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Synthesis of some new pyrazolo-pyrazole derivatives containing indoles with antimicrobial activity

R. Mallikarjuna Rao, G. Nagaraja Reddy, J. Sreeramulu*

Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India

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ABSTRACT

A series of new pyrazolo[3,4-c]pyrazole derivatives bearing indole moiety (3a-c and 5a-c) have been prepared by making by use of 3-methyl-4-((5-methyl-2-phenyl-3H-indol-3-yl)methylene)-1H-pyrazol-5(4H)-one and 3-methyl-4-((4,7-dichloro-2-phenyl-3H-indol-3-yl)methylene)-1H-pyrazol-5(4H)-one as a key intermediates obtained by the reaction of Substituted 2-phenyl indoles-3-carboxaldehydes and 3-methyl-1H-pyrazol-5(4H)-one. The structure of the newly synthesized compounds have been confirmed on the basis of their I.R, H^1NMR and elemental analysis data and the newly synthesized compounds have been screened for their antibacterial activities.

Key Words: pyrazole, indole, pyrazolone, anti-microbial activity.

INTRODUCTION

Heterocycles bearing nitrogen, oxygen and sulphur atoms in their structure constitute the core structure of the biologically interesting compounds. Heterocycles such as pyrazole and indole rings are associated with wide range of biological properties. Pyrazole and pyrazolone ring systems represent an important class of compounds not only for their theoretical interest but also for their Anti-inflammatory, postmenopausal osteoporosis, angiotension, antagonists, and anti coagulant activities [1-3]. Recently some aryl pyrozole are reported to have non nucleoside HIV-1 reverse transcriptase inhibitor activities[4]. Over the past two decades, pyrazole containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. Literature survey revealed that some pyrazoles have been implemented as antileukemic [5-7] antitumor [8-11] and antiprolifere [12-13] agents, besides their capability to exert remarkable anticancer effects [14-16] through inhibiting different types of enzymes that play important roles in cell division. On the other hand indole nucleus is frequently found in medicinal chemistry and is considered as "privileged scaffolds"[1]. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years [17-19]. Indole derivatives constitute an

important class of therapeutic agents in medicinal chemistry including anticancer [20] antioxidant [21] antirheumatoidal and anti-HIV[22-23] and also play a vital role in the immune system [24-25]. Many indole derivatives are considered as the most potent scavenger of free radicals [26]. Artificial receptors for biologically active molecules have attracted attention from the view point of molecular recognition [27].

In addition, it was reported that various substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals and perfumes [28]. Combination of the pyrazolo-pyrazole moiety with the indole nucleus may enhance these activities. In view of these previous findings, and in continuation of our interest in the fictionalization of Pyrazolyl-indoles, we report here in on the synthesis of some new pyrazolo-pyrazole derivatives containing indoles with antimicrobial activity.

MATERIALS AND METHODS

Thin layer chromatography was used to monitor the completion of the reaction and homogeneity of the synthesised compound. Melting points were determined in open capillary tubes and uncorrected. I.R spectra in KBr pellets were recorded Perkin-Elmer Spectrum 100 FT IR spectrometer (400 MHZ)in DMSO-d_6 /$CDCl_3$ using TMS as an internal standard (chemical shifts are expressed in ppm). The homogeneity of the compounds was checked on silica gel–G coated plates by using chloroform and ethylacetate (5:2) as the eluent and observed in U.V light. All the synthesised compounds gave satisfactory elemental analysis.

Synthesis of phenacyl bromide:
To a solution of Acetophenone (66 ml) acetic acid (75 ml) bromine (20 ml) in acetic acid (75 ml) was added. The content were shaken for 10- 20 min and allowed to stand for 20-30 min. Then the reaction was quenched in crushed ice, the solid separated was filtered and washed with little absolute alcohol. m.p. 60 ^0C[147]. Yield 88 %.

Synthesis of phenacyl aniline:
A solution of phenacyl bromide (0.01mol) in ethanol (l00 ml) was added slowly to the corresponding aniline (0.02 mo1) dissolved in ethanol (50 ml). The reaction mixture was warmed on water bath for 15-25 min till the colour of mixture turned to dark brown. The contents were cooled to room temperature and solid obtained was collected, washed with rectified spirit. It was recrystallized from ethanol.

