Industrial Engineering Journal
ISSN: 0970-2555
Volume : 52, Issue 11, No. 2, November : 2023

SYNTHESIS OF NEW PYRIMIDINE DERIVATIVES AND THEIR DIVERSE POTENTIAL IN DRUG DEVELOPMENT AND MEDICINE

Ranvir Kumar[1] Department of Chemistry, Rameshwar College, B.R.A. Bihar University, Muzaffarpur, Bihar, India
Dr. Avinash Kumar Jha[2] Department of Chemistry, Rameshawar Mahavidyalya, B.R.A.B.U, Muzaffarpur, Bihar, India

Abstract- Changes in therapeutic targets lead to the difficult and more concerning phenomena of anticancer treatment resistance. Even if the development of new chemotherapeutic agents is moving quickly, further study and treatment planning are necessary due to the growing frequency of this problem. We recently reported on RDS 344, a novel amino pyrimidine molecule, as a possible novel anticancer agent. Techniques: Here, we present the creation, synthesis, and anti-proliferative properties of novel amino pyrimidine derivatives that are structurally connected to RDS 3442. These derivatives were produced by substituting on the 2-aniline ring of our hit or at position 6 of the pyrimidine core. Several tumor forms, including glioblastoma, triple-negative breast cancer, oral squamous cell carcinomas, colon cancer, and human dermal fibroblasts selected as a control of normal cells, were used to assess the capacity to limit cell proliferation.
Keywords— *Synthesis of new Pyrimidine Derivatives, Diverse Potential, Drug Development, Medicine.*

INTRODUCTION

Since the United States declared the "war on cancer" in 1971, numerous scientists and pharmaceutical corporations have worked to find a cure for the disease during the past fifty years. Many of the novel molecules being developed for the treatment of cancer do not meet the expectations of fully curing cancer, despite the fact that this development is still ongoing, particularly in the case of anticancer medications. In fact, the complexity and heterogeneity of cancer continue to be linked to high rates of morbidity and death and the main obstacle to finding a solution for the disease is still medication resistance. Resistance to treatment with anticancer drugs depends on several factors including individual variations in patients and somatic cell genetic differences in tumors, even those from the same tissue of origin. Principal mechanisms of drug resistance in cancer chemotherapy may include one or more altered energy-dependent membrane transporters that detect and eject anticancer drugs from cells (for example, the overexpression of the P-glycoprotein), altered target enzyme, decreased drug activation, increased drug degradation due to altered expression of drug-metabolizing enzymes, drug inactivation due to conjugation with increased glutathione, subcellular redistribution, drug interaction, enhanced DNA repair and failure to apoptosis as a result of mutated cell cycle proteins such as p53. For the above reasons, standard approaches are not enough to treat some tumor types, such as glioblastoma, triple-negative breast cancer, oral squamous cell carcinoma, lung and colon cancer. Among them, a major challenge is the treatment of head and neck squamous cell carcinomas (HNSCCs), including the tongue squamous cell carcinoma and pharynx squamous cell carcinoma. The group of HNSCC is the sixth most frequent cancer worldwide, with a global incidence of more than half a million annual cases and about 65,000 of new cases only in the United States in 2019, and it is highly resistant to a wide range of structurally different drugs with diverse cytotoxic mechanisms of action. Indeed, the efficacy of pharmacological treatment is limited as patients acquire drug resistance, showing poor response to chemotherapeutics and therefore pushing physicians to use radiations and surgical interventions that often lead to a permanent impairment of oral functions. Thus, despite many drugs have demonstrated promising ability, the development of new therapeutic options is still urgently needed. Recently, we synthesized

Industrial Engineering Journal
ISSN: 0970-2555
Volume : 52, Issue 11, No. 2, November : 2023

and reported a new aminopyrimidine compound as a potential innovative anticancer agent namely RDS 3442 (1a, Figure 1). Notably, this compound was evaluated on three different human cancer types chosen on the basis of their unsatisfactory therapeutic strategies and poor prognosis: glioblastoma multiforme, triple-negative breast cancer and colon adenocarcinoma. We demonstrated that compound 1a is a potent inhibitor of replication, a negative regulator of cell cycle progression and an inducer of apoptosis for human cancer cells of different histotypes. Indeed, compound 1a led to the upregulation of p21 and p27 and blockage of the cell cycle at G0/G1 at lower concentration (20 μM), while it induced apoptosis at higher concentrations (30–50 μM).

