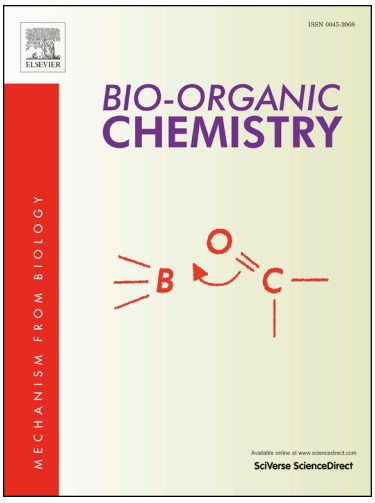

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PII: S0045-2068(18)30566-2
DOI: https://doi.org/10.1016/j.bioorg.2018.08.031
Reference: YBIOO 2488

To appear in: *Bioorganic Chemistry*

Received Date: 10 June 2018
Revised Date: 14 August 2018
Accepted Date: 26 August 2018

Please cite this article as: N.G. Mohamed, M.M. Sheha, H.Y. Hassan, L.J.M. Abdel-Hafez, F.A. Omar, Synthesis, Antimicrobial activity and Molecular Modeling Study of 3-(5-Amino-(*2H*)-1,2,4-triazol-3-yl]-naphthyridinones as Potential DNA-gyrase inhibitors, *Bioorganic Chemistry* (2018), doi: https://doi.org/10.1016/j.bioorg.2018.08.031

Synthesis, Antimicrobial activity and Molecular Modeling Study of 3-(5-Amino-(*2H)*-1,2,4-triazol-3-yl]-naphthyridinones as Potential DNA-gyrase inhibitors

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Abstract

Four series of triazolylnaphthyridinone derivatives were synthesized as structural surrogates of nalidixic acid. The targeted derivatives involve: 3-(5-acylamino-2H-1,2,4-triazol-3-yl)-naphtyridin-4-ones **6(a-e)**; 3-(5-benzylidineamino-2H-1,2,4-triazol-3-yl)-naphthyridin-4-ones **8(a-g)** and their 6-bromonaphthyridin-4-one analogs **7(a-e)**; **9(a-g).** The synthesized compounds were evaluated *In vitro* for their antimicrobial activity against selected resistant strains of *G+ve, G-ve*, and *Mycobacterium phlei*. The results revealed remarkable selectivity, of the tested compounds, against *Bacillus subtilis* and *Aggregati-bacter actinomycetemcomitans,* which are resistant to nalidixic acid. The growth inhibition zones were ranging from 20 – 40 *mm* at 10 *mg/ml* and the respective *MIC*-values ~ *3.68–6.3 µM*. The results illustrate that the 6-bromo derivatives **7(a-e)** and **9(a-g)** were more potent than the non-brominated counterparts **6(a-e)** and **8(a-e)** respectively. Inhibition of E. coli *DNA-gyrase* supercoiling activity is also evaluated. The 5-(4-methoxybanzamido)-triazolyl-6-bromonaphthyridinone **(7e)** exhibits IC_{50} = 1.94 *ug/ml*, which is comparable to that of nalidixic acid (IC_{50}:1.74 *ug/ml*). In addition, the most prominent IC_{50}-values are displayed by: (**7a;** IC_{50}:2.77 *µg/ml*); (**8g**; IC_{50}:3.78 *µg/ml*); and **(9d;** IC_{50}*:* 3.21 *µg/ml*). Molecular docking to the active site of *DNA–gyrase* cleavage complex of *Acinetobacter baumannii* (PDB code: 2xkk) co-crystallized with moxifloxacin revealed similar binding modes in addition to new interactions. Assessment of drug-likeness characteristics illustrate that the synthesized compounds showed agreement to Lipinski's and Veper's parameters. The study could offer an exceptional framework that may lead to the discovery of new potent antimicrobial agents.