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Anti-*Helicobacter pylori* Activity of Quinolin-2-one/ Chalcone Hybrids as Urease Inhibitors

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Abstract

The present research explores the urease inhibitory potential of a designed set of quinoline-2-one/ chalcone hybrid derivatives (4a-e). The biological assessment demonstrated that these molecules exhibit strong urease inhibition, with IC_{50} values ranging from 0.58-1.90 µM. Their inhibitory potency notably surpasses that of the reference compound, thiourea (IC_{50} = 21.50 µM). Within this series, compounds 4a, 4c, and 4e emerged as the most active inhibitors, displaying IC_{50} values of 0.93 ± 0.08 µM, 0.75 ± 0.06 µM, and 0.58 ± 0.04 µM, respectively. In addition, the anti-*Helicobacter pylori* potential of these hybrids was assessed against three metronidazole-resistant *H. pylori* strains using the disk diffusion technique. The outcomes revealed a strong association, indicating that methoxy-bearing analogs 4c and 4e identified as the most effective urease inhibitors also exhibited pronounced antibacterial action against *H. pylori*. Collectively, these observations underscore the promising dual therapeutic profile of this hybrid framework.

Keywords: Urease, *Helicobacter pylori*, Antibacterial, Paper Disk, Inhibition Zone

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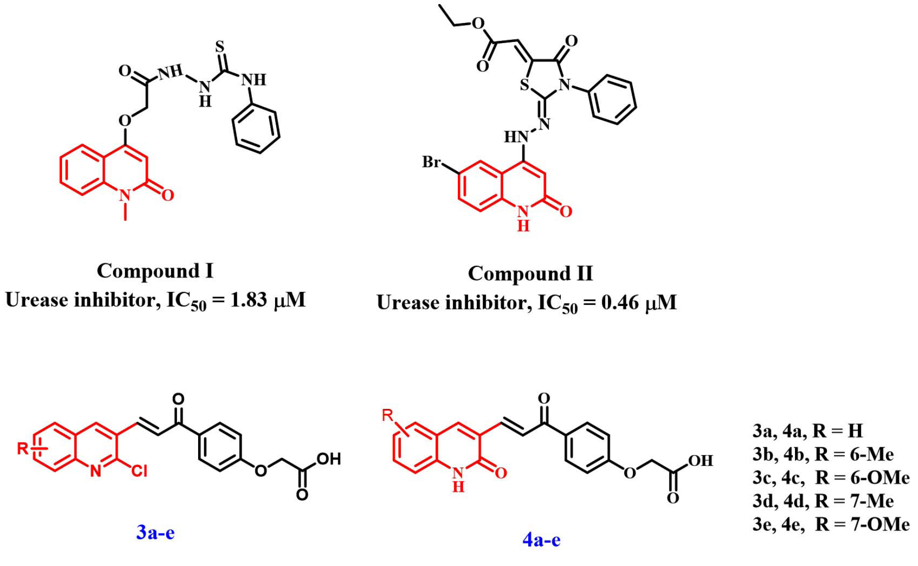
INTRODUCTION

Urease is a nickel-dependent metalloenzyme responsible for catalyzing the hydrolysis of urea into ammonia and carbamate.[1,2] This enzyme is structurally diverse and occurs in multiple isoforms identified across a wide range of biological systems, including plants, fungi, and numerous bacterial species.[3,4] Within pathogenic microorganisms, urease functions as a major virulence determinant, critically contributing to the onset and progression of various disorders such as peptic ulcer disease, gastric carcinoma, urinary tract infections, hepatic encephalopathy, and several renal complications.[5]

