J. Chem. Sci. Vol. 127, No. 12, December 2015, pp. 2201–2209.
DOI 10.1007/s12039-015-0983-y

One-pot synthesis of N-aryl 1,4-dihydropyridine derivatives and their biological activities

ISAIVANI DHINAKARAN[a], VEDIAPPEN PADMINI[a,*] and NATTAMAI BHUVANESH[b]
[a]Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, Tamil Nadu, India
[b]Department of Chemistry, Texas A&M University, College Station, TX 77842, USA
e-mail: padimini_tamilenthi@yahoo.co.in

MS received 2 March 2015; revised 19 September 2015; accepted 20 September 2015

Abstract. Highly efficient, one pot synthesis of N-aryl, 1,4-dihydopyridines was carried out by four component reaction. Synthesized 1,4-dihydropyridines were screened for their cytotoxicity against A549 cell line. All the synthesized compounds exhibited better DPPH radical scavenging activity.

Keywords. One-pot synthesis; enamine; radical scavenging; cytotoxicity; dihydropyridine.

1. Introduction

In general, chemotherapy is fraught with negative side effects such as nausea, vomiting, fatigue and hair loss. Thus, several new anti-cancer drugs were developed with reduced side effects.[1] The pyridine substituted compounds exhibited wide range of pharmaceutical and biological activities.[2,3] Many natural products contain 1,4-dihydropyridines (DHP), which can be used in pharmaceutical, agrochemical and other chemical industries.[4] Synthesis of 1,4-DHP was started by Hantzsch in 1881.[5] In the early days, only symmetrical 1,4-DHP derivatives were synthesized due to non availability of simple procedures to make unsymmetrical analogues.[6] Currently, researchers are interested in making unsymmetrical and biologically important 1,4-DHP molecules. The library of 1,4-DHP derivatives by multi-component reactions consists of different reaction conditions such as catalysts, microwave, thermal, different solvents, etc.[7] Researchers are interested in synthesis of 1,4-DHP analogues due to its significant biological applications,[8–11] such as anticonvulsant, HIV protease inhibition, anticancer, antioxidant, antitumor, anti-mutagenic, anti-diabetic, anti-hyperplasia, antimicrobial and antitubercular activities.[12–21]

Tandem reaction is a one of the most attractive method for making diverse organic molecules that contribute particularly to form C-C and C-N bonds to give a final polysubstituted target products Onepot atom economy synthesis is a powerful method to avoid molecular complexity, to enhance the yield and reduce the waste and time compared to their stepwise reactions. 1,4-dihydropyridine derivatives have been reported by using multicomponent reactions (MCR).[4,22–30]

In this paper, we report the synthesis of N-aryl 1,4-dihydropyridine derivatives by using a four-component reaction of naphthaldehyde, p-toluidine, ethyl propiolate and malononitrile in the presence of triethylamine as a base. The best results are obtained using ethanol as the solvent at room temperature. The DPPH radical scavenging and cytotoxicity activities of these compounds are evaluated at different concentrations.

2. Experimental

The requisite chemicals were purchased from Aldrich, Alfa-Aesar and local companies and used as received. The solvents purchased from Merck Company were purified and dried as per the literature methods. Thin layer chromatography was performed using aluminium sheets pre-coated with silica gel. Melting points were determined with sigma melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker (300 MHz) spectrometer. For ^{1}H NMR spectra, the chemical shifts are reported in ppm relative to $SiMe_4$ (TMS) as an internal standard and coupling constants are presented in Hz. FT-IR spectra of the compounds were recorded by using JASCO-FTIR spectrophotometer (4000-400 cm^{-1}). Electrospray ionization mass spectrometry (ESI-MS) analysis was performed in the negative ion mode on a liquid chromatography–ion trap mass spectrometer (LCQ Fleet, Thermo Fisher Instruments Limited, USA). Antioxidant properties were

*For correspondence

recorded by using JASCO-V325 spectrophotometer. DFT and Mulliken Atomic Charge calculations were studied at B3LYP/6-31G level.

Crystallographic data (excluding structure factors) for N-Aryl 1,4-dihydropyridine **5h** in this paper have been deposited with the Cambridge crystallographic data center as supplementary publication numbers CCDC 1006593 and copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [e.mail-deposit@ccdc.cam.ac.uk]

2.1 *Typical experimental procedure for the synthesis of N-Substituted 1,4- dihydropyridines **5h***

In a round-bottom flask, a mixture of aniline (1 equivalent, 0.2 g) and ethyl propiolate (1 equivalent, 0.208 g) in 5.0 mL of ethanol was stirred at room temperature for 10 h. Then, aromatic aldehyde (1 equivalent, 0.292 g), malononitrile (1 equivalent, 0.217 g) and triethylamine (1 equivalent, 0.141 g) in 5.0 mL of ethanol were added. The solution was stirred at a room temperature for additional two hours. After completion of the reaction, the solvent was removed under reduced pressure. The solid product was collected by filtration and washed with cold ethanol to give the pure product **5h** without further purification or recrystallization.

Compound **5h:** White solid; yield-80%; M.p.173-175°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS, δppm) 7.53-7.36 (m, 3H, ArH), 7.34 (d, $J = 6.6$ Hz, 2H, ArH), 7.30-7.25 (m, 3H, ArH, CH), 6.86 (d, $J = 8.7$ Hz, 2H, ArH), 4.59 (s, 1H, CH), 4.17 (s, 2H, NH_2), 4.00 (q, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 1.14 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS, δppm) δ 166.35, 158.41, 149.64, 139.64, 138.08, 137.99, 136.19, 130.90, 128.35, 127.30, 121.31, 113.83, 107.93, 62.71, 60.18, 55.18, 38.32, 14.13; IR (KBr) υ/cm^{-1} 3464, 2187, 1699, 1608, 1573; LC-MS calcd. m/z 375.16 found 374.36, (MH). Anal. Calcd. for $C_{24}H_{27}N_3O_3$ calcd. C, 70.38; H, 5.64; N, 11.19% Found C, 70.35; H, 5.66; N, 11.21%.

