that the addition of monosubstituted aniline to the benzoxazin-4-ones gives two zwitterionic intermediates respectively. These cyclic intermediates can give the open product 2, which is relatively stable, or directly the closed product 3. It should be noted that the main effect of this ring-opening competition is due to the transfer of the negative charge from nitrogen to oxygen to give the closed product or from oxygen to nitrogen to give the open compound. Given that oxygen is more electronegative than nitrogen, pathway (2) is therefore more favoured (in the case of R=Ph). The 2-aryl-benzoxazin-4-ones have two nucleophilic attack sites, which can either open the heterocycle to give compound

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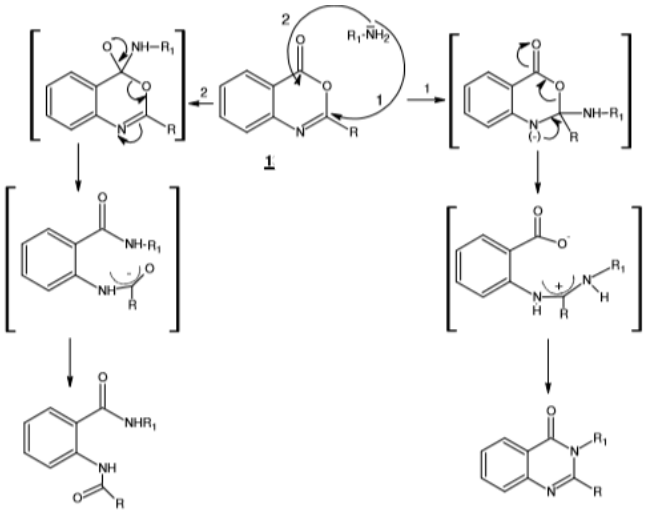
3 or form compound 2. The competition between the two nucleophilic attacks depends on a number of parameters, such as the size and the nature of the nucleophile. The mechanism, is given in the following:



2 **3**

Scheme 1. Mecanisme for the condensation of anilines with benzoxazin-4-one reaction.

Method

Experimental Method

All melting points were measured on a Stuart Scientific SMP3 apparatus fitted with a microscope and uncorrected. The IR absorption spectra (KBr disks) were measured on a Nicolet Magna 550 series II IR Spectrophotometer. 1H-RMN (300.13 MHz) and 13C-RMN (75.47 MHz) spectra were recorded in deuterated chloroform ($CDCl_3$) on a Brucker DRX 300 spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ values (ppm). Mass spectra were recorded on a Nermag R 10-10C quadruple mass spectrometer at 70 eV. All the compounds gave satisfactory elemental analyses. The multimode microwave reactor (a modified microwave oven Candy MGA 20M) has a single magnetron (2.45 GHz) with a maximum delivered power of 800 W. It was directly graduated in W (from 100 to 800 W). Experiments were carried out in a Pyrex reactor fitted with a condenser.

Computational Method

Prediction of the Pharmacokinetic Properties And Toxicological Properties Using ADMET

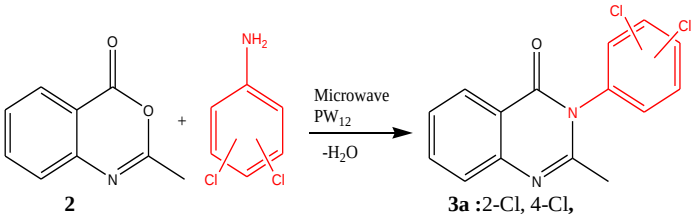
The pharmacokinetic properties of the compounds studied. The following properties, (i) absorption, Lipinski's rule of five, water solubility, Caco-2 permeability, intestinal absorption (human), skin permeability and P-glycoprotein interactions, (ii) distribution: VDss, Fu, Log BB and CNS permeability, (iii) metabolism and (iv) excretion were selected. Also, online pkCSM pharmacokinetics were used to predict the toxicity of the molecules, including skin sensitization, hepatotoxicity, etc. The results obtained were analyzed and compared with the reference values of the pkCSM pharmacokinetics prediction properties (Pires et al., 2015).