A notable example is *Helicobacter pylori*, a microaerophilic bacterium characterized by exceptionally high urease activity. This pathogen is one of the most common bacterial inhabitants of the human stomach, colonizing more than half of the global population.[6] The urease enzyme produced by *H. pylori* enables the organism to survive within the stomach's acidic environment by generating ammonia, which forms a protective alkaline microenvironment surrounding the bacterium.[7] The resulting accumulation of ammonia damages the gastroduodenal epithelium, contributing to the development of severe gastrointestinal conditions such as duodenal ulcers, gastric adenocarcinomas, and lymphomas, affecting approximately 15%-20% of infected patients.[8,9] Supporting this, Eaton et al. demonstrated that urease-deficient mutant strains of *H. pylori* failed to colonize the stomachs of gnotobiotic piglets,[10,11] confirming the enzyme's indispensable role in bacterial survival and pathogenesis. Consequently, the design and discovery of potent urease inhibitors are of substantial therapeutic relevance.

In recent years, significant attention has been directed toward the antimicrobial potential of quinoline-containing scaffolds, as many derivatives have shown enhanced biological performance compared with conventional agents.[12-15] For instance, Elshaier et al. reported the synthesis and biological evaluation of a novel group of quinoline derivatives as urease inhibitors, identifying Compound I (Figure 1) as the most active molecule in the series with an IC_{50} of 1.83 µM.[16] Similarly, Elbastawesy et al. developed a distinct quinoline-based collection of compounds, among which Compound II (Figure 1) exhibited strong urease inhibition, with an IC_{50} value of 0.46 µM.[17]

Chalcones, chemically defined as 1,3-diaryl-2-propen-1-ones, represent another prominent class of naturally occurring molecules widely recognized for their diverse pharmacological activities, notably their antimicrobial potential.[18-20] Their natural abundance and the relative simplicity of their synthesis have generated significant



Compound I
Urease inhibitor, IC_{50} = 1.83 µM

Compound II
Urease inhibitor, IC_{50} = 0.46 µM

3a-e

4a-e

3a, 4a, R = H
3b, 4b, R = 6-Me
3c, 4c, R = 6-OMe
3d, 4d, R = 7-Me
3e, 4e, R = 7-OMe

Figure 1. Structures of quinoline-based urease inhibitors I, II and target compounds 3a-e and 4a-e

interest in utilizing chalcone frameworks for the creation of new therapeutic leads.[21-23]

At the same time, molecular hybridization, a strategy that combines two or more pharmacologically active moieties within a single molecular structure, has emerged as a powerful tool for developing multifunctional bioactive compounds. Such hybrid architectures can integrate distinct mechanisms of action, often resulting in synergistic or dual biological properties that enhance therapeutic efficacy against pathogenic microorganisms.[21,24-27]

In our previous work[28] we described the design and synthesis of a novel library of quinoline–chalcone hybrids (3a-e and 4a-e, Figure 1), created by uniting these two privileged structural motifs into a single molecular entity. Upon biological screening, compounds within the 3a-e subset demonstrated the most pronounced antibacterial activities against a panel of six bacterial strains.

Encouraged by the promising antibacterial outcomes obtained from the 4a-e series (Figure 1) and inspired by the well-documented urease-inhibitory potential of quinoline derivatives such as Compounds I and II (Figure 1), the present study was designed to explore the urease inhibitory capabilities of compounds 4a-e. Moreover, this work further investigates the anti-*Helicobacter pylori* efficacy of these hybrid molecules to assess their broader therapeutic potential.

