



SYNTHESIS OF SOME NEW IBUPROFEN DERIVATIVES CONTAINING CHIEF HETEROCYCLIC MOIETY LIKE S-TRIAZINE AND EVALUATED FOR THEIR ANALGESIC ACTIVITY

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ABSTRACT

A new series of Ibuprofen derivatives, N-[2-(3-H/nitro-4-isobutyl phenyl) propanoyl]-N'-[4,6-bis-(2-Aryl aniline)-1,3,5-triazin-2-yl] hydrazine have been synthesized by the condensation of N-[2-(3-H/nitro-4-iso butyl phenyl) propanoyl] hydrazine and 2-chloro-(4,6-bis aryl anilido)-s-Triazine in 1,4-dioxane solvent and Potassium carbonate using as a neutralizing agent. The structures of all these compounds were confirmed on the basis of their analytical and spectral data¹⁷. The title compounds were characterized by IR, ¹H NMR and elemental analysis. Some of these compounds showed significant analgesic activity.

Keywords: Ibuprofen, Cyanuric chloride, hydrazine hydrate, N-[2-(3-H/nitro-4-iso butyl phenyl) propanoyl] hydrazide, s-Triazine and analgesic activity.

INTRODUCTION

Certain s-Triazine derivatives have been found to possess a wide variety of biological activities viz, antitubercular¹, anticancer^{2,4}, antitumour³, and antiinflammatory⁵ activities. In addition, many s-Triazine derivatives have been found to exhibit antiviral⁶, antibacterial⁷ and herbicidal⁸ activities. The chemistry of s-Triazine has been extensively studied because many drugs include this ring. Melamine derivatives have been found to exhibit antineoplastic⁹ and insecticidal activity. Also some of these organic molecules which containing s-Triazine moiety have been extensively used as therapeutic agents such as Sulfasymazine¹⁰, Irsoglandin¹¹, Trocloses K¹² and Prometryn¹³...etc. Substituted s-Triazine derivatives exhibit remarkable Tuberculostatic activity of high therapeutic significance. s-Triazine derivatives also have been reported to possess good diuretic and saluretic activity¹⁴⁻¹⁵.

EXPERIMENTAL

Melting points were taken in open capillary tubes. IR spectra (KBr in cm⁻¹) were recorded on Shimadzu 8201 PC FTIR spectrophotometer. ¹H NMR spectrum was recorded using variation 300 MHz NMR Spectrophotometer and chemical shifts are reported in δ ppms relative to TMS as internal standard in CDCl₃ Solvent. Purity of the compound was monitored by TLC (silica gel 60 F₂₅₄ 1.05554.0007) and was visualized by UV light of 254 nm.

General Procedure:

• **2-(3-nitro-4-isobutyl phenyl) Propanoic acid (Nitration of Ibuprofen).**

0.1 mole of 2-(4-isobutyl phenyl) propanoic acid (Ibuprofen) was dissolved in 80 ml sulfuric acid. To that 0.13 mole 8N nitric acid was then added slowly at such a rate that the temperature of the reaction mixture did not rise above 5 °C, the mixture was stirred at room temperature till reaction was completed. The homogeneous reaction mass was quenched in crushed ice and the solid obtained was

filtered, washed with water till it was acid free. Material dried and crystallized in methanol to get light yellow colored crystalline powder, yield equal to 80% with M.P. equal to 84 °C. Purity of the compound was confirmed by,

TLC (Rf value-0.52) in solvent eluent: n-Hexane (5) + EA (3) + Acetic acid (1)

- **2-(3-H/nitro-4-isobutyl phenyl) ethyl propanoate (II).**

The above compound (I) was esterified by dissolving 0.1 mole in 80 ml of ethyl alcohol and then to that 2.0 ml of sulfuric acid was added. The mixture was refluxed for 6-8 hrs. Reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, solvent was removed by distillation and to which add 100 ml cold water. Followed by extracted with Carbon tetrachloride. Separated The organic layer was washed with water, then with 5% Na₂CO₃ solution and with water till it is free from acid, dried over Na₂SO₄ and removed solvent. The pale yellow colored liquid was obtained was distilled to get desired product. Yield 90% and BP: 260-262 °C. (Where R=H) / 281-282 °C. (Where R=nitro)

