CHAPTER- Ⅰ

SECTION-C

One-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketones or its analogues catalyzed by Silica-gel

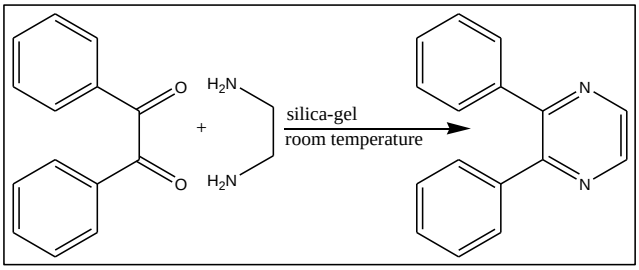
Ⅰ.C. Present Investigation

Ⅰ.C.1. Background of the present Investigation

Heterocyclic compounds are wide spread in nature[1] and compounds containing *N*-heterocyclic moieties are of immense importantance in pharmaceuticals as well as in medicines[2]. Likewise, pyrazine is a class of privileged *N*-heterocycle that is vital components of aroma fragrances,[3] and forms the active core of large number of biologically active substances[4-6]. Pyrazinamide is used against *Mycobacterium tuberculosis* to treat tuberculosis[7]. Cephalostatin, a bis-steroidal marine natural product with a pyrazine core, has been reported to induce apoptosis without the prerequisite of an active caspase-8 and apoptosome formation[8]. Despite their wide agrochemical uses[9], pyrazine derivatives are also used as relaxing cardiovascular, uterine smooth muscle, anti-aggregation, anti-thrombotic, COX-2 inhibiting as well as analgesic effects[10]. These N-heterocyclic compounds, pyrazine and its congeners have broad spectrum of biological activities[11] such as anticancer, antituberculosis[12], antimicobacterial, antimalarial, anti-HIV activity and cytotoxicity[13]. Besides these, pyrazines are widely applied to other industrial fields, for example, in the preparation of pharmaceuticals, perfumes, and agricultural chemicals[14]. It also plays an important role in making flavor ingredient in food and pheromones in various insect[15-16]. It also acts as versatile synthetic intermediates[17]. Due to these wide applications of pyrazine derivatives, their synthesis has always been important for organic chemists. Several synthetic strategies have been developed so far for their synthesis over the years.[18] Pyrazines were formed through catalytic dehydrogenation of the vapour of

ethanolamine. The catalysts used were copper oxide, zinc oxide, copper, sodium carbonate[19]. Condensation of α-amino ketone[20], Pd-catalysed cross coupling reaction also produced pyrazine derivatives[21]. Further, pyrazine compounds were prepared by the reaction of diamine with diol in vapour phase, catalysed by granular alumina[22]. Catalytic system such as copper-zinc-chromium[23], zinc-phosphoric acid-manganese[24], copper-chromium[25] and silver[26] were also used for the preparation of 2-methyl pyrazine from propyleneglycol and ethylenediamine. Pyrazines were synthesized from the condensation of epoxides and diamines using copper-chromium catalyst[27]. Piperazines gets dehydrogenated in the presence of palladium catalyst to produce pyrazines in high yield[28]. α-hydroxy ketones and 1, 2-diamine also produce pyrazines via MnO_2 catalyzed tandem oxidation reaction under refluxing conditions, but the yields were not so encouraging[29], moreover this reaction requires an excess amount of MnO_2 catalyst that detracts from the commercial point of view and green condition[30]. Direct condensation of 1, 2-diketones with 1,2-diamine has so far been the better procedure of pyrazine synthesis through dihydropyrazine[31]. Although there are several methods of pyrazine synthesis in literature, most of them are regarded as ineffective because of poor yield, long reaction time, tedious work-up process and drastic reaction condition[32]. Therefore development of efficient, mild and environmental friendly method for pyrazine synthesis has been a long cherished goal for organic chemists. Since the primary demands of green synthesis include minimization of steps, that is one-pot tandem reactions as well as catalytic processes under metal-free conditions,[33] we explored a greener process for the synthesis of pyrazines directly from simple synthons like ethylenediamine and 1, 2-dicarbonyl compounds or α-hydroxy or α-bromo ketone at room temperature. In recent days, solvent-free synthesis has attracted the attention of chemists because they are environmentally benign processes. In continuation of our interest in the development of solvent-free synthesis,[34] herein we report a new synthetic strategy for the preparation of pyrazine derivatives