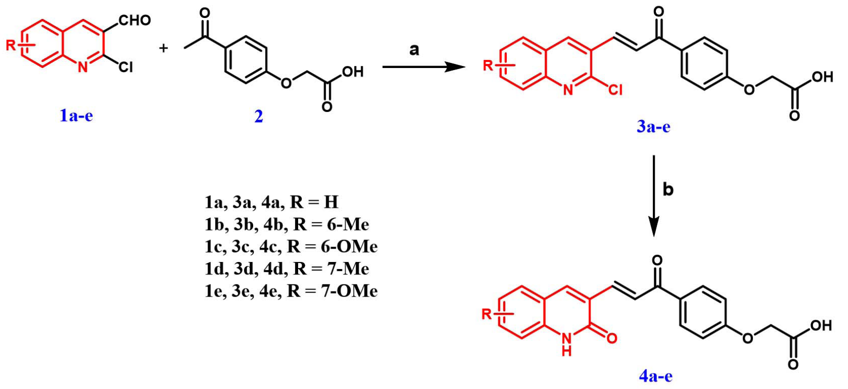
Experimental

Urease inhibition assay

The in vitro urease inhibitory potential of the synthesized compounds was examined using Jack bean urease, according to the Berthelot phenol assay protocol.[29,30] This colorimetric method quantifies the amount of ammonia released during the enzymatic hydrolysis of urea, thereby reflecting the enzyme's catalytic activity. All assays were performed in triplicate, and results are reported as the mean ± standard deviation (SD). A comprehensive and sequential description of the experimental procedure is provided in the Supplementary file.

Bacterial growth inhibition assay (disk diffusion method)

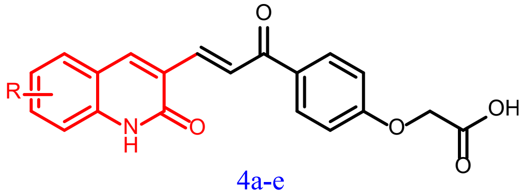
The antibacterial activity of the prepared compounds against *Helicobacter pylori* was determined using the standard filter paper disk diffusion approach. Experimental assays were performed on Brucella agar medium supplemented with 7% defibrinated horse blood and incubated at 37 °C under microaerophilic conditions. Dimethyl sulfoxide (DMSO) was utilized as the dissolution medium for all tested samples.[31] Each disk diffusion test was conducted in triplicate. The diameters of the inhibition zones were analyzed using One-way ANOVA to determine significant differences between the synthesized compounds and the positive control, with a P-value <0.05 defined as the threshold for significance. The complete and



1a, 3a, 4a, R = H
1b, 3b, 4b, R = 6-Me
1c, 3c, 4c, R = 6-OMe
1d, 3d, 4d, R = 7-Me
1e, 3e, 4e, R = 7-OMe

Figure 2. Synthesis of target compounds 3a-e and 4a-e
Reagent and Reactions conditions: (a) Ethanol, 10% NaOH, r.t. 15 mins, 79%-82% (b) Acetic acid, reflux, 6 hrs, 68%-75%.

Table 1. IC_{50} of compounds 4a-e against urease



4a-e

Compd. No.	R	Urease inhibition (IC_{50}, µM)
4a	H	0.93 ± 0.08
4b	6-Me	1.90 ± 0.15
4c	6-OMe	0.75 ± 0.06
4d	7-Me	1.45 ± 0.10
4e	7-OMe	0.58 ± 0.05
Thiourea	-	21.50 ± 0.80

detailed experimental protocol is outlined in the Supplementary file.

RESULTS AND DISCUSSION

Chemistry

The intended quinoline–chalcone hybrid derivatives (3a-e and 4a-e) were efficiently prepared following established synthetic routes previously reported in the literature,[28] as illustrated in Figure 2. Structural elucidation and confirmation of product identity were accomplished by comparing their physical characteristics and spectroscopic profiles (^{1}H NMR and ^{13}C NMR) with the corresponding literature data, ensuring complete consistency with reported values.

Biology

Urease inhibition assay

The newly synthesized quinoline-based hybrid molecules (4a-e) were assessed for their inhibitory efficacy against the urease enzyme in vitro, using thiourea as the reference standard inhibitor.[29] The obtained results, represented as IC_{50} values, are summarized in Table 1.

