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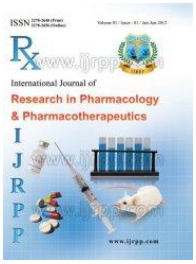

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Synthesis and biological evaluation of piperazine derivatives as anthelmintic agents

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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 acid chlorides **(3a-3j)** through reaction of substituted acid with thionyl chloride in the presence of a drop of dimethyl formamide as a catalyst. The second step involves the reaction of compounds **(3a-3j)** with methyl piperazine, affording target compounds **(5a-5j).**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 **(5a-5j)** was investigated in vitro against Eisenia fetida. All the investigational compounds **(5a-5j)** exhibited promising anthelmintic activity at minimal dose of 5mg/ml in comparison with reference drug Piperazine citrate.

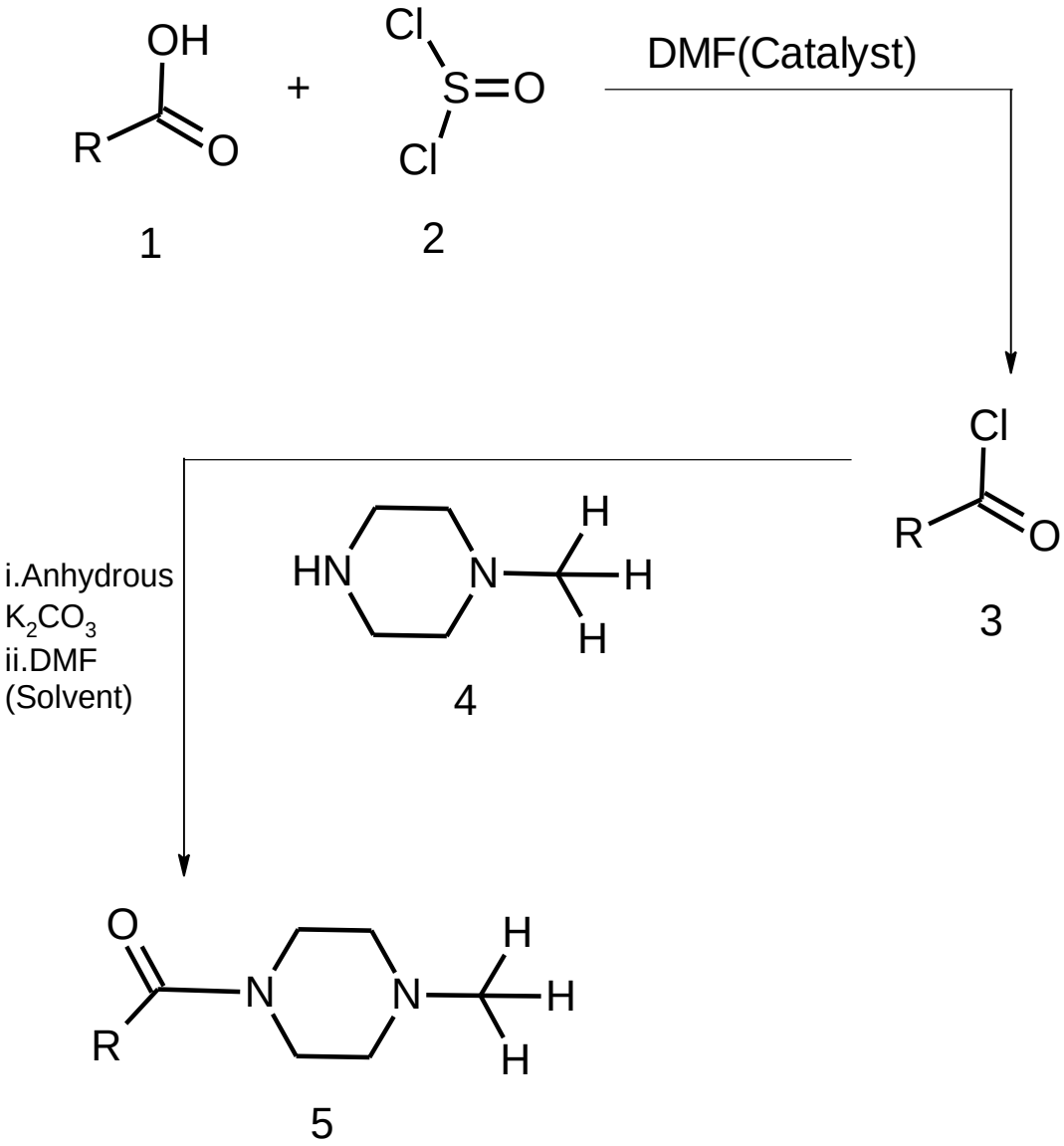
Keywords: Methyl piperazine, Acyl chlorides, Anthelmintic.

