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RESEARCH ARTICLE

Synthesis and Screening of Some New Piperazine Derivatives as Potential Anthelmintic Agents

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ABSTRACT

The purpose of this study is based upon synthesis of a series of 1,4-disubstituted piperazine derivatives through two step reaction. This protocol involves the formation of various mannich base derivatives (N-01 to N-07) through reaction in which microwave synthesis is carried out to prepare 1-phenyl piperazine The second step involves the reaction of 1-phenyl piperazine (N-01 to N-07) with substituted aniline to afford target compounds. (N-01 to N-o7). The structures of target compounds were elucidated from the data of the different spectral methods of analysis. In addition, a mass spectrum, for a representative example, was carried out where the expected fragmentation pattern is in accordance with the structure of the proposed compound. The anthelmintic activity of the synthesized derivatives (N-01 to N-07) was investigated in vitro against Eisenia fetida. All the investigational compounds (N-01 to N-07) and) exhibited promising anthelmintic activity at minimal dose of 5mg/ml in comparison with reference drug Piperazine citrate.

KEYWORDS

1-Phenyl Piperazine, Anthelmintic Activity, Mannich Base, Anthelmintic Activity

INTRODUCTION

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesize pharmacologically interesting piperazine derivatives of widely different composition.

Substituted piperazine has received considerable attention during last two decades as they are endowed with variety of biological activities. Literature survey showed that methyl piperazine is a versatile lead molecule for design of potential bioactive agents.

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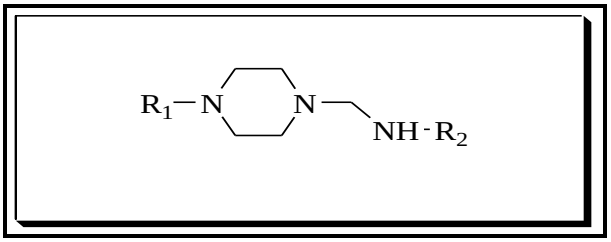
Piperazine is a main ingredient of anthelmintics used to treat intestinal roundworms (ascariasis) infection in human. This observation is a guiding thought in the present work in exploring the synthesis of some new compounds with a desire to obtain highly potent, more specific molecules.

Mannich reaction is a versatile reaction and it is also reported in the treatment of helminth infection, our proposed aim is to prepare Mannich base of prepared N-aryl and N-methyl piperazine, the reaction is done with extreme care to obtain the desired result. In the helminth infection the need of more potential and broad spectrum drug is needed, the development of resistance as well as other side effects is problem, So our aim is to prepared the derivatives with potency as a good anthelmintic agents as well as

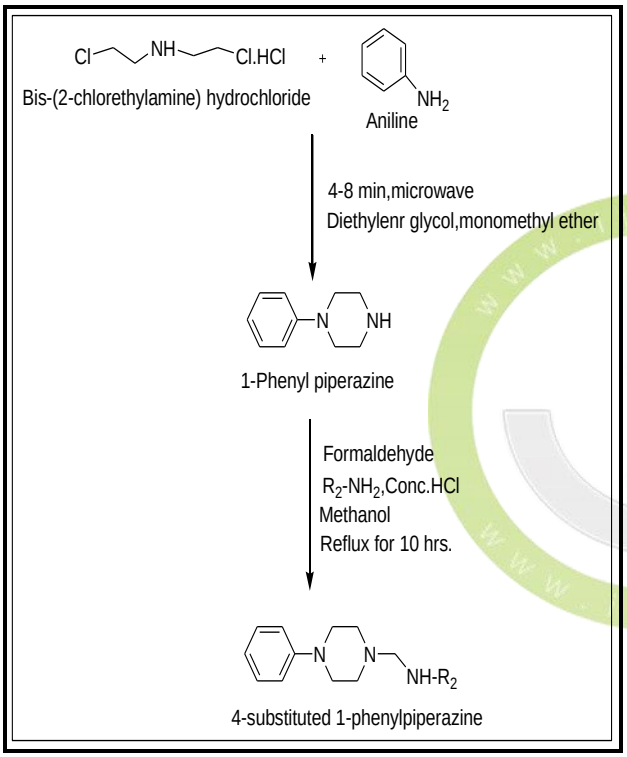
having less side effects for betterment of the health.

