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ANALGESIC ACTIVITY OF SOME NEW SYNTHETIC DIBENZO- α -PYRONES DERIVATIVES

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ABSTRACT

Following standard Hurltley reaction, by using 2-Bromobenzoic acid, resorcinol and NaOH in the presence of CuSO₄ solution as a catalyst, a clay coloured solid of dibenzo- α -pyrone was prepared. This resulting solid of DB α P was then reacted with various amines respectively, formaldehyde and ethanol and refluxed for 1.5 h as per Mannich reaction resulting into eleven new synthetic Mannich derivatives of DB α P. The characterisation of synthesised new compounds were done by various spectral (UV, IR and NMR) and analytical methods. The synthesised derivatives were also evaluated for their analgesic activity using different animal models (Tail clip test and Hot plate method). Some of these compounds exhibited promising activities.

Keywords: Dibenzo- α -pyrone, Mannich derivatives, Hurltley synthesis, Analgesic activity.

INTRODUCTION

From decades, Non-Steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation as therapeutic agents. They act primarily on peripheral pain mechanisms. They do not produce physical dependence, have no abuse liability and are weaker analgesics. However, their long term clinical usage produces significant side effects such as bleeding, gastrointestinal lesions and nephrotoxicity. Therefore, it's a challenging goal in the research field for the discovery of new and safer synthetic analgesics and anti-inflammatory agents. Generally, NSAIDs block PG generation, which is considered the major mechanism of action of NSAIDs. Prostaglandin (PG), prostacyclin (PGI₂) and thromboxane (TXA₂) are produced from arachidonic acid by the enzyme cyclo-oxygenase which exists in two isoforms constitutive (COX 1) and inducible (COX 2) isoforms. COX 1 serves physiological 'house keeping' functions while the COX 2 serves the generation of PGs and inflammation action. PGs induce hyperalgesia by affecting the transducing property of free nerve endings. NSAIDs block the pain sensitizing mechanism induced by bradykinin, TNF α , interleukins (ILs) and other algescic substances. Therefore, more effective against inflammation associated pain. Literature reports shows that Shilajit is a rejuvenator of Ayurvedic origin and is found in layers of rocks in many mountain ranges especially Himalayas and Hindukush ranges. DB α P is an active constituent of herbal drug Shilajit. Clinical research reported its analgesic, anti-inflammatory, anti-oxidant, anti aging, antialzheimer, anti-ulcerogenic, immunomodulator, adaptogenic activities and nutritive tonic.¹⁻⁷

MATERIALS AND METHODS

Chemistry

The target compounds were synthesised as outlined in scheme 1 and scheme 2. The starting material dibenzo- α -

pyrone was prepared using a solution of 2- Bromobenzoic acid, resorcinol and NaOH in (round bottom flask) RBF and was heated under reflux for 30 minutes to 60°C and treated with CuSO₄ solution (10 %). Then, the mixture is heated at 80°-90°C for 10 minutes and it was stirred vigorously until it was thicken.⁸⁻⁹ The resulting DB α P was mixed with various amines (2a-k) respectively followed by formaldehyde and ethanol in a RBF and refluxed for 1.5 h as per Mannich reaction.

Experimental

All melting points were in degree centigrade and were determined using open capillary method with Perfit melting point apparatus and were uncorrected. The progress of the reaction and the purity of the product were determined by thin layer chromatography (TLC) using hexane: ethyl acetate as solvent system. IR spectra were recorded as KBr pellets on a Jasco FT/ IR- 4100 type. ¹H NMR was recorded on Bruker 400 MHz NMR spectrometer using DMSO as a solvent. UV spectra were recorded on Shimadzu- 1800 type.

Pharmacology

Eddy's Hot Plate and Tail clip method was used for determination of analgesic activity.¹⁰⁻¹⁵ The activity was performed using standard procedures and ethics (Institutional Ethical Clearance number ITS/05/IAEC/2013)

Animals

The healthy Swiss albino mice of both sexes weighing 25-30 g were taken for the study. The animals were kept in hygienic cages with proper space during the course of experimental period. The animals are kept on standard commercial diet and water *ad libitum* and were kept in rooms maintained at 22 $\pm$ 1°C with 12 h dark life cycle.

