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Physicochemical and pharmacological study of some newly synthesized furan imine derivatives

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Abstract

Furan ring systems are abundantly available in secondary plant metabolites. Due to their remarkable properties, many synthetic furans are utilized as pharmaceuticals. Hence a series of N-(furan-2-ylmethylene) benz- imines derivatives has been synthesized by reaction between furan-2--carboxaldehyde and various aromatic anilines to yield the schiff's bases. The newly synthesized compounds showed potent CNS depressant and analgesic activities. Prior to determination of the Pharmacological activity $LD_{50\ was}$ determined. The pharmacological data obtained were tested for statistical significance.

Keyword: Furfuraldehyde, Column chromatography, P^{Ka} Value, LD^{50}, Analgesic, CNS depressant.

Introduction

Furan is a 5-membered heterocyclic oxygen-containing unsaturated ring compound. From a chemical perspective it is the basic ring structure found in whole class of industrially significant products. The furan nucleus is also found in a large number of biologically active materials. Though not found in animal metabolism, furan ring systems are abundantly available in secondary plant metabolites,(l). Many of these furan natural products show inspiring biological activities, such as cytotoxic and antitumor properties,(2) antispasmodic,(3) and antifeeding

activities(4) . More natural furan containing molecules continue to be uncovered at a rapid speed(5). Due to their remarkable properties ,many synthetic furans are utilized as pharmaceuticals.(l) In addition to being building blocks found in natural molecules, poly-substituted furans(6) are important precursors for the synthesis of natural and non natural products(7). Lea Grinblat, Claudia M. Sreider, Andrés O.M. Stoppani (8) showed that nitrofuran derivatives bearing unsaturated five- or six-membered nitrogen heterocycles or related substituents were more effective inhibitors of yeast and rat tissue glutathione reductases than those bearing other groups, such as nitrofurtimox, nitrofurazone and 5-nitro-2-furoic acid. The inhibitory action proved independent of electron withdrawal from the reduced enzyme, as a consequence of redoxcycling of the nitro group. Joshi, *et al.* (9) discovered potent furan piperazine sodium channel blockers for treatment of neuropathic pain . Yiqiu Fu et al (10) designed and synthesized a novel class of furan-based molecules as potential 20S proteasome inhibitors.

Materials and methods

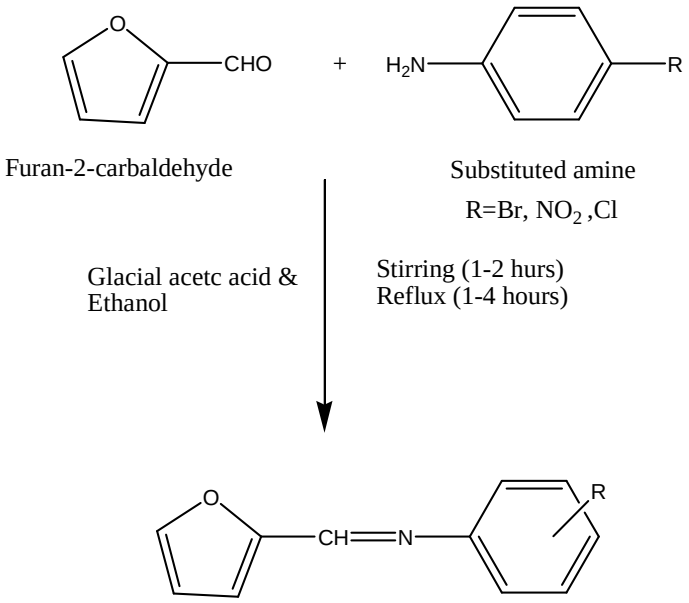
The synthesis of the titled compound is given in scheme-1. All the melting points were determined in concord apparatus in °C. The UV spectra were recorded on Shimadzu UV-1201 spectrophotometer. The IR spectra of the compounds were recorded in BX-II FTIR Perkin Elmer. The 1H-NMR was determined on 500 MHz JEOL. MS spectra were recorded on MS-MASS FIGGEAN. PKa value was determined on pH meter Toshniwal Mfg.Pvt.Ltd.Ajmer.The. The CNS activity was determined on actophotometer, INCO.

