

Synthesis, Characterization and Biological Applications of Triazolo-Thiadiazepine Derivatives

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Abstract:

Heterocyclic compounds containing Nitrogen and Sulfur atoms have attracted considerable attention in Medicinal Chemistry[1-5] because of their diverse biological and pharmacological properties[6-9]. In the present study, a series of Novel Triazolo and thiadiazepines derivatives were designed and synthesized through suitable cyclization and condensation reactions[10-13]. The synthesized compounds were characterized by various analytical and spectroscopic techniques including FT-IR, ¹H NMR, ¹³C NMR and Mass spectrometry. Structural features and the formation of the desired heterocyclic systems were established on the basis of their spectral data. The synthesized derivatives were evaluated for their potential biological activities against selected Microbial/biological targets. Several compounds exhibited promising activity, which may be attributed to the presence of Nitrogen and Sulfur containing heterocyclic moieties and their ability to interact with biological targets. This complete study demonstrates that Triazolo and Thiadiazepines scaffolds can serve as valuable structural frameworks for the development of biologically heterocyclic compounds.

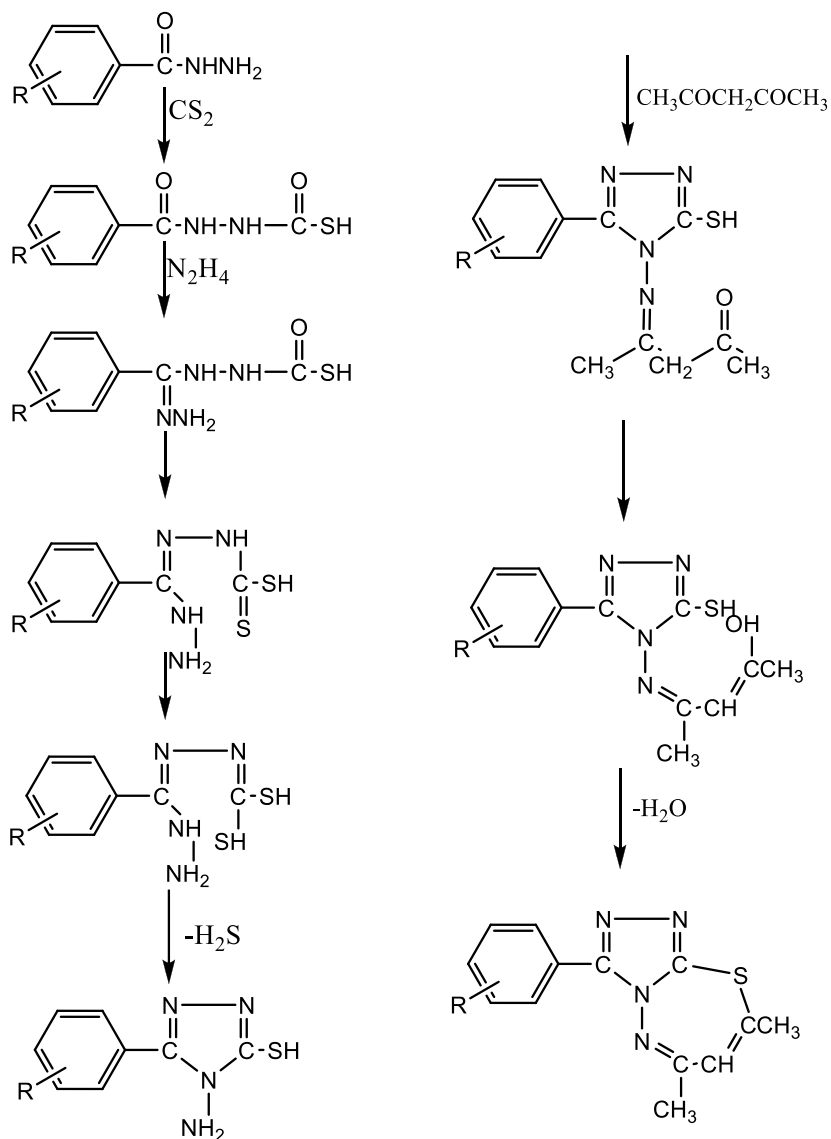
Introduction:

Heterocyclic compounds constitute an important class of organic molecules and play a significant role in medicinal chemistry due to their wide range of biological and pharmacological activities[14-24]. Among various heterocyclic scaffolds, Triazole have attracted considerable attention because of their good chemical stability and diverse activities including Antimicrobial[25-26], Antifungal[27-29], Anti-Inflammatory[30-34] and Anticancer properties[35-38].

