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Research Article

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Synthesis and biological activity of some new indole derivatives containing pyrazole moiety

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ABSTRACT

Ethyl Acetoacetate reacted with hydrazine hydrate in the presence of absolute alcohol at 50 ^{0}C to give 3-methyl - 1H-pyrazole-5 (4H)-one (1). Which upon reacted with various substituted Indole aldehydes (1a-b) in presence of aceticacid and sodiumacetate afforded the corresponding pyrazole derivatives (2a-b). 1H- 3 methyl - 4-(4-sustituted indole nucleus)- 2a,4-di hydro pyrazolo [3,4-c] pyrazole derivatives (3a-d), (4a-d) were obtained due to cyclocondensation reaction between 2a-b and hydrazine hydrate , phenyl hydrazine hydrochloride , semicarbazide, thiosemicarbazide . Structures of the synthesized compounds have been elucidated by means of IR , H^1NMR , and Mass spectral data. Finally obtained compounds were screened for biological activities namely antibacterial, antifungal activities.

Key words: Indole, pyrazolo [3,4-c] pyrazole, semicarbazide, hydrazinehydrate, antibacterial , antifungal activity

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INTRODUCTION

Heterocyclic compounds play vital role in biological activities with containing pyrazolone nucleus. Pyrazole and its anologues have been found to exhibit industrial , agricultural and biologically active Applications[1-5]. Indole and its derivatives display a wide range spectrum of biologically activity[6].In addition , it was reported that various 3-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals , pharmaceuticals and perfumes. Accordingly the synthesis of indole derivatives has been a major topic in organic and medicinal chemistry over the past several decades. However the fisher indole synthesis suffers from low yields and numerous side products[7] , for over 100 years the fisher indole synthesis has been one of the most used methods for the preparation of indoles[8]. Nitrogen containing heterocycles are ubiquitous systems in nature and are consequently considered as privileged structures in drug discovery. Literature survey revealed that some pyrazoles plays an essential role in biologically active compounds and also in medicinal chemistry[9-10], Such as anti bacterial[11], anti fungal[12], antiviral[13], antioxidant[14], antitubercular[15], antiandrogenic[16], anti inflammatory[17], anti-diabetic[18], anticancer[19] etc. Indole derivatives have been found to posses wide spectrum activities antiparkinsonian[20-22], anticonvulsant[23-25] it has been reported that substitution of different heterocyclic moieties at 3rd position of indol nucleus these observations prompted the synthesis of nes series of indol derivatives by incorporating of the pyrazolo-pyrazole moieties at 3rd position of indol nucleus. In this article explain antibacterial, antifungal activity of indole derivatives containing pyrazole moiety. In addition pyrazoles have played a crucial role in the development of theory in heterocyclic chemistry and also used extensively as useful synthon in organic synthesis[26-30]. Here it is interesting to note that fused by pyrazoles are reported as well known pharmacophores. The activities of pyrazole derivatives are muscle relaxant,[31-33] hypoglycemic and sex stimulating agents.

EXPERIMENTAL SECTION

Melting points were determined with Melting point apparatus using open capillary tubes and uncorrected . IR spectra (KBr Pellets) were recorded on a Perkin-Elmer spectrum 100 FT-IR spectrometer .The IR spectra of compounds were recorded in the ranges 4000-500 cm^{-1}. The H^1-NMR and C^{13}-NMR spectra were recorded using Brucker DRX-400 MHz spectrometer in DMSO- d_6 using TMS as an internal standard for H^1-NMR. Chemical shifts are reported in δ ppm with respect to TMS. Elemental Analyses were carried out using a Perkin-Elmer 240 C Micro analyzer . The mass spectra were recorded on a jelo SX-102 (FAB) spectrometer.

preparation of 3-methyl-1H-pyrazol-5(4H)-one (1) :
Ethylacetoacetate (0.01) was taken in a conical flask and hydrazinehydate (0.01) was added drop wise to it with stirring in ethanol about 1-hr at room temperature . Here ethanol is used as a solvent. Solid separated out was filtered , washed with ethanol and recrystallized from ethanol to afford white crystalline compound 1, 80 % ; M.Pt. 211-210 ^{0}C ; I.R : 1640(C=O), 1540(C=N), 3381(NH) , 2982 cm^{-1}.

