International Journal of Pharmaceutical Drug Design
IJPDD (August, 2024)
ISSN: 2584-2897
Website: https://ijpdd.org/

Research

Synthesis And Characterization of Indazole N-oxide Derivatives as antimicrobial activity

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Article History
Received: 04/07/2024
Revised : 25/07/2024
Accepted : 02/08/2024

DOI:
10.62896/ijpdd.1.9.2

Abstract:
The synthesis and characterization of Indazole N-oxide derivatives were carried out with the aim of evaluating their antimicrobial potential. Indazole N-oxide is a heterocyclic compound known for its diverse biological activities, including antimicrobial properties. In this study, a series of Indazole N-oxide derivatives were synthesized through a multistep reaction process. The synthesized compounds were then characterized using various spectroscopic techniques, including Nuclear Magnetic Resonance (NMR) spectroscopy, Infrared (IR) spectroscopy, and Mass Spectrometry (MS). The antimicrobial activity of the synthesized derivatives was assessed against a panel of bacterial and fungal strains. The results demonstrated that several of the Indazole N-oxide derivatives exhibited significant antimicrobial activity, with certain compounds showing superior efficacy compared to standard antimicrobial agents. The structure-activity relationship (SAR) analysis indicated that the presence of specific functional groups on the Indazole N-oxide core significantly influenced the antimicrobial properties. These findings suggest that Indazole N-oxide derivatives have the potential to be developed as novel antimicrobial agents, offering an alternative approach to combat microbial resistance.

Keywords: *Indazole N-oxide derivatives, antimicrobial activity, Synthesis*

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Introduction:

The species initially named "protozoa" are not firmly connected with one another and just have shallow similitudes (eukaryotic, unicellular, motile, however with exemptions). The expressions "protozoa" and "protist" are generally put in current biosciences down. Notwithstanding, this wording is as yet experienced in medication. This is somewhat a result of the moderate person of clinical characterization and somewhat because of the need of making recognizable pieces of proof of life forms in view of morphology.

Inside the ordered characterization, the four protist supergroups (Amoebozoa, Excavata, SAR, and Archaeplastida) fall under the space Eukarya. Protists are a counterfeit gathering of north of 64,000 different single-celled living things. This implies that it is challenging to characterize protists because of their outrageous contrasts and uniqueness. Protists are a polyphyletic [(of a gathering of creatures) got from more than one normal transformative predecessor or familial gathering and in this way not reasonable for putting in the equivalent taxon][2] an assortment of living beings and they are unicellular, and that implies that they miss the mark on degree of tissue association which is available in additional complicated eukaryotes. Protists fill in a wide assortment of wet environments and a greater part of them are free-living creatures. In these damp conditions, microscopic fish and earthbound structures can likewise be found. Protists are chemoorganotrophic [organisms which oxidize the substance bonds in natural

mixtures as their energy source][3] and are answerable for reusing nitrogen and phosphorus. Parasites likewise are answerable for causing sickness in people and tamed creatures[3-6].

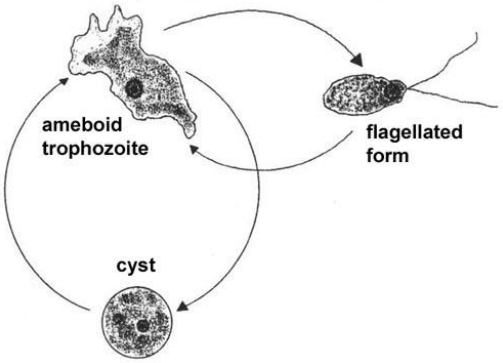
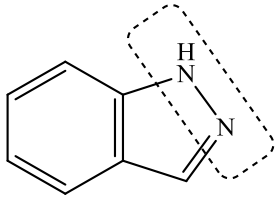


Figure:1 Free-living Protozoa and Human Disease.

