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ORIGINAL ARTICLE

Design, synthesis and biological evaluation of quinazolin-4(3*H*)-one Schiff base conjugates as potential antiamoebic agents

Saba Tariq [a], **Fernando Avecilla** [b], **Guru Prasad Sharma** [c], **Neelima Mondal** [c], **Amir Azam** [a,*]

[a] *Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India*
[b] *Departamento de Química Fundamental, Universidade da Coruña, Campus da Zapateira s/n, 15071 A Coruña, Spain*
[c] *School of Life Sciences, Jawaharlal Nehru University, New Delhi 110062, India*

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Abstract In an effort to develop novel antiamoebic scaffolds having better efficacy than the standard drug metronidazole (IC_{50} = 1.80 μM) used against *Entamoeba histolytica*, quinazolin-4(3*H*)-one Schiff base conjugates were synthesized and evaluated against HM1: IMSS strain of *E. histolytica*. Out of the thirteen compounds (**S2-S14**), six compounds (**S2**, **S3**, **S4**, **S5**, **S6** and **S11**) were found to be better inhibitors than metronidazole and showed low cytotoxicity on HeLa cells, a cervical cancer cell line. The structure of intermediate compound **S1** was confirmed by crystal structure studies.

1. Introduction

Amebiasis, caused by gastrointestinal protozoan *Entamoeba histolytica* is the third principal cause of death among parasitic diseases worldwide. Its prevalence is greatest in the countries with poor sanitation, poverty, ignorance, and malnutrition [1–3]. It is estimated to result in 110,000 deaths and more than 500 million people get infected annually [4]. *E. histolytica* is primarily found in the colon as inactive, but after certain period it becomes lethal to human being by causing severe complications like dysentery, colitis and liver abscess [5–7]. Amoebic colitis characterized by ulceration and inflammation of the colon and amoebic liver abscesses are the two major clinical features of *E. histolytica* infection. Amoebic colitis when accompanied with extreme gut inflammation can closely mimic inflammatory bowel disease [8,9]. Therefore it is important to identify and treat amebiasis appropriately. Although the availability of a large number of antibacterial agents for clinical treatment has proved propitious for the health status of mankind [10]. The existence of antimicrobial resistance for the past few years has threatened their therapeutic utility thereby, exhibiting severe global crisis [11–14]. The antiamoebic drug

* Corresponding author. Fax: +91 11 26980229.
E-mail address: amir_sumbul@yahoo.co.in (A. Azam).
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metronidazole is the treatment of choice for this disease but certain side effects [15–18] such as neurologic toxicity [19], genotoxicity, carcinogenicity [18,20,21] spermatozoid damage [22] are associated with it. Moreover resistance of *E. histolytica* to metronidazole and recurrence of intestinal and hepatic amebiasis have been reported [23,24]. This situation has necessitated the development of novel anti-amoebic agents with increased efficacy and lesser toxicity for the host [25]. Because of their high therapeutic index and clinical utility, quinazolin-4(3*H*)-one and its derivatives are promising scaffolds for the synthesis of potential bioactive agents [26]. Quinazolin-4-(3*H*)-ones and 1,2,4-triazoles exhibited a diverse range of bioactivities such as analgesic [27,28], anti-inflammatory [29,30], anti-tumour [31,32], anticancer [33–35], antibacterial [36–38] and anticonvulsant [39–41] therefore, these two important heterocyclic scaffolds have been incorporated into a wide variety of interesting molecules to transform them into better drugs. Due to the important and versatile biological activities, Schiff bases [42] can be used as ideal lead structures in drug development. Therefore, we synthesized quinazolin-4(3*H*)-one Schiff base conjugates with the aim to develop compounds with enhanced antiamoebic efficacy than the standard drug metronidazole [25]. To the best of our knowledge, this is the first report of quinazolin-4-(3*H*)-one derivatives showing promising antiamoebic activity against *E. histolytica*.

2. Experimental

2.1. Materials and measurements

All the required chemicals were purchased from Merck and Aldrich Chemical Company (USA). Precoated aluminium sheets (Silica gel 60 F254, Merck Germany) were used for thin-layer chromatography (TLC) and spots were visualized under UV light. The melting points were recorded on Veego instrument with model specifications REC-22038 A2 and are uncorrected. Elemental analyses were performed on Elementar Vario analyser and the results are within ±0.4% of the theoretical values. IR spectra (KBr) were acquired at Bruker FT-IR spectrophotometer. ^{1}H and ^{13}C NMR were recorded on a Bruker Spectrospin DPX 400 MHz and Bruker Spectrospin DPX 75 MHz spectrometer respectively, using DMSO-d_6 as a solvent and trimethylsilane (TMS) as the internal standard. Splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values are given in ppm. Mass spectra were recorded by ESI-MS (AB-Sciex 2000, Applied Biosystem).

2.2. General procedure for the synthesis of methyl 2-(2-chloroacetamido)benzoate (*S*)

An aromatic amine (0.12 mol) was dissolved in glacial acetic acid and saturated solution of sodium acetate. The mixture was warmed and then cooled in ice bath with stirring. To this solution was added drop wise a solution of chloro acetyl chloride (0.12 mol). The progress of the reaction was monitored by thin layer chromatography. After half an hour white product was formed. This was separated, filtered, washed with cold water and purified by crystallization from aqueous alcohol [43].

