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Synthesis and Molecular Docking of Novel 1,3-oxazole and 1,3-thiazole Derivatives of Ciprofloxacin for their Anticancer Activity

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Abstract

In this study, cioprofloxacin served as the starting point for the preparation of the new compounds. It underwent a ring expansion to form 1,3-oxazole and 1,3-thiazole, both of which have five atoms. First, ciprofloxacin was reacted with thionylchloride and absolute ethanol to produce compound [2]. Next, compound [2] was reacted with urea to produce compound [3A], and finally, compound [2] was reacted with thiourea to produce compound [3B]. Finally, compound [3B] was reacted with 4-phenylphenacylbromide in the presence of absolute ethanol to produce a 1,3- Compounds were synthesised, their purities were evaluated using TLC, and their structures were determined using FT-IR, 1H-NMR, and 13C-NMR spectroscopy. Target molecule binding interactions with the 2BIP receptor were analysed using molecular docking.

Key words: Ciprofloxacin, 1,3-oxazole, 1,3-thiazole, molecular docking, Gastric cancer

Introduction

As a second-generation fluoroquinolone, Bayer's ciprofloxacin (fig 1, chemical name 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4dihydroquinoli-ne -3-carboxylic acid) has remarkable anti-microbial efficacy and outstanding pharmacokinetic features.(1).

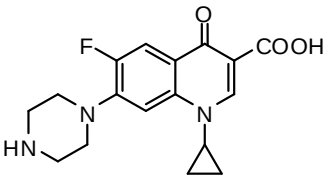


Fig.1 chemical structure of ciprofloxacin

Worldwide, cancer ranks among the leading killers (2). Traditional cancer chemotherapy is ineffective because it harms healthy cells and causes cancer cells to become resistant to drugs. (3). Heterocyclic compounds having oxazole, thiazole, or pyrazole functionalities are effective drug design scaffolds because of their branching conjugated systems. (4-7).

The 1,3-oxazole molecule is a five-membered ring with three-carbon, one-nitrogen, and one-oxygen atoms. [8].

The 1,3-oxazole moiety is promising for use in the development of new biologically active medicines with anticancer properties[9-12], Anti-microbial[13], Antihelmenthic[14], Antipathogenic[8], analgesics[15], Antiinflam-matory[16] and Antifungal [17].

Sulphur and nitrogen are found in 1,3-thiazole, a heterocyclic molecule with a carbon atom separating them. [18]. The N and S heteroatoms in heterocyclic compounds have significant biological activity. [19]. 1,3-Thiazole holds significant prominence within the realm of heterocyclic chemistry, as well as in the fields of drug design and detection. [20] such as Antimicrobial[21, 22], Antitumor[23]and antioxidant activity[24].

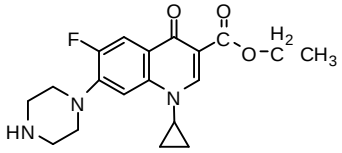
Materials and Methods

The ciprofloxacin used in this synthesis was acquired from Energy Chemical, and all other compounds used were of the highest analytical quality. The synthesised derivatives' final melting points were measured without correction. All quoted melting points were measured with a Gallen kamp equipment. After exposing the chromatograms to iodine vapour, single round spots appeared, indicating the purity and the completion of the reactions, when the intermediates and final products were separated using thin layer chromatography (TLC) on aluminium precoated silica gel 60 F254 sheets (Merck). A Shimadzu FT-IR spectrophotometer was used to acquire infrared spectra from a KBr disc. The BRUKER model Ultrashield spectro-photometer (500 MHz) was utilised to acquire the ^{1}HNMR and ^{13}C-NMR spectra and DMSO-d_6 was used as the solvent.

Chemical synthesis of ethyl ciprofloxacin (2)[25] A precisely metered quantity of ciprofloxacin (1) (4g, 0.012 mol) was added to (10 ml) thionyl chloride, which was then refluxed for five hours with (2-3) drops of DMF.

After chilling the mixture, 15 ml of abs was added to it. EtOH was then chilled at room temperature, and the resulting solid was filtered and recrystallized from 70% EtOH.Brown powder, yield = 80%, m.p. (115-117 °C). Rf = 0.78, IR (KBr disc), (ύ cm^{-1}): 3182.55 (NH) str., 3028.24 Aromatic (C-H) str., 2924.09 Aliphatic (C-H), 1651.07 (C=O) str. ester, 1203.58 (C-O-C)str.

