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A Study on the Biological Evaluation of Dihydropyridines

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Abstract – By substituting 1-(4-Nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-Nitrobenzyl)-5-imidazolyl for the orthonitrophenyl group on location 4, new analogues of nifedipine, an established calcium channel blocker, were synthesised. In male rats, the effects of the newly synthesised compounds on blood pressure were analysed using an indirect tail-cuff procedure at 15, 30, and 60 minutes after administration and compared to nifedipine.

Keywords – Antibacterial Activity, 1, 4-Dihydropyridine, Antihypertensive Activity; Rat.

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INTRODUCTION

1, 4-dihydropyridine has played an important role in the development of a broad range of heterocyclic molecules for medicinal use. Antimicrobial, antitubercular, antiulcer, anticonvulsant, analgesic, and anti-inflammatory substances containing the 1, 4-dihydropyridine nucleus have earned a lot of publicity. Because of their intriguing pharmacological properties, 1, 4-dihydropyridines and their derivatives have attracted a lot of attention in the area of organic and medicinal chemistry. Most calcium channel blockers have the 1, 4-dihydropyridine skeleton, and they are most often used in medications like nifedipine, nicardipine, and amlodipine, which have been discovered as coronary agents for the treatment of hypertension.

1, 4-Dihydropyridines (DHPs), including Ca2+ antagonist (CA) drugs, are large group of structurally diverse compounds. They are functionally equivalent to dihydronicotinamide redox-active synthetic compounds with radical scavenging and antioxidant (AO) effects, and they may be used to guard against oxidative stress and related disorders. Oxidative stress plays a crucial role in mitochondrial pathogenesis, controlling the redox modulation of cellular signalling pathways in particular. The existence of oxygen and nitrogen free radicals, classified as reactive oxygen and nitrogen species, is strongly linked to oxidative stress (ROS and RNS, resp.). As cells are exposed to numerous endogenous and/or exogenous insults, they accumulate. ROS and RNS have a "two-faced" personality, acting as both harmful and beneficial organisms. While OS has been studied in a variety of diseases, the different phenomena linked to OS have probably been better studied in cancer cells, where OS can have anticancer-like consequences based on a variety of factors. Its protumorigenic results are largely due to the activation of oxidative DNA lesions (8-OH-G) and the resulting rise in DNA mutations, which can contribute to genome instability and accelerated cellular proliferation if not repaired. Antitumorigenic properties of OS, on the other hand, have been related to cellular processes of senescence and apoptosis, two main molecular pathways that prevent tumour growth.

The formation and development of molecules of therapeutic potential is one of the most significant goals of organic and medicinal chemistry. Heterocyclic compounds have proved to be flexible support mechanisms with a high degree of structural diversity in this respect. 1.4 Dihydropyridines have a variety of pharmacological functions, including calcium channel antagonists, and the heterocyclic ring is a typical characteristic for antihypertensive, antianginal, antitumor, anti-inflammatory, antitubercular, analgesic, and antithrombotic properties. It binds to the L-type channel and also acts on the N-type channel. Other activities such as vasodilation, anticonvulsant, stress protective effect cardio depressant activity, antibacterial, antileishmanial agents, cystic fibrosis transmembrane conductance regulator activity, mineralocorticoid receptor antagonist activity, neuroprotection properties, HIV-1 protease inhibitors, Alzheimer's disease, and antifertility agent have been reported.

Calcium-channel blockers are commonly used to treat a variety of cardiovascular diseases. They've been widely used for hypertension, angina pectoris, heart failure, and Raynaud's disease since 1996, according to Parmley. Calcium channel antagonists are known to be a structurally diverse group of

compounds. The most powerful antagonists are 1, 4-dihydropyridine compounds, such as nifedipine, which is commonly used today. Dihydropyridines work by blocking calcium ion entry into vascular smooth muscle cells through L-type calcium channels. Their capacity to calm vascular smooth muscles accounts for their beneficial effects in the treatment of cardiovascular diseases.

