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An Economically and Environmentally Sustainable Synthesis and Characterization of Indole Pyrazole Carbothioamide Derivatives

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Abstract: *Indoles, both naturally occurring and synthetic, exhibit wide-ranging biological activity. Unusual and complex molecular architectures occur among their natural derivatives. As a result, this important ring system continues to attract attention from the international chemical community. The indole scaffold is found in a wide range of bioactive heterocycles and natural products. In the present work we have successfully synthesized and characterized some indole pyrazole carbothioamide derivatives.*

Keywords: Indole, Chalcones, Vilsmeier hack, Pyrazole Thiocarbamide

I. INTRODUCTION

Several Indole derivatives possess important pharmacological activities and therefore they are useful materials in drug design**.** Now a day, cancer therapy interfering with a single biological molecule or pathway has been successfully utilized for the treatment in clinics. When a normal cell turns cancerous, they develop into tumours, which produce various proinflammatory and inflammatory cytokines and chemokines that attract leukocytes to the site of growth.(1-2) The leukocyte, in turn, produces an assorted array of cytokines, cytotoxic mediators including reactive oxygen species, serine and cystine proteases, matrix metalloproteinases (MMPs) and soluble mediators of cell killing such as tumour necrosis factor-alpha (TNFa), interleukins and interferons (IFNs). The leukocyte then to kill the tumour cells to regulate the inflammation. When they are not successful, it results in chronic inflammation and progression of tumours. The growth of tumours thus depends on the balance between pro and anti-inflammatory cytokines.

Cancer is one of the leading diseases responsible for deaths in society. Cancer cells will invade and damage healthy tissue that is near a tumour, causing many complications. According to the American cancer society, there will be 95,270 new cases of colon cancer in the U.S. in 2016. Age is an important risk factor for colon cancer; around 90 percent of those diagnosed are over 50. Overall, the lifetime risk of developing colorectal cancer is about 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women. This risk is slightly lower in women than in men. It is expected to cause about 50, 260 deaths during 2017.

Based upon these observations and in continuation of our ongoing research interest on the development of novel anticancer and anti-inflammatory agents, herein we have synthesized a diverse library of novel asymmetric 1-thiocarbamoyl Indole derivatives

II. LITERATURE SURVEY

Review of biologically active compounds summarizes strategies to synthesize Indolyl pyrazole carbothioamide derivatives and demonstrate that this class of compounds can be targeted for the discovery of new drugs. By taking into consideration this fact, we have synthesized novel asymmetric 1-thiocarbamoyl Indole derivatives.

Indole and several N-substituted Indole derivatives are known to possess various medicinal applications because of their versatile biological activities such as anticancer (3-7) , anti-inflammatory (8-17) , antioxidant (18,19) , antimicrobial (20-23) , anticonvulsant (24) , insecticidal (25), antidepressant (26-29) and antitubercular (30-31) . Various traditional nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, diclofenac, indomethacin, aspirin and flurbiprofen are available in the market but have some limitations in clinical treatment like hemorrhage, ulceration and