- **N-[2-(3-H/nitro-4-iso butyl phenyl) propanoyl] hydrazide(III)**

0.1 mole of above ester, that is compound (II) was dissolved in 30 ml 80 % hydrazine hydrate at 70 °C, 80 ml ethyl alcohol was added through condenser and the reaction mass was refluxed for 12-14 hrs. The progress of the reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, solvent was removed by distillation and 100 ml of cold water was added to the reaction mass to get solid mass, which was then filtered and wash with water. The material was re-crystallized in 50% aqueous methanol to get pure product

Where R=H, Yield equal to 90% with melting point was 77-78 °C

Found: C: 70.78, H: 9.18 & N: 12.70 % [C₁₃H₂₀N₂O requires C: 70.87, H: 9.15 & N: 12.72%]

Where R=Nitro, Yield equal to 90% with melting point was 112 °C

Found: C: 58.65, H: 7.19 & N: 15.87%, [C₁₃H₁₉N₃O₃ requires C: 58.85, H: 7.22 & N: 15.84%]

- **2-chloro-(4,6-bis aryl anilino)-s-Triazine (IV)**

0.1 mole of Cyanuric chloride was dissolved in 100 ml of 1,4 dioxan and to that solution of 0.095 mole of aromatic amines in 50 ml 1,4 dioxan was added at < 5 °C. Then 0.12 mole of anhydrous K₂CO₃ was added and mixture was stirred the for 2 hrs. The progress of reaction was confirmed by TLC (eluent: Toluene-7ml + MeOH-3ml). To the above reaction mass, again solution of 0.095 mole of same aromatic amine in 1,4 dioxan was added below 35 °C. Then 0.12 mole of anhydrous K₂CO₃ was added and mixture was stirred for 2 hrs until amine spot disappears by TLC. After completion of reaction, cool the mixture to 10°C and to that 10 times cold water added below maintaining 10 °C and the solid material obtained was filtered, dried at 50 °C under vacuum.

- **N-[2-(4-isobutylphenyl)propanoyl]-N'-[4,6-bis(2-arylanilino)-1,3,5-triazin-2-yl]hydrazine (V)**

To the solution of 0.1 mole 2-chlro-(4,6-bis aryl anilino)-1,3,5-Triazine (IV) in 1,4-Dioxan. Which was further heated to 90 °c., to this solution of 0.09 mole of N-[2-(4-iso butyl phenyl) propanoyl] hydrazine (III) in 6 ml 1,4 dioxan was added below maintaining 95 °C. Then 0.12 mole anhydrous K₂CO₃ was added. The reaction mixture was refluxed for 6-8 hrs. The progress of the reaction was monitored by TLC (Eluent: Toluene-7ml + MeOH-3ml).

After completion of reaction the heating was discontinued and the reaction mass was poured in to 200 ml cold 1 % dilute HCl solution. Which Stir it and filter, wash with water till free from any acidic or alkaline elements.

Yield of crude material had been purified by dissolve in minimum quantity methanol. This methanolic solution was further poured in cold 1% dilute HCl solution at temperature not exceeds 10 °C to get solid mass. Filtered the solid material and wash with water till it becomes acid free.

