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# Synthesis of oxindole Substituted imidazothiadiazole

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**Abstract:** In this experiment a mixture of 4-Chlorophenyl acetic acid (1 eq) and thiosemicarbazide (1.5 eq) was added slowly to the round bottom flask containing concentrated H2SO4 with constant stirring in ice bath. After complete addition, ice bath was replaced by water bath and slowly heated to 70-80 $^{0}$C and maintained at that temperature for 7 hrs. After cooling to room temperature, the contents of the reaction were poured into ice water and made basic with ammonia and the precipitate was filtered, washed with water and recrystallized from ethanol. All work relating to analytical thin layer chromatography were performed with silica gel 60F254 aluminum plates and were visualized with UV light. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. The following mobile phases were employed for TLC : hexane and ethyl acetate in different ratios. The instrumental techniques employed for the characterization of the newly synthesized compounds include 1H and 13C NMR spectroscopy. 1H and 13C NMR spectra were recorded on a (400 and 300 MHz).

**Keywords:** Thin layer chromatography, Silica gel, UV light, mobile phase, 13C NMR and 1H.

## INTRODUCTION

### Imidazothiadiazole

A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring. Heterocyclic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of these heterocycles [Cotter, T. G, 2009].

Examples: nucleic acids, the majority of drugs, and many natural and synthetic dyes.

The bridgehead nitrogen atom heterocycle, imidazo (2, 1-b) (1, 3, 4) thiadiazole consisting of four heteroatoms and two condensed heterocycles with different π-conjugations was first discovered in the early fifties of nineteenth century. This heterocycle is an isoster of biologically significant imidazo (2, 1-b) (1, 3, 4) thiazole, in which the 3-CH group of thiazole ring is substituted by 3-N atom [Campos, L. *et al*., 1993].

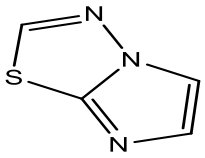


**Figure 1:** Structure of Imidazo (2, 1-b) (1, 3, 4) thiadiazole

During the past six decades, significant development has been observed in the field of chemistry and biology of imidazo (2, 1-b) (1, 3, 4) thiadiazoles. The synthesis and biological activities of numerous imidazo (2, 1-b) (1, 3, 4) thiadiazoles possessing a variety of substitutions at C-2, C-5 and/or C-6 positions of the general structures [Iyer, D. 2013].

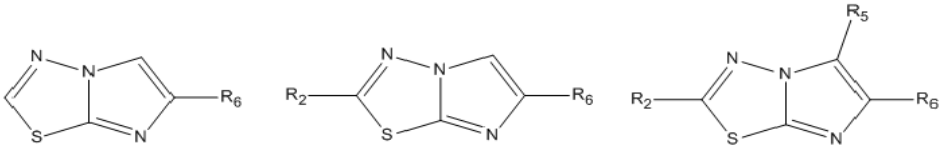


**Figure 2:** General structure of Imidazo (2, 1-b) (1, 3, 4) thiadiazole (Iyer, D. and Raghavan, S.C., 2013).

Most of the synthesized derivatives are reported to exhibit diversified biological activities as well as inhibition of some specific enzymes. The biological activities includes antibacterial, antifungal, leishmanicidal, herbicidal, antitubercular, anticancer, antihelmintic, anticonvulsant, analgesic, anti-inflammatory, antipyretic, local anesthetic, cardiotonic and diuretic [Iyer, D. *et al*., 2016].

The recent review provides a comphrensive summary on the chemistry of imidazo(2,1-b)(1,3,4) thiadiazole highlighting an overview on the methods of synthesis, spectral studies, physicochemical properties, reactivity as well as ring fused imidazo (2,1-b)(1,3,4) thiadiazoles (Khazi et al., 2011). To the best of our knowledge, this is the first comphrensive review of biological





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profiles of the imidazo(2,1-b)(1,3,4) thiadiazole heterocycle provides a medicinal and bioorganic chemists a collective insights into the biological profiles of imidazo(2,1-b)(1,3,4) thiadiazole derivatives, thus helping them adopt a more focused and speedy target oriented drug discovery process[Ferri, K.F. *et al*., 2001].

