

ORIGINAL ARTICLE

Synthesis, Characterization and Study of Antibacterial Activity of Some Novel Substituted Sulphonamide Phthalazine-Tetrazole Derivatives

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ABSTRACT

Phthalazine nucleus has attracted attention of medicinal chemists, due to wide spectrum of biological activities exhibited by them. A series of new Phthalazine Sulphonamide-Tetrazole Derivatives have been Synthesised in excellent yields. The chemical structures of the synthesized compounds were confirmed by FT-IR, ¹H NMR, ¹³C NMR, and mass spectral studies. The new compounds (8a– 8i) were tested for their antimicrobial activity. Variable and modest activities were observed against the investigated strains of bacteria and fungi. Compounds 8i, 8g, and 8f demonstrated good antimicrobial activity against all the tested microbial strains.

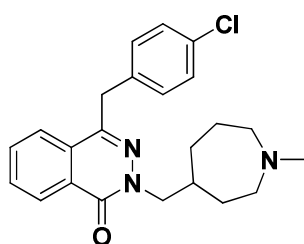
Key words : 1,4-dichlorophthalazine, Tetrazoles, sulfonamides, [3+2] cyclo addition reactions, Synthesis, Antimicrobial activity

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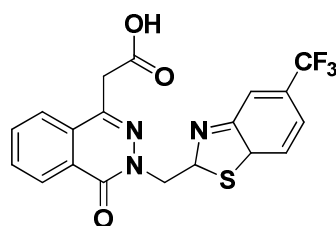
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Introduction

Phthalazine derivatives, like the other members of the isomeric benzodiazine series, have been widely applied as therapeutic agents due to their anticonvulsant, cardiotoxic, vasorelaxant and anti-inflammatory properties [1-2]. Majorities of the drugs used in human medicine are heterocyclic compounds. Common drugs such as Morphine, Lipitor, Penicillin, and non steroidal anti-inflammatory agents contain at least one heteroatom in their structure [3]. Heterocyclic compounds containing nitrogen group have large are a in nature, and their utilization is becoming progressively important as biologically active pharmaceuticals, agrochemicals, and functional materials [4]. In particular, hydrazine containing heterocyclic compounds have been considered of great importance on account of pharmacological properties and clinical applications [5]. Moreover, these of combined phthalazines have biological properties such as inhibition of p38MAPkinase [6] for selective binding of GABA receptor [7], anti-anxiety drug [8], antitumor agent [9], and high affinity ligand to the $\alpha_2\text{-}1$ sub unit of calcium channel [10]. Phthalazine derivatives have been greatly used as therapeutic agents owing to their anticonvulsant, cardiotoxic, vasorelaxant, anti-inflammatory properties [11-16], and antimicrobial activity [17]. Like azelastine, the phthalazine derivatives have antihistaminic effects in the treatment of allergic rhinitis [18], and hydralazine is used as antihypertensive agent in the treatment of pulmonary hypertension [19-21]. Some commercially used phthalazine derivatives are shown in FIG 1.



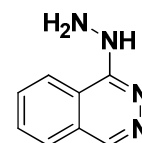
Azelastin



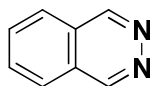
Zopolrestat



Luminol



Hydralazine

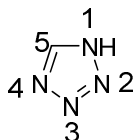


phthalazine

FIG 1: Some commercially used phthalazine derivatives & Structure of Phthalazine.

Tetrazole are class of synthetic organic heterocyclic compounds consisting of five-member ring of four nitrogen and one carbon atom (plus hydrogen). The simplest is tetrazole itself CN_4H_2 . It is white to pale yellow crystalline solid with weak characteristic odour, soluble in water and alcohol. It is acidic in nature due to presence of four nitrogen atoms. Numbering of tetrazoles is as shown below (**Fig :1**)

Synonym – Tetrazole, Tetraza cyclo pentadiene, 1-H Tetrazole.



Tetrazole

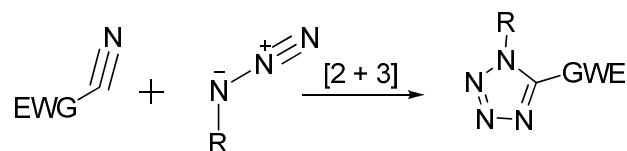
Fig :2 Structure of tetrazole

Tetrazole and its derivatives have important applications in major areas, such as medicine, agriculture and imaging technology, and are very stimulating heterocycles from an academic viewpoint. Tetrazoles are a class of heterocycles that have received attention due to their wide range of applications.[22] In general, this nitrogen-rich ring system is used in propellants[23], explosives[24], and in pharmaceuticals[25]. In addition, tetrazoles are important synthons in synthetic organic chemistry[26] and also used as precursors of carbenes in flash vacuum pyrolysis[27]. Various tetrazole-based compounds have also shown good coordination properties and are able to form stable complexes with several metal ions[28] Furthermore, the tetrazole ring has strong electron withdrawing property and tetrazolyl halides have been successfully used in organic synthesis as derivatising agents for the chemical modification of alcohols [29].

