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Synthesis, Characterization and Anticancer Screening of Novel 2-Substituted Benzothiazole Derivatives of Pyrimidine

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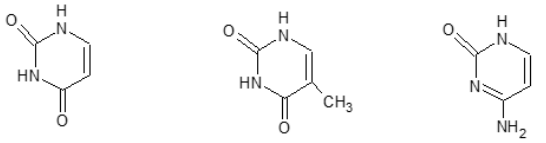
***Abstract*: A series of 1- (6- Derivative of 1, 3- benzithiazol -2-yl) -3-methyl -2-sulfanylidene-1, 3-diazinane-4,6-dione synthesized by treating malinix acid in acetyl chloride. Elemental analysis, IR, 1H, NMR and Mass spectral data's are confirmed structure of the newly synthesized compounds. Synthesized benzothiazole derivatives of pyrimidine were investigated for their Anti-Cancer activity.**

***Keywords*: Benzothiazole, Pyrimidine, Anticancer activity.**

1. Introduction

The small and simple benzothizole nucleus is present in compound involved in research aimed at evaluating new products that possess interesting biological activities like-antitumour1-4, antimicrobial, antitubercular, antimalarial, analgesic and anti-inflammatory activity. The benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Heterocycles containing the thiazole moiety are present in many natural products such as bleomycin, epothilone A, lyngbyabellin A & dolastatin Benzothiazole is a privileged bicycilc ring system.

Three pyrimidine derivatives that are integral part of DNA and RNA well as to structure of medicinally actives agents.



Pyrimidine derivatives occur very widely in the living organisms and are among the first compounds to have been studied by the organic chemist. The barbiturates, valuable soporific and hypnotic drugs, and a number of useful antibacterial and antimalarial drugs also contain pyrimidine nucleus. Vatamins B1 and B2 also contains pyrimidines moiety.

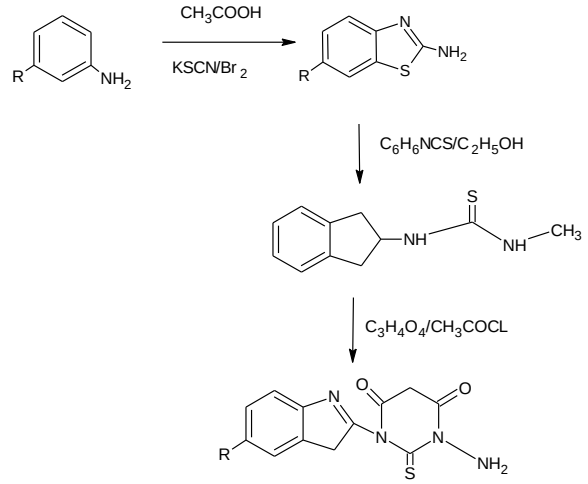
Pyrimidines are the class of drugs, known to possess various biological activies. They are shown to produce their action through the inhibition of the enzyme Dihydrofolate Reductase(DHFR). DHFR is essential for the folate metabolism in the organism or any cell. The inhibition of the enzyme has shown to be one of the most promising ways to control the bacterial and parasitic diseases. They are also shown to possess anticancer activity.

Dihydrofolate Reductase is the enzyme, which is essential part of any living system. Its inhibition is found to affect the growth of the cell. Some of the derivatives of pyrimidines like Trimethoprim, Methotrexate and Pyrimethamine have shown to exhibit antimicrobial, anticancer and antimalarial activities respectively. Some recent studies have shown that pyrimidines also possess antinflammatory activity.

Though there is similarity in the shape of pyrimidine to that of benzene and pyridine, the differences between the bond angles and distance of these ring systems suggest that the pyrimidine is least aromatic amongst them [1].

Chemically they are considered as the derivatives of pyridine and to a lesser exent as cyclic amidines. They are weaker base than pyridine, imidazole, or amidines in general. This is because the addition of protons does not increase the possibilities for the resonance and resonance energy [5].

