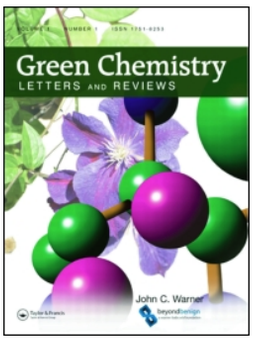

Green Chemistry Letters and Reviews

ISSN: 1751-8253 (Print) 1751-7192 (Online) Journal homepage: https://www.tandfonline.com/loi/tgcl20

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To cite this article: Mohammed H. Geesi, Azzam Ahmed Mohammed AL-Hadedi, Mohammed A. Bakht, Abdellah Kaiba, Meryem Boukili, Mohammed B. Alshammari, Oussama Dehbi & Yassine Riadi (2018) A simple and eco-friendly microwave mediated route the synthesis of novel antimicrobial substituted quinoline-2-thiones, Green Chemistry Letters and Reviews, 11:4, 469-475, DOI: 10.1080/17518253.2018.1536228

To link to this article: https://doi.org/10.1080/17518253.2018.1536228

GREEN CHEMISTRY LETTERS AND REVIEWS
2018, VOL. 11, NO. 4, 469–475
https://doi.org/10.1080/17518253.2018.1536228

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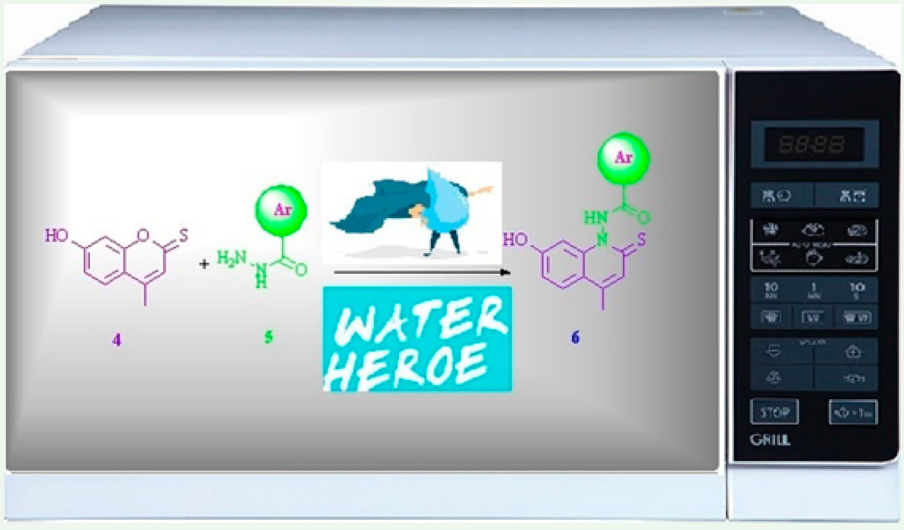
A simple and eco-friendly microwave mediated route the synthesis of novel antimicrobial substituted quinoline-2-thiones

Mohammed H. Geesi[a], Azzam Ahmed Mohammed AL-Hadedi[b], Mohammed A. Bakht[a], Abdellah Kaiba[c], Meryem Boukili[d], Mohammed B. Alshammari[a], Oussama Dehbi[e] and Yassine Riadi[f]

[a]Department of Chemistry, College of Science and Humanities Studies, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia; [b]Department of Chemistry, College of Science, University of Mosul, Mosul, Republic of Iraq; [c]Department of Physics, College of Science and Humanities Studies, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia; [d]Team of Microbiology and Health, Laboratory of Chemistry-Biology Applied to the Environment, Moulay Ismail University Faculty of Sciences, Meknes, Morocco; [e]Department of Chemistry, College of Sciences and Arts, Jouf University, Al Qurayyat, Saudi Arabia; [f]Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia

ABSTRACT

An eco-friendly and efficient method was developed for the preparation of a new series of sulfur-containing quinolinthiones. Compounds **6a–o** were synthesized from 4-methyl-2-thiocoumarin and arylhydrazides using water as a solvent under microwave irradiation. Some noteworthy features of our novel method are its cleanliness, short reaction time and high conversion rate, and the reaction proceeds (profiles) using a simple procedure. All of the prepared compounds were screened for their antibacterial efficacy *in vitro* using the disc diffusion method against bacterial strains. Compound (**6j**) showed the greatest potency with a 16 and 19 mm inhibition zone against *Klebsiella pneumonia* and *Staphylococcus aureus*, respectively.



