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Research Article

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Synthesis of aryl {4-[({5-[3-(methylsulfonyl)phenyl]pyrazin-2-yl}-oxy)methyl]piperidin-1-yl}methanones

B. Sriramudu*, B. Satyanarayana, P. Muralikrishna and D. Ramachandran

Department of Chemistry, Acharya Nagarjuna University, Guntur, (A.P), India

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ABSTRACT

Pyrazine nucleus potent biological activities with remarkable pharmaceutical importance and some of their derivatives occur as natural products. In view of these findings, it made interest to synthesize 2-(piperidin-4-ylmethoxy) pyrazines derivatives by the condensation of 2-[3-(methylsulfonyl) phenyl]-5-(piperidin-4-ylmethoxy) pyrazine with various aromatic acid chlorides in the presence of diisopropyl amine (DIPA).

Keywords: 2-(piperidin-4-ylmethoxy) pyrazines, aromatic acid, diisopropyl amine, synthesis

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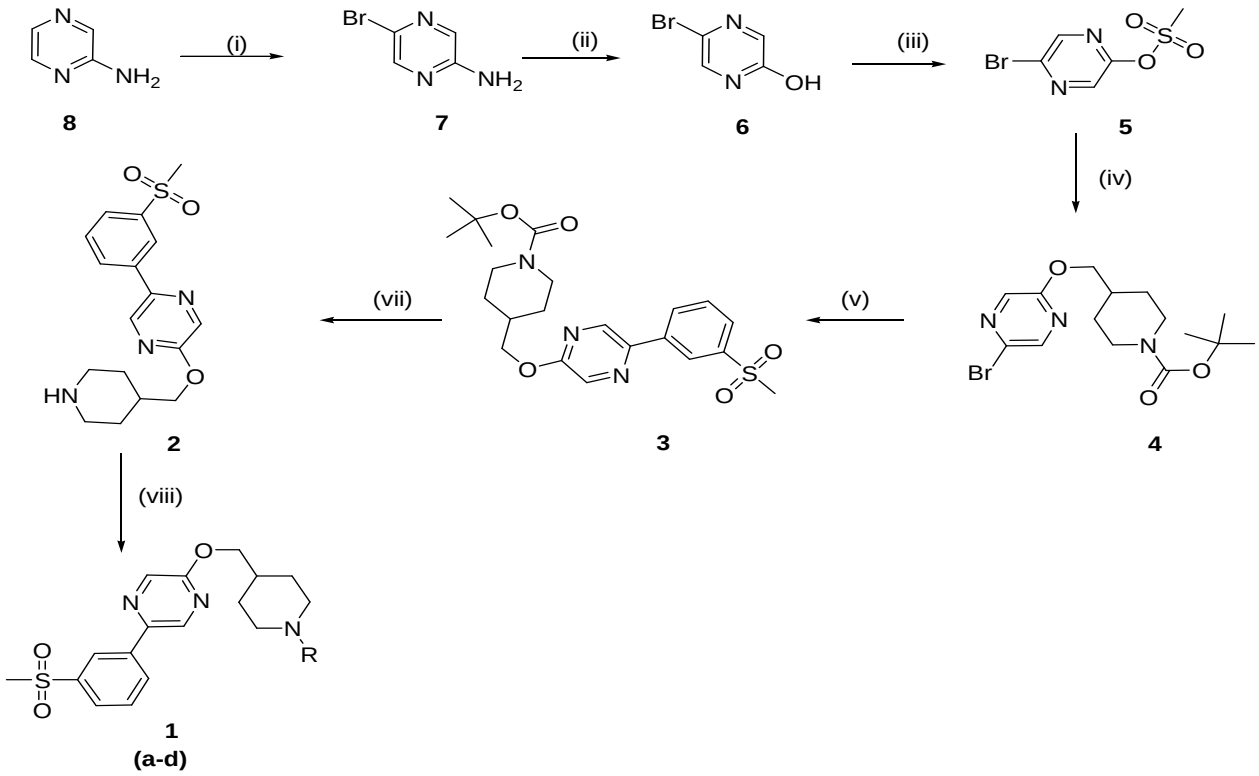
INTRODUCTION

Pyrazine contains two nitrogen atoms in its aromatic ring[1]. Pyrazine play an important role as intermediates for perfumes[2], pharmaceuticals, agricultural chemicals[3] and food spices. Especially, amides and sulfonamides of pyrazines are being used as anti-tuberculosis, nutrition supplement, insecticides, fungicides dyes and pigments[4].

In general pyrazine is prepared by the catalytic reaction of diamines with dioles in a vapour phase, dehydrogenation of piperazine or dealkylation of methyl pyrazine. Pyrazine and their derivatives form an important class of compounds present in several natural flavors and complex organic molecules, it is also responsible for flavour in foodstuffs, like cheese, tea coffee, cooked meats nice aroma[5]. Over recent years there has been an increasing interest in the chemistry of pyrazine derivatives because of their biological significance. L. E. Seitz[6] have synthesized and evaluated antimycobacterial activity of pyrazine derivatives **(1)**. H. Foks[7] have synthesized and screened antibacterial activity of 1*H*-pyrazolo [3, 4-*b*] pyrazine derivatives such as Analgesic[8], Antibacterial[9], Antifungal[10], Anti-inflammatory[11], Antiviral[12], Anticancer [13] and Anti HIV [14]. The primary goal of the our research work is to find and develop new chemical entities (NCEs) which can be used against untreatable diseases, or which have superior properties when compared to currently available drugs. As pyrazine nucleus and some of their derivatives possesses potent pharmaceutical and biological, it made interest for the authors to synthesize 2-(piperidin-4-ylmethoxy) pyrazines derivatives by the condensation of 2-[3-(methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acid chlorides in the presence of diisopropyl amine (DIPA), as shown in reaction scheme. All the synthesized compounds by the author have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy.



