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Highly Efficient Synthesis of Vasorelaxant Quinazolinone Derivatives under Ultrasonic Irradiation in the Presence of TiO_2 Nanoparticles

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Abstract

Quinazolinone compounds are interesting pharmacophores with a wide range of biological activities. Among the most valuable quinazolinones are the 3-substituted 2-methylquinazolin-4(3H)-one derivatives. There are some reports about the vasorelaxant effects of these compounds.Various methods have been suggested to synthesize these molecules, but most of them suffer from many disadvantages such as long reaction times, low yields, harsh reaction conditions, and toxic residues. Therefore, developing convenient methods for the synthesis of these valuable medicinal scaffolds is of great importance. In the first part of this study, we presented an efficient procedure for the preparation of a series of 3-substituted 2-methylquinazolin-4(3H)-one derivatives from anthranilic acid, acetic anhydride and primary amines using TiO_2 nanoparticles under ultrasonic irradiation in solvent-free conditions at room temperature. In the second part of this research, we analyzed the vasorelaxant activity of the synthesized compounds in isolated rat thoracic aorta. Based on the results, all of the synthesized quinazolinone derivatives showed vasorelaxant properties and some of them were as potent as acetylcholine.

Keywords: Quinazolinones; Ultrasonics; Vasorelaxant; Nanoparticles; Titanium dioxide.

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1. Introduction

Quinazolinones are very interesting pharmaceutical scaffolds with a wide range of biological properties such as anticancer, antimicrobial, antiprotozoal, anti-inflammatory, diuretic, and anticonvulsant (1-7). These compounds are found in wonderful natural products with active medicinal properties (8). Due to their broad biological activities, these valuable pharmacophores have attracted much attention in medicinal chemistry (9). Among the most widely encountered quinazolinones are the 3-substituted 2-methylquinazolin-4(3H)-one derivatives (10). Some authors have reported the vasorelaxant effects of compounds containing this molecular skeleton (8, 11, 12). Structure-activity relationship studies suggest that the presence of an aromatic group attached to nitrogen 3 and an active methyl group attached to the carbon atom of the heterocyclic ring may be involved in the vasorelaxant activities of these substances (13). Various methods have been used for the synthesis of quinazolinone derivatives including the reaction of nitriles with lithiated anthranilamides (14),

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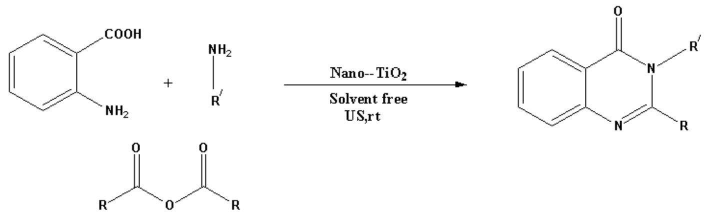


Scheme 1. Synthesis of 3-substituted 2-methylquinazolin-4(3H)-one compounds using TiO_2 nanoparticles as green catalysts under ultrasonic irradiation (U.S.) in solvent-free conditions at room temperature (rt) using anthranilic acid, anhydrides and primary amines.

thermolysis of 3-arylidene amino 1,2,3, benzotriazin-4-one (15), direct condensation of aldehydes and anthranilamide in the presence of copper chloride (16), and metal-catalyzed synthesis of quinazoline diones (17). Unfortunately, most of these methods suffer from significant disadvantages such as long reaction times (hours), low yields, harsh reaction conditions, laborious purification, and the need to use expensive and environmentally toxic catalysts or reagents. Therefore, developing convenient and efficient methods for the synthesis of these valuable substances is of great importance. Recently, some green methods have been developed, including ultrasonic and metal-catalyzed solid-phase synthesis (18). Ultrasonic irradiation as an alternative source of energy has attracted an increasing interest in organic synthesis. This technique accelerates chemical reactions, reduces energy consumption, and increases the yield of products (19). Continuing our previous studies in an attempt to develop a facile and practical one-pot multicomponent synthesis of quinazolinone derivatives, we would like to report another efficient method for the preparation of a series of 3-substituted 2-methylquinazolin-4(3H)-one derivatives using anthranilic acid, acetic anhydride, and primary amines as reactants under ultrasonic (US) irradiation in the presence of TiO_2 nanoparticles (Scheme 1).

