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Synthesis and Biological Evaluation of Novel Quinoline Derivatives as Antibacterial and Antifungal Agents

M. Shiri[a,*], A. Nejatinejhad-Arani [a], Z. Faghihi [a], S.A. Shintre [b] and N.A. Koorbanally[b]

[a]*Department of Chemistry, Faculty of Physics and Chemistry, Alzahra University, Vanak, Tehran 1993893973, Iran*

[b]*School of Chemistry and Physics, University of KwaZulu-Natal, Private Bag X54001, Durban, 4000, South Africa*

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Vilsmeier Several diamide derivatives containing 2-chloroquinoline scaffolds were synthesized *via* Ugi reaction of 2-chloroquinoline-3-carboxaldehydes, amines, carboxylic acids and isocyanides. The diversity of these quinolinyl Ugi-adducts was increased by using 2-chloroquinoline-3-carboxylic acids as a source of acid. Among them, compounds **2d, 2n, 2p, 4a, 4c** and **4e** displayed moderate to good antibacterial and antifungal activity.

Keywords: Multicomponent condensation, Quinolines, Diamides, Antibacterial, Antifungal

INTRODUCTION

The Ugi four-component reaction (Ugi 4-CR) involves the condensation of aldehydes, amines, isocyanides and carboxylic acids to form diamides [1-4]. This reaction has the capability of rapid construction of diverse and complex molecules by changing four different starting materials. Recently, some applications of Ugi reaction in polymer chemistry for instance [5], macrocyclization of peptide side chains [6] along with the synthesis of the inhibitors of the MDM2-p53 interaction [7] have been published. The Ugi reaction has also been mentioned in a recent review regarding the isocyanide-based multicomponent reactions for the synthesis of heterocycles [8] and as well as cyclic constrained peptidomimetics [9]. Recent advances for generation of small-molecule libraries using this significant name reaction has been lately reviewed, too [10].

As a one-pot reaction, it saves time and costs, reduces wastes leading to an increase in the total yield. These factors align with the principles of green chemistry. Various synthetic and naturally occurring quinoline derivatives with pharmaceutical applications have been described in the literature [11-15]. Quinolines are well-known bioactive molecules, which exhibit anti-malarial [16], anti-bacterial [17], anti-inflammatory [18], anti-hypertensive [19], hypotensive [20], anti-rheumatic [21] and anti-asthmatic properties [22]. There is therefore an ongoing search for novel quinoline derivatives in the search for new and sophisticated pharmaceuticals. Ma *et al.* have prepared two new types of quinoline scaffolds with combinatorial format *via* the Ugi 4CR and the Pd-catalyzed intramolecular arylation reaction [23]. Tetrahydroisoquinoline was oxidized to the corresponding imines by singlet oxygen generated from oxygen and a porphyrin photosensitizer was then used in Ugi-type reactions to produce functionalized tetrahydroisoquinolines [24]. Synthesis of Ugi adducts incorporating the 4-aminoquinoline moiety has been described by Musonda *et al.* [25]. The same group reported the preparation of 4-aminoquinoline γ- and δ-lactams *via* the Ugi 3-component 4-centre multicomponent reaction [26]. These compounds were active against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. The stereoselective Ugi condensation of (*S*)-glutamic acid 5-methyl ester, quinoline aldehyde and an isonitrile in the presence of $TiCl_4$ has been reported [27]. Fluorite has been also used as a catalyst for the Ugi 4-CR under microwave irradiation [28]. In some reports 2-chloroquinoline-3-carbaldehyde was used in

*Corresponding author. E-mail: mshiri@alzahra.ac.ir

isocyanide-based reactions [29-31].

On the basis of these reports and our experience in the chemistry of quinoline as well as Ugi reactions [15,32-43], we herein report an easy and catalyst-free synthesis of novel quinolinyl diamides using Ugi 4-CR and their antibacterial and antifungal activity.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. IR spectra were acquired on a Shimadzu Infra-Red Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 Spectrometer in DMSO-d_6 or $CDCl_3$ as solvent. A Leco CHNS, model 932 was used for elemental analysis.

