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RESEARCH ARTICLE

MICROWAVE ASSISTED PICTET-SPENGLER SYNTHESIS OF SOME TETRAHYDROISOQUINOLINE DERIVATIVES AND THEIR BIOLOGICAL EFFICACY STUDIES.

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Abstract

In the present research article, a one pot synthesis of novel 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(substitutedphenyl)isoquinoline(THIQ) derivatives using 2-(3,4-dimethoxy)phenylethylamine, substituted benzaldehyde with toluene in tetrahydrofuran(THF) under microwave condition is reported. The structures of the newly synthesised compounds were confirmed using modern analytical IR, NMR and MS techniques. The synthesized THIQ derivatives were screened for antibacterial activities against gram positive and gram negative bacteria. The biological efficacies of the synthesized derivatives were investigated in the form of zone of inhibition (mm) against *E. coli*, *S. aureus* and *P. aeruginosa*. Few of the derivatives have been found to possess significant antibacterial activities and can have potential applications in pharmacological/medical science.

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Introduction:-

Isoquinoline, a low melting solid (mp 27°C) was synthesized in 1885 and its structure was established by oxidation to a mixture of phthalic acid and pyridine-3,4-dicarboxylic acid [1-3]. Isoquinoline in the form of 1,2,3,4-tetrahydroquinoline scaffold occurs in a large number of alkaloids [2-9]. The Bischler-Napieralski [10] suggested the new method for the synthesis of isoquinoline. Bergstrom [11] reported Pictet-Spengler Reaction (PSR) for synthesis of substituted isoquinolines. These two methods have been found to be reliable methods for synthesis of tetrahydroisoquinoline wherein N-acyl-β-arylethylamine or β-arylethylamine derivative is treated with an aldehyde under acidic condition to generate imine. The imine then can undergo ring closure to give tetrahydroisoquinoline which can be oxidised to isoquinoline.

The Pictet-Spengler reaction suffers from many drawbacks [12]. For instance the reaction needs high temperature and large excess amount of strong Bronsted acids required for unreactive substrate while conversion. It has also been reported that the reactive substrates in PSR necessarily do not need harsh reaction conditions [13]. In the present investigation an effort is made to minimize the need of prolonged heating and use of harsh reagents in order to synthesize THIQs which is in need of green synthesis approach.

Recently, Microwave Assisted Organic Synthesis (MAOS) protocols have been described for Bischler-Napieralski [14] and for Pictet-Spengler reaction [15-20]. Newer strategies and synthetic methods for the preparation of libraries of substituted isoquinolines have also been reported [21]. In order to eradicate the problems associated with the

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conventional methods, the present investigation offers microwave assisted method which is environment/user friendly due to minimized use of harsh materials and shorter reaction time.

Experimental:-

Materials and Methods:-

All chemicals/reagents used were of AR/chemically pure grade purchased from reputed companies like Merck/Sigma Aldrich and used as received. Melting points were determined in open capillary tube using melting point apparatus. The completion of reaction was monitored with alumina coated TLC plates. The spots were visualized with UV radiation or iodine vapour. Column chromatography was performed in silica gel (60-120 mesh) with ethyl acetate-hexane(20:80) mixture as eluent. NMR spectra were recorded on a Bruker Avance II NMR spectrometer operating at 400MHz for ^1H NMR and 200MHz for ^{13}C NMR using TMS as an internal standard. IR spectra were recorded on Perkin Elmer - Spectrum RX-IFTIR. Mass spectra were recorded on a Waters Micromass Q-ToF Mic.

General procedure for the synthesis of substituted quinolines (IQ₁-IQ₈):-

2-(3,4-dimethoxy phenyl)ethanamine (1mmol), substituted benzaldehyde (1.5mmol), TFA (8mmol) and toluene (1mL) was taken in a round bottom flask and the mixture was refluxed by irradiating in temperature assisted microwave oven at 540W for 30 min. The completion of the reaction was monitored by TLC. After completion of the reaction, the crude mixture was suspended into ice cold water (5mL). The solvent was evaporated under reduced pressure and treated with aqueous NaOH(2M) for maintaining pH 8 and extracted with ethyl acetate (5×6mL). The extracted organic phase was dried over Na₂SO₄, concentrated and purified with column chromatography using silica gel (60-120 mesh), where ethyl acetate-hexane (20:80) mixture was used as eluent to yield the pure substituted quinolines. The purified product was re-crystallized using proper solvent. The structures of the substituted quinolines were established on the basis of spectral analysis. The scheme for synthesis of THIQs is presented in Fig. 1.