TiO_2 nanoparticles are inert, nontoxic, and stable heterogeneous catalysts. Due to their unique morphology and surface chemistry, TiO_2 nanocatalyst have been widely used to drive a variety of organic reactions (20). In this study, we investigated the effect of using ultrasound irradiation combined with TiO_2 nanocatalyst on increasing the rate and yield of the reaction between anthranilic acid, acetic anhydride, and primary amines to produce a series of 3-substituted 2-methylquinazolin-4(3H)-one derivatives. The synthesized compounds were subsequently pharmacologically evaluated for vasodilator activity on isolated rat thoracic aorta.

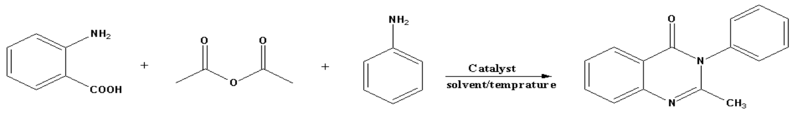
2. Materials and Methods

2.1. Chemicals and equipments

All chemicals were of analytical grade and purchased from Sigma or Merck. The reactions were followed by thin layer chromatography (TLC) using SILG/UV 254 silica-gel plates. Sonication was performed using a Dr Hielscher UP200H ultrasonic device with a frequency of 24 kHz and a nominal power of 600 W/cm^2. Melting points were measured in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. IR Spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. 1H- and 13C-NMR Spectra were obtained using a Brüker Avance-DPX-250 spectrometer operating at 250/62.5 MHz, respectively (δ in ppm, J in Hz). GC/MS were performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z; rel %). Elemental analyses were performed on a Perkin–Elmer 240-B microanalyzer.

2.2. Animals

Male Sprague-Dawley rats (200-250 g) were used. The animals were allocated in groups of 6-7 under standard conditions (12 h light/dark cycle, temperature: 20-25 °C, and



Scheme 2. Synthesis of 2-methyl-3-phenyl-3H-quinazolin-4-one as a template molecule from the reaction between anthranilic acid, acetic anhydride and aniline.

humidity: 25- 30%) with standard food and tap water *ad libitum*. All animal procedures were approved by the Institution of Animal Care and Use Committee of Shiraz University of Medical Sciences.

2.3. Methods

2.3.1. Synthesis of 3-substituted 2-methylquinazolin-4(3H)-one derivatives

A series of 3-substituted 2-methylquinazolin-4(3H)-one derivatives were prepared by a one-pot reaction between anthranilic acid, anhydrides and primary amines in the presence of TiO_2 nanoparticles under ultrasonic irradiation (U.S.) in solvent-free conditions at room temperature. For these reactions, the ultrasound reactor was set at 80% amplitude, with a pulse cycle of 1, a frequency of 24 kHz, and an output power of 600 W.

The reaction between acetic anhydride the template reaction (Scheme 2). We first investigated the yield and rate of the reaction between anthranilic acid (1 mmol), acetic anhydride (1.5 mmol), and aniline (1 mmol) under different conditions in terms of temperature, solvent, catalyst, and ultrasonic irradiation. The results are summarized in Table 1.

In our first attempt, we carried out the reaction in acetonitrile as the solvent and refluxed the reaction mixture for 24 h (entry 1). No products were identified. In another experiment, the solvent was changed to ethanol, but this change didn't lead to a product (entry 2). In the next two experiments, we investigated the effect of catalysts titanium dioxide and titanium dioxide nanoparticles on the rate and efficiency of the first reaction (entries 3-4). The results showed that only nano TiO_2 increased the yield of the first reaction by 53%. In the next two steps, we investigated the reaction process under solvent-free conditions at

Table 1. Effect of different conditions on reaction time and product yield for the synthesis of the template 3-substituted 2-methylquinazolin-4(3H)-one compound.

Entry	Catalyst	Source of energy	Solvent	Time	Yield (%)
1	-	Reflux	Acetonitrile	24 h	NR
2	-	Reflux	Ethanol	24 h	NR
3	TiO_2	Reflux	Acetonitrile	24 h	NR
4	Nano TiO_2	Reflux	Acetonitrile	24 h	53
5	-	100 °C	-	24 h	NR
6	TiO_2	100 °C	-	24 h	NR
7	Nano TiO2	100 °C	-	24 h	92
8	-	Ultrasonic irradiation Room temperature	-	1 min	90
9	TiO_2	Ultrasonic irradiation Room temperature	-	1 min	90
10	Nano TiO_2	Ultrasonic irradiation Room temperature	-	1 min	95
11	Nano TiO_2	Ultrasonic irradiation Room temperature	-	5 min	96

Reaction condition: aniline (1 mmol), anthranilic acid (1 mmol), acetic anhydride (1.5 mmol) and TiO_2 catalyst (0.04 g, 5 mol%).
NR: No products were identified.

