European Journal of Medicinal Chemistry 44 (2009) 3680–3686

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis of new acridines and hydrazones derived from cyclic β-diketone for cytotoxic and antiviral evaluation

Osama I. El-Sabbagh [a,*], Hanaa M. Rady [b]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
[b] Department of Chemistry of Natural Compounds, National Research Centre, Cairo, Egypt

ARTICLE INFO

Article history:
Received 2 September 2008
Received in revised form
18 March 2009
Accepted 2 April 2009
Available online 8 April 2009

Keywords:
Acridines
Hydrazones
Cytotoxic
Antiviral activity

ABSTRACT

Cyclic β-diketone namely, dimedone was utilized to prepare different chemical entities whether cyclic such as acridines, thiadiazole and triazole or acyclic systems as hydrazide, hydrazones, thiosemicarbazide and semicarbazide. The structures of the novel compounds were determined using elemental analyses and various spectroscopic methods. Most acyclic derivatives especially semicarbazide **19**, hydrazide **9** and thiosemicarbazide **16** showed a higher *in vitro* cytotoxic activity against hepatoma cell line (HepG2) than the cyclized acridine derivatives. The antiviral activity of the new compounds against *Hepatitis A Virus* (HAV) using the plague infectivity reduction assay revealed that the acridine **4** and the hydrazone **12** were more active than the reference drug amantadine.

1. Introduction

Malignant tumor and viral infections are the most serious threats against human health in the world. *Hepatitis A Virus* (HAV) is a picornavirus, a common causative agent of acute self-limited hepatitis that sometimes leads to fulminant hepatic failure [1,2].

Therefore, treatment of severe infections [1] is still an issue of major concern especially the clinically used drugs remains relatively poor.

Furthermore, there exist a number of acridine (amsacrine) [3–7], thiadiazole [8,9] and triazole (ribavirin) [10–12] derivatives having anticancer and antiviral activities. Moreover, some hydrazones [13,14] and thiosemicarbazone [15] derivatives were reported to exhibit anticancer and antiviral properties, respectively.

Based on the above findings and coupled with our interest of the chemistry of cyclic β-diketone especially dimedone gave us the opportunity for preparation of diverse heterocyclic ring systems such as acridine, thiadiazole and triazole derivatives in addition to acyclic systems e.g. hydrazone, thiosemicarbazide as well as semicarbazide derivatives with the aim to evaluate their cytotoxic and antiviral activities.

2. Results and discussions

2.1. Chemistry

In this work, the novel derivatives **4**–**19** were designed and prepared as illustrated in Schemes 1 and 2.

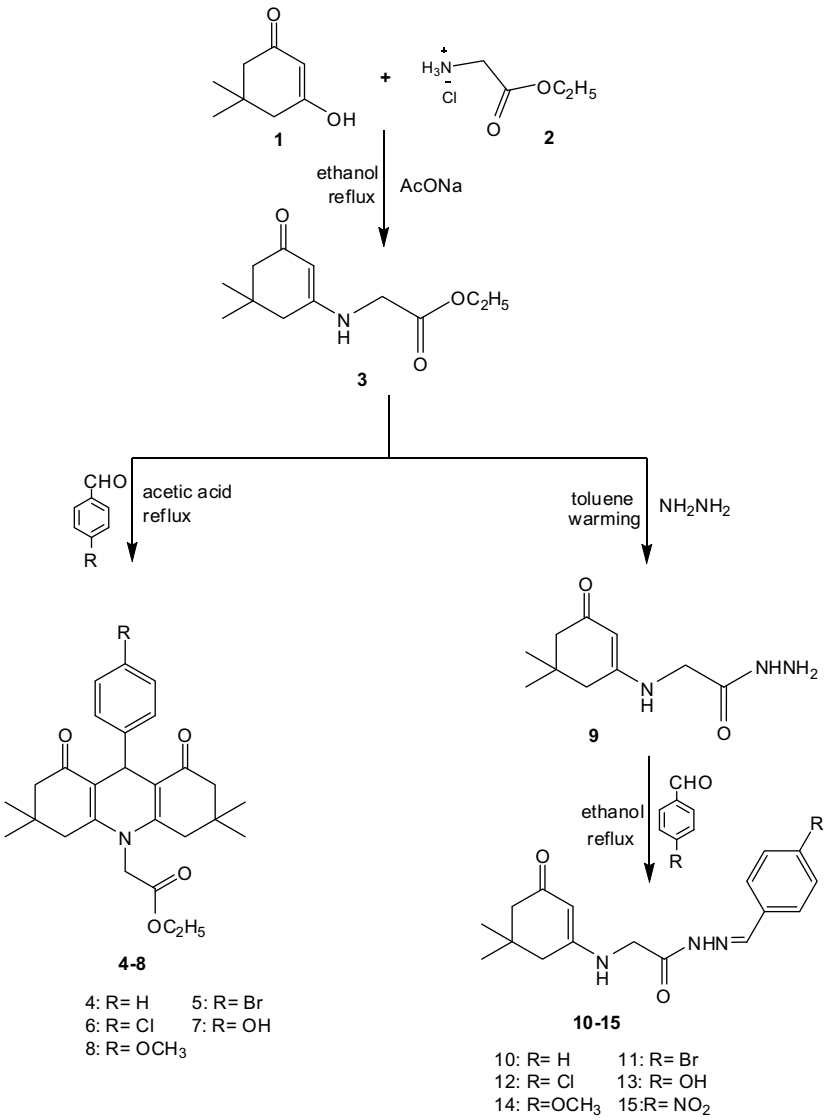
The key intermediate ethyl 2-(5,5-dimethyl-3-oxocyclohex-1-enyl amino) acetate (**3**) was prepared by condensation of equimolar amounts of 5,5-dimethyl-1,3-cyclohexandione (**1**) with ethyl glycinate HCl (**2**) in the presence of anhydrous sodium acetate adopting two procedures either via heating the reactants under reflux in toluene for 15 h to produce 65% yield [16–19] or in ethanol for 2.5 h giving 85% yield. The latter method was preferred than the former one due to it afforded pure product with higher yield in shorter time.