2.2 *Biological Assay*

2.2a *DPPH radical scavenging activities*: The DPPH radical scavenging activities of the compounds were measured by the conventional method.[29] The radical scavenging of the compound can be determined on the basis of its capacity to scavenge stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. The absorption maximum of DPPH radical is at 517 nm. The DPPH scavenging was determined by the decrease of the absorbance. Ascorbic acid is used as a standard. Experiments were carried out in triplicate. Concentration of the compounds were taken in methanolic solution like 25, 50, 75 and 100 μg/mL. The stock solution of DPPH (0.1 mM) in methanol was prepared. 2 mL of the stock solution was added to 2 mL of methanol and absorbance was recorded at 517 nm, which is blank (X). Test solution was diluted to 2 mL using methanol and 2 mL of stock solution of DPPH was added and then the absorbance recorded at 517 nm (Y). The percentage scavenging was calculated[31,32] as % Scavenging = [(XY)/X] × 100.

2.2b *Cell lines and reagents*: A549 cell line was obtained from National Centre for Cell Sciences, Pune (NCCS). The cells were maintained in Minimal Essential Media supplemented with 10% FBS, penicillin (100 U/mL), and streptomycin (100 μg/mL) in a humidified atmosphere of 50 μg/mL CO_2 at 37°C. Reagents: MEM was purchased from Hi Media Laboratories. Fetal bovine serum (FBS) was purchased from Cistron laboratories. Trypsin, methylthiazolyl diphenyl-tetrazolium bromide (MTT) and Dimethyl sulfoxide (DMSO) were purchased from Sisco research laboratory chemicals, Mumbai. All other chemicals and reagents were obtained from Sigma Aldrich, Mumbai.

2.2c *In vitro assay for cytotoxicity (MTT assay)*: The anticancer activity of samples on A549 cells was determined by the MTT assay.[33] Cells (1×10^5/well) were plated in 0.2 mL of medium/well in 96-well plate and incubated at 5% CO_2 incubator for 72 h. Then, added various concentrations of the samples in 0.1% DMSO for 48 h at 5% CO_2 incubator. After removal of the sample solution and washing with phosphate-buffered saline (pH 7.4), 20 μL/well (5 mg/mL) of 0.5% 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-tetrazolium bromide (MTT) in phosphate- buffered saline solution was added. After 4 h incubation, 1 mL of DMSO was added. Viable cells were determined by the absorbance at 540 nm. Measurements were performed and the concentration required for a 50% inhibition of viability ($\mathbf{IC_{50}}$) was determined graphically.

The effect of the samples on the proliferation of A549 cells was expressed as the % cell viability, calculated using the formula: % cell viability = (treated cells/control cells) × 100.

3. Results and Discussion

The four-component reaction of naphthaldehyde, p-toluidine, ethyl propiolate and malononitrile was

investigated as a model reaction in ethanol and in the presence of triethylamine at room temperature. The use of stronger bases such as NaOH was tested but low yield of the target product was obtained. (table 1, entry 4). Interestingly the basicity of the common weaker organic base has not shown any effect on the product yield (table 1, entry 5). However, Et_3N afforded a slightly better yield than others. We tried different bases and solvents but optimized with Et_3N and ethanol as the reaction medium (table 1, scheme 1).

Next, the scope of this reaction was explored with various substituted anilines and aldehydes which provided the corresponding products in good yields (table 2). Various electron withdrawing/donating groups e.g., Cl, Br, OMe, Me, etc., present on the aryl ring of aldehydes and anilines were well tolerated. Reactions of 1-naphthaldehyde, 4-butoxybenzaldehyde and p-toluidine proved to be more potent leading to the formation of products in **5c, 5i** and **5l** in 88% yield. Using substituted anilines and aldehyde derivatives with electron donating substituents afforded the products in high yield of 80–85% (table 2, **5a, 5b, 5d, 5f, 5g** and **5h**). The presence of an electron withdrawing group in anilines such as halogens, -3,5-Di-Cl and -CF_3, slightly decreased the formation of products with yields ranging from 60–80%. The use of ethyl propiolate was well tolerated. All these reactions were successfully carried out under open air conditions.

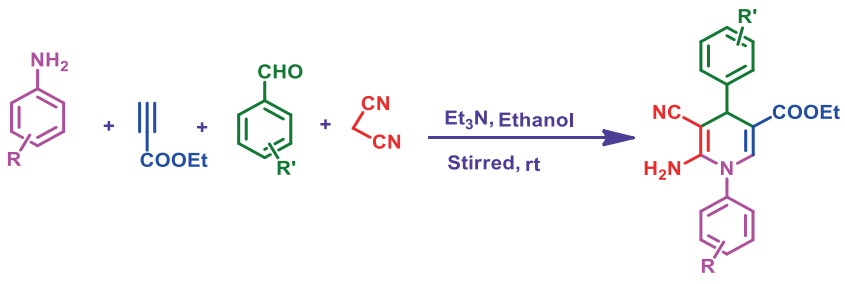
Table 1. Optimization of the four-component reaction for the synthesis of N-aryl 1,4-dihydropyridines.