catalyzed by silica-gel under solvent-free condition. Silica-gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product because of its insolubility in organic solvents. Silica-gel supported catalysts such as SiO_2/BF_3, $SiO_2/NaHSO_4$, $SiO_2/FeCl_3$ and SiO_2/H_2SO_4[35] have also been used in various types of organic transformations. With this background of Silica-gel and in connection with our present interest, we envisioned that silica-gel itself could serve as an ecofriendly, easily available and cheap alternative catalyst for the synthesis of pyrazines through the metal-free, solvent-free tandem reduction condensation in one-pot protocol (**Scheme**. Ⅰ.C.1).

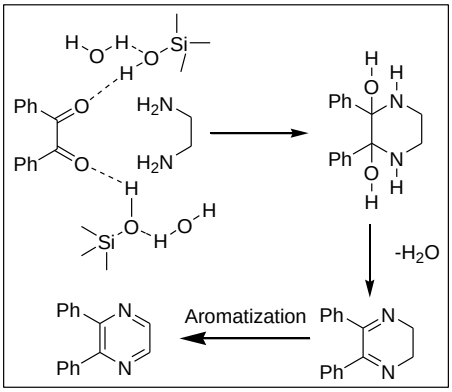


Scheme . Ⅰ.C.1. Silica-gel mediated one-pot synthesis of pyrazines from ethylenediamine and 1, 2-diketones or their analogues.

Ⅰ.C.2.Results and Discussion

In our present investigation we have selected ethylenediamine and benzil for expected transformation.We optimized time(h) for the transformation of ethylenediamine(1mmol) and benzil(1mmol) into pyrazine(Table. Ⅰ.C.1) catalyzed by silica-gel.We mixed benzil(1mmol) and ethylenediamine(2mmol) into silica-gel(2g) at 100^0C under magnetic stirrer for 6h and found no product(**entry 1,table. Ⅰ.C.2.**).Then we took ethylenediamine (1.5mmol), benzil(1.5mmol) and silica-gel(1.5g) at 50^0C and got 42% desired product.Then we conducted the reaction at room

temperature and got 75% product(**entry 3, table. Ⅰ.C.1.**) in identical condition.We added a few drops of water into silica-gel and conducted the reaction at room temperature and got even better result. Finally we optimized the reaction condition as ethylenediamine (1mmol), benzil(1mmol) and silica-gel (1g) with few drops of water and conducted the reaction at room temperature and got 87% yield(**entry 5,table. Ⅰ.C.2.**). In order to show the general applicability, we attempted the developed optimized protocol to a number of chemically diversified ketone and ethylenediamine to synthesize a library of pyrazine derivative (**Table. Ⅰ.C.3.**) and got the desired transformation in each case. The same protocol also gave excellent result (entry 20) when applied on 1, 2-diketo derivative of pentacyclic triterpenoids of lupane or friedelin skeleton (A, B or C). Moreover, it was found that silica-gel was recyclable and only one gram moistened silica-gel is much more effective in the shortest time.The progress of reaction was monitored by TLC. In the present investigation, it is observed that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the early methods and this is the main advantage of this procedure. Optimization of the reaction condition by changing the temperature, time and other condition led us to achieve only pyrazine derivatives as the sole product in (87%) isolated yield. The study also indicates that a trace amount of water on silica-gel is very much effective and a pre-calcined silica-gel is ineffective to bring about the reaction. We depicted a plausible mechanism (**Scheme. Ⅰ.C.2**)



Scheme. Ⅰ.C.2. Plausible mechanisms for the synthesis of pyrazine derivatives using moistened silica gel.