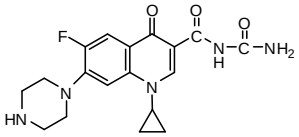
The ^{13}C-NMR spectrum of compound [2] a carbon atom in the carbonyl ester group can be linked to the signal at 166.29 ppm, but the signal at 172.03 ppm cannot. At 164.73 ppm, the carbon atom signal for the C=N group in the 1,2,3.6-tetrahydropyrazine ring was detected. Many signals were also observed in the range of (151.81-94.62) ppm, which is associated with the aromatic car-bon atoms of the quinoline ring. For OCH2, the aliphatic carbon atom causes a signal at 60 ppm. However, 1,2,3,6-tetrahydropyrazine showed two signals at -46.83 ppm and -43.01 ppm to aliphatic carbon atoms for -CH2-N. At 35.29 and 14.70 ppm, respectively, the carbon atoms of the -CH- and -CH2- groups in cyclopropyl make their appearance.



Chemical synthesis of N-carbamoyl-1-cyclopropyl-7-(5,6-dihydropyrazin-1(2H)-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (3A)[26]

In abs. EtOH (20 ml), urea (0.08 g, 0.001 mol) was combined with ethyl ciprofloxacin (2) (0.5 g, 0.001 mol). After 7 hours of refluxing, the mixture passed TLC. The solid product was obtained after cooling and filtering the mixture, and it was subsequently recrystallized from 70% EtOH to produce compound (3A).

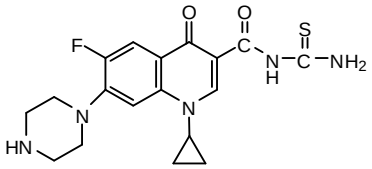
Brown powder, yield = 65%, m.p. (159-161°C). Rf = 0.84, IR (KBr disc), (ύ cm^{-1}): 3417.86 and 3321.42 (NH_2) str., 3194.12 (NH) str., 2958.80 and 2843.07 Aliphatic (C-H), 1670.35 (C=O) str. Amide.



Chemical synthesis N-carbamothioyl-1-cyclopropyl-7-(5,6-dihydropyrazin-1(2H)-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (3B)[26]

For 7 hours, thiourea (0.06g, 0.001mol) and Ethyl ciprofloxacin (2) (0.5g, 0.001mol) were refluxed in abs. EtOH (25ml). There was a cooling of the reaction mixture. A product was obtained by filtering and washing the precipitate with extremely cold EtOH, and then recrystallizing it from 70% EtOH.

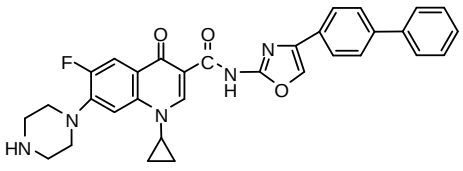
Brown powder, yield = 68%, m.p. (138-140°C). Rf = 0.78, IR (KBr disc), (ύ cm^{-1}): 3371.57 and 3286.70 (NH_2) str., 3182.55 (NH) str., 3020.53 (C-H) aromatic, 2924.09 and 2850.79 Aliphatic (C-H), 1620.21 (C=O) str. Amide.



Chemical synthesis N-(4-(biphenyl-4-yl)oxazol-2-yl)-1-cyclopropyl-7-(5,6-dihydro-pyrazin-1(2H)-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxamide (4A)[26]

compound (3A) (0.3g, 0.0008mol) was dissolved in abs. The p-phenylphenacylbromide was dissolved in EtOH (30ml) at a concentration of 0.24g/mol. The mixture was then cooled and neutralised with ammonium hydroxide solution after being treated to an 8-hour period of reflux. The precipitate was then filtered and rinsed with water before being recrystallized in petroleum ether (80-100). Dark yellow, yield = 50%, m.p. (100-102°C). Rf = 0.75, IR (KBr disc), (ύ cm^{-1}): 3273.20 (NH) str., 3057.17, 3030.17 Aromatic (C-H) str., 2920.23 and 2850.79 Aliphatic (C-H), 1678.07(C=O) str. amide, 1602.85 (C=N) str.

^{1}HNMR-(δppm): 9.5 (s, 1H, O=C-NH), 8.56-7.22 (m, 13H, Ar-H), 4.16 (t, 2H, CH_2 in pyrazin), 3.4 (p, 1H, CH in cyclopropan), 2.50 (s, 1H, NH), 1.26 (q, 2H, CH_2 in cyclopropan).

