



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF NOVEL BIPHENYL TETRAZOLE DERIVATIVES

Pineshkumar N. Patel^{*1}, Denish C. Karia²

¹Huntsman International India Pvt Ltd, Vadodara, Gujarat, India

²Department of Chemistry, Patel J D K Davolwala Science College, Borsad, Gujarat, India

*E-Mail: ppinesh41891@gmail.com

Received 20 May 2015; Accepted 18 June 2015

Abstract: Biphenyl Tetrazole and their derivatives are well known for valuable medicinal properties. The present work describes the synthesis of novel Biphenyl Tetrazole derivatives and evaluation of their medicinal value. The reaction of 4'-Methyl-biphenyl-2-carbonitrile with Sodium azide and tri-n-butyl-tin chloride produced 5-(4'-Methyl-biphenyl-2-yl)-1H-tetrazole (**T1**) which upon reaction with Triphenyl methyl chloride was converted to 5-(4'-Methyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (**T2**). The Bromination of **T2** resulted 5-(4'-Bromomethyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (**T3**). Finally, the **T3** was reacted with Hydroxy Aldehyde, Hydroxy Acetophenone and Hydroxy Coumarine derivatives to produce **TB (A-G)**. The **TB (A-G)** was heated in presence of acidic media to produce **TB (H-N)**. The chemical structures of synthesized compounds were characterized by ¹H-NMR, ¹³C-NMR and FT-IR. All synthesized compounds were screened for their antimicrobial activity. The compounds TB-A, TB-B, TB-E and TB-K were found to be the most potent antimicrobial agent among all synthesized compounds.

Keywords: Biphenyl, Tetrazole, Coumarine, Aldehyde, Antibacterial, Antifungal.

INTRODUCTION:

The development of novel chemotherapeutic agent is an important and challenging task for the medicinal chemist. Many research programs are directed towards design and synthesis of new drugs. Research on new substances possessing improved antimicrobial activity has attracted

considerable attention due to continuous increase in the resistance of microbes to the existing drugs. Further, the infection caused by such microorganism posed serious challenge to medicinal scientists and sought for development of efficient drugs.

Biphenyl compounds are one of the valuable

classes in the organic chemistry which constitutes structural moiety of various compounds with important medicinal properties. Initially, Biphenyl compounds were used in chemical and agrochemical industries as an intermediate but with emerging trends in synthetic medicinal chemistry, variety of Biphenyl derivatives were prepared by researchers and evaluated their therapeutic significance. The intense research work is the evidence of importance of Biphenyl moiety as pharmacologically important compound. Some of the compounds having Biphenyl moiety possess valuable medicinal properties like antihypertensive and calcium channel blocker [1,2]. The molecules having Biphenyl moiety are also known to exhibit anti-inflammatory [3], diuretic [4], anti-diabetic [5] activity. Some of the Biphenyl containing compounds possesses antipsychotic and anxiolytic activity [6]. Some of the Biphenyl hydrazide-hydrazone are known to exhibit very good antimicrobial activity [7,8].

In addition to the Biphenyl compounds, the pharmacologically important heterocyclic with N-bridge derived from Tetrazole also carved the way toward the active research in Tetrazole heterocyclic compounds. Tetrazole compounds possess many important medicinal properties in heterocyclic compounds. Tetrazole is much more stable towards biological degradation and therefore, important moiety for the development of various biologically active compounds. Tetrazole consists of 5-membered ring having four Nitrogen atoms and one Carbon atom. Owing to maximum numbers of Nitrogen, it exhibits extreme acidity, basicity and complex formation constants. Tetrazole is bioisostere of carboxylic acid group. Tetrazole compounds possesses wide variety of medicinal properties and therefore under continuous attention of many researcher. Tetrazole are well known to possess antimicrobial [9-13], anti-inflammatory and analgesic [14-16], anticancer [17-18], anticonvulsant [19-20], antihypertensive [21-24], antinociceptive [25], hypoglycemic [26-

28], antiproliferative [29], cyclo-oxygenase-2-inhibitor and ACE-amylase inhibitor [30-31] activity. Some of the Tetrazole having Coumarine moiety are also known to possess antibacterial and anticancer activity [32-33].

The recent trend in research shows that Biphenyl Tetrazole derivatives are under continuous attention to many research programs. A number of attempts were made to improve and explore the pharmacological properties by varying the substitution on the Tetrazole derivatives. Thus, prompted by diverse biological activity of Tetrazole and its derivatives, attempt has been made to incorporate Tetrazole nucleus in compound containing Biphenyl-aryl ether group to develop novel potential antibacterial and antifungal agent.

MATERIALS AND METHOD:

Materials:

All key raw materials, reagents and solvents were highly pure and of commercial grade, used without further purification. All melting points were determined using open capillaries in a liquid paraffin bath and were uncorrected. The completion of reaction was monitored by thin layer chromatography using silica gel-G as absorbent and Toluene: Ethyl acetate was employed as mobile phase. The visualization of TLC was accomplished by UV light and Iodine. IR spectra (KBr pallet) were recorded on FT-IR, Perkin Elmer RX1 spectrophotometer and NMR spectra on BRUKER AVANCE II (400 MHz) using TMS as internal standard (chemical shifts in δ ppm).

