

Fabricating Green Mansion for the Synthesis of (2HB) INH and Its Scaffolds: UV-Visible Determinations for Selective Probe towards Co^{+2} ions

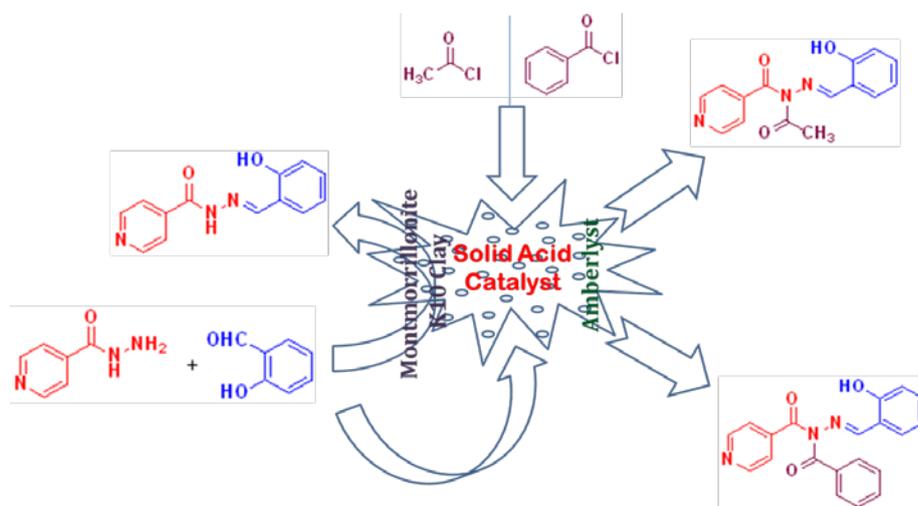
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Abstract. The present work is emphasizing on the use of solid acid catalysts for the condensation of INH with 2-hydroxy benzaldehyde and its acetyl and benzoyl scaffolds. The Montmorillonite K 10 clay and Amberlyst are proved highly efficient in catalysing the reactions. Both catalysts offer several advantages like energy efficiency, short reaction time and easy separation techniques over conventional methods and provide safer pathways. The synthesized isonicotinohydrazide (INH) derivative is showing the excellent binding ability with some transition metal ions. The (2HB) isonicotinohydrazide is readily forming complexes with the transition metal ions like Zn^{+2} , Cu^{+2} , Co^{+2} , Ni^{+2} etc. The (2HB) INH is found to have selective probe towards the Co^{+2} ions estimated from UV-Visible spectrometric analysis. The synthesis of complex could be easily observed by simple visual determinations.

Keywords: Green Chemistry, INH, Amberlyst, Montmorillonite K 10 clay, Chemo selectivity etc



1 Introduction

In the present era of “Green Chemistry”, the heterogeneous catalysts have attracted tremendous attention due to their higher catalytic efficiencies and easy separation techniques. There are many catalysts have govern the growing interest by scientific communities and industries [1-3]. The heterogeneous catalyst has remarkable impact on environment safety not only in the way of energy efficiency and catalytic effectiveness but also in terms of environmental benign nature, reducing the waste generation during reactions, easy separation methods, reusability, easy availability, low cost etc. The inorganic solid materials with very mild acidic nature are most often in use nowadays [4-7].

The most prominent candidates are often zeolites, zeotypes, clays, polymer resins, MOFs (metal organic frameworks), mesoporous materials, nanomaterials, biomaterials etc [9-10]. Zeolites are nothing but the hydrous aluminosilicates available naturally [11-12]. Their porous crystalline nature accompanied with the definite array of packing atoms in its crystal lattice usually provides good absorption and separation selectivity⁵. Their pores are of molecular dimensions; so the guest molecules of higher sizes get entrapped in the holes through which those of lower sizes get passed easily [13-14]. They also possess mild acidic nature; that's why they act as solid acid catalysts in organic transformations accessing the reacting substrate molecules for getting adsorbed in its surface and pores; partial polarization of molecules ultimately results in activation towards reactions [15-16].

