Available online on 15.06.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Anti-inflammatory and Anti-arrhythmic Activities of 1-(Alkanoylphenoxy/ Thiophenoxy)-3-(N^4-Phenylpiperazinyl) Propane

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ABSTRACT

Synthesis and pharmacological screening of 1-(o-, m-,p-alkanoyl-, p-benzoyl-, p-cinnamoyl-, p-α-hydroxypropyl- p- α -acetoxypropyl-, p- α-oximainopropyl-, p- α -ureidiminopropyl-phenoxy/ p-propionylthiophenoxy)-3-N^4-(phenylpiperazinyl)propanes, 1-(p-propionylphenoxy)-3-substituted aminopropane, 1-(p-propionylphenoxy)-3-N^4-(phenylpiperazinyl) ethane and butanes and B-(p-propionylphenoxy)-N^1-(N^4-phenylpiperazinyl) propionamide are reported. Some of the compounds possess Anti-inflammatory and Anti-arrhythmic activity.

Keyword: pharmacological screening, Anti-inflammatory, Anti-arrhythmic activity, anti-depressant activity, IR spectra, etc.

Article Info: Received 03 May 2019; Review Completed 03 June 2019; Accepted 06 June 2019; Available online 15 June 2019

Cite this article as:

Parashar K, Starling SK, Anti-inflammatory and Anti-arrhythmic Activities of 1-(Alkanoylphenoxy/Thiophenoxy)-3-(N^4-Phenylpiperazinyl) Propane, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):420-424

http://dx.doi.org/10.22270/jddt.v9i3-s.2872

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INTRODUCTION

During the course of structure-activity relationship study of 1-(P-Propionylphenoxy)-2-hydroxy -3-(N^4-phenyl piperazinyle) as antidepressant, it was found that the corresponding 2-desoxy compound 5 though devoid of any antidepressant activity in had significant anti-diabetic activity in carrageenan-induced oedema in mice and anti-arrhythmic activity in electrically driven isolated guinea-pig auricles. This lead to the synthesis and pharmacological screening of other analogues of 5, which are described in this paper.

Condensation of alkanoyl- and aroylphenols and thiophenols (1) with 1-choloro 3-(N^4-phenylpiperazinyl) propane (2) gave compounds 5-11 and 16, $NaBH_4$ reduction of 5 furnished the corresponding hydroxyl compound 12 which on acetylation gave the actoxy compound 13. Treatment of 5 with $NH_4OH.HCl$ and $H_2N.NHCONH_2.HCl$ gave the corresponding oxime 14 and semicarbazone 15 respectively.

Compounds with varying amino substituents such as 22-25 and 27, 28 were synthesized by condensation of 1-(p-propionylphenoxy)-ω-haloroxypropiophenone (3) with 1,2_dibromoethane (4a), 1,3-chlorobromopropane (4b) and 1,4 –chlorobromobutane (4c) , with various amines in the presence of Na_2CO_3 and NaI. Acetylation of 25 with Ac_2O-pyridine gave26 and treatment of 27 with HCl-AcOH furnished 29. The amide 30 was prepared by the condensation of the acid chloride 21 with N_4-phenylpiperazine. 21 was obtained by reaction of 3 with 3-chloropropionic acid (4d) followed by treatment of the resulting acid 20 with oxalyl chloride.