The Bioactivity Scores Prediction

The bioactivity scores of the quinazolin-4(3*H*)-ones toward G protein-coupled receptor (GPCR) ligand, ion channel modulator, a kinase inhibitor, nuclear receptor ligand, protease inhibitors, and enzyme inhibitor were predicted by using the Molinspiration bioactivity score v2018.03. The predicted results are written in Table 9. The rule for the bioactivity scores estimation is the following: when the bioactivity score was more than 0.00; the compound was considered active. While if the bioactivity score in the range between -0.50 and 0.00; the compound was moderately active. But if the bioactivity score was less than -0.50, the compound was inactive.

Synthesis

The action of aromatic amines on 2-methylbenzoxazin-4-ones in the presence of an aprotic solvent has been described in the literature (Kidwai, 2003). In the present work, we have replaced these aromatic amines with dichloanilines. The reaction of dichloroanilines with 2-methylbenzoxazin-4-ones was performed under microwave irradiation in the presence of PW_{12} catalyst and in the absence of solvent. The dichloroanilines and 2-methyl-benzoxazin-4-one, in the presence of PW_{12} in catalytic quantity, were ground and then subjected to microwave irradiation for 3 minutes at 300W and 9 minutes at 400W. The results obtained are summarized in Table 1.



2

3a :2-Cl, 4-Cl**,**
3b : 2-Cl, 5-Cl,
3c : 2-Cl, 6-Cl,
3d : 3-Cl, 4-Cl.

Scheme 2. Synthesis of 3-(dichlorophenyl)-2-methylquinazolin-4(3*H*)-ones under solvent free conditions.

Results and Discussion

Caracterization

The compounds 3a-d were prepared in good yields (53-67 %). It was found that yields of products 3 depend on position of two chlorine atoms. In the 3,4-position of the chlorine, the yield of compound 3d is higher than that of compound 3c (53%). This difference in the yield is due to the steric hindrance of the chloro groups (Table 1).

Table 1. Melting points Mp and yields of compounds 3a-d

Compounds	ArNH	Yields (%)	Melting points (^{0}C)
3a	2,4-diCl_2-C_6H_3	59	142
3b	2,5-diCl_2-C_6H_3	60	128
3c	2,6-diCl_2-C_6H_3	53	130
3d	3,4-diCl_2-C_6H_3	70	219

The UV-Visible spectra of compounds 3a-d reveal two absorptions, with the most intense one attributed to the π→π* transition, and the weaker one characterizing the n→π* electronic transition (Table 2).

Table 2. UV-vis spectral analysis

Compounds	λ(nm)		Transition
		264.1	π→ π*
3a	306.0		π→ π*
	317.9		n→ π*
		255.0	π→ π*
3b	365.0		π→ π*
	305.0		n→ π*
		206.0	π→ π*
3c	305.0		π→ π*
	317.0		n→ π*
		267.0	π→ π*
3d	305.0		π→ π*
	317.0		n→ π*

The IR spectrum also confirms the structure of compounds 3a-d by the appearance of two characteristic bands at 1687.69-1692.20 cm^{-1} and 1602.14-1605.76 cm^{-1} corresponding to the carbonyl and imine functions, respectively.

Table 4. IR bands for the compounds 3a-d as KBr pellets.

Fonction / Compounds	ν C=O	υC=N
3a	1692.14	1602.14
3b	1687.69	1604.62
3c	1692.20	1605.76
3d	1689.00	1604.00

The structures of the synthesised compounds 3a-d were further confirmed by mass spectra and elemental analysis (Table 5). The mass spectrum of product 3b shows a molecular peak with even number (304) and even number (2) of nitrogens, satisfying the nitrogen rule. This peak is accompanied by two peaks at m/z=306 (3.11%) and m/z=308 (1.55%). This is due to the contribution of chlorine isotopes.

Table 5. Elemental analysis and mass spectrometry data.