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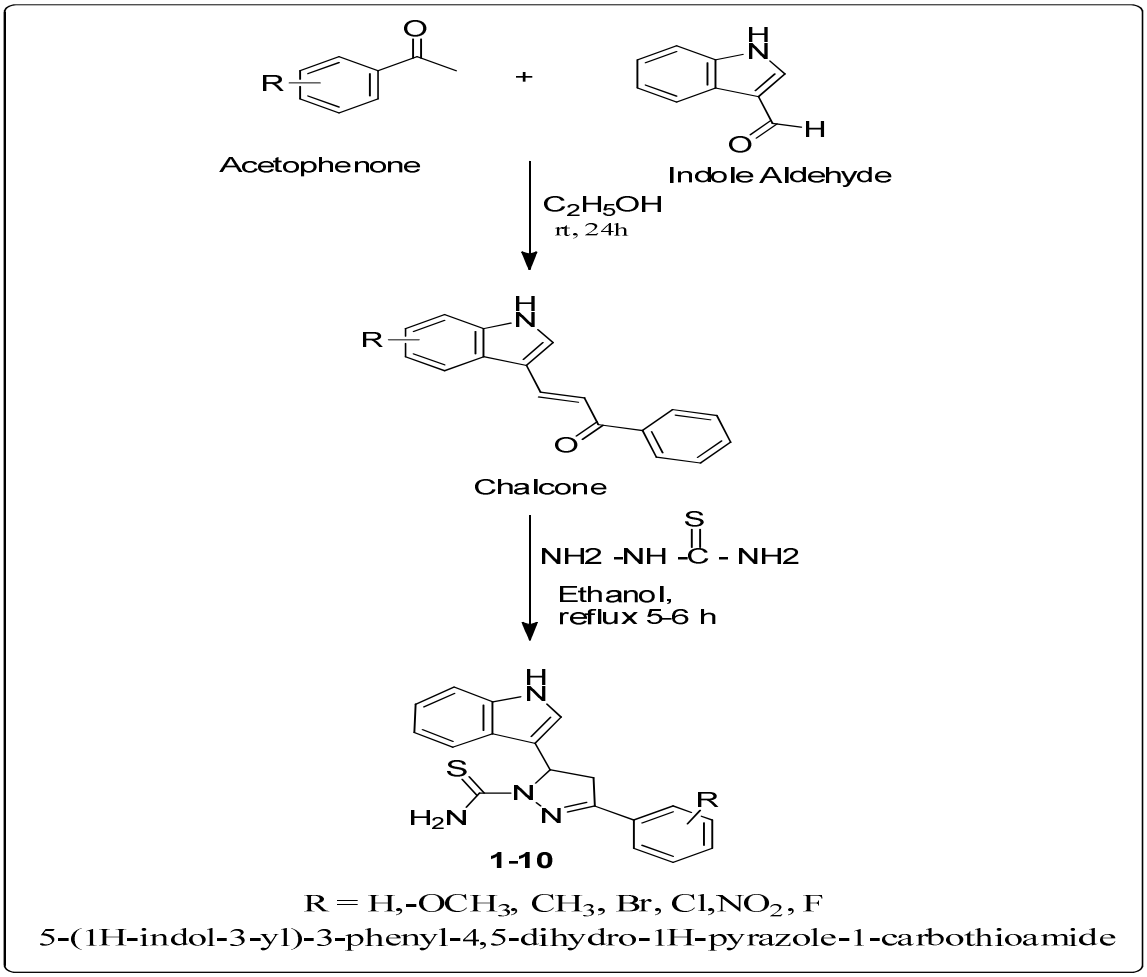
gastrointestinal (GI) addiction tolerance especially for opiates. Nowadays, NSAIDs having side-effects hence the development of alternatives to NSAIDs is going all over the world.

Several methods were reported in the literature. The Vilsmeier Haack reaction (also called the Vilsmeier reaction) is the chemical reaction of a substituted amide with phosphorous oxychloride to produce an aryl aldehyde or ketone. The reaction is named after Anton Vilsmeier and Albrecht Haack. Solid supported synthesis has been used to generate small organic libraries and solution phase preparation of combinatorial libraries have been prepared in DMF.

Medicinal chemistry which is becomes an important field in chemistry because the joining between chemistry and the medicinal life issues by trying to study the common diseases and how should we solve it. According to literature review heterocyclic compounds represents important place in medical chemistry. Heterocycles have been found a key structure in medical chemistry and frequently found in large percent in boimolecules. Such as enzyme, vitamins, natural products and biological active compounds including antifungal, antiinflammatory, antibacterial, antioxidant, anticonvulsant, antiallergic, enzyme inhibitors, herbicidal activity, anti-HIV, antidiabetic, anticancer activity, insecticidal agents.

Numerous catalytic syntheses of N-substituted pyrazole derivatives have been presented over the last decade. However, some often suffer from high coast, long reaction time, low availability, the narrow application scope of substrates, and drastic reaction conditions [32-37].