Entry	Base (Equivalent)	Solvent	Time (h)	Yield (%)
1	K_2CO_3(1.0)	C_2H_5OH	24	30
2	$KHCO_3$(1.0)	C_2H_5OH	30	20
3	NH_4OH (5N)(1.0)	CH_3CN	10	Trace
4	NaOH(1.0)	C_2H_5OH	10	50
5	pyridine(1.0)	C_2H_5OH	24	25
6	Et_3N(1.0)	DMF	24	–
7	Et_3N(1.0)	CH_3OH	12	70
8	Et_3N(1.0)	C_2H_5OH	12	89

The poly-substituted 1,4-dihydropyridines were fully characterized by ^1H and ^{13}C NMR, and mass spectroscopies. The structure of the N-Aryl 1, 4-dihydropyridine **5h** was further confirmed by single crystal X-ray crystallographic study (figure 2). In the ^1H NMR spectrum of compound **5h**, the CH_2 proton of ester group is observed as a quartet in the region of 4.05 ppm and the CH_3 protons of ester group appears as triplet at 1.14 ppm (t, 3H, $J = 6.9$ Hz). A sharp and intense singlet with 3 protons integral value observed at 3.79 ppm is due to methoxy proton. The ^1H-^1H COSY spectrum further confirmed the methylene and methyl protons merged and correlate with aromatic methoxy protons (figure S15, see Supplementary Information). The benzylic proton (H-4) appeared at 4.59 ppm as a singlet. The HMBC experiment acted as a firm proof to substantiate the formation of **5h** which revealed that the singlet at 4.59 ppm showed correlation with many carbon bonds such as ester attached carbon, methoxy carbon, aromatic carbon of methoxy substituent phenyl group C-4' carbon, carbonyl carbon, cyano group of carbon at 108.0, 60.15, 113.75, 166.20, 121.18 ppm, respectively in the HMBC spectra. HMB Correlation of the compound **5h** is shown in figure 1.

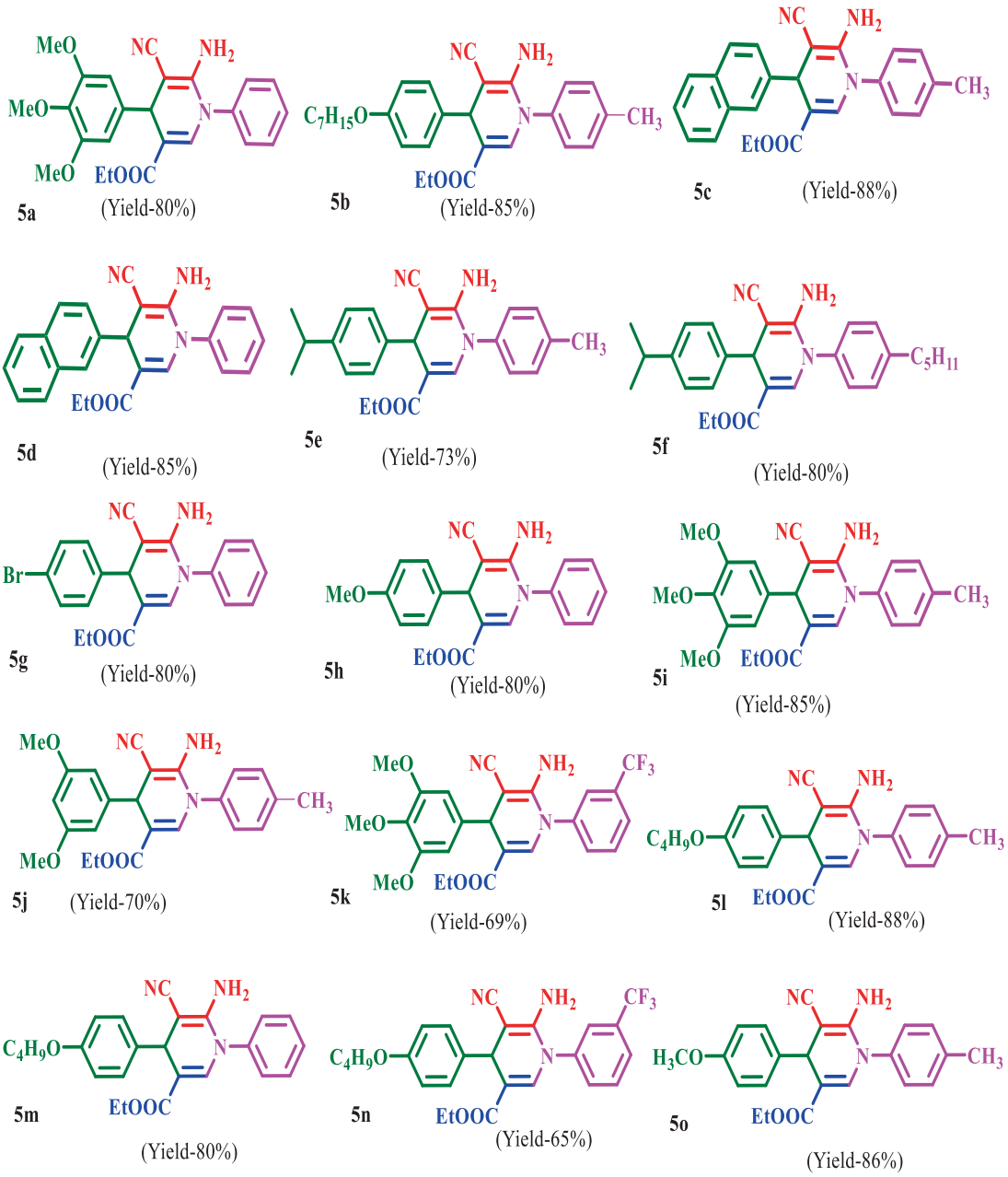
All the aromatic protons appeared as three doublets and one multiplet at 6.88 (d, $J = 9$ Hz), 7.23 (d, $J = 9$ Hz), 7.31 (d, $J = 9$ Hz) and 7.49–7.41 ppm, respectively. In the ^1H NMR spectrum the $-NH_2$ protons appeared at 4.17 ppm indicating the discrete characteristic peak of the amino group at the C-2 position of the compound **5h**. The ^{13}C NMR spectrum further confirmed the formation of dihydropyridine by exhibiting a singlet at 158.3 ppm for the C-2 carbon of compound **5h** (figure S16). From the DEPT-135 spectrum (figure S17), the methylene carbon is confirmed by the negative peak and the quaternary carbon C-5 is confirmed by appearance at 108.02 ppm because the region has not appeared, as well as 8 quaternary carbons also not appeared in DEPT-135 spectrum.