Compounds	Chemical formula	Elemental analysis
3a	$C_{15}H_{10}Cl_2N_2O$	C 59.04, H 3.30, Cl 23.23, N 9.18, O 5.24
3b	$C_{15}H_{10}Cl_2N_2O$	C 59.04, H 3.30, Cl 23.23, N 9.18, O 5.24
3c	$C_{15}H_{10}Cl_2N_2O$	C 59.04, H 3.30, Cl 23.23, N 9.18, O 5.24
3d	$C_{15}H_{10}Cl_2N_2O$	C 59.04, H 3.30, Cl 23.23, N 9.18, O 5.24

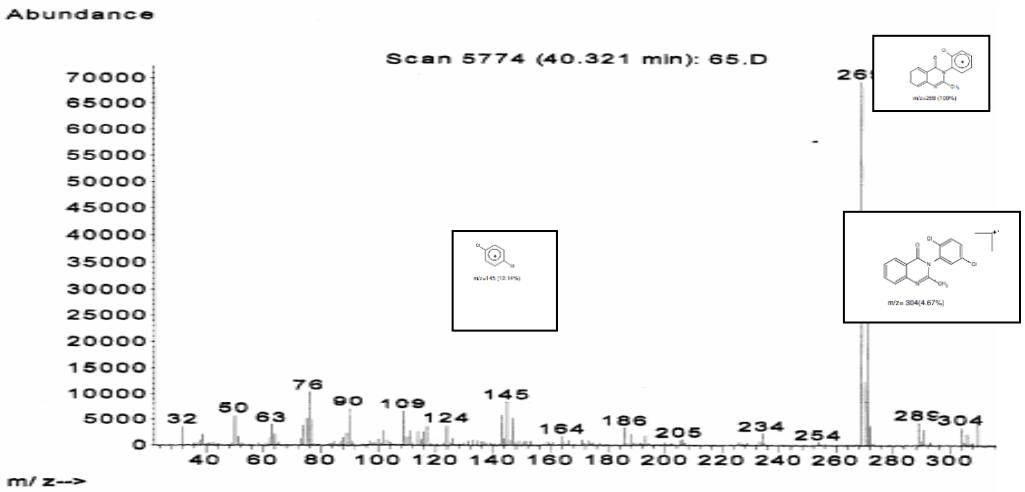


Figure 1. Mass spectra of 3-(2,4-dichlorophenyl)-2-methylquinazolin-4(3*H*)-one 3a.

The 1H-NMR spectrum of compound 3 shows six signals, whose integration is compatible with the total number of protons in the molecule and the presence of a singlet at 2.13 ppm, corresponding to the methyl group. This confirms the structure of our compound 3a-d.

Table 6. NMR data of the compounds 3a-d.

Compounds	1H-NMR (DMSO)	13C-NMR ($CDCl_3$)
3a	δppm = 8.12 (d, 1H), 7.95 (d, 1H); 7.85 (t , 1H); 7.66 (m, 3H); 7.53 (t, 1H), 2.13 (s, 1H).	δppm = 160.93; 154.15; 147.45; 135.61; 135.45; 134.61; 133.12; 132.49; 130.35; 129.50; 127.41; 127.15; 126.88; 120.40; 23.55.
3b	δppm = 8.46 (d, 1H); 7.13 (d, 1H); 7.93 (t, 1H), 7.66 (m, 3H), 7.55 (t, 1H); 2.14 (s, 3H).	δppm = 160.90; 153.92; 147.43; 136.66; 135.13; 133.17; 132.01; 131.68; 131.48; 130.95; 127.42; 127.16; 126.86; 123.02; 23.48.
3c	δppm = 8.12 (d, 1H); 7.94 (d, 1H); 7.80 (t, 1H); 7.55 (m, 3H); 7.12 (t, 1H); 2.11 (s, 1H).	δppm = 161.30; 153.52; 147.52; 135.97; 133.74; 132.70; 129.90; 129.05; 127.74; 127.47; 126.97; 120.06; 25.39.
3d	δppm = 8.12 (d, 1H) ; 7.81 (m, 3H) ; 7.72 (d, 1H) ; 7.63 (m, 2H), 2.20 (s, 1H).	δppm = 161.06; 156.41; 144.90 ; 137.24 ; 135.90, 132.91 ; 132.48 ; 132.10 ; 131.18 ; 129.51 ; 127.82 ; 127.12 ; 125.18 ; 120.32 ; 23.42.

