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ECO FRIENDLY SYNTHESIS OF SOME NOVEL DIPYRANO-PYRROLE DERIVATIVES FROM 1-(2, 6-DICHLORO-4-TRIFLUOROMETHYL-PHENYL)-PYRROLIDINE-2,5-DIONE.

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ABSTRACT:
Environmentally friendly chemical synthesis is most interesting and popular in today's research. The novel synthons have been successfully developed in the current context. Instead of using organic solvent, use of a PbO nanoparticle catalyst that produced a respectable yield. It is one of the classified greener techniques which replaces hazardous solvents. This method does not require potentially harmful piperidine. The structures of these compounds are supported by their IR, NMR spectral data. The compounds have been screened for their antibacterial and antioxidant activities.

KEYWORDS: pyrano-pyrrole, cyclic imide, malononitrile, PbO nanoparticals.

1.0 INTRODUCTION:

An Imide is considered as a functional group in synthetic chemistry having two acyl substituents that are attached to the nitrogen which is found in both form chain and cyclic.[i.] Cyclic imides were prepared from primary amine and cyclic anhydrides which emerged as an important class of organic substrates for agricultural, biological and chemical applications.[ii] Cyclic imides, which are composed of the most abundant heterocyclic components such as nitrogen, oxygen, and sulphur, are important in the pharmacological, medical, chemical, and agricultural areas. Cyclic imides are extensively utilized for advanced derivatization through multifarious chemical transformation. Now a days, the renovated attraction has been affectionate globally towards a classic legacy of these compounds for their significant applications and advantages specifically in the field of pharmaceutical and innovative drug designing.[iii]

Recently benzopyran derivatives sparked a lot of attention due to their several significances in therapeutics such as anticoagulants, diuretics, and spasmolytic[iv-vii]. Benzo-pyrans are also determined for their remarkable medicinal values against mortal diseases[viii] which include anti-

ancaphylactia, antitumor, anti-cancer and so on.[ix] According to Literature survey, benzo-pyrans have been found in numerous biologically active natural compounds[x]. Additionally, they are utilized as a pigments[xi], photo-active material[xii] and biodegradable agrochemicals.[xiii]

As we know that in today's main stream research, the researchers are working too hard for developing modern synthetic strategies with complimenting and exploration of novel methodologies in the domain of heterocyclic compounds. They are also focusing on significant level of molecular complexity, higher practical organization compatibilities and minimum cost solvent and reagents. In addition to the traditional methods, plenty of ecofriendly methodologies have been described in literature withinside the current instances permitting stepped forward to get complex heterocycles moieties from convenient precursors and under milder reaction conditions. In all this research heterocyclic chemistry plays significant role for synthesizing most efficient molecules.

As we discussed earlier in order to maintain synthetic interest, ecofriendly technical enhancements were required for the initial reaction conditions. It is possible to synthesize dipyrano derivatives with the assistance of PbO nanoparticles by reacting cyclic imide with malononitrile in the presence of a substituted aromatic aldehyde. In conventional synthesis techniques of dipyrano have used a basic catalyst such as piperidine or triethylamine in an organic solvent such as ethanol, DMF, or acetic acid[xiv-xx] and microwave irradiation also be used to make them.[xxi] Despite the fact that each of these techniques has its own merits, they do not completely satisfy. Long reaction times, non-renewable solvents, toxic chemicals, poor yield, and complex set-up are all disadvantages of these techniques.

PbO nanoparticles were used to perform a solvent-free synthesis of pyranopyran derivatives which is an efficient catalyst at room temperature. PbO nanoparticles have been shown to be a highly efficient, renewable, and environmentally acceptable heterogeneous catalyst. The procedure, which is simple to set up, fast reaction times, solvent-free, and avoids hazards chemicals. N-phenyl succinimides with substituted aromatic aldehyde and malononitrile yielded a new class of pyranopyran (5a-e).