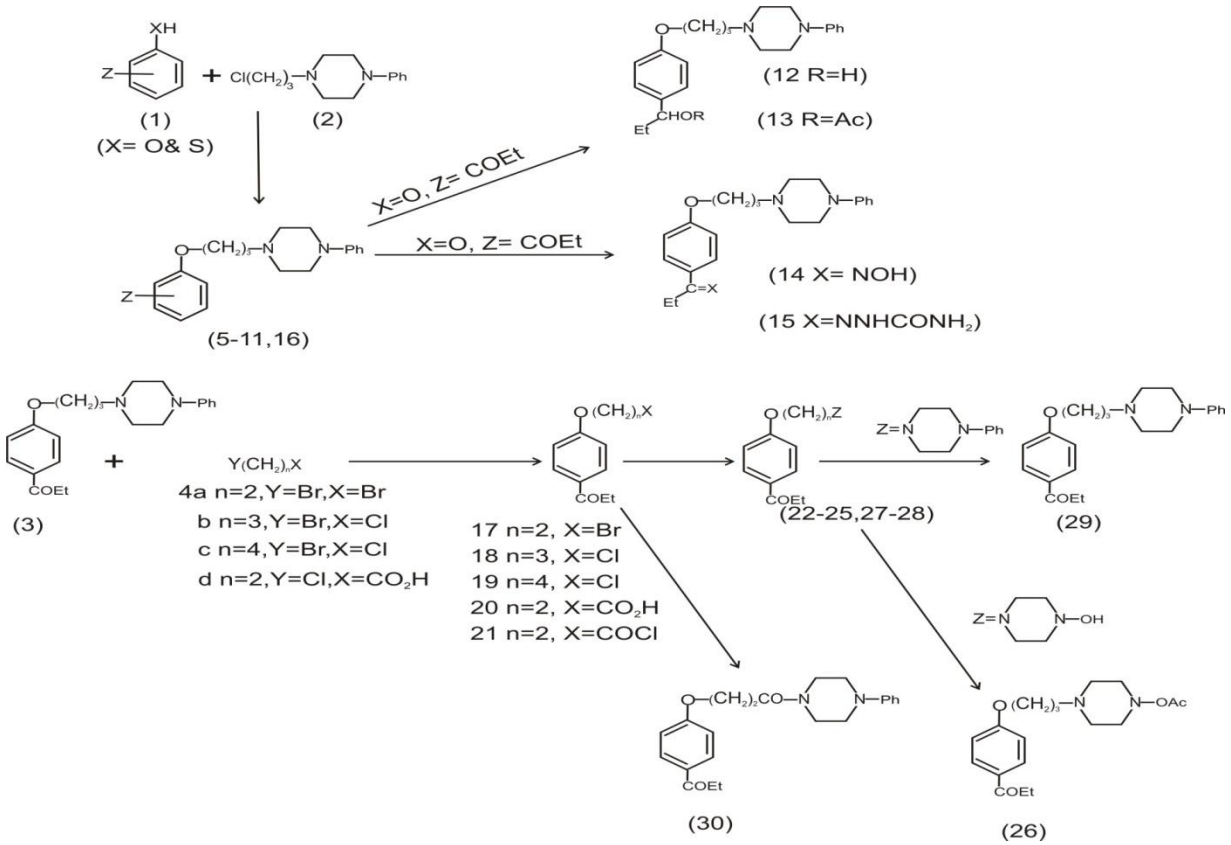
Pharmacological activity- The approximate lethal dose in 50% of animals (ALD_{50}) and gross behavioral effects were studied in mice by intra-peritoneal administration of graded doses of compounds using five animals at each dose level. The effect on blood pressure and respiration, and respiration, and interaction with acetylcholine and epinephrine on these parameters were studied in anesthetized (pentobarbitone, 35 mg/kg) cats.

Anti-diabetic screening was carried out according to the described methods. All the compounds were tested in mice for their ability to antagonize carrageenan-induced oedema at 0.2 of ALD_{50} dose. Compounds showing significant activity in this test were also studied by carrageenin induced edema and cotton pellet test in rats.

The in vitro anti-arrhythmic activity of these compounds was tested by the method of Dawes in isolated guines-pig auricle

and the effect was compared with a 3×10^{-6} g/m concentration quinidine. Interaction of the compounds with histamine and acetylcholine was studied on isolated guinea-pig ileum.

The in vivo anti- arrhythmic activity was studied in anesthetized (urethane, l g/kg ip) rats of either sex weighing between 150 and 300g. The jugular vein was cannulated for infusion of cotinine (100 µg/ml; 4.15 µg/min) by slow injection apparatus. The ECG (Lead II) changes were monitored and recorded on encardiorite polygraph before and after the administration of test compounds and during the infusion of aconitine. The test compounds were injected 2 min before starting the infusion. Quinidine was used as a reference standard. Results were expressed as the amount of aconitine required for the onset of early arrhythmia (EA), ventricular fibrillation (VF) and cardiac arrest (CA) per 100g of body weight.



