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Synthesis and anticancer activity of novel 2-(benzo[d]thiazol-2-yl)-5-(4-(4-chloro phenylsulfonyl)piperazin-1-yl)phenol.

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ABSTRACT

Novel 2-(benzo[d]thiazol-2-yl)-5-(4-(4-chlorophenylsulfonyl)piperazin-1-yl)phenol was synthesized by nucleophillic substitution reaction of 2-(benzo[d]thiazol-2-yl)-5-(piperazin-1-yl)phenol with 4-chlorobenzene-1-sulfonyl chloride with good yield. The synthesized compound was characterized by spectral analysis and tested against its anticancer activity.

INTRODUCTION

The benzothiazole core became an important template for a wide range of biologically active molecules. These molecules and their derivatives were posses a wide variety of activity such as antitumor agents [1], calmodulin (CAM) antagonists [2], neurotransmission blocker [3], and neuroprotective agent [4]. Benzothiazole kind compounds attracted considerable attention in anticancer drug development [5]. The simple benzothiazole nucleus is present in several biological active systems such as antimicrobial[6], antitumoral [7], antimalarial [8], and antitubercular [9]. After reviewing the literature modified benzothiazole core structure with additional functional groups will enhance the biological potential of the synthesized compounds. On the other hand N-sulfonyl-containing benzothiazoles showed considerable activity against hepatocellular carcinoma, acute breast cancer, leukemia, myelogenous, and non- small cell lung carcinoma [10]. Benzothiazole has been exploited to enhance the donor-acceptor effects in the chromophores.

Compounds containing 2-(benzo[d]thiazol-2-yl)-5-bromophenol derivatives and its N-sulfonyl substituted-derivatives are associated with diverse pharmacological activities which have made them important chemotherapeutic agents. Based on the above observations, we herein report the synthesis of 2-(benzo[d]thiazol-2-yl)-5-(4-(4-chlorophenylsulfonyl)piperazin-1-yl)phenol and its anti cancer activity.

MATERIALS AND METHODS

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (200-400

mesh) using a proper eluent. ^{1}H NMR was recorded on Varian MR400 (400 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br= broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet. Coupling constants, J, were reported in hertz unit (Hz). Melting points (°C) were taken in open capillary tubes using silicon oil on Gallen Kamp apparatus. Mass Spectra were recorded on Schimadzu GCS-QP1000EX Spectrometer at 70 eV. The IR Spectra were recorded with a Philips Infra cord Spectrophotometer Model PU 9712 in KBr discs.

Methyl 4-bromo-2-hydroxybenzoate (2):
To a stirred solution of 4-bromo-2-hydroxybenzoic acid **1**(6.5 g, 29.9 mmol) in MeOH (325 mL) at 0 ^{o}C was added Conc H_2SO_4 (5 mL) dropwise and stirred at 80 ^{o}C for 4 h. After consumption of the starting material (by TLC), the reaction mixture was neutralized with aqueous $NaHCO_3$ solution and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel (100-200 mesh) column chromatography eluting with 2% EtOAc/Hexane to afford (5 g, 84%), TLC system: 10 % EtOAc/Hexane, $R_{f:}$ 0.85; ^{1}H NMR (DMSO-d_6, 500 MHz):δ 10.64 (s, 1H), 7.68 (d, *J* = 8.5Hz, 1H), 7.23 (s, 1H), 7.13 (d, *J* = 8.5Hz, 1H), 3.87 (s, 3H).

2-(benzo[d]thiazol-2-yl)-5-bromophenol (3)
The mixture of **2** (0.5 g, 2.16mmol) and 2-amino thiophenol (0.27 g, 2.16 mmol) was taken in PPA (5 mL) and stirred at 180 ^{o}C for 4 h. After consumption of the starting material (by TLC), the reaction was poured in to ice cold water and neutralized with ammonia solution and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel (100-200 mesh) column chromatography eluting with 2% EtOAc/Hexane to afford **3** (0.3g, 45%), TLC system: 10 % EtOAc/Hexane, $R_{f:}$ 0.54; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 12.70 (br s, 1H), 8.01-7.88 (m, 2H), 7.56-7.43 (m, 3H), 7.39-7.26 (m, 1H), 7.11-7.06 (m, 1H); Mass: 307 [M^++1].