MATERIAL AND METHODS

Title Moiety



Synthetic Route



Substitution at R_1 and R_2 position

R_1	R_2
$-C_6H_5$	2-Cl-C_6H_4
	4-Br-C6H4
	4-F-C6H4
	4-OCH3-C6H
	4-NO_2-C_6H_4

Experimental

All the chemicals and reagents were obtained from Sigma Aldrich (India) and were used without purification. All the reactions were carried out under prescribed laboratory conditions. The products were purified by vacuum distillation. All the melting points were determined by open capillary method and were uncorrected. Thin layer chromatography was performed on microscopic slides (2 x 7.5cms) coated with silica gel-G and spots were visualized by exposure to iodine vapours and by ultraviolet light. Ultra Violet spectra were recorded on UV-VIS 1700A Pharmaspec Spectrophotometer. Infrared spectra were recorded in KBr discs on Perkin-Elmer model spectrophotometer.[1] H NMR spectra were recorded on (Bruker AMX 400 MHz) spectrometer in DMSO. Mass spectra were recorded on (LCQ Fleet and TSQ quantum Access with surveyor plus HPLC system) spectrometer in methanol.

Synthetic Procedure

General Synthetic Procedure for Preparation of Substituted N-aryl piperazine Derivatives

0.61gm (6.6mmol) of aniline, 0.79 gm (4mmol) of bis(2-chlorethyl)amine hydrochloride were taken in a round bottom flask and irradiated at the MW oven (KELVINATOR T-37, OUTPUT 700W) For 1 minute. HCl gas evolved was trapped into NaOH solution kept outside the oven. The mixture was basified with NaOH and extracted with CHCl3, was distilled out and the resulting oil was subjected to column chromatography using silica gel of 60-120 mesh to give 1-phenylpiperazine weighing 0.52 gm (73%).[73] And characterized by PMR data. Boiling Point : 287.2ºC (std.) 282-285ºC (prepared) TLC (R_f Value): 0.58 ($CHCl_3$: MeOH, 4:1)

Attempted Synthetic Procedure for Step 2

Prepared solution of 1-phenyl piperazine is taken and the respective substituted anilines were taken. Formaldehyde and concentrated hydrochloride were taken. Here all these reagents are in 0.01 mol in quantity. In round bottom flask

all the reagents were kept and stirring for an hour followed by reflux to them for 10 hrs. Reaction mixture was poured into the crushed ice and keep in refrigerator overnight. Product obtain was recrystallized by ethanol.

Synthesis of N-((4-phenylpiperazine1-yl)methyl)benzamine(N-01)

A solution of 1-phenyl piperazine (0.01 mole) along with aniline (0.01mol) was take and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added and stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture was poured into the crushed ice and sodium bisuphate solution (10% in concentration) was added. The solution was kept in refrigerator overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table 1

Synthesis of 4-nito-N-((phenylpiperazine 1-yl)methyl)benzamine(N-02)

A solution of 1-phenyl piperazine (0.01 mole) along with para nitro aniline (0.01mol) was taken and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added and stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture was poured into the crushed ice and sodium bisuphate solution (10% in concentration) was added. The solution was kept in refrigerator overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table 1

Synthesis of 4-bromo-N-((phenylpiperazine 1-yl)methyl)benzamine (N-03)

A solution of 1-phenyl piperazine (0.01 mole) along with para nitro aniline (0.01mol) were taken and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added and stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture was poured into the crushed ice and sodium bisuphate solution (10% in concentration) was added. The solution was kept in the refrigerator overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table1

Synthesis of 4-chloro-N-((phenylpiperazine 1-yl) methyl)benzamine(N-04)

