Bioorganic & Medicinal Chemistry Letters 24 (2014) 2324–2328

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and biological evaluation of compounds which contain pyrazole, thiazole and naphthalene ring as antitumor agents

Ji-Wen Yuan †, She-Feng Wang †, Zhong-Liang Luo, Han-Yue Qiu, Peng-Fei Wang, Xin Zhang, Yong-An Yang, Yong Yin, Fei Zhang, Hai-Liang Zhu *

State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, PR China

ARTICLE INFO

Article history:
Received 9 January 2014
Revised 5 March 2014
Accepted 24 March 2014
Available online 3 April 2014

Keywords:
EGFR inhibitors
Anti-tumor activity
Cell migration
Structure–activity relationship

ABSTRACT

A series of compounds which contain pyrazole, thiazole and naphthalene ring (**1a**–**7a**, **1b**–**7b**, **1c**–**7c**, **1d**–**7d**) were firstly synthesized and their anti-proliferative activity, EGFR inhibitory activity, cytotoxicity and inhibition to Hela cell migration were evaluated. Compound 2-(3-(3,4-dimethylphenyl)-5-(naphthalen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-one (**7d**) displayed the most potent inhibitory activity (IC_{50} = 0.86 μM for Hela and IC_{50} = 0.12 μM for EGFR). Structure–activity relationship (SAR) analysis showed that the anti-proliferative activity was affected by A-ring-substituent (–OCH_3 > –CH_3 > –H > –Br > –Cl > –F). Docking simulation of compound **7d** into EGFR active site showed that naphthalene ring of **7d** with LYS721 formed two *p*–π bonds, which enhanced antitumor activity. Therefore, compound **7d** may be developed as a potential antitumor agent.

Pyrazole ring was a prominent skeleton motif in a lot of pharmaceutically active compounds, and pyrazole derivatives possess a wide range of biological activities, such as anti-inflammatory,[1] antifungal,[2,3] antimicrobial,[4,5] anticoagulants,[6] analgesic,[7] antithrombolic,[8] anti-tumor activity,[9,10] and so on. A series of pyrazoleoxime ether derivatives were prepared and examined as cytotoxic agents, among which 5-phenoxypyrazole exhibited very potent cytotoxicity against XF 498 and HCT15.[9] While 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives were showed inhibitory effects on the growth of A549 cells.[10]

Thiazole and its derivatives were widely used in pesticides and medicine. For example, 4-(4-chlorophenyl)-2-(3-(3,4-dimethylphenyl)-5-p-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl) thiazole displayed the potent EGFR TK inhibitory activity and anti-proliferative activity against MCF-7,[11] 4-substituted methoxybenzoyl-aryl-thiazoles exhibited anti-proliferative activity of against melanoma and prostate cancer cells from μM to nM range.[12] Besides, thiazole and its derivatives also showed other biological activities in antimicrobial,[5] antifungal,[13] antifilarial,[14] anti-inflammatory,[15] antiviral,[16] and so on. Compounds containing naphthalene ring displayed potent bioactivity in anti-arrhythmia,[17] anti-tumor[18] and antioxidant.[19]

Due to potent biological activities and low toxicities,[20,21,4,22–25] we designed and synthesized a series of compounds containing pyrazole, thiazole and naphthalene ring and evaluated their anti-proliferative activity. As everyone knows, EGFR (epidermal growth factor receptor) plays a very important role in cell proliferation, survival, migration, differentiation and metastasis of many tumors. EGFR was often used as targets for the development of novel anticancer agents, such as Gefitinib and Elotinib.[26,27] To further understand the antitumor effect of designed compounds, docking simulation was performed to position compound **7d** into the EGFR active site to determine the probable binding model.