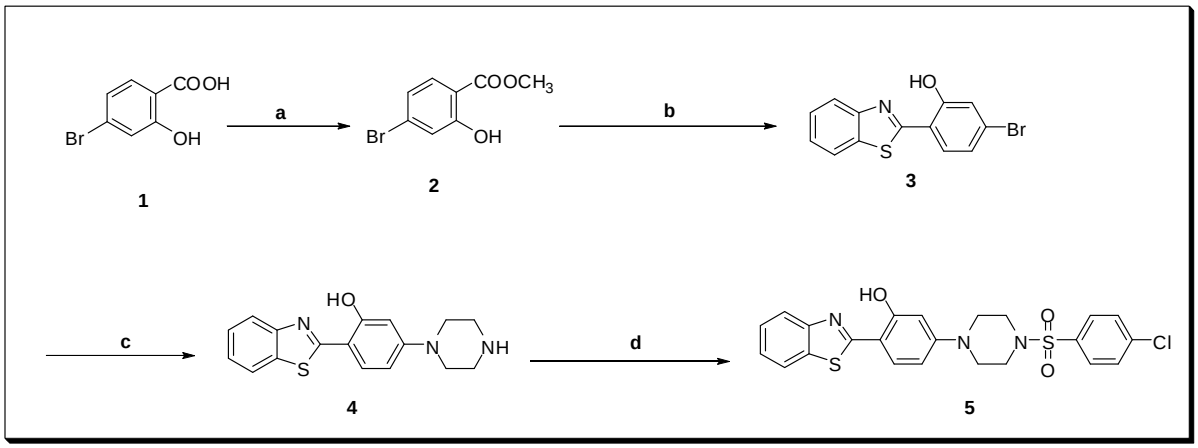
2-(benzo[d]thiazol-2-yl)-5-(piperazin-1-yl)phenol (4)
To a stirred solution of **3** (0.01 g, 0.32 mmol) in DMSO (10 mL) in a sealed tube was added piperazine (0.056 g, 0.65 mmol), K_2CO_3 (0.11g, 0.81 mmol), CuI (0.18 g, 0.09 mmol) and Proline (0.01 g, 0.09 mmol) were added and stirred at 90 ^{0}C for 3 h. After consumption of the starting material (by TLC), the reaction was diluted with water and the aqueous layer was extracted with EtOAc (2 x 20 ml). The combined organic extracts were dried over anhy Na_2SO_4 and concentrated under reduced pressure. The crude was purified by preparative TLC eluting with 10% MeOH/DCM to afford **4** (17 mg, 16%), TLC system: 10 % MeOH/DCM, $R_{f:}$ 0.15; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 10 Hz, 1H), 7.79 (d, *J* = 10 Hz, 1H), 7.50-7.47 (m, 1H), 7.38-7.35 (m, 1H), 6.62 (d, *J* = 10 Hz, 1H), 6.45 (s, 1H), 3.22-3.20 (m, 4H), 2.83-2.81 (m, 4H). HPLC Purity: 98.09% at 1.50 RT; Mass: 312 [M^++1].

2-(benzo[d]thiazol-2-yl)-5-(4-(4-chlorophenylsulfonyl)piperazin-1-yl)phenol (5)
To a stirred solution of **4** (0.05 g, 0.16mmol) in CH_2Cl_2 (5 mL) was added 4-Chloro benzene sulfonyl chloride (**4**) (0.037 g, 0.17mmol) followed by compound Et_3N (0.03 mL, 0.24 mmol) and stirred at RT for 1 h under inert atmosphere. After consumption of the starting material (by TLC), the reaction was diluted with water and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by preparative HPLC eluting with 20% EtOAc/Hexane to afford **5** (0.02g, 25%), TLC system: 20 % EtOAc/Hexane, $R_{f:}$ 0.1; ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.73 (s, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.81-7.73 (m, 5H), 7.50-7.48 (m, 1H), 7.39-7.36 (m, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 6.46 (s, 1H), 3.39 (s, 4H), 3.04 (s, 4H); Mass : 486 [M^++1].

RESULTS AND DISCUSSION

Chemistry:
2-(benzo[d]thiazol-2-yl)-5-bromophenol derivatives and its N-sulfonyl substituted-derivative were prepared by the method summarized in Scheme.

Scheme:



Scheme: a) H_2SO_4, MeOH, 80 °C, 4h; b) 2-Amino thiophenol, PPA 180 ^{0}C , 4 h; c) Piperazine, K_2CO_3, CuI, Proline, DMSO, 90 ^{0}C, 3 h. in a sealed tube. d) 4-Chloro benzene sulfonyl chloride, Et_3N, CH_2Cl_2, RT, 1 h.

