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Effect of catalyst and Solvent in Synthesis of Tacrine-Terpenoid Hybrid Analogues: Friedlander Annulation Approach

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ABSTRACT

Several investigations were carried on the modification of tacrine (THA), an acetyl cholinesterase inhibitor, used in the treatment of Alzheimer's disease. THA can be prepared by several methods, among those Friedlander condensation is the simplest and convenient approach. As an attempt to synthesize tacrine analogues with less/no hepatotoxicity, we designed some novel thienopyridine derivatives by incorporating terpenoids into the structure. From the designed series, we synthesized three tetracyclic THA analogues by conventional and microwave methods using different catalysts in the presence/absence of solvent. We found the formation of byproducts and some charged species along with desired THA analogues. The reaction mixture was subjected to LC-MS and the title compounds were confirmed. Promising yields were found with anhydrous aluminum chloride in dichloroethane.

KEY WORDS: Alzheimer's disease, Thienopyridine, Tacrine, Acetyl cholinesterase, Terpenoids.

1. INTRODUCTION

Tacrine, the amino derivative of acridine (9-amino-1, 2, 3, 4-tetrahydroacridine, THA) and known as one of the "polymethylene quinoline" derivative (4-amino-2, 3-tetramethylene quinoline), was the most potent and clinically effective AChEI for the symptomatic treatment of Alzheimer's disease (AD) (Crismon, 1994; Davis, 1995). Quinolone derivatives can be prepared by using numerous approaches such as Skraup, Friedlander, Doebner von Miller, Pfitzinger, Combes and Conrad- Limpach methods with different combinations of catalyst-solvent systems (Mohamed, 2005; Kouznetsov, 2005; Alan and Katritzky, 1998; Narasimhulu, 2007; Ecjhao, 2010; Sanjay, 2003; Mitsuhiro, 2001). Among these methods, the Friedlander annulation approach (FAA) is still considered to be one of the simplest and straightforward approaches for the preparation of quinoline derivatives (Marco-Contelles, 2009).

The classical form of the FAA involves the acid or base promoted condensation between a 2-aminoaryl carbonyl compound (ketone, aldehyde, nitrile or an equivalent) and substituted carbonyl compound possessing a reactive α-methylene group followed by cyclodehydration. Generally, by refluxing the reactants in aqueous or alcoholic solvent with base catalyst or cooking the reactants without catalyst at 150-220°C (Mabire, 2005; Zong, 2006; Dingqiao, 2007; Sarkis, 2007). Bronsted-Lowry and Lewis acids also are known to promote these reactions (Liang Zhang, 2007; Subhas Bose, 2006; Guan-Wu Wang, 2006; Yadav, 2005; Prabhakar Reddy and China Raju, 2008; Jia, 2006). In the past few decades, there has been enormous investigations carried out in the FAA to improve the reaction conditions to minimize its drawbacks (such as harsh reaction conditions, longer reaction times, low yields, usage of dangerous organic solvents and complications in the work-up procedures) and also extended the synthesis of wide range of nitrogen-containing heterocycles (Khalilzadeh and Hosseini, 2007; Marco-Contelles, 2006; Marco, 2001; Li, 2008; Sestili, 2004; Jia, 2007; GR, 2000). The modified method of FAA, the reaction between anthranilonitrile and ketones have been considered to the synthesis of tacrine and its analogues. The tetracyclic systems such as thienopyridines, pyrrolo pyridines and several other heterocycles were reported with fusion of cycloalkanes of different ring sizes as acetyl cholinesterase inhibitors (Madapa, 2008; McKenna, 1997; Jossan, 1992; Jann, 1989).

