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Synthesis, Characterization and Biological Activity Evaluation of Some 2-(1, 1-Dimethyl Guanidinyl)-4,5-Diaryl Imidazoles

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A B S T R A C T

A series of 2-(1,1-dimethyl guanidinyl)-4,5-diaryl imidazoles are synthesized by condensing 2-hydroxy -1,2-diaryl ethanones with metformin. All the compounds were characterized and screened for their anthelminthic and anti-tubercular activity. Most of the compounds exhibit both the activities.

Keywords: Aromatic aldehydes, 2-hydroxy-1,2-diaryl ethanones, metformin, anthelminthic activity, anti-tubercular activity

A R T I C L E I N F O

CONTENTS

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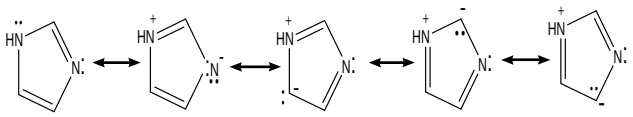
1. Introduction

The synthesis of a complex organic compound requires a synthetic analysis and planning, the most efficient method consists in the retro synthetic analysis which is based on proper disconnections that virtually generate smaller fragments that are in turn disconnected till commercially available compounds are reached. Imidazole is an aromatic heterocyclic compound, classified as a diazole and as an alkaloid with the formula $C_3H_4N_2$. Many drugs contain an imidazole ring, such as antifungal drugs, nitroimidazole, and the sedative midazolam.

Structure and Properties

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because the proton can be located on either of the two nitrogen atoms. Some resonance structures of imidazole are shown below.



Amphotericity

Imidazole is amphoteric so it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5 and as a base, the pK_a of the conjugate acid is approximately 7.

2. Materials and Methods

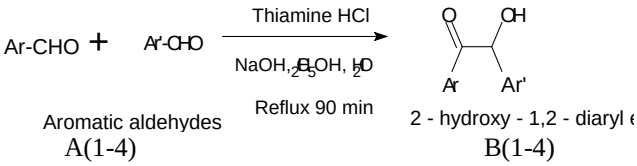
Benzaldehyde, Furfuraldehyde, Veratraldehyde, p-Dimethyl aminobenzaldehyde, p-Chloro benzaldehyde, p- Bromo benzaldehyde, Metformin, Thiamine hydrochloride.

Experimental Work

Melting points were determined in open capillary tube using Digital melting point apparatus and uncorrected. Infrared spectra (υ-cm^{-1}) were recorded on a SHIMADZU FT-IR 4000; using KBr disks. Mass spectra were obtained on JEOL GC mate II GC-Mass spectrometer at 70 ev using direct insertion probe method. ^{1}H NMR spectra were taken on BRUKER AV500 MHz High Resolution Multi nuclear FT-NMR spectrometer using TMS as internal standard. Experimental part has been divided into three parts viz., Synthetic methodology; *In silico* methodology; Evaluation of anti-tubercular activity by MABA assays method and anthelminthic activity.

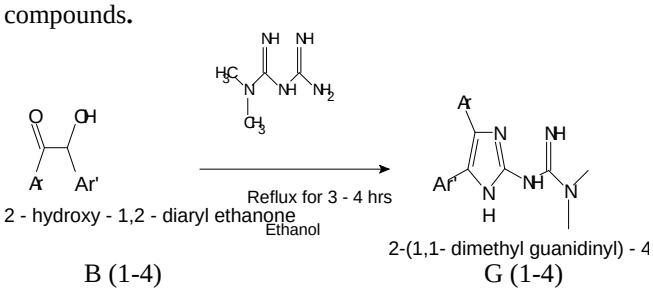
Synthetic Methodology

Step 1: Synthesis of 2-hydroxy -1, 2- diaryl ethanones (B_{1-4}): To a solution of thiamine hydrochloride (1.75 g, 0.005 M, 5ml), ethanol (95%, 5ml), aqueous sodium hydroxide solution (0.4 g 5ml) and aromatic aldehydes $A_{(1-4)}$ were added. The mixture was heated gently on a water bath for about 90 min. The mixture was cooled to room temperature and then in ice bath to induce crystallization.