The benzthiazole compounds were prepared starting from commercially available methyl 4-bromo-2-hydroxybenzoic acid **1**, which was transformed into methyl ester **2** by the reaction of sulfuric acid in methanol (Scheme **1**). On treatment of 2-aminothiophenol with the corresponding substituted benzoic acids **2** in PPA at 180 ^{o}C gave compounds **3**. This route also afforded from the reaction of substituted benzoic acids **2** and 2-aminothiophenol in PPA. As expected, PPA can mediate the reactions. Even at room temperature, the conversion rate after 4 h reached 10%, which increased to 45% under reflux conditions. Due, to the low yields in benzothiazole ring formation alternatively, 2-alrylbenzothiazoles can be prepared from *via* palladium mediated Suzuki coupling between aryl boronic acids and 2-halo benzothiazoles. Recently, 2-alrylbenzothiazoles were used in bioimaging of an integrin-targeting water-soluble fluorenyl probe.[11]

Recently, great progress has been made in copper-catalyzed C-N bond formation between aryl halides and N-containing nucleophiles.1.The use of special ligands makes this transformation work under significantly milder conditions compared with those for the traditional Ullmann reaction[11]. This progress has greatly expanded the reaction scope because more N-containing nucleophiles could be employed as coupling partners. As a continuing effort on exploring amino acid-promoted Ullmann type reactions, we found that using L-proline as a ligand could solve the above problems, leading to coupling of 2-aryl benzthiazole derivative **3** with piperazine and potassium carbonate proceeded smoothly to afford N-arylation product **4**. The synthesis of the target compounds **5** was accomplished from commercially available substituted sulfonyl chlorides in the presence of triethylamine to the corresponding sulfonamides **5**.

Table 1

Compound	IC 50 (μM)		
	K562	Colo-205	MDA-MB 231
3	17	10	39
4	15	8	32
5	10	5	22
Harmine	14	8	32

We evaluated the synthesized compounds for their anti-proliferative properties in vitro against a number of cancer cell lines for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and Human breast cancer cell line (MDA-Mb 231MR32). The test compounds were examined at various concentrations in a MTT (3-(4, 5-dimethyl thiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) assay and the IC_{50} values obtained for each compounds are summarized in Table 1. Harmine, a member of β-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines was used as a reference compound. While the title compound showed

inhibition of leukemia cell growth as reflected by their IC_{50} values the good results. Similarly, the synthesized compounds 4 and 5 were found to be active against colon carcinoma cells and breast cancer cells. (Table 1)

In conclusion we have reported the synthesis of novel -(benzo[d]thiazol-2-yl)-5-(4-(4-chlorophenylsulfonyl)piperazin-1-yl)phenol and their antitumor activities. Further this approach for the synthesis N-sulfonyl substituted-derivatives of 2-(benzo[d]thiazol-2-yl)-5-bromophenol was a novel and it can be applied for the analogue preparation.

REFERENCES:

[1] Hutchinson. I, Bradsha. T. D, Matthews. S. C, Stevens. F. G. M, Westwell. A. D. B, *Bioorg Med Chem. Lett.* **2003**, 13, 471.
[2] T. Tanaka, H. Umekawa, M. Saitoh, T. Ishikawa, T. Shin, M .Ito, H. Itoh, Y. Kawamatsu, H Sugihara, H. Hidaka, *Mol Pharmacol*, **1986**, 29, 264.
[3] Jimonet. P, Audiau. F, Barreau. M, Blanchard. J. C, Boireau. A, Bour. Y, Coléno. M. A, Doble. A, Doerflinger. G, Huu. C. D, Donat. M. H, Duchesne. J. M, Ganil. P, Guérémy. C, Honoré. E, Just. B, Kerphirique. R, Gontier. S, Hubert. P, Laduron. P. M, BlevecJ. L, Meunier. M, MiquetJ. M, Nemecek. C, Pasquet. M, Piot. O, Pratt. J, Rataud. J, Reibaud. M, Stutzmann. J. M, Mignani. S, *J Med Chem*, **1999**, 42, 2828.
[4] Benavides. J, Camelin.J. C, Mitrani. N, Flamand. F, Uzan. A, Legrand, J. J, Gueremy. C, Le Fur. C. G, *Neuropharmocology*, **1985**, 24, 1085.
[5] Yamazaki. K, Kaneko. Y, Suwa. K, Ebara. S, Nakazawa. K, Yasuno. K, *Bioorg Med Chem*, **2005**, 13, 2509.
[6] Ambrogi. V, Grandolini. G, Perioli. L, Ricci. M, Rossi. C, Tuttob. L, *Eur J Med Chem*, **1990**, 25, 403.
[7] Chua. M. S, Shi. D. F, Wrigley. S, Bradshaw. T. D, Hutchinson .I, Shaw. P. N, Barrett. D. A, Stanley. L. A, Stevens. M. F.G, *J Med Chem*, **1999**, 42, 381.
[8] Burger. A, Sawhney. S. N, *J Med. Chem*, **1968**, 11, 270.
[9] Palmer. P. J, Trigg. R. B, Warrington. J. V, *J Med Chem*. **1971**, 14, 248.
[10] Ley. S. V, Thomas. A. W, *Angew. Chem., Int. Ed*. **2003**, 42, 5400.
[11] Maheswaran. H, Krishna. G. G, Prasanth. K. L, Srinivas. V, Chaitanya. G. K, Bhanuprakash. K, *Tetrahedron* **2008**, 64, 2471.