Clays are also the composition of aluminosilicates generally possessing mild acid character [17-18]. Clays are nothing but the finely grinded forms of natural zeolites generated during the volcanic eruptions [19-20]. Montmorillonite K 10 clay has growing interest as it is proved an excellent catalyst in many organic reactions [21]. Amberlyst 15 is strongly acidic, sulfonic acid, macro reticular, polymeric resin based on cross linked styrene divinyl benzene copolymers¹⁰. Due to its higher acid nature and easy separation; many industries are using this as promising catalyst [22].

The host-guest chemistry has attracted much attention due to the strong affinity of compounds or materials for another particular one from the range of similar type of compounds i.e. called as chemo-selectivity [23]. Co^{+2} ions have higher biological significance as they are the active center of coenzymes called cobalamins, the most common example of which is vitamin B12. It is an essential trace dietary mineral for all animals. Cobalt in inorganic form is also micronutrient for bacteria, algae and fungi [24].

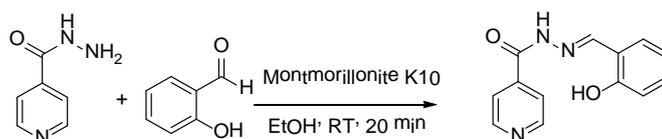
The INH and its scaffolds are well known prodrug in the treatment of mycobacterial tuberculosis. They possess many bactericidal activities and enormous applications in the field of pharmacology [25-27]. The present study focuses on development of green pathway for the synthesis of (2HB) INH by using Montmorillonite K 10 clay as heterogeneous reusable catalyst and its acyl and benzoyl derivatives using Amberlyst wet 15 resin as efficient catalyst. The study also shows the applicability of here synthesized (2HB) INH as a Co^{+2} ion receptor at lowest concentrations of 10-5 M.

2 Experimental

All the materials (like Amberlyst wet 15 resin, INH, 2-Hydroxy benzaldehyde and metal chlorides) are purchased from SD Fine Chemicals Pvt. Ltd, Mumbai (India). The Montmorillonite K10 clay is purchased from Sigma-Aldrich, Bangalore Division (India).

2.1 Synthesis

Reaction Schemes:



Scheme 1. Synthesis of (2HB) INH.

INH (10 mmol), 2-Hydroxy benzaldehyde (10 mmol) and catalytic amount of Montmorillonite K 10 clay (10% w/w of reaction mass) are taken in EtOH and mixed thoroughly. The condensation reaction yields (E)-N'-(2-hydroxybenzylidene) isonicotinohydrazide [(2HB) INH] in 20 min. The reaction is continuously monitored on TLC technique for the formation of product. After that reaction mass is filtered and washed with water (3 X 10 ml). The obtained product then recrystallized with pure ethanol separates the Montmorillonite K 10 clay as residue on filter paper and pure product reappears in filtrate on cooling.

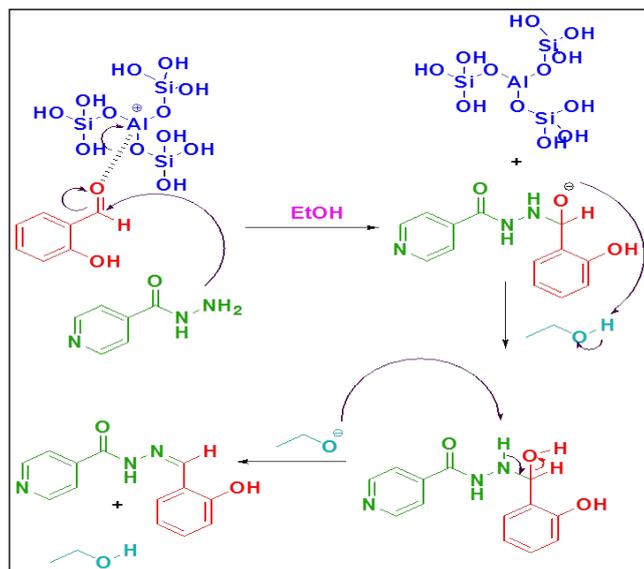
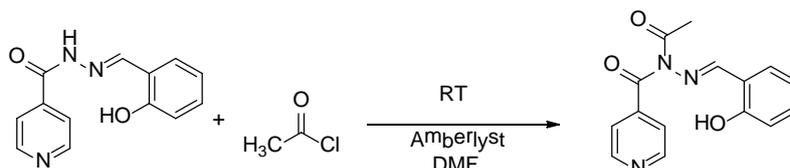