Similarly, Thiadiazepines, containing both Nitrogen and Sulfur atoms in their heterocyclic framework[40-42], have emerged as promising compounds with potential biological applications. The combination and structural modification of these heterocyclic moieties may provide new molecules with enhanced biological properties[43-44]. Therefore the synthesis and characterization of novel Triazolo-Thiadiazepines derivatives is of considerable interest in the search of biologically active compounds[45-46].

Keywords: Triazole, thiadiazepines, heterocyclic compounds, Antifungal, antibacterial, IR, NMR

Reaction



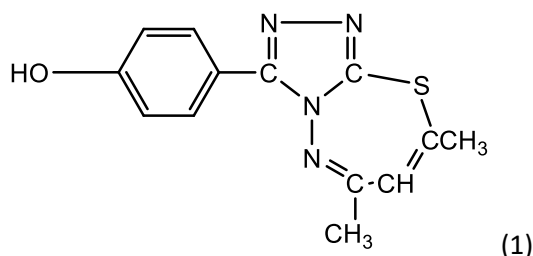
Scheme-1

Table-1

S.No	R	mp(⁰ C)
1.	H	87-89
2.	2-CH ₃	112-114
3.	4-CH ₃	105-106
4.	3-CH ₃	124-125

5.	2-Cl	119-120
6.	4-Cl	140-141
7.	2,4-Cl ₂	136-137
8.	2-OCH ₃	148-150
9.	4-OCH ₃	165-170

IR, NMR, & Elemental analysis of the final compounds



4-(6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-3-yl)phenol

Chemical Formula: C₁₃H₁₂N₄OS

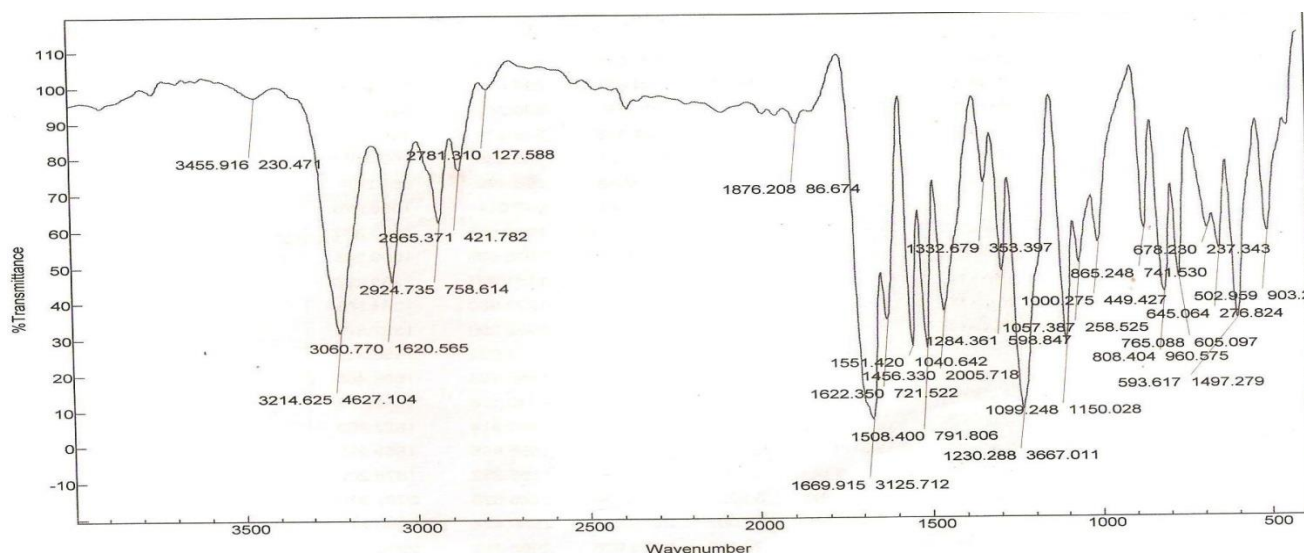
Exact Mass: 272.07

Molecular Weight: 272.33

m/z: 272.07 (100.0%), 273.08 (14.2%), 274.07 (4.7%), 273.07 (2.3%), 274.08 (1.3%)

