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EFFICIENT, MICROWAVE ASSISTED SYNTHESIS OF 4-(substituted fluoro-phenyl)-substituted-*6H*-1-thia-5, 7, 8, 9a -tetraaza-cyclopenta[*e*]azulenes And Their MICROBIAL ACTIVITY

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ABSTRACT

Organic compounds having heterocyclic ring and fluorine atom are most widely studied in the last decade. Present work focus on the synthesize of 4-(substituted fluoro-phenyl)-substituted-6*H*-1-thia-5,7,8,9a-tetraaza-cyclopenta[*e*]azulenes using microwave irradiation technique. Reported ten derivatives were efficiently synthesized using (2-Amino-5-substituted-thiophen-3-yl)-(fluoro-phenyl)-methanone and (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid. This microwave assisted synthetic protocol is interestingly rapid with good percent yield. Synthesized compounds were screened for microbial activity and 50% of them found good active against tested microorganisms.

Keywords: Microwave assisted, T3P, Hydrazine, Carboxylic acid hydrazide, DMF, Microbial activity

INTRODUCTION:

Heterocycles are most important and powerful building blocks for number of pharmaceutical candidates[1]. Deep literature survey on the heterocyclic compound revels that the hydrophilic and lipophilic characters of hetero atoms provide greater importance to heterocycles in pharmacy sector.

The compounds of thiophenes are widely used intermediate for the synthesis of number of compounds with huge biological importance. Thiophene derivatives are most potent pharmaceutically important and showing various type of bioactivities such as anticancer[2,3,4,5], antimycobacterial activity[6], antimicrobial activity[7], anti-inflammatory activity[8], anticonvulsant activity[9], Cardiovascular activity[10].

Different triazole derivatives are also showing broad range of biological activities, out of that the triazole and its different derivatives, are well known as anti-cancer[11], anti-inflammatory[12], antiviral activity[13], antitubercular[14], antileishmanial and antitrypanosomal activity[15], antimicrobial activity[16], antibacterial activity[17], miscellaneous agents[18].

Fused and multi-cyclic derivatives of heterocycles show important biological activities such as anticonvulsant[19,20], antifilarial[21], Anticancer[22], antidibetic[23], CNS depressant[24], analgesic[25], antifungal and antibacterial[26], antihelmintic and antitumoral[27]. Chemists working on organic synthesis, were reported various synthetic roadmaps for the synthesis of heterocycles such as non metal and metal catalysis[28]. Green techniques were also used for the synthesis of triazoles such as microwave irradiated synthesis[29], solvent free synthesis[30,31], grindstone chemistry[32], ultra sound chemistry, one pot multicomponent synthesis[33,34,35].

