Synthesis and Characterization of Novel Imidazo (1, 2-a) pyrimidine Derivatives and their Evaluation for Antiepileptic and Analgesic activity

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Abstract

Affordable and practical synthesis methods in drug development have always been very attractive. Herein, microwave assisted synthesis was utilized to prepare Imidazo[1,2-a] pyrimidine derivatives were obtained by the reaction between 2-aminopyrimidine, aldehyde, and benzyl isocyanide. It gives 82-92 % yields. As well as demonstrating the Anti-MES efficacy of compound 2, its potency against seizures induced by pentylenetetrazole, were also established, with the results suggesting that GABA-mediated mechanisms might be involved in its anticonvulsant activity, such as enhancing of GABAergic neurotransmission or activity, activate GAD or inhibit GABA-T, and $GABA_A$-mediated mechanisms. For the analgesic activities, hot-plate method were employed. Derivative-II was found to have the significant activity by hot-plate method.

Keywords: *Imidazo[1,2-a]pyrimidine derivatives, Microwave assisted synthesis, Antiepileptic activity, Analgesic activity.*

1. INTRODUCTION

Significant efforts have been dedicated to new synthetic methods and chemical reactivities regarding these ring systems[1]. Many biologically active compounds contain bicyclic heterocycles

with a position nitrogen atom. The bicyclic system of imidazo[1,2-a]pyrimidines, the A ring is π-deficient and typically subjected to nucleophilic attack, whereas electrophilic addition/substitution typically occurs on the π-excessive B ring (Figure 1) [2].

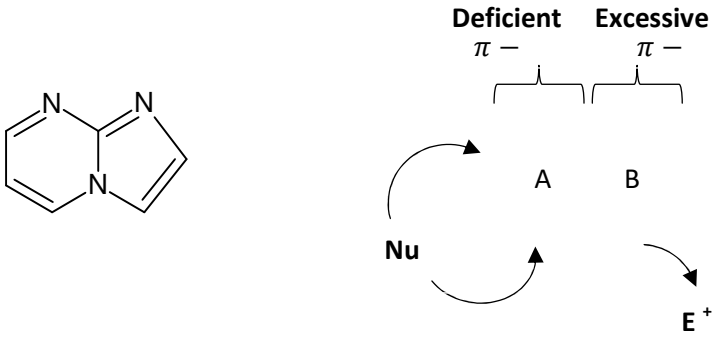


Figure 1. Electrophilic addition/substitution typically occurs on the π-excessive B ring

There are now huge numbers of multicomponent reactions (MCRs) known in the literature. Passerini established one of the first in 1921, with the treatment of an isonitrile with a carboxylic acid and an aldehyde or ketone to give acyloxy amides. This reaction was further prolonged by Ugi in 1961, to give bis-amides, by the introducing of ammonia (or an amine component) giving the four-component MCR knew today. Recently, a new revised of this the reaction was designated by Blackburn, Bienayme, and Groebke, which enabled the ready synthesis of imidazo[1,2-a]azines by the acid-catalyzed condensation of an aldehyde, an isonitrile, and a 2-aminoazine to give 3-alkyl-amino-2- substituted-imidazo[1,2-a]azines. Since imidazo[1,2-a]azines have established as versatile drug patterns in broad areas of medicinal chemistry, ranging from cardiac stimulant, anti-inflammatory, antiulcer, and anti-viral based therapies, an equivalent synthesis to these compounds is theatrically enhanced by a route containing an efficient one-pot MCR. Subsequently, imidazo[1,2-a]azine libraries have been prepared both in solution and on the solid phase where one object of the MCR is used to 'capture' the desired final product on the resin, with the Rink amine linker often proving to be the linker of choice for the establishment of the amine component. During the synthesis of a library of imidazo [1, 2-a] -pyrimidines, while seeking to estimate the performance of different catalysts ($Sc(OTf)_3$, AcOH, and $HClO_4$) in a model reaction using 2-aminopyrimidine as the amine component with five different aldehydes and two different isonitrile components. In the case of 2-aminopyrimidine,

