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Simple, Convergent Synthesis and Characterization of benzimidazole derivatives (pyrazole linked pyridine): Micro-wave, Sonication and Conventional methods

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A B S T R A C T

The preparation of skeleton is an important in the novel drug development. Herein, the skeleton is developed based on anti-ulcerative drugs. A convergent synthesis, approached to simplify the synthesis and succeeded to prepare novel pyrazole-pyridine (benzimidazole) linked derivatives **.**Finally, coupled both pyrazole and pyridine derivatives by approaching micro-wave, Sonication and conventional techniques. The efficient technology identified as Sonication technique basically time and yield.

Keywords: Antiulcer, Conventional, Convergent synthesis, Micro-wave, Sonication

A R T I C L E I N F O

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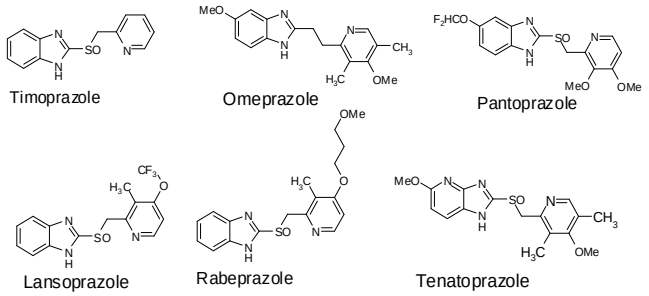
1. Introduction

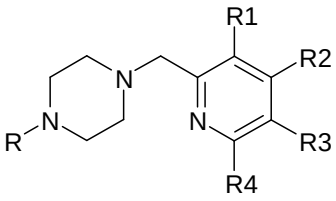
The therapeutic purposes, a drug substance with well-known chemical structure are used for developing more efficient drugs. The basic idea is to prepare more analog compounds that related drug candidates with efficient technologies. Organic molecules owe their biological activity to a variety of structural features. Sometimes a set of activities is associated with the structural backbone of a molecule. The inhibitory effect is dose-related. Omeprazole inhibits both basal and stimulated acid secretion irrespective of the stimulus[22]. The absorption of omeprazole

takes place in the anti-ulcer drugs, Omeprazole and Lansoprazole is a proton pump inhibitor (PPIs) and inhibits the action of hydrogen/potassium adenosine triphosphatase (Hþ/KþATPase) in parietal cells. Pantoprazole suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (Hþ, Kþ)-ATPase enzyme system at the secretary surface of the gastric parietal cell. Rabeprazoleis also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers. Ilaprazole (e) is a proton pump inhibitor (PPI) used in the treatment of dyspepsia, peptic ulcer disease (PUD), and duodenal ulcer.

Benzimidazole derivatives



The art has endeavoured to synthesize a variety of piperazine derivatives. Among the piperzine derivatives available as anti-ulcer drugs, 1-[2-(orthochloro-robenzydryloxy) ethyl]-4-(ortho- methyl benzyl) piperzine well known. The selection of well-known skeleton, strategic synthetic approach, technologies applied for reactions. The maximum anti-ulcerative drugs are prazoles. The prazoles skeleton considered for development of novel moieties into literature. The idea to incorporate the piperazine with pyridine derivatives of prazoles considered to design new skeleton.



A strategy of convergent synthesis, that aims to improve the efficiency of multi-step chemical synthesis, most often in organic synthesis. In linear synthesis the overall yield quickly drops with each reaction step. Here in, the synthesis of two tiles derivatives and coupled considered easy and found excellent literature for easy synthesis of both ends approached convergent than linear.

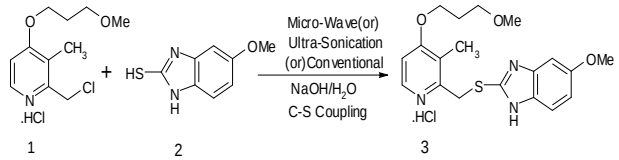
The reliable technology useful for reaching target is very important to reach target very simple and cost effective. The second technology is the way of reaction conditions are using, for getting lesser reaction timings and high yield. The N-alkylation step differentiated via Micro Wave, Sonication and Conventional method.

