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RESEARCH ARTICLE

SOLVENT FREE SYNTHESIS OF PYRROLO[2,1-a]ISOQUINOLINES UNDER MICROWAVE-IRRADIATION: AN ANTIOXIDANT POTENT.

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Abstract

An environmentally benign protocol has been described for the synthesis of substituted pyrrolo[2,1-a]isoquinolines from 3-formyl chromone and 2-aryl/alkoxycarbonylmethylisoquinolium bromide using basic alumina as solid base in a solvent-free condition under microwave irradiation. All the synthesized compounds have also been screened for their antioxidant activities by DPPH method and were found to be significantly active with respect to Butylatedhydroxytoluene (BHT).

Introduction:-

In recent years, microwave-assisted organic synthesis using recyclable and less expensive solid mineral supports (*e.g*., silica gel, alumina) has attracted a great deal of attention[1-3]. Microwave assisted solid supported reactions not only eliminates the use of solvents and requirement of sealed vessels, furthermore, it enables microwave-accelerated reactions to occur at atmospheric pressure, and extending it to preparative scale[4,5].On the other hand, the homogenous dispersion of active sites, improved selectivity, enhanced reaction rates,easy work-up procedure make the microwave-assisted solid-supported reactions attractive compare to the conventional solution phase reactions or in presence of transition metal catalyzed reactions[6-8].

Synthesis of pyrrolo[2,1-*a*]isoquinoline moieties have received much attention as they possess various biological activity[9,10] and serve as intermediates for the synthesis of bioactive alkaloids[11]. Moreover, this type of compounds can be used as Positron Emission Tomography(PET) radiotracers for imaging serotonin uptake sites[12].The varied biological activities of pyrrolo[2,1-*a*]isoquinoline derivatives have attracted the attention of organic chemists and a number of synthetic methodologies have been developed for this system[13-20].

Despite the availability of different methodologies, there is scope for the development of green protocol with greater efficiency and simpler operation, as synthetic steps and from simple starting materials. In this communication we have developed a green protocol for the one of the recent challenges in organic synthesis is the demand for novel environmentally benign methodologies that afford products of structural complexity in fewer synthesis of pyrrolo[2,1-*a*]isoquinoline from 3-formyl chromone and alkyl/aryl carbonylmethyl isoquinolium bromide using basic alumina as solid base in a solvent-free condition under microwave irradiation. The use of basic alumina used

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in the strategy serves dual role, eliminating the use of additional base and the requirement of hazardous solvents.Recently,chemists have increased interest in the synthesis of active antioxidant compound because medical scientific research indicates that antioxidants can reduce the risk for chronic diseases including cancer, heart attack, atherosclerosis, aging, inflammation, diabetes, hair loss, immunosupression, Alzheimer's and Parkinson's diseases[21-22].

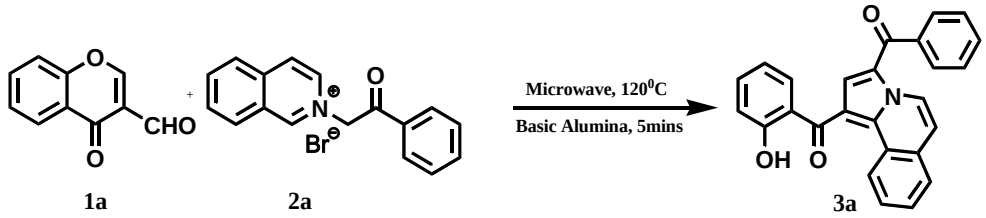
Antioxidant can be synthetic or natural. Primary sourcedantioxidants such as Vit-C, Vit-E, carotenes, Phenolic acids etc. have been recognized as having the potential to reduce disease risk[23]. Practically, during the normal course of metabolism in human body free radicals [Reactive Oxygen or Nitrogen Species (ROS/RNS)] are generated as a byproduct of cellular aerobic respiration with odd electron[24]. Over production of ROS (superoxide radicals, hydroxyl radicals, singlet oxygen, hydrogen peroxide radical) and RNS can damage to biomolecules such as DNA, nucleic acids, carbohydrates, lipids or proteins[25]. Antioxidants are basically free radical scavengers which can neutralize the unwanted free radicals present in our body system by interfering with oxidative process, oxygen scavengers and chelating with the metals. Normally, by using different enzymes and body defense mechanism can balance the production and elimination of ROS in human body. Virtually, antioxidant can slow down the oxidation of other molecules and can combine with radicals to prevent the damage of ROS. In conclusion, it is a way to overcome the oxidative stress of human body. So, synthesis of active antioxidant supported compound in chemical history is now a pressing issue and a great deal of chemistry.

Therefore, the present research was designed to synthesize variously substituted pyrrolo[2,1-*a*]isoquinolines with its synthetic strategy, mechanistic pathway, chracterization including spectroscopy and also examined their antioxidant potentiality using a reference compound BHT.

Results and Discussions:-

Initially, 1 mmol 3-formyl chromone (**1a**) and 1 mmol of 2-phenyl carbonylmethyl isoquinolium bromide (**2a**) were added to the basic alumina (0.5 g) in a mortar and mixed thoroughly. The resulting mixture was transferred into a beaker and exposed to microwave irradiation at 120 ^{0}C for 5 minutes to afford (3-benzoyl-pyrrolo[2,1-*a*]isoquinolin-1-yl)-(2-hydroxy-phenyl)methanone (**3a)** in excellent yield (Scheme 1).

