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REVIEW ARTICLE

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 5, 5-DIPHENYL N (3)-SUBSTITUTED IMIDAZOLIDINE 2, 4-DIONE DERIVATIVES

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ABSTRACT

A *Convenient high yield synthesis of pharmaceutically interesting 5,5-diphenyl N(3)-substituted imidazolidine 2,4-dione derivatives from benzil and urea is described. The structures of compounds were established on the basis of IR,NMR and GC-MS spectral data. The title compounds were investigated for anti-inflammatory and antibacterial activity. The tested compounds exhibited good antiinflammtory and antibacterial activity as compared to standard drugs. The 5,5-diphenyl imidazolidine dione was generated from the condensation between benzil and urea and then converted to the desired derivatives by condensation with aryl compounds.*

Key words: *Synthesis, benzil, urea, sodium hydroxide, aryl compounds, anti-inflammatory and antibacterial activity.*

INTRODUCTION

Medicinal chemistry or pharmaceutical chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs[1].Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties, and their quantitative structure-activity relationships (QSAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products[2].However, inorganic compounds and metal-containing compounds have been found to be useful as drugs. For example, the cis-platin series of platinum-containing complexes have found use as anti-cancer agents[3].

Medicinal chemistry is a highly interdisciplinary science combining organic chemistry with biochemistry, computational chemistry, pharmacology, pharmacognosy, molecular biology, statistics, and physical chemistry. Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with creation of new synthetic drug compounds[4]. Medicinal chemistry is almost always geared toward drug discovery and development.

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Medicinal chemistry is the branch of science that provides these drugs either through discovery or through design. In the last century, the classical drugs were primarily discovered either by alteration of natural substances or entirely by chemical synthesis. In the recent years, an ever-increasing understanding of pathophysiology of disease has increasingly led to novel opportunities to deliberate design synthesis and evaluation of candidate drug molecules[5].

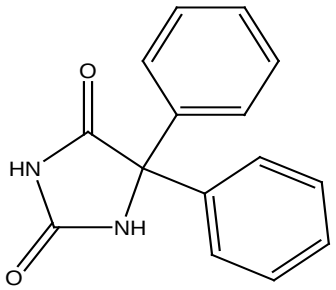
Drugs are chemicals that prevent disease or assist in restoring health to the diseased individuals as such they play an indispensable role in modern medicine.

5, 5-diphenyl imidazolidinedione is a commonly used as antiepileptic. Phenytoin acts to suppress the abnormal brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage-gated sodium channels. Aside from seizures, it is an option in the treatment of trigeminal neuralgia in the event that carbamazepine or other first-line treatment seems inappropriate.

5, 5-diphenyl imidazolidinedione (diphenylhydantoin) was first synthesized by German chemist Heinrich Biltz in 1908. Biltz sold his discovery to Parke-Davis, which did not find an immediate use for it. In 1938, outside scientists including H. Houston Merritt and tracy putnam discovered phenytoin's usefulness for controlling seizures, without the sedative effects associated with phenobarbital[6].

According to goodman and gilman's pharmacological basis of therapeutics, in contrast to the earlier accidental discovery of the antiseizure properties of bromide and phenobarbital, phenytoin was the product of a search among nonsedative structural relatives of phenobarbital for agents capable of suppressing electroshock convulsions in laboratory animals.

There are some indications that phenytoin has other effects, including anxiety control and mood stabilization, although it has never been approved for those purposes by the FDA. Jack Dreyfus, founder of the Dreyfus Fund, became a major proponent of phenytoin as a means to control nervousness and depression when he received a prescription for Dilantin in 1966. It was approved by the USA Food and Drug Administration in 1953 for use in seizures. Dilantin made an appearance both as an anticonvulsant and as a mechanism to control inmate behaviour[7].



5, 5-diphenylimidazolidine-2, 4-dione

A few 5, 5-diphenyl imidazolidinedione derivatives have already been known, but N (3)-substituted imidazolidine dione derivatives were not synthesized and evaluated for any biological activity. So, 5, 5-diphenyl –N(3) Substituted imidazolidine dione derivatives were synthesized and evaluated for its anti-inflammatory and antibacterial activity.

MATERIALS AND METHODS

Chemicals and equipments:

Benzil, Urea, DMF, Sodium hydroxide, Hydrochloric acid, Ethanol, 2-Chloro-4-Nitro aniline, Octyl bromide, Allyl bromide, Ibuprofen, Aspirin, Para bromo aniline, Glycine, Paracetamol, Domperidone, Dimethyl Sulfoxide, Chloroform, reflux condenser, heating mantle, RBF, hot plate, Denver single pan electronic balance, hot air oven, GUNA digital melting point apparatus, desiccators, shimadzu FTIR spectrometer, JEOL GC Mate II GC-MS spectrometer.

