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Synthesis and characterization, derivatives of 2-(4-chlorophenyl)-2, 3-dihydrobenzo[d]thiazole with their antibacterial action

Abstract

A newly synthesized molecules of 2-chloro-1-(2-(4-chlorophenyl)benzo[d] thiazol-3(2H)-yl)ethanone, 4-(2-(4-chlorophenyl) benzo [d]thiazol-3(2H)-yl)thiazol -2-amine and 4-(2-(4-chlorophenyl) benzo[d] thiazol-3(2H)-yl)thiazol-2-amine have been synthesized by the reaction2-chloro-1-(2-(4-chlorophenyl) benzo[d]thiazol-3(2H)-yl)ethanone with urea/ thiourea and checked their in vitro as antimicrobials activity. The synthesized molecules showed the good and scenic antimicrobial activity.

Keywords: Synthesis, Spectral Characterization, Antimicrobial Activity.

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Introduction

The molecules containing a ring self-possessed of two or more different kinds of atoms commonly known as carbon [C], nitrogen [N], oxygen [O] and sulfur[S] like indole, oxadiazole, chroman, pyran, furan, thiophene, pyrrole and thiazole etc. are called as heterocyclic moieties. The chemistry of heterocyclic compounds now formed one of the most extensive areas of organic chemistry with rapid expansion of investigation. Due to increased application of a large number of heterocyclic compounds such as pesticides, herbicides, pharmaceuticals etc. in recent times the development in heterocyclic che `mistry has been very rapid. Intensive investigation of synthetic compounds, which are many times analogues of known pharmaceutical agents results in the development of new drugs. The main aim in all such studies is always to have a more efficacious medicine with minimum adverse effect.

Review of Literature

2-(4-chlorophenyl)-2,3-dihydrobenzo[d]thiazole is a heterocyclic compound, The small and simple thiazol nucleus is present in compounds evaluating new products that possess interesting biological activities like antitumor[1], anticonvulsant[2], antimicrobial[3], anthelmintic[4], antileishmanial[5], anti-tubercular[6], schictosomicidal[7], antifungal[8], anti-inflammatory[9] antipsychotic[10] and anti-diabetic activities[11]. And benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Due to their importance in pharmaceutical, the synthesis of various benzothiazole derivatives is a considerable area of current discussion. The classical method involves condensation of *o*-aminothiophenols with substituted aldehydes, acyl chlorides, carboxylic acids or esters, nitriles. Other most commonly used methods include Pd/Cu/Mn/chloranilne catalyzed cyclization of *o*-halothioformanilides. The Benzothiazole are prepared by treatment of 2-mercaptoaniline with acid chlorides [12].

The present investigation describes a simple, facile procedure for the synthesis of 2-chloro-1-(2-(4-chlorophenyl) benzo[d] thiazol-3 (2H)-yl) ethanone derivatives from 2-(4-chlorophenyl)-2,3-dihydrobenzo[d]thiazole their pharmacological activity. The newly synthesized derivatives were characterized by modern physico-chemical techniques such as IR, NMR spectroscopic studies and by their chemical analysis. The homogeneity and purity of these compounds were checked by TLC& HPLC.

Aim of the Study

The present investigation describes a simple, facile procedure for the synthesis of 2-chloro-1-(2-(4-chlorophenyl) benzo [d]thiazol-3 (2H)-yl) ethanone derivatives from 2-(4-chlorophenyl)-2,3 their pharmacological

dihydrobenzo[d]thiazoleactivity. The newly synthesized derivatives were characterized by modern physico-chemical techniques such as IR, NMR spectroscopic studies and by their chemical analysis. The homogeneity and purity of these compounds were checked by TLC& HPLC.

