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SYNTHESIS OF QUINAZOLINONE DERIVATIVES USING SELECTED GREEN METHODS AND THEIR POTENTIAL ANTIBACTERIAL ACTIVITY

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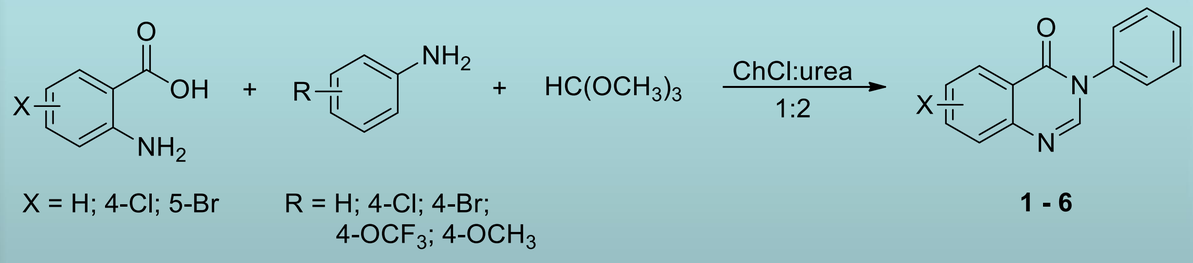
Introduction

Quinazolinones are a group of heterocyclic compounds which are of great interest to scientists, especially in the fields of medicine and pharmacy. Due to their structural diversity, they are proven to have antibacterial, antifungal, antivirus and antimicrobial properties. In this study synthesis of quinazolinone derivatives was performed by mixing different substituted anthranilic acids, anilines and trimethyl orthoformate in choline chloride:urea (1:2) deep eutectic solvent (DES) using a magnetic stirrer, ultrasound bath and microwave reactor as green methods. DES was prepared by mixing choline chloride with urea in 1:2 molar ratio at 80 °C. Because of their antibacterial property, the antibacterial activity was examined by a modified microdilution method in terms of minimum inhibitory concentrations (MICs) on two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria.



X = H; 4-Cl; 5-Br — R = H; 4-Cl; 4-Br; 4-OCF_3; 4-OCH_3 — **1 - 6**

Scheme 1. Synthesis of substituted quinazolin-4(3*H*)-ones **1 – 6** by green methods

Synthesis by mixing and heating

Synthesis of quinazolinone derivatives was performed by mixing 2 mmol of different substituted anthranilic acids, 2.4 mmol of trimethyl orthoformate and 2.4 mmol of substituted anilines for 4 hours at 80 °C. The mixture was stirred in 2.5 mL choline chloride:urea (1:2). The progress of the reaction was monitored by TLC. Water was added to the reaction mixture and the crude product was filtered and washed with water.

Ultrasound-assisted synthesis

Ultrasound-assisted synthesis was performed in an ultrasound bath for 4 hours at 80 °C and 50 W. The reaction mixture included 2 mmol of different substituted anthranilic acids, 2.4 mmol of trimethyl orthoformate and 2.4 mmol of substituted anilines in 2.5 mL choline chloride:urea (1:2). The progress of the reaction was monitored by TLC. Water was added to the reaction mixture and the crude product was filtered and washed with water.

Fig 1. Ultrasound-assisted synthesis

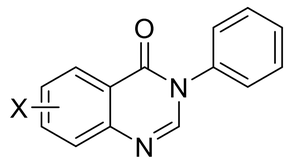
Microwave-assisted synthesis

Microwave-assisted synthesis was performed in a microwave reactor for 2 hours at 80 °C and 1800 W. Anthranilic acids (2.4 mmol), substituted anilines (2.4 mmol) and trimethyl orthoformate (2.4 mmol) were added to 2.5 mL of choline chloride:urea (1:2) DES. The progress was monitored by TLC. Water was added to the reaction mixture and the crude product was filtered and washed with water.

Fig 2. Microwave-assisted synthesis

Results

Table 1. A comparison of substituted quinazolin-4(3H)-ones obtained with selected green methods



1 - 6

Compound	X	R	Stirring (%)	Microwave-assisted synthesis (%)	Ultrasound-assisted synthesis (%)
1	H	H	*	13	14
2	H	4-Cl	27	*	13
3	H	4-Br	13	*	11
4	H	4-OCF_3	9	*	9
5	6-Br	4-OCH_3	10	*	7
6	7-Cl	4-OCF_3	11	*	10

*Product was detected in traces

Table 2. Minimum inhibitory concentrations (MIC) of quinazolinone derivatives against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus* (mg mL^{-1})

	MIC (mg mL^{-1})			
	G-		*G+*	
Compound	***E. coli***	***P. aeruginosa***	***B. subtilis***	***S. aureus***
1	0.06250	0.06250	0.06250	0.06250
2	0.06250	0.06250	0.06250	0.06250
3	0.06250	0.06250	0.12500	0.06250
4	0.06250	0.06250	0.06250	0.06250
5	0.06250	0.06250	0.06250	0.06250
6	0.06250	0.06250	0.06250	0.06250
CIPROFLOXACIN	0.003125	0.00078	0.00156	0.003125

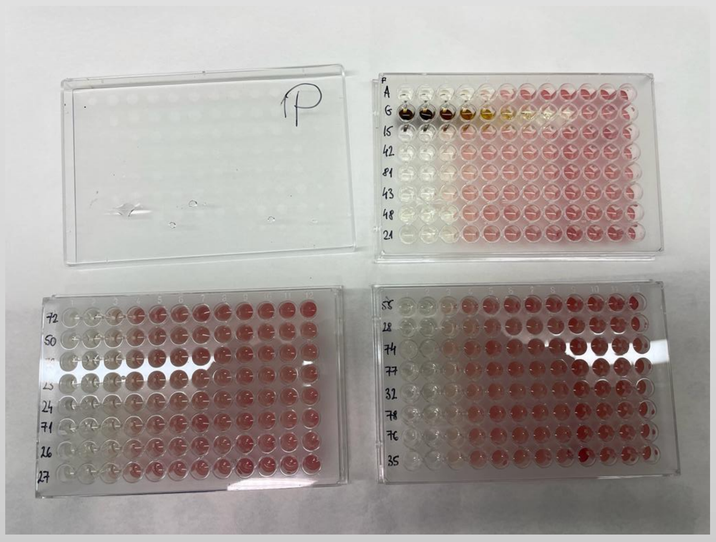


Fig 3. Antibacterial assay against *P. aeruginosa*

Conclusion

- Choline chloride:urea (1:2) was used as solvent with no use of catalysts.
- Best reaction time was 4 h for stirring and ultrasound-assisted synthesis, and 2 h for microwave-assisted synthesis at 80 ˚C.
- Microwave-assisted synthesis gave products in traces.
- All products have shown antibacterial activity.

Acknowledgment

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