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Comparative studies on conventional and microwave-assisted synthesis of a series of 2,4-di and 2,3,4-trisubstituted benzimidazo[1,2-a] pyrimidines and their antimicrobial activities

Research Article

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Abstract: Comparative studies were performed on a series of 2,4-di and 2,3,4-trisubstituted benzimidazo[1,2-a]pyrimidines, which were synthesized with conventional and microwave heating methods. In microwave irradiation method, approximately, 95 - 97.5% of the reaction time was increased and 1 - 45% yield increase was obtained. All compounds were able to inhibit the growth of the screened microorganisms *in vitro* with MIC values between 3.9-250 μg mL^{-1}. The highest activity was expressed by compound IIId (2,4-diphenyl-benzo[4,5]imidazo[1,2-a] pyrimidine), which has the MIC value of 3.9 μg mL^{-1} and 31.2 μg mL^{-1} for *Penicillium natatum* ATCC 24791 and *E. faecalis* ATCC 29212, respectively.

Keywords: *Benzimidazo[1,2-a]pyrimidines • Fused azole heterocycles • Microwave irradiation • Antimicrobial activity*

1. Introduction

The frequency of infectious diseases in humans has increased dramatically due to multi-drug resistance [1,2]. The increasing clinical significance of drug-resistant bacterial and fungal pathogens has lent additional urgency to research for more effective agents.

Benzimidazole compounds are of significant importance in medicinal chemistry because of the wide spectrum of their biological and pharmaceutical applications. Specifically, 2-aminobenzimidazole and its derivatives, such as Astemizole, Mebendazole, Enviroxime, Carbendazim, and Benomyl [3] have been widely used in clinics. In biologically active derivatives, which possess a 2-aminobenzimidazole nucleus, the usually substituted amine group at the 2-position is condensed with heterocyclic rings. Recent studies have focused on the synthesis of these derivatives [4-7]. In addition, it is well established that benzimidazol[1,2-a] pyrimidines have demonstrated a wide spectrum of biological activities, such as antimicrobic, herbicid, bactericid, fungucid and virucid [8], immunotropic [9], antiulcer [10]. Moreover, these compounds have been evaluated for their benzodiazepine receptor binding affinity [11], interactions with DNA [12], anti-HIV [13] and antiviral [14] properties. WIN51708 and WIN62577 which possess a benzimidazol[1,2-a]pyrimidine structure, may have use as neurokinin-1 (NK1) receptor

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antagonist in schizophrenia treatment [15] and as allosteric enhancer of acethylcholine (Ach) affinity at muscarinic M_3 receptors in Alzheimer's disease [16]. Benzimidazol[1,2-a]pyrimidines were also found as anti-inflammatory, analgesic and antiamoebic compounds [17]. Therefore, preparation of benzimidazol[1,2-a] pyrimidines has attracted considerable attention in recent years.

Rather than employing conventional heating techniques to this study, we decided to employ microwave assisted organic synthesis, which has been shown to be superior in many ways to conventional heating [18,19]. The advantages of microwave assisted organic synthesis are high speed, increased yield and clear chemistry [18]. Nowadays, microwave assisted organic synthesis has become a new era in the field of synthetic chemisty [20]. Through cyclization reactions, substituted benzimidazole derivatives have been synthesized in a variety of conditions, using solvents, such as dry benzene and toluene, and ring-closing agents, such as polyphosphoric acid (PPA) and p-toluene sulfonic acid [21,22].

In our previous study, we synthesized benzimidazol[1,2-a]pyrimidine derivatives by reacting 2-aminobenzimidazole with *β*-keto esters or 1,3-alkanediones in toluene/methanol or in PPA by one-pot operation. The cytotoxicities of the compounds were then evaluated on the non-tumoral cells (F2408) and tumor cells (5RP7) [23]. Consequently, in this work, our aim was to compare the synthesis of benzimidazo[1,2-a] pyrimidine derivatives in the presence of PPA through microwave and conventional methods and optimize the auxiliary group present in the aryl ring of the title compounds, which might possess potent antimicrobial activity.

2. Experimental Procedures

2.1 Chemistry

Microwave reaction was carried out in 10 mL Erlenmeyer Pyrex flasks in a focused mono-mode microwave oven (Discover by CEM). Melting points were determined using an Electrothermal-9300 Digital Melting Points Apparatus (Electrothermal Inc., Essex, UK). The room temperature attenuated total reflection Fourier transform infrared (FT-IR ATR) spectrum of the title compounds were recorded using Varian FTS1000 FT-IR spectrometer with Diamond/ZnSe prism (4000–525 cm^{-1}; number of scans: 250; resolution: 1 cm^{-1}) in the solid.