Methods:

In the present work, novel Biphenyl Tetrazole derivatives were prepared by following general reaction scheme as shown in figure 1.1. Several methods have been reported in the literature for the synthesis of Tetrazole compounds. Most of them have limited application to the preparative

organic synthesis only because of the toxic and explosive nature of hydrazoic acid. In the present work, the hydrazoic acid has been replaced by inorganic azide and organotin compounds to synthesize Tetrazole. The 4'-Methyl-biphenyl-2-carbonitrile was cyclized using Sodium azide and tri-n-butyl tin chloride in Monochlorobenzene solvent to afford good yield of **T1**. The compound **T1** upon reaction with Triphenyl methyl chloride and Triethyl amine in Monochloro benzene produced **T2**. The **T2** was Brominated using Hydrogen Bromide and Hydrogen peroxide to produce **T3**. The reaction of **T3** with various substituted Hydroxy aromatic compound produced various derivatives of Biphenyl Tetrazole **TB (A-G)**. The heating of **TB (A-G)** in presence of glacial Acetic acid produced various Biphenyl Tetrazole **TB (H-N)**. The physical constants of synthesized compounds are mentioned in Table 1.1. All synthesized compounds were evaluated for antibacterial and antifungal activity. The results of antibacterial and antifungal activity are depicted in Table 1.2 and Table 1.3.

Procedure for the synthesis of 5-(4'-Methyl-biphenyl-2-yl)-1H-tetrazole (T1) [34]

A solution of 4'-Methyl-biphenyl-2-carbonitrile (19.3 g, 0.10 moles), Sodium azide (6.5 g, 0.14 moles) and tri-n-butyl-tin chloride (32.5 g, 0.13 moles) in Monochlorobenzene were refluxed at 135-138°C for 24 hours. The progress of the reaction was monitored by Silica gel thin layer chromatography. Toluene: Ethyl acetate (75:25) was used as eluent in TLC chromatography. After completion of reaction, the mass was cooled to 45°C and filtered to separate generated sodium chloride. 12 ml 32% Hydrochloric acid was added to the filtrate under stirring and controlling temperature 25-30°C, then the reaction mass was stirred for 1 hour to precipitate out 5-(4'-Methyl-biphenyl-2-yl)-1H-tetrazole. The precipitated product was isolated by filtration. The crude product was purified from Methanol and obtained 5-(4'-Methyl-biphenyl-2-yl)-1H-tetrazole as

white amorphous powder in 94% yield having melting point 148-150°C.

Procedure for the synthesis of 5-(4'-Methyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (T2)

To a solution of 5-(4'-Methyl-biphenyl-2-yl)-1H-tetrazole (**T1**) (10 g, 0.040 moles) and Triphenyl methyl chloride (13.6 g, 0.049 moles) in Monochloro benzene, Triethyl amine (5.8 g, 0.057 moles) was charged and the reaction mass was heated to 75-80°C for 8 hours. The progress of the reaction was monitored by Silica gel thin layer chromatography. Toluene: Ethyl acetate (75:25) was used as eluent in TLC chromatography. After completion of reaction, the mass was cooled to 40°C and filtered to separate generated salt. The filtrate was then, concentrated under vacuum to distill out Monochloro benzene. Then, the Methanol was added in the residual mass and stirred at 30-35°C. The product was isolated by filtration and washed with Methanol and dried. Yield: 89%, white amorphous powder, m.p: 167-169°C.

Procedure for the synthesis of 5-(4'-Bromomethyl-biphenyl-2-yl)-1-trityl-1H-tetrazole (T3)

A mixture of **T2** (10 g, 0.021 moles), 48% Hydrogen peroxide (1.79 g, 0.025 moles), Azo bis isobutyronitrile (0.25 g, 1.5 mmoles) and 100 ml Methylene dichloride were cooled to 10-15°C and 48% Hydrogen Bromide (3.82 g, 0.023 moles) was added to the cooled solution over period of 4 hours in controlled way so that temperature during addition remained 10-15°C. The progress of the reaction was monitored by Silica gel TLC using Toluene: Ethyl acetate (65:35) as eluent. After completion of reaction, the mass was treated with Sodium sulfite solution at 15-20°C. Then, the organic layer was washed with water at 15-20 °C and neutralized with Sodium Bicarbonate solution. Methylene dichloride was distilled out from the Organic layer and then, Methanol was added in the mass. The resultant mixture was cooled to 15-20°C. Finally, the precipitated mass was

filtered to recover white product. Yield: 82%, white amorphous powder, m.p: 152-155°C.

General procedure for the synthesis of 4-[2'-(1-Trityl-1H-tetrazol-5-yl)-biphenyl-4-yl-methoxy]-benzaldehyde TB (A-G).

The mixture of T3 (1 g, 1.79 mmoles), Sodium Carbonate (0.23 g, 2.15 mmoles) and 4-hydroxy benzaldehyde (0.23 g, 1.88 mmoles) in Dimethyl Formamide (25 ml) were stirred at room temperature. Then, Tetra butyl ammonium bromide was added as catalyst and the mass was heated to 75-80°C for 5 hours. The progress of reaction was monitored by Silica gel TLC using Toluene: Ethyl acetate (95:05) as eluent. After completion of reaction, the mass was drawn in 500 ml water within 30 minutes. The resultant solids were filtered and washed with water. The crude product was purified in mixture of Methanol and Ethyl acetate to afford amorphous powder. Yield: 87%, white amorphous powder, m.p: 170-172°C.

General procedure for the synthesis of 4-[2'-(1H-Tetrazol-5-yl)-biphenyl-4-yl-methoxy]-benzaldehyde TB (H-N).

