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A Convenient Synthesis and Reactions of some Substituted 1,2,4-Triazine, and Their Derivatives with Carbazole, Sulfonamide and Trityl Chloride Moiety of Biological Interest

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ABSTRACT:

A series of 1,2,4-triazine derivatives [**1-9]** were synthesized by various analogous methods. In this investigation 5,6-diphenyl-1,2,4-triazine-3-thiol compound [1] was prepared by cyclization of benzil with thiosemicarbazide. Further 5-(prop-2-en-1-yl)-5H-[1,2,4] triazino [5,6-b]indole-3-thiol compound [3] was prepared by treating 1-(prop-2-en-1-yl)-1h-indole-2,3-dione compound [2] with thiosemicarbazide. Further a variety of compounds were prepared by hydrogen replacement of compound [1] and compound [3] by differently active halogen containing scaffolds. Compound [1] was reacted with 9-(2-bromoethyl)-9H-carbazole to produce 9-(2-(5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethyl)9-H-carbazole compound [4].After that, the compound [1] was allowed to react with 2-chloro-N-(4-methylbenzene-1-sulfonyl)-N-(pyridine-2-yl)acetamide to synthesize 2-((5,6-diphenyl-1,2,4-triazin-3-yl)-N-(Pyridin-2-yl)-N-tosylacetamide compound [5].In addition to this ,5,6-diphenyl-3-(tritylthio)-1,2,4-triazine compound [6] was also prepared by condensation reaction between trityl chloride and compound [1]. Further, Compound [3] was reacted with 9-(2-bromoethyl)-9H-carbazole to produce 3-((2-(9H-Carbazol-9-yl)ethylthio)-5-allyl-5H-[1,2,4]triazino[5,6-b]triazino[5,6-b]indole compound [7].After that, the compound [3] was allowed to react with 2-chloro-N-(4-methylbenzene-1-sulfonyl)-N-(pyridine-2-yl) acetamide to synthesize 2-((5-allyl-5H-[1,2,4]triazino[5,6-b]infol-3-yl)thio)-N-(pyridine-2-yl)-N-tosylacetamide compound [8].In addition to this ,5-allyl-3-(tritylthio)-5H-[1,2,4]triazino compound [9] was also prepared by condensation reaction between trityl chloride and compound [3]. All the synthesized compounds were confirmed by spectral data **(Table 1)** and analytical data **(Table 2)**.

KEYWORDS:

Benzil, Isatin, 1,2,4-Triazine, Trityl chloride, N-bromoethyl carbazole, Sulfonamide.

INTRODUCTION:

1,2,4-Triazine is a prominent structural core system found in numerous natural and synthetic biologically active compounds with a wide range of biological activity and are also known to be active pharmacologically[1-9]. Some new anti-HIV and anticancer agents have also been searched by incorporating new heterocyclic additional moieties in the 1,2,4-triazine nucleus by allowing interaction between 1,2,4-triazine, different nucleophilic and electrophilic reagents in different media[10-19]. In this article, This article includes the study of different factors influencing the orientation of cyclization reactions of functionalized derivatives of 1,2,4-triazine.

RESULT & DISCUSSION:

The required 5,6-diphenyl-1,2,4-triazine-3-thiol [1] was prepared by cyclization of Benzil with thiosemicarbazide in water and 5-(prop-2-en-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol [3] was prepared by cyclization of 1-(prop-2-en-1-yl)-1*H*-indole-2,3-dione [2] with thiosemicarbazide in acetic acid. Formation of the product is authenticating by the presence of a singlet δ: 8.21 [s, 1H, NH of triazino] and multiplet δ: 7.09-7.64 [m,10H,Ar-H] in NMR and 3307 [NH, Str.], 3106 [Ar-H, CH str.], 1639 [C=N str.] and 1209 [C=S str.] in IR for compound [1] and singlet δ: 8.12 [s, 1H, NH of triazino], 4.71 [quintett, 1H $CH=CH_2$], 2.13 [d, 2H $N-CH_2-CH=CH_2$], 1.89 [d, 2H $CH_2=CH-CH_2-N$] and multiplet δ: 7.21-7.69 [m, 4H, Ar-H] in NMR and 3289 [NH, Str.], 3051 [Ar-H, CH str.], 1644 [C=N str.] and 1226 [C=S str.] in IR for compound [3].

