Design, Synthesis and Biological Evaluation of New Substituted Pyrimidine Derivatives.

Ahmed M. Soliman[1]*, Heba A. Allam[2], Walaa R. Mahmoud[2], Bassem H. Naguib[1,3]

[1]Pharmaceutical Chemistry Department, Faculty of Pharmacy, The British University in Egypt, Cairo, Egypt.
[2]Department of pharmaceutical chemistry, faculty of pharmacy, Cairo University, Cairo, Egypt.
[3]Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University; Cairo, Egypt.
**Corresponding author: ahmed.soliman@bue.edu.eg*

PC-06

Introduction

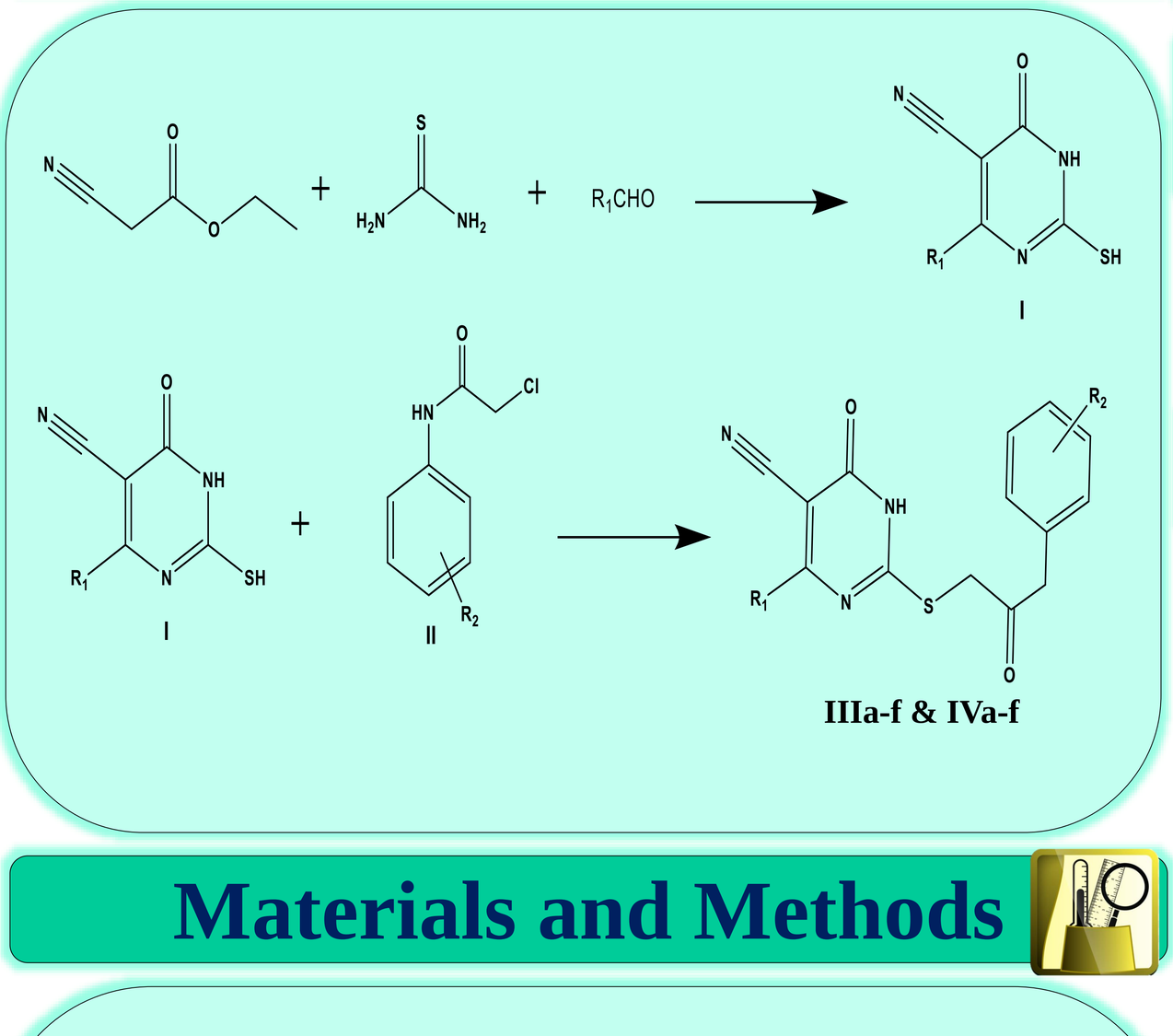
The antimicrobial resistance is a major medical threat nowadays, with low economic incentives for pharmaceutical industries and poor antibiotic use and awareness by the public, there is an increased importance for developing more potent antimicrobial agents (1).

Pyrimidines are important component in antimicrobial, antiviral and antineoplastic pharmaceutical synthesis. They have been recently reported as antimicrobial agents for their S-alkylation derivatives (2). Pyrimidine derivatives have been proved to be effective against different microorganisms including Staphylococcus aureus, Bacillus subtilis, Escherichia coli and antifungal active against Candida Albicans and Aspergillus Niger (3).

On the other hand, Pyrimidines are considered as parent scaffold for different anticancer agents as the pyrimidine skeleton is present in nature in different nucleic acids such as cytosine, thymine and uracil (4).