The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Tetrazoles are medicinally important heterocycles incorporated in a large number of drugs. Tetrazole, an aromatic azapyrrole group, is metabolically stable and has acidic characteristics closely similar to that of the carboxylic group[30]. Tetrazole and its derivatives possessing a wide spectrum of biological activities including antibacterial[31, 32] antifungal and anti-convulsant[33], analgesic[34], anti-inflammatory[35], antitubercular activity[36], anticancer activity[37] and antihypertensive[38] activities.

Generally preparation of tetrazoles carried out by the most direct method is via the formal [2+3] cyclo addition of azides and nitriles. However, evidence in the literature indicates that the mechanism of the reaction is different for different azide species. When an organic azide is used as the dipole, only certain highly activated nitriles are competent dipolarophiles [39]. In these cases the reaction is regioselective, and only the 1-alkylated product is observed[40]. It is commonly accepted that in these cases the reaction proceeds via a traditional [2 + 3] mechanism [41] (Scheme-1) addition of azide salts and nitriles to give 1H-tetrazoles (Fig : 3).

Scheme-1: traditional [2 + 3] mechanism:

**(FIG : 3 2+3 cyclo addition of Nitrile and azide ion)**

sulfonamides have a variety of biological activities such as antibacterial [42-44], insulin releasing [45], carbonic anhydrase inhibitory [46, 47], anti-inflammatory [48] and antitumor [49] activities. Sulphonamide core Structure present in various Drugs Such as Losartan, Irbesartan, Valsartan,.[**Fig : 4** Structures Of Sulphonamide Core Containing Various Biologically Active Drugs.]

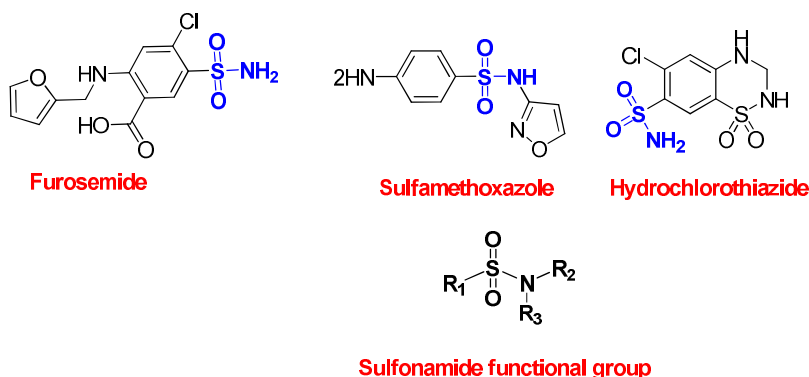


Fig : 4 Structures Of Sulphonamide Core Containing Various Biologically Active Drugs

These findings encouraged us to explore the synthesis of sulfonamides containing Phthalazine with tetrazole moieties and to examine their antibacterial and antifungal properties.

Tetrazoles are medicinally important heterocycles incorporated in a large number of drugs [50-51]. In recent years, the growth of the tetrazole chemistry has been significant [52, 53], mainly as a result of the central roles played by tetrazoles in coordination chemistry as nitrogen-containing heterocyclic ligands [54], in materials applications as specialty explosives, information recording systems, rocket propellants and in agricultural applications [55, 56]. In particular, tetrazoles can be used as equivalent replacements for carboxylic moiety in drug design, with the advantage over carboxylic moieties being that they are resistant to many biological metabolic degradation pathways [57]. In fact, several leading compounds have been synthesized and tested for pharmaceutical purposes [58-60]. Furthermore, tetrazole moieties can be used as important synthons in synthetic organic chemistry due to their characteristic electronic property [61-63]. Tetrazole core unit present in various Drugs Such as Losartan, Irbesartan, Valsartan, [Fig : 5 Structures Of Tetrazole Core Containing Various Biologically Active Drugs.]

