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Anti-uropathogenic activity, drug likeness, physicochemical and molecular docking assessment of (E-)-N′-(substituted-benzylidene)-2-(quinolin-8-yloxy) acetohydrazide

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ABSTRACT

Objective: To deal with the anti-uropathogenic and in silico screening of (E-)-N′-(substituted-benzylidene)-2-(quinolin-8-yloxy)acetohydrazide analogues in order to search the potential anti-uropathogenic agents.

Methods: Three (E-)-N′-(substituted-benzylidene)-2-(quinolin-8-yloxy)acetohydrazide analogues were synthesized. Structure elucidation was done using various spectroscopic techniques including infrared radiation, 1hydrogen-nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, *etc*. Physicochemical score, bioactivity score and molecular docking studies were carried out using Lipinski's rule of five, Molinspiration (web based software), Autodock 4.2 tools. *In vitro* anti-uropathogenic activity was carried out against four pathogens named as *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis*, *Proteus mirabilis* and *Escherichia coli* by disc diffusion method and macro-dilution test following their morphological and biochemical characterization.

Results: The formation of (E-)-N′-(substituted-benzylidene)-2-(quinolin-8-yloxy)aceto-hydrazide is confirmed from the spectroscopic results. All the compounds were found in compliance with Lipinski's rule of five and exhibited bioactivity score from −0.50 to 0.00. Docking results revealed that compound-1 is forming one hydrogen bond with TYR 576 and two hydrogen bond with GLU 569, while compound-2 is forming one hydrogen bond with ARG 599, and compound-3 forming 0 hydrogen bond. The anti-uropathogenic evaluation exhibited that compound one exhibited better activity against *S. aureus*, while it was found to possess moderate to good activity against both Gram-positive bacteria and Gram-negative bacteria excluding *S. aureus*.

Conclusions: Our study revealed that compound one exhibited better activity than the standard in case of *S. aureus* and moderate to good activity against rest of the pathogens. Molecular docking, physicochemical and bioactivity studies strongly supported the experimental results. From the well obtained results it was concluded that compound-1 can lead as potential anti-uropathogenic agents.

1. Introduction

Multidrug-resistant strains of uropathogenic microorganisms have evolved as unmanageable infections of urinary tract and emerged as the second most common disease after respiratory tract infection [1]. Multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (*S. aureus*), penicillin resistant *Streptococcus pneumoniae* (*S. pneumoniae*), and vancomycin-resistant *Enterococci*, compounded problems in the therapeutics [2,3]. Quinolines and its derivatives have been known to possess diverse pharmacological activities such as antibacterial, antifungal, antimycobacterial, antidepressant, antimalarial, anticonvulsant, antiviral, anticancer, hypotensive and anti-inflammatory activities [4–11]. Quinine, which is extracted from Cinchona bark, has provided the basis for the development of synthetic quinoline-containing drugs, and many of them are presently available such as chloroquine, amodiaquine and mefloquine [12]. Hydrazones owing to their physiological activity and co-ordination capability yielded a number of pharmacophores

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with antiplatelet, antiulcer, antitumor, antiprotozoal, antibacterial and antifungal activities [13–29]. Some of the hydrazone derivatives have been found to represent the potential antimicrobial activity such as 2,5-diformyl-1H-pyrrole bis(methan-1-yl-1-ylidene)dimalonohydrazone [30], Benzylidene/2-aminobenzylidene hydrazides [30], 1,3-benzothiazole-2-yl-hydrazone [31], metal complexes with 2-acetylpyridine phenoxyacetyl hydrazone [32], pyrrole dihydrazones and their metal complexes [33–36], cholic acid hydrazone analogues [37], macrocyclic bis hydrazone [37], 3-oxido-1H-imidazole-4-carbohydrazides [38]. On the other hand, the evaluation of physicochemical parameters of a chemical entity plays a vital role in generation and escalation of bioactivity of chemical entity which is obtained by Molinspiration, web based software [39]. Docking studies were also carried out to find out the interaction of the synthesized compounds with the receptor in comparison to the standard drug Ciprofloxacin. Keeping in mind the importance of quinoline nucleus and hydrazones functionality, we designed our research in such a way that the combination of this functionality together will be important to enhance the biological activity.

2. Materials and methods

Solvents and organic reagents were purchased from Sigma Aldrich, Merck (Germany) and were used without further purification. Melting points (m.p.) were performed using a Mel-Temp instrument, and the results were uncorrected. Precoated aluminium sheets (silica gel 60 F254, Merck Germany) were used for thin-layer chromatography (TLC) and spots were visualized under UV light. Elemental analyses were performed on Heraeus Vario EL III analyzer. Infrared radiation (IR) spectra were recorded on Perkin–Elmer model 1600 FT-IR RX1 spectrophotometer as KBr discs. 1Hydrogen-nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on Bruker AVANCE 300 spectrometer using $CDCl_3$ and dimethyl sulfoxide (DMSO) as solvents with tetramethylsilane as internal standard. Splitting patterns are designated as follows; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Chemical shift values are given in ppm. Electrospray ionisation mass spectrometry (ESI-MS) was recorded on a Micromass Quattro II triple quadrupole mass spectrometer.

2.1. General procedure for the synthesis of ethyl-2-(quinolin-8-yloxy)acetate (A)

A mixture of 8-hydroxyquinoline (10 mmol), ethyl chloroacetate (10 mmol) and potassium carbonate (15 mmol) in dry acetone (100 mL) was refluxed for 24 h. The reaction mixture was filtered hot and the solvent was distilled off from the filtrate. The crude ester thus obtained was purified by recrystallization from ethanol.