Emil Fisher was the researcher who initially characterized indazole as a heterocyclic wherein benzene ring is melded with pyrazole ring. Indazole is artificially benzpyrazole and it tends to be functionalized to high selectivity at various positions. Planarity of the indazole ring, side chain length and fuctionalizations at various positions can bear the cost of a huge number of subsidiaries of indazole, furnishing new particles with natural and restorative properties.[4] 1H-indazole is thermodynamically more steady than 2H-indazole and consequently, is prevalent tautomer.[5] Trifluoro-methyl gathering or fluorine replacement at a fitting place of atom elevates lipophilicity to the atom and results in expanded dissolvability and transport of the atom in lipid framework. In this manner indazole-based compounds with fluorine or trifluoromethyl group(s) at determined position have acquired importance as powerful natural particles, which eventually serve like drugs.[1]



Indazole

In nature, indazoles are found seldom. It is available in a portion of the alkaloids to be specific nigellicine, nigeglanine and nigellidine. Nigellicine was disengaged from the plant Nigella sativa L (dark cumin). Nigeglanine was detached from the concentrates of Nigella glandulifera[6-9]

Subordinates of indazole have been accounted for to have different powerful pharmacological exercises, for example, antitumor, antiplatelet, antiviral, cancer prevention agent, antispermatogenic, mitigating, against tubercular, COX-hindrance, antimicrobial and neuroprotection exercises. In addition, a few subsidiaries of indazole were purportedly found as inhibitors of protein kinase C-B/AKt, strong double inhibitors of IDO1/TDO, and furthermore as bad guys of 5-HT4, 5-HT3 and 5-HT2 receptors.

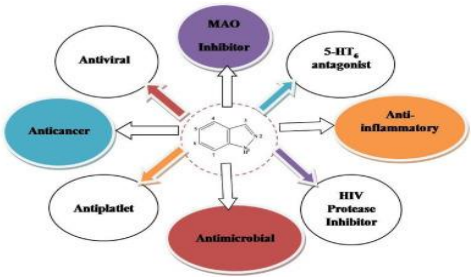


Fig. 2. Indazole heterocyclics with a broad spectrum of pharmacological activities.

Parasitic sicknesses are the premier overall medical condition today, especially in the immature nations. In South America, Chagas' sickness possesses the third spot in number of passings each year, after jungle fever and schistosomiasis.1-4 Trypanosoma cruzi (T. cruzi) the aetiological specialist of this sickness, has a perplexing pattern of life that doesn't allow to get a proficient medication. Just two medications are financially accessible for the treatment of this sickness, Nifurtimox (Nfx, at present stopped) and Benznidazole (Bnz), being these chemotherapeutic specialists still insufficient because of their undesired side effects.[7]

Then again, the leishmaniases are a progression of infections brought about by Leishmania species. There are roughly 1.5 million instances of leishmaniases every year from Focal and South America, West Asia and Europe.5 The medications, which have been most often used to treat the leishmaniases, are the pentavalent antimonials, Pentostam and Glucantime.

In any case, these medications are very harmful and in certain areas opposition can be essentially as high as 40%.7 At present, WHO/TDR is fostering an exploration program with Miltefosine, an exceptionally encouraging leishmanocidal drug, yet new restorative choices ought to be found to build the drug munititions stockpile[10].

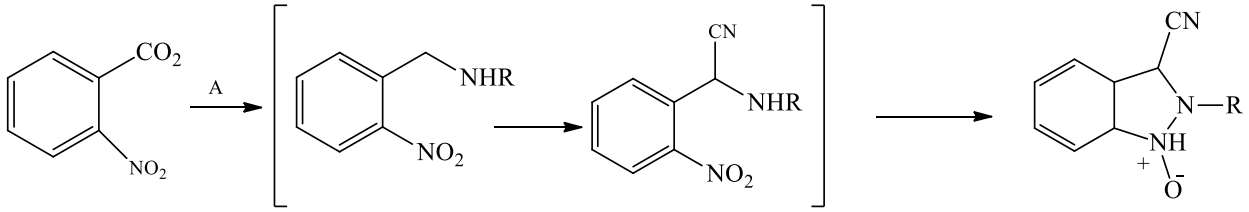
Material Methods and Synthesis

In this, we report the union of indazole N1-and N2-oxide subsidiaries and their antiprotozoa movement (against T. cruzi, Leishmania amazonensis, Leishmania infantum and Leishmania braziliensis). Likewise, we present the electrochemical and ESR concentrates on that permitted to make sense of their natural way of behaving. Also, we concentrate on the adjustment in the take-up of oxygen advanced by indazole.