The mixture of TB-A (1 g, 1.67 mmoles) and glacial Acetic Acid (2 ml) in Methanol (25 ml) was heated to reflux temperature for 5-8 hours. The progress of reaction was monitored by Silica gel TLC using Toluene: Ethyl acetate (10:90) as eluent. After completion of reaction, the mass was drawn in 500 ml water. The resultant solids were filtered and washed with water. The crude product was purified in Acetone to afford amorphous powder. Yield: 77%, white amorphous powder, m.p: 120-122°C.

REPRESENTATIVE SPECTRAL DATA

4-[2'-(1-Trityl-1H-tetrazol-5-yl)-biphenyl-4-yl-methoxy]-benzaldehyde (TB-A)

¹H NMR (DMSO) δ ppm: 5.17 (2H, s, -CH₂-), 6.85-7.88 (27H, m, Ar-H), 9.87 (1H, s, -CHO). ¹³C NMR (DMSO) δ ppm: 69.3 (-C-Ph₃), 82.27 (-CH₂-O), 115-163 (Aromatic

-C), 191.29 (-C=O, Aldehyde), FT-IR, (KBr, cm⁻¹): 761 (o-substituted Benzene), 829 (p-Substituted Benzene), 1158 (-C-O-, ether), 1267, 1687 (>C=O, Aldehyde), 1578 (-N=N-, Tetrazole ring), 1597 (-C=N-, Tetrazole ring), 3032 (C-H, aromatic).

BIOLOGICAL EVALUATION

Synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity. For evaluation of antibacterial activity, the representative strains of Gram-negative bacteria (*Escherichia Coli*, *Pseudomonas Aeruginosa*) and Gram-positive bacteria (*Staphylococcus Aureus*, *Streptococcus Pyogenus*) were used. For antifungal activity, *Candida Albicans*, *Aspergillus Niger* and *Aspergillus Clavatus* were used. All standard strains were procured from Institute of Microbial Technology, Chandigarh, Punjab, India. The Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin were used as standard antibacterial drugs for the comparison. While, Nystatin and Griseofulvin were used as standard antifungal drugs. The Agar diffusion and broth dilution test method were followed and each test compounds were dissolved in Dimethyl Sulfoxide (DMSO). Muller Hinton Broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. Inoculums size for the test strain was adjusted to 10⁸ Cfu/ml by comparing the turbidity. The synthesized compounds and standard drugs were dissolved in DMSO, adjusted the concentration to 2000 μ g/ml and then, used as stock solution. Serial dilutions were prepared for primary and secondary screening for the test compounds. The test compound tubes were incubated for 24 hours at 37°C. The turbidity produced in each tube was recorded by UV/Visible spectrophotometer. The turbidity produced by the Broth (without inoculums) was considered as 100% transparency. The minimum inhibitory concentration (MIC) was noted as the minimum concentration of the test substance, which completely inhibits the growth of the

