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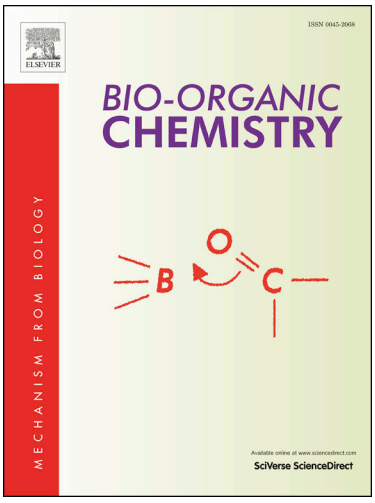

Dual active 1, 4-Dihydropyridine derivatives: Design, green synthesis and *in vitro* anti-cancer and anti-oxidant studies

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PII: S0045-2068(20)31677-1
DOI: https://doi.org/10.1016/j.bioorg.2020.104379
Reference: YBIOO 104379

To appear in: *Bioorganic Chemistry*

Received Date: 21 February 2020
Revised Date: 5 September 2020
Accepted Date: 12 October 2020

Please cite this article as: P. Anaikutti, P. Makam, Dual active 1, 4-Dihydropyridine derivatives: Design, green synthesis and *in vitro* anti-cancer and anti-oxidant studies, *Bioorganic Chemistry* (2020), doi: https://doi.org/10.1016/j.bioorg.2020.104379

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Dual active 1, 4-Dihydropyridine derivatives: Design, green synthesis and *in vitro* anti-cancer and anti-oxidant studies

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Abstract

The present work describes the design of 1,4-dihydropyridines (1,4-DHPs) with diverse variations in structural and functional groups. The physico-chemical properties and drug-like molecule nature evaluations were carried out using SWISSADME. A simple, economical, eco-friendly, water-mediated and *Para*-Toluene sulfonic acid catalysed multicomponent and one-pot synthetic method from nitroketene *N*, *S*- acetals (NMSM) and corresponding aldehydes has been developed. All compounds (**6a-u** and **13a-h**) were subjected to *in vitro* assays against two important human cancer cell lines *Viz*. are Laryngeal carcinoma (Hep2) and Lung adenocarcinoma (A549) cells. The reduction level of DPPH (%) used to evaluate the anti-oxidant properties. The 1,4-DHP derivatives, **6o, 6u** and **6l** displayed the potent anti-cancer activity with IC_{50} value of 10 μM, 14 μM and 10 μM against the Hep2 and 8 μM, 9 μM and 50 μM against the A549 cells. Similarly, the anti-oxidant properties of **6o, 6l** and **6u** at a standard concentration of 50μg, are found to be 70.12%, 63.90% and 59.57% respectively favours the 1,4-DHP derivatives dual activity potentials. The compounds, **6o** and **6l** found to be equivalent with standard drug, Doxorubicin.

Keywords: *Green Chemistry; Nitroketene N, S-Acetals; 1, 4-Dihydropyridine; anti-cancer, anti-oxidant.*

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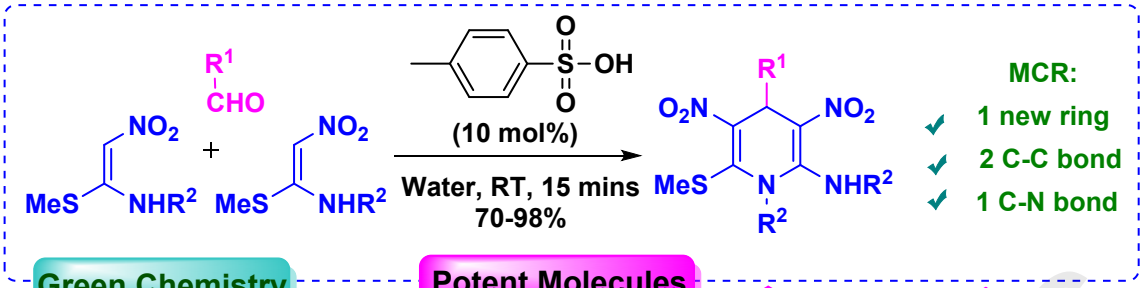
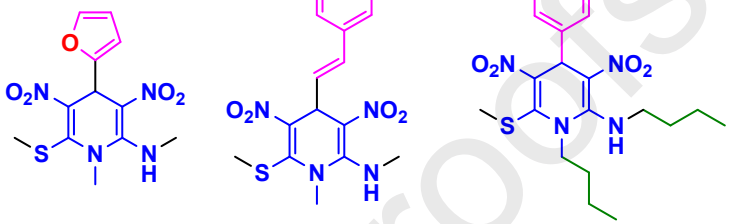
Graphical abstract



Green Chemistry

- Water Solvent
- PTSA Catalyst
- No tedious workup
- No column chromatrpohy

Potent Molecules



	6o	6l	6u
Hep2 ($IC_{50;}$ µM):	10	10	14
A549 ($IC_{50;}$ µM):	08	50	09
DPPH Reduction (%):	70.12	63.90	59.57

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1. Introduction

Over a century, 1,4-dihydropyridines (1,4-DHPs) derivatives have been gaining momentum and becoming the choice of synthetic chemists and medicinal chemists for developing novel molecules with therapeutic importance. Owing to their diversity in structural and medicinal applications, the 1,4-DHPs scaffold has been categorized as one of the privileged structures.[1] The reviewed biological importance of 1,4-DHPs include - calcium channel blockers, cardiovascular, anti-hypertensive, antitumor, anti-inflammatory, analgesic, neuroprotectant, platelet anti-aggregator, anti-ischemic, anti-Alzheimer, anti-microbial and insecticidal *etc*.[1-6] The noticeable drug candidates in this class are Nifedipine **1**, Felodipine **2** and Amlodipine **3** *etc*.[3, 4, 6]

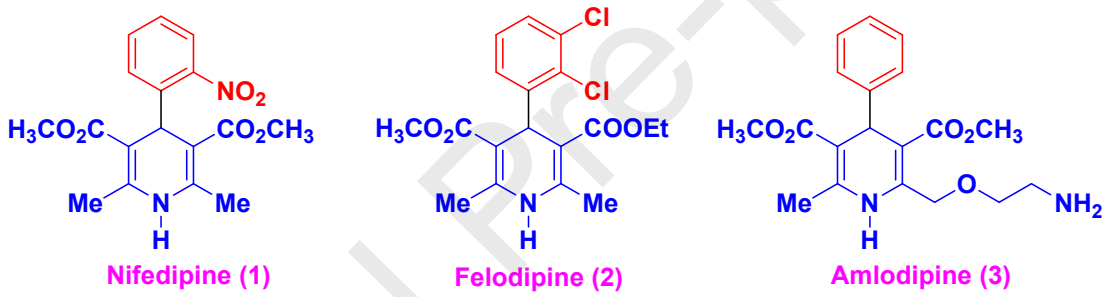

Figure 1. Biologically important 1, 4-DHPs.

In addition to the biological importance, 1, 4-DHPs are useful source of hydride for reductive amination and synthetic intermediates for producing biologically important molecules.[7] Since from 1882, first classical report for the synthesis of 1, 4-DHPs through multicomponent reactions (MCR) by Hantzsch,[8] the advances towards improving and development of new methods have been under progress with great interest to generate therapautically important molecules.[3, 6, 9] The MCRs are one of the simplest, eco-friendly and widely used in organic synthesis. This is due to their ability of simultaneous and selective formation of more than two or three bonds by domino mechanism within a single step with high yields and purity. In recent years, MCR has been paying much attention to the generation

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of highly diverse and functionalized molecules [10-14] Thus, developing an environmentally benign MCR has been recognized as one of the most important methods for developing the molecules with ease and advantages like stereo and regio-selective synthesis, biocatalysis and green chemistry[14-19].

