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SYNTHESIS AND CHARACTERIZATION OF *N*-METHYL INDOLE DERIVATIVES VIA DESULFITATIVE DISPLACEMENT BY VARIOUS ANILINE DERIVATIVES

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Abstract:

The present work indicates a facile and efficient synthesis of some new 3- ((Substitutedphenyl)amino)-2-(1-methyl-1H-indole-3-carbonyl)-3-(methylthio) acrylonitrile derivatives bearing indole moiety via desulfitative displacement by various amines. The synthetic route is well designed in such a way that reaction required minimum time for completion with catalyst-free reaction, and easy workup and purification process. The range of yield is moderate to good with maximum purity. All the synthesized compounds were characterized by various spectroscopic technique. All the synthesized compounds were tested for in-vitro antimicrobial biological evaluation in which the antibacterial activity of some compounds showed promising activity in comparison to standard drug streptomycin and ciprofloxacin, while the antifungal activity of all compounds showed higher to moderate activity against standard drug Nystatin. This study would be beneficial for further bio-evaluation.

Keywords: *desulfitative, in-vitro antimicrobial activity, Nystatin.*

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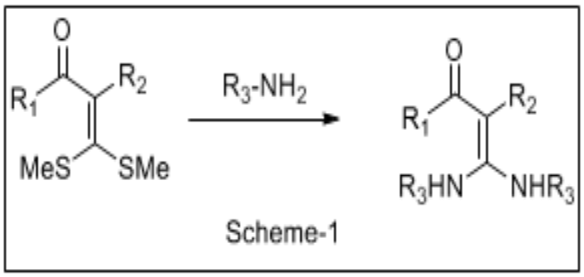
INTRODUCTION:

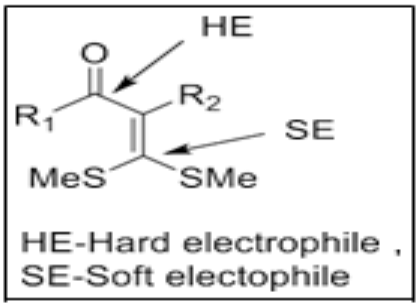
α-Oxoketene dithioacetals:

α-Oxoketene dithioacetals are important intermediate in organic chemistry[1]. The α- oxoketene dithioacetals having three carbon synthons are applied widely for the synthesis of a different heterocyclic compounds[2]. It contains 1,3-electrophilic center which was used to design different methodologies for the synthesis of both carbocyclic and heterocyclic[3]. The intermediate has β-alkylthio groups[4], which was activated by the reaction of polar substituents at the α-position and can be substituted by either one or both by various carbon, nitrogen and oxygen nucleophiles providing new opportunity to create more scope for introducing new functionalities in the product. (Scheme-1)



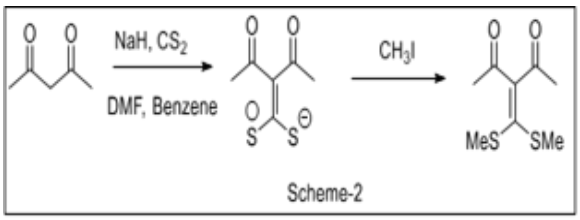
Scheme-1

α-Oxoketene dithioacetals possess carbonyl as a hard electrophilic center because carbonyl is adjacent to the hard-base oxygen and the β-carbon atoms as a soft electrophilic centre because β-carbon is attached by soft-base thiomethyl groups[5]. Depending on the regio-selectivity in the molecule, the reagent can be selected from hard nucleophiles or soft nucleophiles in which hard nucleophiles can undergo 1,2- addition while soft nucleophiles can undergo 1,4-addition[6]. Hard-soft dissymmetry can be reversed either under appropriate reaction conditions or by structural modifications, by replacing a thiomethyl group with an amino group so that the same group of nucleophiles can be made to react with either of the carbon atoms to yield the respective regioisomers.



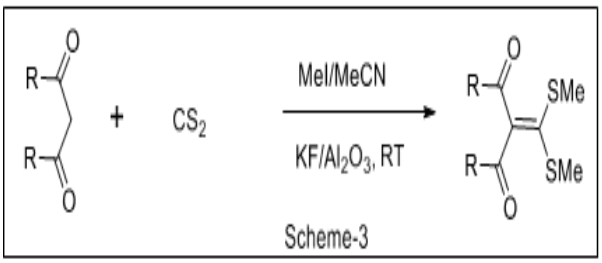
Synthetic aspect of α-oxoketene dithioacetals:

Kelber and co-workers[7] have reported first α-oxoketene dithioacetals in the year of 1910. Later, Sandstrom and Wennerbeck have reported the synthesis of α-oxoketene dithioacetals from the reaction between 2,4-pentanedione and carbon disulphide (CS2) in the presence of sodium hydride (NaH) in a mixture of DMF and benzene followed by alkylation with methyl iodide. (Scheme 2)



Scheme-2

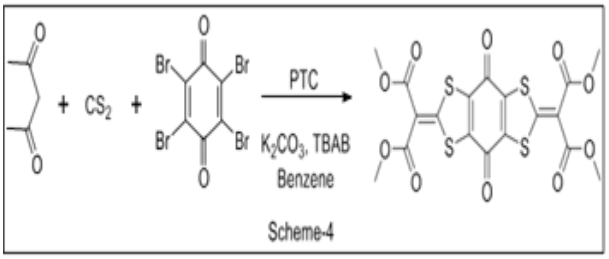
Abdelkrim Ben Alloum[8] has discovered an excellent method for the synthesis of ketene dithioacetals by the condensation reaction of active methylene compound and carbon disulfide followed by alkylation. The reaction was carried out in the presence of potassium fluoride on alumina. (Scheme-3)



Scheme-3

Soliman *et al*[9] have reported one-pot reaction for the synthesis of ketene dithioacetals. The synthesis of 2,6-Di-(1-Acetyl-2-oxopropylidene)-bidithiolo-(4,5-b:4'5'-e)-4,8- benzoquinone have achieved by the reaction of acetyl acetone, carbon disulfide and tetrabromobenzoquinone using phase transfer catalyst (K_2CO_3/benzene/tetrabutyl ammonium bromide

(TBAB)). (Scheme-4)



Scheme-4

Reaction of *α*-oxoketene dithioacetals:

In the last few decades, the number of *α*-oxoketene dithioacetals intermediate were reported, which have great utility in the synthesis of new design product. Synthetic application of *α*-oxoketene dithioacetals is described below **(Figure-1)**. Reaction with hydride and organometallic reagent generally give 1,2-addition[10] but regio-selectivity can be changed with appropriate reagent under suitable reaction condition to obtain 1,4-addition product[11]. Thus *α*-oxoketene dithioacetals form most important synthons with the active electrophilic and nucleophilic center. Reduction of α-oxoketene dithioacetals with sodium borohydride form carbinolacetals with chemoselective 1,2- addition path way[12]. If reduction of *α*-oxoketene dithioacetals with sodium borohydride take place in the presence of acetic acid chemoselective with 1,4-addition fashion produce corresponding *β*-oxodithioacetals[13] and reduction with sodium borohydride also take place in the presence of ethanol produce carbinolacetals. The Grignard reagent reacts with *α*-oxoketene dithioacetals in 1,2-addition fashion to form *β*-hydroxyvinylsulphides. *α*-oxoketene dithioacetals react with nickel borides (NiCl4/NaBH4) to form *β*-methylthioalkenylketones.[14]

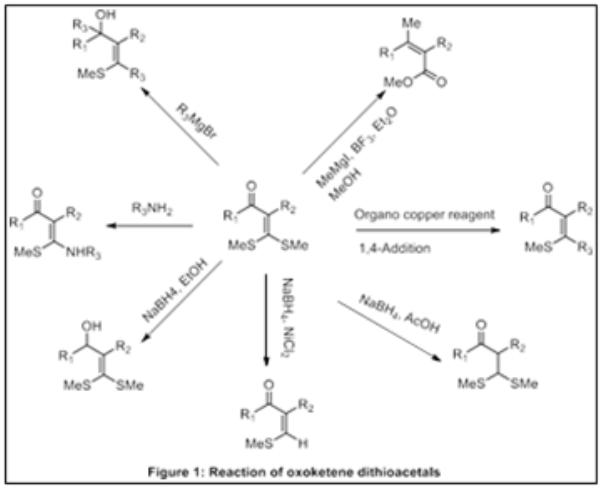


Figure 1: Reaction of oxoketene dithioacetals

Significance of indole derivatives:

The study of biologically active heterocyclic compounds has fascinating in the medicinal chemistry field. Various heterocyclic motif possessing nitrogen atom have given great utility in drug discovery. Indole has a pyrrole ring which fused with benzene ring[15]. It is an aromatic compound with 10 electron system[16]. Indole is a bicyclic heterocyclic compound containing both five and six-membered ring **(Figure- 2)**. Indole scaffolds are present in natural product and also in protein as a form of amino acid tryptophan[17].

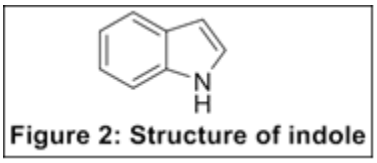
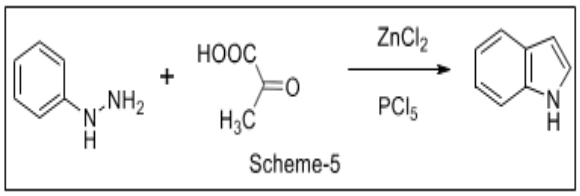


Figure 2: Structure of indole

Synthetic aspect of indole derivatives:

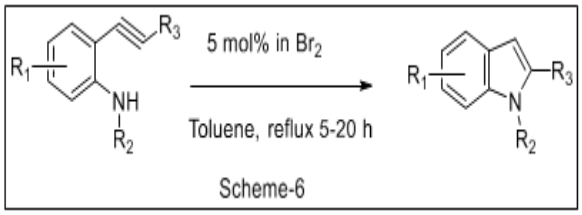
G. Bratulescu[18] has synthesized indole from the condensation reaction of phenylhydrazine and pyruvic acid using a Lewis acid catalyst zinc chloride ($ZnCl_2$). The function of phosphorus pentachloride (PCl_5) as water scavenger. (Scheme-5)



Scheme-5

N. Sakai *et al*[19] reported the synthesis of indole derivatives. The synthesis was carried out by the cyclization reaction of 2-ethynylanilines using

indium as a catalyst. (Scheme-6)



Scheme-6

MATERIAL AND METHODS:

All chemicals were purchased and used without any further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, visualization was done with ultraviolet light (254 65 nm), or with iodine vapour chamber and aq. $KMnO_4$ reagent. Melting points were determined by using a Buchi B-540 open capillary apparatus and are uncorrected. IR spectra were recorded on an FTIR-8400 S, CE Shimadzu instrument and are expressed in cm-1 (KBr). NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 MHz for 1H NMR and 101 MHz for 13C NMR) respectively in deuterated solvents $CDCl_3$. Chemical shift values (δ) were expressed in parts per million (ppm) relative to TMS. 1H-NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, coupling constants in Hz. Elemental analysis was carried out on Euro EA 3000 elemental analyser and the results are in agreement with the structures assigned. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70eV) model using direct inlet probe technique and m/z was reported in atomic units per elementary charge. Solvents were evaporated with a Büchi rotary evaporator.

Experimental procedures:

Synthesis of 3-(1-Methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (Int-1):Take 1-Methyl-1*H*-indole (19 mmol), cyanoacetic acid (19 mmol), and acetic anhydride (20 mL) in 100 mL RBF. Stir the reaction mass at room temperature to prepare a homogeneous solution. After that, the resulting solution was heated at 90 °C temperature for 30 minutes. The progress of the reaction was monitored on TLC plate. After completion of the reaction, the mixture was allowed to cool at room temperature, the crystal obtained was filtered through *vacuum*, and washed with methanol and dried to obtain 3-(1-Methyl-1*H*-indol-3-yl)-3-oxopropanenitrile as a solid pure product. **(Int- 1)**

Synthesis of 2-(1-Methyl-1*H*-indole-3-carbonyl)-3,3bis(methylthio)acrylonitrile (Int-2):

Take 3-(1-Methyl-1*H*-indol-3-yl)-3-oxopropanenitrile **(Int-1)** (15 mmol), potassium carbonate (37 mmol) and DMF (50 mL) dissolved in 100 mL RBF. Stir at room temperature for 10 minutes. Then keep RBF on an ice bath to keep 0 °C temperature, then stir the reaction mass for 30 minutes followed by dropwise addition of Carbon disulfide (CS_2) (22 mmol). The reaction mixture was further stirred for 1 hour followed by dropwise addition of methyl iodide over a period of 20 minutes, and then the reaction mixture was stirred overnight at room temperature. The progress of reaction mass was monitored on TLplate. After completion, the reaction mass was ured into ice-cold water to obtain the solid product, filter it through *vacuum*, wash it with n-Hexane, dry it to obtain analytically pure 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio) acrylonitrile as a solid with excellent yield. **(Int-2)**

