European Journal of Medicinal Chemistry 46 (2011) 229–235

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and in vitro anti-tumor activity of new oxadiazole thioglycosides

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ARTICLE INFO

Article history:
Received 12 April 2010
Received in revised form
3 November 2010
Accepted 5 November 2010
Available online 12 November 2010

Keywords:
1,3,4-Oxadiazole
Thiogycosides
Tamoxifen
5-Flurouracil
Anti-tumor activities
Toxicity

ABSTRACT

A facile, convenient and high yielding synthesis of novel thioglycosides incorporating 1,3,4-oxadiazole, triazole and or triazine moieties from readily available starting materials has been described. The key step of this protocol is the formation of 3-*iso*butyl-1-phenyl-*1H*-pyrazole-4-carbaldehyde (**3**) *via* condensation between methyl *iso*-butyl ketone and phenylhydrazine followed by application of Vilsmeier–Haack reaction. **3** was converted either to 1,3,4-oxadiazole derivative or condensed with *O*-aminothiols to give the bases **8**, **19** and **20** in good yields, respectively. The aglycons **8**, **19**, and **20** were coupled with different activated halosugars in the presence of basic medium. Pharmacological evaluation of compounds **8**, **14**, **16** and **22** in vitro against 2-cell lines MCF-7 (breast) and HEPG2 (liver) revealed them to possess high anti-tumor activities with IC_{50} values ranging from 2.67–20.25 (μg/mL) for breast cell line (MCF-7) and 4.62–43.6 (μg/mL) for liver cell line (HEPG2). None of the tested compounds exhibited any toxicity in doses up to 500 mg kg^{-1} of the animal body weight.

1. Introduction

The incidence and mortality of cancer patients have become one of the important issues discussed worldwide. Unfortunately, development of resistance to chemotherapeutic agents is a common obstacle in the treatment of different types of cancers [1,2]. Several important drugs including tamoxifen (TAM), 5-flurouracil (5FU), adriamycin (ADR) and vincristin (VCR) with different structures and mechanisms of anti-tumor activities fail to end these problems completely. Due to the several side effects, drug resistance and failure of anti-tumor drugs to exert their effects in certain cases of cancers [3–5], looking for new chemotherapeutic agents with synthetic or natural origins is one of the hot topics in cancer research laboratories.

1,3,4-Oxadiazole derivatives have attracted significant attention in the field of drug discovery because of their wide array of pharmacological activities, including antibacterial–antifungal, analgesic, anti-inflammatory, antihypertension, muscle relaxing and anticancer activities [6–16]. Additionally, pyrazole and N-arylpyrazole derivatives are very important class of heterocyclic compounds that have remarkable pharmacological activities as antibacterial–antifungal, hypoglycemic, hyperlipidemia, kinase inhibitor for treatment of type 2 diabetes, anti-inflammatory and tumor necrosis inhibitor [17–21].

In view of the above mentioned findings and our previous reports [22–26], the purpose of the present work was to design, synthesize and investigate the anti-tumor activity of some novel 1H-pyrazolo-1,3,4-oxadiazole derivatives carrying carbohydrate residues through S-glycosidic bond formation.

2. Chemistry

The synthesis of our desired pyrazole derivatives began with commercially available aliphatic ketones **1a**,**b** (namely, 2-butanone and methyl *iso*-butyl ketone) and phenylhydrazine as starting materials. Condensation between the ketone and hydrazine provided a hydrazones **2a**,**b** in high yields. The Vilsmeier–Haack reaction using 2.5 eq of reagent performed a double addition of reagent to afford, ultimately after hydrolysis, the desired cyclized aldehyde **3** in 80% yield unfortunately, the application of the Vilsmeier–Haack reaction at the hydrazone **2a** did not led to desired product, instead 3,4-dimethyl-1-phenyl pyrazole (**4**) was obtained as a sole product (Scheme 1).

The reaction sequence of preparing the desired aglycon [5-(3-*Iso*butyl-1-phenyl-1H-pyrazole-4-yl)-1,3,4- oxadiazle-2-thiol (**8**)] is some what long and linear with few common intermediates. To this aim, aldehyde **3** is oxidized using a mixture of sulphuric acid (30%) and $K_2Cr_2O_7$ to yield the acid **5** which esterified using absolute ethanol in presence of few drops of conc. sulphuric acid, affording **6** in fairly good yield. The ^1H NMR of acid **5** showed the

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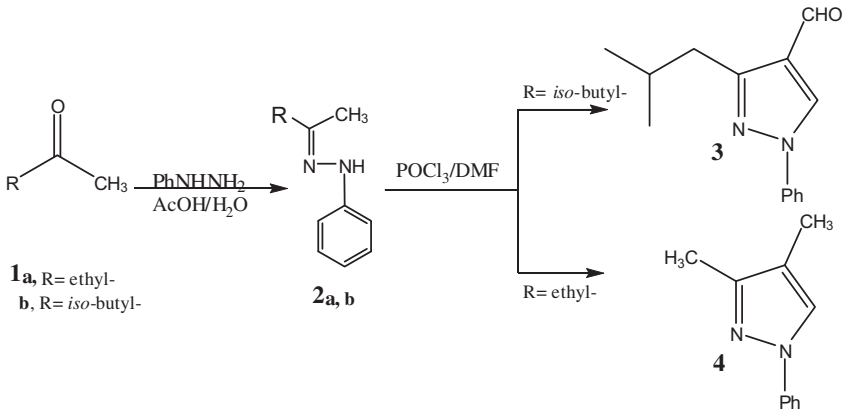
doi:10.1016/j.ejmech.2010.11.008



Scheme 1. Synthesis of 1-phenylpyrazoles **3** and **4**.