Scheme 1:-

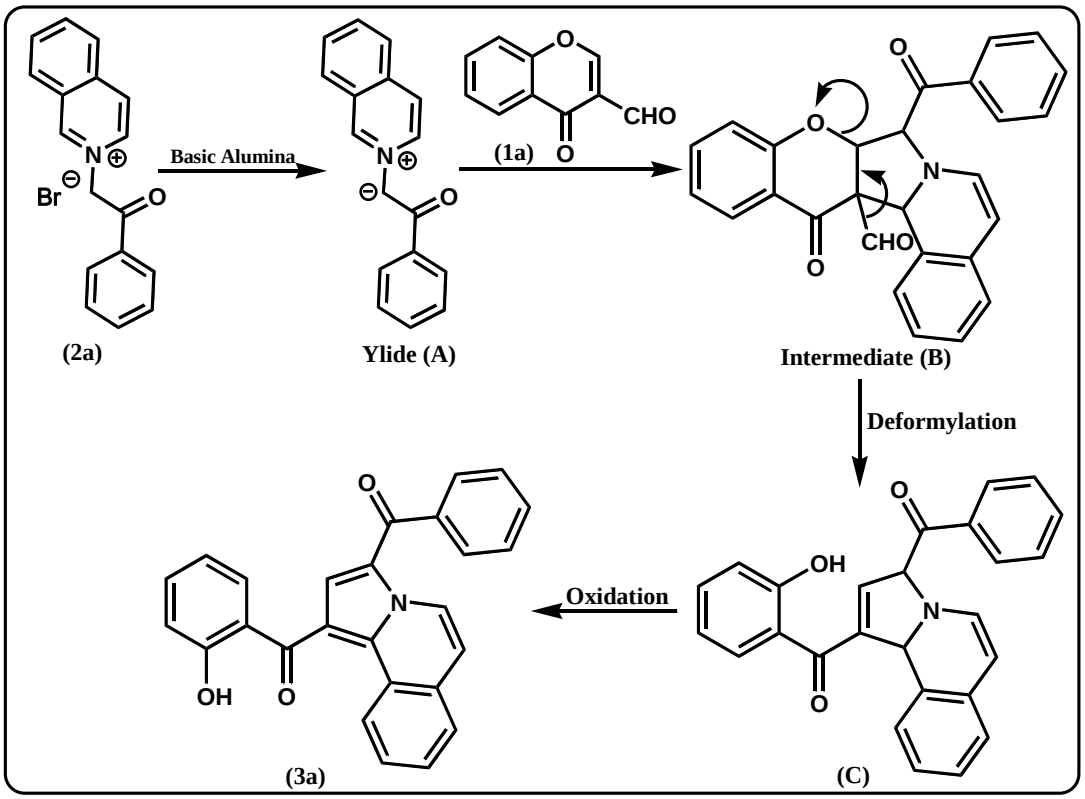


1a **2a** **3a**

The above reaction was also performed using some organic (DBU, Et_3N) and inorganic base (K_2CO_3, Na_2CO_3) instead of basic alumina, but the yield of the reaction was not satisfactory. Even the use of silica gel, titanium dioxide(TiO_2) or montmorillonitrile-K10 as solid support and Et_3N as base proved less effective compared to basic alumina alone. In order to evaluate the effect of microwave irradiation in comparison with conventional heating, a pre-heated oil-bath was used as heat source in a comparative experiment. The very poor yield (≤5%) under thermal condition, even after prolong reaction time clearly indicated the effect of microwave is not purely thermal and the reason may be attributed to the easy excitation of electronic energy levels due to microwave heating.

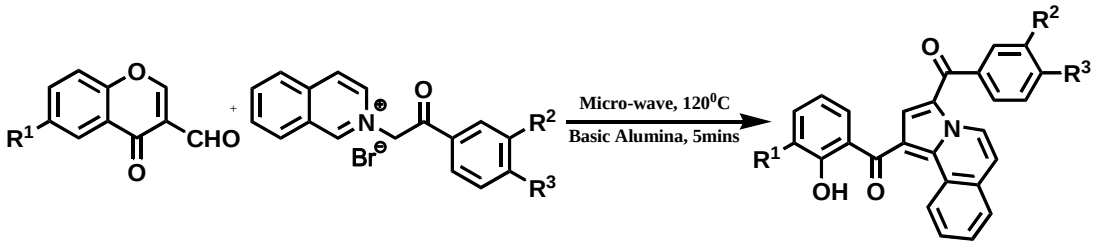
A plausible pathway for the formation of **3a** is depicted in Scheme 2. Initially, the oxide ions of basic alumina help to easy formation of isoquinolinium ylide (**A**) through de-protonation of the isoquinolium salt (**2a**). Then, a regioselective 1,3-dipolar cycloaddition occurs between the electron deficient C_2-C_3 π bond of 3-formyl chromone(**1a**) and the isoquinoliun ylide(**A**), forming an unstable pentacyclic fused intermediate **B**. The intermediate **B** after subsequent deformylation[26] and pyrone ring cleavage[27] leads to intermediate **C**, which finally oxidizes to afford **3a**.

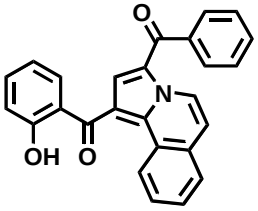
Scheme 2:-



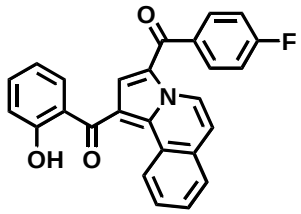
In order to establish the generality and feasibility of the above protocol, differently substituted 3-formyl chromone derivatives (1a: R^1=H, 1b: R^2=Me, 1c: R^1=Cl) were reacted with different derivatives of and 2-phenyl carbonylmethylisoquinolium bromide (2a-2e). All the derivatives reacted smoothly to produce substituted pyrrolo[2,1-*a*]isoquinoline (3b-3l) in high yield. (Scheme 3, entries 2-12).In order to further establish the generality of the method, 3-formyl chromone (**1a**) was reacted with different 2-alkoxy carbonylmethyl isoquinolium bromide (**4a-4c**) to produce ester substituted pyrrolo[2,1-*a*]isoquinoline (**5a-5c**) in excellent yield (Scheme 4).