2.2. General procedure for the synthesis of 2-(quinolin-8-yloxy)acetohydrazide (B)

A mixture of A (10 mmol) and hydrazine hydrate (99%, 10 mmol) in ethanol (50 mL) was refluxed for 8 h. The solution on cooling gave a solid mass of hydrazide, which was collected by filtration, and recrystallized from ethanol.

2.3. General procedure for the synthesis of Schiff bases (1–3)

A mixture of compound B (10 mmol), appropriate aldehyde (10 mmol) and few drops of glacial acetic acid in ethanol (50 mL) was refluxed for 12 h. The product was precipitated, collected by filtration and re-crystallized from ethanol.

(E-)-N′-(4-methoxybenzylidene)-2-(quinolin-8-yloxy)aceto-hydrazide (1).

Yellow solid; yield: 80%; m.p. 162–164 °C Anal. Calc. for $C_{19}H_{17}N_3O_3$: C 68.05, H 5.11, N 12.53%, found C 68.12, H 5.14, N 12.54%; IR ν (cm^{-1}): 3134 (NH), 3011 (Ar, C–H), 1720 (C═O), 1612 (C═N); ^{1}H-NMR (DMSO) δ (ppm): 9.14 (s, 1H, NH), 8.12 (s, 1H, CH═N), 7.87 (d, 1H, J = 8.1 Hz, Ar–H), 7.78 (d, 1H, J = 8.1 Hz, Ar–H), 7.68 (m, 1H, Ar–H), 7.64 (m, 2H, Ar–H), 7.56 (d, 1H, J = 9.0 Hz, Ar–H), 7.31 (d, 2H, J = 8.0 Hz, Ar–H), 7.24 (d, 2H, J = 8.0 Hz, Ar–H), 5.68 (s, 2H, –CH_2–), 3.85 (s, 3H, –OCH_3); ^{13}C-NMR (DMSO) δ/ppm: 167.6 (C═O), 165.56 (C═N), 160.72, 158.64, 151.63 (Ct), 150.45, 148.53, 139.27, 131.62, 129.90, 129.52, 129.13, 128.41, 127.22, 119.43, 115.33, 112.52, 55.62 (–OCH_3), 52.21 (–CH_2–); ESI-MS m/z: [M^++H] 336.13.

(E-)-N′-(3,4-dimethoxybenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (2).

Yellow solid; yield: 84%; m.p. 166–168 °C Anal. Calc. for $C_{20}H_{19}N_3O_4$: C 65.74, H 5.24, N 11.50%, found C 65.75, H 5.26, N 11.54%; IR ν (cm^{-1}): 3136 (NH), 3017 (Ar, C–H), 1724 (C═O), 1610 (C═N); ^{1}H-NMR (DMSO) δ (ppm): 9.10 (s, 1H, NH), 8.11 (s, 1H, CH═N), 7.89 (d, 1H, J = 8.2 Hz, Ar–H), 7.74 (d, 1H, J = 8.6 Hz, Ar–H), 7.65 (m, 1H, Ar–H), 7.60 (m, 2H, Ar–H), 7.56 (d, 1H, J = 8.5 Hz, Ar–H), 7.35 (d, 2H, J = 8.0 Hz, Ar–H), 7.30 (d, 2H, J = 7.0 Hz, Ar–H), 5.60 (s, 2H, –CH_2–), 3.81 (s, 3H, –OCH_3), 3.79 (s, 3H, –OCH_3); ^{13}C-NMR (DMSO) δ/ppm: 167.63 (C═O), 165.55 (C═N), 160.76, 158.62, 151.62, 150.47, 148.50, 139.23, 131.61, 129.90, 129.51, 129.13, 128.40, 127.29, 119.43, 115.37, 112.56, 55.60 (–OCH_3), 52.2 (–CH_2–); ESI-MS m/z: [M^++H] 366.14.

(E-)-N′-(3,4,5-methoxybenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (3).

Yellow solid; yield: 83%; m.p. 170–172 °C Anal. Calc. for $C_{21}H_{21}N_3O_5$: C 63.79, H 5.35, N 10.63%, found C 63.76, H 5.35, N 10.65%; IR ν (cm^{-1}): 3130 (NH), 3017 (Ar, C–H), 1725 (C═O), 1614 (C═N); ^{1}H-NMR (DMSO) δ (ppm): 9.10 (s, 1H, NH), 8.14 (s, 1H, CH═N), 7.82 (d, 1H, J = 8.6 Hz, Ar–H), 7.76 (d, 1H, J = 8.8 Hz, Ar–H), 7.65 (m, 1H, Ar–H), 7.62 (m, 2H, Ar–H), 7.54 (d, 1H, J = 9.5 Hz, Ar–H), 7.34 (d, 2H, J = 8.4 Hz, Ar–H), 7.27 (d, 2H, J = 7.0 Hz, Ar–H), 5.63 (s, 2H, –CH_2–), 3.85 (s, 3H, –OCH_3), 3.80 (s, 3H, –OCH_3), 3.78 (s, 3H, –OCH_3); ^{13}C-NMR (DMSO) δ/ppm: 167.67 (C═O), 165.52 (C═N), 160.71, 158.63, 151.60, 150.40, 148.55, 139.24, 131.63, 129.97, 129.56, 129.11, 128.49, 127.27, 119.45, 115.33, 112.52, 55.61 (–OCH_3), 52.23 (–CH_2–); ESI-MS m/z: [M^++H] 336.13.

2.4. Physicochemical properties [40]

Physico-chemical properties of compounds 1–3 and ciprofloxacin were checked with the help of software Molinspiration physicochemical properties calculator available online (www.molinspiration.com). The properties of partition coefficient (log P), molar refractivity, molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation were calculated.