METHODS

Synthesis of 5, 5-Diphenyl imidazolidine dione:

A mixture of 5.3gm of benzyl (1), 3gm of urea (2), 15mL of 30% aqueous sodium hydroxide and 25mL of ethanol was taken in a 100mL round bottomed flask. The reflux condensation was carried out for 2 hours. Then the mixture was cooled out to room temperature and solutions was poured into 125mL of water, mix thoroughly and allowed it to stand for 15min. Then the solution was filtered under suction and filtrate was made strongly acidic with concentrated hydrochloric acid, cooled in ice water, filtered and recrystallized from industrial sprit. Completion of the reaction was determined by thin layer chromatography using toluene: cyclohexane (2:1) as mobile phase and yield was 85% & m. p 228^0-230^0C.

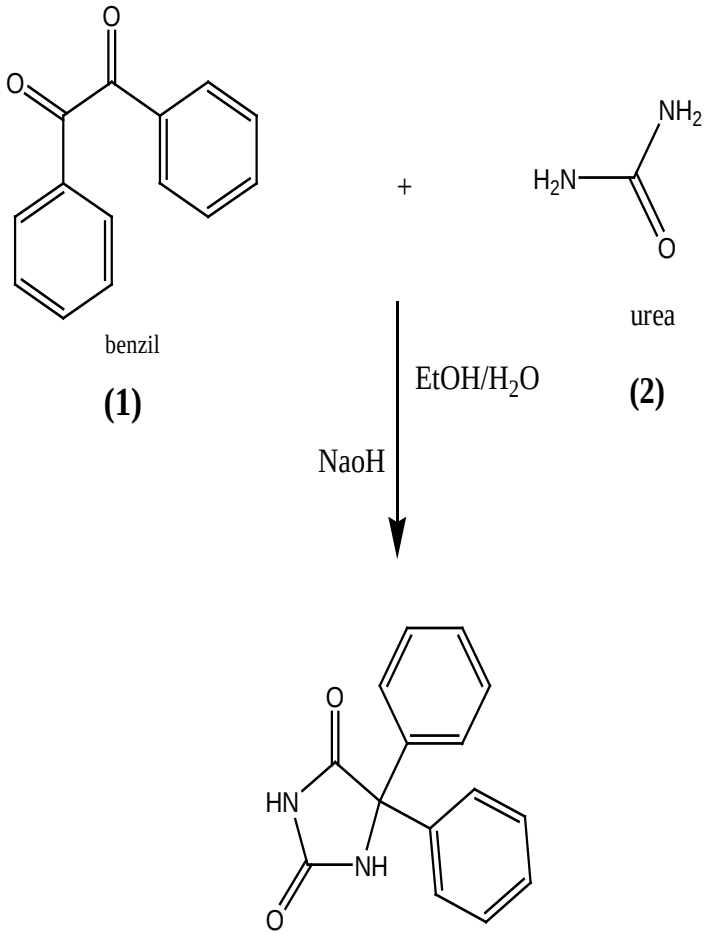
Synthesis of 5, 5-diphenyl-N(3) substituted imidazolidine dione derivatives: (3_a-3_d)

A mixture of 5,5-diphenylimdazolidine-2,4-dione(3)2.65gm (0.01moL)with the compounds such as 5-cholro-1-(1-(3-(2-oxo-2,3-dihydrobenzoimidazl-1-yl)propyl)piperidin-4-yl)-1*H*-benzoimidazole-2(3*H*)-one,3-bromoprop-1-ene,1-bromooctane, 2-chloro-4-nitro benzamine (4.26g, 2.92g, 3.64g, 1.72g 0.01 moL) in 20 mL dimethylformamide (DMF) were refluxed for 4 hours at 30-40^{0}C. The reaction mixture was poured into cold water. The precipitate were filtered off and washed with water. After drying, the precipitate was purified by recrystallization from ethanol. Completion of the reaction was determined by thin layer chromatography using toluene: cyclohexane (2:1) as solvent system.