General procedure for the synthesis of 3-((Substitutedphenyl)amino)-2-(1- methyl-1*H*-indole-3-carbonyl)-3-(methylthio)acrylonitrile (VD-201 to VD-215):

Take 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitrile **(Int-2)** (16 mmol), aniline substrate (16 mmol) and ethanol (10 mL) in 25 mL RBF. Stirred the reaction mass at 65 °C temperature for 1 hr. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was cooled at room temperature, to obtain the crystalline product, filtered through *vacuum*, and washed with n-Hexane and dried it to furnished yellow colour analytically pure solid final compounds which were labeled as **(VD-201 to VD-215).**

RESULTS AND DISCUSSION:

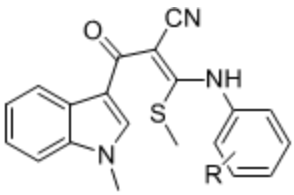


Table 2: Physical parameters of 3-((Substitutedphenyl)amino)-2-(1-methyl-1*H*- indole-3-carbonyl)-3-(methylthio)acrylonitrile (VD-201 to VD-215):

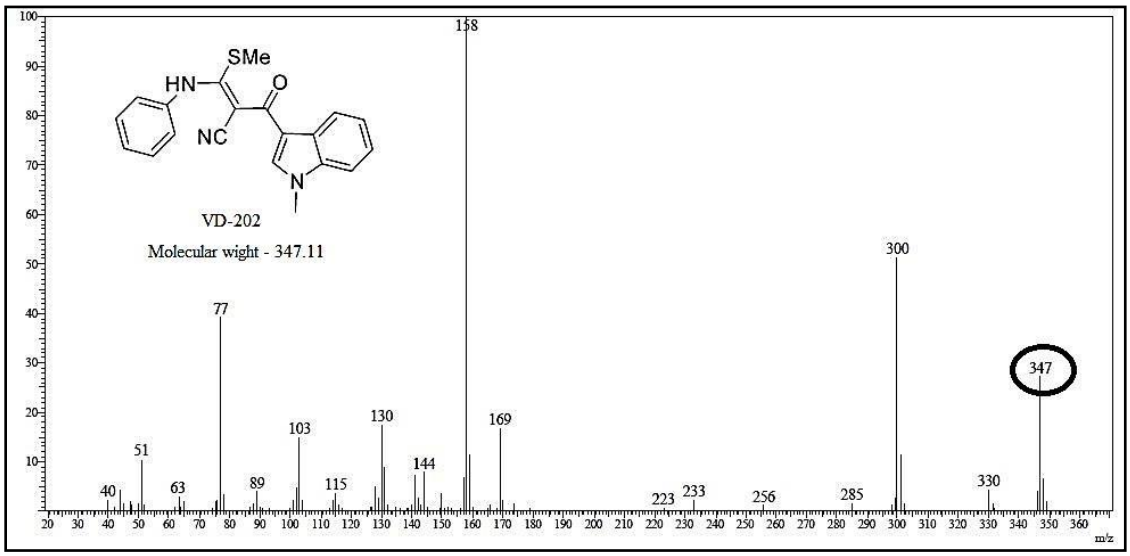
Comp. Code	Substituent R=	Molecular Formula	Molecular Weight	Yield (%)	M.P. (^{0}C)
VD-201	4-OCH_3	$C_{21}H_{19}N_3O_2S$	377.12	81	176-178
VD-202	-H	$C_{20}H_{17}N_3OS$	347.11	83	196-198
VD-203	2-Cl	$C_{20}H_{16}ClN_3OS$	381.07	76	168-170
VD-204	2,4-di F	$C_{20}H_{15}F_2N_3OS$	383.09	78	178-180
VD-205	4-Cl	$C_{20}H_{16}ClN_3OS$	381.07	71	182-184
VD-206	2,4-$(CH_3)_2$	$C_{22}H_{21}N_3OS$	375.14	63	170-172
VD-207	2-OCH_3	$C_{21}H_{19}N_3O_2S$	377.12	86	172-174
VD-208	-Py	$C_{19}H_{16}N_4OS$	348.10	83	164-166
VD-209	4-n-Propyl	$C_{23}H_{23}N_3OS$	388.16	76	156-158
VD-210	4-tert. butyl	$C_{23}H_{23}N_3OS$	403.17	80	190-192
VD-211	-Benzyl	$C_{21}H_{19}N_3OS$	361.12	81	182-184

VD-212	4-Br	$C_{20}H_{16}BrN_3OS$	425.02	71	174-176
VD-213	2,4,6-$(CH_3)_3$	$C_{23}H_{23}N_3OS$	389.16	75	196-198
VD-214	4-OH	$C_{20}H_{17}N_3O_2S$	363.10	69	186-188
VD-215	2,4-di Br	$C_{20}H_{15}Br_2N_3OS$	502.93	78	194-196