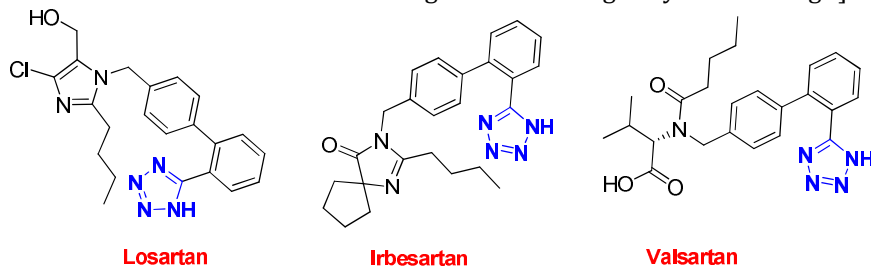


Fig.5 Tetrazole Core Structure Present in Various Biologically Active Drug Molecules

Encouraged by the diverse biological activities of Phthalazine compounds, it was decided to prepare a new series of Phthalazines derivatives. The synthesis of the compounds as per the following Scheme I given below.

The synthetic route was depicted in scheme I

The structures of all synthesized compounds were assigned on the basis of IR, Mass, ¹H NMR spectral data. Further these compounds were subjected for antifungal and anti-bacterial activity.

MATERIALS AND METHODS

Laboratory chemicals were provided by Rankem India Ltd. and Fisher Scientific Ltd. Melting points were determined by the open tube capillary method and are not correct. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system Petether:ethyl acetate (8:2). The spots were observed by exposure to iodine Vapours or by UV light or P-Anisaldehyde Stain Solutions. The IR spectra were received by PerkinElmer 1720 FT-IR spectrometer (KBr pellets). The ¹H NMR & ¹³C NMR spectra were obtained by Bruker Advance II 400 spectrometer using TMS because the internal standard in CDCl₃.

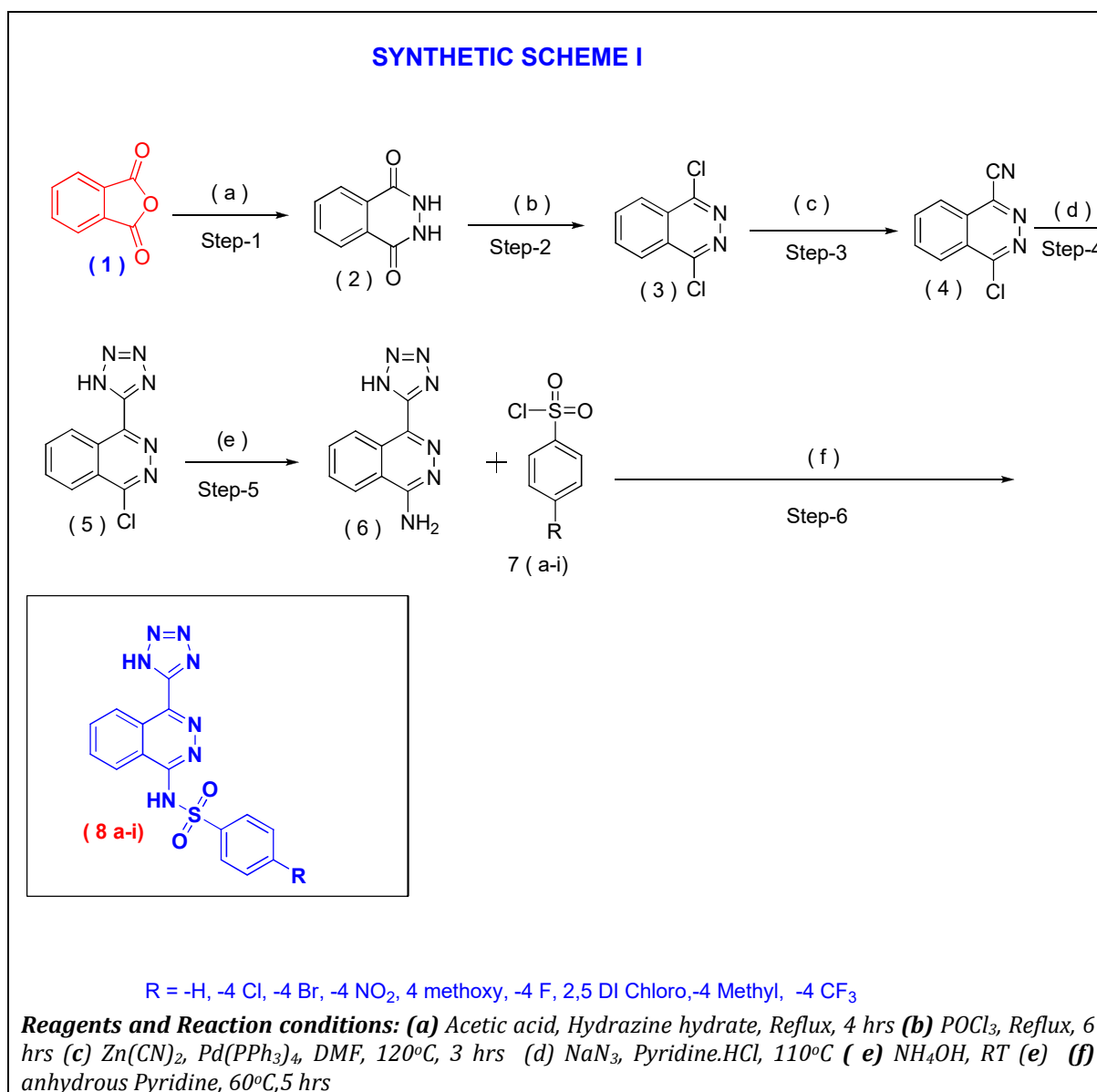
General Information.