Such drugs reduce resistance in the systemic and coronary arterial beds in angina pectoris, lowering cardiac oxygen demand and increasing cardiac oxygen supply, respectively. The design and synthesis of 4-substituted 1, 4-dihydropyridine derivatives, as well as their hypotensive effect on rat blood pressure measurements using an invasive in vivo technique on canulation with the right carotid artery system, are described in this paper.

Several researchers have established and reviewed the haemodynamic, antianginal, and antihypertensive effects of 1, 4-dihydropyridine calcium channel blockers. Nifedipine, the prototype of 1, 4-dihydropyridines, is an effective drug that is used in clinical practise, but it has some undesirable clinical characteristics. There have been several attempts to develop new drugs in this class with better pharmacokinetic and pharmacodynamic properties. Because of their vessel selectivity, some of these drugs have an effect on the vascular beds and effectively lower blood pressure. Nifedipine's activity and tissue selectivity are affected by changes in the substitution pattern at the C-3, C-4, and C-5 positions. As a result, it's intriguing to see how different C-3 and C-5 substituents affect blood pressure when combined with C-4 1–(4-nitrobenzyl)-5-imidazolyl or 2-methylthio-1- (4-nitrobenzyl)-5-imidazolyl substituents. The synthesis of new alkyl 1, 4-dihydro-2, 6- dimethyl-4-(1-(4-nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-nitrobenzyl)-5-imidazolyl or 2-methylthio-1-(4-nitrobenzyl)-5-imidazolyl)- 3,5-pyridinedicar

BIOLOGICAL ACTIVITIES OF 1, 4-DIHYDROPYRIDINES

For over a century, 1, 4-dihydropyridines (1, 4-DHPs) have been identified. They're relevant biologically because they're analogues of the reactive portion of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH), which are also cofactors in oxidation-reduction enzymes. 4-DHPs, which are synthetic, have a wide range of therapeutic uses, including calcium channel antagonists, antitumor agents, and anti-inflammatory molecules. Nifedipine, Felodipine, and Amlodipine are variants of 1, 4-DHPs, which have a high specific activity as calcium channel blocking agents and are easy to synthesise in large quantities. Nifedipine, for example, has been a common medication for coronary heart failure. In addition to medicinal uses, certain 1, 4-DHPs, such as neonicotinoids, have insecticidal properties without being particularly harmful to humans. Aside from the above uses, 1, 4-DHPs are used as hydride sources in reduction reactions and as synthetic intermediates on the path to alkaloids. Due to its wide range of applications, 1, 4-DHP has emerged as a preferred scaffold for the preparation of structurally diverse six-membered nitrogen heterocycles as well as technique growth.

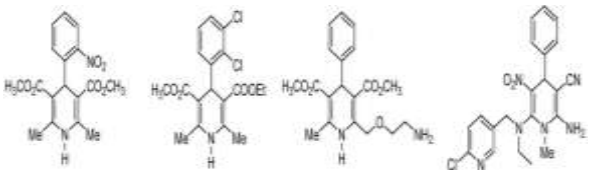

Figure 1.1: Structure of dihydropyridine based calcium channel blockers (Nifedipine, Felodipine and Amlodipine) and neonicotinoid insecticide analogue.

1, 4-DIHYDROPYRIDINES: A SEPARATE GROUP OF BIOANTIOXIDANTS

Because of their structural similarity to 1, 4-dihydronicotinamide, 1, 4-dihydropyridines could be used as model compounds for functioning molecular mechanisms of action modulated by cellular enzymes NADH and NAD (P) H. This composition is the active portion of these reduced coenzymes, which are essential modulators of enzymatic redox reactions and involved in electron transfer.

1, 4-dihydropyridines are hydrogenated N-heteroaromatic compounds that are synthesised. At locations 2, 6, 3, 5, and 1, 4, they may have a variety of substituents. The Hantzsch style cyclic condensation reactions may be used to synthesise their derivatives.