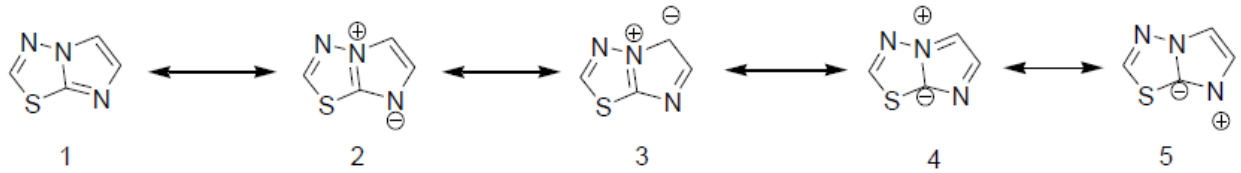


**Figure 3:** Structure and reactivity of imidazo (2, 1-b) (1, 3, 4) thiadiazole [Ferri, K.F. *et al*., 2001].

These resonance structures indicate greater delocalization of π-electrons in the imidazole ring, while the double bond of the thiadiazole ring is almost localized. Structure (1) is the maximum contributing structure [Gutiérrez-Puente, Y. *et al.*, 2002].

The imidazo (2, 1-b) (1, 3, 4) thiadiazole ring system is pseudo aromatic in behavior containing imidazole moiety as electron rich center. Chlorine or bromine does not add to the double bond at 2$^{nd}$ and 3rd position. On the other hand, electrophilic substitution reactions like bromination, nitration etc. takes place at 5th position [Li, J. *et al*., 1996].

**Oxindole**

Oxindoles are credited to have a wide range of applications and are reported to exhibit an extensive range of biological effects which include the antiviral, antifungal, antibacterial, antiproliferative, anticancer, anti-inflammatory antihypertensive and the anticonvulsant activities. The chemistry of oxindoles is very interesting and the biological activity of the oxindoles and their derivatives has made them very important in synthetic organic and medicinal chemistry [Reed, J.C, 1997].

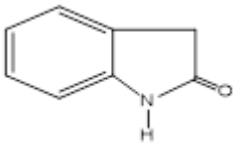

**Figure 4:** Structure of Oxindole [Reed, J.C, 1997]

Oxindole is an aromatic heterocyclic organic compound that are found in the tissues and body fluids of mammals, and in the natural products of some plants. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing ring. Oxindole is a modified indoline with a substituted carbonyl at the second position of the 5-member indoline ring [Li, J. *et al*., 2012].

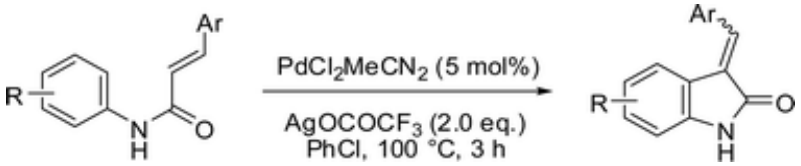


**Figure 5:** Oxindole synthesis by palladium-catalysed aromatic C–H alkylation [Dancey, J.E. *et al*., 2001].

**Instrumentation**

All work relating to analytical thin layer chromatography were performed with E. Merck silica gel $60F_{254}$ aluminum plates and were visualized with UV light. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. The following mobile phases were employed for TLC: hexane and ethyl acetate in different ratios [Kirkin, V. *et al*., 2004]. The instrumental techniques employed for the characterization of the newly synthesized compounds include $^{1}H$ and $^{13}C$ NMR spectroscopy. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a (400 and 300 MHz) Fourier transform spectrophotometer and reported in ppm using $CDCl_3$or DMSO-$d_6$ solution and tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS. Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz.