Materials and Methods (Analgesic activity¹⁶):

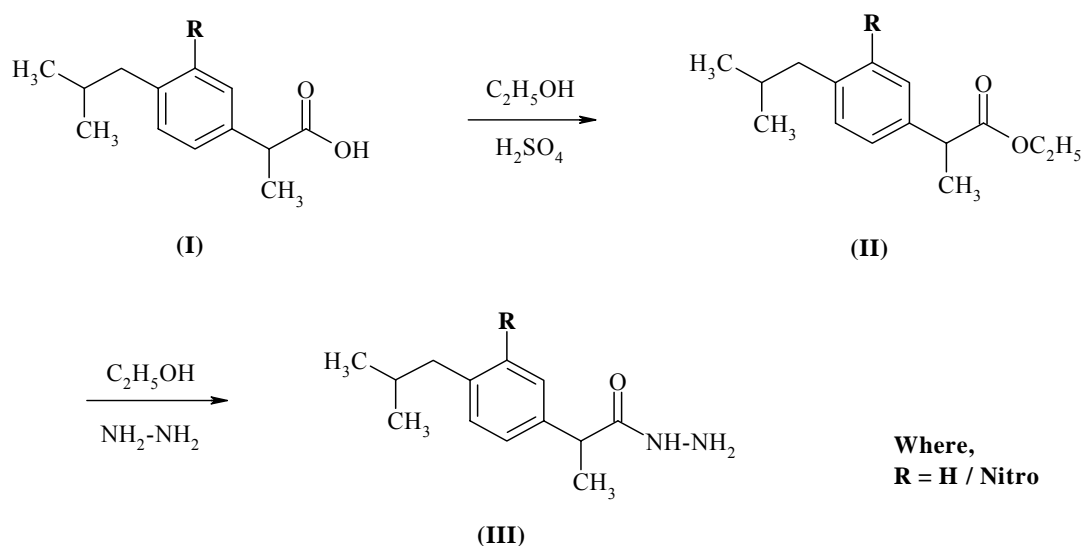
The analgesic activity screening was carried out by Tail-Flick method as described by Ther, Linder and Vogel¹⁶ against albino swiss mice.

Animal room was maintained at the temperature between 26-28 °C and relative humidity was about 65 - 68%.

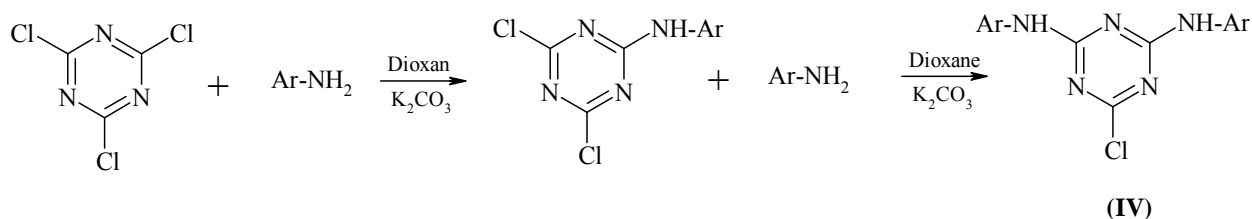
The tested samples were dissolved in 5-10% aq. ethanolic solution by adding slight alkali hydroxide. Dry Mices feed pellets for each cage supplied by Amrut Laboratory Animal Feed; Maharashtra.

In this method, Albino Swiss Mice of both sexes is used for each dose 1 ml of the test sample was administered orally to the mice. The concentration of the dose was 0.1 mg per mL. The efficacy of the samples was evaluated by comparing the results with those obtained by dosing the reference standards like Ibuprofen and Disprin.

We had synthesized about 16 compounds and 10 of them were screened for their analgesic activity. Activities of standard drugs such as Ibuprofen and Disprin are also given for comparison.



Scheme-1; Synthesis of N-[2-(3-H/nitro-4-iso butyl phenyl) propanoyl] hydrazine (III)



Scheme-2: Synthesis of 2-chloro-(4,6-bis aryl anilido)-s-Triazine (IV)

RESULTS AND DISCUSSION

Scheme-1 involves esterification of α -methyl-3H/nitro-4-(2-methyl propyl) benzene acetic acid (I) under inert condition in ethanol in presence of acid-catalyst sulfuric acid to afford 2-(3-H/nitro-4-isobutyl phenyl) ethyl propanoate (II). Hydrolysis of this ester compound (II) by hydrazine hydrate gave the desired hydrazide compound (III).