Commercial chemicals were treated as follows: 1,4 di oxane, DMF (N,N di methyl formamide) distilled from CaH₂ and degassed (freeze and thaw) three times prior to use; THF, ether, distilled from Na/benzophenone.

The synthesis of the compounds as per the following Scheme I given below.

The synthetic route was depicted in scheme I

The title compounds 8(a-i) were synthesised in Six sequential steps using different reagents and reaction conditions, the 8 (a-i) were obtained in moderate yields. The structure were established by spectral (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and mass) and analytical data.



Experimental Section

General Methods: Column chromatography was performed using Silica gel 100-200 mesh size. THF and dioxane were distilled from sodium-benzo phenone and dried over MS 5A⁰ and MS 4A⁰, respectively. MeCN and 1,2-dichloroethane (DCE) were distilled from CaH₂. EtOH was distilled from Mg/I₂ and dried over MS 3A⁰. Prior to use, POCl₃ was distilled. All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na₂SO₄, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–100 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C , respectively, in CDCl₃ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetra methyl silane (TMS) in the solvent of CDCl₃-d or

DMSO- d_6 as the internal standard (^1H NMR: TMS at 0.00 ppm, CDCl_3 at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: CDCl_3 at 77.16 ppm, DMSO at 40.00 ppm).

General procedure for the preparation of 2,3-dihydrophthalazine-1,4-dione (Compound 2) [64] :

The starting material Phthalic anhydride (1) (1 m.mol) was dissolved in Acetic acid (10 Vol.). To this mixture hydrazine hydrate (3 m.mol) drop wise under ice bath. The reaction mixture was stirred at room temperature for 20 mins, and then raise temperature at 110°C for 4 hrs. The off white solid was precipitated was collected through filtration and washed the chilled water and dried to afford compound 2 (Yield 77 %).

m.p.: 300°C above also not melted.

^1H NMR (DMSO- d_6 , 400 MHz): 8.1(d, 2H), 7.9 (d, 2H), 11.2 (bs, 2 H).

^{13}C NMR (DMSO- d_6 , 100 MHz): 120,134,117,169

IR (KBr, cm^{-1}): O-H (3510, sharp), Ar stretch C-H (3130.34), C-O (1060), C=N (1608.69), C=C (1344.43) m/z (LC-MS Shows 95% purity.):163 [M+H]⁺

General procedure for the preparation of 1,4-dichlorophthalazine (Compound 3) [65] :

The compound (2) (10 m.mol) was added to a stirred solution of phosphorus oxychloride (15 ml). The mixture was heated to 110°C for 1 h. After the reaction was complete (monitored by TLC), The reaction mixture was cooled to room temperature. The mixture was added dropwise to crushed ice with stirring for 10 minutes. Then the mixture was filtered through a buchner funnel. the filter cake was washed with H_2O until neutral and dried in a vacuum. Compound(3) (90.1 percent) was obtained as a white solid.

m.p.: $160\text{--}161^\circ\text{C}$.

^1H -NMR (400 MHz, CDCl_3) δ ppm: 8.12(d, 2H), 7.89 (d, 2H)

^{13}C NMR (DMSO- d_6 , 100 MHz): 123,155, 126, 138

IR (KBr, cm^{-1}): Ar stretch C-H (3120), C=N (1618), C=C (1540), C-Cl (767).

EI-MS (m/z): 199 [M⁺], 201[M+2], 203[M+4] (9:6:1, it indicates molecule contains two chlorine atoms).