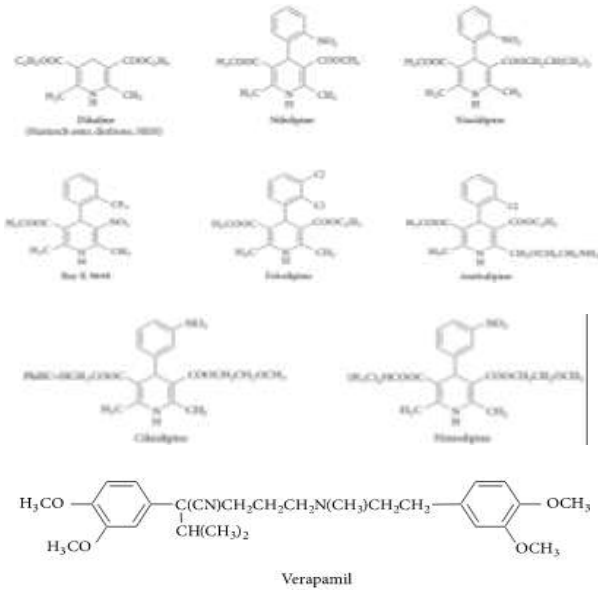

Figure 1.2: Structures of the most known 1, 4-dihydropyridine derivatives and some non-DHP Ca2+ antagonists.

LITERATURE REVIEW

Uppalaiah Kusampally et al. (2020) the authors have established an easy and environmentally safe metal switch over Zeo-catalyst Zr-ZSM-5 in this paper. It is a reusable heterogeneous strong catalyst that can be used to make triphenyl pyridine-3,5-dicarboxamide and 2,6-dimethyl-1,4- dihydropyridine-3,5-dicarboxylate from Acetoacetanilide/ethyl acetoacetate, ACOONH4/NH4OH, and various Aromatic Aldehydes in one jar. In ethanol at an acceptable temperature, reactions yielded very good product yields (87–95%) in a fast reaction period (27–35 minutes). The prepared catalyst could be reused four to five times (4–5 runs) without losing significant catalytic operation. Zr-ZSM-5 is often used as a green catalyst in dihydropyridine combinatorial syntheses. XRD, SEM/EDS, and BET SA-PSD were used to characterise the strong catalyst, and 1H and 13C NMR, IR, and elemental spectral details were used to characterise and validate the substituted dihydropyridine derivatives.

Saddala Madhu Sudhana et al. (2019) the use of MOM-Cl, a controlled carcinogen, is avoided in a novel process for the preparation of MOM-protected carbamates. The two-step, one-pot process yields MOM-protected carbamates by generating a reactive N-chloromethyl carbamate that is quenched with methanol. Various functionalities, such as Boc, sulfonamide, and acetamide shielding groups, are tolerated by the operation. The elimination of the MOM group under mild conditions is also identified, as is selective deprotection of the MOM group in the presence of a Boc group.

DattatrayaK. Jamale et al. (2018) One pot four component Hantzsch condensation of 1,3diphenyl1Hpyrazole4carbaldehydes, ammonium acetate, dimedone, and alkyl acetoacetate in glycerol as a green reaction medium yielded a sequence of 4 (1Hpyrazol4yl)polyhydroquinolines. The compounds' structures are confirmed using spectroscopic techniques, and their antimicrobial efficacy against the Mycobacterium tuberculosis H37RV strain is tested. Centered on the minimum inhibitory concentration, almost all of the synthesised derivatives display excellent antitubercular efficacy. With a minimum inhibitory concentration of 1.6 g/mL, the compounds 5h and 5k, in particular, show excellent antitubercular efficacy. Additionally, molecular docking of synthesised scaffolds against M. tuberculosis enoylacyl carrier protein reductase was conducted to suggest binding modes.