Table. Ⅰ.C.1. Optimization of time(h) for the synthesis of pyrazine from ethylenediamine(1mmol) and benzil(1mmol) catalyzed by silica-gel(1g) at room temperature

Entry	**Time (h)**	**Conversion(%)[a]**
1	12	72
2	5	42
3	7	75
4	8	76
5	**6**	**77[b]**
6	2	34
7	0.5	25

[a]Isolated yield . [b]Optimized condition

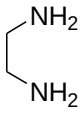
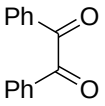
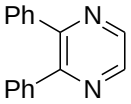
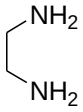
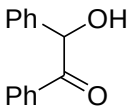
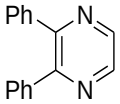
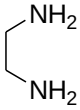
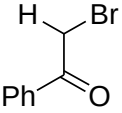
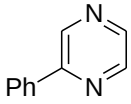
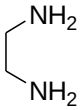
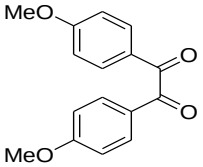
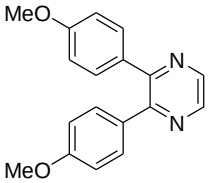
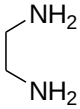
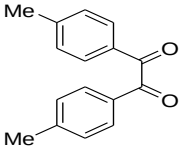
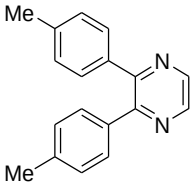
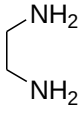
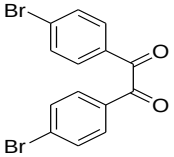
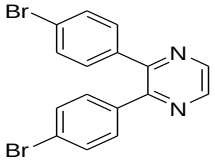
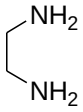
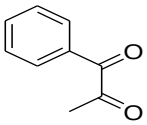
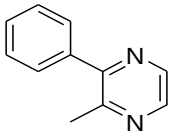
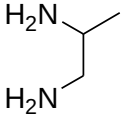
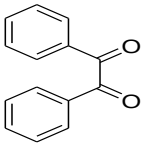
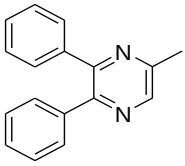
Table. Ⅰ.C.2. Optimization of reaction conditions for silica-gel catalyzed one-pot condensation of ethylenediamine (mmol) with benzil (mmol).[a]

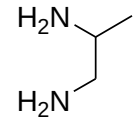
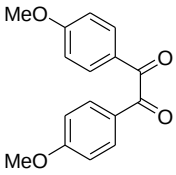
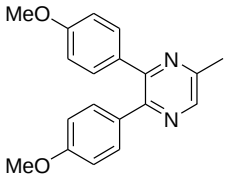
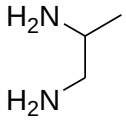
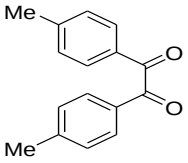
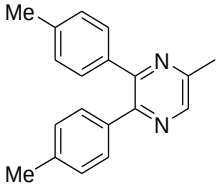
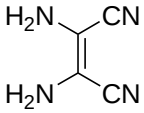
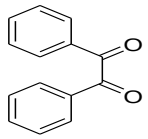
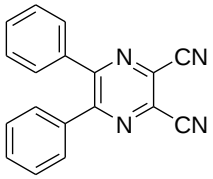
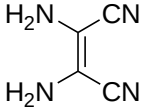
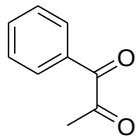
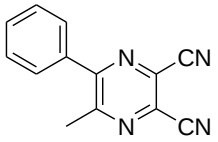
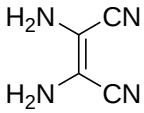
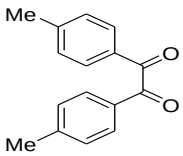
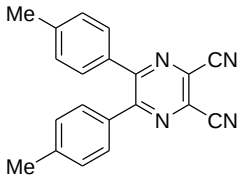
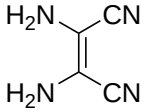
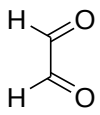
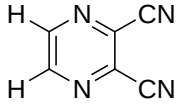
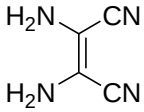
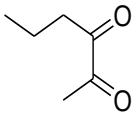
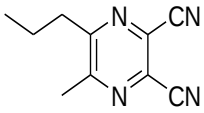
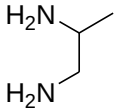
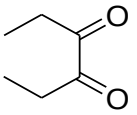
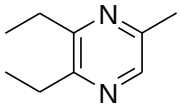
Entry	Silica-gel(g)	Temp(° C)	Solvent	Ethylenedi Amine(mmol)	Benzil(mmol)	Conversion (%)[b]
1	2	100	No	2	1	Nil
2	1.5	50	No	1.5	1.5	42
3	1.0	RT[d]	No	1.0	1.0	75
4	0.5	RT	No	1.0	1.0	62
5	**1.0**	**RT**	**water**	**1.0**	**1.0**	**87[c]**

