Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (2):
Pg. 435-443

Microwave-Assisted Synthesis of Potent Antimicrobial Agents of Flavanone Derivatives

ABDULLAH S. AL-BOGAMI[1]*, HAMAD Z. ALKHATHLAN[2], TAMER S. SALEH[1] and AHMED M. ELAZZAZY[3]

[1]Department of Chemistry, Faculty of Science, King Abdulaziz University, North Jeddah, P.O Box 80203 Jeddah 21589, Saudi Arabia.
[2]Department of Chemistry, Faculty of Science, King Saud University, P.O.Box 2455 Riyadh - 11451, Saudi Arabia.
[3]Biological Sciences Department, Faculty of Science, North Jeddah, King Abdulaziz University, P.O. Box 80327, Jeddah 21454, Saudi Arabia.
*Corresponding author E-mail: chem_org@hotmail.com

http://dx.doi.org/10.13005/ojc/300205

(Received: March 02, 2014; Accepted: April 07, 2014)

ABSTRACT

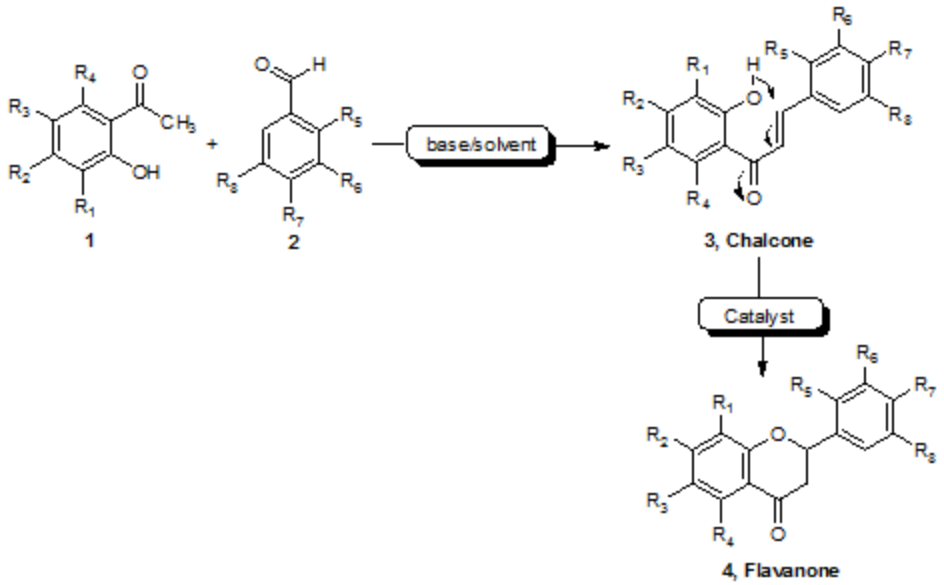
The currently available antimicrobial drugs suffer from toxicity, interactions with other drugs, insufficient pharmacokinetic properties, and the development of resistance. Thus, development of new antimicrobial agents with optimum pharmacokinetics and low toxicity is important. In this study, a series of flavanone, hydrazone derivatives have been prepared from flavanone under microwave irradiation after a very short reaction time (1-2 min.) with good yields. The structures of the synthesized compounds were elucidated using various spectroscopic methods. The screening of the synthesized compounds for antimicrobial activity was performed against *Staphylococcus aureus, Escherichia coli*, *C. Albicans* and *Aspergillus niger*. Some of the synthesized compounds show potent anti microbial activity.

Key words: Microwave irradiation, Flavanone, Hydrazone, Isoniazide, Antimicrobial activity.

INTRODUCTION

Flavanones, which exhibited broad spectrum of biological activities, have long attracted the interest of chemists. The most commonly reported biological activities include neuron protection, anti-tumor, anti-metastasis, anti-microbial, anti-oxidant, anti-inflammatory, and anti-viral activities[1-8]. Flavanones, which have chemical structures embedded with a 2-aryl chroman-4-one skeleton, are widely distributed in plants[9] and are available from synthetic sources. The major and most commonly reported synthetic methods for flavanones 4 usually involve the Claisen Schmidt

reaction of o-hydroxyacetophenones **1** with benzaldehydes **2** to produce chalcone intermediates **3** using various catalysts[10-14], followed by cyclization with various bases[15], acids[16], or other materials (Scheme 1)[17].



