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Research Article

Synthesis and antimalarial activity of new quinazolinone-4 derivatives

Ali Gamal Al-kaf[1]*, Anas Ahmad Almahbashi[2], M'Hammed Ansar[4], Azeddine Ibrahimi[3], Abdul-Malik Abudunia[3]

[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Sana'a University, Yemen
[2]Department of Biology, Division of microbiology, Faculty of Science-Sana'a University Yemen
[3]Department of Biotechnology Laboratory (Med-Biotech), Faculty of Medicine and Pharmacy, Mohammed V University Rabat, Morocco
[4]Department of Medicinal Chemistry Laboratory, Faculty of Medicine and Pharmacy, Mohammed V University-Rabat, Morocco

ABSTRACT

In this study, we have two new compounds of quinazolinone-4 derivatives were synthesized and evaluated for some of their pharmacological activities that were predicted by computer program (PASS), and also testified for their yield obtained by using some of strong polar aprotic solvents.

The new compounds were synthesized in the lab by allowing interaction of 2-phenylbenzoxazinones-4 with p-aminobenzenesulfonamides in a medium of acid catalyst and strong polar aprotic solvents DMSO.In the pharmacological studies, the synthesized compounds have been investigated in vitro for their toxicity and antimalarial activity according to WHO method.

The pharmacological studies approved that the new compounds have low toxicity, since compound A gave class VI (harmless) and compound B gave class V (practically non toxic) according to Sidorov's classification. For the antimalarial activity, the investigated compounds (A&B) inhibit the maturation of ring form of plasmodium falciparum to schizont form.

We concluded from our study that the new synthesized quinazolinone-4 derivatives were preferably obtained with usage of strong polar aprotic solvents especially DMSO. In addition, the pharmacological investigations have confirmed the prediction of PASS that testifies the high reliability of the obtained results.

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***Correspondence to:**
Dr. Ali Gamal Al-kaf
Email: alialkaf21@gmail.com

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INTRODUCTION:

One of the actual problems of the modern public health is target searching for new high effective medicinal preparation. Amongst those medicinal preparations are the natural and synthetic origins of quinazolinone-4 derivatives. Quinazoline derivatives were reported to be physiologically and pharmacologically active [1].
They also exhibit a wide range of activities such as anticonvulsant, anti-inflammatory, antifungal, antimalarial and sedative [2-6]. Some of these compounds are identified as drugs used as diuretics, vasodilators and antihypertensive agents [7]. Moreover, sulfonamide derivatives have been widely used as bacteriostatic agents [8, 9]. Prompted by the above mentioned facts and in conjunction with our ongoing program on the utility of readily obtainable starting material for the synthesis of heterocyclic systems of biological interest [10-13], we have decided to synthesize a series of quinazoline derivatives having sulfonamide moiety with potentially wide spectrum of biological responses.

MATERIALS AND METHODS:

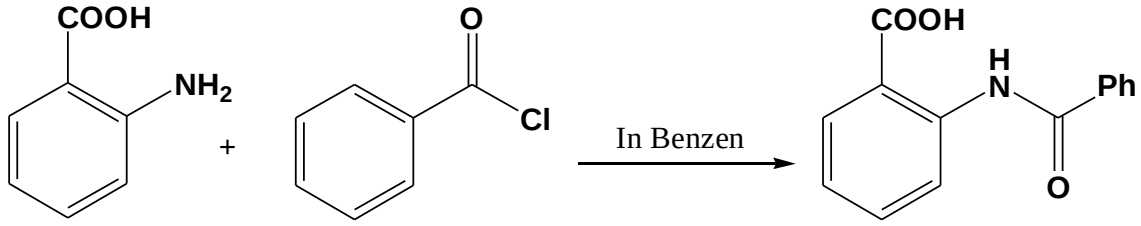
1- Synthesis of O-Benzoyl amino benzoic acid (OBABA)

- Benzylation of anthranilic acid acid in benzene medium

Dissolve 119 g of anthranilic acid in 300 ml of benzene by mixing and add 100 ml of Benzoyl chloride drop by drop, upon heater.

In the process of the reaction, the precipitate of O - Benzoyl amino benzoic acid is formed and after the addition of all quantity of benzoyl chloride the reaction mixture may crystallized. Precipitate must be recrystallized from ethanol with charcoal three times.