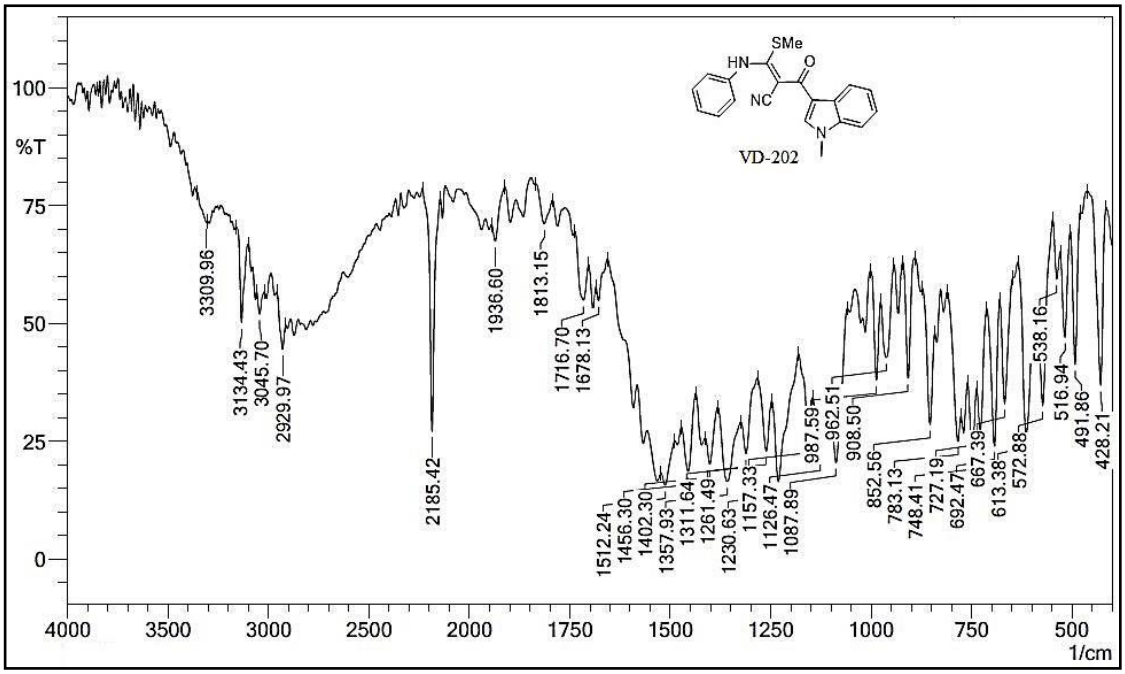
Characterization Studies:

VD-202		2-(1-Methyl-1*H*-indole-3-carbonyl)-3-(methylthio)-3-(phenyl amino) acrylonitrile		
Mol. Formula		$C_{20}H_{17}N_3OS$		
Physical Appearance		Yellow solid		
M.P. °C		196-198		
Mol. Wt.(gm/mol)		347.11		
Mass (m/z)		347 (M+)		
Ele. Ana.	Value	C	H	N
	Cal.	69.14	4.93	12.09
	Obs.	69.07	4.88	12.02
IR (KBr, ν_{max}, cm^{-1})		3309 (-NH str.), 2929 (C-H Str. in aromatic), 2185 (C≡N str.), 1769 (C=O str.), 1681 (C=N str.), 1566, 1357, 1230, 1155, 1126, 1087.		
^{1}H-NMR (400 MHz, $CDCl_3$) in δ ppm		14.17 (s, 1H), 8.46 (s, 1H), 8.43-8.36 (m, 1H), 7.45-7.40 (m, 3H), 7.40-7.29 (m, 5H), 3.87 (s, 3H), 2.23 (s, 3H).		
^{13}C-NMR (100 MHz, $CDCl_3$) in δ ppm		184.32, 170.37, 138.33, 136.99, 135.80, 129.56, 127.92, 127.02, 124.76, 123.44, 122.95, 122.65, 122.04, 114.32, 109.84, 85.62, 33.84, 17.46.		

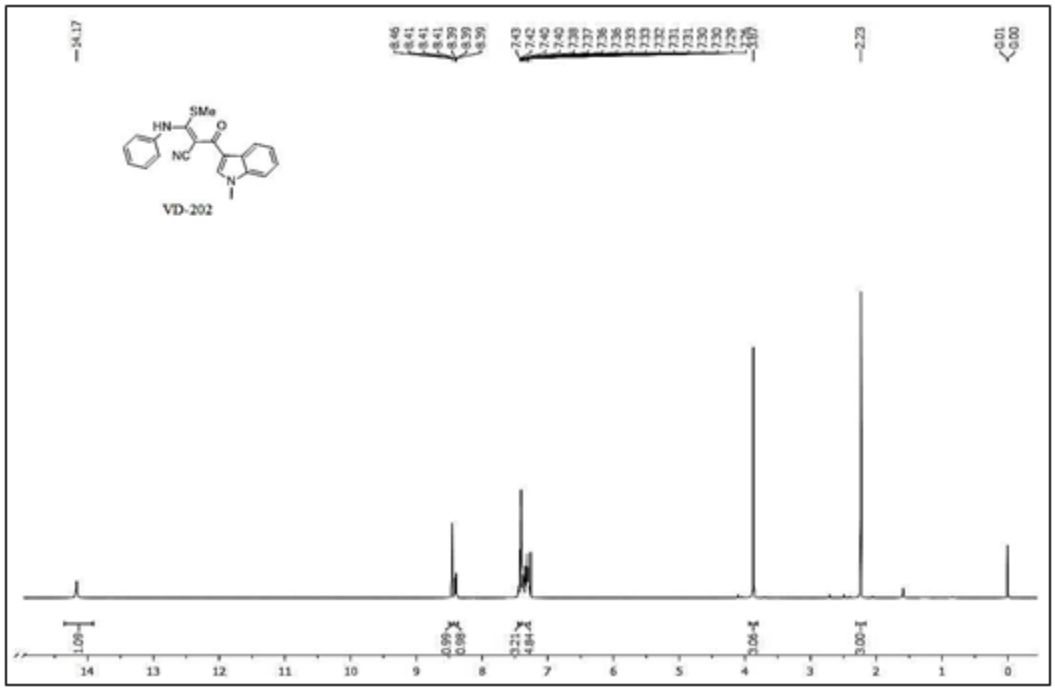
Mass spectrum of compound VD-202:



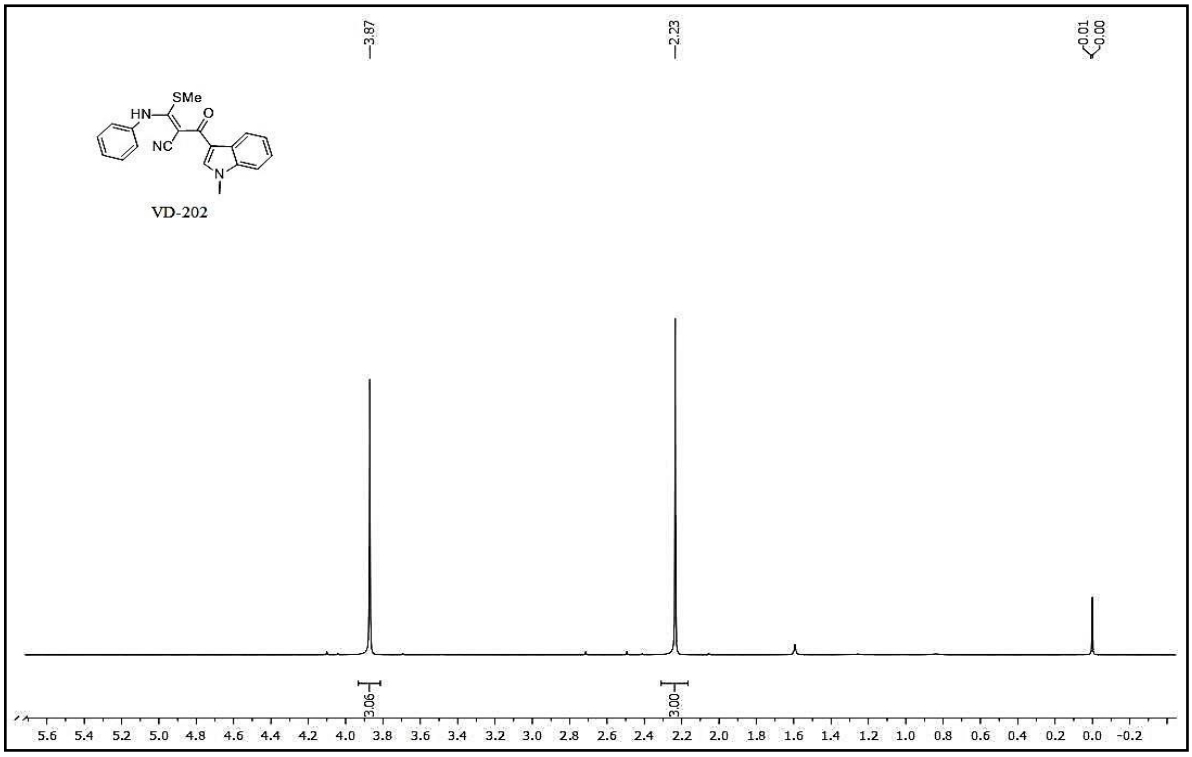
IR spectrum of compound VD-202:



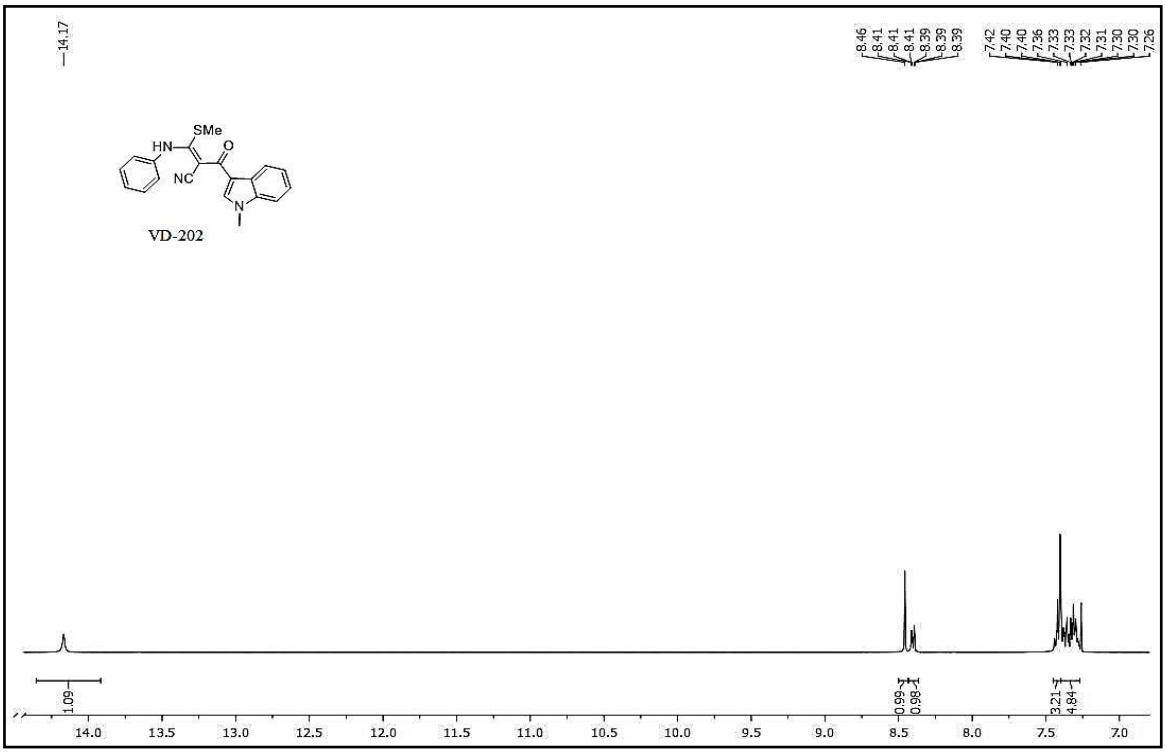
H-NMR of compound VD-202:



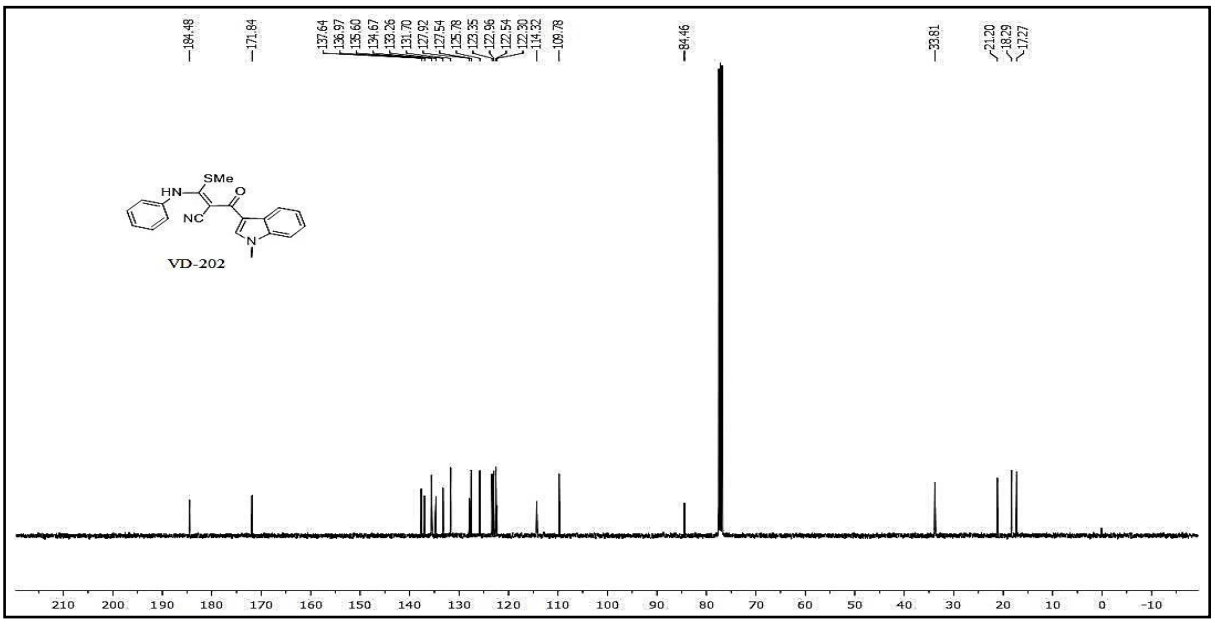
Expanded (Aliphatic region) ^{1}H-NMR of compound VD-202 :