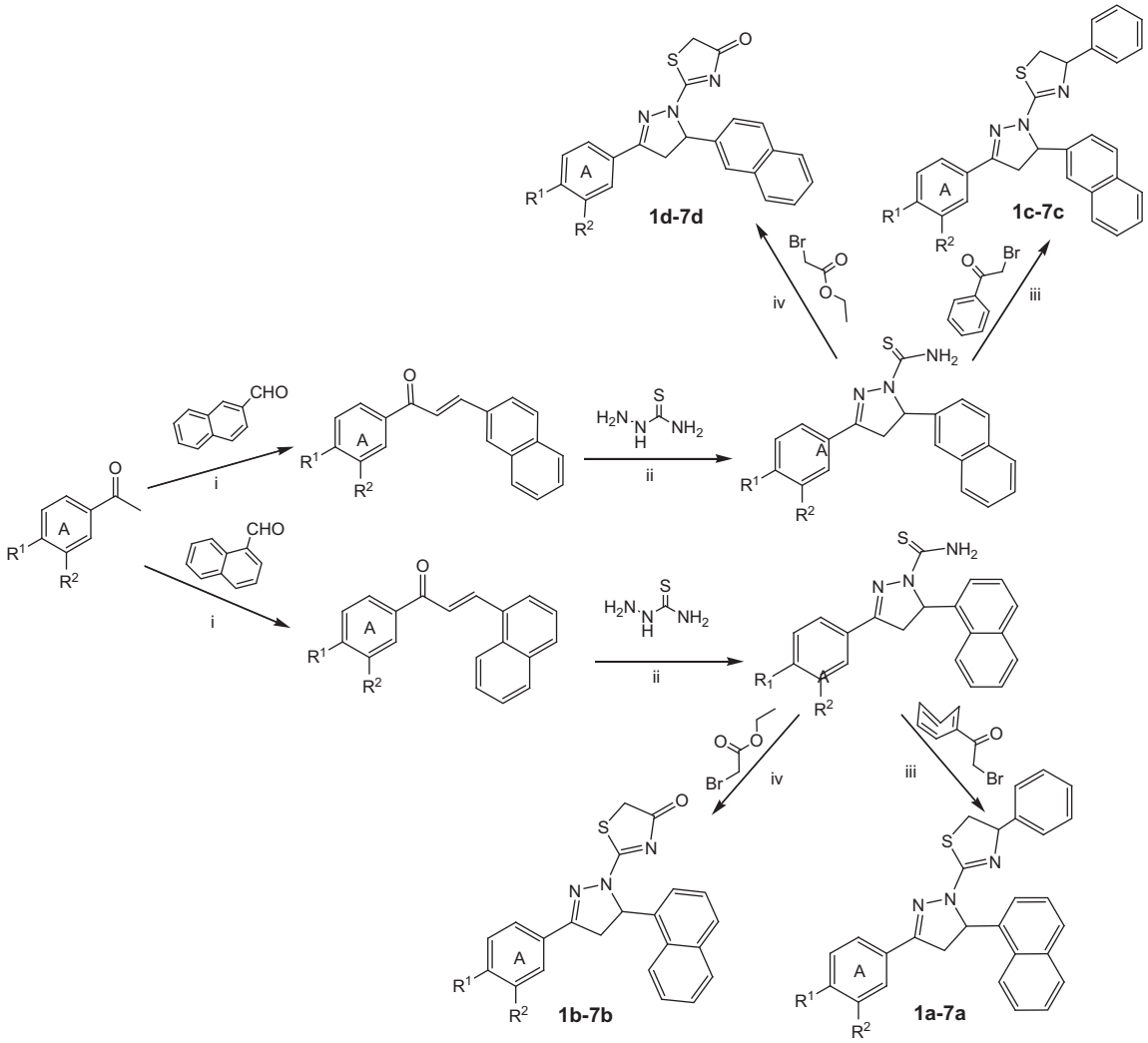
The synthetic procedures of compounds **1a**–**7a**, **1b**–**7b**, **1c**–**7c** and **1d**–**7d** were outlined in Scheme 1, Tables 1 and 2 and their structures were confirmed by one ^{1}H NMR and MS. The structures of compounds **1d** and **5d** were demonstrated by X-ray diffraction analysis. The crystal data were presented in Table 3, Figures 1 and 2 and have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication Nos. 987465 and 978466.