M.P = 170^0 c Yield = 50%

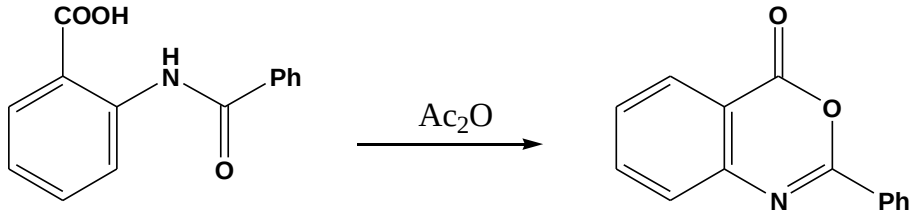


2-aminobezoic acid Benzoyl chloride 2-(benzoylamino)bezoic acid

2-Synthesis of quinazolinone ring (2-phenyl benzoxazinone):

38 ml acetic anhydride (Ac2O) distilled to 27 ml by boiling, then add 13 g (0.05mole) of O-Benzoyl amino benzoic acid in 10 minutes, the precipitate is formed. Then crumbled, filtered and recrystallized from ethanol.

M.P = 116^0c Yield = 50%

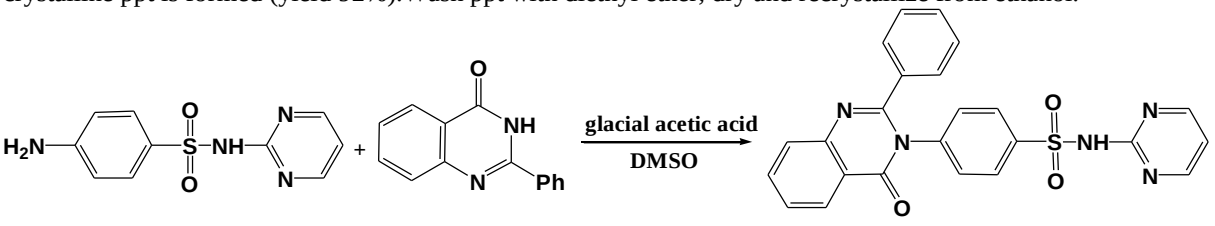


2-(benzoylamino)benzoic acid 2-phenyl-4-*H*-3,1-benzoxazin-4-one

B-Synthesis of compounds (A & B):

1- Synthesis of 4-(4-Oxo-2-phenyl-4H-quinazolin-3-yl)-N-pyrimidin-2-yl-benzenesulfonamide (Compound A):

2.23 gm (0.01mole) 2 phenyl-1,3-benzoxazinone-4 and 2.50 gm. (0.01mole) 2-(p-aminobenzenesulfamido)-pyrimidine are dissolved in 7 ml glacial acetic acid and 0.5 ml DMSO and boil during 2 hours , after that white crystalline ppt is formed (yield 92%).Wash ppt with diethyl ether, dry and recrystallize from ethanol.



Sulfadiazine **2-phenyl-4*H*-3,1-benzoxazin-4-one** **Compound B**

Fig (1)

Formula: $C_{24}H_{17}N_5O_3S$

Properties: white crystalline powder without odour, soluble in DMSO, slightly soluble in ethanol, insoluble in water and ether.

- M.P. crystallization from ethanol=265-269 C°
- RF from ethanol =0.89
- Elemental analysis:

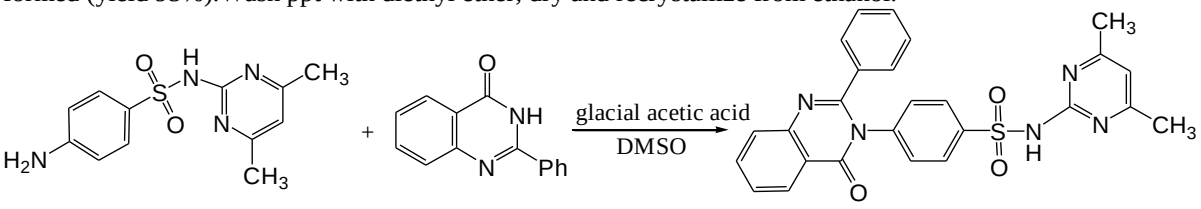
Calculated %: C(63.29 %), H(3.76%), N(15.38%)

Found %: C (62.79%), H (3.66 %), N (15.22 %)

- IR: C=O: 1638, C=N: 1588, S=O: 1159. UV: 220, 270 nm.

2- Synthesis of N-(4,6-Dimethyl-pyrimidin-2-yl)-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzenesulfonamide (Compound B)

2.23 gm (0.01mole) 2 phenyl-1,3-benzoxazinone-4 and 2.78 gm (0.01mole) N-acetyl-p-aminobenzenesulfonamide are dissolved in 7 ml glacial acetic acid and 0.5 ml DMSO and boil during 4 hours, after that white crystalline ppt is formed (yield 95%).Wash ppt with diethyl ether, dry and recrystallize from ethanol.



Sulfadimidine 2-phenyl-4*H*-3,1-benzoxazin-4-one Compound D

Fig (2)

Formula: $C_{26}H_{21}N_5O_3S$.

Properties: white crystalline powder without odour, soluble in DMSO, slightly soluble in ethanol, insoluble in water and ether.

