ORIGINAL ARTICLE

A C G publications *Bioorg. Med. Chem. Rep.* X:X (2023) X-X

Bioorganic & Medicinal Chemistry Reports

Fluorinated benzimidazole derivatives: *In vitro* antimicrobial activity

Kajeen Hassan Jasim [1], Ronak Haj Ersan [1, 2*], Roaida Sadeeq [1] Soad Salim [1], Somaya Mahmood [1] and Zina Fadhil [1]

[1] *Department of Medical Laboratory, College of Health Science, Cihan University, Duhok, Iraq*
[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Mersin University, 33169, Mersin, Türkiye*

(Received January 30, 2023; March January 30, 2023; Accepted April 11, 2023)

Abstract: Given the pharmacological significance of fluorine-containing heterocycles, in the present paper, a series of benzimidazole having fluoro-benzene moiety within a single molecular framework were screened for their *in vitro* antimicrobial activity against four Gram-positive bacteria, two Gram-negative bacteria and two fungal strains. The results of antimicrobial activity demonstrated that fluoro-substituted compounds (**13-15** and **17-19**) have good antibacterial and antifungal properties as compared to unsubstituted parent compounds (**12** and **16**). Compound **18** which hold fluorine atom in *meta*-positions of phenyl ring side chain of benzimidazole displayed high activity against Gram-negative bacteria with a MIC value of 31.25 µg/mL. Similarly, 2-(*m*-fluorophenyl)-benzimidazole derivatives **14** and **18** showed good anti-*B. subtilis* with a MIC value of 7.81 µg/mL. SAR studies suggested that the presence of methyl substitution group at position 5 of benzimidazole is recommended for significant antifungal activity against *C. parapsilosis*. The high potency suggested that compound **18** could be a starting point for the discovery and optimization of novel antimicrobial agents.

Keywords: Benzimidazole; fluorine; MIC; antibacterial; antifungal. ©2023 ACG Publication. All right reserved.

1. Introduction

Current antimicrobials are in danger of losing effectiveness due to the progressive development of antibiotic and antifungal resistance among pathogenic bacteria and fungi.[1] In order to prevent this major medical problem, the discovery of new types of antimicrobial agents is a very important but challenging task. In search to create a new set of effective antimicrobials, aryl benzimidazole compounds have attracted great attention for their wide range of biological activities.[2-4] Especially, phenyl benzimidazole derivatives were identified as a potential target to further study and explored for identifying the lead antimicrobial agent.[5-7]

The isosteric substitution of hydrogen by fluorine could modulate the chemical and physical properties, biological activity, pharmacodynamics, and pharmacokinetics of organofluorines.[8,9] Also, the presence of fluorine atom(s) could increase drugs' selectivity and lipophilicity, thus resulting in increased antimicrobial activities by enhancing the rate of cell penetration.[10,11]

The discovery of the fluoroquinolones such as norfloxacin, lomefloxacin, enoxacin, ofloxacin, and ciprofloxacin as antibacterials is a striking example of the strong effect of fluorine atoms on molecular properties[12]. Ciprofloxacin (**1**) is a stellar example of a fluoroquinolone to date with a broad spectrum of biological activities. The introduction of fluorine at position-6 resulted in increasing antibacterial activity, especially, against Gram-positive bacteria, compared to other analogues.[12]

* Corresponding author: E-Mail: ronak.arsan@duhokcihan.edu.krd, Phone: + 9647502206580

The article was published by ACG Publications
http://www.acgpubs.org/journal/bioorganic-and-medicinal-chemistry-reports © Month-Month 2023 EISSN:2667-6028
DOI: http://doi.org/10.25135/bmcr.30.23.01.2692
Available online: April 27, 2023

Fluorinated benzimidazole derivatives

It is known that fluconazole (**2**), one of the most used anti-candidiasis drugs,[13] is an azole compound containing a fluorinated phenyl group. Fluconazole structure and the essential role of mono-fluorine on the phenyl ring in the antifungal activity have been reported by Xie et al.[14]