**Chemicals Required**

6-Chloro oxindole and 5-bromo oxindole
Acetophenone and 4-Methoxyacetophenone
N-bromosuccinimide (NBS)
Para-toluene sulphonic acid (p-TSA)
Acetonitrile



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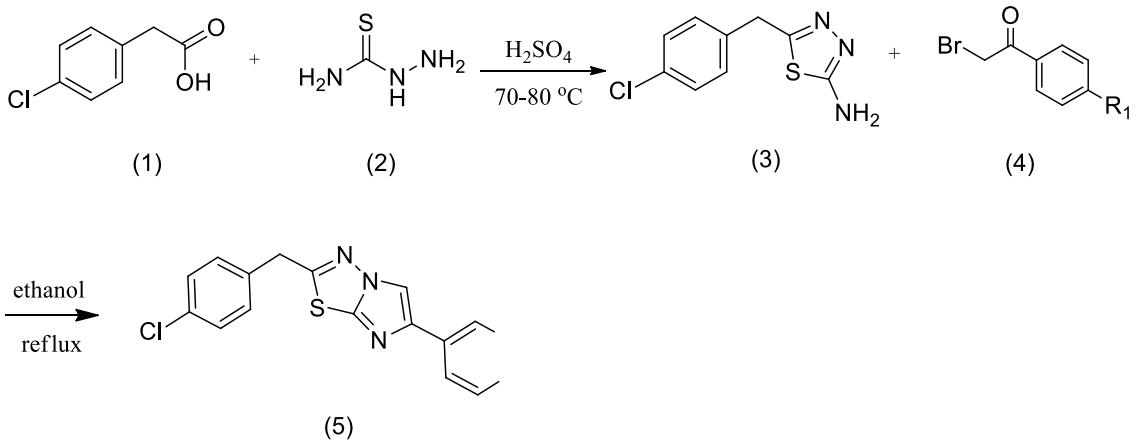
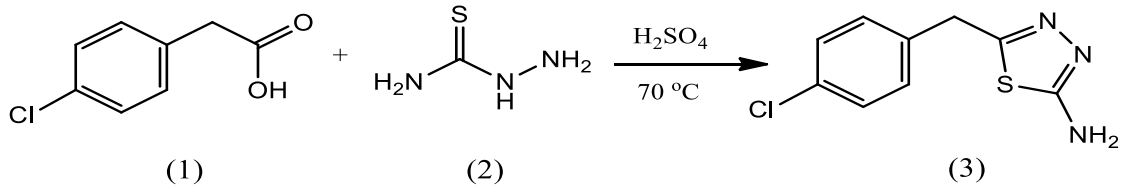
| | |
|---|---|
| 4-Chlorophenylacetic acid | Dimethylformamide (DMF) |
| Thiosemicarbazide | Sodium Carbonate |
| Sulphuric acid | Sodium Bicarbonate |
| Ethanol | Methanol |
| Ammonia | Piperidine |
| $POCl_3$ | |

**General scheme for synthesis of oxindole substituted imidazothiadiazole**




**Scheme 1:** Reaction protocol for the synthesis of oxindole substituted imidazothiadiazole [Kamal, A. *et al*., 2014].

**Synthesis of 5-(4-chlorobenzyl)-1, 3, 4-thiadiazol-2-amine**




**Scheme 2:** Synthesis of 5-(4-chlorobenzyl)-1,3,4-thiadiazol-2-amine [Zitvogel, L. *et al*., 2013].

The mixture of 4-Chlorophenyl acetic acid (1 eq) and thiosemicarbazide (1.5 eq) was added slowly to the round bottom flask containing concentrated $H_2SO_4$ with constant stirring in ice bath. After complete addition, ice bath was replaced by water bath and slowly heated to 70-80 $^0$C and maintained at that temperature for 7 hrs. After cooling to room temperature, the contents of the reaction were poured into ice water and made basic with ammonia and the precipitate was filtered, washed with water and recrystallized from ethanol [Etgar, L. *et al*., 2012].