ARTICLE HISTORY
Received 6 June 2018
Accepted 17 September 2018

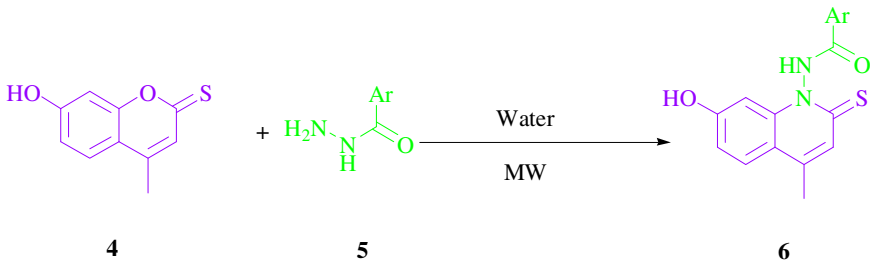
KEYWORDS
Green chemistry; quinolinthiones; methyl-2-thiocoumarin; water; microwave

1. Introduction

The Quinoline skeleton is a key structural element in a variety of bioactive natural compounds, pharmaceuticals and other functional materials (*1*). They are also one of the important groups of heterocyclic scaffolds as synthetic precursors (*2*). Only a few ways have been reported to access these structures (*3*).

Quinoline rings containing a thioxo group are of interest and biologically active owing to the potential chemical and physical properties of this heterocycle (*4–6*). Among these are quinoline-2-thiones are an important skeleton, which has been used as NS ligands (*7*), synthetic intermediates (*8*) and drug candidates (*9*). Despite these attributes, a few general protocols have

CONTACT Mohammed H. Geesi m.geesi@psau.edu.sa; Yassine Riadi yassinriadi@yahoo.fr
Supplemental data for this article can be accessed https://doi.org/10.1080/17518253.2018.1536228.



Scheme 1. Green synthesis of substituted quinoline-2-thiones from 2-thiocoumarin under microwave irradiation.

been developed for the preparation of quinoline-2-thiones which show great biological efficiency (*10*). A typical synthesis of this group of compounds involves sulfurizing quinoline-2-ones using P_2S_5, also based on reacting 2-haloquinolines with thiourea or sodium sulfide, which requires tedious multistep transformations (*11*). Saito and Otani recently developed a new method of constructing the quinoline-2-thiones entity by the Friedel–Crafts alkenylation-cyclization of 2-alkynylphenyl isothiocyanates promoted by indium at a higher temperature (*12*). Recently, chromenes with a thioxo group increased antibacterial activity (*13*). In view of all these facts, two entities, namely, arylated hydrazides and 2-thiocoumarin, were combined in a single molecule to synthesize a series of new quinoline-2-thiones as antibacterial agents.

This was as a continuation of our previous research based on the synthesis of therapeutic and heterocyclic agents (*14*) and the development of more new eco-friendly synthesis and methods (*15*). Thus, we decided to optimize the synthesis of novel substituted quinoline-2-thiones derivatives and *in vitro* anti-bacterial (Scheme 1).

2. Results and discussion

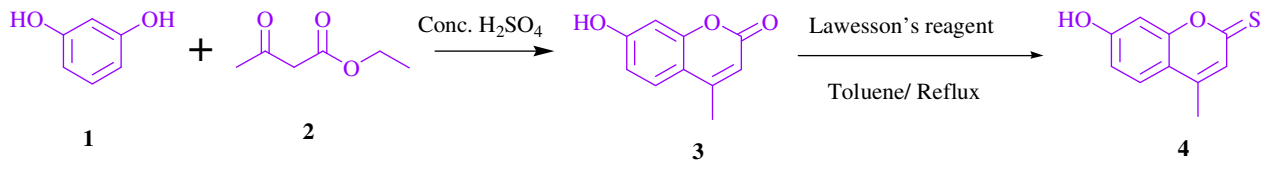
To synthesize the target molecules, the key molecule 7-hydroxy-4-methyl-2-thiocoumarin **4** was obtained by Pechmann condensation of ethyl acetoacetate **2** with resorcinol **1** in the presence of sulfuric acid (*16*). Then, the resulting compound was successfully transferred to the corresponding 2-thiocoumarin **4** using Lawesson's reagent in toluene under reflux (Scheme 2) (*17*).

