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AN EFFICIENT, GREENER MICROWAVE ASSISTED MULTI-COMPONENT ONE POT SYNTHESIS OF [1, 3, 4] THIADIAZIN-2-YL-THIAZOLIDIN-4-ONES

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ABSTRACT: This work involves synthesis of [1, 3, 4] thiadiazin-2-ylamine 3(a-c) derivatives from various substituted acetophenone derivatives 1(a-c), and thiosemicarbazide 2 mixed in ethanol and irradiation with microwaves which were directly used for next step. [1, 3, 4]Thiadiazin-2-yl)-thiazolidin-4-one 6(a-f) were synthesized in the second step from substituted-6H-[1, 3, 4] thiadiazin-2-ylamine 3(a-c), substituted aromatic aldehyde 4(a-b), and thioglycolic acid mixed in ethanol. After completion of the reaction products obtained 6(a-f) was confirmed by spectroscopy. Library of such [1, 3, 4] thiadiazin-2-ylamine and [1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one derivatives has been generated and the structures were subjected to PASS for their probabilities of being biologically active. Biological prediction study of the library was done to find out most active molecules. Computer programme PASS predicted for three activities with top probability for compound 3(a-c) as- 1. Mucomembranous protector, 2. Arylacetonitrilase inhibitor, 3. Macrophage elastase inhibitor. Similarly Compounds 6(a-f) were predicted for two activities with top probability as- 1. CC chemokine-4-receptor antagonist, 2. Phosphatase inhibitor.

INTRODUCTION: 1, 3, 4-thiadiazine derivatives involve in many biological processes and serve as medicinally interesting compounds^{1, 2}. The wide range of therapeutic activities of 1, 3, 4-thiadiazine are antifungal³, antibacterial⁴, antimicrobial⁵, anti-inflammatory⁶ cardiovascular⁷, anti-HIV⁸, antidiabetic⁹, antidepressant¹⁰ etc. 4-Thiazolidinone derivatives have also been known to exhibit diverse bio-activities such as anti-convulsant¹¹, anti-diarrheal¹², anti-platelet activating factor¹³, antihistaminic¹⁴, anti-diabetic¹⁵,

Cyclooxygenase (COX) inhibitory¹⁶, Ca²⁺-channel blocker¹⁷, platelet activating factor (PAF) antagonist¹⁸, cardioprotective¹⁹, anti-ischemic²⁰, anti-cancer²¹, tumor necrosis factor- α antagonist²² and nematicidal activities²³. 2-Phenylimino-3-aryl-4-S-benzyl-6-tetra-O-acetyl- β -D-galactosylimino-2, 3-dihydro-1, 3, 5-thiadiazine (hydrochloride) derivatives²⁴ show antimicrobial activity against various pathogenic bacteria and fungi.

These biologically active spiroheterocycle inspired us to integrate thiadiazine moiety in a triazole framework²⁵. Some new 1, 3, 4-thiadiazines with coumarin moieties and their derivatives²⁶ were shown to have antioxidant activity, employing different antioxidant assays (DPPH scavenging activity, iron chelating activity, power reducing activity).

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Again some new series of novel 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1, 2, 4] triazolo[3,4b] [1,3,4] thiadiazine derivatives²⁷ shown antibacterial activity against four human pathogenic bacteria viz. *Escherichia coli*, *Klebsiella pneumoniae*, *Shigella dysenteriae* and *Shigella flexnei*. Herein we report the synthesis of a new series of spiro-thiadiazines and their antimicrobial activity. The synthesis of heterocycles containing such multistructure in a molecule has received much attention in recent years²⁸.

PASS: PASS is a software application that predicts 565 possible biological activities of a user selected (set of) compound(s). These activities include 5-hydroxytryptamine antagonists, neuromuscular blocking agents, antibiotics, antidepressants, antiviral agents (AIDS), contraceptives, tumor necrosis factor antagonists and many others. Using PASS predictions, novel pharmaceutical agents have been discovered with anxiolytic, anti-inflammatory, antihypertensive, anticancer and other activities. PASS is applicable to chemical libraries containing millions of compounds.

The "the biological activity spectrum" is defined as the "intrinsic" property of a compound depending only on its structure and physico-chemical characteristics. Prediction of this spectrum by PASS is based on SAR analysis of the training set containing thousands of compounds which have many kinds of biological activities. In PASS biological activities are described qualitatively ("active" or "inactive").