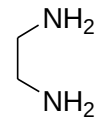
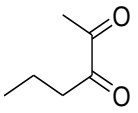
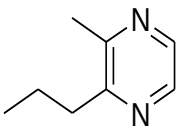
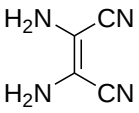
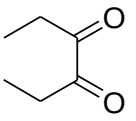
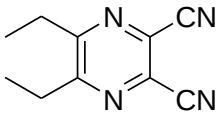
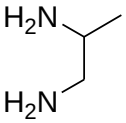
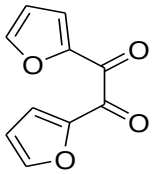
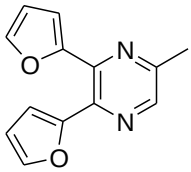
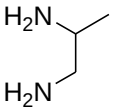
[a]Rection of benzil with ethylenediamine in silica-gel (60-120mesh); [b]Isolated yield; [c]Optimized condition; [d]Room temperature.

In order to show the general applicability, we attempted the developed optimized protocol to a number of chemically diversified ketone and ethylenediamine to synthesize a library of pyrazine derivative (**Table. Ⅰ.C.3**) and got the identical result in each case.The same protocol also gave excellent result (**entry 20, Table. Ⅰ.C.3**) when applied on 1, 2-diketo derivative of pentacyclic triterpenoids of lupine or friedelin skeleton (A, B,or C). Moreover, it was found that silica-gel was recyclable and only one gram moistened silica-gel is much more effective in the shortest time. In the present investigation, it is observed that no additional steps required to aromatize the dihydropyrazine derivatives as reported in the earlier methods and this is the main advantage of this procedure.Melting point of the known compounds are provided in supporting information.[38-39]

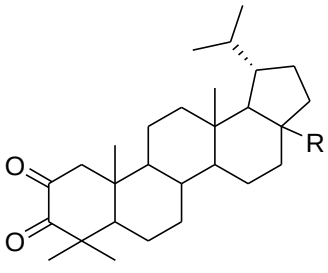
Table. Ⅰ.C.3. Silica-gel catalyzed condensation of ethylenediamine with 1, 2-dicarbonyl compounds or with α-hydroxy ketones or with α-bromo ketone at room temperature

Entry no	Ethylenediamine	1,2-dicarbonyl compound/ analogues	Time(h)	Product	Yield(%)
1			6		87
2			6		75
3			6		68
4			10		76
5			8		81
6			7		80
7			6.5		75
8			5		73

9			5.5		73
10			6		85
11			5		85
12			7		86
13			6		75
14			6.5		82
15			5.5		75
16			7		73

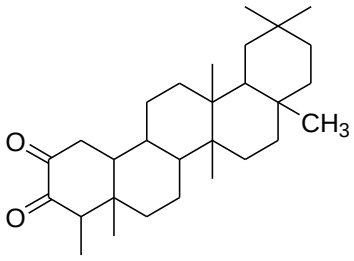
17			8		76
18			7		72
19			5.5		81
20		A/B/C	6	D/E/F	80