INTRODUCTION

Heterocyclic compounds play a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in heme and chlorophyll. Heterocyclic nitrogenous compounds and their fused analogues represent an important class of heterocyclic compounds. They display a wide range of biological and pharmaceutical activities [1-4]. Piperazines have been exploited over the past few decades because of the wide range of activities like antihistamines, hypotensive, anaesthetics, analgesics, anticonvulsants, antifungals, antimicrobials, anthelmintics. Many important biochemical compounds of natural origin contain heterocyclic ring structures. Among these eg: carbohydrates, essential amino acids, vitamins, alkaloids, glycosides etc., the presence of heterocyclic structures in such diverse types of compounds is strongly indicative of the diverse types of the pharmacological activity and recognition of this is reflected in efforts to find useful synthetic drugs [5].Taking in view of the applicability of heterocyclic compounds, efforts were made for the preparation of derivatives with piperazine nucleus.

The placement of a wide variety of substituents of these nuclei has been designed in order to evaluate the synthesized products for their pharmacological profile against worms.

Synthetic Scheme



1 substituted carboxylic acids
2 thionyl chloride
3 substituted acid chlorides (3a-3j)
4 N-methyl piperazine
5 1-4 disubstituted piperazine derivatives (5a-5j)

Compound	R	Compound	R
5a	$-C_6H_5$	5f	$-C_6H_5OH$
5b	$-C_6H_5Cl$	5g	$-CH_2\ C_6H_5$
5c	$-C_6H_5OCH_3$	5h	$-CH_2C_6H_5NO_2$
5d	$-C_6H_5CH_3$	5i	$-CH_2\ C_6H_5Cl$
5e	$-C_6H_5NO_2$	5j	$-CH{=}CH\ C_6H_5$

RESULTS AND DISCUSSION

From the literature survey, method A and method B were applied for synthesis of piperazine derivatives **(5a-5j).** Method A was used for synthesis of piperazine derivatives **(5a-5j)**, but reaction did not proceed and failed to give desired product [6-8].

Method B was tried for synthesis of piperazine derivatives **(5a-5j)**, but this also failed to give fruitful result. Finally, another method was employed for the synthesis of piperazine derivatives **(5a-5j)** and good yield was obtained. Ten substituted acid chloride derivatives **(3a-3j)** and ten 1,4-disubstitutedpiperazine derivatives **(5a-5j)** were prepared according to the scheme. The physical data of synthesized derivatives **(3a-3j)** and **(5a-5j)** are given in **table 1.**Their physical constants and thin layer chromatography primarily confirmed purity of the synthesized compounds [9].

Structures of synthesized compounds **(5a-5j)** were confirmed by IR, ^{1}H NMR and Mass spectroscopy. The spectral data of synthesized derivatives **(5a-5j)** are given in **table 1.**