Importance of PASS:

1. Experimental determination of biological activity of a drug is time and cost consuming procedure, so making the use of PASS is generally important.
2. PASS can be effectively used for finding of compounds with required properties and without undesirable side effects.
3. It used for selecting the most prospective compounds from the set of available samples for specific screening.
4. For determining of more relevant screens for particular compound.

Due to this significance of PASS, it is used in the present study as a tool to design the drug with highest probable activity.

MATERIALS AND METHODS: All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin layer chromatography was performed on percolated silica gel 60-F 254 plates. IR spectra on KBr disks were recorded on a Shimadzu IR - 470 FT-IR spectrophotometer. The routine nuclear magnetic resonance spectra were taken in DMSO/CDCl₃ using a Bruker 300 MHz spectrophotometer with TMS as an internal standard. Chemical shift δ was given in ppm relative to TMS. The data found were in consistent with the proposed structure. Elemental analysis was done using EURO Vector Elemental Analyzer. Melting points are determined in an open capillary tube and are uncorrected.

Synthetic Procedure for the 5-phenyl-6H-[1, 3, 4] thiadiazin-2-ylamine 3(a): In 100 mL round bottom flask, acetophenone 1.20 g, (0.01 mole), and thiosemicarbazide 0.91 g, (0.01 mole) were mixed in ethanol (20 mL) and the reaction mixture was irradiated with microwaves at 20% microwave power (140 W) for 5 min. The completion of the reaction was confirmed by TLC (Ethyl acetate: Hexane 1:9). The reaction mixture was allowed to cool at room temperature, poured into crushed ice. The solid separated was filtered, washed with little ethanol and purified by recrystallization from ethanol to get pure products.

5-Phenyl-6H-[1, 3, 4] thiadiazin-2-ylamine 3(a):

Molecular Formula: C₉H₉N₃S,

Melting Point: 222 °C,

IR (KBr) ν_{\max} : 1200 (C=S), 3318 (>NH) 3552 (-NH₂) cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 2.60 (s, 2H, CH₂), 6.94-7.36 (m, 5H, Ar-H), 9.45 (s, 2H, NH₂) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ 21.09, 127.91, 129.90, 133.30, 140.00, 150.01, 154.91 ppm. Similarly derivatives 3b and 3c are synthesized.

5-(3-Nitro-phenyl)-6H-[1, 3, 4] thiadiazin-2-ylamine 3(b):

Molecular Formula: C₉H₈N₄O₂S,

Melting Point: 206 °C,

IR (KBr) ν_{\max} : 1330(C=S), 3010 (>NH), 3345 (-NH₂) cm⁻¹. H¹ NMR (CDCl₃, 300 MHz): δ 2.71 (s, 2H, CH₂), 7.66-8.99 (m, 4H, Ar-H), 9.78 (s, 2H, NH₂) ppm. ¹³C NMR(CDCl₃, 100 MHz): δ 21.18, 120.51, 126.41, 128.58, 132.28, 140.61, 142.27, 146.26, 150.55 ppm.

5-(4-Methoxy-phenyl)-6H- [1, 3, 4] thiadiazin-2-ylamine 3(c):

Molecular Formula: C₁₀H₁₁N₃OS,

Melting Point: 202 °C,

IR (KBr) ν_{\max} : 1120 (C=S), 2965 (>NH), 3317 (-NH₂) cm⁻¹. H¹ NMR (CDCl₃, 300 MHz): δ 2.56 (s, 2H, CH₂), 3.87 (s, 3H, OCH₃), 6.90-7.98 (m, 4H, Ar-H), 9.67 (s, 2H, NH₂) ppm. ¹³C NMR(CDCl₃, 100 MHz): δ 18.09, 67.42, 121.97, 124.51, 127.55, 128.93, 124.12, 156.67 ppm. The products thus obtained 3(a-c) were directly used for next step.

Synthetic procedure for the 2-(2,4dichloro-phenyl)-3-(5-phenyl-6H-[1,3,4] thiadiazin-2-yl)-thiazolidin-4-one 6(a-f): In a 100 mL round bottom flask, the product of step I *i.e.* 5-phenyl-6H-[1,3,4]thiadiazin-2-ylamine(3a) (0.001 mole), 2,4-dichlorobenzaldehyde (0.001 mole), and thio glycolic acid (2-mercapto acetic acid) (0.001 mole) were mixed in ethanol (15 mL). The reaction mixture was irradiated with microwaves at 20% microwave power (140 W) for 4 mins. The completion of the reaction was confirmed by TLC (Ethyl acetate: Hexane 1:9). The reaction mixture was allowed to cool at room temperature and poured into crushed ice. The solid separated was filtered, washed with little ethanol and purified by recrystallization from ethanol to get pure product 6a.