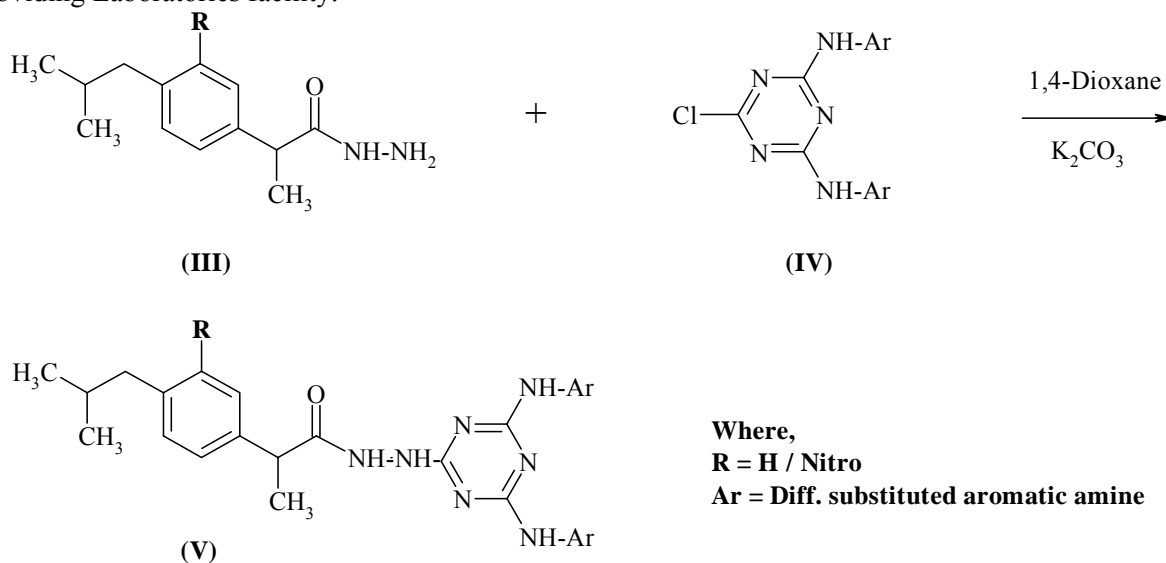
Scheme-2 involves preparation of 2-chloro-(4,6-bis aryl anilido)-s-Triazine (IV) via condensation of Cyanuric chloride and substituted aromatic amines in 1,4-dioxan.

Scheme-3 involves condensation of hydrazide compound (III) and 2-chloro-(4,6-bis aryl anilino) -s-Triazine (IV) to afford desired derivative (V).

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N-[2-(3-H/nitro-4-isobutylphenyl)propanoyl]-
 N'-[4,6-bis(2-Aryl anilino)-1,3,5-triazin-2-yl] hydrazine

Scheme-3: Synthesis of compounds [V (C-01 to C-08 and D-01 to D-08)]

Table-1: Analgesic activity data of some selected compounds

Ibuprofen	3.01	3.90	5.05	6.18	7.25	2.41
Tested Compound	Time required to Flick Tail (In Seconds)					PAS After 120 mins.
	Before Dosing	After Drug administration				
		30 mins.	60 mins.	90 mins.	120 mins.	
C-01	4.09	4.41	3.95	3.79	3.71	0.91
C-02	4.16	4.85	4.72	4.25	3.97	0.95
C-04	3.69	3.62	3.58	3.49	3.45	0.93
C-05	3.98	4.29	4.08	3.94	3.88	0.97
C-07	3.78	3.94	3.91	3.80	3.72	0.98
D-01	3.35	4.79	5.88	7.17	8.00	2.37
D-02	3.49	4.55	6.14	7.03	8.12	2.33
D-04	2.85	3.60	5.75	6.97	7.92	2.78
D-05	3.23	4.31	5.92	7.05	8.01	2.48
D-07	3.11	3.92	4.24	6.48	7.98	2.47
Disprin	3.08	4.92	6.90	8.26	9.17	2.97

CONCLUSION

Evaluation of analgesic activity reveals that, new synthesized Ibuprofen derivatives possess poor analgesic activity, whereas the synthesized nitrated Ibuprofen derivatives possesses either moderate analgesic activity or little but higher analgesic activity.