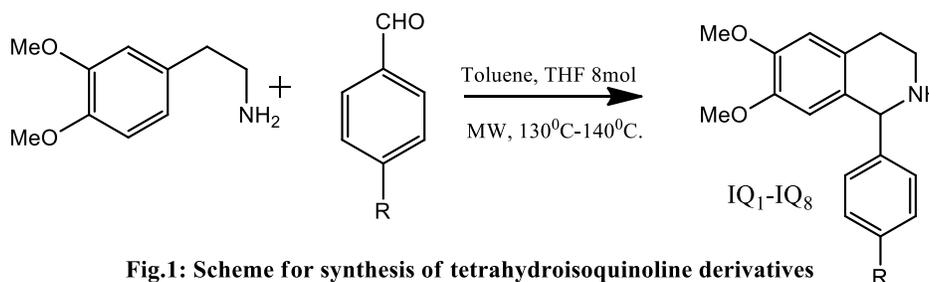


Fig.1: Scheme for synthesis of tetrahydroisoquinoline derivatives

The structures, yields and melting points of the synthesized THIQ compounds are tabulated in Table 1.

Table 1:- Synthesized isoquinoline derivatives with their yield and melting point.

Sr. No.	Compound	R	Molecular formula	Yield (%)	M.P.(°C)
1.	IQ ₁	H	C ₁₇ H ₁₉ NO ₂	82	276
2.	IQ ₂	CH ₃	C ₁₈ H ₂₁ NO ₂	79	293
3.	IQ ₃	OCH ₃	C ₁₈ H ₂₁ NO ₃	80	305
4.	IQ ₄	OH	C ₁₇ H ₁₉ NO ₃	77	-
5.	IQ ₅	NO ₂	C ₁₇ H ₁₈ N ₂ O ₄	78	-
6.	IQ ₆	Cl	C ₁₇ H ₁₈ ClNO ₂	72	303
7.	IQ ₇	Br	C ₁₇ H ₁₈ BrNO ₂	66	319
8.	IQ ₈	COOH	C ₁₈ H ₁₉ NO ₄	80	316

Spectral Data:-

1,2,3,4-tetrahydro-6,7-dimethoxy-1-phenylisoquinoline (IQ₁): M.F.- C₁₇H₁₉NO₂; ^1H NMR (δ ,ppm,TMS)-7.14-7.06(m,5H), 6.41-6.40(d,2H), 5.19(s,1H), 3.73(s,6H), 3.61(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ^{13}C NMR-147.5, 147.2, 142.8, 136.8, 129.8, 129.3, 128.3, 126.3, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR(cm^{-1})- 3450(N-H, str), 2960(C-H, str, aromatic), 2850(C-H, str, O-CH₃), 2830(C-H, str, O-CH₃), 1650(N-H, bend), 1605(C=C, str),