Step 2: Synthesis of 2-(1,1- dimethyl guanidinyl)- 4,5-diaryl imidazole's $G_{(1-7)}$:

A mixture of 2- hydroxy-1, 2- diaryl ethanone $B_{(1-7)}$ (0.01 moles) and metformin **(**0.01 moles) were intimately mixed in ethanol and refluxed for 4 hrs. The reaction mixture was cooled and triturated with crushed ice (approx. 150 g).The crude product separated was filtered, washed thoroughly with small portions of cold water and dried. The products were recrystallized from ethanol to get crystalline compounds**.**



By adopting the above synthetic procedures, compounds G_1 G_2, G_3, and G_4 were synthesized.

Structures and IUPAC Names of the Title Compounds ($G_1 – G_4$)

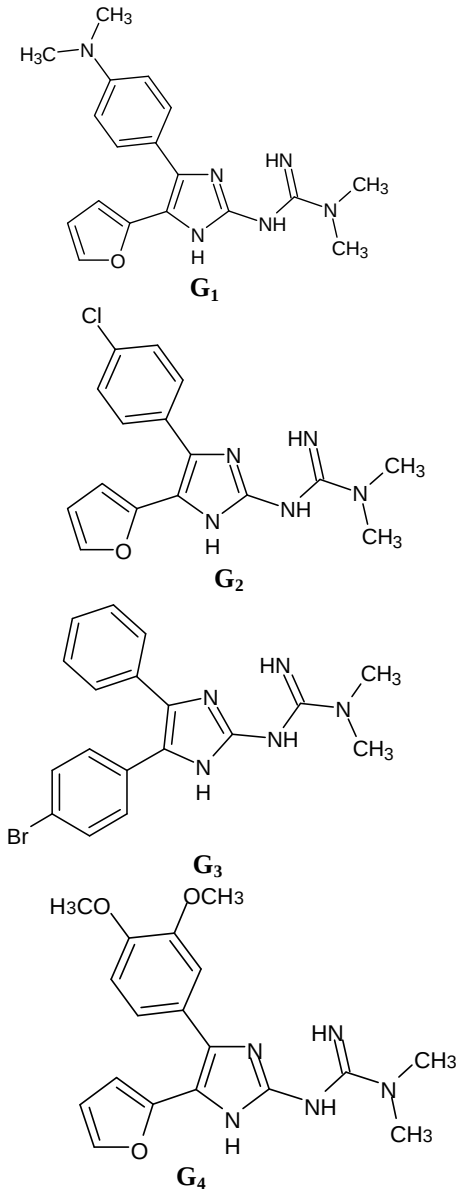


Table 1: IUPAC Names of the Title Compounds

Compound Code	IUPAC Nomenclature
G_1	3-{4-[4-(dimethylamino)phenyl]-5-(furan-2-yl)-1*H*-imidazol-2-yl}-1,1-dimethylguanidine
G_2	3-[4-(4-chlorophenyl)-5-(furan-2-yl)-1*H*-imidazol-2-yl]-1,1-dimethylguanidine
G_3	3-[5-(4-bromophenyl)-4-phenyl-1*H*-imidazol-2-yl]-1,1-dimethylguanidine
G_4	3-[4-(3,4-dimethoxyphenyl)-5-(furan-2-yl)-1*H*-imidazol-2-yl]-1,1-dimethylguanidine

Insilico Methodology

PASS (Prediction of activity spectra for substances) is a software product designed as a tool for evaluating the general biological potential of an organic drug like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. $P_{a\ is}$ Probability "to be active" and P_i is Probability "to be inactive".

Table 2: Predicted Biological Activity Spectrum of synthesized compounds by using PASS

S.No	Compound Code	Pa	Pi	Activity
1	G_1	0.273	0.137	Antihelmintic (Nematodes)
		0.226	0.143	Antimycobacterial
2	G_2	0.350	0.068	Antihelmintic (Nematodes)
		0.252	0.117	Antimycobacterial
3	G_3	0.474	0.022	Antihelmintic (Nematodes)
		0.250	0.119	Antimycobacterial
4	G_4	0.281	0.128	Antihelmintic (Nematodes)

Evaluation of Biological Activity

1. Anthelminthic Activity:

Animals

Healthy adult Indian earthworms, *Pheretima posthuma*, were used in the study. All earthworms were collected from vermin compost, Kurnool, washed with normal saline to remove faecal matter. All earthworms of equal size 8cm in length were used for all experimental protocol due to its anatomical and physiological resemblance with the human intestinal parasites (Vidyarathi et al., 1977, 1984)