Some derivatives of nitrated Ibuprofen like **D-01, D-02, D-05 and D-07** showed analgesic activity same as Ibuprofen, while for **D-04** the activity increases to 15% compare to Ibuprofen. Other samples showed poor analgesic activity.

It can be concluded that the synthesized Ibuprofen derivatives have lost their activity, whereas derivatives of nitrated Ibuprofen were either moderate or higher than the parent compound.

It can be also concluded that because of the introduction of Nitro functional group or in presence of Nitro group, the activity of synthesized Ibuprofen derivatives becomes stable and in certain cases the analgesic effect increases.

On consideration of structure-activity it has been observed that the introduction of nitro group in benzene ring enhance the analgesic activity and without introduction of nitro group show less analgesic activity.

Table-2: Physical and analytical data of compounds (C-01 to C-08 and D-01 to D-08)

Compd. Code	R	Ar	Yield %	Rf value By TLC	M.P. (°C)	Mol. Formula Mol. Wt.	Found (Calcd.) %		
							C	H	N
C-01	H	2-Methoxy Phenyl	76	0.58	112-113	C ₃₀ H ₃₅ N ₇ O ₃ (541.66)	66.52 66.33	6.51 6.54	18.10 18.17
C-02	H	4-Methyl Phenyl	78	0.61	145	C ₃₀ H ₃₅ N ₇ O (509.66)	70.70 70.51	6.92 6.89	19.24 19.29
C-03	H	4-Nitro Phenyl	52	0.62	126	C ₂₈ H ₂₉ N ₉ O ₅ (571.60)	58.84 58.74	5.11 5.12	22.05 21.97
C-04	H	3-Chloro Phenyl	79	0.56	111-112	C ₂₈ H ₂₉ Cl ₂ N ₇ O (550.50)	61.09 61.18	5.11 5.10	17.81 17.78
C-05	H	4-Chloro Phenyl	78	0.61	158	C ₂₈ H ₂₉ Cl ₂ N ₇ O (550.50)	61.09 61.02	5.11 5.12	17.81 17.85
C-06	H	2-Hydroxy-4-Nitro Phenyl	59	0.51	133-134	C ₂₈ H ₂₉ N ₉ O ₇ (603.60)	55.72 55.50	4.84 4.83	20.88 20.92
C-07	H	Phenyl	79	0.62	128	C ₂₈ H ₃₁ N ₇ O (481.61)	69.83 69.61	6.49 6.52	20.36 20.36
C-08	H	2,3-Dimethyl Phenyl	81	0.65	122	C ₃₂ H ₃₉ N ₇ O (537.71)	71.48 71.55	7.31 7.32	18.23 18.19
D-01	NO ₂	2-Methoxy Phenyl	80	0.58	100-102	C ₃₀ H ₃₄ N ₈ O ₅ (586.66)	61.42 61.50	5.84 5.79	19.10 19.06
D-02	NO ₂	4-Methyl Phenyl	79	0.53	149-150	C ₃₀ H ₃₄ N ₈ O ₃ (554.66)	64.97 64.71	6.18 6.19	20.20 20.12
D-03	NO ₂	4-Nitro Phenyl	49	0.34	190	C ₂₈ H ₂₈ N ₁₀ O ₇ (616.60)	54.54 54.42	4.58 4.58	22.72 22.65
D-04	NO ₂	3-Chloro Phenyl	82	0.55	144	C ₂₈ H ₂₈ Cl ₂ N ₈ O ₃ (595.49)	56.48 56.72	4.74 4.72	18.82 18.75
D-05	NO ₂	4-Chloro Phenyl	84	0.49	154	C ₂₈ H ₂₈ Cl ₂ N ₈ O ₃ (595.49)	56.48 56.40	4.74 4.70	18.82 18.75
D-06	NO ₂	2-Hydroxy-4-Nitro Phenyl	61	0.41	210	C ₂₈ H ₂₈ N ₁₀ O ₉ (648.60)	51.85 51.65	4.35 4.35	21.60 21.63
D-07	NO ₂	Phenyl	82	0.39	145	C ₂₈ H ₃₀ N ₈ O ₃ (526.60)	63.86 63.62	5.74 5.77	21.28 21.24
D-08	NO ₂	2,3-Dimethyl Phenyl	79	0.51	160	C ₃₂ H ₃₈ N ₈ O ₃ (582.71)	65.96 65.77	6.57 6.59	19.23 19.24

