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Original Research Article

Synthesis and Characterization of 5, 6 Diphenyl Pyrrole Derivatives and it's Pharmacological Profile

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Abstract

Novel series of pyrrole derivatives were synthesized with an approach to develop more potent and less side effects having antimicrobial anti-inflammatory and anti-tubercular. An efficient synthesis of different novel 2-methyl-7(4-nitrophenyl)-5,6 diphenyl-3,7 dihydro-4H-pyrrolo [2,3-d]pyridine-4-one derivatives by the Paal-knorr Condensation. Benzoin with primary aromatic amines refluxing in ethanol resulted the formation of α-aminoketone intermediates, which were condensed, without isolation, with malononitrile to yield the various 2-amino-4,5-diphenyl-1-substituted-1H-pyrrole-3-carbonitriles (Ia-e). Pyrrole (Ia-e) further reacted with acid such as acetic acid to yield compound (IIa-e). The synthesized compounds were confirmed through spectral characterization using IR (JASCO 4100-FT/IR), Mass (QP 2013 Shimadzu) and 1H NMR. Result indicated that these compounds showed promising antimicrobial activity, anti-tuberculosis activity and anti-inflammatory activity in comparison to standard drugs was used.

Keywords: Pyrrole derivatives, acetic acid, antimicrobial activity, anti-tuberculosis and anti-inflammatory activity.

1. Introduction

Pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacy involved with designing and developing pharmaceutical drugs. These are chemical compounds that may be used in diagnosis, treatment, cure and mitigation of disease or other abnormal conditions. Pyrrole derivatives are display diverse biological activity. In the preparation of pyrrole derivative many disadvantages including harsh reaction condition and poor yields by applying Paal-Knorr reaction. Pyrrole derivatives are considerable attention of synthetic importance and extensively used in drug discovery and pharmacological activity such as anti-microbial[6,7] anti-inflammatory and anti-tubercular[2].

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2. Experimental

Synthesis of substituted 5,6-diphenyl pyrrole derivatives was carried out in two steps.

1] Synthesis of 2-amino-5,6-diphenyl-1-substituted-1H-pyrrole-3carbonitrile [Ia-e].
2] Synthesis of derivatives [IIa-e]

Step 1

1. Synthesis of 2-amino-4, 5-diphenyl-1-substituted-1H-pyrrole-3carbonitrile [Ia-e].

A mixture of benzoin, the appropriate amine aniline and conc. HCl in ethanol was heated under reflux and cooled. Malononitrile was added, followed by a catalytic amount of pyridine portion wise and left to reflux until a solid formed. The solvent was evaporated under reduced pressure and the residue was recrystallized from methanol. Yield: 63-69% MP- 145-148 ºC.

Step 2:

Synthesis of 2-methyl-7-(amine)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIa-e]

The appropriate, 2-amino-4,5-diphenyl-1-substituted-1H-pyrrole-3carbonitrile [Ia] in acetic acid was refluxed for 3 h, cooled, poured onto ice water, filter off dried to give 2-methyl-7-(amine)-5,6 diphenyl-3,7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one [IIa-e] and recrystallized from methanol.

1. Synthesis of 2-methyl-7-(4-nitrophenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one.[IIa]

IR (cm^{-1}): 3356(NH Str), 3030(Aro C-H), 2350(Aryl nitro), 1710(C=O), 1680(C=N), 1450(C-N); NMR (δ, ppm): 7.3-7.9(m, Ar-14H of 4,5 diphenyl ring), 4.6(s,1H CH3 of pyrimidin).

2. Synthesis of 2-methyl-7-(4-bromophenyl)-5,6 diphenyl-3,7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one. [IIb]

