Archives of Pharmaceutical Sciences Ain Shams University 2022; Vol. 6(1): 29-36

OPEN ACCESS

Medicinal chemistry

Original Article

Synthesis, Biological Evaluation, and In-silico ADME Study of Novel Hybridized Benzimidazole-Chalcone Compounds with Potential Antimicrobial Activity

Mai I. Shahin[a*], Asmaa I. AbdAlhafiz[b], Khaled A. M. Abouzid[a,c], Wesam E. Mehanna[a]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt*

[b]*Department of Microbiology and Immunology, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt*

[c]*Department of Organic and Medicinal Chemistry, Faculty of Pharmacy, University of Sadat City, Sadat City, Menoufia, Egypt*

ABSTRACT

The intractable emergence of bacterial resistance worldwide urges the need for developing new effective antimicrobial agents to face such virulent strains. Based on the reported effectiveness of both chalcones and benzimidazoles on different bacterial strains including MRSA (Methicillin-Resistant *Staphylococcus aureus*), a hybridization strategy to design a scaffold comprising both moieties was achieved and a series of novel chalcone-benzimidazole based compounds were synthesized and tested for their antimicrobial activity. This was performed against *Staphylococcus aureus* as a representative of Gram-positive bacteria and *Escherichia coli* representing Gram-negative bacteria. The satisfactory activity shown against *Staphylococcus aureus* was a great promoter to test the compounds versus *linezolid-resistant MRSA.* Promising antimicrobial activity against MRSA was observed for three compounds **3b**, **3c,** and **3e** where compound **3e** is the most active showing MIC of 3.05 mg/ml. Modest chemical modification revealed a great difference in the activity profile which is intriguing to accomplish further modifications.

Keywords: *Chalcones; Benzimidazole; Antimicrobial activity; MRSA; Escherichia coli.*

***Correspondence** | Mai I. Shahin; Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Abbassia, Cairo 11566, Egypt. Email: maishahin@pharma.asu.edu.eg

Citation | Shahin MI, AbdAlhafiz AI, Abouzid KAM, Mehanna WE, 2022. Synthesis, Biological Evaluation and In-silico ADME Study of Novel Hybridized Benzimidazole-Chalcone Compounds with Potential Antimicrobial Activity. Arch Pharm Sci ASU 6(1): 29-36

DOI: 10.21608/aps.2022.126565.1083

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 10 March 2022. **Accepted** 19 March 2022.

Published by: Ain Shams University, Faculty of Pharmacy

1. INTRODUCTION

It is of great notice now the enormous development of bacterial resistance towards currently used antimicrobials. The great alarm was when the methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the 1960s **[1]**. MRSA is considered one of the leading causes of bacterial infections in populations **[2]**. Chalcones have always proved their importance as biologically active moieties having anti-inflammatory, antitumor, and antimicrobial activities **[3]**. Many chalcone-based molecules were reported to have significant antimicrobial activity. Even simple unsubstituted biphenyl chalcone exhibited MIC equal to 125 µg/mL against *Staphylococcus aureus* **[4]** (**Fig. 1**). Same for the benzimidazole nucleus which is considered a privileged scaffold for investigations due to its potential activity profiles

as anticancer, anti-inflammatory, antimalarial, and antiviral **[5]**. It has also proven its prospective effect as antimicrobial **[6]**. There are already many benzimidazole-based drugs that are marketed as effective antimicrobials **[7]**. A novel antimicrobial small molecule is being investigated as an effective drug for *Clostridium difficile* infection with benzimidazole as the main core of its structure (**Fig. 1**) **[8]**.

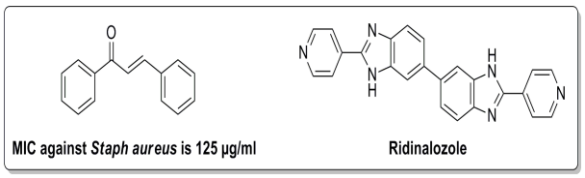


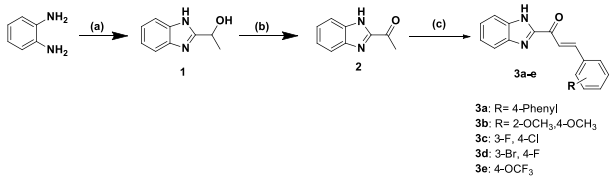
Fig. 1. Simple chalcone exhibiting good MIC against *S. aureus* and Ridinalozole

