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International Journal of Current Research
Vol. 9, Issue, 11, pp.60346-60348, November, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4, 5 – DIPHENYL PYRROLE DERIVATIVES

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ARTICLE INFO

Article History:
Received 17th August, 2017
Received in revised form
18th September, 2017
Accepted 22nd October, 2017
Published online 30th November, 2017

Key words:

Paal Knorr Condensation,
Pyrrole Derivatives,
Anti-Microbial.

ABSTRACT

New series of Pyrrole derivatives were synthesized with an approach to reduce the growing anti-microbial resistance and to develop more potent and less side effects having antimicrobial, anti-inflammatory and anticancer activity. An efficient synthesis of different novel 2-amino-4, 5-diphenyl-1-substituted-1H-pyrrole-3-carbonitriles derivatives by the Paal- Knorr Condensation of benzoin with primary aromatic amines in refluxing ethanol resulted in the formation of α-amino ketone intermediates, which were condensed without isolation, with malononitrile to yield the various 2-amino-4,5-diphenylpyrrole-3-carbonitriles(a-d). Pyrroles a-d reacted with different reagents such as acetic anhydride, sodium azide, hydroxyl amine hydrochloride to yield compound (a1-d1). The synthesized compounds were confirmed through spectral characterization using IR, 1H NMR and Mass. The Pyrrole derivatives examined for their in vitro antimicrobialtesting using disc diffusion method. Activity of the synthesized compounds was carried out against Gram-positive, Gram-negative bacteria. Result indicated that these compounds showed promising antimicrobial activity in comparison to amoxicillin (the standard antimicrobial drugs).

Citation: Jaya lakshmi, Soumithran.C.S., Pallav Kumar Kinra, Manoj Joseph Michael, Deepak Passi and Vikram Ahuja, 2017. "Synthesis and antimicrobial activity of 4, 5 – diphenyl pyrrole derivatives", *International Journal of Current Research*, 9, (11), 60346-60348.

INTRODUCTION

Pyrrole and its derivatives are important heterocycles in organic and bio-chemistry and have been found in many pyrrole-containing natural products such as heam, chlorophyll, vitamin BI2 and bile pigments. The pyrrole derivatives are widespread in numerous natural products, and many of them display diverse biological activities. Besides Pyrroleis one common structural unit in many organic materials. In the preparation of Pyrrole derivatives, however, many disadvantages including harsh reaction conditions and poor yields limit the application of classical methods, such as Knorr reaction and Paal-Knorr reaction (Joule, 2000). Although some novel strategies have been developed to synthesize Pyrrolederivatives recently (Joule, 2000). Pyrrole and the simple alkyl Pyrrole are colorless liquids, with relatively weak odors rather like that of aniline, whichalso like anilines, darkens by autooxidation (Joule, 2000). The Pyrrole scaffold is an useful structural pattern for exhibitingchemical functionality in biologically active molecules [1a].it has established broad application in drug development for the treatment as antibacterial, anti-inflammatory, antiviral, antitumor, and antioxidant agent (Bansal, 2005).

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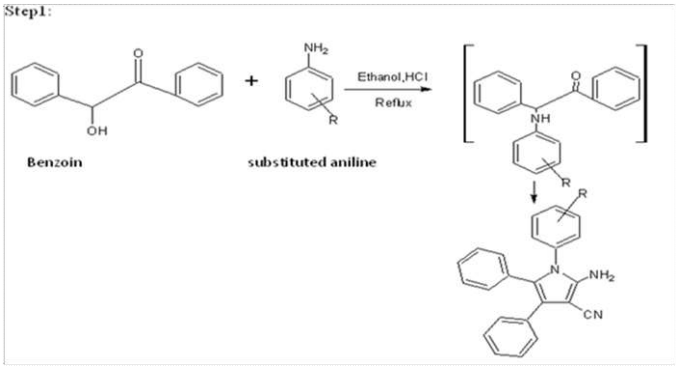
The pyrrole ring system is one of the most important substructures forbiologically active compounds such as indolizidine alkaloids, unsaturated β-lactam and bicyclic lactams. Thesestructural units are found in a wide array of natural products, synthetic materials and bioactive molecules such as vitamin b12, heam and cytochromes therefore, preparation of pyrroles has attracted considerable attention of chemists in recent years.

