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Synthesis, biological screening and DFT studies of the new tetrahydropyrimidine-benzo[d]imidazol compounds

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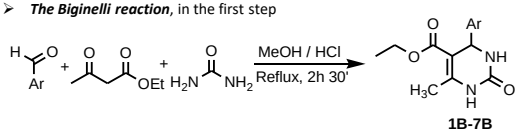
Abstract

A series of the tetrahydropyrimidines obtained through the Biginelli condensation was used to synthesize new tetrahydropyrimidine-benzo[d]imidazoles, by two types of reactions: 1. Mannich reaction; or 2. reaction with a benzimidazole halogen compound. The structures of all compounds were confirmed by ^{1}H, ^{13}C-NMR, FTIR, UV-VIS spectra and elemental analysis. All derivatives were evaluated by qualitative and quantitative methods against a panel of selected bacterial and fungal strains. A DFT analysis of molecular structure and frontier molecular orbitals HOMO-LUMO was performed using the GAMESS 2012 software. Antimicrobial activity was correlated with electronic parameters (chemical hardness, electronic chemical potential, global electrophilicity index), Mullikan atomic charges and geometric parameters of the tetrahydropyrimidines calculated with GAMESS. It has been found that the symmetry of the molecule and the presence of nucleophilic group are advantages for a high antimicrobial activity.

Synthesis of the compounds

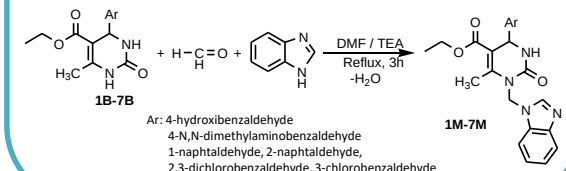
The synthesis of benzimidazolo-dihydropyrimidinone compounds by multicomponent reactions, namely:

- ***The Biginelli reaction***, in the first step



1B-7B

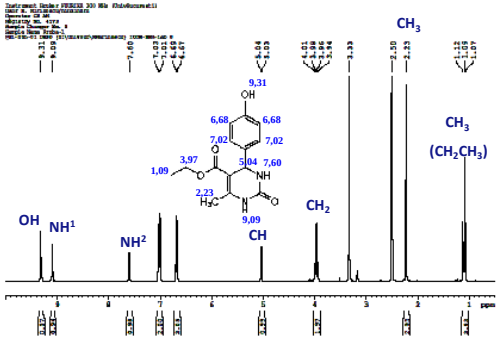
- ***The Mannich reaction***, in the second step



1B-7B → **1M-7M**

Ar: 4-hydroxibenzaldehyde
4-N,N-dimethylaminobenzaldehyde
1-naphtaldehyde, 2-naphtaldehyde,
2,3-dichlorobenzaldehyde, 3-chlorobenzaldehyde
thiophene 2-carbaldehyde

^{1}H NMR spectrum of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate 1B



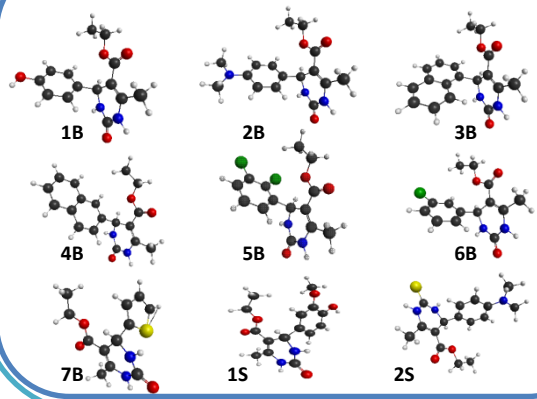
Study of the potential antimicrobial activity of dihydropyrimidinones and synthesized Mannich bases

Table 1 Inhibitory activity on microbial strains tested by qualitative method (diameter of halos in mm)

Compound/strain	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*
1B	-	6	-	6
2B	-	-	-	-
3B	-	-	-	-
4B	-	-	-	-
5B	-	-	-	7
6B	-	8	8	7
7B	-	7	-	7
1M	-	7	-	6
2M	-	-	-	-
3M	-	-	-	-
4M	-	7	-	8
5M	-	8	10	8
6M	-	7	6	7
7M	-	6	7	7

The results of qualitative screening of the compounds studied on *Escherichia coli* (left), *Pseudomonas aeruginosa* (center), *Candida albicans* (right)

DFT optimized structures of the Biginelli compounds



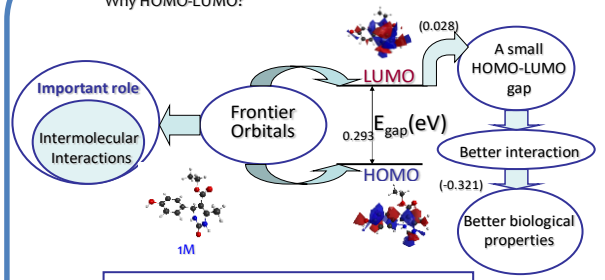
Study of the potential antimicrobial activity of dihydropyrimidinones and synthesized Mannich bases

Table 2. Quantitative screening of antimicrobial activity to determine quantitative antimicrobial activity parameters (MIC, in mg/mL) on clinically isolated bacterial strains and reference microbial strains

Comp/strain	*S. aureus*	*Escherichia coli*	*P. aeruginosa*	*C. albicans*
1B	0,0625	0,01562	0,0625	>1
2B	0,004	0,008	0,004	>1
3B	>1	0,125	>1	>1
4B	>1	1	1	>1
5B	>1	>1	1	1
6B	>1	1	1	0,002
7B	0,5	0,002	0,5	0,01562
1M	0,01562	0,01562	0,002	>1
2M	>1	1	0,0625	>1
3M	>1	>1	>1	>1
4M	1	0,125	>1	1
5M	>1	>1	>1	0,002
6M	0,002	0,002	0,004	0,002
7M	0,01562	0,004	>1	0,002
Ciprinol	0,004	0,002	0,002	0,008
DMSO	0,002	0,004	0,002	0,002

The Density Functional Theory (DFT) at M11/ at ktzvp level

Why HOMO-LUMO?



HOMO: High Occupied Molecular Orbital

LUMO: Low Unnocupied Molecular Orbital

Conclusions

- ✓ 14 Compounds, 7 Biginelli and 7 Mannich were synthesized and characterized by 1H, 13C-NMR spectra, FTIR and UV-VIS.
- ✓ The electronic and structural parameters of the benzimidazole compounds are correlated well with their antimicrobial activity.
- ✓ All compounds exhibited microbicidal and antibiofilm features, both in planktonic and adherent state, therefore they can be used as antimicrobial and antibiofilm agents.