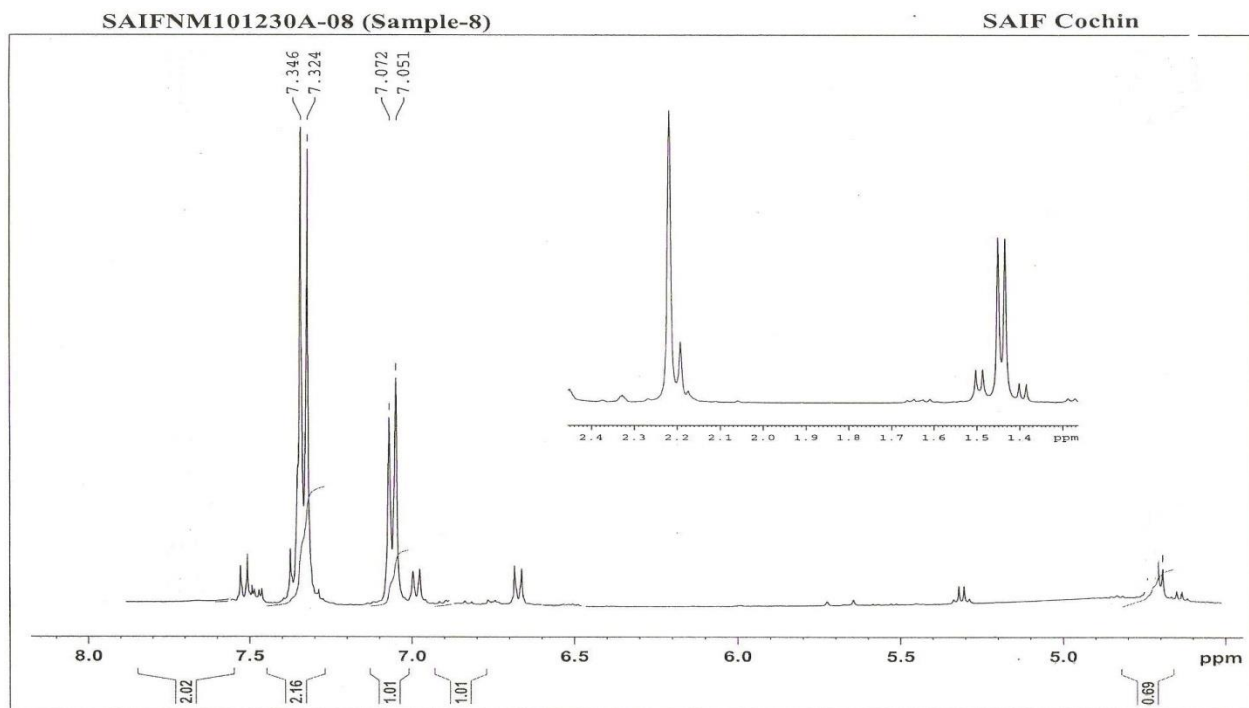
Elemental Analysis: C, 57.34; H, 4.44; N, 20.57; O, 5.88; S, 11.77