Ece Baydar et al. (2017) Under microwave irradiation, a sequence of alkyl 4-(5/6-bromo-1H-indole-3-yl)-2,6,6/2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives were synthesised using an easy, rapid, and convenient updated Hantzsch condensation reaction. Different spectral methods, such as IR, 1H-NMR, COSY, 13C-NMR, and mass analysis, were used to deduce the structure of the target compounds. Furthermore, single crystal X-ray research verified the proposed structure of compound 3. The compounds' anti-tubercular efficacy was tested in vitro against Mycobacterium tuberculosis H37Rv. According to the findings, certain substances had high antimycobacterial activity but low cytotoxicity. Compounds of ethyl or isopropyl groups in their ester moiety were found to be the most involved in this sequence of compounds. To learn more about the active compounds' mechanisms of action, researchers used molecular simulation. The associations were observed to be very identical with the co-crystallized ligand of M. tuberculosis enoyl reductase, according to the findings (InhA).

Ghorbani Vaghei (2016) N,N,N′,N′-Tetrachlorobenzene-1,3-disulfonamide and poly(N,N′-dichloro-N-ethyl-benzene-1,3-disulfonamide) are new catalysts that allow one-pot, four-component synthesis of new substituted 1,4-dihydropyridine derivatives from ammonium acetate, aldehydes, and various 1,3- Antibacterial and anti-oxidant processes were assessed in all of the synthesised compounds. Antibacterial behaviour was assessed using 2, 2-diphenyl-1-picrylhydrazyl free radical scavenging against four Gram-positive and Gram-negative bacteria, and anti-oxidant activity was assessed using 2, 2-diphenyl-1-picrylhydrazyl free radical scavenging. The bioassay findings showed that the synthesised 1; 4-dihydropyridine derivatives had antioxidant and antibacterial properties.

ANTIHYPERTENSIVES

A class of medication used to control hypertension. Antihypertensive drugs come in a variety of forms that act in various ways to relieve blood pressure. Some people want to get rid of excess fluid and salt from their bodies. Others pause the pulse or calm and open the blood vessels. With one prescription, an individual can react better and experience less side effects than with another. To reduce their blood pressure, certain people need more than one antihypertensive medication. Antihypertensives are a type of medications used to control elevated blood pressure (high blood pressure) Antihypertensive treatment aims to avoid elevated blood pressure problems such as stroke and myocardial infarction. Evidence shows that lowering blood pressure by 5 mmHg will minimise the risk of stroke by 34%, ischaemic heart disease by 21%, diabetes, heart failure, and cardiovascular mortality. Antihypertensives are divided into many categories, each of which lowers blood pressure in a particular way. Thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers are among the most effective and commonly utilised drugs.

EXPERIMENTAL

Materials and methods

Tolidarou Pharmaceuticals supplied the nifedipine (Tehran, Iran). Dimethyl sulphoxide was used to dissolve both of the chemicals (DMSO). Merck Company provided additional analytical grade reagents (Darmstadt, Germany). Dimethyl sulphoxide was used to dissolve nifedipine and all newly synthesized compounds.

Chemical procedures

Following the steps shown in Figure 1.3, the 1, 4-dihydropyridine derivatives 6a-h (Table 1.1) were synthesised. Denner's protocol for producing 5-hydroxymethyl-1-(4-nitrobenzyl)-2-thio imidazole was followed. The corresponding substituted methylthioimidazole 3 or desulfurated imidazole 4 is obtained by reacting 2 with methyl iodide or dilute nitric acid solution, respectively. The corresponding aldehyde 5a or 5b was obtained by oxidising 3 or 4 with manganese dioxide in chloroform. The classical Hantzsch condensation, in which the aldehyde 5a or 5b was reacted with the acetoacetic ester and ammonium hydroxide, yielded the symmetrical 1, 4-dihydropyridine derivatives 6a-h (25-56 percent yield, Table 1.2). 1H nuclear magnetic resonance, infrared spectroscopy, and mass spectrometry were used to classify the compounds. Thin layer chromatography was used to assess the quality of all materials, with many solvent methods with varying polarity.

Nuclear magnetic resonance (NMR)

The NMR spectra were obtained using a 90 MHz FT NMR instrument (Jeol) and chloroform-D as the solvent.