the symmetry of the starting material might be expected to improve the yield of the 2-alkylamino product that might be obtained compared to other aminoazines. The proportional nucleophilicity of the mines is another thought. To the best of our knowledge, this is the first described synthesis of 2-alkyl-amino-3-substituted-imidazo [1, 2-a] pyrimidine derivatives using MCR protocols. There was little difference with the choice of the catalyst being the dominant feature. This side reaction potency well explains the low yields reported by others when using pyrimidines in these MCRs. The imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrazine and imidazo [1,2-a]pyrimidine structural moieties can be originate in pharmacologically active compounds such as benzodiazepine receptor agonists, anti-inflammatory agents, inhibitors of gastric acid secretion, calcium channel blockers and antibacterial. The classical synthesis of imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrazines and imidazo[1,2-a]pyrimidines contains the condensation of α-haloketones with 2- amino-pyridines, 2-amino-pyrazines or 2-amino-pyrimidines, respectively. The use of Ugi-type multicomponent reactions for the generation of compound libraries both by solution and solid phase chemistry has been described by several groups. In the course of our own studies of the Ugi reaction using a wide variety of isonitriles, aldehydes, amines and carboxylic acids. We observed that the structure of the product formed depends strongly on the structure of the primary amine involved. We found now that the condensation with 6-membered heteroaromatic amines containing a H_2N-C=N substructure leads efficiently to the generation of imidazo[1,2-a]-annulated heterobicyclic compounds. Thus, 2-amino-pyridine, 2-amino-pyrazine or 2-amino-pyrimidine gave 3-amino-imidazo[1,2-a]pyridines 4, 3-amino-imidazo[1,2-a]pyrazines 5 and 3-amino-imidazo[1,2-a]pyrimidines respectively. This reaction may be viewed as a special type of the Ugi four- component reaction. For synthetic modification chalcones are versatile scaffolds and exhibit diverse pharmacological properties. Because of their better bioavailability and high tolerance in the body, research on chalcones and derived compounds are gaining interest worldwide for the development of pharmacological compounds. Now a day's number of chalcone moiety is currently available in the market and in clinical trials. Chalcone derivatives show pharmacological properties like anti-malarial, anti-microbial, anti-viral, anti-inflammatory, anti-oxidant, anti-tumor, and anti-cancer. Chalcone is available abundant in edible plants like vegetables, fruits, spices, tea, and natural foodstuffs. In pyrimidine 2-Amino pyrimidine has great importance is widely spread in living organisms. In 1899 Gabriel & Colman first isolated pyrimidine. 2-Amino pyrimidine and its derivatives showed a broad-

spectrum activity. The ring system of pyrimidine has chemical &biological importance. Pyrimidine compounds were prepared by the cyclization of aliphatic raw materials, polysubstituted pyrimidines compound were synthesized from acyclic compounds[3-4]. Microwave Assisted Organic Synthesis had developed in now years which has been considered superior to traditional heating. Microwave assisted organic synthesis has as a new "lead" in the organic synthesis[5-15]. The technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis[16-25]. Important advantage of this technology includes highly accelerated rate of the reaction time with an improvement in yield and quality of product[26-36]. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry, screening, medicinal chemistry and drug development. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution. Computational studies are the crucial steps in the drug designing. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search[37-45]. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations can help to have good biological activity from any heterocyclic compound modification. Someday soon, you might be making your own medicines at home. That's because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series[45-51]. Epilepsy, a ubiquitous disease characterized by recurrent seizures. For epilepsy