MATERIAL AND METHODS

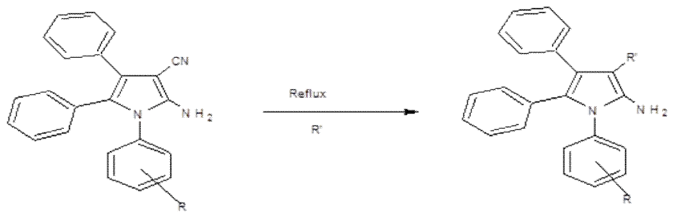
In 2013 all chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required the reagents were purchased from Samarth Lab, Loba Research lab.IR spectra were recorded using KBR disc on JASCO FTIR-410.H^1NMR spectra were performed in DMSO solution and their chemical shifts are reported in δ unit with respect to TMS as internal standard at IIT Powai, Mumbai. Mass spectra were obtained from Oxygen Healthcare Research P. Ltd, Ahmedabad in same year.

EXPERIMENTAL

Synthesis of 2-amino-4, 5-diphenyl-1-substituted-1H-pyrrole-3-carbonitriles (a): A mixture of benzoin (1 g, 0.01 mol), the appropriate amine (4-ethyl aniline, 3- ethyl aniline) (1.10ml, 0.01 mol), and conc.



Step 2:



Derivative of 4, 5- diphenyl pyrrole (a1-a4)

HCl (5–7 drops) in ethanol (20 mL) was heated under reflux for 4h, 8h respectively and cooled. Malononitrile (1ml 0.01 mol) was added, followed by a catalytic amount (0.5 mL) of pyridine portion wise and left to reflux until a solid was formed. The solvent was evaporated and the residue was re crystallized from ethanol to give compounds a-b respectively. Yield: 40%; M.P. 140-144 ^{0}C; IR (KBr) (cm $^{-1}$) 3090.1,(Ar C-H str)3335.6, 3434.0(NH,NH_2) 3278.5(OH) 3040.2(Ali-C-H str);^{1}H NMR (DMSO-d6,300 MHz) δ(ppm):7.408-7.920m, Ar-14H of 1,4,5 phenyl ring4.319s, 1H of OH5.195 s, 1H of NH5.560S, 1H of NH5.239 s,2H of NH2 2.54,4.439,S,3H of CH3, s, 2H of CH2.

Synthesis of 5, 6-diphenyl (4-ethylphenyl)-7H-pyrrolo [2, 3-d] pyrimidin-4(3H)-ones (a1): An appropriate amino pyrrole, **a** (3.35 g, 0.01 mol), in formic acid (20 ml, 85%) was heated under reflux for 3 h, cooled,poured onto ice-water to give compounds in the form of precipitates which werefiltered off, dried, and recrystallized from ethanol.

Synthesis of 3-[2-amino-1-(3-ethylphenyl)-4,5-diphenyl 1H pyrrole) amidoximes (a2): The appropriate cyano pyrrole **b** (3.49 g, 0.01 mol) , hydroxyl amine hydrochloride (0.33 g, 0.01 mol) and anhydrous sodium carbonate (5.3 g, 0.05 mol) in absolute ethanol (40 mL) was refluxed for 4 h, filtered while hot and the residue was washed with hot ethanol. The collected filtrate was cooled, poured onto ice-water to yield precipitates which were filtered, dried and re crystallized from ethanol to give compound.

Synthesis of 2-amino-1-(3-ethylphenyl)-4, 5-diphenyl-3-tetrazolo-1Hpyrroles. (a3): A mixture of the appropriate cyano pyrrole **b** (3.35 g, 0.01 mol), sodium azide (0.65 g, 0.01 mol) and ammonium chloride (1.06 g, 0.02 mol) was refluxed in DMF (30 mL) for 4 h, filtered while hot and the residue was washed with hot DMF. The collected filtrate was concentrated, cooled, poured onto ice-water to yield precipitates which were filtered, dried and recrystallized from methanol to give compound.

Synthesis of 3-[2-amino-1-(4-ethylphenyl)-4,5-diphenyl1 Hpyrrole)amidoximes(a4): The appropriate cyano pyrrole **a** (3.49 g, 0.01 mol) , hydroxyl amine hydrochloride (0.33 g, 0.01 mol) and anhydrous sodium carbonate (5.3 g, 0.05 mol) in absolute ethanol (40 mL) was refluxed for 4 h, filtered while hot and the residue was washed with hot ethanol. The collected filtrate was cooled, poured onto ice-water to obtain precipitates which were filtered, dried and re crystallized from methanol to give compound.