2.1. Optimizing the conditions for the preparation of the target molecule

Initially, optimizing the reaction conditions started by coupling of 7-hydroxy-4-methylcoumarin **4** with 4-chloro-benzoic acid hydrazide **5a**, which was chosen as the reaction model (Table 1). As indicated in Table 1, the effects of several solvents were studied (entries 1–7). Low yields were obtained using CH_3CN or toluene as a solvent (entry 1 and 2). Using MeOH or dioxane led to an increase of the yields with 44% and 48%, respectively (entries 3 and 4). Moreover, using either DMF, THF or EtOH gave the desired compound with good yields. Interestingly, we noted that a high yield (92%) was obtained in just 20 min when water was used as the most efficient solvent under microwave irradiation (entry 9). In addition, irradiating the reaction under microwaves gave a better result than the classical reflux (entries 8, 9).

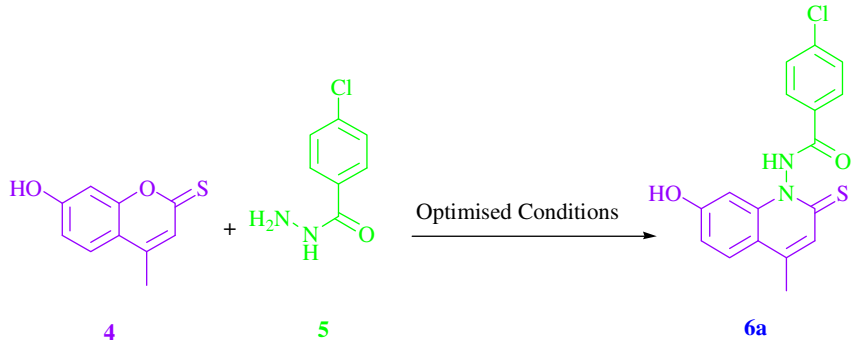
2.2. Typical procedure for preparing 4-chloro-N-(7-hydroxy-4-methyl-2-thioxo-2H-quinolin-1-yl)-benzamide 6a

A microwave glass vial (10 mL) was charged with an equimolar mixture of 7-hydroxy-4-methyl-2-thiocoumarin **4** (0.25 mmol) and 4-chloro-benzoic acid hydrazide **5a** (0.25 mmol) along with 5 mL of water. The reaction was irradiated under microwaves for 20 min (160 W, 120°C). The reaction mixture was cooled to rt, then filtered to produce the crude compound. The compound was purified by recrystallization from water/ethanol (1/3) to produce 4-chloro-N-(7-hydroxy-4-methyl-2-thioxo-2H-quinolin-1-yl)-benzamide **6a**.



Scheme 2. The synthetic route of 7-hydroxy-4-methyl-2-thiocoumarin.

Table 1. Optimizing the reaction conditions.[a]



4 5 6a

Entry	Solvent	Reflux/MW	Reaction time (min)	Yield (%)[b]
1	CH_3CN	MW	20	18
2	Toluene	MW	20	14
3	CH_3OH	MW	20	44
4	Dioxane	MW	20	48
5	DMF	MW	20	56
6	THF	MW	20	61
7	EtOH	MW	20	69
8	Water	Reflux	180	84
9	Water	MW	20	92

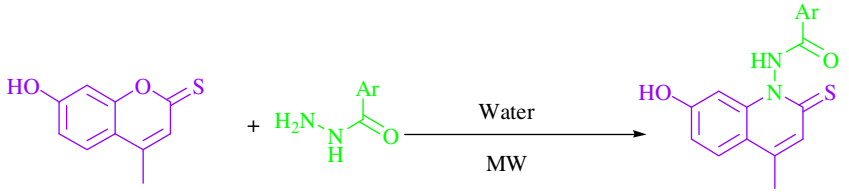
[a]Reaction conditions: 7-hydroxy-4-methylcoumarin (0.25 mmol, 1 equiv), 4-Chloro-benzoic acid hydrazide (0.25 mmol, 1 equiv), solvent (5 mL).
[b]The isolated product yield.