treatment, nearly 95% of clinically available drugs were approved before 1985 and they are only effective in reducing the severity and number of seizures in less than 70% of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia. Research to find more effective and safer antiepileptic drugs are, therefore, imperative and challenging in medicinal chemistry[52-56]. Analgesics, which are most widely used drugs for the treatment of pain, can be divided into two groups: morphine and related drugs and nonsteroidal anti-inflammatory drugs (NSAIDs). The fear of addiction and tolerance associated with morphine and related drugs has led to the restriction and withdrawal of these drugs. NSAIDs act primarily by inhibiting cyclooxygenase (COX) enzymes, which catalyze the first step in the prostaglandin biosynthesis. The long-term use of NSAIDs may also lead to severe gastrointestinal side effects, which limit the use of these drugs[57-58]. The adverse effects accompanying the use of non-selective NSAIDs arise from the reduction of the levels of protective prostaglandins in the gastrointestinal (GI) tract due to the inhibition of COX-1. Although selective COX-2 inhibitors cause less GI adverse effects than nonselective NSAIDs, their use in the treatment is also limited due to their serious cardiovascular effects. From the above discussion, it is clear that the search for new effective compounds has gained great importance[57-60].

2. MATERIALS AND METHODS

Chemistry

All chemicals and solvents were procured from commercial sources, purified and dried using standard procedures from literature whenever required the regents were purchased from Sigma Aldrich and solvents and anilines were purchased from Research Lab. Melting points were determined by open capillary tube method and are uncorrected. Thin layer chromatography was used to assess the course of reaction and the purity of the intermediate and the final compounds were confirmed by applying a single spot on TLC plate (silica gel G) using various solvents such Ethyl acetate and n-hexane as system.

General procedure for Synthesis of chalcone

A mixture of substituent acetophenone (0.01 mole) and aryl aldehyde (0.01 mole) was stirred in ethanol (10ml), then add dropwise with constant stirring10 ml of 10% NaOH into the mixture.

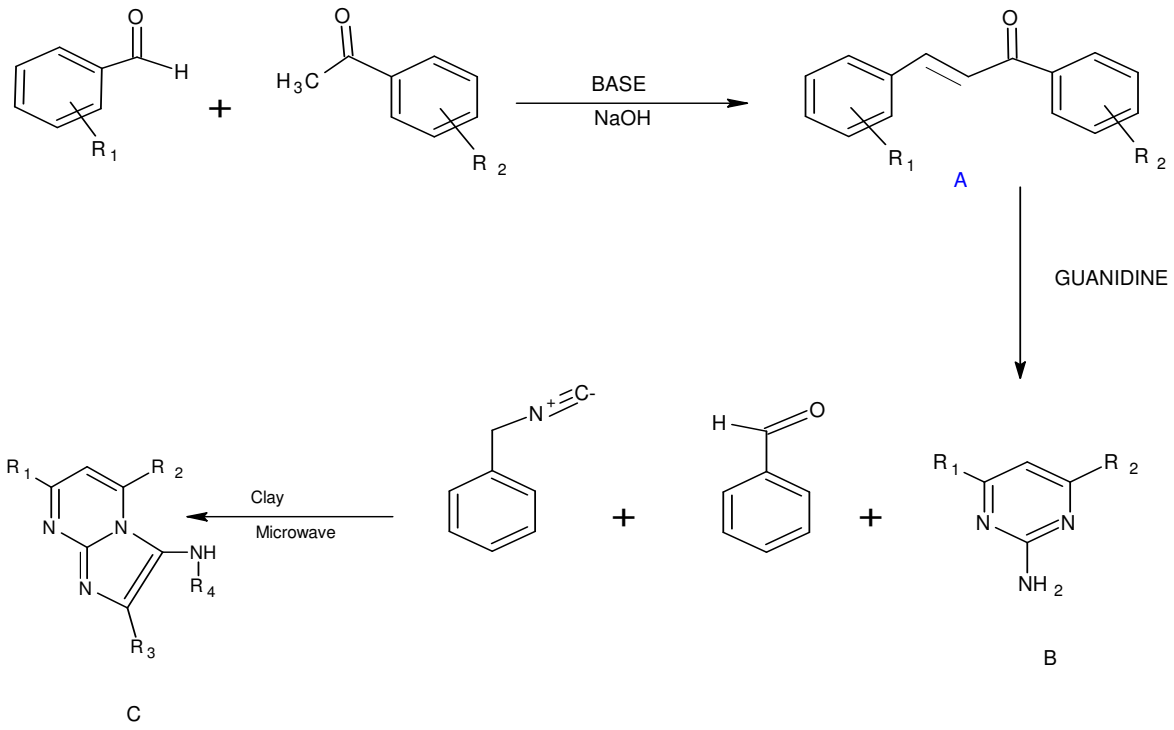
The reaction mixture was stirred for 4-5 hr at R.T. In between, TLC was checking the completion of reaction condition. After completion of reaction neutralization of the mixture by adding dilute HCl. The solid separated was filtered and recrystallized from rectified spirit to get pale yellow colored solid chalcone.