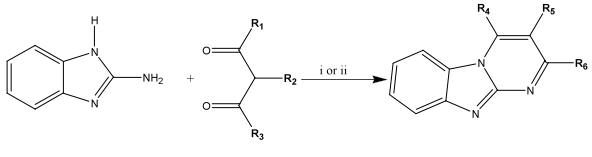
2.2 Synthesis of 2,4-di- and 2,3,4-trisubstituted benzimidazo[1,2-a]pyrimidine compounds (IIIa-g)

2.2.1 Conventional method

In the presence of PPA, equimolar amounts of 2-aminobenzimidazole (2.5 mmol) and dicarbonyl compound (2.5 mmol) were heated in oil bath at 110 - 120°C for 1 - 2 h in 50 mL round-bottomed glassware. The reaction was heated until completion as determined by TLC analysis (1:1 chloroform:methanol developing system). The mixture was allowed to cool to room temperature and then poured into 50 mL cold water. Stirring was continued for several minutes and the mixture was neutralized with sodium bicarbonate, and then the solid products were filtered off. The crude products obtained were purified by column chromatography.

2.2.2 Microwave irradiation method

2-Aminobenzimidazole (2.5 mmol), dicarbonyl compounds (2.5 mmol) and 5 g PPA were mixed in a 50 mL Erlenmeyer Pyrex flask. The Erlenmeyer Pyrex flask was placed in a microwave oven and irradiated at low power for 3 - 5 min. The reaction was heated until completion as determined by TLC analysis (1:1 chloroform:methanol developing system). The reaction mixture was poured over ice, precipitated with sodium carbonate solution, washed with water, and dried. The crude products obtained were purified by column chromatography.



II III

R_1=OCH_2Ph, OEt, Ph, CH_3; **R_2**=H, CH_3, C_2H_5; **R_3**=CH_3, Ph; **R_4**=OH, CH_3, Ph; **R_5**= H, CH_3, C_2H_5; **R_6**=CH_3, Ph

i) Toluene, Methanol or Ethanol, reflux 1 - 2 h; **ii)** PPA, 120°C 3 - 5 min.

Scheme 1. Synthesis of the target compounds.

2-Phenyl-benzo[4,5]imidazo[1,2-a]pyrimidine-4-ol (**IIIa**) [24]; Yield: 75% m.p.=316°C. (Lit. m.p. = 315-17°C, 40%). $C_{16}H_{11}N_3O$. (MW=261.29). IR u_{max} cm^{-1} (KBr): 3440 (OH), 3018 (Ar C-H), 1570 (C=C), 1254 (C-N). ^{1}H-NMR (DMSO-d_6): δ 7.23-7.38 (*m*, 2H), 7.45-7.53 (*m*, 5H), 8.01-8.15 (*m*, 2H), 8.39 (*d, J*=7.8 Hz, 1H), 12.89 (*br s*, OH).

2,3-Dimethyl-benzo[4,5]imidazo[1,2-a] pyrimidine-4-ol (**IIIb**) [24]; Yield: 90%. m.p.=320°C. (Lit. m.p.=320-321°C, 83%). $C_{12}H_{11}N_3O$. (MW=213.24). IR υ_{max} cm^{-1} (KBr): 3421 (OH), 2984-2822 (Ar C-H), 1645 (C=N), 1600-1580 (C=C). ^{1}H-NMR (DMSO-d_6): δ 2.10 (*s*, 3H), 2.30 (*s*, 3H), 7.20-8.20 (*m*, 4H), 12.89 (*br s*, OH).

2-Methyl-4-phenyl-benzo[4,5]imidazo[1,2-a] pyrimidine (**IIIc**) [24]; Yield: 85%. m.p.= 209°C. (Lit. m.p.=206-208°C, 69%) $C_{17}H_{13}N_3$. (MW=259.31). IR υ_{max} cm^{-1} (KBr): 2994 (Ar C-H), 1630 (C=N). ^{1}H-NMR (DMSO-d_6): δ 2.55 (*s*, CH_3), 6.52 (*d*, 1H), 6.86 (*s*, 1H), 7.12-7.38 (*t*, 2H), 7.60-7.20 (*m*, 5H), 7.85 (*d*, 1H).