IR Data



Tuesday, May 06 16:02:26

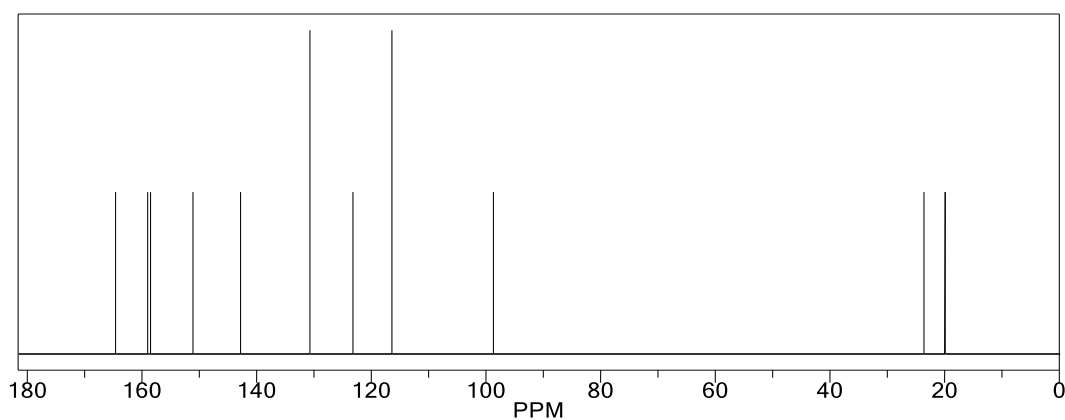
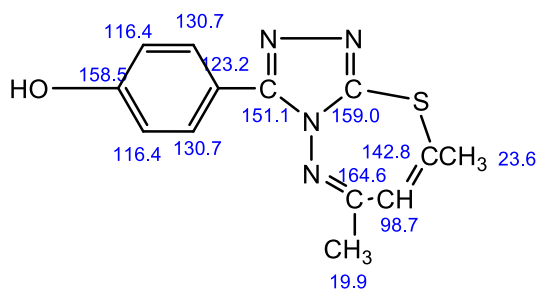
3455 (O-H stretching), 3060 (C-H arom.), 2924 (C-H aliph), 1669 (C=O) 2180 (C=N), 1456 (C=C),



¹H NMR

¹H NMR (DMSO-d₆): δ 7.34-7.05 (dd, 4H, aromatic proton), 2.2 (s, 1 H Ethylene proton), 1.5 (s, 6H, methyl proton);

¹³C NMR Data



1. **6,8-Dimethyl-3-phenyl-[1,2,4]-triazolo-[3,4-b][1,3,4]-thiadiazepine**

Black solid; IR: 3010 (C-H arom), 2980 (C-H aliph), 2190 (C=N), 1410 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.99-6.49 (m, 6H, aromatic proton), 7.40 (s, 1 H Ethylene proton), 2.53 (s, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.0, 112.3, 112.9, 115.8, 117.2, 127.5, 127.9, 128.4, 128.8, 132.5, 135.0, 145.9, 150.8. Chemical Formula: $\text{C}_{13}\text{H}_{12}\text{N}_4\text{S}$, Exact Mass: 256.08, Molecular Weight: 256.33, m/z : 256.08 (100.0%), 257.08 (16.5%), 258.07 (4.5%), 258.08 (1.2%), Elemental Analysis: C, 60.91; H, 4.72; N, 21.86; S, 12.51

2. **6,8-Dimethyl-3-o-tolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine**

White solid; IR: 3020 (C-H arom), 2975 (C-H aliph), 2182 (C=N), 1400 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.52-6.36 (m, 4H, aromatic proton), 7.40 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.0, 21.0, 112.6, 113.5, 115.0, 117.9, 126.5, 127.5, 128.2, 129.6, 131.5, 135.7, 144.6, 152.8. Chemical Formula: $\text{C}_{14}\text{H}_{14}\text{N}_4\text{S}$, Exact Mass: 270.09, Molecular Weight: 270.35, m/z : 270.09 (100.0%), 271.10 (15.3%), 272.09 (4.8%), 271.09 0(2.3%), 272.10 (1.2%), Elemental Analysis: C, 62.20; H, 5.22; N, 20.72; S, 11.86

3. **6,8-Dimethyl-3-p-tolyl-[1,2,4]triazolo-[3,4-b][1,3,4]-thiadiazepine**

White crystalline solid; IR: 3015 (C-H arom), 2960 (C-H aliph), 2100 (C=N), 1405 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.44-6.29 (dd, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $\text{C}_{14}\text{H}_{14}\text{N}_4\text{S}$, Exact Mass: 270.09, Molecular Weight: 270.35, m/z : 270.09 (100.0%), 271.10 (15.3%), 272.09 (4.8%), 271.09 (2.3%), 272.10 (1.2%), Elemental Analysis: C, 62.20; H, 5.22; N, 20.72; S, 11.86