Predication of the Pharmacokinetic Properties and Toxicological Properties via ADMET

In this study, the pharmacokinetic predictions of the quinazolinone 3a-d were estimated. The results revealed that all the investigated molecules show significant values for oral absorption. Compound 3d shows the highest water solubility value among the other analogues. All of the evaluated compounds are predicted to have high cellular permeability, especially for intestinal cells (95.994-96.444%) (Table 7). Generally, it is known that an orally available molecule that satisfies both Lipinski's and Veber's rules has a balance between lipophilicity and hydrophilicity. As shown from table 7, compounds 3a-d follow both Lipinski's and Veber's rules and thus qualify as possible drug-like molecules. The Caco-2 cell line is generally utilized as an in vitro example of the human intestinal mucosa to calculate drug absorption by assessing the log of the apparent permeability coefficient (log Papp; log cm/s). A chemical is considered to have high-level Caco-2 permeability for the pkCSM webserver if its log Papp value is more than 0.90 cm/s. Table 7 shows that all products 3a-d have high Caco-2 permeability.

In terms of the BBB, which determines a drug's capacity to enter the brain while boosting effectiveness (fewer adverse effects), a molecule is capable of moving across the blood-brain barrier quickly when log BB is greater than 0.3. As a result, because the log BB values of all examined derivatives are highest than 0.3, they can only cross the blood - brain barrier marginally. All of the synthesized compounds showed relatively high activity as they inhibit CYP1A2, CYP2C19, and CYP3A4. This can be positively correlated to the lipophilicNity of the compounds to metabolism related toxicity. These results show that these compounds could be involved in drug-drug interactions, and could initiate oxidative stress.

Table 7. ADMET proporties of the synthesis compounds.

Property		Compound **3a**	Compound **3b**	Compound **3c**	Compound **3d**
Absorption	Water solubility (log mol L^{-1})	-4.21	-4.545	-4.545	-4.625
	Caco2 permeability (log Papp in 10^{-6} cm s^{-1})	1.077	1.635	1.629	1.625
	Intestinal absorption (%)	95.994	95.994	96.244	96.444
	Skin permeability (log Kp)	-2.675	-2.339	-2.351	-2.335
	P-Glycoprotein substrate	No	No	No	No
	P-Glycoprotein I	No	No	No	No
	P-Glycoprotein II	Yes	Yes	Yes	Yes
Distribution	VDss (log L kg^{-1})	0.002	-0.133	-0.093	-0.076
	Fraction unbound (Fu)	0.221	0.179	0.181	0.149
	BBB permeability (log BB)	0.556	0.612	0.548	0.565
	CNS permeability (log PS)	-1.354	-1.338	-1.356	-1.328
Metabolism	CYP2D6 substrate	No	Yes	No	No
	CYP3A4 substrate	Yes	Yes	Yes	Yes
	CYP1A2 inhibitor	Yes	Yes	Yes	Yes
	CYP2C19 inhibitor	Yes	Yes	Yes	Yes
	CYP2C9 inhibitor	Yes	No	No	No
	CYP2D6 inhibitor	No	No	No	No
	CYP3A4 inhibitor	No	No	No	Yes
Excretion	Total clearance (log ml mim^{-1} kg^{-1})	0.154	0.205	0.327	0.27
	Renal OCT2 substrate	No	Yes	Yes	Yes
Toxicity	AMES toxicity	Yes	No	No	No
	Max. tolerated dose (log mg kg^{-1} day^{-1})	0.302	-0.123	-0.096	-0.055
	hERG I inhibitor	No	No	No	No
	hERG II inhibitor	No	No	No	No
	Oral rat acute toxicity (LD50) (mol kg^{-1})	2.527	2.132	2.135	2.165
	Oral rat chronic toxicity (LOAEL)	0.776	1.178	1.230	1.301
	(mol kg^{-1}	No	No	No	No
	bw day^{-1})	No	No	No	No
	Hepatotoxicity	0.463	0.885	0.850	0.909
	Skin sensitisation	-0.360	0.133	-0.045	-0.212
	T. pyriformis toxicity (log mg L^{-1})				
	Minnow toxicity (log mM)				