Synthesis of phenacyl bromide :
Bromine (20ml) in acetic acid (100ml) was added drop wise to the solution of Acetophenone (70ml) in acetic acid (120ml) with continuous stirring . After the complete addition of bromine, the reaction mixture further stirred for 30min at room temperature then the reaction mixture was poured into crushed ice , the solid separated was filtered and washed with little absolute alcohol. M.Pt: 60 ^{0}C ,Yield 78 % .

Synthesis of phenacyl aniline :
A solution of phenacyl bromide (0.01) in ethanol (100ml) was added slowly to the corresponding aniline (0.02 mol) dissolved in ethanol (50ml). The reaction mixture was warmed on water bath for 15-20 min till the colour of mixture to dark brown . the contents were cooled to room temperature and solid obtained was collected , washed with rectified spirit . It was recrystallised from ethanol to obtain light yellow colour solid.

Preparation of Aniline hydro bromide :
The Aniline (5ml) merge with water (10ml) suspension was formed . To this suspension adding hydrobromic acid (5ml) , the aniline was converted into the respective hydrobromide and warming the mixture on a water bath. On cooling the aniline hydrobromide separated out was filtered , washed with ether and dried to obtained white needle shape crystalline solid .

Synthesis of 5-substututed -2-phenyl indoles :
An equimolar mixture of the appropriate aniline (0.04mol),the corresponding phenacylaniline (0.02mol) and the catalytic amount of respective anilinehydrobromide(0.05g) was heated in an oil bath at required temperature. Then the reaction mixture was poured into dil HCl(50ml,20%)and extracted with ether . The ether layer was washed with dilute HCl to remove an excess of aniline and dried(Na_2SO_4). The solvent was evaporated and the residue obtained was crystallized from a suitable solvent.

Synthesis of substituted-2-phenylindoles-3-carboxaldehyde: (1a-b)
A solution of substituted-2-phenyl indoles (0.01mol) in minimum amount of DMF(dimethyl formamide) was added to a Vilsmier-Haack complex, prepared from $POCl_3$(1ml) and dimethyl Formamide (3.10ml), maintaining the temperature between 10-20 ^{0}C . The reaction mixture was kept at 45 ^{0}C for 30min and poured into ice water (100ml) containing NaOH (20ml,10%). This was boiled for 1min , then cooled and filtered washed with water dried and crystallized from suitable Solvents.

Synthesis of 3-methyl-4-((substituted-2-phenyl-1H-indol-3-yl)methylene)-1H-pyrzol-5(4H)-ones (2a-b)
3-methyl-1H-pyrazol-5(4H)-one(1) (0.01 mol) and substituted-2-phenylindoles-3carboxaldehyde (1a-b) (0.01mol) were in acetic acid in the presence of anhydrous sodium acetate (0.01mol) for 6-7hours.The reaction mixture was cooled to room temperature and poured into ice cold water. The solid separated out was filtered washed with water and recrystallised from ethanol.

(2a) Yield: 70%, Yellow colour compound , m.p: 270-271 ^{o}C IR (KBR) cm^{-1} : 3392 ($NH_{str.}$,), 3010 (C-$H_{str.}$, Ar-H), 1690 ($C=O_{str.}$),1595($C=C_{str}$),1410-1440(indole nucleus), H^1-NMR($CDCl_3$)δ:7.4-7.7(m,5H, Ar-H), 7.1(s,1H, =CH), 2.34(s,3H, CH_3), 8.7(s,1H,indole), 7.83(d,1H,indol), 7.65 (d,1H,indol). Mass (m/z) :346.11. (2b) IR (KBR) cm^{-1}: 3440cm^{-1}, 2950cm^{-1}, 1655cm^{-1}, 1610cm^{-1} ,1492cm^{-1},1390cm^{-1},1240cm^{-1},749cm^{-1},690cm^{-1}. H^1-NMR :δ 2.3,δ7.3,δ7.98, δ7.55 Mass (m/z): 380.07.