General procedure for Synthesis of pyrimidine

A mixture of chalcone (0.01 mol) and Guanidine (0.01 mol) was dissolved in 10 ml ethanol (95%) in a beaker. In this 40%, aqueous KOH solution (10 ml) was added slowly with continuous stirring. The reaction mixture was placed in the microwave and irradiated at power level-3 (245W) for 7-10 min. In between, TLC was a check for the completion of the reaction condition. After completion of the reaction, the reaction mixture was cooled to R.T. and poured into ice-cold water and neutralized by adding dil.HCl. The ppt. obtained was filtered, washed with water and dried. The product was recrystallized from the rectified spirit.

General procedure for Synthesis of imidazo[1,2-a]pyrimidine

A mixture of aldehyde (1mmol) and 2-aminopyrimidine in presence of a small amount of Bentonite clay with microwave for 1 min (at power of 850 W). Then add isocyanide (1mmol) the reaction mixture was further irradiated successively (2min) at 50% power (425W) duration of 1 minute followed by a cooling period of 1 min. The resulting product was dissolved in dichloromethane (10ml) and clay was filtered off. The solution was removed by under reduced pressure and the crude product was purified by crystallization.



A- Substituent chalcone

B- Substituent pyrimidine

C- Imidazo(1,2-a) pyrimidine derivatives

Scheme 1. *Synthetic route for the preparation of the Imidazo (1,2-a) pyrimidine and their analogs*

Table 1. Physicochemical characteristics of Imidazo(1,2-a)pyrimidine derivatives

Comp.	**R_1**	**R_2**	**R_3**	**R_4**	**M.P. (^{0}C)**	**%yield**	**R_f value**
1	$N(CH_3)$	OH	C_7H_6O	C_8H_7N	140	84	0.34
2	Cl	CH_3	C_7H_6O	C_8H_7N	135	90	0.34
3	Cl	CH_3	C_7H_6O	C_8H_7N	141	89	0.33
4	NO_2	OH	C_7H_6O	C_8H_7N	138	88	0.34

5	NO_2	C_6H_5	C_7H_6O	C_8H_7N	159	82	0.33
6	Br	$CH_3(OH)$	C_7H_6O	C_8H_7N	145	92	0.35

Table 2. Analytical data of Imidazo(1,2-a)pyrimidine derivatives

Sr. No.	**Compound**	**IR (cm^{-1})**	**NMR**	**MASS g/mol.**
1	N,N-dimethyl aniline	Benzene=1500 1450-1550 Amine=3300-3550	H_1=2-4 C_{13}=125-130	121.08
2	Phenol	3200-3550	$H_{1=}$6.2-6.4 $C_{13=}$118ppm	94.113
3	Benzaldehyde	1200-1250	$H_{1=}$6-8 $C_{13=}$130-140	108.12
4	4-amino-phenylacetonitril	1500-1550	$H_{1=}$7 $C_{13=}$128-130	132.16
5	Toluene	650-850	$H_{1=}$7-8(7-7.2) $C_{13=}$125-130	92.14
6	Chlorobenzene	650-800	$H_{1=}$7-8 (7.2-7.4) $C_{13=}$129-134	112.55

Pharmacological Evaluation:

I. Antiepileptic Activity:

Maximal electro shock-induced convulsion

The rats were divided into following different groups and each group comprised of 6 animals. Before the study animals were kept for acclimatization for 10 days. Animal was grouped and treated as per the following groups[61-63].