Table 1: Physical characterization data of the compounds 3 and 5

Compd	Molecular Formula (M.W)(g/mole)	b.p (^{o}C)	% Yield	Compd	Molecular Formula (M.W)(g/mole)	b.p (^{o}C)	% Yield
3a	C_7H_5OCl(140.57)	-	-	5a	$C_{12}H_{16}ON_2$ (204.13)	180-185	65
3b	$C_7H_4OCl_2$(175.04)	221-223	85	5b	$C_{12}H_{15}ON_2Cl$ (238.71)	40-44	68
3c	$C_8H_7O_2Cl$(170.59)	259-263	73	5c	$C_{13}H_{18}O_2N_2$ (234)	250-253	71
3d	C_8H_7OCl(154.60)	222-226	88	5d	$C_{13}H_{18}ON_2$ (218)	50-52	75
3e	$C_7H_4O_3NCl$(185)	69-73	75	5e	$C_{12}H_{15}O_3N_3$ (249)	84-89	64
3f	$C_7H_5O_2Cl$(156.56)	274-277	73	5f	$C_{12}H_{16}O_2N_2$ (220)	210	65
3g	C_8H_7OCl(154.54)	91-95	75	5g	$C_{13}H_{18}ON_2$ (218)	198-200	79
3h	$C_8H_6O_3NCl$(199.59)	-	85	5h	$C_{13}H_{17}O_3N_3$ (263)	80-85(mp)	75
3i	$C_8H_6OCl_2$ (189.04)	83- 86	69	5i	$C_{13}H_{17}ON_2Cl$ (252.5)	156-159	78
3j	C_9H_7OCl(166.06)	31-35	72	5j	$C_{14}H_{18}ON_2$ (230)	70-74(mp)	65

Table 2: Spectral characterization of data of compound 5.

Compd	Molecular Formula (M.W) (gm/mole)	max (nm)	IR Spectra (cm^{-1}) (KBr)	Mass Spectra (m/e)	^{1}H NMR (δ)
5a	$C_{12}H_{16}ON_2$ (204.13)	226.5	1704.85(C=O), 3062.60(ArCH),2875.20(C-H)	-	
5b	$C_{12}H_{15}ON_2Cl$ (238.71)	230	1632.77(C=O),1087.74(Ar-Cl) 2971.47 (SP^3C-H Stretch)	239.18 $(M+H)^+$ 240(M+2)	
5c	$C_{13}H_{18}O_2N_2$ (234)	248	1252.08&1023.7 (Ar-O-R	-	
5d	$C_{13}H_{18}ON_2$ (218)	238.5	2931.21(Alkane C-H *sp3 stretch)* 3001.91(ArCH)	219.18 $(M+H)^+$	
5e	$C_{12}H_{15}O_3N_3$ (249)	269	-	250.15 219.10 191	δ 2.289 (s, 3H, C$\underline{H_3}$) δ 3.315(s,4H,^{3,5}C$\underline{H_2}$) δ 3.755(s,4H,^{2,6} C$\underline{H_2}$) δ7.4-7.52(d,2H,$^{2'6'}$C$\underline{H}$-Ar) δ 8.20-8.22(d, 2H, $^{3'5'}$ C$\underline{H}$-Ar)
5f	$C_{12}H_{16}O_2N_2$ (220)	241	3421.55 (O-H) 1160.26(C-O) 1660.79(C=O)	-	
5g	$C_{13}H_{18}ON_2$ (218)	221.5	-	219.20 (M+H)$^+$ 101.03	δ 2.201 (s, 3H, C$\underline{H_3}$) δ 3.688 (s, 2H, C$\underline{H_2}$) δ 2.1-2.3 (m, 4H, ^{3,5} C$\underline{H_2}$) δ2.4-3.6 (m, 4H, ^{2,6} C$\underline{H_2}$) δ 7.1-7.2 (m, 5H, C$\underline{H}$-Ar)
5h	$C_{13}H_{17}O_3N_3$ (263)	259	1345.43,1594.9 (NO_2), 1632.76(C=O	-	
5i	$C_{13}H_{17}ON_2Cl$ (252.5)	228	1089.86(Ar-Cl) 1641.92(C=O), 2935.26(sp^3 *C-H* strech)	-	
5j	$C_{14}H_{18}ON_2$ (230)	280	3079.90(Alkene CH),1644.92 (AlkeneC=C), 1644.92(C=O)	-	

DISCUSSION

Physical characteristics

The aryl amide derivatives **(5b, 5e, 5j)** are yellowish crystalline compounds. The compound **(5d)** is white crystalline compound. The derivatives **(5a, 5c, 5g, 5i) a**re in liquid form and they have pale yellow color. The derivatives **(5b, 5d, 5e, 5h, 5j)** have low melting points. The derivatives **(5a-5j)** are soluble in nonpolar solvent chloroform. The derivatives **(5a-5j)** have solubility in polar solvent ethyl acetate. The derivatives **(5a-5j)** have low aqueous solubility.