Synthesis of N-(furan-2-ylmethylene) benzenimine Deriatives

Taken 50 ml of dry ethanol, to that added 1gm of furfuraldehyde and stirred for 15 minutes for proper mixing. To the resulting mixture glacial acetic acid was added and the reaction was ran for 1hr. After that to the resulting mixture the substituted anilines were added in different proportions: p- bromo aniline (1 meq), p- nitro aniline (1.5 meq), p- chloro aniline (1.2 meq).Then the reaction was stirred for an hour followed by 2-3 hrs reflux in water bath. At the end there was colour change observed. The completion of the reaction was determined by TLC using iodine chamber. The reaction was kept for overnight. To the cooled reaction mixture crushed ice was added. Formation of precipitate took place. The purification of the compound was done by coloumn chromatography using petroleum ether and ethyl acetate as mobile phase.

Estimation of pKa by Potentiometric method (11)

0.01 M solution of compound in 10% acetone water solvent system was prepared in 50 ml. and 0.01 N aqueous hydrochloric acid were prepared in 100 ml. The pH meter was calibrated by pH tablet before 30 min of titration. A burette containing solution B was filtered appropriately for individual respective compounds 47.5 ml solution of A in titrating vessel was taken and pH was recorded. The titration was performed by addition of 0.5 ml portion of solution B appropriately for individual respective compound from burette and pH of each condition of titration was measured. Addition of titration was continued up to 5ml (10 nos. addition).The pKa was calculated by applying Henderson Hasselbach equation for each addition of titrant and then mean value was reported.



Sheme-1:-Synthesis of N-(furan-2-ylmethylene) benzenimine derivatives

Animal Experimentation

Healthy three months old male mice weighing around 25-30g were bread and maintained in Central Animal House Facility, IIMT College of medical sciences, Meerut were used for study. The experimental protocol was submitted to Institutional animal ethical committee and continued after approval Swiss albino mice used for acute toxicity studies were also locally bread .The animals were maintained on standard rodent diet and water *ad labium* . The animals were maintained on 12hrs/12hrs dark cycle at temperature of 25+2°C, Humidity of 45%-55% and ventilation of 10-12 exchanges/hrs.

Procedure for toxicity study(12-15)

Based on the short term toxicity study, the dose of the animals were determined as per OECD guidelines. Prior to studying different pharmacological activity of the compounds, it was essential to determine toxicity of drug. Healthy and adult male albino mice weighing between 20-25 gm were used in present investigation. Animals were fed with sample test compound suspended in 10% solution of Tween 80 (water as vehicle), was administered intra- peritonially in dose of 5-300 mg/kg. A control group of the animals received only vehicle. Animals were observed for 48 hrs from the time of administration of test compound (T1, T2, T3) to record the mortality. The results of acute toxicity study were found to be supportive in regard to fix the doses further for other pharmacological investigations.

Evaluation of CNS activity

Procedure for actophotometer(16,17)

Healthy and adult albino mice were weighed and numbered. Actophotometer calibration was done prior to experimentation. Each mouse was placed separately in the activity cage for 600 seconds and the basal activity score of each mouse was noted. The tested compounds were

administered intra-peritonially and the activity scores for 600sec were note after 30 min and 1hr. The difference in activity before and after drug administration was noted. The percent decrease in the motor activity was then calculated.

Evaluation of Analgesic activity

Procedure for tail immersion test(18)

Healthy and adult male albino mice (20-25gm) were used. They were placed into individual restraining cages leaving the tail hanging out freely. The animals were allowed to adapt to the cages for 30 min before testing. The lower 5cm portion of the tail was immersed in a cup of freshly filled water of exactly 55ºC. within a few seconds the mice reacts by withdrawing the tail. The reaction time was recorded in 0.5sec units by a stopwatch. After each determination the tail was dried carefully. The reaction time is determined before and periodically after intra peritoneal administration of the test substance, e.g., after 30 mins and 1hr. The cut off time of the immersion was 15secs. The withdrawal time of untreated animals is between 1-5.5secs. A withdrawal time of more than 6 secs therefore regarded as positive response.