Scheme 3:-

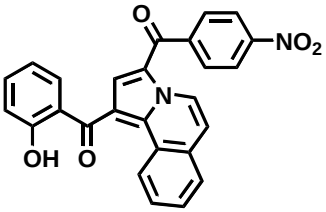




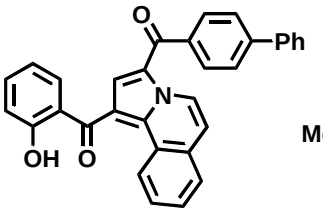
3a: Yield 98%



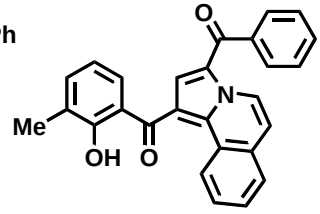
3b: Yield 96%



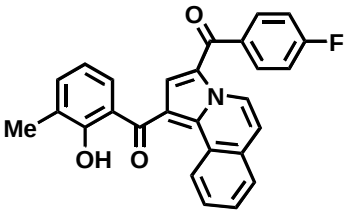
3c: Yield 96%



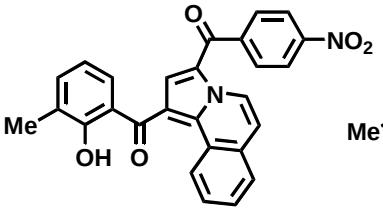
3d: Yield 97%



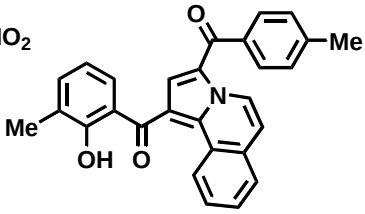
3e: Yield 98%



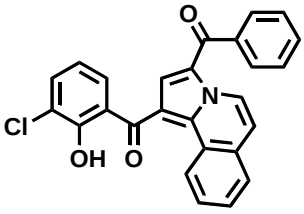
3f: Yield 98%



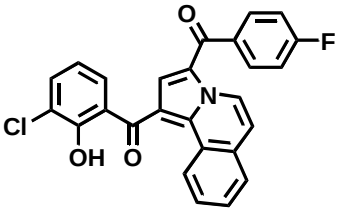
3g: Yield 96%



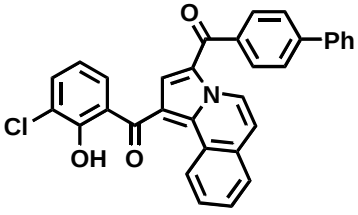
3h: Yield 97%



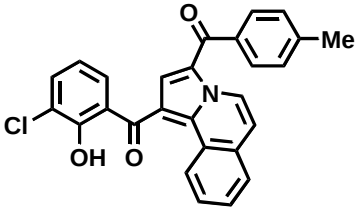
3i: Yield 98%



3j: Yield 98%



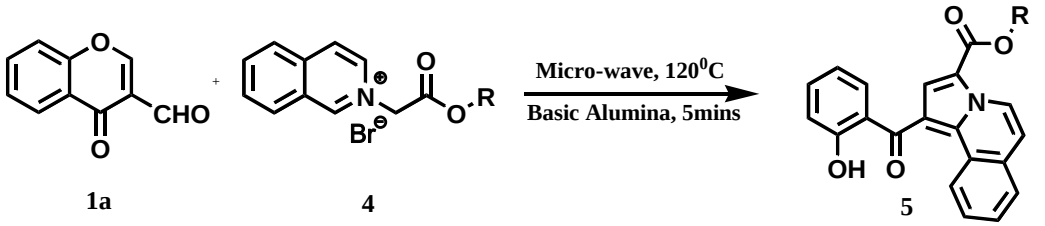
3k: Yield 96%



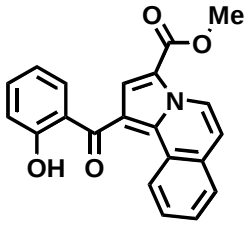
3l: Yield 96%

We also investigated the above reaction with 3-formyl thiochromone (6a) instead of 3-formyl chromone, but in that case no product was isolated (Scheme 5). The observed striking difference in reactivity between 3-formyl chromone and 3-formyl thiochromone is due to lesser reactivity of C_2-C_3 π bond and greater aromaticity of the thiochromone system as compared with chromones[28]. We also performed the above reaction with **1a** andthiazolium salt **6b**, in that case a pyrrolo[2,1-*b*]thiazole derivative **7** was isolated as anticipated (Scheme 6) but the yield of the product was very poor (≤10%).

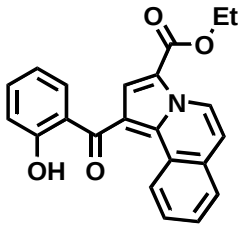
Scheme 4:-



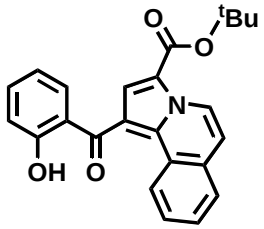
1a **4** **5**



4a: R=Me; **5a:** Yield 98%

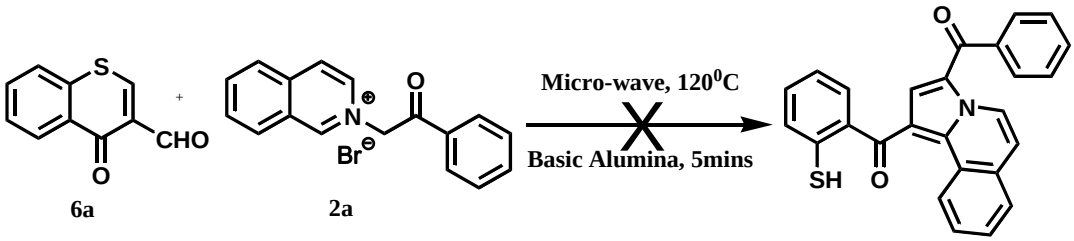


4b: R=Et; **5b:** Yield 96%



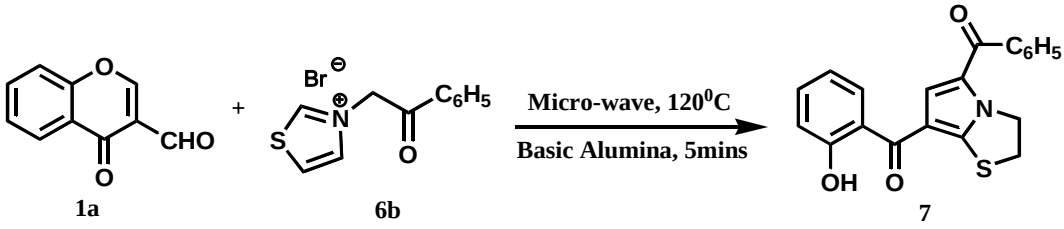
4c: R=^{t}Bu; **5c:** Yield 96%

Scheme 5:-



6a **2a**

Scheme 6:-



1a **6b** **7**

All the products (3a-l, 5a-c and 7) were characterized by IR, NMR and Mass spectroscopy also by comparison of the data reported in the literature.

Assay for DPPH radical scavenging activity:-

Phenolic compounds are well behaved free radical scavengers by virtue of their hydrogen donating ability, forming phenoxyl radicals (Scheme 7). According to their stability factor of such radicals by other functional groups in their structure enhances the antioxidant activity. It is well established that ortho and para substitution with electron donating groups (EDG) increases the stability of the aryloxyl/phenoxyl radicals through inductive effect (I-effect) or resonance effect (R-effect) and thus the antioxidant activity and consequently has lower IC_{50} value. Substitutions with electron withdrawing groups (EWG) have just the opposite effect.