General Procedure

Synthesis of Ugi adduct bearing quinoline derivatives. To a solution of aldehyde (0.5 mmol) and amine (0.5 mmol) in MeOH (3 ml), carboxylic acid (0.5 mmol) and isocyanide (0.5 mmol) were added at room temperature. The reaction mixture was stirred for 24 h. The completion of the reaction was monitored by TLC. The product was precipitated out of the solution and filtered. It was then washed with cold methanol. In the case of formation of diamides as a side product, column chromatography is required to get purified.

***In vitro* antibacterial studies.** The microbial cultures were grown overnight at 37 °C in nutrient broth (UKZN Biolab, South Africa), adjusted to 0.5 McFarland standard using distilled water and lawn inoculated onto Mueller-Hinton agar (MHA) plates. A volume of 10 µl of each sample (18.15-19.98 mM, 1 ml DMSO) was inoculated onto antibiotic assay discs (6 mm diameter) and placed on the MHA plates which incubated overnight at 37 °C for 24 h. After the incubation period, zones of inhibition were measured in mm. Compounds showing an inhibition zone of > 9 mm were selected to determine their MBC values using the broth dilution assay with Ampicillin and Ciprofloxacin as the controls following the method in Andrews J. M. (2001). Compounds **2d**, **2n**, **2p**, **4a**, **4c** and **4e** were chosen for the broth dilution method to determine their MBCs.

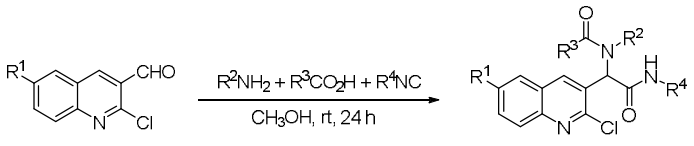
For the broth dilution method the microbial cultures (adjusted to 0.5 McFarland) were prepared as described previously for the disc diffusion method. The test compounds were dissolved in DMSO (10 mg ml^{-1}) and subjected to a 50% serial dilution in 1 mL Eppendorf tubes with Mueller-Hinton Broth (MHB), inoculated with bacterial cultures (20 µl) and then incubated at 37 °C for 18 h. The total volume in each Eppendorf was 200 µl. 10 µl volume of each dilution was spotted on MHA plates and incubated at 37 °C for 18 h to determine the MBC (mM). Ampicillin, ciprofloxacin and tioconazole served as the standard drugs for the antibacterial and antifungal studies respectively. All experiments were performed in duplicate.

RESULT AND DISCUSSION

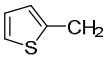
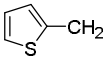
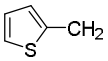
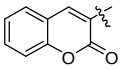
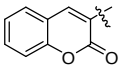
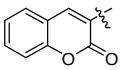
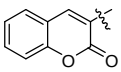
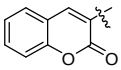
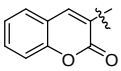
In the first step, 2-chloroquinoline-3-carbaldehyde (**1a**) was prepared as reported in the literature [44]. It was then reacted with *p*-toluidine, acetic acid and cyclohexyl isocyanide in methanol at room temperature for 24 hours to produce the diamide **2a** in 75% yield (Table 1, entry 1). By varying the reactants in this reaction, a total of twenty compounds were synthesized which varied at C-6 of the quinoline as well as the substituents on the amide groups. Besides, the 2-chloroquinoline-3-carbaldehyde (**1a**), 6-methoxy-2-chloroquinoline-3-carbaldehyde (**1j**) and 6-methyl-2-chloroquinoline-3-carbaldehyde (**1k**) were used in the reaction. Five amines and seven carboxylic acids were used in different combinations, which included the amines, aniline, benzylamine, *p*-toluidine, *p*-methoxyaniline, *p*-bromoaniline and the carboxylic acids, acetic acid, benzoic acid, chloracetic acid, bromoacetic acid, 3-chloropropanoic acid, 2-thiophenylacetic acid and coumarin-3-carboxylic acid.

