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Design, solvent free synthesis, and antimicrobial evaluation of 1,4 dihydropyridines

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ABSTRACT

Here in, we report the usage of cellulose sulfuric acid as a heterogeneous eco friendly catalyst for the synthesis of 1,4 dihydropyridines under solvent free conditions via Hantzsch three component reaction of an aldehyde, ethyl acetoacetate and ammonium acetate at 100 °C for 2–5 h. In silico studies were performed on twenty two possible 1,4 dihydropyridines (DHPs) analogues against K^+ channel receptor (KcsA). In order to validate in silico studies, thirteen compounds were synthesized and evaluated as antibacterials against twenty seven ESBL isolates of *Klebsiella pneumoniae* and *Escherichia coli*.

Bacterial resistance is emerging world wide as a threat to clinical therapeutics. β-lactamases production by bacterial species is one of the most important mechanisms of resistance to *penicillins* and *cephalosporins*. The mechanism of this resistance is the production of extended spectrum β-lactamases (ESBL). ESBLs are capable of hydrolysis and inactivating the β-lactam rings in the third generation antibiotics like *penicillins*, *cephalosporins* and *aztreonam*. Wide spread use of third generation antibiotics has led to mutations in these enzymes leading to the emergence of ESBLs. Although ESBL isolates were first discovered in the mid 1980's in Western Europe their occurrence is currently a worldwide problem ESBL isolates are very predominant in *Klebsiella pneumoniae* and *Escherichia coli*. Rise of drug resistance in many human pathogens necessitates the development of new drug therapeutic agents. Development of drugs for new targets is the need of the hour. In the present scenario synthesis of DHPs and their derivatives emerged as a hot area of research.

1,4 dihydropyridines (DHPs) class of drugs are well known for their calcium channel modulation,[1] recent studies have shown that they play an important role in K^+ and Na^+ channel modulation.[2] These compounds have a remarkable significance, because of their wide range of pharmacological and biological activity such as cardiovascular diseases including hypertension,[3] anti-inflammatory,[4] antiviral,[5] cytotoxicity,[6] anticonvulsants,[7] anti tuberculosis,[8] antithrombotic,[9] in the treatment of Alzheimer's diseases,[10] calcium agonists and antagonists,[11] more recently as enhancers of the vanilloid receptor 1 (TRPV1)[12] and screened as the human multidrug resistance protein[13].

DHPs were first synthesized by Hantzsch in 1882 via three component synthesis[14] of an aldehyde, ethyl acetoacetate and ammonium acetate in ethanol or acetic acid at 80 °C. This reaction was further fine tuned by the development of several synthetic strategies and methodologies including microwave irradiation,[15] ultrasounds,[16] ionic liquids,[17] phase transfer catalysts,[18] Brønsted bases,[19] solvent free synthesis,[20] Lewis acids,[21] Brønsted acids[22] and Lewis base[23] catalyzed solvent free synthesis of DHPs. Here in, we report a simple and practical method for the synthesis of DHPs by impressive Hantzsch protocol using catalytic amount (0.05 g) of cellulose sulfuric acid as a heterogeneous catalyst under solvent free conditions. More recently, in silico studies are being performed for rational design and synthesis of new analogues with improved pharmacological profile. Preliminary studies in our lab have shown that DHPs are very effective antimicrobial agents

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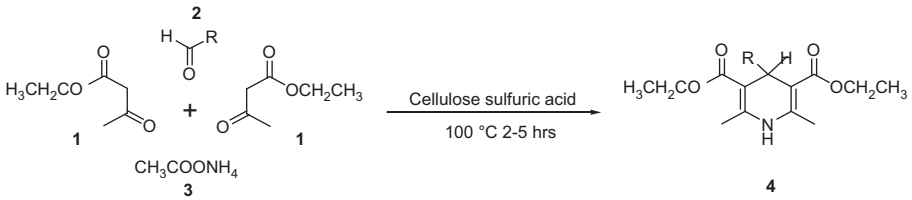

Scheme 1. Solvent free synthesis of 1,4 dihydropyridines catalyzed by 10 mol % of Cellulose sulfuric acid.