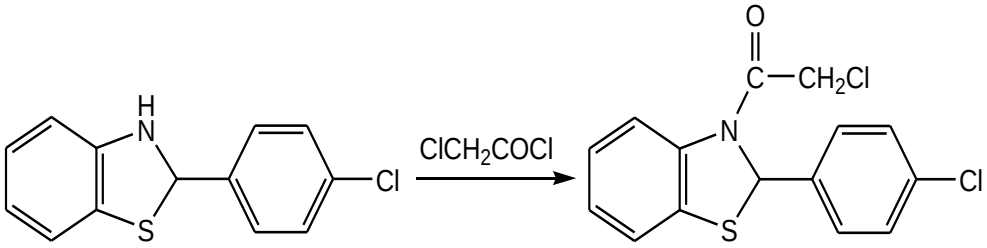
Materials

All compounds and chemicals were purchased from Sigma-Aldrich Chemicals and Merck. Melting points were determined using an open-ended capillary tube method and are uncorrected. TLC wasperformed on pre-coated plastic sheets of silica gel G/UV of 0.2 mm thickness (Macherey-Nagel, Germany). The homogeneity and purity of the synthesized compounds was checked by TLC. A FT-IR spectrum was recorded on a Perkin-Elmer 1605 series FT-IR in a KBr disc. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker FT-NMR spectrophotometer using TMS as internal standard.

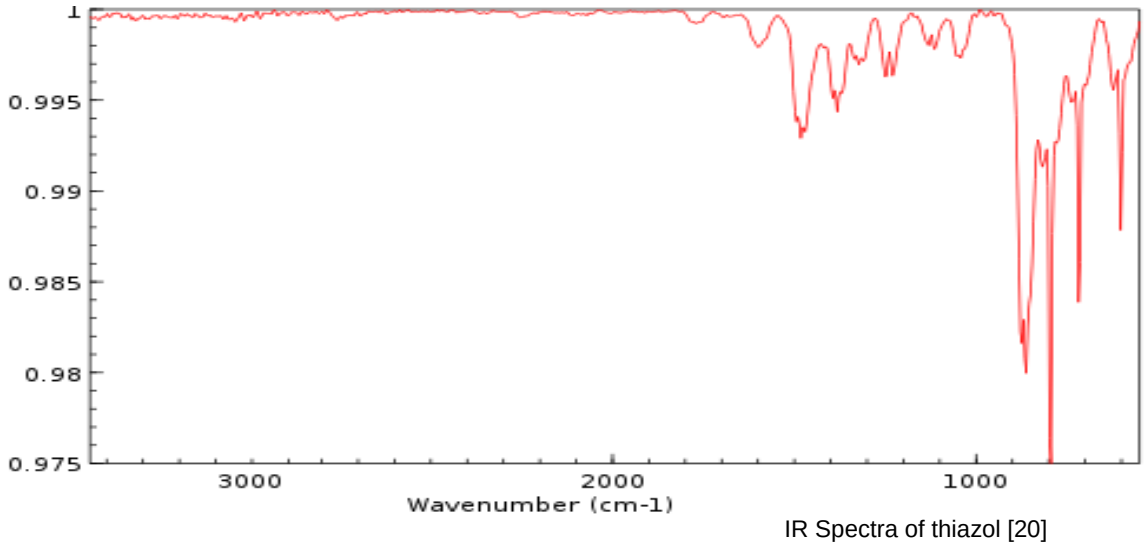
Experimental

2-chloro-1-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)ethanone.

2-chloro-1-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)ethanone has been prepared by following the method of Arya et al. [13]. A solution of 2-(4-chlorophenyl)-2,3-dihydrobenzo[d]thiazole (0.01 mol) in dry dioxane (50 mL) was added dropwise 2-chloroacetyl chloride (0.01 mol) and dry dioxane (150 mL) at 60^{o}C. The reaction mixture was stirred and reflux for 4 h, cooled and poured into ice cold water. The resulting mixture was filtered to afford an orange solid which was recrystallised from ethanol. Analytical data for $C_{15}H_{11}Cl_2NOS$ (324.22) Calcd C, 55.57; H, 3.42; N, 4.32; Found: C, 55.55; H, 3.50; N, 4.36, M.p.253^{o}C.