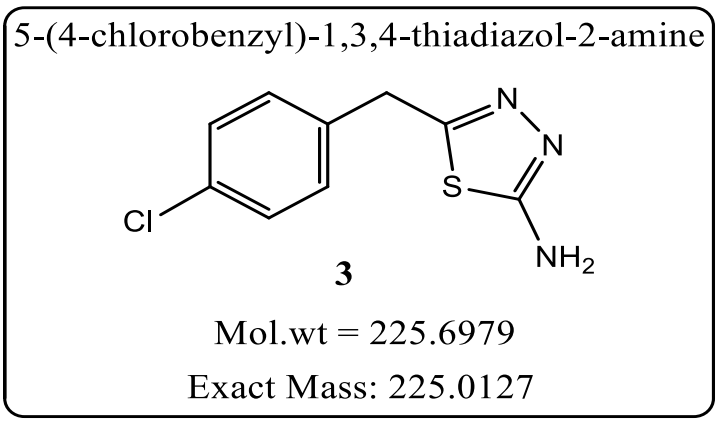



**Figure 6:** Structure of 5-(4-chlorobenzyl)-1,3,4-thiadiazol-2-amine



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Yield 65 %; MP. 181-183 °C; brown solid; $^{1}$H-NMR (400 Hz, DMSO-$d_6$): δ ppm: 4.123 (s, 2H, -$CH_2$-), 7.022 (s, 2H, -$NH_2$), 7.260-7.280 (d, 2H, Ar, J=8 Hz), 7.348-7.367 (d, 2H, Ar, 7.6 Hz); $^{13}$C- NMR (400 Hz, DMSO-$d_6$): δ ppm: 35.123, 129.002, 130.949, 131.998, 137.420, 157.520, 169.382; HRMS-(ESI): m/z calculated for [$C_9H_8ClN_3S$ + $H^+$] = 226.0127: found = 226.4298.