Figure: 1.1: General Synthesis scheme

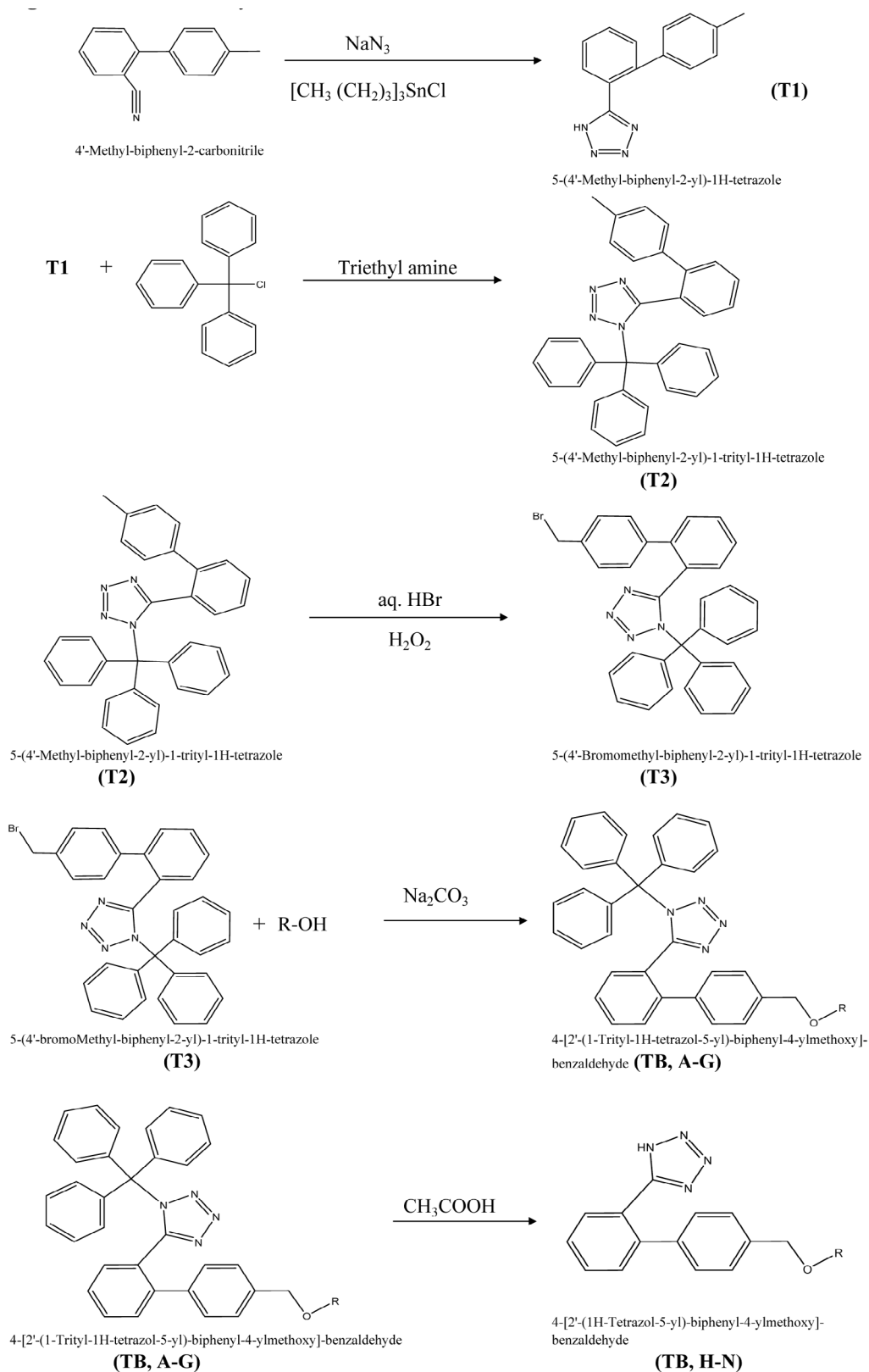


Table 1.1: Physical constants of synthesized compounds

Compound Name	R	Molecular Formula	Mol. Weight	Melting Point [°C]	Rf Value
TB-A		$C_{40}H_{30}N_4O_2$	598.69	170-172	0.44*
TB-B		$C_{41}H_{32}N_4O_3$	628.72	192-195	0.41*
TB-C		$C_{44}H_{39}N_5O_2$	669.81	82-85	0.19*
TB-D		$C_{41}H_{32}N_4O_2$	612.72	138-141	0.40*
TB-E		$C_{43}H_{32}N_4O_3$	652.74	164-167	0.39*
TB-F		$C_{42}H_{30}N_4O_3$	638.71	178-180	0.37*
TB-G		$C_{40}H_{30}N_4O_2$	598.69	102-105	0.49*
TB-H		$C_{21}H_{16}N_4O_2$	356.38	120-122	0.68**
TB-I		$C_{22}H_{18}N_4O_3$	386.4	92-95	0.67**
TB-J		$C_{25}H_{25}N_5O_2$	427.5	142-145	0.30**
TB-K		$C_{22}H_{18}N_4O_2$	370.4	176-178	0.64**
TB-L		$C_{24}H_{18}N_4O_3$	410.42	230-232	0.59**
TB-M		$C_{23}H_{16}N_4O_3$	396.4	86-88	0.68**
TB-N		$C_{21}H_{16}N_4O_2$	356.38	94-96	0.62**

*Toluene: Ethyl acetate : : 95 : 05, **Toluene: Ethyl acetate : : 10 : 90

Table 1.2: Antibacterial Activity, Minimum Inhibition Concentration. (MIC^a)

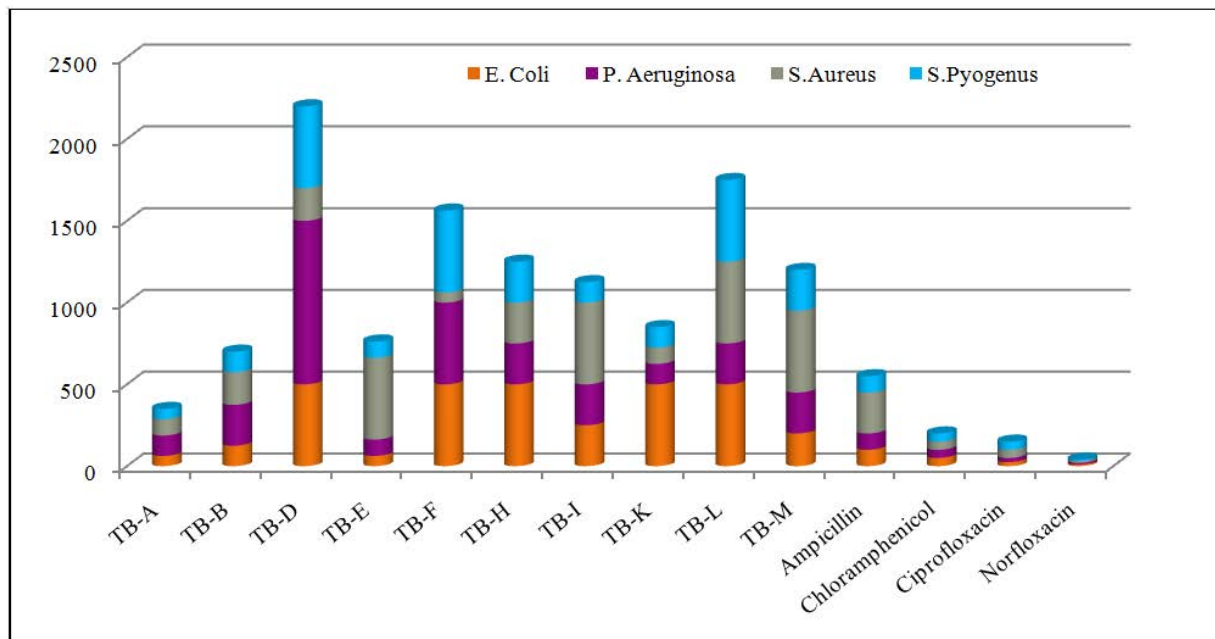
Compound Name	E. Coli (MIC) ^a	P. Aeruginosa (MIC) ^a	S.Aureus (MIC) ^a	S.Pyogenus (MIC) ^a
	MTCC 443 Gram-Negative	MTCC 1688 Gram-Negative	MTCC 96 Gram Positive	MTCC 442 Gram-Positive
TB-A	62.5	125	100	62.5
TB-B	125	250	200	125
TB-D	500	1000	200	500
TB-E	62.5	100	500	100
TB-F	500	500	62.5	500
TB-H	500	250	250	250
TB-I	250	250	500	125
TB-K	500	125	100	125
TB-L	500	250	500	500
TB-M	200	250	500	250
Standard drugs				
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