Scheme 1:

Recently, we reported the simple and efficient microwave-assisted synthesis of 2'-hydroxychalcones and flavanones in one step with high yield and no side products[14] highlighting the role of different substituent in directing the reaction to pure chalcone or flavanone product (Figure 1).

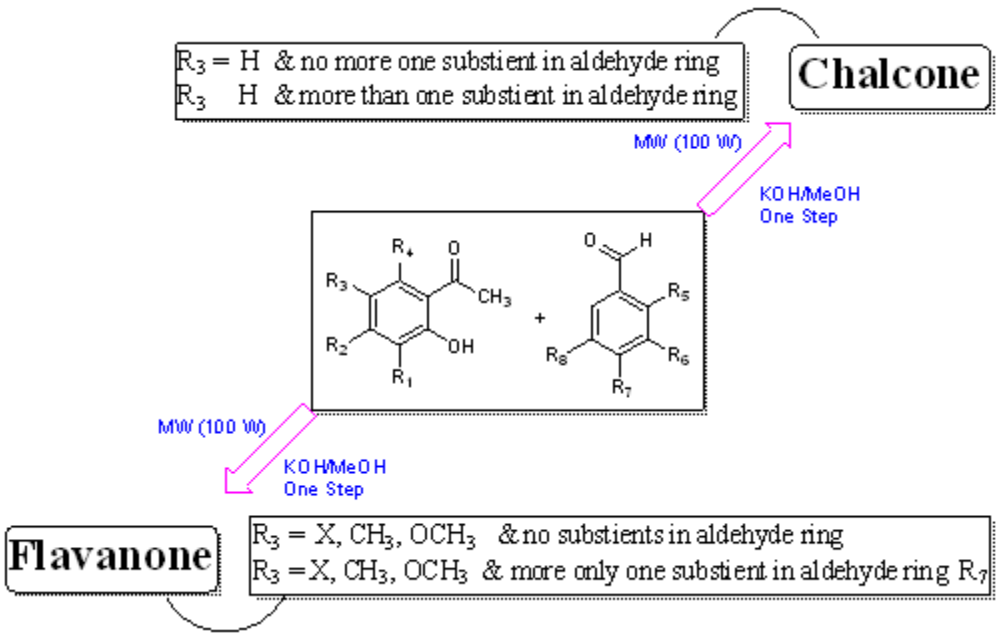


Fig. 1: Substitution effect in synthesis of flvanone

The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic areas, as a new technology enabling drug discovery and development[18,19]. By taking advantage of this efficient source of energy (enhanced reaction rates, high yields, improved purity, ease of work up after the reaction and eco-friendly reaction conditions relative to conventional methods), compound libraries for lead generation and optimization can be assembled in a fraction of the time required by classical thermal methods.

Prompted by these observations and the importance of flavanones, we report the microwave-assisted synthesis of new flavanone derivatives and the evaluation of their antimicrobial activity.

EXPERIMENTAL

Materials and methods

All materials and reagents of the best available quality were purchased from commercial sources and used without further purification. Melting points are uncorrected and were determined on Gallenkamp-melting point apparatus. NMR spectra were recorded on JEOL ECP 400 (400 MHz) in $CDCl_3$ and expressed as ´ in ppm. Mass spectra were recorded on Shimadzu QP-5050A GC/MS system. Microwave experiments were carried out using CEM MARS synthator™ microwave apparatus. TLC was performed on (TLC plates silica gel $60F_{245}$ pre-coated 20×20 cm layer thickness 0.25 mm). Elemental analyses were carried out on EuroVector instrument C, H, N, S analyzer EA3000 Series. Microwave experiments were carried out using CEM MARS synthator™ microwave apparatus with temperature control for MW experiments using IR sensor. Flavanone 4a-d[14] was prepared according to the reported literature.

Typical procedure for synthesis of flavanone derivatives 5a-d and 10a-d

An equimolar amount of flavanone 4a-d and phenyl hydrazine or isoniazide were mixed in a process vial in presence of 1 ml acetic acid and irradiated with microwave (Power 300 watt) for 1-2 min (as examined by TLC), after reaction completion the precipitate was filtered and washed with ethanol and the products (81-92% yield) were crystallized from ethanol. The synthesized compounds with their physical data are listed below.