Table 1: Spectral Analysis

Derivatives	UV spectra	IR spectra	NMR spectra
DBP	332.5(0.158), 276 (1.231), 235(0.707), 208(0.724)	3297 (C-OH), 3046 (C-H), 1708 (C=O), 1473 (C=C), 1392 (C-O), 840 (C-C) cm^{-1}	10.3 (s, 1H, OH), 6.7-8.2 (m, 7H, Ar-H).
Methylamine derivative	332.5(0.150), 276.5(0.815), 233.5(0.622), 208(0.689)	3309 (C-NH), 3239 (C-OH), 2792 (C-H), 2750 (-CH ₃), 2715 (-CH ₂), 1704 (C=O), 1454 (C=C), 1280 (C-O), 1064 (C-N), 833 (C-C) cm^{-1}	10.3 (s, 1H, OH), 8.1-8.2 (m, 6H, -NH), 6.7-7.8 (m, 6H, Ar-H), 3.3 (s, 1H, -CH ₂), 2.4 (s, 1H, -CH ₃).
Ethylamine derivative	332(0.146), 275.5(1.239), 236(0.677), 208(0.689)	3386 (C-OH), 3305 (C-NH), 2985 (-CH ₃), 2976 (C-H), 2865 (-CH ₂), 1704 (C=O), 1392 (C=C), 1240 (C=C), 1218 (C-O), 1164 (C-C) cm^{-1}	8.2 (s, 1H, OH), 8.1 (m, 5H, NH), 6.6-7.8 (m, 6H, Ar-H), 3.8-4.2 (d, 2H, -CH ₂), 2.4 (t, 3H, -CH ₃).
Butylamine derivative	332(0.145), 277(0.735), 234(0.46), 211.5(0.397)	3424 (C-OH), 3212 (C-NH), 3043 (C-H), 2981 (-CH ₃), 2861 (-CH ₂), 1720 (C=O), 1420 (C=C), 1388 (C-O), 1198 (C-N), 1168 (C-C) cm^{-1}	: 10.3 (s, 1H, OH), 8.1-8.2 (m, 5H, -NH), 6.7-7.8 (m, 6H, Ar-H), 3.3 (s, 1H, -CH ₂), 2.4 (s, 1H, -CH ₃).
Isobutylamine derivative	332(0.226), 277(0.878), 247(0.552), 233.5(0.736), 214.5(0.718)	3432 (C-NH), 3216 (C-OH), 2985 (-CH ₃), 2908 (-CH ₂), 2830 (C-H), 1704 (C=O), 1423 (C=C), 1240 (C-N), 1214 (C-O), 1164 (C-C) cm^{-1}	10.3 (s, 1H, OH), 8.1-8.2 (m, 5H, -NH), 6.7-7.8 (m, 6H, Ar-H), 3.3 (s, 1H, -CH ₂), 2.4 (s, 1H, -CH ₃).
Dimethylamine Derivative	332(0.168), 276.5(0.784), 234(0.554), 211(0.498)	3355 (C-OH), 3189 (-CH ₃), 3043 (-CH ₂), 3000 (C-H), 1704 (C=O), 1330 (C=C), 1258 (C-N), 1226 (C-O), 1164 (C-C) cm^{-1}	: 10.3 (s, 1H, OH), 6.7-8.2 (m, 6H, Ar-H), 3.3 (s, 2H, -CH ₂), 2.5 (s, 3H, -CH ₃).
Diethylamine derivative	332(0.157), 276.5(0.983), 235(0.568), 211(0.459)	3293 (C-OH), 3046 (C-H), 2989 (-CH ₃), 2892 (C-H), 2850 (-CH ₂), 1704 (C=O), 1457 (C=C), 1222 (C-O), 1087 (C-N), 879 (C-C) cm^{-1}	: 10.3 (s, 1H, OH), 6.7-8.2 (m, 6H, Ar-H), 3.3 (s, 2H, -CH ₂), 2.5 (s, 3H, -CH ₃).
Dibutylamine derivative	332.5(0.163), 276.5(0.81), 234.5(0.527), 214(0.445)	3301 (C-OH), 3043 (C-H), 2977 (-CH ₃), 2857 (-CH ₂), 1700 (C=O), 1562 (C=C), 1222 (C-O), 991 (C-N), 836 (C-C) cm^{-1}	10.3 (s, 1H, OH), 6.7-8.2 (m, 6H, Ar-H), 2.8 (t, 3H, -CH ₂), 2.5 (s, 1H, -CH ₂), 1.5 (m, 5H, -CH ₂), 1.3-1.2 (m, 6H, -CH ₂), 0.9-0.8 (t, 3H, -CH ₃).
Benzylamine derivative	332(0.15), 276.5(0.668), 268.5(0.8), 234.5(0.522)	3475 (C-OH), 3359 (C-NH), 3073 (C-H), 2873 (-CH ₂), 1754 (C=O), 1423 (C=C), 1376 (C-O), 1220 (C-N), 1184 (C-C) cm^{-1}	10.3 (s, 1H, OH), 4.0 (s, 5H, -NH), 6.7-8.2 (m, 11H, Ar-H), 3.4 (s, 1H, -CH ₂), 2.5 (s, 1H, -CH ₃).
Morpholine derivative	332(0.156), 268.5(1.117), 235.5(0.609)	3297 (C-OH), 3050 (C-H), 2857 (-CH ₂), 1727 (C=O), 1531 (C=C), 1357 (C-N), 1172 (C-O) cm^{-1}	10.3 (s, 1H, OH), 6.8-8.2 (m, 6H, Ar-H), 3.4 (s, 3H, O-CH ₂), 2.5 (s, 3H, N-CH ₂).
Pyrrolidine derivative	332(0.159), 268.5(1.232), 236(0.614)	3293 (C-OH), 3093 (C-H), 2749 (-CH ₂), 1697 (C=O), 1419 (C=C), 1380 (C-N), 1230 (C-O), 1191 (C-C) cm^{-1}	10.3 (s, 1H, OH), 6.7-8.2 (m, 6H, Ar-H), 3.3 (s, 1H, -CH ₂), 2.5 (d, 3H, N-CH ₂).
Piperazine derivative	339.5(0.012), 302(0.026), 291.5(0.027), 261.5(0.155), 210(2.463)	: 3502 (C-NH), 3197 (C-OH), 3073 (C-H), 2954 (-CH ₂), 1751 (C=O), 1542 (C=C), 1450 (C-N), 1168 (C-O), 1079 (C-C) cm^{-1}	9.8 (s, 1H, OH), 6.7-8.2 (m, 6H, Ar-H), 4.4 (d, 3H, -NH-), 3.3 (s, 1H, -CH ₂), 2.5 (s, 3H, N-CH ₂).