Synthesis of aniline hydrobromide
The aniline was converted into the respective hydrobromide by adding hydrobromic acid (5g) to a suspension of aniline (5g) in water (5ml) and warming the mixture on a water bath. On cooling the aniline hydrobromide separated out was filtered, washed with ether and dried.

Synthesis of substituted-2-phenyl indoles
An intimate mixture of the appropriate aniline (0.04mo1), the corresponding phenacyl aniline (0.02mo1) and the catalytic amount of respective anilinehydrobromide (0.059) was heated in an oil bath at required temperature. Then, the reaction mixture was poured into dilute hydrochloric acid (50mL, 20%) and extracted with ether. The ether layer was washed with dilute hydrochloric acid to remove the 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 (**1**):
A solution of substituted-2-phenylindoles (0.0lmol) in minimum amount of dimethyl formamide was added to a Vilsmier-Haack complex, prepared from phosphorous oxy chloride (lml,) and di methyl formamide (3.15ml), maintaining the temperature between 10-20 ^{0}C. The reaction mixture was kept at 45 ^{0}C for 30min and poured in to ice water (100ml) containing sodium Hydroxide (20ml, 10%). This was boiled for l min, cooled and filtered washed with water dried and crystallized from suitable solvents.

Preparation of 3-methyl-lH-pyrazol-5(4H)-one (**2**):
Ethyle aceto acetate (0.01mo1) is cyclised with hydrazine hydrate (0.01mo1) by stirring in ethanol about 3-4hrs. Solid separated out was filtered, washed with ethanol and recrystallized from ethanol to afford white crystalline compound 2, 85%; m.p. 211-212 ^{o}C; I.R :1640 (C=O) 1542 (C=N) 3380cm^{-1} (NH), 2980 cm^{-1} (C-H aliph.).

Preparation of (4Z)-3 – methyl - 4 - ((5-methyl-2-phenyl -3H –indol -3-yl) methylene) -1H-pyrazol - 5(4H) – one (3):
A mixture of compound (2) (0.01mo1) and 5-Substituted-2-phenylindoles-3- carboxaldehyde (1) (0.0lmol) were refluxed in acetic acid in presence of anhydrous sodium acetate (0.01mo1) for 8 hrs. The 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 to afford **3**, 63% as yellow crystals. m.p. 233-234 ºC I.R : 3394 ($NH_{Pyrazole}$), 1620 (C=N), 1645(C=O) , 1590(C=C), 2923cm^{-1}(CH alipatic), 1448(indole nucleus),3068 (=CH,Ar). ^{1}H NMR (500 MHz, DMSO-d_6), δ 9.5 (s, 1H, N-$H_{Pyrazole}$), 10.58(s, 1H, N-H_{Indole}), 8.22 (d, 1H, H-4), 8.03 (d, 1H, H-7), 7.35 (d, 1H, H-6), 2.57 (s, 3H, CH_3), 6.8 (s, 1H, =C-H),7.62 (m, 2H, Ar-H), 7.4 (m, 3H, Ar-H), 2.5 (s, 3H, CH_3). Anal. Calcd. for $C_{20}H_{17}N_{3O}$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.10; H, 5.42; N, 13.27.

3,3a-dihydro-4-methyl-3-(5-methyl-2-phenyl-1H-indol-3-yl)pyrazolo[3,4-c] pyrazole-2(6H)-carboxamide (**3a**):
A mixture of compound (3), (0.01mo1) and Semicarbazide (0.01mo1) refluxed in acetic acid in presence of anhydrous sodium acetate (0.01mo1) for 5-6 hrs. Reaction mixture was cooled to room temperature and poured in ice cold water. The solid separated out was firtered washed with water and recrystallized from ethanol. To afford **3**a: 60% as buff crystals, m.p 240-241^{o}C; I.R(KBr): 3433(NH_2), 3365(NH) 1690cm^{-1} (C=O), 1602 cm^{-1} (C=N), 1448(indole nucleus); ^{1}H NMR (500 MHz, DMSO-d_6), δ 10.1 (s, 1H, N-$H_{Pyrazole}$), 10.22 (s, 2H, NH_2), 11.2(s,1H,N-H_{indole}), 8.32 (d, 1H, H-4), 7.80 (d, 1H, H-7), 7.25 (d, 1H, H-6), 2.57 (s, 3H, CH_3), 7.6(m, 2H, Ar-H), 7.4 (m, 3H, Ar-H), 2.5 (s, 3H, CH_3). Anal. Calcd. for C21H18N6 O: C, 68.09; H, 4.90; N, 22.69. Found: C, 68.05; H, 4.80; N, 21.98.