Conceivable plan

The manufactured course depicted for the planning of this framework includes the arrangement of the Schiff base between 2-nitrobenzaldehyde and the comparing amines. Treatment with sodium cyanide changes over the Schiff base to its aaminonitrile subsidiaries, which thusly go through fundamental cyclization.

Reagents and conditions: (i) H2NR, KCN, CH3CO2H, rt. (ii) Et3N, rt. (iii) NaHCO3, rt.



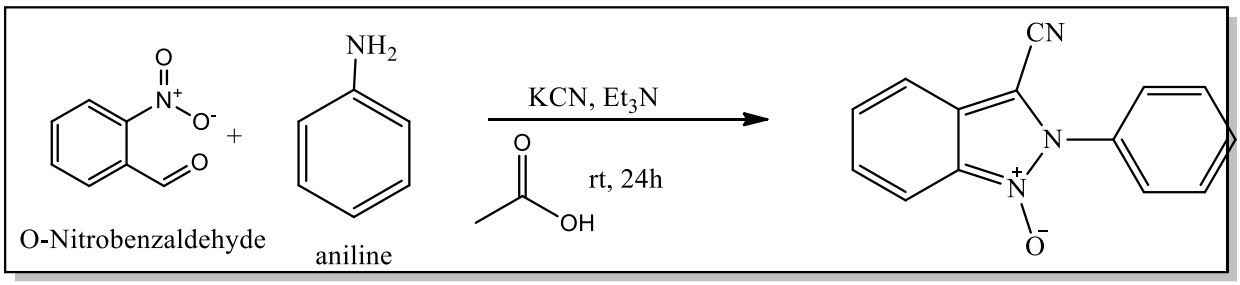
R =
1.ph ,
m-OHPh,
P-CH_3-Ph,
m-NO_2Ph
COOH
ArCHO
haloges

Synthesis of Indazole N^1-oxide derivatives

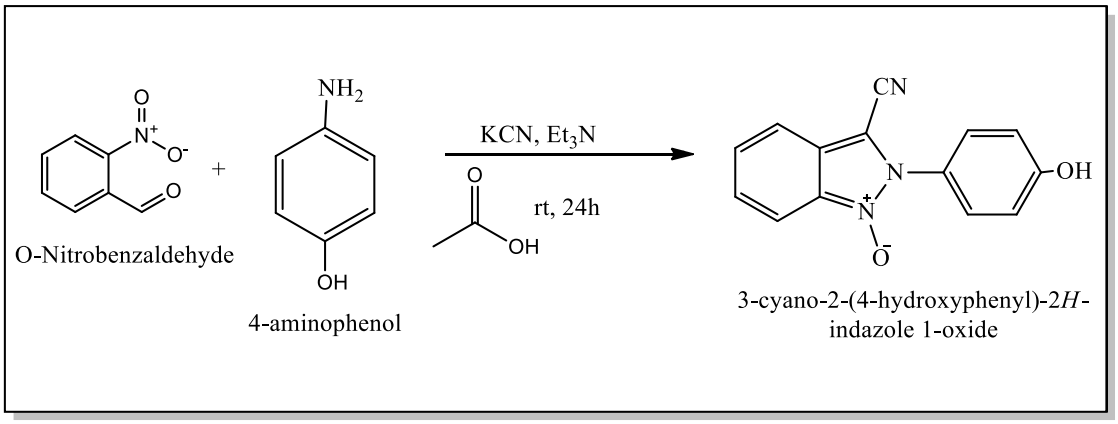
1. **2-(2-Nitrophenyl)-2-phenylaminoacetonitrile**

   Procedure: A combination of o-nitrobenzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the comparing amine (3.3 mmol) in chilly acidic corrosive (30 mL) was mixed at room temperature for 24 h. After expansion of 20 mL water, the accelerated item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the hastened item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was refined by crystallization from the showed dissolvable.

Yeildlow solid 0.51 g (61%). 1 H NMR (400 MHz, DMSOd6) d ppm: 6.44 (1H, d, J = 9.8 Hz), 6.78 (4H, m), 7.19 (2H, t, J = 8.1 Hz), 7.74 (1H, m), 7.90 (2H, m), 8.1 (1H, d, J = 8.1 Hz).



