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A convenient & general procedure for the preparation of Methyl-4-phenyl-3-oxo butyrate derivatives

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ABSTRACT

A convenient and general procedure for the preparation of methyl-4-phenyl-3-oxo butyrate derivatives is accomplished by the treatment of benzyl cyanides with potassium methyl malonate & anhydrous $ZnCl_2$ in EDC. The protocol is applied successfully to various phenylacetonitriles by decarboxylative Blaise reaction [1].

Keywords: Benzyl cyanides, Potassium methyl malonate, anhydrous $ZnCl_2$, EDC, Decarboxylative Blaise reaction.

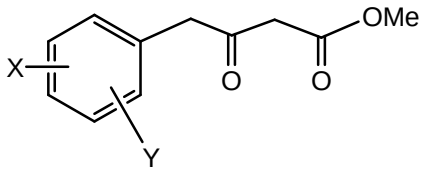
INTRODUCTION

Methyl-4-phenyl-3-oxo butyrate derivatives (β-keto esters) and their precursors β-aminoacrylates are among the most important intermediates in organic synthesis and medicinal chemistry. Several methods have been developed previously by acylation of acid chlorides with diethyl malonate followed by selective partial hydrolysis and subsequent decarboxylation of one of the two-ester groups in the acylated malonate intermediate [2, 3]. By the same methodology β-ketoesters are prepared using ethyl malonic acid [4, 5], meldrum's acid [6, 7], on acid chlorides or acids in the presence of magnesium chloride and pyridine or triethyl amine or carbonyldiimidazole. β-ketoesters are also prepared by treating benzonitriles with potassium ethyl malonate and zinc [8, 9, 10] based on Blaise reaction.

A century old Blaise reaction is an important method for the preparation of β-keto esters and their precursors. β-keto ester functional group in the product is highly versatile for further transformations and moreover the Blaise reaction can be truncated to produce β-amino-α, β-unsaturated esters, which are useful for the synthesis of heterocycles and β-amino acids. However in spite of its straightforward introduction of versatile functionalities from nitrile group, its use in synthetic chemistry is limited due to problems of low yield, narrow scope and undesired side reactions. These early problems are greatly improved by Kishi's modifications

that use activated zinc. Additional useful protocols like ultrasonic assistance [11] and zinc oxide addition [12] in the Blaise reaction are more advantageous.

Although these modifications are significant improvements over the original procedure, there is a substantial need for further refinement for synthesizing 4-phenyl-3-oxo butyrate derivatives starting from phenylacetonitriles.



1

MATERIALS AND METHODS

^{1}H & ^{13}C NMR spectra are recorded using a Bruker 400 Spectrometer (400 & 100 MHz respectively) with TMS as internal standard. IR spectra are recorded on Perkin Elmer Spectrophotometer as KBr pellets or neat. Analytical TLC is conducted on E-Merck 60F254 aluminum-packed silica gel plates (0.2mm). Developed plates are visualized using UV light or Iodine chamber. HPLC spectra are recorded on shimadzu 2010.

General Procedure for the synthesis of Methyl-4-phenyl-3-oxo butyrate derivatives (1a-m).
To a stirred solution of phenylacetonitriles **2** (1.0 M), potassium methyl malonate **3** (2.0 M) in ethylene dichloride under nitrogen atmosphere is added anhydrous zinc chloride (2.0 M) at room temperature. The temperature of the reaction mixture is raised to reflux temperature (80 – 85°C) and stirred for 60 to 90 hours. The completion of the reaction is checked on precoated silica gel plates and observed under UV light or Iodine vapors. After cooling the reaction mixture to ambient temperature (20 - 25°C) and then treating with water the organic layer is separated. The aqueous layer is extracted with EDC. The combined organic portions were washed with water (till pH comes to neutral) and then dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue in desired solvent furnished the methyl-4-phenyl-3-oxo butyrate derivatives.