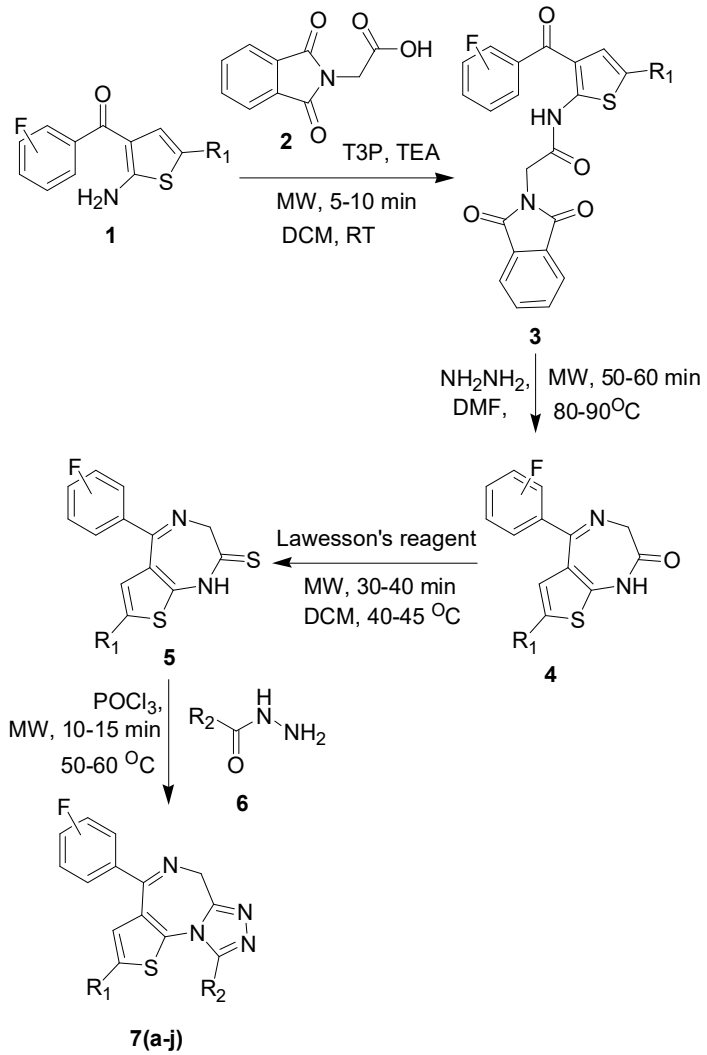
The compounds incorporated with multi heterocycles may possess various biological activities due to multiple heteroatom's and various ring size incorporated with them. In the present study, here we reported synthesis of multi heterocyclic compounds having azulenes, triazole and thiophene rings containing compounds. We are screened the synthesized compounds for their microbial activities and found some compounds were potent active against tested microorganism compared with standards.

Results and Dicussion:

In the present work we have synthesize 4-(substituted fluoro-phenyl)-substituted-6*H*-1-thia-5,7,8,9a-tetraaza-cyclopenta[*e*]azulene derivatives **7(a-j)** using

(2-Amino-5-substituted-thiophen-3-yl)-(substituted-fluoro-phenyl)-methanone **1** and (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid **2** with the help of microwave irradiation technique.

Initially equimolar solution of (2-Amino-5-substituted-thiophen-3-yl)-(substituted-fluoro-phenyl)-methanone **1** and (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid **2** in DCM were reacted in presence of amide coupling agent T3P (3%) and triethyl amine catalyst in microwave at RT for 5-10 min. to form intermediate 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[3-(fluoro-benzoyl)-5-substituted-thiophen-2-yl]-acetamide **3** with 50-60 % of isolated yield.



Scheme 1:- Synthesis of 7a-j using microwave irradiation

Compound 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[3-(fluoro-benzoyl)-5-substituted -thiophen-2-yl]-acetamide **3** were irradiated with excess of hydrazine hydrate

and DMF in microwave at 80-90 ^{O}C for 50-60 min to afford compounds 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepin-2-one **4** with 74-80 % of isolated yield.

Microwave irradiation of 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepin-2-one **4** with Lawessons reagent in DCM at 40-45 ^{O}C afford compounds 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepine-2-thione **5** with 74-80 % of isolated yield. Finally equimolar solution of 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepine-2-thione **5** and substituted acid hydrazide **6** were reacted in presence of $POCl_3$ in microwave at 90-95 ^{O}C for different time interval. After completion reaction mass were quenched with ice cold water and neutralized with saturated sodium bicarbonate solution resultant solids were filtered out washed with excess of water. Obtained crude were purified by flash chromatography (Eluting with 10 EA : Hex.) to afford compounds 4-(substituted fluoro-phenyl)-substituted-6*H*-1-thia-5,7,8,9a-tetraaza-cyclopenta[*e*]azulene derivatives **7(a-j)** (Scheme 1) with 80-89 % of isolated yield (Table 1).

Synthesized compounds were confirmed by NMR techniques. NMR was taken at 100 MHz in DMSO and chemical shift reported in δ ppm.

Micro broth dilution method was used for the screening of microbial activities of the synthesized compounds. Anti bacterial activity of the compounds were tested against two gram positive and two gram negative bacteria while antifungal activity against three different fungal spores. Anti bacterial activity was compared with standards drugs like Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin and Norfloxacin while anti fungal activity of the synthesized compounds were compared with Nystatin and Greseofulvin as standards (Table 2).