Synthesis of 5, 5-diphenyl-N (3) substituted imidazolidine dione derivatives: (3_e-3_h)

A mixture of 5,5-diphenylimdazolidine-2,4-dione (3)2.65gm (0.01mol)with the compounds such as2-(4-isobutylphenyl)propanoyl chloride,2-(chlorocarbonyl)phenyl acetate,2-aminoacetyl chloride,2-aminopropanoyl chloride (2.06g, 1.08g, 3.09g, 3.23g 0.01 mol) in 20 mL *N,N*-dimethylformamide (DMF) were refluxed for 4 hours at 30-40^{0}C. The reaction was terminated, using monitoring of products with TLC. The reaction mixture was poured into cold water. The precipitate were filtered off and washed with water. After drying, the precipitate was purified by recrystallization from ethanol. Completion of the reaction was determined by thin layer chromatography using toluene: cyclohexane (2:1) as solvent system.

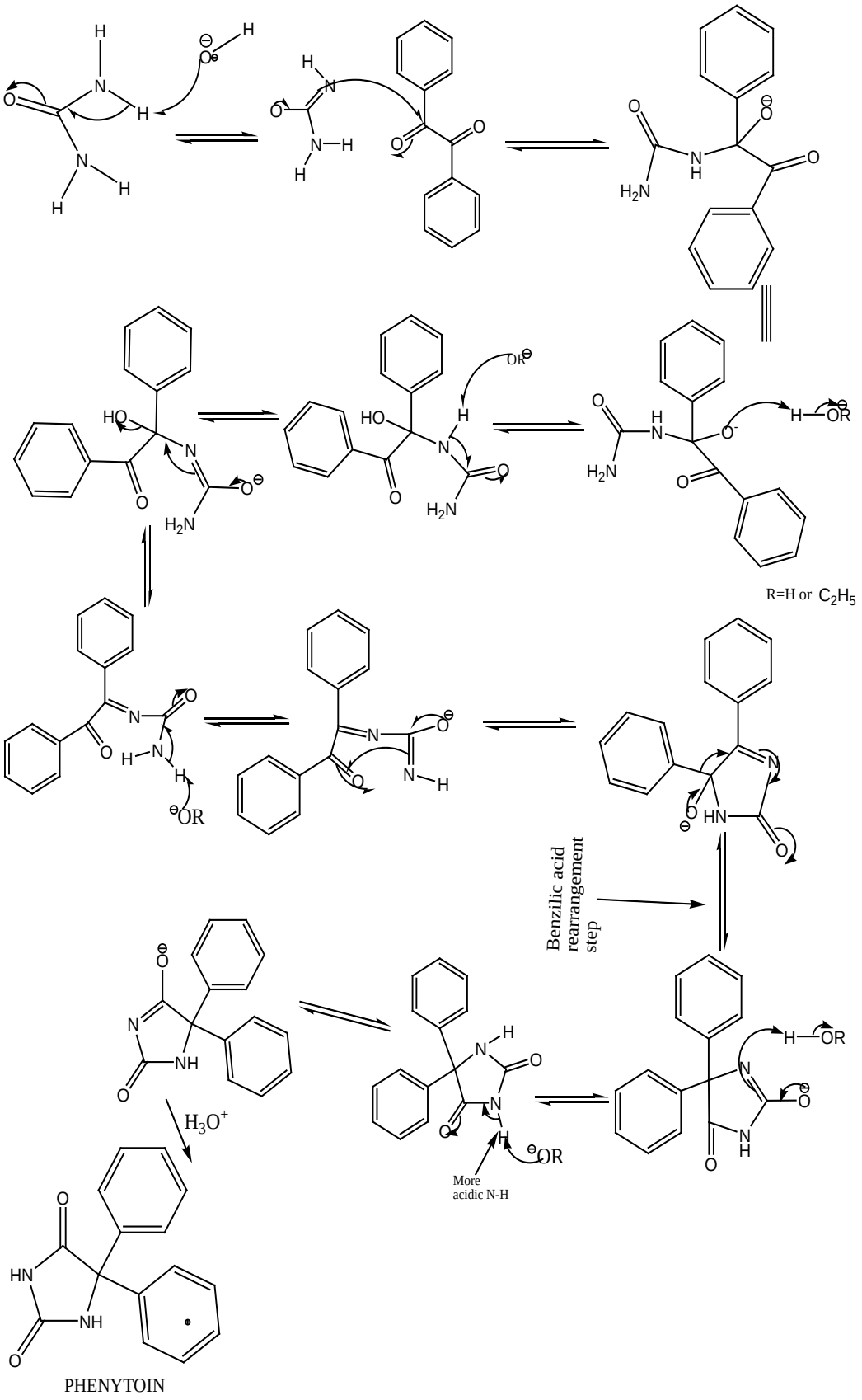
SCHEME-I:



5,5-diphenylimidazolidine-2,4-dione

(3)

Mechanism involved in the synthesis of 5, 5-di phenylimidazolidine2, 4-dione:



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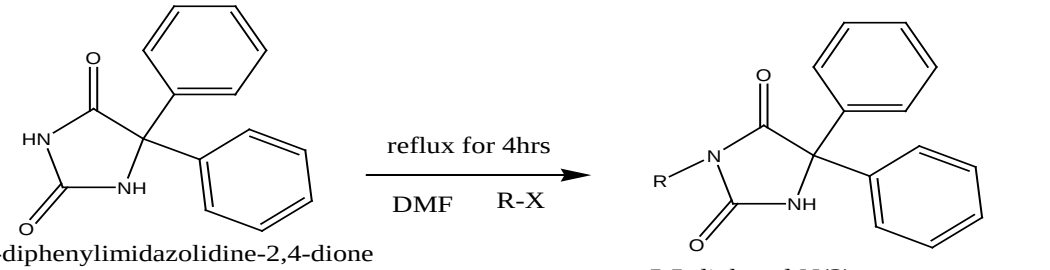


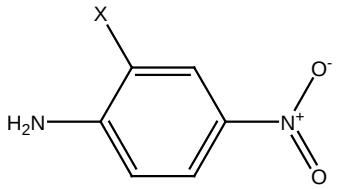
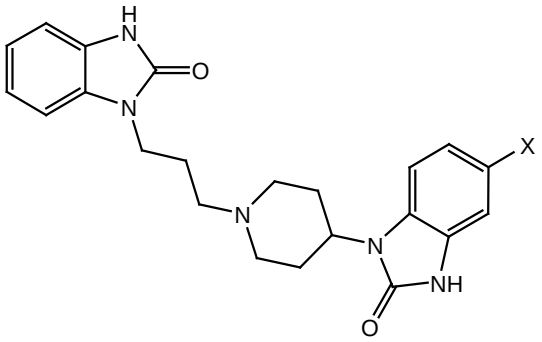
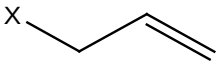
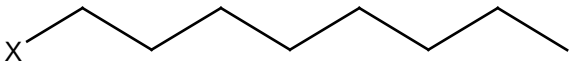
5,5-diphenylimidazolidine-2,4-dione

(3)

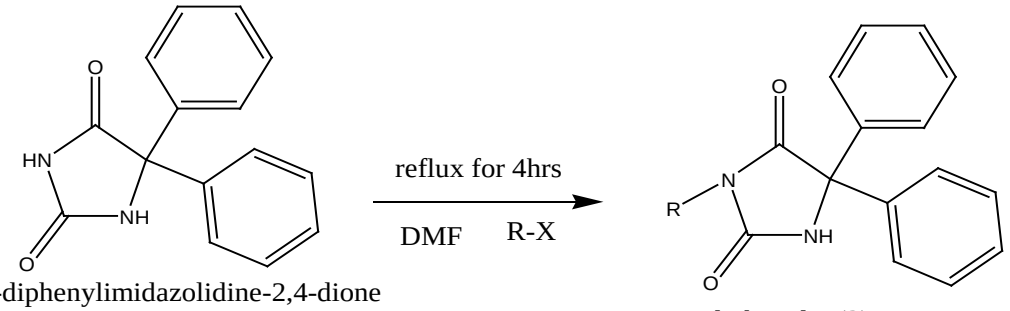
5,5-diphenyl N(3)-substitutedimidazolidine 2,4-dione

(3_{a-d})

Table - 1:

Compound code	R	X in R
3_a		Cl
3_b		Cl
3_c		Br
3_d		Br

SCHEME-III:



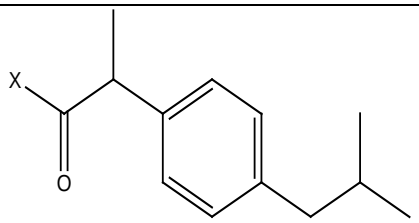
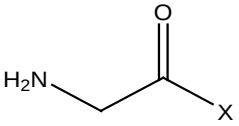
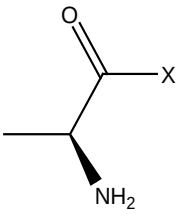
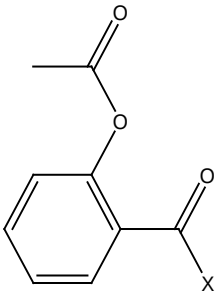
5,5-diphenylimidazolidine-2,4-dione