Synthesis of Methyl-4-(2,4,5-trifluorophenyl)-3-oxo butyrate **(1a)**
White crystalline powder. Yield: 52 %; HPLC Purity: 99 %; mp: 39-41°C; FT-IR (cm^{-1}): 1737 (C=O of ester), 1635 (C=O of ketone); ^{1}HNMR (ppm, $CDCl_3$): δ 3.5 (s, 2H, $-CH_2$), δ 3.7 (s, 3H, $-OCH_3$), δ 3.8 (s, 2H, $-CH_2$), δ 6.9 (m, 1H, Ar), δ 7.0 (m, 1H, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 41.91, 48.28, 52.41, 105.43, 116.67, 119.25, 145.42, 148.01, 150.62, 154.69, 157.08, 167.09, 172.64, 174.20 and 197.89; ESI-MS (m/z %): 247.4 (M+1).

Synthesis of Methyl-4-(4-fluorophenyl)-3-oxo butyrate **(1b)**
Yellow Oil. Yield: 55 %; HPLC Purity: > 90 %; FT-IR (cm^{-1}): 1749 (ester C=O), 1718 (C=O of ketone); ^{1}HNMR (ppm, $CDCl_3$): δ 3.4 (s, 2H, $-CH_2$), δ 3.7 (s, 3H, $-OCH_3$), δ 3.8 (s, 2H, $-CH_2$), δ 7.0 (t, 2H, *J* = 8.6 Hz, Ar), δ 7.1 (dt, 2H, *J* = 2.0 & 6.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 47.87, 48.63, 52.12, 115.52, 128.79, 129.50, 130.59, 131.01, 160.66, 167.29 and 199.99.

Synthesis of Methyl-4-(4-chlorophenyl)-3-oxo butyrate **(1c)**
Pale yellow crystalline powder. Yield: 63 %; mp: 48-50 °C; FT-IR (cm^{-1}): 1742 (C=O of ester), 1714 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.4 (s, 2H, $-CH_2$), δ 3.7 (s, 3H, $-OCH_3$), δ 3.8 (s, 2H, $-CH_2$), δ 7.1 (dd, 2H, *J* = 2.0 & 6.5 Hz, Ar) and δ 7.3 (dd, 2H, *J* = 2.0 & 6.5 Hz, Ar); ^{13}CNMR

($CDCl_3$/TMS): δ 48.03, 48.96, 52.33, 128.86, 130.82, 131.45, 133.28, 167.29 and 199.63; ESI-MS (m/z %): 227.2 (M+1) & 229.3 (M+2).

Synthesis of Methyl-4-(4-bromophenyl)-3-oxo butyrate **(1d)**
Pale yellow crystalline powder. Yield: 48 %; mp: 48-50 °C; HPLC purity: 100 %; FT-IR (cm^{-1}): 1743 (ester C=O), 1714 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.4 (s, 2H, $-CH_2$), δ 3.72 (s, 3H, $-OCH_3$), δ 3.79 (s, 2H, $-CH_2$), δ 7.07 (d, 2H, *J* = 8.0 Hz, Ar), δ 7.46 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 48.05, 49.03, 52.35, 121.36, 131.19, 131.61, 131.81, 131.97, 167.29 and 199.55.

Synthesis of Methyl-4-(2-chlorophenyl)-3-oxo butyrate **(1e)**
Pale Yellow Oil. Yield: 50 %; HPLC purity: > 98 %; FT-IR (cm^{-1}): 1749 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.52 (s, 2H, $-CH_2$), δ 3.73 (s, 3H, $-OCH_3$), δ 3.97 (s, 2H, $-CH_2$), δ 7.21-7.26 (m, 3H, Ar), 7.37-7.40 (m, 1H, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 47.47, 48.35, 52.28, 127.03, 128.91, 129.49, 131.76, 134.34, 167.32 and 198.99.