Spectral characteristics

U.v. spectra

The UV spectra of all the final compounds **(5a-5j)** were studied in methanol. All the compounds show two peaks in methanol. The λmax of the compounds **(5a,5b, 5c,5d,5f,5g,5i)** was found around 220-250 nm. The λmax of the compound **(5e,**

5h) was found around 260 due to the presence of nitro group. The λmax of the compound **(5j)** was found around 280 due the presence of alkene group.

Ir spectra

The IR spectra of all the 1,4-disubstituted piperazine derivatives **(5a-5j)** were recorded on KBr discs. The IR spectra of the compounds **(5a-5j)** has showed a peak of (C=O) stretching vibration at 1630-1680 cm^{-1}. The IR spectra of **4-methyl-1-(4- chloro benzoyl) piperazine(5b)** has showed a peak of (Ar-Cl) stretching vibration at 1087.74 cm^{-1} which confirms presence of chloro group. The IR spectra of **4-methyl-1-(4- methoxy benzoyl) piperazine(5c)** has showed a peak of (Ar-O-R) stretching vibration at (1252.08&1023.7cm^{-1}), which confirms phenyl alkyl ether group. The IR spectra of **4-methyl-1-(4-methyl benzoyl) piperazine (5d)** has showed a peak of (alkane SP^3C-H) stretching vibration at 2931.21 cm^{-1}, which confirms methyl group. The IR spectra of **4-methyl-1-(4- hydroxy benzoyl) piperazine (5f)** has showed a peak of (O-H) stretching vibration at 3421.55 cm^{-1}, which confirms H-bonded (O-H) group. The IR spetra of **1-(4-Methylpiperazin-1-yl)-2-(4-nitrophenyl)ethanone (5g)** has showed (NO_2) stretching vibration at (1345.43&1594.96 cm^{-1}) , which confirms nitro group. The IR spetra of **1-(4-Methylpiperazin-1-yl)-2-(4-chlorophenyl)ethanone (5i)** has showed (Ar-Cl) stretching vibration at (1089.86 cm^{-1}) , which confirms chloro group The IR spectra of **1-(4-methylpiperazin-1-yl)-3-phenylprop-2-en-1-one (5j)** has showed a peak of (sp^2C-H stretch) at 3079.90 cm^{-1} , which confirms alkene moiety.

^{1}HNMR spectra

The ^{1}H NMR spectra of compounds **(5e and 5g)** were studied in $CDCl_3$. In compound **(5e),** methyl protons appear at δ value (2.289) as a singlet, methylene protons at 3rd and 5th position appear at a δ value 3.315 as a singlet, methylene protons at 2nd and 6th position appears downfield at a δ value 3.755 as a singlet. Aryl protons at 2' and 6' position appear at a δ value (7.4-7.52) as a doublet, while aryl protons at 3' and 5' position appear downfield at a δ value (8.20-8.22) as a doublet. In compound **(5g),** methyl protons appear at δ (2.201) as a singlet, methylene protons at 3rd and 5th position appear at a δ value (2.1-2.3) as a multiplet, methylene protons at 2nd and 6th position appears downfield at a δ value (2.4-3.6) as a multiplet. Methylene protons attached to carbonyl carbon, appear downfield at a δ value 3.688 as a singlet. Aryl protons appear at a δ value 7.1-7.2.