1575(C=C, str), 1525(C=C, str), 1496(N-H, str), 1460(C=C, str), 1310(C-N, str), 1250(C-O-C, str, asym), 1165 (C-C, str), 870(C-N, str), 743(C-H, bend); **Mass- MS: m/z** – 269.14(100%), 270.14(18.8%), 271.15(2.1%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methylphenyl)isoquinoline(IQ₂): M.F.-C₁₈H₂₁NO₂; ¹H NMR (δ,ppm,TMS) – 6.94(s,4H), 6.41-6.40(d,2H), 5.19(s,1H), 3.74(s,6H), 3.62(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H), 2.35(s,3H); ¹³C NMR- 147.5, 147.2, 139.8, 136.8, 135.9, 129.8, 129.6, 128.2, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9, 24.3; **IR(cm⁻¹)** 3428(N-H, str), 2990(C-H, str, aromatic), 2860(C-H, str, O-CH₃), 2840(C-H, str, O-CH₃), 1670(N-H, bend), 1610(C=C, str), 1570(C=C, str), 1520(C=C, str), 1490(N-H, str), 1455(C=C, str), 1300(C-N, str), 1245(C-O-C, str, asym), 1160(C-C, str), 871(C-N, str), 750(C-H, bend); **Mass- MS: m/z** - 283.16(100%), 284.16(19.8%), 285.16(2.3%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxyphenyl)isoquinoline(IQ₃): M.F.- C₁₈H₂₁NO₃; ¹H NMR (δ,ppm,TMS) – 6.95(d,2H), 6.65(d,2H), 6.41-6.40(d,2H), 5.19(s,1H), 3.73(s,9H), 3.60(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 158.2, 147.5, 147.2, 136.8, 135.1, 129.8, 129.3, 114.8, 113.2, 57.1, 56.9, 56.2, 41.8, 29.9; **IR(cm⁻¹)**- 3433(N-H, str), 2980(C-H, str, aromatic), 2845(C-H, str, O-CH₃), 2825(C-H, str, O-CH₃), 1660(N-H, bend), 1615(C=C, str), 1580(C=C, str), 1529(C=C, str), 1498(N-H, str), 1469(C=C, str), 1306(C-N, str), 1258(C-O-C, str, asym), 1153 (C-C, str), 875(C-N, str), 760(C-H, bend); **Mass- MS: m/z** - 299.15(100%), 300.16(19.8%), 301.16(2.5%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-hydroxyphenyl)isoquinoline(IQ₄):M.F.-C₁₇H₁₉NO₃;¹H NMR(δ,ppm,TMS) – 6.89(d,2H), 6.61(d,2H), 6.41-6.40(d,2H), 5.19(s,1H), 5.0(s,1H), 3.72(s,6H), 3.62(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 156.0, 147.5, 147.2, 136.8, 135.4, 129.8, 129.7, 116.4, 113.3, 57.1, 56.2, 41.8, 29.9; **IR(cm⁻¹)**- 3610(O-H, str), 3456(N-H, str), 3110(C-H, str, aromatic), 2863(C-H, str, O-CH₃), 2813(C-H, str, O-CH₃), 1678(N-H, bend), 1608(C=C, str), 1522(C=C, str), 1505(C=C, str), 1491(N-H, str), 1453(C=C, str), 1309(C-N, str), 1205(C-O-C, str, asym), 1118 (C-C, str), 873(C-N, str), 748(C-H, bend); **Mass- MS: m/z** -285.14(100%), 286.14(18.7%), 287.14.16(2.3%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-nitrophenyl)isoquinoline(IQ₅): M.F.-C₁₇H₁₈N₂O₄; ¹H NMR(δ,ppm,TMS)– 8.07(d,2H), 7.32(d,2H), 6.41-6.40(d,2H), 5.19(s,1H), 3.73(s,6H), 3.60(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 148.9, 147.5, 147.2, 145.9, 136.8, 129.8, 129.2, 121.6, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; **IR(cm⁻¹)**- 3510(N-H, str), 3125(C-H, str, aromatic), 2867(C-H, str, O-CH₃), 2834(C-H, str, O-CH₃), 1676(N-H, bend), 1600(C=C, str), 1593(C=C, str), 1547(C=C, str), 1500(N-H, str), 1485(C=C, str), 1335(NO₂, str), 1242(C-O-C, str, asym), 1108 (C-C, str), 870(C-N, str), 730(C-H, bend); **Mass- MS: m/z** - 314.13(100%), 315.13(18.7%), 316.13(2.6%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-chlorophenyl)isoquinoline(IQ₆): M.F.-C₁₇H₁₈ClNO₂; ¹H NMR (δ,ppm,TMS) – 7.15(d,2H,Ar-H), 7.00(d,2H,Ar-H), 6.41-6.40(d,2H,Ar-H), 5.19(s,1H), 3.74(s,6H), 3.61(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 147.5, 147.2, 140.9, 136.8, 131.8, 129.8, 129.7, 129.4, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; **IR(cm⁻¹)**- 3487(N-H, str), 3113(C-H, str, aromatic), 2867(C-H, str, O-CH₃), 2843(C-H, str, O-CH₃), 1670(N-H, bend), 1643(C=C, str), 1580(C=C, str), 1521(C=C, str), 1491(N-H, str), 1455(C=C, str), 1306(C-N, str), 1289(C-N, str), 1245(C-O-C, str, asym), 1145 (C-C, str), 865(C-N, str), 750(C-H, bend), 720(C-Cl, str); **Mass-MS: m/z** - 303.10(100%), 305.10(32.0%), 304.11(18.7%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-bromophenyl)isoquinoline(IQ₇): M.F.-C₁₇H₁₈BrNO₂; ¹H NMR (δ,ppm,TMS)– 7.31(d,2H), 6.95(d,2H), 6.41-6.40(d,2H), 5.19(s,1H), 3.73(s,6H), 3.63(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 147.5, 147.2, 141.8, 136.8, 132.2, 130.5, 129.8, 120.6, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; **IR(cm⁻¹)**- 3498(N-H, str), 3120(C-H, str, aromatic), 2878(C-H, str, O-CH₃), 2856(C-H, str, O-CH₃), 1681(N-H, bend), 1656(C=C, str), 1589(C=C, str), 1529(C=C, str), 1498(N-H, str), 1469(C=C, str), 1315(C-N, str), 1295(C-O-C, str, asym), 1153 (C-C, str), 873(C-N, str), 761(C-H, bend), **Mass- MS: m/z** -347.05(100%), 349.05(97.30%), 348.06(18.7%), 350.05(18.3%), 349.06(2.1%), 351.06(1.6%)

