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Development of Novel Indole Molecules for the Screening Of Anti-Oxidant Activity

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Research Article

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ABSTRACT

In the present work, some new 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-diones were prepared from 5-hydroxy isatin. A mixture of 5-hydroxy isatin, dialkylamino alkylhalide in alcoholic potassium hydroxide was stirred at room temperature for 6 hours to get the 5-[2(3)-dialkylamino alkoxy] Indole 2,3-diones. The structures of the products were characterized by IR, NMR, MASS Spectral studies. All the compounds were examined for antioxidant activity by using 1, 1-diphenyl-2-picryl-hydrazyl and hydrogen peroxide (H_2O_2), and the total antioxidant capacity by a phosphomolybdenum assay. In general, the derivatives were found to exhibit antioxidant activity. Further, the compounds with dialkylamino alkoxy at the C5 position demonstrated significant antioxidant activity.

KEYWORDS:

Synthesis, 5-[2(3)-dialky amino alkoxy] Indole 2, 3-diones, Antioxidant activity.

1. INTRODUCTION

Isatin is an endogenous compound isolated in 1998 and reported[1] to possess a wide range of central nervous system activities. Surendranath pandya[2] et al. reported the synthesis and anticonvulsant activity of some novel n-methyl/acetyl, 5-(un)-substituted isatin-3-semicarbazones. In the last few years, Isatin derivatives have been discovered which show potential hypnotic[3], antibacterial[4-6] and MAO inhibitory[7], antihistaminic[8]activity. It is evident from the literature survey that Isatin derivatives showing more promising antioxidant activities.

We are reporting in the present communication the synthesis and characterization of some new compounds. 5-[2(3)-dialky amino alkoxy] Indole 2, 3-diones.5-Hydroxyisatin condensed with dialkylamino alkyl halide by using Williamson synthesis to prepare the 5-[2(3)-dialkylamino alkoxy] Indole 2, 3-dione derivatives. All the compounds of the series have been screened for antioxidant activity and the structures of these compounds were identified by IR, NMR and Mass Spectrums.

2. EXPERIMENTAL

2.1 Materials and methods

The compounds were mostly synthesized by conventional methods and described in experimental selection and also by the methods established in our laboratory.

2.2 Chemicals

DPPH, phosphomolybdenum, H_2O_2, Dialkyl amino alkylhalides purchased from Sigma- Aldrich Chemicals Private Limited, Hyderabad, India. p-amino phenol, hydroxylamine hydrochloride, sodium sulfate were purchased from Merck Chemicals Private Limited, Hyderabad, India.

2.3 Chemistry

Solvents were dried or distilled before use. Melting points were obtained on a Thoshniwall melting point apparatus in open capillary tubes and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel –G plates(Merck).Infrared spectra(IR) were recorded with KBR pellet on a Perkin-Elmer BX series, Infrared spectrophotometer. Mass spectra were recorded by the direct inlet method on Thadmam-mass-quantam API 400H mass spectrophotometer.^{1}H NMR spectra were recorded on Brucker spectrospin 400 MHz spectrophotometer in DMSO-d_6.

5-hydroxy Isatin was synthesized from p- amino phenol by using Sandmayer[8] method It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield.

2.3.1 Preparation of 5-[2(3)-dialkyl amino alkoxy] Indole 2,3 dione derivatives:

A mixture of 5-hydroxyisatin (0.01 Moles) and dialkylamino alkylhalide (0.01 Moles) placed in 10% alcoholic potassium hydroxide and this mixture was stirred at room temperature for 6 hours .The alcohol was reduced to half of its volume and cooled. The product separated was filtered, washed with small portions of cold alcohol repeatedly and dried .It was purified by recrystalisation from hydro alcoholic mixtures to get a crystalline solid. Similarly other 5-Hydroxy Isatin derivatives were prepared and their melting points were determined in Open capillary tubes using Toshniwall melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC.

The physical data of the title compounds were presented in **Table –I.** The compounds were characterized by spectral data.