M.P. crystallization from ethanol=234-235 C°

RF from ethanol = 0.73

Elemental analysis:

Calculated %: C (64.6%), (H=4.38%), N (14.48%)

Found %: C (64.10%), H (4.20%), N (14.89%)

IR: C=O: 1638, C=N: 1588, S=O: 1159

UV: 225, 270 nm

NMR integrals of (Compound B) spectrum correspond to protons quantity of the suggested structure. The multiples of aromatic protons are in the field of 8.1–9.0 ppm the signal of one proton is strongly enough displaced into a weak field area and observed as a doublet in the field of 9.7 ppm, that unequivocally testifies of quinazolinone nucleus formation.

Study of acute toxicity:

Acute toxicity study was carried out according to kerber's method [16,17] on mice (18-24 gm).The examined substances were given to mice in the form of suspension with tween-20 intraperitonealy.

Antimalarial activity Screening:

The antimalarial activity screening in vitro was carried out at department of microbiology, Shephaco Pharmaceutical industry, Sana'a-Yemen.

On the bases of the anti-malarial activity of chloroquine salts, synthesized compounds having quinazolinone-4 nucleus have been studied for anti-malarial effect. In which the activity was studied on vitro-test according to (WHO. 2003) [18]. As chloroquine is classified according to its action on plasmodium life cycle stages in human hosts [19] as blood schizonticides, which attack parasites in red blood cells, preventing or terminating the clinical attack.

WHO in-vitro test of anti-malarial drugs susceptibility test was performed in duplicate in a 96-well micro-titter plate, according to the World Health Organization method (WHO) (in vitro micro test) that is based on assessing the inhibition of schizont maturation [19] and the RBMI 1640 was the culture media that was used for cultivation of P. falciparum [18].

Data analysis:

Data analysis was carried out using a computerized mathematical long-concentration-response-Probit analyzing model for result interpretation [20], based on the method of Litchfield and Wilcoxon to fit a regression line to the data points which were directly derived from the counting results. This method is presently the most widely accepted analytic approach to dose-effect experiments showing a long-normal distribution of results. The 50% and 90% effective concentration (EC50 and EC90, respectively), i.e. the drug concentration at which 50 and 90% shcizont maturation inhibition had occurred, were calculated from mathematically derived regressions. Cutoff points, the lowest drug concentration at which no schizont maturation was observed, were used as measure of full inhibition.

RESULTS:

The following table (1) represents the results of acute toxicity of N-sulfonamide derivatives of quinazolinone-4;

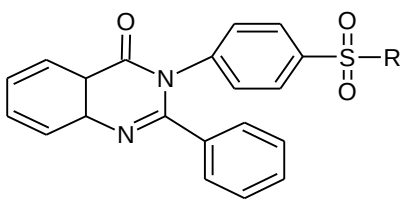
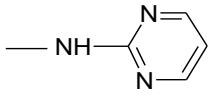
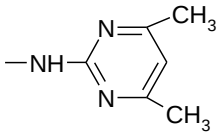


Table. 1:

Laboratory index.	R	LD_{50} mg/kg (IPR-MUS)*	Class of toxicity
Compound A		**3500**	**VI (harmless)**
Compound B		**2800**	**V (practically nontoxic)**
***IPR-MUS: intraperitonealy in mouse.**			

Acute toxicity of new quinazolinone-4 derivatives investigation has shown that these substances according to the classification of K.K.Sidorov [15] are related to substances V1 classes of toxicity, which means that they are practically nontoxic and harmless.

Specifically follows to emphasize that preparation "sulfanilamide" has LD_{50}-930 mg/kgs at intraperitonealy introduction for mice [14], and related to substances with toxicity of class IV [15].

Elemental analysis:

According to the prediction, the structures of the synthesized compounds were confirmed on the basis of the elemental analysis data, and UV, IR -and NMR-spectroscopy. Electronic absorption spectrums are measured on the spectrophotometers of CF-103 in quartz cuvettes of 1 cm thickness, ethanol solvent.IR-spectrums are measured on spectrometer Specord IR-75 in a suspension in vaseline oil .NMR spectrums were registered on Brucker-300Mhz device at 20°C in HMDS, as the internal standard. All reagents corresponded to BDH, SIGMA and ELDRICH."

For a thin-layer chromatography, plates of «Silufol UV-254" were used. As a developer, iodine vapors were used. Ultraviolet spectrums of absorption of the synthesized compounds are characterized by two wide absorption bands.

For quinazolinones-4 the front strip in most cases is within the limits of 240-290 nm, rarely of 250-320 nm and it is high-intensity one, the second strip is more intensive in the field of 200-220 nm. In IR-spectrums of all quinazolinones-4 we can observe the absorption strips in the field of 1640-1675 (Ar-C=O), 1590-1650, 1520-1580, 1460-1500 cm which are characteristic for quinazolinone cycle [22,23, 24].