The isocyanide was mostly kept constant at cylcohexyl isocyanide with the exception of *t*-butyl isocyanide, which was reacted with *p*-toluidine and benzoic acid together with 2-chloroquinoline-3-carbaldehyde (**1a**) to produce **2b**. Three different anilines were used with 2-thiophenylacetic acid and the quinoline carbaldehyde (**1a**), *p*-toluidine, aniline and *p*-methoxyaniline to produce the Ugi products **2c-e**. In the next four products **2f-i**, the anilines, were varied using aniline itself, *p*-toluidine, *p*-bromoaniline and *p*-methoxyaniline with coumarin-3-carboxylic acid, cyclohexylisocyanide and the quinoline carbaldehyde (**1a**). Only one compound was made with the 6-methoxy-2-

Table 1. Ugi 4-CC of Aldehyde **1**, Amine, Acid and Isocyanide



1 **2**

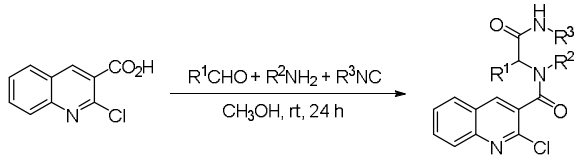
Entry	R^1	R^2	R^3	R^4	Product **2**	Isolated yield (%)
1	H	4-MeC_6H_4	CH_3	CycHex	**a**	75
2	H	4-MeC_6H_4	Ph	*t*-Butyl	**b**	70
3	H	4-MeC_6H_4		CycHex	**c**	96
4	H	Ph		CycHex	**d**	72
5	H	4-$MeOC_6H_4$		CycHex	**e**	85
6	H	Ph		CycHex	**f**	74
7	H	4-MeC_6H_4		CycHex	**g**	72
8	H	4-BrC_6H_4		CycHex	**h**	91
9	H	4-$MeOC_6H_4$		CycHex	**i**	62
10	MeO	4-$MeOC_6H_4$		CycHex	**j**	86
11	Me	4-$MeOC_6H_4$		CycHex	**k**	78
12	Me	4-MeC_6H_4	Ph	CycHex	**l**	68
13	H	$PhCH_2$	Ph	CycHex	**m**	62
14	Me	Ph	CH_3	CycHex	**n**	92
15	H	4-$MeOC_6H_4$	$ClCH_2$	CycHex	**o**	91
16	H	4-MeC_6H_4	$BrCH_2$	CycHex	**p**	90
17	H	4-BrC_6H_4	$BrCH_2$	CycHex	**q**	82
18	H	4-MeC_6H_4	$ClCH_2CH_2$	CycHex	**r**	75
19	H	Ph	$ClCH_2CH_2$	CycHex	**s**	84
20	Me	4-MeC_6H_4	$BrCH_2$	CycHex	**t**	76

chloroquinoline-3-carbaldehyde (**1j**). This product incorporated *p*-methoxyaniline, coumarin-3- carboxylic acid and cyclohexyl isocyanide to produce **2j**. Four Ugi products (**2k**, **2l**, **2n** and **2t**) were made with 6-methyl-2-chloroquinoline-3-carbaldehdye, keeping the cyclohexyl isocyanide constant but varying the amine (aniline, *p*-methoxyaniline and *p*-toluidine) and the carboxylic acid (coumarin-3-carboxylic acid, benzoic acid, acetic acid and bromoacetic acid). In the remaining compounds, **2m** and **2o-2s**, the five different anilines were used with **1a**, cyclohexyl isocyanide and either benzoic acid, chloracetic acid, bromoacetic acid or 3-chloropropanoic acid.