2,4-Diphenyl-benzo[4,5]imidazo[1,2-a]pyrimidine (**IIId**) [24]; Yield: 70% m.p.=276°C. (Lit. m.p.=277°C, 55%) $C_{22}H_{15}N_3$. (MW=321.38). IR υ_{max} cm^{-1} (KBr): 3012 (Ar C-H), 1656 (C=N). ^{1}H-NMR ($CDCl_3$): δ 6.68 (*d*, 1H), 7.00-7.46 (*m*, 3H), 7.51-7.57 (*m*, 3H), 7.60-7.81 (*m*, 4H), 7.98 (*d*, 1H), 8.22-8.35 (*m*, 3H).

2,4-Dimethyl-benzo[4,5]imidazo[1,2-a] pyrimidine (**IIIe**) [24]; Yield: 98%. m.p.=240°C. (Lit. m.p.=241-242°C, 97%) $C_{12}H_{11}N_3$. (MW=197.24). IR υ_{max} cm^{-1} (KBr): 3050 (Ar C-H), 1600 (C=N). ^{1}H-NMR (DMSO-d_6): δ 2.60 (*s*, CH_3), 3.10 (*s*, CH_3), 6.90 (*s*, 1H), 7.35-7.55 (*t*, 2H), 7.78 (*d*, 1H), 8.20 (*d*, 1H).

2,3,4-Trimethyl-benzo[4,5]imidazo[1,2-a]pyrimidine (**IIIf**) [24]; Yield: 88% m.p.=203°C. (Lit. m.p.=202-203°C, 77%) $C_{13}H_{13}N_3$. (MW=211.27). IR υ_{max} cm^{-1} (KBr): 2985 (Ar C-H), 1640 (C=N). ^{1}H-NMR ($CDCl_3$): δ 2.20 (*s*, CH_3, 3H), 2.65 (*s*, CH_3, 3H), 2.95 (*s*, CH_3, 3H), 7.265-7.45 (*m*, 2H), 7.94 (*dd*, 1H), 7.95 (*dd*, 1H).

3-Ethyl-2,4-dimethyl-benzo[4,5]imidazo[1,2-a] pyrimidine (**IIIg**) [24]; Yield: 70%m.p. = 132°C. (Lit. m.p.=132-133°C, 48%) $C_{14}H_{15}N_3$. (MW=225.30). IR υ_{max} cm^{-1} (KBr): 29954 (Ar C-H), 1630 (C=N). ^{1}H-NMR (DMSO-d_6): δ 1.25 (*t*, 3H), 2.70 (*s*, 3H, CH_3), 2.70 (*q*, 2H), 3.05 (*s*, 3H, CH_3), 7.27-7.50 (*t*, 2H), 7.80 (*d*, 1H), 8.25 (*d*, 1H).

2.3 Biological Activity

2.3.1 Antimicrobial activity

Stock solutions of the synthesized compounds were prepared by dissolving in dimethyl sulfoxide and then diluting in Mueller-Hinton broth (Merck Cat. No:1.10298) and Triptic soy broth (Merck Cat. No:1.05459) to give an initial concentration of 500 µg mL^{-1}. Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities at concentrations of 500, 250, 125, 62.5, 31.25, 15.62, 7.8, 3.9 and 1.9 µg mL^{-1}. To ensure that the solvents had no effect on microbial growth, a control test was also performed containing inoculated broth supplemented with dimethyl sulfoxide at the same dilutions used for the test compounds and was determined to be inactive. The minimal inhibitory concentrations (MIC) for each compound was investigated against standard bacterial strains: *Escherichia coli* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 25853), *Staphylococcus aureus* (ATCC 25813) and *Bacillus subtilis* (ATCC 6633), *Aeromonas hydrophila* (ATCC 95080), *Acinetobacter baumanii* (ATCC 02026) and yeast-like fungi; *Candida parapsilosis* (ATCC 22019), *Candida glabrata* (ATCC 4322), *Penicillium notatum* (ATCC 24791), and *Saccharomyces cerevisae* (ATCC 9763) obtained from the Refik Saydam Hıfzısıhha Institute, Ankara, Turkey. Flucanazole and Ampicillin were used as control drugs. The observed data on the antimycotic activity of the compounds and the control drugs are given in Table 2.