All tested compounds exhibited notable urease inhibition, with IC_{50} values ranging between 0.58 µM and 1.90 µM, indicating substantial potency. This inhibitory activity was significantly superior to that of the benchmark compound thiourea (IC_{50} = 21.50 µM). Among the series, compound 4e (R = 7-OMe) emerged as the most powerful inhibitor, displaying an IC_{50} of 0.58 ± 0.05 µM approximately 37 times more active than thiourea. The inhibitory efficiency was strongly affected by the position of the methoxy substituent: compound 4c (R = 6-OMe, IC_{50} = 0.75 µM) was about 1.3-fold less active than 4e. The unsubstituted derivative 4a (R = H, IC_{50} = 0.93 ± 0.08 µM) showed slightly lower potency, being 1.6 and 1.3 times less effective than 4e and 4c, respectively.

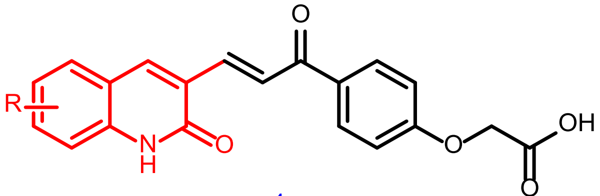
A marked decline in inhibitory capability was detected when the methoxy functionality was replaced by a methyl group. This structural modification generated compounds 4d (R = 7-Me, IC_{50} = 1.45 ± 0.10 µM) and 4b (R = 6-Me, IC_{50} = 1.90 ± 0.15 µM), which were the least potent members of the series. Specifically, 4d displayed 2.5-fold lower activity compared with its methoxy analogue (4e), whereas 4b was 2.6-fold weaker than 4c. Collectively, these findings demonstrate that both the electronic effects and the positional orientation of substituents on the quinoline phenyl ring play a decisive role in determining urease inhibition. The established structure activity relationship (SAR) for this set follows the order: 7-OMe > 6-OMe > H > 7-Me > 6-Me.

Anti-*Helicobacter pylori* assay

The antibacterial potential of the hybrid molecules 4a-e was examined against three *Helicobacter pylori* strains resistant to metronidazole using the standard disk diffusion approach. The average inhibition zone diameters (IZDs) observed at varying concentrations (100, 50, 25, and 12.5 µg per disk) for the three isolates are presented in Table 2. According to the accepted evaluation guidelines, antibacterial activity was categorized as high (>20 mm), moderate (16-20 mm), weak (11-15 mm), or negligible (<10 mm).[31]

As shown in Table 2, most of the synthesized hybrids demonstrated notable growth inhibition against *H. pylori* within the concentration range of 100-25 µg/disk. Interestingly, their antibacterial performance corresponded closely to their urease inhibitory behavior. Compound 4e (R = 7-OMe), identified earlier as the most active urease inhibitor, also exhibited the strongest antibacterial response, producing inhibition zones exceeding 26 mm across all concentrations. It surpassed the reference antibiotic metronidazole,

Table 2. Inhibition zone diameters of compounds 4a-e



4a-e

Comp.	R	Average of inhibition zone diameters (range, mm)*			
		100 µg/disk	50 µg/disk	25 µg/disk	12.5 µg/disk
4a	H	22 (20-24)	17 (21-23)	15 (11-19)	9 (7-11)
4b	6-Me	11 (10-12)	10 (8-11)	7 (6-9)	7 (5-9)
4c	6-OMe	32 (30-34)	26 (23-29)	24 (20-27)	21 (18-23)
4d	7-Me	15 (12-19)	12 (10-13)	10 (8-12)	8 (6-10)
4e	7-OMe	38 (36-39)	34 (32-35)	30 (28-31)	27 (24-29)
Metronidazole	-	26 (24-31)	24 (20-31)	18 (14-21)	12 (8-15)

which showed a 26 mm zone at 100 µg/disk. The next most potent derivative, 4c (R = 6-OMe), generated inhibition zones between 21 mm at 12.5 µg/disk and 32 mm at 100 µg/disk. At every concentration, compound 4c proved superior to metronidazole approximately 1.5-fold stronger at 100, 50, and 25 µg/disk, and nearly 2.3-fold more active at 12.5 µg/disk. These findings highlight the dual bioactivity of the methoxy-bearing analogues 4c and 4e, confirming their role as both efficient urease inhibitors and potent anti-*H. pylori* agents.

