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Synthesis of the new ring system 6,8-dihydro-*5H*-pyrrolo[3,4-*h*]quinazoline

Paola Barraja, Virginia Spanò, Patrizia Diana, Anna Carbone, Girolamo Cirrincione *

Dipartimento Farmacochimico, Tossicologico e Biologico Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

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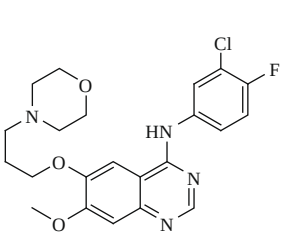
ABSTRACT

A convenient synthesis of the pyrrolo[3,4-*h*]quinazoline ring system is reported. Our synthetic approach consisted of the annelation of a pyrimidine ring to an isoindole moiety using tetrahydroisoindole-4-ones as building blocks. The antiproliferative activity of the new compounds was investigated and one of them showed antitumor activity against all the 59 tested cell lines at micromolar concentrations (1.46–18.4 μM).

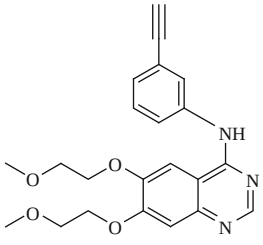
The quinazoline nucleus is the scaffold of many antitumor drugs mainly acting as inhibitors of tyrosine kinase receptors (RTK). Overexpression of these receptors is found in a number of cancers (e.g., breast, ovarian, colon, and prostate). In particular VEGF (vascular endothelial growth factor) has been recognized as a key factor promoting neovascularization of many tumors.[1,2] Leading examples of quinazoline-based inhibitors are the clinically approved anticancer agent Iressa (ZD1839) **1** and Tarceva (OSI 774/CP358,774) **2** which is in Phase III clinical trials for cancer.[3,4] Both compounds inhibit the receptor tyrosine kinase of the epidermal growth factor (EGFR/HER1). Other compounds containing the quinazoline moiety which target the vascular or endothelial growth factor receptors have been advanced into clinical trials[5,6] and quinazoline RTK inhibitors of the platelet-derived growth factor receptors (PDGFRs) with potent activity have been also reported.[7]

Moreover fused tricyclic quinazolines such as pyrrolo- and pyrazoloquinazolines **3** and **4**, respectively, showed IC_{50} values in the nanomolar range in the inhibition of VEGFR.[8] In addition pyrrolo[3,2-*f*]quinazolines of type **5** are effective for neoplastic diseases as inhibitors of the dihydrofolate reductase (DHFR).[9]

We have recently studied the synthesis of isoindole-based ring systems such as the pyrano[2,3-*e*]isoindol-2-one[10] **6** and the pyrrolo[3,4-*h*]quinolin-2-one[11] **7** as heteroanalogues of Angelicin.



1



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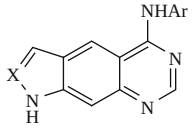
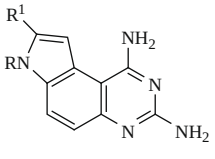


3 X=CH
4 X=N



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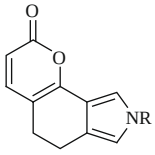

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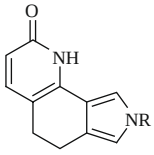

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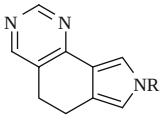

8

Considering our interest in the chemistry of pyrrole and encouraged by the potent antitumor activity of the above mentioned quinazoline derivatives we decided to investigate the synthesis of another pyrrolo-fused heterocycle, the pyrrolo[3,4-*h*]quinazoline **8**. Our synthetic strategy for this new ring system consists of the annelation of a pyrimidine moiety to an isoindole moiety as described in Scheme 2. The 1-phenyl derivative **12a** was obtained by a multistep sequence starting from 2-[(dimethyl-

* Corresponding author. Tel.: +39 0916161606; fax: +39 0916169999.
E-mail address: gcirrinc@unipa.it (G. Cirrincione).