Cancer, broadly a collection of more than 100 diseases with the abnormal and uncontrolled division of cells and affecting major parts of the body. [20, 21] Globally by causing 1 in 6 deaths, cancer has become the second leading cause of deaths with the total accountability of 9.6 million deaths in 2018. The women and men populations have been effected with diverse types of cancers.[22] The accessible and existing anticancer drugs have distinctive mechanisms of action which ultimately make variations in their effects on diverse types of cancer and normal cells. In addition, there is very insufficient evidence of biochemical alterations between normal cells and cancerous cells and hence, a particular cure for cancer has demonstrated indefinable. The advancement of resistance to existing multi-drug chemotherapy and their slow cure rate, dreadful and toxic effects on patients are serious and pragmatic concerns of cancer.[23] Hence, the impeccable efforts are required for the identification of newer, efficient and less toxic chemotherapeutic agents for treating the cancers.[24]

The reactive oxygen species (ROS), are highly reactive and unstable species that are produced during many metabolic activities in the body. The produced ROS disturbs the function and structure of healthy cells by quickly pairing up their odd free electrons with cells and creating an unstable redox equilibrium leading into the origin and growth of different human cancers, in addition to various other ailments.[25-28] Controlling the intracellular ROS generation by antioxidants is one of the key strategy to overcome cancer.[29] Hence, developing chemotherapeutic agents with the dual action of anti-cancer and anti-oxidant properties are of great importance.

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Hence in continuation of our efforts in medicinal chemistry research[30-38] and considering the importance of the 1, 4-DHP derivatives, the present work aimed to design, synthesise and validate the dual action properties of 1, 4-DHP derivatives by *in vitro* anti-cancer and anti-oxidant studies. Considering the hurdles in the reported synthetic methods, the present work demonstrates construction of the highly functionalized 1, 4-DHP derivatives by simple, convenient and eco-friendly synthetic methodology by using simple starting materials ((*E*)-*N*-Methyl-1-(methylthio)-2-nitroethenamine) (NMSM), **4a** and corresponding aldehydes (**5a-r**) in the presence of catalytic PTSA and in water medium.

2. Results and Discussion

2.1. Design and evaluation of Physico-chemical and Drug like molecule (DLM) properties of 1, 4-DHP derivatives

In the design of the molecules, the privileged 1,4-DHP scaffold with nitro groups at 3rd and 5th positions have been kept intact and the structural and functional variations have been intended at the 1st, 2nd, 4th and 6th positions of the 1,4-DHP scaffold as shown in figure 2. The designed 1, 4-DHP derivatives intended for the synthesis with diverse structural and functional variations were shown in Figure 3. The designed molecules were subjected to evaluate for their DLM nature, which is ultimately dependent on their physicochemical properties. These properties further aid in designing a molecule with better Absorption, Distribution, Metabolism, Excretion (ADME) and Toxicity.[39, 40] One of the highly influential rules in guiding the small-molecule drug design is the 'rule of 5' (Ro5). The Ro5 summarizes that the molecule with a Log *P* not greater than 5, molecular weight (MW) less than 500, hydrogen bond acceptors (HAs) and donors (HDs) less than 10 and 5 respectively could lead to good DLM character.[41-43] The other rules by Veber's group revealed that the molecules containing total polar surface area (TPSA), rotatable bonds (RBs) and HAs and HDs equal to or less than, 140 Å, 10 and 12 respectively found to possess better oral bioavailability.[44] The works of Leeson and co-workers have

identified that there was a 16 to 23% increase in the number of rings, hydrogen bonding groups, a number of RBs and MWs in the molecules approved between 1983 and 2002 than the drugs approved before 1983.[45] Hence, a precise understanding and modulation of physicochemical properties became an important component for a drug candidates to contribute overall quality at different important drug discovery stages.

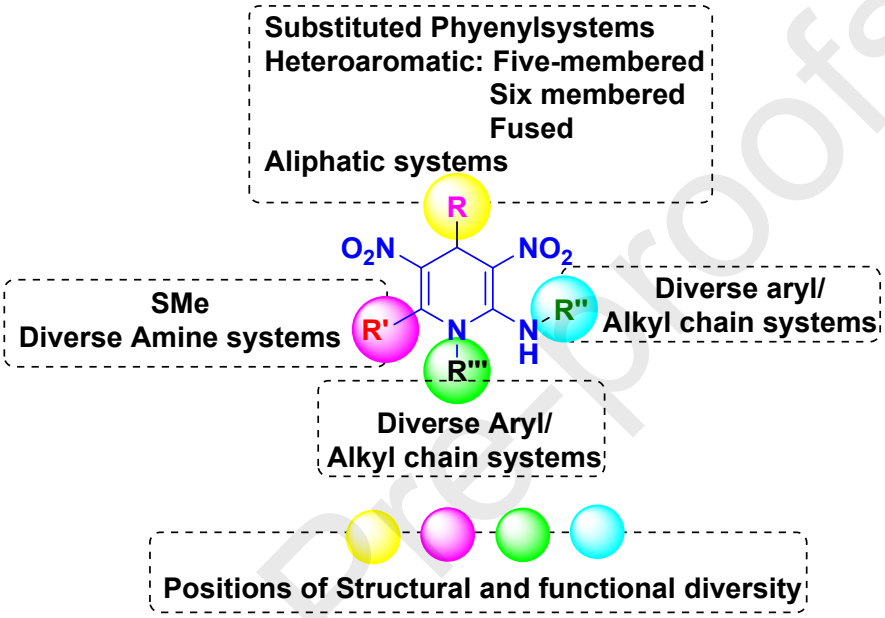

Figure 2. Design of the 1,4-DHP derivatives

The physicochemical properties of 1, 4-DHP derivatives were evaluated using the SwissADME online website [46, 47] and the key parameters are being summarized in table 1 (for the complete profile can be found in the supporting information). The physicochemical properties data reveal that the MWs of the intended compounds are in the range from 326.33 to 576.66 with **6o** as the lowest and **6t** as the highest respectively. The molecule, **6t** violated the Lipinski's standard of MW less than 500. The iLogP values varied between 1.58 to 4.47 with the **6q** as lowest and **6t** as highest respectively. The HAs and HDs of the molecules have been found in the range from 4 to 6 and 1 to 2 respectively. The compounds have shown to have number of RBs between 5 to 13. The molecules **6t, 6u** and **13d** revealed to be the molecules with the highest number of RBs with 13, 11 and 10 respectively. The molecules, **6e** stand top with the highest PTSA value of 178.03 and the molecules, **13f**, **13g** with the the lowest TPSA value of 110.15. Hence, a blend

of molecules with wide variations in their physicochemical properties have been designed with violations of Lipinski's rule with molecules **6e** and **6t** and rest all the other compounds are in accordance with the Lipinski and Veber proposals.

