International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

Research Article **Open Access**

Synthesis, characterization and Biological Evaluation of 3,4-bis(substituted-Phenyl)-7-(2,6- dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-C:5,4- C'] diisoxazoles from 2, 6- dichloro-4-trifluoro methyl aniline

Shankarsing Sardarsing Rajput*[1], Rahebar Ali Mohammed Ali Sayyed[2]

[1]*Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha, Dist.Dhule, (M.S) 425408, India*
[2]*Department of Chemistry, PSGVPM's Arts, Commerce and Science College, Shahada, Dist. Nandurbar (M.S) 425409, India*

A B S T R A C T

The five membered cyclic imide derivative of 2, 6 dichloro-4-trifluoromethyl aniline was synthesized by reacting succinic anhydride with 2, 6 dichloro-4-trifluoro methyl aniline in presence of acetyl chloride and benzene. The resulting imide derivative was condensed with substituted aromatic aldehydes in presence of acetic acid gives bis-heterocyclic chalcones. These chalcones underwent ring closure with hydroxylamine hydrochloride afforded bis-isoxazole derivatives of 2, 6 dichloro-4-trifluoromethyl aniline. The synthesized compounds were screened for their spectral analysis and biological evaluation.

Keywords: Cyclic imides, chalcone, isoxazole

A R T I C L E I N F O

CONTENTS

Article History: Received 18 November 2016, **Accepted** 19 December 2016, **Available Online** 15 January 2017

***Corresponding Author**
Shankarsing Sardarsing Rajput
Department of Chemistry,
SVS's Dadasaheb Rawal College
Dist.Dhule, M.S, India-425408
Manuscript ID: IJCTPR3261

PAPER-QR CODE

Citation: Shankarsing Sardarsing Rajput. Synthesis, characterization and Biological Evaluation of 3,4-bis(substituted-Phenyl)-7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-C:5,4- C'] diisoxazoles from 2, 6- dichloro-4-trifluoro methyl aniline. *Int. J. Curnt. Tren. Pharm, Res.*, 2017, 5(1): 17-22

1. Introduction

The heterocyclic chemistry is an emerging branch of chemistry due to its medicine manufacturing characteristics, it is exposed by Literature survey that there is extremely large research going on cyclic imides, isoxazole and

chacones from last two decades by virtue of their effective nature towards disease causing microorganism. This effective nature of these compounds bring core assiduity for chemist, pharmacist and researchers all over the globe. Cyclic imides act as precursors for many heterocyclic compounds such as pthalimide, 1, 8-naphthalimide and diphenimide etc. Cyclic imides and their derivatives brought much attention to chemist and pharmacist in the field of research and development, they have used as antibacterial[1] ,nerve conduction blocking[2], analgesic[3], antitumor[4], muscle relaxant[5], hypotensive[6] and antitubercular agents[7].

Chalcones are aromatic ketones as well as enones which are essential biological active compounds. They are inclusively accepted as chaconnes or chalconoids and are found in edible plants and their derivatives act as building block for many important heterocycles such as flavones, pyrrozoline and benzothiazepine etc. They exhibit comprehensive variety of pharmacological features such as anti-bacterial[8], anti-fungal[9] anti-cancer[10], anti-malerial[11] anti-oxidant[12], anti-inflammatory[13], anti-ulcer[14], anti-tumor[15], anti-bacterial[16], chaconnes also act as vase relaxant agent[17] and tyrosine inhibitors[18].

Isoxazole is heterocyclic organic compound also referred as azole having 3 carbon atoms with 1 oxygen and 1 nitrogen atom adjacent to each other. It is found in some natural products such as ibotenic acid which is a chemical compound and referred as psychoactive drug[19-20]. It is one of important heterocyclic compound which is known to synthesized some unique drugs like C0-x-2 inhibitor valdecoxide[21] (Bextra) and a neurotransmitter agonist AMPA[22]. There are some antibiotics which contain isoxazolyl group such as dicloxacillin and flucloxacillin.