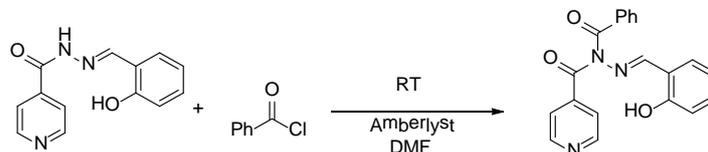
Figure 1. Plausible Mechanism for Synthesis of (2HB) INH.

The mechanism proposed reveals the catalytic role of Mont. K 10 clay in the synthesis of (2HN) INH derivatives. The core functional group responsible for its catalytic behaviour is aluminosilicates having the Al-O-Si linkages present on the surface and in the pore voids of Mont. K10 which polarizes the 2-hydroxy benzaldehyde and increases the electron deficiency at carbonyl carbon centre. The lone pair of primary amine nitrogen present in INH easily attacks on sufficiently electron deficient carbonyl carbon through conjugation followed by loss of water molecule yields the required product.



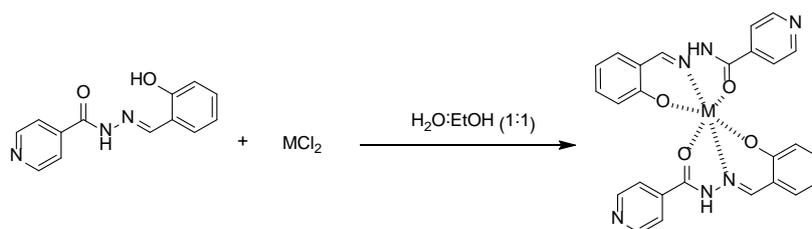
Scheme 2. Synthesis of Acyl derivative of (2HB) INH.

(2HB) INH (10 mmol), acetyl chloride (10 mmol) and catalytic amount of Amberlyst (10% w/w of reaction mass) are taken in EtOH and mixed thoroughly. The condensation reaction yields (E)-N-acetyl-N'-(2-hydroxybenzylidene)isonicotinohydrazide.



Scheme 3. Synthesis of Benzoyl derivative of (2HB) INH.

(2HB) INH (10 mmol), Benzoyl chloride (10 mmol) and catalytic amount of Amberlyst (10% w/w of reaction mass) are taken in EtOH and mixed thoroughly. The condensation reaction yields (E)-N-benzoyl-N'-(2-hydroxybenzylidene)isonicotinohydrazide.



Scheme 4. (2HB) INH – Metal Complexes.

Dissolve (2HB) INH (10 mmol) in EtOH (5 ml) and Dissolve Metal Chloride (10 mmol) in distill water and catalytic amount of Amberlyst (10% w/w of reaction mass) are taken in EtOH and mixed thoroughly. The condensation reaction yields (E)-N-benzoyl-N'-(2-hydroxybenzylidene) isonicotinohydrazide.

3 Result and Discussions

3.1 Catalyst Study

Table 1. Catalyst Study for Synthesis of (2HB) INH.

Sr. No	Catalyst	Time	RT/Reflux	Yield
1)	Acetic Acid	180 min	Reflux	90%
2)	Montmorillonite K-10 clay	5 min	RT	95%
3)	Fly Ash	120 min	RT	94%
4)	MFA	7 min	RT	93%
6)	Amberlyst wet 15*	30 min	RT	92%
7)	Kaolin light clay	150 min	RT	90%
8)	Without Catalyst	180 min	Reflux	88%

Table 1 indicates the efficiency of different catalysts. The conventional methods are using acetic acid and reflux conditions for the synthesis. It is clearly evident that Mont K 10 is the most effective and efficient catalyst as it requires less reaction time and the reaction occurs at room temperature. The amberlyst is also showing good catalytic activity but slightly more reaction time and also comparatively low yield.