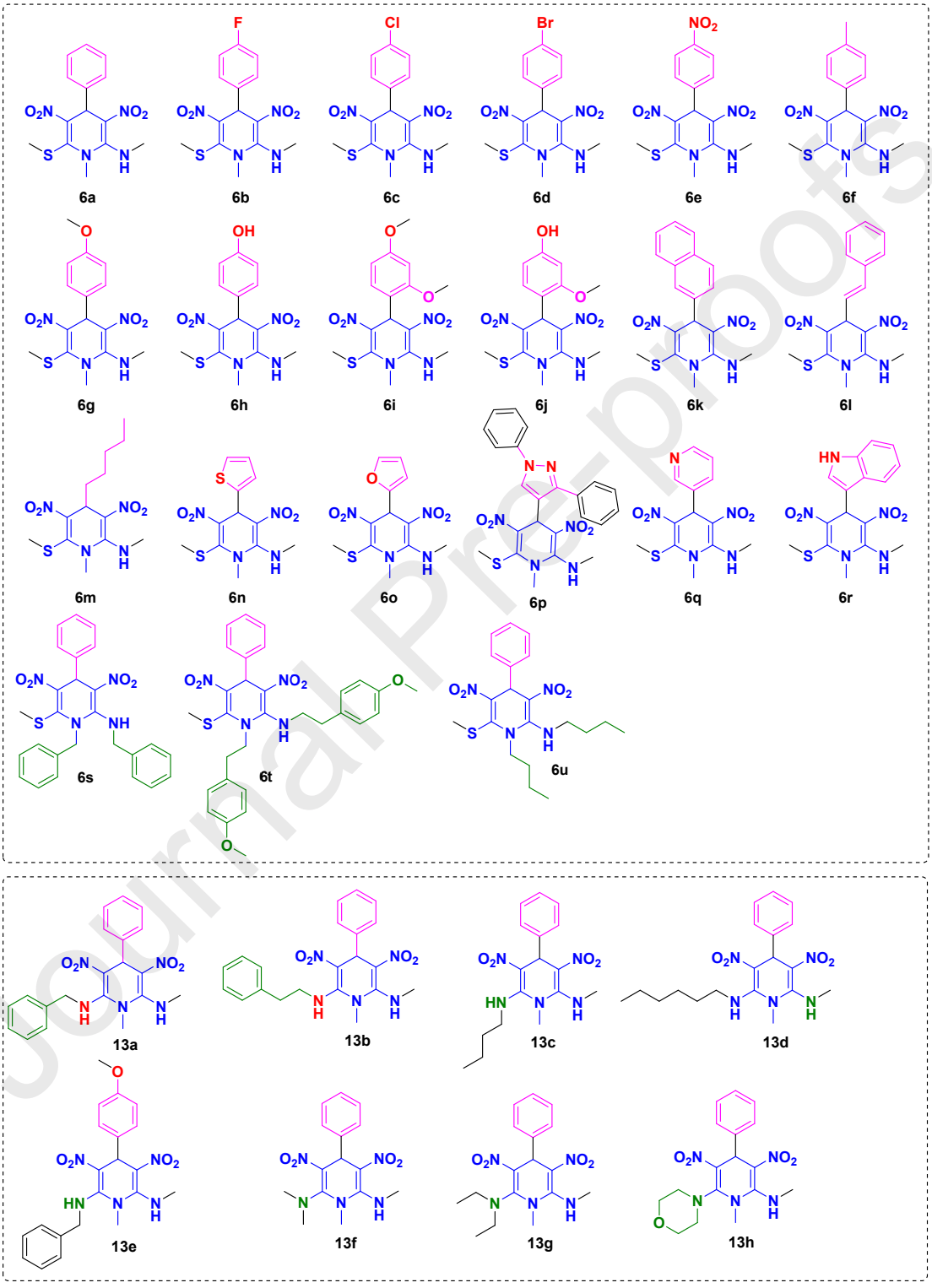

Figure 3. Library 1,4-DHPs with diversity: C6-methylthio group (**6a-u**) and with amines replacement of C6-SMe **(13a -h).**

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Additionally, based on all the physicochemical properties, the pharmacokinetic behaviours *Viz*. are Gastrointestinal absorption and brain access of the of 1, 4-DHP derivatives have been predicted and depicted graphically by the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) by computing the lipophilicity (WLOGP) againt the TPSA. The molecules falling in the region of the white ellipse, yellow ellipse and grey area predicted to have high intestinal absorption (HIA), Brain-Blood barrier (BBB) crossing and non-permeant either in HIA or BBB. The colour-coding by blue dot and red dots of the points indicates the predicted active effluation of the molecules or not by the P-glycoprotein of the Central Nervous System (CNS) respectively. It is predicted that none of the molecule is falling in the yellow ellipse, hence the molecules are with poor BBB permeation. Majority of the molecules are in the white ellipse and predicted to have HIA. Rest of the compounds are falling in the grey region predicted to have poor GI and BBB. Except for molecules, **13h**, **6r** and **6j,** all are predicted to have non-efflux action from the CNS by the P-glycoprotein.

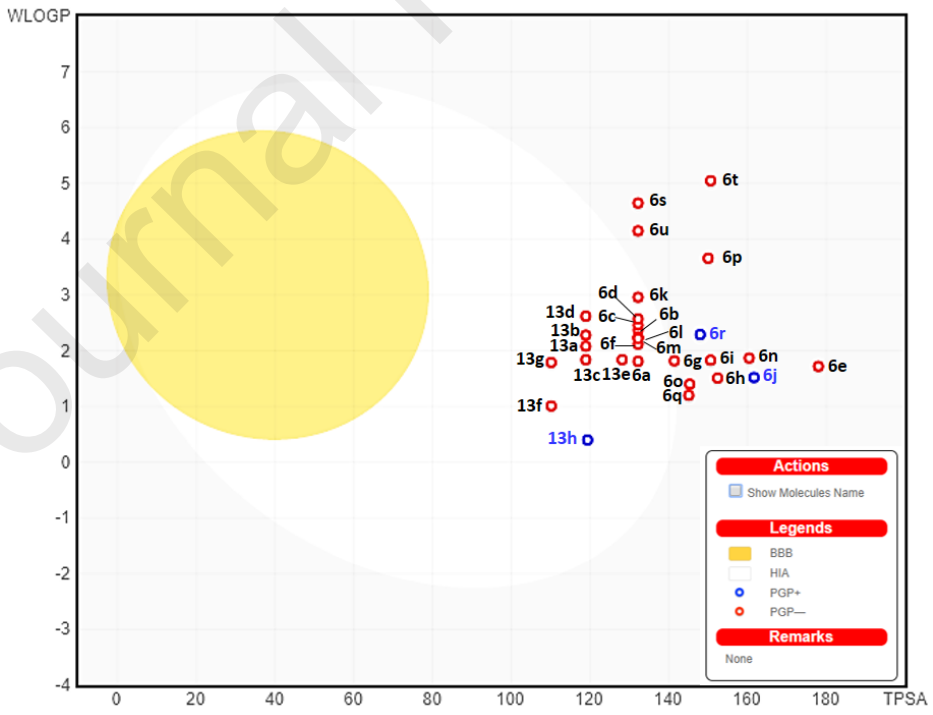

Figure 4. The BOILED-Egg depiction of the designed and synthesized molecules.