In the field of heterocyclic chemistry isoxazole and their derivatives widely playing important role for synthesizing contemporary drugs and draw attention of organic chemist, their moieties are base for number of crucial drugs like anti-cancer, anti-tumor etc. It shows the wide spectrum of pharmacological and biological activities such as Muscle relexant[23], anti-convulsant[24], anti-inflammation[25], anti-tuberculer[26], analgesic[27], anti-anxiety[28], anti-bacterial[29], anti-viral[30], anti-cancer[31] etc. In view of the important of heterocyclic compounds. In previous work we have synthesized cyclic imides using selective aniline[32-36] (2,6 dichloro 4 trifluoro methyl aniline).In present work we have focused to synthesize some novel bis chalcones and bis-isoxazole using cyclic imides with the hope of good microbial activity of synthesized compound to get.

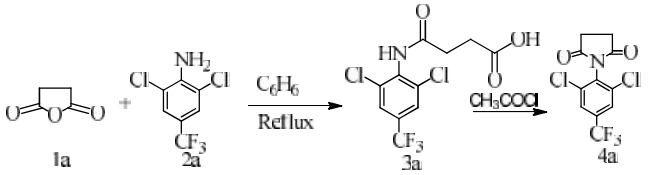
2. Materials and Methods

Entire chemicals utilized for synthesized compounds are chemically classic, melting points were driven in open capillary method and were found uncorrected. FTIR spectra are recorded on Perkin-Elmer spectrum. H^1NMR spectra are recorded on Bruker DRX 500 MHz NMR spectrometer with DMSO-d^6 solvent and TMS used as internal reference (chemical shift in δ ppm) these all newly synthesized compounds were formed according to following scheme1, 2 and 3.

1. Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione:

Succinic anhydride (0.01mol) was dissolved in benzene (10ml) then 2, 6-dichloro-4-trifluoromethyl aniline (0.01mol) was added to it vigorously hence 4-((2, 6-dichloro-4-(trifluoromethyl) phenyl) amino)-4-oxobutanoic acid was formed. This acid was cyclized by using (0.09) mole of fresh acetyl chloride at reflux conditions. The product (4a) was obtained and recrystallized from methanol.

1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a): M.F: $C_{11}H_6Cl_2F_3N$, M.W: 312, Yield 90%, M.P.165-167°C, C, H, N Elem. Anal. Calculated: C, 38.34; H, 1.94; N, 4.49. Obtained: C, 38.24; H, 1.83; N, 4.34.

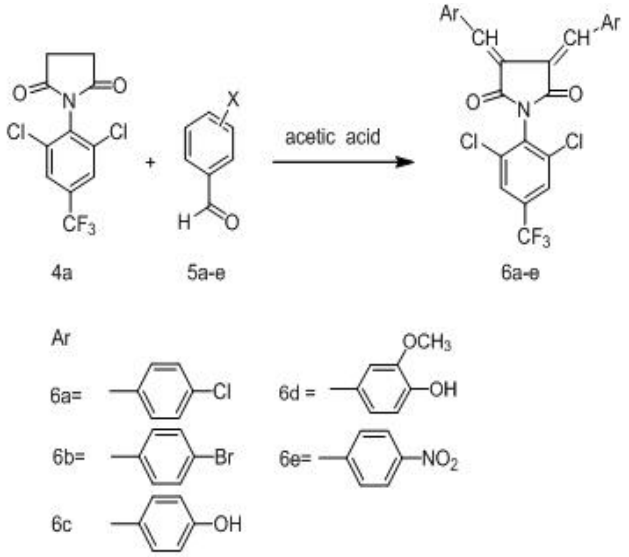


Scheme I

IR (KBr) cm^{-1}: 2900-3000 cm^{-1} (CH_2), 1650-1700 cm^{-1} (C=O), 1470-1500 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (C-N).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 2.5 (s, 4H), 7.7 (s, 2H, Ar-H).