Herein, we reported the synthesis of hybridized novel compounds based on both of these potent antimicrobial moieties, chalcone, and benzimidazole. Other than the reported potency of both benzimidazole and chalcone as antimicrobials, the choice of the basic structure of the compounds synthesized was based on their ease of synthesis, so a library of different novel compounds with preferable pharmacokinetic and pharmacodynamics properties can be further synthesized and explored. Moreover, the fragment synthesized is of desirable drug-like properties. *In silico* ADME study was performed to confirm that the synthesized structures have acceptable Mwt, clogP, and PSA values. The synthesized compounds were tested versus *Escherichia coli*, *Staphylococcus aureus*, and three clinical isolates of *linezolid-resistant MRSA*. The results revealed a substantial activity profile that can be considered for further optimization to develop second-generation compounds for *in-vivo* studies.

2. Materials and methods

2.1. Chemistry

All chemicals either starting materials or reagents used were purchased from Aldrich (USA) or Alfa-Aesar Organics and used without further purification. All reactions were monitored using analytical thin-layer chromatography (TLC) purchased from Merck (Merck, Darmstadt, Germany) and performed on 0.255 mm silica gel plates, with visualization under U.V. light (254 nm). Melting points were determined using Stuart Scientific apparatus and were uncorrected. ^{1}HNMR and ^{13}C NMR spectra were run at Bruker 400 MHz spectrometer using TMS as a reference at the Center for Drug Discovery and Development Research, Ain Shams University. The proton of NH was not noticed in the ^{1}HNMR unless noted. LC-MS was performed on a Shimadzu LC-MS-2020 system. The purity of the final products was confirmed to be >95%. 70% Acetonitrile/water solvent mixture was used as an eluent.



Reagents and conditions: (a) Lactic acid, conc. HCl, reflux, 5 h; (b) $K_2Cr_2O_7$, H_2SO_4, rt, 4 h; (c) Corresponding aldehydes, 10% KOH, rt , 24 h.

Synthetic route to targeted compounds

2.1.1. 1-(*1H*-benzo[d]imidazol-2-yl)ethanol (1) was prepared as previously reported **[9]**.

2.1.2. 1-(*1H*-benzo[d]imidazol-2-yl) ethanone (2) was prepared as previously reported **[10]**.

2.1.3. General synthetic method for compounds (3a-e).

Compound **2** (0.5 g, 3.12 mmol) was suspended in ethanol and the corresponding aldehydes (3.75mmol, 1.2 eq.) were added to that suspension. 10% KOH (6.24 mmol, 2 eq.) was added dropwise while stirring. The whole mixture was left stirred overnight at room temperature. The day after, the solution formed was poured onto ice/water and the product was

filtered and recrystallized from ethanol.

2.1.4. (*E*)-3-([1,1'-biphenyl]-4-yl)-1-(1H-benzo[d]imidazol-2-yl)prop-2-en-1-one (3a):

Yellow solid (35% yield); m.p. 216-220 ^{o}C; LC-MS m/z 325 [M+H]+; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.26 (d, *J* = 16.2 Hz, 1H), 7.98 – 7.89 (m, 3H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.78 – 7.74 (m, 2H), 7.70 (dd, *J* = 6.1, 3.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.41 (dd, *J* = 8.3, 6.3 Hz, 1H), 7.32 – 7.23 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d6) δ 139.64 , 134.22 , 129.89 , 129.53 , 128.52 , 127.73 , 127.19 , 123.73 , 117.97 .

2.1.5. (*E*)-1-(*1H*-benzo[d]imidazol-2-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3b):

Orange solid (48% yield); m.p. 198-200 ^{o}C; LC-MS m/z 309 [M+H]+; ^{1}H NMR (400 MHz, DMSO-d6) δ 13.39 (s, 1H), 8.15 (d, *J* = 15.9 Hz, 1H), 8.01 (d, *J* = 16.1 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 6.4 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 3H);^{13}C NMR (101 MHz, DMSO-d6) δ 181.49 , 164.04 , 160.88 , 149.81 , 139.72 , 131.11 , 119.24 , 116.17 , 107.11 , 98.93 , 56.41 , 56.07;