The microwave mediated organic reactions 13b, 13 and 13a take place more rapidly, safely, and in an environmentally friendly manner, with high yields. Very little solvent and even the use of water as a solvent is a big advantage of microwave chemistry. Recently, microwave, and ultrasonication[14] assisted synthesis in organic chemistry is quickly growing. Many organic reactions proceed much faster with higher yields under microwave irradiation compared to conventional heating. It has long been know that molecules undergo excitation with electromagnetic radiation is a technique for microwave synthesis[15]. Ultra-Sonication reactions enhances the reaction rates up to a million times, believed to be due small cavities (100 microns) which implode, creating tremendous heat and pressure, shock waves, and particular accelerations[16].

2. Experimental

General procedure for preparation of pyrazole-pyridine derivatives (1–9): All the reactions routinely monitored by Thin-layer chromatography (TLC**)** using Merck silica gel 60 F_{254} coated aluminium plates using several solvent systems of different polarity. The following mobile phases were employed ethylacetate/hexane, ethylacetate/ dichloromethane, methanol/dichloromethane and methanol-ethyl acetate with different percentage combinations. The Column chromatography by using all vensil columns are used for purification of compounds used (60–120 mesh) silica-gel. The Melting points were determined in open capillaries on a Thermonick melting point apparatus and found uncorrected. ^{1}H NMR (400 MHz) and 13C NMR (100 MHz) recorded on $CDCl_3$ and DMSO-d_6 solution in a 5 mm tube on Varian 400 MHz Unity Inova using TMS internal reference standard (chemical shifts in δ).Mass spectra were recorded on Agilent 6310 Ion Trap and Shimadzu LCMS (e/z and relative intensity). Microwave reactions are carried out in SEM Discovery (sixty). Ultra Sonication reactions performed in Sonirex sonicator.

(1) Derivatives: 5-methoxy-2-(4-(3-methoxypropexy)-3-methylpyridine-2-yl) methylthio)-1H benzo[d] imidazole hydrochloride.



Scheme-1

Conventional method (A)

To a mixture of **(Int-1)** or **(Int-2)**; **(Int-3),** or **(Int-4),** or **(Int-5),** or **(Int-6),** or **(Int-7),** and potassium carbonate in anhy.DMF at r.t. The reaction mixture was stirred at 40 °C for 5–6 h. The reaction mixture was diluted with water and extracted product into ethyl acetate. The resultant crude product purified through silica-gel (60–120 mesh) column chromatography to afford yield (calculated (cal.) 30%–50%) (**1**–**9**).

Micro-wave method (B)

To a mixture of **(Int-1),** or **(Int-2)**; **(Int-3),** or **(Int-4),** or **(Int-5),** or **(Int-6),** or **(Int-7), 8,9** and potassium carbonate in anhy.DMF at r.t. in a micro tube. The reaction mixture was stirred at 80 °C for 30 min, 100–200 watts. The reaction mixture was diluted with water and extracted

product into ethyl acetate. The resultant crude product purified through silica-gel (60–120 mesh) column chromatography to afford yield (cal.33%–46%) (**1**–**9**).

Ultra-Sonication method (C) (**1**–**9**):

To a mixture of **(Int-1),** or **(Int-2)**; **(Int-3),** or **(Int-4),** or **(Int-5),** or **(Int-6),** or **(Int-7),**8,9 and potassium carbonate in anhy.DMF at r.t. The reaction mixture was sonicated at 40 °C for 30 min. The reaction mixture was diluted with water and extracted product into ethyl acetate. The resultant crude product purified through silica-gel (60–120 mesh) column chromatography to afford yield (cal.40%–70%).

Synthesized compounds by using above methods (A), (B) and (C)

5-methoxy-2-(2-(4-(3-methoxypropoxy)-3-methyl pyridine -2-yl) ethyl)-1H-benzo[d]imidazole.