MATERIAL AND EXPERIMENTAL PROCEDURE

Melting points were determined in capillary tubes in a bath and are uncorrected. IR spectra were determined on a Perkin-Elmer infrared and NMR spectra on Varian A-60D spectrometer. All compounds showed the expected spectral characteristics. The reaction products were checked routinely by NMR and IR spectroscopy and TLC. Analysis are indicated by symbols of the elements and were within ±0.4% of the calculated values. The preparations described illustrate the general methods of synthesis employed.

l-(p_Cinnsmoylphenoxy)-3-(N⁴_(phenylpiperazinyl)propane (11) - To a stirred solution of p-cinnamoylphenol (2.24 g, 10 mmoles) in DMF containing 2 ml of 20% NaOH was added drop wise l-chloro-3(N⁴-phenylpiperazinyl) propane (2) (203 g, 10 mmoles) during 30 min at room temperature. After stirring for 10 min at this temperature it was heated to 60-65 for 12 hr. under stirring. The reaction mixture was diluted with water, extracted with C_6H_6 and the extract washed with water, 5% NaOH solution, saturated NaCl solution and dried (Na_2SO_4) and concentrated to give 307 g of 11 m.p. 115-16 (C_6H_6-hexane).

1-(p-α Hydroxy propyl phenoxy) -3- (N⁴-phenyl piperazinyl) propane (12) – A solution of l-(p-propionylphenoxy)-3- (N⁴-phenylpiperazinyl) propane (5) (3g, 9 mmoles) in MeOH was stirred at 5-10 and treated with powdered $NaBH_4$ (2.4g) in three parts in 20 min. The reaction mixture was stirred for l hr. at this temperature and then refluxed for l hr. on a steam-bath. Concentration of the solution and decomposition of the residue with hot water followed by extraction with $CHCL_3$ and the usual workup gave 2.6 g of 12, m.p. 84-85 (C_6H_6-hexane) ; hydrochloride, m.p. 178 (MeOH-Et_2O).

l-(p-α-Acetoxy propyl phenoxy)-3- (N⁴-phenyl piperazinyl) propane (13)- A solution of 12 (1.8 g, 5 mmoles) and Ac_2O (6 ml) in pyridine (10 ml) was stirred for 24 hr. Excess of pyridine and AC_2O were removed in vacuum and the residue diluted with water, extracted with C_6H_6 and the extract washed with water 5% $NaHCO_3$ solution, saturated NaCl and dried (Na_2SO_4) Removal of C_6H_6 by distillation and crystallization of the residue form C_6H_6 – hexane gave 1.8 g of 13 m.p. 1687 ; hydrochloride, m.p. 176 (MeOH-Et_2O).

l-(p-Propionylphenoxy_-3-(N⁴-phenylpiperazinyl) propane oxime (14)– A mixture of 5 (0.5 g, 1.3. mmoles), $NH_2OH.HCl$ (0.5 g, 6.5 mmoles) and 0.5 mole pyridine in 5 ml EtOH was refluxed for l hr. The solution was concentrated and diluted with water to give 0.5 g of 14 m.p. 185 dihydrochloride, m.p. 182 (MeOH_Ht_2O).

l-(p-propionylphenoxy)-3-(N⁴-phenylpiperazinyl)propanesemicarbazone (15) – A mixture of $H_2NNHCONH_2.HCl$ (1.0 g, 1 mmoles), NaOAc (1.5g,

16 mmoles) and 5 (0.5g, 1.3 mmoles) in 10 ml water was warmed on a steam-bath for 5 min. On cooling the semicarbazone 15 separated out, yield 0.5 g, m.p. 197 dihydrochloride, m.p. 173 (MeOH-Et_2O).

l- (p-propionylphenoxy)-3-chloropropane (18) -To a stirred solution of NaOH (8g, 200 mmoles) in water (20ml) and p-hydroxypropiophenone (3, 30 g , 200 mmoles) in DMF (180 ml) at room temperature was allied l-chlore-3-bromopropane (4b, 31.5 g, 200 mmoles) drop wise during30 min. After 10 min at this temperature, it was kept under stirring at 60-65 for 12 hr. The reaction mixture was worked up in the usual manner to give 24 g of 18, B.P. 162-64/0.04 mm.

l- (p-propionylphenoxy)-3- (N-morpholinyl) propane (24)- A mixture of 18 (4.5 g, 20 mmoles) morpholine (1.74 g, 20 mmoles), anhydrous K_2CO_2(4g) and KI (0.1 g) in dry Me_2CO (50 ml) was refluxed for 8 hr., filtered Me_2CO evaporated and the residue after dilution with water extracted with C_6H_6 The extract was washed NaCl, dried (Na_2SO_4) and concentrated to give 4.8 g of 24 m.p. 126 (C_6H_6-hexane) hydrochloride, m.p. 188-89 (MeOH-Et_2O).