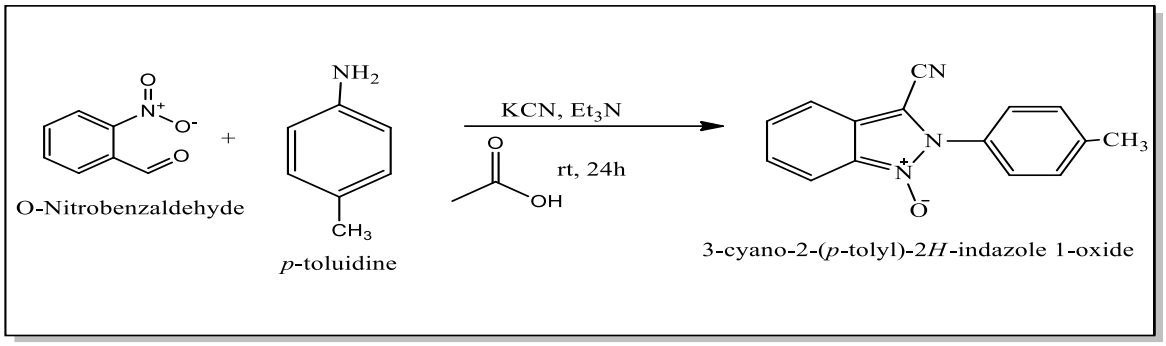
2. **Procedure:** A combination of o-nitrobenzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the 4-aminophenol (3.3 mmol) in cold acidic corrosive (30 mL) was blended at room temperature for 24 h. After expansion of 20 mL water, the accelerated item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the hastened item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was purged by crystallization from the showed dissolvable.
3. Yellow solid 0.29 g (62%) (method A); mp 193.6–194.3 C (ethanol). 1 H NMR (400 MHz, DMSO-d6) d ppm: 7.50 (2H, m), 7.73 (3H, m), 7.85 (4H, m). IR (KBr, cm 1): 2206, 1507, 1474, 1344, 1287, 1237, 1035, 865, 742. Anal. Calcd for C14H9N3O (235.07): C 71.48; H 3.86; N 17.86. Found: C, 71.32; H, 3.95; N, 17.89.



4. A combination of o-nitrobenzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the 4-aminophenol (3.3 mmol) in chilly acidic corrosive (30 mL) was mixed at room temperature for 24 h. After expansion of 20 mL water, the hastened item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was mixed at room temperature for 24-48 h. After expansion of 20 mL water the hastened item was gathered by filtration and air-dried, yielding the comparing indazole N1 - oxide. The item was cleansed by crystallization from the demonstrated dissolvable.

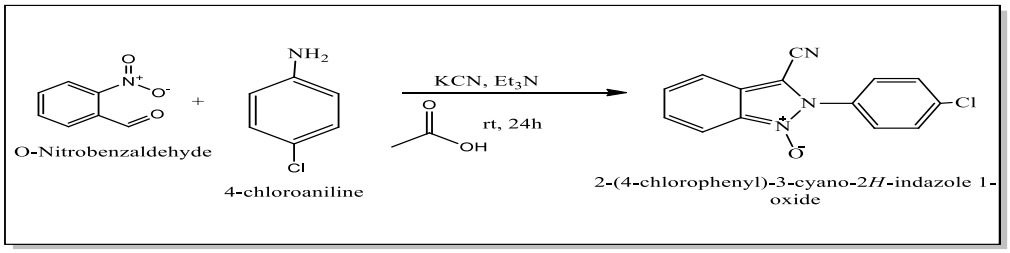
Interpretation:

Yieldlow solid 0.75 g (60%). 1H NMR (400 MHz, DMSOd6) d ppm: 2.19 (3H, s), 6.38 (1H, d, J = 10.0 Hz), 6.59 (1H, d, J = 10.0 Hz), 6.71 (2H, d, J = 8.2 Hz), 7.00 (2H, d, J = 8.2 Hz), 7.72 (1H, m), 7.86 (1H, m), 7.93 (1H, d, J = 7.3 Hz), 8.09 (1H, d, J = 7.8 Hz).



A combination of o-nitrobenzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the 4-Chloroaniline (3.3 mmol) in cold acidic corrosive (30 mL) was mixed at room temperature for 24 h. After expansion of 20 mL water, the encouraged item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the accelerated item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was purged by crystallization from the demonstrated dissolvable.