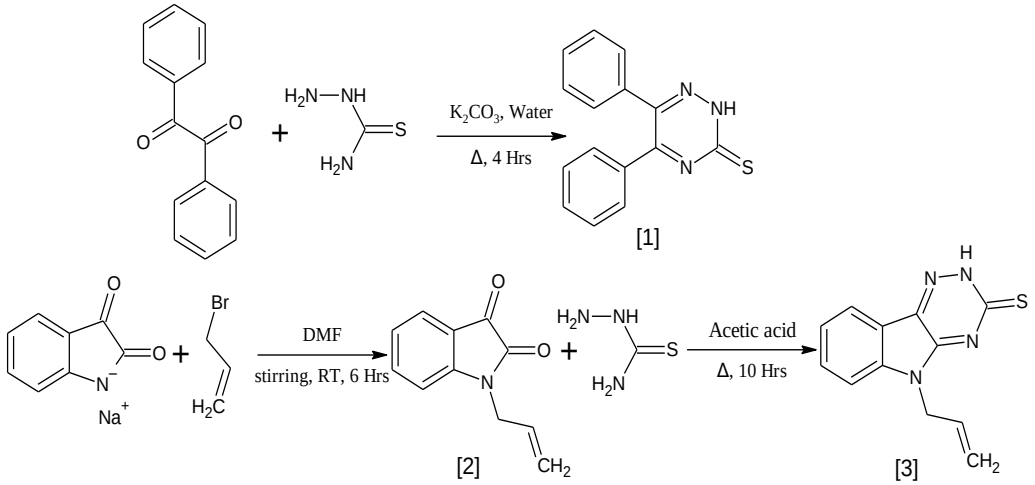
In the next step compound [1] rearrange and transfer hydrogen from nitrogen to thio & condensation reaction with some halo alkyl/halogen-substituted moieties (compound a, b, c). Among these moieties compound (a) was prepared by the literature procedure [20] and compound (b) was prepared by the literature method [21]. The compound (c) was directly purchased from the supplier.

In the next process Hydrogen of SH. from the triazine, ring linkage was replaced by halogen derivative. Firstly compound [1] get reacted with 9-(2-bromoethyl)-9*H*-carbazole [a] to give Synthesis of 9-(2-((5,6-diphenyl-1,2,4-triazine-3-yl)thio)ethyl)-9*H*-carbazole [4]. Which was confirmed by the disappearance of singlet δ: 8.21 [s, 1H, N.H. of triazino] and I.R. & NMR and the I.R. band at 1209 cm-1 due to the C=S group and appearance of a new band at 699 cm-1 due to the C-S bond. Respectively 2-((5,6-diphenyl-1,2,4-triazine-3-yl)thio)-N-(pyridin-2-yl)-N-tosylacetamide compound [5] were also prepared by the treatment of 2-chloro-N-(4-methylbenzene-1-sulfonyl)-N-(pyridin-2-yl) acetamide (b) on compound [1]. It was confirmed by the disappearance of the singlet δ: 8.21 [s, 1H, N.H. of triazino] and I.R. band at 1209 cm-1 due to the C=S group and appearance of a new band at 691 cm-1 due to the C-S bond. Furthermore, the appearance of sulfonyl bands at 1619, 1609 [O=S=O] linkage in I.R. and two singlet δ: 4.12 [s, 2H, CH_2], 2.58 [s, 3H, CH_3] as well as 5,6-diphenyl-3-(tritylthio)-1,2,4-triazine compound [6] was also formed by the direct condensation of compound [1] with Trityl chloride (c). It was also confirmed by the disappearance of the singlet δ: 8.21 [s, 1H, N.H. of triazino] and I.R. band at 1209 cm-1 due to the C=S group and appearance of a new band at 684 cm-1 due to the C-S bond.