III. METHODOLOGY



Scheme

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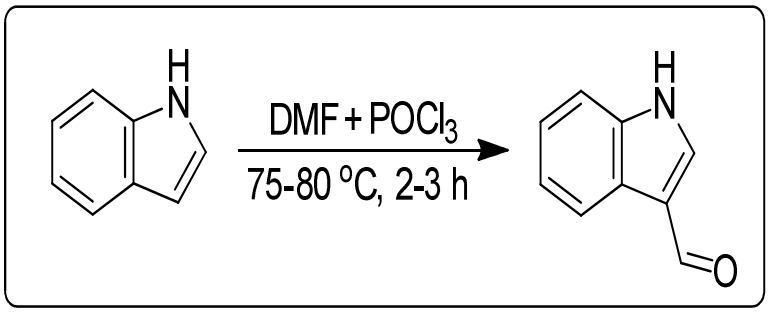
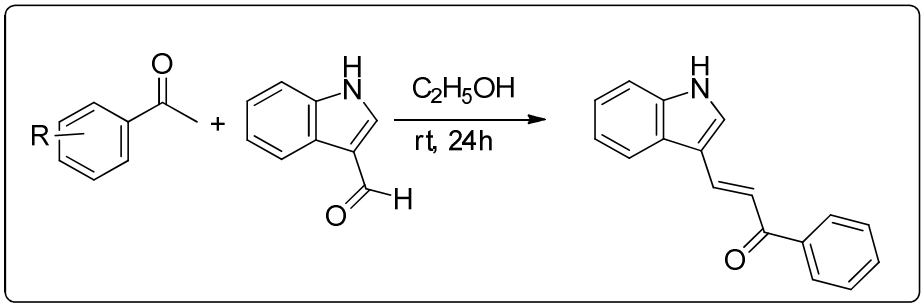
Step 1: Preparation of indole aldehyde

Add indole (1mmol) in Vilsmeier- Haack reagent (DMF + $POCl_3$} 10 ml at 0 °C for 15-20 minutes and then heated for 2-3 hrs. at 75-80 °C. Then reaction mixture was cooled poured to ice cold water the precipitate was filtered, dried & recrystallized from ethanol.



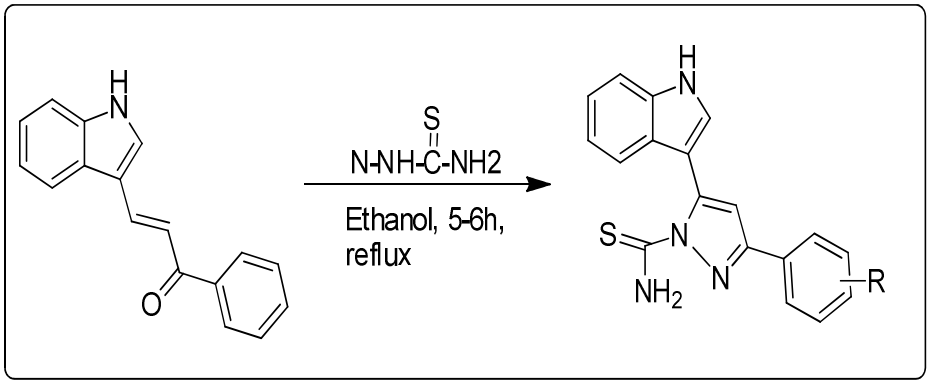
Step 2: Preparation of Chalcone

Equimolar quantity of the appropriate Indol aldehyde (1 mmol, 1 equiv) and substituted acetophenones (1 mmol, 1 equiv) were dissolved in approximately 15-20 ml of ethanol. The mixture was allowed to stir for 10-15 minute at 0 °C. Then 40% aqueous potassium hydroxide solution was added dropwise to the reaction flask *via* an addition funnel. The reaction solution was allowed to stir at room temperature for approximately 24 h. The reaction mass was poured in ice cold water to precipitated out. The crude product was purified by recrystallization from ethanol to obtain pure product



Step 3: Preparation of Indolyl pyrrazole carbothioamide derivatives.

A mixture of chalcone (1 mmol), thiosemicarbazide (1.2 mmol), and KOH (2 mmol) was refluxed in absolute ethanol (20 ml) for 5-6 h. The progress of reaction was monitored by TLC, after completion of reaction the mass was poured into ice cold water and stirred for a few minutes. The precipitate was filtered and crystallized from ethanol to obtain titile product. Remaining substituted 1-thiocarbamoyl pyrazole derivatives were also prepared by same procedure.