Synthesis of Methyl-4-(2-bromophenyl)-3-oxo butyrate **(1f)**
Pale Yellow Oil. Yield: 52 %; HPLC purity: > 97 %; FT-IR (cm^{-1}): 1748 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.53 (s, 2H, $-CH_2$), δ 3.74 (s, 3H, $-OCH_3$), δ 4.0 (s, 2H, $-CH_2$), δ 7.16 (dt, 1H, *J* = 2.0 & 8.0 Hz, Ar), δ 7.23 (dd, 1H, *J* = 2.0 & 8.0 Hz, Ar), δ 7.58 (d, 1H, *J* = 8.0 Hz, Ar), δ 7.58 (d, 1H, *J* = 8.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 48.40, 49.83, 52.20, 124.83, 127.47, 129.0, 131.73, 132.69, 133.65, 167. 24 and 198.88.

Synthesis of Methyl-4-(3-chlorophenyl)-3-oxo butyrate **(2g)**
Pale Yellow Oil. Yield: 50 %; HPLC purity: > 98 %; FT-IR (cm^{-1}): 1749 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.52 (s, 2H, $-CH_2$), δ 3.73 (s, 3H, $-OCH_3$), δ 3.97 (s, 2H, $-CH_2$), δ 7.21-7.26 (m, 3H, Ar), δ 7.37-7.40 (m, 1H, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 47.47, 48.35, 52.28, 127.03, 128.91, 129.49, 131.76, 134.34, 167.32 and 198.99.

Synthesis of Methyl-4-(4-methylphenyl)-3-oxo butyrate **(2h)**
Pale Yellow Oil. Yield: 40 %; HPLC purity: > 96 %; FT-IR (cm^{-1}): 1749 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 2.32 (s, 3H, $-CH_3$), δ 3.44 (s, 2H, $-CH_2$), δ 3.70 (s, 3H, $-OCH_3$), δ 3.76 (s, 2H, $-CH_2$), δ 7.08 (d, 2H, *J* = 8.0 Hz, Ar), δ 7.14 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 21.08, 47.88, 49.71, 52.34, 89.75, 129.32, 129.42, 129.59, 130.11, 137.08, 167.61 and 200.66.

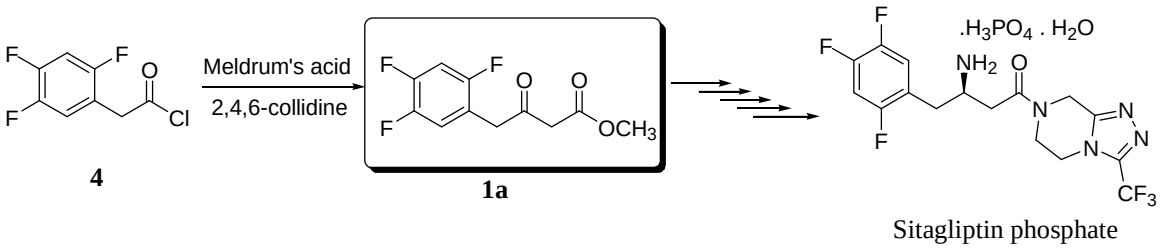
Synthesis of Methyl-4-(3,5-dimethylphenyl)-3-oxo butyrate **(2i)**
Pale Yellow Oil. Yield: 45 %; HPLC purity: > 93 %; FT-IR (cm^{-1}): 1747 (ester C=O), 1716 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 2.29 (s, 6H, 2($-CH_3$), δ 3.43 (s, 2H, $-CH_2$), δ 3.71 (s, 3H, $-OCH_3$), δ 3.73 (s, 2H, $-CH_2$), δ 6.81 (s, 1H, Ar), δ 6.85 (s, 1H, Ar), δ 6.91 (s, 1H, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 21.12, 46.78, 49.51, 51.14, 127.75, 128.32, 129.42, 129.59, 137.01, 137.18, 170.61 and 200.66.

