European Journal of Medicinal Chemistry 98 (2015) 179–189

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis, characterization and antiamoebic activity of chalcones bearing *N*-substituted ethanamine tail

Saadia Leeza Zaidi [a], Sonam Mittal [b], Maitreyi S. Rajala [b], Fernando Avecilla [c], Mohammad Husain [d], Amir Azam [a, *]

[a] Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India
[b] School of Biotechnology, Jawaharlal Nehru University, New Delhi 110067, India
[c] Departamento de Química Fundamental, Universidade da Coruña, Campus da Zapateira s/n, 15071 A Coruña, Spain
[d] Department of Biotechnology, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India

ARTICLE INFO

Article history:
Received 6 February 2015
Received in revised form
4 May 2015
Accepted 8 May 2015
Available online 18 May 2015

Keywords:
Chalcones
Amoebiasis
E. histolytica
MTT assay
A549

ABSTRACT

A series of chalcones (4–21) possessing N-substituted ethanamine were synthesized by the aldol condensation reaction of 1-(4-(2-substituted ethoxy)phenyl)ethanones with different aldehydes preceded by the reaction of 2-chloro N-substituted ethanamine hydrochloride and 4-hydroxy acetophenone. The structure of all the synthesized compounds was elucidated by various spectral and X-ray diffraction studies. The compounds were screened against HM1: IMSS strain of *Entamoeba histolytica* and cytotoxicity was performed on A549 (non-small cell lung cancer cell line) cells by MTT assay. Out of eighteen compounds twelve showed better activity then the standard drug metronidazole. The compound 9, 14 and 19 showed good cell viability, hence were least toxic.

1. Introduction

Amoebiasis, the devastating disease of the gastrointestinal tract is caused by a parasitic protozoan *Entamoeba histolytica*. It is responsible for 100,000 fatalities worldwide per annum [1]. The spread of the infection is accelerated by poor sanitation. The treatment is usually done by nitroimidazoles such as metronidazole (MNZ) and tinidazole but they have shown several side effects [2]. MNZ is known to be carcinogenic in rodents and some major side effects such as irritation of the gastric mucus lining, spermatozoid damage, convulsions, central nervous system disorders, blood in urine [3–7]. Recent reports have shown clinical resistance towards the conventional drugs [8].

Chalcones are 1, 3-diaryl-2-propen-1-ones possessing a diverse range of biological activities including anticancer [9,10], antimicrobial [11,12], anti-HIV [13,14], anti-oxidant [15,16], anti-inflammatory [17,18] and anti-protozoal activities [19,20]. Modification in their structure leads to an enhancement in their biological activity and therapeutic efficacy [21]. Thus chalcones are a very promising structural motif to be explored in the quest for newer drugs. Literature review revealed that chalcones have been studied for their activity against various protozoal diseases but their potential against the neglected diseases such as amoebiasis remains to be explored. Previously, we have reported antiprotozoal activity of a series of chloroquinoline based chalcones (Fig. 1) which showed some promising results against *E. histolytica* [22]. Compounds containing morpholine, piperadine (Fig. 2) and N, N-dimethylamino scaffolds have shown promising antiprotozoal and antibacterial activities [23–25].

In our continuous effort towards the development of more potent antiamoebic agents and taking into consideration that aliphatic and cyclic amine bearing heterocycles and chalcones are biologically active. We herein, report the synthesis, characterization, antiamoebic activity and toxicity of a series of hybrid molecules containing chalcone and N-substituted ethanamine tail (Fig. 3).

2. Results and discussion

2.1. Chemistry

A series of chalcones (4–21) containing N-substituted ethanamine were synthesized as outlined in Scheme 1. 4-hydroxy

* Corresponding author.
E-mail address: amir_sumbul@yahoo.co.in (A. Azam).

http://dx.doi.org/10.1016/j.ejmech.2015.05.013
0223-5234/

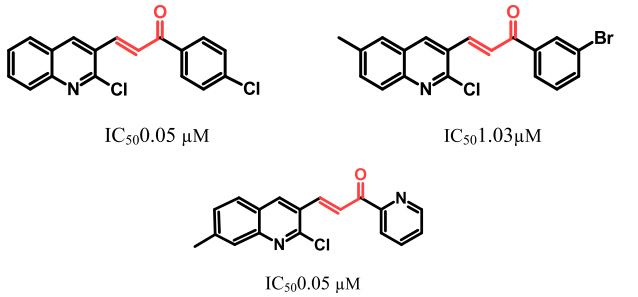


Fig. 1. Structures of antiprotozoal chalcones showing promising antiamoebic activity.

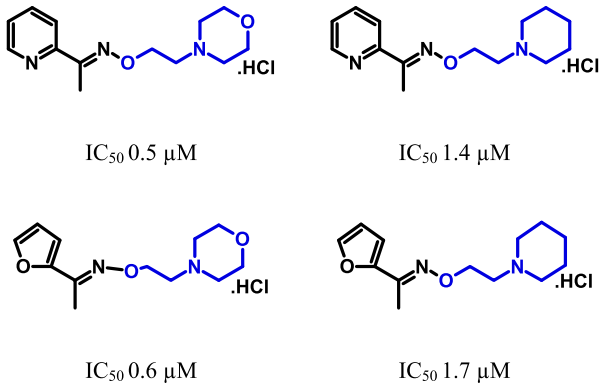


Fig. 2. Structures of compounds containing N-substituted ethanamine side chain showing good antiamoebic activity.

