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An Efficient Multicomponent Synthesis Of 1,4-dihydro-2,6-dimethyl-N3,N5-diphenyl-4-(4-phenylthio)Phenyl)dyridine-3,5-dicarboxamide

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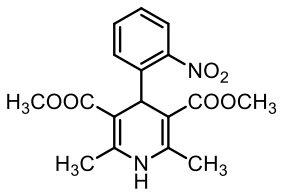
Abstract
Synthesis of 1, 4-dihydropyridine consists of some novel Hantzsch dihydropyridines. The synthesized compounds were screened for their in vitro antibacterial activity against two gram-positive bacteria: Staphylococcus aureus and Bacillus subtilis. The structures of the newly synthesized compounds were confirmed by IR, Mass and ^{1}H NMR spectral data

Keywords: Hantzsch, dihydropyridines.

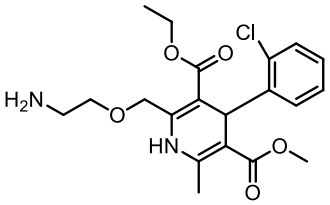
Introduction

The Arthur Rudolf Hantzsch in 1881 reported dihydropyridine synthesis as a multi-component organic reaction. The reaction carried out between an aldehyde, β-keto ester and a nitrogen donor. The reaction product is called as Hantzsch compound or 1, 4-dihydropyridine dicarboxylate or 1, 4-DHP compound [1]. Pyridine is a parent molecule for dihydropyridine. The one double bond of pyridine is replaced with two substituent's and it gives dihydropyridine. Pyridine derivatives are widely used in medicine [2]. Dihydropyridines are especially used in the treatment of hypertension [3] and well known in pharmacology as L-type calcium channel blockers [4]. Compared with certain other L-type calcium channel blockers verapamil [5] have significant action at the heart, it is relatively vascular selective in its mechanism of action in lowering blood pressure by decreasing heart rate.

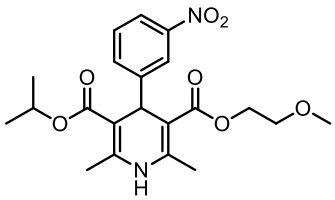
The most applied drugs contain pyridine or hydrogenated pyridine rings. As these 1,4-DHP compounds are important class of calcium channel blockers and derivatives such as nifedipine [6], amlodipine[7], nimodipine [8], aranidipine [9], azelnidipine [10], Barnidipine [11], Benidipine [12]clinidipine [13],clevidipine [14] etc.



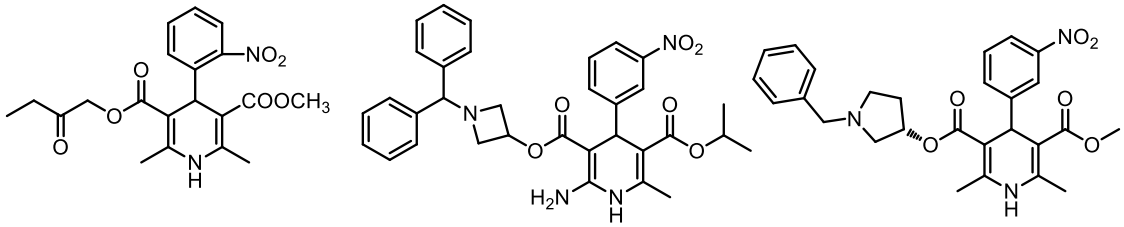
Nefidipine



Amlodipine



Nimodipine



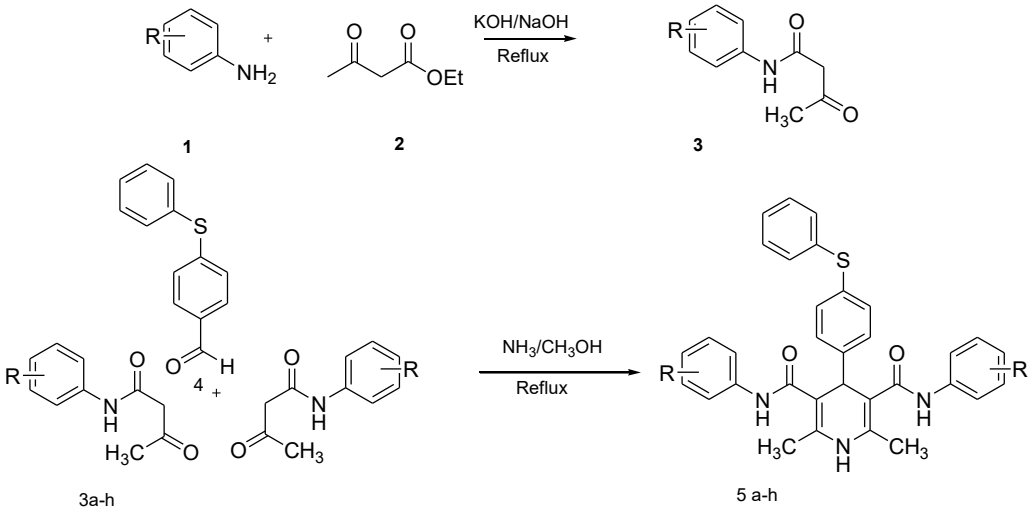
Aranidipine **Azelnidipine** **Barnidipine**