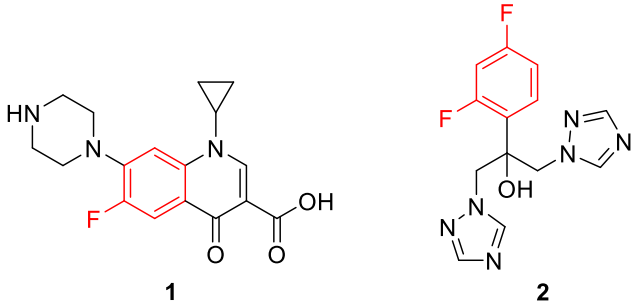


Figure 1. Structure of ciprofloxacin and fluconazole

It was also reported that the benzimidazole compounds bearing fluorine substituent can have improved biological activities, especially for the antibacterial and antifungal activities.[15] El-Gohary and co-workers synthesized a series of benzimidazole derivatives and tested their antimicrobial activity, among the tested benzimidazole compounds, fluorinated benzimidazole (**3**) showed good activity toward *S. aureus* and *C. albicans* with MIC value 156.25 µg/mL and 78.125 µg/mL respectively.[16] Pardeshi et al. synthesized new benzimidazole derivatives and evaluated their antifungal and antibacterial activity. The result showed that the presence of fluorine in benzimidazole (**4** and **5**) is responsible for their reactivity.[17] In addition, Zhang et al. developed a new series of arylbenzimidazoles with improved efficacy. Their results indicate that the presence of a strong electron-withdrawing atom such as fluorine at phenyl side chain of benzimidazole (**6**) improves the antifungal activity against *C. albicans*, *S. cerevisiae*, and *A. flavus fungi*.[18]

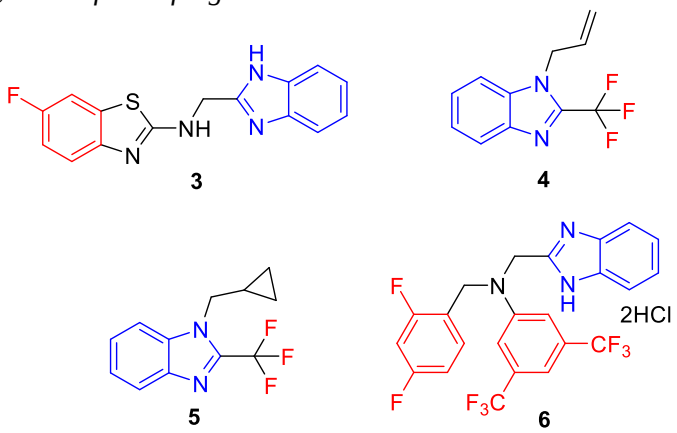


Figure 2. Benzimidazole derivatives incorporating fluorine

In view of the above considerations, and the known some antimicrobial agents have a halogenated phenyl ring, presumably in order to give them good antibacterial and antifungal activity, we decided to investigate the antimicrobial potency of our previously synthesized 2-phenyl benzimidazole which hold fluorine atom in the *ortho*-, *meta*- or *para*-positions of phenyl ring side chain of benzimidazole.

2. Experimental

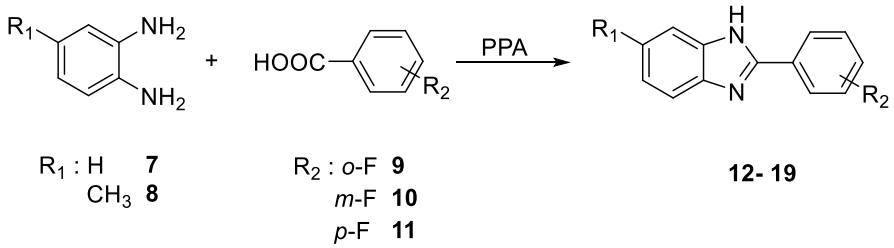
2.1. Chemistry

The synthetic route of the compounds is shown in Scheme 1. All compounds were synthesized by using polyphosphoric acid methods. ^{1}H NMR spectra were taken on a 400 MHz spectrometer with

tetramethylsilane (TMS) as an internal standard, and chemical shifts were recorded in ppm values. The IR spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer. The synthesis procedure and results are detailed in our previous study.[19]

2.1.1. General Synthesis Procedure

A mixture of 1,2-phenylenediamine derivatives (1 eq.) and the corresponding carboxylic acid derivatives (1.1 eq.) were heated for a period of 13–18 h in 5 mL polyphosphoric acid (PPA) at 120-150 °C (Scheme 1).[20-22] The reaction mixture was poured onto ice water and neutralized by mixing it with 5 M NaOH until a slightly basic pH (8–9) was obtained to get the precipitate. The resulting precipitate was filtered off, washed with cold water, and recrystallized with ethanol-water. The resulting crystalline compounds were filtered, and the vacuumed product was dried (Figure 3).