Scheme-1

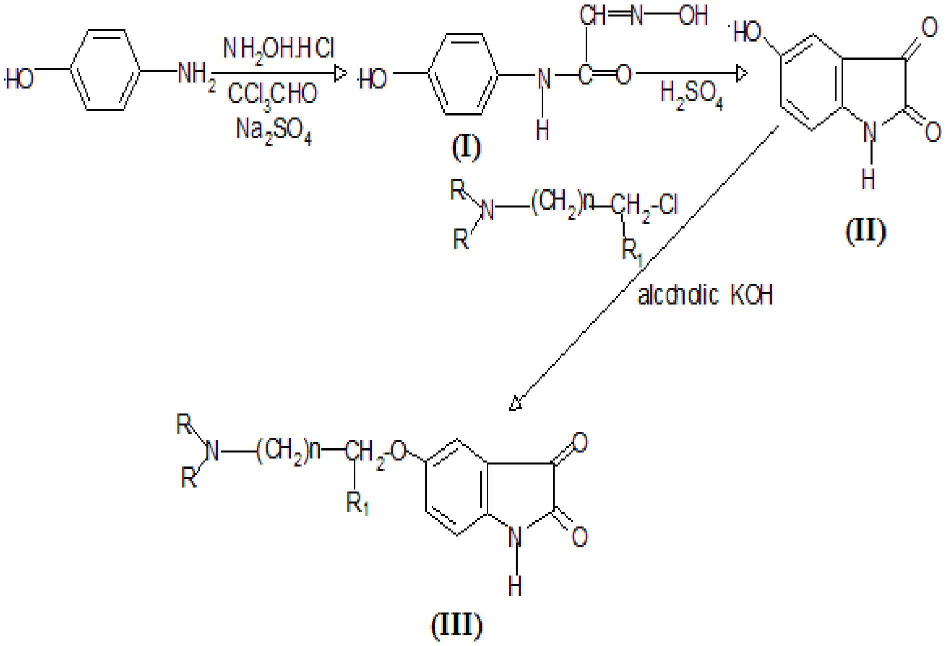
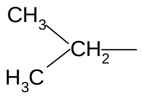
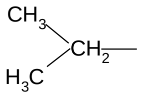


Table- 1: Characterization Data of 5 - [2(3) -Dialkylamino Alkoxy] Indole 2, 3-Diones

S.No	Compound	R	R_1	n	X	M.F	% YEILD	M.P	M.Wt
1	IIIa	CH_3	H	1	O	$C_{12}H_{14}N_2O_3$	91%	<320	234
2	IIIb	C_2H_5	H	1	O	$C_{14}H_{18}N_2O_3$	86%	<320	252
3	IIIc	CH_3	CH_3	1	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
4	IIId	C_2H_5	CH_3	1	O	$C_{15}H_{20}N_2O_3$	85%	<320	276
5	IIIe		H	1	O	$C_{16}H_{22}N_2O_3$	81.8%	<320	290
6	IIIf	CH_3	H	2	O	$C_{13}H_{16}N_2O_3$	93%	<320	248
7	IIIg	C_2H_5	H	2	O	$C_{15}H_{20}N_2O_3$	75%	<320	276
8	IIIh		H	2	O	$C_{17}H_{24}N_2O_3$	74%	<320	304
9	IIIi	CH_3	H	0	O	$C_{11}H_{12}N_2O_3$	85%	<320	220
10	IIIj	C_2H_5	H	0	O	$C_{13}H_{16}N_2O_3$	90%	<320	238

2.4 Spectral Data

The compounds have been characterized by the spectral data IR, PMR and Mass.

IR spectrum (KBr) of compound **(III)** exhibited absorption bands (cm-1) 3421.47 (OH), 1630.08 (C = O), 1548 (Ar, C=C), 1282(C-O-C), 883.85-579.8 (Ar). Its PMR spectrum (DMSO, **III**) showed characteristic peaks at (d ppm) 300 MHz 13.3 (s, 1H, OH), 10.36(s, 1H,-CONH), 6.65-7.29(m, 3 H, Ar-H). Mass spectrum of compound III showed molecular ion(M+) base peak at m/z (164.1).

Compound (**IIIa)** showed characteristic IR peaks at 3276(NH), 1651.96 (C=O), 1569.82 (Ar, C=C), 1276(C-O-C), 1080(C-N), 2860(C-C), 807.93(Ar). Its PMR spectrum (DMSO, **IIIa**) showed characteristic peaks at (d ppm) 300 MHz 10.36(s, 1H,-CONH), 7.21(d, H,Ar-H), 7.26(d, H,Ar-H), 7.01(s, H,Ar-H),3.2 (t,2H,O-CH_2) ,2.9 (t,2H,N-CH_2), 1.36 (s,6H,N-$(CH_3)_2$). Mass spectrum of compound **IIIa** showed molecular ion (M+) base peak at m/z 234 (100%).It also shows peak at m/z (72) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIb)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21(Ar, C=C), 1243(C-O-C), 1084(C-N), 2890(C-C), 845.51 (Ar). Its PMR spectrum (DMSO, **IIIb**) showed characteristic peaks at (d ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.99 (t,2H,O-CH_2) ,2.72 (t,2H,N-CH_2) , 1.24 (s,4H,N-$(CH_2$ -C$)_2$), 1.22 (s,6H,(N-C-$CH_3)_2$). Mass spectrum of compound **IIIb** showed molecular ion (M+) base peak at m/z 252 (100%).It also shows peak at m/z (90) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIc)** showed characteristic IR peaks at 3274(NH), 1651.96 (C=O), 1579.72(Ar, C=C), 1266(C-O-C), 1095(C-N), 2898(C-C), 805.91(Ar). Its PMR spectrum (DMSO, **IIIc**) showed characteristic peaks at (d ppm) 300 MHz 10.46(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.84 (m,H,O-CH) , 2.51 (d,3H, R_1=CH_3),2.48 (d,2H,N-CH_2), 1.25 (s,6H,N-$(CH_3)_2$).