Table-3: IR and ¹H NMR data of compounds-V (C-01 to C-08 and D-01 to D-08)

Compounds	Spectral Data
C-01	IR (KBr cm ⁻¹): 2866 (C-H, aromatic), 2838 (C-H, O.CH ₃) 1658 (C=O, ketone), 1642 (C=N, aromatic), 1394 (C-H, isobutyl), 850 (C-H, subst ^d . ring). ¹ H NMR [δ ppms (multiplicity, protons, assignments)]: 0.80 (d, 6H, isobutyl), 1.50(d, 3H, CH-CH ₃), 1.6-2.0 (m, 1H, CH ₃ -CH-CH ₂), 2.40 (m, 2H, (CH ₃) ₂ -CH-CH ₂), 3.6-3.7 (m, 1H, CH-CH ₃), 3.8 (m, 3H, Benzylic-NH), 3.95 (s, 6H, 2×O.CH ₃), 6.6-8.4 (d, 4H, ArH), 8.60 (broad lump, 1H, NH).
C-05	IR (KBr cm ⁻¹): 2867 (C-H, aromatic), 1658 (C=O, ketone), 1650 (C=N, aromatic), 1390 (C-H, isobutyl), 826 (C-H, subst ^d . ring), 770 (C-Cl mono Cl). ¹ H NMR [δ ppms (multiplicity, protons, assignments)]: 0.80 (d, 6H, isobutyl), 1.52(d, 3H, CH-CH ₃), 1.8 (m, 1H, CH ₃ -CH-CH ₂), 2.5-2.8 (d, 2H, (CH ₃) ₂ -CH-CH ₂), 3.6-3.8 (m, 1H, CH-CH ₃), 4.0 (m, 3H, Benzylic-NH), 6.8-7.6 (d, 4H, ArH), 7.9(broad lump, 1H,NH).
C-06	IR (KBr cm ⁻¹): 2867 (C-H, aromatic), 1658 (C=O, ketone), 1650 (C=N, aromatic), 1512 & 1349 (N=O, Ar-Nitro), 1390 (C-H, isobutyl), 826 (C-H, subst ^d . ring), 770 (C-Cl mono Cl).
C-08	IR (KBr cm ⁻¹): 2868 (C-H, aromatic), 3052 (O-H, Ar-OH), 1678 (C=O, ketone), 1512 & 1346 (Nitro), 1649 (C=N, aromatic), 1190 (C-O, Ar-OH), 1381 (C-H, isobutyl), 850 (C-H, subst ^d . ring).
D-01	IR (KBr cm ⁻¹): 2868 (C-H, aromatic), 2838 (C-H, O.CH ₃) 1678 (C=O, ketone), 1650 (C=N, aromatic), 1512 & 1350 (N=O Ar-Nitro), 851 (C-H, subst ^d . ring). ¹ H NMR [δ ppms (multiplicity, protons, assignments)]: 0.80 (d, 6H, isobutyl), 1.52 (d, 3H, CH-CH ₃), 1.6-2.0 (m, 1H, CH ₃ -CH-CH ₂), 2.4-2.8 (m, 2H, (CH ₃) ₂ -CH-CH ₂), 3.6-3.7 (m, 1H, CH-CH ₃), 3.8 (m, 3H, Benz-NH)3.95 (s, 6H, 2×O.CH ₃), 6.6-8.4 (d, 4H, ArH), 9.00 (broad lump, 1H, NH).
D-05	IR (KBr cm ⁻¹): 2869 (C-H, aromatic), 1658 (C=O, ketone), 1529 & 1347 (N=O Ar-Nitro), 1288 (C-N, 2° amine), 826 (C-H, subst ^d . ring), 769 (C-Cl, mono chloro). ¹ H NMR [δ ppms (multiplicity, protons, assignments)]: 0.89 (d, 6H, isobutyl), 1.52(d, 3H, CH-CH ₃), 1.6-2.0 (m, 1H, CH ₃ -CH-CH ₂), 2.2-2.6 (d, 2H, (CH ₃) ₂ -CH-CH ₂), 3.4-3.8 (m, 1H, CH-CH ₃), 4.0-4.2 (m, 3H, Benzylic-NH), 6.6-8.0 (d, 4H, ArH), 8.9-9.0 (broad lump, 1H, NH).
D-06	IR (KBr cm ⁻¹): 2869 (C-H, aromatic), 1659 (C=O, ketone), 1515 & 1340 (Nitro), 1485 (C=C, aromatic), 1315 (C-N, 2° amine), 1199 (C-O, Ar-OH), 812 (C-H, subst ^d . ring).
D-08	IR (KBr cm ⁻¹): 2869 (C-H, aromatic), 1668 (C=O, ketone), 1528 & 1356 (Nitro), 1484 (C=C, aromatic), 1321 (C-H, Ar-CH ₃), 1287 (C-N, 2° amine), 850 (C-H, subst ^d . ring).