Scheme:



The IR, ^{1}H NMR, Mass and Elemental analysis supported the structure of title compounds. Physical and analytical data of

title compound and its other substituted derivatives are given in Table 1.

2. Experimental works

All the chemicals were purchased from Merck and used without purification. Analytical TLC was performed on silica Gel F254 plates (Merck) with visualization by UV light. The melting range of the synthesized compounds was performed by LAB INDIA visual melting point apparatus and is uncorrected. The IR spectra of the compounds were recorded on Shimadzu FT-IR spectrometer with potassium bromide pellets. Mass spectra were recorded on Shimadzu GCMS QP 5000. The 1H-NMR and spectra of the synthesized compounds were recorded on a Bruker 300 NMR spectrometer in MeOD. X-ray diffraction study of synthesize derivatives was performed by PAN analytical techniques with model PW3040/60 X'pert PRO with the help of source X-ray tube 3kW with copper and cobalt target. The IR, 1H-NMR, and Mass spectra were consistent with the assigned structure.

Table 1
Physical and analytical data of title compound and its other substituted derivatives

Compound Name	Where R=	Molecular Formula	Yield of %	Melting Point
S1	4 – OCH_3	$C_{18}H_{13}N_3O_3S_2$	88.5%	186-188^{O}C
S2	4 – F	$C_{17}H_{10}N_3O_2FS_2$	59.7%	154-156 ^{O}C
S3	4 – CL	$C_{17}H_{10}N_3O_2C1S_2$	76.3%	178-180 ^{O}C
S4	4 – Br	$C_{17}H_{10}N_3O_2BrS_2$	73.3%	112-114 ^{O}C
S5	4 – NO_2	$C_{17}H_{12}N_4O_2S_2$	83.8%	146-148 ^{O}C

3. General procedure [6] for S1 to S5

A. *Step-1*

A mixture of 4- substituted aniline (0.01mol) and potassium thiocynate (0.01mol) in glacial acetic acid (20 ml) was cooled and stirred to this solution bromine (0.01 mol) was added dropwise at such a rate to keep the temperature below 10^{0}c throughout the addition. Stirring was continued for additional 3 h and the separated hydro bromide salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralized with aqueous ammonia solution (25%) filtered, washed with water and dried, recrystalised with benzene to obtain 1-(6-substituted-1, 3-benzothiazol1-2-yl).

B. *Step-2*

1-(6-substituted-1, 3- benzothiazol-2-yl) (2.24 g, 0.01 mol) in ethanol (20 ml) phenyl isothiocynate (1.49 g, 0.01 mol). The mixture was heated at reflux for 5 h, the reaction mixture was cooled and the product separated was filtered, dried and crystallized from dioxane, yield- 1.12 g.

C. *Step-3*

3- (6 – substitute debenzothiazol - 2- yl) – 1 – phenyl – 2 - thioxo dihydropyrimidine-4,6-dione was prepared by heating a mixture of 5 (0.268g, 0.75 mmol) and malonic acid (1.50 in acetyl chloride (10ml) was heated for 6 h at 40^{0}.the reaction mixture was cooled and poured into crushed ice; the solid separated was collected and crystallized from ethanol, yield 0.186 g (76%).

Synthesis of 3-(6-methoxybenzothiazol-2-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione (S1):

IR (KBr) (v cm^{-1}) 3426.78(Ar-C –H), 1021.10(C-N,) 834.05(C- S), 3117.75(N-H), EI-MS m/z 372.73 ^{1}H-NMR (MeOD) (δ ppm) 7.81-8.51(3H of Benzene),3.07(2H of methylene), 2.71 (3H of Methyl). Percentage of Yield is 88.5%. Melting point is 186 – 188^{0}c.

