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Synthesis and Characterization of Novel Highly Functionalized Indole Derivatives.

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ABSTRACT

A series of novel (Z)-3-(3-((3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)methyl)-1H-indol-1-yl)-N-arylpropanamide ***7a-j*** *have been synthesized starting from various 3-(3-formyl-1H-indol-1-yl)-N-arylpropanamide* ***5a-j****. Synthesis of various* ***5a-j*** *were prepared by reacting 1H-indole-3-carbaldehyde with 3-chloro-N-arylpropanamide* ***2a-j*** *and K_2CO_3 as a base in acetone under room temperature. Further reaction of* ***5a-j*** *with 5-methyl-2,4-dihydro-3H-pyrazol-3-one* ***6*** *in the presence of alcohol was yielded novel highly functionalized indole* ***7a-j*** *with excellent yields.*

Keywords: *Indole, 3-methyl-5-pyrazolone, Vilsmeier-haack reaction.*

1. INTRODUCTION

The indole moiety is found in various pharmacologically and biologically active compounds [1,2]. Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties [3-6]. For example, five novel indole alkaloids [7,8]. They show cytotoxicity toward murine tumor cell lines and have potent inhibition against several protein kinases [9,10]. Amongst the various N-heterocycles, indole motifs have received significant attention due to their presence in proteins, amino acids, bioactive alkaloids, and drugs [11–15]. In this context, a large number of indole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties, such as antimicrobial, antiviral, anticancer, anti-inflammatory, inhibitors, and antioxidant [16–18]. Generally, indoles substituted at 2nd or 3rd position [19-23], are known to exhibit certain bioactivity. On the other hand, the importance of N1-substituted indole derivatives in marketed drug molecules, natural products, and marine organisms are at great extent [24-27]. Despite the structural novelties and valuable biological activities of N1-substituted indoles [28], it remains challenging due to the inertness of the nitrogen atom (-NH-) towards electrophilic reagents [29].

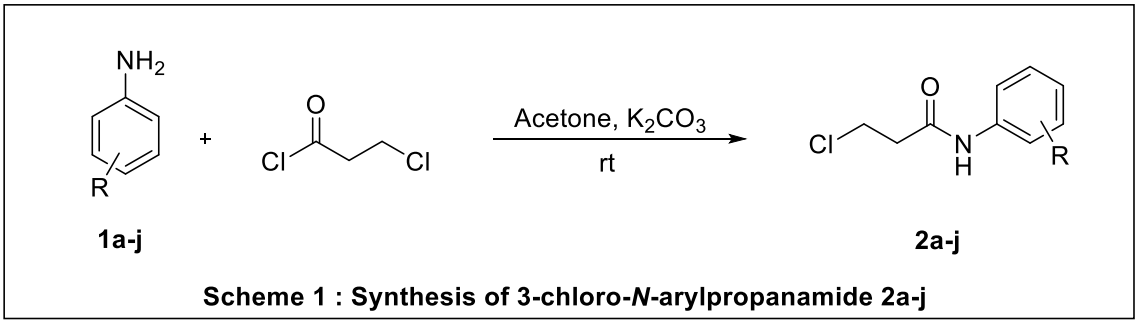
2. EXPERIMENTAL

2.1. General

Melting points were determined on an electrothermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was performed on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with iodine vapor. ^{1}H spectra were recorded on a Bruker AVANCE III (400 MHz) spectrometer in DMSO-d6. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were recorded using a direct inlet probe on Shimadzu GCMS QP2010 Ultra mass spectrometer. All reagents were purchased from Molychem, Loba, and CDH and used without further purification.

2.2. General synthesis of 3-chloro-*N*-arylpropanamide 2a-j

A mixture containing the various substituted aniline **1a-j** (10 mmol), 3-chloropropanoyl chloride (10 mmol), and catalytic amount of K_2CO_3 in acetone was stirred at rt for the approximately 1 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under vaccuo and the solid or oil was crystallized from methanol which afforded pure product **2a-j**.