Table 1: Microwave assisted synthesis of 4-(substituted fluoro-phenyl)-substituted-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulenes.

Entry	F	R_1	R_2	Time (min.)	(%) Yield[a]	M. p. ^{O}C[b]
7a	2-F	$-CH_3$	$-CH_3$	5	88	185-187
7b	2-F	$-CH_3$	$-C_2H_5$	5	86	201-205
7c	2-F	$-CH_3$	$-C_6H_5$	5	88	228-231
7d	2-F	$-C_2H_5$	$-CH_3$	10	89	191-194
7e	2-F	$-C_2H_5$	$-C_2H_5$	5	80	230-233
7f	2-F	$-C_2H_5$	$-C_6H_5$	5	89	269-271
7g	4-F	$-CH_3$	$-CH_3$	15	86	220-222
7h	4-F	$-CH_3$	$-C_2H_5$	15	85	241-244

7i	4-F	$-CH_3$	$-C_6H_5$	15	89	180
7j	4-F	$-C_2H_5$	$-CH_3$	5	82	178-180

[a]Isolated yield, [b]Melting point.

Table 2: In Vitro anti-microbial activities of the synthesized compounds 7a-e

Entry	Minimal inhibition concentration (µg mL^{-1})						
	Bacterial species				Fungal species		
	Gram-positive		Gram-negative				
	S. a.	*S. p.*	*E. c.*	*P. a.*	*C. a.*	*A. n.*	*A. c.*
7a	50	100	100	50	100	500	100
7b	250	60.2	50	250	500	100	200
7c	50	50	100	100	900	100	100
7d	50	100	55	100	100	250	500
7e	10	50	500	450	500	100	100
Gentamycin	0.25	0.5	0.05	1	--	--	--
Ampicilin	250	100	100	100	--	--	--
Chloramphenicol	50	50	50	50	--	--	--
Ciprofloxacin	50	50	25	25	--	--	--
Norfloxacin	10	10	10	10	--	--	--
Nystatin	--	--	--	--	100	100	100
Greseofulvin	--	--	--	--	500	100	100

S. a. = Staphylococcus aureus, S. p. = Streptococcus pyogenus,
E. c. = Escherichia coli, P. a = Pseudomonas aeruginosa,
C. a. = Candida albicans, A. n. = Aspergillus niger, A. c. = Aspergillus clavatus.

Antibacterial activity of the synthesized compounds

Synthesized compounds **7a-j** was evaluated for their in vitro anti microbial activity against two gram positive *S. Aureus* and *S. pyogenus* and two gram negative *E. Coli* and *P. aeruginosa* bacteria and only compound **7a-e** was found potent active.

From screening data, some of them possessed excellent antibacterial activity compared with standard drugs Ampicilin entry **7b** active against gram positive *S. aureus,* compounds **7a, 7c,** and **7d** active against *S. aureus* compared with standard Chloramphenicol or Ciprofloxacin. **7a** and **7d** were active against *S. Pyogenus* compared with Ampicilin while **7c** and **7e** compared with Chloramphenicol or Ciprofloxacin. The entry **7a** and **7c** were potent active against gram negative *E. coli* bacteria compared with Ampicilin. The compounds active against *P. Aeruginosa* such as **7c** and **7d** compared with Ampicilin and **7a** compared with Chloramphenicol (Table 2).

Antifungal activity of the synthesized compounds

Three fungal species like *C. Albicans. A. niger* and *A. clavatus* were used for in vitro antifungal activity, and Nystatin and Greseofulvin as standard drugs. Synthesized compounds found to potent antifungal such as compound **7b** and **7e** comparing with Greseofulvin against *Candida albicans*, compound **7a** active against *Candida*

albicans compared with Nystatin. **E**ntry **7b**, **7c**, **7e** are showing good activity against *Aspergillus niger* compared with both the standards Greseofulvin and Nystatin. Compound **7a**, **7c** and **7e** are found very good antifungal activity against *Aspergillus clavatus* compared with the standard Greseofulvin and Nystatin (Table 2).