Table 2. Catalyst Study for Synthesis of Acyl derivative of (2HB) INH.

Sr. No	Catalyst	Time	RT/Reflux	Yield
1)	Acetic Acid	240 min	Reflux	84%
2)	Montmorillonite K-10 clay	50 min	RT	88%
3)	Fly Ash	180 min	RT	82%
4)	MFA	70 min	RT	90%
6)	Amberlyst wet 15*	20 min	RT	92%
7)	Kaolin light clay	180 min	RT	84%
8)	Without Catalyst	360 min	Reflux	Nil

Table 2 indicates the efficiency of different catalysts. It is clearly evident that Amberlyst wet 15* resin is the most effective and efficient catalyst for this synthesis.

Table 3. Catalyst Study for synthesis of Benzoyl derivative of (2HB) INH

Sr. No	Catalyst	Time	RT/Reflux	Yield
1)	Acetic Acid	280 min	Reflux	64%
2)	Montmorillonite K-10 clay	60 min	RT	70%
3)	Fly Ash	180 min	RT	72%
4)	MFA	120 min	RT	68%
6)	Amberlyst wet 15*	30 min	RT	70%
7)	Kaolin light clay	240 min	RT	68%
8)	Without Catalyst	360 min	Reflux	Nil

Table 3 indicates the efficiency of different catalysts. It is clearly evident that Amberlyst wet 15* resin is the most effective and efficient catalyst for this synthesis.

Table 4. Details of synthesized metal complexes

Sr. No.	Complex with	Time (min)	Melting Point	Colour	Yield (%)
1)	Zn ⁺²	5	>300	Yellow	94%
2)	Cu ⁺²	5	>300	Dark greenish	94%
3)	Co ⁺²	5	>300	Dark brown	98%
4)	Fe ⁺³	5	>300	Black	96%
5)	Mn ⁺²	5	>300	Light brown	94%
6)	Ni ⁺²	5	>300	Orange	94%

The synthesis of metal complex is achieved using water-ethanol (1:1) as solvent at room temperature. The synthesized metal complexes of (2HB) INH with some biologically important transition metal ions are listed in table 3.

3.2 UV-Visible Study

The synthesized (2HB) INH readily forms metal complexes with transition metal ions. The UV-Visible spectra reveal its selective probe towards Co⁺² ions at very low concentrations.

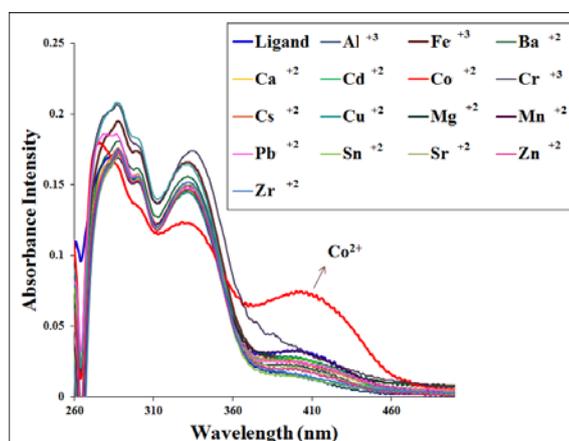


Figure 2. UV-Visible study spectra of synthesized metal complexes.

The host is dissolved in DMF at concentration of 10^{-5} M. The metal chlorides are dissolved into distilled water (10^{-3} M concentrations). Firstly the base line is set with DMF as a standard solvent and blank reading is drawn with host solution. The binding study is executed by taking the host solution (2 ml) in cuvette and adding metal salt solution (20 μ l); slightly shaking is applied and UV-Visible spectra are studied. The process is repeated with each metal salt and all the graphs are taken into account.

From the graph, it is clearly evident that the ligand shows selectivity for Co^{+2} ions as there is shift in λ_{max} observed in visible region at the lowest concentrations of 10^{-5} M where the metal concentration is also 10^{-5} M. The binding at such a low concentrations proves it as Co^{+2} ion selective receptor. While the same study with other transition metal ions does not show any binding at such low concentrations, though they too form complexes at higher concentrations.