Mass spectrum of compound **IIIc** showed molecular ion (M+) base peak at m/z 248 (100%).It also shows peak at m/z (86) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIId)** showed characteristic IR peaks at 3257(NH), 1679.64 (C=O), 1546.86 (Ar, C=C), 1245(C-O-C), 1180(C-N), 2960(C-C), 812.71(Ar). Its PMR spectrum (DMSO, **IIId**) showed characteristic peaks at (d ppm) 300 MHz 10.51(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.76 (m,2H,O-CH) , 2.45 (t,3H, R_1=CH_3), 2.48 (d,2H,N-CH_2), 1.24 (s,4H,N-$(CH_2$ -C$)_2$), 1.22 (s,6H,(N-C-$CH_3)_2$). Mass spectrum of compound **IIId** showed molecular ion (M+) base peak at m/z 276 (100%). It also shows peak at m/z (114) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIe)** showed characteristic IR peaks at 3257(NH), 1689.46 (C=O), 1576.34 (Ar, C=C), 1228(C-O-C), 1170(C-N), 2870(C-C), 814.53(Ar). Its PMR spectrum (DMSO, **IIIe**) showed characteristic peaks at (d ppm) 300 MHz 10.26(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),2.96 (t,2H,O-CH$_2$) ,2.82 (t,2H,N-CH$_2$), 1.35 (s, 2H,N-(CH)$_2$) ,1.21 (d,12H,N-C -(CH$_3$)$_2$). Mass spectrum of compound **IIIe** showed molecular ion (M+) base peak at m/z 290 (100%).It also shows peak at m/z (128) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIf)** showed characteristic IR peaks at 3286(NH), 1651.96 (C=O), 1566.82 (Ar, C=C), 1266(C-O-C), 1150(C-N), 2910(C-C), 808.93(Ar). Its PMR spectrum (DMSO, **IIIf**) showed characteristic peaks at (d ppm) 300 MHz 10.46(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H),3.2 (t,2H,O-CH$_2$) ,2.9 (t,2H,N-CH$_2$), 3.01(m,2H,C-CH$_2$-C), 1.36 (s,6H,N-(CH$_3$)$_2$). Mass spectrum of compound **IIIf** showed molecular ion (M+) base peak at m/z 248 (100%).It also shows peak at m/z (86) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIg)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21 (Ar, C=C), 1243(C-O-C), 1210(C-N), 2885(C-C) 845.51(Ar). Its PMR spectrum (DMSO, **IIIg**) showed characteristic peaks at (d ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.99 (t,2H,O-CH$_2$) , 3.04(m,2H,C-CH$_2$-C), 2.72 (t,2H,N-CH$_2$) ,1.23 (s,4H,N-(CH$_2$-C)$_2$), 1.21 (s,6H,(N-C-CH$_3$)$_2$). Mass spectrum of compound **IIIg** showed molecular ion (M+) base peak at m/z 276 (100%).It also shows peak at m/z (114) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIh)** showed characteristic IR peaks at 3257(NH), 1689.46 (C=O), 1576.34 (Ar,C=C), 1228(C-O-C), 1280(C-N), 2970(C-C) 814.53(Ar). Its PMR spectrum (DMSO, **IIIh**) showed characteristic peaks at (d ppm) 300 MHz 10.26(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.96 (t,2H,O-CH$_2$) , 3.06(m,2H,C-CH$_2$-C),2.82 (t,2H,N-CH$_2$), 1.35 (s, 2H,N-(CH)$_2$) ,1.21 (d,12H,N-C -(CH$_3$)$_2$). Mass spectrum of compound **IIIh** showed molecular ion (M+) base peak at m/z 304 (100%).It also shows peak at m/z (142) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIi)** showed characteristic IR peaks at 3276(NH), 1651.96 (C=O), 1569.82 (Ar, C=C), 1276(C-O-C), 1089(C-N), 2865(C-C) 807.93(Ar). Its PMR spectrum (DMSO, **IIIi**) showed characteristic peaks at (d ppm) 300 MHz 10.36(s, 1H,- CONH), 7.21(d, H,Ar-H), 7.26(d, H,Ar-H), 7.01(s, H,Ar-H) , 2.8 (s,2H,N-CH$_2$-O), 1.36 (s,6H,N-(CH$_3$)$_2$). Mass spectrum of compound **IIIi** showed molecular ion (M+) base peak at m/z 220 (100%).It also shows peak at m/z (58) may be due to the fragmentation of the alkyl chain from the molecule ion.