2.3.2 Antibacterial assay

The cultures were prepared in Mueller-Hinton broth for all the bacteria and incubated for 24 h at 37 ± 1°C. Testing was carried out in Mueller-Hinton broth at pH 7.4 and the two-fold serial dilution technique was applied. The microorganisms were grown overnight in Mueller-Hinton broth at 37 ± 1°C and the final inoculum

Table 1. Chemical structures of all the synthesized compounds and their physical and spectral data.

No	Compound III			Conventional heating				Microwave heating			
	R_4	R_5	R_6	Yield (%)	Time (min)	M.p. (°C)	IR KBr (cm^{-1})	Yield (%)	Time (min)	M.p. (°C)	IR (cm^{-1})
IIIa	OH	H	Ph	62	120	314-315	OH: 3444	75	3	316	OH: 3440
IIIb	OH	CH_3	CH_3	83	120	320-321	OH : 3421	90	4	320	OH : 3421
IIIc	Ph	H	CH_3	69	120	206-208	C=N:1527	85	4	209	C=N:1530
IIId	Ph	H	Ph	55	120	277-278	C=N: 1652	70	5	276	C=N: 1656
IIIe	CH_3	H	CH_3	97	60	241-242	C=N: 1608	98	3	240	C=N: 1600
IIIf	CH_3	CH_3	CH_3	77	120	202-203	C=N: 1635	88	4	203	C=N: 1640
IIIg	CH_3	CH_3CH_2	CH_3	48	120	132-133	C=N: 1647-1635	70	5	132	C=N: 1630

size was 10^5 CFU mL^{-1} for the antibacterial assay. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 h at 37 ± 1°C, the lowest concentration that showed no growth of microorganism was recorded as the MIC expressed in µg mL^{-1}. These experiments were duplicated to define the MIC values.

2.3.3 Antifungal assay

The fungi were maintained in Triptic soy broth (Merck, pH 5.6) and incubated for 24 h at 37 ± 1°C. The two fold serial dilution technique was applied. The microorganisms were grown overnight in Triptic soy broth at 37 ± 1°C and the final inoculum size was 10^5 CFU mL^{-1} for the antifungal assay. A set of tubes containing only inoculated broth was kept as a control. After incubation for 48 h at 37 ± 1°C, the lowest concentration that showed no growth of fungi was recorded to represent the MIC expressed in µg mL^{-1}. Each experiment was duplicated in order to define the MIC values.

3. Result and Discussion

As part of our research program on searching for new antimicrobial agents, we would like to report the synthesis and antimicrobial activities of novel 2,4-di and 2,3,4-trisubstitue benzimidazo[1,2-a]pyrimidines. Approaches for the synthesis of benzimidazo[1,2-a] pyrimidine derivatives generally involve using harsh dehydrating reaction conditions [8,25-30]. These reactions are often carried out under high pressure and require long reaction time. Therefore, discovery of mild and practical routes for the synthesis of benzimidazo[1,2-a]pyrimidine continues to attract the attention of researchers. To accomplish this, we employed microwave irradiation, which has been extensively used for the rapid synthesis of a variety of heterocyclic compounds.

In the present work, 2,4-di and 2,3,4-trisubstitue benzimidazo[1,2-a]pyrimidines **IIIa-g** first were synthesized according to the procedure described by Meric *et al*. [23]. The representation of our microwave based synthesis method depicted in Scheme 1 was proved to be a viable alternative. The reaction time using the microwave based technique (3 - 5 min) was a 95 - 97.5% improvement over the conventional method (1 - 2 hours) for the benzimidazo[1,2-d]pyrimine derivatives. Furthermore, the microave based technique improved yields by 1 - 45%. The comparative data of the synthesized compounds was shown in Table 1. The structures and formulas of all the synthesized compounds were supported by physical and spectral data and found to be in good agreement with the target compounds.

To investigate antimicrobial activity of the synthesized compounds, MIC values of the synthesized compounds were determined for Gram-positive and Gram-negative bacteria as well as for fungi, using the standard macrodilution susceptibility test. The results of the antibacterial and antifungal screening tests were summarized in Table 2. MIC values of the synthesized compounds were compared to those of the control drugs, Fluconazol and Ampicillin. It was found that the growth of Gram-positive bacterial strains (*S. aureus*, *B. subtilis*, *E. faecalis*) was inhibited by compound **IIId**, **IIIf** and **IIIg** at the tested concentrations of 31.2-250 µg mL^{-1}. The MIC values of the compounds obtained for Gram-negative (*E.coli*, *P. aeruginosa*, *A. baumanii* and *A. hydrophila*) bacteria were found in the range of 62.5 - 250 µg mL^{-1} and for fungus (*C. parapsilosis*, *C. glabrata*, *S. cerevisiae* and *P. notatum* spp.) between 3.9 - 250 µg mL^{-1}.