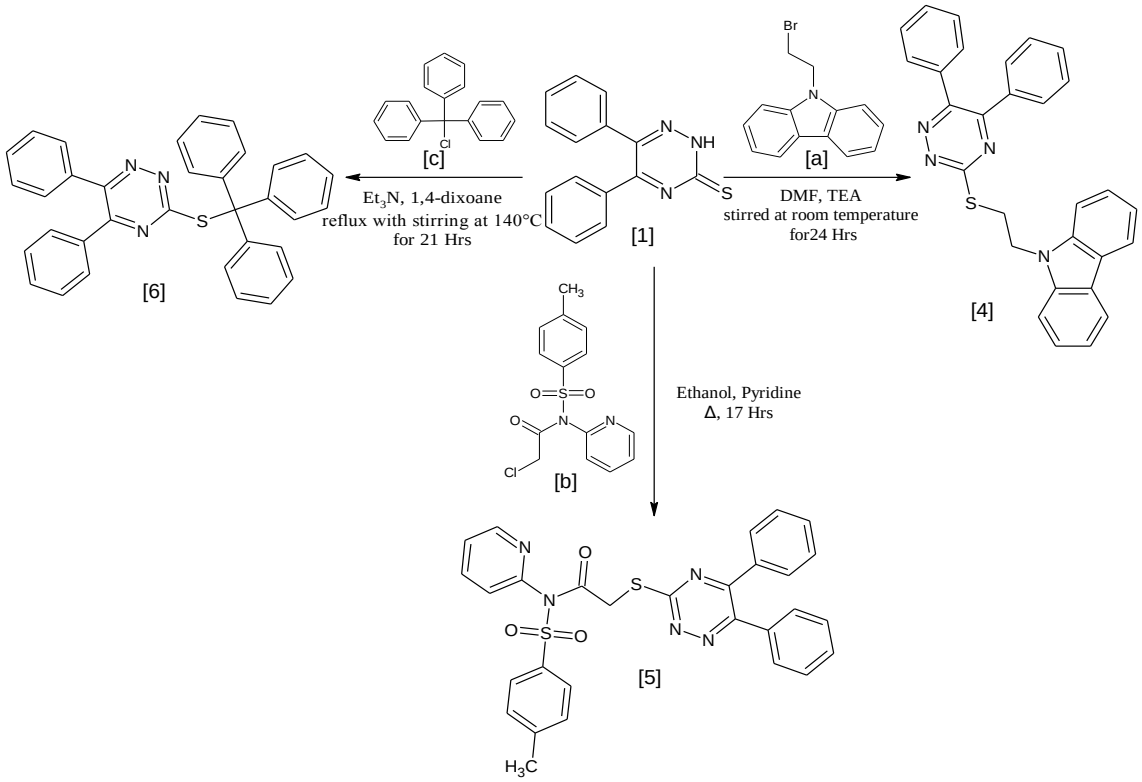
Furthermore, compound [7], [8], [9] were prepared respectively by the direct treatment on compound [3]. They were confirmed by the disappearance of the singlet δ: 8.21 [s, 1H, N.H. of triazino] and I.R. band at 1226 cm-1 due to the C=S group and appearance of a new band at 687 cm-1, 697 cm-1, 693 cm-1 respectively for compound [7], [8], [9] due to the C-S bond.

METHOD & MATERIALS

All the chemicals and solvents (analytical grade) were procuring from economical sources and put into practice without additional purification. All melting points were resolute in an open capillary tube and are uncorrected. TLC aluminium sheets were used for thin-layer chromatography (TLC), and spots were visualized under U.V. absorption chamber of variety range of U.V. light. Reaction completion was monitored by Thin layer Chromatography by using the required solvent system.For spectroscopy FTIR Perkin Elmer, H^1 NMR on Joel Resonance Delta2 400-MHz & Joel SX-102 (FAB) mass spectrometer was used. Structure of all the synthesized compounds was assigned on the basis of their analytical data **(Table 1)** and spectral data.