General procedure for the preparation of 4-chlorophthalazine-1-carbonitrile (Compound 4) [66] :

In a sealed tube a mixture of 1,4-dichlorophthalazine (1 eq), $\text{Zn}(\text{CN})_2$ (1.05 eq) and tetrakis (tri phenyl phosphine) palladium(0) (0.1 eq) in anhydrous DMF was degassed with argon for 10 minutes and then warmed at 120°C for 2 hours. After cooling, the reaction was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane. The major fractions were combined and the solvent was concentrated in vacuum to afford 4-chlorophthalazine-1-carbonitrile (Compound 4).

m.p.: $130\text{--}132^\circ\text{C}$.

^1H -NMR (400 MHz, CDCl_3) δ ppm: 8(d, 2H), 7.89 (d, 2H)

^{13}C NMR (DMSO- d_6 , 100 MHz): 123,132, 138, 135, 160, 125, 122, 118(Nitrile carbon).

IR (KBr, cm^{-1}): Ar stretch C-H (3110), C=N (1628), C=C (1530), C-Cl (763), 2210($\text{C}\equiv\text{N}$).

EI-MS (m/z): 189 [M⁺], 191[M+2], (3:1, it indicates molecule contains one chlorine atom).

General procedure for the preparation of 1-chloro-4-(1H-tetrazol-5-yl)phthalazine(Compound 5) [67] :

4-chlorophthalazine-1-carbonitrile (Compound 4) (10 m.mol), NaN_3 (12m.mol), and $\text{Py}\cdot\text{HCl}$ (10m.mol) in 20ml of DMF were added to a 50-mL round-bottomed flask. The reaction mixture was heated at 110°C for 8h with vigorous stirring. Conversion was monitored by thin-layer chromatography (TLC). After that, the reaction mixture was cooled to room temperature and dissolved in 4mL of NaOH aqueous solution (5M) with 30min of stirring. The solution was concentrated under reduced pressure by the removal of DMF and Py; the reaction residue was dissolved in 10mL water. The pH value was adjusted to 1 with HCl (3M, 10mL) to form a precipitate. The precipitate was then filtered, washed with 20 mL of 3M HCl, and dried at 80°C overnight to furnish pure 1-chloro-4-(1H-tetrazol-5-yl)phthalazine(Compound 5) as a white solid.

m.p.: $168\text{--}169^\circ\text{C}$.

^1H -NMR (400 MHz, CDCl_3) δ ppm: 8(d, 2H), 7.89 (d, 2H), 4.5(1H,bs).

^{13}C NMR (DMSO- d_6 , 100 MHz): 151,127,137,134,124, 156,125, 164.

IR (KBr, cm^{-1}): Ar stretch C-H (3120), C=N (1618), C=C (1540), C-Cl (767), 3310(N-H).

EI-MS (m/z): 232 [M⁺], 234[M+2], (3:1, it indicates molecule contains one chlorine atom).

General procedure for the preparation of 4-(1H-tetrazol-5-yl)phthalazine-1-amine (Compound 6) [68] :

A mixture of 1-chloro-4-(1H-tetrazol-5-yl)phthalazine(Compound 5) (1g)and 30 ml of concentrated ammonium hydroxide was stirred at ambient temperature overnight. The solid which had precipitated was collected by filtration and was recrystallized from ethanol. The yield of 4-(1H-tetrazol-5-yl)phthalazine-1-amine was 0.7g (72%) ;

m.p. 127°-129°C

¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.85(2H,bs).

¹³C NMR (DMSO-d₆, 100 MHz): 144, 127, 133, 132, 120, 166,116, 164

IR (KBr, cm⁻¹): Ar stretch C-H (3110), C=N (1618), C=C (1540), C-Cl (777), 3320 & 3420 (N-H, two bands it indicates presence of primary amine).

EI-MS (m/z): 213 [M⁺,100%], 214[M+1, 9.7%], (it indicates molecule contains 9 Carbon atoms).

General procedure for the preparation of

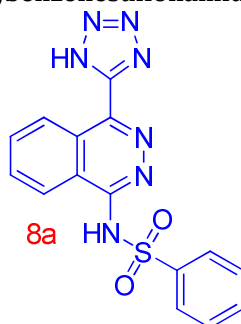
General procedure for the preparation of N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl) benzenesulfonamide (8a), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-chlorobenzenesulfonamide(8b), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-bromobenzenesulfonamide (8c), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-nitrobenzenesulfonamide (8d), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-methoxybenzenesulfonamide (8e), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-fluorobenzenesulfonamide (8f), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-2,5-dichlorobenzenesulfonamide (8g), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-methylbenzenesulfonamide (8h), N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-(trifluoromethyl) benzenesulfonamide (8i) [69]:

To the starting amine (Compound 6) (6 m.mol) suspended in anhydrous pyridine (10 mL), appropriate sulfonyl chlorides (7 a-i) (6.3 m.mol) was added gradually.The reaction mixture was heated at 60°C for 2-5 hours, then poured into ice water and acidified with 2N HCl. The solid product was filtered, washed well with water, and re crystallized from Ethanol.