Table 1. Evalauation of physico-chemical properties and *In vitro* biological activities of 1, 4-DHP derivatives

Compound	Physico-chemical properties[a]								*In vitro* Biological Activities		
	Lipinski rule of five						Veber rule		Anti-Cancer (IC_{50})		Anti-Oxidant Reduction level of DPPH (%)[b]
	MW	iLOGP	HAs	HDs	Violations	RBs	TPSA	Violations	Hep2 (μM)	A549 (μM)	
6a	336.37	2.01	4	1	0	5	132.21	0	20	25	51.31098
6b	354.36	2.21	5	1	0	5	132.21	0	**16**	**10**	67.89634
6c	370.81	2.37	4	1	0	5	132.21	0	>100	>100	46.52439
6d	415.26	2.48	4	1	0	5	132.21	0	30	25	72.86585
6e	381.36	1.77	6	1	1	6	178.03	0	>100	>100	75.67073
6f	350.39	2.38	4	1	0	5	132.21	0	>100	>100	62.13415
6g	366.39	2.51	5	1	0	6	141.44	0	50	45	59.72561
6h	352.37	1.7	5	2	0	5	152.44	0	>100	>100	49.96951
6i	396.42	2.7	6	1	0	7	150.67	0	20	10	69.39024
6j	382.39	1.84	6	2	0	6	161.67	0	40	30	22.07317
6k	386.42	2.53	4	1	0	5	132.21	0	>100	>100	63.35366
6l	362.4	2.62	4	1	0	6	132.21	0	**10**	**50**	63.90244
6m	330.4	2.75	4	1	0	8	132.21	0	45	50	73.71951
6n	342.39	2.23	4	1	0	5	160.45	0	>100	>100	52.40854
6o	326.33	1.82	5	1	0	5	145.35	0	**10**	**8**	70.12195
6p	478.52	3.02	5	1	0	7	150.03	0	**15**	**25**	39.81707

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6q	337.35	1.58	5	1	0	5	145.1	0	>100	>100	52.04268
6r	375.4	1.88	4	2	0	5	148	0	>100	>100	53.81098
6s	488.56	3.41	4	1	0	9	132.21	0	24	30	66.76829
6t	576.66	4.47	6	1	1	13	150.67	0	>100	>100	66.82927
6u	420.53	3.44	4	1	0	11	132.21	0	**14**	**9**	59.57317
13a	395.41	2.8	4	2	0	7	118.94	0	>100	>100	22.07317
13b	409.44	3.1	4	2	0	8	118.94	0	>100	>100	39.81707
13c	361.4	2.73	4	2	0	8	118.94	0	>100	>100	65.36585
13d	389.45	3.02	4	2	0	10	118.94	0	>100	>100	39.81707
13e	391.42	2.78	5	2	0	9	128.17	0	24	29	71.40244
13f	333.34	2.37	4	1	0	5	110.15	0	>100	80	46.52439
13g	361.4	2.46	4	1	0	7	110.15	0	>100	>100	56.58537
13h	375.38	2.56	5	1	0	5	119.38	0	>100	>100	55.60976
Doxorubicin	-	-	-	-	-	-	-	-	10±0.8	0.65±0.04	-
Paclitaxel	-	-	-	-	-	-	-	-	1.8±0.12	0.175±0.01	-
Ascorbic Acid	-	-	-	-	-	-	-	-	--	--	100.9146

[a] calculated using SwissADME online; [b]Results are the average of three independent experiments. [c]Evaluated at standard concentration of 50μg

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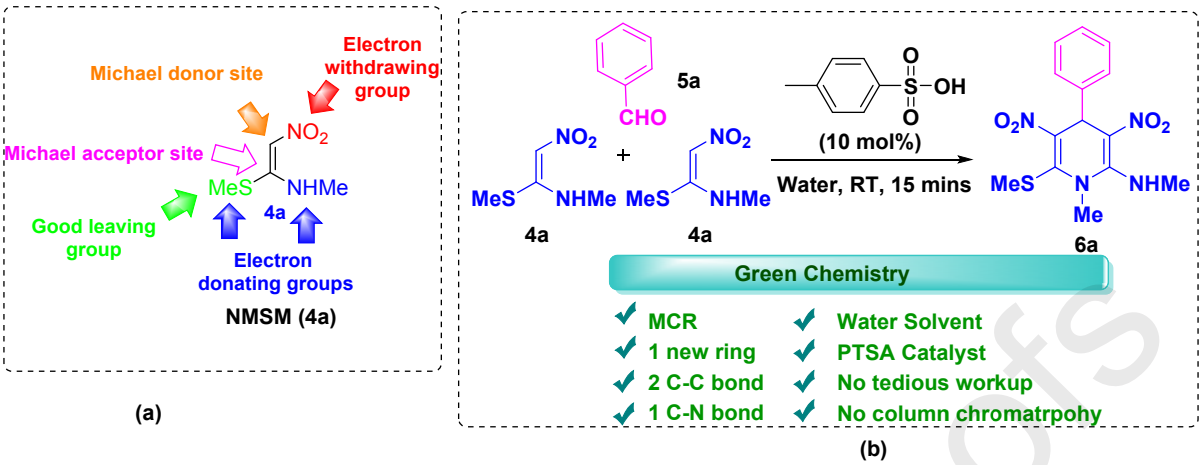
2.2. Synthesis



Scheme 1: (a) Reactivity profile of NMSM; (b) General synthesis method of 1,4-DHPs with **6a** as the example.

The NMSM is a versatile intermediate, with an ethylene motif containing three functional groups - NO_2, S-methyl and N-methyl. Due to the presence of strong electron-withdrawing nitro group on ethylene carbon, the NMSM can act as an excellent Michael acceptor. The methylsulfanyl group is a good leaving in nucleophilic substitutions and also an electron donor.[48] It is considered to be one of the key intermediate in industrial scale synthesis of ranitidine and nizatidine, marketed anti-ulcer drugs.[48]

The development of new methods by using NMSM to synthesised polysubstituted 1,4-DHP *via* an efficient and convenient procedures are of great interest. Previously, the synthesis of 1,4-DHP derivatives are reported from NMSM by various methods using the 2-aminopyridine catalyst[34] and microwave conditions.[49] However, the above mentioned reaction suffers from the following drawbacks i) high temperatures ii) there is no chance for molecular diversity for various derivatives in the amine functional group and iii) toxic catalyst. To overcome these, in the present work, a simple, greener and eco-friendly synthetic methodology has been developed towards the synthesis of highly functionalized 1,4-dihydropyridine by using simple starting materials ((*E*)-*N*-Methyl-1-(methylthio)-2-nitroethenamine) NMSM **4a** and aldehydes **5a** in the presence of PTSA in water medium at ambient temperature. This method provides clean

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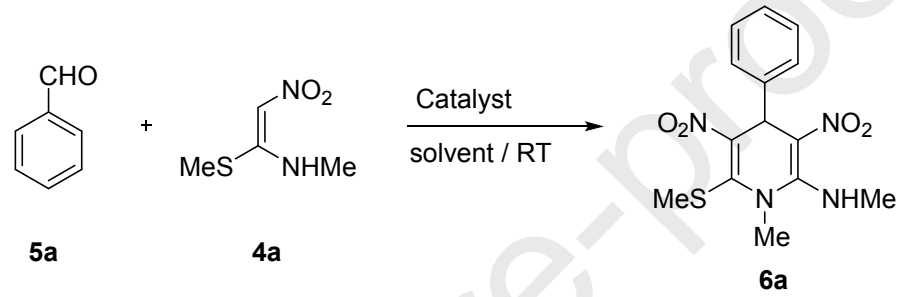
reaction with shorter reaction time, easy work-up and purification of products by nonchromatographic method with high yields. To the best of our knowledge, no research group has reported the reaction of two moles of NMSM with wide spectrum of aldehydes in the presence of PTSA in water to afford corresponding highly functionalized multi-substituted 1,4-DHP derivatives in a single step and with excellent yield. The NMSM reactivity attributes and synthetic scheme are depicted in scheme 1.