Tacrine, the molecule of significance with broader pharmacological profile (Korabecny, 2011; Badran, 2010; Barreiro, 2003; De Los Ríos, 2010; Santos Pisoni, 2010) was also found to form several toxic hydroxy metabolites on the cycloalkane ring by the Cytochrome P450 enzymes, especially CYP1A2. To counter the toxicity of tacrine, we initiated the synthesis of molecules with several terpenoids fused to the 4-amino pyridine nucleus to evaluate them for their acetyl cholinesterase inhibition. The synthesis of the designed molecules was carried out by the Lewis acid-mediated FAA of substituted thiophene amino nitriles with various terpenoids to afford the corresponding tetracyclic THA analogue under solvent-free and solvent-reflux conditions.

2. EXPERIMENTAL

All the chemicals were purchased from Sigma-Aldrich, Fluka, Merck and Finar Chemicals Ltd. All the solvents were of laboratory grade and were purified and dried by standard procedures. Menthone and Carvone were purchased from Fluka. They were enantiomerically pure. Camphor was purchased from Sigma Aldrich, MI, USA. Aluminium choride (anhydrous) and Dichloroethane (DCE) used were of Merck make. Anhydrous Zinc Chloride, Toluene, Tetrahydrofuran, Ethylacetate, Chloroform, Sodium hydroxide pellets, Sulfur, Malononitrile, Morpholine

were purchased from Finar chemicals, Mumbai. LG Microwave oven (domestic) was used. A temperature controllable magnetic stirrer of Remi make was used. The reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck, Germany); spots were visualized with UV light. Merck silica gel (80–120 mesh; Merck, Germany) was used for column chromatography.

Synthesis of 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (Ia & Ib): Equimolar quantities (0.01 mole) of cyclopentone/cyclohexone, malononitrile and sulphur were taken in a round bottomed flask containing ethanol (30 ml) and the reaction mixture was allowed to stir till to get a homogeneous mixture. Then Morpholine (0.01 mole) was added drop wise to the contents of the flask at 45-50°C. The reaction was continued with stirring at room temperature for about 4-5 hours and the reaction was monitored by TLC. The contents of the flask were kept in the freezer overnight. Later, the reaction mixture was filtered and the precipitate was washed twice with cold ethanol (2 X 10 ml). The filtrate was dried and purified by recrystallization using methanol to yield yellowish-brown crystals (Frideling, 2004).

General Synthesis of Tetracyclic Thienopyridine derivatives of Terpenoid (IIa-IIf):

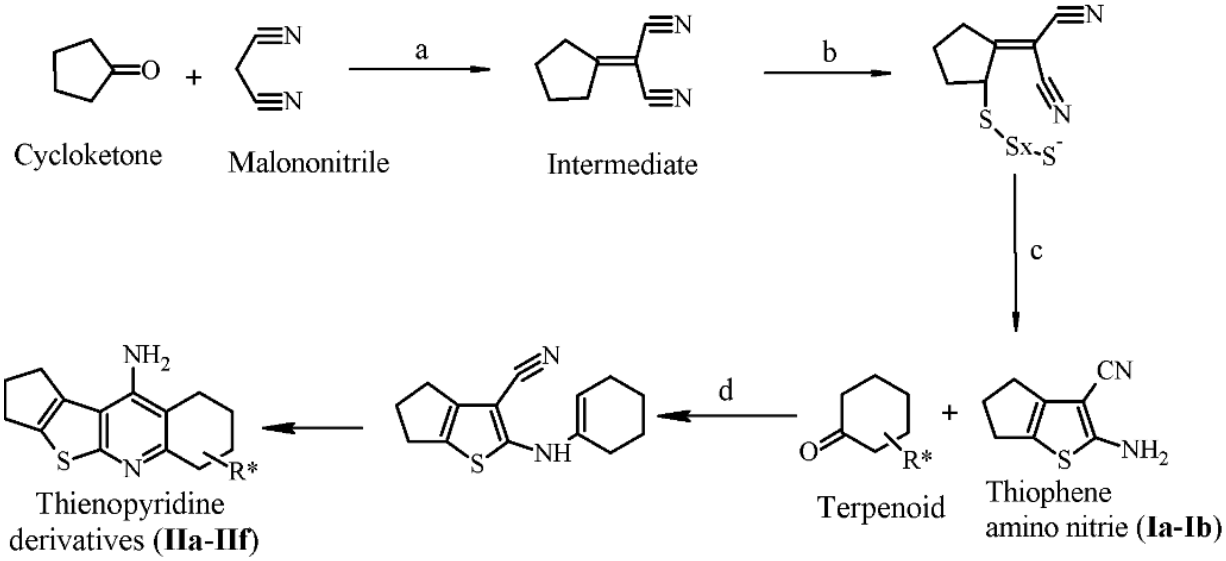
Microwave Irradiation Using $ZnCl_2$ as catalyst: Equimolar quantities (0.01 mol) of the thiophene amino nitrile (Ia/Ib), menthone and anhydrous zinc chloride was irradiated under the sequential order of conditions in a domestic microwave. The product formation was monitored constantly by TLC.