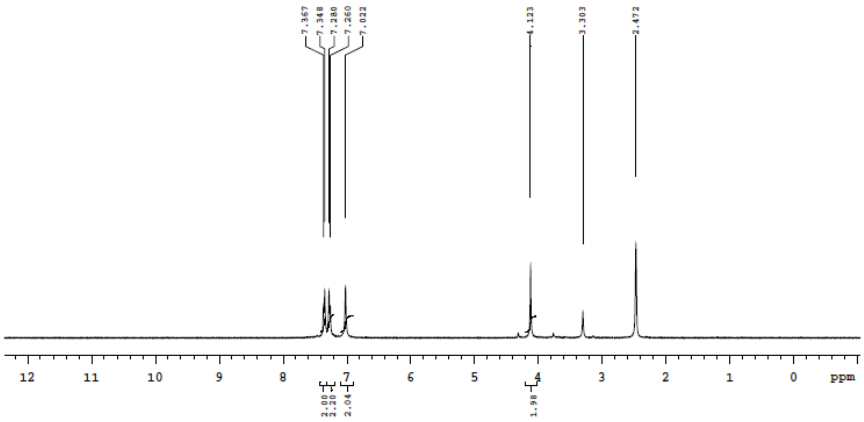


**Figure 7:** $^{1}$H NMR (400 Hz-DMSO-d6) of compound (3)

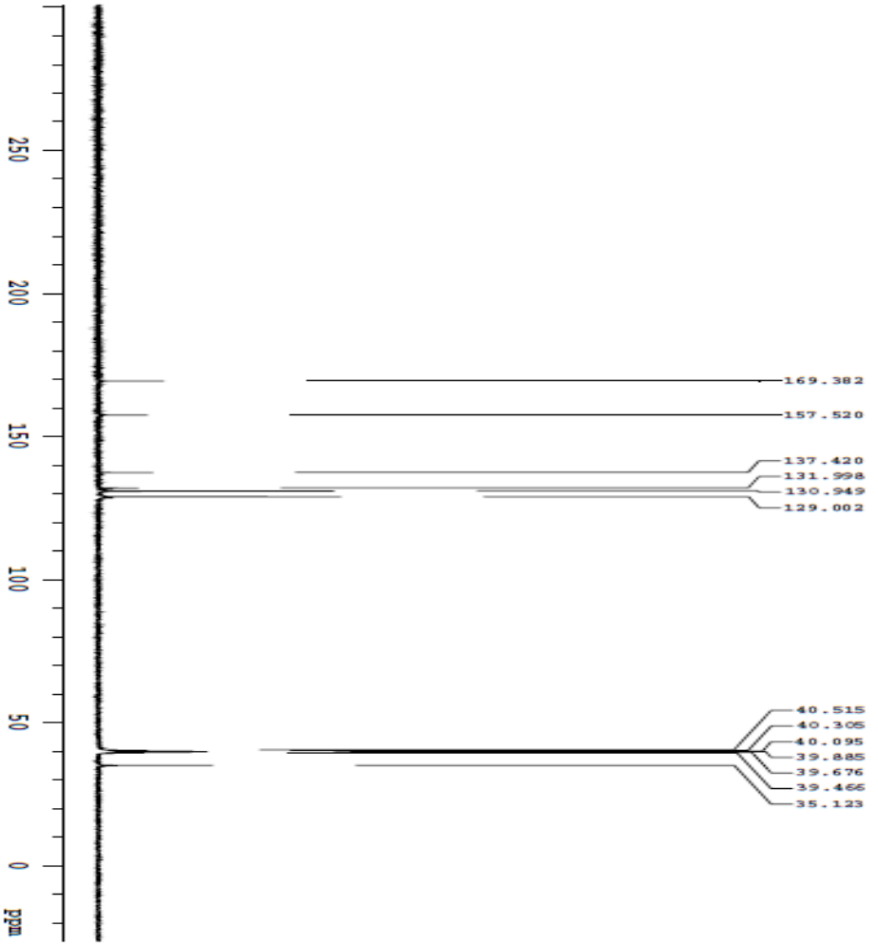


**Figure 8:** $^{13}$C-NMR(400MHz-DMSO-$d_6$) of compound (3)



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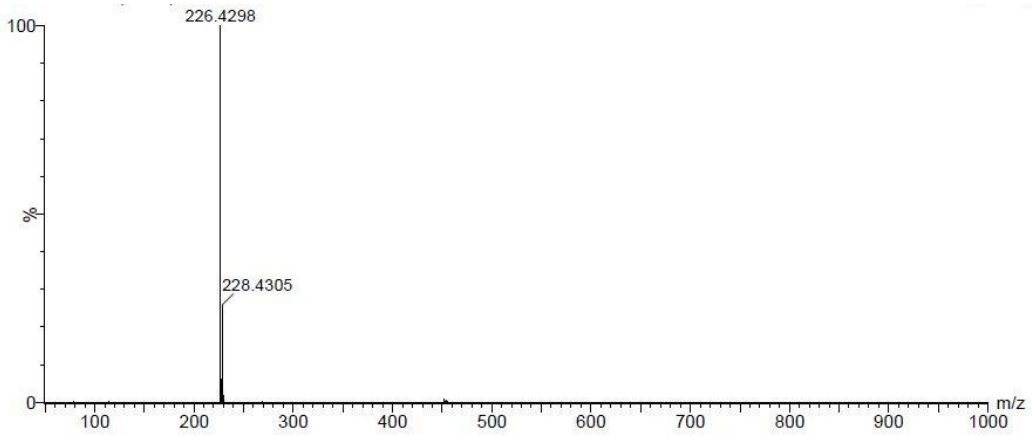
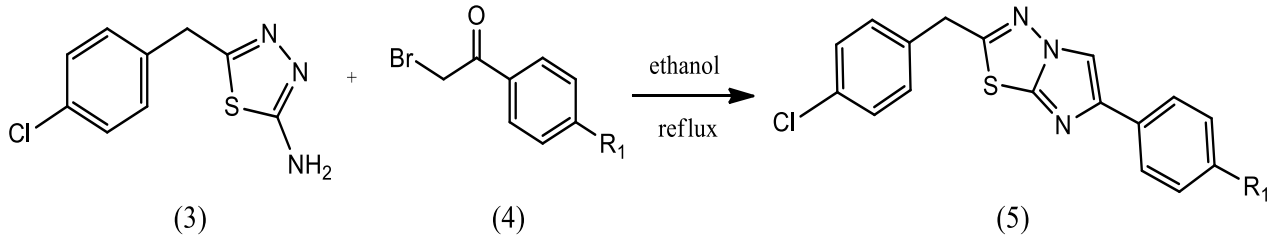