Table 8. Lipinski's and Veber's for the synthesis compounds

Property	Compound **3a**	Compound **3b**	Compound **3c**	Compound **3d**
log P	3.69	3.69	3.69	3.69
Molecular weight	391.14	391.14	391.14	391.14
H-bond acceptors	2	2	2	2
H-bond donor	0	0	0	0
No. of Lipinski's rule violations	0	0	0	0
TPSA	34.89	34.89	34.89	34.89

In conclusion, in this study, pkCSM software was used to predict the toxicological properties of the target compounds. Furthermore, this software has a system that performs predictions on the type of toxicity that a compound presents, such as mutagenicity, hepatotoxicity, cardiotoxicity, and skin sensitization. Herein, the bacterial mutagenic potential of the quinazoline derivatives through Ames toxicity testing showed that three analogues, namely 3b-d, could be considered as non-mutagenic agents. Yet, the toxicities of all of the compounds in T. pyriformis are high. Also, the investigated compounds were predicted for one of the important parameters regarding toxicity, which is cardiotoxicity, in the form of human ether-a-go-go-related gene I/II (hERG I/II), which was found to be at an acceptable level. G protein-coupled receptor (GPCR) ligand: The quinazoline (3a, 3b, and 3c) were found to be active with the bioactivity scores in the range from 0.02 to 0.04. the compound 3d was inactive.

• Ion channel modulator: the quinazoline 3a was found to be active with the bioactivity scores 0.01 while the other compounds were found to be moderately active with the bioactivity scores in the range from -0.04 to -0.13.

• Kinase inhibitor: all the quinazoline were found to be moderately active with the bioactivity scores in the range from -0.10 to -0.36.

• Nuclear receptor inhibitor: the two quinazoline 3a and 3d were found to be inactive with the bioactivity scores less than -0.50 (the range from -0.51 to -0.52). While the two compounds 3b-3c were found to be moderately active with the bioactivity scores -0.48.

• Protease inhibitor: all the quinazoline were found to be moderately active with the bioactivity scores in the range from -0.17 to -0.33.

Table 9. The bioactivity scores prediction of the compound 3a-d.

The bioactivity scores	Compound **3a**	Compound **3b**	Compound **3c**	Compound **3d**
GPCR ligand[a]	0.03	0.04	0.02	-0.05
Ion channel modulator	0.01	-0.13	-0.04	-0.13
Kinase inhibitor	-0.30	-0.18	-0.10	-0.36
Nuclear receptor ligand	-0.52	-0.48	-0.48	-0.51
Protease inhibitor	-0.50	-0.22	-0.46	-0.52
Enzyme inhibitor	-0.33	-0.33	-0.17	-0.28

[a]G protein-coupled receptor (GPCR) ligand

Conclusion

We developed an efficient synthesis of 2-methylquinazolin-4(3*H*)-ones using the 2-methylbenzoxazin-4-one and substituted anilines under PW_{12}-mediated catalysis, microwave irradiation and solvent-free conditions. Mildness of the catalysts, avoidance of solvents, short reaction times and good yields are the outstanding advantages of the present protocol. The structures of synthesized compounds were performed by UV-visible, IR, 1H-NMR, 13C-NMR and spectroscopy mass. Furthermore, ADMET and bioactivity scores properties were calculated and showed satisfactory pharmacokinetic and toxicological properties.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

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