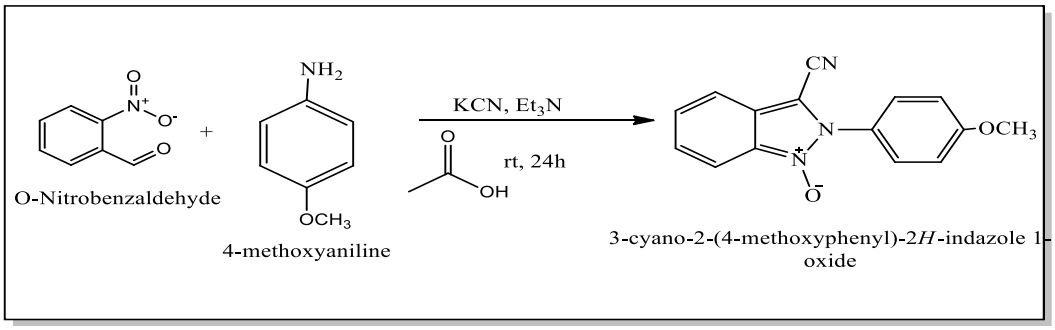
Brown solid 0.20 g (21%). 1 H NMR (400 MHz, DMSO-d6) d ppm: 6.45 (1H, d, J = 9.5 Hz), 6.82 (2H, d, J = 8.6 Hz), 6.99 (1H, d, J = 9.5 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.67 (3H, m), 8.11 (1H, d, J = 8.0 Hz).



5. A combination of o-nitrobenzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the 4-Chloroaniline (3.3 mmol) in icy acidic corrosive (30 mL) was mixed at room temperature for 24 h. After expansion of 20 mL water, the encouraged item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the hastened item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was sanitized by crystallization from the showed dissolvable.

Interpretation: H NMR (400 MHz, DMSO-d6) d ppm: 2.46 (3H, s), 7.52 (4H, m), 7.80 (2H, d, J = 8.2 Hz), 7.84 (1H, d,J = 6.6 Hz), 7.86 (1H, d, J = 8.4 Hz129.59, 130.92, 142.61.

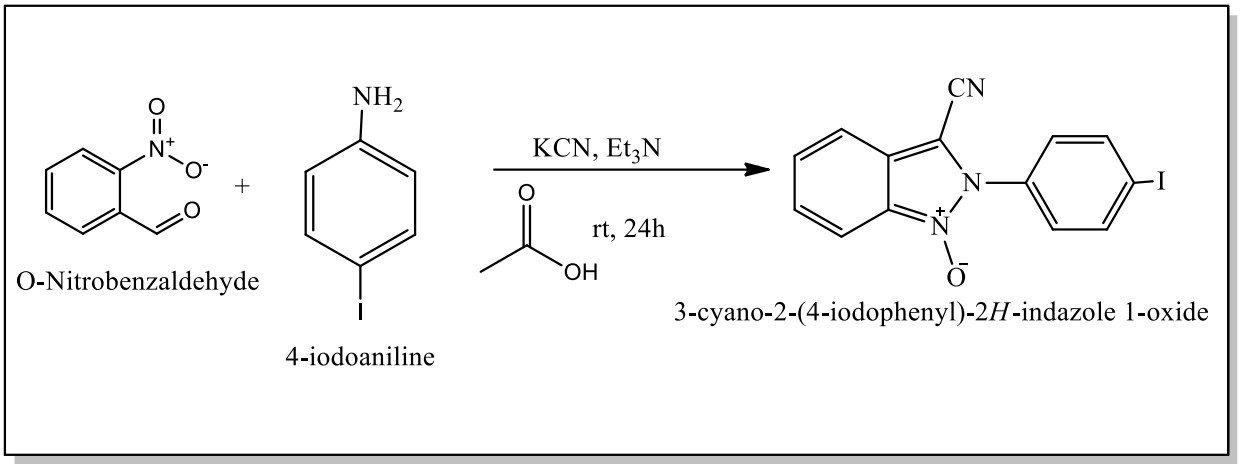
IR (KBr,cm 1): 2201, 1516, 1488, 1438, 1348, 1242, 1035, 809, 745. Anal. Calcd for C15H11N3O (249.09): C, 72.28; H, 4.45; N, 16.86. Found: C, 72.08; H, 4.62; N, 16.80.