The novel nonclassical acridine derivatives (**4**–**8**) were obtained in one-pot synthesis reaction via cyclocondensation of enaminone **3** with half equivalent of aromatic aldehyde through heating the reactants at reflux for 4 h in glacial acetic acid (Scheme 1). This method gave the acridines in one step without passing through the formation of bis intermediates. Moreover, acetic acid was found to be the solvent of choice for conducting the cyclocondensation whereas it provided the reaction with a higher temperature necessary for its completion and also maintained the expelled amine residue, thus it favors the formation of acridines.

The structures of the novel acridines were confirmed using IR spectra which showed the disappearance of NH stretching band at

* Corresponding author. Tel.: +20 109610300; fax: +20 552303266.
E-mail addresses: elsabbagh_59@yahoo.com, elsabbagh_59@zu.edu.eg (O.I. El-Sabbagh).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.04.001



Scheme 1. Synthetic pathway for compounds **3**–**15**.

$\upsilon = 3260\ cm^{-1}$ for the starting enaminone. ^1H NMR proved the absence of vinylic H singlet peak around $\delta = 4.992$ ppm as well as NH singlet peak around $\delta = 7.25$ ppm for the starting enaminone. In addition, the appearance of singlet signal at $\delta = 5.168$ ppm assignable to 9-H of acridine nucleus.

An interesting observation is the appearance of geminal methyl groups at different chemical shifts (0.954 and 1.065). This observation of the different values for geminal methyl groups may be due to either the nonbonding interaction between the aromatic residue at position 9 and the 1,8-dioxo functions.

This may allow the former to occupy angular position to the tricyclic plane of the acridine skeleton. The other possibility for the distinguished chemical shifts of the methyls may be due to the limited free rotation of the phenyl group at position 9. One of the geminal methyl may also be affected by the anisotropy of the ring current. Thus, it appears at higher chemical shift value which was supported by constructing models for these compounds.

Moreover, the acid hydrazide **9** was synthesized through the reaction of enaminone ester **3** with hydrazine hydrate either in ethanol by heating the reactants at reflux for 3 h (50% yield) or by just warming them in toluene with continuous stirring for 10 min only (83% yield). The latter method was characterized by affording pure product in an excellent yield.

Condensation of the hydrazide **9** with different aromatic aldehydes was conducted by heating the reactants in ethanol containing catalytic amount of glacial acetic acid to afford the novel hydrazone derivatives **10**–**15**.

The structures of these hydrazones were confirmed using ^1H NMR spectra which showed the disappearance of NH_2 singlet broad peak around $\delta = 4.322$ ppm for the starting hydrazide. In addition, the appearance of singlet signal at $\delta = 7.939$–8.031 ppm assignable to azomethine proton as well as multiplet peaks around $\delta = 6.827$–7.794 ppm due to aromatic residue. Furthermore, the presence of vinylic H singlet around $\delta = 4.7$ ppm as well as NH broad singlet around $\delta = 7.0$ ppm of enaminone system exclude the formation of acridine nucleus under the reaction condition.

The formation of the novel thiosemicarbazide derivative **16** was accomplished through the reaction of equimolar amounts of hydrazide **9** and phenyl isothiocyanate in refluxing ethanol. In addition, the thiosemicarbazide **16** was cyclized either under acidic