Table 2. Optimization of reaction conditions **6a.**



5a **4a** **6a**

Entry	Catalyst in (equivalents)	Solvent	Time	Yield (%)
1	PTSA (0.1)	Toluene	10 h	35
2	PTSA (0.1)	Acetone	5 h	45
3	PTSA (0.1)	MeCN	5 h	60
4	PTSA (0.1)	Ethanol	1h	70
5	PTSA (0.1)	Water:Ethanol	30 min	80
6	**PTSA (0.1)**	**Water**	**10 min**	**98**
7	DNSA	Water	1h	45
8	CH_3SO_3H	Toluene	5h	40
9	CF_3COOH	Toluene	1h	45
10	TfOH	Toluene	1h	35
11	$InCl_3$	Ethanol	2h	82
12	$ZnCl_2$	Ethanol	5h	70
13	CuCl	Ethanol	1h	80
14	No catalyst	Water	24h	-

[a] General conditions; **5a** (1 equi), **4a** (2 equi) and PTSA (0.1 equi) under water at room temperature conditions. [b] Isolated yield after washing water solvent.

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PTSA=*Para*-Toluenesulfonic acid, DNSA=2,4-Dinitrobenzenesulfonic acid, CH_3SO_3H= Methanesulfonic acid, CF_3COOH= Trifluoroacetic acid, TfOH=trifluoromethanesulfonic acid (Triflic acid), $InCl_3$= Indium(III) chloride, $ZnCl_2$ = Zinc chloride, CuCl = Cuprous chloride.

Our initial studies are focused towards the identification of the optimum reaction conditions test reactions of benzaldehyde **5a** with NMSM **4a** afforded *N*, 1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine **6a** was investigated by using various Bronsted acids (Table 2). To begin with, the reaction was performed with PTSA in toluene medium afforded poor yield of the product (0.1 equiv; Table 2, entry 1) at room temperature. The reation was conduted with diverse polar solvents such as acetone, acetonitrile, ethanol and ethanol-water mixture (1:1) (0.1 equiv; Table 2, entries 2-5) furnished moderate yields of products. To our delight, a breakthrough result was achieved when the reaction was carried out in green solvent, water medium (0.1 equiv; Table 2, entry 6) **6a** afforded good yield 98% and the reaction time was shortened to just 5-10 minutes. This test reaction was then investigated using DNSA in water medium (0.1 equiv; Table 2, entry 7) which resulted in poor yield. Furthermore this test reaction was carried out other Bronsted acids like CH_3SO_3H, CF_3COOH and TfOH in toluene (0.1 equiv; Table 2, entries 8-10) medium furnished the desired products but yield of the products was not satisfactory. The reaction was performed by using $InCl_3$, $ZnCl_2$ and CuCl in ethanol medium (0.1 equiv; Table 2, entris 11-13) gave moderate yields. However, product has to isolate in conventional workup and column chromatography. The reaction did not take place in the absence of any catalyst in water medium (entry 14). Based on the optimization result, PTSA-water condition was found to be the ideal for this MCR, which afforded good yield. Further, it is important to note that in the PTSA-water condition furnished the product as precipitate in the reaction vessel which can easily purified by simple filtration technique, hence no need of extra purification techniques is required to get pure desired product **6a**. Hence, The optimised reaction involves simple stirring two reactants at the ambient temparature using water as a solvent and PTSA as a catalyst. The

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reaction completes with in 15 mins and can be observed from the thin layer chromatography (TLC) and precipitation formation in the in the reaction vessel. The crude products were further purified by the simple recrystallization from dichloromethane and hexane mixture (9:1) to obtain analytically pure products (**6a-u).** The desired product was characterized by spectral analysis *Viz.* are IR, ^{1}H NMR, ^{13}C NMR and HRMS. The spectral data of the compounds are found to be in accordance with the reported literature (See supporting information).[34] For instance, the ^{1}H NMR spectrum of **6a** displaye a singlet peak at 5.94 ppm, a characteristic signal for C4*H*. The singlet peak observed at 3.42 ppm corresponds to NMe and doublet peaks observed at 3.09 ppm corresponds to NHMe peaks. The characteristic peak of good leaving group, SMe is observed at 2.53 ppm as a singlet. The singlet peak located at 10.05 ppm confirms the presence of NH. Similarly, in the ^{13}C NMR spectrum, the **6a** compound has displayed 12 distinctive signals corresponding the its crabons. Among these, four, three and five were observed in the regions corresponding to the aliphatic, aromatic CH and quaternary carbons respectively. The plausible mechanism for the formation of 1,4-DHPs has been represented in Scheme 2.

Based on the optimization results mentioned above (Scheme 1, Table 2), a plausible reaction mechanism was proposed as shown in scheme 2. First an aldehydes **5a** reacts with PTSA condensed to give protonated benzaldehyde 7 which reacts with NMSM **4a** through Michael addition to generate the intermediate **8** which rearrange to give intermediates **9** and **10** by through PTSA. The intermediate **10** undergoes a *N*-cyclization with another mole of NMSM **4a** to give intermediate **11** with loss of water molecule. Finally an intramolecular elimination of thiomethanol to furnish *N*, 1-dimethyl-6-(methylthio)-3,5 dinitro-4-phenyl-1,4-dihydropyridin-2-amine **6a.**