In present work we have used 2, 6 dichloro 4- Fluro methyl aniline for synthesizing novel pyrano-pyrrole derivatives via cyclic imide 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (3a) with various substituted benzaldehyde. Literature survey shows that 2, 6 dichloro 4-fluromethyl aniline is selectively utilized for synthesis of pesticide such as Fipronil.[xxii-xxiii] An overview of this amine shows that the addition of trifluoro methyl on the benzene ring significantly utilized in the agrochemical and pharmaceutical industries.[xxiv-xxvi]

2.0 MATERIAL AND METHODS:

Melting Points were recorded in open glass capillaries and were uncorrected. The chemical structures of the obtained compounds were confirmed by spectral analyses. IR spectra in KBr pallets were recorded on Shimadzu and ATR Brucker alpha FT-IR spectrophotometer. 1H NMR spectra were recorded at 500 MHz by a Brucker spectrophotometer. The rection was monitored by thin layer chromatography, which was performed by using pre-coated silica gel aluminium plates with a mixture of diethyl ether and ethyl acetate in a 6:4 proportion.

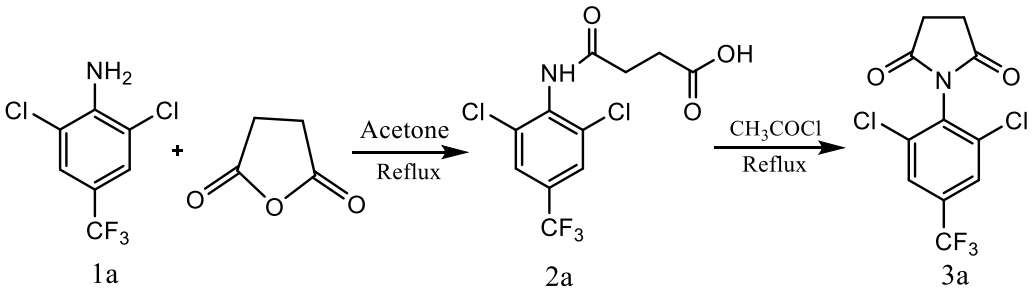
3.0 EXPERIMENTAL SECTION:

3.1 General Procedure for the Synthesis of N-phenyl Succinimide :

Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (3a):

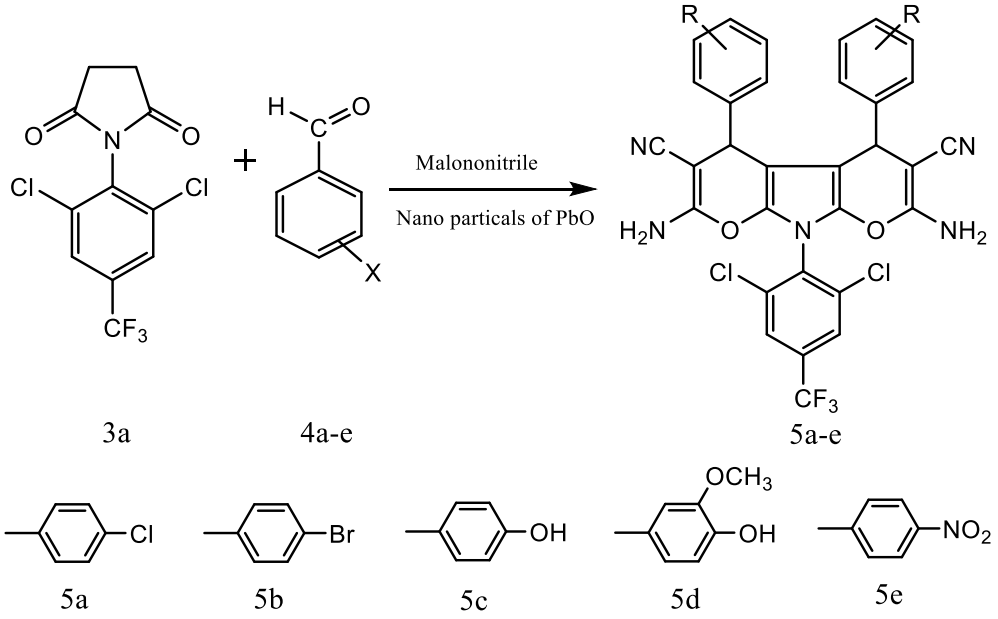
Succinic anhydride (0.01mol) was dissolved in benzene (10ml) then 2, 6-dichloro-4-trifluoromethyl aniline (0.01mol) was added to it vigorously. The 4-((2, 6-dichloro-4-(trifluoromethyl) phenyl) amino)-4-oxobutanoic acid (2a) was formed. This imic acid was cyclized by using (0.09) mole of fresh acetyl chloride under reflux conditions leads to give

product (3a). It is recrystallized from ethanol (Scheme 1).