A series of novel substituted 5-cyano pyrimidine series III & IV were designed, synthesized and evaluated for their antibacterial activity against different microorganisms furthermore their cytotoxic activity against different cancer cell lines and targeting EGFR and CDK2 enzymes were investigated.

Experimental protocol



Materials and Methods

A- Chemistry

Compounds Ia,b were synthesized through cyclo-condensation of aromatic aldehydes, thiourea and ethyl cyanoacetate. Compounds II were synthesized by adding chloroacetyl chloride to different amines (4).

Finally, reacting compounds Ia,b and II gave the candidate compounds' series IIIa-f and IVa-f.

B- Antimicrobial assay and cytotoxic activity:

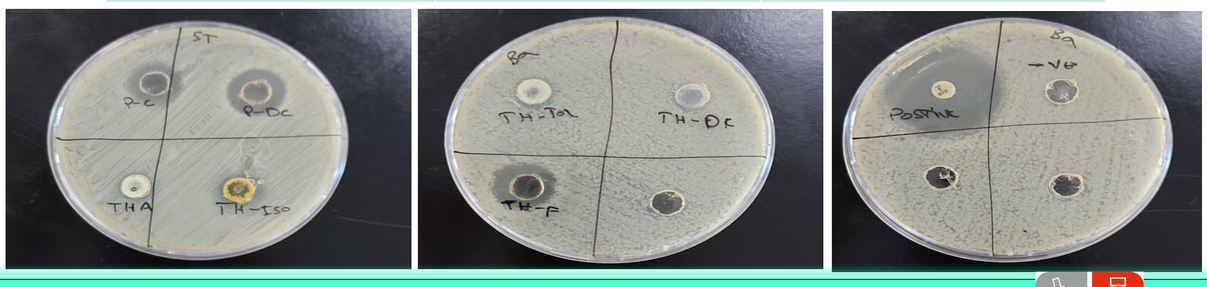
Series IIIa-f & IVa-f were tested for their antimicrobial activity through disc agar diffusion method in the British university DRD-G labs against different microorganisms as S. aureus, B. subtilis compared to reference drug amoxicillin.

Selected compounds of candidate series III were evaluated for their cytotoxic activity against 60 cell lines through the National Cancer institute (NCI-MSD,USA) screening program. compounds IIIa and IVa has been screened against EGFR and CDK2 enzymes in cytotoxicity lab in Azhar university.

Results

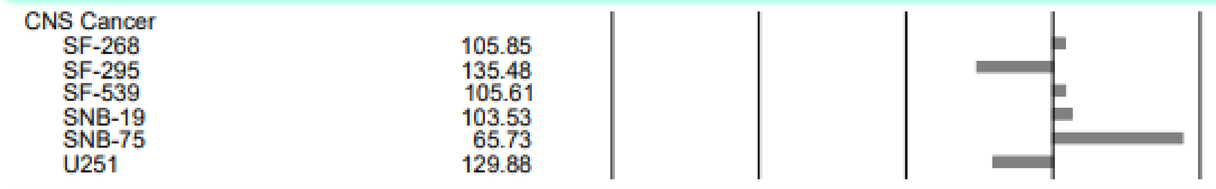
A- Antimicrobial assay

Compound	*S. aureus*	*B. subtilis*
IIIa	----------	----------
IIIb	1.5 cm	----------
IIIc	----------	----------
IIId	----------	----------
IIIe	1.6 cm	----------
IIIf	1.6 cm	1.7 cm
IVa	----------	----------
IVb	----------	----------
IVc	1.5 cm	1.5 cm
IVd	1.6 cm	1.8 cm
IVe	----------	----------
IVf	----------	----------
Amoxicillin	2.5 cm	3 cm



B- Cytotoxic activity

The preliminary screening results showed that compound IIIa has moderate cytotoxic activity against CNS cancer SNB 75 cell lines with 35% Growth inhibition



Compounds IIIa and IVa displayed enzymatic inhibition effect against EGFR and CDK2 enzymes.

Compound	*EGFR (IC50)*	Compound	*CDK2(IC50)*
IIIa	56.57±1.81 µM.	IIIa	84.68 ±2.06 µM
IVa	25.02 ±0.94 µM	IVa	63.48±2.14 µM.
Erlotinib	0.69 ±0.13 µM.	Staurosporine	0.72 ±0.16 µM

Conclusion

The preliminary studies of the antimicrobial assay distinguish promising results which needs more investigations with different methods.

The cytotoxicity report for III series candidates showed a moderate inhibition against CNS cancer SNB 75 cell lines which encourage further investigation.

The results of enzymatic inhibition for both IIIa and IVa showed weak IC50 results against EGFR and CDK2 compared to their reference drug Erlotinib and Staurosporine respectively, which indicated the need of further screening for the appropriate target.

Reference

1. Kobayashi-Matsunaga, Y. (2005). Synthesis and Characterization of a Novel Protein Tyrosine Phosphatase. *Letters in Drug Design & Discovery*.
2. Marston, H. D. (2016). Antimicrobial Resistance. *JAMA*.
3. Rizk, S. (2017). Synthesis, spectroscopic. *Journal of Molecular Structure*.
4. Synthesis and antimicrobial evaluation of some 6-aryl-5-cyano-2-thiouracil derivatives. (2011). *Acta Pharm. 61*.

Acknowledgment

NATIONAL CANCER INSTITUTE DCTD Division of Cancer Treatment & Diagnosis