A solution of 1-phenyl piperazine (0.01 mole) along with para chloro aniline (0.01mol) was taken and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added and stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture was poured into the crushed ice and sodium bisuphate solution (10% in concentration) was added. The solution was kept in refrigerator overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table1

Synthesis of 4-fluro-N-((phenylpiperazine 1-yl)methyl)benzamine (N-05)

A solution of 1-phenyl piperazine (0.01 mole) along with para fluro aniline (0.01mol) was taken and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added, stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture is poured into the crushed ice. Sodium bisuphate solution (10% in concentration) was added. The solution was kept in the refrigerator for overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table1

Synthesis of 4-methoxy-N-((phenyl-piperazine 1-yl) methyl) benzamine (N-06)

A solution of 1-phenyl piperazine (0.01 mole) along with para anisidine (0.01mol) was taken and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added, stirred for an hour followed by refluxing for 10-12 hrs. The reagent mixture was poured into the crushed ice. Sodium bisuphate solution (10% in concentration) was added.

The solution was kept in the refrigerator for overnight. The product obtained was filtered and

recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table1

Synthesis of 4-methyl-N-((phenylpiperazine 1-yl) methyl) benzamine(N-07)

A solution of 1-phenyl piperazine (0.01 mole) along with para toludine (0.01mol) was take and poured into the round bottom flask. Formaldehyde and concentrated Hydrochloride (both in 0.01 mole) were added, stirred for an hour followed by refluxing for 10-12 hrs.

The reagent mixture was poured into the crushed ice. Sodium bisuphate solution (10% in concentration) was added. The solution was kept in the refrigerator for overnight. The product obtained was filtered and recrystallized from ethanol. Physiochemical and spectral data of the prepared derivative is shown in table1

Biological Evaluation

Anthelmintic Activity

Helminth is a general term meaning worm. The most common worm is the earth worm, a member of *Eisenia fetida.* Adult worms collected from moist soil and washed with normal saline to remove all faecal matter were used for anthelmintic study.

The earthworms of 3-5 cm in length and 0.1-0.2 cm in breadth were used for all experimental protocols due to their anatomical and physiological resemblance with the intestinal round worm parasites of human being.

Method[48, 74]

The synthesized compounds (**N-01 to N-07**) were evaluated *in vitro* for their anthelmintic activities according to a standard protocol mentioned below. The worms were transferred in saline immediately to the lab of study. The worms were washed several times by saline. The worms were divided into the respective group containing six – earth worms in each group. All the compounds were dissolved in minimum quantity of 2%v/v Tween 80 and the volume was adjusted to 10 ml with normal saline for making the concentration of 5, 10 and 20 mg/ml. All the compounds and the standard drug solution were freshly prepared before commencement of the experiments. All the earth worms were released into 10 ml of respective formulation as follows, vehicle (2% v/v Tween 80 in normal saline), piperazine citrate (20 mg/ml) and compounds (5, 10, 20 mg/ml). Six worms of about the same size per petridish were used. They were observed for their spontaneous mobility and evoked responses. Observations were made for the time taken to paralysis and death of individual worms. Paralysis was said to occur when the worms do not revive even in normal saline. Death was concluded when the worms lost their motility followed with fading away of their body color. The time taken by the earthworms to become motionless was noted as paralytic time (PT). The time of death was noted as death time (DT).

RESULTS

From the literature survey, method A and method B were followed for synthesis of piperazine derivatives (N-01 to N-07). The physical data of synthesized derivatives (N-01 to N-07) and are given in table 1. Their physical constants and thin layer chromatography primarily confirmed purity of the synthesized compounds. Structures of synthesized compounds are checked by NMR, IR, MASS spectroscopy

From the literature survey, method A and method B were followed for synthesis of piperazine derivatives (N-01 to N-07) the spectral data of synthesized derivatives (N-01 to N-07) and are given in table 2, table 3, table 4 and 5

In the same way the results of the biological evaluation data of the prepared derivatives is also shown in table 5and table 6 (N-01 to N-07).