2-(2, 4-Dichloro-phenyl)-3-(5-phenyl-6H-[1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one 6(a):

Molecular Formula: C₁₈H₁₃Cl₂N₃OS₂,

Melting Point: 228 °C,

IR (KBr) ν_{\max} :750 (C-Cl), 1040 (C-N), 1750 (C=O), 3000 (Ar-CH), cm⁻¹. H¹ NMR (DMSO, 400 MHz): δ 2.49 (s, 2H, >CH₂), 3.26 (s, 2H, >CH₂), 6.06(s, 1H, >CH), 7.31-8.27(m, 8H, Ar-H), ppm. ¹³C NMR(DMSO, 100 MHz): 21.29, 33.50, 67.50, 107.18, 117.95, 127.02, 128.07, 129.43, 130.58, 132.56, 132.87, 134.60, 135.07, 137.83, 152.18, 171.18 ppm. Similarly derivatives 6(b-f) are synthesized.

2-(4-Chloro-phenyl)-3-(5-phenyl-6H-[1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one 6(b):

Molecular Formula: C₁₈H₁₄ClN₃OS₂,

Melting Point: 202 °C,

IR (KBr) ν_{\max} :700 (C-Cl), 1040 (C-N), 1750 (C=O), 2950 (Ar-CH), cm⁻¹. H¹ NMR (DMSO, 400 MHz): δ 2.66 (s, 2H, >CH₂), 3.26 (s, 2H, >CH₂), 6.08 (s, 1H, >CH), 7.31-8.11(m, 9H, Ar-H), ppm. ¹³C NMR(DMSO, 100 MHz): 21.00, 25.22, 71.50, 117.65, 127.02, 128.07, 129.63, 130.56, 132.50, 132.87, 134.60, 135.00, 137.89, 174.02 ppm.

2-(2, 4 Dichloro-phenyl)-3-[5-(3-nitro-phenyl)-6H-[1,3,4]thiadiazin-2-yl]-thiazolidin-4-one 6(c):

Molecular Formula: C₁₈H₁₂Cl₂N₄O₃S₂,

Melting Point: 210 °C,

IR (KBr) ν_{\max} :700 (C-Cl), 1020 (C-N), 1355-1375 (N=O), 1740 (C=O), 2950 (Ar-CH), cm⁻¹. H¹ NMR (CDCl₃, 400 MHz): δ 2.50 (s, 2H, >CH₂), 3.55 (s, 2H, >CH₂), 5.97 (s, 1H, >CH), 7.11-8.04 (m, 7H, Ar-H), ppm. ¹³C NMR(CDCl₃, 100 MHz): 22.54, 29.48, 63.64, 114.81, 124.69, 130.65, 133.32, 136.62, 138.68, 141.81, 144.14, 145.44, 148.26, 149.59, 154.65, 161.33, 163.49, 180.08 ppm.

2-(4-Chloro-phenyl)-3-[5-(3-nitro-phenyl)-6H-[1, 3, 4]thiadiazin-2-yl]-thiazolidin-4-one 6(d),

Molecular Formula: C₁₈H₁₃ClN₄O₃S₂,

Melting Point: 204 °C,

IR(KBr) ν_{\max} :700 (C-Cl), 1020 (C-N), 1355-1375 (N=O), 1740 (C=O), 2950 (Ar-CH),cm⁻¹. H¹ NMR (CDCl₃, 400 MHz): δ 2.50 (s, 2H, >CH₂), 3.55 (s, 2H, >CH₂), 6.01 (s, 1H, >CH), 6.79-7.65 (m, 8H, Ar-H), ppm. ¹³C NMR(CDCl₃, 100 MHz): 21.08, 29.48, 67.48, 115.84, 118.84, 121.48, 124.69, 127.77, 130.65, 132.25, 135.21, 149.05, 153.03, 160.49, 161.33, 181.01 ppm.