Table 2: Physico- Chemical Properties

Compound	Molecular formula	Molecular weight	m. p. (°C)	R _f value	Solubility in DMSO	Partition coefficient
DBP	C ₁₃ H ₈ O ₃	211 g	230°-240°C	0.33	soluble	Lipophilic
Methylamine Derivative	C ₁₅ H ₁₃ O ₃ N	253 g	210°-215°C	0.54	soluble	Hydrophilic
Ethylamine Derivative	C ₁₆ H ₁₅ O ₃ N	267 g	190°-210°C	0.69	soluble	Hydrophilic
Butylamine Derivative	C ₁₈ H ₁₉ O ₃ N	295 g	180°-185°C	0.56	soluble	Lipophilic
Isobutylamine Derivative	C ₁₈ H ₁₉ O ₃ N	295 g	200°-220°C	0.66	soluble	Lipophilic
Dimethylamine Derivative	C ₁₆ H ₁₅ O ₃ N	267 g	200°-210°C	0.66	soluble	Lipophilic
Diethylamine Derivative	C ₁₈ H ₁₉ O ₃ N	295 g	210°-220°C	0.53	soluble	Lipophilic
Dibutylamine Derivative	C ₂₂ H ₂₇ O ₃ N	351 g	210°-215°C	0.64	soluble	Lipophilic
Benzylamine Derivative	C ₂₁ H ₁₇ O ₃ N	331 g	230°-240°C	0.50	soluble	Lipophilic
Morpholine Derivative	C ₁₈ H ₁₇ O ₄ N	311 g	220°-230°C	0.56	soluble	Lipophilic
Pyrrolidine Derivative	C ₁₈ H ₁₇ O ₃ N	295 g	218°-220°C	0.69	soluble	Lipophilic
Piperazine derivative	C ₁₈ H ₁₈ O ₃ N ₂	310 g	140°-150°C	0.52	soluble	Lipophilic