1a-j **2a-j**

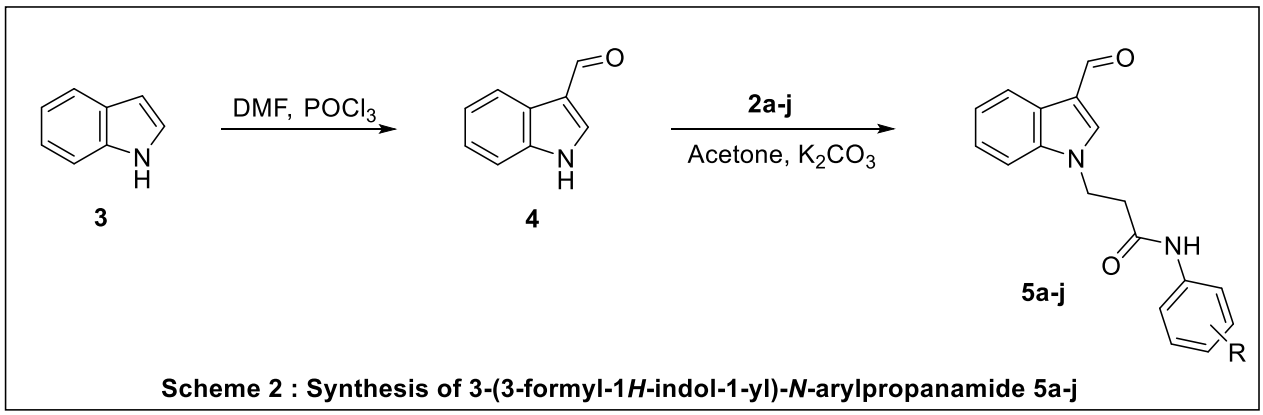
Scheme 1 : Synthesis of 3-chloro-*N*-arylpropanamide 2a-j

2.3. General synthesis of 2-methyl-1*H*-indole-3-carbaldehyde

To a three-necked round flask was introduced anhydrous DMF (12.92 mmol) at 0°C followed by slow addition of phosphorus oxychloride (2.05 mmol). Solution was mixed at 0°C for 40min. A solution of an appropriate 2 methyl indole (1.86 mmol) in 1mL of DMF was slowly added maintaining the temperature below 10°C. The mixture was stirred at this temperature for 40 min and then at 35°C for additional 40 min. Pilled ice was added to the flask and a solution of sodium hydroxide (23.27 mmol dissolved in 2.5mL of water) was introduced dropwise. Solution was vigorously stirred during the addition, then heated to 100°C for 30 min and left to reach room temperature. Mixture was diluted with water (100mL) and product was extracted with ethyl acetate (3×30mL). Organics layers were combined, dried over anhydrous sodium sulphate, filtered and concentrated in vacuo.[31]

2.4. General synthesis of 3-(3-formyl-1H-indol-1-yl)-N-phenylpropanamide 5a-j

In the stirring solution of 1*H*-indole-3-carbaldehyde **4** (10 mmol) in acetone, K_2CO_3 (10 mmol), and the different 3-chloro-*N*-arylpropanamide **2a-j** (11 mmol) were added. The reaction mixture was stirred until reaction completion which was monitored by TLC. The reaction mixture was poured into crushed ice. Thus, the obtained solid was filtered, washed with water, and dried at rt to afford analytically pure product.



3 **4** **5a-j**

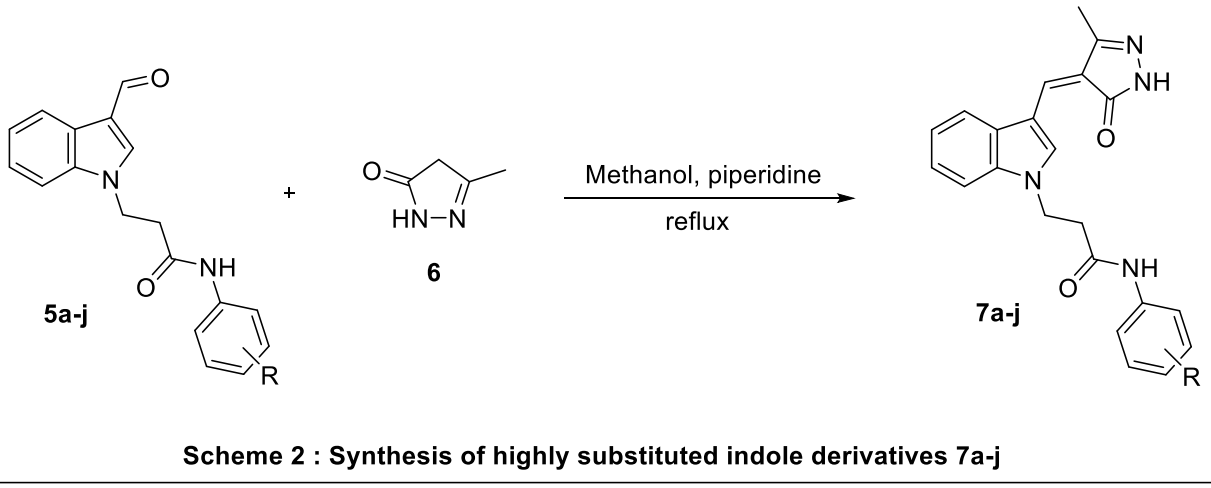
Scheme 2 : Synthesis of 3-(3-formyl-1*H*-indol-1-yl)-*N*-arylpropanamide 5a-j

2.5. General synthesis of (*Z*)-3-(3-((3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)-1H-indol-1-yl)-*N*-arylpropanamide 7a-j

A mixture containing the compound **5a-j** (10 mmol), 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one **6** (10 mmol), and catalytic amount of piperidine in methanol was reflux for the approximately 2 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under vaccuo and the solid was crystallized from methanol which afforded pure product.