100 °C with or without the use of TiO_2 catalyst (Entries 5–7). It was shown that after 24 hours the reaction did not proceed (entry 5). Even more, the use of TiO_2 catalyst also failed to lead to the formation of the product under these conditions (entry 6). However, the nano-TiO_2 catalyst significantly increased the yield of the products to 92% after 24 hours at 100 °C (entry 7). Next, we investigated the effect of using ultrasound radiation on the reaction rate under different conditions. Under solvent-free conditions, ultrasound irradiation significantly increased the reaction rate and yield (entry 8). The addition of TiO_2 catalyst did not lead to a significant change in the reaction time and product yield (entry 9). The simultaneous use of TiO_2 nanoparticles along with ultrasound irradiation increased the reaction efficiency by 95% (entry 10). Extending the reaction time to 5 minutes did not lead to a significant increase in product yield (entry 11). Therefore, the most effective method for synthesizing the model compound at room temperature was the use of ultrasound irradiation in the presence of TiO_2 nanoparticles under solvent-free conditions. After establishing the feasibil¬ity of the proposed method for the synthesis of the template compound, the scope of the methodology was assessed by employing a set of various primary amines to produce a series of 3-substituted 2-methyl-4(3H)-quinazolinone compounds. At room temperature, a number of aromatic or aliphatic amines were reacted separately with anthranilic acid and acetic anhydride in the presence of catalytic amounts of nano TiO_2 (5.0 mol %) under ultrasonic irradiation (25 kHz) in solvent free conditions (Table 2). Thin layer chromatography was performed throughout the reaction time to monitor the completion of the reactions and the purity of the products. The molecular structure of the synthesized compounds was determined using spectroscopic data including infrared (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS), elemental analysis, and melting point. The relevant reports are provided in the experimental section.

2.3.2. Evaluation of vasorelaxant activity of the 3-substituted 2-methylquinazolin-4(3H)-one derivatives

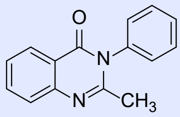
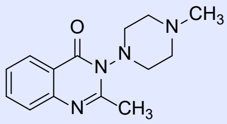
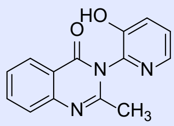
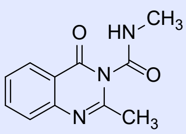
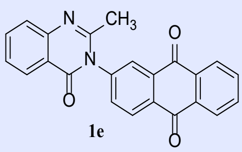
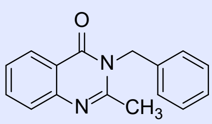
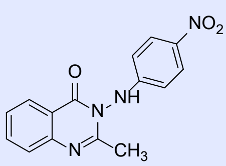
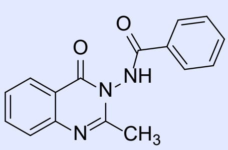
After identifying all the newly synthesized quinazolinone derivatives, they were screened for their vasodilator activity on isolated rat thoracic aorta.

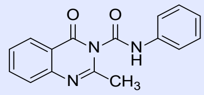
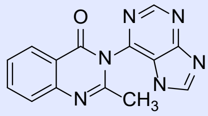
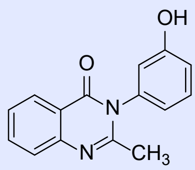
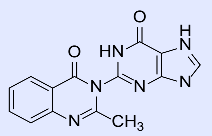
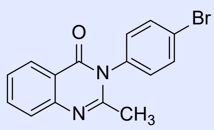
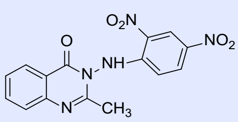
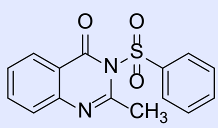
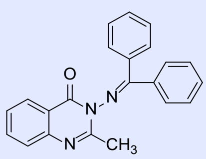
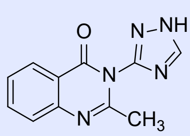
Male Sparque-Dawley rats (200-250 g) were anesthetized using ketamine (60 mg/kg) and xylazine (8 mg/kg) intraperitoneally. The thoracic aorta was isolated and divided into four rings of approximately 2-3 mm length. The rings were mounted on some hooks in an organ bath filled with bicarbonate-buffered physiological saline solution (PSS buffer) which was continuously bubbled with 95% O_2 and 5% CO_2 and refreshed every 20 minutes. The temperature was set at 37 °C and the pH at 7.4. Vascular tension was recorded by a force transducer (K 30, Hugo Sachs Elektronik, Germany) that was attached to a software (HSE-ACAD, Hugo Sachs Elektronik, Germany). Aortic rings were left to stabilize for 60 minutes with a resting vascular tension of 1g. The rings then were preincubated with phenylephrine (10^{-6} M) to achieve their maximal vascular tension. Subsequently, cumulative concentrations of quinazolinone compounds (10^{-9}–10^{-4} M) were added to the organ bath and at the same time, vascular tension of the aortic rings was recorded. Concentration-response curves were plotted and log IC_{50} (the logarithm of the concentration that relaxes the vessel to 50% of its initial tension), and maximal vasorelaxant effects (Emax) were achieved. Acetylcholine was used as a reference standard for vasorelaxant activity.