Table 3. Groups and Treatment

Sr. No.	Groups	Treatment
1	Normal	Distilled Water
2	Standard	Phenytoin (25mg/kg;I.P)
3	Derivative-I	Imidazo[1,2-a]pyrimidine derivative-I
4	Derivative-I	Imidazo[1,2-a]pyrimidine derivative-II

General procedure for the maximal electro shock induced convulsion

Animals was divided into 4 groups. Phenytoin was administered by I.P. route and imidazo[1,2-a]pyrimidine derivative was administered by oral gavage to the rats. After 30 min animals were subjected to electro convulsions.The reduction in time or abolition of tonic extensor phase of MES-convulsions was measured[64-65].

II. Analgesic activity:

Hot plate method

The mice were divided into following different groups and each group comprised of 6 animals. Before the study animals were kept for acclimatization for 10 days. Animal was grouped and treated as per the following groups:

Table 4. Groups and treatment

Sr. No.	Groups	Treatment
1	Normal	Distilled Water
2	Standard	Pentazocine (5mg/kg;I.P)
3	Derivative-I	Imidazo[1,2-a]pyrimidine derivative-I
4	Derivative-I	Imidazo[1,2-a]pyrimidine derivative-II

General procedure for the Hot plate method

Animal was divided into 4 groups. In each group was taken 6 animals having a weight between 20-25 g. Take the basal reaction time when mice start licking their paw or started jumping, which appears first. The normal response time is around 7-9 second if they not respond up to 15 second these animals were removed from the experiment. Hot plate temperature (55^0C) was regulated. Inject the given drug (Pentazocine) by subcutaneous route was given to the animals and animal was placed on a hot plate. Note reaction time of animals on the hot plate at 15, 30, 60 and 120 minutes and the stopwatch has registered the movement until either paw leaking or jumping take place. When the drug administered the reaction time was increased and 15 sec is the max time for response. Calculate the percent increase in reaction time at each time interval, as before and after administration of the drug. The same procedure used for derivative I & II administration[66-68].

3. RESULTS AND DISCUSSION

The main objective of the study was to synthesize derivatives of Imidazo[1,2]pyrimidine. In total synthesis six derivatives of Imidazo[1,2]pyrimidine were synthesized. This reaction afforded desired derivatives ranging from 82 to 92% of yields. Thin Layer Chromatography was used to assess the completion of reaction and purity of the final product, giving a single spot on TLC plate with the various solvent systems. Solvent system Ethyl acetate: n-hexane (5:5) was found to be an appropriate system. The test compound was screened for biological activities i.e. analgesic and antiepileptic activity. Two synthesized derivatives were screened for analgesic activity. The compound SS-I and SS-II show good analgesic activity at concentration 0.40 mg/kg compare with pentazocine as a standard. Compound SS-II shows good analgesic activity than SS-Ion mice. After getting a satisfactory result for the analgesic activity of synthesized compounds was further screened for antiepileptic activity and was compared with standard drug phenytoin. Derivative-II gives good results than derivative–I. The derivative-II of the synthesized compounds shows good antiepileptic activity on rats at concentrations 40 mg/kg.

Derivatives used in anticonvulsant and analgesic activity:

Derivative-I [SS-I or Test-1]: 2-(4-((7(4-(dimethylamino)phenyl)-2-(4-formylphenyl)-5-(4-hydroxyphenyl)-2,3-dihydroimidazo[1,2-a]pyrimidin-3-yl(amino)phenyl)acetonitrile.