Reaction Scheme-1:



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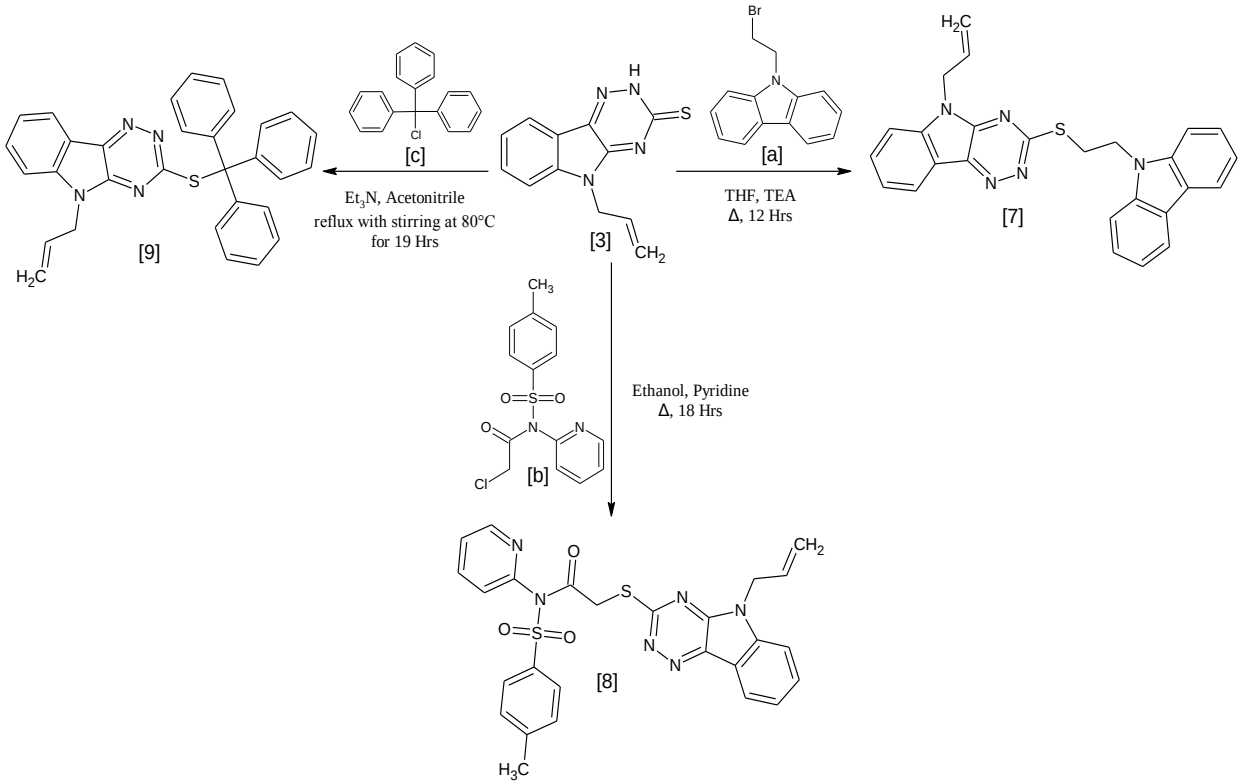

Reaction Scheme-3:

Synthesis of 1-(prop-2-en-1-yl)-1*H*-indole-2,3-dione [2]:

The sodium salt of indole **(1)** (0.02 mol) was suspended in DMF and with the aid of dropping funnel allyl bromide (0.02 mol) was added dropply in DMF with continuous stirring. The mixture was stimulated for 6 hrs until the colour of the solution changed. Crystals of NaBr were separated by filtration, and then the filtrate was poured in crushed ice. The clumpy solid strained was washed with methanol to get solid of compound **(2) which** was filtered, dehydrated and purified from ethanol.