Oxidation of **1a** to the 2-chloroquinoline-3-carboxylic acid **3** produced a new source of acid [45]. Carboxylic acid **3** reacted with 2-formylindole, *p*-toluidine and cyclohexylisocyanide to form **4a** as a novel type of quinoline containing diamide (Table 2, entry 1). By varying mainly the aldehyde, eight compounds of this type were synthesized (**4a-h**). Compound **4b** was synthesized with *p*-methoxyaniline instead of *p*-toluidine and **4f** with *t*-butylisocyanide instead of cyclohexyl isocyanide. All other compounds were formed from *p*-toluidine and cyclohexyl isocyanide with various aldehydes.

The compounds were evaluated for their *in vitro* antibacterial activity against two Gram +ve strains *S. aureus* (ATCC 25923) and *MRSA* (ATCC BAA-1683) and three Gram -ve strains *E. coli* (ATCC 25922), *K. pneumonia (*ATCC 31488) and *P. aeruginosa* (ATCC 27853) as well as one fungal strain *C. albicans* (ATCC 10231). Compounds **2d**, **2n**, **2p**, **4a** and **4e** all showed strain specific activity better than ampicillin against at least one of the bacterial strains tested against (Table 3). Compounds **2n**, **4a** and **4e** were all active against *K. pneumonia* whilst **4e** was also active at 0.22 mM against *P. aeruginosa*. Compounds **2n** and **2p** were active against the Gram +ve *S. aureus* and MRSA. Compounds **2d**, **4a** and **4c** were all much more active than tioconazole against *C. albicans* (Table 3). Amongst the three active compounds, **2d**, **2n** and **2p**, no real trend could be observed with the functional groups on the molecules and bioactivity, however with **4a**, **4c** and **4e**, it was evident that compounds with the 2-indolyl carbaldehyde, *p*-methylbenzaldehyde and cinnamaldehyde

