European Journal of Medicinal Chemistry 45 (2010) 572–580

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis, antitumor activity and molecular docking study of novel Sulfonamide-Schiff's bases, thiazolidinones, benzothiazinones and their C-nucleoside derivatives

Mohsen M. Kamel [a], Hamed I. Ali [b], Manal M. Anwar [a,*], Neama A. Mohamed [a], AbdelMohsen M. Soliman [a]

[a] Medicinal Chemistry Department, National Research Centre, Dokki, Cairo, Egypt
[b] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Helwan University, Helwan, Egypt

ARTICLE INFO

Article history:
Received 31 August 2009
Received in revised form
22 October 2009
Accepted 23 October 2009
Available online 11 November 2009

Keywords:
Sugar-Schiff's base
Thiazolidin-4-one
Benzothiazin-4-one
Antitumor activity
Autodock
Protein tyrosine kinase

ABSTRACT

A series of sulfapyridine-polyhydroxyalkylidene (or arylidene)-imino derivatives (Schiff's bases) **2a–c** and **4a–e** were prepared by condensation of 4-amino-*N*-pyridin-2-ylbenzenesulfonamide (**1**) with different monosaccharides or with aromatic aldehydes. Treatment of **2a–c** with thioglycolic acid led to the formation of the C-nucleosides (**3a–c**), while treatment of **4a–e** with thioglycolic and/or thiosalicylic acids afforded the corresponding 2-arylthiazolidin-4-one or 2-arylbenzothiazin-4-one derivatives **5a–e** and/or **6a–e**, respectively. Some representative examples of the newly prepared compounds showed considerable cytotoxic effect against breast carcinoma cell line **MCF7** and cervix carcinoma cell line **HELA** in comparison with 5-flurouracil and doxorubicin. AutoDock molecular docking into PTK has been done for lead optimization of the compounds in study as potential PTK inhibitors.

1. Introduction

The chemistry of sulfanilamides [1,2], thiazolidinones [3] and benzothiazines [4] have been of increasing interest since many of these derivatives produce useful applications as chemotherapeutic agents especially against pathogenic bacteria and tumor cells. On the other hand, it has been reported that a wide range of Schiff's bases with their reactive azomethine linkage shows interesting inhibitory activity against experimental tumor cells [5–8]. It is also suggested that the Schiff's bases could be hydrolyzed selectively by the tumor cells to act as alkylating agents at the same time as the active amine becomes free to act as antimetabolite [9]. Besides, the Schiff's bases represent active intermediates to develop various heterocyclic systems of biological importance as the above mentioned pyridines, thiazolidines, benzothiazines and their C-nucleoside analogues. Based on all of these findings, it was of interest to synthesize some new sulfapyridine-Schiff's bases and their cyclic products and/or their C-nucleoside analogues to be evaluated for their cytotoxic activity.

The role of tyrosine kinase in the control of cellular growth and differentiation is central to all organisms and the tyrosine kinase has been found to participate in human neoplastic diseases. Tyrosine kinase inhibitors and their potentials in the clinical applications are well documented by dramatic examples such as Gleevec, Iressa and Herceptin. Several tyrosine kinase inhibitors are undergoing human trials and several are in the pipeline of drug discovery [10]. Molecular docking has been a focus of attention for many years. Generally speaking, today's flexible docking programs such as AutoDock are able to predict protein–ligand complex structures with reasonable accuracy and speed [11]. One of the most reliable, robust and popular energy-based docking packages is AutoGrid/AutoDock (Morris et al., 1998) because it allows a very efficient docking of flexible ligands (*e.g.* substrates, drug candidates, inhibitors, peptides, *etc.*) onto receptors (*e.g.* enzymes, antibodies, nucleic acids, *etc.*) [12].

2. Chemistry

The discovery of C-nucleosides and continuous study of their biological activities [13,14] led us to construct compounds containing sulfapyridine Schiff's bases incorporated into different aldoses, thiazolidinones, benzothiazines and/ or their C-nucleoside analogues which might be of potential anticancer properties against experimental tumor cell lines. Thus the reaction of

* Corresponding author. Tel.: +20 123956970; fax: +20 233370931.
E-mail address: manal.hasan52@yahoo.com (M.M. Anwar).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.10.044

sulfapyridine **1** dissolved in DMF containing few drops of acetic acid with various monosaccharide (aldoses) namely, D-arabinose, D-xylose and/ or D-mannose dissolved in water, gave the corresponding Schiff's bases: *N*-[1- (1,2,3,4-tetrahydroxypentylidene)]-imino 4-[(pyridinylamino)sulfonyl]benzenes (**2a**, **b**) and/ or *N*-[1-(1,2,3,4,5- pentahydroxyhexyl idene)- imino-4-[(pyridin-2-ylamino)sulfonyl]benzene (**2c**), respectively. Cyclocondensation of Schiff's bases **2a**–**c** with thioglycolic acid in dry dioxane, afforded the corresponding thiazolidinones, namely; 2-[1-(1,2,3,4- tetrahydroxybutyl)]-3-[4-[(pyridin-2-yl amino) sulfonyl]phenyl] thiazolidin-4-one (**3a**,**b**) and/ or 2-[1-(1,2,3,4,5-penta- hydroxyl- pentyl)]-3-[4-[(pyridin-2-ylamino)]sulfonyl]-phenyl]thiazolidin-4-one (**3c**), respectively (Scheme 1).

