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Synthesis and initial biological evaluation of substituted 1-phenylamino-2-thio-4,5-dimethyl-1*H*-imidazole derivatives

Leyla Yurttaş [a,*], Murat Duran [b], Şeref Demirayak [c], Hülya Karaca Gençer [d], Yağmur Tunalı [d]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey
[b] Department of Chemistry, Faculty of Science & Letters, Eskisehir Osmangazi University, 26480 Eskisehir, Turkey
[c] Department of Pharmaceutical Chemistry, School of Pharmacy, Medipol University, 34083 Istanbul, Turkey
[d] Department of Microbiology, Faculty of Pharmacy, Anadolu University, 26470 Eskisehir, Turkey

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ABSTRACT

In this work, some new 2-[(4,5-dimethyl-1-(arylamino)-1*H*-imidazol-2-yl)thio]-1-(aryl)ethanone derivatives were synthesized and investigated for their antibacterial, antifungal and anticancer activities. Toxicity of the most effective compounds was established by performing Brine-Shrimp lethality assay. Antifungal activity of the compounds was found to be higher than antibacterial and anticancer activities of the compounds.

In general, imidazoles and azoles are important family of heterocyclic compounds with a broad interest due to their bioactive properties. Various imidazole derivatives have been reported with a broad range of bioactivities, such as antifungal, antiprotozoal, antiinflammatory, antiallergic, antihistaminic, antiulcer, antihelmintic, analgesic, antihypertensive, antineoplastic activity and neuroleptic antipsychotic and thromboxane synthetase inhibitory activity.[1–4] It is well-known that the azole scaffold is a major chemical group with antifungal activity acting as a pharmacophoric group. Imidazole derivatives (clotrimazole, econazole, miconazole, misonidazole, metranidazole, ketoconazole, itraconazole, fluconazole, fenticonazole) control fungal infections by blocking ergosterol biosynthesis which is an essential component of fungal cell wall, causing its depletion and accumulation of lanosterol and some other 14-methylsterols.[5–8] Imidazole ring is also present in some of the clinically used drug structures (asetomidate, cimetidine, omeprazole, lansoprazole, azomycine, flumazenil, thyroliberin, methimazole, pilocarpine and etomidate) acting as a pharmacophoric group or a substituent (space).[9,10] Although there is a lot of imidazole including drugs, the activity is not always directly related with the imidazole structure.

Imidazoles form the main structure of some well-known biomolecules of human organisms, such as the amino acid histidine, vit B_{12}, histamine and biotin.[11] Ribotide 4(5)-aminoimidazol-5(4)-carboxamide is an another imidazole containing biomolecule which is a key compound in the biosynthesis of natural purine component of RNA and DNA. Imidazole moiety containing compounds are also known as antimetabolite drugs.[12,13] Imidazole-containing anticancer drugs currently undergoing clinical studies are known to act by the same mechanism as mercaptopurine;[14] imidazolfurin which is evaluated for its ability to inhibit the growth of human myelogenous leukemia K562 cells;[15] thioguanine which is an antimetabolite classically used as an alternative drug in children with acute lymphoblastic leukaemia;[16] cytarabine a nucleoside antimetabolite frequently used in the treatment of hematological malignancies;[17] pentostatin, a purine nucleoside analog, which is highly efficacious in the treatment of many indolent lymphoproliferative disorders, including hairy-cell leukemia, chronic lymphocytic leukemia, and low-grade non-Hodgkin's lymphomas.[18]

Motivated by the above data and as an extension of our previous works,[19,20] we attempted to prepare a new series of compounds containing imidazole structure as the pharmacophoric group.

Forty new imidazole compounds (**1**–**40**) were synthesized by two steps. The synthesis pathway of the compounds is shown in Figure 1.[21] and all the synthesized compounds are listed in Table 1. The structures of the synthesized compounds were confirmed by means of ^{1}H and ^{13}C NMR spectra, while the molecular weights of the compounds were confirmed by molecular ions detected by

* Corresponding author. Tel.: +90 222 335 05 80/3783; fax: +90 222 335 07 50.
E-mail address: lyurttas@anadolu.edu.tr (L. Yurttaş).

