FUNCTIONAL BIOLOGICALLY ACTIVE DERIVATIVES AS ANTICANCER AND ANTIBACTERIAL AGENTS BASED ON MEFENAMIC ACID

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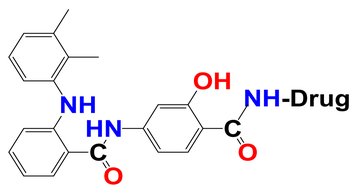
1. Introduction and Objectives

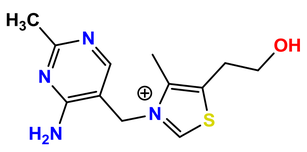
Mefenamic acid (MA) 6-[(6,4-dimethylphenyl)amino]benzoic acid, or (2-(2,3-xylyl)-2-aminobenzoic acid) is a compound belonging to the family of N-aryl anthranilic acid. It is amongst the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs); having both anti-inflammatory and analgesic activities. Three new heterocyclic compounds were prepared based on the structure of mefenamic acid. Firstly, mefenamic acid was reacted with (5-aminosalicylic acid) 5-ASA to produce a novel heterocyclic compound. In turn this new compound was used as a starting material to produce more complex pharmaceutical compounds by reacting it with three different heterocyclic compounds (thiamine, cefotaxime, and 2-amino-5-mercapto-1,3,4-thiadiazole) to produce three biologically active heterocyclic compounds (I, II, III) respectively. Spectroscopic data and microanalyses of the newly synthesized compounds confirmed their structures. The physical properties of these compounds as well as their solubility in different solvents were also investigated.

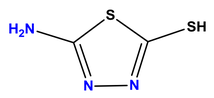
Antibacterial activities against gram-negative bacteria Escherichia Coli (E. coli) and the gram-positive bacteria Staphylococcus aureus (S. aureus) were also studied. The new compounds (I, II and III) were more active as antibacterial agents against S. aureus than Mefenamic acid itself. The activity of compounds I and II against E. coli was very close to that of the standard drug (13, 12, and 9). Meanwhile, compound III showed poor activity against E. coli (19 and 29).

The anticancer activity of the new compounds I, II and III were investigated. The results showed considerably high cytotoxic activity against the human cancer cell (breast cancer cell (MCF-7 cell line) (IC50=14.94, 23.24, and 24.98 µg/mL respectively). These findings are encouraging since I, II and III may have the potential to inhibit the diffusion of cancer cell lines.

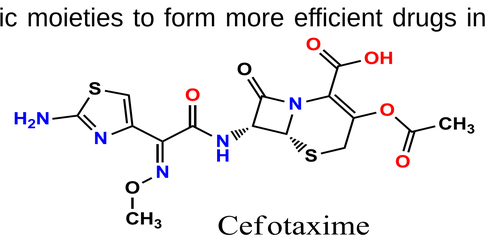
In general, this class of compounds could expand our knowledge and understanding of the effectiveness of combining two or more organic moieties to form more efficient drugs in the treatment of bacterial diseases as well as in the treatment of cancer.





