SYNTHESIS OF PYRROLO OXINDOLE FROM 3-PHENACYLIDENE OXINDOLE AND METHYL ACETOACETATE

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The conventional procedures in organic synthesis utilize stepwise formation of individual bonds and therefore require many synthetic steps. In contrast to such multistep processes, one-pot transformations based on multicomponent reactions (MCRs) have gained great importance in modern organic synthesis. The focal theme of this thesis is the exploration of new multicomponent reactions for the synthesis of biologically important heterocycles. In order to put things in perspective, a brief introduction to MCRs, their applications in organic synthesis and introduction on pyrroles are given in the following section.

Multicomponent reactions

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In a MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct a MCR in such a way that the network of pre-equilibrated reactions channel into

the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, nature of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.[1]

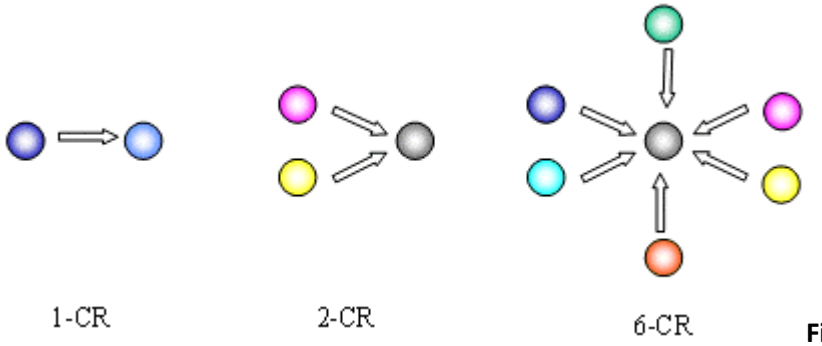
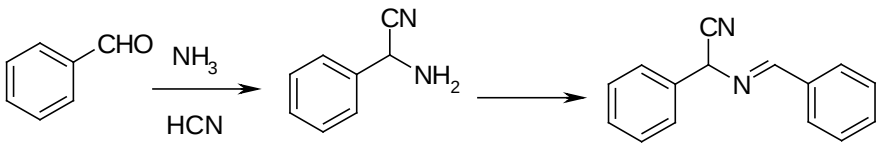


Figure 1. A divergent 1-component reaction and convergent 2- and 6-component reaction.

Multicomponent reactions with carbonyl compounds

Some of the first multicomponent reactions to be reported function through derivatization of carbonyl compounds into more reactive intermediates, which can react further with a nucleophile. Carbonyl compounds played a crucial role in the early discovery of multicomponent reactions, as displayed by a number of name reactions.

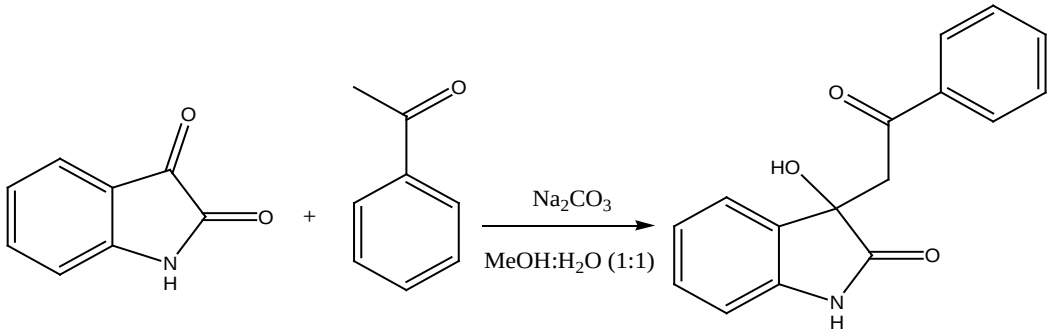
The history of MCRs can be traced back to the work of Laurent and Gerhardt, who in 1838, from the reaction of bitter almond oil and ammonia, isolated a poorly soluble product which they called “benzoyl azotid”.[2] In this reaction, the cyanohydrin derived from benzaldehyde and hydrocyanic acid, reacts with ammonia giving amino benzyl cyanide whose schiff base with benzaldehyde was called “benzoyl azotid”.



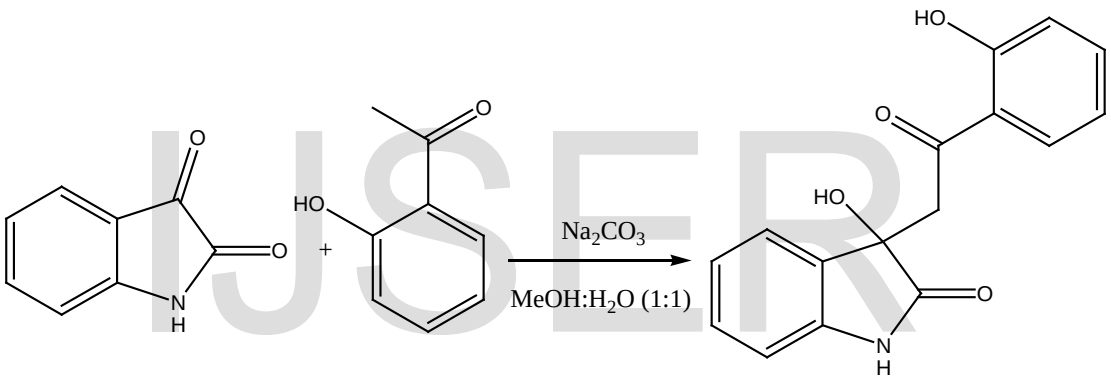
2. SCOPE AND SCHEME OF THE WORK

3-substituted 3-hydroxyindolin-2-ones are important substrates for studies of biological activities as well as useful synthetic intermediates for drug candidates and alkaloids. The development of practical methods for their preparation is of interest. 3-Substituted 3-hydroxyoxindoles are encountered in a large variety of natural products with a wide spectrum of biological activities, such as convolutamydines,[1] donaxaridines,[2] maremycins,[3] dioxibrassinines,[4] celogentin K,[5] 3'-hydroxy glucoisatisin,[6] and TMC-95A.[7] 3-Alkenyl- and 3-aryl-substituted 3-hydroxyindoles,[8] and their derivatives [9] have been used in a number of recent pharmaceutical studies. The formation of quaternary carbon centers via addition of nucleophiles to ketone derivatives still constitutes a major challenge for synthetic chemistry.