Derivative-II [SS-II or Test-2]: 2-(4-((7(4-chlorophenyl)-2-(4-formylphenyl)-5-(4-tolyl)-2,3-dihydroimidazo[1,2-a]pyrimidin-3-yl(amino)phenyl)acetonitrile.

Dose:-1. Antiepileptic activity

SS-I- 35 mg/k

SS-II-40 mg/kg

For Analgesic activity

SS-I-0.35 mg/kg

SS-II-0.40 mg/kg

Table 5. Antiepileptic results of different stages on Derivatives –I &II (Test-I &Test-II)

7th day

Sr. No.	Treatments	Dose	Tonic Hind limb flexion (sec)	Tonic Hind limb Extension (sec)	Clonus Duration (sec)	Stupor (sec)
I	Control	10ml/kg	17.67±0.33	15.67±1.453	16±0.5774	102.3±2.404
II	Standard	25mg/kg	6.25±0.52	8.698±0.658	12.25±1.08	66.459±3.568
III	Deri. -1	35mg/kg	10.333±0.33	7.333±0.33	9.333±0.66	58.33±3.18
IV	Deri. - 2	40mg/kg	6±0.57	5.667±0.33	4±0.57	78.67±2.84

14th day

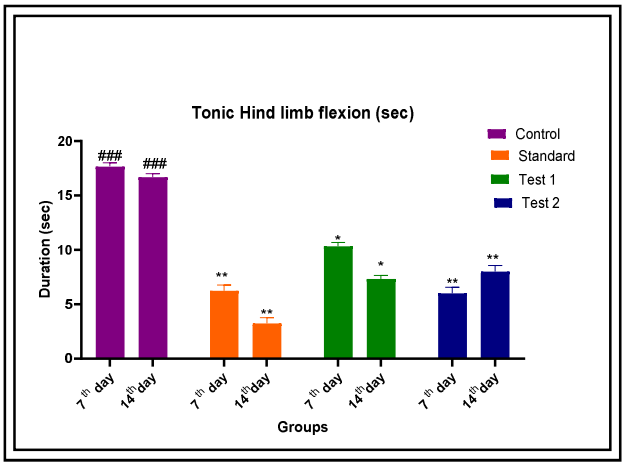
Sr.no.	Treatments	Dose	Tonic Hind limb flexion	Tonic Hind limb Extension	Clonus Duration (sec)	Stupor (sec)

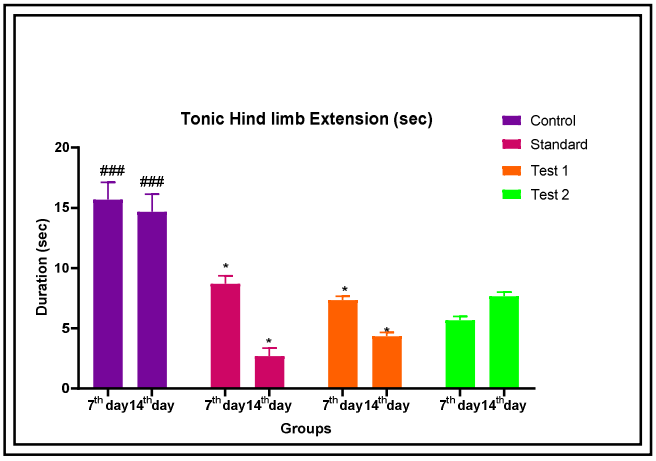
			(sec)	**(sec)**		
I	Control	10ml/kg	16.67±0.33	14.67±1.453	15±0.5774	100.3±2.404
II	Standard	25mg/kg	3.25±0.52	2.698±0.658	9.25±1.08	60.459±3.568
III	Deri. -1	35mg/kg	7.333±0.33	4.333±0.33	6.333±0.66	64.33±3.18
IV	Deri. - 2	40mg/kg	8±0.57	7.667±0.33	7±0.57	70.67±2.84