The unsubstituted compound 4a (R = H) displayed substantial antibacterial activity at the highest dose (22 mm IZD at 100 µg/disk). However, its efficacy gradually declined to moderate (17 mm) and weak (15 mm) levels at 50 and 25 µg/disk, respectively, and it exhibited no measurable activity at 12.5 µg/disk. In contrast, the methyl-substituted counterparts 4b (R = 6-Me) and 4d (R = 7-Me) consistently showed only mild inhibitory effects throughout all tested concentrations, indicating the diminished antibacterial impact of methyl substitution compared to methoxy analogues.

Briefly, the synthesised hybrids demonstrated significant potential for dual action. In the urease inhibition assay, compounds 4c (IC_{50} = 0.75 µM) and 4e (IC_{50} = 0.58 µM) shown markedly superior potency relative to the reference Thiourea (IC_{50} = 21.50 µM). This sub-micromolar activity is comparable to or superior to that of previously documented benzimidazole and thiosemicarbazide derivatives, which typically exhibit IC_{50} values ranging from 1 to 10 µM.[32,33] Moreover, compound 4e exhibited an inhibitory zone of 38 mm (at 100 µg/disk), significantly above the clinical standard Metronidazole, which measured 26 mm. At the lowest tested concentration (12.5 µg/disk), 4e (27 mm) demonstrated greater efficacy in inhibiting growth compared to Metronidazole at its maximum concentration (100 µg/disk, 26 mm). The methoxy-substituted hybrids exhibit superior enzyme inhibition and enhanced membrane permeability or intrinsic toxicity against *H. pylori* compared to standard nitroimidazole-based therapies.

CONCLUSION

This study systematically evaluated a designed series of quinoline-2-one/chalcone hybrid molecules (4a-e) to explore their dual pharmacological profile as urease inhibitors and anti-*Helicobacter pylori* agents. Biochemical assays confirmed that most of these synthesized hybrids exhibit strong urease inhibition, presenting IC_{50} values within the range of 0.58 µM to 1.90 µM. Their activity was markedly superior to that of the reference standard, thiourea (IC_{50} = 21.50 µM). Within the set, compounds 4a, 4c, and 4e stood out as the most active members. A notable and direct correlation was observed between urease inhibitory potential and antibacterial efficiency, as these same derivatives displayed pronounced inhibitory effects against *H. pylori* at concentrations from 100 down to 25 µg/disk. Collectively, these findings reinforce the potential of the quinoline-2-one/chalcone hybrid framework as an attractive and versatile scaffold for developing future anti-*H. pylori* therapeutics. Further investigations focusing on systematic modification and structure activity optimization of this molecular template are justified and may lead to promising lead compounds for subsequent preclinical evaluation.

Future perspectives

The remarkable efficacy of these hybrids, particularly compound 4e, highlights their potential as leading candidates for the treatment of *H. pylori* infections. Subsequent investigations will focus on testing the cytotoxicity of these compounds in mammalian cells, utilising established cell lines such as Vero or HEK-293, to further examine their translational significance and clinical safety. To ascertain the safety of these sub-micromolar urease inhibitors for humans, it is essential to determine the Selectivity Index (SI), defined as the ratio of the cytotoxic concentration (CC_{50}) to the inhibitory concentration (IC_{50}).

SUPPLEMENTARY INFORMATION

Supplementary information accompanies this article at https://doi.org/10.22207/JPAM.20.2.44

Additional file: Supplementary information.

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None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript and/or in the supplementary files.

ETHICS STATEMENT

Not applicable.

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