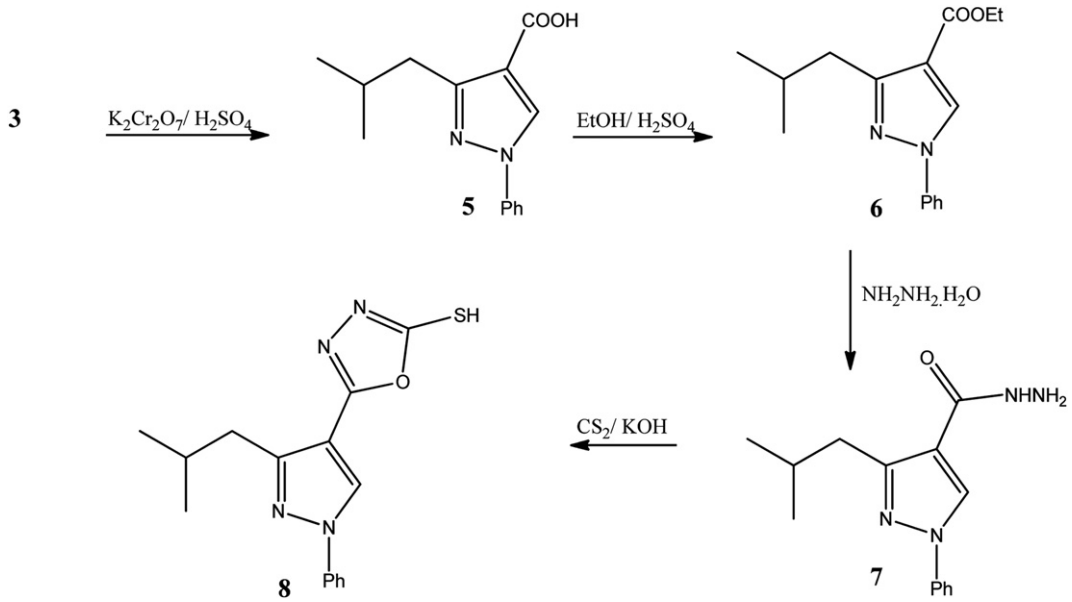
absence of aldehydic proton which detected at the parent **3**, while, the ester **6** showed the ethyl protons at their expected locations.

Treatment of **6** with hydrazine hydrate in boiling ethanol afforded the hydrazide derivative **7** in good yield. Finally the oxadiazole derivative **8** was achieved following our previously reported method [27] by adopting a simple one pot procedure that involves reacting of **7** with carbon disulphide under strong basic conditions followed by acidification with diluted hydrochloric acid (Scheme 2).

The coupling between the aglycon and the activated sugars was achieved in the presence of basic medium. Thus, aglycon **8** was reacted with NaH in dry DMF followed by addition of the activated cyclic sugars (2′,3′,4′,6′-tetra-*O*-acetyl-α-D-gluco (or galacto)) pyranosyl bromide **9** and **10**, or the activated acyclic sugar analogues, chloromethyl methylthioether (**11**), or chloromethyl ethyl ether (**12**), to give the corresponding thioglycoside derivatives **14**–**17** in a good yields, respectively.

The structures of thioglycosides **14** and **15** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (^{1}H NMR, ^{13}C NMR and MS, cf. experimental). Thus, their ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ = 5.68 and 6.24 ppm with a spin–spin coupling constant ($J_{1',2'}$ = 9.95 and 10.39 Hz) corresponding to a *trans* orientation of H-1′ and H-2′ protons indicating the β-configuration. On the other hand, the formation of S-glycosides **14** and **15** and not the corresponding N-glycosides **13** were proved using ^{13}C NMR spectroscopy which revealed the absence of a signal at δ 178 ppm for the thione carbon and the appearance of a signal at δ = 162.21 and 161.55 ppm corresponding to the C-2 carbon of the 1,3,4-oxadiazole ring, whose chemical shift is the same as that of the corresponding S-methyl derivative [28–30], the same results were obtained with compounds **16** and **17** (Scheme 3).

Additionally, when compound **3** was condensed with selected examples of bidentate ligands (**18a**, **b**), the condensing adducts **19**, **20** were obtained in high yields. The ^{1}H NMR of **19**, **20** showed the methine CH proton at 7.97 and 8.22 ppm supported the condensing adduct structures. Finally, the S-glycosides **21**, **22** were obtained in fairly good yields, on treatment of compounds **19** and **20** with **9** in the presence of NaH/DMF following the above mentioned conditions whereas the β-isomers were obtained ($J_{1',2'}$ = 9.75 and 9.20 Hz) (Scheme 4).



Scheme 2. Synthetic pathway for the synthesis of 5-(3-isobutyl-1-phenyl-1*H*-pyrazol-4-yl)-1,3,4-oxadiazole-2-thiol **8**.