Solvent-free reaction, using $ZnCl_2$ as catalyst: Equimolar quantities (0.01 mol) of the thiophene amino nitrile (Ia/Ib), menthone and anhydrous zinc chloride was taken in a 50 ml round bottom flask, attached to a reflux condenser and heated at 180-190°C on electric mantle for about 16 hrs. The reaction was monitored by TLC.

Benzene as a solvent, using $ZnCl_2$ as catalyst: Equimolar quantities (0.01 mol) of the thiophene amino nitrile (Ia/Ib) and menthone dissolved in benzene (25 ml) then added anhydrous zinc chloride (0.03 mol) in a 50 ml round bottom flask, attached to a reflux condenser and heated at 80-90°C on electric mantle for about 20 hrs and the reaction progression was monitored by TLC.

Toluene as solvent, using $ZnCl_2$ as catalyst: Thiophene amino nitrile (0.01 mol), menthone (0.01 mol), anhydrous zinc chloride (0.03 mol) in toluene (50 ml) and was heated at 170-180°C for about 32 hrs. The reaction was monitored by TLC. The reaction mixture was cooled, 5% sodium hydroxide was added and stirred. It was extracted ether (3 X 30 ml) and dried under *in vacuo*. Purified the product by performing column chromatography using hexane as solvent by increasing its polarity with ethyl acetate (0-20 %).

Using $AlCl_3$ as catalyst and dichloroethane as solvent: $AlCl_3$ (0.01 mmol) was suspended in anhydrous 1, 2-dichloroethane (10 ml). The corresponding thiophene (Ia/Ib, 0.02 mol) and terpenoid (0.017 mol) were added and the reaction mixture was heated under reflux for about 60 hrs to offered tetracyclic thiophene series of tacrine (IIa-IIf). The reaction was monitored by TLC and after the completion of reaction, a mixture of Tetrahydrofuran-water (2:1) was added at room temperature and 10% Sodium hydroxide was added drop wise until the solution became basic. After stirring for 30 min, the mixture was extracted with chloroform (3 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulphate, filtered and evaporated the solvent *in vacuo* to obtain brownish waxy solid (Hu, 2009).



Scheme.1. Reaction sequence of the IIa–IIf synthesis

(a) Morpholine (1.0 equiv. amount), Methanol or Ethanol, RT-45°C; (b) addition of sulfur, Sulphur (1.0 equiv. amount); c. ring-closure. d. $ZnCl_2$/$AlCl_3$, Toluene/Dicloroethane

3. RESULTS AND DISCUSSION

The proposed compounds (IIa-IIf) were synthesized through two steps by following reaction sequence given in Scheme I, one involves the synthesis of thiophene amino nitrile (Ia & Ib) by Knoevenagel-Cope condensation and later condensing Ia/Ib with terpenoids (Menthone, Carvone and Camphor) by Friedlander's Annulation Approach. High Resolution Mass spectrum of thiophene amino nitrile (Ia) is given in Fig.1. The reaction between a cyclic ketone having an activated methylene group and an amino nitrile in the presence of a Lewis acid as catalyst and an anhydrous solvent. During the transition stage, the keto group reacts with the amino and forms a secondary amine along with the double bond formation between the keto carbon and active methylene carbon. Then, the condensation completes by further reacting with the carbon of cyano group thereby forming a 4-amino pyridine group.