Results and Discussion

Our present work involves synthesis of some furan imine derivatives and characterization of the synthesized compounds followed by their pharmacological evaluation. These compounds were synthesized by reaction between furan-4-carboxyaldehyde, substituted aniline and glacial acetic acid in the presence of dry ethanol as a solvent. Purification of the compounds was done by coloumn chromatography using ethyl acetate and petroleum ether in different proportions. The chemical analysis of the compound was done for aldehyde, primary amine, nitro and halogens. It gives negative result for aldehyde and amine which indicated formation of imine derivatives. The Physicochemical data of the compound is shown in the (Table no-1). Structural elucidation of the compounds was done by UV analysis (Table-2,3), ^{1}H NMR ,IR and MS(Table-4,5,6).The λ_{max}, A_{max}, $^{1\%}E_{1cm}$ and Є values were also recorded from UV analysis. Based on the spectral analysis the compound are named as 4-bromo-N-(furan-2-ylmethylene) benzenamine; N-(furan-2-ylmethylene)-4 –nitro benzenamine, and 4-chloro-N-(furan-2-ylmethylene) benzenamine respectively.The pharmacological screening against analgesic and CNS activity was determined for all the compounds but prior to pharmacological evaluation, toxicity study was determined & dose is fixed as 10mg/kg body weight for compound no. 1 & 2 and 5mg for compound no. 3.The pharmacological deata was subjected to statistical validity shown in the (Table -7,8) .

The UV analysis on test solutions of 10µg / ml in methanol+water (1:1) mixture showed the expected λ max in nm (Єmax in dm^3/mol/cm) values 258(2398.36); 379(3114.82); 299(1024.46) respectively with allowed transition which also indicate that compounds are aromatic. The presence of HC=N is proved due to weak intense band at 258nm;289nmand 360nm which also showed in all the compounds n-π^* transitions are predominating.

From the ^{1}HNMR spectra it was found that in all the compounds the protons were aromatic in nature due to the formation of peak on δ value 6-8.The formation of CH=N was further confirmed due to the singlet peak at δ value (for the compound):-7.25(Compound no-1) ,7.40(Compound no-2) ;7.45 (Compound no-3) respectively.

IR (KBr) spectra of the compounds showed streching for C=N at 1590.27,1597.54 and 1479.12 respectively .The formation of peak at 595.26b (str.) indicates the presence of C-Br incompound-1. The presence of C-NO_2 in case of the compound-2 is confirmed by peak at 1303.78 (str.) and C-Cl in compound -2 is confirmed by peak at 752.13 (str.) .

The molecular mass was confirmed on mass spectroscopy using acetonitrile as solvent by peak at m/e (%) 250.13 (97%) ; 216.05(100%) ;206.13 (33%) .From the pKa values it was confirmed that all the compound are acidic in nature .

After toxicity study dose was fixed as 10mg/kg body weight for compound no. 1 & 2 and 5mg for compound no. 3. The analgesic & CNS depressant activities were determined for all the compounds except compound 1, all the compound shown significant analgesic activity and all the compound shown the potent CNS depressant activity.

Table-1: Physical data of Compounds

CompoundNo.	MP (°C)	Colour	R_f Value*	% Yield	Solubility	P^{ka} Value
1	96	Dark brown	0.7	80 %	MeOH	3.46525
2	132	Yellow orange	0.53	82 %	MeOH	3.49925
3	92	Brown	0.79	75 %	MeOH	3.44625

Table-2: UV Analysis of the compound

Compound no.	λ_{max}	A_{max} of µg/ml	$^{1\%}E_{1cm = Abs/0.001}$	Molecular Weight	$Є_{max} = {}^{1\%}E_{1cm}$ x M.Wt/100
1	258	0.959	959	250.09	2398.36
2	379	1.436	1436	216.91	3114.82
3	299	0.497	497	206.13	1024.46

Table-3: Electronic Transitions of U.V. Visible Spectra

Compound No.	λmax	Absorbance	Types of Peaks	Transitions	Transition due to
1.	258	0.959	Weak band- not intense	n-π*	C=N
	289	0.395	Band- intense	π -π*	C=C
2.	289	1.410	Band- intense	n-π*	C=N
	299	0.495	Weak band-not intense	π -π*	C=C
3.	226	0.789	Broad band	n-σ*	C-N
	360	1.39	Sharp band with shoulder	n-π*	C=N
	379	1.436	Broad band- intense peak	n -π*	C=C