All the twelve synthesized compounds with substitution at the *ortho*position of phenolic -OH, can be sub-divided into three classes as follows: **set-A** (3a, 3b, 3c, 3d) contains simple -H, **set-B** (3e, 3f, 3g, 3h) contains -Me and **set-C** (3i, 3j, 3k, 3l) contains –Cl. The compounds of**set-B** have electron donating –Me group at *ortho* position of –OH group. As a result they are most potent antioxidants and have lower value of IC_{50} than the others. Similarly, compounds of **set-C** have electron withdrawing –Cl group at *ortho* position of –OH group and as a result show

lower antioxidant activity than the compounds of **set-A** and **set-B** due to stabilize factors of the phenoxyl radical and have highest IC_{50} value for **set-C**. Now, in case of **set-A** i.e. in absence of any EDG or EWG shows moderate antioxidant potency. Interestingly, in case of antioxidant activity, highly efficient antioxidant potents are methyl substituted compounds of **set-B** and in conclusion the antioxidant potentialities are as follows: **set-B**>**set-A**>**set-C**.

Scheme 7:-Plausible mechanistic pathway of DPPH radical scavenging process.

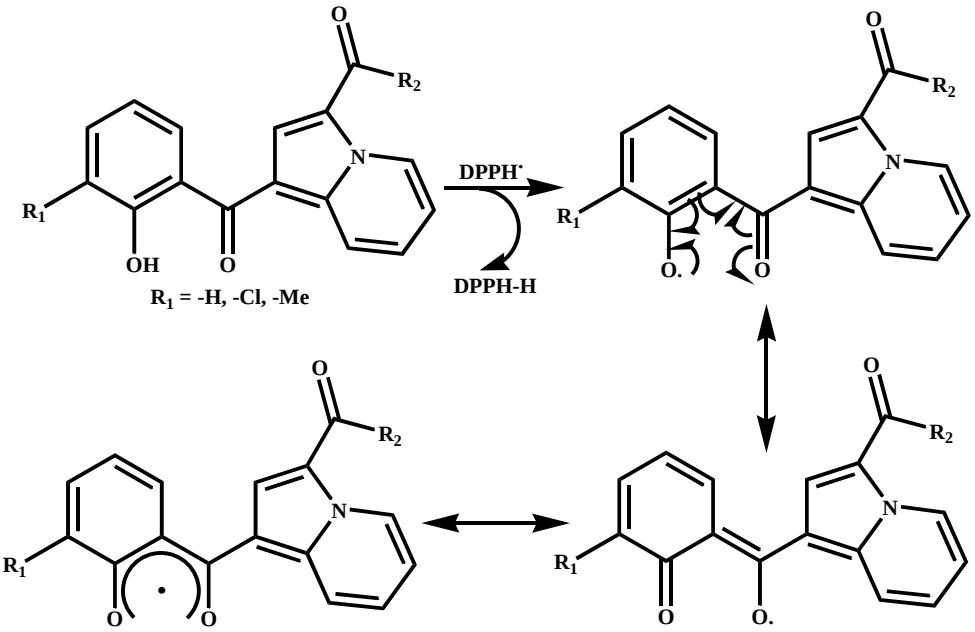
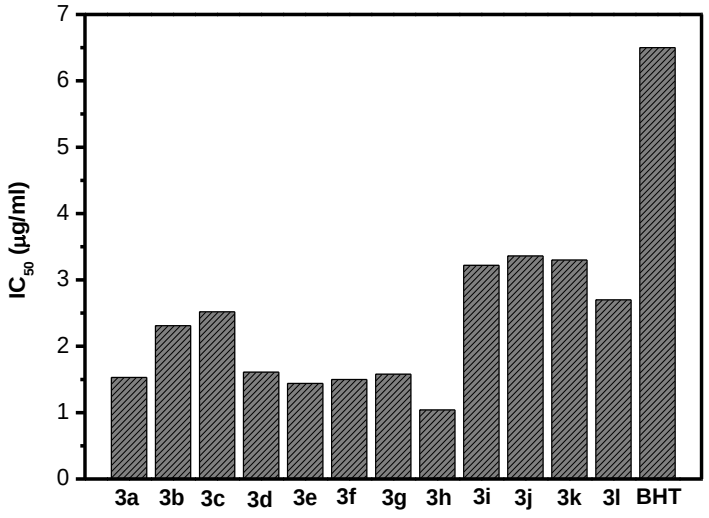


Chart 1:-IC_{50} values of the synthesized compounds (**3a-3l**) by DPPH method**.**



Experimental:-

All chemicals were purchased from Sigma Aldrich Chemical Co. and used without further purification. The solvents used for spectroscopic studies and for syntheses were purified and dried by standard procedures prior to use. Ethanol used for antioxidant study is of HPLC grade and was purchased from Merck.

The Fourier transform infrared (FT-IR) spectra were recorded on Thermo Nicolet iS10 spectrometer using KBr pellet in the range 4000–400cm^{-1}. The electronic spectra were recorded on Thermo-Scientific Orion Aquamate-8000 spectrophotometer for antioxidant study. Elemental analyses were carried out on a Perkin-Elmer 2400 series-II CHNS Analyzer& NMR spectra were recorded on Bruker DPX-300.

General Procedure:-

Basic alumina (0.5 g) was placed in a mortar followed by either 1mmol 3-formyl chromone derivatives (**1a-1c**) and 2-phenyl carbonylmethylisoquinolium bromide derivative (**2a-2e**) [for the synthesis **3a-3l**] or either 1mmol 3-formyl chromone (**1a**), 1mmol 2-alkoxy carbonylmethylisoquinolium bromide derivative (**4a-4c**) [for the synthesis **5a-5c**]. The reactants were mixed well for 5 minutes using a pestle. The homogenized mixture was placed in a beaker, preheated in a microwave oven for 2min at 120^{0}C (250 W) and the heating was continued for 5 minutes to complete the reaction (monitored by TLC). The contents were cooled to room temperature and mixed thoroughly with 10mL of acetone. The solid inorganic material was filtered off and the filtrate was evaporated to dryness. The residue was crystallized from chloroform-hexane mixture to afford pure **3a-3l** or **5a-5c** and also **7**.

DPPH radical scavenging activity:-

The antioxidant activity of the synthesized compounds was assessed in vitro by the 1,1 diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. 1mL of various concentrations of test compounds (0.25, 0.52, 0.76, 1.51, 3.10 and 6.25 µg/mL) was mixed with 1.0 mL of 0.1mM methanolic solution of DPPH[29,30]. The mixture was shaken vigorously and was incubated for 30mins at room temperature in dark. The absorbance of the resulting solutions were measured at 517nm against methanol as blank using a spectrophotometer. Free radical scavenging ability of the sample was calculated according to the following equation:

$$\% \text{ Activity (DPPH)} = \{(A_{Control} - A_{Sample}) / A_{Control}\} \times 100$$

Where $A_{Control}$ and A_{Sample} are the absorbances in the absence and presence of the tested compounds.Butylatedhydroxytoluene (BHT) was used as a standard antioxidant. All the analyses were carried out in triplicate.