Synthesis of 3-(4-methyl-2-phenyl-2,3,3a,6-tetrahydropyrazolo[3,4-c]pyrazol-3-yl)-5-nitro-2-Phenyl-1H-indol (3a):- Yield - 68% , Yellow colour compound, m.p.-210-212 ^{0}C.
A mixture of compound (2a)(0.01ml) and phenyl hydrazine hydrochloride (0.01ml) were refluxed in acetic acid in presence of anhydrous sodium acetate (0.01ml) for 6-7hours. Reation mixture was cooled to room temperature and poured in ice cold water. The solid separated out was filtered washed with water and recrystallized from ethanol. IR (KBR) 3430 cm^{-1} (N-H_{str}), 3120 cm^{-1} (=CH), 2100 cm^{-1} (CH_3), 1641 cm^{-1} (C=N), 1590 cm^{-1} (N-$H_{bending}$), 1420-1510 cm^{-1} (indole nucleus). H^1-NMR($CDCl_3$): δ1.95(s,3H,CH_3), δ 4.0(d,2H,CH-CH), δ 7.4-8.7 (m,10H, Ar-H),δ 8.89 (s,1H,indol), δ 7.8-8.0 (d,2H,indol), δ 7.0(s,1H,NH), δ11.3 (s,1H,indol N-H). Mass (m/z):436.16, 437.17, 438.17.

Synthesis of 4-methyl-3-(5-nitro-2-phenyl-1H-indol-3-yl)-3,3a-dihydropyrazolo[3,4-c]pyrazol-2(6H)-carboxamide (3b):- Yield – 62 %, Yellow colour compound, m.p.- 240-242 ^{0}C.
A mixture of compound (2a) (0.01mol) and semicarbazide (0.01mol) refluxed in EtOH presence of NaOH /H_2O (0.01mol) for 8hours. Reaction mixture was cooled to room temperature and poured in ice-cold water . The solid separated out was filtered washed with water and recrystallized from ethanol. IR (KBR) cm^{-1}:3400 cm^{-1} (N-H_{str}), 3120 cm^{-1} (=C-H), 2930 cm^{-1} (CH_3),1690 cm^{-1} (C=O),1620 cm^{-1} (C=N), 1580 cm^{-1}(N-$H_{bending}$), 1518-1450 cm^{-1} (indol nucleus) . H^1-NMR($CDCl_3$): δ 4.4-3.2 (d, 2H, CH-CH), δ8.2 (s,2H,NH_2), δ8.9(s,1H,NH), δ7.4-7.5 (m,5H,Ar-H). Mass (m/z) : 403.14 (M) , 404.14(M+1).

Synthesis of 4-methyl-3-(5-nitro-2-phenyl-1H-indol-3-yl)-3,3a-dihydropyrazolo[3,4-c]pyrazol-2(6H)-carbothioamide (3c):- Yield – 60 % , Light yellow colour compound, m.p.-242-244 ^{0}C.
A mixture of compound (2a)(0.01mol) and thiosemicarbazide (0.01mol) in 50ml of ethanol , a solution of NaOH (0.02mol) in 5ml of water was added and refluxed for 7-8hours. The product was poured into crushed ice, which was filtered, dried and recrystallized from DMF. IR(KBR)cm^{-1}: 3420 cm^{-1}(N-H_{str}), 3020 cm^{-1}(=C-H), 2980 cm^{-1}(CH_3), 1650 cm^{-1}(C=N), 1610,1585 cm^{-1}(N-Hbending),1310cm^{-1}(C-N),1267(C=S),1440-1475cm^{-1}(aromaticring). H^1-NMR($CDCl_3$)δ: 1.94(s,3H,CH_3),δ3.9(d,2H,CH-CH), δ 7.56(s,2H,NH_2), δ 7.4-7.5(m,5H,Ar-H), δ 8.2(s,1H,NH), δ 10.8 (s,1H,NH). Mass (m/z) : 419.12.

Synthesis of 3-(4-metyl-2,3,3a,6-tetrahydropyrazolo[3,4-c]pyrazol-3-yl)-5-nitro-2-phenyl-1H-Indole (3d):- Yield – 58% , Light yellow crystals, m.p.-235-237 ^{0}C.
A mixture of compound (2a) (0.01mol) and hydrazine hydrate (0.01mol) and anhydrous sodium acetate (0.02mol) were dissolved in acetic acid refluxed for 8hours. The reaction mixture was poured on crushed-ice and then filtered. The solid was separated out and recrystallized from ethanol. IR (KBR) cm^{-1}: 3250 cm^{-1} (N-H_{str}), 3025 cm^{-1} (=C-H), 2900 cm^{-1}(CH_{3str}), 1690 cm^{-1} (C=N), 1320 cm^{-1}(C-N), 1520-1420 cm^{-1}(indol nucleus). H^1-NMR ($CDCl_3$): δ 3.9-2.1(d,2H,CH-CH), δ8.1-9.2 (s,2H,N-H/$NH_{(pyrazol)}$), 11.5(s,1H,NH), δ 7.3-7.4(m,5H,Ar-H). Mass (m/z): 360.13.

