



Vilsmeier-Haack Methodology as a Key Step to Novel Heterocycles: Synthesis of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde

Manisekar Sathiyaseelan¹, Amaladoss Nepolraj¹, Pandian Pitchai^{1*},
Gengan Robert Moonsamy²

¹Department of Chemistry, Government Arts College (Auto), Kumbakonam, Thanjavur - 612 001, Tamil Nadu, India. ²Department of Chemistry, Steve Biko Campus, Durban University of Technology, Durban 4000, South Africa.

Received 26th January 2016; Revised 02th April 2016; Accepted 12th April 2016

ABSTRACT

The synthesis of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde is achieved through a dual utility of Vilsmeier-Haack reaction. The utility of cheaper precursors in addition to easy work-up procedures contributes to an important synthetic strategy.

Key words: Vilsmeier Haack, 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde, 2-chloro-3-phenylquinoline.

1. INTRODUCTION

A parallel growth of horrible diseases and attempted solutions by chemists and biologists is increasing at a tremendous rate. Although ancestral concoctions using a variety of plant materials to serve as anti-inflammatory, antimalarial, antihypertensive, and antivasculature is encouraging; however, identifying the active components in this group is difficult yet essential [1-4]. The major components with biological activities are usually alkali in nature and belong to the class of alkaloids [5,6]. Even though terpenoids, steroids carbohydrates, flavones, flavonoids, and anthocyanins also display good biological activities, their application is marginal. The indole and quinoline alkaloids are abundant in plants belonging to *Rutaceae* [7-12]. Our laboratory has surveyed the applications and reported a variety of approaches to synthesis derivatives in excellent yield [13-18].

Although the natural abundance of organic compounds containing the pyrazole moiety is quite uncertain, their synthesis especially with fused and condensed systems of other heterocycles shows unimaginable applications in pharmaceuticals. With the continuous exploration of synthesis of some pyrazoloquinazolines as reported earlier by us [18], we herein successfully synthesized a novel condensed pyrazoloquinoline using readily available chemicals via an economic route (Scheme 1).

2. EXPERIMENTAL

2.1. General Methods

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform IR spectrophotometer as potassium bromide discs unless otherwise indicated. ¹H nuclear magnetic resonance (NMR) spectra were obtained on a Bruker (400 MHz) instrument in CDCl₃ solutions using tetramethylsilane as an internal standard. *J* values are given in Hz. Mass spectra were obtained at the Vellore Institute of Technology, Vellore, Tamil Nadu, India. Column chromatography utilized Merck silica gel 60 and hexane and ethyl acetate as eluents. All the basic chemicals were purchased from Merck (India).

2.2. Synthesis of 2-hydrazinyl-3-phenylquinoline 3

About 0.01 mole (2.39 g) of 2-chloro-3-phenylquinoline 1 was dissolved in methanol and excess of hydrazine hydrate was added with a trace amount of sodium carbonate. The initial color of the mixture was yellow; it was allowed to reflux at 75°C for 5 h. The red coloration and thin layer chromatography (TLC) observation indicate the reaction progress, then it was poured into the crushed ice; it was extracted with ethyl acetate, concentrated and purified through column chromatography using petroleum ether and ethyl acetate (95:5) as an eluent.

*Corresponding Author:

E-mail: pitchaipandian@gmail.com

Phone: +91-9952455611

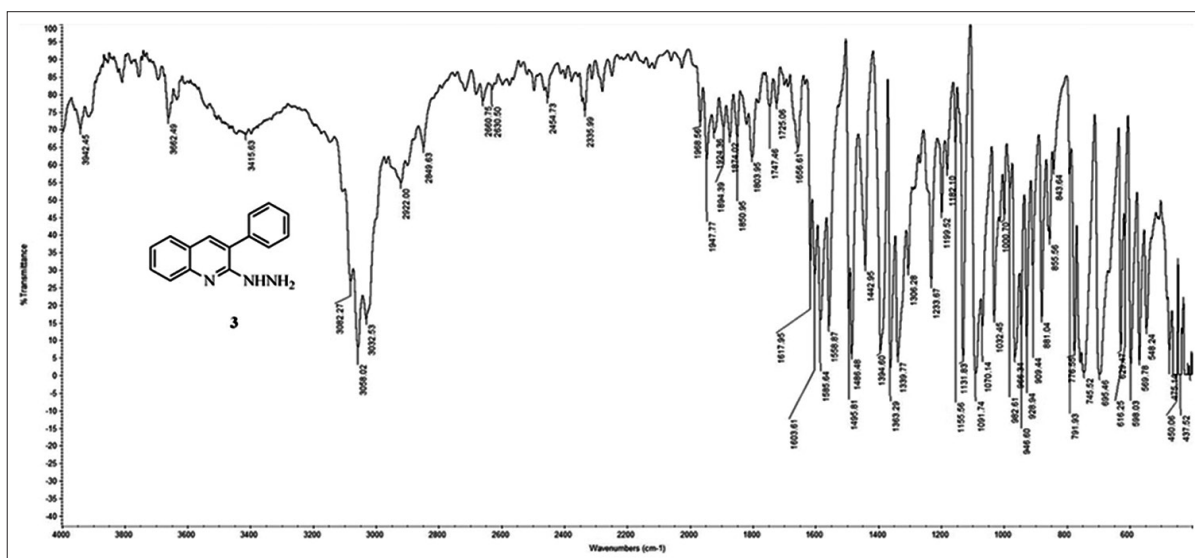


Figure 1: Infrared spectrum of 2-hydrazinyl-3-phenylquinoline 3.