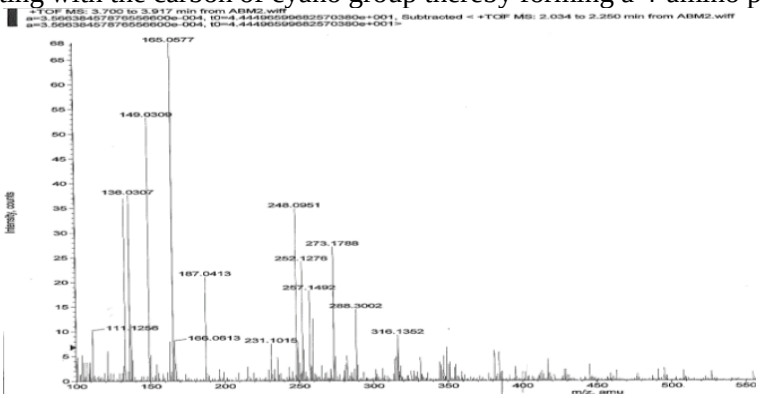


Figure.1. High Resolution Mass spectrum of thiophene amino nitrile (Ia)

Synthesis of menthone adduct (IIa) was tried in various conditions. Though, microwave irradiation (using a bomb) was reported as method of preparation, we could not achieve it using domestic microwave conditions. Details of microwave irradiation conditions and % Yield of compound IIa given in Table.1. Also, same is the case with using anhydrous zinc chloride as a catalyst without using any solvent when heated using an electric mantle. Used benzene as solvent and the quantity of anhydrous zinc chloride was increased to 3 times, we observed its effect on the reaction progress but it was not productive. The product formation could be observed and heated to reflux.

Table.1. Details of Microwave Irradiation Conditions and % Yield of IIa

Power	Pulse (Seconds)	% Yield
160 W	8 X 10	2.8
320 W	6 X 10	3.5
320 W	6 X 10	5.2
480 W	3 X 10	6.2

The use of Anhydrous Zinc Chloride as a catalyst in toluene as a solvent was reported to yield 21 % of a Tacrine analogue (Marco, 2002). It was observed that the complete conversion of the Ia was not achieved after continuing the reaction even for 32 hours later the detection of the product formation. The Ia was removed by column chromatography and both were analyzed for their molecular weights (Fig.2 & 3). The mass spectrum of compound Ia (Menthone derivative of thienopyridine) showed a high intensity signal at m/z 259.1226 (Fig.3) which was thought to be a fragment ion formed due to the loss of isopropyl group. The yield of compound Ia was around 3 %. For the synthesis of compound 2, carvone adduct, toluene was used as solvent and the reaction was continued till the complete product formation.