Note: % Yield refers to the isolated yield of all compounds. For known compounds, melting points [36-37] and for rest of the compounds respective characterization data are provided in the supporting information

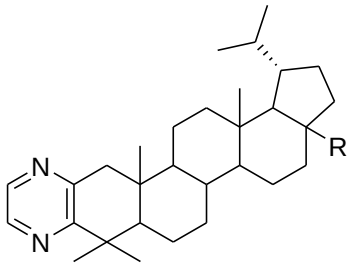


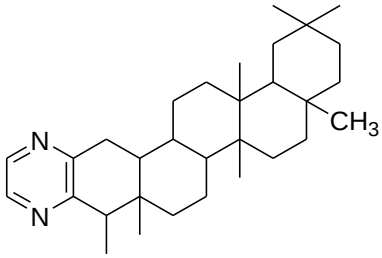
A, R= -CH_3

B, R= -$COOCH_3$



C





D, R= -CH_3 F

E, R= -$COOCH_3$

We also tested the reusability of the catalyst silica-gel (**Table. Ⅰ.C.4**). The catalyst was recovered from the reaction mixture as follows: The reaction mixture was taken in ethylacetate (2 mL), subjected to the centrifugation at 5000 rpm and removed the supernatant liquid. The residue was washed with ethylacetate followed by acetone. Drying under vacuum furnished the powder, which is identical as compared to the first-time used silica-gel.

Table. Ⅰ.C.4. Recycling of the silica-gel tested with ethylenediamine and benzil in one-pot reaction.

Entry	Recovered silica-gel(g)	Silica-gel used	Time(h)	Yield(%)
1st run	___	1g	6	87
2nd run	1g	1g	8	75
3rd run	1g	1g	7	76

Ⅰ.C.3. Experimental

Ⅰ.C.3.1. Reaction procedure and purification

Our studies began with the reaction of ethylenediamine and benzil in the presence of silica-gel. We set-up the reaction by adding the reacting components i.e mixture of ethylenediamine (1mmol) and benzil (1mmol) to the silica-gel(1g) in a mortar, then the mixture was grinded for a few minutes and finally was transferred to a 50 ml round-bottom bottle and was kept under magnetic stirring at room temperature for 6hrs. The completion of reaction was monitored by TLC. Ethylacetate (3×15ml) was added to the reaction mixture and the extract was filtered through anhydrous Na_2SO_4. Finally 2, 3-diphenyl pyrazine was separated by column chromatography over silica-gel(60-120 mesh) where pet-ether and ethylacetate mixture was used as eluent. The desired isolated products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The reaction condition was optimized in **Table 1**.

Ⅰ.C.3.2. Spectroscopic measurements

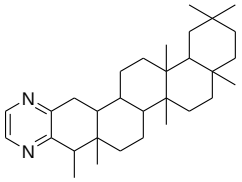
IR spectra was recorded on KBr disks and nujol on Perkin-Elmer FT IR spectrometer. H NMR was recorded on 300 MHz C NMR was recorded on 75 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

Ⅰ.C.4. Conclusion

In conclusion, the author has demonstrated the synthesis of bio-active scaffold pyrazine derivatives directly from ethylenediamine and 1, 2-diketone or with its analogues via one-pot condensation reactions using silica-gel as the catalyst under complete metal-free conditions. The conditions are

straightforward, mild and no other side-products are obtained. Green process of preparation of pyrazines from ethylenediamine and keto-compounds are developed that could override existing metal-catalyzed reaction conditions.