Analgesic activity using Hot plate test

The experiment was carried out using Vogel's method, using hot plate apparatus, maintained at 55°± 0.5°C. The mice were divided into 14 groups of 6 animals each and used for each dose. The hot plate, which is commercially available, consists of an electrically heated surface. The animals are placed on the hot plate and the time until either licking or jumping occurs is recorded by a stopwatch. The reaction time was measured prior to administration of synthesised compounds and drug administration (0 minute). Group 1 was kept as normal control group. Group 2 was served as standard and were treated with diclofenac 10 mg/kg orally. The synthesised compounds were injected orally to mice of group 3-14 at three different doses 10 mg/kg, 20 mg/kg and 30 mg/kg.

The reaction time was measured after the treatment at 0, 30, 60, 90 minutes. To avoid tissue damage to the mice paws, cut-off time for the response to the thermal stimulus was set at 60 s.

Analgesic activity using Haffner's Tail clip method

The experiment was carried out using Vogel's method, using an artery clip. An artery clip is applied to the root of the tail of mice and the reaction time is noted. Mice with a weight between 18 to 25 g were used. The mice were divided into 14 groups of 6 animals each and used for each dose. The test compounds were administered orally to fasted animals. The reaction time was measured after the treatment at 0, 30, 60, 90 minutes. An artery clip was applied to root of the tail (approximately 1 cm from the

body) to induce pain. The animal quickly responds to the location of the clip.
noxious stimuli by biting the clip or the tail near the

RESULTS AND DISCUSSION

Table 3: Result of analgesic activity using hot plate test (Eddy's hot plate method)

Derivatives	10 mg/kg				20 mg/kg				30 mg/kg			
	0 min	30 min	60 min	90 min	0 min	30 min	60 min	90 min	0 min	30 min	60 min	90 min
Vehicle	7.66 ± 2.51*	9.00 ± 1.73*	9.66 ± 1.52**	7.33 ± 2.08*								
Positive Control	10.66 ± 2.08*	11.66 ± 1.52**	11.33 ± 1.15**	10.33 ± 3.05*								
DBP	10.33 ± 0.57**	11.33 ± 0.57**	11.00 ± 1.73**	7.00 ± 1.00**	10.33 ± 0.57**	10.66 ± 2.51*	9.00 ± 1.00**	9.33 ± 1.15**	7.66 ± 0.57**	11.00 ± 1.00**	9.33 ± 1.15**	9.33 ± 2.08*
Methylamine Derivative	14.33 ± 1.15**	14.00 ± 1.00**	10.66 ± 3.05*	10.66 ± 1.15**	10.66 ± 2.08*	13.66 ± 1.15**	14.00 ± 1.00**	9.00 ± 1.00**	10.66 ± 2.08*	11.33 ± 3.21*	7.66 ± 2.51*	11.33 ± 3.21*
Ethylamine Derivative	11.66 ± 4.16*	12.00 ± 1.00**	14.00 ± 1.00**	14.00 ± 1.00**	11.66 ± 3.51*	13.00 ± 1.73**	11.00 ± 1.00**	13.33 ± 1.52**	12.33 ± 0.57**	14.00 ± 1.00**	12.66 ± 2.51*	8.66 ± 1.15**
Butylamine Derivative	9.66 ± 0.57**	8.33 ± 2.08*	8.00 ± 1.73*	8.00 ± 3.60	10.66 ± 1.15**	9.33 ± 5.13	12.33 ± 3.05*	9.33 ± 1.15**	10.33 ± 2.51*	10.33 ± 4.50	9.66 ± 4.72	8.33 ± 1.52
Isobutylamine Derivative	10.00 ± 1.00**	6.00 ± 1.00**	9.33 ± 4.93	7.33 ± 2.30*	11.00 ± 3.00*	9.00 ± 1.00**	8.66 ± 0.57**	7.33 ± 2.30*	9.00 ± 2.64*	8.33 ± 3.21*	11.00 ± 1.00**	12.00 ± 2.00**
Dimethylamine Derivative	9.66 ± 2.08*	5.66 ± 2.08*	12.33 ± 2.51*	9.33 ± 0.57**	11.00 ± 1.00**	11.66 ± 1.52**	12.00 ± 3.00*	6.33 ± 3.21	9.66 ± 4.04	12.66 ± 2.51*	10.00 ± 4.00*	10.33 ± 2.51*
Diethylamine Derivative	11.66 ± 2.88*	10.66 ± 2.08*	11.00 ± 2.64*	13.00 ± 2.64*	10.00 ± 2.00*	8.33 ± 2.57**	7.66 ± 2.51*	10.00 ± 2.00*	11.00 ± 1.41	11.00 ± 1.41	8.50 ± 0.70*	9.00 ± 1.41
Dibutylamine Derivative	13.00 ± 1.73**	11.66 ± 1.52**	7.66 ± 2.08*	7.33 ± 2.51*	11.33 ± 1.52**	8.00 ± 3.00*	7.66 ± 2.51*	10.66 ± 4.04*	9.00 ± 2.64*	9.66 ± 1.52**	9.66 ± 0.57**	8.66 ± 2.30*
Benzylamine Derivative	7.66 ± 2.57*	10.00 ± 1.00**	10.33 ± 0.57**	4.33 ± 1.15*	7.00 ± 2.64*	9.33 ± 1.15**	7.66 ± 3.21	10.33 ± 1.52**	10.66 ± 1.15**	10.00 ± 3.00*	12.00 ± 2.00**	10.66 ± 1.15**
Morpholine Derivative	8.33 ± 2.08*	10.33 ± 0.57**	8.33 ± 3.51	7.66 ± 3.21	10.66 ± 1.15**	11.66 ± 1.52**	13.00 ± 1.00**	4.66 ± 1.52*	9.00 ± 1.41	10.50 ± 0.70*	7.00 ± 4.24	5.00 ± 1.41
Pyrrolidine Derivative	10.33 ± 0.57**	10.33 ± 3.21*	8.66 ± 1.15**	10.00 ± 4.00*	12.00 ± 2.64*	10.66 ± 1.15**	9.00 ± 1.73*	12.66 ± 3.21*	9.00 ± 1.00**	9.00 ± 1.73*	9.00 ± 3.46*	11.00 ± 3.60*
Piperazine Derivative	13.00 ± 2.64*	8.33 ± 2.88*	13.00 ± 2.64*	7.33 ± 1.15**	10.33 ± 1.52**	10.66 ± 1.15**	10.00 ± 2.00*	9.33 ± 0.57**	12 ± 2.00**	11.00 ± 2.64*	10.33 ± 1.52**	11.33 ± 2.30*