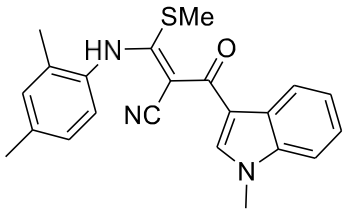
Expanded (Aromatic region) ^{1}H-NMR of compound VD-202 :



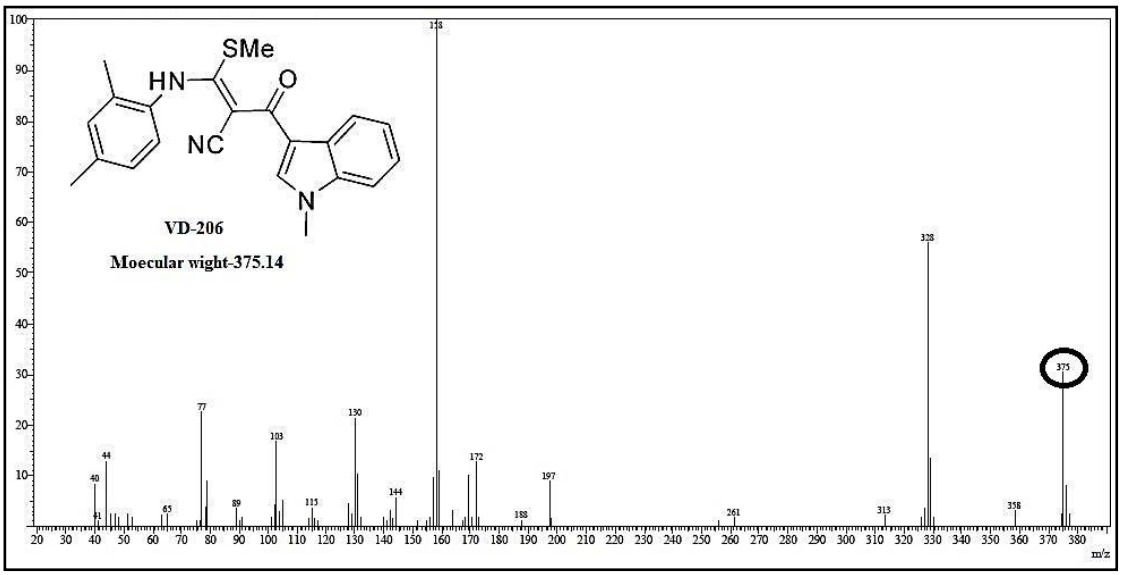
C-NMR of compound VD-202 :



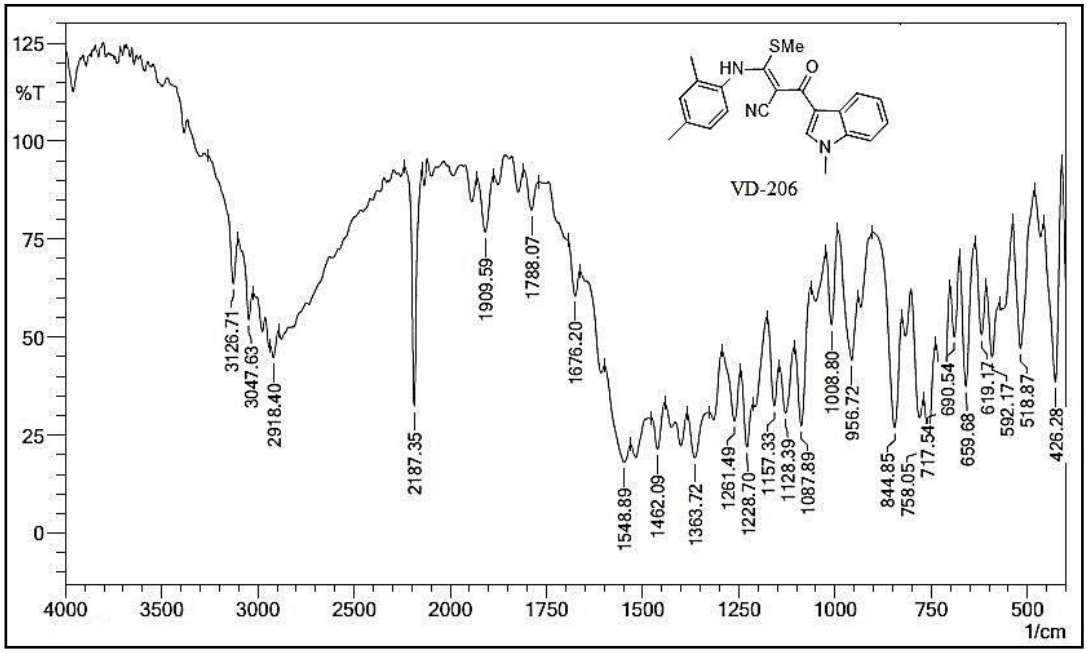
VD-206		3-((2,4-Dimethylphenyl)amino)-2-(1-methyl-1*H*-indole-3- carbonyl)-3-(methylthio)-acrylonitrile		
Mol. Formula		$C_{22}H_{21}N_3OS$		
Physical Appearance		Yellow solid		
M.P. °C		170-172		
Mol. Wt.(gm/mol)		375.14		
Mass (m/z)		375 (M^+)		
Ele. Ana.	Value	C	H	N
	Cal.	70.37	5.64	11.19
	Obs.	70.31	5.58	11.11
IR (KBr, νmax, cm^{-1})		3379 (-NH str.), 2928 (C-H Str. in aromatic), 2187(C≡N str.), 1790 (C=O str.), 1678(C=N str.), 1519, 1361, 1261, 1230, 1157, 1087.		
^{1}H-NMR (400 MHz, $CDCl_3$) in δ ppm		13.98 (s, 1H), 8.44 (s, 1H), 8.39-8.41 (m, 1H), 7.39-7.27 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H).		
^{13}C-NMR (100 MHz, $CDCl_3$) in δ ppm		184.38, 171.74, 137.53, 136.87, 135.49, 134.57, 133.15, 131.60, 127.81, 127.44, 125.68, 123.24, 122.86, 122.43, 122.20, 114.22, 109.68, 84.35, 33.70, 21.09, 18.18, 17.17.		