The structure is confirmed by the single-crystal X-ray analysis performed for the representative compound **5h**. Compound **5h** is a Triclinic crystal with space group P-1.



Scheme 1. Synthesis of N-aryl 1,4-dihydropyridines.

Table 2. N-aryl 1,4-dihydropyridine derivatives synthesized using the four-component reaction.



The cell dimensions are a = 9.8518 Å, b = 10.2278 Å and c = 10.5705 Å. ORTEP diagram of compound **5h** is presented in figure 2. It shows the 1,4-dihydropyridine unit is planar. The dihedral angles between the planes of the two phenyl rings are 103.75(12)° and 103.60(12)°, respectively, packing diagram shown in figure 3.

3.1 *Natural bond orbital (NBO) analysis*

The NBO analysis of calculations using B3LYP/6-31G was carried out for compound **5h**. The second order perturbative estimates of donor–acceptor interactions are displayed in table 3. The importance of hyper conjugative interaction and electron density transfer from lone pair electrons to the antibonding orbital has been analyzed. Several donor-acceptor interactions are observed for **5h** and among the strongly occupied NBOs, the most important delocalization sites are in the π system and in the lone pairs (n) of the oxygen and nitrogen atoms. The σ system shows some donation to the delocalization, and the important contributions to the delocalization correspond to the donor-acceptor interactions are C1–C2 → C5–C6, C3–C4 → C1–C2, C5–C6 → C3–C4, C17–C18 → C21–C22, C19–C20→ C17–C18, C19–C20→ C21–C22, C21–C22→ C17–C18, C42–C45→ C42–H43. These are the strong

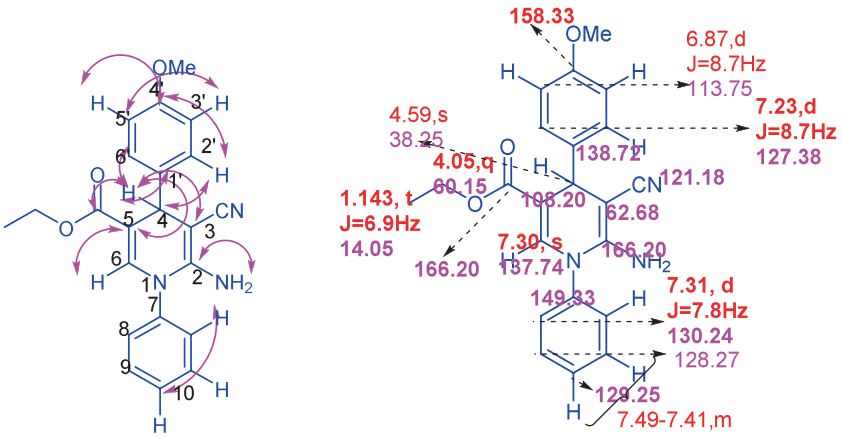


Figure 1. Selected HMB correlation of compound **5h**.

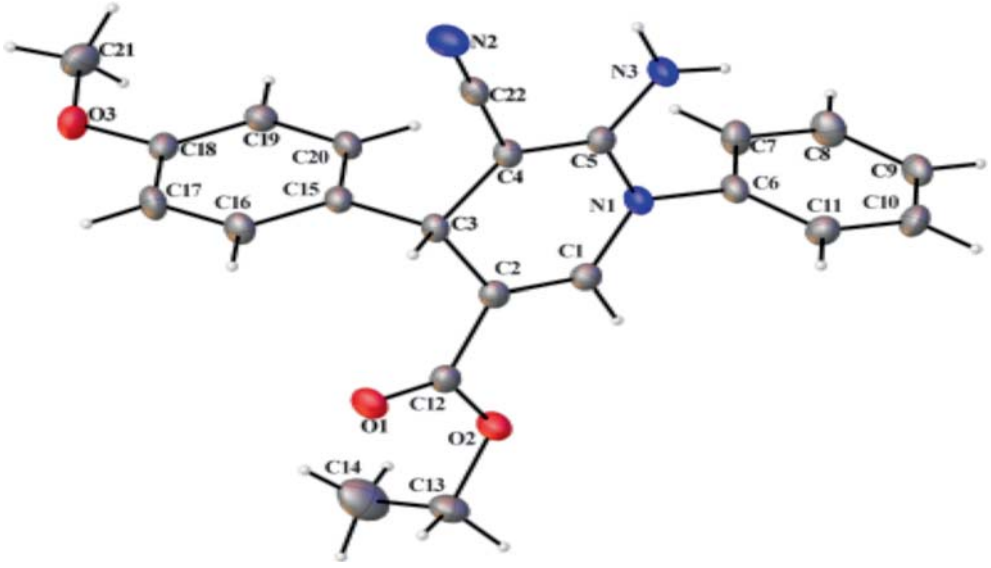


Figure 2. ORTEP diagram of compound **5h** (CCDC no. 1006593).

intermolecular hydrogen bonding between methoxy substituent of O3 and the amino group of H3A. The electron transfer is from the lone pair electrons of N35 to the antibonding orbital of C21–H27 bond and lone pair of O40 to the antibonding orbital of C39-O41 bond. Among these two, O40 bond to C39-O41 delocalization energy is high due to electron releasing CH_3 group present at the adjacent of O41. All these theoretical (DFT) data are in good agreement with the experimental (XRD) values listed in table 3. However, from the theoretical values, it is clear that the most of the optimized bond lengths, bond angles and dihedral angles are slightly higher than that of XRD values. These deviations can be attributed to the isolated molecule in the gaseous phase in theory whereas the XRD results are about the molecule in the solid state.

