Hetero-annulation reaction between 2-acylnaphthoquinones and 2-aminobenzothiazoles. A new synthetic route to antiproliferative benzo[g]benzothiazolo[2,3-b]quinazoline-7,12-quinones

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Abstract

A convenient two-step method is developed for the preparation of benzo[g]benzothiazolo[2,3-b]quinazoline-7,12-quinones from 2-acylnaphthohydroquinones and 2-aminobenzothiazoles. The structure of the heterocyclic quinones is supported by X-ray crystallography. This protocol provides an operationally simple strategy to prepare the title compounds and shows good functional flexibility and easily available starting materials. Evidences are reported on the significant in vitro antiproliferative activities of some of the obtained heterocyclic quinones on prostate, bladder, and breast human-derived tumor cell lines.

Introduction

Quinones are ubiquitous in nature and comprise one of the largest classes of anticancer agents. Anticancer quinones are currently the focus of intensive research because of their biological activity and complex modes of action, which differ depending on their particular structure. The biological processes involved with the antitumor activity of quinones are based mainly on DNA intercalation, bioreductive alkylation of biomolecules, and generation of reactive oxygen species (ROS) through redox cycling. The DNA intercalative ability of quinonoid antitumor agents, such as daunorubicine, doxorubicine, mitoxantrone, and mitomycin C, is due to their large and planar polycyclic structures, which facilitates the binding between the base pairs through hydrogen bonds and π-stacking interactions. Our research group has especially focused on biologically active compounds based on quinone cores fused to heterocyclic rings. In this context we have reported the synthesis and antiproliferative activity on cancer cells of a variety of isoquinoline-containing polycyclic quinones. It is worth mentioning that a number of the reported N-heterocyclic quinones exhibit inhibition of topoisomerase I and activation of caspase-3 in HL-60 cells. Our synthetic strategy to entry into isoquinoline-containing polycyclic quinones is based on the hetero-annulation reaction of 2-acyl-1,4-quinones with primary acyclic- and endocyclic enaminones, where the electrophilic α,β-unsaturated acyl fragment of the quinone and the ambident nucleophile H$_2$N- group of the enaminone are involved in the N-heterocyclic ring formation. Taking into account the similar chemical reactivity of enaminones and 2-aminobenzothiazoles to act as ambident nucleophiles with α,β-unsaturated carbonyl compounds to give heterocycles, we decided to explore the synthesis of benzo[g]benzothiazolo[2,3-b]quinazoline-7,12-quinones from 2-acylnaphthoquinones and 2-aminobenzothiazoles. To the best of our knowledge, the sole precedent regarding the synthesis of antiproliferative benzo[g]benzothiazolo[2,3-b]quinazolinequin ones is the recent report on amberlyst-15 catalyzed three-component condensation of 2-aminobenzothiazole, aromatic aldehydes, and 2-hydroxy-1,4-naphthoquinone. Herein, we wish to report that benzo[g]benzothiazolo[2,3-b]quinazoline-7,12-quinones...
quinone derivatives can be conveniently obtained from easily available 2-acyl-1,4-naphthoquinones and 2-aminobenzothiazoles. Preliminary antiproliferative evaluation of some members of the series on cancer cell lines is also described.

Results and discussion

To explore the possibility of heterocyclic annulation reactions, 2-acetyl-1,4-naphthoquinone 2a and aminobenzothiazole 3a were initially chosen. Quinone 2a, prepared by oxidation of acylhydroquinone 1a with silver(I) oxide, was reacted with 3a in dichloromethane at room temperature to give a red solid product. The IR spectrum of the product revealed the presence of O–H and C=O bands at 3421, 1680 and 1644 cm⁻¹. The ¹H NMR spectrum showed hydroxyl and naphthoquinone peri aromatic protons at δ 6.37 (br s), 8.10 (dd) and 8.17 (dd). The ¹³C NMR spectrum displayed characteristic signals at δ 28.6, 88.5, 182.7, and 185.7 due to a methyl, an aliphatic quaternary carbon, and two carbonyl groups. The mass spectrum showed the molecular ion [M+1] peak at m/z = 348.05649. Based on these data, together with the high electrophilic character of the C-3 in 2-acyl-1,4-naphthoquinones and the behavior of 2-aminobenzothiazole to act as ambident nucleophile with α,β-unsaturated carbonyl compounds, two possible alternative structures derived from benzog[benzothiazol][2,3-b]quinazoline (4a) and benzog[benzo][4,5]-thiazolo[3,2-d]quinazoline (4a‘), were assigned for the reaction product isolated in 66% yield (Scheme 1).

Encouraged by these results we explored the substrate scope for the synthesis of dibenzothiazolquinazolinequinones such as 4a or 4a‘. A variety of 2-acyl-1,4-naphthoquinones 2b–2e, generated by oxidation from their corresponding acylhydroquinones 1b–1e with silver(I) oxide, were reacted with different 2-aminobenzothiazoles 3a–c, under standard conditions. The spectral data of the new products 4b–4k were closely similar to those described above for compound 4a or 4a‘. In order to unequivocally establish the structure of the benzothiazolquinazolinequinones formed in the reaction of acylnifiones 2 with the aminobenzothiazoles 3, compound 4b was submitted to X-ray diffraction analysis (Fig. 1).