TLC is done for the all prepared derivatives by taken mobile phase with the ratio as below.

Chloroform: Methanol (4:1)

Physical Characteristics of Prepared Derivatives (N-01 to N-07)

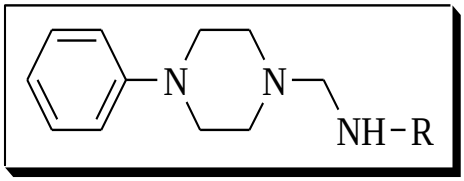


Table 1: Physical characteristics of prepared derivatives (N-01 to N-07)

Code No.	R	Molecular weight	Molecular formula	%Yied	Melting point	R_f value
N-01	$-C_6H_5$	267.17gm/mole	$C_{17}H_{21}N_3$	52.5%	160-165°C	0.45
N-02	$-C_6H_4NO_2$	312.37gm/mole	$C_{17}H_{20}N_4O_2$	69.5%	175-180°C	0.49
N-03	$-C_6H_4Br$	346.26gm/mole	$C_{17}H_{20}BrN_3$	78.8%	132-135ºC	0.51
N-04	$-C_6H_4Cl$	301.21gm/mole	$C_{17}H_{20}ClN_3$	69.5%	145-150ºC	0.56
N-05	$-C_6H_4F$	285.36gm/mole	$C_{17}H_{20}FN_3$	74.8%	125-128ºC	0.63
N-06	$-C_6H_4OCH_3$	297.30gm/mole	$C_{18}H_{23}N_3O$	58.7%	195-198ºC	0.59
N-07	$-C_6H_4CH_3$	281.4gm/mole	$C_{18}H_{23}N_3$	61.2%	210-215ºC	0.62

Spectral Characteristics Data of Prepared Derivatives (N-01-N-07)

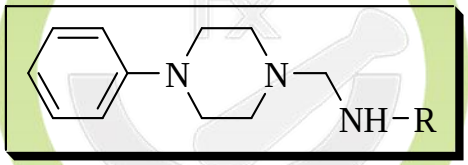


Table 2: Spectral characteristics data of prepared derivatives (N-01-N-07)

Code No.	Molecular formula (M.W) (gm/mole)	λmax (nm)	IR spectra (cm^{-1}) (KBr)	Mass spectra (m/e)
N-01	$C_{17}H_{21}N_3$ (267.17gm/mole)	249.5	3435.72(Ar-NH), 1105.96(C-N stretch), 1454.25(Ar-c-C Str)	268.7(M+H)
N-02	$C_{17}H_{20}N_4O_2$ (312.37gm/mole)	294.5	3387.48(Ar-NH str), 1594.71(NO_2), 1454.25(Ar-N), 749.58(C-H str In aromatic)	313.129 (M+H)
N-03	$C_{17}H_{20}BrN_3$ (346.26gm/mole)	256.6	3432.65(Ar-NH), 1458.63(CH_2), 1228.35(C-N str), 579.87(C-Br str) 820.52(C-H def)	347.26(M+2)
N-04	$C_{17}H_{20}C_lN_3$ (301.21gm/mole)	255.5	3428(N-H str), 1454.03(CH2) 726.36,778.02 (C-Cl str)	-

Code No.	Molecular formula (M.W.) (gm/mole)	λmax (nm)	IR spectra (cm^{-1}) (KBr)	Mass spectra (m/e)
N-04	$C_{17}H_{20}ClN_3$ (301.21gm/mole)	255.5	3428(N-H str), 1454.03(CH_2) 726.36,778.02 (C-Cl str)	-
N-05	$C_{17}H_{20}FN_3$ (285.36gm/mole)	246.5	3418(N-H str) 1121.31, 1156.26(C-F str). 1453.23(CH_2)	-
N-06	$C_{18}H_{23}N_3O$ (297.30gm/mole)	251.3	3416(N-H str), 1451.17(CH_2), 1074.48,1118.11 (C-O str)	-
N-07	$C_{18}H_{23}N_3$ (281.4gm/mole)	253.3	3416(N-H str), 1451.17(CH_2), 2924.73 (C-H str in sp^3)	-