3.2 *Biological evaluation*

3.2a *DPPH radical scavenging*: DPPH assay is a well-known technique to evaluate the antioxidant activity of synthesized compounds due to its simple procedure and reliability. The results of the DPPH radical scavenging activity (IC_{50} values) of the compounds are shown in table 4. From the table, it is clear that almost all the compounds showed radical scavenging activities. It is important to note that compounds **5b, 5c, 5e, 5f, 5i, 5j, 5l**, and **5o** showed better DPPH radical scavenging activity when compared to the standard ascorbic acid. The remaining compounds of **5a, 5d, 5g, 5h, 5k, 5m** and **5n** have shown low to moderate radical scavenging activities because of those compounds contain electron withdrawing groups such as -Br, $-CF_3$. The compounds **5b** and **5e** showed promising radical

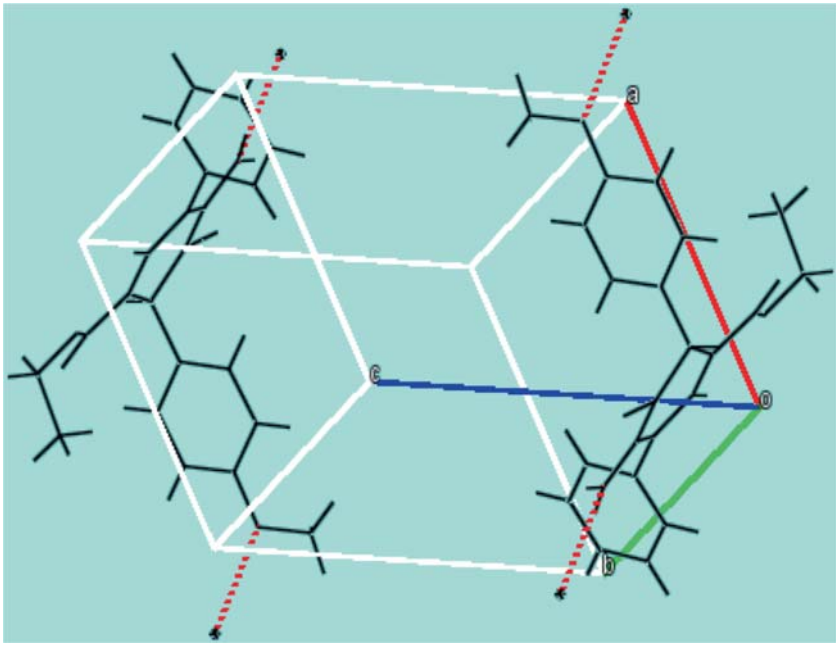


Figure 3. Packing diagram of compound **5h**.

Table 3. Selected bond length (Å), bond angle (°) and Torsion angles (°) of compound **5h**.

Bond length (Å)	Exp(Theo) (Å)	Bond angle (°)	Exp(Theo) (°)XRD	Bond Torsion (°)	Exp(Theo) (°)XRD
O1-C12	1.210(1.265)	C12-O2-C13	116.6(118.0)	O3-C18-C19-C20	178.5(−178.5)
O2-C12	1.350(1.281)	C18-O3-C21	117.1(119.1)	N1-C1-C2-C3	4.44(−1.454)
O2-C13	1.448(1.461)	C1-N1-C5	119.3(119.8)	N1-C1-C2-C12	−178.7(−178.7)
O3-C18	1.372(1.382)	C1-N1-C6	118.1(118.5)	N1-C6-C7-C8	−178.2(178.6)
O3-C21	1.426(1.455)	C5-N1-C6	122.4(121.6)	N1-C6-C11-C10	178.5(−178.1)
N1-C1	1.379(1.380)	H3A-N3-H3B	120.2(118.9)	C1-N1-C5-N3	171.9(−174.7)
N1-C5	1.386(1.375)	C5-N3-H3A	120.5(119.5)	C1-N1-C5-C4	−6.20(3.672)
NI-C6	1.444(1.457)	C5-N3-H3B	118.9(121.4)	C1-N1-C6-C7	103.6(−116.8)
N2-C22	1.154(1.176)	N1-C1-H1	118.1(117.6)	C1-N1-C6-C11	−74.88(60.9)
N3-H3A	0.879(1.009)	C2-C1-N1	123.9(123.9)	C1-C2-C12-O1	170.9(−19.64)
N3-H3B	0.891(1.007)	N3-C5-N1	116.1(119.2)	C1-C2-C12-O2	−9.82(−19.64)
N3-C5	1.352(1.358)	N3-C5-C4	124.2(122.3)	C3-C2-C12-O1	−12.1(−17.88)

*Theo- Theoretical values

Table 4. DPPH radical scavenging activity IC_{50} (μg/mL) for the N-aryl1,4-dihydropyridines **5a-o**.

S. No.	Sample code	IC_{50} (μg/mL) of DPPH scavenging	S. No.	Sample code	IC_{50} (μg/mL) of DPPH scavenging
1	**5a**	23.25	9	**5i**	13.82
2	**5b**	19.23	10	**5j**	15.79
3	**5c**	16.68	11	**5k**	20.65
4	**5d**	29.20	12	**5l**	18.98
5	**5e**	17.13	13	**5m**	27.23
6	**5f**	20.15	14	**5n**	29.14
7	**5g**	22.27	15	**5o**	26.59
8	**5h**	21.43	Std	Ascorbic acid	32.00

scavenging due to the presence of an electron releasing group such as methoxy group on phenyl ring in N-aryl,4-dihydropyridine derivatives. It is clear that, the substituents of polysubstituted dihydropyridines on the aromatic ring have a major effect on their radical scavenging. The presence of methoxy group in aromatic

ring enhanced their free radical scavenging activity. The radical scavenging activity increased with one methoxy and alkyloxy group in **5b, 5c, 5e, 5f, 5i, 5j, 5l** and **5o** and further enhanced when there are two or three methoxy groups as in compounds **5c** and **5e**.