Table 1 Yields & Melting Points of Corresponding Compounds (8a-8i) :

S.NO	Yield (%)	Melting Point (°C)	Physical Appearance
8a	80	208-210	White Solid
8b	82	230-231	Off white Solid
8c	80	215-216	White Solid
8d	81	235-236	white Solid
8e	83	239-240	Off white solid
8f	84.2	243-245	White solid
8g	84	182-184	White solid
8h	85	190-192	White solid
8i	86	187-189	White solid

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)benzenesulfonamide (8a) :



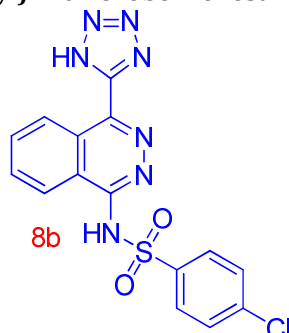
IR (KBr, cm⁻¹): Ar stretch C-H (3095), C=N (1526.15), C=C (1575), N-H (3266), 1362 & 1153(S=O Stretching in Sulfonamide group).

¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.9-7.6 (5H, m), 4.2(1H,bs).

¹³C NMR (DMSO-d₆, 100 MHz): 120-165.5 (15 aromatic carbons)

Mass : 354(100%, M+H)

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-chlorobenzenesulfonamide(8b) :



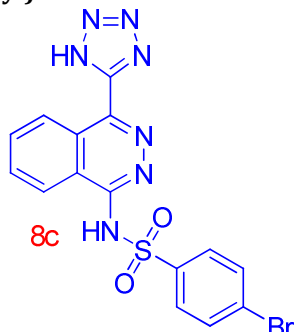
IR (KBr, cm^{-1}): Ar stretch C-H (3078), C-Cl (740), C=C (1593), N-H (3359), 1365 & 1159(S=O Stretching in Sulfonamide group).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.04(d, 2H), 7.87 (d, 2H), 7.9 (2H,d, 7.45(2H.d), 4 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 120-167(15 aromatic carbons)

Mass : 387(100%, M^+), 389(33%, $\text{M}+2$) It indicates molecule contains one chlorine molecule.

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-bromobenzenesulfonamide (8c)



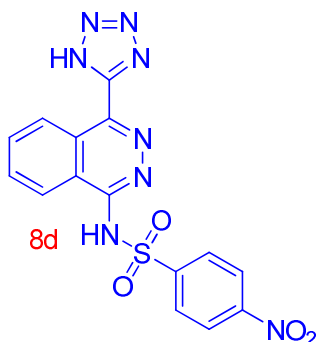
IR (KBr, cm^{-1}): Ar stretch C-H (3033), C=C (1590), N-H (3393), C-Br(540), 1365 & 1159(S=O Stretching in Sulfonamide group).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.8 (2H,d, 7.6(2H.d), 4 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 120-167(15 aromatic carbons)

Mass : 430(100%, M^+), 432(98%, $\text{M}+2$) It indicates molecule contains one bromine molecule.

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-nitrobenzenesulfonamide (8d)



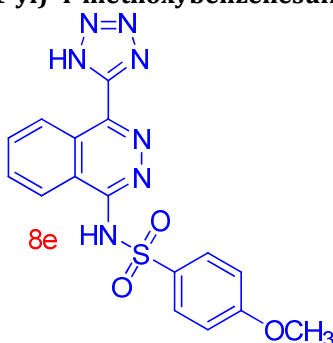
IR (KBr, cm^{-1}): Ar stretch C-H (3064), C=C (1595), N-H (3249), 1361& 1151(S=O Stretching in Sulfonamide group), 1340 & 1550 (N-O Stretching in nitro group).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 8.2 (2H,d, 8.6(2H.d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 120-165(15 aromatic carbons)

Mass : 399(100%, $\text{M}+\text{H}$)

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-methoxybenzenesulfonamide (8e) :



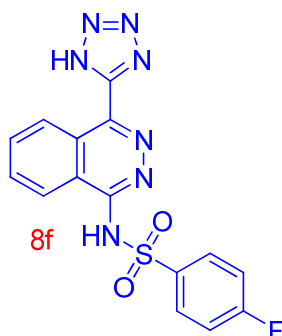
IR (KBr, cm^{-1}): Ar C-H stretch (3068), C=C (1585), N-H (3293), 1365& 1159(S=O Stretching in Sulfonamide group), 2958 (C-H).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 3.85(3H,s), 7.7 (2H,d, 7.2(2H.d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 115-168(15 aromatic carbons), 57(Methoxy Carbon).