Synthesis of 2-(4-chlorophenyl)-3-(4-methyl-2-phenyl-2,3,3a,6-tetrahydropyrazolo[3,4-c] pyrazol-3-yl)-5-nitro-1H-indol (4a) :- Yield-60 %, Yellow colour compound, M.P: 225-230 ^{0}C.
A mixture of compound (2b) (0.01mol) and phenyl hydrazine hydrochloride (0.01mol) refluxed in EtOH presence of NaOH/H_2O(0.01mol) for 8hrs. Reaction mixture was cooled to room temperature and poured in ice-cold water. The solid separated out was filtered washed with water and recrystallized from ethanol. IR (KBR) cm^{-1}: 3306 cm^{-1} (N-H_{str}), 3055cm^{-1} (C-H_{str} ,Ar-H), 1490cm^{-1} (C=C_{str}), 1376cm^{-1} (C-N_{str} ,NO_2), 1260cm^{-1} (C-N_{str} ,C-NH), 956cm^{-1}(C-Cl). H^1-NMR ($CDCl_3$): δ 6.77-7.23(m,5H,Ar-H), 1.95(s,3H,CH_3), 7.55-7.98(d,4H,Ar-H), 7.0 (s,1H,NH), 3.9-2.1(d,2H,CH-CH),10.98(s,1H,indol NH),8.89(s,1H,C-H), 7.8-8.0(d,2H,C-H). Mass (m/z) : 470.13.

Synthesis of 3-(2-(4-chlorophenyl)-5-nitro-1H-indol-3-yl)-4-methyl-3,3a-dihydropyrazolo [3,4-c]pyrazol-2(6H)-carboxamide(4b):-Yield-61%,Lightyellow colour compound,M.P:240^{0}C.
A mixture of compound (2b) (0.01mol) and semicarbazide (0.01mol) refluxed in EtOH presence of NaOH/H_2O (0.01mol) for 8hrs. Reaction mixture was cooled to room temperature and poured in ice-cold water. The solid separated out was filtered washed with water and recrystallized from ethanol. IR(KBR) cm^{-1}: 3440cm^{-1} (N-H_{str}), 1687cm^{-1} (1^0 amide), 1710cm^{-1}(C=O), 1499cm^{-1}(C=C),1620cm^{-1} (C=N_{str}), 920cm^{-1}(C-Cl). H^1-NMR ($CDCl_3$): δ7.55-7.98(d,4H,Ar-H), 1.94(s,3H,CH_3),6.0(s,2H,NH_2), 7.0(s,1H,NH), 2.5-4.9(d,2H,CH-CH). Mass (m/z) : 437.10