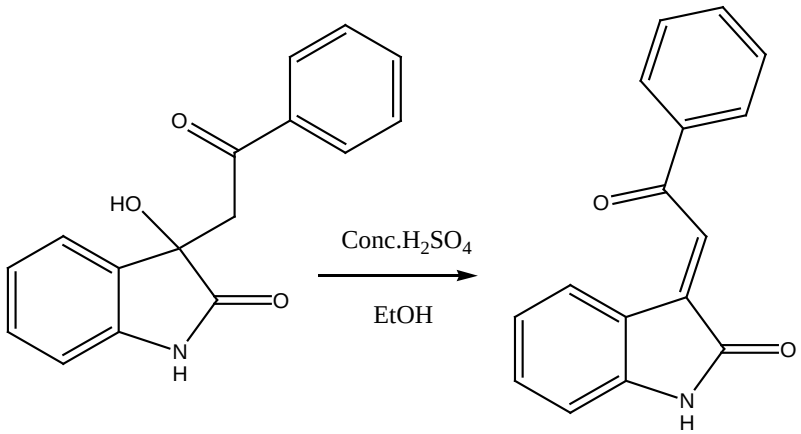
Scheme 1: Synthesis of 3-hydroxy-3-phenacyl oxindole from isatin and acetophenone at room temperature



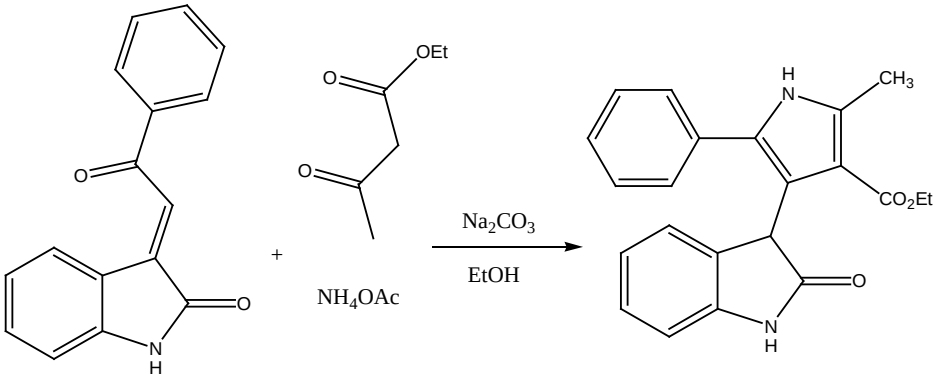
Scheme 2. Synthesis of 3-hydroxy-3(2'-hydroxy)phenacyl oxindole from isatin and 2-hydroxy acetophenone at room temperature



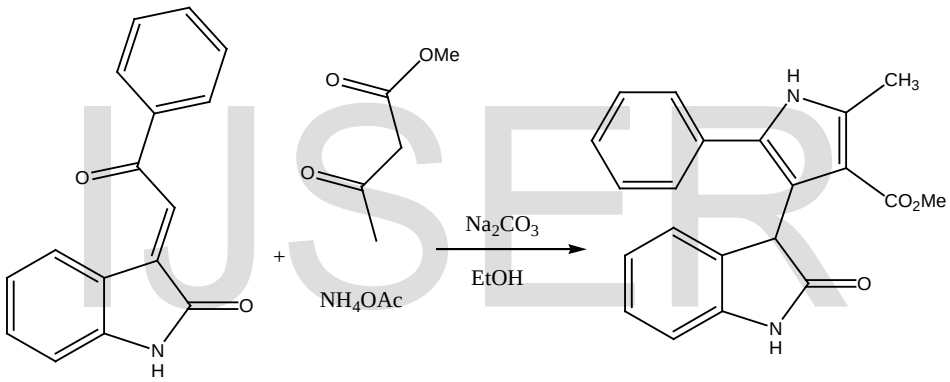
Scheme 3. Synthesis of 3-phenacylidene oxindole at room temperature



Scheme 4. Synthesis of pyrrolo oxindole from 3-phenacylidene oxindole, ethyl acetoacetate and ammonium acetate (reflux)



Scheme 5. Synthesis of pyrrolo oxindole from 3-phenacylidene oxindole, methyl acetoacetate and ammonium acetate (reflux)



OBJECTIVE OF THE PROJECT

To synthesize pyrrolo oxindole by one-pot three-component reaction of 3-phenacylideneoxindole, ethyl acetoacetate and ammonium acetate.

- To study the scope and limitation of this method by substituting ethyl acetoacetate by methyl acetoacetate.
- To study the effect of various solvents on the one pot reaction and also to catalytic activity of Na_2CO_3
- To synthesize the precursor (3-hydroxy-3-phenacyloxindole) by a simple and convenient method superior to the previously reported procedures
- To characterize the products through

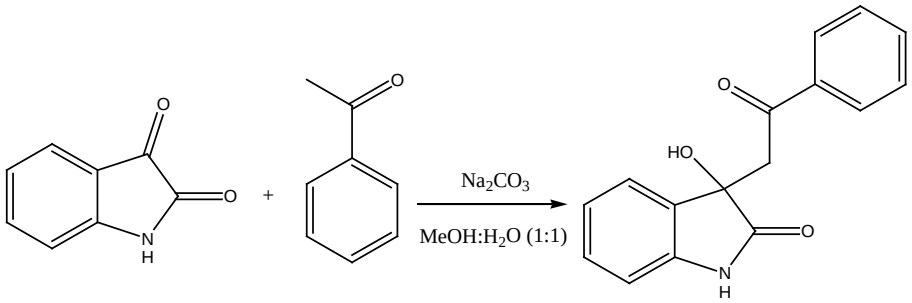
- FT-IR
- ^{1}H NMR
- ^{13}C NMR
- Mass spectral analysis