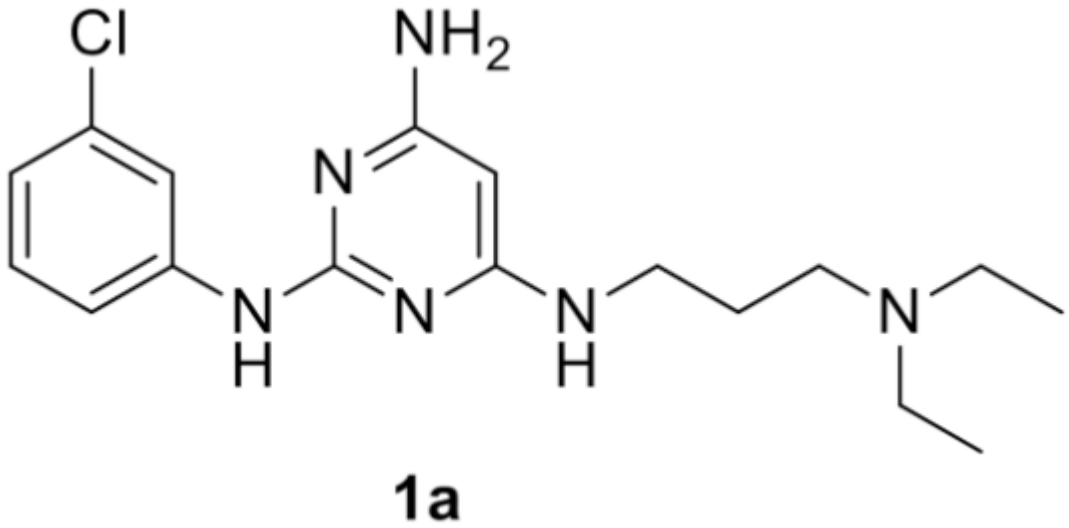

Figure 1- Structure of our previously reported anticancer aminopyrimidine derivative RDS 3442 (1a)

PYRIDINE DERIVATIVES AS ANTICANCER AGENTS (2019–2021)

Numerous synthetic drugs are good chemotherapeutic agents. Pyridines constitute the class of nitrogenous heterocycles which undergo different chemical synthesis routes for generation of novel compounds demonstrating anticancer/anti-tumor properties. There are many synthetic derivatives prepared for the pyridines, however, in this review we will discuss the novel ones past 3 years i.e. between the years 2019–2021 which have been characterized in vitro or through in silico studies.

Year	Author	Compound	In vitro studies	In silico studies/Possible targets
2019	Bathula et al.	11-(1-Benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline	Cytotoxic, anti-clonogenic; G_0/G_1 cell cycle phase inhibitor	EGFR kinase
2019	Fayed et al.	Coumarin-pyridine/fused pyridine hybrids	Growth inhibitors at G_2/M phase, apoptotic cell death	
2020	Jian et al	Pyrazolo[3,4-b]pyridine-bridged derivatives of combretastatin A-4 acquiring 3,4,5-trimethoxylphenyl groups	nti-proliferative actions, G_2/M stage arrest	Tubulin polymerization inhibition
2020	Behbehani et al.	Substituted 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine and 5,6-dihydrobenzo[h]quinoline systems	Cytotoxicity	
2021	Zwergel et al.	za-analogues like the regioisomers from the N-hydroxy-3-(4-(2-phenylbutanoyl)amino)phenyl)acrylamide comprising pyridine nucleus	G_2/M stage inhibition	HDACs
2021	Hassan et al.	Pyridine and fused pyridine derivatives	Anti-tumor action	

Table 1- Synthetic pyridine derivatives with anticancer activity

LITERATURE REVIEW

Bathula et al. (2019) reported newly designed Pyrido[2,1-b] quinazoline fused derivatives having good medicinal properties. These designed compounds were tested for cytotoxic actions via the in vitro studies countering to an array of malignant cell lines including NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145. Compound **1 i.e.** 1-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoli exhibited the highest cytotoxic action over the lung cancer cell lines, A549 and NCI-H460. In addition, the same compound was demonstrated to have a potent anti-clonogenic impact on lung cancer cells. Under flow cytometry this unique compound was observed to block the G_0/G_1 cell cycle phase in the A549 malignant cell lines. Molecular docking studies of the compounds **2a** and **2b** with erlotinib as control for predicting the binding to the EGFR kinase were also performed. The compounds under investigation showed the analogous interactions in comparison to erlotinib. The study concluded that the compound 11-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline could serve as a lead anticancer agent.