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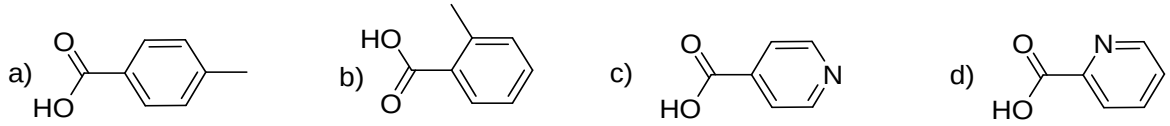


(i) NBS/Dichloromethane (ii) $NaNO_2/H_2SO_4$ (iii) CH_3SO_2Cl/ DIPA, Dichloromethane (iv) tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate/ potassium carbonate (v) $Pd(PPh_3)4$, K_2CO_3/ 3 (methylsulfonyl) phenylboronic acid (vi) 2N HCl (vii) HBTU, DIPA / R-COOH

EXPERIMENTAL SECTION

Preparation of 5-Bromopyrazin-2-amine (7)

To the cooled solution of 2-aminopyrazine (10.0 g, 0.105 mol) in dry dichloromethane (DCM) (250mL), *N*-bromosuccinamide (18.72g, 0.105mol) was added portion wise. The mixture was stirred at 0^oC for 24 hour. The reaction was monitored on thin layer chromatography (TLC). After completion of the reaction, saturated aqueous solution of sodium carbonate was added (200 ml) to quench the reaction. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the resulting crude product was purified by column chromatography on silica gel (Eluent: 2 : 8 = Ethylamine : Hexane) to obtain pure product.

Yield: 70 %, MP: 133-135^{o}C; MS: m/z = 174, 176 [M], [M] $^{+2}$

Preparation of 5-Bromopyrazin-2-ol (6)

Sodium nitrite (8.9 g, 0.129 mol) was added portion wise with constant stirring to concentrated H_2SO_4 (49 mL) at 0^oC and the mixture was warmed to dissolved the solid. The mixture was cooled to 5^oC. To this a solution of 5-bromopyrazin-2-amine (15.0 g, 0.086 mol) in concentrated H_2SO_4 (71mL) was added slowly. Later the reaction mixture was stirred below 5^oC for 30 minute and warmed to 40^oC for 2hrs. The reaction mixture was poured onto crushed ice and the aqueous solution was extracted with ethyl acetate (250mL x 3) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the solid product so obtained was subjected to spectral analysis.

Yield: 75%, MP: 80-82^{o}C; MS: m/z = 174.6, 176.5 [M], [M] $^{+2}$

Preparation of 5-Bromopyrazin-2-yl methanesulfonate (5)
To a stirred cooled (ice bath) solution of 5-bromopyrazin-2-ol (5.0 g, 0.028 mol) in dry DCM (25 mL), DIPA (5.65 g, 0.056 mol) and CH_3SO_2Cl (2.80 ml, 0.034 mol) was added dropwise in solution at 0^oC. The reaction mixture was stirred for 2 hour at room temperature (monitored by TLC), and the solvent was removed *in vacuo*. The product was filtered, washed with water and dried to give analytical pure product which is subjected to spectral analysis.
Yield: 85 %, MP 85-87 ^oC; MS: m/z = 253, 255 [M], [M] $^{+2}$

Preparation of *tert-butyl 4-((5-bromopyrazin-2-yloxy) methyl) piperidine-1-carboxylate* (4):
To a stirred suspension of K_2CO_3 (3.036g, 0.022mol) and 5-bromopyrazin-2-yl methanesulfonate (3.0 g, 0.011 mol) in dry DMF (30 ml), *tert*-butyl 4- (hydroxymethyl) piperidine-1-carboxylate (2.54g, 0.011 mol) was added. Later the solution was heated on a water bath for 2 hrsour (monitored by TLC). The reaction mixture was poured onto crushed ice, to obtain and is finally filtered, washed with pure distilled water to give pure product.
Yield: 80 %, MP: 99-101^oC; MS: m/z = 373, 374 [M]$^{+1}$, [M] $^{+2}$.

Preparation of *tert-butyl 4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidine-1-carboxylate* (3):
A solution of *tert*-butyl 4-{[(5-bromopyrazin-2-yl) oxy] methyl} piperidine-1- carboxylate (1.5 g, 0.004 mol) in toluene (20 mL) was stirred at room temperature under nitrogen atmosphere. The obtained solution was further stirred for 5.0 minute. To this solution 3-(methylsulfonyl) phenylboronic acid (0.66g, 0.004 mol), isopropyl alcohol (20mL) was added at room temperature. To the above reaction mixture a solution of K_2CO_3 (10.0ml, 0.02 mol) in water was added drop wise under nitrogen atmosphere and stirred for 5.0 minute. Palladium tetrakis triphenylphosphine (0.231g, 0.0002 mol) was added to the above reaction mixture and the reaction mixture was heated to reflux for 6hrs (monitored by TLC). The reaction mixture was poured into water with stirring. The aqueous layer was extracted with ethylacetate (100mL × 3), and the combined organic layers were washed with water followed by brine solution and dried over anhydrous Na_2SO_4. Finally the solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.
MS: m/z = 448 [M]$^{+1}$

Preparation of 2-[3-(Methylsulfonyl) phenyl]-5-(piperidin-4-ylmethoxy) pyrazine (2)
A mixture of HCl in dioxane (10 mL) and *tert*-butyl 4-((5-(3-(methylsulfonyl) phenyl) pyrazine-2-yloxy) methyl) piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate was added to the above crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 mL × 3). The combined organic layers were washed with water followed by brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product.
Yield: 60 %, MP: 138-139^oC; MS: m/z = 348 [M]$^{+1}$

General procedure for the preparation of Aryl {4-[({5-[3- (methylsulfonyl) phenyl] pyrazin-2-yl} oxy) methyl] piperidin-1-yl} methanones (1).
To a stirred cooled (ice bath) solution of 2-[3-(methylsulfonyl)phenyl]-5- (piperidin-4-ylmethoxy) pyrazine (0.2g, 0.576 mmol) and aryl acid (0.576 mmol) in dry DMF (3.0mL), HBTU (2-(1*H*-benzotriazole-1-yl) -1,1,3,3-tetramethyl uranium hexafluoro phosphate) (0.262 g, 0.691 mmol) and DIPA (0.1ml, 0.864 mmol) was added at 0^oC. The reaction mixture was stirred for 10hrs at room temperature and monitored by TLC. The reaction mixture was poured onto crushed ice, thus the precipitate separated was filtered and washed with water to give pure product.