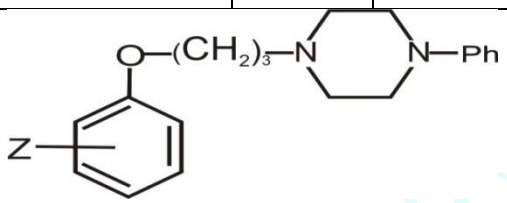
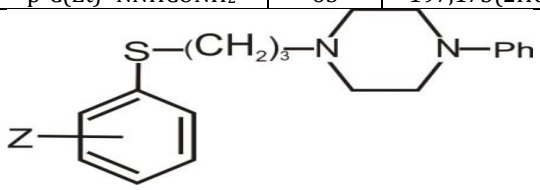
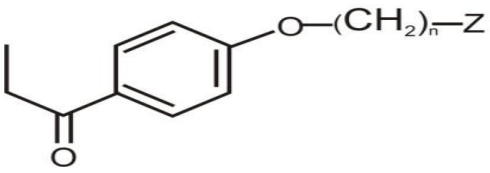
l- (p-propionylphenoxy)-3- (N^1-morpholinyl) propane (26) – A mixture of 25 (1.5 g, 5 mmoles), Ac_2O (2 ml) in pyridine (30 ml) was stirred for 24 hr. at room temperature. Excess of pyridine and Ac_2O was removed in vacuum, the residue diluted with water, extracted with C_6H_6 and the extract washed with water, 5% NaOH solution, saturated Nacl, dried (Na_2SO_4) and concentrated to give 0.95 g of 26 m.p. 88-89 ; hydrochloride, m.p. 137-38 (MeOH-Et_2O)

l- (p-propionylphenoxy)-3- N^1-(4-phenyl-3-piperidienyl) propane (29) - A mixture of 27 (l g, 3 mmoles), conc, HCl (2 ml) and glacial AcOH (2ml) was refluxed for 20 min and the hot solution poured on ice water. The solid was filtered and crystallized from C_6H_6 to yield 0.85g of 29, m.p 116^0; hydrochloride, m.pm. 176^0 (MeOH-Et_2O).

β-(p- propionylphenoxy) propenoic acid (20) - NaOH (2 g, 50 mmoles) in 10ml water was added drop wise to mixture of 3(3.8g, 25mmoles) at β-chloropropinoic acid (2.8g, 25 mmoles) 70^0. The reaction mixture was stirred for 10 min at the temperature and then refluxed for 3hr. cooled and the reaction mixture acidified with dil.HCl to give 20, m.p. 73-74.

β-(P-propionylphenoxy)propionylchloride(21):-oxalyl chloride (0.6g,5mmoles) in dry C_6H_6 was added drop wise to a stirred solution of 20 (1.2g, 5mmoles) in dry C_6H_6 and solution allowed stir overnight at room temperature. Benzene was removed under vacuum to give 1.0g of 21 as an oil.

N'-(N^4-phenylpropionyl)-β-(p-propionylphenoxy) propionamide (30)- N-phenylpiperazine (1.54g, 10mmoles) in dry C_6H_6 (15ml) was added drop wise to a solution of the chloride (21, 1.2g, 5mmoles) in dry C_6H_6. The mixture was refluxed for 1hr and treated with water. The C_6H_6 layer was washed with 1% aq.NaOH, water, saturated NaCl dried (Na_2SO_4) and concentrated to give 1.3g of 30, m.p. 100^0 (C_6H_6-hexane); hydrochloride m.p. 186^0 (MeOH-Et_2O).