On the basis of the established anticancer properties of thieno[2,3-b] pyridines Hassan et al. (2019) planned to synthesize new thieno[2,3-b]pyridine analogues assimilating diverse biologically active heterocycles via several chemical reactions. Total 44 compounds were synthesized, and these newly synthesized derivatives were assayed for anti-tumor activity over HepG-2 and MCF-7 cell lines with respect to doxorubicin (standard anticancer drug). Outcomes of the study suggested that out of the total 44 compounds, compound 1, 2, 3 and 4 acquired highest potency over both the cell

lines and compound **2** was found to be more potent than doxorubicin standard against HepG-2 cell line.

New series of 16 coumarin-pyridine/fused pyridine hybrids was created by Fayed and coworkers (Fayed et al., 2019) and tested for the anticancer property over human cancer cell lines HCT-116, MCF-7, A549, and HepG-2. Out of the 16 compounds in total, compound **1, 2** and **3** were found to be most potent growth inhibitors against cell line MCF-7 detaining the cell cycle in the G_2/M phase and subsequently apoptotic cell death. In coherence with these results, caspase-3 activity in MCF-7 cells was also evaluated. The results designated the significant augmentation of caspase-3 activity by compounds **1, 2,** and **3** in comparison to the control group. Additionally, binding affinity of all the three compounds for caspase-3 was established by docking analysis using MOE software (MOE 2008.10). Altogether, it was deciphered that these coumarin derivatives might prove to be promising anti-proliferative agents.

Jian et al. (2020) reported synthesis of 26 new pyrazolo[3,4-*b*]pyridine-bridged derivatives of combretastatin A-4 acquiring 3,4,5-trimethoxylphenyl groups, and assessed their tubulin polymerization inhibitory and anti-proliferative actions. Initial biological assessment established that few of the candidate compounds showed considerable anti-proliferative action countering four varying cell lines comprising MDA-MB-231, MCF-7, Kyse150 and HeLa. Compound **1** proved to be the highly potent pyridine derivative as it induced HeLa cells arrest in the G_2/M stage *via* dose dependent manner. Molecular modeling investigation suggested that analogue **1** apparently dwells in the colchicine spot of tubulin. The preliminary outcomes are indicative in proving 3,4,5-trimethoxyphenyl substituted pyrazolo[3,4-*b*]pyridine to be a competent scaffold intended in developing effective tubulin barrier as antineoplastic agents.

Murugavel et al. (2019) presented in their work, the computational quantum compound investigation in addition to the biological assessment of a newly synthesized heterocyclic sulfur thiophene analogue including pyridine and 1,2,3-triazole components *viz.* BTPT [2-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-6-methoxy-4-(thiophen-2-yl) pyridine]. Drug resemblance factors of BTPT were searched *via in silico* medicinal ADMET attributes evaluation. Human topoisomerase IIα targeting ATP binding site was used to perform molecular docking studies. MTT assay was conducted over the three human malignant cell lines PC-3, A549 and MDAMB-231 for the *in vitro* cytotoxicity test of BTPT/doxorubicin. The lead compound BTPT showed considerable cytotoxicity against MDAMB-231 (breast cancer cell), mild activity with A-549 (human lung cancer cell) and least inhibition with PC-3 (human prostate cancer cell) in comparison to the known cancer drug doxorubicin. It was inferred that BTPT could serve as a potent candidate for anticancer drug.