ELEMENTAL ANALYSIS RESULTS AND DISCUSSION

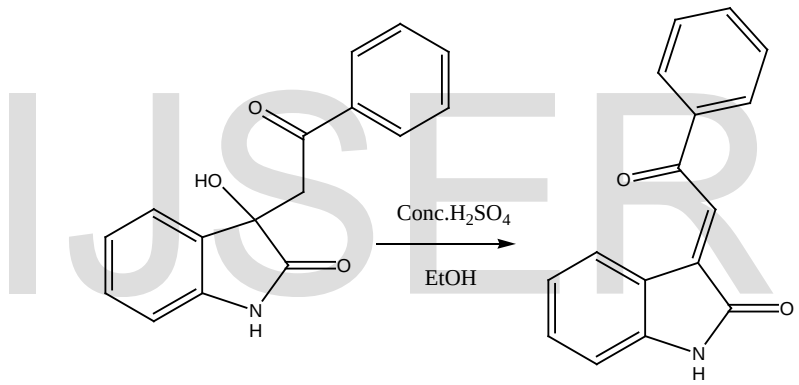
Among various nitrogen heterocycles, pyrroles were found to display a wide spectrum of biological applications. In our continued interest in the development of a highly expedient methodology for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we describe herein an one-pot three component reaction 3-phenacylidene oxindole, ethyl acetoacetate and ammonium acetate.

Pyrrole and its derivatives are ubiquitous among naturally occurring organic compounds. They are commonly found as structural motifs in bioactive molecules such as porphyrins, alkaloids and co-enzymes. In view of their importance, there has been continuing interest in developing novel synthetic routes.

For the synthesis of pyrrolo oxindole, the precursor 3-hydroxy-3-phenacyl oxindole was synthesized by a new, simple and efficient method. The reaction was conducted at room temperature by stirring a mixture of isatin and acetophenone in methanol:water (1:1) containing a catalytic amount of Na_2CO_3 (20 mol %). The product precipitated from the reaction mixture. No column chromatography or recrystallization was required for its purification.



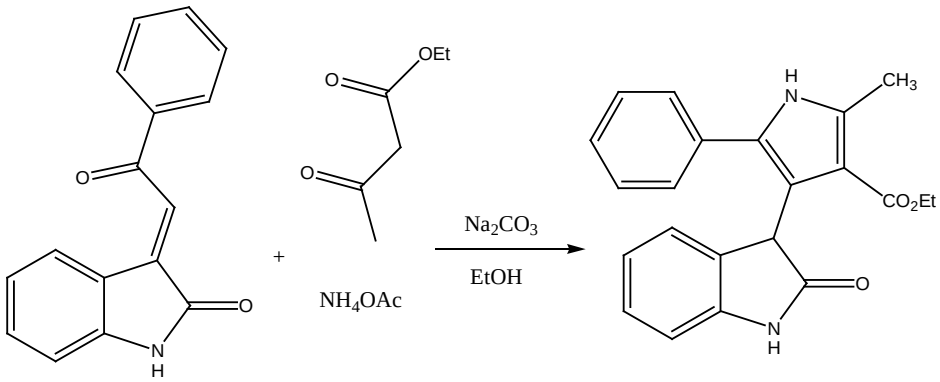
The starting material, 3-phenacylidene oxindole required for the synthesis of pyrrolo oxindole was synthesized by acid catalyzed dehydration of 3-hydroxy-3-phenacyl oxindole.



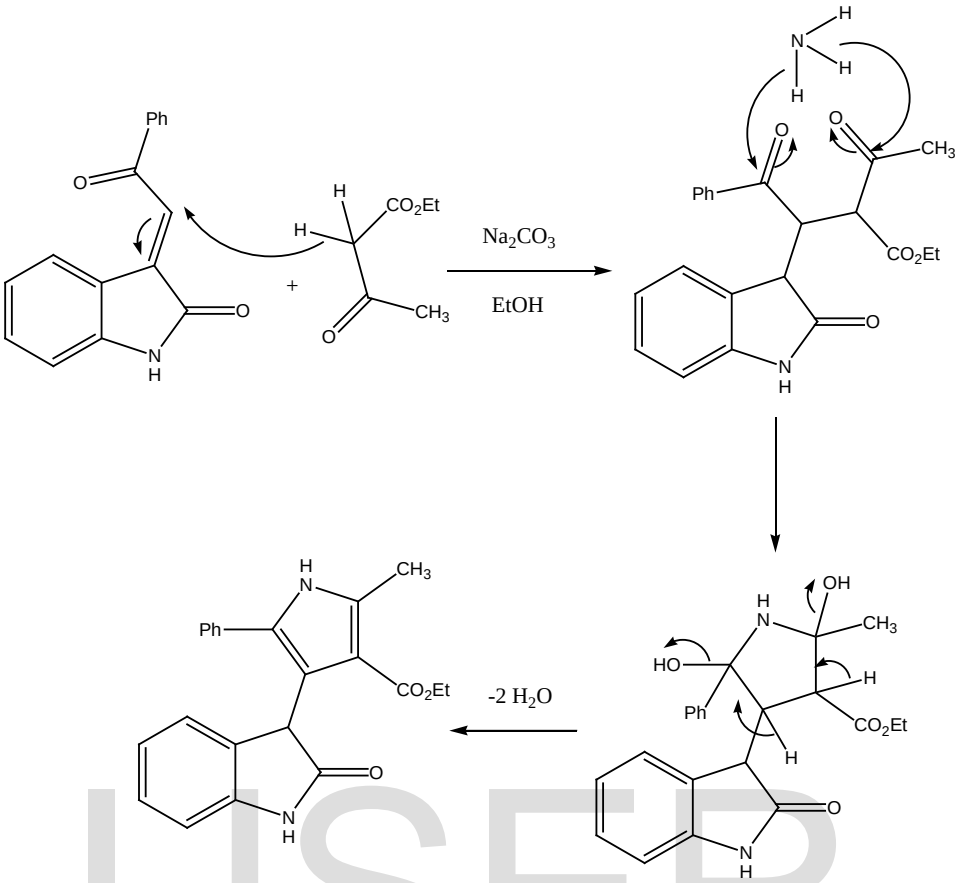
In our initial endeavour, we investigated the three component reaction of 3-phenacylideneoxindole, ethyl acetoacetate and ammonium acetate with various catalysts, namely triethyl amine and sodium carbonate and solvent systems (methanol and ethanol) for the synthesis of pyrrolo oxindole. After systematic screening, sodium carbonate and ethanol were found to be the optimum catalyst (20 mol %) and solvent.