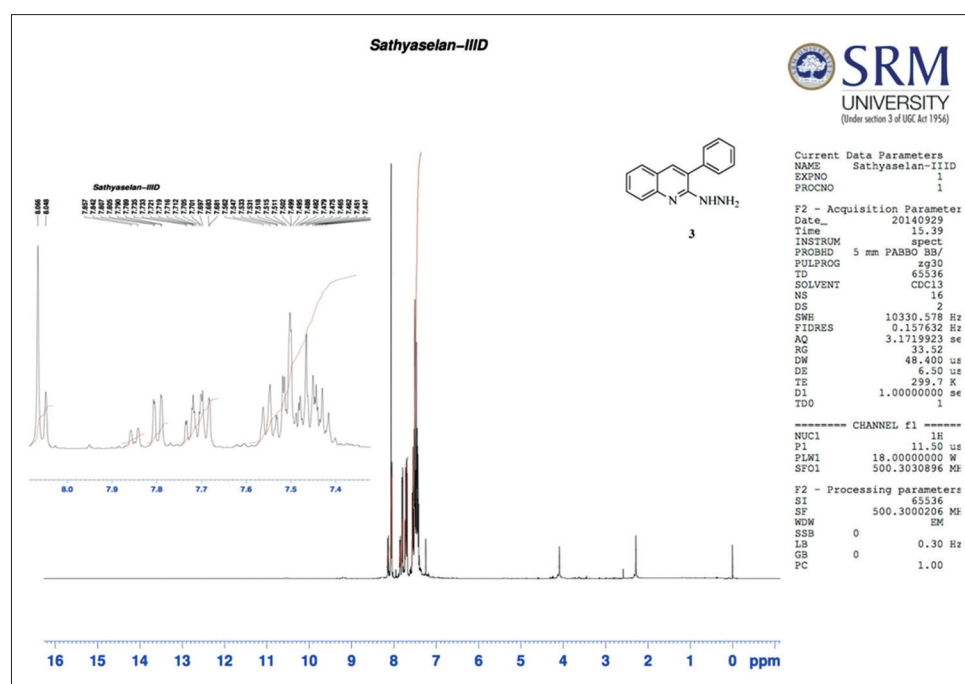


Figure 2: ^1H nuclear magnetic resonance spectrum of 2-hydrazinyl-3-phenylquinoline 3.

2.2.1. Preparation of 2-hydrazinyl-3-phenylquinoline 3

Dark brown greasy mass 90% (2.07 g) yield with unidentified melting point (Figure 1). IR (KBr): 3082, 3058, 3032, 2883, 1603 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) (Figure 2): 8.06 (s, 1H, $\text{C}_4\text{-H}$), 7.68-7.89 (m, 4H, C_5 , C_6 , C_7 and $\text{C}_8\text{-H}$), 7.41-7.56 (m, 5H, Ph-H), 4.10 (s, 1H, NH-H), 2.30 (s, 2H, $\text{NH}_2\text{-H}$). ^{13}C NMR (125 MHz, CDCl_3) (Figure 3): 149.93, 147.36, 138.84, 137.98, 137.65, 134.83, 133.86, 133.25, 130.45, 129.69, 129.23, 128.87, 128.14, 127.44.

2.3. Synthesis of 3-phenyl-2-(2-(1-phenylethylidene)hydrazinyl)quinoline 5

2-Hydrazinyl-3-phenylquinoline 3 (0.01 mole,

2.30 g) was weighed and mixed with acetophenone 4 (0.01 mole, 1.8 ml) in methanol and a catalytic amount of glacial acetic acid was added and allowed to reflux at 75°C for 5 h. The condensed material was then poured into ice-cold water; the precipitate was extracted with ethyl acetate, concentrated and purified through column chromatography with petroleum ether and ethyl acetate mixture (90:10).

2.3.1. Preparation of 3-phenyl-2-(2-(1-phenylethylidene)hydrazinyl)quinoline 5

Red color semisolid in 89% (2.86 g) yield greasy mass unidentified melting point. IR (KBr) (Figure 4): 3057, 3025, 2918, 1655 cm^{-1} . ^1H NMR (400MHz, CDCl_3)