^{1}HNMR chemical shifts of compound (N-01)

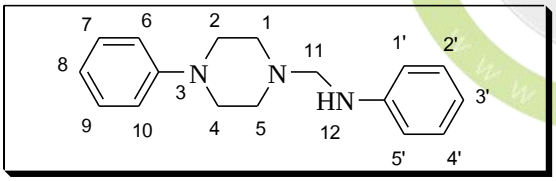


Table 3: ^{1}HNMR chemical shifts of compound (N-01)

Code no.	1HNMR data
N-01	2.52 (d, 2H,1,5 CH_2) 3.34 (t, 2H,2,4 CH_2) 4.82 (S, 1H,12 NH) 5.00 (d, 1H,1 $2H_2$) 6.58 (td, 2H, 6,10 CH) 6.60 (t, 1H, 8CH) 7.04 (tq, 2H, CH) 8.27 (t, 2H, 2',4'CH)

^{1}HNMR chemical shifts of compound (N-02)

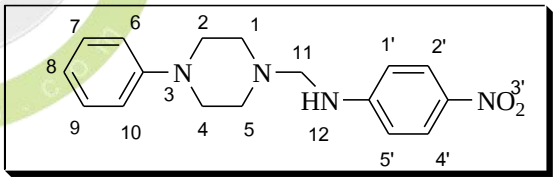


Table 4: ^{1}HNMR chemical shifts of compound (N-02)

Code no.	^{1}HNMR data (δ ppm)
N-02	2.52 (d, 2H,^{1,5} C<u>H</u>$_2$) 3.34 (t, 2H,^{2,4} C<u>H</u>$_2$) 4.82 (S, 1H,^{1,2} N<u>H</u>) 5.00 (d, 1H, $2H_2$) 6.59 (td, 2H,^{6,10} C<u>H</u>) 6.60 (t, 1H, ^{8}C<u>H</u>) 7.21 (tq, 2H, C<u>H</u>) 8.07 (t, 2H,$^{2',4'}$ C<u>H</u>)

Anthelmintic Activity

The anthelmintic activity of the target compounds **(N-01 to N-07)** were tested against *Eisenia fetida* according to a reported protocol described in the experimental part.

Table 5: Anthelmintic activity prepared piperazine derivatives (N-01 to N-07)

	Paralysis time (PT) (Sec)			**Death time (DT) (sec)**		
Test compounds	5mg/ml	10mg/ml	20mg/ml	5mg/ml	10mg/ml	20mg/ml
Control	-	-	-	-	-	-
N-01	46±3	39±3	28±3	106±5	92±5	85±5
N-02	55±3	48±3	40±3	150±5	141±5	132±5
N-03	45±3	33±3	23±3	55±3	45±3	32±3
N-04	56±3	44±3	37±3	56±3	43±3	38±3
N-05	46±3	40±3	32±3	50±5	44±3	32±3
N-06	65±3	55±3	44±3	92±3	87±3	74±3
N-07	92±3	85±3	70±3	135±3	120±3	110±3
Std	-	-	45±1	-	-	52±1

All determinations were done in duplicate and results are expressed as Mean ± SEM.
P values was calculated by comparing with control by one –way ANOVA. Control worms were alive up to 24 hrs of observation.
P< 0.05, significantly different when compared with reference compound, Piperazine citrate.

The data of anthelmintic activity of prepared derivatives can also be analyzed with the help of the charts as follows.

