Bioorganic & Medicinal Chemistry Letters 24 (2014) 1685–1691

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and evaluation of some new pyrazoline substituted benzenesulfonylureas as potential antiproliferative agents

Pooja Rathore [a], Shafiya Yaseen [a], Syed Ovais [a], Rafia Bashir [a], Raed Yaseen [a], Alhamzah D. Hameed [a], Mohammed Samim [a], Rakesh Gupta [b], Firasat Hussain [b], Kalim Javed [a,*]

[a] Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110 062, India
[b] Department of Chemistry, University of Delhi, Delhi 110 007, India

ARTICLE INFO

Article history:
Received 6 December 2013
Revised 15 February 2014
Accepted 20 February 2014
Available online 28 February 2014

Keywords:
Benzenesulfonylureas
Pyrazolines
Anti-cancer
Antiproliferative activity
Sulfonamides

ABSTRACT

Twenty six new pyrazoline substituted benzenesulfonylureas (**2a**–**z**) were synthesized and tested for in vitro anticancer activity. Fourteen derivatives (**2i**, **2k**–**2p**, **2r**, **2s**–**2x**) were screened for their antiproliferative activity towards 60 human cancer cell lines by the National Cancer Institute (USA). Among them four compounds (**2i**, **2n**, **2v** and **2x**) exhibited significant growth inhibition and further screened at 10-fold dilutions of five different concentrations (0.01, 0.1, 1, 10 and 100 μM). The compounds **2i**, **2n**, **2v** and **2x** showed effective growth inhibition (GI_{50} MID) values of 2.62, 3.93, 3.33, 3.74 μM respectively beside cytostatic activity TGI (MG-MID) values of 8.42, 65.80, 24.00 and 36.06 μM respectively. The compound **2i** displayed remarkable antiproliferative activity in 8 different cell lines with GI_{50} less than 2 μM. Compounds **2n**, **2v** and **2x** also displayed good antiproliferative activity against 11, 18 and 14 different cell lines respectively with GI_{50} less than 3 μM.

Cancer is a group of illness that results from cells in the body growing abnormally. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs. Cancer treatment includes many strategies and chemotherapy plays a central role.[1] Chemotherapy involves the use of low-molecular-weight drugs to selectively destroy tumour cells or at least limit their proliferation. Despite immense advances in the field of basic and clinical research, which have resulted in higher cure rates for a number of malignancies, cancer remains the second leading cause of death after heart disorders in developing as well as advanced countries.[2] Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the difficult task of discovering new anticancer agents remains critically important.

Among the wide range of compounds tested as potential anticancer agents, derivatives comprising the sulfonamide, N^1,N^3-diarylsulfonylurea and -thiourea functionalities have attracted great attention.[3,4] Recently three sulphonamides derivatives E7010, ER-34410 and E7070 (Fig. 1I–III) have been reported as potent antitumor agents and are in advanced clinical trials.[5] Sulofenur (Fig. 1IV) is a sulfonylurea that has been clinically evaluated in lung, breast, colon, ovarian, pancreatic and gastric cancer.[6] The antitumor properties of the diarylsulfonylurea is due to the uncoupling of mitochondria[7,8] but other mechanisms, such as inhibition of the mitochondrial isozyme V of carbonic anhydrase (CA V), have also been hypothesized, since hydrolysis of the cytotoxic agent, leading to the formation of unsubstituted sulfonamides as the principal products, has been reported both in vivo and in vitro.[9] However, clinical trials of sulofenur have yielded unsatisfactory results because of its high protein binding and dosing being limited by the appearance of anemia due to methemoglobinemia, a side effect likely associated with its aniline-related metabolites.[10]

Pyrazol(in)e derivatives have attracting continuing attention over the years because of their broad spectrum biological activities and strong efficacy. Some representative of this heterocyclic exihibit antiproliferative,[11–13] anti-inflammatory,[14–16] anti-infective,[17] antidepressant[18] and analgesic[19] activity.

Recently, Lv et al.,[11] discovered (V) (Fig. 1) displayed the most potent EGFR TK inhibitory activity with IC_{50} of 0.06 μM, which was comparable to positive control Erlotirib. This compound (I) also showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.07 μM. The present work is an extension of our ongoing efforts towards developing promising biologically active agents using a hybrid pharmacophore approach. We made the design (Fig. 1) and synthesized hybrid compounds by linking pyrazoline ring system with benzene sulfonylurea. In these derivatives we

* Corresponding author. Tel.: +91 9873463272.
E-mail addresses: kjaved@jamiahamdard.ac.in, kjavedchem@yahoo.co.in (K. Javed).