Mass spectra

The mass spectral fragments of some of the target compounds under electron impact (60 eV) were also studied. The compounds showing intense molecular ion peaks at their corresponding molecular weights. The daughter ions were also exhibited their molecular ion peaks. The mass fragmentation pattern of the compound **(5d)** is depicted in the following way.

Anthelmintic activity

The anthelmintic activity of the target compounds **(5a-5j)** were tested against *Eisenia fetida*according to a reported protocol described in the experimental part.

Table 3: Anthelmintic activity data of compounds (5a-5j)

	Paralysis time (PT) (Sec)			Death time (DT) (sec)		
Test compounds	**5mg/ml**	**10mg/ml**	**20mg/ml**	**5mg/ml**	**10mg/ml**	**20mg/ml**
Control	-	-	-	-	-	-
47a	68 ± 2	61 ±1.5	29.5 ±2.5	161 ±1	153 ±1.5	73.5 ±3.5
47b	369 ± 2	360 ±1	178.5±0.5	482 ±3	476 ±4	238 ±1
47c	130 ±2	122 ±2	60.5±1.5	230 ±2	223 ±1.5	111.5±3.5
47d	93 ±1	82 ±4	40.5±1.5	175 ±3	169 ±1	87.5 ±7.5
47e	129 ±2	118 ±1	58.5±1.5	190 ±1	183 ±2	90.5±20.5
47f	123 ±5	110 ±3	54 ±1	220 ±0.5	214 ±1	105.5±5.5
47g	140 ±1	131 ±5	65.5 ±4.5	264 ±1	253 ±1	126 ±2
47h	142 ±2	132 ±1	64 ±1	221 ±4	213 ±2	106.5±5.5
47i	125 ±0.5	116 ±4	55.5 ±1	208 ±2	197 ±1	97.5 ±3.5
47j	121 ±1	113 ±2	54 ±3	212 ±1	209 ±1	104.5±8.5
Std	-	-	50 ±1	-	-	110 ±2

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.

Anthelmintic activity

Helminth is a general term meaning worm. The most commom 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 lenth 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 [6, 7]

The synthesized compounds **(5a-5j)** 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).

Statistical Analysis

Results were expressed as Mean± SEM. Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Dunnett's test, with the level of sifnificance at *P*< 0.05.

DISCUSSION

All the investigational compounds **(5a-5j)** exhibited the anthelmintic activity at minimal dose of 5mg/ml. Compound (**5a)** had shown its significant activity at 5mg/ml for time taken to paralysis and death when compared to the standard drug Pipetazine citrate used at 20mg/ml. At the concentration of 10mg/ml, compounds **(5d, 5f, 5i and 5j)** exhibited their significant action for time taken to paralysis and death. In which compounds **(5c)** and **(5e)** 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 **(5b)** significantly reduced the paralysis and death time as well. Compounds **(5e, 5g, 5h)** showed their moderate significant action for time taken to paralysis and death when compared to standard. Compounds **5a** and **5d** exhibited highly significant action for time taken to paralysis and death and which is almost equipotent action when compared to standard drug Piperzine citrate. In the higher concentration all the compounds showed their time taken to paralysis and death was drastically reduced and almost comparable to standard drug.

Experimental Section

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 7.5 cms) coated with silicagel-G and spots were visualized by exposure to iodine vapours and by ultraviolet light. Ultra Violet spectra were recorded on UV-VIS 160A Shimadzu 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.

General procedure for synthesis of substituted acyl chloride derivatives (3a-3j) [8, 9]

Substituted acid (0.13 mole), 75ml of freshly distilled thionyl chloride and a drop of dimethyl formamide (DMF) were refluxed in a boiling water bath for 2 hrs. In order to remove traces of thionyl chloride from crude acid chloride, the reaction mixture was concentrated under reduced pressure and then an inert solvent (carbontetrachloride) was added and the solution was evaporated under vacuum to obtain the product. The physical data of compounds synthesized are recorded in **Table 1.**

Synthetic procedure for 4-methyl-1-(4-benzoyl) piperazine (5a)