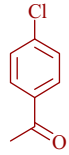
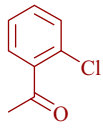
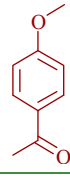
2.3. Methodology extension

With the optimal conditions to hand, the scope of the reaction was developed using 7-hydroxy-4-methyl-2-thiocoumarin **4** (0.25 mmol) and a series of aryl hydrazides **5.** The aryl hydrazides were readily synthesized according to the literature (*18*).

The presence of an electron donating group (CH_3 or OCH_3) on the phenyl ring decreased the aryl hydrazines' reactivity toward 7-hydroxy-4-methyl-2-thiocoumarin

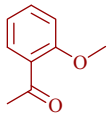
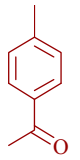
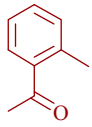
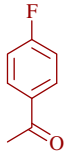
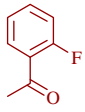
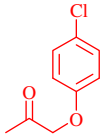
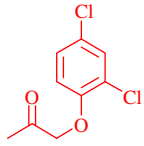
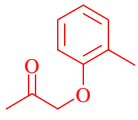
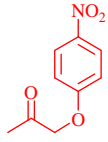
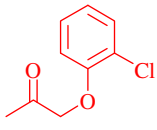
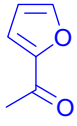
Table 2. Reactions of 7-hydroxy-4-methylcoumarin with various arylhydrazides.[a]



Entry	Ar	Product	Yield[b] (Time, min)[b] Classical reflux	MW
1		**6a**	82% (120)	92% (20)
2		**6b**	71% (120)	88% (20)
3		**6c**	52% (150)	68% (30)

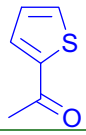
(*Continued*)

Table 2. Continued.

Entry	Ar	Product	Yield[b] (Time, min)[b]	
			Classical reflux	MW
4		**6d**	49% (150)	62% (30)
5		**6e**	50% (150)	58% (30)
6		**6f**	41% (150)	61% (30)
7		**6g**	75% (120)	90% (20)
8		**6h**	62% (120)	88% (20)
9		**6i**	78% (120)	94% (15)
10		**6j**	68% (120)	91% (15)
11		**6k**	56% (150)	69% (25)
12		**6l**	65% (150)	81% (25)
13		**6m**	70% ((120)	90% (15)
14		**6n**	36% (150)	52% (30)

(*Continued*)

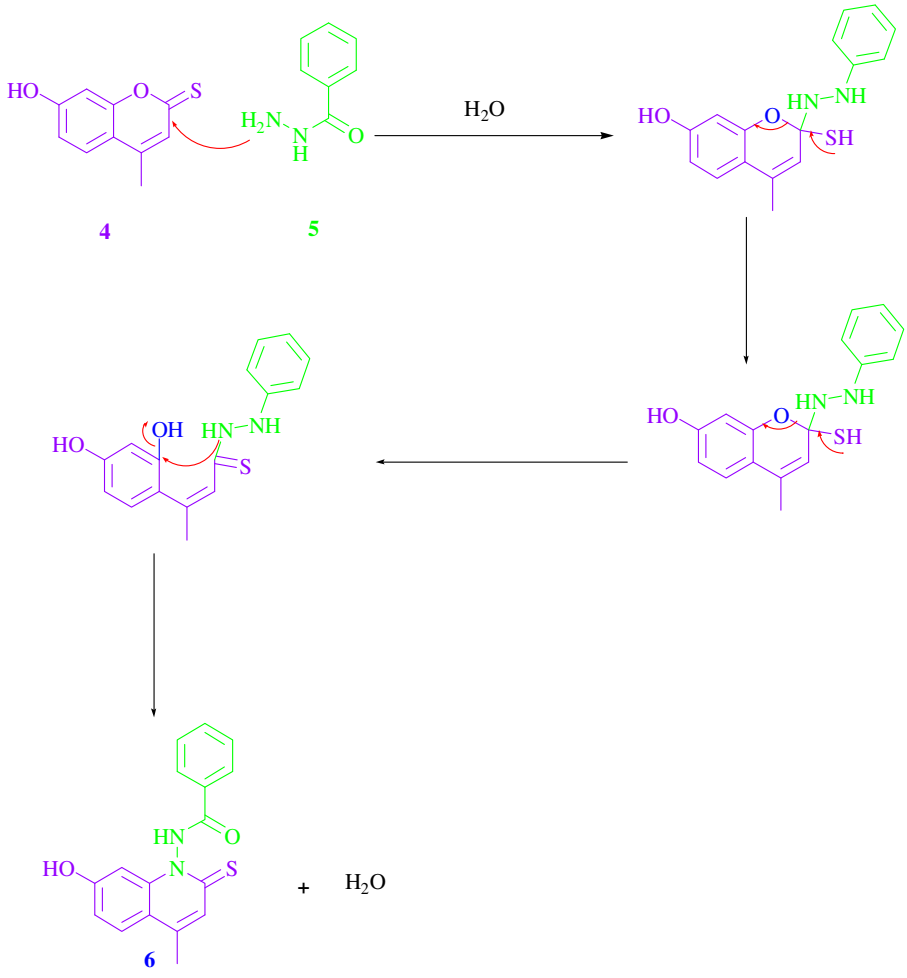
Table 2. Continued.