1-(6-Bromo-2-phenylchroman-4-ylidene)-2-phenylhydrazine.

m.p. 112-114 °C, yield 81%; IR (KBr): 3327 (NH), 1605 (C=N), cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.76 (dd, 1H, *J* = 16.8, 5.1 Hz, H_{3a}), 3.34 (dd, 1H, *J* = 2.9, 16.8 Hz, H_{3b}), 5.25 (dd, 1H, *J* = 2.9, 11.7 Hz, H_2), 7.26-7.85 (m, 13H, Ar-H), 9.56 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.9, 77.2, 112.5, 114.9, 116.6, 121.7, 124.3, 127.0, 127.6, 128.0, 128.8, 129.7, 134.1, 139.9, 143.1, 147.9, 155.1. MS (m/z): 392 (M^+). (Found: C, 64.38; H, 4.28; N, 6.95 $C_{21}H_{17}BrN_2O$ Calc. C, 64.13; H, 4.36; N, 7.12%).

1-(6-Chloro-2-phenylchroman-4-ylidene)-2-phenylhydrazine. 5b

m.p. 194-195 °C, yield 88%; IR (KBr): 3323 (NH), 1599 (C=N), cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 2.77 (dd, 1H, *J* = 16.8, 4.4 Hz, H_{3a}), 3.36 (dd, 1H, *J* = 4.4, 16.8 Hz, H_{3b}), 5.22 (dd, 1H, *J* = 2.2, 11.7 Hz, H_2), 7.19-7.77 (m, 13H, Ar-H), 9.55 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.7, 77.2, 112.1, 114.2, 119.8, 121.00, 125.1, 126.1, 127.5, 128.0, 128.9, 129.9, 134.0, 139.5, 143.0, 145.2, 154.7. MS (m/z): 348 (M^+). (Found: C, 72.64; H, 4.78; N, 7.83; $C_{21}H_{17}ClN_2O$ Calc. C, 72.31; H, 4.91; N, 8.03%).

1-(6-Methoxy-2-phenylchroman-4-ylidene)-2-phenylhydrazine. 5c

m.p. 174 °C, yield 81%; IR (KBr): 3298 (NH), 1605 (C=N), cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (dd, 1H, *J* = 16.9, 5.1 Hz, H_{3a}), 3.33 (dd, 1H, *J* = 16.9, 2.9 Hz, H_{3b}), 3.83 (s, 3H, OMe), 5.16 (dd, 1H, *J* = 2.9, 11.7 Hz, H_2), 7.21-7.88 (m, 13H, Ar-H), 9.42 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.7, 50.1, 77.1, 112.3, 115.0, 116.5, 119.0, 121.6, 126.5, 127.8, 128.1, 129.4, 139.1, 143.0, 147.2, 148.9, 154.4. MS (m/z): 344 (M^+). (Found: C, 77.02; H, 5.73; N, 7.95; $C_{22}H_{20}N_2O_2$ Calc. C, 76.72; H, 5.85; N, 8.13%).

1-(2-(4-Chlorophenyl)-6-methoxychroman-4-ylidene)-2-phenylhydrazine. 5d

m.p. 133-135 °C, yield 82%; IR (KBr): 3322 (NH),

1602 (C=N), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ´: 2.71 (dd, 1H, *J* = 16.8, 4.5 Hz, H_{3a}), 3.35 (dd, 1H, *J* = 2.9, 17.6 Hz, H_{3b}), 3.81 (s, 3H, OMe), 5.20 (dd, 1H, *J* = 2.9, 11.8 Hz, H_2), 7.20-7.78 (m, 12H, Ar-H), 9.44 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.9, 51.0, 76.3, 112.2, 114.9, 116.5, 119.1, 121.0, 126.2, 129.0, 129.9, 134.0, 136.6, 143.2, 147.2, 149.5, 154.5. MS (m/z): 378 (M^+). (Found: C, 70.08; H, 4.92; N, 7.19; $C_{22}H_{19}ClN_2O_2$ Calc. C, 69.75; H, 5.05; N, 7.39%).