ANALYTICAL DATA:
(4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidin-1-yl) (p-tolyl) methanone (1a). MP: 160-162 ^oC; **IR (KBr):** 3001, 2929, 2846, 1622, 1538, 1461, 1341, 1301, 1149, 1015, 827 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm 1.40-1.47 (m, 2H, 2CH), 1.75-1.78 (d, J=12.64 Hz, 1H, CH), 1.98-2.02 (d, J=13.08 Hz, 1H, CH), 2.11-2.17 (m, 1H, CH), 2.29 (s, 3H, CH3), 2.83-2.97 (m, 1H, CH), 2.98-3.05 (m, 1H, CH), 3.09 (s, 3H, CH3), 3.54-3.57 (d, J=12.40 Hz, 1H, CH), 4.27-4.28 (d, J=6.40 Hz, 2H, CH2), 4.87-4.90 (d, J=12.92 Hz, 1H, CH), 7.21-7.30 (m, 4H, ArH), 8.02-8.05 (m, 2H, ArH), 8.21-8.14 (m, 2H, ArH), 8.31 (s, 1H, ArH), 8.56-8.57 (d, J=1.24 Hz 1H, ArH). **^{13}C NMR (100 MHz, $CDCl_3$):** δ ppm 26.23, 30.10, 35.46, 42.10, 44.59, 46.19, 70.16, 120.18, 123.51, 126.84, 128.08, 130.94, 135.78, 138.14, 140.62, 144.29, 152.55, 156.16, 159.28, 170.21. **MS: m/z** = 465 [M] $^+$.

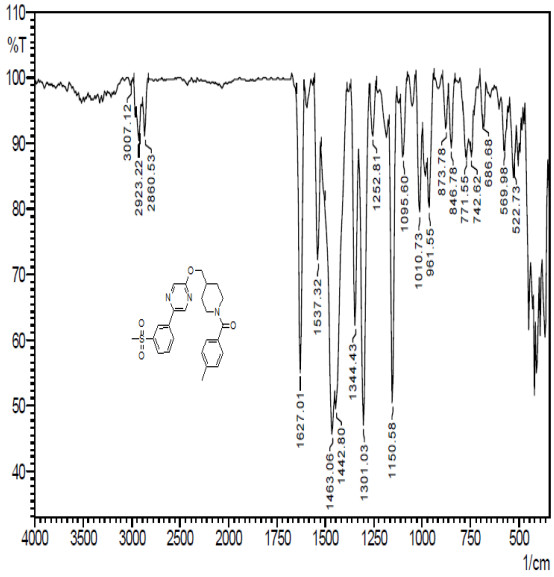
(4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidin-1-yl) (o-tolyl) methanone (1b)
MP: 182-184 ^oC. **IR (KBr):** 3007 (Ar, C-H str), 2923 (C-H str), 2860 (C-H str), 1627 (amide, C=O str), 1537 (Ar, C=C str), 1463 (Ar, C=C str), 1344 (C-H ban), 1301 (S=O str asym), 1150 (S=O str sym), 1095 (C-N str), 1010 (C-O-C str), 742 (C-H o.p. ban) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm 1.40-1.47 (m, 2H, 2CH), 1.75-1.78 (d, J=12.64 Hz, 1H, CH), 1.98-2.02 (d, J=13.08 Hz, 1H, CH), 2.11-2.17 (m, 1H, CH), 2.29 (s, 3H, CH3), 2.83-2.97 (m,

1H, CH), 2.98-3.05 (m, 1H, CH), 3.09 (s, 3H, CH3), 3.54-3.57 (d, J=12.40 Hz, 1H, CH), 4.27-4.28 (d, J=6.40 Hz, 2H, CH2), 4.87-4.90 (d, J=12.92 Hz, 1H, CH), 7.21-7.30 (m, 4H, ArH), 8.02-8.05 (m, 2H, ArH), 8.21-8.14 (m, 2H, ArH), 8.31 (s, 1H, ArH), 8.56-8.57 (d, J=1.24 Hz 1H, ArH).

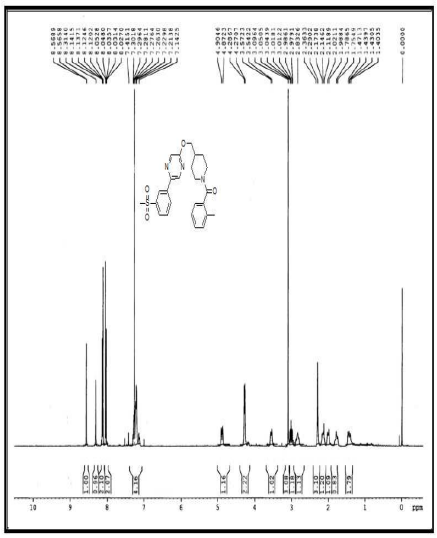
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 19.70, 30.10, 35.46, 42.10, 44.59, 46.19, 70.16, 120.18, 123.51, 126.84, 128.08, 130.94, 135.78, 138.14, 140.62, 144.29, 152.55, 156.16, 159.28, 170.21. **MS: m/z** = 465 $[M+1]^+$.

(4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidin-1-yl) (pyridin-4-yl) methanone (1c)
MP: 233-235^{o}C. **IR (KBr):** 3001, 2916, 2869, 1617, 1535, 1449, 1339, 1300, 1148, 1010, 750 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm 1.45-1.54 (m, 2H, 2CH), 1.82-1.85 (d, J=12.56 Hz, 1H, CH), 1.98-2.01 (d, J=12.88 Hz, 1H, CH), 2.17-2.18 (m, J=13.48 Hz, 1H, CH), 4.28-4.29 (d, J=6.52 Hz, 2H, CH2), 4.81-4.84 (d, J=13.12 Hz, 1H, CH), 7.33-7.36 (m, 1H, ArH), 7.61-7.63 (d, J=7.76 Hz, 1H, ArH), 7.78-7.82 (m, 1H, ArH), 8.02-8.05 (m, 2H, ArH), 8.11-8.14 (m, 2H, ArH), Hz, 1H, ArH). **^{13}C NMR (100 MHz, $CDCl_3$):** δ ppm 28.10, 35.92, 42.25, 44.59, 46.17, 70.61, 120.08, 123.61, 126.83, 128.07, 131.74, 135.43, 137.10, 138.16, 140.23, 144.16, 152.15, 156.64, 159.94, 172.94. **MS: m/z** = 453 $[M+1]^+$;