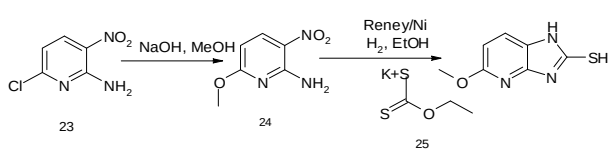
White powder, mp 80–85 °C. IR (KBr) υ 622, 1086, 1150, 1294, 1407, 1580, 2859, 3067 cm.-1;^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10-2.15 (m, 2H), 2.25-2.28 (s, 3H), 3.30 (s,3 H), 3.56–3.71 (s, 3H), 3.84 (t, 2H), 4.15 (t, 2H),4.30-4.60 (s,2H), 6.70-6.85 (m, 3H),(j = 8.46Hz,Hz,) δ 8.31-8.35 (d, 2H),. MS (*e/z*).568 (M^+). 1054(20), 895(15), 770(80), 748(90)

5-(difluoro methoxy)-2-(((3-methyl-4-(2, 2, 2-trifluoro ethoxy)pyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole: Yellow gummy solidmp 80–85 °C. IR (KBr) υ 665, 807, 1042,1105,1160,1255,1456,1740,2952,3043cm.-1;^{1}HNMR (400 MHz,$CDCl_3$): δ2.34(s,2H), 4.454.90(2H), 6.55(s,1H), 6.80.(d,1H),7.01(d,1H).7.03(*J* = 8.44 Hz,(d.1H),7.05(d,1H), 8.4(bro.1H.NH). MS (*e/z*): 420, (M^-, M^+). 374(15),

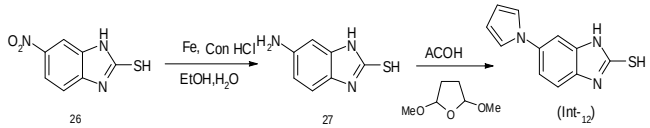
2-(((3,4-dimethoxypyridin-2-yl)methyl)thio)-5-methoxy-1H-benzo[d]imidazole hydrochloride: Pale yellow colour syrup.mp 80–85 °C. IR (KBr) υ 634, 1044, 1235, 1738, 2986cm.-1; 1H NMR (400 MHz, $CDCl_3$): δ3.36 (s, 2H), 3.84 (s, 6H), 4.30 (s, 3H), 6.76-6.90 (m, *J* = 8.46 Hz, 3H), 7.45 (d, 1H), 8.40 (d, *J* = 5.6 Hz, 1H).), 12.09(bros, 1H, NH); MS (*e/z*): 381, 383 (M^-, M^+).

3. Results and discussion

The reaction of 6-chloro-3-nitro-pyridine-2-yl-amine with sodium methoxide in methanol to afford 6-methoxy – 3-nitro-pyridine -yl amine (24) and further reduction with Raney Ni and cyclisation with potassium ethyl xanthenes (25) leads. Scheme.



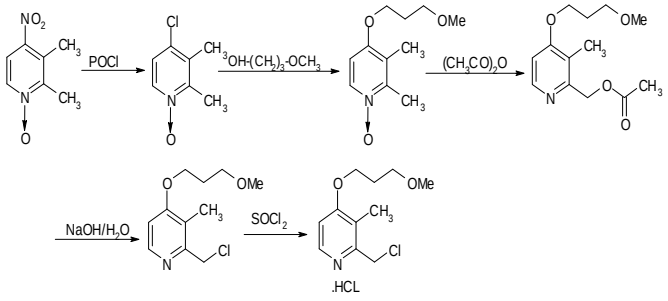
The reaction of 2-mercapto-6-5-nitrobenzimidazole (26) with iron and concentrated HCl in refluxing ethanol and water gives mono amine (27). Which by condensation with 2,5-dimethoxytetra hydrofuran (28) in acetic acid yield 2-mercapto -5-(1-pyrrolys) benzimidazole (int 12). Scheme.