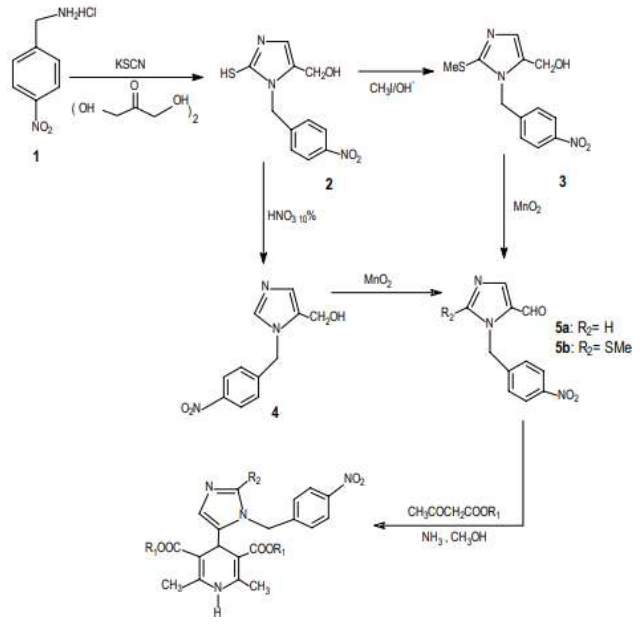

Figure 1.3: Chemical procedures for the synthesis of 1, 4-dihydropyridine derivatives 6a-h.

Table 1.1: Physical properties of synthesized symmetrical esters 6a-h

Compound	R1	R2	Mp (° c)	Yield (%)
6a	Me	H	200-201	27
6b	Et	H	203-204	25
6c	Bz	H	198-199	25
6d	TBu	H	193-194	30
6e	Me	SMe	200	43
6f	Et	SMe	212-213	36
6g	Bz	SMe	248	56
6h	TBu	SMe	213-214	31
	Nifedipine		174	

Mass spectrometry

An MAT CH5/DF (Finnigan) mass spectrometer was used to obtain low-resolution mass spectra, while an A.E.I. Kratos MS30 spectrometer was used to obtain high-resolution mass spectra and precise mass measurements. A Data General DS 50 data device was used to link both spectrometers. Ionization by electron impact was carried out at a 70 eV ionising force and a source temperature of 250oC.

Biological Assays

The rats used were adult male sprauge–Dawlley rats weighing 250–300 g. Animals were kept in groups of four in a temperature-controlled space (21oC) and subjected to a 12-hour light-dark period. Entry to food and drink is unrestricted. Each dose and compound were tested on six rats. Only DMSO (1 ml/kg, i.p.) was provided to the control group. Animals were adjusted to the experimental cage 3-4 days until the start of the trial over duration of 30-60 minutes to minimise random fluctuations in blood pressure. The indirect tail-cuff system was used to assess blood pressure changes. A pressure transducer (International Biomedical Inc., USA) on an 8 channel polygraph apparatus provided automatic measurement of systolic blood pressure (Narcotrace 80, Narco Bio-System USA). In rats, all of the test compounds were dissolved in DMSO (Sigma Chem. Co.) and provided intraperitoneally (10 mg/kg). Blood pressure was taken before, 15, 30, and 60 minutes after the medication was administered. As a standard compound, nifedipine was provided. Systolic Blood Pressure Was Determined Before, 15, 30, And 60 Minutes After Drug Administration.