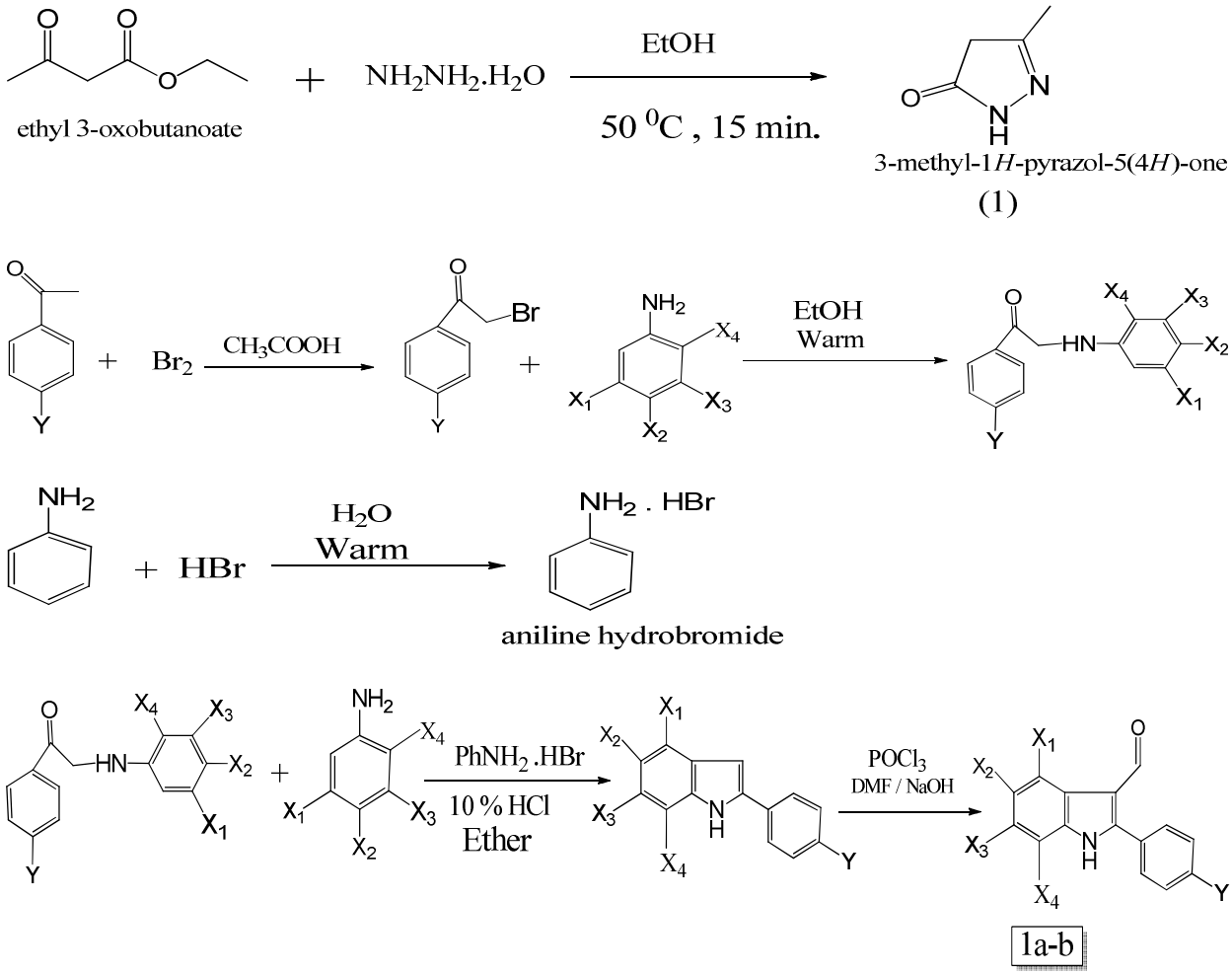
Synthesis of 3-(2-(4-chlorophenyl)-5-nitro-1H-indol-3-yl)-4-methyl-3,3a-dihydropyrazolo [3,4-c]pyrazol-2(6H)-carbothioamide(4c):-Yield-59%,Yellow colour compound,M.P:235^{0}C.
A mixture of compound (2b) (0.01mol) and thiosemicarbazide(0.01mol) refluxed in EtOH presence of NaOH/H_2O (0.01mol) for 7-8hrs.Reaction mixture was cooled to room temperature and poured in ice-cold water. The solid separated out was washed with water and recrystallized from ethanol. IR(KBR) cm^{-1}: 3461cm^{-1} (N-H_{str}), 3060cm^{-1} (C-H_{str}), 1376cm^{-1} (C-N), 1448cm^{-1} (C=C_{str}), 1624cm^{-1} (C=N_{str}), 1280cm^{-1} (C=S_{str}). H^1-NMR ($CDCl_3$): δ7.0