http://dx.doi.org/10.1016/j.bmcl.2014.02.059
0960-894X/

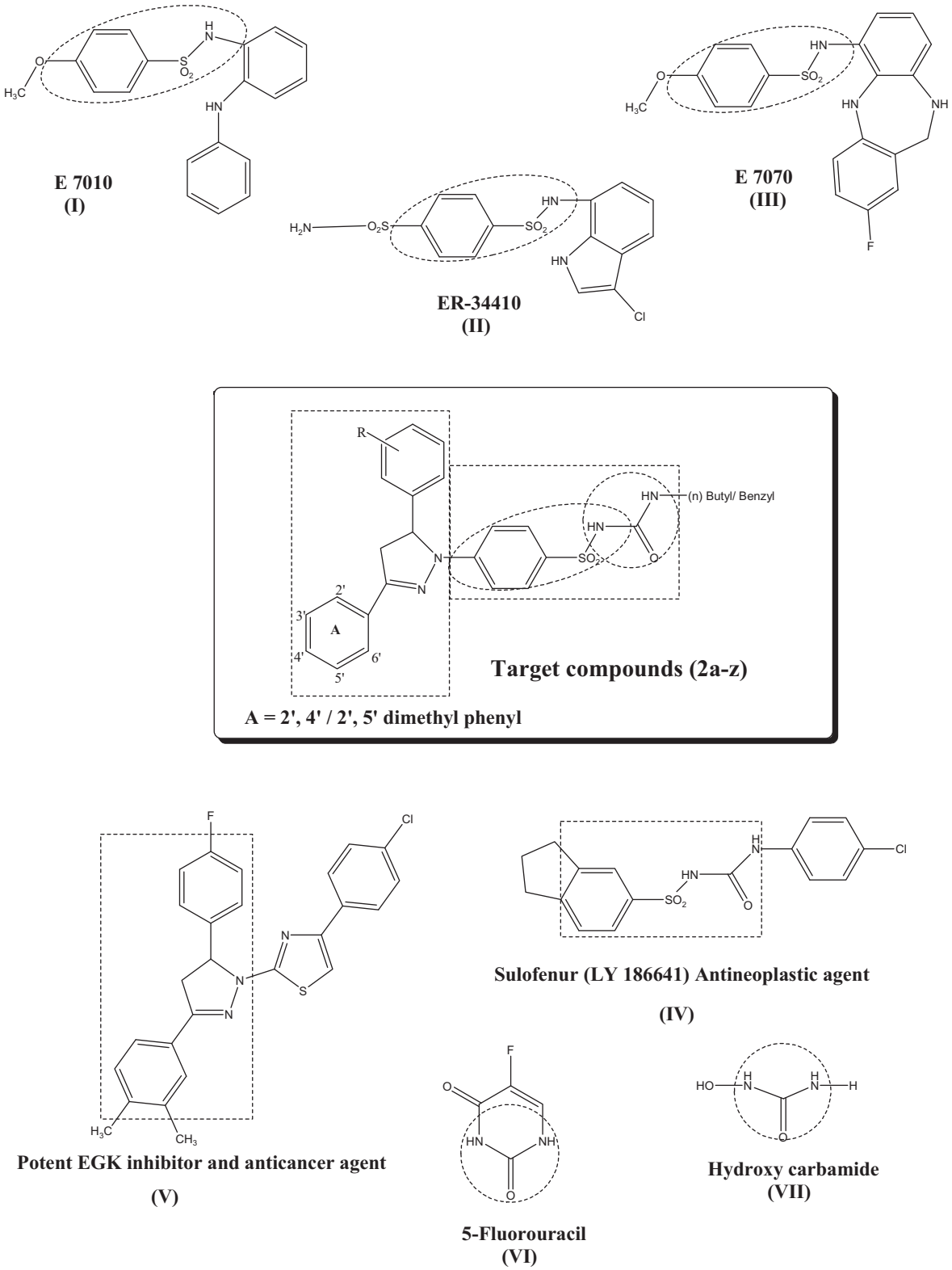

Figure 1. Structure of some biologically active anticancer drugs and rationally designed template for target compounds (**2a**–**z**).

introduced butyl or benzyl group at N^3 position in order to avoid possible side effects associated with aniline-related metabolites generating from the aryl substituted derivatives.[10] As per the protocol of NCI, only fourteen representative compounds **2i**, **2k**–**2p**, **2r**, **2s**–**2x** were selected and granted NSC codes Viz; NSC 765376, NSC 772443, NSC 765379, NSC 772444, NSC 765378, NSC 765377, NSC 762442, NSC 765372, NSC 762441,NSC 772440, NSC 765373, NSC 765371, NSC 765375 and NSC 765374 respectively and screened at NCI for antiproliferative activity at a single high dose (10^{-5} M) in full 60 cell panel. Four compounds namely **2i**, **2n**, **2v** and **2x**