The title compounds were evaluated for their ability to inhibit cell proliferation against Hela, BGC823 and HepG2 cell lines using CCK8 assay. The results in Table 4 showed good anti-proliferative activities on Hela cancer cell line (IC_{50} values between 0.86 and 12.35 μM). Among them, compound **7d** showed the most potent inhibiting activity with IC_{50} 0.86 μM.

SAR studies were carried out to determine how compounds affected the anti-proliferative activity. Firstly, compound **7d** (IC_{50} = 0.86 μM) with two -CH_3 in A-ring displayed stronger anti-proliferative activity than those with one -OCH_3 (**5d**,

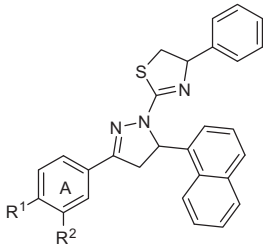
* Corresponding author. Tel.: +86 25 83592572; fax: +86 25 83592672.
E-mail address: zhuhl@nju.edu.cn (H.-L. Zhu).
† These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bmcl.2014.03.072
0960-894X/



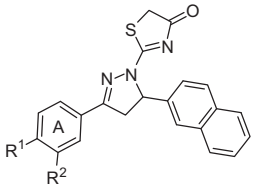
Scheme 1. General synthesis compounds **1a**–**7a**, **1b**–**7b**, **1c**–**7c**, **1d**–**7d**. Reagents and conditions: (i) 40% aqueous KOH solution, ethanol, rt; (ii) thiosemicarbazide, KOH, ethanol, reflux; (iii or iv) bromoacetic acid (or 2-bromo-1-phenylethanone), acetic anhydride, sodium acetate, acetic acid, 80 °C, 7–9 h.

Table 1
Chemical structure of compounds **1a**–**7a**, **1c**–**7c**



Compounds	R^1	R^2	Compounds	R^1	R^2
1a	H	H	**1c**	H	H
2a	F	H	**2c**	F	H
3a	Cl	H	**3c**	Cl	H
4a	Br	H	**4c**	Br	H
5a	OCH_3	H	**5c**	OCH_3	H
6a	CH_3	H	**6c**	CH_3	H
7a	CH_3	CH_3	**7c**	CH_3	CH_3

Table 2
Chemical structure of compounds **1b**–**7b**, **1d**–**7d**



Compounds	R^1	R^2	Compounds	R^1	R^2
1b	H	H	**1d**	H	H
2b	F	H	**2d**	F	H
3b	Cl	H	**3d**	Cl	H
4b	Br	H	**4d**	Br	H
5b	OCH_3	H	**5d**	OCH_3	H
6b	CH_3	H	**6d**	CH_3	H
7b	CH_3	CH_3	**7d**	CH_3	CH_3

IC_{50} = 1.48 μM), $-CH_3$ (**6d**, IC_{50} = 1.76 μM), –H (**1d**, IC_{50} = 3.48 μM), –Br (**4d**, IC_{50} = 4.22 μM), –Cl (**3d**, IC_{50} = 6.32 μM) and F (**2d**, IC_{50} = 9.17 μM), the order was **5d** > **6d** > **1d** > **4d** > **3d** > **2d**. The same results were also found in compounds **1a**–**7a**, **1b**–**7b** and **1c**–**7c**. This meant that compounds with stronger activating substituents in A-ring showed better anti-proliferative activity. The results indicated that the anti-proliferative activity was affected by A-ring-substituent ($-OCH_3$ > $-CH_3$ > –H > –Br > –Cl > –F). Secondly,