Table 1.2: Reduced mean systolic blood pressure after administration of the test compounds

Compound	Time After Adminstration (min)		
	15	30	60
DMSO	6.66±0.56	6.33±0.76	3.66±0.56
Nifedipine	29±1.02***	33.95±0.88***	27.55±0.90***
6a	16.93±0.75***	22.48±1.22***	10.46±1.32***
6b	11.05±0.66**	14.1±0.98***	8.34±0.53***
6c	4.99±0.26	10.56±0.82**	6.73±0.74*
6d	6.67±0.5	11.18±0.5***	4.36±0.51*
6e	5.88±0.93	11.79±0.44***	3.67±0.79*
6f	11.29±1.23**	14.74±1.46***	6.84±1.21
6g	7.76±2.66	15.75±1.09***	5.75±1.03***
6h	16.29±0.82***	17.91±0.75 ***	111.78±0.37***

* P<0.05, ** P<0.01, *** P<0.001 compared to DMSO

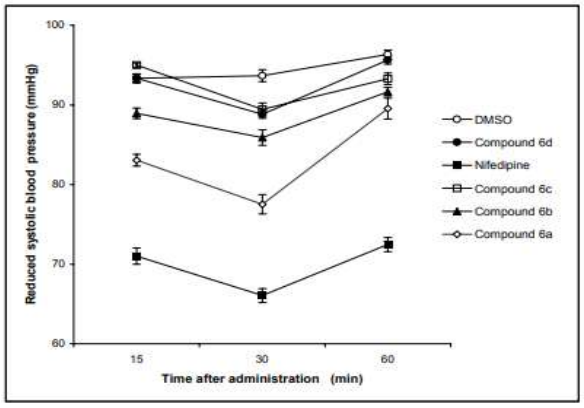

Figure 1.4: Effects of Nifedipine (), DMSO (o), 6a (◊), 6b (), 6c (..), 6d(y) on the mean systolic blood pressure of rats.

Each point reflects the mean ± sem, for each of the six experimental classes. The systolic blood pressure was set at 100 mmHg as the starting point.

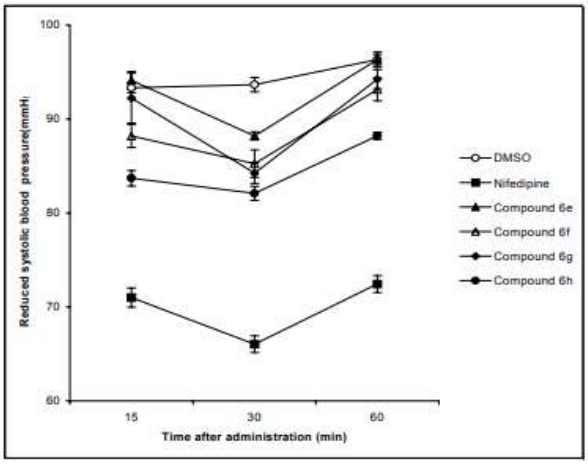

Figure 1.5: Effects of Nifedipine(), DMSO(¶), 6e(), 6f(ì), 6g(•), 6h(y) on the mean systolic blood pressure of rats.

Each point represents mean ± sem, n=6 in each experimental groups. Baseline of systolic blood pressure was considered 100 mmHg

STATISTICAL METHODS

Analysis of variation (ANOVA) and Dunnett's test is used to determine the statistical importance of variations. The significance level was set at $p< 0.05$.

RESULTS AND DISCUSSION

Both of the finished goods were pure and secure, according to our findings. They were lipophilic molecules with low water solubility, similar to other nifedipine analogues. Many of the compounds were crystalline powders that ranged from yellow to orange in colour. When subjected to natural and artificial illumination, they remained stable. The mean blood pressures before and after DMSO administration were not significantly different. The actions of compounds 6a-6h (10 mg/kg, i.p.) were compared to those of nifedipine (10 mg/kg, i.p.). Both compounds lowered mean systolic blood pressure, but none were as effective as nifedipine in lowering blood pressure.

CONCLUSION:

In conclusion, 1, 4-dihydropyridine derivatives were synthesised, structural characterization and biological evaluation of C (4) substituted 4H-chromenes were performed, and 1, 4-dihydropyridines were synthesised, characterised, and biologically evaluated. The findings show that both compounds lower mean systolic blood pressure, but they are less successful than nifedipine. Compounds 6c, 6d, 6e, and 6g have a delayed onset of action than the parent substance.

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