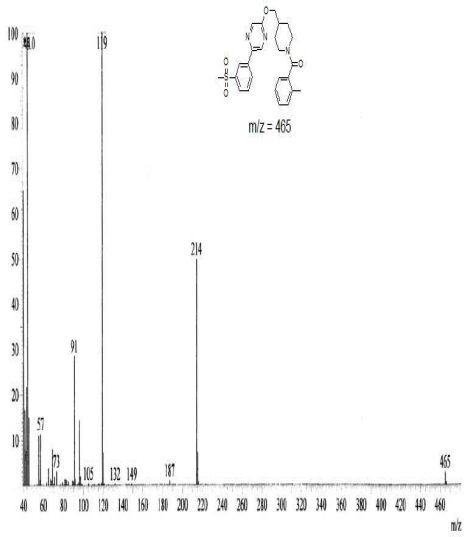
(4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidin-1-yl) (pyridin-2-yl) methanone (1d).
MP: 219-221^{o}C. **IR (KBr):** 3003, 2919, 2867, 1616, 1534, 1463, 1340, 1300, 1148, 1089, 1058 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm 1.45-1.54 (m, 2H, 2CH), 1.82-1.85 (d, J=12.56 Hz, 1H, CH), 1.98-2.01 (d, J=12.88 Hz, 1H, CH), 2.17-2.18 (m, J=13.48 Hz, 1H, CH), 4.28-4.29 (d, J=6.52 Hz, 2H, CH2), 4.81-4.84 (d, J=13.12 Hz, 1H, CH), 7.33-7.36 (m, 1H, ArH), 7.61-7.63 (d, J=7.76 Hz, 1H, ArH), 7.78-7.82 (m, 1H, ArH), 8.02-8.05 (m, 2H, ArH), 8.11-8.14 (m, 2H, ArH), Hz, 1H, ArH). **^{13}C NMR (100 MHz, $CDCl_3$):** δ ppm 28.10, 35.92, 42.25, 44.59, 46.17, 70.61, 120.08, 123.61, 126.83, 128.07, 131.74, 135.43, 137.10, 138.16, 140.23, 144.16, 152.15, 156.64, 159.94, 170.94. **MS:** m/z = 453 $[M+1]^+$;



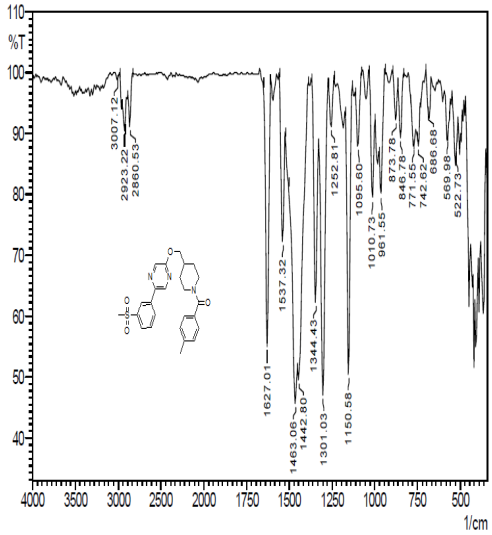
1HNMR 1a



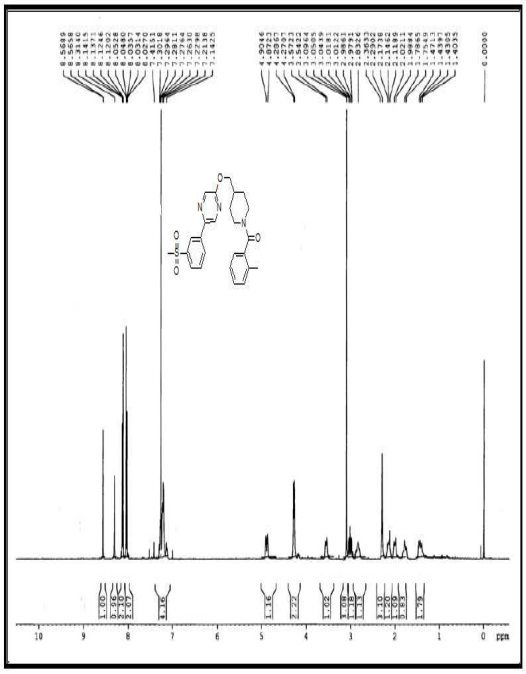
Mass Spectra 1a



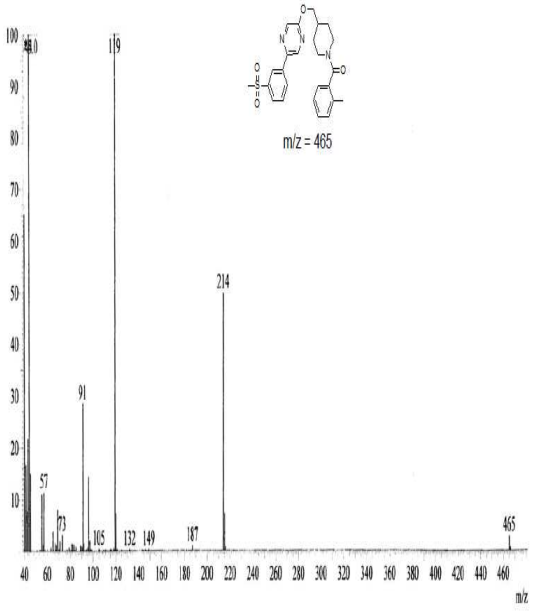
IR spectra of 1b



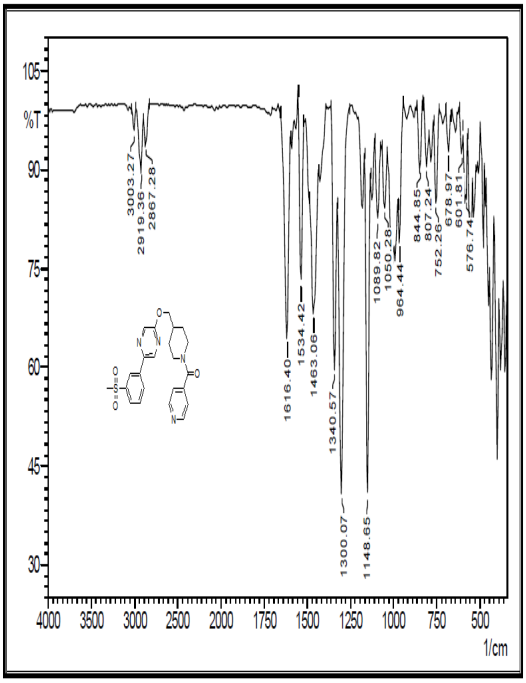
1HNMR 1b



Mass of 1b



IR of 1c



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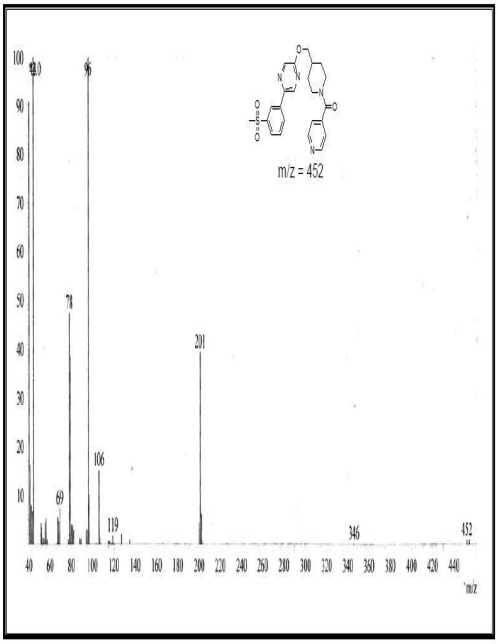