Table-4: NMR (^{1}H) Spectra of the compounds

COMPOUND No.	δ VALUE (ppm) & J (Hz)	TYPES OF PEAK	POSITION OF THE PROTON
1.	7.69-7.68 (J=5)	doublet	C_2=1H
	6.58-6.57 (J=5)	doublet	C_3=2H
	7.9-7.89 (J=5)	doublet	C_8=2H
	6.23-6.22 (J=5)	doublet	C_7=2H
	7.25	singlet	C_{12}=1H
2.	7.90-7.89 (J=5)	doublet	C_2=1H
	6.56-6.55 (J=5)	doublet	C_3=2H
	7.90-7.89 (J=5)	doublet	C_8=2H
	6.58-6.57 (J=5)	doublet	C_7=2H
	7.40	singlet	C_{12}=1H
3.	7.80-7.79 (J=5)	doublet	C_2=1H
	6.53-6.52 (J=5)	doublet	C_3=2H
	7.71-7.70 (J=5)	doublet	C_8=2H
	6.33-6.5732 (J=5)	doublet	C_7=2H
	7.45	singlet	C_{12}=1H

Table-5: FTIR Spectra of the compounds

COMPOUND No.	Peak at (cm^{-1})	Stretching/Vibration	Group responsible
1.	595.26	Str	C-Br
	1290	Str	C-H
	1489.12	Skeletal vibration	C-C
	1590.27	str	C=N
	1865	Out of plane	C-H
2.	832.82	Vibration	C-N
	1303.78	Symmetric str	C-NO_2
	1597.54	Vibration	C=N
3.	752.13	Str	C-Cl
	1279	In plane deformation	C-H
	1479.12	Skeletal vibration	C=N
	1580.27	Str	C=N
	1863.57	Out of plane	C-H

Table-6: Mass Spectra of the compounds

COMPOUND NO.	m/e	TYPE OF PEAK (%)
1.	252.13	M+ (100.0 %)
	250.13	M+1 (97.0 %)
2.	216.05	M+ (100 %)
	217.06	M+1 (12.1 %)
	218.06	M+2 (1.3 %)
3.	307	M+ (100.0 %)
	206.13	M+1 (33.0 %)

Table 12: CNS Depressant Activity (Actophotometer)

Treatment (i.p.)	Drug (mg/kg)	Mean reaction without drug (sec)	Reaction Response	
			30 min	1 hr
Control	0.2ml	839.66±6.489	837.66±06.825*	841.66±8.861*
Standard	1-3	665.00±76.453*	515.00±76.385*	166.00±2.082*
Test 1	10	975.00±14.194	862.33±14.591*	53.33±1.085
Test 2	10	491.33±38.299*	369.16±14.515*	55.33±1.926*
Test 3	5	392.33±18.342*	216.33±12.593*	35.00±1.000*

*Counts taken after every 600 sec; Values are mean ±SEM; n=6 in each group; * represents the values less than P<0.05 were considered to be significant*