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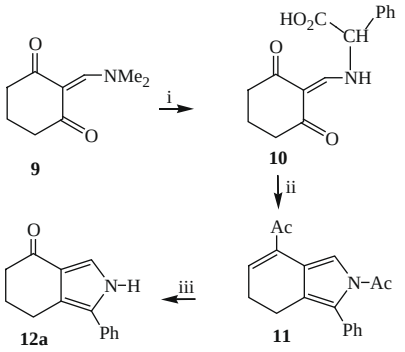


Scheme 1. Synthesis of intermediate **12a**. Reagents and conditions: (i) phenylglycine, $AcONa{\cdot}3H_2O$, ethanol, reflux, 4 h, 95%; (ii) Et_3N, Ac_2O, 30 min, reflux, 83%; (iii) 80% acetic acid, 37% HCl, 30 min, 60 °C, 94%.

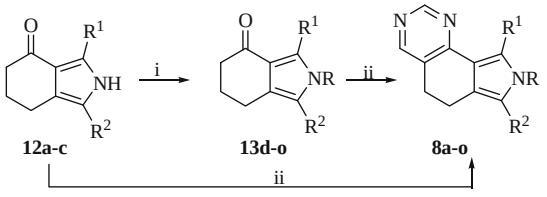
amino)methylene]cyclohexane-1,3-dione **9** which was reacted with phenylglycine to give the enaminoacid **10**. Cyclization of this latter in acetic anhydride and triethylamine gave the expected dihydroisoindole **11**. The tetrahydroisoindole-2-one **12a** was obtained upon desacetylation by heating in aqueous acetic acid (80%) and HCl (37%) (Scheme 1).[12] Tetrahydroisoindole-4-ones **12b,c** were conveniently prepared as described before.[10]

Ketones **12a–c** were functionalized on the nitrogen atom in THF or DMF using NaH as the base and an alkylating agent such as MeI, BnCl, ClBn*p*Me, or ClBn*p*OMe to give the corresponding N-substituted derivatives **13d–o** (60–98%).

The annelation of the pyrimidine ring on the isoindole moiety was achieved by the Bredereck method widely used for the synthesis of pyrimidine and their fused derivatives, such as pyrimidinocarbazoles, starting from ketones.[13] Thus, heating under reflux tetrahydroisoindole-4-ones **12a–c** or **13d–o** in formamide with tris-(formylamino)-methane in the presence of catalytic amount of *p*-toluenesulfonic acid, derivatives **8a–o** were obtained in moderate to good yields (45–90%).[14] (Scheme 2, Table 1)

All the new compounds were submitted to the NCI of Bethesda for antiproliferative studies. Derivatives **8b–e,g,i,l,m,o** were selected for the one dose (10^{-5} M) screening on the full panel of 60 human cancer cell lines derived from nine human cancer cell types, that have been grouped in disease sub-panels including leukemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumor cell lines.

Derivative **8o** was further tested at five concentrations at 10-fold dilution (10^{-4}–10^{-8} M), showing activity against all the 59



a R=R^1=H, R^2=Ph; **b** R=R^1=R^2=H; **c** R=H, R^1=Me, R^2=CO_2Et; **d** R=Me, R^1=R^2=H; **e** R=Bn, R^1=R^2=H; **f** R=Bn*p*Me, R^1=R^2=H; **g** R=Bn*p*OMe, R^1=R^2=H; **h** R=Me, R^1=Me, R^2=CO_2Et; **i** R=Bn, R^1=Me, R^2=CO_2Et; **j** R=Bn*p*Me, R^1=Me, R^2=CO_2Et; **k** R= Bn*p*OMe, R^1=Me, R^2=CO_2Et; **l** R=Me, R^1=H, R^2=Ph; **m** R=Bn, R^1=H, R^2=Ph; **n** R=Bn*p*Me, R^1=H, R^2=Ph; **o** R=Bn*p*OMe, R^1=H, R^2=Ph.