Compound (**IIIj)** showed characteristic IR peaks at 3274(NH), 1681.53 (C=O), 1570.21. (Ar, C=C), 1243(C-O-C), 1180(C-N), 2940(C-C), 845.51 (Ar). Its PMR spectrum (DMSO, **IIIj**) showed characteristic peaks at (d ppm) 300 MHz 10.25(s, 1H,-CONH), 7.22(d, H,Ar-H), 7.26(d, H,Ar-H), 7.11(s, H,Ar-H), 2.78 (s,2H,N-CH_2-O)1.24 (s,4H,N-(CH_2-C)$_2$), 1.22 (s,6H,(N-C-CH_3)$_2$).

Mass spectrum of compound **IIIj** showed molecular ion (M+) base peak at m/z 238 (100%).It also shows peak at m/z (76) may be due to the fragmentation of the alkyl chain from the molecule ion.

3. PHARMACOLOGY

3.1 DPPH radical scavenging method

Blios[9] (1958) showed that α, α -diphenyl-β-picryl hydrazyl radical can be used for determining antioxidant activity. DPPH in ethanol shows a strong absorption band at 517 nm (independent of pH from 5 to 6.5), and the solution appears to be deep violet in color. As the DPPH radical is scavenged by the donated hydrogen from the antioxidant, the absorbance is diminished according to the stoichiometry. Briefly, 0.5 ml of DPPH solution (0.2 mM) was mixed with 0.1 ml of various concentrations of test compounds and 1.5 ml ethanol added. The mixture was kept at room temperature for 30 min, and then absorbance (OD) was read at 517 nm against blank. The % reduction of free radical concentration (OD) with different concentrations of test compounds was calculated and compared with the standard, Ascorbic acid. The results were expressed as IC_{50} values (the concentration of test required to scavenge 50% free radicals).

3.2 Hydrogen peroxide scavenging activity

The ability of test compounds to scavenge hydrogen peroxide was determined by using the method of Sanchez (2001) and Famey et al[10]. (1998). The solution of hydrogen peroxide (20 mM) was prepared in phosphate buffered saline (pH 7.4). Various concentrations of 1 ml of test compounds and standards were added to 2 ml of H_2O_2. Absorbance of hydrogen peroxide at 230 nm was determined 10 min later against the blank. Ascorbic acid was used as a reference standard.

3.3 Total antioxidant capacity by a phosphomolybdenum assay

The in vitro antioxidant activity of the synthesized compounds was evaluated by the phosphomolybdenum method according to the procedure of Prieto, Pineda, and Aguilar[11] (1999). The principle of the assay is based on the reduction of Mo (VI) to Mo (V) by test compounds and subsequent formation of a green phosphate/Mo (V) complex at acid pH.

An aliquot of 0.1 ml of the test solution in methanol was mixed with 1 ml of a reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate).

The tubes were capped and incubated at 95°C for 90 min. The samples were cooled at room temperature and then absorbance was measured at 695 nm against the blank. The blank solution was containing 1 ml of the reagent solution and an appropriate volume of the same solvent used in the test compound. The total antioxidant capacity of the tested compounds was calculated according to the equation

$$\mathbf{TAC\ (\%) = [(A_0\text{-}A_t/A_0)\ *]\ 100}$$

Where A_t is the absorbance value of the test compound and Ao is the absorbance of the blank sample. The reference standard is Ascorbic acid.

4. RESULTS AND DISCUSSIONS

Physical data TLC, IR, 1H NMR and mass spectra confirmed the structures and purity of the synthesized compounds. All the title compounds de-composed before melting. All the compounds were examined for antioxidant activity by using 1, 1-diphenyl-2-picryl-hydrazyl and hydrogen peroxide (H_2O_2), and the total antioxidant capacity by a phosphomolybdenum assay.