Scheme 1: Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)- pyrrolidine-2,5-dione

1)1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (3a):
Molecular Formula: $C_{11}H_6Cl_2F_3NO_2$, **Physical Appearance:** Off white powder, **Nature of compound:** Amorphous, **Percentage Yield (%):** 88, **Melting Point (ºC):** 164-166, **Molecular Weight (g/mol):** 312.
C, H, N Elem. Anal.: Calculated: C, 38.34; H, 1.94; N, 4.49. Obtained: C, 38.24; H, 1.83; N, 4.34.
FT-IR (KBr) cm^{-1}: 3000 (C-H stretching CH_2), 2936 (C-H stretching of Ar-H), 1710 (C=O), 1537 and 1490 (ArC=C), 1220 (C-N stretching), 1010 (C-F stretching), 826 (Cl stretching).
^{1}H-NMR (500 MHz, DMSO-d$_6$, δ ppm): 2.50 (t, 4H), 7.94 (s, 2H, Ar-H)**.**
3.2 General procedure for the synthesis of Dipyrano-pyran using cyclic imide (3a) and aromatic aldehydes:
Synthesis of Dipyrano-pyrrole derivatives of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrrolidine-2,5-dione (5a-e):
Mixture of N-phenyl succinimide derivatives (0.01mole), aromatic aldehydes (0.02mole), malononitrile (0.02mole) and 100 mg PbO nanoparticles were ground for half hour at a room temperature with a mortar and pestle. The reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the product was washed with distilled water. The novel developed compounds were dried and recrystallized from ethanol to furnished pure compounds with maximum yield. **(**Scheme 2).



Scheme 2: Synthesis of Dipyrano-pyrrole derivatives of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrrolidine-2,5-dione.