2.6. (*Z*)-3-(3-((3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)-1H-indol-1-yl)-*N*-phenylpropanamide 7a

Yellow Crystals; mp 230-232 °C; MS (m/z): 386 (M+); ^{1}H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 10.03 (s, 1H), 9.82 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.79 – 7.72 (m, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.40 – 7.24 (m, 5H), 7.03 (s, 1H), 4.68 (s, 2H), 2.97 (s, 3H), 2.25 (s, 2H).



Scheme 2 : Synthesis of highly substituted indole derivatives 7a-j

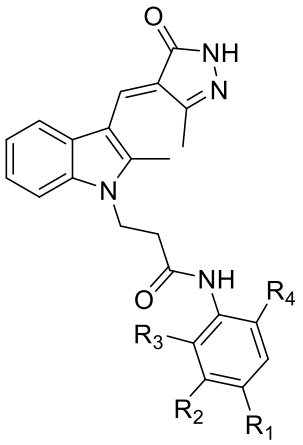
2.7. (*E*)-*N*-(4-methoxyphenyl)-3-(3-((3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)-1*H*-indol-1-yl)propanamide 7b

Yellow Crystals; mp 232-234 °C; MS (m/z): 416 (M+); ^{1}H NMR (400 MHz, DMSO) δ 11.06 (s, 1H), 9.90 (s, 1H), 9.81 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.35 (t, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.67 (t, *J* = 6.4 Hz, 2H), 3.70 (s, 3H), 2.92 (t, *J* = 6.7 Hz, 2H), 2.25 (s, 3H),

2. RESULT AND DISCUSSION

Preparation of the desired compounds are illustrated in **Schemes 1-3**. Initially various substituted 3-chloro-N-arylpropanamide **2a-j** were prepared by reacting substituted anilines with chloroacetyl chloride in acetone with a catalytic amount of potassium carbonate **(Scheme 1)**. The reaction mixtures were stirred at rt for 1-2 h to yield the targeted derivatives **2a-j.** indole-3-carboxaldehyde **4** was easily synthesized from the reported literature [31] threw Vilsmeier-Haack Reaction of indole **3(Scheme-2)**. Further reaction of **4** with **2a-j** in acetone and K_2CO_3 as a base yielded **5a-j**. The resulting compounds **5a-j** was further reacted with 5-methyl-2,4-dihydro-3H-pyrazol-3-one **6** in methanol and catalytical amount of piperidine under reflux condition to affords the desired highly substituted indole derivatives in excellent yield with short reaction time **(Scheme 3)**. The synthesized compounds were confirmed by Mass and ^{1}H NMR spectroscopy.

Table 1. Physicochemical characteristics of the novel indole derivatives 7a-b



Entry	R^1	R^2	R^3	R^4	Molecular weight	Molecular formula	Yield (%)	Melting point (°C)
7a	H	H	H	H	386.46	$C_{23}H_{22}N_4O_2$	87	230-232
7b	OCH_3	H	H	H	416.48	$C_{24}H_{24}N_4O_3$	82	232-234
7c	F	H	H	H	404.45	$C_{23}H_{21}FN_4O_2$	78	210-212
7d	Br	H	H	H	465.35	$C_{23}H_{21}BrN_4O_2$	78	235-236
7e	H	H	CH_3	CH_3	414.51	$C_{25}H_{26}N_4O_2$	82	240-242
7f	H	Cl	H	H	420.90	$C_{23}H_{21}ClN_4O_2$	80	232-234
7g	H	F	H	H	404.45	$C_{23}H_{21}FN_4O_2$	75	212-213
7h	H	F	F	H	422.44	$C_{23}H_{20}F_2N_4O_2$	72	206-208
7i	OCH_3	OCH_3	H	H	446.51	$C_{25}H_{26}N_4O_4$	65	240-242
7j	H	OCH_3	H	H	416.48	$C_{24}H_{24}N_4O_3$	84	236-238

3. CONCLUSION

In conclusion, the results of the present study indicate that the indole molecules are useful precursor for many organic synthesis because of its highly functionality, for the facile and convenient synthesis of different functionalized 2-chloro acetamido thiophenes. The compounds prepared are expected to be of pharmacological interest.

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