**Figure 9:** Mass spectra of compound (3)

**Synthesis of imidazothiadiazoles**




(3) (4) (5)

**Scheme 3:** Synthesis of imidazothiadiazoles

The appropriate 5-(4-chlorobenzyl)-1,3,4-thiadiazol-2amine(1eq) was treated with the appropriate p-substituted phenacyl bromide (1 eq), in ethanol. The mixture was refluxed for 10-12 hrs. Excess of solvent was removed under reduced pressure and the solid hydrobromide was separated by filtration, washed with cold ethanol and dried. Neutralization of hydrobromide salt with cold aqueous solution of sodium carbonate yielded the corresponding free base which was filtered [Liu, M. *et al*., 2001].

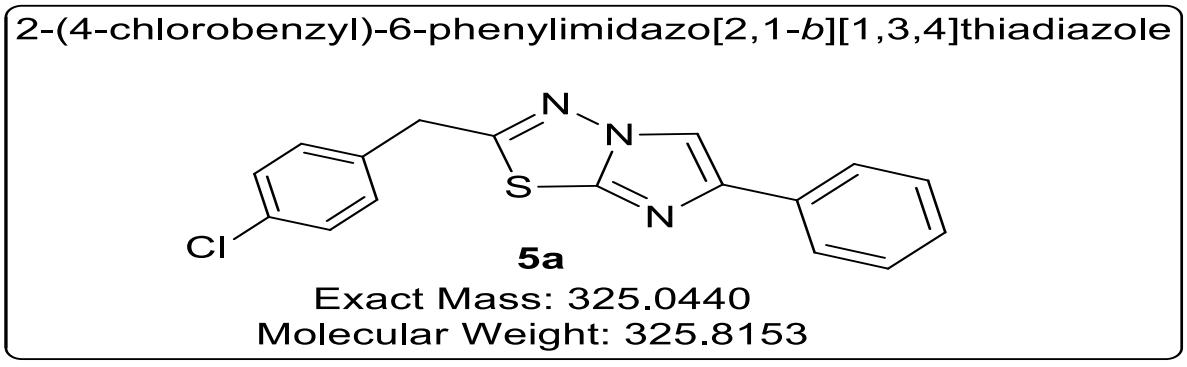



**Figure 10:** 2-(Chlorobenzyl)-6-phenylimidazol[2,1-b][ Cotter, T. G, 2009; Campos, L. *et al*., 1993; Iyer, D, 2013]thiadiazole

Yield 55%; MP. 155-157 °C; pale yellow solid; $^{1}$H-NMR (400 Hz, DMSO-$d_6$): δ ppm : 4.421 (s, 2H, -$CH_2$-), 7.210-7.247 (t, 1H, Ar, J=7.6 Hz), 7.339-7.377 (t, 2H, Ar, J=8 Hz), 7.406 (s, 4H, Ar), 7.803-7.822 (d, 2H, Ar, J=7.6 Hz), 8.612 (s, 1H, -CH= imidazole); $^{13}$C- NMR (400 Hz, DMSO-$d_6$) : δ ppm: 36.508, 110.741, 125.042, 127.689, 129.080, 129.245, 131.493, 132.631, 134.305, 135.462, 145.337, 164.406; HRMS-(ESI): m/z calculated for [$C_{17}H_{12}ClN_3S + H^+$] =326.0440: found = 326.5780.