(MIC)^a: Minimum Inhibitory concentration in µg/ml**Table 1.3:** Antifungal activity, Minimum Fungicidal Concentration

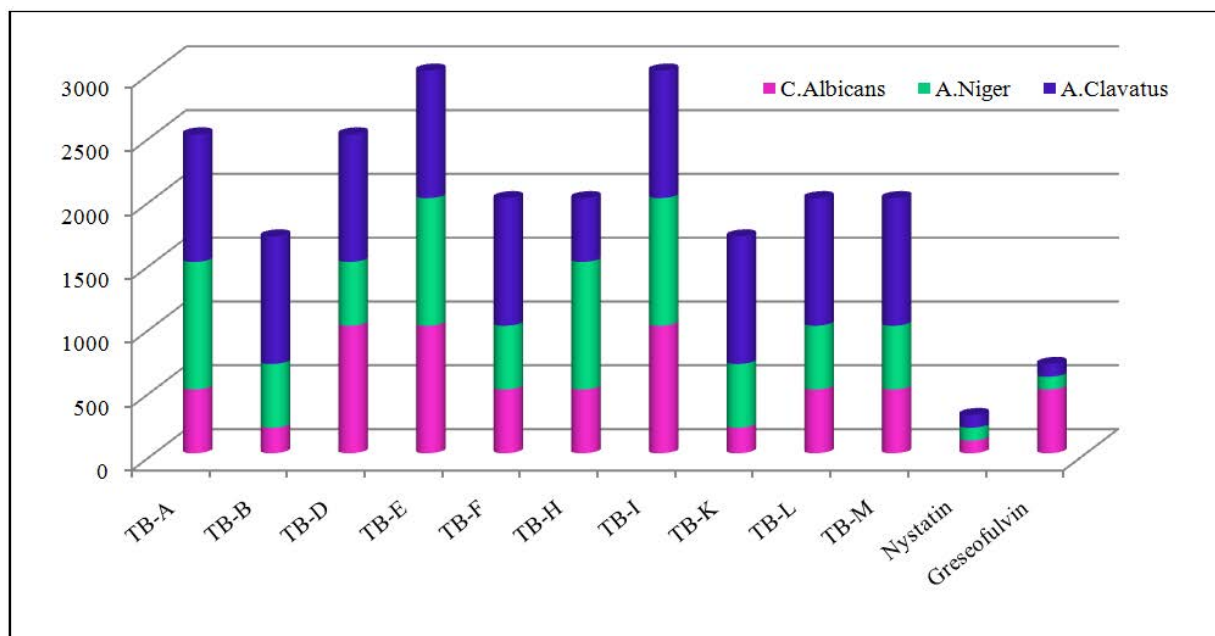
Compound Name	C.Albicans (MIC) ^b	A.Niger (MIC) ^b	A.Clavatus (MIC) ^b
	MTCC 227	MTCC 282	MTCC 1323
TB-A	500	1000	1000
TB-B	200	500	>1000
TB-D	>1000	500	>1000
TB-E	>1000	>1000	>1000
TB-F	500	500	>1000
TB-H	500	>1000	500
TB-I	>1000	>1000	>1000
TB-K	200	500	>1000
TB-L	500	500	>1000
TB-M	500	500	>1000
Standard drugs			
Nystatin	100	100	100
Greseofulvin	500	100	100