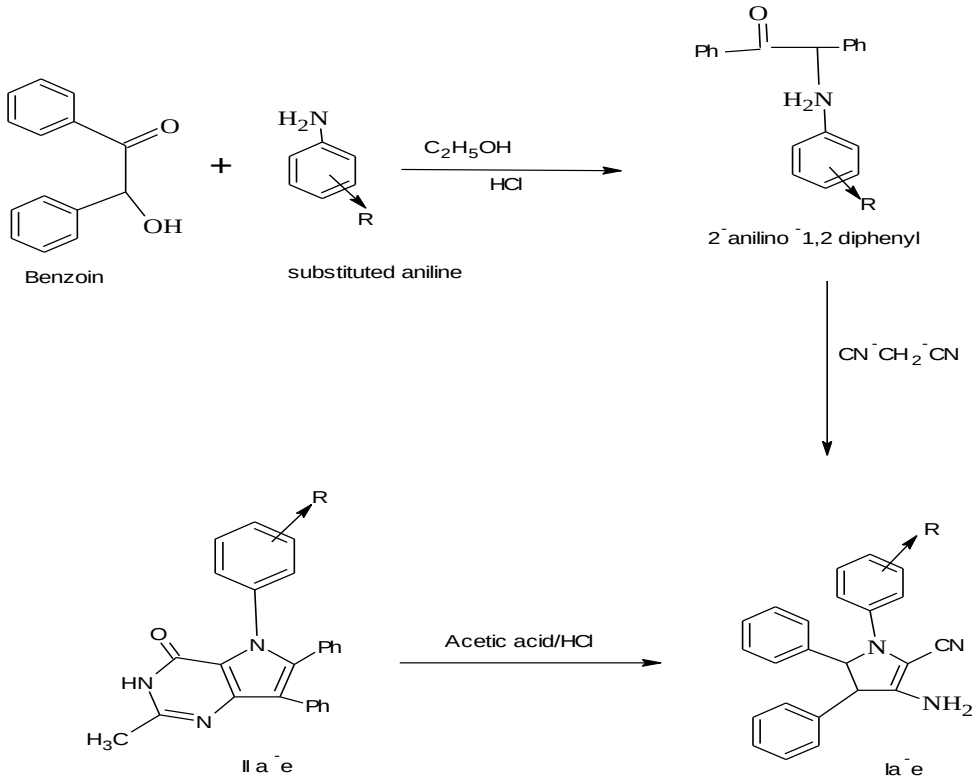
IR (cm^{-1}): 3400(NH Str), 3020(Aro C-H str), 1705(C=O), 1610(C=N), 1460(C-N), 470(Aro-br); NMR (δ, ppm):

3. Synthesis of 2-methyl-7-(4-ethylphenyl)-5, 6, diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIc]

4. Synthesis of 2-methyl-7-(2,4 dinitrophenyl)-5,6 diphenyl-3,7-dihydro-4H-pyrrolo [2,3-d]pyrimidin-4-one. [IId]

5. Synthesis of 2-methyl-7-(N, N dimethylphenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIe]

The appropriate aminopyrrole, Ie in acetic acid was refluxed for 2 h, cooled, poured onto ice water, filter off dried to give IIe and recrystallized from methanol.



Where, R=P-nitro, P-bromo, 4-ethyl, 2,4dinitro, NN dimethyl aniline.

Scheme

Table 1: Properties of Synthesized Compound.

Name	Molecular formula	Rf value	% yield	Melting Point
IIa	C25H18N4O3	0.59	55.61	112-114ºC
IIb	C25H18N3Br1	0.83	67.37	108-110ºC
IIc	C27H23N3O1	0.79	63.27	108-112ºC
IId	C25H17N5O5	0.69	60.37	116-118ºC
IIe	C27H24N3O1	0.70	71.12	112-116ºC

Anti-Microbial activity

The compounds (IIa-e) were evaluated for their invitro antimicrobial activity against E. coli, S. aureus, B. substilis and S. typhi by disk diffusion method was performed using MacConkeys agar and Nutrient agar medium. Each compound was tested at a concentration at 100µg/ml in DMSO. The zone of inhibition was measured after 24h incubation at 37ºC.

Anti-tubercular activity

The compounds (IIa-e) were evaluated for their invitro antitubercular activity against Mycobacterium TB H37RV by nitrate reductase assay method was performed using LJ media. Each compound was tested at a concentration at 100µg/ ml, 150 µg /ml and 200µg/ ml in DMSO. If bottles didn't show any colour change and remain the same then it was confirmed that M.TB H37RV it was sensitive to that test samples.

Anti-inflammatory activity

The compounds (IIa-e) were evaluated for their invitro anti-inflammatory activity by Protein denaturation method. The reaction mixture consisted of 0.4ml egg albumin, 5.6ml phosphate buffer saline (pH6.4) and 4ml varying concentration of compounds. Each compounds was tested at a concentration at 50 µg /ml in DMSO. Mixture were incubated at 37ºC and then heat at 70ºC.after cooling, there absorbance was measured at 660 nm, by using vehicle as a blank and their viscosity was determined by using Ostwald viscometer. Diclofenac sodium 50 µg /ml was used as reference drug and treated similarly for determination of absorbance and viscosity.