Table 1:-% of *in vitro* radical scavenging activity of the synthesized compounds (3a-3l).

Entry	Concentration (µg/mL)						
	0.25	**0.52**	**0.76**	**1.51**	**3.10**	**6.25**	**IC_{50}**
3a	13.65	41.45	52.35	62.60	71.45	89.90	1.53
3b	9.60	36.55	46.20	58.00	67.12	71.34	2.31
3c	7.15	34.20	45.75	56.25	65.50	70.25	2.52
3d	13.61	41.00	51.30	62.60	70.20	86.65	1.61
3e	10.15	42.75	53.60	64.50	76.00	92.20	1.44
3f	10.00	42.60	53.40	63.20	74.15	91.15	1.50
3g	9.75	42.15	50.15	66.15	71.20	90.00	1.58
3h	13.80	46.50	59.90	69.75	76.25	98.75	1.04
3i	5.60	26.00	37.10	51.50	63.15	63.25	3.22
3j	5.90	25.15	32.75	52.50	60.15	63.00	3.36
3k	4.95	26.15	36.15	50.50	61.35	63.25	3.30
3l	6.15	32.50	39.50	53.40	64.95	71.25	2.70
BHT[a]	-	4.75	12.02	24.15	29.90	44.75	6.50

- No activity

[a]Butylatedhydroxytoluene as standard substance.

(3-Benzoyl-pyrrolo[2,1-a]isoquinolin-1-yl)-(2- hydroxy-phenyl)-methanone (3a): Yellow needles (98% yield), Mp 195-197 °C (lit.[20] Mp 194-196 °C); R_f (Hexane/EtOAc 9:1) 0.51; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (1H, t, *J*= 7.5 Hz), 7.09 (1H, d, *J*= 8.1 Hz), 7.33 (1H, d, *J*= 7.5 Hz), 7.43 (1H, s), 7.53 (5H, m), 7.62 (1H, m), 7.69 (1H, d, *J*= 8.1 Hz), 7.79 (1H, d, *J*= 7.8 Hz), 7.85 (2H, m), 8.51 (1H, d, *J*= 8.4 Hz), 9.68 (1H, d, *J*= 7.5 Hz), 12.28 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.7 (CH), 116.3 (C), 118.4 (CH), 118.8 (CH), 120.6 (C), 123.4 (C), 123.9 (C), 125.1 (CH), 126.0 (CH), 127.2 (CH), 127.9 (CH), 128.4 (2xCH), 128.9 (CH), 129.1 (CH), 129.3 (2xCH), 130.3 (C), 131.8 (CH), 133.3 (CH), 135.5 (C), 136.4 (CH), 139.6 (C), 163.2 (C), 185.8 (CO), 197.6 (CO); MS: (ESI-MS, positive

mode) *m/z* 392 $[M+H]^+$, 414 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{26}H_{17}NO_3Na$: 414.1106; found: 414.1102.

[3-(4-Fluoro-benzoyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-(2-hydroxy-phenyl)-methanone(3b): Yellow needles (96% yield), Mp 196-198 °C (lit.[20] Mp 198-200 °C); R_f (Hexane/EtOAc 9:1) 0.51; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (1H, m), 7.10 (1H, d, *J*= 8.4 Hz), 7.18 (2H, t, *J*= 8.7 Hz), 7.34 (1H, d, *J*= 7.5 Hz), 7.40 (1H, s), 7.52 (2H, m), 7.65 (2H, m), 7.80 (1H, d, *J*= 7.8 Hz), 7.89 (2H, m), 8.51 (1H, d, *J*= 8.4 Hz), 9.63 (1H, d, *J*= 7.5 Hz), 12.26 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.5 (2xCH, $^2J_{C-F}$= 21.75 Hz), 115.8 (CH), 116.4 (C), 118.5 (CH), 118.8 (CH), 120.6 (C), 123.3 (C), 123.9 (C), 125.0 (CH), 126.0 (CH), 127.2 (CH), 128.0 (CH), 128.6 (CH), 129.4 (CH), 130.3 (C), 131.5 (2xCH, $^3J_{C-F}$= 9 Hz), 133.2 (CH), 135.6 (C), 135.8 (C, $^4J_{C-F}$= 3 Hz), 136.5 (CH), 163.3 (C), 166.6 (C, $^1J_{C-F}$= 252), 184.3 (CO), 197.6 (CO); MS: (ESI-MS, positive mode) *m/z* 410 $[M+H]^+$, 432 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{26}H_{16}FNO_3Na$: 432.1012; found: 432.1008.

(2-Hydroxy-phenyl)-[3-(4-nitro-benzoyl)pyrrolo[2,1-a]isoquinolin-1-yl]-methanone(3c): Yellow needles (96% yield), Mp 196-198 °C (lit.[20] Mp 194-196 °C); R_f (hexane/EtOAc 9:1) 0.34; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (1H, m), 7.11 (1H, d, *J*= 8.4 Hz), 7.34 (1H, s), 7.39 (1H, t, *J*= 7.5 Hz), 7.54 (2H, m), 7.66 (2H, m), 7.83 (1H, d, *J*= 7.8 Hz), 7.98 (2H, d, *J*= 8.4Hz), 8.35 (2H, d, *J*= 8.4 Hz), 8.49 (1H, d, *J*= 8.1 Hz), 9.72 (1H, d, *J*= 7.2 Hz), 12.20 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 116.4 (CH), 117.0 (C), 118.6 (CH), 119.0 (CH), 120.5 (C), 122.8 (C), 123.69 (2xCH), 123.74 (C), 125.0 (CH), 126.1 (CH), 127.3 (CH), 128.3 (CH), 129.2 (CH), 129.8 (CH), 129.9 (2xCH), 130.6 (C), 133.1 (CH), 136.2 (C), 136.7 (CH), 145.1 (C), 149.5 (C), 163.4 (C), 183.3 (CO), 197.4 (CO); MS: (ESI-MS, positive mode) *m/z* 437 $[M+H]^+$, 459 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{26}H_{16}N_2O_5Na$: 459.0957; found: 459.0951.