The reaction was carried out with 3-phenacylideneoxindole (1 eq), β-keto ester (1 eq) and ammonium acetate (2.5 eq) catalyzed by Na_2CO_3 (20 mol %) in ethanol and refluxed for 2 hours. After completion of the reaction (as indicated by TLC), the solid

obtained was filtered and dried. This protocol is remarkably simple and requires no purification technique like column chromatography



Mechanism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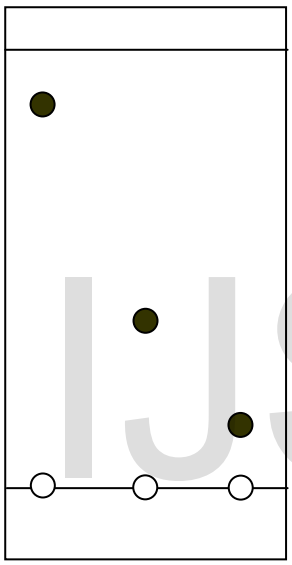
CHARACTERISATION

Result for the Synthesis of Pyrrolo oxindole from ethyl acetoacetate:

UV-254 nm visualization

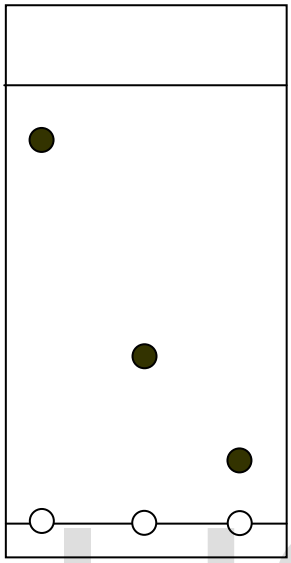


1. ethyl acetoacetate
2. 3-phenacylideneoxindole
3. Reaction mixture

Eluent : 50 % EA in Pet. ether

Result for the Synthesis of Pyrrolo oxindole from methyl acetoacetate:

UV-254 nm visualization

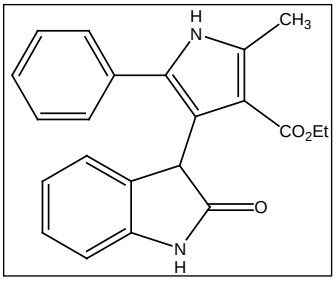


1. methyl acetoacetate
2. 3-phenacylideneoxindole
3. Reaction mixture

Eluent : 50 % EA in Pet. ether

Product Interpretation

Ethyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate



Structure determination by using NMR Spectrum

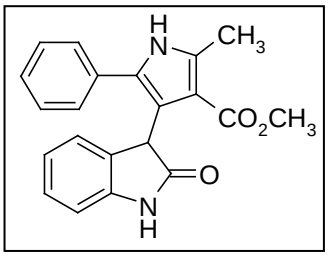
^{1}H NMR (500 MHz, DMSO-d_6) δ:	
2.46 (s, 3H),	-CH_3
0.84 (t, 3H, *J* = 6.9 Hz),	-$CO_2CH_2\underline{CH_3}$
3.69 (m, 2H)	-$CO_2\underline{CH_2}CH_3$
4.59 (s, 1H)	Methine proton (oxindole)
11.63 (s, 1H, NH, D_2O exchangeable)	-NH (pyrrole)
10.35 (s, 1H, NH, D_2O exchangeable)	-NH (oxindole)
6.76 (m, 3H), 6.97 (m, 1H), 7.09 (m, 5H)	Aromatic protons
^{13}CNMR (125MHz, DMSO-d_6) δ:	
13.9	-CH_3

13.1	$-CO_2CH_2\underline{CH_3}$
57.8	$-CO_2\underline{CH_2}CH_3$
178.4	$-CO_2CH_2CH_3$
163.9	-C=O (oxindole)
44.7	Methine carbon
108.7, 109.7, 113.7, 120.8, 122.4, 126.9, 127.3, 127.7, 127.8, 128.8, 131.6, 131.7, 131.8, 136.6, 142.9	Aromatic carbons

Structure determination by using FT - IR Spectrum

(KBr)ν_{max} cm^{-1} :	
3354,	-NH (pyrrole)
3211	-NH (oxindole)
1668	-C=O (oxindole)
1700	-C=O (ester)

Methyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate



Structure determination by using NMR Spectrum

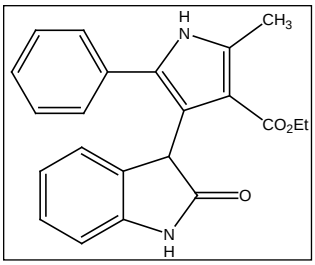
^{1}H NMR (500 MHz, DMSO-d_6) δ:	
2.40 (s, 3H)	-CH_3
3.17 (s, 3H)	-$CO_2\underline{CH_3}$
4.55 (s, 1H)	Methine proton (oxindole)
11.61 (s, 1H, NH, D_2O exchangeable)	-NH (pyrrole)
10.32 (s, 1H, NH, D_2O exchangeable)	-NH (oxindole)
7.08 (m, 1H), 7.31 (t, 1H, *J* = 7.65 Hz), 7.42 (t, 2H, *J* = 7.65 Hz), 7.52 (d, 2H, *J* = 7.65 Hz)	Aromatic protons
^{13}CNMR (125MHz, DMSO-d_6) δ:	
12.9	-CH_3
44.6	-$CO_2\underline{CH_3}$
178.5	-$\underline{C}O_2CH_3$
164.4	-C=O (oxindole)
49.2	Methine carbon
108.6, 109.4, 113.9, 120.9, 122.4, 127.0, 127.3, 128.8, 131.5, 131.7, 131.8, 136.5, 142.9	Aromatic carbons