CLASSIFICATION OF PYRIDINE DERIVATIVES BASED ON THE BIOLOGICAL ACTION

(i)Synthetic pyridine derivatives involved in cell cycle regulation- Bathula et al. (2019) reported newly designed Pyrido[2,1-b] quinazoline fused derivatives having good medicinal properties. These designed compounds were tested for cytotoxic actions via the in vitro studies countering to an array of malignant cell lines including NCI-H460, A549, HCT-15, HT-29, HFL, and DU-145. Compound **1 i.e.** 1-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoli exhibited the highest cytotoxic action over the lung cancer cell lines, A549 and NCI-H460. In addition, the same compound was demonstrated to have a potent anti-clonogenic impact on lung cancer cells. Under flow cytometry this unique compound was observed to block the G_0/G_1 cell cycle phase in the A549 malignant cell lines. Molecular docking studies of the compounds **2a** and **2b** with erlotinib as control for predicting the binding to the EGFR kinase were also performed. The compounds under investigation showed the analogous interactions in comparison to erlotinib. The study concluded that the compound 11-(1-benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline could serve as a lead anticancer agent.

(ii) ynthetic pyridine derivatives acquiring anti-tumorigenic properties- On the basis of the established anticancer properties of thieno[2,3-b] pyridines Hassan et al. (2019) planned to synthesize new thieno[2,3-b]pyridine analogues assimilating diverse biologically active heterocycles via several chemical reactions. Total 44 compounds were synthesized, and these newly synthesized derivatives were assayed for anti-tumor activity over HepG-2 and MCF-7 cell lines with respect to doxorubicin (standard anticancer drug). Outcomes of the study suggested that out of the total 44 compounds, compound **1, 2, 3** and **4** acquired highest potency over both the cell lines and compound **2** was found to be more potent than doxorubicin standard against HepG-2 cell line.

(iii) Synthetic pyridine derivatives exhibiting cytotoxicity- A novel synthetic platform has been developed by Behbehani et al. (2020) utilizing a new, convenient and efficient procedure to produce markedly substituted 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine systems. The initial cytotoxicity examination of these synthesized 10 pyridine derivatives were performed towards human malignant cell lines viz. A549 (lung cancer) and MCF-7 (breast cancer) by employing the MTT colorimetric test. The results revealed that the all 10 pyridine derivatives are potent cytotoxic agents as tested on MCF-7 and A549 malignant cells. Outcome of this study assures the possibility of the aforementioned compounds to serve as an appropriate primary source for future research in anticancer drug designing.

BIOLOGICAL TARGETS OF PYRIMIDINE DERIVATIVES

Pyrimidines have also been shown to have anticancer properties by inhibiting a variety of targets including the tyrosine kinase of the Epidermal Growth Factor Receptor (EGFR), Janus Kinase (JAK), Mitotic Checkpoint Protein Kinase (Mps1), carbonic anhydrase, and MDM-2 (Kilic-Kurt et al., 2018). They have a high selectivity for CDK9 over other CDKs and can activate caspase 3, decrease Mcl-1 anti-apoptotic protein levels, and induce cancer cell death (Shao et al., 2013). We used a reverse virtual screening (RVS) approach to associate protein targets to our initial set's most active **c**ompounds 3d**,** 3h**,** 3e**,** and 3f. RVS proceeded through several steps, which we implemented in a semiautomated procedure (Fig. 2 and Methods section for details). First, we scanned PharmMapper to search PDB codes of proteins featuring active sites compatible with each of the four query compounds. The compatibility criterion is based on the complementarity between the pharmacophoric features of ligand and protein. The four resulting rankings of proteins are annotated with the name, classification and diseases associated with each protein. More than 200 entries were obtained for each active compound, which corresponded to 379 unique PDB codes. Next, we assumed that the four active compounds would bind a common target due to their high similarity.