Drug: Albendazole (Standard)

Chemicals: Normal saline

Procedure:

The anthelminthic assay was carried as per the method of Ajaiyeoba et al. (Bate smith, 1962) with minor modifications (Deore et al., 2009). The assay was performed on the adult earthworm, *Pheretima posthuma.* All the test solutions and standard drug solutions were prepared freshly before starting the experiment. Samples of standard drug and test drug was prepared at the concentrations 100,200,500 and 1000µg/ml in distilled water and eight earthworms of approximately 8 cm in length were placed in each nine centimetre petridish containing 25ml of above test solutions of drugs. Albendazole was used as standard drug and normal saline as control. Observations were made for the time taken to paralysis and death of individual worms.

Anti Tubercular Activity (MABA method)

Tuberculosis is a chronic granulomatous disease the causative organism of the disease is *Mycobacterium tuberculosis.* Compounds, synthesized in the present investigation were screened for anti-tubercular activity against *Mycobacterium tuberculosis* H37 RV strain in the Middle brook 7H9 (MB 7H9 broth) by using Streptomycin, Ciprofloxacine and Pyrazinamide as standard drug at a concentration of 6.25µg/mL, 3.125µg/mL and 3.125µg/mL respectively. The MIC of a compound is concentration of that which inhibits 90% of standardized bacterial inoculums.

Materials:

96 well plate, Middle brook 7H9 broth with M.tuberculosis H37 RV strain, Deionized water, Almar Blue reagent, 10% Tween 80, Incubator, Micropipettes.

Procedure:

a. The anti-mycobacterial activity of compounds were assessed against *M tuberculosis* using Micro plate Alamar Blue Assay (MABA).
b. This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method.
c. Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation.
d. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate.
e. The final drug concentrations tested were 100 to 0.8 µg/ml.
f. Plates were covered and sealed with parafilm and incubated at 37ºC for five days.
g. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% Tween 80 was added to the plate and incubated for 24 hrs.
h. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth.
i. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

The results of the title compounds were tabulated as shown below

3. Results and discussions

All the title compounds were synthesized and the yields were satisfactory and they were purified by recrystallization. The title compounds were characterised by FT-IR, ^{1}H NMR and MASS spectral studies and their structures were established. All the title molecules were predicted for biological properties by using PASS (Prediction of Activity Spectrum of Substances). All the compounds show maximum anti tubercular activity. From the results of anthelminthic activity tabulated it was shown that compound $G_{1\ is}$ comparatively active with that of standard drug. The remaining compounds also exhibit activity. From the results of anti-tubercular activity the compounds G1 and G_4 exhibits significant activity in comparison with standard, may be due to the presence of electron donating groups like $-N(CH_3)_2$ and $-OCH_3$.

Table 3: Effect of ethanolic extract of rhizomes of *Curculigo orchioides* in paracetamol induced hepatotoxicity

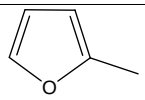
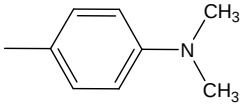
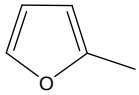
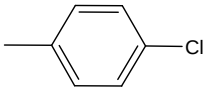
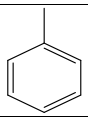
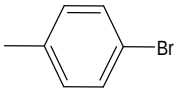
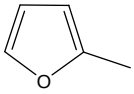
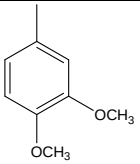
S.No.	Compound code	Ar	Ar'	Molecular formula	Molecular weight	Melting point	Yield (%)
1	G_1			$C_{18}H_{22}N_6O$	338.40	92-94^{0}C	**76.9**
2	G_2			$C_{16}H_{16}ClN_5O$	329.78	94-98^{0}C	**74.8**
3	G_3			$C_{18}H_{18}BrN_5$	384.27	_	**70.5**
4	**G_4**			$C_{18}H_{21}N_5O_3$	355.39	_	64.6