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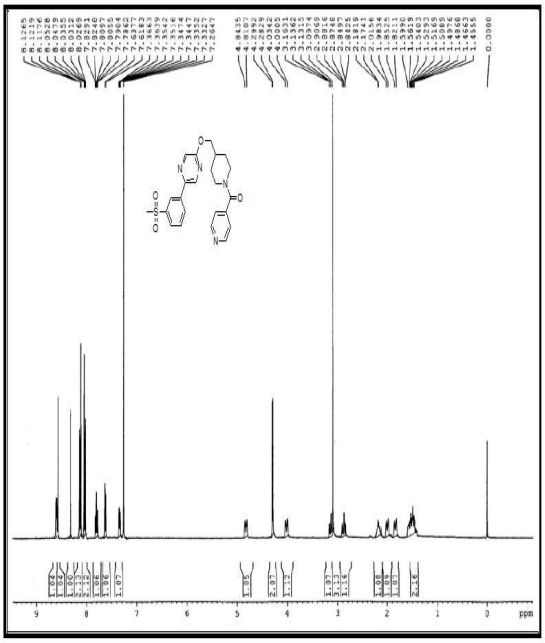
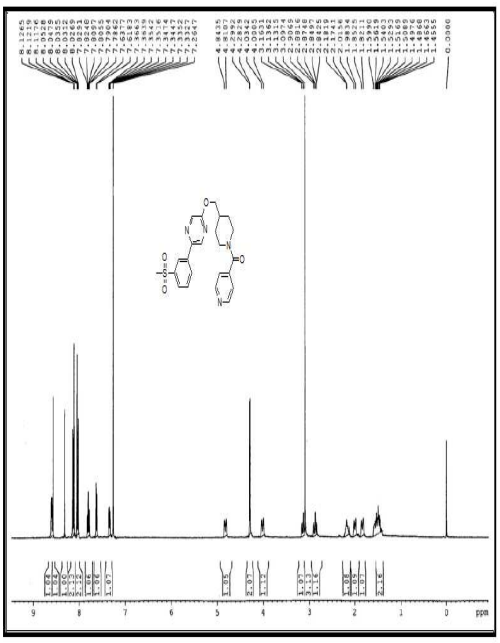
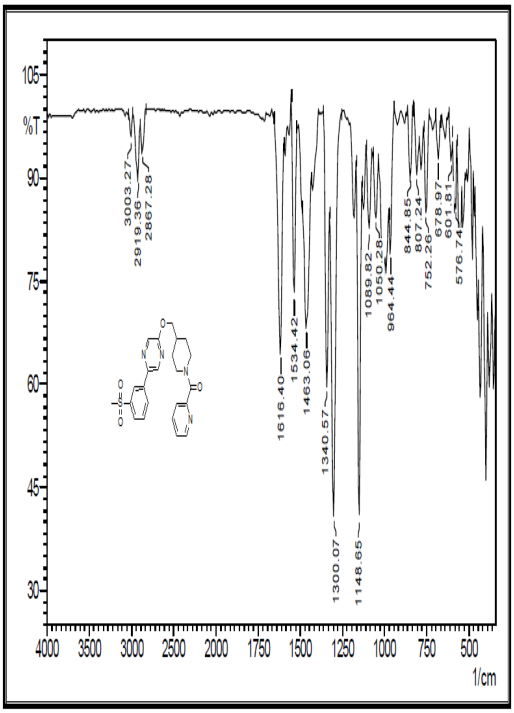