Scheme 1. Synthesis of 2-(fluorophenyl)-benzimidazole derivatives.

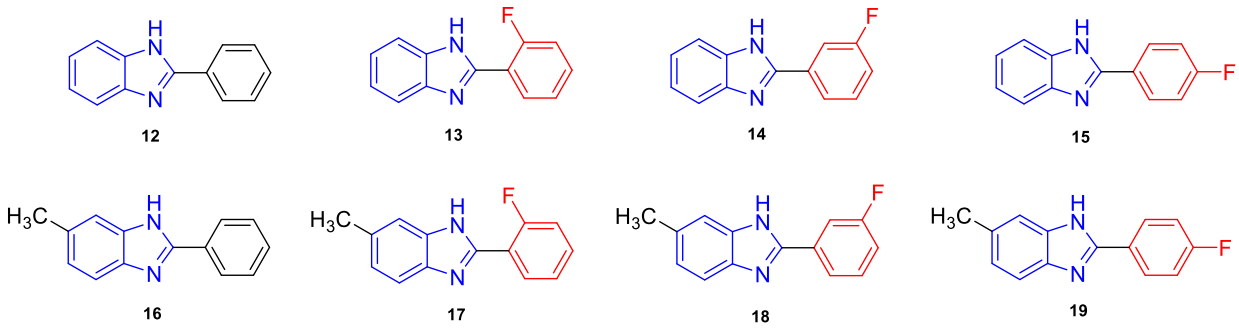


Figure 3. Structures of the 2-(fluorophenyl)-benzimidazole derivatives (**12-19**).

*2-Phenyl-1H-benzo[d]imidazole (**12**)*[23]: Light yellow crystalline; 66%; R_f ($CHCl_3$/MeOH 95:05) = 0.50; mp = 290-294 °C; IR (KBr, cm^{-1}) ν_{max} 3411, 1540, 1450, 1408, 967, 774; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.18 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.60 (m, 2H, Ar-H), 7.57-7.50 (m, 3H, Ar-H), 7.22-7.19 (m, 2H, Ar-H).

*2-(2-Fluorophenyl)-1H-benzo[d]imidazole (**13**)*[24]: Yellow crystalline; 66%; R_f ($CHCl_3$/MeOH 95:05) = 0.62; mp = 210-215 °C; IR (KBr, cm^{-1}) ν_{max} 3320, 3048, 1585, 1444, 109.5, 743; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.55 (br s, 1H, NH), 8.23 (m, 2H, Ar-H), 7.61-7.53 (m, 2H, Ar-H), 7.47-7.37 (m, 2H, Ar-H), 7.27-7.21 (m, 2H, Ar-H).

*2-(3-Fluorophenyl)-1H-benzo[d]imidazole (**14**)*[25]: yellow crystalline; 54%; R_f ($CHCl_3$/MeOH 95:05) = 0.51; mp= 253-257 °C; IR (KBr, cm^{-1}) ν_{max} 3307, 3021, 1535, 1404, 1075, 733; ^{1}H NMR (400 MHz, CD_3OD) δ 7.90–7.79 (m, 2H, Ar-H), 7.62–7.49 (m, 3H, Ar-H), 7.28–7.18 (m, 3H, Ar-H).

*2-(4-Fluorophenyl)-1H-benzo[d]imidazole (**15**)*[23]: Beige crystalline; 42%; R_f ($CHCl_3$/MeOH 95:05) = 0.58; mp= 250-255 °C; IR (KBr, cm^{-1}) ν_{max} 3429, 3060, 1604, 1440, 964, 743; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.23-8.21 (m, 2H, Ar-H), 7.59 (d, *J* = 2.7 Hz, 2H, Ar-H), 7.38 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.22-7.18 (m, 2H, Ar-H).

Fluorinated benzimidazole derivatives

6-Methyl-2-phenyl-1H-benzo[d]imidazole ***(16)***[26]: Red crystalline; 45%; R_f ($CHCl_3$/MeOH 95:05) = 0.54; mp = 250-255 °C; IR (KBr, cm^{-1}) ν_{max} 3375, 3052, 2919, 1504, 1420, 944, 723; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.10 (s, 1H, NH), 8.68 (d, *J* = 1.8 Hz, 1H, Ar-H), 8.54 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.40 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.50 – 7.57 (m, 2H, Ar-H), 7.46 (s, 1H, Ar-H), 7.14 (d, *J* = 8.0 Hz, 1H, Ar-H), 2.50 (s, 3H, CH_3).