4-(2-(6-bromo-2-phenylchroman-4-ylidene) hydrazinyl)pyridine. 10a

m.p. 200-202 °C, yield 84%; IR (KBr): 3365 (NH), 1690 (C=O), 1598 (C=N), cm^{-1}; ^1H NMR (400 MHz, DMSO) δ: 2.77 (dd, 1H, *J* = 17.6, 5.1 Hz, H_{3a}), 3.38 (dd, 1H, *J* = 16.8, 2.9 Hz, H_{3b}), 5.25 (dd, 1H, *J* = 2.9, 11.7 Hz, H_2), 6.92-7.88 (m, 12H, Ar-H and Pyridine-H), 9.56 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, DMSO) δ: 39.6, 77.2, 113.4, 114.1, 114.8, 119.5, 122.7, 126.5, 127.6, 128.0, 133.0, 134.0, 139.1, 140.1, 145.9, 154.6, 160.2. MS (m/z): 421 (M^+). (Found: C, 60.03; H, 3.69; N, 9.78; $C_{21}H_{16}BrN_3O_2$ Calc. C, 59.73; H, 3.82; N, 9.95%).

4-(2-(6-chloro-2-phenylchroman-4-ylidene) hydrazinyl)pyridine. 10b

m.p. 194-195 °C, yield 92%; IR (KBr): 3359 (NH), 1697(C=O), 1605 (C=N), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.75 (dd, 1H, *J* = 16.8, 5.1 Hz, H_{3a}), 3.39 (dd, 1H, *J* = 17.6, 4.4 Hz, H_{3b}), 5.29 (dd, 1H, *J* = 2.9, 12.4 Hz, H_2), 6.89-7.91 (m, 12H, Ar-H and Pyridine-H), 9.56 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.6, 77.2, 113.5, 114.0, 117.1, 122.9, 126.0, 127.6, 127.9, 128.5, 128.7, 132.0, 138.2, 139.9, 145.9, 154.6, 159.2. MS (m/z): 377 (M^+). (Found: C, 66.99; H, 4.18; N, 10.98; $C_{21}H_{16}ClN_3O_2$ Calc. C, 66.76; H, 4.27; N, 11.12%).

4-(2-(6-Methoxy-2-phenylchroman-4-ylidene)hydrazinyl)pyridine. 10c

m.p. 144-145 °C, yield 88%; IR (KBr): 3361 (NH), 1691 (C=O), 1601(C=N), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.73 (dd, 1H, *J* = 16.8, 4.4 Hz, H_{3a}), 3.36 (dd, 1H, *J* = 2.9, 16.8 Hz, H_{3b}), 3.77 (s, 3H, OMe), 5.18 (dd, 1H, *J* = 2.9, 11.7 Hz, H_2), 7.01-7.84 (m, 12H, Ar-H), 9.45 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.8, 50.8, 77.1, 112.2, 114.7, 116.2, 117.0, 117.3, 121.9, 126.9, 127.1, 128.0, 138.0, 139.6, 147.1, 150.4, 154.4, 160.0. MS (m/z): 373 (M^+). (Found: C, 70.98; H, 5.07; N, 11.09; $C_{22}H_{19}N_3O_3$ Calc. C, 70.76; H, 5.13; N, 11.25%).

4-(2-(2-(4-chlorophenyl)-6-methoxychroman-4-ylidene)hydrazinyl)pyridine. 10d

m.p. 124-126 °C, yield 86%; IR (KBr): 3359 (NH), 1690 (C=O), 1602 (C=N), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.71 (dd, 1H, *J* = 16.8, 4.4 Hz, H_{3a}), 3.36(dd, 1H, *J* = 2.9, 16.8 Hz, H_{3b}),3.71 (s, 3H, OMe), 5.20 (dd, 1H, *J* = 2.9, 12.4 Hz, H_2), 6.89-7.92 (m, 11H, Ar-H), 9.45 (s, 1H, NH, D_2O-exchangeable), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.4, 51.0, 76.3, 112.8, 114.0, 116.1, 117.2, 117.9, 122.0, 126.2, 128.7, 134.1, 135.2, 139.7, 146.8, 150.2, 154.5, 160.0. MS (m/z): 407 (M^+). (Found: C, 65.07; H, 4.33; N, 10.14. $C_{22}H_{18}ClN_3O_3$ Calc. C, 64.79; H, 4.45; N, 10.30 %).