Results of antimalarial activity:

The in vitro test for the compounds (A & B) was performed .The schizonts maturation inhibition (SMI) (the lowest drug concentration in which no such schizonts were observed) was determined by using probit analysis for individual drugs.The frequency of schizonts maturation growth of plasmodium falciparum in different concentrations of the drugs is described in the table (2).

The schizonts minimum inhibition percentage and effective concentration (EC_1, EC_{16}, EC_{34}, EC_{50}, EC_{90} and EC_{99}) for each drug are described in the table (4).

Table No. 2:

Table No. (2): Number. of schizonts/100 ring forms :						
Conc./well	**Cpd A (1)**	**Cpd A (2)**	**Cpd B (1)**	**Cpd B (2)**	**+ve control (Chlq.Ph) (1)**	**+ve control (Chlq.ph) (2)**
-ve control	15%	10%	16%	16%	13%	19%
7.8	2%	2%	1%	1%	0%	9%
15.6	2%	1%	1%	0%	2%	3%
31.25	1%	1%	0%	0%	1%	2%
62.5	0%	2%	0%	0%	0%	0%
125	1%	1%	0%	0%	0%	0%
250	0%	0%	0%	0%	0%	0%
500	0%	0%	0%	0%	0%	0%

Table No. 3:

Drug conc. (µg/well)	SMI% Cpd (A)	SMI% Cpd (B)	SMI% Chlq.Ph
7.8	84%	93.7%	71%
15.6	88%	96.8%	84%
31.25	92%	100%	90.6%
62.5	92%	100%	100%
125	92%	100%	100%
250	100%	100%	100%
500	100%	100%	100%

Table No. 4: The efficacy conc. of compounds (A & B) compared with the positive control chloroquin phosphate.

EC	Cpd (A)	Cpd (B)	Chlq.Ph
EC_1	2	1	2
EC_{16}	2	2	4
EC_{34}	4	5	6
EC_{50}	6	6	7
EC_{90}	23	9	28
EC_{99}	224	22	58

Discussion:

Among strategies to compact malaria, the search for new antimalarial drugs including quinazolinone-4 derivatives appears to be a priority. Investigations of drugs of quinazolinone nucleus have provided strong evidence for several compounds with potent antimalarial activity [4-6]. The efficacy of antimalarial drugs depends primarily on their ability to kill malarial parasites by interrupting their essential life function, leading to inhibition of multiplication and allowing the

immune system to remove damaged parasites completely from the circulation [21].This efficacy varies according to the susceptibility of each parasite clone within a natural, often genetically heterogeneous, population of malaria parasites and is generally referred to as drug sensitivity.

The results obtained from *in vitro* tests do not necessarily reflect the clinical outcome of malaria therapy as this is not merely dependent on the intrinsic drug sensitivity of the pathogen, but is also dependent on a several host related factors such as the immune status of the patient. Although the immune status of individuals might at first sight seem to be an obstacle to determining the specific drug response of parasite populations.

The in vitro results of compound (A) show complete inhibition of the schizonts maturation exhibited at 250µg/ml with EC_{50} = 6 and EC_{99}= 224, while chloroquine show complete inhibition of the schizonts maturation exhibited at 62.5µg/ml with EC_{50} = 7 and EC_{99}= 58 that means activity of compound (A) can be increased by increasing the dose.

The compound (B) showed higher effectiveness than chloroquine in which the complete inhibition of the schizonts maturation exhibited at 31.25µg/ml with EC_{50} = 6 and EC_{99}= 22 that approved an activity with a low dose.

Finally, we advice for doing further studies on the investigated compounds for testing activity on chloroquine resistant strains of *plasmodium falciparum* and in vivo studies concerning pharmacodynamic and pharmacokinetic properties of these drugs.

Conclusion:

1. Quinazolinone-4 derivatives, containing in N-3 nucleus of quinazolinone arylsulfonamide fragments were obtained for the first time. Synthesis of 4-(4-Oxo-2-phenyl-4H-quinazolin-3-yl)-N-pyrimidin-2-yl-benzenesulfonamide (Compound A), and N-(4,6-Dimethyl-pyrimidin-2-yl)-4-(4-oxo-2-phenyl-4H-quinazolin-3-yl)-benzenesulfonamide (Compound B) are carried out in the lab by allowing interaction of 2-phenylbenzoxazinones-4 with p-aminobenzenesulfonamides in a medium of acid catalyst and strong polar aprotic solvent DMSO.
2. Introduction of quinazolinone cycle in the place of primary amine of the molecule of sulfanilamide brings to reduce its toxicity and give new and interested pharmacological activity.
3. The investigated compounds (A & B) showed high antimalarial activity compared with chloroquin.
4. Analysis of pharmacological activity predicted by program PASS allow in experiments to confirm the antimalarial activity.

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