METHOD FOR ANTIMICROBIAL ACTIVITY DETERMINATION

All clinicians are guaranteed to be challenged with at some time in their career the treatment of bacterial infections. Because bacteria are constantly changing, the selection of appropriate antimicrobial therapy is crucial in providing efficacious treatment of infect ions. To choose the very effective therapy for their patients it is of the importance that clinicians know the medicinal chemistry of antimicrobial agents. Antimicrobial resistance t rends are constantly changing and vary from institution to institution, so a complete understanding of the structural relationship differences between antibiotics, even in the same class, is helpful in selecting the most appropriate therapy for an individual patient (Idhayadhulla et al., 2012).

Antimicrobial disc- diffusion method (Mohamed, 2011; ChandrakantKokare, 2010)

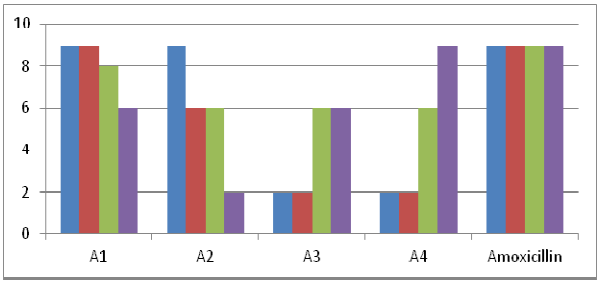
Preparation of culture media for antibacterial sensitivity test
MacConkey agar (50ml) and nutrient agar (100ml) was prepared as per the procedure given for preparation of slants respectively. Then it was sterilized in autoclave at 15lbs pressure (121C) for 15 min. after sterilization the media was cooled up to 45^{0}C, poured 20-25ml in sterile petri plates in aseptic condition and allowed to solidify. Inoculation of suspension of bacteria on culture media Sterile, non-toxic swab were dipped into the standardized inoculum and then the entire agar surface of the plate was streaked with the swab three times, turning the plate at 60 angles between streaking. Then the streaked inoculum was allowed to dry for 5-15min with lid. Sterile Whatman paper disc were dipped separately into the solutions containing synthesized drug (200µg/ml) and standard drug amoxicillin (10mg/ml) in aseptic condition with the help of sterile forceps and placed on the surface of inoculated culture media after which the plates were kept in refrigerator for 30 min. for the diffusion of the compound from the paper disc into the culture media. After 30 min. the plates were incubated at 37^{0}C for 24 hrs. All the synthesized compounds (a-j) were observed for antibacterial activity against gram positive and gram negative species. Observation was recorded in tables by measuring the zone of inhibition in millimeters.

RESULT AND DISCUSSION

Observation table

Table no.1 Antibacterial screening results of synthesized compounds measuring the zone of inhibition in millimeter.

Sr.no.	Comp. No	Name of organisms (zone of inhibition)			
		E.coli	*B.subtilis*	*S. aureus*	*S. typhi*
1.	A1	+++	+++	++	++
2.	A2	+++	++	+	+
3.	A3	+	+	++	++
4.	A4	-	-	++	+++
5.	Amoxicillin	+++	+++	+++	+++



Graph no. 1 Antibacterial screening results of synthesized compound

The antimicrobial activity of synthesized compounds (A1-A4) was carried out by using disc diffusion method and screened against E.coli, Bacilussubtilis. Salmonella Typhae, Styphylococcus Aureus microorganism using standard amoxicillin (10mg/ml) and test compounds 200µg /ml in (DMSO).

Conclusion

An efficient synthesis of different novel 2-amino-4,5-diphenyl-1-substituted-1H-pyrrole-3-carbonitriles derivatives by the Paal- Knorr Condensation of benzoinwith primary aromatic amines in refluxing ethanol resulted in the formation of α-aminoketone intermediates, which were condensed, without isolation, with melononitrile to yield the various 2-amino-4,5-diphenyl pyrrole-3-carbonitriles (a1-a4). Pyrroles (a1-a4) reacted with different reagents such as acetic anhydride, sodium azide, hydroxyl amine hydrochloride to yield compound (1a1-1c1). The yield of product (a1-a4) in the range 37-83% by conventional method and 81-91% by microwave irradiation. The time taken by conventional method was 10 hr where as time by the microwave irradiation method was 16 min. at 210 W. The yield of product (a1-a4). In the range 43-63% by conventional method and 70-80% by microwave irradiation. The time taken by conventional method was 4 hr where as time by the MicrowaveIrradiation method was 10 min. at 210 W.The structural characterization of the synthesized compounds was done by theinterpretation of IR, 1H NMR. All the compounds showed satisfactory IR, 1H NMR. All the synthesized compounds were screened for Antimicrobialactivity.

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