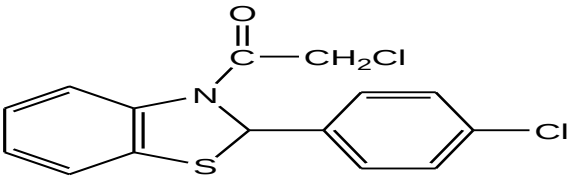
2-(4-chlorophenyl)-2,3-dihydrobenzo[*d*]thiazole 2-chloro-1-(2-(4-chlorophenyl)benzo[*d*]thiazol-3(2*H*)-yl)ethanone



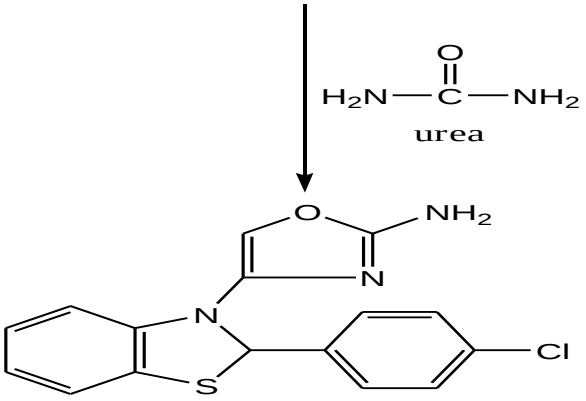
IR Spectra of thiazol [20]

4-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)oxazol-2-amine.

The solution of compound (1) i.e. 2-chloro-1-(2-(4-chlorophenyl) benzo[d]thiazol-3(2H)-yl)ethanone (0.01 mol) in absolute ethanol (250 mL) was added to urea (0.01 mol). The reaction mixture was taken in a beaker and assisted by microwave irradiation using a domestic microwave oven for 10 min. Completion of the reaction was monitored by TLC. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was filtered off. The precipitate was washed with Na_2CO_3solu-tion and water. When the base was completely liberated from the precipitate, it was dried and recrystallised from ethanol/water. Analytical data of $C_{16}H_{12}ClN_3OS$ (329.80) calcu. For C, 58.27; H, 3.67; N, 12.74. Found: C, 58.23; H, 3.66; N, 12.70, M.p.246^{o}C.



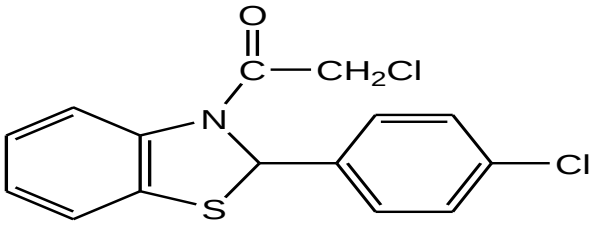
2-chloro-1-(2-(4-chlorophenyl)benzo[*d*]thiazol-3(2*H*)-yl)ethanone



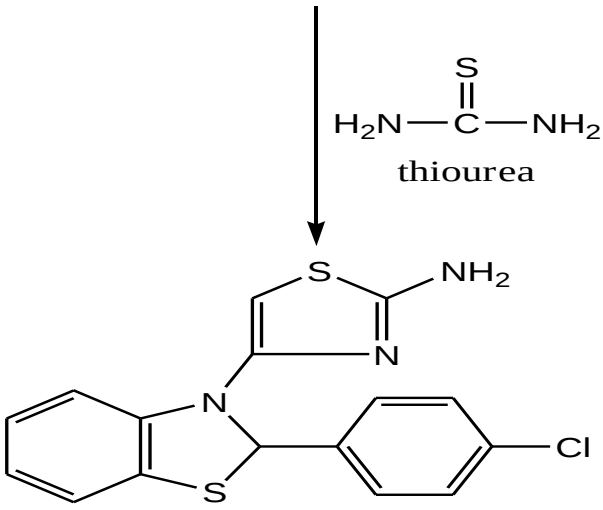
4-(2-(4-chlorophenyl)benzo[*d*]thiazol-3(2*H*)-yl)oxazol-2-amine

4-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)thiazol-2-amine.