1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-carboxyphenyl)isoquinoline (IQ₈): M.F.- C₁₈H₁₉NO₄; ¹H NMR (δ, ppm, TMS)– 11.0(s,1H), 8.01(d,2H), 7.27(d,2H), 6.41-6.40(d,2H), 5.19(s,1H), 3.74(s,6H), 3.64(s,1H), 2.93-2.83(m,2H), 2.69-2.66(m,2H); ¹³C NMR- 169.4, 148.0, 147.5, 147.5, 136.8, 130.8, 129.8, 128.2, 127.8, 113.3, 113.2, 57.1, 56.2, 41.8, 29.9; IR (cm⁻¹)- 3520(R-CO-OH, str), 3498(N-H, str), 3180(C-H, str, aromatic), 2893(C-H, str, O-CH₃), 2843(C-H, str, O-CH₃), 1671(N-H, bend), 1641(C=C, str), 1574(C=C, str), 1536(C=C, str), 1505(N-H, str), 1434(C=C, str), 1308(C-N, str), 1291(C-O-C, str, asym), 1142(C-C, str), 890(R-CO-OH, bend); 734(C-H, bend) **Mass- MS: m/z** -313.13(100%), 314.13(19.8%), 315.14(2.7%)

In-vitro antimicrobial Activity:-

The *in-vitro* antibacterial activities of the 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-substitutedphenyl) isoquinoline derivatives has been investigated against various strains of gram positive and gram negative bacteria. Nutrient agar media was employed for the bacterial growth. Sterile medium was melted on water bath and kept at 45°C at constant temperature. In each sterile petri-dish, molten medium was added so that thickness was approximately 4-5 mm and sub-cultured organism under study was inoculated. The inoculated dishes were allowed to set for 30 min at room temperature. Cups of 6 mm diameter were then made with the help of sterile stainless steel borer and solutions of compounds (100 µgml⁻¹) were added to each cup. Petri-dishes were kept in refrigerator for 30 min so as to allow diffusion of the solutions in the medium and then incubated for approximately 24 hrs. at 37°C for antibacterial activity. Antibacterial activity against three strains i.e. *E. coli*, *S. aureus* and *P. aeruginosa* were determined using Streptomycin as standard. The screening results have been depicted in the Table 2.