(3)

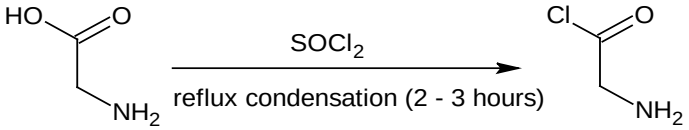
5,5-diphenyl N(3)-substitutedimidazolidine 2,4-dione

(3_{e-h})

Table - 2:

Compound code	R	X in R
3_e		Cl
3_f		Cl
3_g		Cl
3_h		Cl

The carboxylic acid group of 3(e), 3(f), 3(g), 3(h) compound was converted in to acyl group by treating with 0.02M of thionyl chloride by reflux condensation for about 3hrs. Then the reaction mixture was allowed to cool at room temperature. The separated solid was filtered and dried, and then it was used without further purification.



Evaluation of Anti inflammatory activity[8]:
All the title compounds were tested for anti-inflammatory activity using gelatine zymography method.

DETECTION OF MMP-2 AND MMP-9 USING GELATIN ZYMOGRAPHY REQUIRED REAGENT AND ITS COMPOSITION

1. Gelatin Substrate (20mg/mL): Weighed 20mg of gelatin and add 1mL of distilled water. Heated the solution till it becomes transparent. Cooled it and stored it at 4^0C.

2. Acryl amide Bis-acrylamide Solution (30:08): Weighed 7.5gm of Acrylamide +200mg of bis-acrylamide. Made it to 25 mL with distilled water. Stored at 4^0C.

3. TEMED: Commercially available. Stored at 4^0C.

4. 1.5% APS (Ammonium per sulphate): Weighed 75mg of APS and add 5mL of distilled water. Always prepare fresh.

5. Resolving Gel buffer stock: 18.15gm of tris +24mL of 1M HCl Mixed and brought to 50 mL final volume with distilled water. Filtered, stored at 4^0C.

6. Stacking gel buffer stock: 6.0gm of Tris dissolved in 40mL of distilled water. Adjust the pH 6.8 with 1M HCl and brought to 100mL final volume with distilled water. Filtered, stored at 4^0C.

7. Reservoir Buffer stock: 3.03gm of Tris+14.4 gm. glycine+1gm SDS. Make it to 100mL with distilled water. Storedat4^0C. Working Solution: [10mL of Reservoir buffer stock + 90mL of distilled water].

8. 2.5% Triton x -100: Measured 2.5mL of Triton x-100. Made up the volume upto 100mL with distilled water stored at 4^0C.

9. Incubation buffer: Weighed 605mg of Tris HCl +222mg of $CaCl_2$. Make it to 100mL with distilled water. Stored at 4^0C.

10. Coomassie blue R250 [For 100mL]: Coomassie blue 500mg + Methanol 50mL + Acetic acid 10mL + distilled water 40mL. Stored at R.T.

11. De-staining solution: Methanol 50mL + Acetic acid 10mL + distilled water 40mL stored at R.T.

12. Storage buffer i.e. **5% Acetic acid:** 5mL of Acetic acid + 95mL of distilled water. Stored at R.T.

13. 10% SDS: Weighed 100mg of SDS +10mL of distilled water. Stored at 4^0C.

14. 2x Non reducing buffer [For 8mL]: 2.8 mL distilled water + 1mL 0.5M Tris HCl (pH 6.8) + 0.8 mL glycerol + 3.2 mL 10% SDS + 0.2mL 0.2% bromophenol blue.

15. 0.1% Agarose gel: 100mg agarose + 10mL of Saline, Boiled the Solution till it becomes transparent. Stored at R.T or 4^0C.

16. Tris buffer: 600mg Tris (0.05M) + 250/mL triton x-100 (0.25%) + 300mg $CaCl_2$ (0.02M), Made up the final volume 100mL with 0.9% Saline. Stored at 4^0C.

PROCEDURE

1. Clean the electrophoresis apparatus in warm water and clean glass plates in Methanol.

2. Set up plates. Large plate then two spacers (apply little petroleum jelly on both sides of the spacers) and small plate on top. Assemble plates into clamp and gently tighten screws. Do not over tighten, as this will crack the plates.