7.A combination of o-nitro benzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the 4-Chloroaniline (3.3mmol) in cold acidic corrosive (30 mL) was blended at room temperature for 24 h. After expansion of 20 mL water, the accelerated item was gathered by filtration and air-dried. The strong (a-aminonitrile subordinate) was

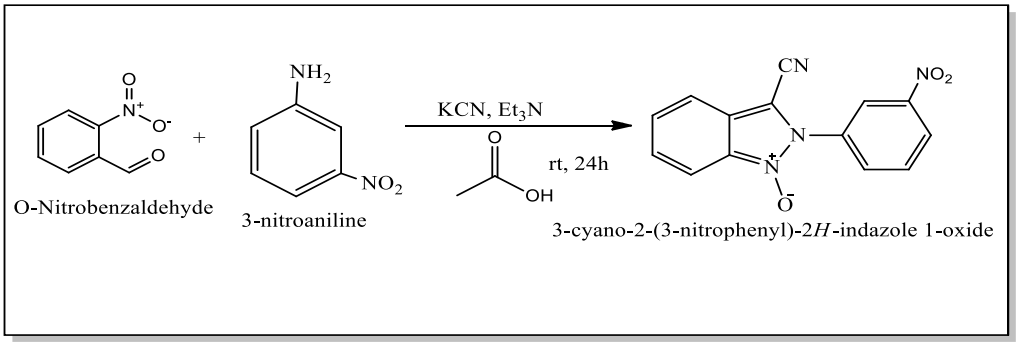
treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the encouraged item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was filtered by crystallization from the showed dissolvable.

H NMR (400 MHz, DMSO-d6) d ppm: 2.46 (3H, s), 7.52 (4H, m), 7.80 (2H, d, J = 8.2 Hz), 7.84 (1H, d, J = 6.6 Hz), 7.86 (1H, d, J = 8.4 Hz). IR (KBr,cm1): 2201, 1516, 1488, 1438, 1348, 1242, 1035, 809,745. Anal. Calcd for C15H11N3O (249.09): C, 72.28; H, 4.45; N, 16.86. Found: C, 72.08; H, 4.62; N, 16.80.



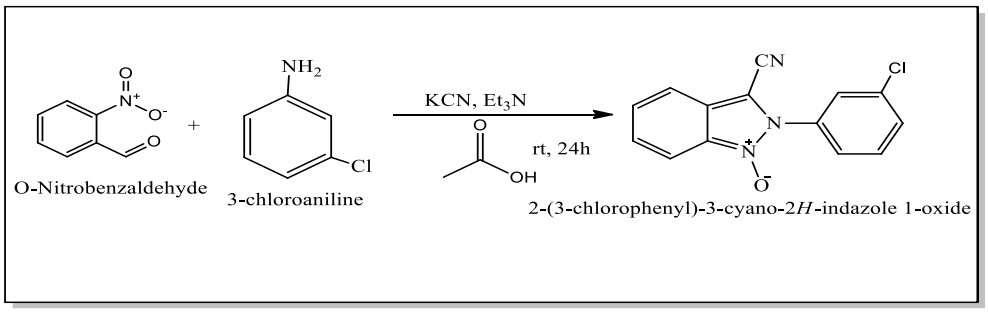
8. A combination of o-nitro benzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the m-nitroaniline (3.3mmol) in frosty acidic corrosive (30 mL) was blended at room temperature for 24 h. After expansion of 20 mL water, the hastened item was gathered by filtration and air-dried. The strong (a-aminonitrile subordinate) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the encouraged item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was cleansed by crystallization from the showed dissolvable.