2.1.6. (*E*)-1-(*1H*-benzo[d]imidazol-2-yl)-3-(4-chloro-3-fluorophenyl)prop-2-en-1-one (3c):

White solid (42% yield); m.p. 244-248 ^{o}C; LC-MS m/z 301 [M+H]+; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.45 (d, *J* = 16.1 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.70 – 7.63 (m, 2H), 7.60 (dd, *J* = 6.2, 3.2 Hz, 2H), 7.11 – 6.97 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d6) δ 183.21 , 143.85 , 139.38 , 131.59 , 126.54 , 126.14 , 122.44 , 118.52 , 116.65 .

2.1.7. (*E*)-1-(*1H*-benzo[d]imidazol-2-yl)-3-(3-bromo-4-fluorophenyl)prop-2-en-1-one (3d):

Yellow solid (62% yield); m.p. 224-228 ^{o}C; LC-MS m/z 345 [M+H]+; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 – 8.17 (m, 2H), 7.91 (ddd, *J* = 7.8, 4.9, 2.2 Hz, 1H), 7.80 (d, *J* = 16.1 Hz, 1H), 7.67 (dd, *J* = 6.2, 3.2 Hz, 2H), 7.45 (t, *J* = 8.6 Hz, 1H), 7.23 (dt, *J* = 6.2, 3.6 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d6) δ 181.85 , 141.20 , 134.27 , 133.48 , 124.26 , 124.02 , 117.96 , 117.77 , 109.49 .

2.1.8. (*E*)-1-(1H-benzo[d]imidazol-2-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (3e):

Yellow solid (65% yield); m.p. 238-240 ^{o}C; LC-MS m/z 333 [M+H]+; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.18 (d, *J* = 16.1 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 16.1 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.20 (m, 2H).

2.2. Assessment of antimicrobial activity

Initial screening for antibacterial activity was done against the Gram-negative *Escherichia coli* ATCC 25922 and the Gram-positive *Staphylococcus aureus* ATCC 29213, by the agar well diffusion method **[11]**. A standardized count of 10^{7} CFU (Colony Forming Unit) of each standard strain was adjusted spectrophotometrically and inoculated on Muller Hinton agar (MHA) plates before wells (12 mm diameter) were perforated. All test compounds were dissolved to a concentration of 50 mg/1 mL in DMSO. Wells were filled with 100 µL of solution. DMSO was used as a negative control, while Ciprofloxacin (1 mg/mL) was used as the positive control. Incubation was done at 37 °C overnight, then the plates were visually examined for inhibition zones and zone diameters were measured.

2.3. Determination of minimum inhibitory concentrations (MIC)

The compounds that have shown promising results in the assessment of antimicrobial activity were further investigated for their MIC. MICs were determined against Gram-negative

Escherichia coli ATCC 25922, Gram-positive *Staphylococcus aureus* ATCC 29213 and MRSA ATCC 43300 via the broth microdilution method as described in the CLSI guidelines **[12]** Solutions of the test compounds in DMSO were serially diluted, in microtiter plates, using Mueller Hinton Broth. The final concentrations of the test compounds in the solution covered the range 512 µg/mL to 0.5 µg/mL. Then, adjusted inocula of the microorganisms were added so that inoculum density was 10^6 CFU/mL in each well. Unioculated wells were used as negative controls, while Ciprofloxacin at the same concentrations was used as a positive control. At the end of the 24 h incubation period at 37 °C, plates were examined visually and MICs were recorded as the lowest concentration that inhibits the growth of microorganisms. Experiments were conducted in triplicates and average data was reported.

3. Results and discussion

3.1. Chemistry

The synthesis of the five targeted compounds was attained according to the outlined synthetic scheme. 1-(1H-benzo[d]imidazol-2-yl) ethanol **(1)** was synthesized by reacting the commercially available o-phenylenediamine with lactic acid in presence of conc. HCl as reported **[9]**. Oxidation of compound **(1)** using potassium dichromate in conc. H_2SO_4 yielded 1-(1H-benzo[d]imidazol-2-yl)ethanone **(2) [10]**. The targeted compounds **(3a-e)** were developed by treating compound **2** with 10% KOH in presence of the corresponding aldehyde through Claisen-Schmidt condensation reactions **[13]**. This was the final step to forming the basic benzimidazole-chalcone hybrid structures bearing five different substituents on the phenyl ring coming from the aldehyde used. As known, chalcones can exist as *cis* or *trans* isomer **[14]**. In our case, the *trans* isomer formation was confirmed by the appearance of the doublet signal in the HNMR chart with a *j*-coupling constant of 15.9 or 16.1 Hz.