3.2b *Cytotoxicity activity*: Cytotoxicity studies were carried out for all the synthesized N-aryl1,4-dihydropyridine derivatives against A549 lung adenocarcinoma cancer cell line. Paclitaxel was used as a standard. Percent of cell viability was calculated and the inhibition of growth of human lung cancer cell line is defined by the nature of the substituents. Compounds **5i**, **5j** and **5g** exhibited prominent cytotoxicity effect (figures 4 and 5). Compound **5i** having electron donating group of three methoxy groups or methyl group has shown promising cytotoxicity activity than standard paclitaxel. Remaining compounds of **5b, 5c, 5e, 5f, 5l** and **5o** have shown moderate activity, when compared to the standard. The IC_{50} values displayed that most of the synthesized compounds showed potent inhibitory effect against the A549 cell line. Some of the compounds have shown the maximum cell death in minimum inhibitory concentration of IC_{50} value in the following order: **5i**>**5j**>**5g**>**5e**>**5c**>**5f**>**5b**>**5l**>**5o**. Replacing of -OCH_3 and -CH_3 by -CF3 and -NH_2 has not exhibited significant activity. From these results, the electronic effect may be one of the factors in determining the cytotoxicity activity of these compounds. Only better cytotoxicity activities of these nine compounds are displayed in figures 6 and 7. Replacement of the substitution of phenyl ring (R) having -CF_3 in ortho position, the activity has not changed significant against A549 cell line. However, due to isomeric effect of tolyl (R′) group on the DHP bearing on para position, the cytotoxicity activity is high. The substituents (R) in

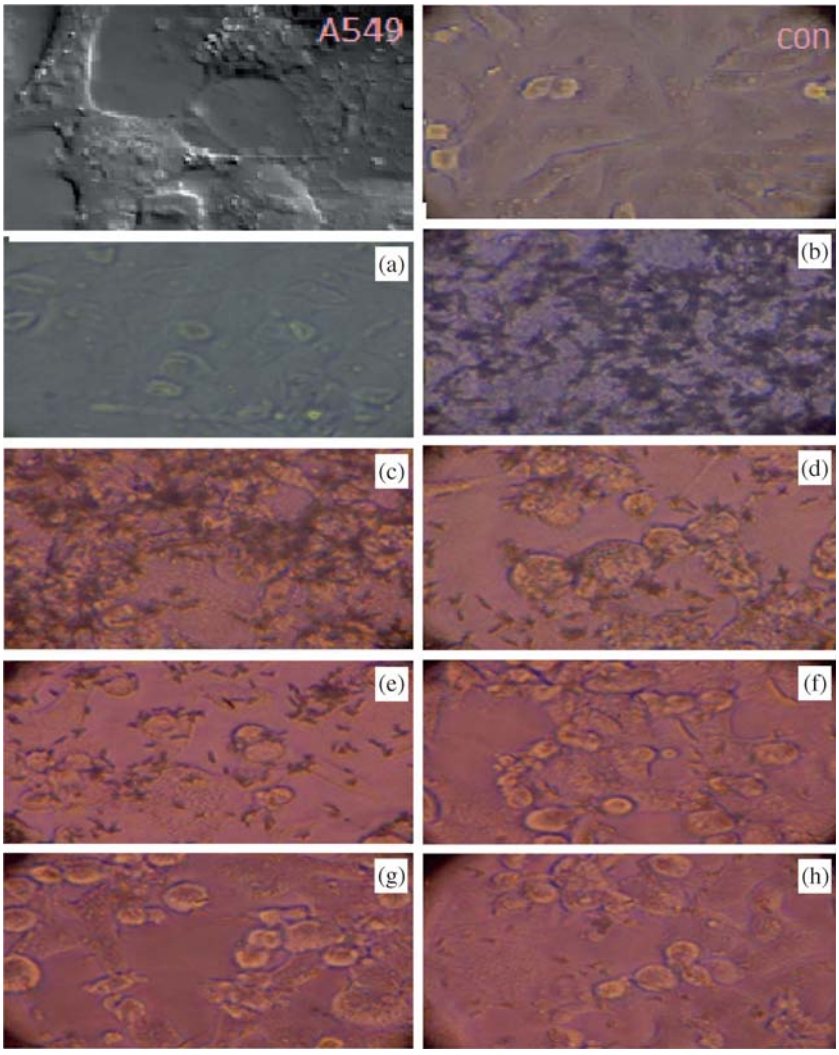


Figure 4. Cytotoxicity effect of compound **5i** on A549 cell line (40X micrographs) at different concentrations (μg/mL). a) 1000, b) 500, c) 250, d) 125, e) 62.5, f) 31.2, g) 15.6 and h) 7.