(MIC)^b: Minimum Inhibitory concentration in µg/ml

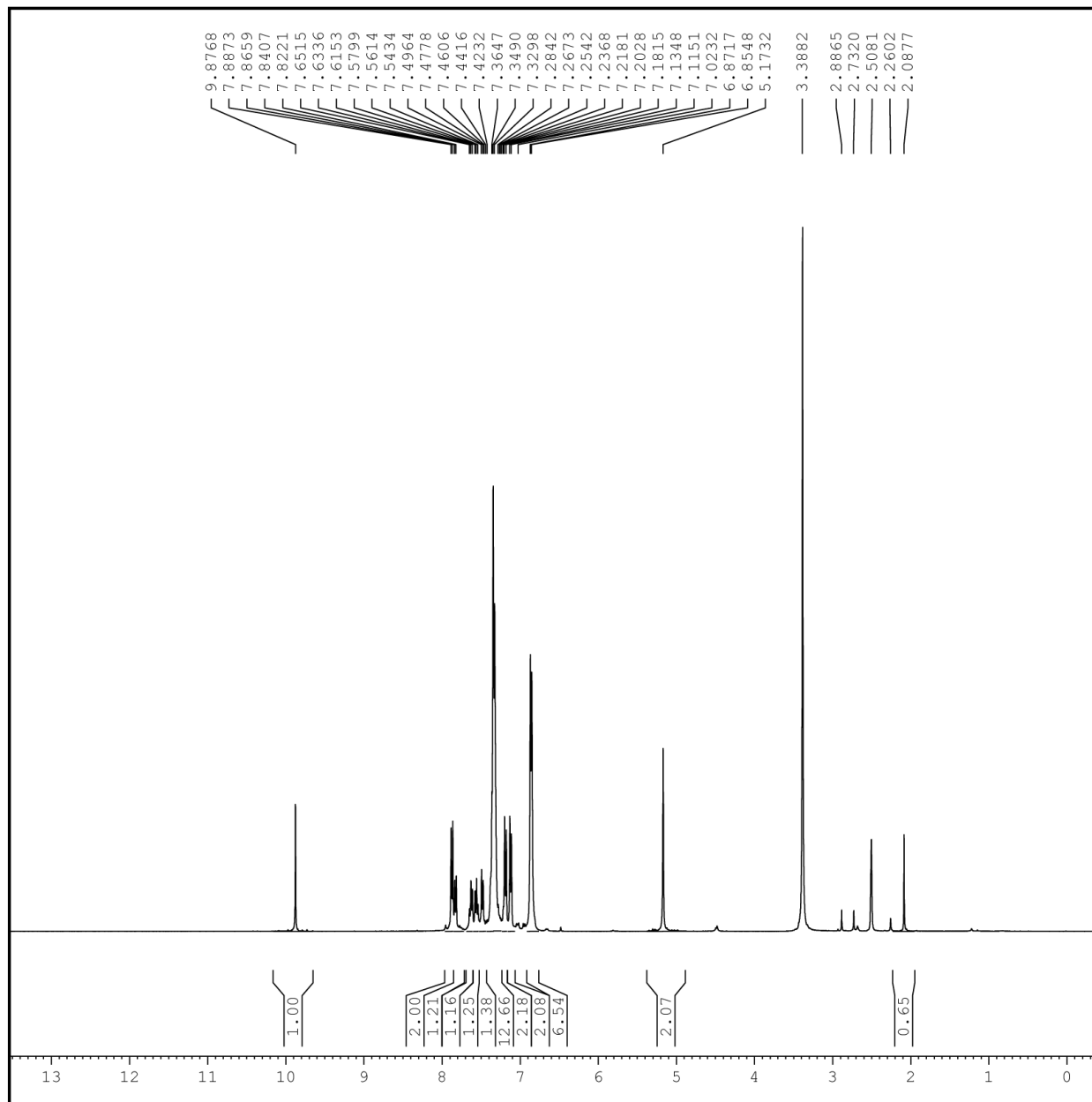
Graph 1.1: Antibacterial Activity, Minimum Inhibition Concentration (Graphical form)

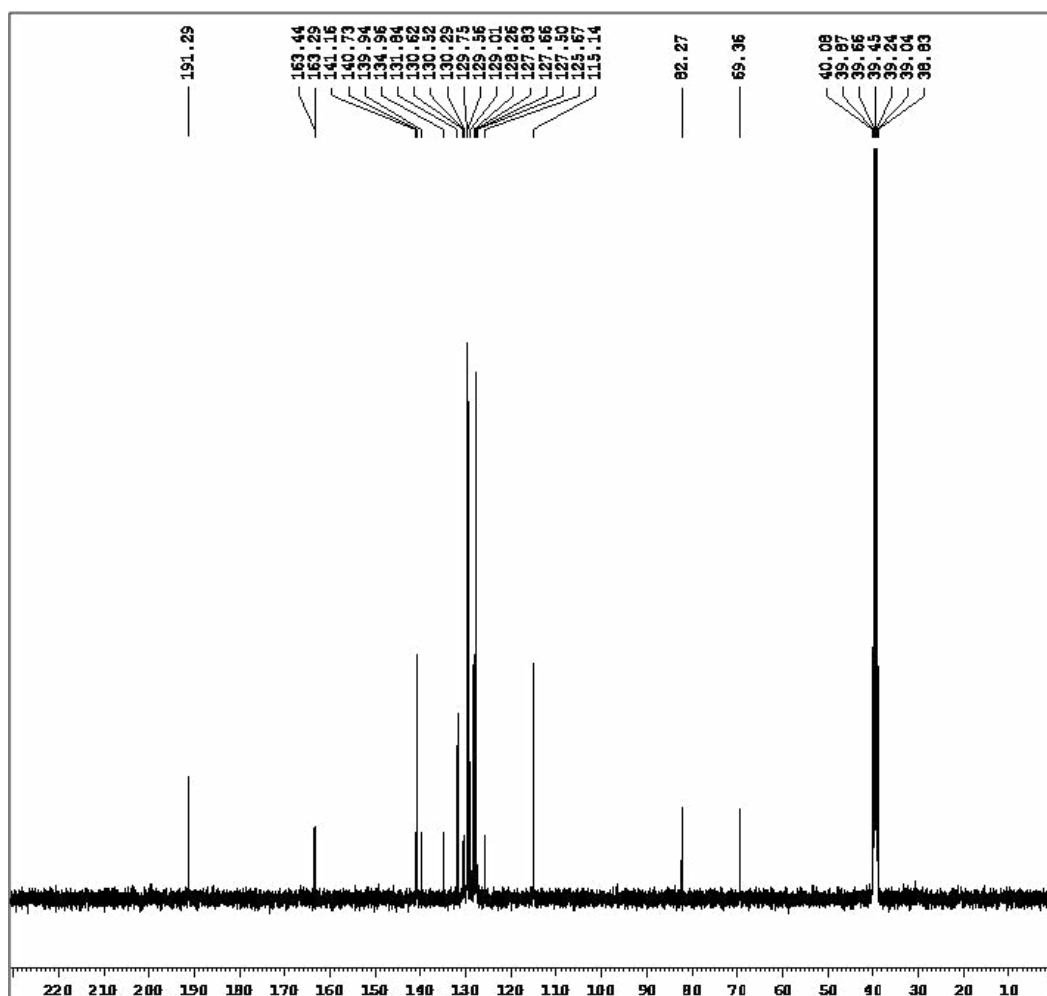


Graph 1.2: Antifungal activity, Minimum Fungicidal Concentration (Graphical Form)