3,3a-dihydro-4-methyl-3-(5-methyl-2-phenyl-1H-indol-3-yl)pyrazolo[3,4-c]pyrazole-2(6H)-carbothioamide (**3b**):
A mixture of compound (3) (0.01mo1) and Thiosemicarbazide (0.01mo1) refluxed in Ethanol in presence of anhydrous sodium acetate (0.01mo1) for 6 hrs. 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. To give **3**b in 58% yield as light yellow Crystals, m.p 244-245^{o}C. I.R (KBr): 3421cm^{-1}(NH_2) 3335(NH) 3.90 (=$CH_{aromatic}$), 2980($CH_{aliphatic}$) 1472 (C=S), 1601(C=N), 1512, 2056 ($NH_{2\ BENDING}$), 1445cm^{-1}(indole nucleus) ^{1}H NMR (500 MHz, DMSO-d_6), δ 10.3 (s, 1H, N-$H_{Pyrazole}$), 9.8 (s, 2H, NH_2), 11.2(s,1H,N-H_{indole}), 8.3 (d, 1H, H-4), 7.79 (d, 1H, H-7), 7.25 (d, 1H, H-6), 2.56 (s, 3H, CH_3), 7.5(m, 2H, Ar-H), 7.4 (m, 3H, Ar-H), 2.3 (s, 3H,

CH_3). Anal. Calcd. forC21H18N6S: C, 65.26; H, 4.69; N, 21. Found: C, 65.22; H, 4.65; N,21.69.

3-(1,3a,4,5-tetrahydro-3-methyl-5-phenylpyrazolo[3,4-c]pyrazol-4-yl)-5-methyl-2-phenyl-1H-indole (**3c**)**:**

A mixture of compound (3) (0.01mo1) and phenylhydrazine (0.01mo1) refluxed in ethanol in presence of anhydrous sodium acetate (0.01mo1) for 10 hrs. 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. To give **3c** in 67% yield as white crystals, mp 204-206 ºC. I.R(KBr): 3437 cm^{-1} ($NH_{pyrazole}$) 1631cm^{-1} (C=N), 3030 (=CH), 2950 ($CH_{aliphatic}$) 1450cm^{-1} (indole nucleus) ^{1}H NMR (500 MHz, DMSO-d_6), δ 9.9 (s, 1H, N-$H_{Pyrazole}$), 11.4(s,1H,N-H_{indole}), 8.22 (d, 1H, H-4), 7.78(d, 1H, H-7), 7.7 (d, 1H, H-6), 2.57 (s, 3H, CH_3), 6.8-7.5(m, 10H, Ar-H), 2.3 (s, 3H, CH_3) Anal. Calcd. for $C_{26}H_{21}N_5$: C, 77.40; H, 5.25; N, 17.36. Found: C, 77.38; H, 5.23; N,17.33.

3-(4,7-dichloro-2-phenyl-3H-indol-3-yl)-4-methylpyrazolo[3,4-c]pyrazole-2(6H)-carboxamide (**5a**):

A mixture of compound (5) (0.5mo1) and Semicarbazide (0.5mo1) refluxed in Acetic acid in presence of anhydrous sodium acetate (0.5mo1) for 6 hrs. Reaction mixture was cooled to room temperature and poured in ice cold water. The solid separated out was firtered washed with water and recrystallized from ethanol. To give **5a** in 55% yield as yellow colour Crystals, m.p 285-286^{o}C, I.R(KBr) : 3467cm^{-1}(NH_2) 330(NH) 3030 (=$CH_{aromatic}$), 2980($CH_{aliphatic}$) 1685(C=O), 1579(C=N), 2056 (NH2 $_{BENDING}$)1440cm^{-1}(indole nuclei) 1411(C-$N_{STRECHING}$) 716(C-Cl); ^{1}H NMR (500 MHz, DMSO-d_6), δ 10.33(s, 2H, NH_2)δ 9.9(s, 1H, N-$H_{Pyrazole}$),11.5(s,1H,N-H_{indole}), 7.84 (d, 2H, H-5,6), 2.57 (s, 3H, CH_3), 7.5-7.2(m 5H, Ar-H), Anal. Calcd. For $C_{20}H_{14}C_{l2}N_6O$ C, 56.48; H,3.32 N,19.76. Found: C, 56.48; H, 3.30; N,19.80.