Synthesis of Methyl-4-(4-methoxyphenyl)-3-oxo butyrate **(2j)**
Pale Yellow Oil. Yield: 47 %; HPLC purity: > 93 %; FT-IR (cm^{-1}): 1749 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.44 (s, 2H, $-CH_2$), δ 3.70 (s, 3H, $-OCH_3$), δ 3.75 (s, 2H, $-CH_2$), δ 3.79 (s, 3H, $-OCH_3$), δ 6.87 (d, 2H, *J* = 8.0 Hz, Ar), δ 7.11 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 47.72, 49.06, 52.22, 55.13, 113.91, 114.18, 125.05, 130.17, 130.49, 158.78 and 167.53.

Synthesis of Methyl-4-(3,4-dimethoxyphenyl)-3-oxo butyrate **(2k)**
Pale Yellow Oil. Yield: 39 %; HPLC purity: > 90 %; FT-IR (cm^{-1}): 1748 (ester C=O), 1718 (keto C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.46 (s, 2H, $-CH_2$), δ 3.71 (s, 3H, $-OCH_3$), δ 3.76 (s, 2H, $-CH_2$), δ 3.87 (s, 6H, 2($-OCH_3$), δ 6.71 (d, 1H, *J* = 2.0 Hz, Ar), δ 6.75 (d, 1H, *J* = 2.0 & 8.0 Hz, Ar), δ 6.82 (d, 1H, *J* = 8.0 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 47.51, 49.38, 52.10, 55.64, 111.22, 112.28, 121.58, 125.39, 148.13, 148.93, 167.43 and 200.60.

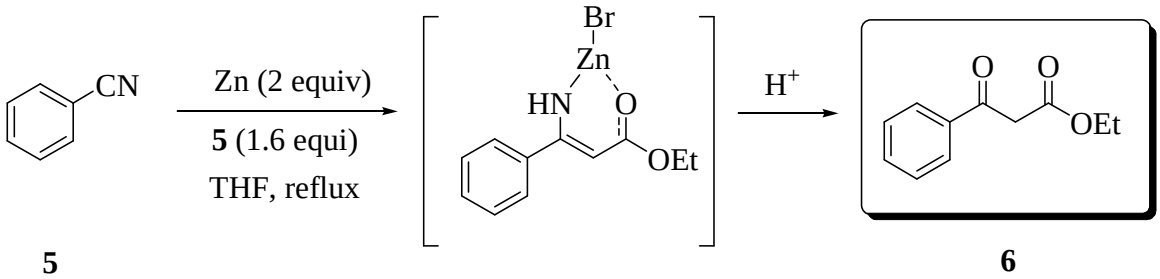
RESULTS AND DISCUSSION

4-phenyl-3-oxo butyrate derivatives **1** are the key structural unit of many potent molecules such as gliptins **(Scheme 1)**[13] and quinolone antibiotics [14]. Most of the reported syntheses to construct this structural segment proceeded from a common synthetic approach, the reaction of phenyl acetyl chloride with meldrum's acid or magnesium enolate of diethyl malonate to give the diester intermediate, which is partially hydrolyzed and decarboxylated to get **1**. But, this process is tedious by the selective partial hydrolysis of the diester intermediate.

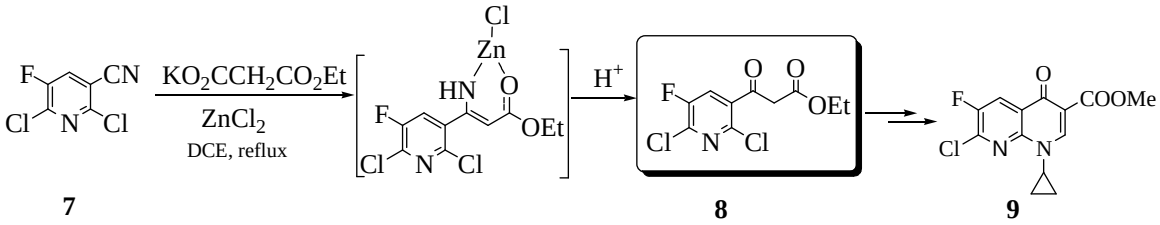


Scheme 1: Synthesis of sitagliptin phosphate

Shin et al. have widely used the application of Blaise reaction in an expedient synthesis of a statin **(Scheme 2)**[8] and quinolone antibiotic intermediates **(Scheme 3)** i.e. Ethyl 2,6-dichloro-5-fluoronicotinoylacetate **8** which is converted to Enoxacin, Tosufloxacin, Trovafloxacin, Gemifloxacin etc.