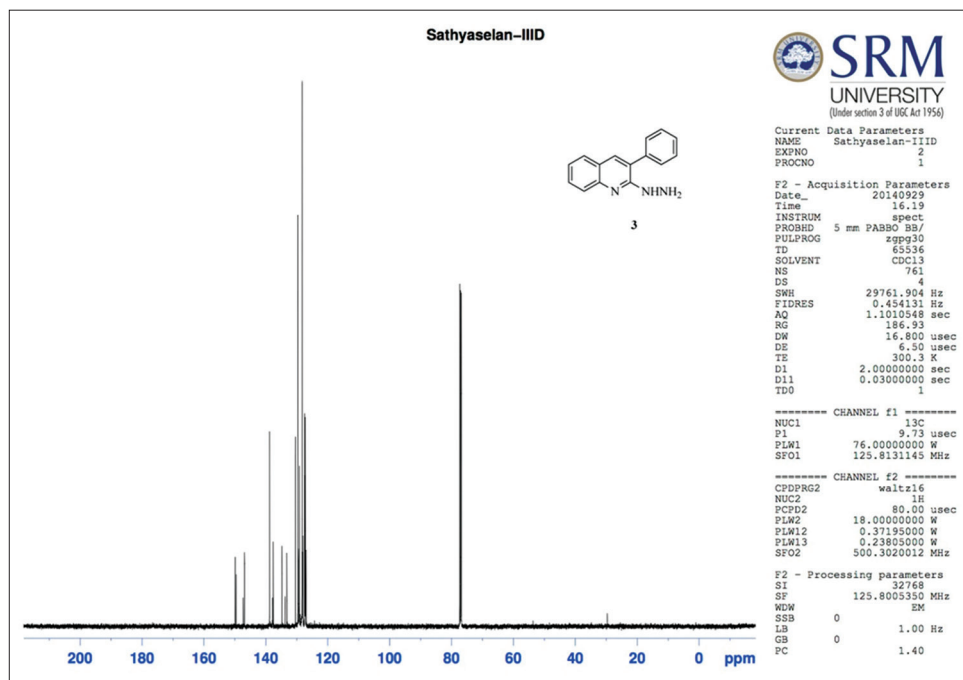


Figure 3: ¹³C nuclear magnetic resonance spectrum of 2-hydrazinyl-3-phenylquinoline 3.

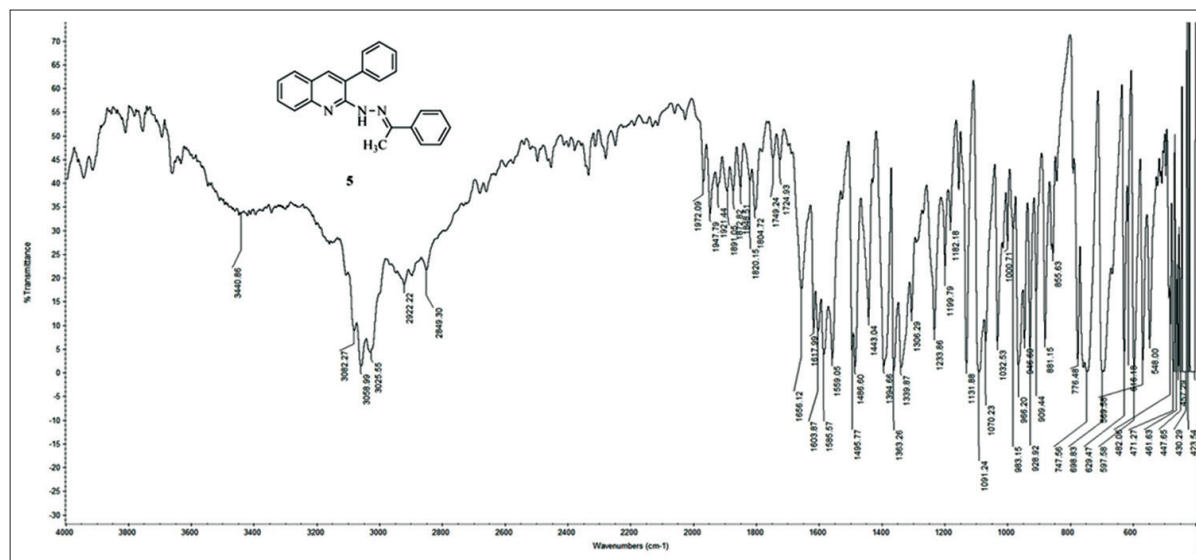


Figure 4: Infrared spectrum of 3-phenyl-2-(2-(1-phenylethylidene)hydrazinyl)quinone 5.

(Figure 5): 8.00 (s, 1H, C₄-H), 7.31-8.08 (m, 12H (for 5 *hy*-Ph-H, 3 Ph-C₂, C₆ and C₄ and Qui-C₅, C₆, C₇ and C₈-H)), 6.67-6.70 (d, 2H, *J*=8.20, Ph-C₃ and Ph-C₅), 7.0 (s, 1H, NH-H), 2.79 (s, 3H, CH₃-H). ¹³C NMR (100 MHz, CDCl₃) (Figure 6): 161.44, 150.89, 149.12, 141.91, 140.20, 137.91, 134.71, 132.27, 129.96, 129.86, 129.82, 127.20, 122.67, 122.39, 117.00, 116.75, 116.51, 111.32, 111.17, 110.54, 30.99.