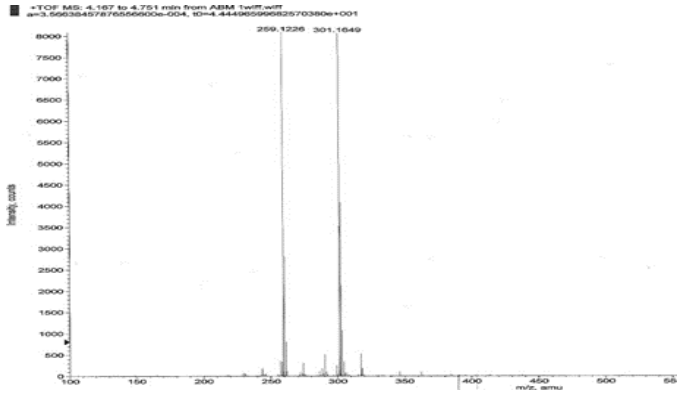


Figure.2. High Resolution Mass spectrum of compound IIa

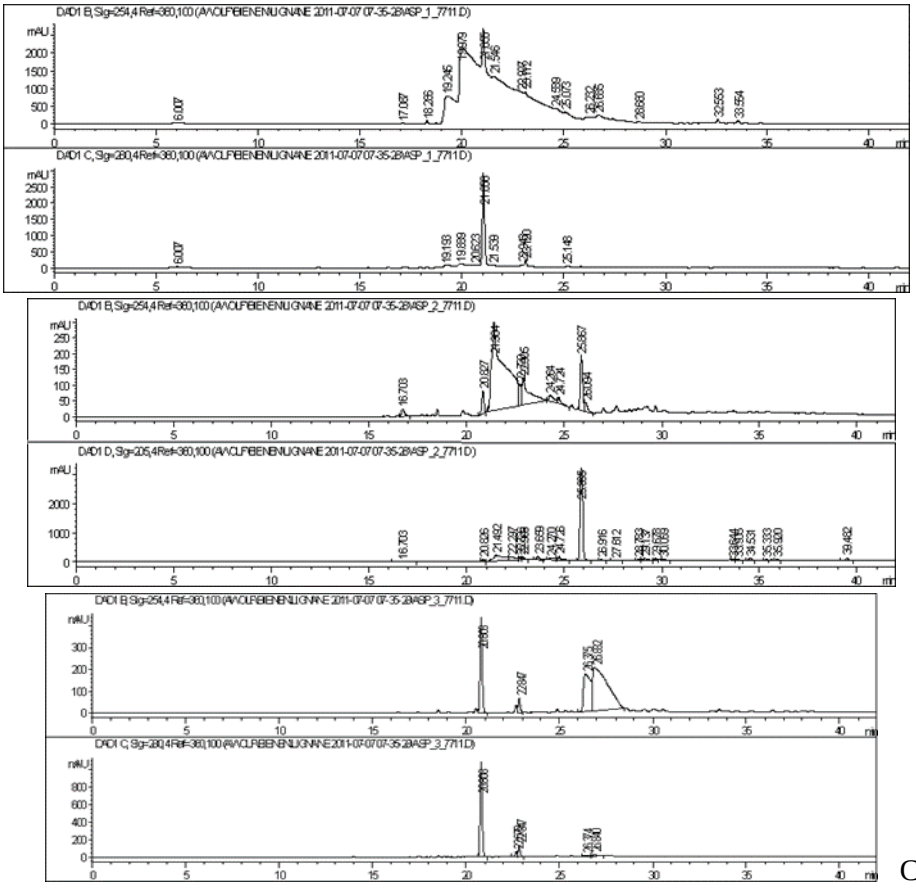
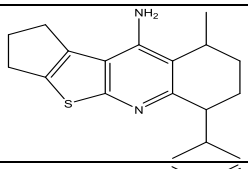
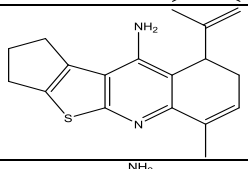
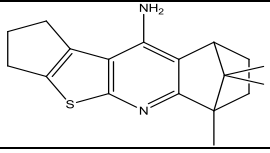
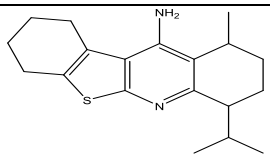
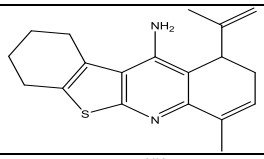
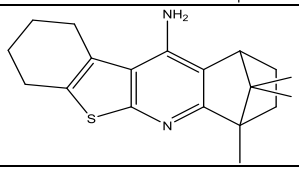