2. Synthesis derivatives of chalcones (6a-e): Cyclic imide 1-(2,6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2,5 dione (0.01 mol) and aromatic aldehyde (5a-e) (0.02 mol) was dissolved in glacial acetic acid (8 ml) and then concentrated on sand bath maintaining low flame. The colorless solid product was obtained (6a-e) and recrystallized from ethanol.



Scheme 2

i) (3E,4E)-3,4-bis(4-chlorobenzylidene)-1-(2,6-dichloro-4- (trifluoromethyl)phenyl)pyrrolidine-2,5-dione (6a):

M.F: $C_{25}H_{12}Cl_4F_3NO_2$, M.W: 554, Yield 91%, M.P. 161-163°C, C, H, N Elem. Anal. Calculated: C, 53.89; H, 2.17; N, 2.51. Obtained: C, 53.59; H, 2.11; N, 2.57.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.08 (s, 2H, C=CH-Ar), 7.70 (s, 2H, Ar-H), 7.68 (dd, 8H, 2Ar-H).

ii) (3E, 4E)-3, 4-bis (4-bromobenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6b): M.F: $C_{25}H_{12}Br_2Cl_2F_3NO_2$, M.W: 646, Yield 90%, M.P. 191-193°C, C, H, N Elem. Anal. Calculated: C, 46.48; H, 1.87; N, 2.17.Obtained: C, 46.40; H, 1.83; N, 2.47.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.01 (s, 2H, 2C=CH-Ar), 7.9 (s, 2H, Ar-H), 7.5-7.8 (8H dd 2Ar-H).

iii) (3E, 4E)-3, 4-bis (4-hydroxybenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6c): M.F: $C_{25}H_{14}Cl_2F_3NO_4$, M.W: 520, Yield 92%, M.P. 120-122°C, C, H, N Elem. Anal. Calculated: C, 57.71; H, 2.71; N, 2.69. Obtained: C, 57.68; H, 2.69; N, 2.67. IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH) **H^1 NMR (500 MHz, DMSO-d^6 δ ppm):** 7.75 (s, 2H, 2C=CH-Ar), 7.77 (s, 2H, Ar-H), 6.9-8.008 (dd, 8H, 2Ar-H), 9.7 (s, 1H, Ar-O-H).

iv) (3E, 4E)-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3,4-bis(4-hydroxy-3-methoxybenzylidene)pyrrolidine-2, 5-dione (6d): M.F: $C_{27}H_{18}Cl_2F_3NO_6$, M.W: 580, Yield 94%, M.P. 91-93°C. C, H, N Elem. Anal. Calculated: C, 55.88; H, 3.13; N, 2.41. Obtained: C, 58.86; H, 3.10; N, 2.43.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 3200-3550 cm^{-1} (Ar-OH), 1000-1300 cm^{-1} (O-CH_3), 3300 cm^{-1} (C-H).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 8.008 (s, 2H, 2C=CH-Ar), 7.4 (s, 2H, Ar-H), 6.9-7.4(6H s 2Ar-H), 9.7 (s, 1H, Ar-O-H), 3.85 (s, 3H OCH_3).