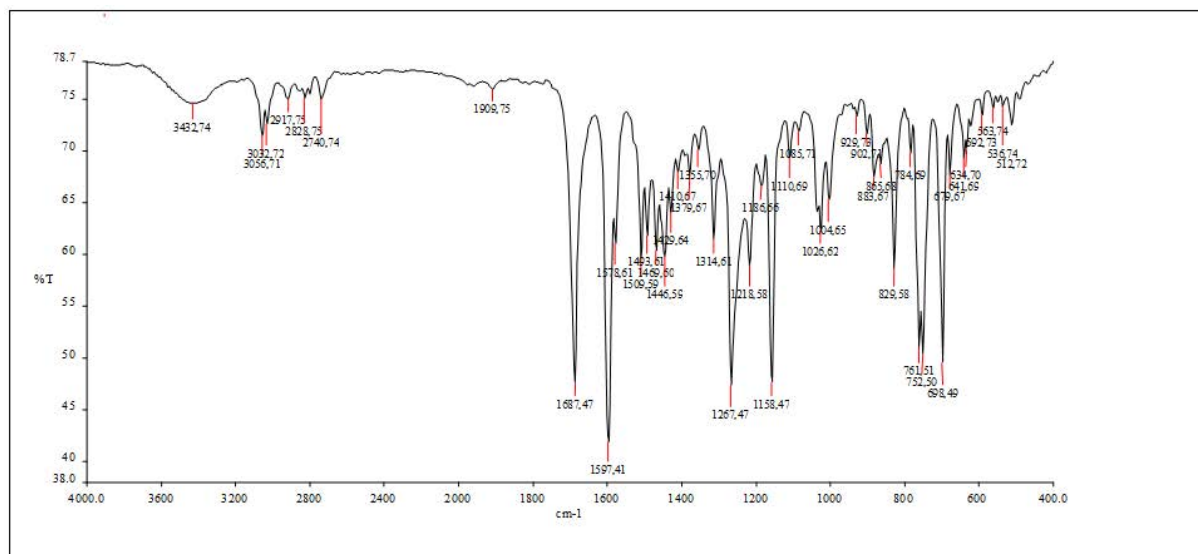


¹H NMR Spectra



^{13}C NMR Spectra

FT-IR Spectra



microorganism i.e. 100% transparency.

RESULTS AND DISCUSSION:

In the present study, fourteen novel Biphenyl Tetrazole compounds were synthesized in reasonably good yield. The presence of stretching at 1577 and 1598 cm^{-1} in FT-IR confirmed the presence of Tetrazole ring. The presence of ether link was also confirmed by presence of characteristic peak in FT-IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$. The synthesized compounds were evaluated for antibacterial and antifungal activity. The test results of antimicrobial activity are mentioned in Table 1.2, Table 1.3 and in Graph 1.1, Graph 1.2.

(1) Antibacterial evaluation: Compounds **TB-A** and **TB-E** found are found to be more potent to Ampicillin ($\text{MIC}=100 \mu\text{g/mL}$) against *E.Coli* (MTCC 443). Compound **TB-E** found equipotent to Ampicillin ($\text{MIC}=100 \mu\text{g/mL}$) against *P.Aeruginosa* (MTCC 1688). Compounds **TB-A**, **TB-B**, **TB-D**, **TB-F**, **TB-H** and **TB-K** possessed very good antibacterial activity against *S.Aureus* (MTCC 96) and found more efficient than Ampicillin ($\text{MIC}=250 \mu\text{g/mL}$). Compounds **TB-A** and **TB-E** possessed very good antibacterial activity against *S.Pyogenus* (MTCC 442) and also found more efficient than Ampicillin ($\text{MIC}=100 \mu\text{g/mL}$).

(2) Antifungal evaluation: Compounds **TB-B** and **TB-K** are found more potent than Greseofulvin ($\text{MIC}=500 \mu\text{g/mL}$) against *C.Albicans* (MTCC 227). While, **TB-A**, **TB-F**, **TB-H**, **TB-L** and **TB-M** are found to be equipotent to Greseofulvin ($\text{MIC}=500 \mu\text{g/mL}$) against *C.Albicans* (MTCC 227). All other synthesized compounds are less potent than standard drugs against *A.Niger* (MTCC 282) and *A.Clavatus* (MTCC 1323).

CONCLUSION:

The novel Biphenyl Tetrazole compounds can be

synthesized in reasonably good yield using less hazardous and commercial grade raw materials. The structures of synthesized compounds were confirmed by FT-IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$. The synthesized compounds were evaluated for biological property. All synthesized compounds were found to possess reasonably good antimicrobial activity and compounds **TB-A**, **TB-B**, **TB-E** and **TB-K** were found to be most potent antimicrobial agent.

ACKNOWLEDGEMENT:

Authors are thankful to SAIF and CIL, Punjab University for extending their support for instrumental analysis. Authors also acknowledge the support provided by Dr. Nimesh Vyas, Head of Chemistry department, Sheth P. T. Arts and Science College, during the research study.