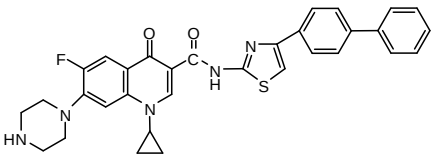


Chemical synthesis N-(4-(biphenyl-4-yl)thiazol-2-yl)-1-cyclopropyl-7-(5,6-dihydropyrazin-1(2H)-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxamide (4B)[26]

Compound (3A) was dissolved in abs. EtOH (25 ml) to get 4B, and then 4-phenyl phenacyl bromide (0.06g, 0.0008 mol) was added. After that, we let the concoction sit and reflux for 8 hours. The precipitate was [analysed by TLC], filtered, and recrystallized in ethanol.

Dark Brown, yield = 61%, m.p. (138-140°C). Rf = 0.83, IR (KBr disc), (ύ cm^{-1}): 3288.63 (NH) str., 3111.18 Aromatic (C-H) str., 1627.92 (C=N) str.

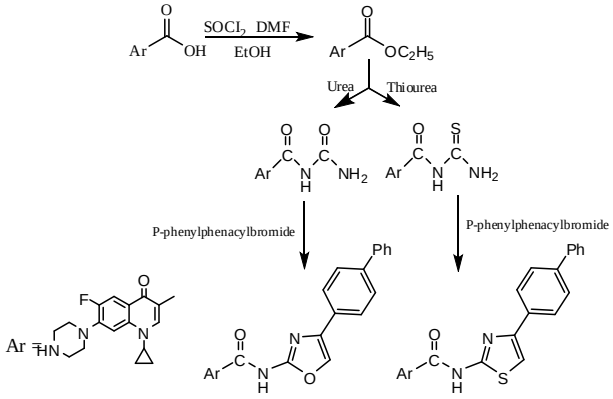
^{1}HNMR-(δppm): 12.6 (s, 1H, O=C-NH), 8.59-6.68 (m, 13H, Ar-H), 4.15 (t, 2H, CH_2 in pyrazin), 3.14 (p, 1H, CH in cyclopropan), 1.8 (s, 1H, NH), 1.27 (q, 2H, CH_2 in cyclopropan).



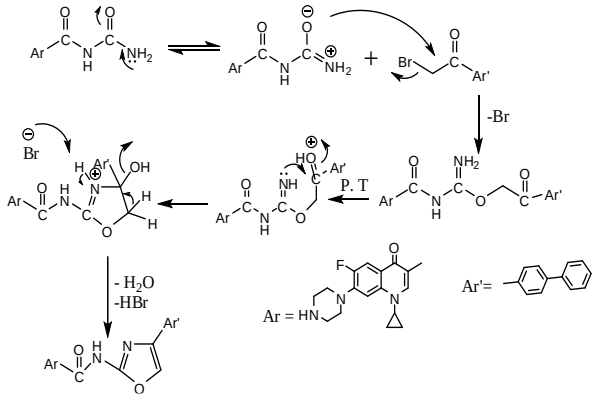
Chemistry

Scheme 1 is a schematic representation of the overall approach taken in the synthesis of new ciprofloxacin 1,3-oxazole and 1,3-thiazole derivatives.

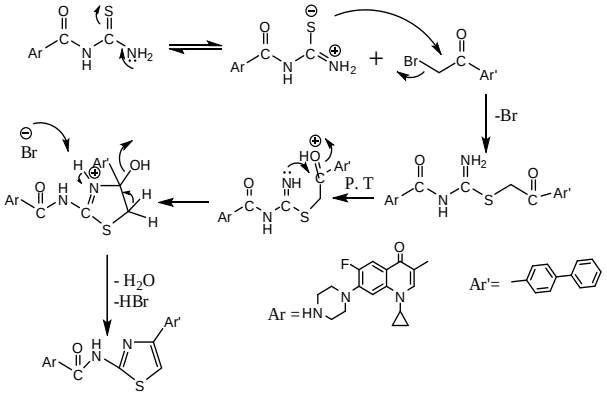
Schemes 2 and 3 depict a likely pathway for the innovative synthesis of oxazole and thiazole derivatives.



Scheme 1: The Synthesis of target compound (4A and 4B)



Scheme 2: The mechanism of the reaction for compound 4A



Scheme 3: The mechanism of the reaction for compound 4B

Molecular docking study

The molecular docking study of the prepared organic derivatives revealed the number and types of bonds through which these prepared derivatives are linked with the amino acid residues present in the active site. For example, the compound (4A) was found to interact with the amino acid residues present in the active site via four distinct bonds, including a carbon hydrogen bond connecting the residue of the amino acid ASP207, which is present in the active site, to the compound itself.