2.4. Synthesis of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde 6

Dimethylformamide (0.05 mole, 3.85 ml) is cooled

to 0°C in a flask equipped with a dropping funnel. Phosphoryl chloride (0.14 mole, 12.97 ml) is added dropwise from the funnel with stirring. The resultant reagent was stirred for a further 30 min at room temperature and then cooled to 5°C then 3.37 g (0.01, mole) 3-phenyl-2-(2-(1-phenylethylidene)hydrazinyl)quinoline 5 is added and the stirring is further continued for 30 min and shifted over water bath and heated for 17 h. After being subjected to the reaction conditions, the reaction mixture was then poured into crushed ice and neutralized with sodium carbonate solution. The solid 3-phenyl-1-(3-phenylquinolin-2-

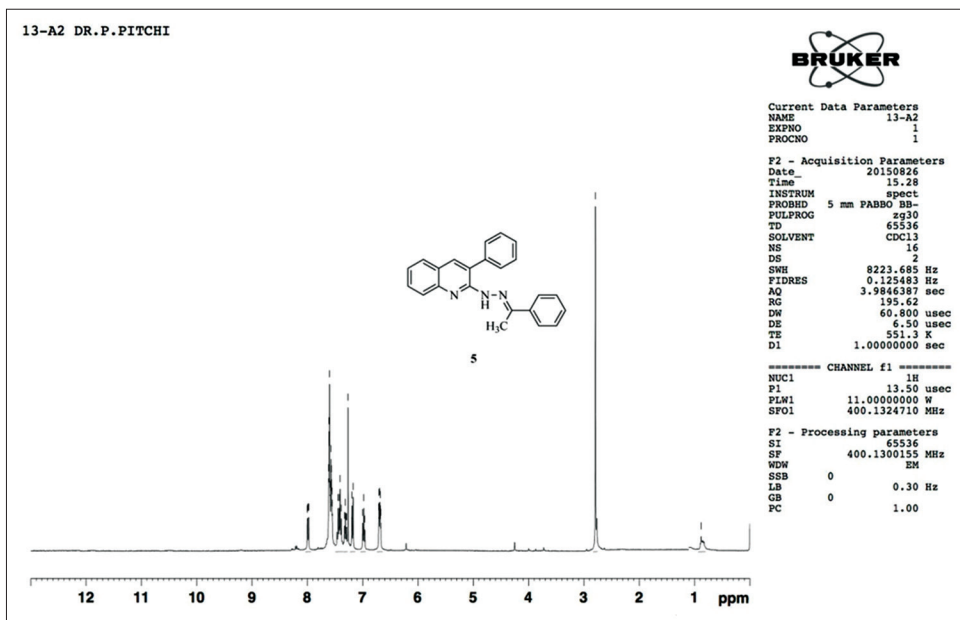


Figure 5: ¹H nuclear magnetic resonance spectrum of 3-phenyl-2-(2-(1-phenylethidene) hydrazinyl)quinone 5.

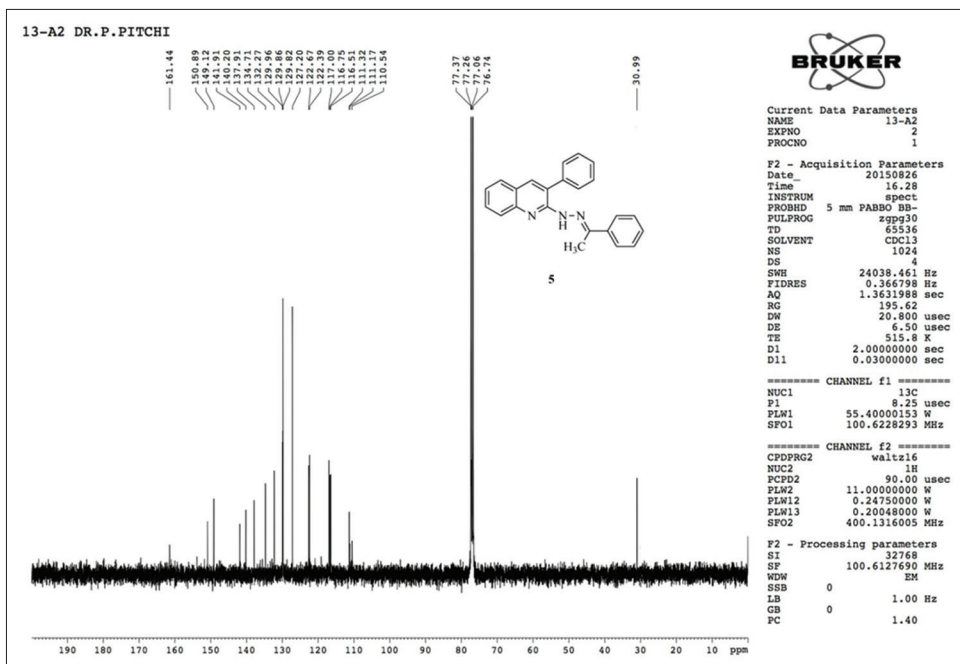


Figure 6: ¹³C nuclear magnetic resonance spectrum of 3-phenyl-2-(2-(1-phenylethidene) hydrazinyl)quinone 5.

yl)-1*H*-pyrazole-4-carbaldehyde 6 was filtered and dried, then purified with column chromatography in petroleum ether elution.