3- (4,7-dichloro-2-phenyl-3H-indol-3-yl)-4-methylpyrazolo [3,4-c] pyrazole -2(6H)-carbothioamide obtained (**5b**)

A mixture of compound (5) (0.5gr) and Thiosemicarbazide (0.5gr) refluxed in Ethanol in presence of anhydrous sodium acetate (05gr) for 6 hrs. 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 to afford **5b** in 63% yield as gray colour pasty mass compound, m.p 292-293^{o}C. I.R(KBr): 3489(NH_2), 3290(NH) 1620cm^{-1} (C=N), 1484,(C=S);1447 (indole nucleus) ,3030 ($CH_{Aromatic}$); 1390 (C-N); ^{1}H NMR (500 MHz, DMSO-d_6), 10.29(s,2H, NH_2) δ 9.8(s, 1H, N-$H_{Pyrazole}$), 11.4 (s,1H,N-H_{indole}), 7.82 (d, 2H, H-5,6), 7.5(d, 2H, Ar-H), 6.8(m 3H Ar-H), 2.4 (s, 3H, CH_3) Anal. Calcd. for: **C20H14Cl2N6S** C, 54.43; H, 3.20; N, 19.04. Found: C, 54.41; H ,3.16; N, 18.98.

4,7-dichloro-3-(1,5-dihydro-3-methyl-5-phenylpyrazolo[3,4-c]pyrazol-4-yl)-2-phenyl-3H-indole (**5c**)

A mixture of compound (5) (0.01mo1) and Phenyl hydrazine (0.01mo1) refluxed in Acetic acid in presence of anhydrous sodium acetate (0.01mo1) for 6 hrs. 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. To afford **5**c:68% as Red colour crystalline compound , m.p 266-267^{o}C; I.R(KBr): 3437(N-H), 1631cm^{-1} (C=N), 1438 (indole nuclei) ,3095 ($CH_{Aromatic}$);1384 (C-N); ^{1}H NMR (500 MHz, DMSO-d_6), δ 9.8(s, 1H, N-$H_{Pyrazole}$),11.53(s,1H,N-H_{indole}), 7.6 (d, 2H, H-5,6), 2.6 (s, 3H, CH_3), 6.8-7.3(m, 10H, Ar-H), Anal. Calcd. for: $C_{25}H_{17}C_{l2}N_5$ C, 65.51; H, 3.74; N, 15.28. Found: C, 65.49; H, 3.72; N, 15.25.

Antimicrobial activity

The in vitro biological screening of the synthesized compound under taken against the bacterial species namely Staphylococuss aureus, EscherichiaColi And Bacillus Subtilis and Fungi species namely Aspergillusniger and Candida albicans by cup plate method using nutrient agar medium .The hole of 6m,mDiametre were punched carefully using asterile cork borerb and these were filled test solutions(1000mg\ml in DMF) and DMF was used as control .The plates were incubated at 35^0Cfor 24hrs,48hrs and 72hrs the results showed that the compounds 3a, 3b, 3c, 5a, 5b and 5c show good activity.