The solution of compound 1 i.e. 2-chloro-1-(2-(4-chlorophenyl) benzo[d]thiazol-3(2H)-yl)ethanone (0.01 mol) in absolute ethanol (250 mL) was added to thiourea (0.01 mol). The reaction mixture was taken in a beaker and assisted by microwave irradiation using a domestic microwave oven for 10 min. Completion of the reaction was monitored by TLC. concentrated and filtered off. The solid thus obtained was washed with Na_2CO_3 solution and then with water to liberate the base completely, dried and recrystallised from ethanol/water to give compound 2. Analytical data of $C_{16}H_{12}ClN_3S_2$ (345.01) calcu. For C, 55.56; H, 3.50; N, 12.15; Found: C, 55.63; H, 3.57; N, 12.14, M.p.268^oC.



2-chloro-1-(2-(4-chlorophenyl)benzo[*d*]thiazol-3(2*H*)-yl)ethanone

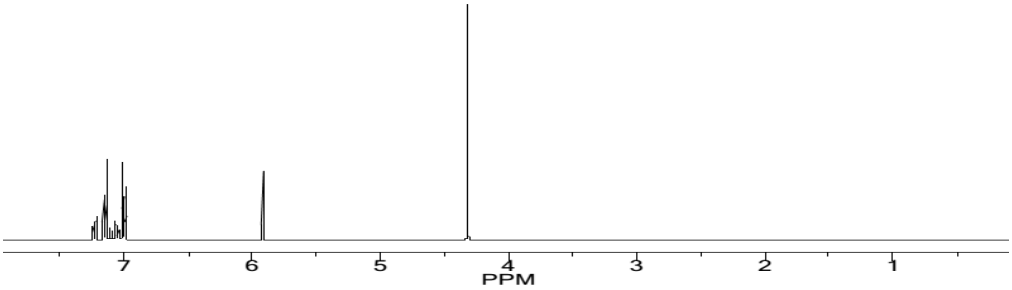


4-(2-(4-chlorophenyl)benzo[*d*]thiazol-3(2*H*)-yl)thiazol-2-amine

Result and Discussion

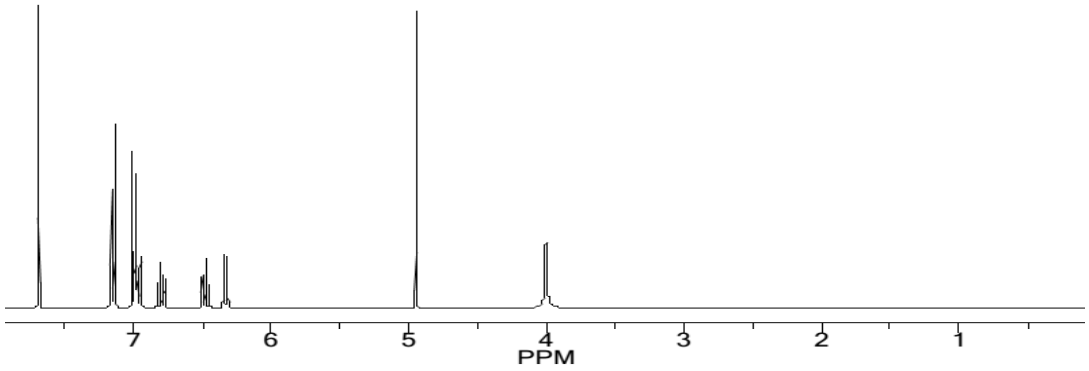
2-chloro-1-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)ethanone.