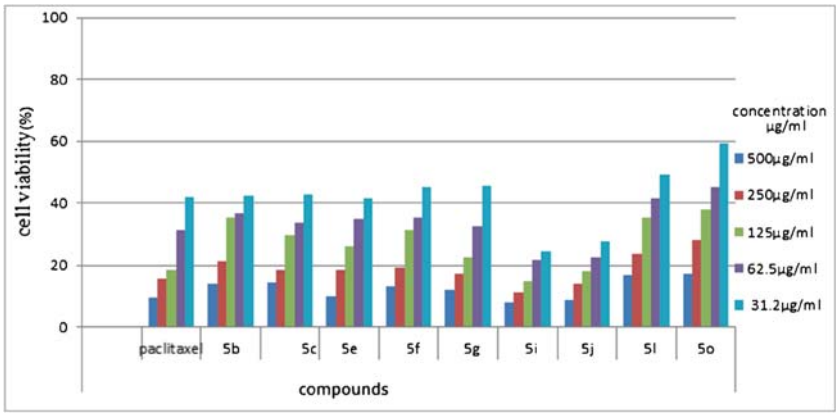


Figure 5. Cytotoxicity effect of compounds **5b, 5c, 5e, 5f, 5g, 5i, 5j, 5l** and **5o** against A549 cell line.

ortho, meta and para position on the phenyl ring such as -OMe, -OC_4H_9, OC_7H_{15} (**5i, 5j, 5b, 5e, 5l** and **5o**) displayed more potent cytotoxicity activity than the standard paclitaxel. Also, DHP bearing bulky substituent such as naphthyl group (**5c**) exhibited significant activity.

4. Conclusions

In summary, a new series of poly-substituted N-aryl,1, 4-dihydropyridine derivatives (**5a-o**) were synthesized with excellent yield. All the synthesized compounds have shown potent DPPH radical scavenging activity when compared to standard ascorbic acid. Further, compounds **5i, 5j** and **5g** exhibited better cytotoxicity effect against A549 cell line when compared to standard paclitaxel.

Supplementary Information

All additional information pertaining to characterization of the compounds using spectroscopic methods ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC and Mass spectra (figures S1–S35) are given in the supporting information. Supplementary Information is available at www.ias.ac.in/chemsci.

Acknowledgements

The authors gratefully acknowledge RGNF No-F-1420(Sc)/2009 SA-III for fellowship and DST and UGC for financial assistance and also thank DST-IRPHA for providing NMR spectrometer.

References

1. Menna P, Gonzalez Paz O, Chello M, Covino E, Salvatorelli E and Minotti G 2012 *Expert. Opin. Drug Saf.* **11** 21
2. Mallea M, Mahamoud A, Chevalier J, Alibert-Franco S, Brouant P, Barbe J and Pages J M 2003 *J. Biochem.* **376** 801
3. (a) Millet J, Torrentino-Mdamet M, Alibert S, Rogier C, Santelli-Rouvier C, Mosnier J, Baret E, Barbe J, Parzy D and Pradines B 2004 *Antimicrob. Agents Chemother.* **48** 2753; (b) Straub T, Boesenberg C, Gekeler V and Boege F 1997 *Biochemistry* **36** 10777; (c) Donkor I O, Zhou X, Schmidt J, Agrawal K C and Kishore V 1998 *Bioorg. Med. Chem.* **6** 563
4. Hantzsch A 1881 *Chem. Ber.* **14** 1637
5. (a) Kikuchi S, Iwai M, Murayama H and Fukuzawa S 2008 *Tetrahedron Lett.* **49** 114; (b) Akbari J D, Tala S D, Dhaduk M F and Joshi H S 2008 *ARKIVOK.* **7** 126
6. (a) Balalaie S, Baoosi L, Tahoori F, Rominger F and Bjanzadeh H R 2013 *Tetrahedron* **9** 738; (b) Ishar M P S, Kamal Kumar, Sumanjit Kaur, Shiv Kumar N, Gridar K, Satish Sachar, Alka Marwaha and Ashish Kapoor 2001*Org. Lett.* **3** 2133
7. Reddy T R, Reddy G R, Reddy L S, Meda C L T, Parsa K V L, Kumar K S, Lingappa Y and Pal M 2013 *Eur. J. Med. Chem.* **62** 395
8. Kumar A and Maurya R A 2008 *Tetrahedron* **64** 3477
9. Kikuchi S, Iwai M, Murayama H and Fukuzaka S 2008 *Tetrahedron Lett.* **49** 114
10. Sirijindalert T, Hansuthirakul K, Rashatasakhon P, Sukwattanasinitt M and Ajavakom A 2010 *Tetrahedron* **66** 5161
11. Sun J, Xia E Y, Wu Q and Yan C F 2010 *Org. Lett.* **12** 3678
12. (a) Schramm M, Thomas G, Towart R and Franckowiak G 1983 *Nature* 303535; (b) Lavilla R 2002 *J. Chem. Soc. Perkin Trans.* **1** 1141; (c) Kappe C O 2000 *Eur. J. Med. Chem.* 351043; (d) Varache-Lemèbge M, Nuhrich A, Zemb V, Devaux G, Vacher P, Vacher A and Dufy B 1996 *Eur. J. Med. Chem.* **31** 547; (e) Borowicz K K, Gasior M, Kleinrok Z and Czuczwar S J 1997 *Eur. J. Pharmacol.* **323** 45
13. Li A H, Moro S, Forsyth N, Melman N, Ji X D and Jacobson K A 1999 *J. Med. Chem.* **42** 706
14. Mai A, Valente S, Meade S, Carafa V, Tardugno M, Nebbioso A, Galmozzi A, Mitro N, Fabiani E D, Altucci L and Kazantsev A 2009 *J. Med. Chem.* **52** 5496