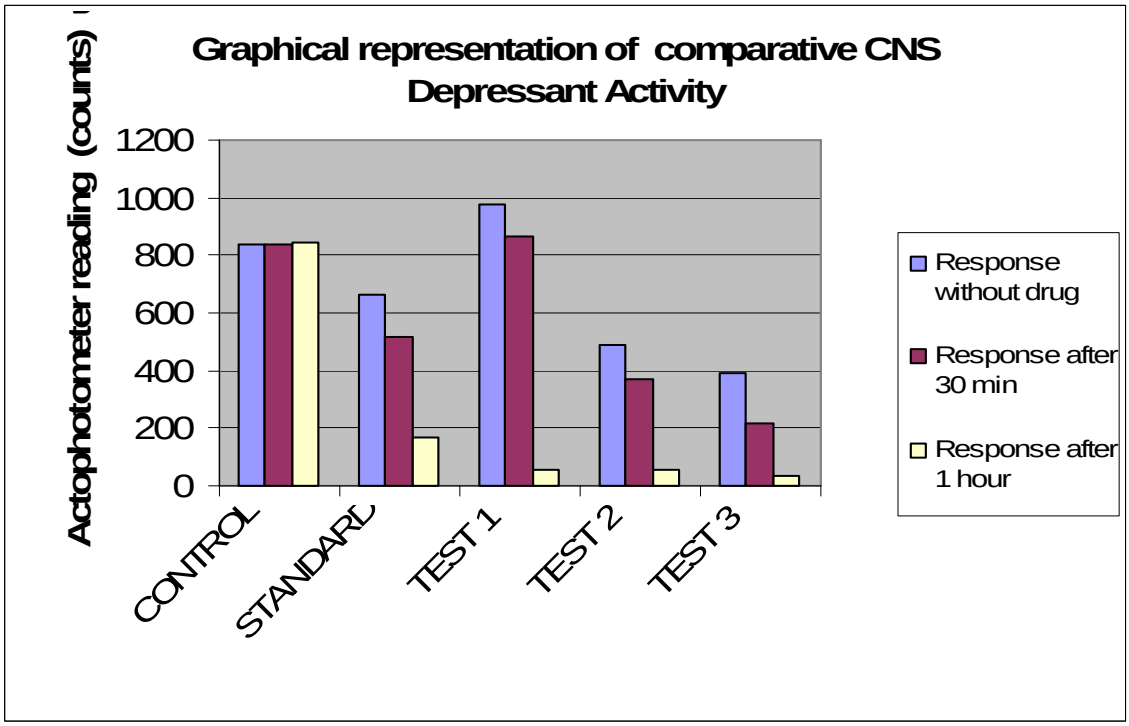
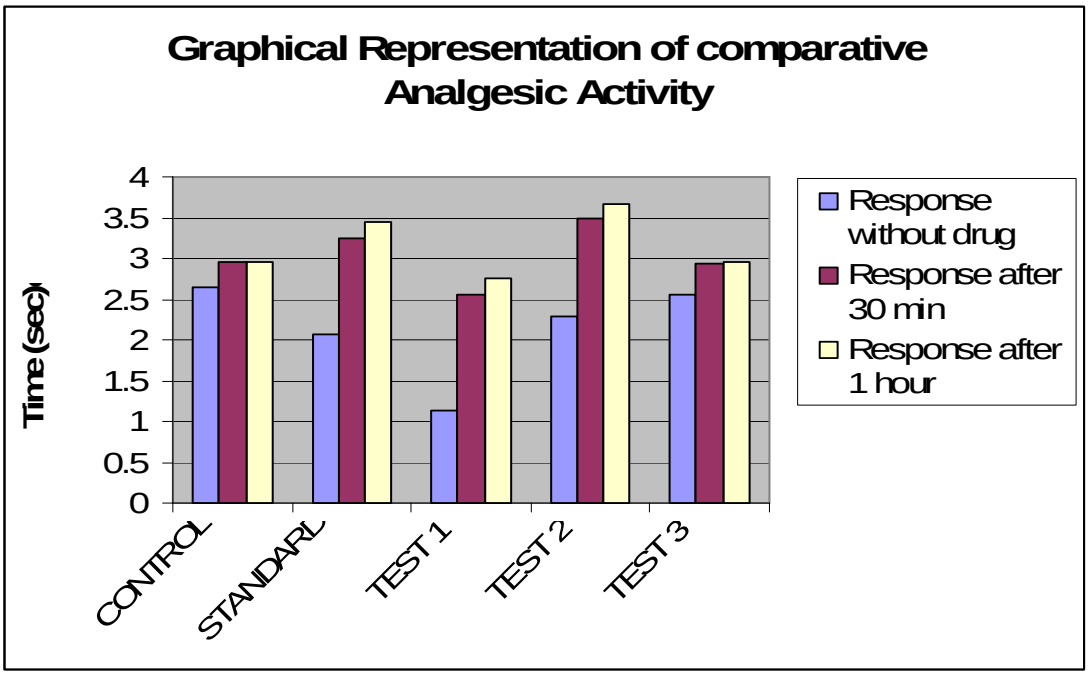


Table 13: Analgesic activity (Tail flick by hot immersion method)

Treatment (i.p.)	Drug (mg/kg)	Mean response without drug (sec)	Mean Reaction Response	
			After 30 min	After 1 hr
Control	0.2ml	2.65±0.0763*	2.9543±0.3868*	2.9543±0.3868*
Standard	1-5	2.076±0.2107*	3.2433±0.4393*	3.44±0.4185*
Test 1	10	1.125±0.2043*	2.5566±1.358*	2.765±0.3324*
Test 2	10	2.2833±0.5492*	3.49±0.4142*	3.6558±0.3829*
Test 3	5	2.5666±0.1202*	2.931±0.2544*	2.965±0.2540*

*After immersion in water at 55ºC; Values are mean ±SEM; n=6 in each group; * represents the values less than P<0.05 were considered to be significant*



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