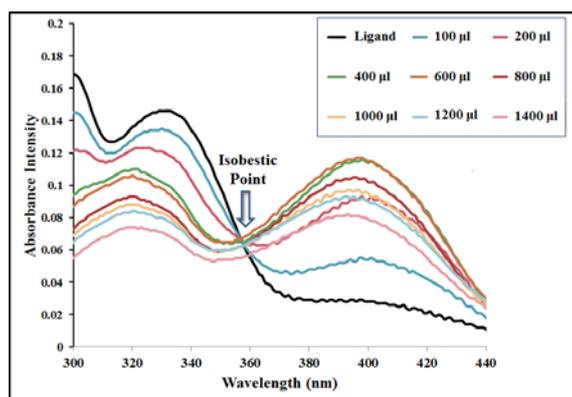


Figure 3. UV-Visible titration spectra of host versus guest.

The UV-Visible titration spectra of (10^{-5} M) host versus (10^{-5} M) guest shows one isobestic point. Isobestic point shows the binding molar ratios as its significance for equal concentrations of both reacting substates. The binding molar ratio is depicted 1:1 because the titration spectra have only one isobestic point.

3.3 Computational Study

In the present work, the bioactivity of synthesized compound is determined using the computational study. At Mol inspiration; the strategy which leads to success is not a universal drug-likeness score, but focuses on particular drug classes and development of specific activity score for each of these classes. The method which is implemented uses sophisticated Bayesian statistics to compare structures of representative ligands active on the particular target with structures of inactive molecules and to identify substructure features (which in turn determine physicochemical properties) typical for active molecules. The mole-inspiration calculation helps in determining the drug-likeness of subjected compounds. The more the negative value represents more drug likeness.

Table 5. Moleinspiration scores for biological activities of (2HB)INH and its scaffolds.

Bioactivity	(2HB) INH	Benzoyl derivative	Acetyl derivative	Albendazole
GPCR	-0.53	-0.21	-0.41	-0.11
Ion channel modulator	-0.90	-0.42	-0.71	-0.10
Kinase inhibitor	-0.49	-0.09	-0.34	-0.04
Nuclear receptor ligand	-0.77	-0.28	-0.60	-0.62
Protease inhibitor	-0.75	-0.27	-0.49	-0.18
Enzyme inhibitor	-0.40	-0.13	-0.23	-0.02

There are many G-protein coupled receptors (GPCRs) for which ligands are yet to discover. GPCRs are playing main role in many diseases. The development of new GPCR ligand may bind many of GPCRs and thereby prove an effective drug. Here synthesized (2HB) INH has higher negative values than the standard drug molecule which ultimately predicts it as an effective anthelmintic drug. Its acyl and benzoyl derivatives are also showing promising GPCR values.

These properties are calculated and discussed on the basis of Lipinski's rule and its component. The compounds V, VIII, IX, X fulfill Lipinski's rule and show good drug likeness score (Table 2). Milog P of these compounds was found below 5 that means these shows good permeability across cell membrane. TPSA below 160 Å², n violatio = 1 or < 0 it means compound easily bind to receptor, molecular mass < 500, n rotb < 5 [10], No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), Number of hydrogen bond acceptor ≤ 10 (The sum of Os and Ns).

The important role of kinases in the control of cell homeostasis resulted in the exploitation of these enzymes as oncologic drug targets. The last 20 years have witnessed a tremendous explosion of novel kinase inhibitors as a lead structures and identification of potential drugs. From the table, it can be concluded that the (2HB) INH and its acetyl derivative possess good kinase inhibition properties even more than standard drugs.

Nuclear receptors are soluble proteins that can bind to specific DNA-regulatory elements and act as cell-type- and promoter-specific regulators of transcription nuclear receptors are important for the control of embryonic development, organ physiology, cell differentiation and homeostasis. Apart from the normal physiology, nuclear receptors have been identified to play a role in many pathological processes, such as cancer, diabetes, rheumatoid arthritis, asthma or hormone resistance syndromes. Therefore, they have great interest in modern biomedical research and drug discovery. (2HB) INH shows the comparative higher values than the standard drug while its acetyl derivative shows the same nuclear receptor ability.