Structure determination by using FT - IR Spectrum

$(KBr)\nu_{max}\ cm^{-1}$:	
3357	-NH (pyrrole)
3207	-NH (oxindole)
1671	-C=O (oxindole)
1694	-C=O (ester)

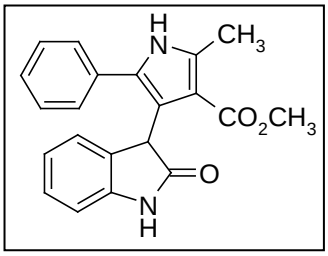
Spectral data

1. Ethyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate

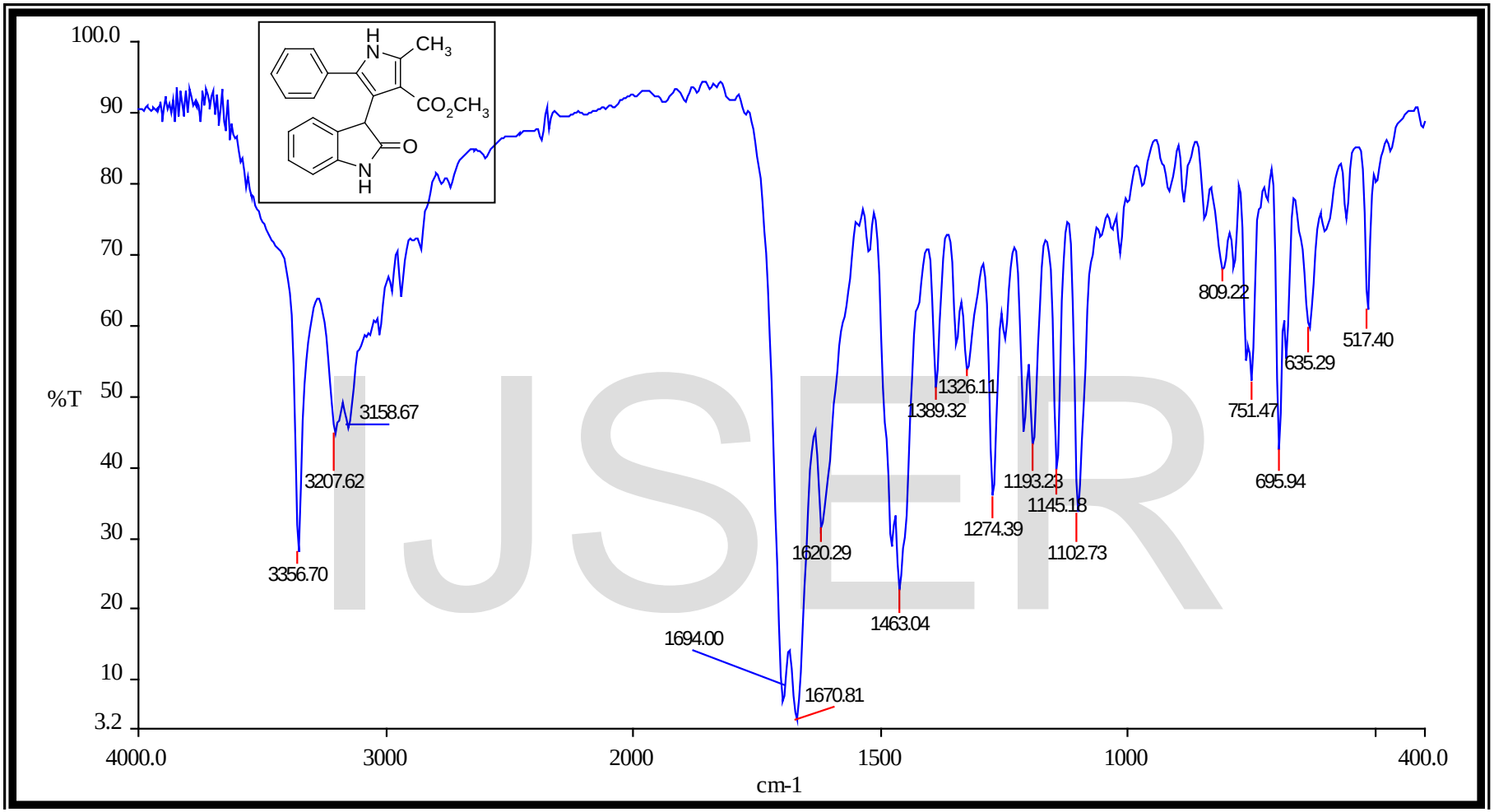


Appearance	White solid
Melting point	317-318^{o}C
FT-IR (KBr)ν_{max} cm^{-1}	3354, 3211, 1700, 1668, 1465, 1100, 699
^{1}H NMR (500 MHz, DMSO d$_6$) δ:	0.84 (t, 3H, *J* = 6.9 Hz), 2.46 (s, 3H), 3.69 (m, 2H), 4.59 (s, 1H), 6.76 (m, 3H), 6.97 (m, 1H), 7.09 (m, 5H), 10.35 (s, 1H, NH, D_2O exchangeable), 11.63 (s, 1H, NH, D_2O exchangeable)
^{13}CNMR(125MHz, DMSOd$_6$)δ:	13.1, 13.9, 44.7, 57.8, 108.7, 109.7, 113.7, 120.8, 122.4, 126.9, 127.3, 127.7, 127.8, 128.8, 131.6, 131.7, 131.8, 136.6, 142.9, 163.9, 178.4
MS *m/z*	360 (M^+)
Elemental Analysis	$C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77 %. Found: C, 73.27; H, 5.52; N, 7.70 %