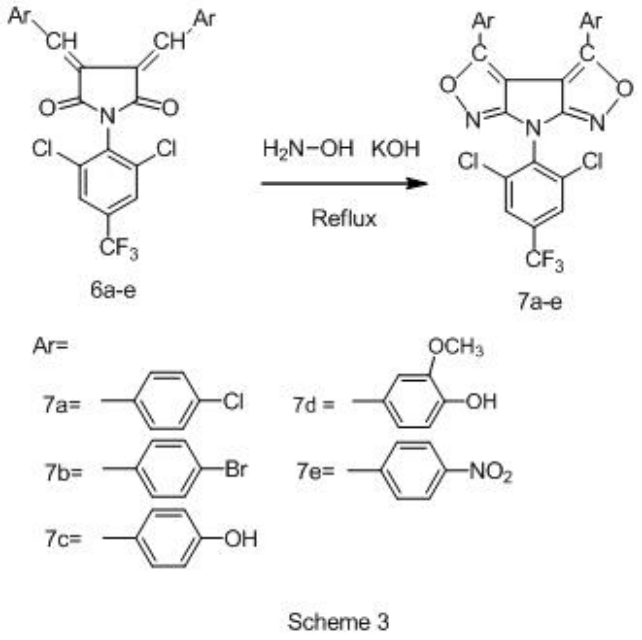
v) (3E, 4E)-3, 4-bis (4-nitrobenzylidene)-1-(2, 6-dichloro-4-(trifluoromethyl) phenyl) pyrrolidine-2, 5-dione (6e): M.F: $C_{25}H_{12}Cl_2F_3N_3O_6$, MF: 578, Yield 89%, M.P. 141-143°C, C, H, N Elem. Anal. Calculated: C, 51.92; H, 2.09; N, 7.27. Obtained: C, 51.90; H, 2.1; N, 7.30.

IR (KBr) cm^{-1}: 3010-3050 cm^{-1} (C=C-H), 1520-1630 cm^{-1} (C=C), 1650-1700 cm^{-1} (C=O), 1425-1600 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (N-C=O), 1550-1600 cm^{-1} (N=O).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.99 (s, 2H, 2C=CH-Ar), 8.17(s, 2H, Ar-H), 8.1-8.4 (dd, 8H, 2Ar-H).

3. Synthesis derivatives of Isoxazole:

Chalcones derivatives (4a-e) (0.01mol) was dissolved to ethanol (8 ml) then hydroxyl amine hydrochloride (0.02 mol) was added. The mixture was refluxed for next 16 hours with maintaining 80° to 90° C .The off white solid compounds (6a-e) obtained and recrystallized from benzene.



Scheme 3

i.3,4-bis(4-chlorophenyl)-7-(2,6-dichloro-4-(trifluoro methyl)phenyl)-7H-pyrrolo[2,3-c:5,4-c']diisoxazole (7a) M.F: $C_{25}H_{10}Cl_4F_3N_3O_2$, M.W: 588, Yield 65%, M.P. 181-183°C, C, H, N Elem. Anal. Calculated C, 51.49; H, 1.73; N, 7.21. Obtained: C, 51.43; H, 1.76; N, 7.25.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.8 (s, 2H, Ar-H), 7.5-7.9 (dd, 8H, 2Ar-H).

ii)3,4-bis(4-bromophenyl)-7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-c:5,4-c']diisoxazole(7b): $C_{25}H_{10}Br_2Cl_2F_3N_3O_2$, M.W: 672, Yield 66%, M.P. 178-180°C, C, H, N Elem. Anal. Calculated: C, 44.68; H, 1.50; N, 6.25. Obtained: C, 44.64; H, 1.52; N, 6.29.

IR (KBr) cm^{-1}: 3300-3400 cm^{-1} (N-H), 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.8 (s, 2H, Ar-H), 7.5-7.7 (dd, 8H, 2Ar-H).

iii) 4,4'-(7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-c:5,4-c']diisoxazole-3,4-diyl)diphenol(7c): $C_{25}H_{12}Cl_2F_3N_3O_4$, M.W: 545, Yield 66%, M.P. 118-120°C, C, H, N Elem. Anal. Calculated: C, 59.97; H, 2.21; N, 7.69. Obtained: C, 59.93; H, 2.24; N, 7.98.

IR (KBr) cm^{-1}: 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.3-7.8 (s, 2H, Ar-H), 7.5-7.7 (dd, 8H, 2Ar-H) 5.1-6.2 (s 1H, Ar-O-H).

iv) 4,4'-(7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-7H-pyrrolo[2,3-c:5,4-c']diisoxazole-3,4-diyl)bis(2-methoxyphenol)(7d): M.F: $C_{27}H_{16}Cl_2F_3N_3O_6$, M.W: 606, Yield 70%, M.P. 198-200°C, C, H, N Elem. Anal. Calculated: C, 53.48; H, 2.66; N, 6.93. Obtained: C, 53.44; H, 2.62; N, 6.89.**IR (KBr) cm^{-1}:** 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C).