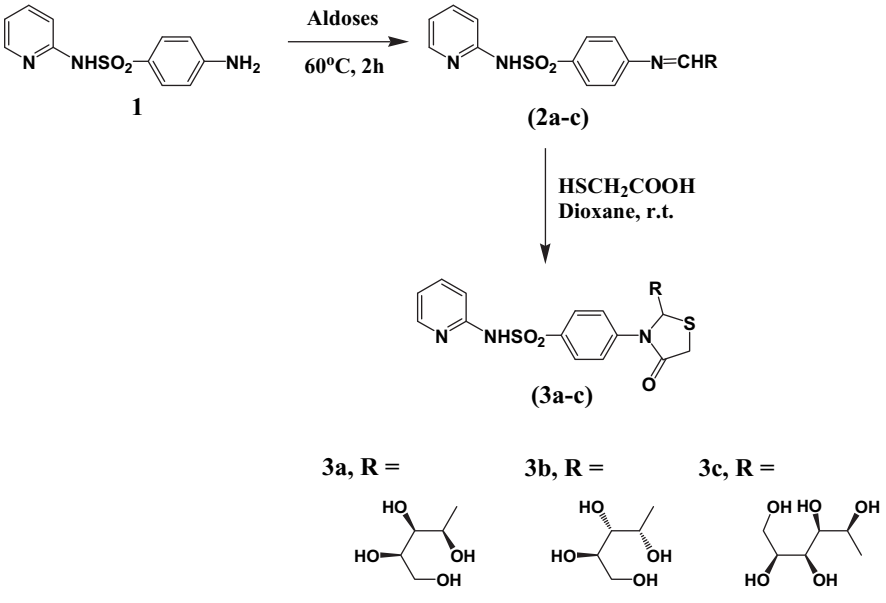
Also, reaction of sulfapyridine **1** with different aromatic aldehydes, namely; *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde, 3,4,5-trimethoxybenzal- dehyde and/ or indol-3-carboxaldehyde in the presence of few drops of acetic acid, afforded Schiff's bases, namely; *N*-(substituted arylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl]benzenes (**4a**–**e**), respectively. Compounds **4a**–**e** were reacted with thioglycolic acid and/ or thiosalicylic acid to give the corresponding 2-aryl- 3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl] thiazolidin-4-ones (**5a**–**e**) and/or 2-aryl-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]-2,4-dihydr- obenzo[e][1,3]thiazin-4-ones (**6a**–**e**), respectively (Scheme 2).

3. Results and discussion

3.1. Biological evaluation

Chemotherapy is a major therapeutic approach for the both localized and metastasized cancers. In the present work, six of the newly synthesized compounds **2b**, **3b**, **4a**, **4e**, **5e**, **6a** were selected to evaluate their in vitro growth inhibitory activities against two human cultured cell lines, which are cervix carcinoma cell line (**HELA**) and breast carcinoma cell lines (**MCF7**) in comparison to the known anticancer drugs: 5-flurouracil and doxorubicin as reference drugs. The six compounds selected being, **2a**, **3b**, **4a**, **4e**, **5e**, and **6a** were carefully selected to be representatives for all the newly synthesized 21 derivatives. And covering all structural variations in these analogs, being of sulfapyridine attached to xylose (**2a**), thiazolidinone (**3b**), sulfapyridine attached to *p*-methoxyphenyl (**4a**), sulfapyridine attached to indole (**4e**), thiazolidinone attached to indole (**5e**), and benzothiazine analogue (**6a**). It has been noticed from Table 1 that all of the tested compounds showed significant antitumor activities and this might be explained that the presence of the phenyl ring of sulfapyridine moiety provided good affinity towards the enzyme on account of the force of electrostatic attraction between the planar phenyl and the target site pocket of the tumor cells. In comparison to 5-flurouracil, the attachment of xylose nucleus to sulfapyridine via azomethine linkage in compound **2b** gave antitumor activity against HELA (IC_{50}: 3.56 μg/mL); about one third that of 5-flurouracil (IC_{50}:1.01 μg/mL), but the activity against MCF7 (IC_{50}: 1.68 μg/mL) was one half that of the reference compound (IC_{50}: 0.67 μg/mL). The antitumor activity of thiazolidinone analogue **3b** against HELA increased (IC_{50}: 2.01 μg/mL), while the activity against MCF7 decreased to be about one fourth of the activity of the comparing drug (IC_{50}: 2.68 μg/mL). Also, combining sulfapyridine moiety with *p*-methoxyphenyl via azomethine linkage in derivative **4a** enhances the antitumor activity against both types of carcinoma cell lines HELA and MCF7 to be very close to that gained by the comparing drug (IC_{50}: 1.88 and 0.74 μ/mL, respectively). The benzothiazine analogue **6a** showed more slight increase in the activity against HELA (IC_{50}: 1.48 μg/mL), but the activity against MCF7 decreased (IC_{50}: 1.61 μg/mL). The derivative **4e** containing indole moiety attached to sulfapyridine through azomethine linkage induced antitumor activity against HELA of about one half that of 5-flurouracil (IC_{50}: 2.82 μg/mL) and against MCF7 of about one third that of the comparing drug (IC_{50}: 2.28 μg/mL). The cyclized analogue bearing thiazolidinone ring **5e** exhibited increase in the antitumor activity against both HELA (IC_{50}:1.95 μg/mL) and MCF7 (IC_{50}: 1.07 μg/mL). It is noteworthy that, comparing to doxorubicin (IC_{50}: 8.72 and 7.71 μg/mL against HELA and MCF7, respectively), all of the tested derivatives showed much higher antitumor activity against both types of carcinoma cell lines (IC_{50}: 0.74–3.56 μg/mL).

Considering the structure activity relationship (SAR) of the aforementioned selected compounds, they exhibited narrow range of variation of IC_{50}, being [0.74–3.56] μg/ml. This indicate that SAR of



Scheme 1.