[3-(Biphenyl-4-carbonyl)-pyrrolo[2,1-a]isoquinolin -1-yl]-(2-hydroxy-phenyl)-methanone(3d): Yellow needles (97% yield), Mp 176-181 °C (lit.[20] Mp 178-180 °C); R_f (Hexane/EtOAc 9:1) 0.50; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (1H, m), 7.10 (1H, d, *J*= 8.4 Hz), 7.34 (1H, d, *J*= 7.5 Hz), 7.40 (1H, m), 7.45 (1H, s), 7.52 (4H, m), 7.63 (3H, m), 7.72 (3H, d, *J*= 8.1 Hz), 7.80 (1H, d, *J*= 7.8 Hz), 7.94 (2H, d, *J*= 8.1 Hz), 8.53 (1H, d, *J*= 8.1 Hz), 9.69 (1H, d, *J*= 7.5 Hz), 12.29 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 115.7 (CH), 116.3 (C), 118.4 (CH), 118.9 (CH), 120.7 (C), 123.6 (C), 124.0 (C), 125.2 (CH), 126.0 (CH), 127.1 (2xCH), 127.2 (2xCH), 127.3 (CH), 128.0 (CH), 128.1 (CH), 128.8 (2xCH), 128.9 (CH), 129.3 (CH), 129.8 (2xCH), 130.4 (C), 133.4 (CH), 135.6 (C), 136.4 (CH), 138.3 (C), 139.9 (C), 144.8 (C), 163.3 (C), 185.4 (CO), 197.7 (CO); MS: (ESI-MS,positive mode) *m/z* 468 $[M+H]^+$, 490 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{32}H_{21}NO_3Na$: 490.1419; found: 490.1412.

(3-Benzoyl-pyrrolo[2,1-a]isoquinolin-1-yl)-(2-hydroxy-5-methyl-phenyl)-methanone(3e): Yellow needles (98% yield), Mp 204-206 °C (lit.[20] Mp 206-208 °C); R_f (Hexane/EtOAc 9:1) 0.53; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.22 (3H, s), 7.00 (1H, d, *J*= 8.4 Hz), 7.32 (2H, m), 7.42 (1H, s), 7.50 (3H, m), 7.57 (2H, m), 7.63 (1H, m), 7.79 (1H, d, *J*=7.8 Hz), 7.87 (2H, d), 8.55 (1H, d, *J*= 7.8 Hz), 9.67 (1H, d, *J*= 7.2 Hz), 12.08 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.5 (CH_3), 115.7 (CH), 116.4 (C), 118.2 (CH), 120.4 (C), 123.4 (C), 124.0 (C), 125.1 (CH), 126.0 (CH), 127.2 (CH), 127.9 (C), 128.0 (CH), 128.4 (2xCH), 129.1 (CH), 129.26 (2xCH), 129.31 (CH), 130.3 (C), 131.9 (CH), 133.1 (CH), 135.5 (C), 137.4 (CH), 139.7 (CH), 161.2 (C), 185.9 (CO), 197.6 (CO); MS: (ESI-MS, positive mode) *m/z* 406 $[M+H]^+$, 428 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{27}H_{19}NO_3Na$: 428.1263; found: 428.1258.

[3-(4-Fluoro-benzoyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-(2-hydroxy-5-methyl-phenyl)-methanone(3f): Yellow needles (98% yield), Mp 215-218 °C (lit.[20] Mp 216-218 °C); R_f (Hexane/EtOAc 9:1) 0.54; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (3H, s), 7.01 (1H, d, *J*= 8.1 Hz), 7.18 (2H, m), 7.33 (2H, d, *J*= 7.5 Hz), 7.39 (1H, s), 7.48 (1H, m), 7.54 (1H, m), 7.63 (1H, m), 7.79 (1H, d, *J*= 7.8 Hz), 7.90 (2H, m), 8.52 (1H, d, *J*= 8.1 Hz), 9.62 (1H, d, *J*=7.5 Hz), 12.06 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4 (CH_3), 115.5 (2xCH, $^2J_{C-F}$= 21.75 Hz), 115.7 (CH), 116.4 (C), 118.2 (CH), 120.4 (C), 123.2 (C), 124.0 (C), 125.0 (CH), 126.0 (CH), 127.2 (CH), 127.9 (C), 128.0 (CH), 128.7 (CH), 129.3 (CH), 130.3 (C), 131.6 (2xCH, $^3J_{C-F}$= 9 Hz), 133.0 (CH), 135.6 (C), 135.9 (C, $^4J_{C-F}$= 3 Hz), 137.5 (CH), 161.2 (C), 163.3 (C, $^1J_{C-F}$= 251.25), 184.3 (CO), 197.5 (CO); MS: (ESI-MS, positive mode) *m/z* 424 $[M+H]^+$, 446 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{27}H_{18}FNO_3Na$: 446.1168; found: 446.1160.

(2-Hydroxy-5-methyl-phenyl)-[3-(4-nitro-benzoyl)-pyrrolo[2,1 a]isoquinolin-1-yl]-methanone(3g): Yellow needles (96% yield), Mp 198-200 °C (lit.[20] Mp 198-200 °C); R_f (Hexane/EtOAc 9:1) 0.35; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.20 (3H, s), 7.01 (1H, d, *J*= 8.4 Hz), 7.34 (1H, m), 7.35 (1H, s), 7.40 (1H, d, *J*= 7.2 Hz), 7.43 (1H, d, *J*= 1.8 Hz), 7.57 (1H, m), 7.66 (1H, m), 7.83 (1H, d, *J*= 7.8 Hz), 8.00 (1H, d, *J*= 8.4 Hz), 8.22 (1H, m), 8.29 (1H, m), 8.35 (1H, d, J= 9 Hz), 8.49 (1H, d, J= 8.4 Hz), 9.71 (1H, d, *J*= 7.2 Hz), 12.00 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ

20.5 (CH_3), 117.1 (C), 118.4 (CH), 120.2 (C), 122.7 (C), 123.5 (CH), 123.7 (CH), 123.8 (CH), 125.0 (CH), 126.1 (CH), 127.3 (CH), 128.0 (C), 128.3 (CH), 129.1 (CH), 129.8 (CH), 129.9 (CH), 130.5 (C), 130.7 (CH), 132.8 (CH), 135.5 (C), 136.2 (C), 137.8 (CH), 145.1 (C), 149.5 (C), 161.3 (C), 183.3 (CO), 197.4 (CO); MS: (ESI-MS, positive mode) *m/z* 451 $[M+H]^+$, 473 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{27}H_{18}N_2O_5Na$: 473.1113; found: 473.1106.