4.1 DPPH radical scavenging activity

The interaction of the synthesized compounds IIIa–Ve with the stable free radical DPPH is presented in Table 2. The values are expressed in IC_{50} i.e., the ability of the test compound required to decrease the concentration of free radicals by 50%. The IC_{50} values of the test compounds were found between 27 and 558 mg/ml. Free radical scavenging of synthesized compounds rose with increase in concentration. Compounds IIIe, IIIj, and IIIiwith IC_{50} values 26.44, 26.46, and 27.18 mg/ml, respectively, demon-strated potent antioxidant activity compared to other compounds and the standard, ascorbic acid. The results of this study revealed that all the compounds are significantly scavenged by the DPPH free radical.

Table 2: In vitro antioxidant activity of DPPH and hydrogen peroxide, total antioxidant capacity by the phosphomolybdenum assay of synthesized isatin derivatives.

S.NO	COMPOUNDS	IC_{50} (µg/ml) DPPH	IC_{50} (µg/ml)H_2O_2	TAC((µg/ml)
1	**IIIa**	56.54±0.041	51.9±1.234	23.96±0.373
2	**IIIb**	49.61±0.042	52.6±0.341	202±1.234
3	**IIIc**	39.42±0.051	35.6±0.234	345.7±0.673
4	**IIId**	31.5±1.204	28.8±0.456	473.4±1.095
5	**IIIe**	26.44±0.042	25.8±0.134	525.7±2.384
6	**IIIf**	54.18±0.036	57.2±1.453	128.2±1,345
7	**IIIg**	56.68±0.034	54.7±1.345	233.7±0.234
8	**IIIh**	45.76±0.063	38.9±0.243	325.8±0.567
9	**IIIi**	27.18±1.036	25.3±0.243	523.8±1.378
10	**IIIj**	26.46±1.0451	29.3±0.653	537.4±1.567
12	**Ascorbicacid**	16.55±0.063	21.96±0.243	-

Values are expressed in mean±SD,N=3;TAC=total antioxidant capacity

4.2 Hydrogen peroxide scavenging activity

H_2O_2 scavenging power is based upon the ability of a compound to convert H_2O_2 into water and was used for the determination of the H_2O_2 scavenging power. The measurement of H_2O_2 scavenging activity may be one of the useful methods for determining the ability of antioxidants to decrease the level of pro-oxidants such as H_2O_2. Hydrogen peroxide is a weak oxidizing agent capable of oxidizing the essential thiol (–SH) groups of proteins, thus inactivating a few enzymes. H_2O_2 readily penetrates cell membranes and inside the cell reacts with Fe+2 to form a hydroxyl radical which exerts several adverse effects. The combination of reduced iron and hydrogen peroxide gives a hydroxyl radical in the well-known Fenton reaction.

$$\mathbf{Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^{\cdot}}$$

The radical scavenging effect of the synthesized compounds against H_2O_2 was measured spectrophotometrically. Values for their IC_{50} are given in Table 2. Compounds, IIIi, IIIe,IIId, IIIj were found to have potent antioxidant activity with IC_{50} below 50 i.e., 25.3,25.8,28.8, and 29.3 mg/ml, respectively. It was observed that compounds IIIf, IIIa, IIIg, IIIb, exhibited less promising antioxidant activity. Among the test compounds IIIc, IIIh, were found to show moderate activity.

4.3 Determination of the total antioxidant capacity

The antioxidant activity of the synthesized compounds was evaluated by the phosphomolybdenum method. The assay is based on the reduction of Mo(VI) to Mo(V) by the test compounds and subsequent formation of a green phosphate/Mo(V) complex at acid pH. TAC ranging from 23.96 to 537.4mg/ml. The most active compound was Ve In addition, experimental data showed compounds IIIj, IIId, , and IIIi possessed significant TAC. The phosphomolybdenum method is an alternative to methods already available for the evaluation of TAC due to its simplicity and the cheap reagents it uses. It is quantitative, since the antioxidant activity is expressed as the number of equivalents of ascorbic acid.

5. CONCLUSION

A new series of five 5-[2(3)-dialkylamino alkoxy] Indole 2, 3 diones were synthesized by reacting 5-hydroxyindole 2,3 dione with 2-N,N dialkylamino alkyl halides. Evaluation of these compounds as antioxidant activity revealed that the compounds IIIi,IIIj,IIId and IIIe with a diisopropyl and diethyl amino ethyl/isoprpyl chain derivatives was found to be relatively superior in antioxidant activity and other compounds(IIIc, IIIh, IIIa, IIIf, IIIb, IIIg) are next in the order of activity.

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