Antimicrobial activity

The antimicrobial activity was investigated on the newly green synthesized Hydrazon, Flavanone and Iso-niazide compounds. The antimicrobial profile was evaluated by measuring the inhibitory effects and the potency of such compounds against Gram positive, Gram negative bacteria and fungi using the agar diffusion technique[29].

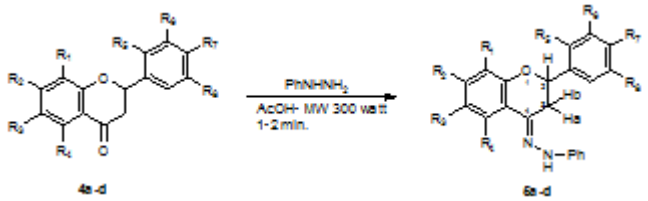
The bacterial strains *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) were cultured on nutrient agar. The fungal strains *Candida albicans* (*C. albicans*) was maintained on Yeast malt extracts medium (YM), while *Aspergillus niger* (*A. niger*) was maintained on Czapeck Dox medium. All the four strains were used against the tested compounds for antimicrobial evaluation.

Suspension of the above mentioned bacterial strains was prepared by inoculating fresh stock cultures into separate broth tubes, each containing 7 ml of nutrient broth. The inoculated tubes were incubated at 27 ± 2°C for 24 h.
Solutions of the tested compounds and reference drugs were prepared by dissolving 0.5 g of the compound in chloroform (5 ml).

RESULTS AND DISCUSSION

As the condensation reactions of amines and hydrazines with ketones are usually catalysed

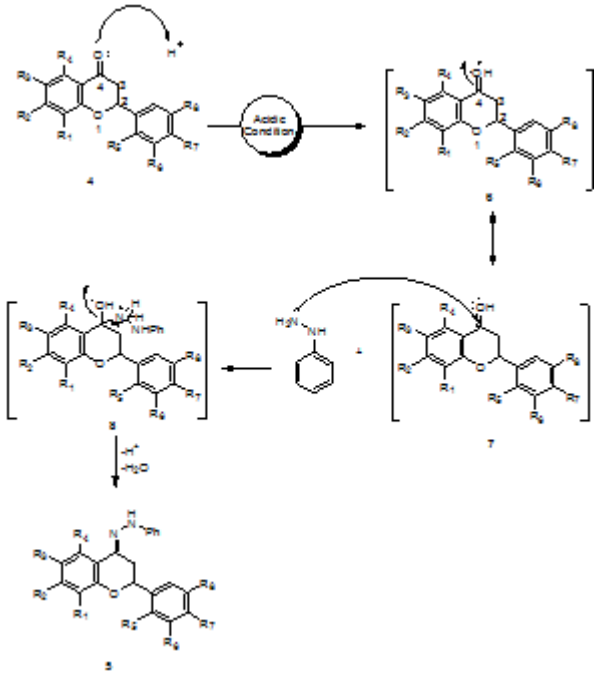
by acids or bases, the synthetic route to phenylhydrazone derivatives 5a-d is illustrated in Scheme 2. The starting flavanone derivatives 4a-d were prepared from the corresponding 2'-hydroxyacetophenones according to the literature method[14]. The synthesis of phenylhydrazone derivatives 5a-d was attempted by the reaction of flavanone 4a-d with phenylhydrazine under microwave irradiation in the presence of 1 ml of acetic acid, which resulted in good to excellent yield of pure phenylhydrazone products in very short reaction times (1-2 min.). The synthetic route to phenylhydrazone derivatives 5a-d is illustrated in Scheme 2.



4,5	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
A	H	H	Br	H	H	H	H	H
B	H	H	Cl	H	H	H	H	H
C	H	H	OMe	H	H	H	H	H
D	H	H	OMe	H	H	H	Cl	H

Scheme 2: synthesis of flavanone hydrazone derivatives 5a-d

Theoretically, the reactivity of flavanone derivatives toward N-nucleophiles, such as substituted hydrazine, is related to two sites: the carbonyl group and C-2 position. The attack of hydrazine to the C-2 position of a chroman ring could result in ring opening and subsequent pyrazoline formation. Previously, the reaction of flavanone derivatives with substituted hydrazines has been investigated under different conditions[20,21]. Kállay *et al.* have reported that flavanone