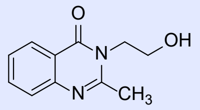
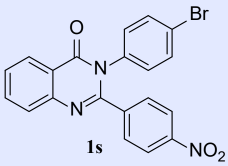
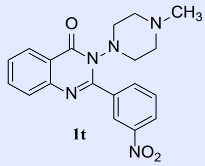
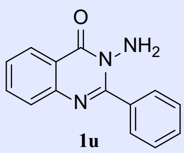
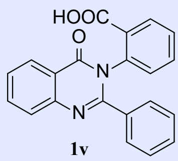
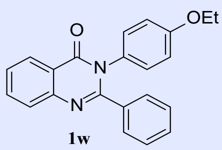
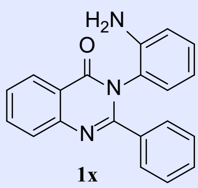
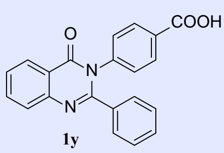
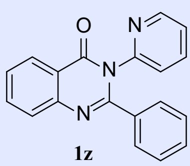
3. Results and Discussion

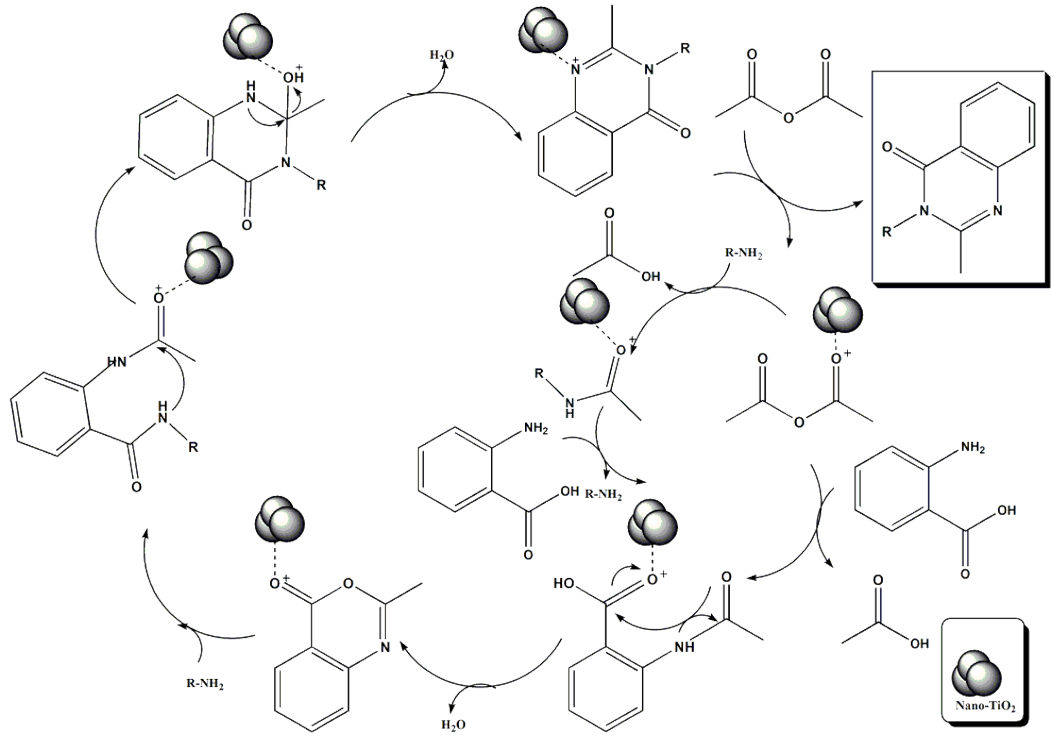
In this study, we synthesized a series of 3-substituted 2-methylquinazolin-4(3H)-one derivatives from anthranilic acid, acetic anhydride, and primary amines in a green and high-yield method using TiO_2 nanocata-