i)2,7-diamino-4,5-bis(4-chlorophenyl)-9-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (5a)
Molecular Formula: $C_{31}H_{16}Cl_4F_3N_5O_2$ **Physical Appearance:** Cremish White solid, **Nature of compound:** Crystalline, **Percentage Yield (%):** 88, **Melting Point (ºC):** 172-174 **Molecular Weight (g/mol):** 689.30.
C, H, N Ele. Analysis: Cal; C, 54.02; H, 2.34; N, 10.16; Obs; C, 54.61; H, 2.43; N, 10.41.
FT-IR (KBr) cm^{-1}: 3093 (-N-H stretching), 2198 (C≡N),1673,1578 and 1528 (Aromatic C=C), 1399 (N-C), 1153 (C-O), 1014 (C-F), 912 (-C-Cl).
^{1}H NMR (500 MHz, DMSO-*d_6*, δ ppm): 4.73 (s, 2H, methine), 6.82 (s, 4H, NH_2), 7.35 7.38 (d, 8H, Ar-H), 7.67 (s, 2H, Ar-H).
ii)2,7-diamino-4,5-bis(4-bromophenyl)-9-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (5b)
Molecular Formula: $C_{31}H_{16}Br_2Cl_2F_3N_5O_2$, **Physical Appearance:** Off-White solid, **Nature of compound:** Needle shape Crystals, **Percentage Yield (%):**91, **Melting Point (ºC):** 148-150, **Molecular Weight (g/mol):** 778.21.
C, H, N Ele. Analysis: Cal; C, 47.85; H, 2.07; N, 9.00 Obs; C, 47.28; H, 2.11; N, 9.08.
FT-IR (KBr) cm^{-1}: 3183 (-N-H), 3021 (C=C-H), 2227 (C≡N), 1668, 1578 and 1528 (Aromatic C=C), 1388 (N-C), 1153 (C-O Stretching), 1075 (C-F stretching), 885 (C-Cl stretching), 695 (C-Br stretching).
^{1}H NMR (500 MHz, DMSO-*d_6*, δ ppm): 4.72 (s, 2H, methine), 6.80 (s, 4H, -NH_2), 7.33 (d, 4H, Ar-H), 7.66 (d, 2H, Ar-H), 7.82 (d, 4H, Ar-H),
iii)2,7-diamino-9-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4,5-bis(4-hydroxyphenyl)-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (5c)
Molecular Formula: $C_{31}H_{18}Cl_2F_3N_5O_4$, **Physical Appearance:** Pale yellow solid, **Nature of compound:** Spongy solid **Percentage Yield (%):** 84, **Melting Point (ºC):**168-170, **Molecular Weight (g/mol):** 652.41.
C, H, N Ele. Analysis: Cal: C, 57.07; H, 2.78; N, 10.73 Obs: C, 58.43; H, 2.74; N, 10.58.
FT-IR (KBr) cm^{-1}: 3345 (-OH stretching), 3132 (-N-H stretching), 3021 (C=C-H stretching), 2227 (C≡N), 1673, 1561 and 1438 (Aromatic C=C), 1412 (O-H bending), 1371 (N-C), 1299 (C-O Stretching), 1114 (C-F stretching), 834 (C-Cl stretching).
^{1}H NMR (500 MHz, DMSO-*d_6*, δ ppm): 4.74 (s, 2H, methine), 6.68 (d, 4H, Ar-H), 6.84 (s, 4H, -NH_2), 7.27 (d, 4H, Ar-H), 6.68 (s, 2H, Ar-H), 9.02 (s, 2H, Ar-H).
iv)2,7-diamino-9-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4,5-bis(4-hydroxy-3-methoxyphenyl)-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (5d)
Molecular Formula: $C_{33}H_{22}Cl_2F_3N_5O_6$, **Physical Appearance:** Lemon yellow solid, **Nature of compound:** Spongy, **Percentage Yield (%):** 85, **Melting Point (ºC):**134-136, **Molecular Weight (g/mol):** 712.46
C, H, N Ele. Analysis: Cal: C, 55.63; H, 3.11; N, 9.83. Obs: C, 56.58; H, 3.08; N, 9.81.
FT-IR (KBr) cm^{-1}: 3406 (-OH stretching), 3121 (-N-H stretching), 3021 (C=C-H stretching), 2221 (C≡N), 1662, 1567 (Aromatic C=C), 1511 (O-H bending),1382 (N-C), 1299 (C-O Stretching),1025 (C-F stretching), 885 (C-Cl stretching).
^{1}H NMR (500 MHz, DMSO-*d_6*, δ ppm): 3.73 (s, 6H, -CH_3), 4.73 (s, 2H, methine), 6.78 (d, 2H, Ar-H), 6.82 (s, 4H, -NH_2), 6.94 (d, 2H, Ar-H), 6.96 (s, 2H, Ar-H), 7.67 (s, 2H, Ar-H), 9.94 (s, 2H, Ar-OH).
v) 5e- 2,7-diamino-9-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4,5-bis(4-nitrophenyl)-5,9-dihydro-4H-dipyrano[2,3-b:3',2'-d]pyrrole-3,6-dicarbonitrile (5e)
Molecular Formula: $C_{31}H_{16}Cl_2F_3N_7O_6$, **Physical Appearance:** Cremish white solid, **Nature of compound:** Needle shape crystal **Percentage Yield (%):** 91, **Melting Point (ºC):** 164-166, **Molecular Weight (g/mol):** 710.41,

C, H, N Ele. Analysis: Cal: C, 52.41; H, 2.27; N, 13.80 Obs: C, 52.68; H, 2.35; N, 13.88.
FT-IR (KBr) cm^{-1}: 3177 (-N-H stretching), 3021 (C=C-H), 2224 (C≡N), 1673,1578 and 1522 (Aromatic C=C), 1475 (N=O), 1321 (N-C), 1153 (C-O), 1008 (C-F), 885 (-C-Cl).
^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 4.72 (s, 2H, methine), 6.80 (s, 4H, -NH_2), 7.68 (s, 2H, Ar-H), 7.72 (d, 4H, Ar-H), 8.16 (d, 4H, Ar-H).

4.0 BIOLOGICAL STUDY:

4.1 Antimicrobial activity:

The series of all synthesized novel compounds (5a-e) were investigated for their antimicrobial activities in vitro against two bacterial strains, Gram positive *Bacillus subtilis*, Gram negative *Escherichia coli* and two fungal strains, *Aspergillus niger* and *Candida albicans* respectively using disc diffusion method.