Table-1

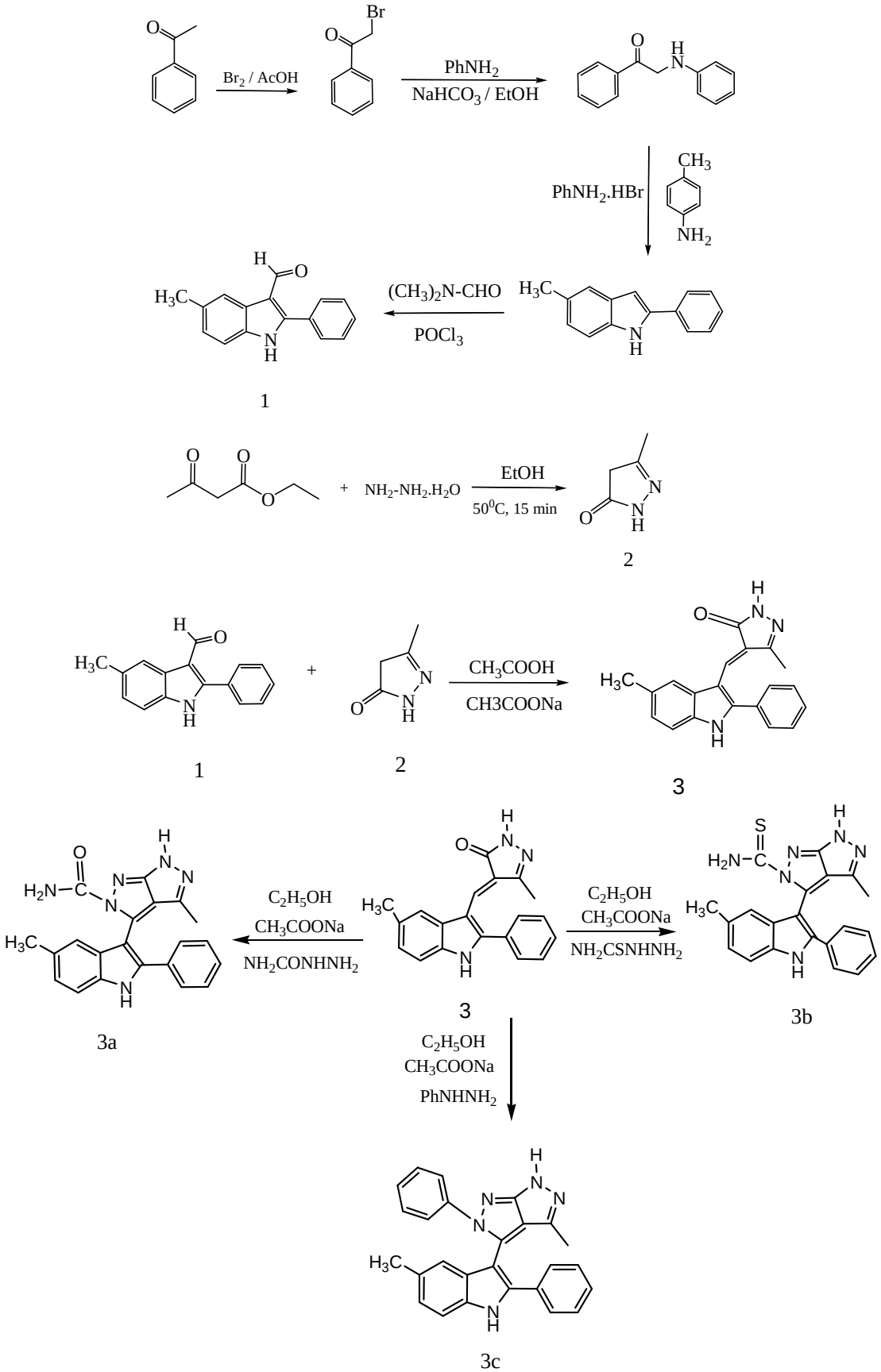
compound	Conc (µg/Ml) In DMF	Zone of inhibition in mm				
Diameter of well (bore size)- 6mm		Antibacterial activity			Anti Fungal Activity	
		S. aureus	*E. coli*	*B. subtilis*	*A. niger*	*C. albicans*
3a	1000	12	15	12	19	17
3b	1000	15	18	17	15	15
3c	1000	15	10	14	17	18
5a	1000	17	19	21	21	19
5b	1000	19	19	20	18	18
5c	1000	12	09	10	10	11
Gentamicin	1000	22	20	21	--	---
Nystatin	1000	---	----	-----	22	21

in the case of antibacterial and anti fungal activity respectively the diameter of zone of inhibition of all tested compounds was mesured and the results were compared with that of standared drug Gentamicin for antibacterial activity and Nistatin for anti fungal activity (Table -1)

Compounds 3b and 3c exibit moderate activity against S.aureus When compared with standard drug Gentamicin. Compounds 5a and 5b showed good activity, Compounds 3a,3b exhibit moderate activity When compared with standard drug Gentamicin against E.Coli. Compounds 5a and 5b showed good activity .Compounds 3b and 3c exhibited moderate activity against B.subtilus When compared to Gentamicin Compounds 5a and 5b showed good activity. Compounds 3b and 3c exhibit moderate activity When compared with standard drug Nystatin against A.niger compounds, 3a, 5a and 5b show good activity. Compounds 3a and 3b exhibited moderate activity. When compared with standard drug Nystatin against C .albicans. Compounds 3c, 5a and 5b showed good activity Rest of the compound showed lower activity against all the micro organism tested when compared to that of Standard drugs at the same concentration as that of test compounds.