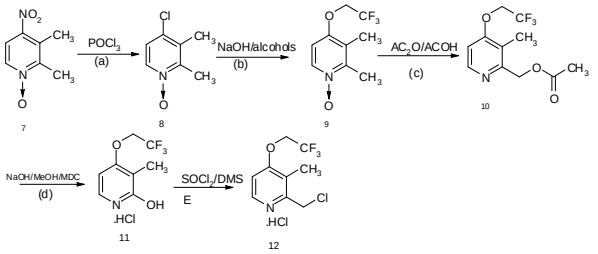
The novel targets were synthesized by simple coupling using different technologies (microwave, ultra-sonication and normal conventional method) , 7-(4-bromo-butoxy) -3-4-dihydro-1H- quinolin-2-one (int-2) reacts with 2-mercapto benzimidazole (int 8-12) in anhydrous DMF and K_2CO_3 as a base the resulting solution was heated at 600C for about 5-6h. (Conventional) 100-200 watts for 5min (microwave) and sonicated at 40 oc for 80 min afforded final targets. (SL-1-9). Basically we observed ultra-sonocation condition cooking comparatively with other techniques used based on yield. In continuation of our research interest was to synthesize a series of new piperzine linked pyridine is furnished.

The novel targets (SLN1-SLN9) were synthesized by simple coupling using different technologies (microwave, ultra- sonication and normal conventional method). Basically, we observed ultra-sonication condition looking better comparatively with other techniques used based on yield reported in Table-1. The reaction sequence leading to the formation of these compounds is outlined in scheme (2-5). In the chapter we described the synthesis and characterization of.

Derivatives: 2-(chloromethyl)-4-(3-methoxy propoxy-0-3-methyl pyridine hydrochloride: In the synthesis of (2-(chloromethyl)-4-(3-methoxy propoxy0-3-methylpyridine hydrochloride) the reaction of 4-nitro-2,3-dimethyl pyridine-1-oxide with $POCl_3$ to give 4-chloro-2,3-dimethyl pyridine-1-oxide, which up on condensation with sodium hydroxide in methoxy propanol yielded 4-methoxy propoxy-2,3-dimethylpyridine-1-oxide , which on further reaction with acetic anhydride give 2-acetoxymethyl-4-(methoxypropoxy)-3-methylpyridine. Hydrolysis of with sodium hydroxide obtained 2-hydroxymethyl-4-(methoxy propoxy)-3-methylpyridine, which on chlorination with thionyl chloride yielded 2-chloromethyl-4-(methoxy propoxy)-3-methylpyridine hydrochloride.

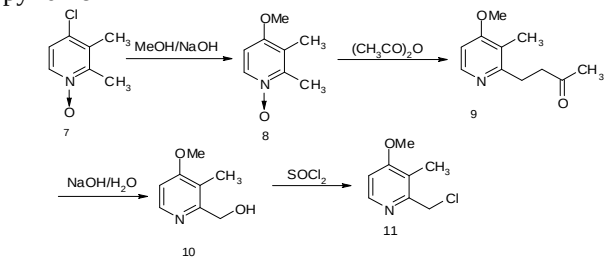


2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride: In the synthesis of reaction of 4-chloro-2,3-dimethylpyridine-hydride (7) with $POCl_3$ to give 4-methoxy-2,3-dimethylpyridine-hydrate (8), which up on condensation with sodium hydroxide in 2,3-dimethyl-4-(2,2,2 trifluoroethoxy) pyridine (9), which on further reaction with acetic anhydride give 3-methyl-4--(2,2,2 trifluoroethoxy) pyridine -2-yl)methyl acetate (10). Hydrolysis of 3-methyl-4--(2, 2,2 trifluoroethoxy) pyridine-2-yl) methanol (11) with sodium hydroxide obtained (9) which on chlorination with thionyl chloride yielded