Synthesis of 3-(6-fluovenzothiazol-2-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione(S2):

IR (KBr) (v cm$^{-1)}$) 3449(Ar-CH stretching), 1628(C=O stretching), 743 (C – S stretching), 1436 (CH_2 bending), 1110 (OC – N stretching), 2922 (-OCH_3 stretching), 583 (C-Br stretching). EI – MS m/z 463.2350, ^{1}H-NMR (MeOD) (δ ppm) 2.5 – 3.5 (3H –OCH_3), 4.5 (2H, s, -CH_2COCI), 6.5 -12 (6H, Ar – CH). Percentage of Yield 59.7% Melting point is 154 – 156^{0}C.

Synthesis of 3-(6-chlorobenzothiazol-2-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione(S3):

IR (KBr) (v CM^{-1}) 3402.41 (Ar-C-H), 1020.83(C-N), 694.56(C-S), 3185.42(N-H), 694.56 (C-C1). EI-MS m/z 375.88, ^{1}H-NMR (MeOD) (δ ppm) 7.56-8.00 (3 H of Benzene), 3.07(2H of methylene), 2.51 (3H of methyl). Yield of Percentage is 76.3%. Melting point is 178 – 180^{0}C.

Synthesis of 3-(6-bromobenzothiazol-2-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione(S4):

IR (KBr) (v cm^{-1}) 3418.17 (Ar-C-H), 1119.17(C-N), 754.69, (C-S), 3151.41(N-H), 693.07 (C-Br). EI-MS m/z422.75. ^{1}H-NMR (MeOD) (δ ppm) 7.02-8.06 (3 H of Benzene), 3.57 (2H of methylene), 2.45 (3H of methyl). Percentage of Yield 73.3% Melting point is 112 – 114^{0}C.

Synthesis of 3-(6-nitrobenzothiazol-2-yl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6-dione(S5):

IR (KBr) (v cm^{-1}) 3426.69 (Ar-C-H), 1114.97(C-N), 751.60, (C-S), 3154.84(N-H), 1453 (C-NO2). EI-MS m/z 397.88. ^{1}H-NMR (MeOD) (δ ppm) 7.34-8.11 (3 H of Benzene), 3.07 (2H of methylene), 2.81 (3H of methyl). Yield of Percentage 83.8% Melting point is 146 - 148^{0}C.

4. Anti-cancer activity

Anticancer activity of the synthesized compounds has done by MTT Assay method was shown in the Table - 2 and Fig. 1.

Table 2
IC_{50} of the synthesized compounds

Compounds	IC_{50}	Status
S1 (Methoxy)	0.25 mM	Active
S2 (Fluro)	0.27 mM	Active
S3 (Chloro)	1.0 mM	Moderately Active
S3 (Bromo)	0.43 mM	Active
S3 (Nitro)	0.46 mM,	Active

Concentration used (µm- micro molar); 0.5 mM, 6.25 mM, 12.5 mM, 25 mM, 50mM

5. Results and discussion

Title compounds (S1 to S5) were found to exhibit mild to moderate anticancer activities in cell lines and the results were summarized below:

- The best mean IC50 values were achieved with compound (S1 and S2) with slight difference among them.
- Compound S2 possess good cytotoxic activity against cells line (IC50 – 0.27µm). The % cell inhibition in maximum concentration 98.97%.
- Compound S1 exhibits potent cytotoxic activity against cells line (IC50 – 0.25µm). The % cell inhibition in maximum concentration 98.35%.
- Compound S3 exhibits moderate cytotoxic activity against cells line (IC50 – 1.0µm). The % cell inhibition in maximum concentration 49.07%.
- Compound S4 exhibits good cytotoxic activity against cells line (IC50 – 0.43µm). The % cell inhibition in maximum concentration 82.04%.
- Compound S5 possess good cytotoxic activity against cells line (IC50 – 0.46µm). The % cell inhibition in maximum concentration 75.33%.
- S1, S2, S3 were found to exhibit good cyotoxicity in the cell line.
- But in overall, compound S2 shows significant activity.

6. Conclusion

This paper presented synthesis, characterization and anticancer screening of novel 2-substituted benzothiazole derivatives of pyrimidine.

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