4. **6,8-Dimethyl-3-m-tolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine**

White solid; IR: 3020 (C-H arom), 2950 (C-H aliph), 2100 (C=N), 1405 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.44-6.29 (m, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $\text{C}_{14}\text{H}_{14}\text{N}_4\text{S}$, Exact Mass: 270.09, Molecular Weight: 270.35, m/z : 270.09 (100.0%), 271.10 (15.3%), 272.09 (4.8%), 271.09 (2.3%), 272.10 (1.2%), Elemental Analysis: C, 62.20; H, 5.22; N, 20.72; S, 11.86

5. **3-(2-Chlorophenyl)-6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine**

Black solid; IR: 3000 (C-H arom), 2868 (C-H aliph), 2110 (C=N), 1425 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.50-6.35 (m, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2,

172.2. Chemical Formula: $C_{13}H_{11}ClN_4S$, Exact Mass: 290.04, Molecular Weight: 290.77, m/z: 290.04 (100.0%), 292.04 (36.8%), 291.04 (16.3%), 293.04 (5.4%), 294.03 (1.5%), Elemental Analysis: C, 53.70; H, 3.81; Cl, 12.19; N, 19.27; S, 11.03

6. 3-(4-Chlorophenyl)-6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine

White solid; IR: 3025 (C-H arom), 2956 (C-H aliph), 2122 (C=N), 1405 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.53-6.44 (dd, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $C_{13}H_{11}ClN_4S$, Exact Mass: 290.04, Molecular Weight: 290.77, m/z: 290.04 (100.0%), 292.04 (36.8%), 291.04 (16.3%), 293.04 (5.4%), 294.03 (1.5%), Elemental Analysis: C, 53.70; H, 3.81; Cl, 12.19; N, 19.27; S, 11.03

7. 3-(2,4-Dichlorophenyl)-6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine

Light green solid; IR: 3054 (C-H arom), 2902 (C-H aliph), 2100 (C=N), 1435 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.60-6.41 (m, 3H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $C_{13}H_{10}Cl_2N_4S$, Exact Mass: 324.00, Molecular Weight: 325.22, m/z: 324.00 (100.0%), 326.00 (68.8%), 325.00 (16.3%), 327.99 (13.1%), 327.00 (10.2%), 329.00 (1.9%), 326.99 (1.0%), Elemental Analysis: C, 48.01; H, 3.10; Cl, 21.80; N, 17.23; S, 9.86

8. 3-(4-Chlorophenyl)-6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine

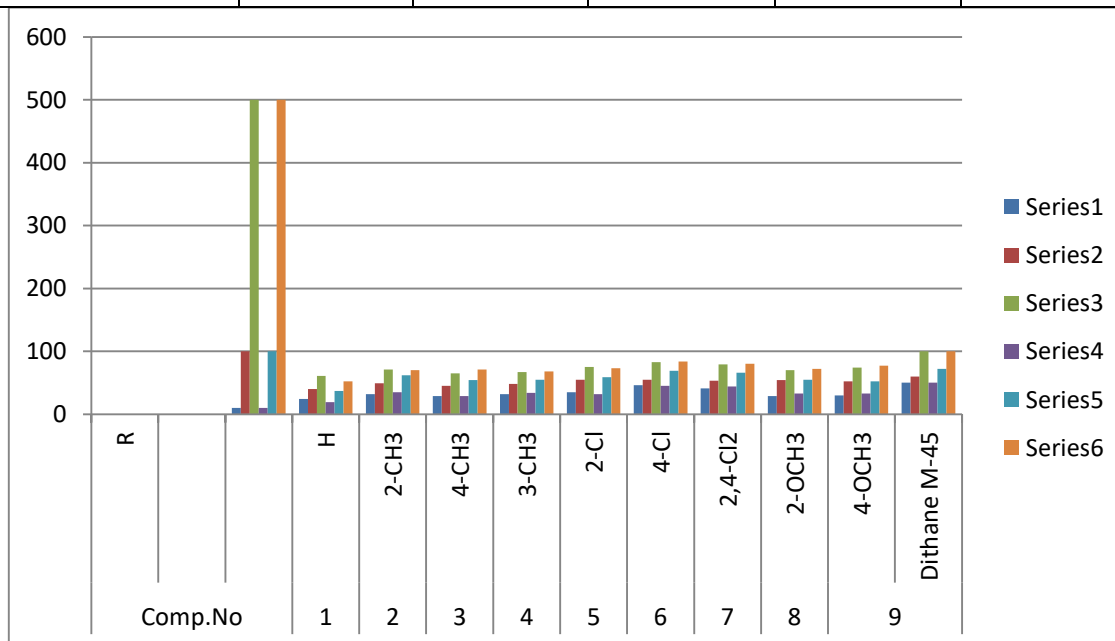
Brown solid; IR: 3020 (C-H arom), 2950 (C-H aliph), 2100 (C=N), 1405 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.44-6.29 (m, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $C_{13}H_{11}ClN_4S$, Exact Mass: 290.04, Molecular Weight: 290.77, m/z: 290.04 (100.0%), 292.04 (36.8%), 291.04 (16.3%), 293.04 (5.4%), 294.03 (1.5%), Elemental Analysis: C, 53.70; H, 3.81; Cl, 12.19; N, 19.27; S, 11.03