Analytical data for $C_{15}H_{11}Cl_2NOS$ (324.22) Calcd C, 55.57; H, 3.42; N, 4.32; Found: C, 55.55; H, 3.50; N, 4.36, M.p.253^oC.
IR (KBr)ν_{max} in cm $^{-1}$, 665 cm $^{-1}$ (C—Cl), 760 cm $^{-1}$ (C—C), 1245 cm $^{-1}$ (C—N), 1540 cm $^{-1}$ (C=C for aromatic compound), 1720 cm $^{-1}$ (C=O), 1270 cm^{-1} (C—S), 3040 cm $^{-1}$ (C—H for aromatic compound)
1H NMR ($CDCl_3$) δ in ppm 3.40 (s, 2H, —CH_2Cl), 7.65-6.85 (m, 8H, Ar—H), 4.95 (s, lH, CH of thiazol exchangeable with D_2O)
GCMS (H^+) m/e 323.22, 288.03, 276.76, 246.74, 136.20, 111.55, 77.49, 48.48, 28.02.



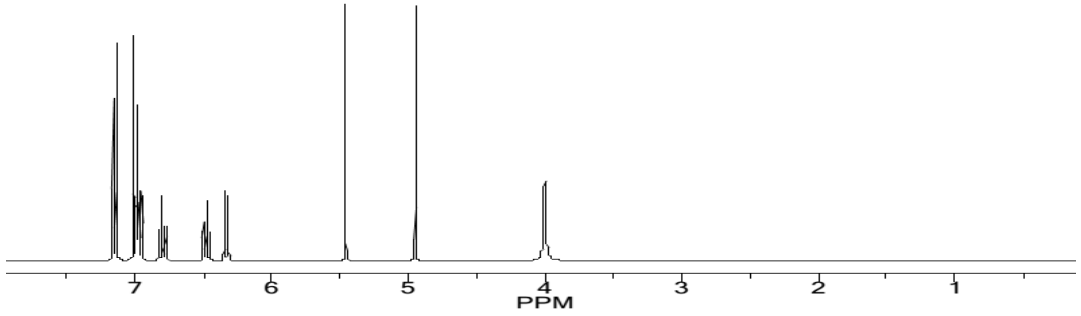
4-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)oxazol-2-amine

The analytical data of $C_{16}H_{12}ClN_3OS$ (329.80) calcu. For C, 58.27; H, 3.67; N, 12.74. Found: C, 58.23; H, 3.66; N, 12.70, M.p.246^oC.
IR (KBr)ν_{max} in cm $^{-1}$, 662 cm $^{-1}$ (C—Cl), 762 cm $^{-1}$ (C—C), 1241 cm $^{-1}$ (C—N), 1544 cm $^{-1}$ (C=C for aromatic compound), 1075 cm^{-1} (C—O—C), 3040 cm $^{-1}$ (C—H for aromatic compound), 1579 cm $^{-1}$ (C=N), 3333 cm $^{-1}$ (—NH_2)
^{1}H NMR ($CDCl_3$) δ in ppm 6.12 (s, 2H, —NH_2), 7.65-6.85 (m, 9H, Ar—H), 4.94 (s, lH, CH of thiazol exchangeable with D_2O)
GCMS (H^+) m/e 328.80, 313.78, 294.35, 279.32, 246.01, 203.23, 136.20, 111.55, 83.06, 77.09, 68.04, 16.03.



4-(2-(4-chlorophenyl)benzo[d]thiazol-3(2H)-yl)thiazol-2-amine.