Entry	Ar	Product	Yield[b] (Time, min)[b] Classical reflux	MW
15		**6o**	42% (150)	54% (30)

[a]Reaction conditions: 7-hydroxy-4-methylcoumarin (0.25 mmol, 1.0 equiv), arylhydrazide (0.25 mmol, 1 equiv), water (5 mL), 160 W, 15–30 min.
[b]The yield of the isolated product.

(Table 2, entries 3–6, 11). On the other hand, the presence of an electron withdrawing a group like (F, Cl, NO_2) increased the reactivity of the corresponding aryl hydrazides and led to the corresponding products having higher yields (entries 1, 2, 7,8, 9, 10, 12, 13). Using aryl hydrazide bearing a furyl or thienyl (Table 2, entries 14, 15) gave a lower yield compared with the other results. Using microwaves as an energy source increased the yields compared with the classical reflux (Scheme 3).

The *in vitro* antibacterial activities of compounds (**6a–6n**) were performed against three bacterial strains, namely, *Escherichia coli* (Ec), *Klebsiella pneumoniae* (Kp) and *Staphylococcus aureus* (Sa); the results are summarized in Table 3. Of the 15 newly prepared compounds, only 6 compounds were found to be active against Kp or/and Sa at a concentration of 250 µg/ml. However, 7-hydroxy-4-methylquinoline-2-thiones (**6a**, **6i** and **6j**) carrying a 4-chlorophenyl substituent was found to be significantly active with an average inhibition zone of 11–19 and 12–16 mm against Kp and Sa, respectively, at a concentration of 250 µg/ml. In addition, 7-hydroxy-4-methylquinoline-2-thiones (**6b** and **6 l**) with a 2-chlorophenyl substituent exhibited moderate activity with an



Scheme 3. The proposed mechanism for the formation of type **6** compounds.

Table 3. The *in vitro* activity of 7-hydroxy-4-methylquinoline-2-thiones (**6a**–**o**) at a concentration of 250 µg/ml.[a]

	Inhibition zone in mm		
Compound N	Ec	Sa	Kp
6a	_	12	11
6b	_	12	13
6c	_	_	_
6d	_	_	_
6e	_	_	_
6f	_	_	_
6g	_	9	
6h	_	_	_
6i	_	14	17
6j	_	16	19
6k	_	_	_
6l	_	16	18
6m	_	_	_
6n	_	_	_
6o	_	_	_

Note: Ec, Escherichia coli; Kp, Klebsiella pneumonia; Sa, Staphylococcus aureus; no inhibition zone.

average inhibition zone of 13–18 and 12–16 mm against Kp and Sa, respectively, at a concentration of 250 µg/ml. In contrast, compound **6 g** with the 4-fluorophenyl group showed poor activity (9 mm average inhibition zone) specifically against a Gram-negative Sa bacterial strain. Surprisingly, all of the obtained products (**6a–6o**) were found to be inactive against *E. coli*.