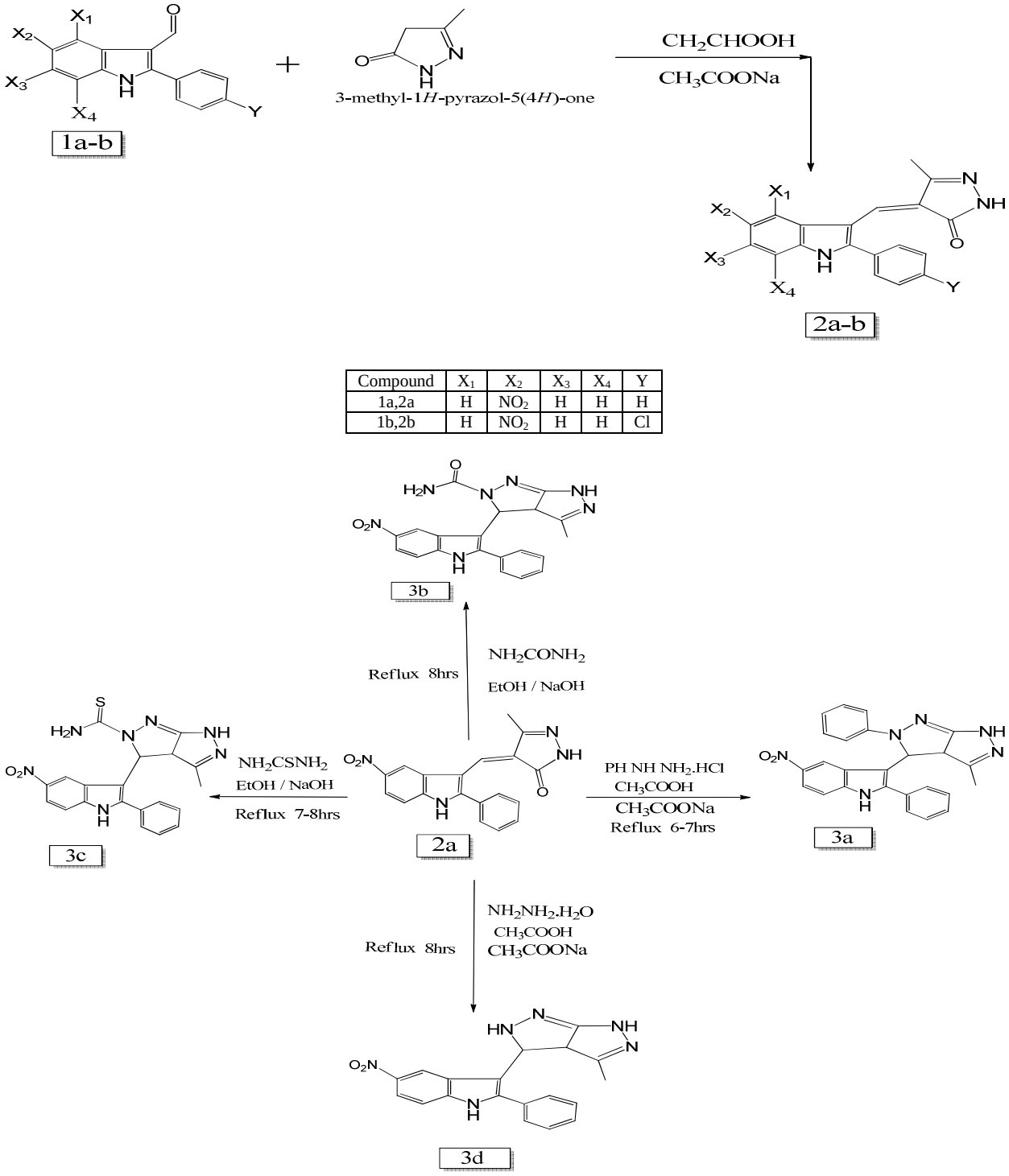
(s,1H,NH), 10.98 (s,1H, indol NH), 8.56(s,2H,amine), 3.9-2.1(d,2H,CH-CH), 7.55-7.98(m,4H,Ar-H), 1.94(s,3H,CH_3), 7.8-8.0 (d,2H,C-H), Mass (m/z) : 453.08.