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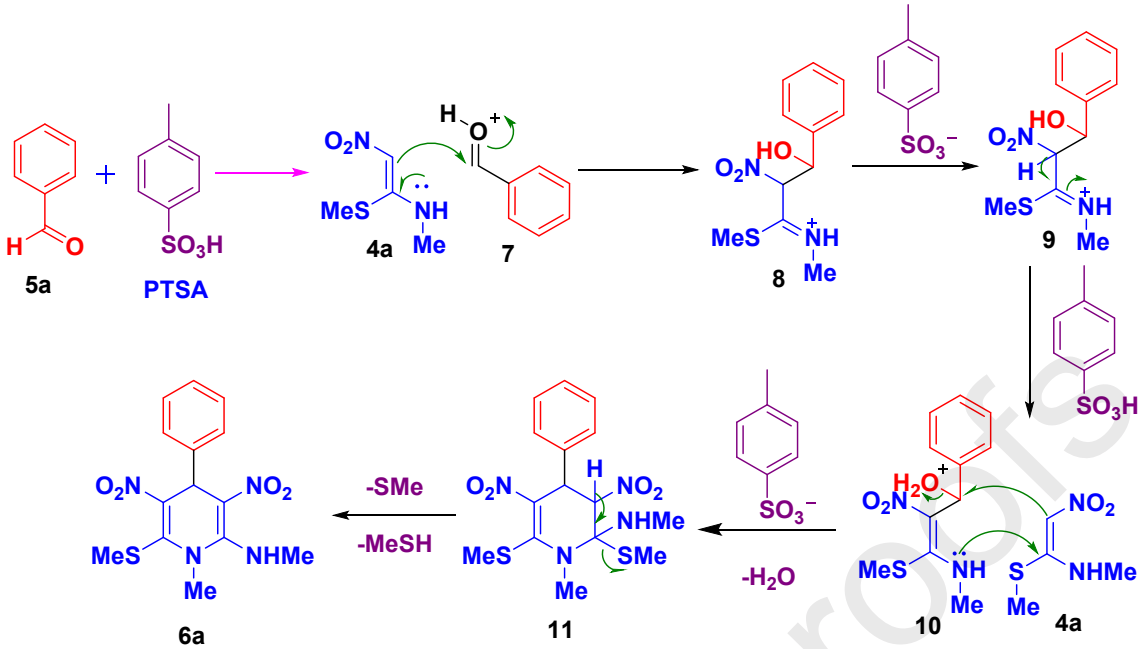
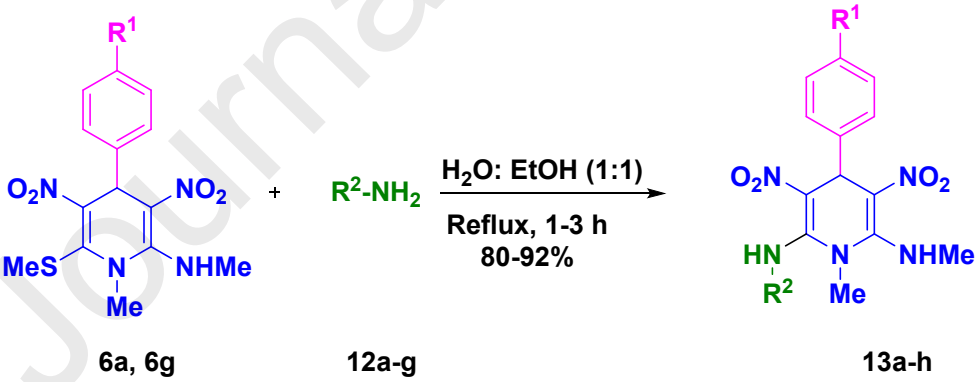


Scheme 2: The plausible mechanism for the formation of 1,4-DHPs

Further, the reactivity of the good labile group, SMe has been tested by reacting the obtained **6a** with the diverse aliphatic amines as nucleophiles in refluxing conditions using water and ethanol (1:1) as solvent mixture to afford the corresponding products with good yields as shown in scheme 3. The library of synthesised 1,4-DHPs with primary and secondary amines substitutions (**13a-h)** have been presented in figure 3.



6a-h, 13a-h: R^1 = H; 6g, 13e: R^1= OMe

12a, 13a: R^2 = Benzyl; 12b, 13b: R^2 = Phenylethyl; 12c, 13c: R^2 = n-Butyl; 12d, 13d: R^2 = n-Hexyl; 12e,13f: R^2 = *N,N*-Dimethyl; 12f, 13g: R^2 = *N,N*-Diethyl; 12g, 13h: R^2 = Morpholine

Scheme 3: The nucleophilic substitution of C2 methylsulfanyl group of 1,4-DHPs with primary and secondary amines.

2.3. Single-crystal X-ray diffraction (SXRD) studies

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In the activity of drug molecules, the isomers play a key role and hence a better understanding of possible and stable isomers of the molecules would benefit in developing the strategies in designing potent molecules.[50] The single crystals of the compound, **13f** has been grown in dichloromethane: hexane (9:1) mixture by slow evaporation at 5 °C - 15 °C. The SXRD analysis of **13f** have been considered as the representative structures of 1,4-DHP derivatives to explicit the spatial orientation of the stable conformer and its crystal packing. In the present study of 1,4-DHPs derivatives, at the chiral carbon, planar phenyl ring is stabilized with the above the plane orientation and has been arranged perpendicular to the 1,4-DHP scaffold (A in figure 5).

The packing of the **13f** in crystal lattice depicts that the one molecule of **13f** has been are arranged in a head to head and are being stabilized by one intramolecular and two intermolecular hydrogen bonds. The intramolecular hydrogen bond is strongly held between one of the Oxygen atom of NO_2 group at 3rd position and the Hydrogen of the N**H**-CH_3 present at 2nd position with a distance of 2.01 Å and an angle of 128.40° between the O, N and H. Similarly, the distance between Oxygen atom of NO_2 group and Nitrogen of the **N**H-CH_3 is found to be 2.632 Å with an angle of 70.63° between the O, N and C. Whereas, the two intermolecular hydrogen bonds have been observed *Viz.* are between the Hydrogen of the N**H**-CH_3 present at 2nd position with the Oxygen atom of NO_2 group at 3rd position of the another molecule with a distance of 2.953 Å and an angle of 45.27° between the O, N and H. Similarly, the other intermolecular hydrogen bond of the same molecules has been observed with the Hydrogen of the N**H**-CH_3 of another molecule with a distance of 2.953 Å and with an angle of 45.27° between the O, N and H. That means one molecule is sandwiched between two other molecules with two intermolecular hydrogen bonds (B in figure 5). The complete alignment of the molecules with all the expanded contacts with hydrogen bonding interactions along the C-

axis has been shown in C in figure 5. The crystal data summary of the **13f** is provided in supporting information.

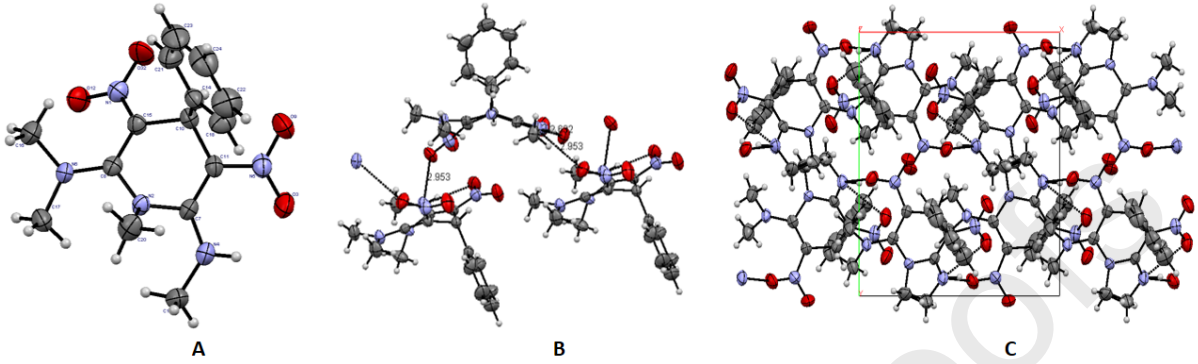

Figure 5. SXRD results of **13f**. **(A)** The ORTEP diagram with 40% ellipsoid probability, **(B)** Hydrogen bonding interactions along the C-axis and **(C)** Cubical packing along the C-axis.