Synthesis of 5-(prop-2-en-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol [3]:

A mixture of 1-(prop-2-en-1-yl)-1*H*-indole-2,3-dione (0.05 mol) and thiosemicarbazide (0.05 mol) were dissolved in 30 ml of acetic acid in a 250 ml RB flask. The resulting reaction mixture was refluxed for 10 hrs consequently. After completing the reaction, the reaction mixture was added to crushed ice and resulted in solid mass was filtered, washed, dried and recrystallized from ethanol to yield compound **[3].**

Synthesis of 2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)-N-(pyridin-2-yl)-N-tosylacetamide [4]:
Into a stirred solution of 9-(2-bromoethyl)-9*H*-carbazole [a] (0.01 mol) and TEA (0.02 mol) in 20 ml DMF and concentrated solution of compound **[1]** (0.01 mol) in DMF was added at cold temperature. The contents were stirred for 8 hrs at 0-8^{0}C and kept for 16 h at R.T. At the completion of reaction with the help of filtration process solid tri-ethyl ammonium bromide was separated and the filtrate was kept in crushed ice. The solid was washed, dried and recrystallized from ethanol.

Synthesis of 2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)isoindoline-1,3-dione [5]:

In a solution of compounds **[1]** (0.01 mol) and 2-chloro-*N*-(4-methylbenzene-1-sulfonyl)-*N*-(pyridin-2-yl) acetamide **(b)** (0.01 mol) in ethanol (20ml) and pyridine (0.01 mol) used as base. The resulting mixture was heated to reflux for 17 hrs. At the completion of the reaction, the R.M. was settled down for cooling and then dumped into icy water. The obtained solid was filtered, dried and recrystallized from ethanol.

Synthesis of 5,6-diphenyl-3-(tritylthio)-1,2,4-triazine [6]:

The solution of compound [1] (0.01 mol) and trityl chloride (0.125 mol) in 1, 4-dioxan (20 ml) was refluxed for 21 h with stirring at 140^0C in the presence of TEA (0.02 mol) as a base in an oil bath. After completing the reaction, the R.M. was settled down to cooling and dumped onto crushed ice. The precipitate of 5,6-diphenyl-3-(tritylthio)-1,2,4-triazine [6] that formed was separated, washed with cold water (twice by 20 ml), dried in hot air oven for 2 hrs and purified by recrystallized from ethanol.

Synthesis of 3-((2-(9H-carbazol-9-yl)ethyl)thio)-5-allyl-5H-[1,2,4]triazino[5,6-b]indole [7]:

Into a stirred solution of 9-(2-bromoethyl)-9*H*-carbazole [a] (0.01 mol) and TEA (0.02 mol) in 40 ml THF and concentrated solution of compound **[3]** (0.01 mol) in THF was added at R.T. The contents were stirred for 2 hrs at R.T. during the addition of compound [3] and then set up to reflux for 12 hrs. At the completion of reaction with the help of filtration process solid tri-ethyl ammonium bromide was separated and the filtrate was kept in crushed ice. The solid was washed, dried and recrystallized from benzene.

Synthesis of 2-((5-allyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)thio)-*N*-(pyridin-2-yl)-*N*-tosylacetamide [8]:

A solution of compounds **[1]** (0.01 mol), 2-chloro-*N*-(4-methylbenzene-1-sulfonyl)-*N*-(pyridin-2-yl) acetamide **(b)** (0.01 mol) in ethanol and as a base pyridine (0.01 mol) was also added. The resulting mixture was heated to reflux for 18 hrs. The excess of solvent from the reaction mixture was distilled off, at the completion of the reaction, and then the residual reaction mixture was cooled and kept in crushed ice. The solid was washed, dried and recrystallized from ethanol.

Synthesis of 5-allyl-3-(tritylthio)-5H-[1,2,4]triazino[5,6-b]indole [9]:

A mixture of compound [3] (0.01 mol) and trityl chloride (0.125 mol) in acetonitrile (20 ml) was heated to reflux for 19 h with stirring at 140^0C in the presence of TEA (0.02 mol) as a base in an oil bath. The extra solvent was distilled off, at workup of reaction and then it was allowed to cool R.T., and the residual R.M. was cooled and dumped into crushed ice. Then with the help of icy water, the obtained solid was washed, dried and by using methanol, the final product was recrystallized.