2.4.1. Preparation of 3-phenyl-1-(3-phenylquinolin-2-yl)-1*H*-pyrazole-4-carbaldehyde 6

Yellow solid in 65% yield (2.44 g), m.p 91°C. IR (KBr) (Figure 7): 3062, 3058, 2849, 1668 cm⁻¹. ¹H NMR (500MHz, CDCl₃) (Figure 8): 12.80 (s, 1H, -CHO-H), 7.25-7.87 (m, 15H, 2 × Ph-H, pyra-H, C₄, C₅, C₆, C₇ and C₈-H). ¹³C NMR (100 MHz, CDCl₃) (Figure 9): 190.22, 145.10, 145.07, 144.94, 143.31, 141.83,

141.72, 140.21, 132.80, 131.71, 130.92, 129.90, 129.88, 129.80, 129.63, 129.30, 129.09, 128.99, 128.92, 128.82, 127.18, 127.13, 126.47, 125.11, 124.79.

3. RESULTS AND DISCUSSION

In the first step of the reaction, 2-chloro-3-phenylquinoline 1 was obtained by the procedure described in our recent report [19]; it was thereafter reacted with hydrazine hydrate 2 with a catalytic amount of sodium carbonate in ethanol and refluxed at 75°C continuously for 5 h. The reaction was monitored

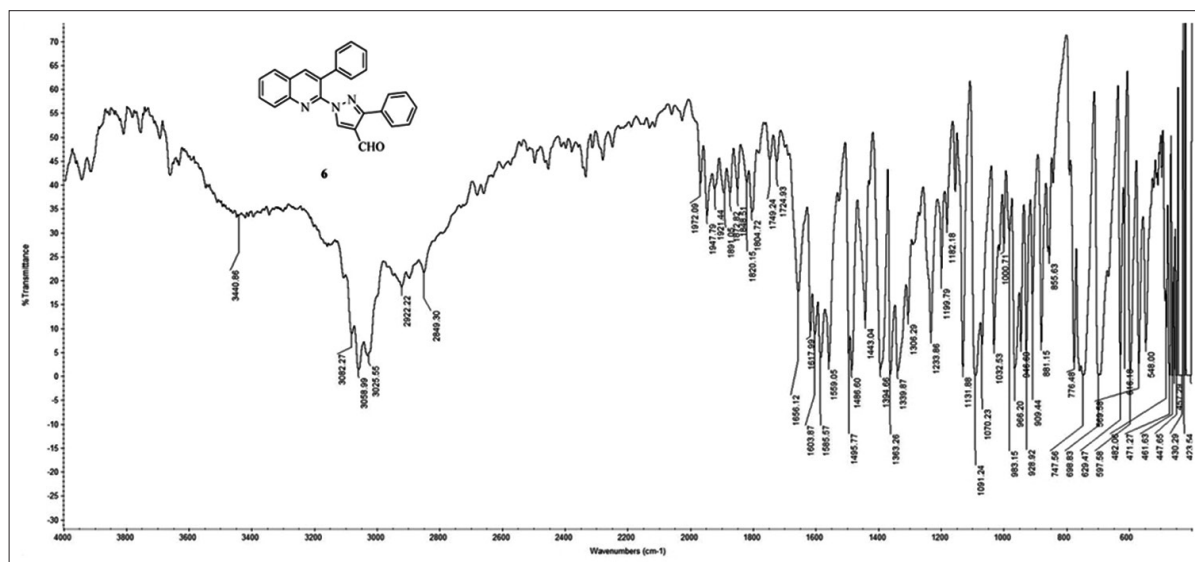


Figure 7: Infrared spectrum of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde 6.

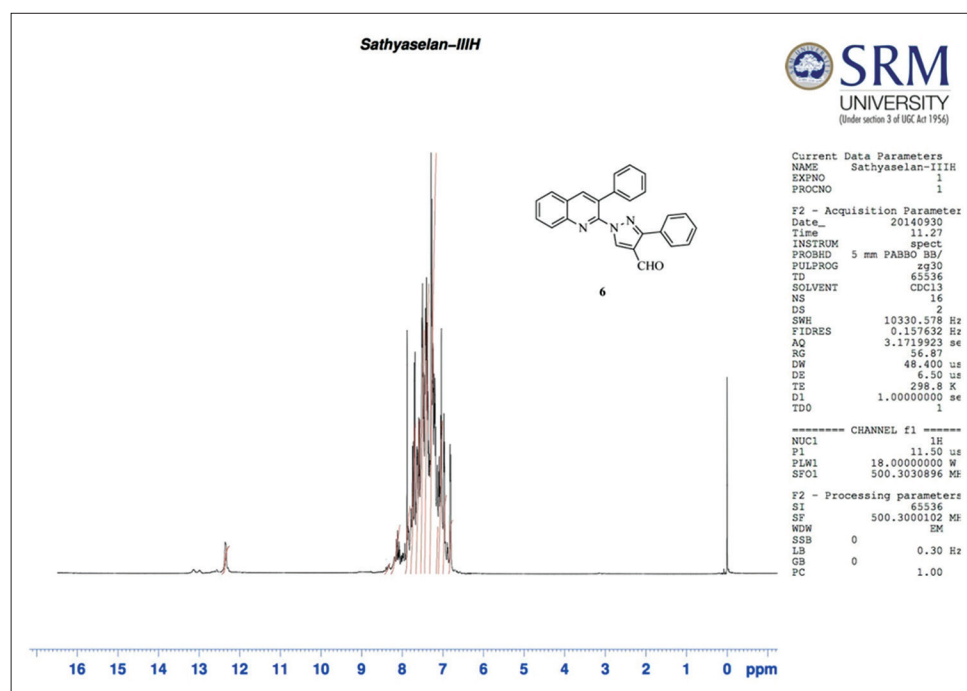


Figure 8: ¹H nuclear magnetic resonance spectrum of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde 6.