3.2. Design strategy of the hybrid benzimidazole-chalcone entity

Merging two important pharmacophores into one single molecule is a well-established approach to getting a new hybrid molecule that can exert a synergistic effect compared to individuals **[15]**. As mentioned above, numerous chalcones have been reported as effective antimicrobials. A comprehensive SAR study was performed revealing the flexibility of changing the groups borne on chalcones while the optimum antimicrobial activity profile was kept (**Fig. 2**). **[16]**.

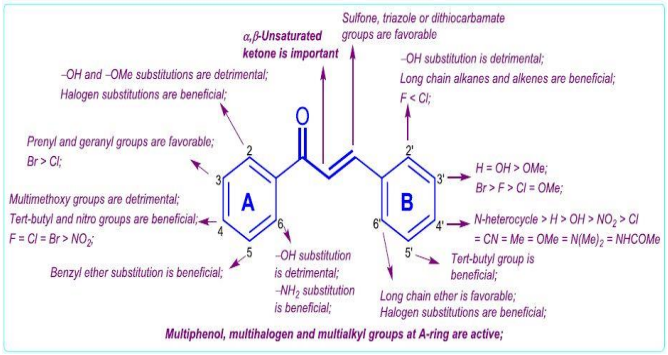


Fig. 2. Comprehensive SAR study of chalcones as antimicrobials **[16].**

Replacement of ring A in the chalcone structure with pyridine and furan rings was found to have good MICs towards MRSA and either alone or with a combination of other antibiotics **[17]**. In light of the above observations, we were prompted to synthesize novel hybrid structures aiming for synergistic antimicrobial activity. As illustrated in **Fig. 3.**, Compound I; with MIC range of 64-512 µg/mL against *MRSA;* and compound II; with MIC of 100 µg/mL against *E. coli* ATCC 25922 and 12.5 mg/mL against *S. aureus;* were used as lead compounds. Hybridization was managed by replacing ring (A) in compound I with a benzimidazole ring due to its announced antimicrobial activities. Substitution of the ring (B) with different substituents in different positions was

accomplished to get variable derivatives to be tested as promising antimicrobial agents. Compound II is considered an effective lead compound with significant antimicrobial activity. Simplification of its structure was a goal in our study to have a benzimidazole ring directly attached to the chalcone seeking a benzimidazole-chalcone hybrid as a novel platform acting as potential antimicrobial agents.

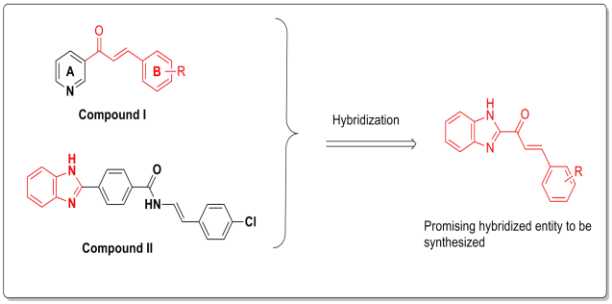


Fig. 3. The design strategy of the targeted compounds. The compound's I derivatives have good MIC towards *MRSA* **[17]**. Compound II has a MIC of 12.5 µg/ml toward *S. aureus and* 100 µg/ml against *E. coli* **[6]**.

3.3. Assessment of antimicrobial activity and MIC determination

The antimicrobial activity of the benzimidazole-chalcone compounds was tested against *E. coli* and *S. aureus* via the cup-plate method. Compounds that have shown inhibition zones were further investigated for MIC using the broth microdilution method. **Table 1** shows the MIC values. When tested against *E. coli*, the common representative of Gram-negative pathogens, compound **3c** was the only compound with a growth inhibitory activity. However, against *S. aureus*, all the tested benzimidazole-chalcone compounds have shown antibacterial activities. The chemical adjustments done resulted in the difference in the antimicrobial activities observed. All the compounds showed moderate inhibition towards *Staphylococcus aureus*. MICs of all the compounds were determined and the most promising antibacterial activities were manifested by compounds **3b** and **3c** with MICs of 5.8 and 5.5 mg/mL, respectively. This was a good start to further investigating the compounds toward more resistant *linezolid-resistant MRSA* isolates (**Table 1**).