2. Methyl 2-methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate



Appearance	White solid
Melting point	316-317^{o}C
FT-IR (KBr)ν_{max} cm^{-1}	3357, 3207, 1694, 1671, 1463, 1103, 696
^{1}H NMR (500 MHz, DMSO d$_6$) δ:	2.40 (s, 3H), 3.17 (s, 3H), 4.55 (s, 1H), 6.79 (m, 3H), 7.08 (m, 1H), 7.31 (t, 1H, *J* = 7.65 Hz), 7.42 (t, 2H, *J* = 7.65 Hz), 7.52 (d, 2H, *J* = 7.65 Hz), 10.32 (s, 1H, NH, D_2O exchangeable), 11.61 (s, 1H, NH, D_2O exchangeable)
^{13}CNMR(125MHz, DMSOd$_6$)δ:	12.9, 44.6, 49.2, 108.6, 109.4, 113.9, 120.9, 122.4, 127.0, 127.3, 128.8, 131.5, 131.7, 131.8, 136.5, 142.9, 164.4, 178.5
MS *m/z*	346 (M^+)
Elemental Analysis	$C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09 %. Found: C, 72.75; H, 5.16; N, 8.01 %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N
CH3
CO2CH3
O
N
H
3356.70
3207.62
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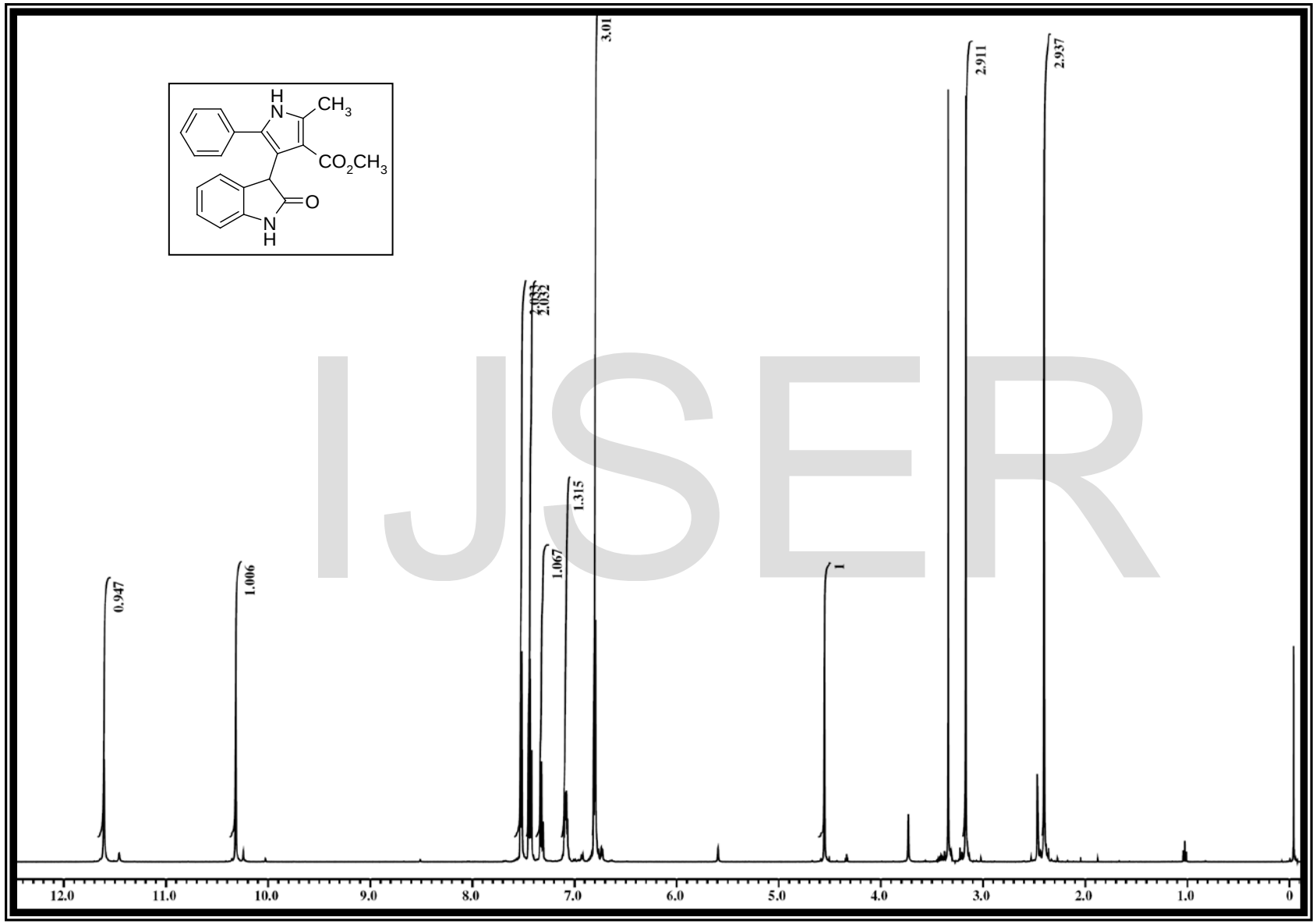
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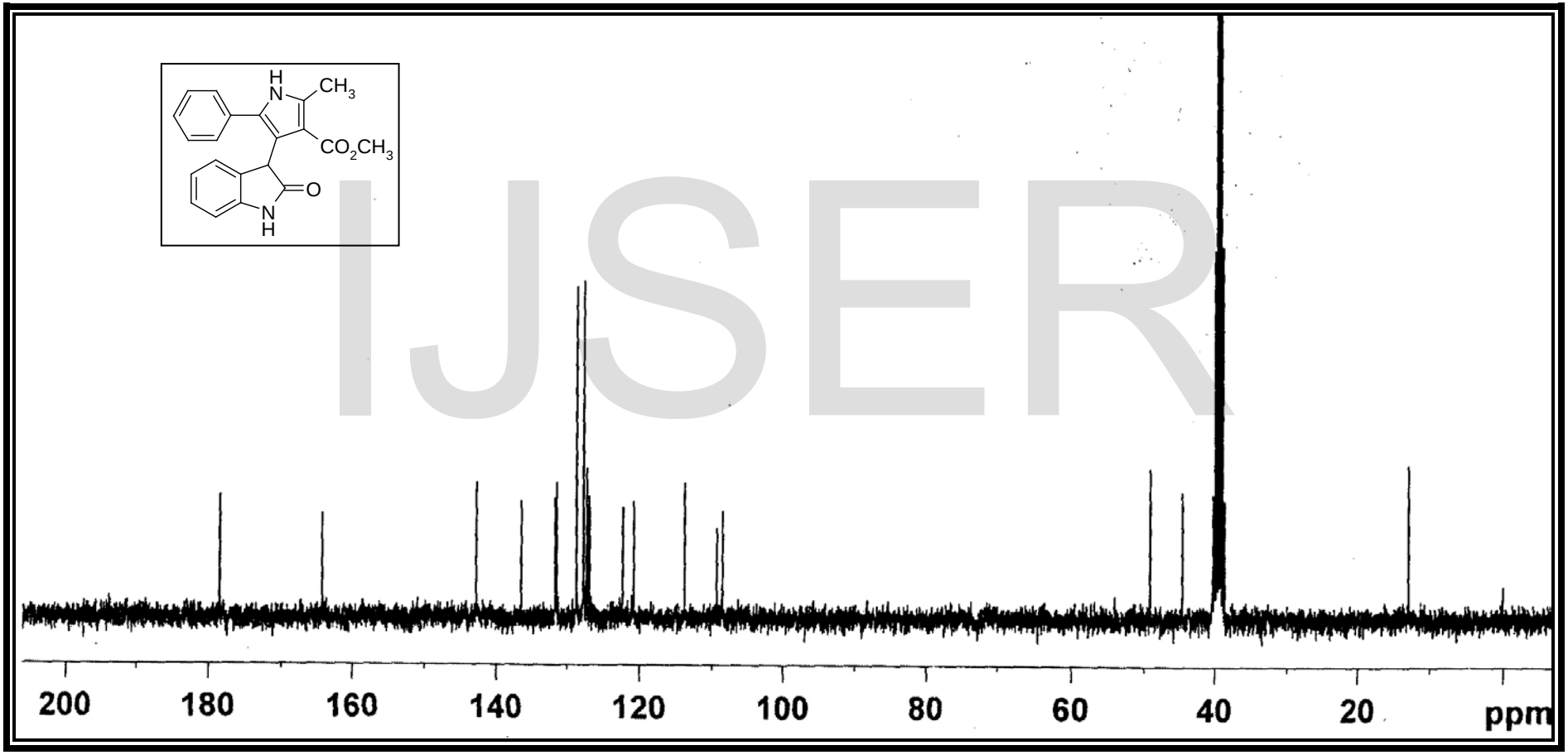