A solution of methyl piperazine (0.09 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then benzoyl chloride (0.2 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water and extracted with ethylacetate (3 x 15 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. After removal of the solvent in vacuum, the oily residue was purified by vacuum distillation**.** The product was obtained at 160^{o}C under reduced pressure. Finally, the product was obtained as yellow liquid.$C_{12}H_{16}ON_2$(204.13)b.p (^{o}C) :180-185^{o}C Yield 65%,TLC:Solvent system = chloroform: methanol (9:1) ,R_f value = 0.78,IR Spectra:1704.85(C=O),3062.60(ArCH),2875.20(C-H)

Synthesis of 4-methyl-1-(4- chloro benzoyl) piperazine (5b)

A solution of methyl piperazine (0.04 mole) in dimethyl formamide was taken, anhydrous powedered potassium carbonate was added to solution and stirred for 10 min and then *p*-chloro benzoyl chloride (0.06 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (60 ml) and extracted with ethylacetate (3 x 30 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** The product was obtained at 110^{o}C under reduced pressure. Finally, the product was obtained as yellow crystals.$C_{12}H_{15}ON_2Cl$(238.71),m.p40-44^{o}C, Yield 68%,TLC:Solvent system = chloroform: methanol (9:1),R_f value = 0.61,IR(KBr):1632.77(C=O),1087.74(Ar-Cl),2971.47 (SP3C-H Stretch),MS:m/z239.18(M+H)+240(M+2)

Synthesis of 4-methyl-1-(4- methoxy benzoyl) piperazine (5c)

A solution of methyl piperazine (0.1 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then *p*-methoxy benzoyl chloride (0.2 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (60 ml) and extracted with ethylacetate (3 x 30 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** The product was obtained at 200-220^{o}C under reduced pressure. Finally, the product was obtained as yellowish brown liquid. $C_{13}H_{18}O_2N_2$ (234), bp250-253^{o}C, Yield 71%, TLC: Solvent system = chloroform: methanol (8:2), R_f value = 0.65, IR (KBr):1252.08&1023.7(Ar-O-R)

Synthesis of 4-methyl-1-(4- methyl benzoyl) piperazine (5d)

A solution of methyl piperazine (0.1 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then *p*-methyl benzoyl chloride (0.4 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (50 ml) and extracted with chloroform (3 x 25 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium

sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** The oily residue was obtained at 180^{o}C under reduced pressure. The residue was kept aside overnight. Finally, the product was obtained as white crystals.$C_{13}H_{18}ON_2$(218),mp50-52^{o}C, Yield 75%,TLC:Solvent system = chloroform: methanol (9:1), $R_f$value = 0.67,IR(KBr): 2931.21(Alkane C-H *sp3 stretch)* 3001.91(ArCH),MS: m/z 219.18 (M+H)+

Synthesis of 4-methyl-1-(4- nitro benzoyl) piperazine (5e)

A solution of methyl piperazine (0.04 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then *p*-nitro benzoyl chloride (0.06 mole) in dimethyl formamide was added. The reaction mixture was stirred for 2 hrs at room temperature and then refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (50 ml) and extracted with chloroform (3 x 25 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** The product was obtained at 120^{o}C under reduced pressure. Finally, the product was obtained as yellow crystals. $C_{12}H_{15}O_3N_3$ (249) mp 84-89^{o}C, Yield 64%,TLC: Solvent system = chloroform: methanol (5:3), R_f value = 0.74,MS:m/z 250.15,219.10,191, 1H NMR(δ):δ 2.289 (s, 3H, CH_3),δ 3.315(s,4H,3,5CH_2),δ 3.755(s,4H,2,6 CH_2),δ 7.4-7.52(d,2H,2'6'CH-Ar),δ 8.20-8.22(d, 2H, 3'5' CH-Ar)

Synthesis of 4-methyl-1-(4- hydroxy benzoyl) piperazine (5f)