Based on the results of the study, it was determined that compound 4B reacted with the active site amino acid residues to generate five distinct types of compounds. Band of the type (Halogen-fluorine) linking the residues of the amino acid ASP186, which are located in the active site, with the electron pair of the fluorine atom substituted on the aromatic ring; three bonds of the type alkyl the residues of the amino acid (CYS182, LEU137, ALA138) which are located in the active site; carbon-hydrogen bond connecting the residue of the amino acid GLU198 with the electronic pair of six-membered

Table (1) values of correlation energy for derivatives prepared

Compound Symble	RMSD	Docking Score
4A	0.038	-8.3
4B	0.053	-7.8

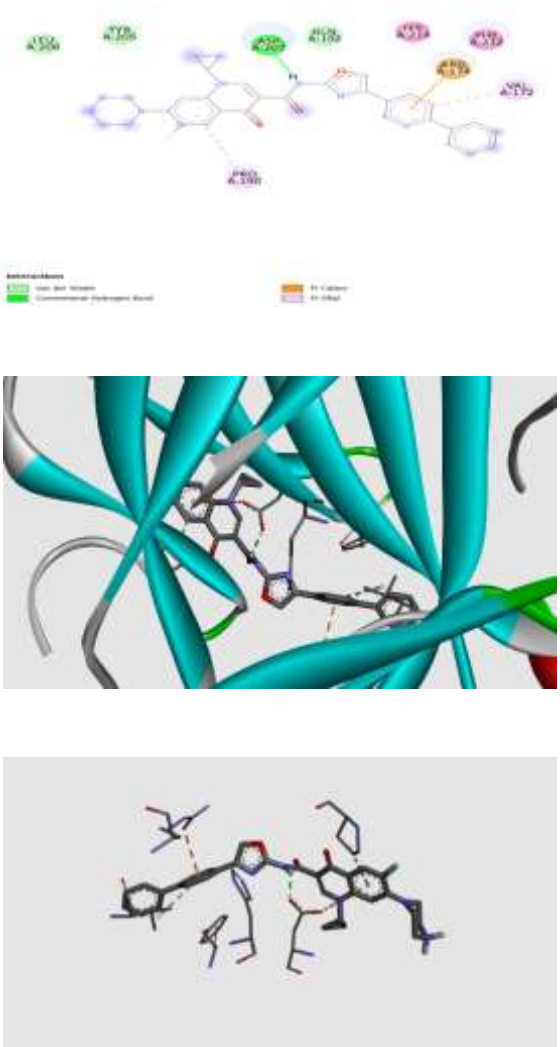


Fig (2): Reactions between compound 4A 2D and 3D dimensions

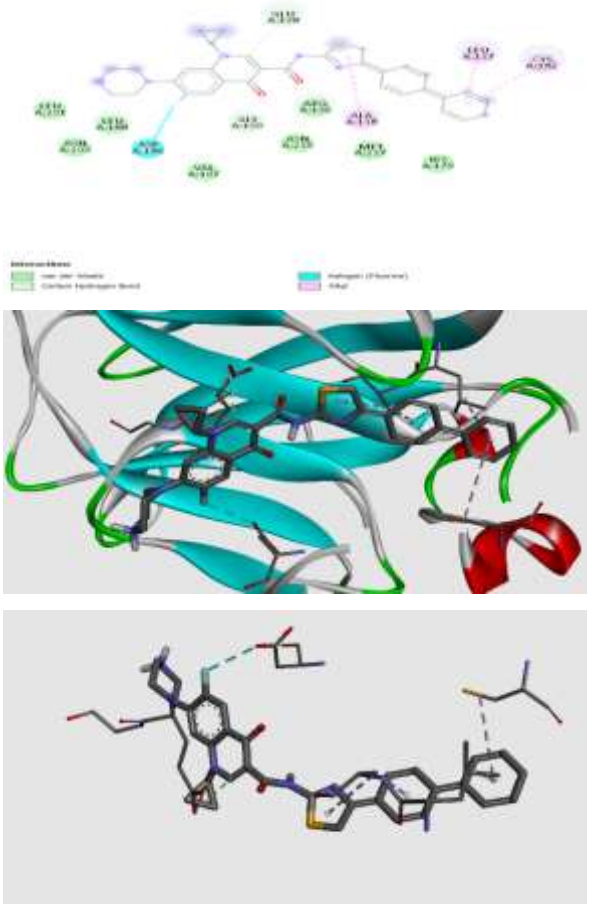


Fig (3): Reactions between compound 4B 2D and 3D dimensions

Conclusion

These proposed chemicals were synthesised using the previously mentioned methods. This investigation found that the strategy for synthesising the designed derivatives was successful because physical and chemical analyses (TLC, melting point, FTIR, 1HNMR, and 13CNMR) showed compound conformity. The anti-cancer activity of these molecules is comparable to commercial compounds.

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