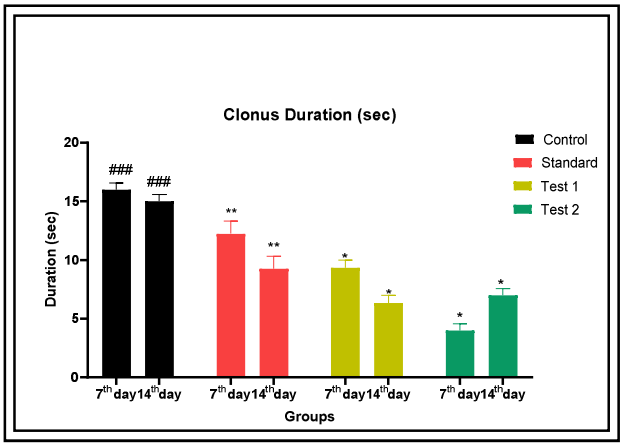
Table 6. Analgesic activity by hot plate method

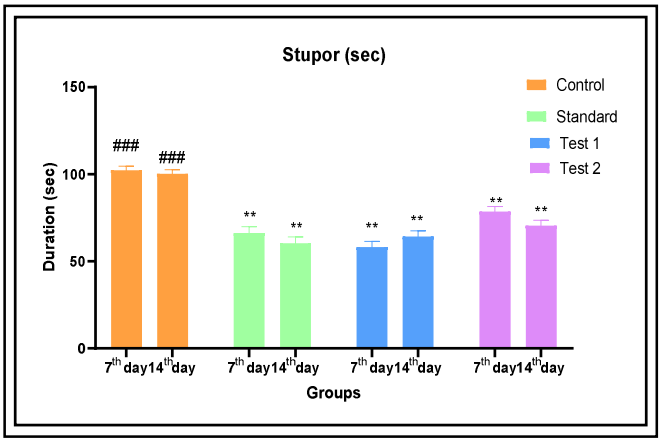
Sr. No.	**Groups**	**Time (min)**					
		0 min	**15 min**	**30 min**	**60 min**	**90 min**	**120 min**
1	Control (10ml/kg)	7.433±0.1476	7.333±0.1282	7.167±0.1282	6.967±0.1282	6.833±0.1116	6.567±0.1116
2	Standard (25mg/kg)	6.9±0.4211	10±0.3651	12.25±0.08851	12.97±0.05578	11.93±0.2974	10.77±0.319
3	Deri. I (0.35mg/kg)	5.333±0.08819	5.95±0.05	6.8±0.1461	7.95±0.04282	7.367±0.3169	8.033±0.1476
4	Deri.II (0.40mg/kg)	5.85±0.06191	6.367±0.1726	7.183±0.09098	8.383±0.1327	8.817±0.06009	8.967±0.1542

Graph 1. Graphical representation of Antiepileptic activity results of different stages on Derivatives –I &II (Test-I &Test-II)









4. CONCLUSION

The synthesis has been carried out by using various compounds like different aldehydes, ketones and benzyl isocyanide. In the present study, we successfully developed a new route for the synthesis of imidazo [1,2] pyrimidine. The method is very simple and takes the advantage of Aldol condensation, Ugi reaction, cyclization and aromatization as key for the thesis of imidazo [1,2] pyrimidine analog. Two synthesized compounds were screened for analgesic and antiepileptic activity. For the analgesic mice was used and antiepileptic rats are used. Synthesized compounds exhibit some interesting results. The compound SS-II was found to be more potent than SS-I.

5. ACKNOWLEDGMENTS

The author are thankful to the principal and management of A.B.C.P. Sangli for providing research facilities to carry out work. Also thankful for the pharmacology department to carry out the biological activity.

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