Experimental:

General

All reactions were performed in electric oven–dried glassware under atmospheric pressure. All the starting reagents, material, and solvents used were of analytical grade (AR) and used as it is received. Melting point of the synthesized compounds was taken on a precision melting point apparatus (DBK instrument), and all are uncorrected. ^{1}H NMR and ^{13}C spectra were recorded in DMSO solvent on a Bruker spectrometer at 100MHz spectrometer. A mass spectrum was recorded on a Waters ZQ-4000 spectrometer. Microwave were used for irradiation is of make 'Catalyst microwave synthesizer'. The yield of the synthesized compounds mentioned is for isolated product. Progress of the reaction was checked by pre coated TLC on silica gel plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine and UV chamber.

General procedure for synthesis of 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[3-(fluoro-benzoyl)-5-substituted-thiophen-2-yl]-acetamide 3:

An equimolar amount of (2-Amino-5-substituted-thiophen-3-yl)-(substituted-fluoro-phenyl)-methanone **1** and (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid **2** were reacted in presence of amide coupling agent T3P (3%), catalytic triethyl amine and 10 volume of dry DCM solvent in microwave tube at RT for 5-10 min. The progress of reaction were monitor on TLC (5% MeOH : DCM) and after completion reaction mass were quenched with ice cold water and extracted with DCM two times and organic layer dried over sodium sulphate and concentrate to afford compounds 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[3-(fluoro-benzoyl)-5-substituted-thiophen-2-yl]-acetamide **3** with 50-60 % of isolated yield.

General procedure for synthesis of 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepin-2-one 4:

1 equivalent of 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-N-[3-(fluoro-benzoyl)-5-substituted-thiophen-2-yl]-acetamide **3** were irradiated with 2

equivalent hydrazine hydrate and 10 volume of DMF in microwave tube at 80-90 ^{O}C for 50-60 min. The progress of reaction were monitor on TLC (30% EA : Hex) and after completion reaction mass were quenched with ice cold water and extracted with EtOAC two times and organic layer dried over sodium sulphate and concentrate to afford compounds 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepin-2-one **4** with 74-80 % of isolated yield.

General procedure for synthesis of 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepine-2-thione 5:

7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepin-2-one **4** (1 equiv.) were irradiated with Lawessons reagent (2 equiv.) and 10 volume of DCM in microwave tube at 40-45 ^{O}C for 30-40 min. The progress of reaction were monitor on TLC (10% EA : Hex) and after completion reaction mass were quenched with ice cold water and neutralized with saturated sodium bicarbonate solution resultant solids were filtered out washed with excess of water to afford compounds 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepine-2-thione **5** with 74-80 % of isolated yield.

General procedure for synthesis of 4-(substituted fluoro-phenyl)-substituted-6*H*-1-thia-5,7,8,9a-tetraaza-cyclopenta[*e*]azulene derivatives 7(a-j):

Equimolar amount of 7-substituted-5-phenyl-1,3-dihydro-thieno[2,3-e][1,4]diazepine-2-thione **5** and substituted acid hydrazide **6** were reacted in presence of $POCl_3$ in microwave tube at 90-95 ^{O}C for 50-60 min. The progress of reaction were monitor on TLC (20% EA : Hex) and after completion reaction mass were quenched with ice cold water and neutralized with saturated sodium bicarbonate solution resultant solids were filtered out washed with excess of water. Obtained crude were purified by flash chromatography (Eluting with 10 EA : Hex.) to afford compounds 4-(substituted fluoro-phenyl)-substituted-6*H*-1-thia-5,7,8,9a-tetraaza-cyclopenta[*e*]azulene derivatives **7(a-j)** with 80-89 % of isolated yield.

Spectral Data

4-(2-Fluoro-phenyl)-2,9-dimethyl-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulene (**7a**).