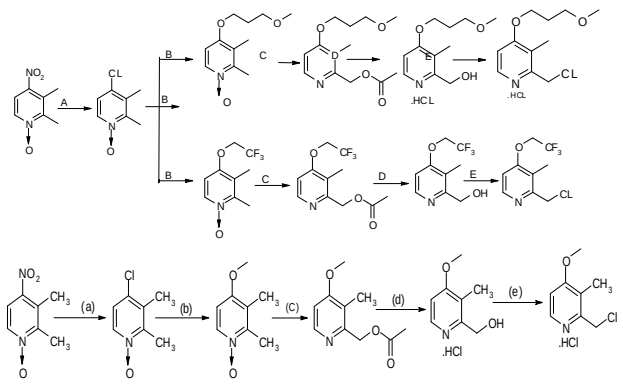
2-(chloromethyl)-4-methoxy-3-methylpyridine

In this synthesis reaction of 4-chloro-2,3-dimethyl pyridinehydride (**7**) with $POCl_3$ gives 4-methoxy-2,3-dimethylpyridine-hydrate (**8**), which on condensation with sodium hydroxide in4-(-4-methoxy-3-methylpyride-2-yl)butan-2-one 9), which on further reaction with acetic anhydride gives (4-methoxy-3-methyl pyridine-2-yl)methanol (10).Hydrolysis of 3-methyl-4--(2,2,2 trifluoro ethoxy) pyridine-2-yl)methanol (11) with sodium hydroxide obtained(9)which on chlorination with thionyl chloride yielded 2-(chloro methyl)-4-methoxyl-3-methyl pyridine



The traditional approach for the synthesis of Int3-Int 7.

The chloro Compouned (10) was obtained by chlorination of compound(9) by using $POCl_3$.which on methylated using DMS to afford methylated compouned (11) which on acetylation by using acetate anhydride in acetic acid to affored acetate product (12) which hydrolyzed by using NaOH to affored hydroxyl compouned (13) . Further which on chlorination by using thionylchloride to affored (Int-3).The 4-chloro-2,3-dimethylpyridine(15) was obtained by chlorination of 2,3-di methyl-4-nitropyridine-n-oxide(14) by using $POCl_3$which on Methylation using 3-methoxypropan-1-ol to 4-(methoxypropoxy)-2-3-dimethylpyridine,(16) which on acetylation by using acetic anhydride in acetic acid to afforded acetate 4-(3-methoxpropoxy)-3- methylpyridin-2-ylmethyl ester (17)w which hydrolyzed by using to (4(3-methoxypropoxy)-3,5-dimethylpyridin-2-yl)-methanol.



Reagents & Conditions: (a) POCl3, reflux for 3-4h (b) appropriate alchohols and NaOH (c)acetic anhydride, acetic acid, MeOH, Toluene (d) NaOH, MeOH, MDC (e) SOCl2 (f) DMS