Based on the X-ray crystallographic data for compound 4b it may be concluded that the products formed by reaction of 2-acylnaphthoquinones 2 with aminobenzothiazoles 3, exhibit the benzog[benzothiazol][2,3-b]quinazoline-7,12-quinone framework (Fig. 1). Table 1 summarizes the results arising from the reaction of acylnifiones 2 with aminobenzothiazoles 3 to produce compounds 4. The possibility to prepare compounds 4 via a one-pot procedure from acylhydroquinone 1, amine 3, and silver(I) oxide in dichloromethane was studied using substrates 1a and 3a. The assays indicate that this procedure is unfeasible to prepare 4a due to oxidative decomposition of amine 3a. A plausible mechanism of this interesting hetero-annulation reaction is shown in Scheme 2 for the formation of compound 4a.

The reaction seems to proceed via an initial attack of the NH₂ group of 3a at the 3-position of the activated quinone 2a to give a Michael intermediate adduct, which by a further 6-exo trig ring closure, followed by aerobic oxidation, yields the heteropentacyclic quinone 4a.

Quinones 4b, 4c, 4f, and 4h were evaluated for their in vitro antiproliferative activity on a panel of three human-derived tumor cell lines, using the conventional MTT (microculture tetrazolium reduction) assay. The data in Table 2 show that compounds 4e,
Table 2

In vitro antiproliferative activity of 4b, 4e, 4f, and 4h on T24 (bladder), DU-145 (prostate) and MCF7 (breast) cancer cell lines

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 ± SEM (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-24</td>
</tr>
<tr>
<td>4b</td>
<td>4.86 ± 0.50</td>
</tr>
<tr>
<td>4e</td>
<td>0.22 ± 0.06</td>
</tr>
<tr>
<td>4f</td>
<td>1.36 ± 0.15</td>
</tr>
<tr>
<td>4h</td>
<td>1.32 ± 0.11</td>
</tr>
<tr>
<td>DOXb</td>
<td>0.65 ± 0.07</td>
</tr>
<tr>
<td>MITc</td>
<td>42.2 ± 5.8</td>
</tr>
<tr>
<td>TFd</td>
<td>32.9 ± 1.5</td>
</tr>
</tbody>
</table>

a Data represent IC50 mean values ± SEM of at least three different experiments.

References and notes

20. Synthesis of 13-hydroxy-t3-(1-propyl)-7H-benzo[g][1,2-b]quinazoline-7,12-quinone (4b): Typical Procedure. A suspension of 2-aminobenzothiazole (3a; 1H, 1.21 mmol), Ag2O (1.1 g, 4.65 mmol), anhydrous MgSO4 (200 mg), and dichloromethane (15 mL) was left at room temperature with stirring at rt for 1 h. The mixture was filtered and, over the completion of the reaction, as indicated by TLC (24 h), the resulting solution was left with stirring at room temperature after removal of the solvent by evaporation. The resulting crude product was purified by column chromatography on a silica gel (petroleum ether/CH2Cl2/DCM, 15:5:20) yield purity 4b (273 mg, 0.73 mmol, 78%) as a red solid; mp 203.5–204.0 °C; IR (KBr, cm−1): 3444 (O–H), 1664, 1641 (C=O); 1H NMR (400 MHz, CDCl3); δ = 0.76 (3H, J= 7.2 Hz, CH3), 0.39 (3H, CH3), 1.35 (3H, CH3), 2.41 (dt; 3H, J= 13.3, 4.2 Hz, CH2), 2.72 (dt; 3H, J= 13.3, 4.7 Hz, CH2), 6.37 (br s, 1H, OH), 7.29 (t; 3H, J= 8.0 Hz, 2- or 3-H), 7.41 (t; 1H, J= 8.0 Hz, 3- or 2-H), 7.56 (d; 1H, J= 7.8 Hz, 4-H), 7.71 (t; 1H, J= 8.0 Hz, 9- or 10-H), 7.75 (t; 1H, J= 8.0 Hz, 10- or 9-H), 8.07 (d; 1H, J= 7.4 Hz; 8- or 11-H), 8.15 (d; 1H, J= 7.3 Hz, 11- or 8-H), 8.22 (d; 1H, J= 8.4 Hz, 1-H); 13C NMR (100 MHz, CDCl3); δ = 123.9, 118.2, 114.2, 91.7, 115.0, 118.1, 122.5, 125.0, 126.3, 127.2, 127.5, 131.7, 133.3, 133.7, 134.5, 137.7, 146.7, 167.5, 182.4, 185.7; HRMS (APCI) calcd for C20H16N2O5S: 376.08816 [M+H]+; found: 376.09454.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.034.