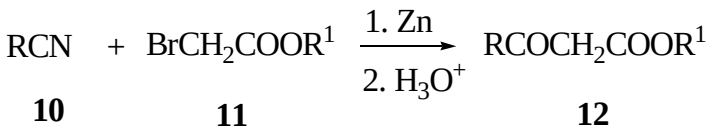


Scheme 2: Synthesis of statin intermediate from benzonitriles



Scheme 3: Synthesis of quinolone antibiotic intermediate

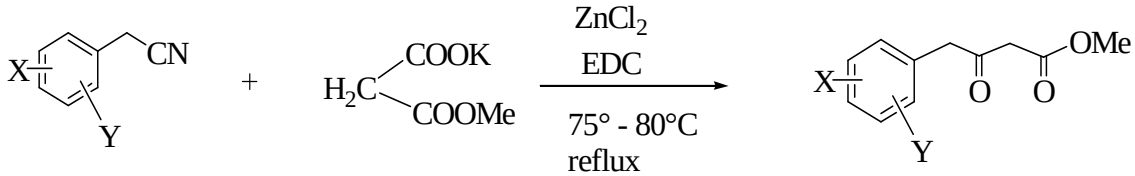
For more than a decade many developments were taken place in the construction of C-C bonds in organic synthesis in an incremental manner through pioneering studies. Wittig reaction, Diels-Alder reaction, Friedel-crafts reaction, Reformatsky reaction, Heck reaction, Suzuki coupling etc. are those reactions named after their discoveries. Similar type of reaction is the Blaise reaction **(Scheme 4)** in which a nitrile **10** is reacted with zinc enolate of ethyl bromoacetate **11** to give the required **12** (β-keto ester).



Scheme 4: Synthesis of β-keto ester through Blaise reaction

In this paper we report the preparation of methyl-4-phenyl-3-oxo butyrate derivatives **1a-m** from phenylacetonitriles by treatment with potassium methyl malonate and zinc chloride. Most of the products are oils and some are crystalline solids with definite melting points. All these derivatives are characterized by their spectral characterization. Although the reaction is effective with benzonitriles, but showed moderate reactivity in case of benzyl cyanides. In most of the cases the reaction did not go to completion. Un reacted starting material is present even after adding excess of zinc chloride, potassium methyl malonate and refluxing for 60 hours. The unreacted starting material (10 to 40%) is recovered and repeated the conversion successfully.

In contrast to the more feasibility of the decarboxylative Blaise reaction in benzonitriles, the initiation and rate of reaction is very slow in case of benzyl cyanides. No product formation is observed for the initial 3 hours of reaction.To force the decarboxylation reaction in benzyl cyanides, the reaction is conducted with 0.5, 1.0, 2.0, 2.5 and 3.0 equivalents of zinc chloride along with 1.0, 1.5, 2.0, 2.5 and 3.0 equivalents of potassium methyl malonate respectively. Among these 2:2 equiv ratios of zinc chloride and potassium methyl malonate showed better conversion. The conversion is also tried with other Lewis acids like magnesium chloride and copper chloride using ethylene dichloride as the reaction medium. Copper chloride showed very low reactivity (only 10%) and magnesium chloride did not show any of the desired reactivity.