by TLC: The appearance of a change of yellow to dark red color indicated evidence in the formation of a new product. Spectroscopic analysis proved the structure as 2-hydrazinyl-3-phenylquinoline 3; the IR spectrum showed the disappearance of a C-Cl stretching at 750 cm⁻¹ which was present in 1. Furthermore, the ¹H-NMR spectrum indicated a two-proton singlet at δ 4.10 and a one-proton singlet at δ 2.30 thereby indicating the nucleophilic replacement of chloride by the hydrazinyl group. When 3 was refluxed with acetophenone 4 with a catalytic amount of glacial acetic acid in methanol at 75°C for 5 h, a

new compound 5 resulted. The ¹H-NMR showed the appearance of a three-proton singlet at δ 2.79 for CH₃ group, the disappearance of a characteristic two-proton singlet of NH₂ at δ 2.30 while the appearance of a signal at δ 30.99 in ¹³C NMR spectrum supported the structure of 3-phenyl-2-(2-(1-phenylethylidene)hydrazinyl)quinoline 5. Compound 5 was finally used by the Vilsmeier-Haack protocol: A POCl₃ and DMF mixture to produce 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde 6. IR spectrum showed C-H stretching frequency at 2849 cm⁻¹ and C=O stretching at 1656 cm⁻¹ are the appreciable area

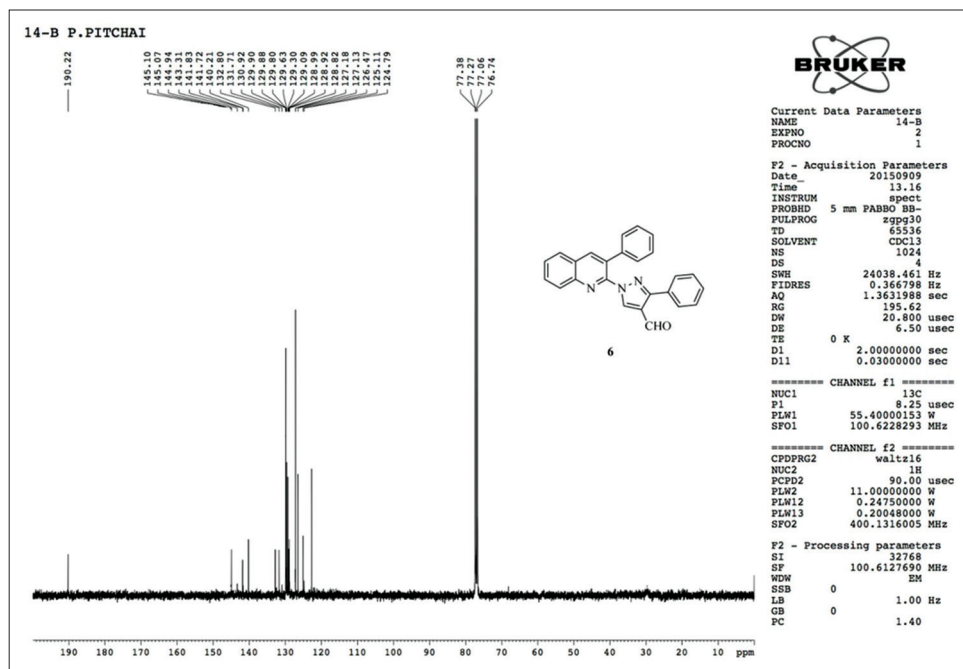
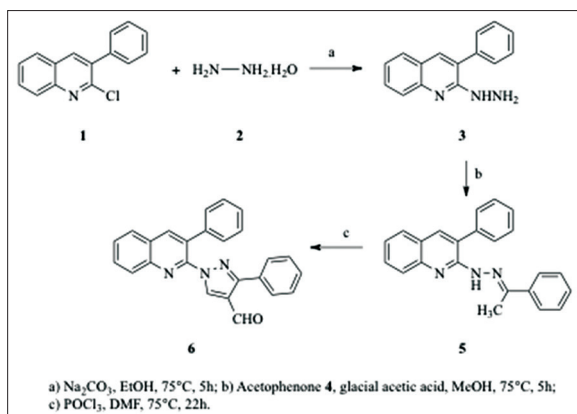


Figure 9: ^{13}C nuclear magnetic resonance spectrum of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde 6.



Scheme 1: Synthesis of 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde.

of aldehyde; δ 12.80 (s, 1H, -CHO-H), δ 7.25-7.87 (m, 15H, 2 Ph-H, pyra-H, C₄, C₅, C₆, C₇ and C₈-H) ^1H NMR, and the supporting ^{13}C NMR data are steadily explain the structure of compound 6.