*2.4. In vitro anti-cancer and anti-oxidant and SAR studies of **6a-u** and **13a-h***

The anti-cancer activities of synthesized 1,4-DHPs (**6a-u** and **13a-h)** have been evaluated by using *in vitro* 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) reduction assay against two human cancer cell lines, Laryngeal carcinoma (Hep2) and Lung adenocarcinoma (A549) cell lines and the results are presented in Table 1. Among all the screened compounds, 4-(furan-2-yl)-*N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydro pyridin-2-amine, **6o** found to the most potent molecule with IC_{50} values of 10 μM and 8 μM against Hep2 and A549 cells respectively. Similarly the styrene substituted molecule, **6l** found to be another potent molecule against Hep2 cell lines with an IC_{50} value of 10 μM but tolerated the activity against A549 cells with an IC_{50} value of 50 μM. The inhibition potentials of **6o** and **6l** against Hep2 cell lines are found to equivalent to that of a standard drug, Doxorubicin's inhibition value of 10 μM. Another molecule, **6u** containing phenyl substitution and *n*-butyl group substitution on both the N atoms of the 1,4-DHP has found to be most potent molecule against A549 cells with an inhibition potential IC_{50} value of 9 μM and also retained the activity against the Hep2 cells with an IC_{50} value of 14 μM. These are the most potent molecules found

in this investigation. The other succeeding molecules, **6p, 6b, 6l** and **6a** have displayed a decent activity against Hep2 cell with an inhibition potential IC_{50} values of 15 μM, 16 μM, 20 μM and 20 μM respectively. Similarly against A549 cells, the **6p, 6b, 6l** and **6a** have displayed better inhibition with 25 μM, 10 μM, 10 μM, 25 μM respectively. The other molecules which could retain the activity with lower IC_{50} values include **13e, 6s, 6d, 6j, 6m** and **6g** with 24 μM, 24 μM, 30 μM, 40 μM, 45 μM and 50 μM respectively against Hep2 cells**.** Similarly, **13e, 6s, 6d, 6j, 6m** and **6g** have retained the activity against the A549 cells with an IC_{50} inhibition potential of 29 μM, 30 μM, 25 μM, 30 μM, 50 μM and 45 μM respectively.

From the interpretation of results, the structure-activity relationship has been drawn and graphically represented in figure 6**.** It is evident that the central core, *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine is an essential requirement for exhibiting the activity. The substitutions at the 4th position have shown to exert a great impact on the activity. The **6a,** the simple phenyl substituted *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine derivative has retained the activity with 20 μM and 25 μM against Hep2 and A549 cells respectively. When the 4th position of Hydrogen replaced with the bioisosteric Fluorine, the resulting molecule **6b** has greatly gained the activity with the 16 μM and 10 μM against Hep2 and A549 cells respectively. Instead of Fluorine, the halogen with bigger in size, Bromine is replaced, the resulting molecule **6d** has lost two folds it's activity with 30 μM and 25 μM against Hep2 and A549 cells respectively. Similarly in **6g** molecule, the 4th position Hydrogen atom of **6a** is replaced with methoxy group, the activity lost to a greater extent with the values of 50 μM and 45 μM against Hep2 and A549 cells respectively. But upon introduction of another methoxy group at the 2nd position of **6g**, the resulting molecule gained the activity to the greater extent and displayed a very good activity with 20 μM and 10 μM against Hep2 and A549 cells respectively. It is interesting to notice that the

activity of the molecule **6j**, which is a result of removing the methyl from the 4th position methoxy group of **6i,** has exhibited more than two folds lesser activity than the **6i.**

Similar to the functional group variations, the molecules derived from the structural variations on the 4th position of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine core have also greatly impacted in varying the the activities. In the case of **6o,** the phenyl system of **6a** is replaced with the furan, a five membered heterocyclic system has been found to be the most potent molecule with the 10 μM and 8 μM against Hep2 and A549 cells respectively. Similarly, when the furan is replaced with the 1,3-diphenyl-1*H*-pyrazole system, the molecule **6p** has lost the activity from two to three folds with 15 μM and 25 μM against Hep2 and A549 cells respectively. Similar to this, the aliphatic structural variations have made their contributions in tailoring the activities. The **6l** and **6m** are the more potent molecules in this category with styrene and *n*-Butyl group substitutions respectively on the *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine core. Among the **6l** and **6m,** the styrene in the **6l** has contributed to exert better activity with 10 μM and 50 μM whereas, the *n*-Butyl group in **6m** has lowered the activity with 45 μM and 50 μM against Hep2 and A549 cells respectively.

The variations of alkyl systems replacing the methyl group on the -N**C**$\mathbf{H_3}$ has also extended its contributions in the exerting the activity. In the case of **6u**, *n*-Butyl group are replaced with the methyl groups of the **6a** and found to have the molecule with great efficiency with the 14 μM and 9 μM against Hep2 and A549 cells respectively. This is another high potent molecule of this series. But replacing the *n*-Butyl groups with benzyl systems resulted in losing the activity with 24 μM and 30 μM against Hep2 and A549 cells respectively. Unfortunately, the replacement of –SCH_3 with the amines could not help in elevating the activity except the molecule **13e**. The **13e** is a structural modification of **6g** with the butan-1-amine has increased

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the activity from 50 μM and 45 μM to 24 μM and 30 μM against Hep2 and A549 cells respectively.

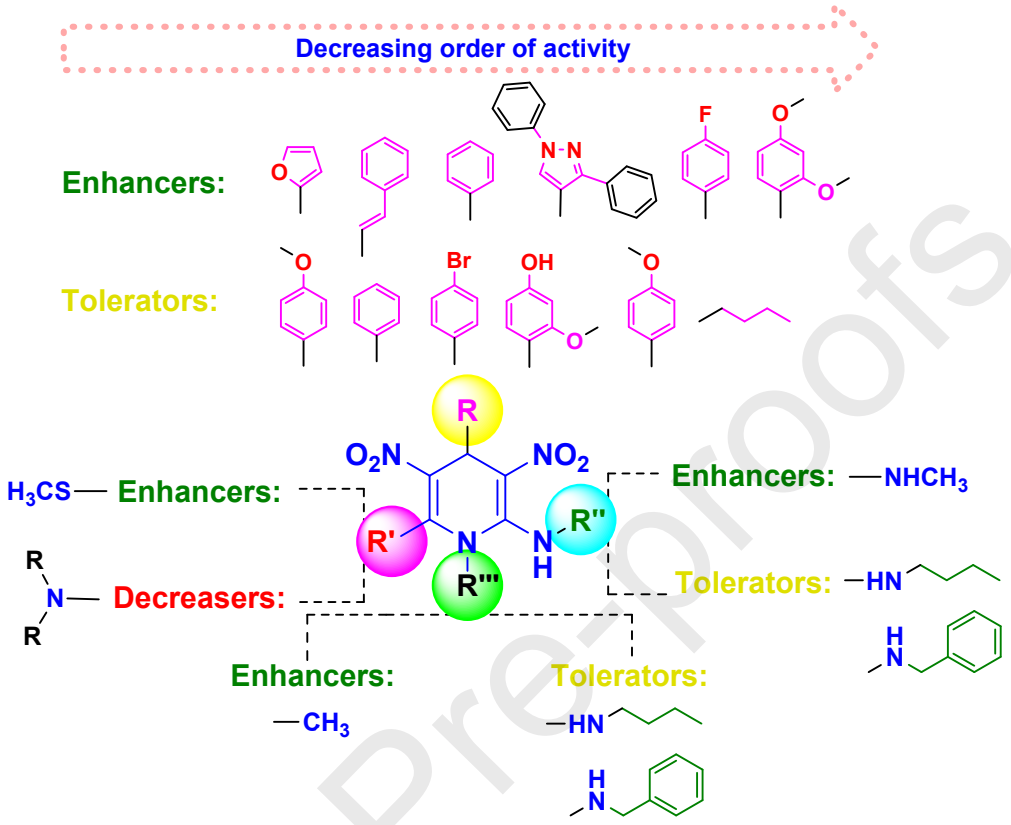

Figure 6. SAR studies

In anti-oxidant activities, the molecules, **6e, 6m, 6d, 13e** and **6o** have displayed better anti-oxidant reduction levels against DPPH with 75.67%, 73.71%, 72.86%, 71.40% and 70.12% respectively. Interestingly, the hit molecule from the anti-cancer activities, **6o** has exhibited better antioxidant activity and validated the 1,4-DHPs dual action capabilities.