Table 4: Spectral details of the synthesized title compounds

Code	IR (KBr disc) position of absorption band(cm^{-1})		^{1}H NMR chemical shift δ (ppm)	Mass Spectra (m/z)
	Functional Group	**Functional Group**		
G_1	Aromatic -C-H -C=C- C-H (CH_3-N) C-O-C(cyclic ether, 5memb) C=N(imines) N-H(aromatic , 2° amine) C-N(2° amine) NH(arylalkyl)	3047.90 1444.86 2822.20 1066.76 1658.98 1593.40 1313.68 3458.79	7.20-7.8(8H,aromatic) 2.5(6H, -N(CH_3) of guanidine) 1.6(6H, -N(CH_3)) 8.5&4.7(NH)	338.40
G_2	Aromatic -C-H -C=C- C-H (CH_3-N) C-O-C(cyclic ether, 5memb) C=N(imines) N-H(aromatic , 2° amine) C-N(2° amine) NH(arylalkyl) C-Cl	3040.18 1452.57 2824.13 1084.13 1645.48 1552.89 1280.89 3464.57 752.33	7.20-7.8(8H,aromatic) 2.8(6H, -N(CH_3) of guanidine) 8.4(NH)	329.78
G_3	Aromatic -C-H -C=C- C-H (CH_3-N) C=N(imines) N-H(aromatic , 2° amine) C-N(2° amine) NH(arylalkyl) C-Br	3060 1506 2836 1574 1587 1295 3390 506	7-8(8H,aromatic) 2.5(6H, -N(CH_3) of guanidine) 8.5(NH)	384.27
G_4	Aromatic -C-H -C=C- C=N(imines)	3063 1506 1684	7.20-7.8(8H,aromatic) 2.6(6H of guanidine)	355.39

	N-H(aromatic , 2° amine) C-N(2° amine) NH(arylalkyl) C-O(aralkyl) Aryl-O Alkyl-O	1587 1331 3451 1234 1039	8.3(NH) 2.5(9H, -OCH_3)	

Table 5: Predicted Biological Activity Spectrum of synthesized compounds by using PASS

S.No.	Compound Code	Pa	Pi	Activity
1	G_1	0.273	0.137	**Antihelmintic (Nematodes)**
		0.226	0.143	**Antimycobacterial**
2	G_2	0.350	0.068	**Antihelmintic (Nematodes)**
		0.252	0.117	**Antimycobacterial**
3	G_3	0.474	0.022	**Antihelmintic (Nematodes)**
		0.250	0.119	**Antimycobacterial**
4	G_4	0.281	0.128	**Antihelmintic (Nematodes)**

Table 5: Effect of substituted diaryl imidazoles on onset of paralysis and onset of death

SNo.	Code	Concentration in µg/ml	Onset of paralysis (min)	Onset of death (min)
1	G_1	100	52±5	58±6
		200	47±7	55±7
		500	40±4	45±4
		1000	37±3	41±5
2	G_2	100	63±7	65±7
		200	55±5	59±9
		500	42±7	46±5
		1000	40±3	45±4
3	G_3	100	63±1	69±3
		200	55±5	60±3
		500	43±3	48±2
		1000	39±4	47±2
4	G_4	100	66±3	69±5
		200	55±3	59±4
		500	43±2	49±2
		1000	41±5	49±3
5	Albendazole (standard)	100	44±4	46±7
		200	43±6	45±5
		500	41±5	42±5
		1000	38±3	40±3

Table 4: Anti-tubercular results of the title compounds

Compounds	100	50	25	12.5	6.25	3.125	1.6	0.8
G_1	S	S	R	R	R	R	R	R
G_2	S	R	R	R	R	R	R	R
G_3	S	R	R	R	R	R	R	R
G_4	S	S	S	R	R	R	R	R

S – Sensitive, R – Resistant, Standard compound are sensitive at below concentrations
Pyrazinamide- 3.125µg/ml, Streptomycin- 6.25µg/ml, Ciprofloxacine-3.125µg/ml

4. Conclusion

All the title compounds were synthesized, characterized and screened for their anthelminthic and anti-tubercular activity. From the results of Anthelminthic activity tabulated it was shown that compound G_1 is comparatively active with that of standard drug. The remaining compounds also exhibit activity. From the results of anti-tubercular activity the compounds G_1 and G_4 exhibits significant activity in

comparison with standard because of presence of electron donating groups like $–N(CH_3)_2$ and $–OCH_3$.

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