2-(2,4Dichloro-phenyl)-3-[5-(4-methoxy-phenyl)-6H-[1,3,4]thiadiazin-2-yl]-thiazolidin-4-one 6(e):

Molecular Formula: C₁₉H₁₅Cl₂N₃O₂S₂,

Melting Point: 212 °C,

IR (KBr) ν_{\max} :700 (C-Cl), 1020 (C-N), 1300 (C-O), 1600 (C=C), 1740 (C=O), 2950 (Ar-CH), cm⁻¹. H¹ NMR (CDCl₃, 400 MHz): δ 2.38 (s, 2H, >CH₂), 3.22 (s, 2H, >CH₂), 3.92 (s, 3H, >OCH₃), 6.00 (s, 1H, >CH), 7.14-7.66 (m, 7H, Ar-H), ppm. ¹³C NMR(CDCl₃, 100 MHz): 21.17, 33.78, 55.10,

70.18, 107.11, 122.20, 126.88, 139.02, 140.07, 142.23, 143.38, 145.14, 145.87, 147.00, 147.77, 150.37, 179.89 ppm.

2-(4-Chloro-phenyl)-3-[5-(4 - methoxy - phenyl)-6H-[1, 3, 4]thiadiazin-2-yl]-thiazolidin-4-one(6f):

Molecular Formula: C₁₉H₁₆ClN₃O₂S₂,

Melting Point: 230 °C,

IR (KBr) ν_{\max} : 700 (C-Cl), 1020 (C-N), 1300 (C-O), 1600 (C=C), 1740 (C=O), 2950 (Ar-CH), cm⁻¹. ¹H¹ NMR (CDCl₃, 400 MHz): δ 2.38 (s, 2H, >CH₂), 3.22 (s, 2H, >CH₂), 3.90 (s, 3H, >OCH₃), 6.01 (s, 1H, >CH), 7.20-7.60 (m, 8H, Ar-H), ppm. ¹³C NMR(CDCl₃, 100 MHz): 21.17, 33.78, 55.10, 70.18, 107.11, 122.20, 126.88, 139.02, 140.07, 142.23, 143.38, 145.87, 147.77, 150.37, 179.89 ppm.

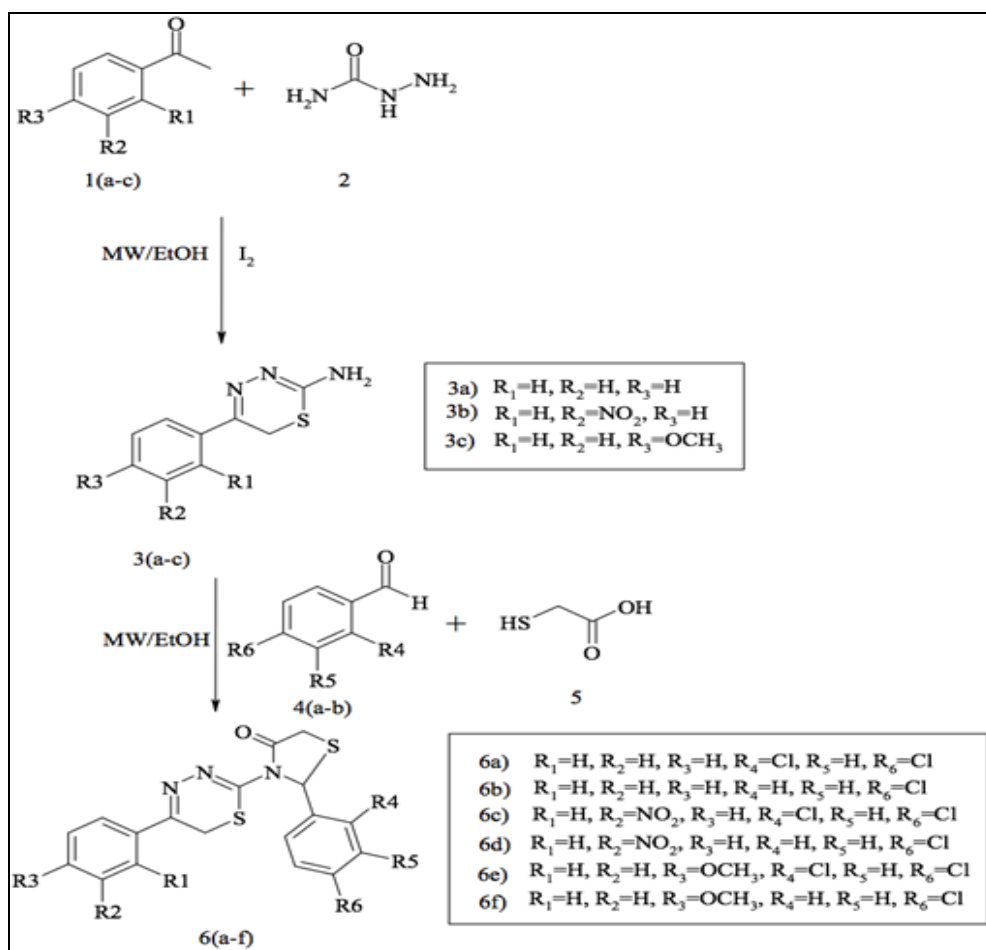


TABLE 1: ANALYTICAL DATA OF THE COMPOUNDS 3(a-c)