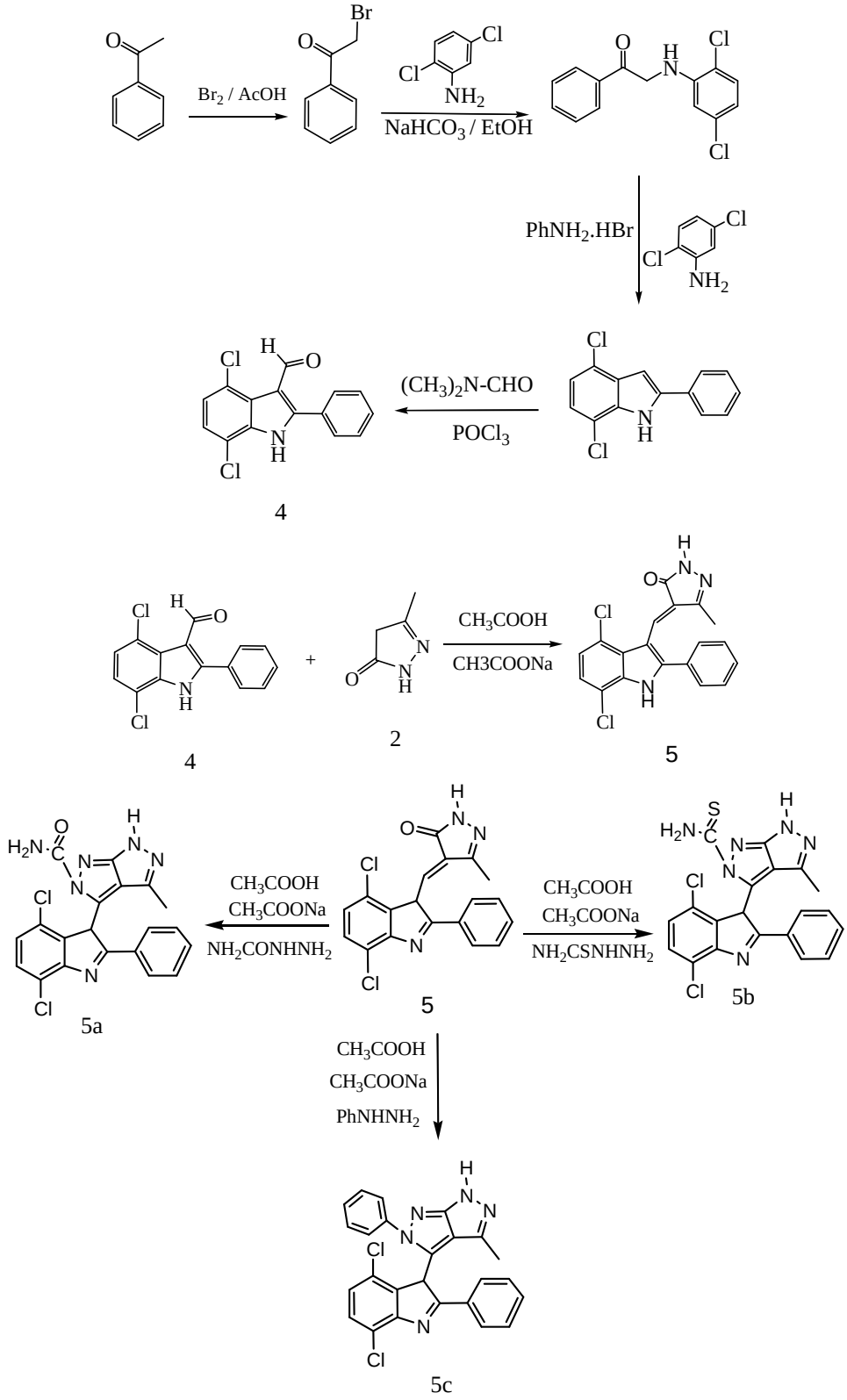
RESULTS AND DISCUSSION

The easily accessible(3-methyl-4-((5-methyl-2-phenyl-3H-indol-3 yl)methylene)-1H-pyrazol-5(4H)-one (3) and 3-methyl-4-((4,7-dichloro-2-phenyl-3H-indol-3-yl)methylene)-1H-pyrazol-5(4H)-one (5), were chosen as starting materials for the synthesis of the new pyrazolo-pyrazole derivatives. Thus, treatment of Pyrazolone (3) with semicarbazide, thiosemicarbazide and phenyl hydrazine in absolute ethanol resulted in the formation of the corresponding 4-methyl-3-(5-methyl-2-phenyl-3H-indol-3-yl)pyrazolo[3,4-c] pyrazole-2(6H)-carboxamide (3a) and 4-methyl-3- (5-methyl-2-phenyl-3H-indol-3-yl) pyrazolo [3,4-c] pyrazole-2(6H)-carbothioamide (3b) 3-(1,5-dihydro-3-methyl-5 –phenyl pyrazolo [3,4-c] pyrazol-4-yl) -5-methyl-2 -phenyl -3H- indole (3c) respectively**. (Scheme-1)**


Br2 / AcOH
PhNH2
NaHCO3 / EtOH
PhNH2.HBr
(CH3)2N-CHO
POCl3
1
2
EtOH
50⁰C, 15 min
CH3COOH
CH3COONa
3
C2H5OH
CH3COONa
NH2CONHNH2
C2H5OH
CH3COONa
NH2CSNHNH2
C2H5OH
CH3COONa
PhNHNH2
3a
3b
3c

Scheme-1

Analogously, when (**5)** was allowed to react with semicarbazide, thiosemicarbazide and phenylhydrazene in refluxing absolute ethanol, gave the expected 3- (4,7-dichloro-2-phenyl -3H-indol-3-yl)-4-methyl pyrazolo [3,4-c] pyrazole-2(6H)-carboxamide (5a) and 3- (4,7- dichloro-2-phenyl-3H-indol-3-yl)-4-methylpyrazolo[3,4-c] pyrazole-2(6H)-carbothioamide (5b) ,and 4,7-dichloro-3-(1,5-dihydro-3-methyl-5-phenylpyrazol [3,4-c]pyrazol-4-yl) -2-phenyl-3H-indole, (5c) respectively (**scheme-2**)



4

4 + 2 → 5

5a 5 5b

5c

Scheme-2