Synthesis of 2-(4-chlorophenyl)-3-(4-methyl-2,3,3a,6-tetrahydropyrazolo[3,4-c] pyrazol-3-yl) -5-nitro-1H-indol (4d) :- Yield-58 %, Yellow colour compound, M.P: 230-235 ^{0}C.
A mixture of compound (2b) (0.01mol) and hydrazinehydrate (0.01mol) refluxed in EtOH presence of NaOH/H_2O (0.01mol) for 7-8hrs. Reaction mixture was cooled to room temperature and poured in ice-cold water. The solid separated out was washed with water and recrystallized from ethanol. IR(KBR) cm^{-1}: 3347cm^{-1} (N-H_{str}), 3041cm^{-1} (=C-H_{str}), 1667cm^{-1} (C=N $_{str}$), 1448cm^{-1} (C=C_{str}), 1379cm^{-1} (C-N,nitro). H^1-NMR ($CDCl_3$): δ7.0(s,2H,hydrazide), 3.9-2.1(d,2H,CH-CH),7.5-7.9(m,4H,Ar-H), 10.98(s,1H,NH), 8.89(s,1H,indol), 7.8-8.0(d,2H,indol). Mass (m/z): 394.09.

RESULTS AND DISCUSSION

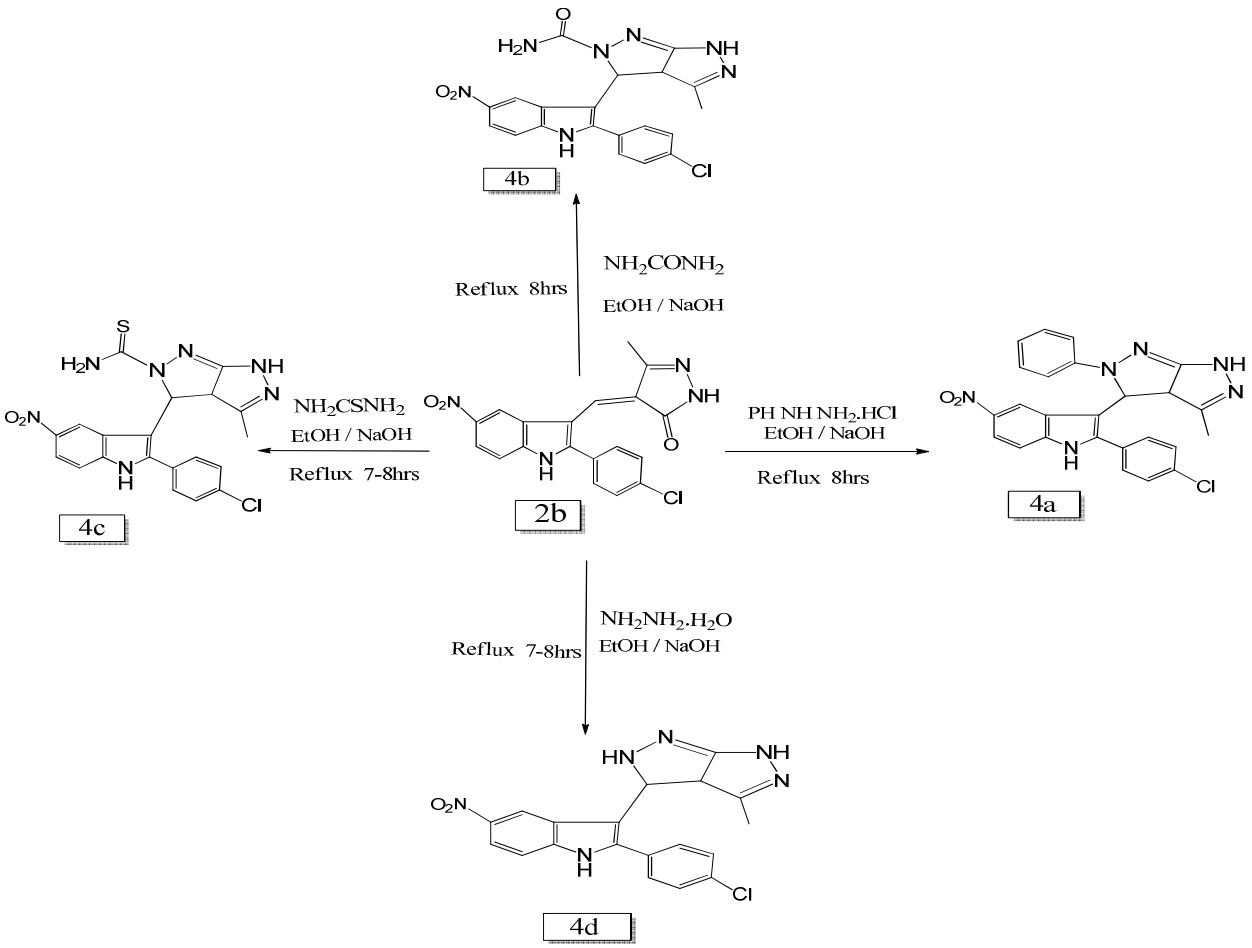
In the present work the synthesis of indole and its derivatives of some pyrazolo pyrazolones 3a-d (scheme-1), 4a-d (scheme-2) from a series of reactions was carried out. To prepare 3-methyl-1H-pyrazol-5(4H)-one (1), hydrazine hydrate was treated with ethyl acetoacetate in absolute alcohol alternatively, (1) was prepared by the reaction of hydrazine hydrate and ethyl acetoaetate in presence of sodium ethoxide solution in EtOH , presence of base reduces the reaction time but yields are not satisfactory. So the base free method is preferred although it takes a longer time. Formation of (1) is confirmed by the disappearance of bands near 3290-3400cm^{-1} for NH_2functionality and presence of band near 2970cm^{-1} for methylene and methyl groups. Analysis of its H^1-NMR spectrum revealed the signals of δ8.2 which confirmed the presence of CONH in pyrazolone nucleus in it transformation of 3-methyl-1H-pyrazol-5(4H)-one (1), to its corresponding indol derivatives (a-d) and (4a-d), was achieved by its treatment with various substituted indole aldehydes (1a-b). Compounds (2a-b) when were subjected to reaction with phenyl hydrazine hydrochloride, semicarbazide, thiosemicarbazide, hydrazinehydrate. A cyclo condensation reaction afforded to the resulting structures of these compounds were determined from their analytical and spectral data.