Figure.3. HPLC-DAD Chromatograms of Compounds IIa-IIc

For the improvement of yield, we tried several combinations of catalyst and solvents using anhydrous Aluminum Chloride along with dichloroethane. The condensation of Ia/Ib with a terpenic cyclanone (Menthone, Carvone and Camphor) to produce novel tetracyclic thiophene series of tacrine (IIa-IIf) with combination of terpene and thiophene rings. The yield in this case was considerably higher, i.e., ~ 60% (Thomae, 2007; Puterova, 2010). Retention times, Molecular weights and ES-MS Spectrum of the compounds IIa-IIf were given in Table.2. The complete conversion of the amino nitrile (Ia/Ib) was not achieved after continuing the reaction even for several hours after the detection of the product formation. Also, unlike the previous experiments, the TLC profile of the product looked differently when tested in various solvent systems with 4 spots apart from the anticipated product and starting material. An in depth analysis of these reaction mixtures was necessary to study the nature of the products formed. HPLC-DAD experiments (Fig.4) were performed using the three reaction products showed asymmetric peaks at λ 254 nm indicating that the charged species are formed during this reaction. Thus, it supported our belief that there could be the formation of some products along with the desired product and so the number of spots increased. This was hitherto unreported in any of the publications dealing with these catalyst and solvent.

Table.2. Retention times, Molecular weights and ES-MS Spectrum of the compounds IIa-IIf

	Structures of compounds	Retention Time (t_R)	Molecular Weight	Molecular ion peak, $[M+H]^+$ observed (*m/z*)
IIa		7.64	300	301
IIb		8.17	296	297
IIc		7.59	298	299

IId		6.89	314	315
IIe		7.94	310	311
IIf		6.84	322	323

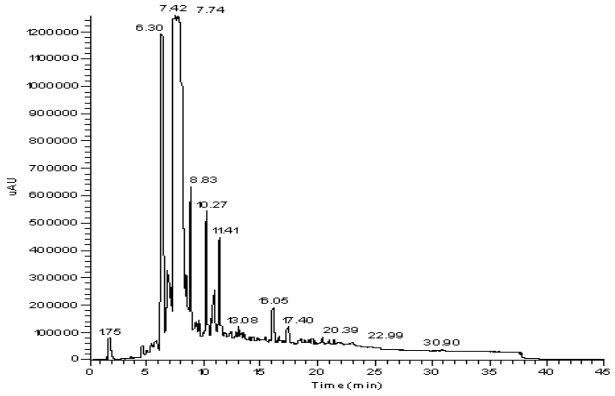


Figure.4. Chromatogram portion of Compound IIa in LC-MS

Then, LC-MS experiments were performed to detect the presence of desired compound. The results indicated the presence of final products. The chromatogram and spectra gave separate peak and signal at m/z 259 (Fig.7), indicating, the mass spectrum signal (at m/z 259.1226) of the compound 1a, the product formed when anhydrous zinc chloride was used as catalyst and benzene as solvent conditions, was not due to the fragmentation but a byproduct. This could not be isolated by the column chromatography and so it appeared with equal abundance in MS. Though the yield of menthone derivative was more in the presence of benzene than with dichloroethane, the results of carvone derivative was just opposite. The yield was less during the use of anhydrous zinc chloride with toluene than with dichloroethane.

The LC-MS (Figs.5, 9 & 12; Mass spectrum of compounds shown in Figs.4, 8, & 11) results were useful to identify the desired product in the chromatogram by mass spectral analysis of the peaks. All the peaks corresponding to the molecular weights of the desired products were high in concentrations. The UV spectra of the compounds (Figs.6, 7, 10 & 13) also suggest that there is no interference of charged species on the products formed. Hence, it can be confirmed that the end products of the reaction are not charged.