Table2:- Antibacterial screening of the synthesized isoquinoline derivatives

Compounds	Diameter of zone of inhibition (mm)		
	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>
IQ ₁	20	21	19
IQ ₂	17	17	18
IQ ₃	19	23	20
IQ ₄	19	22	21
IQ ₅	20	21	22
IQ ₆	23	24	27
IQ ₇	24	23	26
IQ ₈	22	20	24
Streptomycin	25	24	28

Results and Discussion:-

Successful synthesis of a series of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-substitutedphenyl) isoquinoline was carried out using microwave assisted technique. The purity of the synthesized compounds was established by TLC. The structural elucidation of the compounds was done with modern techniques like ¹H/¹³C NMR, IR and MS. The synthesized compounds were screened for their antibacterial activities by cup method. Three gram positive and gram negative bacterial strains were used for the purpose of antibacterial activity. The synthesized isoquinoline compounds were found to possess significant antibacterial activities. Most of the compounds were equally effective against *E. coli* and *S. aureus*. All the compounds have shown a little profound activity against *P. aeruginosa*.

Conclusion:-

Conclusively all the compounds have shown noticeable antibacterial activity. From the present study it may be predicted that the substitution on the phenyl ring with higher polarizability enhances the potency of these compounds as antibacterial agents. Further investigations can be extended to test these compounds in light of their practical applicability as potential antibacterial drugs. Thus these compounds can have potential applications in the field of pharmacological/medical science.

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References:-

1. Hoogerwerff, S.; van Dorp, W. A., Recl. Trav. Chim. Pays-Bas, (1885) 4, 125.

2. Hoogerwerff, S.; van Dorp, W. A., *Recl. Trav. Chim. Pays-Bas*, (1885) 4, 285.
3. Maske, R. H. F., In *The Alkaloids. Chemistry and Biology*, Manske, R. H. F., Ed.; *Academic: New York*, (1960); Vol. 7, p 423.
4. Stanek, J., In *The Alkaloids. Chemistry and Biology*, Manske, R. H. F., Ed.; *Academic: New York*, (1960); Vol. 7, p 433.
5. Kulka, M., In *The Alkaloids. Chemistry and Biology*, Manske, R. H. F., Ed.; *Academic: New York*, (1960); Vol. 7, p 439.
6. Lundstrom, J., In *The Alkaloids. Chemistry and Biology*, Brossi, A., Ed.; *Academic: New York*, (1983); Vol. 21, p 255.
7. Kametani, T., *The Chemistry of Isoquinoline Alkaloids*, *Elsevier: Amsterdam*, (1969).
8. Shamma, M., *The Isoquinoline Alkaloids*, *Academic: New York*, (1972).
9. Philippson, J. D., *The Chemistry and Pharmacology of Isoquinoline Alkaloids*, *Springer: Heidelberg*, (1985).
10. Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* (1893), 26, 1903–1908.
11. Bergstrom, F. W. *Chem. Rev.* (1944), 35, 77–277.
 - (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* (1951), 6, 151; for superacids approach, see: (b) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* (1999), 64, 611.
 - (a) Kametani, T.; Fukumoto, K.; Agui, H.; Yagi, H.; Kigasawa, K.; Sugahara, H.; Hிராgί, M.; Hayasaka, T.; Ishimaru, H. *J. Chem. Soc. (C)* (1968), 112; (b) Kametani, T.; Fukumoto, K. *Heterocycles* (1975), 3, 311; (c) Bates, H. A. *J. Org. Chem.* (1981), 46, 4931.
12. Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* (2003), 33, 2339–2348.
13. Mesangeau, C.; Yous, S.; Peres, B.; Lesieur, D.; Besson, T. *Tetrahedron Lett.* (2005), 46, 2465–2468.
14. Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* (2004), 45, 8137–8140.
15. Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron* (2004), 60, 12075–12084.
16. Campiglia, P.; Gomez-Monterrey, I.; Lama, T.; Novellino, E.; Grieco, P. *Mol. Diversity* (2004), 8, 427–430.
17. Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* (2003), 33, 2339–2348.
18. Gitto, R.; Ferro, S.; Agnello, S.; De Luca, L.; De Sarro, G.; Russo, E.; Vullo, D.; Supuran, C. T.; Chimirri, A. *Bioorg. Med. Chem.* (2009), 17, 3659–3664.
19. Emelia Awuah and Alfredo Capretta *J. Org. Chem.* (2010), 75, 5627–5634