No.	Z	Yield (%)	m.p. ^{0}C	Formula	Analysis	ALD_{50} mg/kg	significant
							
5	p-COEt	78	112	$C_{22}H_{28}N_2O_2$	CHN	800	
6	p-COMe	66	112	$C_{21}H_{26}N_2O_2$	CHN	>800	
7	o-COMe	66	194(2HCl)	$C_{21}H_{26}N_2O_2$	CHN	300	
8	m-COMe	66	93,188(2HCl)	$C_{21}H_{26}N_2O_2$	CHN	400	
9	p-COPr	65	89	$C_{23}H_{30}N_2O_2$	CHN	>800	
10	p-COPh	65	79,144(2HCl)	$C_{26}H_{28}N_2O_2$	CHN	>800	
11	p-COCH=CHPh	88	116,197(2HCl)	$C_{28}H_{32}N_2O_2Cl_2$	CHN	600	
12	p-CH(OH)Et	86	85,178(2HCl)	$C_{22}H_{30}N_2O_2$	CHN	75	
13	p-CH(OAc)Et	83	168,176(2HCl)	$C_{24}H_{22}N_2O_2$	CHN	600	
14	p-C(Et)=NOH	95	185,182(2HCl)	$C_{22}H_{31}N_2O_2$ Cl_2	CHN	400	
15	p-C(Et)=NNHCONH$_2$	65	197,173(2HCl)	$C_{23}H_{33}N_2O_2Cl_2$	CHN	400	
							
16	p-COEt	70	186(2HCl)	$C_{22}H_{30}N_2OSCl_2$	CHN	400	
							

17	Br (n=2)	24	86	$C_{11}H_{13}N_2O_2Br$	CH	-	
18	Cl (n=3)	85	41	$C_{12}H_5O_2Cl$	CH	-	
19	Cl (n=4)	36	170-75/2-3mm	$C_{13}H_{17}O_2Cl$	CH	-	
20	CO_2H (n=2)	58	72	$C_{12}H_{14}O_4$	CH	600	

21	COCl (n=2)	-	-	-	-	-	-
22	4-phyenylpiperazine (n=2)	86	191(2HCl)	$C_{21}H_{28}N_2O_2Cl_2$	CHN	600	
23	Do (n=2)	71	180(2HCl)	$C_{23}H_{32}N_2O_2Cl_2$	CHN	600	
24	Morpholine (n=3)	88	189(HCl)	$C_{16}H_{24}NO_2Cl$	CHN	600	
25	4-Hyroxypiperidyl (n=2)	79	158(HCl)	$C_{17}H_{26}NO_3Cl$	N	600	
26	4-Acetoxylpiperidyl (n=2)	70	138(HCl)	$C_{19}H_{28}NO_4Cl$	CHN	60	
27	4-OH-4-Phenylpiperidyl(n=3)	66	119,159(HCl)	$C_{23}H_{29}NO_3$	CHN	37.5	
28	4-Phenylpiperidyl (n=3)	65	155,155(HCl)	$C_{23}H_{29}NO_2$	CHN	37.5	
29	4-Phenyl-3-piperidienyl (n=3)	76	116,176(HCl)	$C_{23}H_{27}NO_3$	CHN	300	
30	See`expl	66	100,186(HCl)	$C_{22}H_{26}N_2$ O3	CHN	800	

(a) Compound 5-10 and 16 were synthesized as described for 11; 17 and 19 by the method used for 18 and 22-25 and 27-28 by the procedure for 24.

(b) Yield reported here are of based only.

(c) Bases were crystallized form C_6H_6 hexane and hydrochlorides form MeOH-Et_2O.

(d) ALD_{50} refers to approximate LD_{50}.

(e) Compound 5, 7,8,16 &29 were found depressants and 27 stimulant in gross behavior.

(f) AI= anti-diabetic activity. Numbers describe the percent inhibition of carrageenin anducedoedema in mice at doses of 0.2 ALD_{50}.

(g) AA= Anti-arrhythmic activity on isolated guinea-pig auricle. Figures describe the percentage decrease in maximal driving frequency at a concentration of 3×10^{-6}g/ml.

(h) BP = fall in blood pressure measured in mm Hg at 2.5 mg/kg i.e. in cats. Numbers in parentheses represent duration in minutes.