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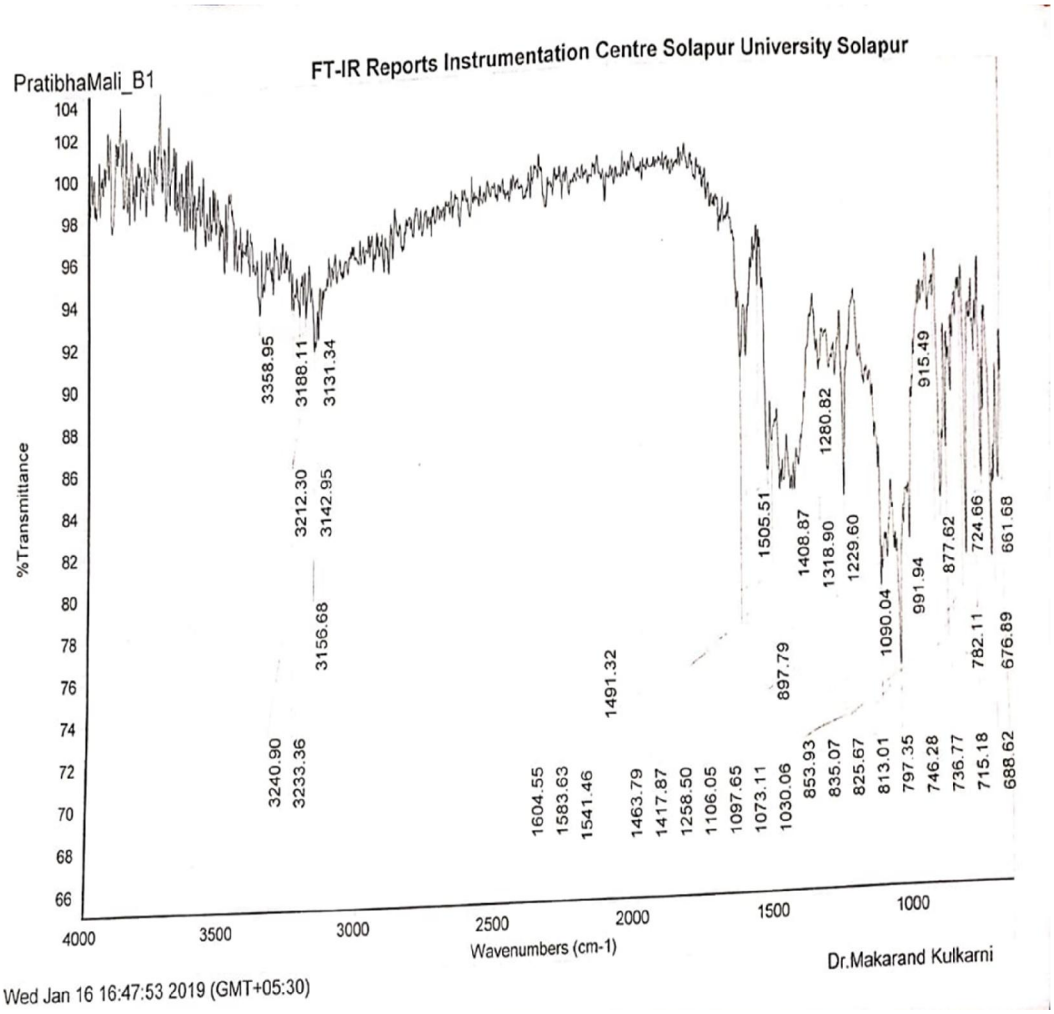
3.1 Spectral Characterization:

R= 4-OMe

IR: - C=N stretching: -1633.97 $cm^{-1,}$ NH_2 stretching: - 3430-3460 $cm^{-1,}$ C-N :- 1350-1000 cm^{-1}C-O:- 1300-1000 cm^{-1}

^{1}H NMR : (400 MHz): 2.24-2.25(d,2H), 2.31-2.32 (t,1H), 2.6(s,1H), 3.8 (s,3H), 5.0(s,2H), 6.9 (m, Ar-H, 4H), 7.4(m, Ar-H, 4H), 9.0(s, 1H), 4.8-5.3 (m, 2H)