A solution of methyl piperazine (0.1 mole) in dimethyl formamide was taken, anhydrous powedered potassium carbonate was added to solution and stirred for 10 min and then *p*-hydroxy benzoyl chloride (0.4 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (50 ml) and extracted with chloroform (2 x 15 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The residue was purified by vacuum distillation**.**$C_{12}H_{16}O_2N_2$ (220)**,**mp 210^{o}C**,** Yield 65%**,**TLC Solvent system = chloroform: methanol (5:3)**,**R_f value = 0.81,IR(KBr): 3421.55 (O-H) 1160.26(C-O) 1660.79(C=O)

Synthesis of 1-(4-methylpiperazin-1-yl)-2-phenylethanone (5g)

A solution of methyl piperazine (0.08 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then phenyl acetyl chloride (0.1mole) in dimethyl formamide was added. The reaction mixture was stirred for 2 hrs in icebath and then refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (50 ml) and extracted with chloroform (2 x 25 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** $C_{13}H_{18}ON_2$(218)**,**bp198-200^{o}C**,**Yield79%**,**TLC Solvent system = chloroform: methanol (5:3)**,**R_f value = 0.63,MS:m/z 219.20(M+H)+101.03,1H NMR(δ): δ 2.201(s, 3H, CH_3),δ 3.688(s, 2H, CH_2),δ 2.1-2.3 (m, 4H, 3,5 CH_2),δ 2.4-3.6 (m, 4H, 2,6 CH_2),δ 7.1-7.2 (m, 5H, CH-Ar)

Synthesis of 1-(4-Methylpiperazin-1-yl)-2-(4-nitrophenyl)ethanone (5h)

A solution of methyl piperazine (0.03 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then *p*-nitro phenyl acetyl chloride (0.05 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (70 ml) and filteration was done. The residue was obtained as product as dark brown crystals.,$C_{13}H_{17}O_3N_3$(263),mp80-85^{o}C,Yield75%,TLC:Solventsystem=chloroform: methanol (8:2),R_f value = 0.71,IR(KBr):1345.43,1594.9 (NO_2), 1632.76(C=O)

Synthesis of 1-(4-Methylpiperazin-1-yl)-2-(4-chlorophenyl) ethanone (5i)

A solution of methyl piperazine (0.03 mole) in dimethyl formamide was taken, anhydrous powedered potassium carbonate was added to solution and stirred for 10 min and then *p*-chloro phenyl acetyl chloride (0.05 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (70 ml) and extracted with ethyl acetate (3x15 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oily residue was purified by vacuum distillation**.** $C_{13}H_{17}ON_2Cl$(252.5),bp156-159 ^{o}C,Yield:78%,TLC Solvent system = chloroform: methanol (8:2), R_f value = 0.72, IR(KBr)1089.86(Ar-Cl),1641.92(C=O), 2935.26(sp3 C-H strech)

Synthesis of 1-(4-methylpiperazin-1-yl)-3-phenylprop-2-en-1-one (5j)

A solution of methyl piperazine (0.07 mole) in dimethyl formamide was taken, anhydrous powdered potassium carbonate was added to solution and stirred for 10 min and then cinnamoyl chloride (0.09 mole) in dimethyl formamide was added. The reaction mixture was refluxed at 80^{o}C for 10 hrs (completion of the reaction was monitored by TLC). After the completion of the reaction, the reaction mass was quenched with distilled water (70 ml) and extracted with ethyl acetate (3x15 ml). Finally, the combined organic layer was washed with distilled water again and dried over anhydrous sodium sulphate. The solvent was removed by simple distillation. The oil residue was purified by vacuum distillation**.** Finally, the product was obtained as yellow solid crystals.$C_{14}H_{18}ON_2$ (230),mp70-74 ^{o}C,Yield 65%,TLCSolvent system=chloroform:methanol(5:5),$R_f$value:0.6,IR(KBr):3079.90(AlkeneCH),1644.92,(AlkeneC=C),1644.92(C=O)

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 **(5a-5j)** exhibited the anthelmintic activity at minimal dose of 5mg/ml. Compounds **5a** and **5d** 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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