The structures of compounds **3a, 3b** and **3c** were confirmed by their spectral data (IR, ^{1}H NMR) together with elemental analyses. The IR spectrum of compounds **3a, 3b** and **3c** reveals the absence of characteristic absorption bands due to C=O ,C=C functions, and NMR spectrum has shown the absence of peak at 6.9 due to =C-H and showed new characteristic bands at 3433, 3380, 1690 and 1602 cm^{-1} due to NH_2,/NH,C=O and C=N. The ^{1}H NMR spectrum of compound expectedly shows characteristic signals near δ 10.1, δ 11.2 and δ 2.57 assignable to N-$H_{pyrazole}$ N-H_{indol} and CH_3 respectively and at δ 6.8-8.22 assignable to Aromatic protons. Further chemical confirmation for the indole bearing pyrazolo-pyrazole carboxamide, pyrazolo-pyrazole carbothioamide and phenyl-pyrazolo-pyrazole was resulted.

The structures of compounds **5a, 5b** and **5c** were confirmed by their spectral data (IR and ^{1}H NMR) together with elemental analyses. The IR spectrum of compounds **5a, 5b** and **5c** reveals the absence of characteristic absorption bands 1645, 1590cm^{-1} due to –C=O, C=C and NMR spectrum has shown the absence of peak at 6.95 due to =C-H Proton and showed new characteristic bands at 3467, 3389, 3030, 1660 and 1578 cm^{-1}due to NH_2/NH, Ar-H, C=O, and C=N respectively. The ^{1}H NMR spectrum of compound expectedly shows characteristic signals near δ 10.56, δ 9.7, δ 11.5, δ 2.6, δ 6.8-8.11 assignable to NH_2 , N-H $_{(Pyrazole)}$, N-$H_{(indole)}$, CH_3 and Aromatic protons respectively. Chemical confirmation for the Chloroindole pyrazolo-pyrazole corboxamide (5a), chloro indole Prazolo-pyrazole corbothioamide (5b) and chloroindole phenyl-pyrazolo-pyrazole (5c) was resulted.

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