4.1.1 Antimicrobial Assay:

Stock solution (1000 microgram per ml) of the test sample was prepared in DMSO solvent. The test was performed by following disc diffusion method using an appropriate volume of test samples. Hi-media antibiotics disc: Chloramphenicol and Amphotericin-B (100 microgram/disc), drizzled with deionized water were used as standard references to detect the antimicrobial activity of synthetic compounds against bacteria and fungi respectively.
Microbial media was used for bacteria nutrient agar (Hi media) with composition (gL-1): Sodium chloride, 5.0; Beef extract 10.0; Peptone 10.0 (pH 7.2). However microbiological media utilized for fungi and yeast is Potato dextrose agar (all ingredients of Hi media) with composition (gL1): Potatoes infusion, 200; Dextrose, 20; Agar, 15; Final pH (at 25°C) 5.6±0.2. Microbiological media was created under the guideline of high-media producers. Using sterile forceps, paper discs of 6 mm in diameter containing a set volume of test sample solution was placed on the surface of inoculated agar plates and simultaneously pushed down to ensure that discs and agar surface were in contact. In the same manner paper discs saturated with controls (DMSO and reference standard) were placed on agar plates and forwarded to incubator at optimum temperature for 24 hours (for antibacterial activity investigation) and 3 to 7 days (for antifungal activity investigation). Ultimately, results were examined carefully. The zone of inhibition around the disc has shown antimicrobial activity. This indicates that microbial growth has been inhibited by effective test samples. The diameter of the zone of inhibition was measured by Vernier Caliper in mm and tabulated in Table (1.0).

5.0 RESULT AND DISCUSSION:

We have synthesized series of (5a-e) molecules from cyclic imide (3a) as shown in (Scheme-1.0) This imide was treated to various benzaldehydes (4a-e), with malononitrile under the catalyst (PbO nanoparticals) to afford pyranopyrrole derivatives (5a-e) as shown in (Scheme-1.1).
We have used PbO nanoparticles as a catalyst which replaces use of hazardous piperidine and costly solvents along with providing high prtactical yield and purity. This method is one of classified ecofriendly method which is conveniently utilized over traditional method to save the time and human efforts.
All these newly developed compounds were characterized by elemental and spectral analysis techniques such as FT-IR, ^{1}H-NMR. These compounds were also investigated for their antimicrobial properties victoriously.

i) Biological activity:

A new series of compounds (5a-e) were evaluated for their antimicrobial activities against two bacterial strains such as gram-positive *"Bacillus subtilis",* gram-negative "*Escherichia coli"* and two fungal strains, *Aspergillus niger* and *Candida albicans* by disc diffusion method in

vitro. 6 mm circular shaped cellular paper discs containing a fixed concentration of test sample solution along with paper discs saturated by controls were placed on inoculated solid agar plates. These plates were kept in the incubator at optimum growth temperature for few days and the final consequences were monitored by observing zone of inhibition Table (1.0).

ii) Results:

All compounds were tested for their antimicrobial properties over bacterial and fungal strains. Compounds 5c, 5d and 5e were observed effective against *Bacillus stibillis* while compound 5b shows mild antibacterial effect against *Escherichia coli*. Similarly, these compounds were investigated for their antifungal properties against two fungal strains. It was observed that compounds 5c and 5e were exhibited antifungal activity against *Aspergillus niger* and *Candida albicans* respectively. However, compounds 5b and 5c were found to be effective against both fungal strains. Table (1.0).

Antibacterial activity of 5a-e series:

Sr. No.	**Sample Code**	**E-Coli**	**B. Subtills**	**A. Niger**	**C. Albicans**
1	5a	-	-	11.2±0.02	-
2	5b	7.14±0.06	-	9..8±0.09	7.14±0.20
3	5c	-	6.84 ± 0.12	14.05±0.14	7.68±0.06
4	5d	-	8.00±0.13	6.45±0.09	-
5	5e	-	7.78 ± 0.18	-	8.67±0.08
Standard	**Chloramphenicol**	20.57± 0.17	19.95±0.28	NA	14.29±0.07
Standard	**Amphotericin-B**	NA	NA	21.84 ±0.17	14.21±0.12

Table 1.0: Antibacterial activity of 5a-e series

6.0 CONCLUSION:

A novel series of pyrano pyrroles (5a-e) was successfully synthesized under milder conditions from cyclic imide (3a), substituted aromatic aldehyde and malononitrile using green approach. We have employed a solvent-free catalyst PbO nanoparticle that provide high yield in short time and also replaces use of harmful reaction conditions. This newly reformed method also avoid use of piperidine as a catalyst.

It is concluded that among these compounds (5a-e) few were exhibited moderate to potent antibacterial activity while some of the compounds recognized as antifungal agents. Although compounds 5c and 5e were observed remarkable effective antifungal agents.

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