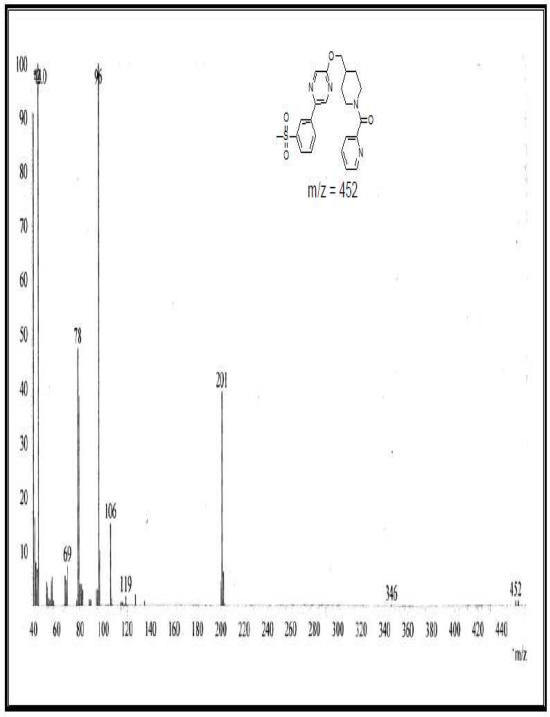
13C NMR 1c



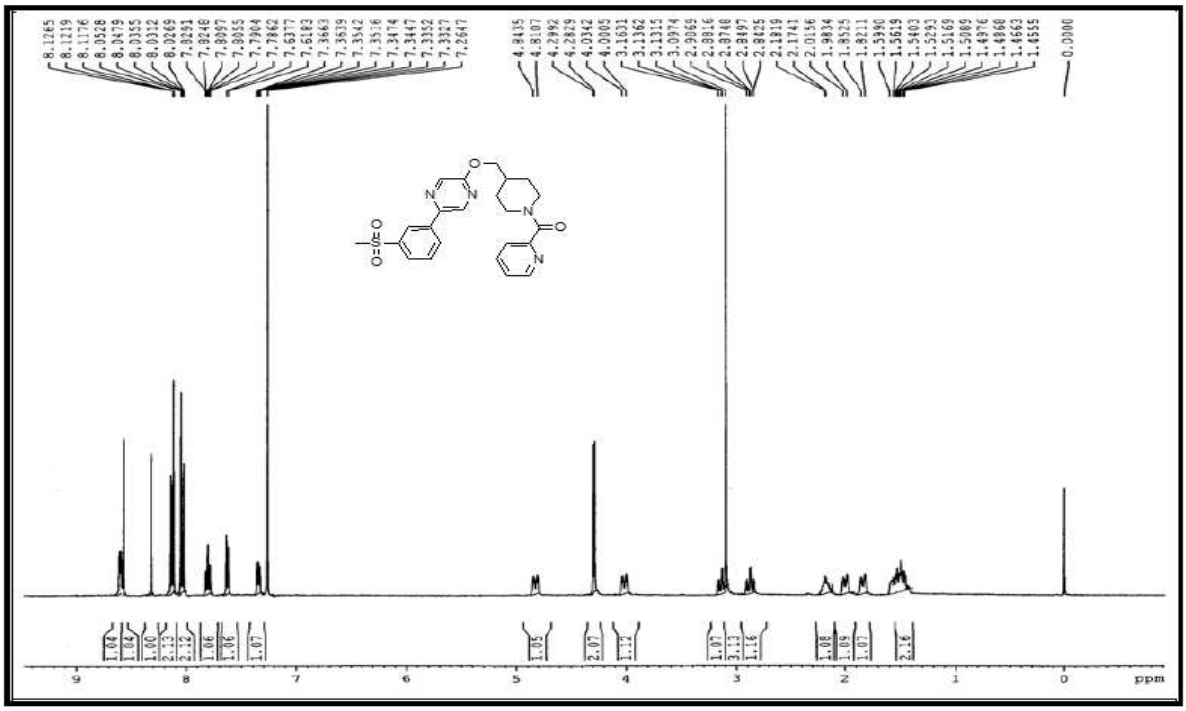
IR of Id



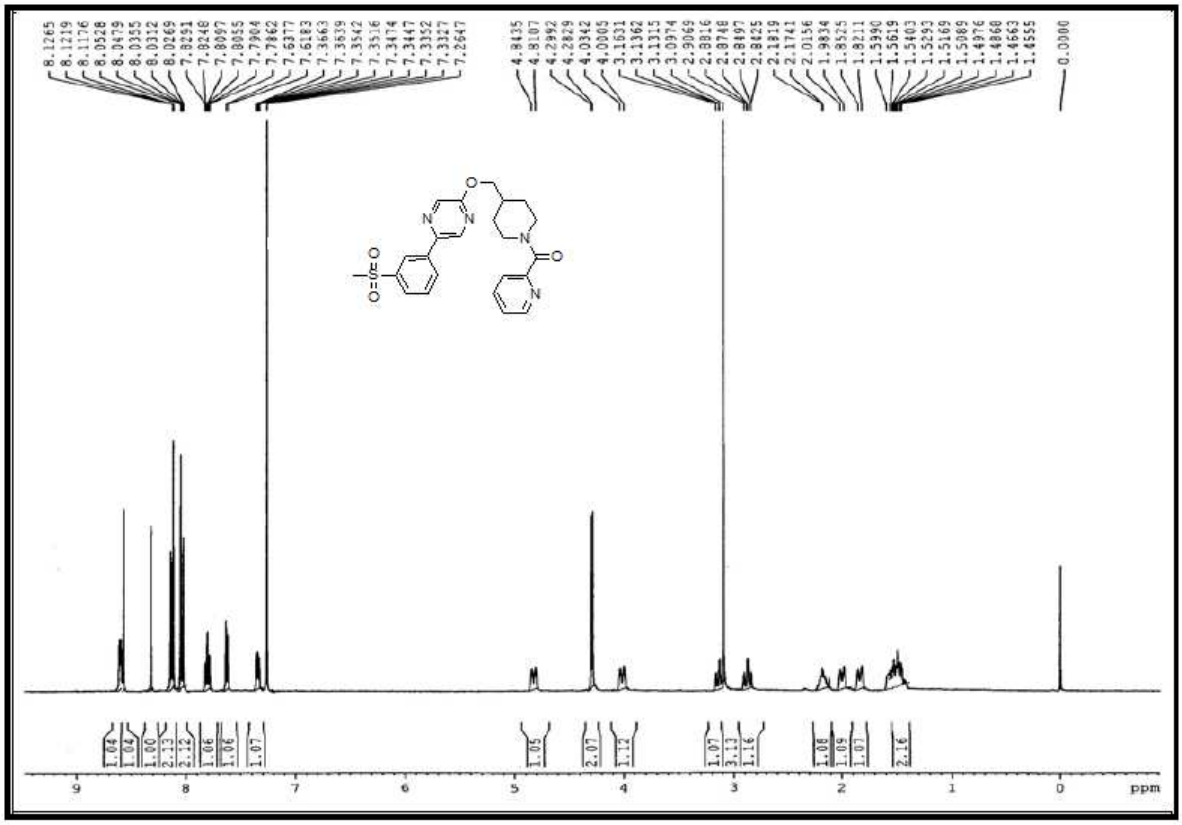
Mass of 1d