Table 2. Ugi 4-CC of Aldehyde, Amine, Acid **3** and Isocyanide

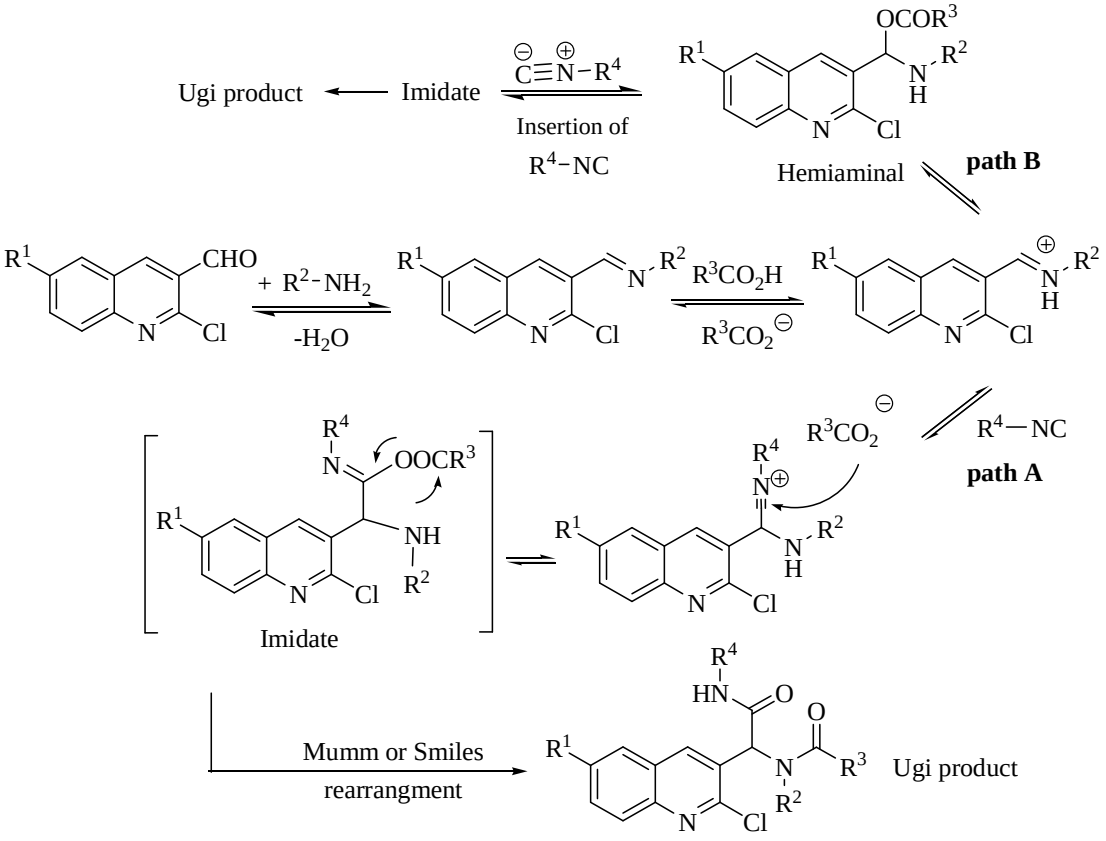


3 **4**

Entry	R^1	R^2	R^3	Product **4**	Isolated yield (%)
1	2-indolyl	4-MeC_6H_4	CycHex	**a**	65
2	2,5-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	CycHex	**b**	83
3	4-MeC_6H_4	4-MeC_6H_4	CycHex	**c**	73
4	4-ClC_6H_4	4-MeC_6H_4	CycHex	**d**	80
5	PhCH=CH	4-MeC_6H_4	CycHex	**e**	66
6	2,5-$(MeO)_2C_6H_3$	4-MeC_6H_4	*t*-Butyl	**f**	71
7	4-$MeOC_6H_4$	4-MeC_6H_4	CycHex	**g**	65
8	2,5-$(MeO)_2C_6H_3$	4-MeC_6H_4	CycHex	**h**	81

Table 3. Antibacterial and Antifungal Activities of Compounds **2** and **4**

Compounds	MBCs in mM				
	Gram-positive bacteria		Gram-negative bacteria		Fungi
	S.aureus	*MRSA*	*P.aeruginosa*	*K.pneumoniae*	*C.albicans*
2d	0.44	-	-	-	0.88
2n	1.83	2.44	-	0.31	-
2p	0.94	0.62	-	-	-
4a	-	-	-	0.43	0.57
4c	-	-	-	-	1.19
4e	-	-	0.22	0.87	-
Ampicillin	0.056	1.789	0.894	3.577	0.894
Ciprofloxacin	0.002	0.007	0.002	0.002	0.004
Tioconazole	-	-	-	-	25.792
DMSO	-	-	-	-	-



Sheme 1. The mechanism of Ugi reaction

group were more active than the Ugi products with other aldehyde groups.

Mechanism

Since the discovery of this reaction in 1959, all synthetic developments about this reaction relied on mechanistic pathway suggested by Ugi himself in about 57 years ago. As shown in path **A** (Scheme 1), some equilibriums concerning nitrilium trapped by oxygenated anion give the corresponding imidate. Due to the greater efficiency of this MCR in polar protic solvents such as methanol, this ionic mechanism was assumed. The alternative mechanism, path **B**, lately considered was the imidate formation involving the insertion of the isocyanide in a hemiaminal. In both cases, the last step is thought to be an irreversible rearrangement displacing the whole equilibriums by developing a CO double bond. For carboxylic acids it is a Mumm rearrangement and a Smiles reaction for phenols [46]. Herein, the nueclephilic center in position 2 of 2-chloroquinoline-3-carbaldehyde does not participate in the reaction.

In conclusion, a series of novel quinolinyl diamide derivatives were easily prepared *via* an Ugi condensation of 2-chloroquinoline-3-carboxaldehydes, amines, carboxylic acids and isocyanides in good yields. This reaction was extended to contain 2-chloroquinoline-3-carboxylic acid as an acid source in the Ugi reaction. All the synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity and among them, compounds **2d**, **2n, 2p, 4a, 4c** and **4e** showed moderate to good activity against *P. aeruginosa*, MRSA, *S. aureus, E. coli* and *K. pneumonia* as well as *C. albicans.*

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