IR



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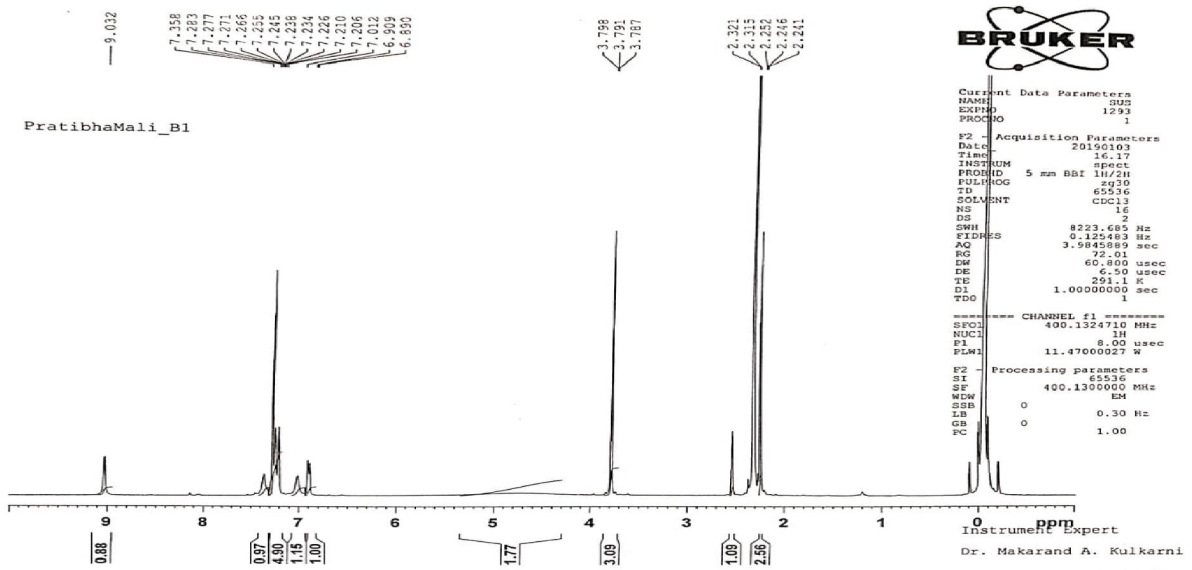
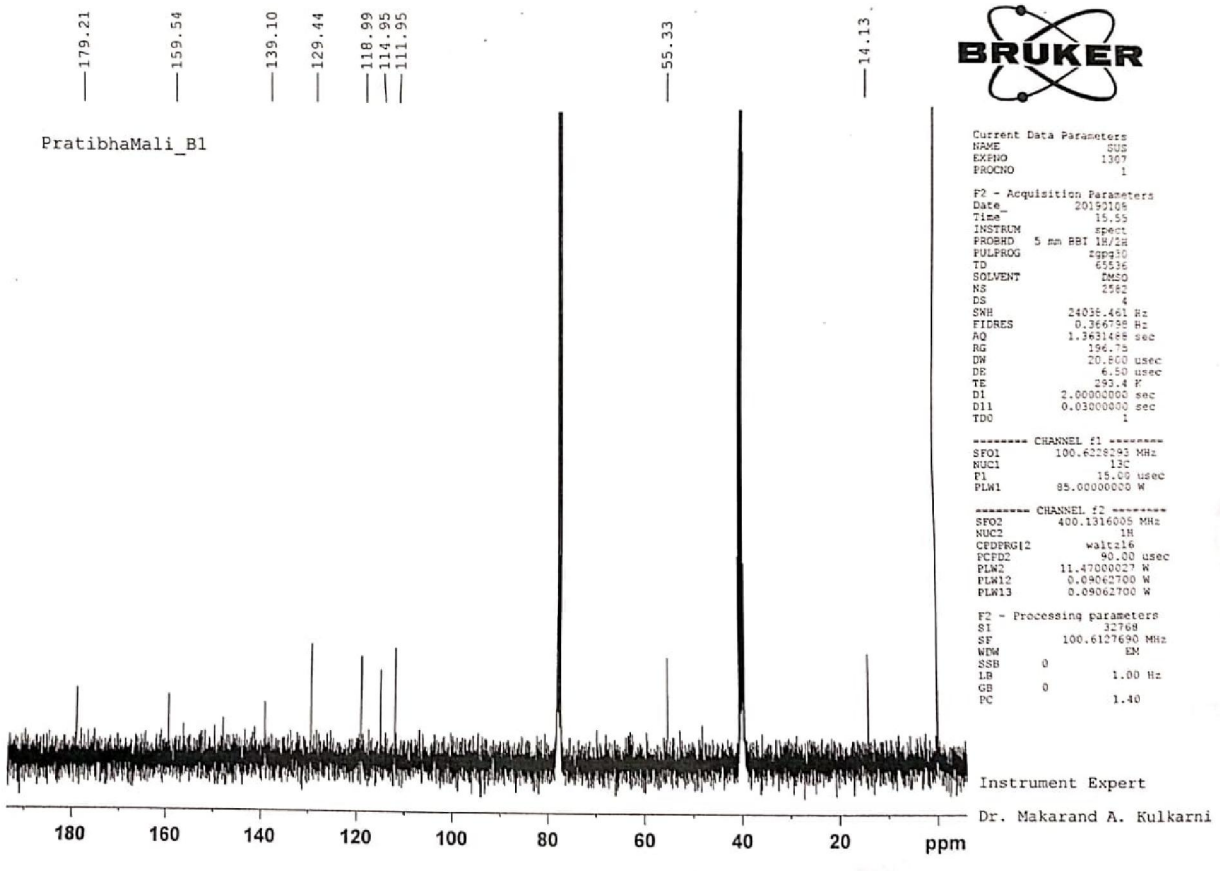
^{1}HNMR