H^1 NMR (500 MHz, DMSO-d^6 δ ppm): 7.8 (s 2H, Ar-H), 7.5-7.7 (s, 2H, dd, 4H, 2Ar-H) 9.8 (s 1H, Ar-O-H), 3.8 (s, 3H, O-CH_3).

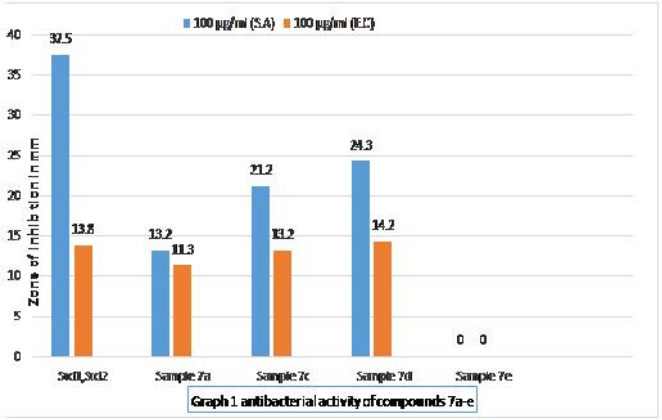
v) 7-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3,4-bis(4-nitrophenyl)-7H-pyrrolo[2,3-c:5,4-c']diisoxazole(7e):
M.F: $C_{25}H_{10}Cl_2F_3N_5O_6$, M.W:604 Yield 80%, M.P. 96-98°C, C, H, N Elem. Anal. Calculated: C, 49.69; H, 1.67; N, 11.59. Obtained: C, 49.61; H, 1.69; N, 11.55. **IR (KBr) cm^{-1}:** 1520-1630 cm^{-1} (C=C), 1000-1250 cm^{-1} (C-N), 1425-1600 cm^{-1} (ArC=C). **H^1 NMR (500 MHz, DMSO-d^6 δ ppm):** 7.3-7.8 (s, 2H, Ar-H), 8.0-8.2 (dd, 8H, 2Ar-H).

3. Results and Discussions

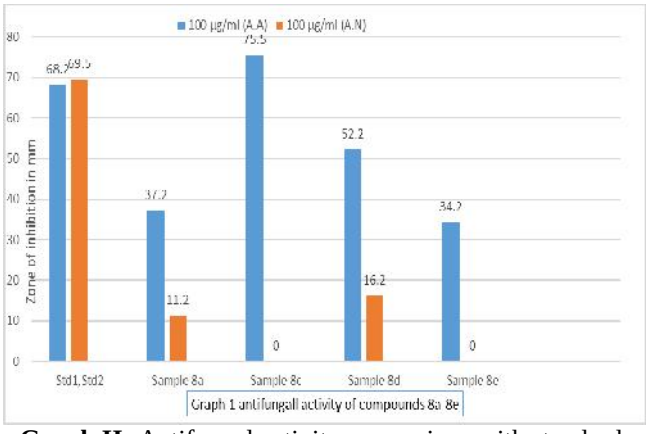
We have successfully synthesized some novel 3,4-bis(substituted-phenyl)-7-(2,6- dichloro-4-(trifluoromethyl) phenyl)-7H-pyrrolo[2,3-c:5,4- c']diisoxazoles (7a-e) from 2, 6- dichloro-4-trifluoro methyl aniline. In starting phase we have synthesized cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2 and then from this cyclic imide we have prepared various chalcone (6a-e) using multifarious substituted benzaldehyde (5a-e). All these chalcones (6a-e) were cyclized by hydroxylamine hydrochloride afforded bis-isoxazole (7a-e). These all novel synthesized compounds were characterized by spectral analysis technique (H^{1}NMR and FTIR) and compounds (7a-e) were screened for their biological evaluation.

