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Synthesis and determination of *in-vitro* anti-urolithiatic activity of quinazolinone derivatives

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Quinazolinone derivatives are a group of heterocyclic compounds known for their diverse biological activities and pharmaceutical applications. However, the potential of quinazolinone-based compounds in preventing or treating urolithiasis remains unexplored. Therefore, this study primarily focused on the synthesis and investigation of the *in-vitro* anti-urolithiatic activities of quinazolinone derivatives, including 2-(2-methoxyphenyl)-3*H*-quinazolin-4-one, 2-(2-hydroxyphenyl)-3*H*-quinazolin-4-one, 2-(3-hydroxyphenyl)-3*H*-quinazolin-4-one, 2-(4-hydroxy-3-methoxyphenyl)-3*H*-quinazolin-4-one, and 2-(4-nitrophenyl)-3*H*-quinazolin-4-one. Quinazolinone derivatives were synthesized *via* oxidative cyclo-condensation of 2-aminobenzamide with substituted aldehydes utilizing $FeCl_3$ as a Lewis acid catalyst. The structures of the synthesized analogues were confirmed using spectroscopic techniques including Fourier-transform infrared spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry. In-vitro anti-urolithiatic activity of the synthesized derivatives was evaluated in triplicates using calcium oxalate crystal initiation assay, calcium oxalate crystal growth assay, and calcium oxalate crystal aggregation assay. Statistical analysis was performed using the one-way ANOVA test. Among the tested compounds, 2-(2-methoxyphenyl)-3*H*-quinazolin-4-one demonstrated the highest crystal initiation inhibition activity, with lowest IC_{50} value (352.23 ± 16.29 µg/mL) outperforming the standard potassium citrate (593.52 ± 53.78 µg/mL); followed by 2-(3-hydroxyphenyl)-3*H*-quinazolin-4-one (392.67 ± 9.86 µg/mL), 2-(4-hydroxy-3-methoxyphenyl)-3*H*-quinazolin-4-one (461.84 ± 26.17 µg/mL), 2-(4-nitrophenyl)-3*H*-quinazolin-4-one (521.89 ± 119.46 µg/mL), and 2-(2-hydroxyphenyl)-3*H*-quinazolin-4-one (528.31 ± 16.29 µg/mL). The highest crystal growth inhibition activity was exhibited by 2-(2-methoxyphenyl)-3*H*-quinazolin-4-one (330.47 ± 9.76 µg/mL) compared to potassium citrate (771.09 ± 22.67 µg/mL); followed by 2-(4-hydroxy-3-methoxyphenyl)-3*H*-quinazolin-4-one (466.44 ± 40.77 µg/mL), 2-(3-hydroxyphenyl)-3*H*-quinazolin-4-one (660.33 ± 17.83 µg/mL), 2-(4-nitrophenyl)-3*H*-quinazolin-4-one (691.49 ± 3.54 µg/mL), and 2-(2-hydroxyphenyl)-3*H*-quinazolin-4-one (691.49 ± 32.23 µg/mL). In the crystal aggregation assay, the IC_{50} values of 2-(3-hydroxyphenyl)-3*H*-quinazolin-4-one, 2-(4-hydroxy-3-methoxyphenyl)-3*H*-quinazolin-4-one, 2-(2-hydroxyphenyl)-3*H*-quinazolin-4-one, 2-(2-methoxyphenyl)-3*H*-quinazolin-4-one, and 2-(4-nitrophenyl)-3*H*-quinazolin-4-one were reported as 455.84 ± 5.48 µg/mL, 501.64 ± 13.33 µg/mL, 521.41 ± 44.37 µg/mL, 545.57 ± 8.78 µg/mL, and 634.50 ± 47.41 µg/mL, respectively. Potassium citrate, used as the standard, showed an IC_{50} value of 333.33 ± 12.39 µg/mL. These findings highlight the potential of quinazolinone derivatives as promising candidates for urolithiasis treatment.

Keywords:

Anti-urolithiatic activity; quinazolinone derivatives; initiation assay; growth assay; aggregation assay