^{13}C NMR



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Derivative 1: 5-(1*H*-indol-3-yl)-3-(3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

Sr. No	Molecular formula	Molecular weight	Melting Pt. (^{0}c)	Yeild in %
1.	$C_{19}H_{18}N_4S_1O$	350	241	96.67
2.	$C_{18}H_{15}N_4S_1NO_2$	365	258	96.57
3.	$C_{18}H_{16}N_4S_1$	320	240	96.97
4.	$C_{18}H_{14}N_5S_1O_2Br$	443	268	96.67
5.	$C_{18}H_{14}N_5S_1C_1Br$	447	264	96.66
6.	$C_{18}H_{14}N_4S_1C_{21}$	388	249	96.36
7.	$C_{18}H_{15}N_4S_1Br$	398	245	96.57
8.	$C_{19}H_{18}N_4S_1$	334	243	96.67
9.	$C_{18}H_{17}N_5S_1$	335	237	96.32
10.	$C_{18}H_{16}N_4S_1O_2$	352	239	96.77

Table 1: Physical data of Indolyl pyrrazole carbothioamide derivatives

IV. Result and Discussion

Based on the facts we have synthesized the series of indole pyrazole carbothiomide derivatives which are synthesized in **Table 1**. The synthesis of indole pyrazole carbothiomide accomplished firstly formation of indol aldehyde by using vilsmeier-haack reagent. Secondly the reaction of indole aldehyde and substituted acetophenones in the presence of ethanolic KOH by Claisen- Schmidt condensation yield chalcone derivatives, which were then react with thiosemicarbazide in the presence of ethanol as a reaction medium as a reaction medium to yield indole pyrazole carbothiomide derivatives. The mechanism of formation of chalcone by reaction between indol aldehyde and substituted acetophenones in presence of base showed aldol condensation type mechanism. The reaction, between thiosemicarbazide and chalcone derivatives are cyclocondensation type gives product indole pyrazole carbothiomide derivatives in impressive yields. The reaction proceeds smoothly without rearranged products. All the products were characterized by IR, ^{1}*H*-NMR, ^{13}C-NMR, mass spectroscopy. ^{1}*H*-NMR spectroscopy is one of the important techniques used for the characterization of these compounds, which show characteristic singlet at δ. 9.0 ppm for – pyrazole proton. These reactions can also take place with other solvents; however, ethanol was chosen as the reaction medium because it is inexpensive and easily accessible.

V. Conclusion

In conclusion, we have shown that the synthesis of Indolyl pyrazole carbothioamide derivatives with ethanol as a solvent not only economical but also environmentally friendly. The significant improvements offered by this procedure are:

1. Simple operation under mild condition.
2. Excellent yield with high purity.
3. Shorter reaction time than reported.
4. Cost efficiency.
5. Environmentally friendliness.
6. Ethanol is used as solvent.
7. Easy work up and isolation.
8. Follows various principles of green chemistry.

The synthesized Indolyl pyrazole carbothioamide derivatives may provide an interesting template for the synthesis of biological active agent.

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