2-(2-Fluorophenyl)-6-methyl-1H-benzo[d]imidazole ***(17)***[26]: Beige crystalline; 53%; R_f ($CHCl_3$/MeOH 95:05) = 0.48; mp = 263-265 °C; IR (KBr, cm^{-1}) ν_{max} 3302, 3042, 2965, 1554, 1470, 974, 833; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.59 (s, 1H, NH), 8.45 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.54 (ddd, *J* = 4.0, 8.0, 3.5 Hz, 2H, Ar-H), 7.47 (s, 1H, Ar-H), 7.32 – 7.42 (m, 2H, Ar-H), 7.10 (d, *J* = 8.0 Hz, 1H, Ar-H). 2.47 (s, 3H, CH_3).

2-(3-Fluorophenyl)-6-methyl-1H-benzo[d]imidazole ***(18)*** (CAS 940703-07-1): Yellow crystalline; 54%; R_f ($CHCl_3$/MeOH 95:05) = 0.53; mp = 272-275 °C; IR (KBr, cm^{-1}) ν_{max} 3307, 3021, 1545, 1407, 1077, 736; ^{1}H NMR (400 MHz, CD_3OD) δ 7.90–7.79 (m, 3H, Ar-H), 7.62–7.49 (m, 3H, Ar-H), 7.32 (s, 1H, Ar-H), 2.40 (s, 3H, CH_3).

2-(4-Fluorophenyl)-6-methyl-1H-benzo[d]imidazole ***(19)***[27]: White crystalline; 63%; R_f ($CHCl_3$/MeOH 95:05) = 0.44; mp = 233-235 °C; IR (KBr, cm^{-1}) ν_{max} 3354, 3035, 2945, 1506, 1423, 944, 743; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.95 (s, 1H, NH), 8.05 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.56 (s, 1H, Ar-H), 7.36 (d, *J* = 7.9 Hz, 3H, Ar-H), 7.11−6.96 (m, 1H, Ar-H), 2.37 (s, 3H, CH_3).

2.2. Antimicrobial Activity

Antimicrobial susceptibility testing was performed by the modification of literature methods.[28] The microbial strains, such as *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25853), *Enterococcus faecalis* (ATTC 29212), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pneumonia* (ATCC 10353), *Bacillus subtilis* (ATCC 6633), *Candida albicans* (ATCC 4322), and *Candida parapsilosis* (ATTC 22019), were used for this purpose. The fungal and bacterial cell inoculums were prepared from a stock culture grown in tryptic soy agar (TSA) at 28 °C for 24 h and in Mueller–Hinton agar (MHA) at 37 °C for 24 h, respectively. The microorganism suspension concentrations were adjusted to 0.5 McFarland turbidity tubes using sterilized saline. Stock solutions of the title compounds were prepared in DMSO at 1000 µg/mL. A modified microdilution test was performed for antimicrobial activity, and the experiments were run in duplicate independently. For the antifungal activity testing, a 100 µL Tryptic Soy Broth (TSB) was added to each of the 11 wells. A 100 µL aliquot of the tested chemical solution was added to the first well, and twofold dilutions were prepared. Then, 5 µL of fungal suspension was added to each tube except the last one, which acted as the control well. For the antibacterial activity testing, a 100 µL Mueller–Hinton broth (MHB) was added to each of the 11 wells. A 100 µL aliquot of the chemical derivative solution was added to the first tube, and twofold dilutions were prepared. Then, 5 µL of the bacterial suspension was added to each tube, except the last control well. A control tube containing 5 µL of the fungal and bacterial suspensions alone without the tested compounds was also prepared. All plates were incubated at 28 °C (for fungi) and 37 °C (for bacteria) for 24 h. After incubation, the MICs (Table 1) were obtained by noting the growth inhibitions. The concentration resulting in a 50% reduction in the optical density (OD) values was compared to a reproduction control at 450 nm by spectrophotometric evaluation and defined as the MIC value. Fluconazole and ampicillin were used as reference drugs. The results were read visually and by measuring the OD for 24 h.