Figure 1.3.1. Calcium Channel Blockers

Hantzsch DHPs synthesis is one of the most broadly used methods for the preparation of Dihydropyridines [15].Pyridines are useful intermediates in natural product synthesis as well as common building blocks found in many biologically active molecules[16]. An efficient synthesis of 3, 5-disubstituted pyridines acts as potential intermediates in the synthesis of some dihydropyridine alkaloids e.g. lyaline, lyadine [17-18]. The Hantzsch synthesis of dihydropyridine has been well studied and is now a very useful method for preparing numerous derivatives [19].

Result and discussion

The 3-oxo-N-phenylbutanamide is prepared using aniline, ethylaceotacetate in toluene and catalytic amount of KOH/NaOH 1. Substituted 3-oxo-N-phenylbutanamide 1 with 4-(phenylthio)benzaldehyde 4 and ammonia 5 in methanol afforded corresponding dihydropyridine derivatives 6a-h. The structures were assigned for 6a-h based on elemental and spectral analyses. For example, the IR spectrum of the isolated product 6b showed absorption at 1642 cm-1 (NH-C=O), 3240 cm-1 (NH) . The 1H NMR spectrum of 6b revealed a singlet at δ 3.80 and δ 6.5 attributed to methyl proton and -NH protons respectively. A multiplet in the region δ 7.1 to 7.72 corresponding to aromatic protons. Elemental analysis and mass spectral data agree with the proposed structures for 6a-h.



Scheme I

Scheme 1: Synthesis of various substituted 1,4-dihydro-2,6-dimethyl-N3,N5-diphenyl-4-(4-(phenylthio)phenyl)pyridine-3,5-dicarboxamide

Table-1: Physical data of compounds 6(a-h)

Comp. No.	R	M. P. (°C)	Yield (%)
6a	$2CH_3$	147-149	65
6b	4-Cl	152-154	62
6c	$2\text{-}OCH_3$	172-174	68
6d	H	167-169	64
6e	$3\text{-}CH_3$	164-166	62
6f	4-F	159-161	68
6g	2-Cl	154-155	64

Table –II Antibacterial activities of 6a-h

Compound	*Staphylococcus aureus*	*Bacillus subtilis*
Tested	Inhibition zone (mm)	Inhibition zone (mm)
6a	**-**	**12**
6b	**-**	**-**
6c	**-**	**16**
6d	**06**	**-** **14**
6e	**-**	**-**
6h	**02**	**15**

Control (Solvent)	**Nil**	**Nil**

Material and Methods

Experimental

The progress of reaction was monitored by thin layer chromatography using silica gel (Merck). Melting points were determined in an open capillary in liquid paraffin bath and are uncorrected.IR spectra were recorded on a SHIMADZU–FT-I spectrophotometer in KBr disc. 1H NMR spectra were recorded on BRUKER ADVANCE–II 400 NMR spectrometer in CDCl3 as a solvent and TMS as an internal standard. Chemical shifts are given in δ (ppm). Mass spectra were recorded on a PEP-SCIUX-APIQ pulsar (electron pre-ionization) mass spectrometer. Elemental analyses were performed on Perkin-Elmer EAL-240 elemental analyzer.

General procedure for synthesis of 3-oxo-N-phenylbutanamide 3.

Anilines (0.1M) and ethyl acetoacetate was refluxed at 110^0 C in 40 ml of toluene and catalytic amount of KOH/NaOH. The completion of reaction was monitored with TLC. After completion of reaction, toluene was distilled out. The residue was cooled at room temperature and was treated with ether. The solid was filtrated and dried. (Yield 64%).

General experimental procedure for the preparation of substituted 4-(bicyclo[2.2.1]hept-5-en-2-yl)-2,6-dimethyl-N3,N5-diphenyl-1,4-dihydropyridine-3,5-dicarboxamide (5a-h) A mixture , of 4-(phenylthio)benzaldehyde (1 equivalent),substituted Acetoacetanilide (2 equivalent and ammonia (1.2 mmol) in methanol was heated at reflux temperature with stirring for 3-4 hr. The progress of the reaction was checked by TLC. The precipitate obtained was filtered and successively washed with water. The solid product thus obtained was recrystallized with alcohol.

