Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 5, Issue 2, 2013

Research Article

SYNTHESIS AND *IN-VITRO* ANTICANCER ACTIVITY OF SOME NOVEL BIS-BENZOTHIAZOLE DERIVATIVES

SEETARAMSWAMY S[1], SEKAR V[1*], GANDHIMATHI S[2], LAXMANADOSS MURUGESAN[3], PERUMAL P[1]

Department of Pharmaceutical Chemistry, J.K.K. Nattraja College of Pharmacy, KomarapalayamDepartment of Pharmaceutical Chemistry, Padmavathi College of Pharmacy, DarmapuriDepartment of Pharmaceutical Chemistry, Jagans College of Pharmacy, Nelloor.
Email: vsekar74@gmail.com

Received: 21 May 2012, Revised and Accepted: 05 January 2013

ABSTRACT

In the present study, six new derivatives (S1-S6) of benzothiazoles were synthesized and evaluated their anticancer activity. 4, 6-di substituted aniline on reacting with potassium thiocynate formed 2-amino benzothiazoles, which on reacted with aromatic aldehyde formed schiff's base derivative. Compounds (S1-S6) were synthesized by reacting schiff's base derivative with thomalic acid (TMA) and o-aminothiophenol. All synthesized compounds were identified by IR, ^{1}H-NMR and Mass Spectra. These newly synthesized compounds were evaluated for their in-vitro anticancer activity towards human cervical cancer cell lines.

Keywords: Benzothiazole, Anticancer, Human cervical cancer cell, Schiff's base.

INTRODUCTION

Amino-benzothiazoles constitute an important class of compounds. In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess biological activities, such as anticancer[7-10], antimicrobial[11], antifungal[12] and anti-inflammatory[13].

Cancer represents one of the most severe health problems worldwide, and it is predicted to continue to become the leading cause of death within the coming years. Chemotherapy, or the use of chemical agents to destroy cancer cells, is a main in the treatment of malignancies.

In the present work, we report the synthesis of new heterocyclic compound, 5-(benzo[d]thiazol-2-ylmethyl)-3-(6-substitutedbenzo [d]thiazol-2-yl)-2-phenyl thiazolidin-4-one and its derivatives. Anticancer activity of the compounds was also evaluated and discussed.

MATERIALS AND METHODS

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded in potassium bromide pellets on FTIR 8300 (Shimadzu) spectrometer; H-NMR spectra were recorded on AVANCE 300 MHz TMS as internal standard. Mass spectra were recorded on SHIMADZU QP 2010 PLUS. All the reactions were monitored by thin layer chromatography carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection (solvent system- toluene: ethyl acetate: formic acid (5:4:1)).

Synthesis of 6-substituted-1, 3-benzothiazole-2-amine (I)

Potassium thiocyanate (0.055mol) was added to a solution of the appropriate aniline (0.01mol) in glacial acetic acid (40 ml). To this mixture a solution of bromine (0.055mol) in acetic acid (8 ml) was added drop wise and the temperature was maintained below 35 ºC with a water bath. After the addition was complete, the reaction mixture was stirred at room temperature for 5 h. Then, the reaction mixture was poured into water, neutralized with ammonia solution, which was purified by column chromatography on silica gel (toluene: ethyl acetate: formic acid) to give the required 2-amino benzothiazole.

Synthesis of 2-(benzylidene)-6-substituted benzothiazoles (II)4

A mixture of compound I (0.001mol), aromatic aldehyde (0.01 mol) and 2-3 drops of glacial acetic acid in ethanol (20ml) was refluxed for 3hrs. The solvents were removed under the reduced pressure. The residue were stirred with ice cold water, filter and dried.

Synthesis of 3-(6-fluorobenzothiazol-2-yl)-4-oxo-2-phenylthiazolidine- carboxylic acid (

A mixture of compounds II, (0.01 mol) and thiomalic acid (TMA) (0.01 mol) was added to small pinch of zinc chloride and DMF (dimethyl formamide) (20 ml) was refluxed for 6 hr. the reaction was neutralized with sodium bicarbonate solution, the formed product was flirted and recrystalized to give the compound III respectively.

5-(benzothiazol-2-ylmethyl)-3-(6-fluorobenzothiazol-2-yl)-2-phenylthiozolidin-4- one (4a-f)

A mixture of compound III (0.01 mol) with 2-aminothiophenol (0.01 mol) in glacial acetic acid (5ml) was heated under reflux for 2hr. the product obtained after cooling was collected by filtration and purified by recrystallization with ethanol to give IV.