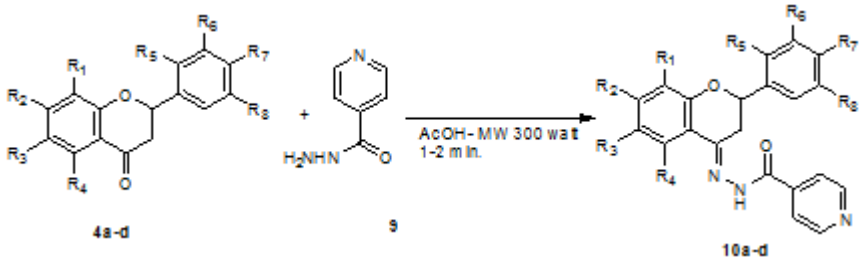


Scheme 3: Proposed mechanism for formation of flavanone hydrazone derivatives.

hydrazones are predominantly obtained under acidic conditions while alkaline conditions give the pyrazolines and the 2-hydroxychalcone derivatives due to the ring cleavage of the hetero ring of chromanone[20]. Similarly, in our experiment with flavanone 4a-d, the hydrazone derivatives were predominantly obtained under mild acidic conditions, Scheme 3.

The structures of compounds 5a-d were characterized by IR, ^{1}H NMR and mass spectroscopy as well as elemental analysis. For example, the IR spectra of compound 5a did not show any absorption due to the presence of C=O groups, and a broad band was observed at 3298-3327 cm^{-1} due to the presence of a N"H bond. The ^{1}H NMR spectrum of 5a showed a singlet D_2O exchangeable signal at d 9.56 for NH; three doublets of doublet signals at d 2.76 (*J* = 16.84, 5.12 Hz), 3.34 (*J* = 2.92, 16.84 Hz) and 5.25 (*J* = 2.96, 11.76 Hz) for H-3a, H-3b and H-2 of the chroman ring, respectively; and a multiplet of aromatic protons at d 7.26-7.85 ppm.

In a similar manner, the isoniazid (isonicotinylhydrazine) (9) reacted with flavanone derivatives 10a-d under microwave irradiation to give the corresponding hydrazone derivatives, Scheme 4.



4,10	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
A	H	H	Br	H	H	H	H	H
B	H	H	Cl	H	H	H	H	H
C	H	H	OMe	H	H	H	H	H
D	H	H	OMe	H	H	H	Cl	H

Scheme 4: Synthesis of flavanone hydrazone derivatives 10a-d

The structure of flavanone derivatives 10a-d was assigned based on their elemental analyses and spectral data. For example, the ^{1}H NMR spectrum of compound 10a revealed a singlet D_2O exchangeable signal at d 9.56 for NH; three doublets of doublet signals at d 2.77 (*J* = 17.60, 5.16 Hz), 3.38 (*J* = 2.92, 16.84 Hz) and 5.25 (*J* = 2.96, 11.76 Hz) for H-3a, H-3b and H-2 of the chroman ring, respectively; and a multiplet of aromatic protons at d 6.92-7.88 ppm. The mass spectrum of the same compound revealed a peak corresponding to its molecular ion at m/z 421.

It was found that microwave irradiation has a beneficial effect on the synthesis of flavanone derivatives. The above reactions took less than 5 min., and provided excellent yields.

Antimicrobial activity

The results in table 1 showed that flavanone compounds were the most potent among the three classes (flavanone, hydrazone and isoniazide) in terms of antibacterial activity. The highest inhibition zone against *E. coli* was detected by flavanone compound 4a followed by 4c, while, 4d was the most potent flavanone compound against *S. aureus*. Compounds 5d, 5c and 5b of hydrazone were the most potent and exhibited the highest inhibition zone against *E. coli* while, 5b was the most potent compound against *S. aureus*. The isoniazide 10c and 10b were the most potent compounds against *E. coli* and the 10b isoniazide was the most potent compound against *S. aureus*.