Ⅰ.C.5. Characterization data

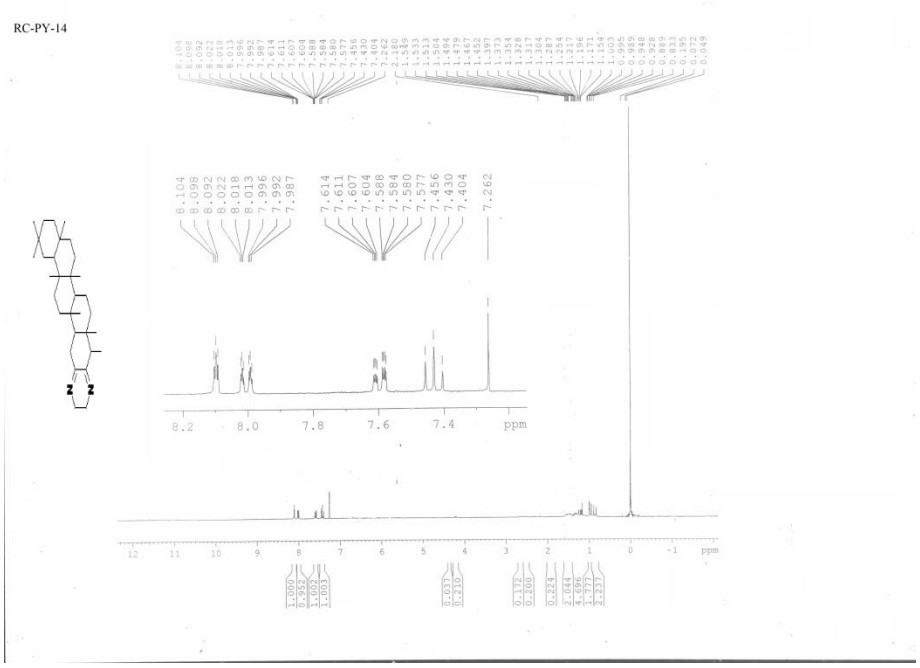


(1) 1, 4-pyrazine derivative of friedelin

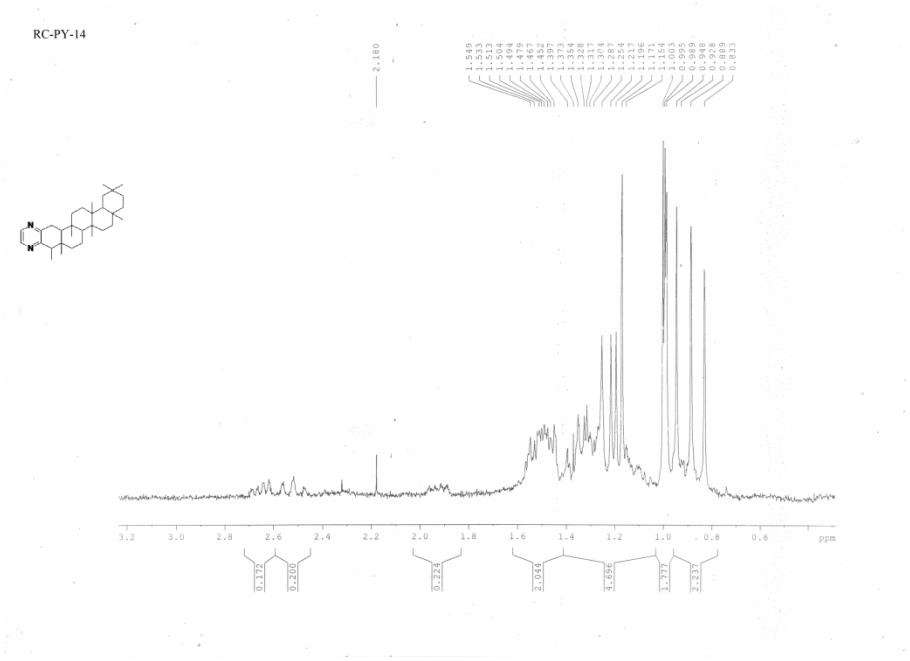
^{13}C NMR($CDCl_3$, 75MHz) : δ 150.8, 150.9, 141.4, 142.3

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.82-1.22(7s, 21H,7t CH_3), 0.99(d, J=6.5 Hz), 8.40 and 8.27 (d, 2H, J=3Hz).