5-(benzo[d]thiazol-2-ylmethyl)-3-(6-fluorobenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S1):

Yield: 74%, m.p.214 ºC, IR (KBr): 751.18 (C-F str), 1328 (C-S str), 3479 (NH str), 3084(Ar-CH str), 1148 (C-N str), 1718 (cyclic C=O str). 1H-NMR (DMSO)(δppm): 6.67-8.87 (m, 12H, Ar-CH), 2-3 (s, 2H, CH), 3.5 (2H, Methylene). EI-MS m/z: 477.

5-(benzo[d]thiazol-2-ylmethyl)-3-(6-chlorobenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S2):

Yield: 70%, m.p.217 ºC, IR (KBr): 811 (C-Cl str), 1357 (C-S str), 3430 (NH str), 3091(Ar-CH str), 1206 (C-N str), 1624 (C=O str). 1H-NMR (DMSO)(δppm): 6.67-8.87 (m, 12H, Ar-CH), 2-3 (s, 2H, CH), 3.5 (2H, Methylene). EI-MS m/z: 493.

5-(benzo[d]thiazol-2-ylmethyl)-3-(6-bromobenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S3):

Yield: 65%, m.p.218 ºC, IR (KBr): 609 (C-Br str), 1344 (C-S str), 3385 (NH str), 3079(Ar-CH str), 1857 (C=O str). 1H-NMR (DMSO) (δppm): 6.67-8.87 (m, 12H, Ar-CH), 2-3 (s, 2H, CH), 3.5-5.6 (2H, Methylene). EI-MS m/z: 538.

5-(benzo[d]thiazol-2-ylmethyl)-3-(6-methoxybenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S4):

Yield: 78%, m.p.221 ºC, IR (KBr): 2852 (C-OCH3 str), 1328 (C-S str), 3084(Ar-CH str), 1718 (C=O str). 1H-NMR (DMSO)(δppm): 7-8 (m, 12H, Ar-CH), 2-3 (s, 2H, Hetero-CH), 3.5-4.0 (m, C-OCH3), 2.5 (2H, Methylene). EI-MS m/z: 487.

5-(benzo[d]thiazol-2-ylmethyl)-3-(6-nitrobenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S5):

Yield: 61%, m.p.218 ºC, IR (KBr): 2852 (C-OCH3 str), 1328 (C-S str),

3408, 3084(Ar-CH str), 1718 (cyclic C=O str). 1H-NMR (DMSO)(δppm):7-8 (m, 12H, Ar-CH), 2-3 (s, 2H, Hetero-CH), 3.5-4.0 (m, C-OCH3), 2.5 (2H, Methylene). EI-MS m/z: 487.

5-(benzo[d]thiazol-2-ylmethyl)-3-(4,6-dinitrobenzo[d]thiazol-2-yl)-2-phenyl thiazolidin-4-one (S6):

Yield: 53%, m.p.214 ºC, IR (KBr):1315 (C-NO2 str), 1355 (C-S str), 3080(Ar-CH str), 1115 (C-N str), 1857 (C=O str).1H-NMR (DMSO)(δppm):6.67-8.0 (m, 11H, Ar-CH), 3.5-3.8 (s, 2H, CH), 2.5 (s, 1H, methylene). EI-MS m/z: 550.

RESULTS AND DISCUSSION

The parent compound 5-(benzo[d]thiazol-2-ylmethyl)-3-(6-fluorobenzo[d]thiazol 2-yl)-2-phenyl thiazolidin-4-one. The structure of this compound was assigned on the basis of analytical and spectral data [Mass: M+ at m/z 477; IR (KBr): 1328 (C-S), 3084(Ar-CH), 1148 (C-N), 1718 (C=O), 1H-NMR (DMSO):6.67-8.87 (m, 12H, Ar-CH), 2-3 (s, 2H, CH), 3.5 (2H, Methylene)].

IR spectra of compounds (**S1, S2, S3, S4, S5 and S6**) showed absorption bands in the range of 2200-2226 cm-1. which can be assigned to CN stretch and absorption bands in the range of 1900-1600 cm-1 are due to C=O stretch. Mass spectra of compounds showed molecular ion peaks which correspond to their molecular weights. ^{1}H-NMR spectral data is also in agreement with structures assigned to compounds.

Anticancer activity studies

All the compounds synthesized were screened for in-vitro anticancer activity against HeLa (Human Epithelial cervix cancer cell line) cell lines by MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrasolium bromide] assay method along with control. The percentage inhibition of each compound was calculated.