The results in table 2 revealed that hydrazone compounds were the most potent among

Table 1: Antibacterial activity of test compounds and reference drug[a]

Compounds	Inhibition zone diameter (mm)			
	G-ve		*G+ve*	
	E. coli	*Potency*	*S. aureus*	Potency
Control	0.0±0.0	0.0	0.0±0.0	0.0
Standard[b]	12.0±0.2	1.0	13.0±0.5	1.0
Flavanone				
4a	19.0±1.4	1.6	16.0±1.4	1.2
4b	16.0±1.4	1.3	14.5±0.7	1.1
4c	17.5±0.7	1.5	16.0±0.0	1.2
4d	17.0±0.0	1.4	16.5±0.7	1.3
Hydrazone				
5a	12.5±0.7	1.04	0.0±0.0	0.0
5b	16.5±0.7	1.4	20.0±0.0	1.5
5c	18.0±0.0	1.5	11.0±0.0	0.8
5d	21.5±0.7	1.8	15.5±0.7	1.2
Isoniazide				
10a	14.0±1.4	1.2	12.0±0.0	0.9
10b	16.0±1.4	1.3	14.0±1.4	1.1
10c	17.0±0.0	1.4	11.0±0.0	0.8
10d	13.5±2.1	1.1	0.0±0.0	0.0

[a] Chloroform has no antibacterial activity at the concentration used to dissolve the test compounds.

[b] Standard for bacteria: chloramphenicol.

Table 2: Antibacterial activity of test compounds and reference drug[a]

Compounds	Inhibition zone diameter (mm)			
	Yeast		*Mould*	
	C. albicans	*Potency*	*A. niger*	*Potency*
Control	0.0±0.0	0.00	0.0±0.0	0.00
Standard[b]	15.5±1.2	1.00	14.0±1.4	1.00
Flavanone				
4a	13.5±2.1	0.9	12.0±0.0	0.9
4b	0.0±0.0	0.0	0.0±0.0	0.0
4c	0.0±0.0	0.0	0.0±0.0	0.0
4d	0.0±0.0	0.0	0.0±0.0	0.0
Hydrazone				
5a	0.0±0.0	0.0	0.0±0.0	0.0
5b	20.0±0.0	1.3	14.5±2.1	1.0
5c	17.5±0.0	1.1	20.0±0.0	1.4
5d	20.0±0.0	1.3	20.0±0.0	1.4
	Isoniazide			
10a	34.0±1.4	2.2	14.0±0.0	1.0
10b	23.5±2.1	1.5	14.0±2.8	1.0
10c	15.5±0.7	1.0	0.0±0.0	0.0
10d	0.0±0.0	0.0	0.0±0.0	0.0

[a] Chloroform has no antibacterial activity at the concentration used to dissolve the test compounds.

[b] Standard for bacteria: chloramphenicol.

the three classes (flavanone, hydrazone and isoniazide) in terms of antifungal activity. None of the flavanone compounds exhibited potency against *C. albicans* and *A. niger*. Compounds 5b and 5d of hydrazone were the most potent and exhibited high inhibition zone against *C. albicans* whereas 5c and 5d were the most potent against *A. niger*. Isoniazide 10a and 10b compounds were the most potent compounds against *C. albicans* and none of the isoniazide compounds had any effect against *A. niger*.

Several recent reviews and studies have reported the antimicrobial efficacy of flavanone molecules[22-24]. The antimicrobial effectiveness of flavonoids is due to their abilities to form complexes with both extracellular and soluble proteins as well as bacterial membranes[25,26]. The penetration into the cell and the maintenance of intracellular concentrations in infecting species becomes a critical concern for the development of flavonoids as the next generation of antibacterial/antifungal agents.

Hydrazone-type compounds containing azomethine constitute an important class of compounds for new drug development. It is well known that the hydrazone group plays an important role in antimicrobial activity[27]. It has been claimed that a number of hydrazide-hydrazone derivatives possess interesting antibacterial and antifungal activities[28].

CONCLUSIONS

A series of flavanone hydrazone derivatives have been prepared from flavanone under microwave irradiation in very short reaction time (1-2 min.) and good yields. Some synthesized compounds show potent anti-microbial activity.