3. Heat the agarose gel, pour between the two glass plates just to seal the bottom surface, leave it for 5-10 minutes.

4. Prepare the resolving gel as given below.

Table 3: Preparation of 10% resolving gel (10mL)

Reagents	**Volume**
Acryl amide – Bis-acrylamide	3.3mL
Resolving gel buffer stock	1.25mL
10% SDS	100µL
1.5% APS	500 µL
Gelatin	1mL
Water	3.8mL
TEMED	10µL

5. Mix the appropriate resolving gel mixture and pipette between the glass plates avoiding bubbles. Fill plates about 80%way up leaving space for the stacking gel and comb. Overlay with a small amount of water to achieve a completely flat interface between resolving gel and stacking gel. Allow to set for about 45 minutes.

6. While resolving gel is setting prepares the stacking gel.

Table 4: Preparation of 5% stacking gel (10mL)

Reagents	Volume
Acrylamide – Bisacrylamide	1.7mL
Stacking gel buffer	1.12mL
10% SDS	100µL
1.5% APS	500µL
Water	6.5mL
TEMED	10µL

7. When resolving gel in set pour off the excess water and added washed between the plates with Distilled water.

8. Pour in stacking gel and inserted comb avoiding bubbles. Allow to set for about 30 mins.

9. When stacking gel is set gently removed comb, washed the wells with distilled water and assembled gels onto the electrode/gasket section of the gel apparatus. Filled top and bottom of the tank with reservoirbuffer. i.e. upper tank with 100mL and lower tank with 150mL.

10. **Preparation of samples:** Taken the tissue sample chop it completely, added 5mL of Tris buffer, centrifuge at 3000 rpm for 15 min, and stored it in -20^{0}C for further use. Before the experiment the samples were centrifuged at 3000 rpm for 10-15min and then use the supernatant. Mixed equal volume of 2x non reducing buffer and sample supernatant. Mixed it and pipette into wells using gel loading tips.

11. **Control:** 50µL of tissue extract were pre-incubated with 50µL of tetracycline (300µg/mL) for 60min at R.T.

12. Loaded 20 µL of sample in each well and 10 µL molecular weight marker in last well.

13. Connected the electrodes. Put lid on tank and plug cables into power supply.

14. Run at about 50V for 15 min and then 100V until the bromophenol blue reaches the bottom of the plates.

15. After electrophoresis, dissembled the apparatus and gently removed the gel and put into a plastic dish and washed the gel with zymogram renaturing buffer i.e.2.5%Triton x-100 for one hour to removed SDS from the gel and allowed proteins to denature.

16. Decanted the zymogram renaturing buffer and incubated the gel in zymogram incubation buffer at 37^{0}C overnight.

Staining

1. Stained with Coomassie blue R-250 for one hour.
2. Gels should be destained with an appropriate Coomassie R-250 destaining solution for about 2 hours.
3. It should look something like this. The background stains blue with Coomassie stain where the gelatin is degraded white bands appear indicating the presence of gelatinases. The lower bands are gelatinases-A (MMP-2) which is about 72KD while the upper bands are gelatinases-B (MMP-9) which runs at about 95KD.

Gel drying

Required Materials

- Gel drying solution
- 20% ethanol
- 10%glycerol
- Gel drying frames from diversified biotech
- Cellophane sheets from diversified biotech.

Procedure

1. Equilibrate gel in gel drying solution for at least 60 min. It reduces gel swelling and results in more flexible dried gel.
2. Place two cellophane sheets in water for 1 to 2 min, cellophane may appear cloudy but will clear upon drying.
3. Lay one sheet of cellophane on solid back plate beveled edge down, avoid air bubbles.
4. Place gel on cellophane, avoid air bubbles. Air bubble can cause cracking.
5. Pipette 1 to 2 mL of gel drying solution on top of gel.

6. Layer a second wet sheet of cellophane on top of gel, match edges with edges of back plate, roll cellophane from bottom of gel towards the well helps avoid air bubble.
7. Place open frame over stack, beveled edge up. Match edges of back plate. Frame should cover all edges of cellophane.
8. Attach plastic chips to all four slides.
9. Leave assembly to dry horizontally for at least two days.
10. Remove chips and dry apart assembly.
11. Peel dried gel/cellophane sandwich from back plate.
12. Trim off access cellophane immediately to avoid curling.