Biological Activity

All the synthesized compounds (7a-e) were screened for their in vitro antimicrobial activity against bacteria and fungi such as *Staphylococcus aurreus*, *Escherichia coli*, *Alternaria altarnata*, *Aspergilus Niger* respectively. Stock solution (100 microgram per ml) of each compound prepared in DMSO solvent. Similarly stock solution of standard drug ciprofloxacin used for antibacterial activity and terbinafine used for antifungal activity have been prepared. Microbiological media used for bacteria is nutrient agar (Hi media) and potato dextrose agar (Hi-media) for fungi. Concentration 100µg/ml per well poured as per well diffusion method and incubated for 24 hours at 37ºC after incubation the results were obtained, where the compounds showed activity there was zone of inhibition occurred, similarly for fungi stock solution 100µg/ml per well poured as per well diffusion method and incubated for next seven days at 29ºC after seven days results noted. The diameter of zone of inhibition where measured by Vernier Caliper in mm and tabulated in table I



Graph I: Graphical comparison of antimicrobial activity



Graph II: Antifungal activity comparison with standard drug

4. Conclusion

An entire new series of compounds are synthesized and confirmed by H^{1}NMR and FTIR spectroscopy and elemental analysis. Compounds (7a-e) are evaluated in vitro for antimicrobial activity. Compound 7a, 7c and 7d showed moderate activity against *Staphylococcus aureus* and good activity against *Escherichia coli.* All these compounds (7a-e) are showed good activity against *Alternaria altarnata* but only compounds 7a and 7d showed moderate activity against *Aspergilus Niger.*

Table 1: Antimicrobial activity of compounds 7a-e

S.No.	Sample Code	*S. aureus*	*E. coli*	*A. altarnata*	*A.niger*
1	7a	13.2	11.3	37.2	11.2
2	7c	21.2	13.2	75.5	-
3	7d	24.3	14.2	52.6	16.3
4	7e	-	-	34.2	-
5	Ciprofloxacin	37.5	13.8	NA	NA
6	Terbinafine	NA	NA	68.2	69.5
7	DMSO (control)	-	-	-	-

Keyword' –'means no zone of inhibition, NA means not applicable

5. Acknowledgement

Authors thank to UGC-MANF, New Delhi (award letter: F1-17.1/2013-14 MUS-MAH-25825/ (SA-III/Website) dated 06-Feb-2014) for financial support, authors are thankful to university of Pune for providing spectral analysis facilities. Authors are also thankful to department of Chemistry and department of Microbiology of

PSGVPM'S ASC College, Shahada for providing research laboratory facility and microbial screening facility.

6. References

[1] SS Rajput, RM Sayyed. Synthesis and formylation of cyclic imides using Vilsmeire-Haack reaction from 2, 6 dichloro-4-triflouromethyl aniline and their anti-microbial activity. World Journal of Pharmaceutical Research, 2015, 12: 1689-1695.

[2] RS Dhivare, SS Rajput. Synthesis and antimicrobial evauation of some novel bis-heterocyclic chalcones from cyclic imides under microwave irradiation. Chemical Science Review and letter, 2015, 4(15): 937-944.

[3] MM Patil, SS Rajput. Succinimides synthesis and biological activity. International Journal of Pharmacy and Pharmaceutical Sciences, 2014, 11: 0975-1491.

[4] JH Mansoory, SS Rajput. Synthesis, characterization and biological evaluation of some novel Schiff's bases from Halovinyl aldehyde and 4- amino-5(pyridine-4-yl)-4H-1, 2, 4-triazole-3-thiol.Der Pharma Chemica, 2015, 7(10): 510-14.

[5] DL Musso, FR Cochran, JL Kelley, EW McLean, JL Selph, GC Rigdon, et al. Design and synthesis of (E)-2-(4,6-Difluoro-1-indanylidene) acetamide, a potent, centrally acting muscle relaxant with anti-inflammatory and analgesic activity.J Med Chem, 2003, 46 (3): 399-408.