Value represents the mean ± SD of 6 animals in each group *p < 0.05, **p < 0.01 (Dunnett test), Diclofenac (dose 10 mg/kg body weight)

Table 4: Result of analgesic activity using Tail clip method (Haffner's Tail clip method)

Derivatives	10 mg/kg				20 mg/kg				30mg/kg			
	0 min	30 min	60 min	90 min	0 min	30 min	60 min	90 min	0 min	30 min	60 min	90 min
Vehicle	1.33 ± 0.57	3.33 ± 1.52	4.33 ± 1.15*	2.66 ± 1.15								
Positive Control	1.66 ± 0.57*	3.66 ± 1.52	3.33 ± 0.57**	6.33 ± 2.51*								
DBP	2.66 ± 2.08	11.66 ± 1.52**	6.33 ± 3.51	7.00 ± 4.00	5.00 ± 3.00	7.33 ± 2.08*	9.00 ± 3.60*	9.33 ± 3.78*	4.00 ± 2.00*	13.00 ± 2.64*	17.33 ± 3.78*	8.00 ± 1.00**
Methylamine Derivative	6.00 ± 3.46	7.66 ± 3.78	5.00 ± 2.64	4.66 ± 3.78	7.33 ± 4.04	14.66 ± 8.96	5.66 ± 0.57**	5.66 ± 2.51	4.00 ± 1.00*	3.33 ± 1.52	5.00 ± 4.35	2.66 ± 1.15
Ethylamine Derivative	4.66 ± 3.05	6.00 ± 5.29	11.33 ± 8.08	9.00 ± 4.58	7.66 ± 2.08*	10.00 ± 5.29	8.66 ± 1.15**	5.66 ± 3.05	8.00 ± 4.00	11.66 ± 4.93	14.66 ± 8.08	8.66 ± 1.52**
Butylamine Derivative	2.33 ± 0.57*	4.00 ± 1.00*	2.66 ± 1.15	2.66 ± 1.15	2.66 ± 1.15	2.33 ± 0.57*	2.33 ± 0.57*	2.66 ± 0.57*	2.00 ± 1.00	2.33 ± 0.57*	5.66 ± 2.88	3.66 ± 1.15*
Isobutylamine Derivative	2.66 ± 0.57*	4.33 ± 1.52*	5.66 ± 2.51	3.33 ± 2.30	4.66 ± 2.08	5.66 ± 3.21	5.66 ± 0.57**	4.66 ± 1.52*	3.33 ± 1.52	2.33 ± 0.57*	2.66 ± 1.15*	2.33 ± 0.57*
Dimethylamine Derivative	4.00 ± 1.73	9.00 ± 3.60*	4.66 ± 3.78	7.66 ± 4.50	9.66 ± 5.50	11.00 ± 7.55	9.33 ± 3.05*	4.66 ± 2.08	6.66 ± 4.72	12.00 ± 2.00**	5.66 ± 0.57**	8.33 ± 2.08*
Diethylamine	8.66 ±	4.66 ±	4.33 ±	8.33 ±	6.66 ±	5.33 ±	9.33 ±	9.66 ±	8.00 ±	11.00 ±	14.00	13.00