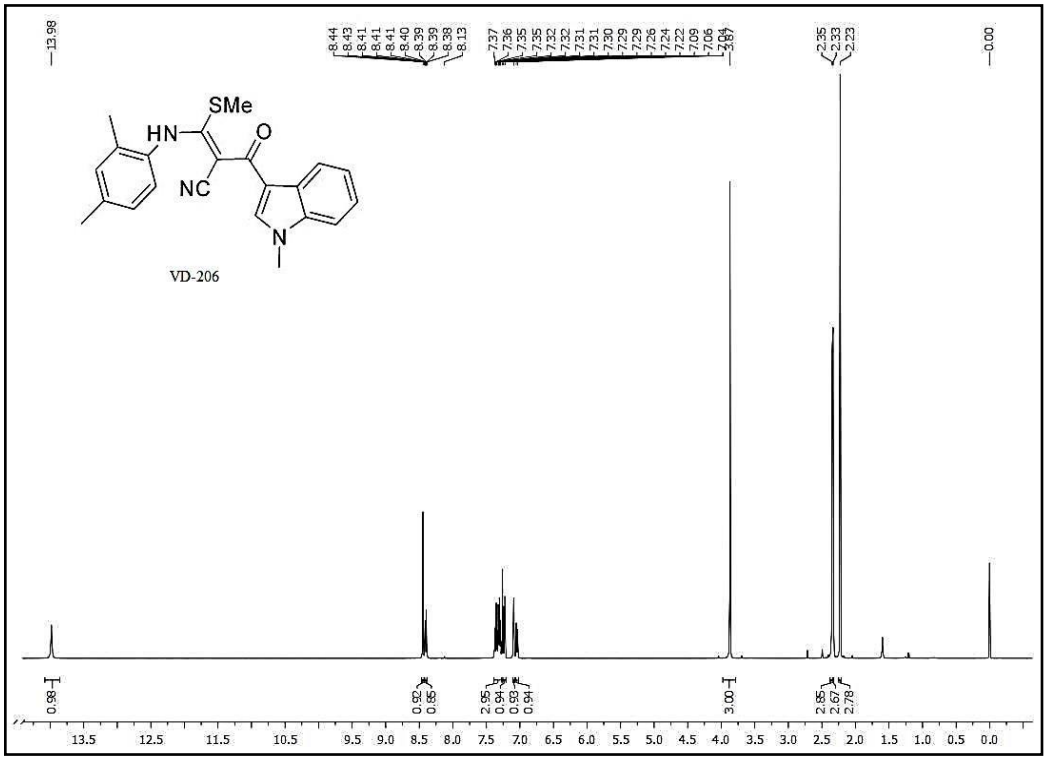
Mass spectrum of compound VD-206:



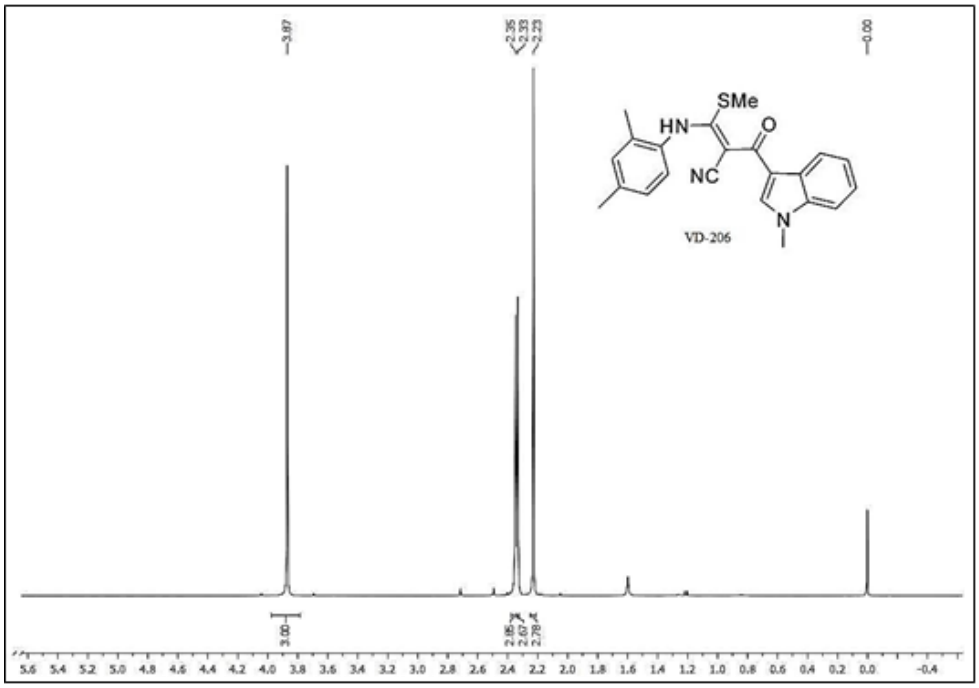
IR spectrum of compound VD-206:



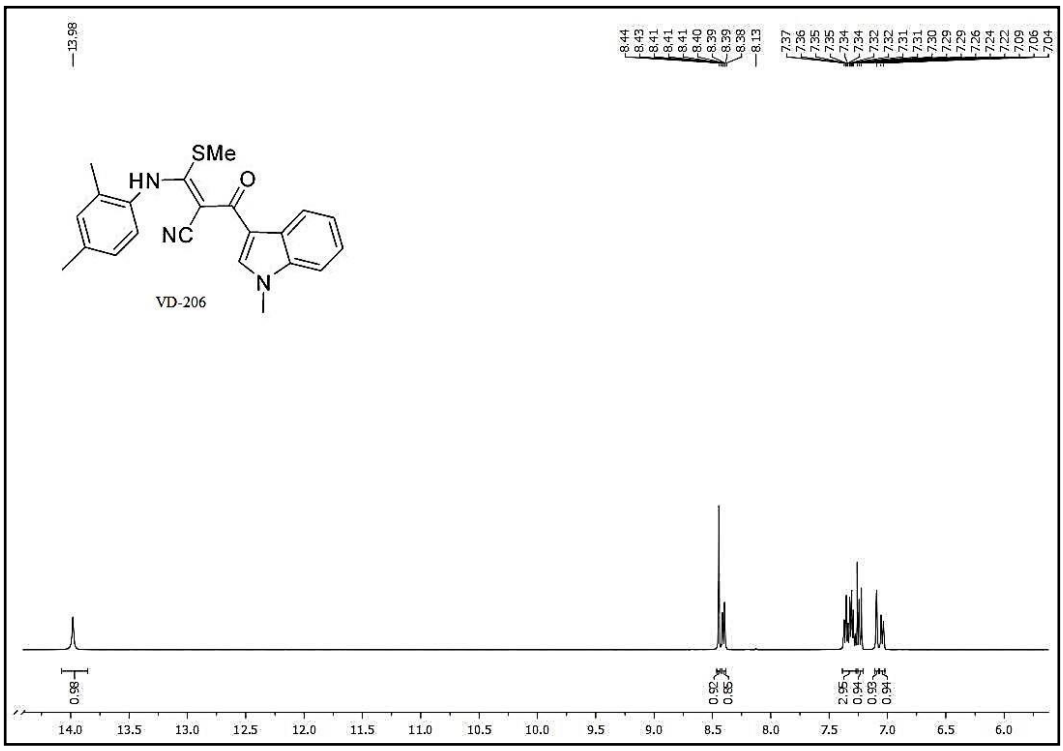
H-NMR of compound VD-206:



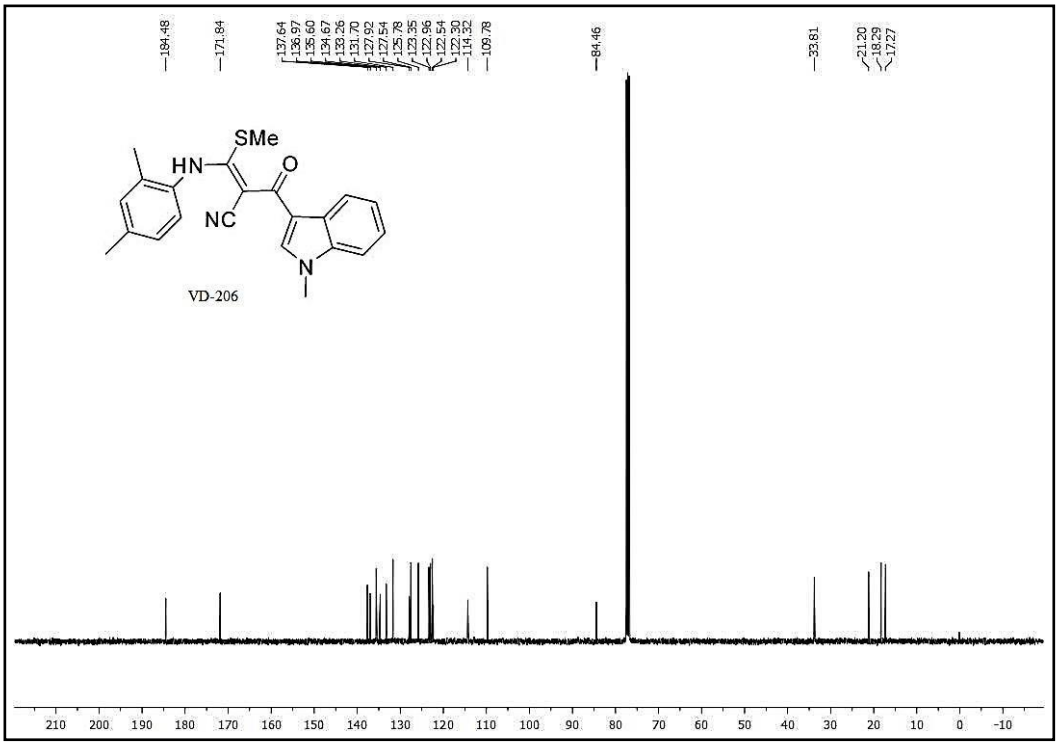
Expanded (Aliphatic region) ^{1}H-NMR of compound VD-206:



Expanded (Aromatic region) ^{1}H-NMR of compound VD-206:



^{13}C-NMR of compound VD-206 :



Spectral Studies of Synthesized Compounds:

Mass spectral study:

Molecular ion peak was observed in agreement with the molecular weight of the respective compound. Systematic fragmentation pattern was observed in mass spectral analysis.

IR spectral study:

The characteristic peaks observed at 3309 cm-1 confirmed the presence of a secondary amine. IR spectrum of all synthesized compounds shows characteristic absorption bands at 3045 cm-1 for C-H stretching in the aromatic ring and characteristic stretching at 2929 cm-1 observed due to alkane starching. One sharp peak observed at 2185 cm-1 which indicates the presence of -CN group. The IR band at 1716 cm-1 confirmed the presence of the carbonyl group.

NMR spectral study:

In 1H NMR spectra, the characteristic peak of secondary amine proton given signal nearest to 14.17 δ ppm. One sharp peak at 3.17 δ ppm was observed for *N*-methyl group and peak at 2.23 δ ppm was observed for S-methyl group. The characteristic signals between 7.40 δ ppm and 7.29 δ ppm are observed indicating the presence of aromatic protons of synthesized compounds.

C NMR spectral data:

13C NMR spectral data has shown the confirmation of carbon atom in the assigned molecular structures of the synthesized compounds.

CONCLUSION:

The present work indicates a facile and efficient synthesis of some new 3-((Substitutedphenyl)amino)-2-(1-methyl-1*H*-indole-3-carbonyl)-3-(methylthio) acrylonitrile derivatives bearing indole moiety via desulfitative displacement by various amines. The synthetic route is well designed in such a way that reaction required minimum time for completion with catalyst-free reaction, and easy workup and purification process. The range of yield is moderate to good with maximum purity. All the synthesized compounds were characterized by various spectroscopic techniques.

All the synthesized compounds were tested for *in-vitro* antimicrobial biological evaluation in which the antibacterial activity of some compounds showed promising activity in comparison to standard drug streptomycin and ciprofloxacin, while the antifungal activity of all compounds showed higher to moderate activity against standard drug Nystatin. This study would be beneficial for further bio-evaluation.

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