Table 2. 3-substituted 2-methylquinazolin-4(3H)-one derivatives synthesized by the reactions between a variety of aromatic or aliphatic amines (1 mmol), with anthranilic acid (1.5 mmol) and acetic anhydride (1 mmol) in the presence of catalytic amounts of TiO_2 nanoparticles (5 mol%) under ultrasonic irradiation in solvent-free conditions.

Entry	Product	Time (min)	Yield (%)
1	 **1a**	5	96
2	 **1b**	20	89
3	 **1c**	30	88
4	 **1d**	15	93
5	 **1e**	30	85
6	 **1f**	9	96
7	 **1g**	30	89
8	 **1h**	15	84

9	 **1i**	15	85
10	 **1j**	22	84
11	 **1k**	8	96
12	 **1l**	25	82
13	 **1m**	12	85
14	 **1n**	13	87
15	 **1o**	19	83
16	 **1p**	14	89
17	 **1q**	22	86

18	 **1r**	12	90
19	 **1s**	10	91
20	 **1t**	10	93
21	 **1u**	13	86
22	 **1v**	18	86
23	 **1w**	15	90
24	 **1x**	10	91
25	 **1y**	15	86
26	 **1z**	16	87



Scheme 3. Molecular mechanism of the reaction between anthranilic acid, acetic anhydride, and primary amines yielding 2-methyl-3-substituted-quinazolin-4(3H)-one derivatives.

lyst and ultrasound (Table 2). This organic synthesis proceeded very quickly at ambient temperature. The molecular mechanism of this reaction involves the amidation of anthranylonitrile, anthranilic acid followed by cyclization of the intermediate (21). The mechanism begins with the acetylation of the aromatic amine group of anthranilic acid by acetic anhydride, producing the key intermediate, N-acetylanthranilic acid. Upon the introduction of the primary amine, a two-step condensation and cyclization reaction occurs. The initial cyclized product then undergoes spontaneous tautomerization to produce the final aromatic the 2-methyl-3-substituted-quinazolin-4(3H)-one (Scheme 3).

3.2. Physical and herbal remedies: Traditional knowledge and contemporary science

The cyclization step proceeds slow and is the rate-limiting step of the reaction (22). Therefore, various methods have been proposed to solve this problem. The use of ultrasound is an effective way to overcome the problem of the low rate of this reaction and helps to carry out the reaction at room temperature. The massive local energy input by ultrasound can directly facilitate chemical steps such as bond breaking and formation, accelerating the rate-determining cyclization step (24). Some researchers have used catalysts to accelerate this reaction. In a study by Khalafinezhad, A. et al, a series of 3-substituted 2-methylquinazolin-4(3H)-one compounds were synthesized using TiO_2 nanoparticles without ultrasonic irradiation, but this reaction required a high temperature (80 °C) to proceed (23). But the benefits of using a catalyst are not limited to speeding up the reaction. TiO_2 nanoparticles allow the reaction to be carried out in a single-step solvent-free condition without the need for toxic and corrosive reagents with high yield which is relatively higher than similar reactions that do not use TiO_2 nanocatalysts or ultrasound. For example, a series of quinazolinone compounds were synthesized by Ajani O. and co-workers under catalyst-free conditions. The best results (yield of about 80%) were obtained at high temperature (100 °C) for 6 hours in ethanol solvent medium (25).

Table 3. Vasorelaxant potencies and maximal efficacies of the 2-methyl-3-phenylquinazoline-4(3H)-one compounds.