In conclusion, we have developed a fast, simple, eco-friendly and efficient method for preparing substituted 7-hydroxy-4-methylquinoline-2-thiones, from 7-hydroxy-4-methyl-2-coumarin and aryl hydrazides in water as a non-toxic, eco-friendly and green benign solvent in mild conditions under microwave irradiation in good yields. The synthesized products were performed against three bacterial strains showing good activity except for the case of *E.coli*. This method is extremely advantageous and attractive and could contribute to reducing environmental problems.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors would like to thank the Deanship of Scientific Research at Prince Sattam Bin Abdulaziz University for providing the financial support for this project (grant no. 2015/01/4784).

Notes on contributors

Mohammed H. Geesi received his Ph.D. in organic chemistry from the University of Southampton in the UK in 2014 under the supervision of Professor Richard C. Brown. Dr Geesi is currently a researcher and assistant professor at the College of Science and Humanities at Prince Sattam Bin Abdulaziz University. His research focuses on the synthesis of natural products, the stereocontrolled synthesis of organic compounds, the development and synthesis of new heterocyclic compounds using green, simple and low-cost processing methods.

Azzam Ahmed Mohammed Al-Hadedi received his Ph.D. in organic chemistry from the University of Southampton, UK. Dr Azzam is a lecturer and researcher at the Department of Chemistry at the College of Science at the University of Mosul in Iraq. His research focuses on the discovery and optimization of new chemical transformations, the synthesis of natural products, the stereocontrolled synthesis of organic compounds, the synthesis of heterocyclic compounds, NMR studies of organic compounds and the use of electrochemistry as an environmentally friendly method to drive chemical reactions.

Mohammed A. Bakht received his Ph.D. in pharmaceutical chemistry in 2009. He is currently working as an associate professor at the College of Science and Humanities at Prince Sattam Bin Abdulaziz University, KSA. His research interest is in the synthesis of potential organic scaffold utilizing new green chemistry technics and studying their pharmacological activities. He has few novel green solvents and catalysts to his name. He has also used ultrasound technology for the synthesis purposes.

Abdellah Kaiba received his Ph.D. in organic physical chemistry from the University of Bordeaux in France. Dr Abdellah is an Assistant Professor and researcher at the Department of Physics at the College of Science and Humanities Studies at Prince Sattam bin Abdulaziz University in Saudi Arabia. His research focuses on the development of new green catalysts.

Mohammed B. Alshammari was born in Saudi Arabia. He received his B.Sc. and M.Sc. degrees in Chemistry from King Saud University in Saudi Arabia. He received his Ph.D. degree from Cardiff University in the UK in 2013 under the supervision of Professor Keith Smith. His research focuses on the use of organolithium reagents as intermediates in organic synthesis. He is currently working as Assistant Professor of Organic Chemistry at Prince Sattam Bin Abdulaziz University in Saudi Arabia.

Meryem Boukili is preparing her Ph.D. in biology, specialty of food microbiology at Moulay Ismail University, Morocco. She is a Ph.D. student and researcher at the group of microbiology and health, laboratory of chemistry–biology applied to the environment. Her research topic concerns the descriptive and epidemiological study of foodborne diseases, and especially those caused by red meat in Morocco, as well as she is working on the hygienic quality of red meats and more specifically those of cattle, to fight against food poisoning, and to highlight the factors influencing its contamination at the city of Meknes in Morocco. In addition to that, she contributes in the isolation of *Listeria monocytogenes* (pathogenic microorganism that is responsible for the listeriosis infection) and study its genetic and resistive property.

Oussama Dehbi received his Ph.D. in organic chemistry from the University of Orleans in France in December 2012. Actually, he is an assistant professor and researcher in the College of Science and Arts, Al Qurayyat, Jouf University, KSA. His research focuses on the design and synthesis of new drug and studies of their structure–activity relationship and also the development of a new eco-friendly method for the synthesis of organic compounds.

Yassine Riadi received his Ph.D. in organic pharmaceutical chemistry from the University of Orleans in France in 2013. Dr Riadi is an assistant professor and researcher at the College of Pharmacy at Prince Sattam Bin Abdulaziz University. His research focuses on the development of new green catalysts using simple and low-cost processing methods and their use in the synthesis of new drugs and compounds.

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