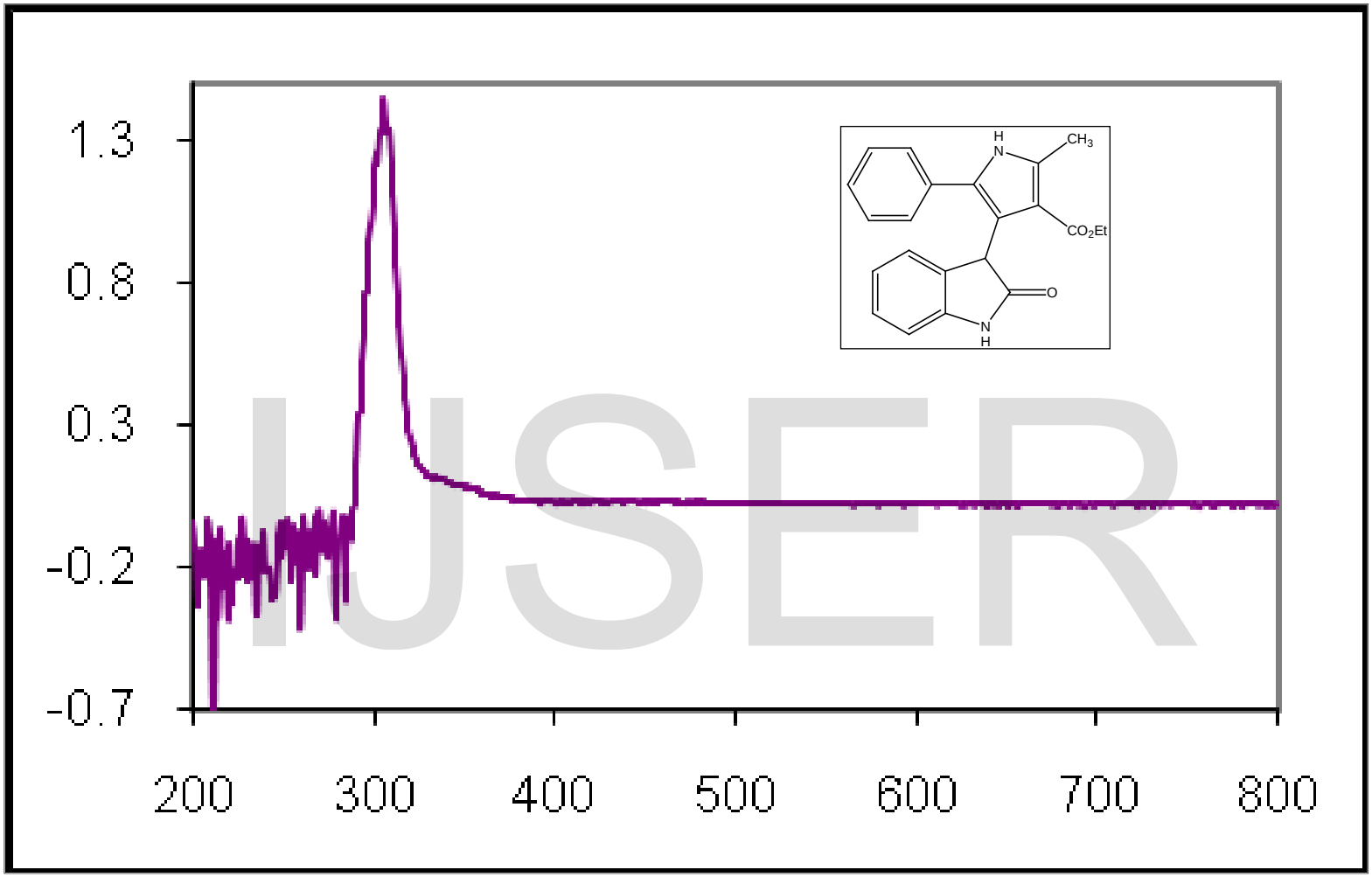

CHAPTER – VI

CONCLUSION

In conclusion, we have described a facile and efficient one pot synthesis of pyrrolo oxindoles in good yields. Easy work-up and no purification technique was required for the isolation of pyrrolo oxindoles. Further, its precursor 3-hydroxy-3-phenacyl oxindole was prepared by a new and efficient method. It was synthesized in good yields by sodium carbonate catalyzed reaction of isatin with acetophenone in methanol:water (1:1). The present methodology offers several advantages such as excellent yields, simple procedure, neat and mild conditions.