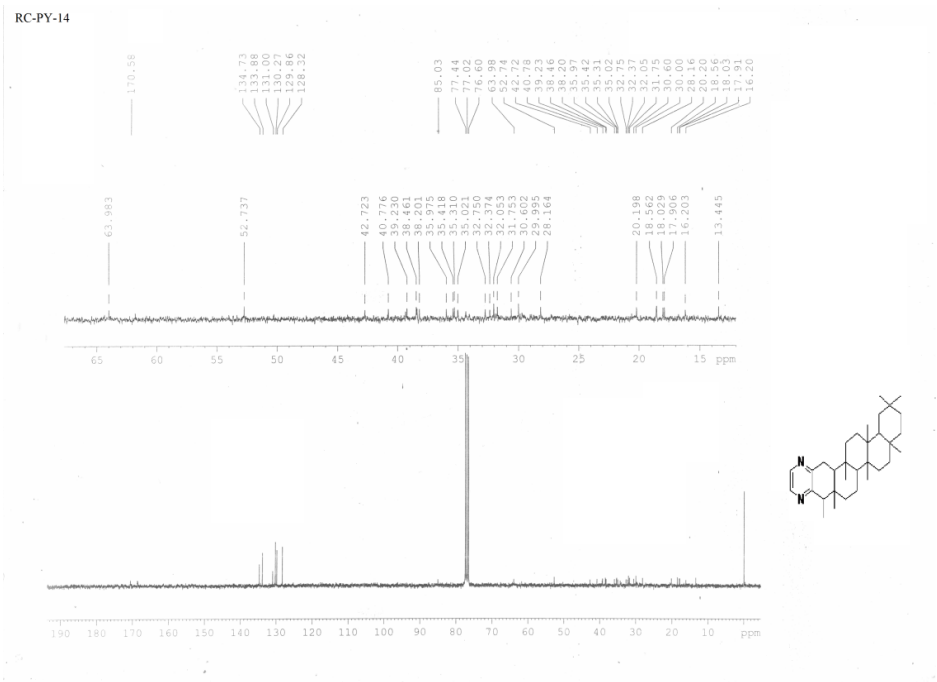
Ⅰ.C.6. Supporting Spectra



Ⅰ.C.6.1. ^{1}H NMR spectrum of pyrazine derivative of friedelin



I .C.6.2. Expanded ^{1}H NMR spectrum of pyrazine derivative of friedelin



I .C.6.3. ^{13}C NMR spectrum of pyrazine derivative of friedelin

Rest characterization data and supporting spetras are attached in Ⅰ-B-6

Ⅰ.C.7. References

[1]. (a) Brahmachari, G.*Green Synthetic Approaches for Biologically Relevant Heterocycles, Elsevier*: Oxford, **2014**, 632; (b) Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern Heterocyclic Chemistry*, John Wiley & Sons: Germany, **2011**; 1

[2]. Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K., P. *Advances in Biological Research*, **2011**, 5, 120.

[3]. Maga, J. A.; Sizer, C. E. *J. Agric. Food. Chem*, **1973**, 21, 22.

[4]. Palacios, F.; Retana, A. M. O.; Munain, R. L. *Org. Lett.*, **2002**, 14, 2405.

[5]. Oldham, N. J.; Morgan, E. D. *J. Chem. Soc*., Perkin Trans. **1993**, 1, 2713.

[6]. Ghosh, P.; Mandal, A. *Green Chemistry Letters and Reviews*, **2012**, 5, 127.

[7]. Zhang, Y.; Wade, M. M.; Scorpio, A.; Zhang, H.; Sun, Z.*Journal of Antimicrobial Chemotherapy*. **2003**, 52, 790.

[8]. Lo´ pez-Anton, N.; Rudy, A.; Barth, N.; Schmitz, L. M.; Pettit, G. R.; Schulze-Osthoff, K.; Dirsch, V. M.; Vollmar, A. M. *The Journal of Biological Chemistry*. **2006**, 281, 33078.

[9].Dubuissona, M. L.; Reesa, J. F.; Marchand-Brynaert, J. *Mini Rev. Med.Chem*., **2004**, 4,421.

[10]. Wu, X.A.; Zhao, Y.M.; Yu, N.J. *J. Asian Natural Products research*, **2007**, 9, 437.