9. 3-(2,4-Dichlorophenyl)-6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepine

Light Brown solid; IR: 3020 (C-H arom), 2950 (C-H aliph), 2100 (C=N), 1405 (C=C), cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.44-6.29 (m, 4H, aromatic proton), 5.59 (s, 1 H Ethylene proton), 2.53 (9, 6H, methyl proton); ^{13}C NMR (δ ppm): δ 19.2, 21.6, 114.6, 118.5, 125.0, 127.6, 136.0, 137.5, 141.2, 149.6, 151.5, 155.7, 160.2, 172.2. Chemical Formula: $C_{13}H_{10}Cl_2N_4S$, Exact Mass: 324.00, Molecular Weight: 325.22, m/z: 324.00 (100.0%), 326.00 (68.8%), 325.00 (16.3%), 327.99 (13.1%), 327.00 (10.2%), 329.00 (1.9%), 326.99 (1.0%), Elemental Analysis: C, 48.01; H, 3.10; Cl, 21.80; N, 17.23; S, 9.86

4-(6,8-dimethyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazepin-3-yl)phenol

Comp. No	R	Percent Mycelial Inhibition			Compound dose (ppm)		
		Aspergillus Flavus			Candida Albicans		
		10	100	500	10	100	500
1	H	24	40	61	19	37	52
2	2-CH ₃	32	49	71	35	62	70
3	4-CH ₃	29	45	65	29	54	71
4	3-CH ₃	32	48	67	34	55	68
5	2-Cl	35	55	75	32	59	73
6	4-Cl	46	65	83	45	69	84
7	2,4-Cl ₂	41	53	79	44	66	80
8	2-OCH ₃	29	54	70	33	55	72
9	4-OCH ₃	30	52	74	33	52	77
	Dithane M-45	50	60	100	50	72	100



Conclusion

In conclusion, the synthesis and characterization of triazolo-thiadiazepene derivatives containing chloro, methyl, and methoxy substituents demonstrate the versatility of this heterocyclic framework for the development of biologically relevant compounds. The incorporation of different substituents on the aromatic ring produced structural variations that can influence the electronic properties, polarity, lipophilicity, and consequently the biological behaviour of the synthesized derivatives. Among the substituted derivatives, the chloro-, methyl-, and methoxy-containing compounds exhibited characteristic spectroscopic features consistent with the proposed structures. The presence of electron-withdrawing chloro and electron-donating methyl and methoxy groups provides useful opportunities for studying structure–activity relationships within the triazolo-thiadiazepene series. Such substitution may affect molecular interactions with biological targets and can therefore play an important role in modulating pharmacological activity.

Overall, the synthesized triazolo-thiadiazepene derivatives represent promising heterocyclic scaffolds for further medicinal-chemistry investigations. Further studies involving detailed biological screening, structure–activity relationship analysis, molecular docking, toxicity evaluation, and optimization of the substituent pattern may help identify more potent and selective derivatives with potential pharmaceutical applications.

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