Table-4: IR and ¹H NMR data of compound (III)

Spectral Data where R=H	
IR-spectra Observed stretching band	3272 (N-H, 2° amine), 2867 (C-H, aromatic), 1642 (C=O, ketone), 1611 (C=C, aromatic), 1379 (C-H, isobutyl), 1284 (C-H, 2° amine), 847 (C-H, subst ^d . ring).

¹ H NMR-spectra δ ppms (multiplicity, protons, assignments)	0.89-0.95 (d, 6H, isobutyl), 1.50-1.52 (d, 3H, CH-CH ₃), 1.78-1.90 (m, 1H, CH ₃ -CH-CH ₂), 2.42-2.46 (d, 2H, (CH ₃) ₂ -CH-CH ₂), 3.46-3.54 (q, 1H, CH-CH ₃), 3.80 (b&s, 2H, NH-NH ₂), 7.27 (s, 1H, NH-NH ₂), 7.09-7.20 (d, 4H, ArH)
Spectral Data where R=NO ₂	
IR-spectra Observed stretching band	3165 (N-H, 1° amine), 2867 (C-H, aromatic), 1678 (C=O, ketone), 1525 & 1352 (N=O, aromatic nitro), 1496 (C=C, aromatic), 1376 (C-H, isobutyl), 1309 & 1291 (C-N, 3° amine), 818 (C-H, subst ^d . ring).
¹ H NMR-spectra δ ppms (multiplicity, protons, assignments)	0.91-0.95 (d, 6H, isobutyl), 1.52-1.54 (d, 3H, CH-CH ₃), 1.828-1.96 (m, 1H, CH ₃ -CH-CH ₂), 2.74-2.78 (d, 2H, (CH ₃) ₂ -CH-CH ₂), 3.46-3.54 (q, 1H, CH-CH ₃), 3.62 (b&s, 2H, NH-NH ₂), 7.27 (s, 1H, NH-NH ₂), 7.26, 7.50 & 7.82 (d, 3H, ArH, C ₆ H, C ₅ H & C ₂ H).

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