[6] FC Pennington, PA Guercio, IA Solomons. The antihypertensive effect of a selective central muscarinic cholinergic antagonist: N-(4-diethylamino-2-butynyl)-succinimide. J. Am Chem Soc, 1953, 75(9): 2261-1.

[7] M Isaka, W Prathumpai, P Wongsa, M Tanticharoen. Hirsutellone F. A dimer of antitubercular alkaloids from the seed fungus Trichoderma species BCC 7579. Org Lett, 2006, 8(13):2815-7.

[8] XL Liu, YJ Xu, ML Go. Functionalized chalcones with basic functionalities have antibacterial activity against drug sensitive Staphylococcus Aureus. European Journal of Medicinal Chemistry, 2008, 43: 681-1687.

[9] KL Lahtchev, DI Batovska, SP Parushev, VM Ubiyvovk, AA Sibirny. Antifungal activity of chalcones: A mechanistic study using various yeast strains. European Journal of Medicinal Chemistry, 2008, 43: 2220-2228.

[10] M Dekarshi, K Bharti, K Sanjay, A vivek. Anticancer Chalcones: Structral and molecular target perspectives" European journal of medical chemistry, 2015, 98: 69-114.

[11] VJ Ram, A Saxena, S Srivastava, S Chandra. Oxygenated chalcones and bischalcones as potential antimalarial agents. Bioorganic & Medicinal Chemistry Letters, 2000, 10: 2159-2161.

[12] A Detsi, M Maya, AK Christos, HL Dimitra, K Panagiotis. Natural and synthetic 20-hydroxy-chalcones and aurones: Synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity. Bioorganic & Medicinal Chemistry, 2009, 17: 8073–8085.

[13] SN Bukhari, I Jantan, M Jasamai. Anti-inflammatory trends of 1, 3-Diphenyl-2-propen-1-one derivatives. Mini-Rev. Med. Chem, 2013, 13: 87–94.

[14] JA Jeffrey, EO Pamela, LR Jared, NJ Jeffrey, DM Peter, MO Linda, SW Pamela, and Beth LE. Synthesis and biological e valuation of flavonoids and related compounds a s gastro-protective agents. Bioorganic & Medic inal Chemistry Letters, 1996, 6 (8): 995-998.

[15] YK Rao, SH Fang, YM Tzeng. Synthesis and biological evaluation of 3,4,5-trimethoxychalcon e analogues as inhibitors of nitric oxide production and tumor cell proliferation. Bioorganic & Medicinal Chemistry, 2009, 17:79 09–7914.

[16] DB Dragana, Marina Milenkovic, B Ivkovic, I Cirkovic. Antibacterial activity of three newly-synthesized chalcones and synergism with antibiotics against clinical isolates of methicillin-resistant Staphylococcus aureus. Indian. J Med Res 140, 2014, pp 130-137.

[17] X Dong, J Chen, C Jiang, T Liu, Y Hu. Design, synthesis, and biological evaluation of prenylated chalcones as vasorelaxant agents. Arch Pharm (Weinheim), 2009, 342(7):428-32.

[18] S Khatib, O Nerya, R Musa, M Shmuel, S Tamir, J Vaya. Chalcones as potent tyrosinase inhibitors: the importance of a 2, 4-substituted resorcinol moiety. Bioorganic & Medicinal Chemistry, 2005, 13: 433-441.

[19] Tommy Liljefors; Povl Krogsgaard-larsen; Ulf Madsen.Textbook of Drug design and discovery, Third Edition.CRC Press. 2002, pp.263-ISBN 978-0-415-28288-8.

[20] A Becker,G Grecksch, HG Bernstein, V Hollt, B Bogerts. Social behavior in rats lesioned with ibotenic acid in the hippocampus: quantitative analysis". Psychopharmacology, 1999, 144 (4): 333-8.