4. CONCLUSION

A novel heterocycle 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde was synthesized via four reaction steps with the Vilsmeier Haack reaction making an important contribution to synthesis.

5. ACKNOWLEDGMENTS

Authors thank DST-SERB for funding this work, VIT, Vellore for Mass Spectral, and SRM University, Chennai for NMR spectral analysis.

6. REFERENCES

1. R. Nandhakumar, T. Suresh, P. S. Mohan, (2002) A photochemical route to synthesize cryptosanguinolone, *Tetrahedron Letters*, **43**: 3327-3328.
2. T. Dhanabal, R. Sangeetha, P. S. Mohan, (2006) Heteroatom directed photoannulation: Synthesis of indoloquinoline alkaloids: cryptolepine, cryptotackieine, cryptosanguinolentine, and their methyl derivatives, *Tetrahedron*, **62**: 6258-6263.
3. (a) E. Gellert, R. Hamet, E. Schlitter, (1951) Die konstitution des alkaloids cryptolepin, *Helvetica Chimica Acta*, **34**: 642-651. (b) D. Dwuma-Badu, J. S. K. Ayim, N. I. Y. Fiagbe, J. E. Knapp, P. L. Schiff Jr, D. J. Slatkin, (1978) Constituents of West African Medicinal Plants XX: Quindoline from *Cryptolepis sanguinolenta*, *Journal of Pharmaceutical Science*, **67**: 433-434. (c) S. Y. Ablordeppey, C. D. Hufford, R. F. Borne, D. Dwuma-Badu, (1990) ^1H -NMR and ^{13}C -NMR assignments of cryptolepine, A 3: 4-Benz- δ -carboline derivative isolated from *Cryptolepis sanguinolenta*, *Planta Medica*, **56**: 416-417. (d) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys, A. Vlietinck, (1996) New alkaloids from *Cryptolepis sanguinolenta*, *Tetrahedron Letters*, **37**: 1703-1706. (e) J. L. Pousset, M. T. Martin, A. Jossang, B. Bodo, (1995) Isocryptolepine from *Cryptolepis sanguinolenta*, *Phytochemistry*, **39**: 735-736. (f) A. N. Tackie, M. M. H. Sharaf, P. L. Schiff Jr, G. L. Boye, R. C. Crouch, G.