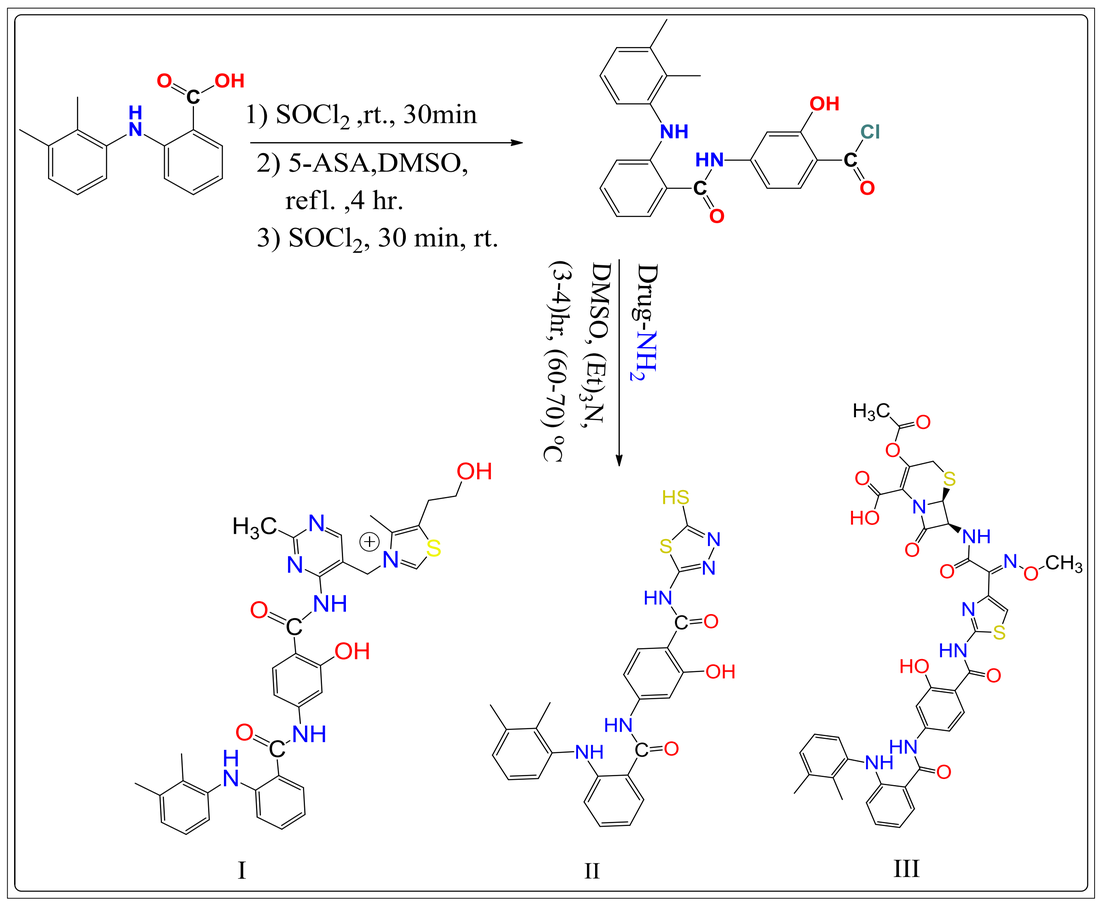


2-Amino-5-mercpto-1,3,4-thiadiazole



Cefotaxime

2. Synthesis



Scheme 1. synthesis of compounds I -III.

3. Characterization

1HNMR spectra: The ^{1}H-NMR spectra of **I**, **II and III** were carried out on a Varian INOVA 500 MHz NMR spectrometer in dimethyl sulfoxide (DMSO-d6), chemical shifts are in δ units (ppm).

- **Compound I:** 10.46 (s, 2H, 2NH sec. amide), 8.58 (s, 1H, CH, thiazole), 8.44- 6.66 (m, 10H, CH, benzene), 8.04 (s, 1H, CH, 2-pyrimidine), 5.42 (s, 2H, CH_2, methylene), 5.31 (s, 1H, OH, phenol), 4.18 (s, 1H, NH, Aromatic amine), 3.66 (qua., 2H, CH_2, methylene), 3.55 (t, 1H, OH, alcohol), 3.05 (s, 3H, CH, methyl), 2.68 (t, 2H, CH_2, methylene), 2.48; 2.41; 2.10 (s; s; s, 9H, $3CH_3$, methyl).
- **Compound II:** 13.17 (s, 1H, aromatic C-S-H), 10.46 s (s, 2H, 2N-H, 2° amide), 8.57-6.77 (m, 10H, CH, benzene), 5.43 (s, 1H, O-H, phenol), 4.16 (s, 1H, N-H, aromatic amine), 2.43; 2.10 (s; s, 6H, $2CH_3$, methyl).
- **Compound III:** 12.31 (s, 1H, COOH), 10.44; 9.64; 8.41 (s; s; d, 3H, 3N-H, sec. amide), 8.23 (s, 1H, C-H, thiazole), 8.76- 6.48 (m, 10H, C-H, benzene), 5.92; 5.07(t; d, 2H, C-H, propiolactam), 5.37 (s, 1H, O-H, phenol), 4.18 (s, 1H, N-H, aromatic amine), 3.08 (s, 2H, CH_2, methylene), 3.93; 2.41; o-2.10 (s; s; s, 9H, $3CH_3$, methyl)