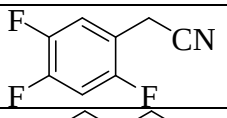
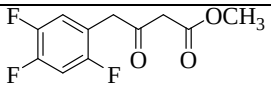
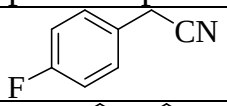
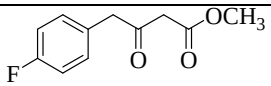
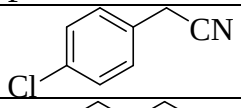
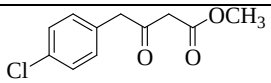
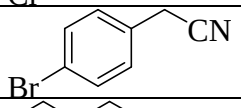
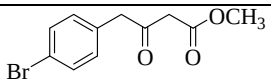
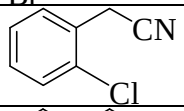
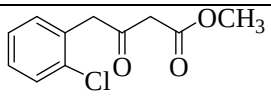
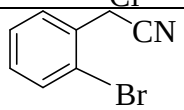
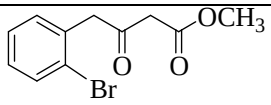
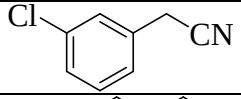
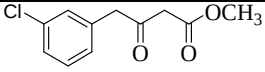
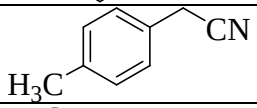
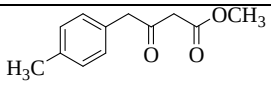
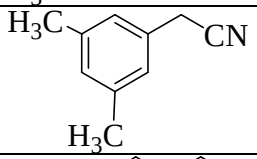
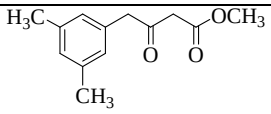
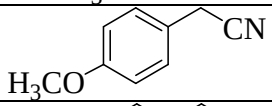
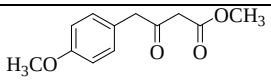
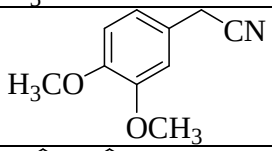
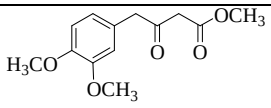
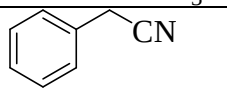
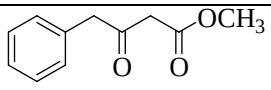
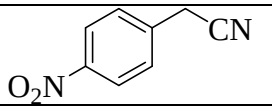
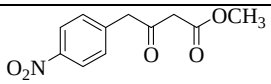
2
Phenylacetonitrile

3
Potassium methyl malonate

1
Methyl-4-phenyl-3-oxo butyrate

Scheme 5: Synthesis of methyl-4-phenyl-3-oxo butyrate derivatives

Table 1. Methyl-4-phenyl-3-oxo butyrate derivatives from phenylacetonitriles 1a-m

Entry	Phenylacetonitrile [STM]	Product	Time (Hrs)	M.P (°C)	HPLC Purity (%)	Recovered STM (%)	Yield (%)
1a			80	39 - 41	99	10	52[a]
1b			60	Oil	90	32	55[a]
1c			85	42 – 43	97	15	63[a]
1d			80	48 - 49	100	29	48[a]
1e			90	Oil	98	28	50[a]
1f			95	Oil	97	26	52[a]
1g			80	Oil	97	30	47[a]
1h			86	Oil	96	42	40[a]
1i			90	Oil	93	20	45[a]
1j			70	Oil	93	40	47[a]
1k			85	Oil	90	28	39[a]
1l			80	Oil	47	45	47[b]
1m			80	-	-	99	NR

a. Isolated yield, b. % conversion in HPLC. NR = No Reaction

CONCLUSION

In conclusion, we have demonstrated a mild and general process for the conversion of phenylacetonitriles to methyl-4-phenyl-3-oxo butyrate derivatives, compared to other commercial processes, which are having drawbacks of lower temperature conditions, exothermic nature, use of expensive materials, lachrymatory bromoacetates and less stable acid chlorides. And the obtained derivatives are important building blocks for many heterocyclic derivatives and potent molecules.

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