Protease inhibitors are the proteins that inhibit protease proteolytic function. The protease inhibition factor of (2HB) INH could be much larger than the standard drug molecule as it bears much higher negative values than the standard drug molecule.

Table 6. Moleinspiration scores for biological activities of synthesized metal complexes.

Bioactivity	Complex with Fe ⁺³	Complex with Co ⁺²	Complex with Cu ⁺²	Complex with Mn ⁺²	Complex with Zn ⁺²	Albendazon
GPCR	-0.04	-0.09	-0.09	-0.09	-0.09	-0.11
Ion channel modulator	-0.26	-0.26	-0.26	-0.26	-0.26	0.10
Kinase inhibitor	-0.06	-0.06	-0.06	-0.06	-0.06	-0.04
Nuclear receptor ligand	-0.15	-0.15	-0.15	-0.15	-0.15	-0.62
Protease inhibitor	-0.12	-0.12	-0.12	-0.12	-0.12	-0.18
Enzyme inhibitor	-0.05	-0.08	-0.08	-0.08	-0.05	-0.02

Computational software (moleinspiration.com). The biological activity scores are compared with the scores of standard drug molecule (Albendazole: an anthelmintic drug) which predicts comparatively equal activeness as standard drug possess.

4 Conclusion

In the present context, we have efficiently achieved the synthesis of (2HB) INH using Mont. K10 as a green catalyst. Subsequently it is further N-acetylated and N-benzylated in presence of Amberlyst wet 15 resin as solid acid catalyst. We have also extended our efforts towards host guest complexation ability of (2HB) INH with different transition metal ions. The all synthesized compounds and metal complexes are predicted of owing moderate to good biological activities by mole-inspiration docking software (Moleinspiration.com); especially, (2HB) INH showing very good scores than the standard drug

Albendazole which attracts the interest towards development of new drug molecule and can be employed for the treatment of a variety of parasitic worm infestations.