REFERENCES:

1. Z. J. Jain, P. S. Gide, R. S. Kankate, Arabian J. Chem., **2013**, doi:10.1016/j.arabjc.2013.07.035
2. J. S. Mojjarad, Z. Zamani, H. Nazemiyeh, S. Ghasemi, D. Asgari, Adv. Pharm. Bull., **2011**, 1, 9.
3. A. Deep, S. Jain, P.C Sharma, Acta Pol. Pharm. Drug Res., **2010**, 67, 63.
4. M. S. Yar, Z. H. Ansari, Acta Pol. Pharm. Drug Res., **2009**, 66, 387.
5. N. Sachan, S. Thareja, R. Agarwal, S. S. Kadam, V. M. Kulkarni, Int. J. Chemtech. Res., **2009**, 1, 1625-1631.
6. G. Ruggero, C. K. Jones, K. Hemstapat, Y. Nong, N. G. Echemendia, L. C. Williams, T. D Paulis, P. J. Conn, J. Pharmacol. Exp. Ther., **2006**, 318, 173.
7. A. Deep, S. Jain, P.C Sharma, P. Verma, M. Kumar, C. P. Dora, Acta Pol. Pharm. Drug Res., **2010**, 67, 225.
8. A. Madhkar, N. Kannappan, A. Deep, P. Kumar, M. Kumar, P. Verma, Int. J. Chemtech. Res., **2009**, 1, 1376.
9. C. X. Wei, M. Bian, G.H. Gong, Molecules, **2015**, 20, 5528-5553.
10. Md Salahuddin, S. Singh, S. M. Shantakumar, Rasayan J. Chem., **2009**, 2, 1, 167-173.
11. M. S. Mohamed, M. A. ELDomany, R. H. ABD EL-Hameed, Acta Pharm. **2009**, 59, 145-158.
12. H. Patil, D. Varadaraji, S. S. Suban, V. R. Ramasamy, K. Kubendiran, J. S. K. G. Raguraman, S. K. Nalilu, Org. Commun., **2010**, 3:3, 45-56.
13. S. J. Chao, X. P. Hui, S. Li, Z. Z. Qiu, P. F. Xu, Z. Y. Zhang, Q. Wang and Z. W. Guan, J. Chinese Chem. Soc., **2005**,

- 52, 539-544.
14. A. A. Bekhit, O. A. el-Sayed, E. Aboulmagd, J. Y. Park, Eur. J. Med. Chem. **2004**, 39, 249-255.
15. U. Natarajan, I. Kaliappan, N. K. Singh, Der Pharma Chemica, **2010**, 2, 1,159-167.
16. A. Rajasekaran, P. P. Thampi, Eur. J. Med. Chem., **2004**, 39, 273-279.
17. C.N.S.S.P. Kumar, D. K. Parida, A. Santhoshi, A. K Kota, B. Sridhar, V. J. Rao, Med. Chem. Commun., **2011**, 2, 486-492.
18. V. H. Bhaskar, P. B. Mohite, J. Optoelectronics and Biomed. Materials, **2010**, 2, 4, 249-259.
19. S. B. Wang, X. Q. Deng, Y. Zheng, Y.P. Yuan, Z. S. Quan, L. P. Guan, Eur. J. Med. Chem. **2012**, 56, 139-144.
20. X. Y. Dun, C. X. Wei, X. Q. Deng, Pharmacological Report, **2010**, 62, 272-277.
21. J. Wu, Q. Wang, J. Guo, Z. Hu, Z. Yin, J. Xu, X. Wu, Eur. J. Pharmacol. **2008**, 589, 220-224.
22. S. Sharma, M. C. Sharma, D. V. Kohli, J. Optoelectronics and Biomed. Materials, **2010**, 1, 3, 151-160.
23. S. Rao, K. S. Babu, Organic Communications, **2011**, 4, 105-111.
24. J. H. Kim, J. H. Lee, S. H. Paik, J. H. Kim, C.H Yong, Arch. Pharm. Res. **2012**, 35, 1123-1126.
25. A. Rajasekaran, A. K. Rajagopal, Acta Pharm. **2009**, 59, 355-364.
26. Y. L. Gao, G. L. Zhao, W. Liu, H. Shao, Y. L. Wang, W. R. Xu, L. D. Tang, J. W. Wang, Indian J. Chem. B. **2010**, 49, 1499-1508.
27. K. Pegklidou, C. Koukoulitsa, I. Nicolaou, V. J. Demopoulos, Bioorg. Med. Chem. **2010**, 18, 2107-2114..
28. A. Sharon, R. Pratap, P. Tiwari, A. Srivastava, P. R. Maulik, V. J. Ram,, Bioorg. and Med. Chem. Letters, **2005**, 15, 2115-2117.
29. A.S. Gundugola, K. L. Chandra, E. M. Perchellet, A. M. Waters, S. Rayat, Bioorg. and Med. Chem. Letters, **2010**, 20, 3920-3924.
30. L. Navidopour, M. Amni, H. Shafarwoodi, K. J. Abdi, M. H. Ghahremani, A. Shafiee, Bioorg. and Med. Chem. Letters, **2006**, 15, 4483-4487.
31. G.Y. Meti, R. R. Kamble, D. B. Biradar, S. B. Margankop, Med. Chem. Res., **2013**, 22, 5868-5877.
32. G. L. V. Damu, S. F. Cui, X. M. Peng, Q. M. Wen, G. X. Cai, C. H. Zhou, Bioorg. and Med. Chem. Letters, **2014**, 24, 15, 3605-3608.
33. R. Sagar, J. Park, M. Koh, S. B. Park, J. Org. Chem., **2009**, 5, 74, 2171-2174.
34. A. V. Reddy, patent, **2010**, US20100222597A1.