Scheme 2. Synthesis of 6,8-dihydro-5*H*-pyrrolo[3,4-*h*]quinazolines **8a–o**. Reagents and conditions: (i) NaH, MeI or BnCl or Bn*p*MeCl or Bn*p*OMeCl, THF or DMF, rt or reflux, 2–24 h, 60–98%; (ii) $CH(NHCHO)_3$, TsOH, formamide, reflux, 3–24 h, 45–90%.

Table 1
Substrates, reaction times, melting points, and yields for compounds **8a–o**

Substrate	product	Reaction time (h)	Mp (°C)	Yield (%)
12a	**8a**	3	241–242	60
12b	**8b**	5	92–94	45
12c	**8c**	17	216–217	70
13d	**8d**	7	Oil	62
13e	**8e**	22	100–101	50
13f	**8f**	22	Oil	45
13g	**8g**	7	Oil	70
13h	**8h**	22	62–63	75
13i	**8i**	24	150–151	60
13j	**8j**	24	111–112	80
13k	**8k**	24	99–100	80
13l	**8l**	20	170–171	70
13m	**8m**	24	Oil	90
13n	**8n**	7	Oil	80
13o	**8o**	5	Oil	60

tested cell lines (see Supplementary data) at micromolar concentration (1.46–18.4 μM).

The best selectivity was achieved for the leukemia (1.46–3.99 μM), and melanoma (2.49–6.81 μM) sub-panels.

In conclusion, we have reported a versatile method for the synthesis of derivatives of the new ring system pyrrolo[3,4-*h*]quinazoline in good overall yields. The antiproliferative activity shown by derivative **8o** makes this class of compounds interesting for further studies directed toward the synthesis of more potent antiproliferative agents.

Acknowledgment

This work was financially supported by Ministero dell'Istruzione dell'Università e della Ricerca.

Supplementary data

Supplementary data (Table 2 containing the GI_{50} of **8o** against 59 tested human tumor cell lines and spectroscopic and analytical data for **8c–o**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.045.

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14. *Preparation of the appropriate 6,8-dihydro-5H-pyrrolo[3,4-h]quinazoline* **8a–o**: To a solution of **12a–c** or **13d–o** (3 mmol) in formamide (5 mL), tris-(formylamino)-methane (0.82 g, 6 mmol) and catalytic amount of *p*-toluenesulfonic acid were added. The mixture was heated under reflux for the designated time, poured onto crushed ice and extracted with ethyl acetate. The crude material was purified by column chromatography, using dichloromethane/ethyl acetate (9:1) as eluent.
Data for 7-phenyl-6,8-dihydro-5H-pyrrolo[3,4-h] quinazoline **8a**: IR ($CHBr_3$): 3139 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.83–2.99 (4H, m, 2 × CH_2), 7.23–7.56 (6H, m, Ar and H-9), 8.47 (1H, s, H-4), 8.84 (1H, s, H-2), 11.71 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 19.8 (CH_2), 25.6 (CH_2), 117.6 (C), 118.4 (CH), 119.9 (C), 125.7 (C), 126.0 (C), 126.3 (2 × CH), 127.1 (CH), 128.7 (2 × CH), 132.4 (C), 154.2 (CH), 156.7 (CH), 157.9 (C). Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.37; H, 5.59; N, 17.26.
Data for 6,8-dihydro-5H-pyrrolo[3,4-h]quinazoline **8b**: IR ($CHBr_3$): 3184 (NH) cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.71 (2H, t, J = 6.2 Hz, CH_2), 2.83 (2H, t, J = 6.2 Hz, CH_2), 6.68 (1H, s, H-7), 7.86 (1H, s, H-9), 8.43 (1H, s, H-4), 8.79 (1H, s, H-2), 11.17 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 19.2 (CH_2), 25.7 (CH_2), 114.5 (CH), 116.7 (CH), 118.3 (C), 120.8 (C), 126.4 (C), 154.1 (CH), 156.6 (CH), 158.1 (C). Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.29; H, 5.12; N, 24.33.