Entry	Compound	Log IC_{50}	E_{max}
1	Acetylcholine	-7.13 ± 0.14	85.31 ± 5.3
2	1a	-6.00 ± 0.55	91.1 ± 5.5
3	1g	-7.31 ± 0.94	86.4 ± 4.0
4	1n	-7.15 ± 0.81	86.1± 8.9
5	1p	-7.77 ± 0.31	90.7± 3.9

Another series of quinazolinone derivatives were synthesized by Hassanzadeh F. and colleagues using several solvents at different temperatures in about 6 hours, with product yields ranging from 25 to 50% (26). The yield of our reaction products in this current study (95%) was still higher than a previous work in which we used only ultrasound irradiation to accelerate the reaction (27). This may be related to the acid-base properties of the TiO_2 surface. The surface of TiO_2 has both Lewis acid sites (Ti^{4+} ions) and Lewis base sites (O^{2-} ions) (20) and provides a confined space where all reactants (acid intermediate and amine) are brought into close proximity. The surface can simultaneously activate both the electrophile (via acid sites) and the nucleophile (via basic sites). The surface also facilitates the critical dehydration step for aromatization (28). Indeed, we combined the advantages of ultrasonic irradiation and nanotechnology for the green synthesis of a number of 3-substituted 2-methylquinazolin-4 (3H)-one compounds.

All synthesized compounds were pharmacologically analyzed for their vascular relaxant effects on isolated rat aorta. It was revealed that all quinazolinone derivatives showed vasorelaxant activity. In some cases (Compounds1a, 1g, 1n, and 1p) this effect was comparable to that of acetylcholine (Ach). These compounds have a quinazolinone core in their molecular structure, which is similar to prazosin, a drug widely used to treat hypertension. Prazosin is a well-known selective antagonist of α-1 adrenergic receptors with potent vasodilator activity (29). Therefore, the vasodilator properties of our quinazolinone compounds may be due to the α-1 receptor antagonism activity. However, this point needs further investigation to be confirmed.

On the other hand, we found that quinazolinone derivatives having a nitro group in their molecular structure (Compounds 1g, 1n) had greater vasorelaxant activity than the others. It can be rationalized by considering the strong electron-withdrawing nature of the nitro group. This feature likely increases the hydrogen bond strength and facilitates stronger interactions with the target. Furthermore, given the critical role of nitric oxide in vasodilatation (28), A proposed hypothesis could be that these derivatives may act as nitric oxide (NO) donors and undergo bioactivation in vascular tissue to directly induce vasodilation via the cGMP pathway (31).

4. Conclusion

In conclusion, in this work we developed an efficient and facile method for the synthesis of some vasorelaxant 3-substituted 2-methylquinazolin-4(3H)-one derivatives under ultrasonic waves in the presence of titanium dioxide nanocatalyst. The nano TiO_2 catalyst drives the one-pot condensation reaction between acetic anhydride, anthranilic acid, and primary amines to proceed under solvent-free conditions. Ultrasound significantly accelerates the reaction and allows the reaction to be carried out at ambient temperature. Some of the synthesized quinazolinone compounds showed strong relaxant properties on isolated rat thoracic aorta and could be used in future pharmacological research.

5. General experimental procedure for the preparation of 3-substituted 2-methyl quinazoline-4(3H)-ones:

The mixture of anthranilic acid (1 mmol), anhydrides (1.2 mmol), with selected aromatic/aliphatic amines (1 mmol) were reacted under ultrasonic irradiation in temperature controled experiments; reactions were performed in a water bath at 25±1 °C. After completion of reaction (monitored by TLC), The reaction mixture was washed with chloroform (3×10 mL). Chloroform was evaporated to give the crude product, which was recrystallized from ethanol. All the products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectroscopy and have been identified by the comparison of the reported spectral data. The spectral and analytical data for the selected compounds are presented.

5.1. 2-methyl-3-phenylquinazoline-4(3H)-one (1a).

White solid, M.p. 145-148 0C. IR (KBr, cm-1): ν= 3100(s) , 2921(s), 1675(s), 1582(s), 755(s).^{1}H NMR (250 MHz, DMSO-d6) δ (ppm): 2.09 (s, 3H), 7.39-7.64 (m, 8H), 8.05 (d, J =7.5 Hz, 1H).^{13}C NMR (62.9 MHz, DMSO-d6) δ (ppm): 24.0 , 120.4, 124.5, 126.2, 126.3, 126.6, 128.4, 128.9, 129.5, 137.8, 147.2, 154.3, 161.4. Anal. Calcd for $C_{15}H_{12}N_2O$ (236.27): C 76.25; H 5.12; N 11.86, Found: C 79.81; H 5.03; N 11.75.

Authors contributions

All authors participated in the design, practical work, and writing of the article. Synthesis, purification, and identification of the compounds were performed at Shiraz University under the supervision of Dr. Ali Khalafinezhad and pharmacological studies were performed at Shiraz University of Medical Sciences under the supervision of Dr. Elahe Sattarinezhad.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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