Derivative	3.51*	2.88	1.15*	5.77	4.72	3.51	3.05*	4.61	4.24	1.41	± 1.41*	± 1.41*
Dibutylamine Derivative	2.66 ± 0.57*	10.00 ± 4.35	8.66 ± 3.78	12.33 ± 2.51*	10.33 ± 1.52**	5.33 ± 2.51	10.00 ± 6.24	13.33 ± 2.28*	6.33 ± 2.88	13.33 ± 2.88*	8.33 ± 2.88*	6.00 ± 2.64
Benzylamine Derivative	5.00 ± 1.73*	6.00 ± 3.60	4.66 ± 1.52	6.00 ± 3.60	6.33 ± 3.21	10.00 ± 2.00**	5.33 ± 2.51	9.66 ± 5.03	3.00 ± 1.00*	4.33 ± 4.04	2.66 ± 1.15	4.33 ± 2.08
Morpholine Derivative	5.00 ± 1.00**	5.33 ± 3.51	4.33 ± 2.08	4.66 ± 3.05	4.33 ± 2.30	2.33 ± 0.57*	7.00 ± 2.64*	2.66 ± 1.15	3.50 ± 2.12	6.00 ± 2.82	2.50 ± 0.70	3.00 ± 1.41
Pyrrolidine Derivative	2.33 ± 0.57*	2.33 ± 0.57*	2.66 ± 1.15*	3.00 ± 1.00*	2.66 ± 1.15	2.66 ± 1.15	2.33 ± 0.57*	2.66 ± 1.15**	2.33 ± 1.15	7.66 ± 3.21	4.00 ± 1.00*	4.00 ± 2.00
Piperazine Derivative	3.33 ± 1.52	6.33 ± 3.51	4.00 ± 1.00*	3.33 ± 0.57**	2.33 ± 0.57*	6.00 ± 2.64	4.66 ± 1.52*	4.66 ± 0.57**	5.33 ± 3.51	6.66 ± 3.21	3.00 ± 1.00*	4.33 ± 1.52*

Value represents the mean ± SD of 6 animals in each group *p < 0.05, **p < 0.01 (Dunnett test), Diclofenac (dose 10 mg/kg body weight)

The results (Table 3 and 4) revealed that most of the tested compounds exhibited significant activity or nearly the same activity as the reference drug (Diclofenac) in central analgesic assays. Few compounds showed even more activity than reference in central analgesic assay. Most of the compounds were found to be good analgesic when compared with reference drug i.e., Diclofenac or even more active using hot plate method. The compound DBP and its synthesised derivatives namely butyl, isobutyl, pyrrolidine and piperazine were found to be active among all the screened compounds using tail clip method.

CONCLUSION

The result showed that by using hot plate method most of the compound were found to be active and by using tail clip method DBP and its derivatives butyl, isobutyl, pyrrolidine and piperazine were found to be active compound against central analgesic assay. Thus the present investigation offers the synthesis of newer potent analgesics having DBP nucleus along.

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