Table 1
Cellulose sulfuric acid catalyzed synthesis of DHPs in different solvents and under solvent free conditions at 100 °C

Entry	Solvent	Catalyst mole (%)	Time (h)	Yield (%)
1	Ethanol	10	10	78
2	Methanol	10	10	63
3	Toluene	10	13	32
4	Acetontrile	10	16	Trace
5	Dioxan	10	20	Trace
6	THF	10	17	55
7	Solvent Free	5	5	56
8	Solvent Free	10	5	80
9	Solvent Free	15	5	81
10	Solvent Free	20	5	78

Table 2
Cellulose sulfuric acid catalyzed synthesis of DHPs at 80 °C under solvent free conditions

Entry	R	Product	Yield (%)	Mp reference	Mp found
1	2-Cl-C6H$_4$	**4a**	87	83–85[15a]	120–125
2	3-NO$_2$-C$_6$H$_4$	**4b**	90	164–165[15a]	144–154
3	4-OH-C$_6$H$_4$	**4c**	91	229–231[15a]	205–210
4	4-OMe-C$_6$H$_4$	**4d**	80	158–160[15a]	132–140
5	4-Cl-C$_6$H$_4$	**4e**	78	145–146[15a]	129–135
6	3-OH-C$_6$H$_4$	**4f**	85	180–182[19e]	105–110
7	2-OH-C$_6$H$_4$	**4g**	78	—	94–99
8	4-OH-3OMe-C$_6$H$_3$	**4h**	85	156–158[15a]	150–151
9	3,4(OMe)$_2$C$_6$H$_3$	**4i**	90	163–165[21d]	160–162
10	3,4,5(OMe)$_3$C$_6$H$_2$	**4j**	85	—	125–127
11	C$_6$H$_6$	**4k**	90	156–158[15a]	142–150
12	H	**4l**	92	—	168–174
13	2,5(OMe)$_2$C$_6$H$_3$	**4m**	80	—	151–153

especially against drug resistant isolates of bacteria (ESBL). We reasoned that DHPs could also be effective against ion channels. Hence, we have attempted to study the effect of DHPs on K^+ channel. In the present study, twenty two possible DHP analogues were docked against K^+ channel receptor (KcsA). In silico predictions have been carried out and analyzed. Based on the docking studies various DHP analogues were synthesized. To validate our in silico studies, we have performed in vitro bioassays of the synthesized analogues against ten bacterial and twenty seven extended spectrum beta lactamase (ESBL) bacterial isolates.

In the present work, Hantzsch-type cyclocondensation reaction was studied for the preparation of 4-aryl-1,4-dihydropyridines (**4a**–**4m**), these were synthesized by the one pot condensation of aromatic aldehyde (0.01 moles), ethyl acetoacetate (0.025 moles) and ammonium acetate (0.02 moles) utilizing the catalyst cellulose sulfuric acid Scheme 1. In an initial attempt the reaction was performed with 10 mol % of catalyst at rt in different solvents viz. ethanol, methanol, *t*-butanol, dioxan, acetonitrile and under solvent free conditions. After 10 h only 30% of the product was obtained under solvent free conditions. When the reaction temperature was increased to 100 °C better results were observed with low reaction times Table 1. To optimize the amount of the catalyst we have carried out the reaction with various mol % of the catalysts. However there is no recognizable change in either % of yield or the reaction time by the increased amounts in catalysts over 0.05 g of cellulose sulfuric acid. For the scope and limitations of the catalyst performance the reaction was carried out with various substituted aromatic aldehydes in the optimized conditions Table 2.

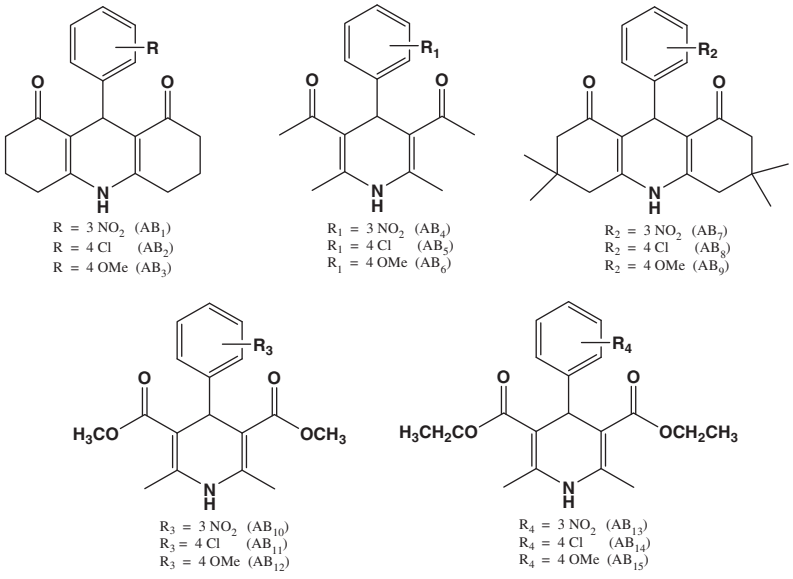

Figure 1. Mole docked DHP analogues (AB_1–AB_{12}) and compounds **4b**, **4d** and **4e**.