Table-1: I.R., NMR and Mass spectra values of the synthesis molecules

Compounds	I.R. (ν cm^{-1})	^{1}HNMR (δ)	Mass
1	3337 [N.H., Str.] 3106 [ArH, CH Str.] 2917, 2887[Ali.-C-H Str.] 1639 [C.N. Str.] 1209 [C.S. Str.]	8.21 [s, 1H, NH of triazino] 7.09-7.64 [m,10H,ArH]	m/z 265 [M^+]
2	3046 [Ar-H, CH Str.] 2936, 2864[Ali.-C-H str.] 1716 [CO] 1675 [CO]	7.35-7.85 [m 4H, ArH] 4.69 [quintett,1H $CHCH_2$] 2.28 [d,2H NCH_2CHCH_2] 1.95 [d,2H CH_2CHCH_2N]	m/z 187 [M^+]
3	3289 [N.H., Str.] 3051 [Ar-H, CH Str.] 2911, 2868[Ali.-C-H Str.] 1644 [C.N. Str.] 1226 [C.S. Str.]	8.12 [s, 1H, NH of triazino] 7.21-7.69 [m, 4H, ArH] 4.71 [quintett,1H $CHCH_2$] 2.13 [d,2H NCH_2CHCH_2] 1.89 [d,2H CH_2CHCH_2N]	m/z 242 [M^+]
4	3094 [Ar-H, CH Str.] 2930, 2872[Ali.-C-H Str.] 1631 [C.N. Str.]	7.11-7.75[(m, 18H, Ar-H] 3.75 [t, 2H, N-CH_2] 2.91 [t, 2H, S-CH_2-triazole]	m/z 458 [M^+]
5	3097 [Ar-H, CH Str.] 2928, 2868[Ali.-C-H Str.] 1753 [C.O. str.] 1619, 1609 [O=S=O Str.] 1641 [C.N. Str.] 1392 [N-S Str.]	7.21-7.69 [m, 18H, Ar-H] 4.12 [s, 2H, CH_2] 2.58 [s, 3H, CH_3-Benzene]	m/z 553 [M^+]
6	3089 [Ar-H, CH Str.] 2936, 2879[Ali.-C-H Str.] 1636 [C.N. Str.]	7.18-8.09 [m, 25H, Ar-H]	m/z 507 [M^+]
7	3094 [Ar-H, CH Str.] 2930, 2872[Ali.-C-H Str.] 1639 [C.N. str.]	7.11-7.75 [m, 12H, Ar-H] 4.71 [quintett,1H $CHCH_2$] 3.81 [t, 2H, N-CH_2] 2.83 [t, 2H, S-CH_2-triazole] 2.13 [d,2H N-CH_2-$CHCH_2$] 1.81 [d,2H CH_2CH-CH_2-N]	m/z 435 [M^+]
8	3085 [Ar-H, CH Str.] 2931, 2879Ali.-C-H Str.] 1755 [C.O. str.] 1615, 1604 [O=S=O Str.] 1649 [C.N. str.] 1395 [N-S str.]	7.11-7.75 [m, 12H, Ar-H] 4.71 [quintett,1H $CHCH_2$] 4.21 [s, 2H, CH_2] 2.65 [s, 3H, CH_3-Benzene] 2.29 [d, 2H N-CH_2-$CHCH_2$] 1.96 [d,2H CH_2CH-CH_2-N]	m/z 530 [M^+]
9	3091 [Ar-H, CH str.] 2932, 2865[Ali.-C-H str.] 1642 [C.N. str.]	7.11-7.75 [m, 19H, Ar-H] 4.71 [quintett,1H $CHCH_2$] 2.34 [d,2H NCH_2CHCH_2] 1.90 [d,2H CH_2CHCH_2-N]	m/z 484 [M^+]

Table-2: Physical and analytical data characterization of the synthesized molecules