Compound	X_1	X_2	X_3	X_4	Y
1a,2a	H	NO_2	H	H	H
1b,2b	H	NO_2	H	H	Cl

Scheme-1



Scheme-2

Antimicrobial activity

The *in vitro* biological screening of the newly synthesized compounds under taken against the bacterial species namely *Staphylococcus aureus, Escherichia coli* and *Bacillus subtilis* and Fungi species namely *Aspergillus niger* and *Candida albicans* by cup plate method using nutrient agar medium. The hole of 6mm Diameter were punched carefully using a sterile cork borer and these were filled test solutions (1000mg/ml in DMF) and DMF was used to control . The plates were incubated at 35^0C for 24hrs , 48hrs, 72hrs the results showed that the compounds 3a, 3b, 3c, 3d, 4a, 4b, 4c, 4d show good activity.

In the case of antibacterial and antifungal activity respectively the diameter of zone of inhibition of all tested compounds was measured and the results were compared with that of standard drug Gentamicin for antibacterial activity and Nystatin for antifungal activity (Table-1).

Table-1

Compound	Conc (µg / ml) In DMF	Zone of inhibition in mm				
Diameter of well(bore size)-6mm		Antibacterial activity			Anti fungal activity	
		S. aureus	*E. coli*	*B. subtilis*	*A. niger*	*C.albicans*
3a	1000	14	10	13	17	18
3b	1000	12	15	12	19	17
3c	1000	14	18	17	15	15
3d	1000	12	13	08	12	15
4a	1000	11	09	10	10	11
4b	1000	17	19	20	20	19
4c	1000	19	19	20	18	18
4d	1000	11	08	12	16	10
Gentamicin	1000	21	20	20	--	---
Nystatin	1000	---	----	-----	22	21

Compound3a and 3c exhibit moderate activity against *S. aureus* When compared with slandered drug Gentamicin. Compounds 4b and 4c showed good activity, Compounds 3b and 3c exhibit moderate activity When compared with standard drug Gentamicin against *E.coli.* Compounds 4b and 4c showed good activity. Compounds 3a and 3c exhibit moderate activity against *B.subtilus* When compared to Gentamicin, Compounds 4b and 4c showed good activity. Compounds 3a and 3c exhibit moderate activity When compared with standard drug Nyastatin against *A.niger* Compounds 3b,4b and 4c show good activity. Compounds 3b and 3c exhibit moderate activity When compared with standard drug Nystatin against *C. albicans* Compounds 3a,4b and 4c showed good activity .Rest of the compounds showed lower activity against all the micro organism tested when compared to that of Standard drugs at the same concentrations as that of test compounds.

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