Mass : 384($\text{M}+\text{H}$).

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-fluorobenzenesulfonamide (8f) :



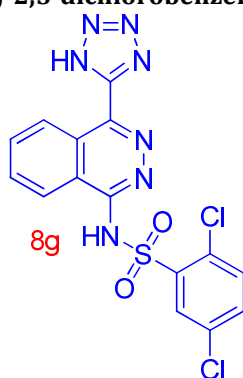
IR (KBr, cm^{-1}): Ar C-H stretch (3038), C=C (1595), N-H (3249), 1365& 1153(S=O Stretching in Sulfonamide group), 1258 (C-F).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.97 (2H, d), 7.4(2H,d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 115-168(15 aromatic carbons).

Mass : 372(M+H).

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-2,5-dichlorobenzenesulfonamide (8g) :



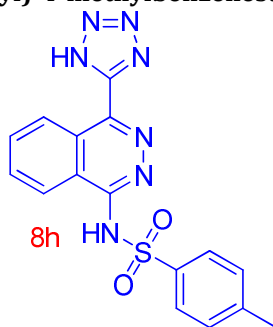
IR (KBr, cm^{-1}): Ar C-H stretch (3068), C=C (1585), N-H (3266), 1364& 1163(S=O Stretching in Sulfonamide group), 758 (C-Cl).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.97 (1H, d) , 7.74(1H.dd), 7.7(1H,d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 115-165(15 aromatic carbons).

Mass : 420(M^+), 422($\text{M}+2$), 424($\text{M}+4$) it indicates molecule contains two chlorine atoms respectively.

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-methylbenzenesulfonamide (8h) :



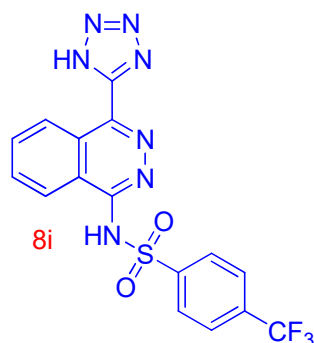
IR (KBr, cm^{-1}): Ar C-H stretch (3098), C=C (1585), N-H (3252), 1360& 1156(S=O Stretching in Sulfonamide group), 2956 (C-H).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 2.3(3H,s), 7.76 (2H,d, 7.42(2H.d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 115-166(15 aromatic carbons), 23(Methyl Carbon).

Mass : 368(M+H).

N-(4-(1H-tetrazol-5-yl)phthalazin-1-yl)-4-(trifluoromethyl)benzenesulfonamide (8i) :



IR (KBr, cm^{-1}): Ar C-H stretch (3088), C=C (1585), N-H (3246), 1363& 1155(S=O Stretching in Sulphonamide group), 1368 (C-F).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ ppm: 8.02(d, 2H), 7.87 (d, 2H), 7.90 (2H, d), 7.79(2H,d), 4.2 (1H, bs).

$^{13}\text{C NMR}$ (DMSO-d_6 , 100 MHz): 115-165(15 aromatic carbons), 124 (trifluoromethyl carbon) .

Mass : 422(M+H).

Biological Activity

Antibacterial activity

Antibacterial activity of the synthesized compounds (8a-8i) were determined against Gram-positive bacteria (*Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 7443) and Gram-negative bacteria (*Xanthomonas campestris* MTCC 7908 and *Escherichia coli* MTCC 7410) in DMF by disc diffusion method on nutrient agar medium (Andrews, 2001). The sterile medium (nutrient agar medium, 15 ml) in each Petri plate was uniformly smeared with cultures of Gram-positive and -negative bacteria. Sterile discs of 10 mm diameter (Hi-Media) was placed in the Petri plates, to which 50 μl (1 mg/ml, i.e. 50 $\mu\text{g}/\text{disc}$) of the different synthesized compounds were added. The treatments also included 50 μl of DMF as negative, bacteriomycin and gentamycin as positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at $37 \pm 2^\circ\text{C}$ for 24 h and the zone of inhibition was determined.

Antifungal activity

The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* MTCC 2480 in DMF by poisoned food technique (Satish *et al.*, 2007). Potato dextrose agar (PDA) media was prepared and about 15 ml of PDA was poured into each Petri plate and allowed to solidify. 5 mm disc of 7 days old culture of the test fungi was placed at the center of the Petri plate and incubated at 26°C for 7 days. After incubation the percentage inhibition was measured and three replicates were maintained for each treatment. Nystatin was used as standard. All the synthesized compounds were tested (at the dosage of 500 μl of the new compounds/Petri plate, where concentration was 0.1 mg/ml) by poisoned food technique.