Table:-2 Anti- diabetic Activity of compound 5

Compound	Carrageenin-induced oedema in mice		Carrageenin-induced oedema in rats		Cotton pellet test in rats	
	Dose mg/kg p.o.	Inhibition %	Dose mg/kg p.o.	Inhibition %	Dose mg/kg p.o.	Inhibition %
5	200	45	100	16.6	50	4.7
	100	42	50	8.3		
	50	32	25	11.1		
Cortisone	40	44	-	-	-	-
phyenylbutazone	-	-	50	20.3	50	14.0

Table:-3 protective effect of test compound on aconitine induced arrhythmia in rats

Compound	Dose mg/kg i.e.	No.of rats used	Mean amount of aconitine (µg/100g) required to produce		
			Early arrhythmia	Ventricular fibrillation	cardiac arrest
5	10	3	8.3	13.8	15.5
7	10	3	13.4	38.2	46.8
8	10	3	12.7	33.2	38.2
10	10	3	15.9	41.4	50.2
15	10	4	12.3	59.2	74.9
27	10	5	23.7	60.4	123.2
Saline	-	5	8.4	15.7	19.5
quinidine	20	5	8.6	18.9	58.0

RESULT AND DISCUSSION

The primary pharmacological screening of the compounds was carried out by the methods described above , and only positive result shown in these tests are given in Tables l. The detailed sand comparative anti-diabetic activity of compound 5 is described in Table 2 and in vivo anti-arrhythmic activity of compounds 5, 7, 8, 10, 15, and 27, in Table 3.

Compound 5 showed marked anti-diabetic activity. A decrease in the length of alkanoyl chain as in 65 retained the activity whereas an increase (9) markedly diminished the activity. Shifting the $-COCH_3$ group of 6 to ortho (7) and Meta (8) positions abolished the activity. Replacement of p-$COCH_3$ group of 6 by p-COPh (10) also resulted in loss of activity while replacement by p-COCH=CHPH retained the activity. Reduction of CO in5 to CHOH (12) lowered the activity which was abolished by acetylation (13). The corresponding oxime 14 gave similar order of activity whereas it semicarvazone 15 showed lower activity. Replacement of the ether group in 5 by thioether group (16) did not affect the activity. Reduction of the chain length to two (22) abolished the activity, while increasing to four (23) lowered the activity. Replacement of N^4-phenylpiperazine residue by morpholine or piperidine with or without a substituted at 4- position as in 24-29 abolished the activity. Replacing tertiary amine part of 5 by an amide function as in 30 markedly lowered the activity.

In in vitro test compounds 5,7,8,10,15 and 27 showed significant anti- arrhythmic activity which suggests that the presence of an alkanoyl part irrespective of its position is necessary for this activity. Compound 5, which showed marked anti-diabetic activity, also had significant anti-arrhythmic activity and was, therefore, selected as a prototype for further structure modification. Reduction of CO to CHOH (12) and its acetyl derivative 13 showed much lower activity than the prototype. The oxime 14 of compound 5 also showed weak activity while its semicarbazone 15 had comparable activity. Replacement of ether function in 5 by thioether (16) abolished the activity. Decreasing the chain length to two (22) also resulted in lowering the activity. 4-hydroxypiperidine compound 25 and 4-phenylpiperidine compound 28 were inactive while 4-hyroxy-4-phenylpiperdine compound 27 was slightly more active than the prototype. All this suggests that in the amino component an additional binding site along with a phenyl group in essential for this activity.

In in vivo test (table-3) compound 7, 8, 10, 15 and 27 were found to delay the onset of EA, VF and CA induced by aconitine in rats. The order of potency in respect of preventing VF was 27>15>10>7>8>quinidine. If CA is taken as the criterion of activity then the order of potency stands as follows: 27>15> quinidine >10>7>8. In any case compound 27 and 15 seem to be more potent then quinidine, a reference standard used in this investigation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONCLUSION

Present study characterized that compound 5-8, 14 and 15 also showed hypotensive activity of this compound 6 had the most mark activity. Compound 5 and 6 both showed Anti-inflammatory and Anti-arrhythmic activity. Compound 7,8,10,15 and 27 show significant Anti-arrhythmic activity.

ACKNOWLEDGEMENT

The author are thankful to Dr. Sushil K. Starling for guidance me and Dr. B.N. Dhawan for providing primary screening data and to Miss Lakhanpal, Mrs. U. Sharma and Mr. M.S.Ansari for technical assistance in pharmacological screening.

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