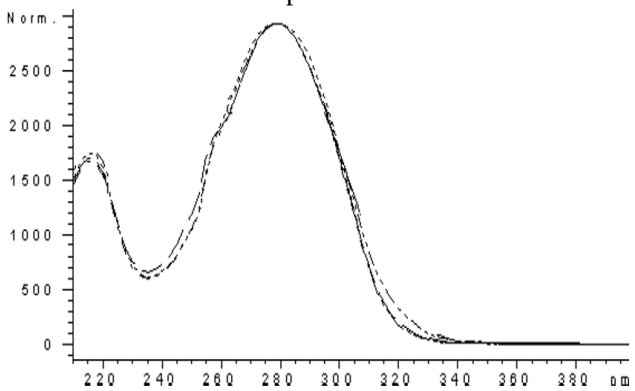


Figure.5. UV Spectrum of Compound IIa

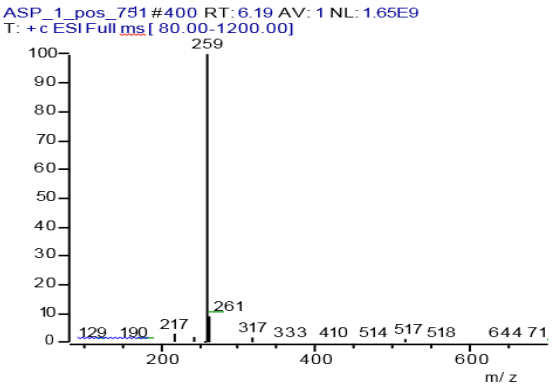


Figure.6. Mass spectrum of degradation product of compound IIa

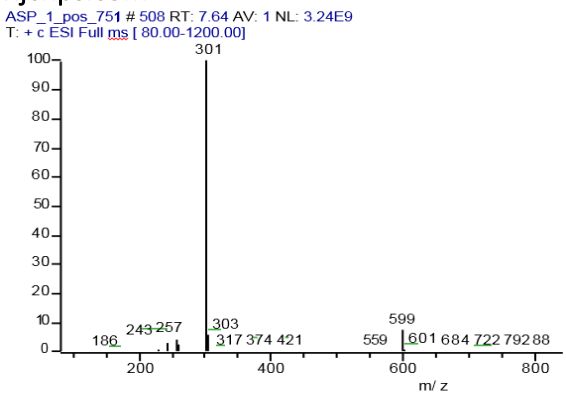


Figure.7. Mass spectrum of compound IIa

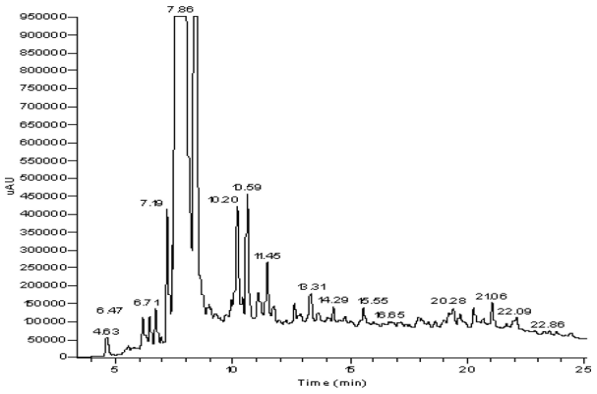


Figure.8. Chromatogram portion of Compound IIb in LC-MS

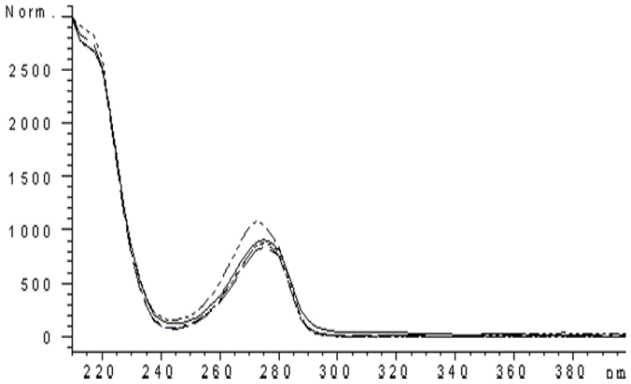


Figure.9. UV Spectrum of Compound IIb

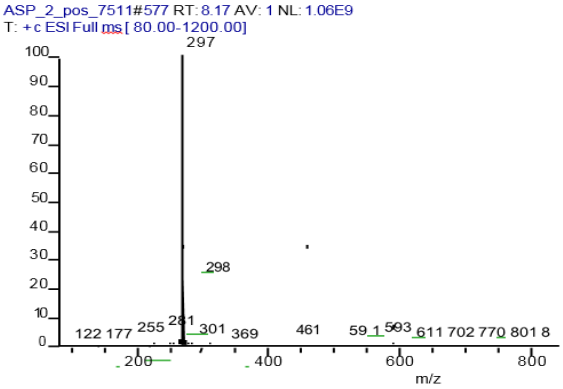


Figure.10. Mass spectrum of compound IIb

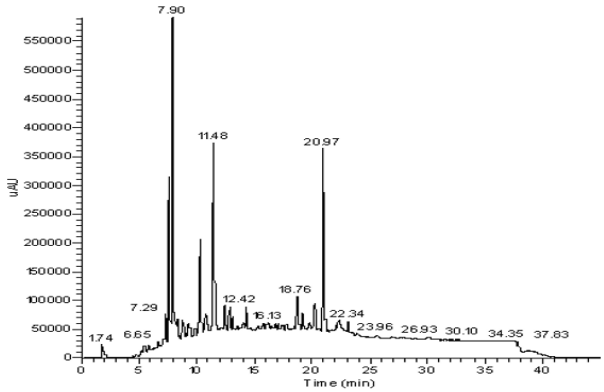


Figure.11. Chromatogram portion of LC-MS of Compound IIc

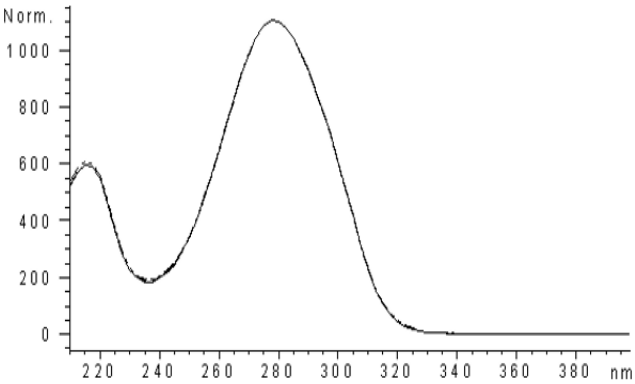


Figure.12. UV Spectrum of Compound IIc

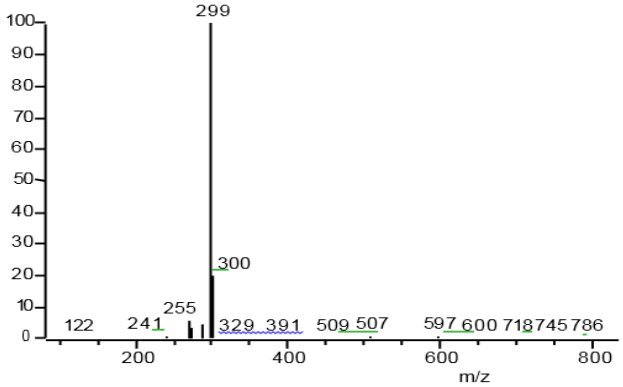


Figure.13. Mass spectrum of compound IIc

4. CONCLUSION

Six new tetracyclic analogues of Tacrine have been synthesized. The use of MW oven for the synthesis did not yield the product. However, the product formation was observed when anhydrous zinc chloride was used as a catalyst along with benzene/toluene as a solvent and also with anhydrous aluminum chloride and dichloroethane as catalyst and solvent respectively. It was also found that anhydrous Zinc Chloride (with or without the presence of solvent, toluene) as a catalyst gave lesser yield when compared to anhydrous Aluminum Chloride in the presence of dichloroethane as solvent. Synthesis of other derivatives and their Acetylcholine Esterase inhibition are under progress from our laboratory.

Conflict of Interest: The authors confirm that this article has no conflicts of interest.

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