(2-Hydroxy-5-methyl-phenyl)-[3-(4-methyl-benzoyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-methanone(3h): Yellow needles (97% yield), Mp 210-212 °C (lit.[20] Mp 212-214 °C); R_f (Hexane/EtOAc 9:1) 0.57; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.22 (3H, s), 2.44 (3H, s), 7.00 (1H, d, *J*= 8.4 Hz), 7.30 (4H, m), 7.42 (1H, s), 7.53 (2H, m), 7.62 (1H, m), 7.79 (3H, d), 8.55 (1H, d, *J*= 8.1 Hz), 9.63 (1H, d, *J*= 7.5 Hz), 12.08 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4 (CH_3), 21.5 (CH_3), 115.5 (CH), 116.2 (C), 118.1 (CH), 120.4 (C), 123.5 (C), 124.0 (C), 125.0 (CH), 125.9 (CH), 127.1 (CH), 127.8 (C), 127.9 (CH), 128.8 (2xCH), 129.0 (CH), 129.2 (CH), 129.4 (2xCH), 130.2 (C), 133.1 (CH), 135.3 (C), 136.9 (C), 137.3 (CH), 142.6 (C), 161.2 (C), 185.6 (CO), 197.5 (CO); MS: (ESI-MS, positive mode) *m/z* 420 $[M+H]^+$, 442 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{28}H_{21}NO_3Na$: 442.1419; found: 442.1412.

(3-Benzoyl-pyrrolo[2,1-a]isoquinolin-1-yl)-(5-chloro-2-hydroxy-phenyl)-methanone(3i): Yellow needles (98% yield), Mp 225-227 °C (lit.[20] Mp 224-226 °C); R_f (Hexane/EtOAc 9:1) 0.62; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (1H, d, *J*= 9 Hz), 7.37 (1H, d, *J*= 7.5 Hz), 7.43 (1H, s), 7.46 (1H, m), 7.52 (2H, m), 7.60 (2H, m), 7.69 (1H, m), 7.76 (1H, m), 7.82 (1H, d, *J*= 7.8 Hz), 7.88 (2H, d), 8.63 (1H, d, *J*= 8.4 Hz), 9.68 (1H, d, *J*= 7.5 Hz), 12.10(1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 115.5 (C), 116.1 (CH), 119.9 (C), 120.0 (CH), 121.5 (C), 123.4 (C), 123.6 (C), 124.0 (C), 125.1 (CH), 126.0 (CH), 127.3 (CH), 128.1 (CH), 128.5 (2xCH), 129.3 (2xCH), 129.5 (CH), 129.6 (CH), 130.5 (C), 132.1 (CH), 132.4 (CH), 136.0 (CH), 139.5 (C), 161.7 (C), 186.0 (CO), 196.1 (CO); MS: (ESI-MS, positive mode) *m/z* 448 $[M+Na]^+$, 450 M+2+$Na]^+$. HRMS (ESI) *m/z*calcd for $C_{26}H_{16}ClNO_3Na$: 448.0716; found: 448.0711.

(5-Chloro-2-hydroxy-phenyl)-[3-(4-fluoro-benzoyl)-pyrrolo[2,1 a]isoquinolin-1-yl]-methanone(3j): Yellow needles (98% yield), Mp 212-214 °C (lit.[20] Mp 212-214 °C); R_f (Hexane/EtOAc 9:1) 0.60; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (1H, d, *J*= 8.7 Hz), 7.21 (2H, m), 7.37 (1H, d, *J*= 7.5 Hz), 7.40 (1H, s), 7.46 (1H, m), 7.58 (1H, t, *J*= 7.2 Hz), 7.66 (1H, m), 7.73 ((1H, m), 7.82 (1H, d, *J*= 7.8 Hz), 7.91 (2H, m), 8.62 (1H, d, *J*= 8.1 Hz), 9.62 (1H, d, *J*= 7.5 Hz), 12.08 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.5 (CH), 115.8 (CH), 116.1 (CH), 120.1 (CH), 121.4 (C), 123.4 (C), 123.9 (2xC), 124.9 (CH), 126.0 (CH), 127.3 (CH), 128.1 (CH), 129.2 (CH), 129.7 (CH), 130.5 (2xC), 131.6 (CH), 131.7 (CH), 132.3 (CH), 135.7 (2xC), 136.0 (CH), 161.7 (2xC), 184.4 (CO), 196.0 (CO); MS: (ESI-MS, positive mode) *m/z* 466 $[M+Na]^+$, 468 M+2+$Na]^+$. HRMS (ESI) *m/z*calcd for $C_{26}H_{15}ClFNO_3Na$: 466.0622; found: 466.0619.

[3-(Biphenyl-4-carbonyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-(5-chloro-2-hydroxy-phenyl)-methanone(3k): Yellow needles (96% yield), Mp 218-220 °C (lit.[20] Mp 216-218 °C); R_f (Hexane/EtOAc 9:1) 0.55; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.05 (1H, d, *J*= 9 Hz), 7.37 (1H, d, *J*= 7.2 Hz), 7.41 (1H, m), 7.45 (1H, dd, J_1= 2.4 Hz, J_2 = 9 Hz), 7.48 (2H, m), 7.50 (1H, s), 7.59 (1H, m), 7.66 (3H, m), 7.74 (2H, m), 7.76 (1H, m), 7.80 (1H, d, *J*= 7.8 Hz), 7.97 (2H, m), 8.65 (1H, d, *J*= 8.4 Hz), 9.68 (1H, d, *J*= 7.2 Hz), 12.10 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 115.6 (2xC), 116.1 (CH), 120.0 (CH), 121.5 (C), 123.5 (C), 123.7 (C), 124.0 (C), 125.1 (CH), 126.0 (CH), 127.2 (CH), 127.30 (2xCH), 127.34 (2xCH), 128.09 (CH), 128.15 (CH), 129.0 (2xCH), 129.4 (CH), 129.6 (2xCH), 129.9 (CH), 130.5 (C), 132.4 (CH), 136.0 (CH), 138.2 (C), 139.9 (C), 145.0 (C), 161.7 (C), 185.5 (CO), 196.1 (CO); MS: (ESI-MS, positive mode) *m/z* 524 $[M+Na]^+$, 526 $[M+2+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{32}H_{20}ClNO_3Na$: 524.1029; found: 524.1018.