The Novel Substituted Sulphonamide Pthalazine-Tetrazole Derivatives containing $-\text{CF}_3$ (8i) and 2,5 di chloro (8g) showed more activity than other substituent's Among the compounds (8a-8i) the antimicrobial inhibitory activity follows the order **8i>8g>8f>8d>8b>8c>8h>8e>8a**

Table 3 In vitro antibacterial and antifungal activities of the synthesized compounds (8a-8i) :

Compounds	Zone of inhibition in diameter (mm)				% inhibition F. oxysporum	
	B. subtilis	S. Aureus	P.aeruginosa	E. Coli		
8a		16	18	16	15	45.2
8b		23	22	21	22	62.4
8c		22	21	22	21	61.2
8d		24	23	21	23	64.5
8e		17	19	18	19	51.9
8f		26	24	24	26	68.8
8g		27	25	25	27	76.3
8h		22	20	21	20	59.2
8i		28	27	29	28	86.6
Bacteriomycin		-	-	34	-	-
Gentamycin		35	30	-	35	-
Nystatin		--	-	-	-	100

RESULTS AND DISCUSSIONS

Chemistry:

According to well-established literature procedures, the thermal reaction of commercially available Phthalic anhydride and hydrazine hydrate produced compound 2, which was further chlorinated with phosphorus oxychloride to produce Compound 3. Intermediate 3 was sequentially nucleophilically substituted with Zinc cyanide ($Zn(CN)_2$) to produce Compound 4. Then, Compound 4 reacts with Sodium azide to produce the corresponding Tetrazole (5). Thereafter, Compound (5) Amination with Aqueous Ammonia to produce the compound (6) respectively. Finally, compound 6 by the condensation reaction of Para Substituted sulfonyl chlorides 7(a-i) in dry pyridine to get desired compounds (8a-8i) with excellent yields. All of the synthesized compounds were characterized using IR, 1H -NMR, ^{13}C NMR and MS analysis.

Characterization:

The FT-IR spectra of 8a-8i were recorded using KBr pellets in the range of 4,000–400 cm^{-1} . The IR spectrum of the title Compounds 8(a-i) has given stretching vibration 3250 cm^{-1} due to the stretching vibration corresponding to N-H Stretching vibrations. 3100 cm^{-1} due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2950 cm^{-1} is due to The stretching vibration corresponding to the SP^3 C-H (methyl gp). The strong Intensity absorption at 1150 & 1350 cm^{-1} is due to The stretching vibration of -S=O Stretching in Sulphonamide group, 1360 cm^{-1} is due to The stretching vibration of C-F bond. 760 cm^{-1} is due to The stretching vibration of C-Cl bond. 560 cm^{-1} is due to The stretching vibration of C-Br bond. The Strong Intensity absorption at 1150 & 1350 cm^{-1} corresponds to a N=O Stretching vibration in nitro group.

It has been observed from chemical structure of compounds 8(a-i) that different pair of protons. The protons of Methyl group which is attached to benzene ring appeared as a singlet at $\delta = 2.3$ ppm, The protons of Methoxy group appeared as a Singlet at $\delta = 3.85$ ppm, . The protons attached Pthalazine ring appeared between $\delta = 7.8$ -8.3 ppm respectively.

The chemical shifts of the final compounds carbon vary from $\delta = 165$ to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, The carbon chemical shift of the methyl group at $\delta = 23$ ppm. The carbon chemical shift of the Methoxy group at $\delta = 58$ ppm.

Readily available starting materials and Simple Synthesizing procedures make this method very attractive and convenient for the synthesis of di substituted Pthalazine derivatives. Formation of products was confirmed by recording their 1H NMR, ^{13}C , FT-IR, mass spectra.

Anti -microbial screening:

The results of Anti -microbial studies of newly synthesized compounds reveal that the compounds possess significant Anti -microbial activities. The results of these studies are given in **Table 3**. From Anti -Microbial screening results, it has been observed that compounds 8i, 8g, 8f possess good activity.

CONCLUSIONS

In conclusion, a series of new Pthalazine Tetrazole containing Sulphonamides were synthesized in good yield, characterized by different spectral studies and their antimicrobial activities have been evaluated. Compounds 8i, 8g, and 8f demonstrated good inhibition against microbial strains tested. The studies reveal that the substituent on phenyl ring in Sulphonamide is responsible for the antimicrobial activity of these classes of agents. On the basis of their activity, these derivatives were identified as viable leads for further studies.

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