Compds	Molecular Formula	M.W.	M. P. °C	Yield (%)	(%) of C Found/cal.	(%) of H Found/cal.	(%) of N Found/cal.	(%) of S Found/cal.	(%) of O Found/cal.
1	C15H11N3S	265	168	80	67.90/67.88	4.18/4.16	15.84/15.81	12.08/12.06	****
2	C11H9NO2	187	191	82	70.58/70.55	4.85/4.83	7.48/7.46	****	17.09/17.06
3	C12H10N4S	242	208	78	59.48/59.46	4.16/4.14	23.12/23.10	13.23/13.21	****
4	C29H22N4S	458	231	72	75.95/75.93	4.84/4.82	12.22/12.20	6.99/6.97	****
5	C29H23N5O3S2	553	262	78	62.91/62.88	4.19/4.16	12.65/12.63	11.58/11.56	8.67/8.64
6	C34H25N3S	507	278	68	80.44/80.42	4.96/4.94	8.28/8.26	6.32/6.29	****
7	C26H21N5S	435	251	74	71.70/71.72	4.86/4.84	16.08/16.05	7.36/7.34	****
8	C26H22N6O3S2	530	282	81	58.85/58.83	4.18/4.15	15.84/15.82	12.09/12.07	9.05/9.03
9	C31H24N4S	484	187	70	76.83/76.81	4.99/4.96	11.56/11.54	6.62/6.60	****

ANTIMICROBIAL ACTIVITY

The antibacterial and antifungal activity of newly nine synthesized compounds were analyzed in N,N-Dimethyl formamide using 500 ppm by the cup and well methodic way.

Table 3: The Micro-organisms used for Antimicrobial activity of the synthesized compounds

S.No.	Bacterial Strains	Screened against Standard	S.No.	Fungal Strains	Screened against Standard
1	Protius Mirabilis	Ciprofloxacin **(S1)**	1	Aspergillus Fumigatus	Flucanazole **(S2)**
2	Bacillus Subtilis				
3	Klebsilla Pneumonia		2	Candida Albicans	
4	Escherichia Coli				

Along with that, the majority of compound gives better activity than stnd. Used against bacterial and fungal strains. The study concluded that compound 4, 7a, 7b, 8a, 8b were discovered as strong amongst all other compounds **(Table 4).** It can be concluded that the newly synthesized compounds showed better antibacterial and antifungal activities.

Table 4: Antimicrobial activity of the synthesized compounds (500 ppm)

		Antibacterial activity				Antifungal activity	
S. No	**Compound name**	**Protius Mirabilis**	**Bacillus Subtilis**	**Klebsilla Pneumonia**	**Escherichia Coli**	**Candida Albicans**	**Aspergillus Fumigatus**
1	1	16 (1.12)	18 (1.11)	16 (1.07)	17(1.23)	18 (.87)	18 (1.12)
2	2	19 (.72)	16 (.97)	18 (1.05)	23 (1.25)	19 (.97)	20 (1.07)
3	3	18 (.88)	17 (1.00)	16 (.83)	22 (1.29)	20 (1.19)	19 (1.29)
4	4	22 (1.15)	23 (1.14)	21 (1.29)	22 (1.25)	23 (1.05)	22 (1.23)
5	5	23 (1.12)	22 (.97)	22 (1.35)	24 (1.27)	22 (1.17)	24 (1.11)
6	6	20 (1.22)	18 (1.03)	20 (.83)	23 (1.29)	23 (1.19)	20 (1.29)
7	7	22 (1.33)	23 (1.21)	23 (1.17)	24 (1.26)	22 (1.21)	22 (1.19)
8	8	23 (1.16)	23 (1.21)	22 (1.19)	23 (1.14)	22 (1.17)	23 (1.21)
9	9	19 (1.33)	16 (.97)	20 (1.17)	20 (1.06)	21 (.89)	22 (1.23)
S1		18	17	18	18	-	-
S2		-	-	-	-	20	20

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug
For antibacterial activity: S1 = Ciprofloxacin
For antifungal activity: S2 = flucanazole

CONCLUSION

In the synthesized compounds **4, 5, 7, 8** give good activity, and others show moderate activity against all four bacterial, and **4, 5, 6, 7, 8, 9** give good activity against two fungal.