Spectral data of the synthesized compounds

6b: IR (KBr, cm^{-1}): 1375 (CN), 1642 (NH-C=O), 1670 (C=O), 3050 (Ar-H), 3240 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 1.68 (s,6H,CH_3), 3.80 (s, 1H, CH), 6.5 (s, 1H, -NH), 7.12-7.72 (m, 17H, Ar-H). 7.7 (s, 1H, -NH), 7.9 (s, 1H, -NH). ES-MS: *m/z*: 599.12

6d: IR (KBr, cm^{-1}): 1370 (CN), 1650 (NH-C=O), 1665 (C=O), 3055 (Ar-H), 3250 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 1.66 (s, 6H, CH_3), 3.82 (s, 1H, CH), 6.40 (s, 1H, -NH), 7.15-7.82 (m, 19H, Ar-H). 7.6 (s, 1H, -NH), 7.78 (s, 1H, -NH). ES-MS: *m/z*: 531.2

6f: IR (KBr, cm^{-1}): 1365 (CN), 1645 (NH-C=O), 1670 (C=O), 3045 (Ar-H), 3240 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 1.72 (s, 6H, CH_3), 6.55 (s, 1H, -NH), 7.22-7.42 (m, 18H, Ar-H). 7.6 (s, 1H, -NH), 7.7 (s, 1H, -NH). ES-MS: *m/z*: 567.18

6g: IR (KBr, cm^{-1}): 1364 (CN), 1652 (NH-C=O), 1675 (C=O), 3054 (Ar-H), 3255 (NH). ^{1}H NMR (400 MHz, DMSO-d_6, δppm): 1.74 (s, 6H, CH_3), 6.54 (s, 1H, -NH), 7.15-7.68 (m, 17H, Ar-H). 7.58 (s, 1H, -NH), 7.74 (s, 1H, -NH). ES-MS: *m/z*: 601.12

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References

[1]. Hantzsch, A. *Chemi*. *Beri*. **1881**, *14*, 1637.
[2]. Scully, C. *Cardio*. *Medici*. **2014**, *5*, 125.
[3]. Vardanyan, R.; Hruby, V. *Synthesis of best seller drug* **2016**, *22*, 329.
[4]. Daschil, N.; Kniewallner, K. M.; Obermair, G. J.; Hutter-Paier, B.; Windisch,
[5]. M.; Marksteiner, J.; Humpel, C. *Neuro*. *of Agi*. **2015**, *36*, 1333.
[6]. Yonekura, M.; Kondoh , N.; Han , C.; Toyama, Y.; Ohba, T. Ono, K; yoichi Itagaki, S.; Tomita, H.; Murakami, M. *J*. *of Pharma*. *Sci* **2018**,1.
[7]. Godfraind, *T*. of *Cardio*. *pharma*. *and Therap*. **2014**, 19, 501.
[8]. Wang, Ji-G.; Yan, P. Jeffers, B. W. *J*. *America*. *Soc*. *Hyperten*. **2014**, *8*, 340.
[9]. Poondra, R. R.; Nallamelli, R. V.; Meda C L. T.; Srinivas, B. N. V.; Grover, A.; Muttabathula, J.; Voleti, S. R.; Sridhar, B.; Pal, M.; Parsa, K. V. L. *Bio*. & *Med*. *Chem*. *Lett*. **2013**, *23*, 1104.
[10]. Masumiya, H.; Tanaka, Y.; Tanaka, H.; Shigenobu, K. *Pharma*. **2000**, *61*, 57.
[11]. Takano, Y.; Ueyama, T.; Ishikura, F. *J*. *of Cardio*. **2012**, *60*, 18.
[12]. Lins, R.; Haerden, Y.; De Vries, C. *High Blood Press*. *Cardio*. *Prevent*. **2017**, *24*, 29.
[13]. Kosaka, H.; Hirayama, K.; Yoda, N.; Sasaki, K.; Kitayama, T. Kusaka, H.; Matsubara, M. *Euro*. *J*. *of Pharma*. **2010**, *635*, 49.
[14]. Sarat Chandra, K.; Ramesh G. *Indian heart J*. **2013**, *65*, 691.
[15]. Erickson, A. L.; DeGrado, J. R.; Fanikos, J. R. *Pharmaco*. **2010**, *30*, 515.
[16]. Drapak, I.; Perekhoda, L.; Tsapko, T.; Berezniakova, N.; Tsapkoc, Y. *J*. *Heterocyclic Chem*. **2017**, *00*.00.
[17]. Dmitriev, M. V.; Salnikova, T. V. Silaichev P. S. Maslivets A. N. *Tetrahedron Lett*. **2017**, *58*, 67.
[18]. Bull J. A.; Mousseau, J. J.; Pelletier, G; Charette, A. B. *Chem. Rev.*, **2012**, *112*, 2642.
[19]. Lluisa, B.; Roca, T.; Monerris, M. *J*. *Org*. *Chem*. **2004**, *69*, 752.