REFERENCES

1. Vauzour, D.; Vafeiadou, K.; Rice-Evans, C.; Williams, R. J.; Spencer, J. P. E. *J. Neurochem.* **2007**, *103*, 1355-1367.
2. Agarwal, C.; Tyagi, A.; Kaur, M.; Agarwal, R. *Carcinogenesis* **2007**, *28*, 1463-1470.
3. Cabrera, M.; Simoens, M.; Falchi, G.; Lavaggi, M. L.; Piro, O. E.; Castellano, E. E.; Vidal, A.; Azqueta, A.; Monge, A.; Lopez de Cerain, A.; Sagrera, G.; Seoane, G.; Cerecetto, H.; Gonzalez. M. *Bioorg. Med. Chem.* **2007**, *15*, 3356-3367.
4. Hsiao, Y. C.; Kuo, W. H.; Chen, P. N.; Chang, H. R.; Lin, T. H.; Yang, W. E.; Hsieh, Y. S.; Chu, S. C. *Chem.-Biol. Interact.* **2007**, *167*, 193-206.
5. Ward, F. E.; Garling, D. L.; Buckler, R. T.; Lawler, D. M.; Cummings, D. P. *J. Med. Chem.* **1981**, *24*, 1073-1077.
6. Choi, Y. J.; Lee, M. K.; Lee, Y. J.; Jeong, Y. J.; Yoon Park, J. H.; Sung, L. S.; Kang, Y. H. *J. Med. Food* **2004**, *7*, 408-416.
7. Njamen, D.; Mbafor, J. T.; Fomum, Z. T.; Kamanyi, A.; Mbanya, J. C.; Recio, M. C.; Giner, R. M.; Manez, S. J.; Rios, L. *Planta Med.* **2004**, *70*, 104-107.
8. Paredes, A.; Alzuru, M.; Mendez, J. *Biol. Pharm. Bull.* **2003**, *26*, 108-109.
9. Reddy, M. V. B.; Kishore, P. H.; Rao, C. V.; Gunasekar, D.; Caux, C.; Bodo, B. *J. Nat. Prod.* **2003**, *66*, 295-297.
10. Wang, X.; Cheng, S. *Catal. Commun.* **2006,** *7***,** 689-695.
11. Drexler, M. T.; Amiridis, M. D. *J. Catal.* **2003**, *214*, 136-145.
12. Chandrasekhar, S.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2005**, *46*, 6991-6993.
13. Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369-1371.
14. Albogami, A. S.; Karama, U.; Mousa, A. A.; Khan, M. S.; Al-Mazroa, A.; Alkhathlan, H. Z. *Oriental J. Chem.* **28**: 619-626 (2012).
15. Coetzee, J.; Mciteka, L.; Malan, E.; Ferreira, D. *Phytochemistry* **1999**, *52*, 737-743.
16. Adams, J. H. *J. Org. Chem.* **1967**, *32*, 3992-3998.
17. Climent, M. J.; Garcia, H.; Iborra, S.; Miranda, M. A.; Primo, J. *Heterocycles* **1989**, *29*, 115-121.
18. Lidstrom, P.; Tierney, J.; Wathcy, B.; Wcstman, J.; *Tetrahedron* **2001**, *57*, 9225-9283.

19. Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; der Eycken, E. V.; Kaval, N.; Kappe, C. O. *Org. Proc. Res. Dev.* **2003**, *7*, 707-716.
20. Kállay, F.; Janzsó, G.; Koczor, I. *Tetrahedron* **1967**, *23*, 4317-4321.
21. Léavai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1-13.
22. Sobolev, V. S.; Neff, S. A.; Gloer, J. B. *J. Agric. Food Chem.*, **2009**, *57*, 62-68.
23. Abdel Ghani, S. B.; Weaver, L.; Zidan, Z. H.; Ali, H. M. W.; Keevil, C. *Bioorg Med Chem Lett.*, **2008**, 18, 518-522.
24. Nowakowska, Z. *Eur. J. Med. Chem.* **2007**, 42, 125-137.
25. Cowan, M. M. *Clin. Microbiol. Rev.* **1999**, *12*, 564-582.
26. Fowler, Z. L.; Baron, C. M.; Panepinto, J. C.; Koffas, M. A. *Yeast* **2011**, *28*, 181-188.
27. Abdel-Fattah, M. E.; Salem, E. E.; Mahmoud, M. A. *Indian J. Heterocycl. Chem.* **2000**, *10*, 121-128.
28. Vicini, P.; Zani, F.; Cozzini, P.; Doytchinova, I. *Eur. J. Med. Chem.* **2000**, *37*, 553-564.