Table 1. MIC of test compounds

Cpd.#	Substituent R	MIC against *E. coli* ATCC 25922	MIC against *S. aureus* ATCC 29213 (mg/mL)	MIC against MRSA ATCC 43300 (mg/mL)*
3a	4-Phenyl	-	11.7 mg/mL	23.4 mg/mL
3b	2,4-Dimethoxy	-	5.8 mg/mL	5.8 mg/mL
3c	4-Chloro,3-fluoro	22 mg/mL	5.5 mg/mL	7.47 mg/mL
3d	3-Bromo,4-fluoro	-	13.3 mg/mL	19.95 mg/mL
3e	4-Trifluoromethoxy	-	24.4 mg/mL	3.05 mg/mL
Ciprofloxacin		32 µg/mL	64 µg/mL	64 µg/mL

*Results are an average of 3 repeats.

Moreover, the synthesized compounds were tested for an effect on the superbug MRSA. Compound **3e**, with the 4-trifluoromethoxy substituent at position 4, was the most potent against MRSA with an average **MIC of 3.05 mg/mL**. Having 2,4 dimethoxy substituents in compound **3b** retained good antimicrobial activity displaying 5.8 mg/mL as MIC.

Compounds **3c**, **3d,** and **3a** were more effective on methicillin-sensitive than on methicillin-resistant *S. aureus*.

3.4. In-silico ADME study

In-silico ADME study was achieved using Accelrys Discovery Studio 2.5 to forecast the ADME of the targeted compounds. Different descriptors to estimate a range of ADME-related properties were calculated for the synthesized compounds. The partition coefficient was of optimum values and didn't exceed the value of 5 except for compounds **3a** and **3e**. Other descriptors such as A logP 98 and PSA 2D were calculated to evaluate solubility level and absorption level. Also, CYP2D inhibition was predicted giving a score of 0 for non-inhibitors and 1 for inhibitors. All the compounds showed good absorption levels (score = 0) with relatively low solubility (score of solubility level = 1–2). All the compounds showed good absorption. Finally, all the compounds were predicted to be CYP2D non-inhibitors (**Table 2**).

Table 2. Results of *in-silico* ADME descriptors

Cpd.#	A log P 98[a]	PSA 2D[b]	Absorption level[c]	Solubility[d]	Solubility level[e]	CYP2D6[f]	CYP2D6 probability[g]
3a	5.142	43.616	0	-6.262	1	0	0.376
3b	3.591	61.477	0	-4.885	2	0	0.227
3c	4.494	43.616	0	-5.812	2	0	0.326
3d	4.578	43.616	0	-5.891	2	0	0.326
3e	5.744	52.547	0	-7.051	1	0	0.227

[a] Lipophilicity descriptor

[b] Polar surface area.

[c] Absorption level (0 = good, 1 = moderate, 2 = low, 3 = very low).

[d] Solubility parameter.

[e] Solubility level (0 = extremely low, 1 = very low but soluble, 2 = low, 3 = good, 4 = optimal).

[f] CYP2D inhibition (0 = non inhibitor, 1 = likely to inhibit).

[g] CYP2D inhibition probability.

Conclusions

Five drug-like novel compounds were synthesized and evaluated versus gram-negative and gram-positive bacteria. The initial screening performed on *S. aureus* and *E. coli* showed moderate inhibitory activity of microbial growth with considerable MICs of values around 5 mg/ml for compounds **3b** and **3c** towards *S. aureus*. Additional exploration using the three clinical isolates of linezolid-resistant MRSA was conducted. Compound **3e** was found to be the most promising antimicrobial agent with **MIC 3.05 mg/mL**. Compound **3c** was also found to be the only active compound against *E. Coli* and with moderate activity towards both *S. aureus* and *MRSA*. The ADME study our predictions towards these compounds have drug-like properties. Our study demonstrates the

importance of developing new antimicrobial agents based on hybridized benzimidazole-chalcone moieties and warrants evolving compounds' library with appreciable antimicrobial activity and pharmacokinetic profile. More derivatives will be further synthesized for better SAR exploration.