- E. Martin, (1991) Assignment of the proton and carbon NMR spectra of indoloquinoline alkaloid cryptolepine, *Journal of Heterocyclic Chemistry*, **28**: 1429-1435, (g) T. D. Spitzer, R. C. Crouch, G. E. Martin, M. M. H. Sharaf, P. L. Schiff Jr, A. N. Tackie, G. L. Boye, (1991) Total assignment of the proton and carbon NMR spectra of the alkaloid quindoline utilization of HMQC-TOCSY to Indirectly Establish protonated carbon connectivities, *Journal of Heterocyclic Chemistry*, **28**: 2065-2070. (h) A. N. Tackie, G. L. Boye, M. H. M. Sharaf, P. L. Schiff Jr., R. C. Crouch, T. D. Spitzer, R. L. Johnson, D. Dunn, J. Minick, G. E. Martin, (1993) Cryptospirolepine, A unique spiro-nonacyclic alkaloid isolated from *Cryptolepis sanguinolenta*, *Journal of Natural Products*, **56**: 653-798. (i) R. C. Crouch, A. O. Davis, T. D. Spitzer, G. E. Martin, M. M. H. Sharaf, P. L. Schiff Jr., C. H. Phoebe Jr., A. N. Tackie, (1995) Elucidation of the structure of quindolinone, a minor alkaloid of *Cryptolepis sanguinolenta*: Submilligram ¹H-¹³C and ¹H-¹⁵N heteronuclear shift correlation experiments using micro inverse –detection, *Journal of Heterocyclic Chemistry*, **32**, 1077-1080. (j) A. Paulo, E. T. Gomes, P. J. Houghton, (1995) New alkaloids from *Cryptolepis sanguinolenta*, *Journal of Natural Products*, **58**: 1485-1491. (k) D. M. Fort, J. Litvak, J. L. Chen, Q. Lu, P. W. Phuan, R. Cooper, D. E. Bierer, (1998) Isolation and unambiguous synthesis of cryptolepinone: An oxidation artifact of cryptolepine, *Journal of Natural Products*, **61**: 1528-1530. (l) C. E. Hadden, M. H. M. Sharaf, J. E. Guido, R. H. Robins, A. N. Tackie, C. H. Phoebe Jr., P. L. Schiff Jr., G. E. Martin (1999) 11-Isopropylcryptolepine: A novel alkaloid isolated from *Cryptolepis sanguinolenta* characterized using submicro NMR techniques, *Journal of Natural Products*, **62**: 238-240. (m) K. Blinov, M. Elyashberg, E. R. Martirosian, S. G. Molodtsov, A. J. Williams, A. N. Tackie, M. M. H. Sharaf, P. L. Schiff Jr., R. C. Crouch, G. E. Martin, C. E. Hadden, J. E. Guido, K. A. Mills, (2003) Quindolinocryptotackieine: The elucidation of a novel indoloquinoline alkaloid structure through the use of computer-assisted structure elucidation and 2D NMR, *Magnetic Resonance in Chemistry*, **41**: 577-584. (n) K. Cimanga, T. D. Bruyne, A. Lasure, B. V. Poel, L. Pieters, M. Claeys, D. V. Berghe, A. J. Vlietinck, (1996) *In vitro* biological activities of alkaloids from *Cryptolepis sanguinolenta*, *Planta Medica*, **62**: 22-27.
4. D. Karou, A. Savadogo, A. Canini, S. Yameogo, C. Montesano, J. Simporé, V. Colizzi, A. S. Traore, (2005) Antimicrobial activity of alkaloids from *sida acuta*, *African Journal of Biotechnology*, **4(12)**: 1452-1457.
 5. J. L. Yang, L. L. Liu, Y. P. Shi, (2011) Limonoids and quinoline alkaloids from *Dictamnus daycarpus*, *Planta Med*, **77**: 271-276.
 6. K. Mohan, R. Jeyachandran, R. Deepa, (2002) Alkaloids as anticancer agents, *Annals of Phytomedicine*, **1(1)**: 46-53.
 7. K. C. Nicolaou, J. L. Gross, M. A. Kerr, (1996) Total synthesis of hamigerans and analogues thereof. Photochemical generation and diels-alder trapping of hydroxy-o-quinodimethanes, *Journal of Heterocyclic Chemistry*, **33**: 735.
 8. G. Bringmann, Y. Reichert, V. Kane, (2004), Enantiopure isoplagiochin C by directed deracemization through axis-to-axis chirality transfer, *Tetrahedron*, **60**: 3539.
 9. I. Jaquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, (1999) Two tetrahydroquinoline alkaloids from *Galipea officinalis*, *Phytochemistry*, **51**: 1167.
 10. P. Pitchai, R. Ulagi, P. S. Mohan, R. M. Gengan, (2013) Derivatives of coumarins, cinnamic acid and tyramine from leaves of *Limonia crenulata*, *International Journal of Research in Phytochemistry and Pharmacology*, **3(1)**: 9-12.
 11. R. Ulagi, P. Pitchai, P. S. Mohan, R. M. Gengan, (2011) Analysis of precipitates from acetone extracts of *feronia limonia*, *Asian Journal of Chemistry*, **23(10)**: 4314-4316.
 12. P. Pitchai, R. Ulagi, P. S. Mohan, R. M. Gengan, (2012) A novel alkaloid, four alkaloid precursors and a coumarin from *Feronia limonia*, *Indian Journal of Chemistry*, **51B**: 1771-1775.
 13. P. Pitchai, C. Uvarani, T. R. Makhanya, R. M. Gengan, P. S. Mohan, (2014) Synthesis of cryptosanguinolentine and its phenyl derivative via eco-friendly sources, *Research and Reviews: Journal of Chemistry*, **3**: 60-71.
 14. R. M. Gengan, P. Pitchai, K. Chandraprakash, P. S. Mohan, (2010) Convenient and efficient microwave-assisted synthesis of a methyl derivative of a fused indoloquinoline alkaloid cryptosanguinolentine, *Molecules*, **15**: 3171-3178.
 15. R. M. Gengan, P. Pandian, H. G. Ndaba, P. S. Mohan, (2015) Utility of vilsmeier- haack reaction in the cyclization of heterocycles: Synthesis of phenyl-dibenzo[b,h][1,6] naphthyridines, *Elixir Applied Chemistry*, **86**: 35088-35089.
 16. P. Pitchai, P. S. Mohan, R. M. Gengan, (2009) Photo induced synthesis of methyl derivative cryptosanguinolentine, *Indian Journal of Chemistry*, **48B**: 692-696.
 17. K. Babu, P. Pitchai, (2015) Multi-component reaction (MCR): Synthesis of unsymmetrical dihydro-1H- Indeno [1, 2-b] pyridines catalyzed

- by $ZrOCl_2 \cdot 8H_2O$, *Elixir Organic Chemistry*, **68**: 22658-22659.
18. K. Babu, P. Pitchai, M. Sathiyaseelan, A. Napolraj, (2015) Novel pyrazoline derivatives: Synthesis, characterization and antimicrobial studies, *Der Pharma Chemica*, **7(6)**: 95-98.
19. P. Pitchai, M. Sathiyaseelan, A. Napolraj, R. M. Gengan, (2015) An elegant synthesis of an indoloquinoline alkaloid cryptackiene via vilsmeier-haack approach, *Indian Journal of Chemistry*, **54B**: 1290-1292.

***Bibliographical Sketch**



Dr. P. Pitchai is currently working as Assistant Professor of Chemistry at Government Arts College, Kumbakonam, Tamil Nadu, India. He finished his Ph.D Degree in organic chemistry at Bharathiar University in the prior months of 2009 and subsequently joint as a post-doctoral fellow at Durban University of Technology, South Africa. During his early studies, he was also awarded as an Visiting Scientist of the same Institution. He is also guiding eight Ph.D students with a major project of DST-SERB, India. He has published 16 papers in reputed journals and consequently visiting several institutions regarding research and conference. The current research focuses to synthesis indoloquinoline alkaloids and some biologically active quinoline heterocycles.