[11]. Wheeler, G. P.; Bowden, B. J.; Temple, C.; Adamson, D. J. *Can Res*., **1983**, 43, 3567.

[12]. Fulda, S.; Jeremias, I.; Pietsch, T.; Debatin, K. M. *Int. J. Cancer.* **1999**, 82, 435.

[13]. Urban, M.; Sarek,J.; Kvasnica, M.; Tislerova, I.; Hajduch, M. *J. Nat. Prod.*, **2007,** 70, 526.

[14]. Taunk, A.; Mishra. R. *International Journal of Scientific Research*. **2014,** 3, 2277.

[15]. Fales, H.M.; Blums, M.S.; Southwick, E.W.; William, D.L.; Roller P.P.; Don, A.W. *Tetrahedron.* **1988**, 44, 5045.

[16]. Wheeler, J.W.; Avery, J.; Olubajo, O.; Shamim, M.T.; Storm, C.B. *Tetrahedron,* **1982**, 38, 1939

[17]. Goel, R.; Luxami, V.; Paul, K. *Org. Biomol. Chem*. **2015**, 13, 3525.

[18]. (a) Darabi, H. R.; Mohandessi, S.; Aghapoor, K.; Mohsenzadeh, F. *Catal. Commun*.**2007**, 8, 389. (b) Mohsenzadeh, F.; Aghapoor, K.; Darabi, H. R. *J. Braz. Chem. Soc***. 2007**, 18. 279 (c) Ghosh, P.; Chakraborty. *J. Chem. Pharm. Res***. 2010**, 2, 154. (d) Giardina, D.; Gulini, U.; Massi, M.; Piloni, M.G.; Pompei, P.; Rafaiani, G.; Melchiorre, C. *J. Med. Chem*. **1993**, 36, 690.

[19]. Aston, J.G.; Peterson, T. E.; Holowchak, J. *J.Am.Chem.Soc*. **1934**, 56, 153.

[20]. Nicole, S. Y. L.; Sunggak, K.; Cheol-Min, P. *Org. Lett*. **2015**, 17, 395.

[21]. Hasrat, A,; Van Lier, J.E.*Tetrahedron Letters*. **2012**, 53, 4824.

[22]. Okada J. Japan Patent 49, 25, 947, 1974.

[23]. Korea Research Institute of Chemical Technology. Japan Patent 05, 52829, 1993.

[24]. Toti Electro-Chemical Co. Japan Patent 55, 50024**,** 1980.

[25]. Koei Chemical Co. Japan Patent 53, 43512, 1978.

[26]. Koei Chemical Co. Japan Patent 09, 48763**,** 1997.

[27]. Koei Chemical Co. Japan Patent 49, 101391, 1974.

[28]. BASF, A.-G. Japan Patent 05, 35140, 1993.

[29]. Raw, S.A.; Wilfred C.D.; Taylor, J.K. *Chem. Commun***. 2003**, 39, 2286.

[30]. Liyan, F.; Wen, C.; Changtao, Q. *Tetrahedron Letters.* **2013**, 54, 231.

[31]. Pradhan, B.P.; Ghosh, P. *Ind. J. Chem*., **1993**, 32B, 590.

[32]. Katritzky, A.R. *Adv. Heterocyclic Chem*. **2003**, 14, 113.

[33]. Allais, C.; Grassot, J. -M., Rodriguez, J.;Constantieux, T. *Chem. Rev*., **2014**, 114, 10829.

[34]. Ghosh, P.; Chakraborty, R.R. *Letters in Organic Chemistry*. **2017**, 14, 566.

[35]. Chari, M. A.; Shobha, D.; Mukkanti, K. *Catal. Commun*. **2006**, 7, 787.

[36]. Badin,G.B. *Chemistry of Heterocyclic compounds*. 1982, 41

[37]. Khodaee, Z.; Yahyazadeh, A.; Mahmoodi, N. O.; Zanjanchi, A.M.; Azimi, V. *Journal of Molecular Structure*. **2012**, 1029, 92.