(5-Chloro-2-hydroxy-phenyl)-[3-(4-methyl-benzoyl)-pyrrolo[2,1-a]isoquinolin-1-yl]-methanone(3l): Yellow needles (96% yield), Mp 206-208 °C (lit.[20] Mp 208-210 °C); R_f (Hexane/EtOAc 9:1) 0.60; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (3H, s), 7.05 (1H, d, *J*= 9 Hz), 7.34 (3H, m), 7.43 (1H, s), 7.46 (1H, m), 7.61 (2H, m), 7.78 (4H, m), 8.64 (1H, d, *J*= 8.4 Hz), 9.64 (1H, d, *J*= 7.5 Hz), 12.11 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6 (CH_3), 115.3 (C), 115.9 (CH), 119.9 (CH), 121.5 (C), 123.3 (C), 123.7 (C), 123.9 (C), 125.0 (C), 125.9 (CH), 127.2 (CH), 127.9 (CH), 129.1 (CH), 129.2 (2xCH), 129.4 (4xCH), 130.4 (CH), 132.4 (C), 135.8 (CH), 136.7 (C), 142.8 (C), 161.6 (C), 185.6 (CO), 195.9 (CO); MS: (ESI-MS, positive mode) *m/z* 440 $[M+H]^+$, 462 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{27}H_{18}ClNO_3Na$: 462.0873; found: 462.0861.

1-(2-Hydroxy-benzoyl)-pyrrolo[2,1-a]isoquinoline-3-carboxylic acid methyl ester(5a): Yellow needles (98% yield), Mp 197-199 °C (lit.[20] Mp 198-200°C); R_f (Hexane/EtOAc 9:1) 0.59; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93 (3H, s), 6.90 (1H, m), 7.11 (1H, d, *J*= 8.1 Hz), 7.24 (1H, m), 7.55 (3H, m), 7.66 (1H, s), 7.76 (2H, m), 8.57 (1H, d,

J= 8.1 Hz), 9.40 (1H, d, *J*= 7.5 Hz), 12.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.6 (CH_3), 115.2 (CH), 115.7 (C), 115.8 (C), 118.3 (CH), 118.8 (CH), 120.8 (C), 124.2 (CH), 124.8 (CH), 125.7 (CH), 127.1 (CH), 127.8 (CH), 128.9 (CH), 129.5 (2xC), 133.5 (CH), 134.8 (C), 136.1 (CH), 161.3 (C), 163.2 (C), 196.4 (CO); MS: (ESI-MS, positive mode) *m/z* 346 $[M+H]^+$, 368 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{21}H_{15}NO_4Na$: 368.0899; found: 368.0895.

1-(2-Hydroxy-benzoyl)-pyrrolo[2,1-a]isoquinoline-3-carboxylic acid ethyl ester(5b): Yellow needles (96% yield), Mp 170-172°C (lit.[20] Mp 172-174°C); R_f (Hexane/EtOAc 9:1) 0.71; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (3H, m), 4.41 (2H, m), 6.91 (1H, t, *J*=7.5 Hz), 7.12 (1H, d, *J*=8.4 Hz), 7.23 (1H, m), 7.55 (3H, m), 7.66 (1H, s), 7.77 (2H, m), 8.54 (1H, d, *J*=8.1 Hz), 9.41 (1H, d, *J*=7.5 Hz), 12.31 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.4 (CH_3), 60.6 (CH_2), 115.2 (CH), 115.8 (C), 116.0 (C), 118.3 (CH), 118.8 (CH), 120.8 (C), 124.3 (C), 124.4 (CH), 124.7 (CH), 125.7 (CH), 127.2 (CH), 127.9 (CH), 128.8 (CH), 129.5 (C), 133.6 (CH), 134.7 (C), 136.2 (CH), 161.0 (C), 163.3 (C), 197.6 (CO); MS: (ESI-MS, positive mode) *m/z* 360 $[M+H]^+$, 382 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{22}H_{17}NO_4Na$: 382.1055; found: 382.1053.

1-(2-Hydroxy-benzoyl)-pyrrolo[2,1-a]isoquinoline-3-carboxylic acid tert-butyl ester(5c): Yellow needles (96% yield), Mp 185-187 C (lit.[20] Mp 186-188 C); R_f (Hexane/EtOAc 9:1) 0.79; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (9H, s), 6.89 (1H, m), 7.11 (1H, d, *J*= 8.4 Hz), 7.20 (1H, d, *J*= 7.5 Hz), 7.51 (4H, m), 7.75 (2H, m), 8.48 (1H, d, J=8.1 Hz), 9.40 (1H, d, *J*= 7.5 Hz), 12.35 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.4 (3xCH_3), 81.7 (C), 114.9 (CH), 115.5 (C), 117.3 (C), 118.3 (CH), 118.8 (CH), 120.8 (C), 124.3 (CH), 124.4 (CH), 124.5 (C), 125.6 (CH), 127.1 (CH), 127.7 (CH), 128.7 (CH), 129.4 (C), 133.6 (CH), 134.3 (C), 136.1 (CH), 160.5 (C), 163.3 (C), 197.8 (CO); MS: (ESI-MS, positive mode) *m/z* 388 $[M+H]^+$, 410 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{24}H_{21}NO_4Na$: 410.1368; found: 410.1357.

[7-(2-Hydroxy-benzoyl)-pyrrolo[2,1-b]thiazol-5-yl]-phenyl-methanone(7): Yellow needles (10% yield), Mp 172-194 °C; R_f (Hexane/EtOAc 9:1) 0.56; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (1H, t, *J*= 7.5 Hz), 7.09 (1H, d, *J*= 8.1 Hz), 7.13 (1H, s), 7.33 (1H, d, *J*= 7.5 Hz) Hz), 7.52 (1H, s, *J*=7.8), 7.52-7.56 (5H, m), 7.72 (2H, t, *J*=8.4), 8.12 (2H, t, *J*=7.8), 12.18 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 110.2 (C), 115.7 (CH), 116.2 (CH), 117.5 (CH), 118.3 (C), 118.4 (CH), 125.1 (CH), 128.2 (2xCH_2), 129.1 (CH), 131.9 (CH), 133.3 (CH), 134.3 (C), 135.4 (CH), 135.5 (C), 145.7 (CH), 157.4 (C), 163.1 (C), 185.6 (CO), 197.2 (CO); MS: (ESI-MS, positive mode) *m/z* 348 $[M+H]^+$, 370 $[M+Na]^+$. HRMS (ESI) *m/z*calcd for $C_{20}H_{15}N_1O_3S_1Na$: 372.0514; found: 372.0510

Conclusions:-

In conclusion, we have developed an eco-friendly methodology for the solvent-free and transition metal free synthesis of substituted pyrrolo[2,1-*a*]isoquinolines using basic alumina as solid base under microwave irradiation. In general, it was found that the compounds with electron donating groups (set-B) at the *ortho* position of the phenolic ring displayed better antioxidant compare to the electron withdrawing group (set-C) or without any substitution at the same position (set-A).

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