References

1. Anastas, Paul T., Warner, John C., "Green chemistry: theory and practice" Oxford, New York: Oxford University Press. ISBN 9780198502340, 1998.
2. James H. Clark, "Catalysis for green chemistry" *Pure Appl. Chem.*, Vol. 73, pp. 103–111, 2001.
3. Devendra S. Raghuvanshi, Pramod P. Mahulikar and Jyotsna S. Meshram, "MFA zeotype catalyst: a greener approach for the synthesis of INH azomethine scaffolds." *RSC Adv.*, Vol. 5, pp. 48071–48078, 2015.
4. Da-Lei Sun, Jian-Ru Deng, and Zi-Sheng Chao, *Chemistry Central Journal*, 27, 2007.
5. Kenneth D. M. Harris "New in situ solid-state NMR strategies for exploring materials formation and adsorption processes: prospects in heterogenous catalysis" *Appl Petrochem Res*, Vol. 6, pp. 295-306, 2016.
6. Sarvesh Kumar Srivastava, Ryosuke Yamada, Chiaki Ogino, Akihiko Kondo, "Biogenic synthesis and characterization of gold nanoparticles by *Escherichia coli* K12 and its heterogeneous catalysis in degradation of 4-nitrophenol" *Nanoscale Research Letters*, Vol. 8, pp. 70- 79, 2013.
7. Debasish Sengupta and Basudeb Basu, "An efficient heterogeneous catalyst (CuO@ ARF) for on-water CS coupling reaction: an application to the synthesis of phenothiazine structural scaffold." *Organic and Medicinal Chemistry Letters*, Vol. 4, pp.17, 2014.
8. Shaobin Wang, "Application of solid ash based catalysts in heterogeneous catalysis" *Environ. Sci. Technol*, Vol. 42, pp. 7055–7063, 2008.
9. Junjiang Zhu, Hailong Li, Linyun Zhong, Ping Xiao, Xuelian Xu, Xiangguang Yang, Zhen Zhao, and Jinlin Li "Perovskite oxides: preparation, characterizations, and applications in heterogeneous catalysis." *ACS Catal.* Vol. 4, pp. 2917–2940, 2014.
10. Noritaka Mizuno and Makoto Misono, "Heterogeneous catalysis" *Chem. Rev.* 98, pp. 199–217, 1998.
11. Jin Y-Q., Ma X-J., Jiang X-G., Liu H-M., Li X-D., Yan J-H., Cen K-F., "Effects of hydrothermal treatment on the major heavy metals in fly ash from municipal solid waste incineration" *Energy & Fuels*, Vol. 27, pp. 394-399, 2013.
12. D. S. Raghuvanshi, J. R. Badgujar, P. P. Mahulikar and J. S. Meshram, "Fly Ash Utilization for Sustainable Environment Management: Waste to Resource Material" pp. 190-203, 2014.
13. I. V. Kuz'min, N. A. Sokolova, I. R. Subbotina, and G. M. Zhidomiro, *Russian Chemical Bulletin, International Edition*, Vol. 64, No. 2, pp. 278–283, 2015.
14. N. G. Grigorieva,^a M. R. Agliullin,^a V. P. Talzi,^b O. V. Vodyankina,^c and B. I. Kutepova, "Nitration of 1, 3, 3-trimethyl-1-phenylindane on mesoporous aluminosilicates." *Russian Chemical Bulletin, International Edition*, Vol. 64, pp. 852–858, 2015.
15. X. Querol, N. Moreno, A. Alastuey, R. Juan, J. M. Andres, A. Lopez-soler, C. Ayora, A. Medinaceli and A. Valero, "Synthesis of high ion exchange zeolites from coal fly ash" *Geol. Acta*, Vol. 5, pp. 49–57, 2007.
16. J. Jiang, J. Yu and A. Corma, "Extra-Large-Pore Zeolites: Bridging the Gap between Micro and Mesoporous Structures." *Angew. Chem.*, Vol. 49, pp. 3120–3145, 2010.
17. Gopalpur Nagendrappa, "Organic synthesis using clay and clay-supported catalysts." *Applied Clay Science*, Vol. 53, pp. 106–138, 2011.
18. A. Vaccari "Clays and catalysis: a promising future." *Applied Clay Science*, Vol. 14, pp. 161–198, 1999.
19. Gopalpur Nagendrappa, "Organic synthesis using clay catalysts" *Resonance*, pp. 64-77, 2002.
20. P. P. Kumavat, D. S. Dalal, "Fabrication of Organic Solar Cells based on Photosensitive Small Molecules and Study of Electron Acceptor Layer Effect on Efficiency" *Modern Organic Chemistry Research*, Vol. 1, pp. 35-42, 2016.
21. Navjeet Kaur and Dharma Kishore, "Montmorillonite: An efficient, heterogeneous and green catalyst for organic synthesis" *Journal of Chemical and Pharmaceutical Research*, Vol. 4, pp. 991-1015, 2012.
22. Pal Rammohan, Taradas Sarkar, and Shampa Khasnobis. "Amberlyst-15 in organic synthesis." *Arkivoc*, pp. 570-609, 2012.
23. Gerhard Wenz, *Clinical Drug Investigation*, Vol. 19, pp. 21–25, 2000.

24. Jump up Schwarz, F. J. Kirchgessner M., Stangl G. I., "Cobalt requirement of beef cattle – feed intake and growth at different levels of cobalt supply" *Journal of Animal Physiology and Animal Nutrition*, Vol. 83, pp. 121–131, 2000.
25. K. Li, J. Valla and J. G. Martinez, "Realizing the commercial potential of hierarchical zeolites: new opportunities in catalytic cracking." *ChemCatChem*, Vol. 6, pp. 46–66, 2014.
26. M. Malhotra, V. Monga, S. Sharma, J. Jain, A. Samad, J. Stables and A. Deep, "Synthesis, characterization and pharmacological evaluation of (E)-N' -(substituted-benzylidene) isonicotinohydrazide derivatives as potent anticonvulsant agents." *Med. Chem. Res.*, Vol. 21, pp. 2145–2152, 2012.
27. R. R. Somani, A. G. Agrawal, P. P. Kalantri, P. S. Gavarkar and E. D. Clercq, "Investigation of 1, 3, 4-oxadiazole scaffold as potentially active compounds." *Int. J. Drug Des. Discovery*, Vol. 2, pp. 353–360, 2011.