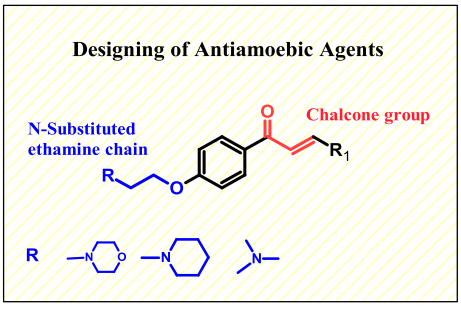
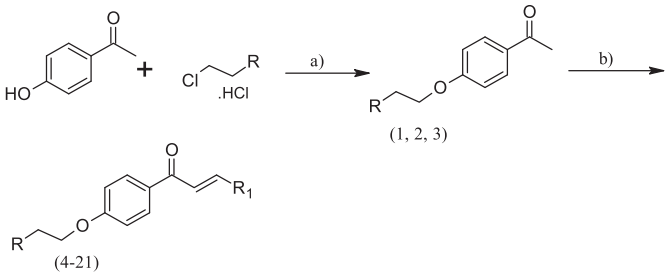


Fig. 3. Designing of hybrid molecule.

acetophenone is converted to 1-[4-(2-dimethylamino/piperidino/morpholinoethoxy)phenyl)ethanone derivative by the reaction with 2-chloro N-substituted ethanamine hydrochloride salts under basic conditions using potassium tert-butoxide (*t*-BuOK) as a base. The aldol condensation reaction of 1-(4-(2-substituted ethoxy)phenyl)ethanones with different aldehydes resulted in the desired chalcones. All the compounds synthesized were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. The molecular composition of the synthesized compounds was established on the basis of their CHNS elemental analysis data. A good agreement between the calculated and the observed values for various elements supported the formation of expected compounds as given in the experimental section. The structures of 1-(4-(2-substituted ethoxy) phenyl) ketones and their chalcones containing N-substituted ethanamine were also supported by their ^{1}H NMR spectra. The chemical shift values for all the compounds are given in the experimental section. The signals due to characteristic olefinic protons (α and β) were found in all the



Scheme 1. Synthesis of N-substituted ethanamine chalcones. *Reagents and Conditions:* (a) *THF, t-BuOK, Reflux* (b) *NaOH, EtOH, rt.*

compounds with *J* values around 15 Hz. In the IR spectra the carbonyl group appeared in the range 1650–1700 cm^{-1} and at around 1580 cm^{-1}for the alkenylic proton was also observed for the final compounds. The values of the ^{13}C NMR are also in good agreement with the proposed structure. The characteristic peak [M+1] in the mass spectra for chalcones helped to further establish the structure.

2.2. Single crystal structures of 1, 8 and 9

1-(4-(2-morpholinoethoxy)phenyl)ethanone(1), *3-(2-methylthiophen-2-yl)-1-(4-(2-morpholino ethoxy)phenyl)prop-2-en-1-*one (8) and *3-(3-bromo-4,5 dimethoxyphenyl)-1-(4-(2-morpholino ethoxy)phenyl)ethanone* (9) crystallize from methanol as colorless prism in 1, as yellow prism in 8 and as orange prism in 9. Figs. 4–6 show an ORTEP representation of 1, 8 and 9 respectively. Hydrogen bonds were not found in the structures. In the crystal packing of 8, the compound forms parallel dimers through π–π interactions between the C=C bonds of propene groups and phenyl rings [26]. The distances between the centroids is for 8:d_{c1-c2} = 3.532 Å [c1 (C14A–C15A), c2 (C7B–C8B–C9B–C10B–C11B–C12B)] (Fig. 7). Instead the compound 9 prefers to form antiparallel dimers in supramolecular structure (Fig. 8). π–π stacking interactions between phenyl rings predominate in this case. The distance between centroids are: d_{c3-c4} = 3.427 Å [c3 (C7A–C8A–C9A–C10A–C11A–C12A), c4 (C16L–C17L–C18L–C19L–C20L–C21L)] and d_{c5-c6} = 3.427 Å [c5 (C7L–C8L–C9L–C10L–C11L–C12L), c6 (C16A–C17A–C18A–C19A–C20A–C21A)]. Crystal data and details of the data collection and refinement for the new compounds are collected in Table 1 and Table 2 contains selected bond lengths and angles for compound 1, 8 and 9.

2.3. Pharmacological screening

2.3.1. Antiamoebic activity

Preliminary experiments were carried out to determine the *in vitro* antiamoebic activity of all the compounds (4–21) by microdilution method using HM1: IMSS strain of *E. histolytica* and their IC_{50} values are reported in Table 3. Metronidazole was used as reference drug having IC_{50} = 1.86 μM in our experiment. The results were estimated as the percentage of growth inhibition compared with the untreated controls and plotted as probit values as a function of the drug concentration. IC_{50} and 95% confidence limits were interpolated in the corresponding dose response curve. Out of the 18 compounds synthesized 12 showed better antiamoebic activity than MNZ. Compounds containing electron withdrawing nitro group were found to have IC_{50} value greater than MNZ. Compound 4, 10, 16 had IC_{50} values 4.76 μM, 4.17 μM and 2.33 μM respectively. Compound 12 containing piperidinoethoxy side chain and anisaldehyde as R_1 was found to have the least IC_{50} value of 0.03 ± 0.01 μM. The activity decreased tenfold when the