^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, -CH_3), 2.70 (s, 3H, -CH_3), 4.60 (s, 1H, -CH_2), 6.51 (s, 1H, Ar-H), 7.12 (d, 1H, Ar-H), 7.20 (dd, 1H, Ar-H), 7.43 (dd, 1H, Ar-H), 7.57 (d, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 16.80, 23.61, 42.28, 115.60, 123.30, 124.24, 124.03, 125.21, 127.12, 130.36, 132.56, 139.55, 160.02, 160.88, 162.62, 164.66.

9-Ethyl-4-(2-fluoro-phenyl)-2-methyl-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulene **(7b).**

^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 1.48 (t, 3H, -CH_3), 2.81 (s, 3H, -CH_3), 2.99 (q, 2H, -CH_2), 4.41 (s, 1H, -CH_2), 6.56 (s, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 7.20 (dd, 1H, Ar-H), 7.52 (dd, 1H, Ar-H), 7.54 (d, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 18.10, 17.78, 20.32, 42.18, 115.60, 123.34, 124.56, 124.84, 125.62, 127.00, 130.06, 132.65, 139.50, 160.23, 160.95, 162.62, 164.60.

4-(2-Fluoro-phenyl)-2-methyl-9-phenyl-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulene **(7c).**

^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 2.15 (s, 3H, -CH_3), 4.02 (s, 1H, -CH_2), 6.56 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 7.24 (dd, 1H, Ar-H), 7.40 (dd, 1H, Ar-H), 7.51 (d, 1H, Ar-H), 7.60-7.98 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 23.30, 42.84, 113.60, 118.20, 123.40, 124.24, 124.99, 125.21, 126.20, 127.18, 130.26, 131.23, 132.60, 139.52, 158.28, 160.00, 160.25, 162.00, 164.23.

2-Ethyl-4-(2-fluoro-phenyl)-9-methyl-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulene **(7d).**

Mass: [ES] $^+$ 327.5. ^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 1.31 (t, 3H, -CH_3), 2.71 (s, 3H, -CH_3), 2.83 (q, 2H, -CH_2), 4.51 (s, 1H, -CH_2), 6.51 (s, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.24 (dd, 1H, Ar-H), 7.43 (dd, 1H, Ar-H), 7.57 (d, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 14.40, 16.81, 23.31, 42.08, 115.62, 123.32, 124.24, 124.03, 125.21, 127.00, 130.06, 132.56, 139.50, 160.02, 160.88, 162.62, 164.60.

2,9-Diethyl-4-(2-fluoro-phenyl)-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulene **(7e).**

^{1}H NMR (100 MHz, $CDCl_3$, δ ppm): 1.10 (t, 3H, -CH_3), 1.95 (t, 3H, -CH_3), 2.28 (q, 2H, -CH_2), 2.80 (q, 2H, -CH_2), 4.60 (s, 1H, -CH_2), 6.48 (s, 1H, Ar-H), 7.22 (d, 1H, Ar-H), 7.30 (dd, 1H, Ar-H), 7.55 (dd, 1H, Ar-H), 7.88 (d, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 14.10, 16.18, 18.20, 23.18, 42.10, 115.24, 123.30, 124.28, 124.29, 125.24, 127.63, 130.66, 132.46, 139.26, 158.14, 160.15, 162.20, 164.00.

CONCLUSION:

In summary, we have developed a convenient, simple and effective method for the synthesis of 4-(substituted fluoro-phenyl)-substituted-6H-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulenes using microwave irradiation technique. The reported derivatives were efficiently synthesized by using (2-Amino-5-substituted-thiophen-3-yl)-(substituted-fluoro-phenyl)-methanone and (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid.

Microbial activity study of the synthesized compounds was show that the 50% screened compounds are potent active against gram positive and gram negative bacterial under investigations. The microwave synthetic pathway is interestingly rapid with good isolated yield.

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Authors do not have any conflict of interest in present work**.**

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