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REFERENCES:

1. M, A. Ibrahim. R. M. A. Rahman, A. M. A.Halim, S. S. Ibrahim, H. A. J. Allimony, *J. Braz. Chem. Soc.* **2009**, *20*, 1275-1286.
2. M. Ashid, P. Yogi, N.Hussain and A. Joshi, *International Journal of Pharma Sciences and Research* Vol 6 No 10 Oct **2015**, 1295-1301.
3. M. Ashid, N. Hussain, G. Tailor, P. Yogi, A. Majid, D. Verma, P.Prajapat and A. Joshi, *J. Chem. & Chem. Sci*., **2017**, Vol.7(7), 495-506.
4. P. Yogi, M. Ashid, N. Hussain, S. Khan And A. Joshi, *Asian journal of chemistry*, Vol. 28, No. 4 (**2016**), 927-932.
5. P. Yogi, M.Ashid**,** N. Hussain, R. Khanam, S. Khan and A. Joshi, *Iranian Journal of Organic Chemistry Vol. 7, No. 2 (***2015***) 1515-1522.*
6. T. E. Ali, *Eur. J. Med. Chem.* **2009**, *44*, 4539-4546.
7. T. E. Ali,. *Eur. J. Med. Chem.* **2009**, *44*, 4385-4392.
8. R. R. Kamble, B. Sudha B. S. *J. Chem. Sci.* **2006**, *118*, 191-194.
9. Ibrahim, M. A.; Abdel-Rahman, R. M.; Abdel-Halim, A. M.; Ibrahim, S. S.; Allimony, H. A. *Arkivoc* **2008**, *16*, 202-215.
10. R. M. Abdel-Rahman, *Trends Heterocycl. Chem*. **1999**, *6*, 126-133.
11. R. M. Abdel-Rahman, *Pharmazie* **1999**, *54*, 791-804.
12. R. M. Abdel-Rahman, *Phosphorus Sulfur, Silicon and Relat. Elem*. **2000**, *166*, 315-357.
13. R. M. Abdel-Rahman, *Pharmazie* **2001**, *56*, 275-286.
14. R. M. Abdel-Rahman, *Trends Heterocycl. Chem*. **2002**, *8*, 187-194.
15. G. J. Collee, G. A. Fraser, P. B. Marmion, A. Sinmons, *Practical medicinal microbiology*. 14th edn. Vol. II. Edinburg: Churchill Livingstone; **1996**. p 163.
16. P. Mullick, S. A. KHAN, T.Begum, S.Verma, D. Kaushik and O.ALAM, *Acta Poloniae Pharmaceutica - Drug Research*, Vol. 66 No. 4 pp. 379-385, **2009**.
17. A.M.El-Agrody1 , M.S.Abd El-Latif, N.A.El-Hady , A.H.Fakery and A.H.Bedair, *Molecules* **2001**, *6, 519-527.*
18. M.Arshad, A. R. Bhat, K. K. Hoi, I. Choi, F. Athar, *Chinese Chemical Letters*, Volume 28, Issue 7, July **2017**, Pages 1559-1565.
19. S. Cascioferro, B.Parrino,V.Spanò, A.Carbone, A. Montalbano, P. Barraja, P.Diana, G. Cirrincione. European Journal of Medicinal ChemistryVolume 142, 15 December **2017**, Pages 328-375
20. L.X. Liu, X.Q. Wang, B. Zhou, L.J. Yang, Y. Li, H.B. Zhang and X.D. Yang, *Scientific Reports* | Nature | 5:13101 | **2015** | DOI: 10.1038/srep13101
21. P. Yogi and A. joshi, *J. Chem. Bio. Phy. Sci. Sec. A*, November 2015 – January **2016**; Vol.6, No.1;117-127