Industrial Engineering Journal
ISSN: 0970-2555
Volume : 52, Issue 11, No. 2, November : 2023

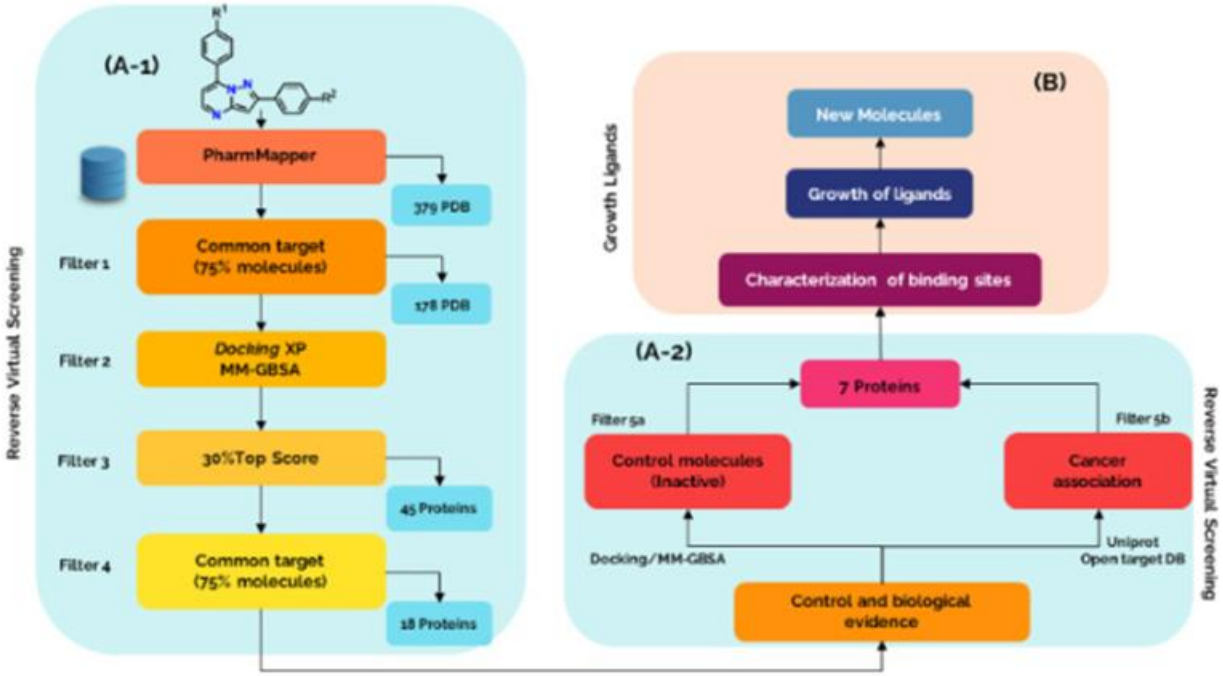

Figure 2-Workflow of the reverse virtual screening strategy used in this work (A-1 and A-2). The targets so identified may be used for the design of new derivatives employing a structure-based approach (B)

CONCLUSION

Recent developments in the field of cancer therapy indicate that pyridine and pyrimidine analogues present promising prospects. Pyridin and pyrimidine's hetrocyclic nitrogen rings are widely used in medication research and development due to their ability to coordinate and their role in a variety of biological processes. Apart from the broad range of chemical alteration, the analogues of pyridine and pyrimidine have exhibited biological action against a diverse array of cancer targets. ROS production, cytotoxicity, apoptosis, and cell cycle arrest are some of the different ways that anticancer activity is mediated. As a first stage, the strategy of mimicking natural sources was applied to create pyridine/pyrimidine analogs that exhibit anti-tumor properties by interfering with the natural source's ability to engage with specific enzymes or receptors. To obtain a variety of pyridine/pyrimidine analogues and complexes, the exchange strategy involving various rings and moieties on the central configuration was used. The coupling of accessible bioactive to pyridine/pyrimidine basic configurations was done in light of the polypharmacological trend in order to create novel compounds with a variety of chemotherapeutic applications.

REFERENCES

[1] Hanahan, D. Rethinking the war on cancer. Lancet 2014, 383, 558–563.
[2] Jo, Y.; Choi, N.; Kim, K.; Koo, H.J.; Choi, J.; Kim, H.N. Chemoresistance of cancer cells: Requirements of tumor microenvironment-mimicking in vitro models in anti-cancer drug development. Theranostics 2018, 8, 5259–5275.
[3] López-Verdín, S.; Lavalle-Carrasco, J.; Carreón-Burciaga, R.G.; Serafín-Higuera, N.; Molina-Frechero, N.; González-González, R.; Bologna-Molina, R. Molecular markers of anticancer drug resistance in head and neck squamous cell carcinoma: A literature review. Cancers 2018, 10, 376
[4] Vasan, N.; Baselga, J.; Hyman, D.M. A view on drug resistance in cancer. Nature 2019, 575, 299–309.
[5] Luqmani, Y.A. Mechanisms of drug resistance in cancer chemotherapy. Med. Princ. Pract. 2005, 14, 35–48.