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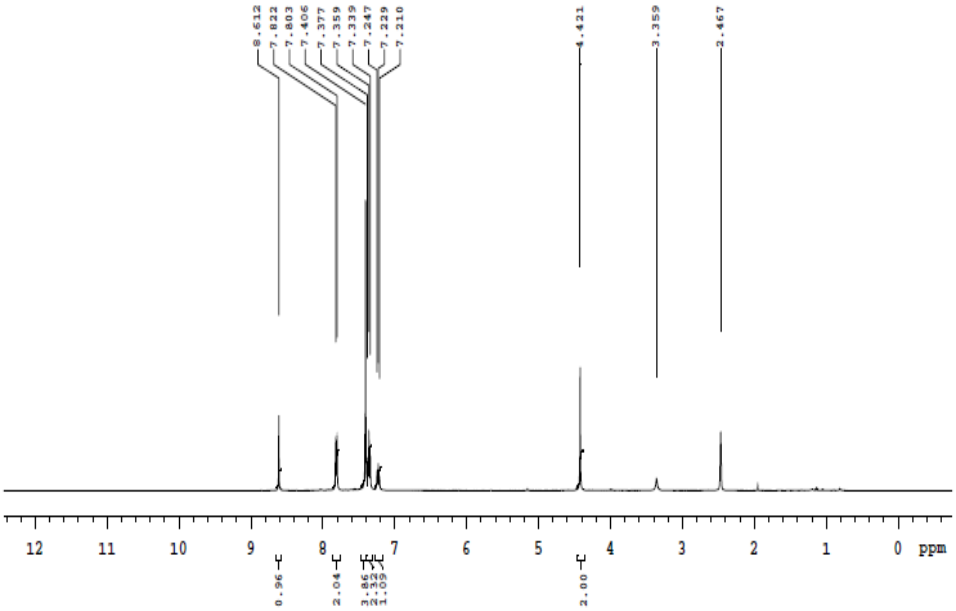