3. Results and Discussion

The *in vitro* antimicrobial screening for all the synthesized compounds was evaluated for four Gram-positive bacteria (*Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pneumonia*, and *Bacillus subtilis*), two gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two fungi

(*Candida albicans* and *Candida parapsilosis*) using a modified microdilution method with the positive control of clinically antimicrobial drugs ampicillin and fluconazole. The values of clog*P*, a partition coefficient as a kind of measurement for molecular hydrophobicity/lipophilicity, were calculated using ChemBioDrawUltra 12.0.3.

The Minimal inhibitory concentration (MIC, μg/mL) values of the synthesized compounds and the control drugs against the tested bacterial and fungal strains are summarized in Table 1.

In general, it could be observed that all of the synthesized compounds of the series have shown moderate to good antimicrobial activity against the tested microorganisms. A visual inspection envisaged that the presence of an electron-withdrawing fluorine atom as a substituent on the phenyl side chain directly attached to benzimidazole moiety increases the antimicrobial activity of compounds (**13-15** and **17-19**) while keeping the phenyl unsubstituted (**12-16**). The notable observation is that the presence of a methyl substitution group at position 5 of the benzimidazole ring leads to the enhancement of the antimicrobial activity of the compounds.

From Table 1, among the 5-unsubstituted benzimidazole derivatives, compound **14** with *meta*-fluoro substitution group on the phenyl ring of the side chain proved to be the most potent antibacterial agent against *B. subtilis* with a MIC value of 7.81 μg/mL.

Among 5-methylbenzimidazole derivatives, compound **18** with *meta*-fluoro substitution group on the phenyl ring of the side chain displayed a potent anti-*E. coli* and anti-*P. aeruginosa* activities with a MIC value of 31.25 μg/mL and good anti-*B. subtilis* with a MIC value of 7.81 μg/mL. The replacement of *meta*-fluoro by *ortho*- and *para*-fluoro substitution groups, which yielded compounds **17** and **19** respectively, resulted in low antibacterial activity.

Two strains of fungi (*C. albicans* and *C. parapsilosis*) were used for determining the antifungal activity of the synthesized compounds. In comparison with *C. parapsilosis*, our compounds were relatively less sensitive to *C. albicans.* Benzimidazole derivatives (**17-19**) having a methyl substituent had higher clog*P* values and displayed better antifungal activity than the unsubstituted parent (**13-15**). Especially, compound **17** with *ortho*-fluoro substitution exhibited good anti-*C. parapsilosis* with MIC value of 15.62 μg/mL in comparison to the reference drug fluconazole. These results suggested the noticeable effects of the methyl group on antifungal activities.

4. Conclusion

The preliminary *in vitro* antibacterial and antifungal screening results the 2-(fluorophenyl)-benzimidazole derivatives reported here have emerged as good antimicrobial agents.

This study has reinforced our speculation about the presence of fluorine atoms as a substituent on the phenyl side chain of benzimidazole. Moreover, the presence of fluorine atom at various positions affects antimicrobial activity and suggested to have different compound-target binding affinities.

From a structural point of view, the *meta*-fluoro substitution group appeared to be the crucial factor for the activity maintenance of tested compounds (**14** and **18**) against *B. subtilis.* However, the presence of methyl group at position 5 of benzimidazole (**18**) didn't improve the activity against *B. subtilis* in comparison with the unsubstituted parent (**14**).

By comparing the antifungal activity of the benzimidazole derivatives, it was found that the introduction of the methyl group at position 5 of benzimidazoles (**17-19**) showed notable enhanced antifungal efficiency against *C. parapsilosis*. The lipophilicity parameters were determined by the theoretical calculation (clog*P*). The results indicate that compounds with high clog*P* have better anti-*C. parapsilosis* than anti-*C. albicans.* A plausible explanation could be the increased lipophilicity of benzimidazole compounds might make them favorable for being delivered to the binding sites.

Our results manifested that fluorophenyl-containing benzimidazole derivatives should be worthy to be of further investigation as potential antimicrobial agents.