Toxicity of test compound in cells was determined by MTT assay based on mitochondrial reduction of yellow MTT tetrasolium dye to a highly colored blue formazan product. 1x105 cells/ml in 96- well plates were incubated and compounds with series of concentrations (100, 10, 1.0 and 0.1 µ M) tested for 48 hrs at 37 ºC in EMEM (Eagles Minimum Essential Medium) containing 10% FBS [Fetal Bovine Serum] medium. Then the above media was replaced with 90µl of fresh serum free media and 15µl of MTT reagent (5mg/ml) and plates were incubated at 37 ºC for 4h. The absorbance at 570nm was measured on a spectrophotometer using micro plate reader IC-50 values were determined and results are summarized in the Table-2.

CONCLUSION

All the newly synthesized compounds were screened for anticancer activity at a concentration of 100, 10, 1, and 0.1µM. All compounds showed good anticancer activity against HeLa cell lines.

The results show that the compound S1 (F), S2 (Cl) and S4 (OCH_3) has significant and moderate anticancer activity against HeLa cell lines than other compounds.

ACKNOWLEDGEMENT

Authors are grateful to P. Perumal, Head and principal, Department of chemistry, J.K.K.Nattraja College of Pharmacy and IIT-Chennai and KMCH, for providing facilities to carryout the work, Spectra and Pharmacological screening.

REFERENCES

1. Arpana Rana, Siddiqui. N, Khan. S. A, Benzothiazole a new profile of biological activities. *Indian Journal of Pharmaceutical Sciences., 2007, 69, 10-17.*
2. Sukhbir L. Khokra, Kanika Arora, Heena Mehta, Ajay Aggarwal and Manish Yadav, Common methods to synthesize benzothiazole derivatives and their medicinal significance. *International Journal of Pharmaceutical Sciences and Research*., 2011, 2, 1356-1378.
3. Yadav P. S, Devprakash, Senthil kumar G. P, Benzothiazole different methods of synthesis and diverse biological activities. *International Journal of Pharmaceutical Sciences and Drug Research,* 2011, 3, 1-7.
4. Shashank. D, Vishawanth. T, Balasubramaniam. V, Perumal. P, Synthesis of some substituted benzothiazole derivatives and its biological activities. *International Journal of Chem Tech Research,* 2009, 4, 1224-1231.
5. Deepak Pareek, Manish Chaudhary, Pawan K. Pareek, synthesis of some bioactive4-thiazolidinone derivatives incorporated benzothiazole moiety; *Der Chemica Sinica*, 2010,1, 22-35.
6. Priyanka Yadav, Deepa Chauhan, Neeraj K. Sharma, Sachin Singhal, 2- substituted Hydrazino-6-fluoro-1, 3-benzothiazole: synthesis and characterization of new novel antimicrobial agents. *International Journal of Chem Tech Research*., 2010,2, 1209-1213.
7. Suvrna Kini, Swain S. P and Gandhi. A.M, Synthesis and evaluation of novel benzothiazole derivatives against human cervical cancer cell lines. *Indian Journal of Pharmaceutical Sciences,* 2007, 69, 46-50.
8. Bradshaw T.D, Westwell A.D, The development of the antitumor benzothiazole prodrug, phortress, as a clinical candidate. *Current Medicinal Chemistry*., 2004, 11, 1241-1253.
9. Devmurari V.P, Pandey Shivanand, Nandanwar R.R, Perumal P, Synthesis and anticancer activity of some novel 2-substituted benzothiazole derivatives. *International Journal of Chem Tech Research*, 2010, 2, 681-689.
10. Giuseppe Trapani, Massimo Franco, Andrea Latrofa, Antonia Reho. Synthesis, in vitro and in vivo cytotoxicity, and prediction of the intentional absorption of substituted 2-ethoxycarbonyl-imidazo [2,1-*b*]benzothiazoles. *European Journal of Pharmaceutical Sciences*, 2001, 14, 209-216.
11. Pandurangan. A, Anjana Sharma, Nitin Sharma, Sharma. P.K, Sharad Visht, Synthesis and structural studies of novel benzothiazole derivative and evaluation of their antimicrobial activity. *Der Pharma Chemica*, 2010, 2, 316-324.
12. Jitender K Malik, Manvil. F. V, Nanjwade. B. N, Sanjiv Singh, Synthesis and screening of some new 2-amino substituted benzothiazole derivatives for antifungal activity. *Drug Invention Today*., 2009, 1, 32-34.
13. Venkatesh. P, and Pandeya. S. N; Synthesis, and anti-inflammatory activity of some 2-amino benzothiazole derivatives. *International Journal of Chem Tech Research*., 2009, 1, 1354-1358.
14. Mosmann. T, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of Immunological Methods*., 1983, 65, 55-63.