Orange solid 0.14 g (30%) (method A); mp 207.1–208.0 C (ethanol). 1H NMR (400 MHz, DMSO-d6) d ppm: 7.48 (1H, dd, J = 6.6, 8.5 Hz), 7.52 (1H, dd, J = 6.6, 8.0 Hz), 7.77 (1H, d, J = 8.0 Hz), 7.89 (1H, d,J = 8.5 Hz), 7.91 (1H, dd, J = 7.9, 8.2 Hz), 8.17 (1H, d,J = 7.9 Hz), 8.54 (1H, d, J = 8.2 Hz), 8.68 (1H, s). IR (KBr, cm1):2207,1536, 1503, 1440, 1353, 1276, 1237, 1167, 1114, 742.Anal. Calcd for C14H8N4O3 (280.06): C, 60.00; H, 2.88; N, 19.99. Found: C, 59.96; H, 2.78; N, 19.68



9. A combination of o-nitro benzaldehyde (0.50 g, 3.3 mmol), KCN (0.40 g, 6.6 mmol) and the m-nitroaniline (3.3mmol) in cold acidic corrosive (30 mL) was blended at room temperature for 24 h. After expansion of 20 mL water, the accelerated item was gathered by filtration and air-dried. The strong (a-aminonitrile subsidiary) was treated with Et3N (30 mL) and was blended at room temperature for 24-48 h. After expansion of 20 mL water the hastened item was gathered by filtration and air-dried, yielding the relating indazole N1 - oxide. The item was purged by crystallization from the demonstrated dissolvable.

Brown solid 0.20 g (21%). 1 H NMR (400 MHz, DMSO-d6) d ppm: 6.45 (1H, d, J = 9.5 Hz), 6.82 (2H, d, J = 8.6 Hz), 6.99 (1H, d, J = 9.5 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.67 (3H, m), 8.11 (1H, d, J = 8.0 Hz).



3.5 Antifungal activity

Following fungus were selected for fungicidal activity,

1. ***Candida albicans*:** is an opportunistic pathogenic yeast that is a common member of the human gut flora.

Methods: In-vitro antifungal activity of all the compounds was performed at 1mg/ml or 1000 ppm concentration against organisms used were ***Candida albicans***. The activities of all the compounds was measured using medium composed of potato 200 gm., dextrose 20 gm., 20 gm. agar and water 1 litre i.e. potato dextrose agar (PDA). One-week old cultures were utilized for this study.

The compounds to be tested were suspended (1 milligram/mL or 1000 ppm) in a previously sterilized Potato Dextrose Agar (PDA) medium separately. The media was poured into sterilized petri-plates and the organisms were inoculated after cooling the petri plates. The zone of inhibition was observed after 72 hours and percentage inhibition for bacteria was calculated using the formula given below.

$$Percentage\ of\ inhibition = 100\left(1 - \frac{y}{x}\right)$$

Where X = Area of colony in control plate; Y = Area of colony in test plate.

The fungicidal activities displayed by various compounds are shown in **Table 3 and Table 4**

Symbol	Zone	% percentage	Activity
(+)	Small clearing	<50%	minor
(++)	Medium clearing	51-55%	moderate
(+++)	Large clearing	56-60%	high
(++++)	Very large clearing	>60%	very high

Table 3: Antifungal activity of standard used as positive control

Sample	% Zone of Inhibition @1000 ppm
	Candida albicans
Ketoconazole	**++++**

Table 4: Antifungal activity of test compounds (PMR-1 to PMR-12)

Sample	% Zone of Inhibition @1000 ppm
	Candida albicans
PMR-1	**+**
PMR-2	**++**

PMR-3	+++
PMR-4	+
PMR-5	++
PMR-6	++
PMR-7	++
PMR-8	++
PMR-9	++
PMR-10	++

Conclusion & future perspective

In rundown, we report on the recognizable proof of new indazole and pyrazoline subordinates that have promising antimicrobial exercises, especially against gram positive microorganisms. The most encouraging lead compound 9 is portrayed by a bicyclic pyrazoline framework including an imide moiety. Critical movement against a few medications safe staphylococcus and enterococcus strains was found for this species, arriving at MIC upsides of 4 mg/mL. Physicochemical and pharmacokinetic information was gathered involving Swiss ADME as an instrument showing that the four most dynamic designs (2, 3, 5 and 9) show great medication similarity properties. The union of all mixtures was worked with by constant stream ways to deal with smooth out and assist the age of these azacyclic structures. Our outcomes exhibit the benefit of screening engineered little particles to recognize new anti-infection lead intensifies whose further examinations are in progress in our labs. Extra investigations are important to distinguish the specific system of activity of this class of atoms.

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