Product	Time (in min.)	Yield	M. P. °C	Mol. Formula	Found / (Calculated) %		
					C	H	N
3(a)	5	75	222	C ₉ H ₉ N ₃ S	56.51 (56.52)	4.65 (4.74)	21.37 (21.97)
3(b)	3	70	206	C ₉ H ₈ N ₄ O ₂ S	45.70 (45.76)	3.29 (3.41)	23.50 (23.71)
3(c)	4	72	202	C ₁₀ H ₁₁ N ₃ OS	54.20 (54.28)	4.99 (5.01)	18.60 (18.99)

TABLE 2: ANALYTICAL DATA OF THE COMPOUNDS 6(a-f)

Product	Time (in min.)	Yield	M. P. °C	Mol. Formula	Found / (Calculated) %		
					C	H	N
6(a)	4	55	228	C ₁₈ H ₁₃ Cl ₂ N ₃ OS ₂	51.02 (51.19)	3.05 (3.10)	9.90 (9.95)
6(b)	5	60	202	C ₁₈ H ₁₄ ClN ₃ OS ₂	55.60 (55.73)	3.61 (3.64)	10.70 (10.83)
6(c)	3	62	210	C ₁₈ H ₁₂ Cl ₂ N ₄ O ₃ S ₂	46.20 (46.26)	2.50 (2.59)	11.90 (11.99)
6(d)	4	65	204	C ₁₈ H ₁₃ ClN ₄ O ₃ S ₂	49.85 (49.94)	3.00 (3.03)	12.90 (12.94)
6(e)	4	60	212	C ₁₉ H ₁₅ Cl ₂ N ₃ O ₂ S ₂	50.40 (50.45)	3.30 (3.34)	9.20 (9.29)
6(f)	4.5	68	230	C ₁₉ H ₁₆ ClN ₃ O ₂ S ₂	54.55 (54.60)	3.63 (3.86)	10.01 (10.05)

RESULTS AND DISCUSSION: The confirmed structures were subjected to computer programme PASS for the prediction of their biological activities. Compound 3(a-c) were predicted for three activities with top probability.

- Mucomembranous protector
- Arylacetonitrilase inhibitor
- Macrophage elastase inhibitor

TABLE 3: BIOLOGICAL PREDICTION ANALYSIS OF ACTIVITIES OF DERIVATIVES 3(a-c)

Activity Comp	Muco-membranous protector	Arylacetonitrilase inhibitor	Macrophage elastase inhibitor
	Pa	Pa	Pa
3(a)	0.802	0.797	0.792
3(b)	0.726	0.794	0.729
3(c)	0.721	0.563	0.776

Compounds 6(a-f) were predicted for two activities with top probability.

1. CC chemokine 4 receptor antagonist
2. Phosphatase inhibitor

TABLE 4: BIOLOGICAL PREDICTION ANALYSIS OF ACTIVITIES OF DERIVATIVES 6(a-f)

Activity Comp	CC chemokine 4 receptor antagonist	Phosphatase inhibitor
	Pa	Pa
6(a)	0.861	0.762
6(b)	0.171	0.774
6(c)	0.800	0.721
6(d)	0.158	0.733
6(e)	0.804	0.733
6(f)	0.164	0.744

CONCLUSION: In summary, we have developed an efficient method for the synthesis of [1, 3, 4] thiadiazin-2-ylamine 3(a-c) and [1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one 6(a-f) derivatives with excellent yield under microwave irradiation, which attains completion in 5 - 7 min in an organic medium and may provide a useful route for the rapid drug discovery. Biological prediction analysis revealed that the 2-(2, 4 dichloro-phenyl)-3-(5-phenyl-6H-[1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one 6(a) is predicted to be moderately active as CC chemokine 4 receptor antagonist. 2-(4-chloro-phenyl)-3-(5-phenyl-6H-[1, 3, 4] thiadiazin-2-yl)-thiazolidin-4-one 6(b) can be most active in the series as phosphatase inhibitor and hence it is recommended for the screening of the same activity.

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