3. Conclusions

In summary, the physico-chemical properties of the designed and synthesized diverse multi-substituted 1,4-DHP derivatives have found to be in accordance with Lipinski and Veber proposals, except three molecules. It is also predicted that these molecules have poor BBB accessibility and moderate HIA attributes. The simple, economical, water-mediated and PTSA catalysed three-component one-pot synthesis procedure has been developed and validated its

wide use by applying it to synthesis molecules from **6a** to **6u** in good yields. The impact of the various structural and functional variations on the biological activities has been evaluated and designed the SAR. The results clearly indicate that furan, pyrrole and styrene substitutions are key for the activity enhancement and the *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-1,4-dihydropyridin-2-amine core is an essential requirement. Interestingly, the hit molecule from the anti-cancer activities, **6o** has exhibited better antioxidant activity. This study established dual action of 1,4-DHP derivatives as anti-cancer and oxidant agents and aids the researchers in finding the potent molecules with the further tuning of the molecules with appropriate structural and functional variations.

4. Materials and methods

All the chemicals, aldehydes, amines, NMSM, MTT, propidium iodide (PI), Dulbecco's Modified Eagle's Medium (DMEM), antibiotics and fetal bovine serum (FBS) were purchased from Sigma–Aldrich, Bangalore, India. The TLC plates procured from Merck are used to monitor the reactions. The melting points were analysed by using open-ended capillary tubes on VEEGO VMP-DS instrument and are uncorrected. Infra-Red (IR) spectra was recorded using Nicolet-6700 spectrometer with KBr pellets. The Bruker Avance 400 spectrometer has been used to record the ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra of the synthesised compounds using either ($CDCl_3$) or (DMSO-d_6 + CCl_4, 1:1) with tetramethylsilane (TMS) as internal standard. The *J* values are calculated in Hz. In reporting the spectral chemical shift values in ^{1}H NMR, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant, integration have been used. The Water's Q-TOF micro mass spectrometer has been used for recording the high-resolution mass spectra in electron spray ionization mode. At 298 K, the SXRD measurements were performed on Oxford CrysAlis CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å).

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4.1. Experimental section

*4.1.1. General procedure for the synthesis of multi-substituted 1,4-DHPs (**6a-u**)*

A mixture of solution containing aldehyde (1.0 equiv), NMSM (2.0 equiv) and PTSA (0.1 equiv) in water (3 mL) was stirred at room temperature for about 15 minutes. The solid formation observed. The TLC with mobile phase of hexane: EtOAc mixture has been used to monitor the completion of the reaction. The resulted solid was cooled to 0-5 °C and filtered under vaccum. The crude products were recrystallized from dichloromethane and hexane mixture (9:1) to obtain analytically pure products (**6a-u).** The spectral characterisation data and spectra are included in the supporting information.

*4.1.2. General procedure for synthesis of nucleophilic substitution of 1,4-DHPs with amines **(13a-h).***

A solution of *N*,1-dimethyl-6-(methylthio)-3,5-dinitro-4-phenyl-1,4-dihydropyridin-2-amine (1 equiv) in water: ethanol mixture (5 mL), added the aliphatic amine (1 equiv) at ambient temparatures and were mixed well. Gradually, the temperature of the reaction mixture has been raised to 80 °C and stirred until the reaction got completed. The progress of the reaction has been monitored by TLC. Upon completion, the reaction mixture was gradually cooled to room temperature and the resulting solid was filtered off. The crude product was purified by the recrystallization from dichloromethane and to obtain spectrally pure products **13a-h**. The spectral characterisation data and spectra are included in the supporting information.

4.2. Biological activity

4.2.1. Cell lines and culture conditions

The cancer cell lines, Hep2 and A549 were obtained from NCCS, Pune, India. The cells were supplemented with 10% fetal bovine serum (FBS) and maintained in 1× Dulbecco's

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Modification of Eagle's Medium (DMEM) at 37 °C in a CO_2 incubator in an atmosphere of humidified 5% CO_2 and 95% air. The cells were maintained by routine subculturing in tissue culture flasks. The culture medium was changed at every 48 h and the cells were split was observed when they reached confluence. The IC_{50} values of the tested compounds were determined by incubating the cells with different concentrations for 48 h.

4.2.2. In vitro anticancer activity

The MTT reduction test was used to determine the cell survival rate. As per the literature described protocol, the MTT colourimetric assay has been performed.[51] The 6 replicates in 96-well flat bottomed culture plates were used to perform the experiments. The phosphate-buffered saline (PBS) was used to dissolve MTT at a concentration of 5 mg/mL. After 48 h of incubation of Hep2 and A549 cells, with different concentrations of tested compounds, 20 µL of a 5 mg/mL MTT solution was added and the plate was further incubated for about 4 h. The 100 µL of DMSO was used to dissolve the compounds. By the absorbance at 570 nm was used to measure the conversion of MTT to formazan by metabolically viable cells. The percentage conversion of compounds with treated cells was used to evaluate the effect of chemicals on the growth of cells and to determine the concentration that inhibited 50% of growth (IC_{50}).

4.2.3. In vitro anti-oxidant activity

As per the literature procedure, all synthesized compounds were tested for their ability of free radical scavenging activity.[52] Different compounds with various concentrations (1, 10, 50, 100, 150 and 200 µg/ml, respectively) were taken in clean and sterile test tubes. 3.9 ml of 2,2-diphenyl-1-picrylhydrazyl (DPPH) solution (0.1 Mm) was dissolved in methanol. This mixture was then added to each test tube and followed by the vigorous shaking. Added DPPH solution with all the test tubes was shaken gradually and permitted to standpoint at 27 ºC in

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place of dark for 45 mins. Then blank and positive controls were equipped in a similar way without any test compounds. With concentrations of 1 to 200 µg/ml, the Ascorbic acid was used as a standard. The UV spectroscopy at a wavelength of 517 nm was used to measure the absorbance of the prepared samples. The experiment was replicated three times for consistant results. Radical scavenging activity of the all synthesized compounds was estimated as an inhibition percentage and was calculated by using the following formula:

Measurement of radical scavenging activity (%): A control – A sample / A control*100

Acknowledgements

The authors thank central instrumentation facilities (CIF) for characterizing the compounds.

Conflict of Interest: The authors declare none

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Supporting information

Supporting information includes spectral analyses data and spectras of all the synthesised compounds.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights:

- Designed and synthesised a library of twenty nine 1,4-dihydropyridines derivatives with diverse structural and functional groups variations.
- The drug-like molecule nature of all the compounds has been evaluated by physico-chemical properties analyses.
- A simple and eco-friendly synthetic and purification methods have been developed.
- The dual action abilities (anti-cancer and anti-oxidant activity) were evaluated.
- Three dual-active potent molecules, **6o, 6u** and **6l** have been identified.
- **6o** and **6l** exhibited equivalent anti-cancer activity against Hep2 cells corresponding with standard drug, Doxorubicin.

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