Upon comparison to the activity of the known compounds, we can find that compound **IIId**, has a potent antimicrobial activity against *Penicillium natatum*

Table 2. MIC values (µg mL^{-1}) for microorganisms of the tested compounds

Microorganisms	Compounds MIC (µg mL^{-1})								
	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	A	B
S. cerevisiae ATCC 9763	0	62.5	31.2	62.5	125	62.5	15.6	3.9	-
Penicillium notatum ATCC 24791	125	125	62.5	3.9	62.5	31.2	0	125	-
C. glabrata ATCC 4322	250	0	62.5	125	125	125	250	31.2	-
C. parapsilosis ATCC 22019	125	125	125	125	62.5	62.5	125	31.2	-
E. coli ATCC 25923	250	0	125	250	125	125	0	-	15.6
S. aureus ATCC 25813	250	0	125	125	125	125	250	-	31.2
B. subtilis ATCC 6633	250	62.5	250	250	125	125	31.2	-	0.9
A. baumanii ATCC 2026	0	0	125	125	62.5	62.5	0	-	125
E. faecalis ATCC 29212	125	0	125	31.2	125	31.2	125	-	250
P. aeruginosa ATCC 25853	0	ND	125	125	125	62.5	0	-	15,6
A. hydrophila ATCC 95080	0	250	250	125	125	125	0		31.2

A: Fluconazole; B: Ampicillin; ND: Not determined

and also antibacterial activity against *E. faecalis*. Most of the compounds were effective against *Penicillium notatum*, *A. baumanii* and *E. faecalis*. When compared with Fluconazol; especially **IIId** exhibited strong activity, while **IIIa**, **IIIb** were similar to reference agent, and **IIIc**, **IIIe**, **IIIf** exhibited moderate activity against *Penicillium notatum*. Similar results were obtained with *A. baumanii*; compounds **IIIe**, **IIIf** exhibited greater activity, whereas **IIIc** and **IIId** exhibited similar activity to Ampicillin. Almost all of the compounds, except **IIIb**, were effective against *E. faecalis*. The compounds **IIId**, and **IIIf** showed strong activity, however, **IIIa**, **IIIc**, **IIIe** and **IIIg** possessed moderate activity. In addition, compound **IIIc** and **IIIg** have moderate activity against *S. cerevisae* in comparison to Fluconazole.

Taking the data obtained from the antifungal and antibacterial tests into account, we can say that entire panel of compounds tested are more active on fungi than bacteria. However, it must be noted that all tested compounds are not active against *C. glabrata*, *C. parapsilosis*, *E. coli*, *S. aureus*, *B. subtilis*, *P. aeruginosa*, *A. hydrophila*. Furthermore, it is very difficult to see any differences in the activity of compounds against Gram-positive and -negative bacteria. We were, however, encouraged by the results was that obtained from antifungal activity screening against *Penicillium notatum*.

4. Conclusions

Based on the data obtained in this study, it can be demonstrated that the synthesis of benzimidazo[1,2-a] pyrimidine derivatives using microwave-assisted synthesis reduced the reaction time and increased the yield. This study also indicates that the developed procedure for synthesis of title compounds using microwave-assisted synthesis is much simple, easier to work with, and safer compared with the reported conventional methods. Furthermore, the inhibition of different types of bacterial and fungal cells by benzimidazo[1,2-a]pyrimidine derivatives depends on certain characteristics of the compounds. This observation leads us to infer that new benzimidazo[1,2-a] pyrimidine derivatives designed to act as antimicrobial agents should include derivation of the R_4, R_5 and R_6 positions of the pyrimidine ring. These compounds were designed considering that changes in potency might be produced by substitution of aryl ring. Structure-activity relationships observations showed that substitution of position 2,4 on the fused heterocyclic system with a pyrimidine ring causes an increase in the antifungal activity compared to substitution 2,3,4 positions.

In conclusion, we have discovered a novel series of benzimidazo[1,2-a]pyrimidine derivatives with potent antimicrobial properties. Some modifications to improve the potency of the series by diversification of the position and the type of substituents are currently under investigation and will be reported in the future.

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