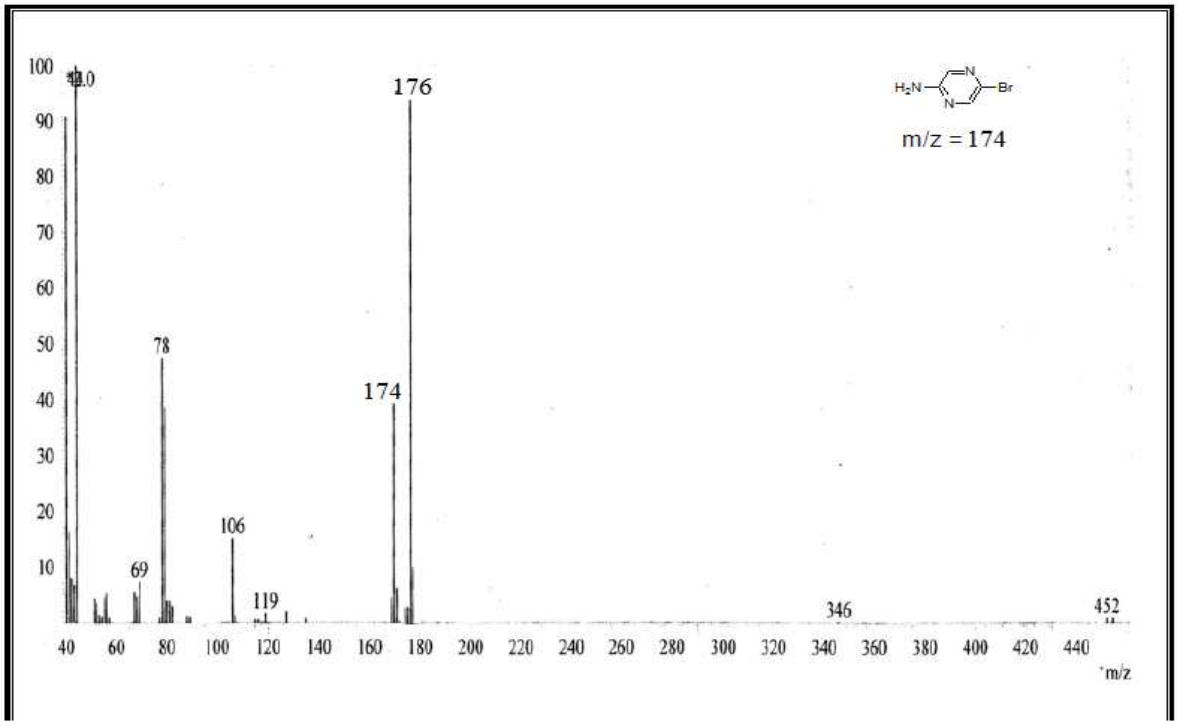
1H NMR of 1d



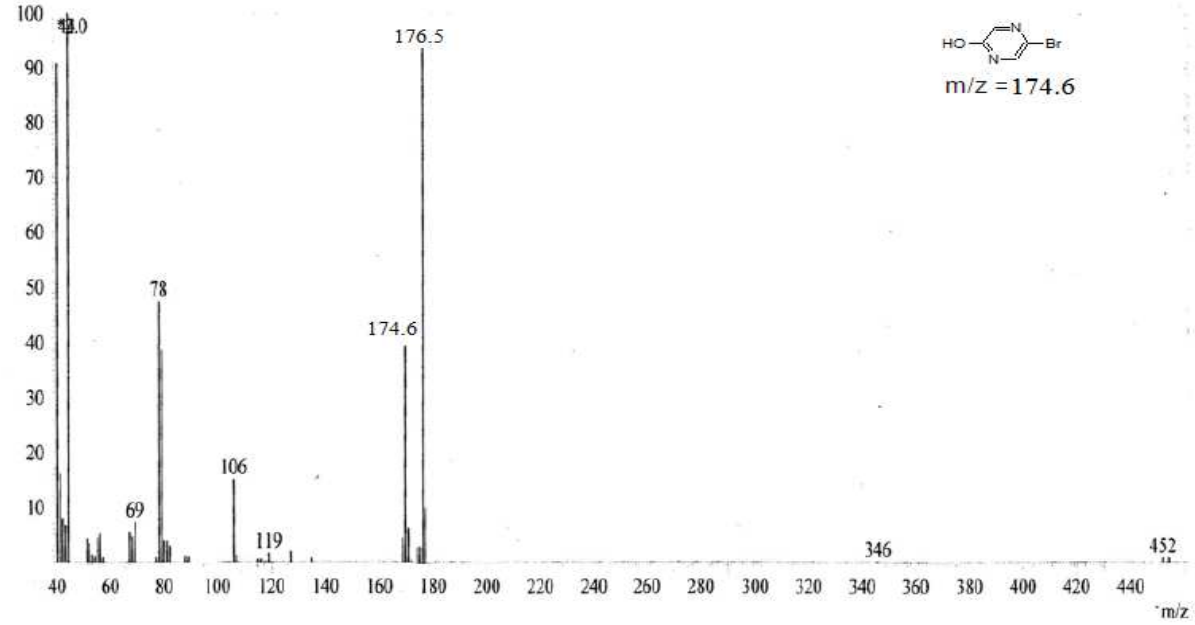
13C of 1d



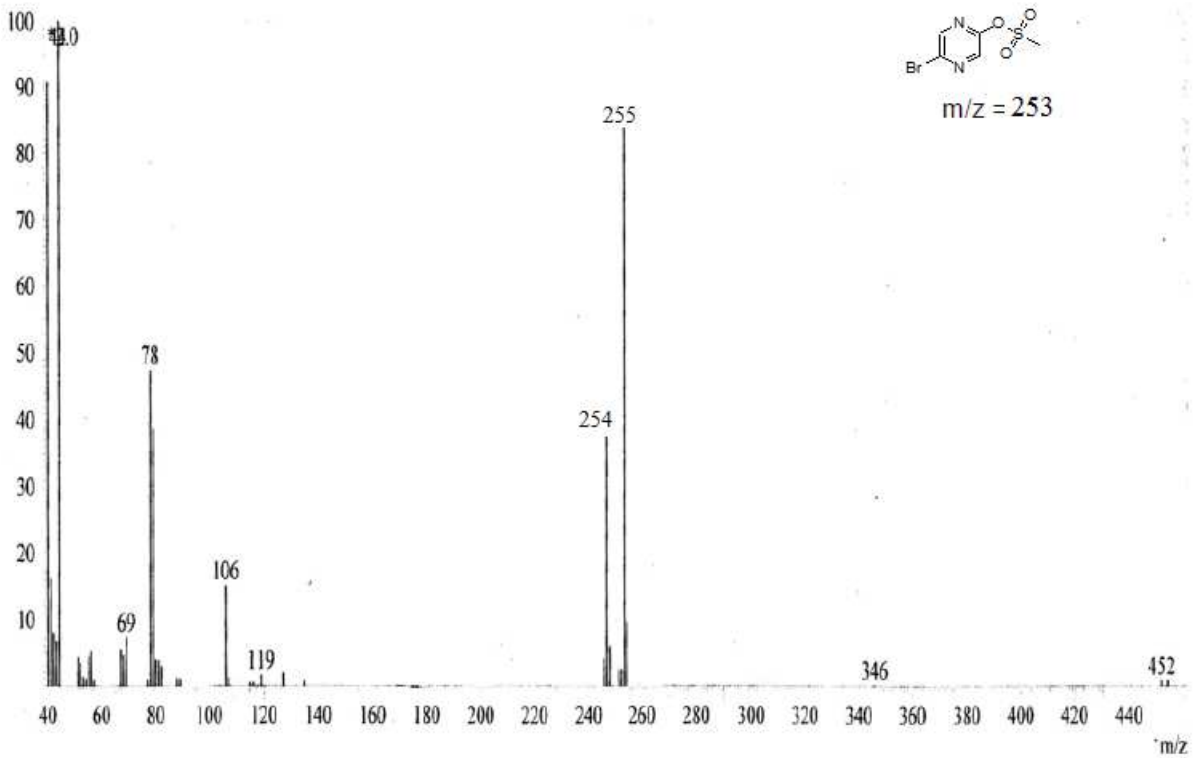
Mass spectra of 5-Bromopyrazin-2-amine (7)