Analytical data of $C_{16}H_{12}ClN_3S_2$ (345.86) calcu. For C, 55.56; H, 3.50; N, 12.15; Found: C, 55.63; H, 3.57; N, 12.14, M.p.268^oC.
IR (KBr)ν_{max} in cm $^{-1}$, 662 cm $^{-1}$ (C—Cl), 762 cm $^{-1}$ (C—C), 1241 cm $^{-1}$ (C—N), 1544 cm $^{-1}$ (C=C for aromatic compound), 681 cm^{-1} (C—S—C), 3040 cm $^{-1}$ (C—H for aromatic compound), 1579 cm $^{-1}$ (C=N), 3333 cm $^{-1}$ (—NH_2)
^{1}H NMR ($CDCl_3$) δ in ppm 6.12 (s, 2H, —NH_2), 7.65-6.85 (m, 9H, Ar—H), 4.94 (s, lH, CH of thiazol exchangeable with D_2O)
GCMS (H^+) m/e 344.86, 310.42, 296.40, 246.74, 234.32, 219.31, 212.29, 136.20, 111.55, 99.14, 84.12, 16.03.



Antibacterial Activity

Antibacterial activities were evaluated using agar well diffusion method [14]. The activity of the free ligand, its metal complexes and standard drug Imipenem were studied against the *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). Bacterial strain were obtained from Microbial Type Collection and Gene Bank, Institute of Microbial Technology (IMTECH) Chandigarh, India. The solution of 2 mg/mL of each compound (free ligand, its metal complexes and standard drug Imipenem) in DMSO was prepared for testing against bacteria. Centrifuged pelletes of bacteria from a 24 h old culture containing approximately 10^4-10^6CFU (colony forming unit) per mL were spread on the surface of Muller Hinton Agar plates. Wells were created in medium with the help of a sterile metallic bore and nutrients agar media (agar 20g+beef extract 3g+peptones5g) in 1000 mL of distilled water (pH 7.0), autoclaved and cooled down to 45^{o}C. Then it was seeded with 10 mL of prepared inocula to have 10^6CFU/mL. Petri plates were prepared by pouring 75 mL of seeded nutrient agar. The activity was determined by measuring the diameter of the inhibition zone (in mm). The growth inhibition was calculated according to reference [14]

The results of the bactericidal study of the synthesized compounds are summarized in table 1. The Schiff base ligand, its metal complexes, standard drug Imipenem ($C_{12}H_{17}N_3O_4S$) and DMSO solution control were screened for their antibacterial activity against the bacteria *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). From the bactericidal activity, it is apparent that the complexes were more toxic towards gram positive strains than gram negative strains. The reason is the difference in the structure of the cell walls. The walls of gram negative cells are more complex than those of gram positive cells. Antibacterial activity of all the compounds towards gram positive and gram negative bacteria is quite significant. Further to it, compounds show moderate to high activities as compared to standard drug towards the all organism. This may be due to the presence of –NH group playing an important role in the biological activity; this group is believed to impart the transformation reaction in biological system. [15], mainly because of the partial sharing of its positive charge with the donor group, this process, in turn increases the lipophilic nature of the central metal atom, which subsequently favors it's permeability through the lipid layer of the cell membrane and blocking the metal binding sites on enzymes of microorganism [16-19]. 4-(2-(4-chlorophenyl) benzo[d] thiazol-3(2H)-yl)thiazol-2-amineshows best antibacterial activity against all the tested pathogen.

Table 1
Bactericidal Screening Data of The Complexes

Compounds	Gram Positive		Gram Negative		
	S A	B S	E C	S T	P A
Compound 1	10	12	22	19	11
Compound 2	10	26	26	22	22
Compound 3	08	40	28	33	33
Imipenem	100	100	100	100	100

Excellent activity (90-100% inhibition), Good activity (60-70% inhibition), Significant activity (30-50% inhibition), negligible activity (08-20% inhibition), *Staphylococcus aureus (S. A), Bacillus subtilis (B S), Escherichiacoli (E C), Salmonella typhi (S T), Pseudomonas aeruginosa (P A),* Imipenem = Standard drug.

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