White solid; Yield: 90%; mp: 118 °C; Anal. Calc. (%) for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; Cl, 15.57; N, 6.15; O, 21.08; found: C, 52.78; H, 4.41; Cl, 15.59; N, 6.14; O, 21.07; ^{1}H NMR (DMSO-d_6) δ (ppm): 11.31 (s, 1H, NH), 8.39 (d, 1H, J = 8.4 Hz, Ar-H), 7.99 (d, 1H, J = 8.4 Hz, Ar-H), 7.67–7.63 (m, 1H, Ar-H), 7.27 (t, 1H, J = 7.5 Hz, Ar-H), 4.44 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3); ESI-MS: m/z = 229 ($M^+ + 1$).

2.3. Synthesis of methyl 2-(2-(1*H*-1,2,4-triazol-1-yl)acetamido) benzoate (*S0*)

Methyl 2-(2-chloroacetamido)benzoate (**S**) (0.1 mol) was treated with (0.1 mol) commercially available 1,2,4 triazole in the presence of (0.05 mol) K_2CO_3 in dimethylformamide under reflux for 18 h to afford methyl 2-(2-(1*H*-1,2,4-triazol-1-yl)acet amido)benzoate.

White solid; Yield: 92%; mp: 102 °C; Anal. Calc. (%) for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53; O, 18.44; found: C, 55.39; H, 4.64; N, 21.52; O, 18.43; ^{1}H NMR (DMSO-d_6) δ (ppm): 10.68 (s, 1H, NH), 8.59 (s, 1H, Ar-H), 8.17 (d, 1H, J = 7.8 Hz, Ar-H), 8.05 (s, 1H, Ar-H), 7.92 (d, 1H, J = 7.8 Hz, Ar-H), 7.64 (t, 1H, J = 7.2 Hz, Ar-H), 7.26 (t, 1H, J = 7.2 Hz, Ar-H), 5.24 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 167.67, 165.71, 152.31, 146.15, 138.98, 134.41, 131.08, 124.52, 122.11, 119.17, 61.72, 52.67; ESI-MS: m/z = 261 ($M^+ + 1$).

2.4. Synthesis of 2-((1H-1,2,4-triazol-1-yl)methyl)-3-aminoquinazolin-4(3H)-one (*S1*)

Methyl 2-(2-(1*H*-1,2,4-triazol-1-yl)acetamido)benzoate (**S0**) (0.1 mol) was reacted with hydrazine hydrate (0.3 mol) in ethanol under reflux for 12 h to give 2-((1*H*-1,2,4-triazol-1-yl) methyl)-3-aminoquinazolin-4(3*H*)-one.

Yellow solid; Yield: 92%; mp: 66 °C; Anal. Calc. (%) for $C_{11}H_{10}N_6O$: C, 54.54; H, 4.16; N, 34.69; O, 6.60; found: C, 54.55; H, 4.14; N, 34.68; O, 6.61; FT-IR ν_{max} (cm^{-1}): 3477 (NH_2), ^{1}H NMR (DMSO-d_6) δ (ppm): 8.64 (s, 1H, Ar-H), 8.16 (d, 1H, J = 7.8 Hz, Ar-H), 8.03 (s, 1H, Ar-H), 7.80 (t, 1H, J = 6.9 Hz, Ar-H), 7.56 (m, 2H, Ar-H), 5.76 (s, 2H, CH_2), 5.69 (s, 2H, NH_2), ^{13}C NMR (DMSO-d_6) δ (ppm): 161.00, 153.29, 151.68, 146.54, 146.31, 134.79, 127.62, 127.35, 126.47, 120.70, 50.63; ESI-MS: m/z = 265 ($M^+ + 23$).

2.5. Synthesis of Schiff bases derived from 2-((1H-1,2,4-triazol-1-yl)methyl)-3-aminoquinazolin-4(3H)-one (*S2-S14*)

An equimolar mixture of compound **S1** (0.01 mol) and substituted aldehydes (0.01 mol) in absolute ethanol (10 mL) was allowed to reflux for 2–4 h, H_2SO_4 (0.5 mL) was added slowly to the reaction mixture and progress of the reaction was monitored through thin layer chromatography. When the reaction was completed, it was allowed to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product was filtered, dried and crystallized from methanol to give title compounds in good yields.

2.5.1. (E)-2-((1H-1,2,4-Triazol-1-yl)methyl)-3-(2-chlorobenzylideneamino)quinazolin-4(3H)-one (*S2*)

Yield: 82.5%; mp: 115 °C; Anal. Calc. (%) for $C_{18}H_{13}ClN_6O$: C, 59.27; H, 3.59; Cl, 9.72; N, 23.04; O, 4.39; found: C, 59.25; H, 3.58; Cl, 9.70; N, 23.06; O, 4.37; FT-IR ν_{max} (cm^{-1}): 1687 (C═O), 1610 (C═N); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.51