Table 1. MIC values of the synthesized 2-(fluorophenyl)-benzimidazole derivatives against Gram + and Gram - bacterial and fungal strains

Compound No	E. coli	P. aeruginosa	E. faecalis	S. aureus	S. pneumoniae	B. subtilis	C. albicans	C. parapsilosis	cLog*P*
12	125	62.5	125	250	250	125	62.5	62.5	3.663
13	62.5	62.5	62.5	62.5	62.5	62.5	62.5	125	3.826
14	62.5	62.5	62.5	250	250	**7.81**	62.5	125	3.826
15	62.5	62.5	62.5	250	250	15.62	62.5	62.5	3.826
16	62.5	62.5	125	250	250	62.5	62.5	62.5	4.162
17	125	125	62.5	62.5	125	125	62.5	**15.62**	4.325
18	31.25	31.25	62.5	62.5	62.5	**7.81**	62.5	31.25	4.325
19	62.5	62.5	62.5	125	125	62.5	62.5	62.5	4.325
Ampicillin	**31.25**	**31.25**	*****	*****	*****	*****	**-**	**-**	-1,2045
Fluconazole	**-**	**-**	**-**	**-**	**-**	**-**	*****	**7,8**	-0,44

*: All tested concentrations are active. -: Not tested

Acknowledgments

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

ORCID
Kajeen Hassan Jasim: 0000-0001-6961-9424
Ronak Haj Ersan: 0000-0001-6651-5910
Roaida Sadeeq: 0000-0001-5683-0554
Soad Salim: 0000-0002-4645-7204
Somaya Mahmood: 0000-0002-4476-020X
Zina Fadhil: 0000-0003-0003-7201

References

[1] Ventola, C. L. The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and therapeutics* 2015, 40, 277.
[2] Tahlan, S.; Kumar, S.; Narasimhan, B. Pharmacological significance of heterocyclic 1H-benzimidazole scaffolds: a review. *BMC chemistry* **2019**, *13*, 1-21.
[3] Beltran-Hortelano, I.; Alcolea, V.; Font, M.; Pérez-Silanes, S. The role of imidazole and benzimidazole heterocycles in Chagas disease: A review. *Eur. J. Med. Chem.* **2020**, *206*, 112692.
[4] Vasava, M. S.; Bhoi, M. N.; Rathwa, S. K.; Jethava, D. J.; Acharya, P. T.; Patel, D. B.; Patel, H. D. Benzimidazole: A milestone in the field of medicinal chemistry. *Mini Rev. Med. Chem.* **2020**, *20*, 532-565.
[5] Saleh, O. R.; Shaldum, M. A.; Goda, R. M.; Shehata, I. A.; El-Ashmawy, M. B. Synthesis and antibacterial evaluation of new2-phenylbenzimidazole derivatives. *ChemistrySelect*. **2019**, *4*, 10307-10315.
[6] Ersan, R. H.; Kuzu, B.; Yetkin, D.; Alagoz, M. A.; Dogen, A.; Burmaoglu, S.; Algul, O. 2-Phenyl substituted Benzimidazole derivatives: Design, synthesis, and evaluation of their antiproliferative and antimicrobial activities. *Med. Chem. Res.* **2020**, 1-17.
[7] Desai, N. C.; Dodiya, A. M.; Shihory, N. R. A search of novel antimicrobial based on benzimidazole and 2-pyridone heterocycles. *Med. Chem. Res.* **2012**, *21*, 2579-2586.
[8] Yadav, P.; Lal, K.; Kumar, L.; Kumar, A.; Kumar, A.; Paul, A. K.; Kumar, R. Synthesis, crystal structure and antimicrobial potential of some fluorinated chalcone-1, 2, 3-triazole conjugates. *Eur. J. Med. Chem*. 2**018**, *155*, 263-274.
[9] Hiyama, T.; Hiyama, T.; Yamamoto, H. Biologically active organofluorine compounds. *Organofluorine Compounds: Chemistry and Applications* 2000, 137-182.
[10] Shah, P.; Westwell, A. D. The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. Med. Chem*. 2007, 22, 527-540.
[11] Saeed, A.; Shaheen, U.; Hameed, A.; Haider Naqvi, S.Z. Synthesis, characterization and antimicrobial activity of some new 1-(fluorobenzoyl)-3-(fluorophenyl) thioureas. *J. Fluor. Chem*. **2009**, *130*, 1028–1034.
[12] Andriole, V. T. The quinolones: prospects. *In The quinolones* 2000, 477-495.
[13] Corrêa, J. C. R.; Salgado, H. R. N. Review of fluconazole properties and analytical methods for its determination. *Crit. Rev. Anal. Chem*. **2011**, *41*, 124-132.
[14] Xie, F.; Ni, T.; Ding, Z.; Hao, Y.; Wang, R.; Wang, R.; Zhang, D. Design, synthesis, and in vitro evaluation of novel triazole analogues featuring isoxazole moieties as antifungal agents. *Bioorg. Chem*. **2020**, *101*, 103982.
[15] Selivanova, G. A.; Tretyakov, E. V. Fluorinated benzimidazoles for medicinal chemistry and new materials. *Russ. Chem. Bull*. **2020**, *69*, 838-858.
[16] El-Gohary, N. S.; Shaaban, M. I. Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and antitumor agents. *Eur. J. Med. Chem*. **2017**, *131*, 255-262.