15. (a) Hilgeroth A 2002 *Mini-Rev. Med. Chem.* **2** 235; (b) Hilgeroth A and Lilie H 2003 *Eur. J. Med. Chem.* **2** 495; (c) Maiti S, Sridharan V and Carlos Menendez J 2010 *J. Comb. Chem.* **12** 713; (d) Straub T, Boesenberg C, Gekeler V and Boege F 1997 *Biochemistry* **36** 10777
16. Donkor I O, Zhou X, Schmidt J, Agrawal K C and Kishore 1998 *Bioorg. Med. Chem.* **6** 563
17. (a) Kawase M, Shah A, Satoh K, Kikuchi H, Nishikawa H, Maki J and Sakagami H 2005 *Anticancer Res.* **25** 2033; (b) Abbas H A S, El Sayed W A and Fathy N M 2010 *Eur. J. Med. Chem.* **45** 973; (c) Zhou X, Zhang L, Tseng E, Scott-Ramsay E, Schentag J J, Coburn R A and Morris M E 2005 *Drug Metab. Dispos.* **33** 321; (d) Bazargan L, Fouladdel S, Shafiee A, Amini M, Ghaffari S M and Azizi E 2008 *Cell Bio. Toxicol.* **24** 165; (e) Teodori E, Dei S, Scapecchi S and Gualtieri F 2002 *Farmaco.* **57** 385; (f) Avendan O C and Menendez J C 2002 *Curr. Med. Chem*. **9** 159; (g) Robert J and Jarry C 2003 *J. Med. Chem*. **46** 4805; (h) Avendano C and Menendez J C 2004 *Med. Chem. Rev*. *Online* **12** 419; (i) Boumendjel A, Baubichon-Cortay H, Trompier D, Perrotton T and Di Pietro 2005 *Med. Res. Rev*. **25** 453
18. (a) Kappe C O 2000 *Eur. J. Med. Chem.* **35** 1043; (b) Alker D, Campbell S F, Cross P E, Burges R A, Carter A J and Gardiner D G 1990 *J. Med. Chem.* **33** 585; (c) Godfraind T, Miller R and Wibo M 1986 *Pharmacol. Rev.* **38** 321; (d) Fasani E, Fagnoni M, Dondi M D and Albini A 2006 *J. Org. Chem.* **71** 2037; (e) Rampe D and Kane J M 1994 *Drug Dev. Res.* **33** 344; (f) Abbas H A S, El Sayed W A and Fathy N M 2010 *Eur. J. Med. Chem.* 45973; (g) Briede J, Stivrina M, Vigante B, Stoldere D and Duburs G 2008 *Cell Biochem. Funct.* **26** 238
19. (a) Ojha K G and Pareek P 2011 *Der. Pharma. Chemica.* **3** 66 (b) Morshed S, Hashinoto K, Murotani Y and Kawase M 2005 *Anticancer Res.* **25** 2033 (c) Srirama D, Yogeeswari P, Dinakaran M, Banerjee D, Bhat P and Gadhwal S 2010 *Eur. J. Med. Chem.* **45** 120
20. (a) Kumar M, Padmini V and Ponnuvel K 2014 *J. Saudi Chem. Soc*. http://dx.doi.org/10.1016/j.jscs.2014.03.006; (b) Pokorny 1991 *J. Trends Food Sci. Technol.* **9** 223
21. (a) Kikuchi S, Iwai M, Murayama H and Fukuzawa S 2008 *Tetrahedron Lett.* **49** 114; (b) Akbari J D, Tala S D, Dhaduk M F and Joshi H S 2008 *ARKIVOK*. **7** 126
22. (a) Kawase M, Shah A, Gaveriya H, Motohashi N, Sakagami H, Varga A and Molnar J 2002 *J. Bioorg. Med. Chem.* **10** 1051; (b) Mojarrad J S, Miria R and Knaus E E 2004 *J. Bioorg. Med. Chem.* **12** 3215; (c) Kumar R and Chandra R 2001 *Adv. Heterocycl. Chem.* **78** 269; (d) Lavilla R 2002 *J. Chem. Soc. Perkin Trans.* **1** 1141
23. Trost B M 1995 *Angew. Chem. Int. Ed. Engl.* **34** 259
24. Wender P A, Hanhdy S T and Wright D L 1997 *Chem. Ind.* 765
25. Weber L 2000 *Curr. Opin. Chem. Biol.* **4** 295
26. Domling 2002 *Curr. Opin. Chem. Biol.* **6** 306
27. (a) Toure B B and Hall D G 2009 *Chem. Rev.* **109** 4439; (b) Candeias N R, Montalbano F, Cal P M and Gois P M P 2010 *Chem. Rev.* **110** 6169; (c) Sunderhaus J D, Dockendorff C and Martin S F 2009 *Tetrahedron* **110** 6454; (d) Wang K, Nguyen K, Huang Y J and Deomling A 2009 *J. Comb. Chem.* **11** 920; (e) Bonne D, Coquerel Y, Constantieux T and Rodriguez 2010 *Tetrahedron: Asymmetry* **21** 1085
28. (a) Huisgen R, Morikawa M, Herbig K and Brunn E 1967 *Chem. Ber.* **100** 1094; (b) R Huisgen and R Castle 1969 (eds.) (New York: John Wiley and Sons) Ch 8 p. 223
29. (a) Nair V, Rajesh C, Vinod A U, Bindu S, Sreekanth A R, Mathen J S and Balagopal A 2003 *Acc. Chem. Res.* **36** 899; (b) Nair V, Menon R S, Sreekanth A, Abhilash N and Biju A T 2006 *Acc. Chem. Res.* **39** 520; (c) Nair V, Devipriya S and Suresh E 2008 *Tetrahedron* **64** 3567; (d) Shibata Y, Noguchi K, Hirano M and Tanaka K T 2008 *Org. Lett.* **10** 2825; (e) Harju K and Vesterinen J 2009 *Org. Lett.* **11** 2219
30. Yanga X H, Zhang P H, Hua L H, Zhanga M, Liua C G, Liua H J and Zhoua Y H 2012 *Ind. Crops Prod.* **38** 14
31. Barbuceanu S F, Ilies D C, Saramet G, Uivarosi V, Draghici C and Radulescu V 2014 *Int. J. Mol. Sci.* **15** 10908
32. Mohamed Youssef M and Ahmed Amin M 2010 *Molecules* **15** 8827
33. Mosmann T J 1983 *Immunol. Methods* **65** 55