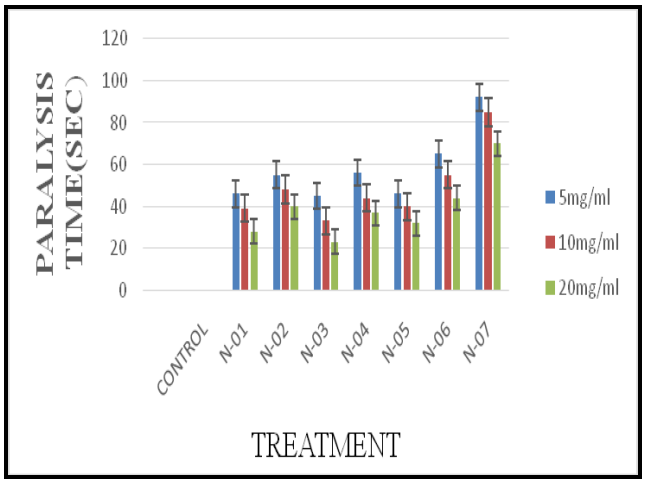


Chart 1: (Paralysis time Vs Treatment) (N-01 to N-07)

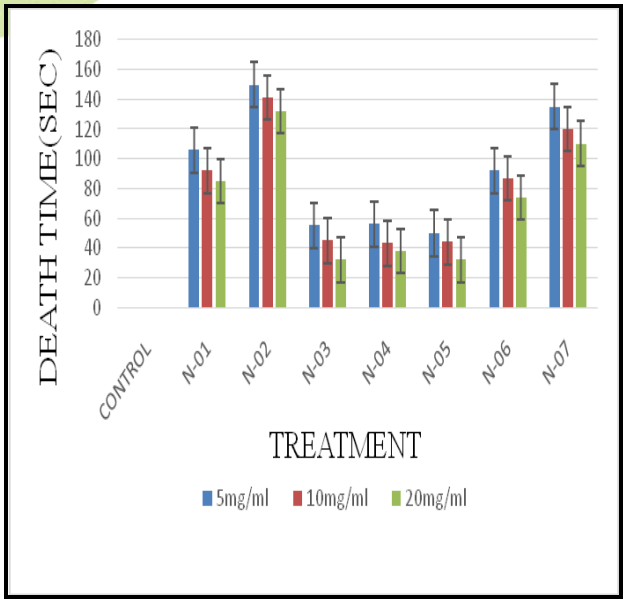


Chart 2: (Death time Vs Treatment) N-01 to N-07)

DISCUSSION

All the investigational compounds **(N-01 to N-07) and (M-01 to M-07)** exhibited the anthelmintic activity at minimal dose of 5mg/ml. Compound (**N-03, N-04)** had shown its significant activity at 5mg/ml for time taken to paralysis and death when compared to the standard drug Piperazine citrate used at 20mg/ml. At the concentration of 10mg/ml, compounds **(N-02, N-03, N-04, N-05)** exhibited their significant action for time taken to paralysis and death. In which compounds **(N-05)** showed their moderate significant action for time taken to paralysis when compared to standard. Used at 20mg/ml. While increasing the concentration (20mg/ml), compounds **(N-03, N-05)** significantly reduced the paralysis and death time as well. Compounds **(N-06, N-07)** showed their delayed action for time taken to paralysis and death when compared to standard. In the higher concentration all the compounds showed their time taken to paralysis and death was drastically reduced and almost comparable to standard drug.

CONCLUSION

A series of 1,4- disubstituted piperazine derivatives were synthesized as the target compounds. From the careful perusal of literature, we have identified new synthetic route, it will prove to be economically feasible and cost-effective for large scale production. The structures of the target compounds were elucidated depending upon the data of the different spectral methods of analysis. In addition, a mass spectrum, for representative example, was carried out where the expected fragmentation mode is in accordance with the structures of the considered compounds. The anthelmintic activity of the synthesized compounds was investigated in *vitro* against *Eisenia fetida*. All the investigational compounds **(N-01 to N-07)** and exhibited the anthelmintic activity at minimal dose of 5mg/ml.

Compounds **N-03, N-04, and N-05**and exhibited highly significant action for time taken to paralysis and death and which is almost equipotent action when compared to standard drug Piperzine citrate. Accordingly, this series of compounds embedding the acyl piperazine moiety in its structure can be considered as promising candidates to be used as anthelmintic agents.

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