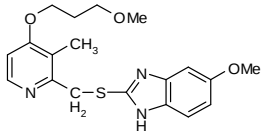
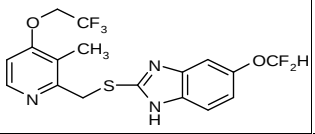
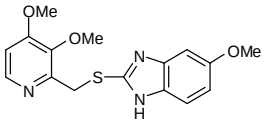
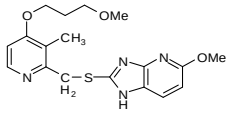
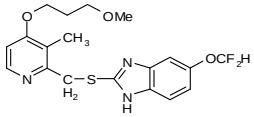
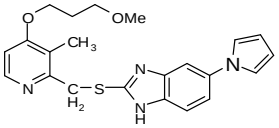
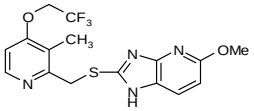
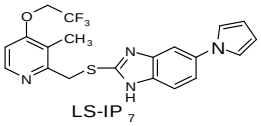
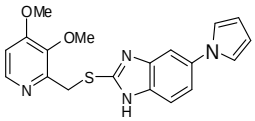
Scheme-V: Synthesis of 2-chloromethyl-4-methoxy-3,5,-dimethylpyridine. HCl (Int-3), 2-chloromethyl-3-methyl-4-(3-methyoxypropoxy) pyridine. HCl (Int-4), 2-chloromethyl-3-methyl4-(2,2,2-trifluoromethoxy)pyridine. HCl (Int-5), 2-Chloromethyl-3-methyl-4-methoxy pyridine. HCl (Int-6) and2-chloromethyl-3,4-dimethoxypyridine.HCl (Int-7). Further which on chlorination by using $SOCl_2$ to afford sython 2-chloro methyl-3-methyl-4-(3-methoxy propoxy) pyridine .HCl (Int-4).the 4- chloro-2,3-di methyl pyridine-n-oxide(15) was obtained by chlorinaton of 2,3 –di methyl-4-nitropyridinr-N-oxide (14) by using poci3. Which on methylated afford 2,3-dimethyl-4-(2,2,2-trifluoro ethoxy)-pyridine (19) which on acetylation by using acetic anhydride in acetic acid to afforded acetic acid 3- methyl-4-(2,2,2-trifluoro-ethoxy)-pyridine-2-ylmethylester(20) which hydrolysed by using NaOH to afford(3- methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl)-methanol.(21) Further which on chlorinaton by using thionylchloride to afford desired sython 2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine.HCl (lnt-5).

The 4-chloro-2,3-dimethyl pyridine (15) on methylation afford 4-methoxy-2,3-dimethyl pyridine(20).which on acetylation by using acetic anhydride in acetic acid to afforded actic acid 4- methoxy-3-methylpyridin-2-ylmethyl ester(23) which hydrolysed by using NaOH to afford (4-methoxy-3-methyl-pyridin-2-yl)-methanol (24) further which on chlorination by using $SOCl_2$ to afford desired synthon 2- chloromethyl-4-methoxy-3- methyl pyridine.HCl(lnt-6). 4- chloromethyl-3-methoxypyridine-N-oxide (26) was obtained by chlorinaton of 4-chloro-3-methyl-3-methoxy-2-methyl-4-nitropyridine. (25) by using $POCl_3$ which on methylation afford 3,4-dimethoxy-2-methyl pyridin (27) which on acetylation by using acetic anhydride in acetic acid to afforded acetic acid 3,4 dimethoxypyridin-2-ylmethyl ester(28) which hydrolysed by using NaOH to afford(3,4- dimethoxy-pyridin-2-yl) methanol.(29). Further which on chlorination by using $SOCl_2$ to afford desired synthon 2- chloromethyl-3,4-dimethoxy pyridine. HCl (lnt-7).

4. Conclusion

The synthesis of (**1**–**9**) successfully synthesised by using good literature. Majorly we selected related drug candidates, prepared skeleton. Simple convergent methodology worked for getting good yields overall. The final **C–N** coupling approached three techniques, where we concluded Sonication technique is good for getting good yield and time. We observed more spots in microwave reaction may be due to microwave other bonds also dislocated and afford low yield. The same conventional reaction yield shown less and taking long time. The explosive reactions, like azide and Mitsunobu reactions *etc*., are not useful for bulk scale. We recommend for small scale reactions in Ultra-Sonication reactions and microwave reactions based on our earlier experience.

Scheme I: The synthetic route was depicted in scheme I.

Entry-1	Entry-2	Product	Conventional Method yield	Microwave Method yield	Ultra- sonication Method yield 1
Int-1	Int-1		**50**	**45**	**72**
Int-1	Int-2		**45**	**55**	**68**
Int-1	Int-3		**45**	**55**	**75**
Int-1	Int-4		**42**	**38**	**50**
Int-1	Int-5		**40**	**45**	**56**
Int 1	Int 6		**47**	**45**	**62**
Int 1	Int 7		**55**	**45**	**58**
Int 1	Int 8	 LS-IP 7	**32**	**38**	**45**
Int 1	Int 9		**35**	**40**	**50**

5. Acknowledgement

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