3-2 CHNS Elemental Analysis

Table 3.1 CHNS Elemental Analysis

Comp.	C		H		N		S	
	Calc. %	Fou. %	Calc. %	Fou. %	Calc. %	Fou. %	Calc. %	Fou. %
I	65.47	62.5	5.66	5.44	13.47	13.11	5.14	4.25
II	58.64	58.08	4.31	3.99	14.25	13.85	13.05	12.80
III	55.56	54.78	4.16	3.90	12.26	11.98	8.02	7.89

3-3 antibacterial activity

Antibacterial activity was screened against (E. coli) and (S. aureus) bacteria using a solution of 0.5 mg from each compound and dissolved in 1 mL of DMSO by using disk-diffusion method. All new compounds (I, II, III) showed antibacterial activity toward S. aureus compared with standard treatments. Meanwhile the antibacterial activity of compounds (I and II) against E. Coli was very close to that of the standard drug, but was lower for the last compound (III).

Table 3-2 Antibacterial activity of compounds (1-3)

Inhibition Zone for *Staph.aurous* for derivative		Inhibition Zone for *Staph.aurous* for Drug alone		Inhibition Zone for *E. Coli* for derivative	Inhibition Zone for *E. Coli* of Drug alone
I	13	Thiamine	0	12	12
II	13	1,3,4-thiadiazol	0	9	10
III	19	Cefotaxime	13	29	35

3-4 Anticancer Activity

The anticancer activity of the new compounds (I, II and III) was investigated, and the results revealed highly considerable cytotoxic activity against human cell cancer (breast cell cancer) as shown in Figures (1, 2 and 3). The findings reveal that (I, II and III) have the potential to inhibit the diffusion of cancer cell lines and that this ability is concentration-dependent.

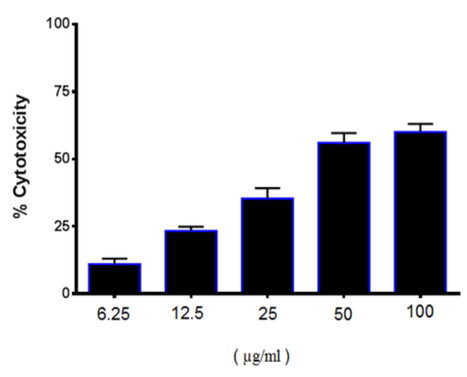


Figure 1. Cytotoxic effect of I IC_{50}=14.94 µg/mL

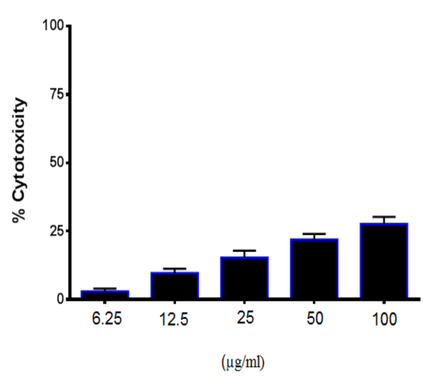


Figure 2. Cytotoxic effect of II. IC_{50}=23.24 µg/mL

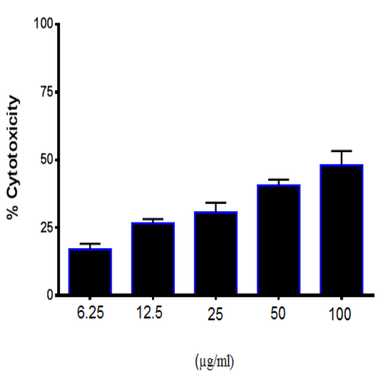


Figure 3. Cytotoxic effect of III IC_{50}=24.98 µg/mL

4- Conclusion

The three prepared compounds have promising properties that enable them to act as anti-cancer agents. The prepared compounds have an inhibitory behavior for the proliferation and growth of Gram-positive Staphylococcus aureus bacteria.

References

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