**Figure 11:** $^{1}$H-NMR (400MHz-DMSO-$d_6$) of compound (5a)

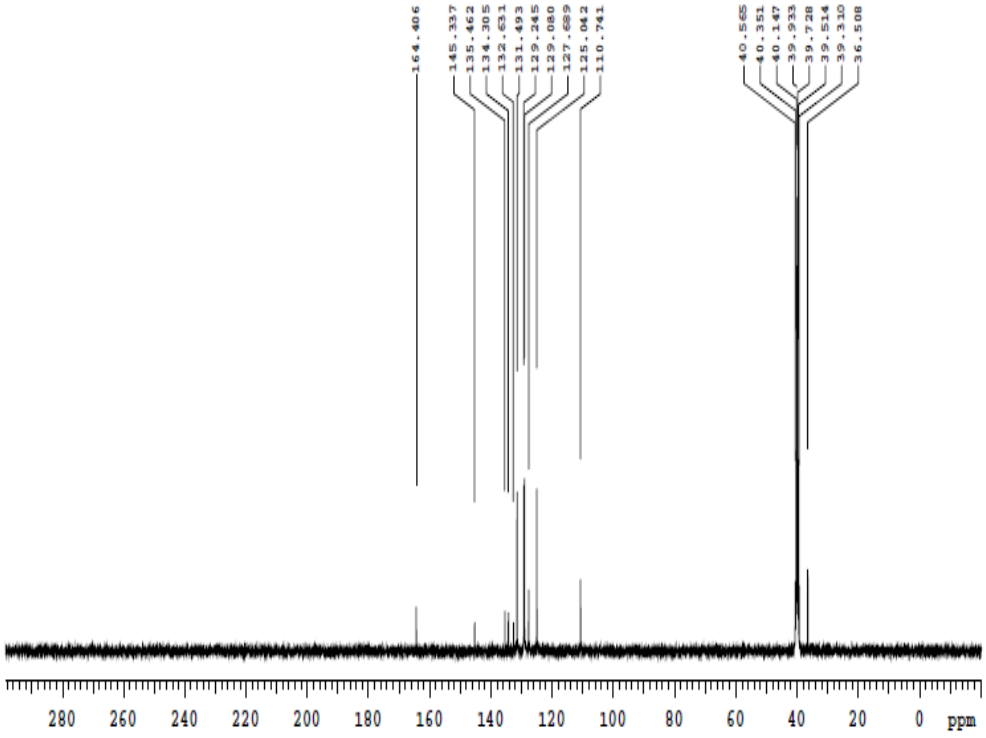


**Figure 12:** $^{13}$C-NMR (400MHz-DMSO-$d_6$) of compound (5a)



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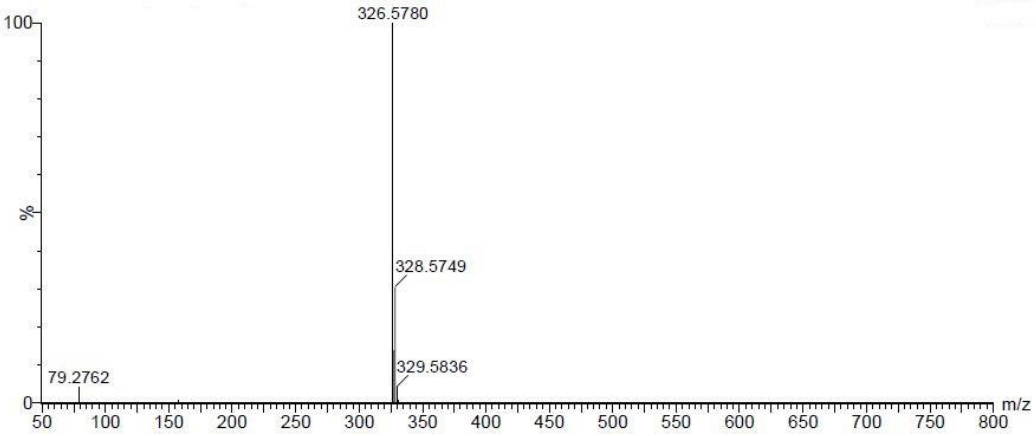


**Figure 13:** Mass spectra of compound (5a)

## RESULTS AND DISCUSSIONS

In this present work, a series of new compounds were synthesized. Scheme (1) illustrates the way used for the preparation of target molecules. As a starting material The mixture of 4-Chlorophenyl acetic acid (1 eq) and thiosemicarbazide (1.5 eq) was added slowly to the round bottom flask containing concentrated $H_2SO_4$ with constant stirring in ice bath. After complete addition, ice bath was replaced by water bath and slowly heated to 70-80 $^0$C and maintained at that temperature for 7 hrs. After cooling to room temperature, the contents of the reaction were poured into ice water and made basic with ammonia and the precipitate was filtered, washed with water and recrystallized from ethanol.

The structural synthesized compounds were confirmed by IR, $^1$H NMR, mass spectra and elemental analysis.

## CONCLUSION

The development of elegant synthetic methods to synthesize disarib and disarib derivatives is of prime importance because of their potential biological and pharmaceutical activities. This compound of disarib have been designed, synthesized and characterized in order to achieve an ideal BCL-2 inhibitor with better efficacy and target specificity, with no/minimum side effects. The reaction of phenyl acetic acid derivative (1) with thiosemicabazide (2) will lead to 2-amino benzyl-3-ylmethyl- (Cotter, T. G. *et al*., 2009; Iyer, D. and Raghavan, S.C. 2013; Iyer, D. et al., 2016) thiadizole (3) which upon condensation with α-haloarylketones (4) will generates imidazothiazoles (5).

I got very good research experience while synthesizing these compounds. It was challenging to synthesis as it was a five step process. But finally I came out with a positive result. I am hoping that these compounds will show very good biological activity and will be helpful in cancer treatment.

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