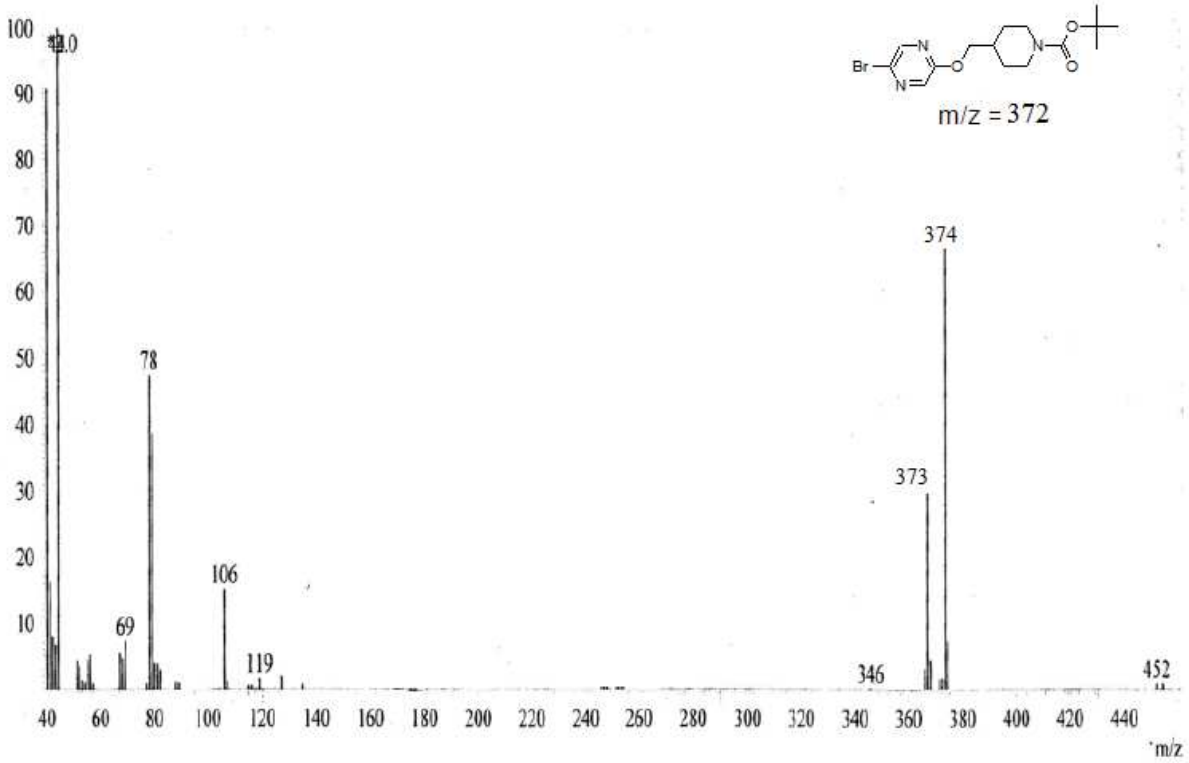
Mass spectra of 5-Bromopyrazin-2-ol (6)



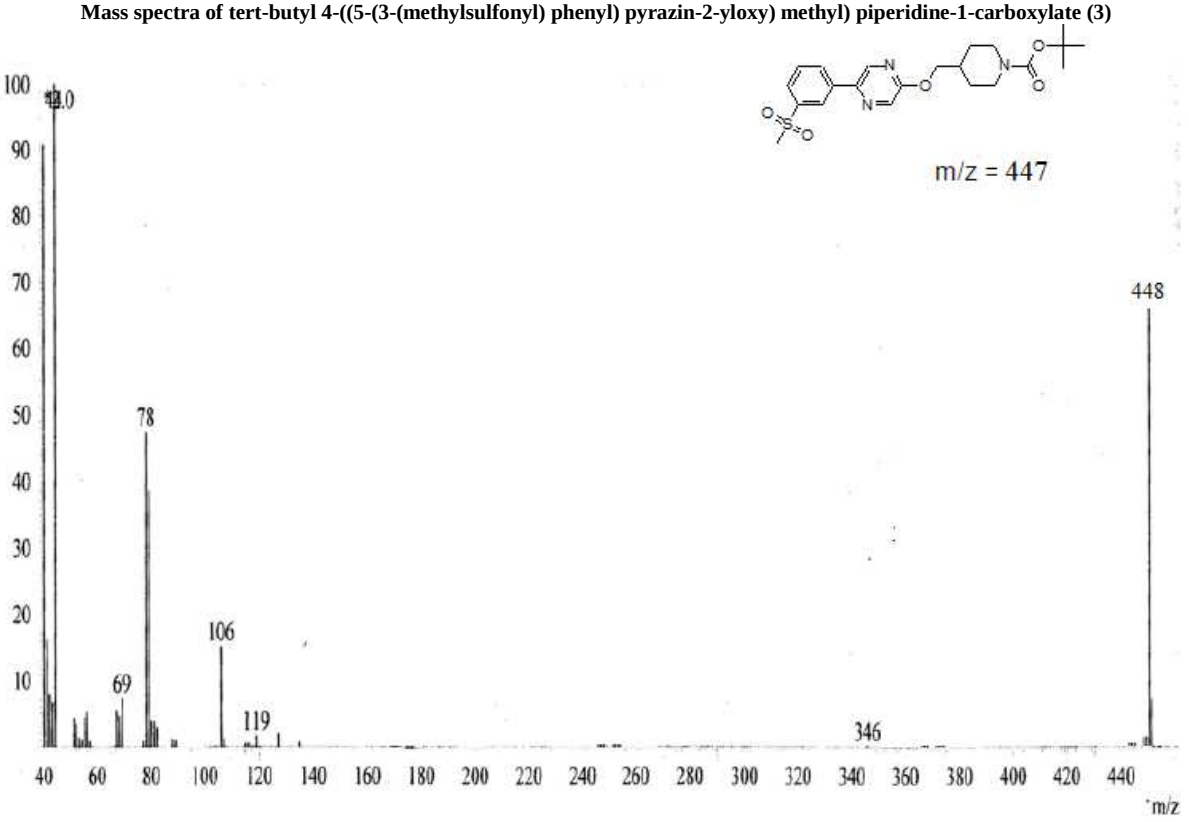
Mass spectra of 5-Bromopyrazin-2-yl methanesulfonate (5)



Mass spectra of tert-butyl 4-((5-bromopyrazin-2-yloxy)methyl)piperidine-1-carboxylate (4)



Mass spectra of tert-butyl 4-((5-(3-(methylsulfonyl) phenyl) pyrazin-2-yloxy) methyl) piperidine-1-carboxylate (3)



Mass spectra of 2-[3-(Methylsulfonyl) phenyl]-5-(piperidin-4-ylmethoxy) pyrazine (2)

Acknowledgement
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