[6] Noch, E.K.; Ramakrishna, R.; Magge, R. Challenges in the treatment of glioblastoma: Multisystem mechanisms of therapeutic resistance. World Neurosurg. 2018, 116, 505–517.
[7] Nedeljković, M.; Damjanović, A. Mechanisms of chemotherapy resistance in triple-negative breast cancer-How we can rise to the challenge. Cells 2019, 8, 957.
[8] Nurwidya, F.; Takahashi, F.; Murakami, A.; Takahashi, K. Epithelial mesenchymal transition in drug resistance and metastasis of lung cancer. Cancer Res. Treat. 2012, 44, 151–156.
[9] Van der Jeught, K.; Xu, H.C.; Li, Y.J.; Lu, X.B.; Ji, G. Drug resistance and new therapies in colorectal cancer. World J. Gastroenterol. 2018, 24, 3834–3848.
[10] Kim, Y.J.; Kim, J.H. Increasing incidence and improving survival of oral tongue squamous cell carcinoma. Sci. Rep. 2020, 10, 7877.
[11] Robert, B.M.; Dakshinamoorthy, M.; Ganapathyagraharam Ramamoorthy, B.; Dhandapani, M.; Thangaiyan, R.; Muthusamy, G.; Madhavan Nirmal, R.; Rajendra Prasad, N. Predicting tumor sensitivity to chemotherapeutic drugs in oral squamous cell carcinoma patients. Sci. Rep. 2018, 8, 15545.
[12] Da Silva, S.D.; Hier, M.; Mlynarek, A.; Kowalski, L.P.; Alaoui-Jamali, M.A. Recurrent oral cancer: Current and emerging therapeutic approaches. Front. Pharmacol. 2012, 3, 149.
[13] Taglieri, L.; Saccoliti, F.; Nicolai, A.; Peruzzi, G.; Madia, V.N.; Tudino, V.; Messore, A.; Di Santo, R.; Artico, M.; Taurone, S.; et al. Discovery of a pyrimidine compound endowed with antitumor activity. Invest. New Drugs 2020, 38, 39–49.
[14] Jain, K.K. A critical overview of targeted therapies for glioblastoma. Front. Oncol. 2018, 8, 419.
[15] Colotti, G.; Saccoliti, F.; Gramiccia, M.; Di Muccio, T.; Prakash, J.; Yadav, S.; Dubey, V.K.; Vistoli, G.; Battista, T.; Mocci, S.; et al. Structure-guided approach to identify a novel class of anti-leishmaniasis diaryl sulfide compounds targeting the trypanothione metabolism. Amino acids 2020, 52, 247–259.
[16] Saccoliti, F.; Angiulli, G.; Pupo, G.; Pescatori, L.; Madia, V.N.; Messore, A.; Colotti, G.; Fiorillo, A.; Scipione, L.; Gramiccia, M.; et al. Inhibition of Leishmania infantum trypanothione reductase by diaryl sulfide derivatives. J. Enzyme Inhib. Med. Chem. 2017, 32, 304–310.
[17] Taglieri, L.; Nardo, T.; Vicinanza, R.; Ross, J.M.; Scarpa, S.; Coppotelli, G. Thyroid hormone regulates fibronectin expression through the activation of hypoxia inducible factor 1. Biochem. Biophys. Res. Commun. 2017, 493, 1304–1310.
[18] S.F. Sousa, P.A. Fernandes, M.J. Ramos, Protein-ligand docking: current status and future challenges
Proteins Struct. Funct. Genet., 65 (2006), pp. 15-26
[19] S. Franco-Ulloa, G. La Sala, G. Pietro Miscione, M. De Vivo, Novel bacterial topoisomerase inhibitors exploit Asp83 and the intrinsic flexibility of the DNA gyrase binding site, Int. J. Mol. Sci., 19 (2018), p. 453