Declarations

Ethics approval and consent of participation

Not applicable

Consent of publication

Not applicable

Data and materials availability

All data produced or analyzed throughout this study are included in the current manuscript.

Competing interests

No competing interests were found between the authors.

Funding

This manuscript was not funded.

4. REFERENCES

1. N.A. Turner, B.K. Sharma-Kuinkel, S.A. Maskarinec, E.M. Eichenberger, P.P. Shah, M. Carugati, T.L. Holland, V.G. Fowler, Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research, Nature Reviews Microbiology, 17 (2019) 203-218.
2. A.S. Lee, H. de Lencastre, J. Garau, J. Kluytmans, S. Malhotra-Kumar, A. Peschel, S. Harbarth, Methicillin-resistant Staphylococcus aureus, Nature Reviews Disease Primers, 4 (2018) 18033.
3. P. Singh, A. Anand, V. Kumar, Recent developments in biological activities of chalcones: A mini-review, European Journal of Medicinal Chemistry, 85 (2014) 758-777.
4. M. Xu, P. Wu, F. Shen, J. Ji, K.P. Rakesh, Chalcone derivatives and their antibacterial activities: Current development, Bioorganic Chemistry, 91 (2019) 103133.
5. B. Pathare, T. Bansode, Review- biological active benzimidazole derivatives, Results in Chemistry, 3 (2021) 100200.
6. S. Tahlan, S. Kumar, B. Narasimhan, Antimicrobial potential of 1H-benzo[d]imidazole scaffold: a review, BMC Chemistry, 13 (2019) 18.
7. D. Song, S. Ma, Recent Development of Benzimidazole-Containing Antibacterial Agents, ChemMedChem, 11 (2016) 646-659.
8. J.C. Cho, M.P. Crotty, J. Pardo, Ridinilazole: a novel antimicrobial for Clostridium difficile infection, Ann Gastroenterol, 32 (2019) 134-140.
9. Y. Wang, S. Xue, R. Li, Z. Zheng, H. Yi, Z. Li, Synthesis and biological evaluation of novel synthetic chalcone derivatives as anti-tumor agents targeting Cat L and Cat K, Bioorg Med Chem, 26 (2018) 8-16.
10. V.M. Reddy, K.R. Reddy, Synthesis and Antimicrobial Activity of Some Novel 4-(1H-Benz[d]imidazol-2yl)-1,3-thiazol-2-amines, Chemical & Pharmaceutical Bulletin, 58 (2010) 953-956.
11. M. Balouiri, M. Sadiki, S.K. Ibnsouda, Methods for in vitro evaluating antimicrobial activity: A review, Journal of Pharmaceutical Analysis, 6 (2016) 71-79.
12. CLSI Performance Standards for Antimicrobial Susceptibility Testing. Twenty-Fourth Informational Supplement. Wayne, PA: Clinical and Laboratory Standards Institute, in, 2015.

13. M.-H. Hsu, S.-M. Hsu, Y.-C. Kuo, C.-Y. Liu, C.-Y. Hsieh, Y.-C. Twu, C.-K. Wang, Y.-H. Wang, Y.-J. Liao, Treatment with low-dose sorafenib in combination with a novel benzimidazole derivative bearing a pyrolidine side chain provides synergistic anti-proliferative effects against human liver cancer, RSC Advances, 7 (2017) 16253-16263.

14. C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing, Z. Miao, Chalcone: A Privileged Structure in Medicinal Chemistry, Chemical Reviews, 117 (2017) 7762-7810.

15. E.B. Mass, G.V. Duarte, D. Russowsky, The Quinazoline-Chalcone and Quinazolinone-Chalcone Hybrids: A Promising Combination for Biological Activity, Mini Rev Med Chem, 21 (2021) 186-203.

16. W. Dan, J. Dai, Recent developments of chalcones as potential antibacterial agents in medicinal chemistry, European Journal of Medicinal Chemistry, 187 (2020) 111980.

17. T.-D. Tran, T.-T.-N. Nguyen, T.-H. Do, T.-N.-P. Huynh, C.-D. Tran, K.-M. Thai, Synthesis and antibacterial activity of some heterocyclic chalcone analogs alone and in combination with antibiotics, Molecules, 17 (2012) 6684-6696.