Evaluation of Antibacterial activity[9]:

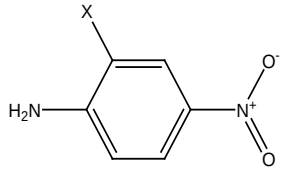
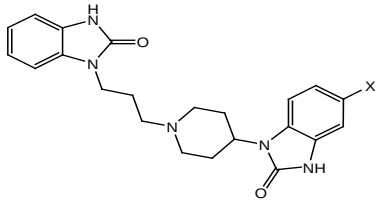
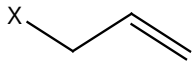
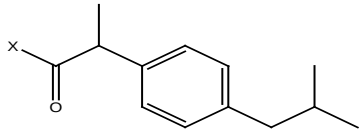
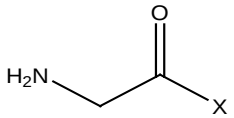
The synthesized compounds were screened for antibacterial activities against the gram positive organisms such as *Staphylococcus albus and Streptococcus pyogens* and gram negative organisms such as *Escherichia coli* and *Klebsilla* by agar diffusion method. Dimethyl formamide was used as solvent control. Procaine penicillin and streptomycin were used as standards for antibacterial screening. The culture medium used was nutrient agar.

RESULTS AND DISCUSSION

The main aim of the present work was to synthesize some 5,5-diphenyl-N(3) substituted imidazolidine dione derivatives. They were confirmed by IR (KBr), GC-MS and ^{1}HNMR spectra. Subsequent purification of crude compounds yielded pure compounds in moderate to high yields. Some of these compounds such as 3_e exhibited significant anti inflammatory activity when compared to that of standard. Rest of the compounds showed mild to moderate anti inflammatory activity when compared to that of standard.

Some of these Compounds such as 3_g and 3_h showed significant activity when compared to that of standard at 50 and 100 µg/ml against gram positive bacteria (*Staphylococcus albus* and *Streptococcus pyogens*) organisms. Compounds such as 3_a, 3_e, 3_f and 3_h showed significant activity when compared to that of standard at 50 and 100 µg/ml against gram negative bacteria (*Klebsilla* and *Escherichia coli*) organisms. Rest of the compounds showed mild to moderate activity against both tested gram positive and gram negative organisms when compared to that of standard.

Table -5:
Characterisation of new substituted 5,5-diphenyl –N(3) substituted imidazolidine dione derivatives[10]:
Physical Characterisation data of 5, 5-diphenyl-N(3) substituted imidazolidine dione derivatives (3_{a-h})

Compound code	R	Molecular formula	Molecular weight	Melting point(^{0}C)	% Yield
3_a		$C_{21}H_{16}N_4O_4$	388.38	185-187	87%
3_b		$C_{37}H_{35}N_7O_4$	641.72	237-240	79%
3_c		$C_{18}H_{16}N_2O_2$	292.33	279-281	89%
3_d		$C_{23}H_{28}N_2O_2$	364.48	290-294	78%
3_e		$C_{28}H_{28}N_2O_3$	440.53	298-231	80%
3_f		$C_{17}H_{15}N_3O_3$	309.32	236-240	88%

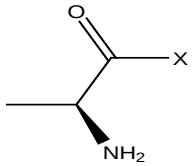
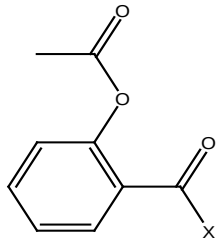
3_g		$C_{18}H_{17}N_3O_3$	323.35	274-279	90%
3_h		$C_{24}H_{18}N_2O_5$	414.41	289-292	82%

Table 4: IR, ^{1}H NMR and Mass spectral data of N (3) -substituted 5, 5-Diphenyl imidazolidine dione derivatives 3_{a-h}:

Compound code	υ_{max} (KBr)cm^{-1}	^{1}H NMR chemical shift δ (ppm)	Mass spectra (m/z)
3_a	1315.61C-N stretching(3^0amine), 1340.69C-N stretching(2^0amine)3375.91 N-H stretching(di alkyl)1741.93 C=O stretching(five membered) 1655.90 C-H (aromatic ring), 1626.90 C-H aromatic out of plane summation bonds, 1718.78 C-O stretching (five membered), 3492.58 N-H stretching, 1259.67 C-N stretching (aromatic primary), 1493.09 N-O stretching (aromatic C-NO_2)	7.2-7.8 (14H, aromatic protons) 3.272 (2H, NH_2) 6.8 (1H, NH)	388.1950
3_b	1348.41C-N stretching(3^0amine),1295.60 C-N stretching(2^0amine),3256.24 N-H stretching(di alkyl),1748.20 C=O stretching (five membered),1675.56 C-H (aromatic ring),1772.88,1882.75 C-H aromatic out of plane summation bonds,2930.07 C-H stretching (CH_2),1471.10 C-H def	7.0-7.4 (17H,aromatic protons) 7.3 (3H,NH) 1.3 (6H,CH_2)	642.4028
3_c	1340.40C-N stretching(3^0amine), 1314.50C-N stretching(2^0amine),3553.50 N-H stretching(di alkyl),1741.90 C=O stretching(five membered),1670.00 C-H (aromatic ring),1639.40 C-H aromatic out of plane summation bonds,2935.88 C-H stretching (CH_2),1450.11 C-H def,1652.20 C=C stretching	---------	--------
3_d	1345.88C-N stretching(3^0amine),1299.90 C-N stretching(2^0amine),3314.11 N-H stretching(di alkyl),1740.00 C=O stretching(five membered),1650.90 C-H (aromatic ring),1633.91,1777.3 C-H aromatic out of plane summation bonds,2964.95 C-H stretching (CH),1448.05 C-H deformation (CH_2)	----------	--------
3_e	1355.30 C-N stretching(3^0amine),1333.20 C-N stretching(2^0amine),3348.80 N-H stretching(di alkyl),1748.30 C=O stretching(five membered),1650.50 C-H (aromatic ring),1695.00 C-H aromatic out of plane summation bonds,1743.30 C=O stretching (acyclic),2872.40 C-H stretching (CH),1338.50 C-H def,2929.40 C-H stretching (CH_2),1474.13 C-H def,2971.00 C-H stretching (CH_3),1472.10 C-H def	7.0-7.4 (14H,aromatic protons) 3.2 (1H,NH_2) 0.8-1.3 (9H,CH_3) 1.3 (2H,CH)	441.8019
3_f	1313.68C-N stretching(3^0amine),1286.68 C-N stretching(2^0amine),3345.28 N-H stretching(di alkyl),1741.93 C=O stretching(five membered),1650.90 C-H (aromatic ring),1880.82 C-H aromatic out of plane summation bonds,1713.00 C-O stretching (five membered)	----------	------
3_g	1315.00C-N stretching(3^0amine),1259.90 C-N stretching(2^0amine),3344.00 N-H stretching(di alkyl),1741.93 C=O stretching(five membered),1660.00 C-H (aromatic ring),1629.19 C-H aromatic out of plane summation bonds,1716.85 C=O stretching(acyclic),1126.57 C-N stretching (aliphatic amine),1587.61 N-H deformation	7.3-7.4 (10H, m,aromatic protons) 3.295 (2H,NH_2) 2.4 (3H,CH) 7.2 (1H, s, NH_2)	323.35
3_h	1340.80C-N stretching(3^0amine),1325.30 C-N stretching(2^0amine),3357.00 N-H stretching(di alkyl),1714.33 C=O stretching(five membered),1670.00 C-H (aromatic ring),1606.99,1717.00 C-H aromatic out of plane summation bonds,1360.80 C-H stretching(CO-CH_3),2905.00C-H def,1717.00 C=O stretching (acyclic),1235.80 C-O stretching(arakyl)	7.0-7.4 (14H,aromatic protons) 6.3 (1H, s, NH_2) 1.507 (3H, s, CH)	414.1511

Table 5: Evaluation of Anti inflammatory activity of synthesised compounds (3_{a-h}):

S.No	Compound	Anti-Inflammatory activity
1	3_a	40%
2	3_b	35%
3	3_c	60%
4	3_d	30%
5	3_e	70%
6	3_f	45%
7	3_g	50%
8	3_h	60%
9	Tetracycline(standard)	70%

Table 6: Evaluation of Anti bacterial activity of synthesised compounds (3_{a-h}):

S. No	Compound	Zone of Inhibition (mm)							
		Staphylococcus albus (+ve)		*Streptococcus pyogens* (+ve)		*Klebsilla* (-ve)		*E.Coli* (-ve)	
		50µg/ml	100µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1.	3_a	16	18	14	16	18	20	19	21
2.	3_b	14	16	15	17	17	19	18	19
3.	3_c	16	18	15	17	18	20	17	19
4.	3_d	15	17	17	19	16	18	17	18
5.	3_e	14	16	15	17	12	15	18	20
6.	3_f	14	15	16	18	19	22	19	21
7.	3_g	17	21	16	21	16	18	17	19
8.	3_h	18	20	16	19	18	21	19	20
9.	Procaine	19	22	20	23	---	---	---	---
10.	penicillin	---	---	---	---	21	23	20	22
11.	Streptomycin	---	---	---	---	---	---	---	---
	Control								

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