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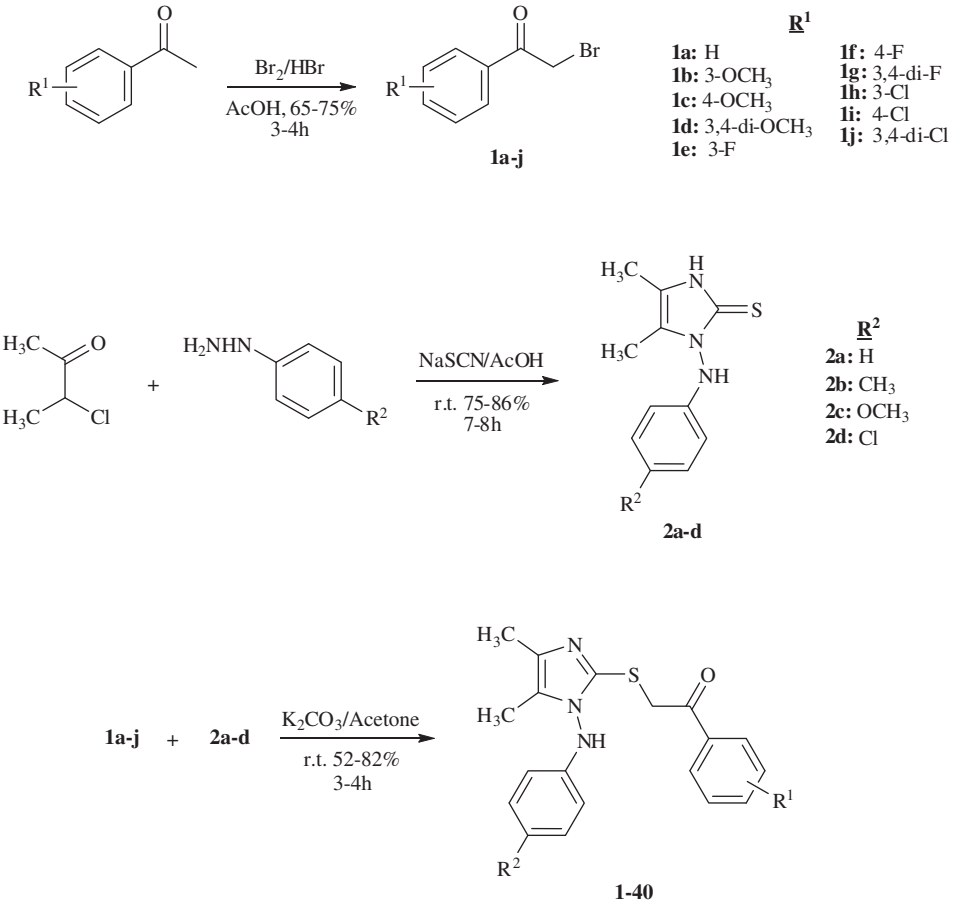

Figure 1. The synthetic protocol of the compounds, reagents and conditions (**1**–**40**).

FAB. Additionally, elemental analyses of all compounds gave satisfactory results as cited in the Supplementary data.

The synthesized new imidazole compounds were screened for in vitro antimicrobial activity against four species of Gram-positive bacteria, *Enterecoccus faecalis* (ATCC 29212), *E. faecalis* (ATCC 51299), *Staphylococcus aureus* (ATCC 25923), *Listeria monocytogenes* (ATCC 19115), and four Gram-negative bacteria, *Escherichia coli* (ATCC 25922), *E. coli* (ATCC 35218), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumonia* (ATCC 13883) and three candida species *Candida albicans* (ATCC 90028), *C. glabrata* (ATCC 90030), *C. krusei* (ATCC 6258). MIC is defined as the lowest concentration of the compounds that completely inhibited microbial growth after 24 h incubation at 35 °C. MIC values of the synthesized compounds were given along with the reference drugs chloramphenicol and ketoconazole.

As shown in Table 2, the tested imidazole derivatives exhibited varying degrees of inhibitory effects on the growth of selected microbial strains. In general, most of the compounds were more active against Gram-positive bacteria than Gram-negative bacteria. The Gram-positive bacterium *L. monocytogenes* (ATCC 19115) was found to be the most susceptible strain. Against *L. monocytogenes* (ATCC 19115), the compounds **7**, **13**, **14**, and **37** were equipotent to chloramphenicol (MIC = 50 μg/mL). Compounds **37** and **40** (MIC = 50 μg/mL) were found to be four times less active than chloramphenicol, while compounds **7** and **13** (MIC = 25 μg/mL) showed half activity to chloramphenicol against *E. faecalis* (ATCC 29212). Compounds **17**, **21** and **22** were most active against *E. faecalis* (ATCC 51255) with MIC values 200, 100, and 200 μg/mL, respectively, whereas the MIC value for chloramphenicol was 100 μg/mL. Compound **7** had the highest activity against *S. aureus* (ATCC 25923) (MIC = 100 μg/mL). The MIC values observed for Gram-negative bacteria were in a similar range, with compound **13** being half as potent as the standard against *E. coli* (ATCC 25922). Compounds **4**, **11**, **12**, **14** and **40** showed some activity against *E. coli* (ATCC 35218), similar to compounds **1** and **3** when tested against *P. aeruginosa*. Another Gram-negative bacterium, *K. pneumonia* (ATCC 13883) was not inhibited by any of the compounds reported here. Also, compounds **16** and **36** lacked antimicrobial activity against all the tested strains.

The antifungal activity of the compounds was studied against three Candida species, the most sensitive *Candida* was established as *C. krusei* (ATCC 6258) and compounds **13**, **14** and **37** were found to be the most active antifungal agent. Against *C. albicans* (ATCC 90028) compounds **13** (MIC = 25 μg/mL), **14** (MIC = 100 μg/mL) and **37** (MIC = 50 μg/mL) were determined as the most active compounds. These three compounds showed antifungal activity similar to ketoconazole with MIC value of 100 μg/mL against *C. glabrata* (ATCC 90030). Compounds **4** and **14** (MIC = 50 μg/mL) displayed same activity of ketoconazole; meanwhile compound **13** (MIC = 25 μg/mL) showed activity two times better than ketoconazole.

The imidazole compounds described herein belong to four structurally related families of derivatives that differ in the substitution pattern on the phenylamino moiety (R^2 = H, CH_3, OCH_3, and Cl). Within each of these four series, various substitution patterns on the acetophenone phenyl ring (R^1 = H, 3-OMe, 4-OMe etc.,) were introduced. A comparison of the properties induced by substitution on the aminophenyl moiety revealed that antimicrobial activities increased for the methyl- and the chloro- substitution, irrespective of electron donating/withdrawing properties of these groups. This