CHAPTER-VII

BIBLIOGRAPHY

1. Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

2. Laurent, A.; Gerhardt, C. F. *Liebigs Ann. Chem.* **1838**, *28*, 265.

3. Ishitani, H.; Komiyama, S. Y.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.

4. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

5. Bossert, F.; Meyer, H.; Wehinger, R. *Angew. Chem.* **1981**, *93*, 755.

6. Biginelli, P. *Gass. Chim. Ital.* **1893**, *23*, 360.

7. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (c) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1.

8. Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.

9. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.* **1998**, *110*, 1096.

10. Robinson, R. *J. Chem. Soc.* **1917**, *111*, 876.

11. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.

12. Ugi, I.; Meyr, R.; Beck, B.; Messer, K.; Herdtweck, E.; Domling, A. *Org. Lett.* **2003**, *5*, 4021.

13. Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotti, P.; Jundo, A. *Tetrahedron* **1995**, *51*, 9045.

14. Lu, E.; Hur, C. U.; Rhee, Y. H.; Park, Y. C.; Kim, S. Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1466.

15. Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235.

16. Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. *Org. Lett*. **2005**, *7*, 4321.

17. Sato, S.; Isobe, H.; Tanaka, J.; Ushijima, T.; Nakamura, E. *Tetrahedron* **2005**, *61*, 11449.

18. Cavicchioli, M.; Sixdenier, E.; Derrcy, A.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **1997**, *38*, 1763.

19. Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 1558.

20. Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038.

21. Anzalone, P. W.; Mohan, R. S. *Synthesis* **2005**, 2661.

22. Zhu, S. -L.; Ji, S. –J.; Su, X. –M; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008,** *49*, 1777.

23. Zhu, S. -L.; Ji, S. -J.; Zhao, K.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 2578.

24. Magedov, I. V.; Luchetti, G.; Evdokimov, N. M.; Manpadi, M.; Steelant, W. F. A.; Slambrouck, S. V. Tongwa, P.; Antipin, M. Y.; Kornienko, S. *Bioorg. & Med. Chem. Lett.* **2008**, *18*, 1392.

25. Wang, B.; Li, J. -Q.; Cheng, Y. *Tetrahedron Lett.* **2008**, *49,* 485.

26. Alizadeh, A.; Rezvanian, A.; Zhu, L. -G. *Tetrahedron* **2008**, *64,* 351.

27. Sun, C.; Ji, S. -J.; Liu, Y. *Tetrahedron Lett.* **2007**, *48,* 8987.

28. Kumar, A.; Akanksha *Tetrahedron Lett.* **2007**, *48* ,8730.

29. Heravi, M. M.; Ranjbar, L.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal. A: Chem.* **2007**, *276,* 226.

30. Teimouri, M. B.; Khavasi, H. R. *Tetrahedron* **2007**, *63,* 10269.

31. Ahmadi, E.; Ramazani, A.; Haghighi, M. N. *Tetrahedron Lett.* **2007**, *48,* 6954.

32. Elinson, M. N.; Vereshchagin, A. N.; Feducovich, S. K.; Zaimovskaya, T. A.; Starikova, Z. A.; Belyakov, P. A.; Nikishin, G. I. *Tetrahedron Lett.* **2007**, *48,* 6614.

33. Alizadeh, A.; Zohreh, N.; Rostamnia, S. *Tetrahedron* **2007**, *63,* 8083.

34. Sridhar, M.; Rao, R. M.; Baba, N. H. K.; Kumbhare, R. M. *Tetrahedron Lett.* **2007**, *48,* 3171.

35. Maghsoodlou, M. T.; Marandi, G.; Hazeri, N.; Aminkhani, A.; Kabiri, R. *Tetrahedron Lett.* **2007**, *48,* 3197.

36. Jimenez-Alonso, S.; Estevez-Braun, A.; Ravelo, A. G.; Zarate, R.; Lopez, M. *Tetrahedron* **2007**, *63,* 3066.

37. Yu, L.; Chen, B.; Huang, X. *Tetrahedron Lett.* **2007**, *48,* 925.

38. Crich, D.; Bowers, A. A. *Org. Lett.* **2007**, *9,* 5323.

39. Rosamilia, A. E.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2007**, *9,* 1245.

40. Ghosh, A. K.; Xu, C. -X.; Kulkarni, S. S.; Wink, D. *Org. Lett.* **2005**, *7,* 7.

41. Cui, S. -L.; Lin, X. -F.; Wang, Y. -G. *Org. Lett.* **2006**, *8,* 4517.

42. Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72,* 1811.

43. Xu, X.; Cheng, D.; Li, J.; Guo, H.; Jie, Y. *Org. Lett.* **2007**, *9,* 1585.

44. Cui, S. -L.; Wang, L.; Wang, Y. -G. *Org. Lett.* **2008**, *10*, 1267.

45. Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72,* 8611.

46. Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*, *Academic, London*, **1977**.

47. Furstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3528.

48. Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Lin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

49. Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2004**, *66*, 4058.

50. Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C. Pereira, L. O. R. Ferreira, M. L. G. *Org. Prep. Proceed. Int.* **2001**, *33*, 441.

51. Oda, M.; Fukuchi, Y.; Ito, S.; Thanh, N. C.; Kuroda, S. *Tetrahedron Lett.* **2007**, *48*, 9159.

52. Shastri, L.; Kalegowda, S.; Kulkarni, M. *Tetrahedron Lett.* **2007**, *48*, 7215.

53. Pridmore, S. J.; Slatford, P. A.; Daniel, A.; Whittlesey, M. K. Williams, J. M. J. *Tetrahedron Lett.* **2007**, *48*, 5115.

54. Azizian, T.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 1471.

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