[21] K Prafulla, KR Sahu, M.Mathrusri Annapurna. Determination of Veldecoxib in human plasma using Reverse Phase HPLC, E-Journal of Chemistry, 2011, 8(2): 875-881.

[22] Zoltewicz J.A, Deady L.W. Quaternization of heteroaromatic compounds. Quantative aspects. Adv. Heterocycl. Chem. (1978).22, 71-121.

[23] T Tatee, S Kurashige, A Shiozawa, K Narita, M Takei. Isoxazole derivatives as centrally acting muscle relaxants. I. Synthesis and activity of 5-(3-aminopropyl) amino-3-phenylisoxazole

derivatives. Chemical & pharmaceutical bulletin, 1986, 34(4): 1634-42.

[24] Hemlata Kaur, Sunil Kumar and Ashok Kumar; Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/ isoxazolinylindol-2-ones; International Journal of Chem Tech Research, April-June 2010, 2(2): 1010-1019.

[25] SA El-Hawash, R Soliman, AM Youssef, HM Ragab, PA Elzahhar, IM El-Ashmawey, AE Abdel Wahab, Shaatl. Design, synthesis and biological screening of some pyridinylpyrazole and pyridinylisoxazole derivatives as potential anti-inflammatory, analgesic, antipyretic and antimicrobial agents. Med.Chem, 2014, 10(3): 318-38.

[26] Khanage et al. Synthesis and pharmacological evaluation of isoxazole derivatives containing 1, 2, 4-triazole Moiety. Marmara Pharm J, 2012; 16: 134-140.

[27] Mastan. M et al. Synthesis and evaluation of analgesic activity of novel series of Indole derivatives linked to isoxazole moiety. Der Pharmacia Lettre, 2012; 4(5): 1431-1437.

[28] DS Garvey, JT Wasicak, MW Decker, JD Brioni, MJ Buckley, JP Sullivan, GM Carrera , MW Holladay, SP Arneric, M Williams. Novel isoxazole which interact with brain cholinergic channel receptors have intrinsic cognitive enhancing and antianxiety activities. J.Med. Chem, 1994, 37: 1055-59.

[29] G Mohamed. Badrey, M Sobhi, Gomha. Synthesis and antibacterial activity of fused isoxazole derivatives using grinding method. Int J Pharm Pharm Sci, 6(7): 236-239.

[30] Artemenko et al, QSAR analysis of [(biphenyloxy) propyl] isoxazoles: agents against coxsackievirus B3. Future Med. Chem, 2011: 3(1): 15–27.

[31] R.M. Kumbhare et al. Synthesis and biological evaluation of novel triazoles and isoxazoles linked 2-phenyl benzothiazole as potential anticancer agents. Bioorganic & Medicinal Chemistry Letters, 2012, 22: 5424–5427.

[32] SS Rajput, RM Sayyed. Synthesis and formylation of cyclic imides using Vilsmeire-Haack reaction from 2,6 dichloro-4-triflouro methyl aniline and their anti-microbial activity.Wourld Journal of Pharmaceutical Research., 2015, 12: 1689-1695.

[33] R Shimajawa, H Takayama, F Kato, M Kato, Y Hashimoto. Non-peptide small-molecular inhibitors of dipeptidyl peptidase IV: N-phenylphthalimide analogs. Bioorg Med chem lett, 1999, 9: 559-69.

[34] Tomlin CDS. The Pesticide Manual. England Hampshire; 14th ed.; British Crop Protection Council, 2006, 462-464.

[35] A Aajoud, P Ravanel, M Tissut. Fipronil metabolism and dissipation in a simplified aquatic ecosystem. J. Agric. Food. Chem., 2003, 51: 1347-1352.

[36] D Hainzl, GE Casida. Fipronil insecticide: novel photochemical desulfinylation with retention of neurotoxicity. Proc. Natl. Acad. Sci, 1996, 93: 12764-12767.