[17] Pardeshi, V. A.; Pathan, S.; Bhargava, A.; Chundawat, N. S.; Singh, G. P. Synthesis and evaluation of novel benzimidazole derivatives as potential antibacterial and antifungal agents. *Egypt. J. Basic App. Sci*. **2021**, *8*, 330-344.

[18] Zhang, H. Z.; Damu, G. L.; Cai, G. X.; Zhou, C. H. Design, synthesis and antimicrobial evaluation of novel benzimidazole type of Fluconazole analogues and their synergistic effects with Chloromycin, Norfloxacin and Fluconazole. *Eur. J. Med. Chem.* **2013**, *64*, 329-344.

[19] Ersan, R. H.; Duran, N. In vitro antiproliferative activity of some fluoro-substituted benzimidazole-based scaffolds. *Bioorg. Med. Chem. Rep*. **2021**, *4*,10-17.

[20] Ersan, R. H.; Yuksel, A.; Ertan-Bolelli, T.; Dogen, A.; Burmaoglu, S.; Algul, O. One-pot synthesis of novel benzimidazoles with anaphthalene moiety as antimicrobial agents andmolecular docking studies. *J. Chin. Chem. Soc*. **2021**, *68*, 374-383

[21] Algul, O.; Ersan, R. H.; Alagoz, M. A.; Duran, N.; Burmaoglu, S. An efficient synthesis of novel di-heterocyclic benzazole derivatives and evaluation of their antiproliferative activities. *J. Biomol. Struct. Dyn. 2021*, *39*, 6926-6938.

[22] Ersan, R. H.; Alagoz, M. A.; Ertan-Bolelli, T.; Duran, N.; Burmaoglu, S.; Algul, O. Head-to-head bisbenzazole derivatives as antiproliferative agents: design, synthesis, in vitro activity, and SAR analysis. *Mol. Divers*. **2021**, *25*, 2247-2259.

[23] Nguyen, T. T.; Nguyen, X. T. T.; Nguyen, T. L. H.; Tran, P. H. Synthesis of benzoxazoles, benzimidazoles, and benzothiazoles using a Brønsted acidic ionic liquid gel as an efficient heterogeneous catalyst under a solvent-free condition. *ACS Omega* **2019**, *4*(*1*), 368-373.

[24] Weires, N. A.; Boster, J.; Magolan, J. Combined Pd/C and montmorillonite catalysis for one-pot synthesis of benzimidazoles. *Eur. J. Org. Chem. **2012***, *33*, 6508-6512.

[25] Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. Sodium sulfide: a sustainable solution for unbalanced redox condensation reaction between o-nitroanilines and alcohols catalyzed by an iron–sulfur system. *Synthesis* **2015**, *47*(*12*), 1741-1748.

[26] Ke, F.; Zhang, P.; Xu, Y.; Lin, X.; Lin, J.; Lin, C.; Xu, J. Microwave-assisted nickel-catalyzed synthesis of benzimidazoles: ammonia as a cheap and nontoxic nitrogen source. *Synlett* **2018**, *29*(*20*), 2722-2726.

[27] Ravi, O.; Shaikh, A.; Upare, A.; Singarapu, K. K.; Bathula, S. R. Benzimidazoles from aryl alkyl ketones and 2-amino anilines by an iodine catalyzed oxidative C (CO)–C (alkyl) bond cleavage. *J. Org. Chem.* **2017**, *82*(*8*), 4422-4428.

[28] Jorgensen, J. H.; Ferraro, M. J. Antimicrobial susceptibility testing: general principles and contemporary practices. *Clin. Infect. Dis*. **1998**, 973-980.

A C G
publications

© 2023 ACG Publications