%inhibition = [control-test/control] x 100

Results and Discussion

Experimental

I] Synthesis of 2-methyl-7-(4-nitrophenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIa]

II] Synthesis of 2-methyl-7-(4-bromophenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIb]

III] Synthesis of 2-methyl-7-(4-ethylphenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIc]

IV] Synthesis of 2-methyl-7-(2, 4 dinitrophenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IId]

V] Synthesis of 2-methyl-7-(N, N dimethylphenyl)-5, 6 diphenyl-3, 7-dihydro-4H-pyrrolo [2, 3-d] pyrimidin-4-one. [IIe]

The step 1 reaction afforded the yield of product (Ia-e) in the range of 63-69% and time taken by this method is 5-7h.

The step 2 reaction afforded the yield of product (IIa-e) in the range of 55-71% and time taken by this method is 2-5h.

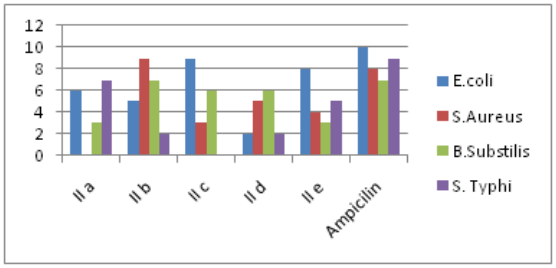
IR, MASS, NMR Spectra studies

The structural elucidation of the synthesized compounds was done by the interpretation of IR, MASS and NMR spectra's. All the compounds show satisfactory IR, MASS and NMR.

Pharmacological Studies

Graph No. 1: The Antimicrobial activities of synthesized compounds (IIa-e)

Graph 1: The Antimicrobial activities of synthesized compounds (IIa-e)



IIc and IIe showed highly active compounds, IIa, IIb showed moderately active compounds while IId showed inactive compounds against E.coli. IIb showed highly active compounds, IId and IIe showed moderately active compounds while IIc inactive compounds against S.Aureus. IIb showed highly active compounds, IIc and IId showed moderately active compounds while IIa and IIe showed inactive compounds against B.Substilis. IIa showed highly active compounds, IIe showed moderately active compounds while IIb, IIc and IId showed inactive compounds against S.typhi.

Where Standard (ampicilin) showed highly active against E.coli, S.aureus, B.Substilis, and S.typhi.

Table 2: Antitubercular Activity.

Comp. Name	Concentration (µg/ml)		
	100	150	200
IIa	NC	C	NC
IIb	C	C	C
IIc	C	C	NC
IId	NC	NC	C
IIe	C	NC	NC
Control	Yellowish pink colour		
Standard (Isoniazide and Rifampicin)	NC		

Where, C-Change, NC-not change.

From the observation of Nitrate Reductase Assay it has been showed that the compounds IIa and IIc are active against M.tuberculosis H37RV as compare to standard drugs Rifampicin and Isoniazid.

Table 3: Effect of pyrrole derivatives on protein denaturation.

Compound No.	Concentration(µg/ml)	% Inhibition	Viscosity(cps)
Control	50	-------	1.38
Standard	50	89.51	0.98
IIa	50	77.18	0.71
IIb	50	83.74	0.82
IIc	50	81.43	0.86
IId	50	71.93	0.91
IIe	50	80.94	0.94

Denaturation of proteins is a well documented cause of inflammation and rheumatoid arthritis. Production of auto antigens in certain arthritic disease may b due to denaturation of proteins invivo. Several anti-inflammatory drugs have shown dose dependent ability to inhibit thermally induced protein denaturation. It has been reported that one of the features of several non-steroidal anti-inflammatory drugs is their ability to stabilize (prevent denaturation) heat treated albumin at the physiological pH.

This anti-denaturation effect was further supported by the change in viscosities. It has been reported that the viscosities of protein solutions increase on denaturation. In the present study, the relatively high viscosity of control dispersion substantiated this fact. Ability of pyrrole derivatives to bring down thermal denaturation of protein is possibly a contributing factor for its anti-inflammatory activity.

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