Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(8):514-517

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of Some Imidazo[1,2-a]pyrazine derivatives and evaluation of their antimicrobial activity

Darshitkumar M. Dave[1], Dharmesh Pansuriya[2], A. H. Bapodra[1] and K. D. Ladva[2]

[1]Department of Chemistry, M. D. Science College, Porbandar-360575, Gujarat, India
[2]Department of Chemistry, Sree M & N Virani Science College, Rajkot-360005, Gujarat, India

ABSTRACT

Some new Imidazo[1,2-a]pyrazine derivatives were prepared. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Key words: Imidazo [1, 2-a] pyrazine, Diazine, hydrazine derivatives, antimicrobial activities

INTRODUCTION

The imidazo [1, 2-a] pyrazine nucleus has been reported with a wide range of bioactivities, such as anti-inflammatory, antimicrobial, antiviral, anticancer, antiulcer, anticonvulsant, analgesic, and hypoglycemic activities [1–4]. Moreover, the imidazo [1, 2-a] pyrazine derivative have exhibited theophylline-like pharmacological properties, such as muscle relaxant, cardiotonic, and antibronchospasm activity, because of their similarity to the theophylline molecule, which includes an imidazo [1, 2-a] pyrimidine ring in its structure [5–7]. According to the literature [8], imidazo [1, 2-a] pyrazine-3-(7H)-on derivative compounds were designed as a prodrug of ibuprofen, a strong non-steroidal anti-inflammatory drug. Furthermore, there are many studies regarding the effect of imidazopyrazines on the central nervous system (CNS) [9-11].

Imidazo[1,2-a]pyrazine have attracted attention of medicinal chemistry for both with regard to heterocyclic chemistry and the pharmacological activities associated with them, inspired us to synthesize N-[2-(3-methoxyphenyl)imidazo[1,2-a]pyrazine-8-yl] substituted benzene sulfonohydrazide derivatives (3a – j).

EXPERIMENTAL SECTION

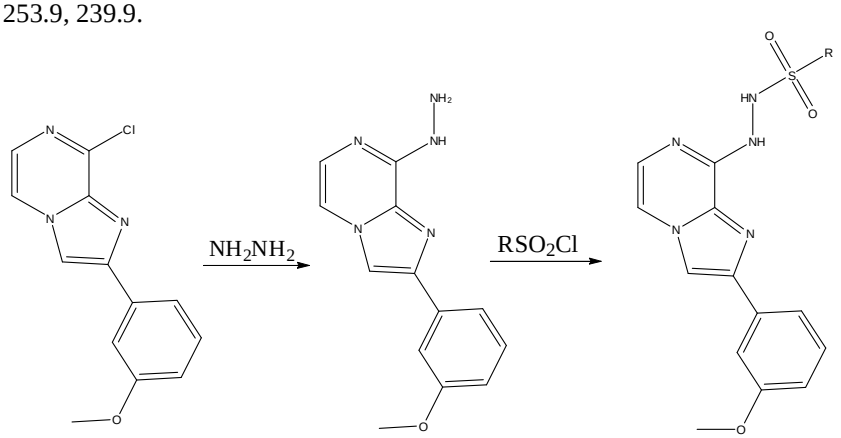
All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrophotometer. ^{1}H NMR spectra recorded on a Bruker 300 MHz spectrometer with DMSO as a solvent and tetra methyl silane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet), *d* (doublet) and *m* (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25mm thickness eluted with Hexanes : Ethyl acetate (7 : 3 v/v) and visualized with UV (254 nm) or iodine to check the purity of the synthesised compounds.

The antimicrobial activity was assayed by using the cup-plate agar diffusion method [12–13] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against varieties of bacterial strains such Staphylococcus aureus, Escherichia coli, Bacillus megaterium, Pseudomonas aeruginosa fungi Aspergillus niger and Aspergillus flavus at various concentration. Standard drugs like Streptomycin, Ampicillin and Nystatin were used for comparison purpose (Table-2).

General procedure for the synthesis of compounds (2) and (3) are as under.

Synthesis of 1-(2-(3-methoxyphenyl)imidazo[1,2-a]pyrazine-8-yl)hydrazine (2):
A mixture of 8-chloro-2-(3-methoxyphenyl)imidazo[1,2-a]pyrazine (1) (0.01 mol, 2.59 gm) and hydrazine hydrate (0.05 mol, 2.5 gm) in ethanol were reflux for 16 hrs and after completion of reaction cool the solution at R.T. The content was poured in to crushed ice. The solid was obtained by filtration, washed with water and crystallised from methanol to give (2). MP = 155 ° C

IR (KBr,cm^{-1}) : 3740 & 3392 (-NH_2, N-H sym. & asym. Str.), 3291 & 3216 (sec. N-H bonded, str.), 3034 (Heterocyclic ring, =C-H, str.), 2996 (1,3 substituted phenyl ring, =C-H, str.), 1646 & 1514 (N-H def plus C-N str.), 1249 (Ar-O-CH_3 ,ether, sym. str.), 1033 (Ar-O-CH_3 ,ether, asym. str.); ^{1}H NMR (DMSO – d_6, δ, ppm): 3.3 (3H, s, -OCH_3), 3.8 (1H, s, -NH-), 4.6 (2H, s, -NH_2), 6.8-7.7 (4H, m, Ar-H), 7.8-8.6 (3H, s, Imidazo[1,2-a]pyrazine moiety),; Mass m/z = 256.9, 253.9, 239.9.



1 **2** **3a - j**

Scheme – 1

Synthesis of compound -3a
A mixture of 1-(2-(3-methoxyphenyl)imidazo[1,2-a]pyrazine-8-yl)hydrazine (2) (0.01 mol, 2.55 gm), 4-methylbenzenesulfonyl chloride (0.012 mol) in pyridine (5 ml), was stirred at room temperature for 5-6 hrs. The content was poured in to 15% aqueous hydrochloric acid solution. The solid was obtained by filtration, washed with water and crystallised from methanol to give **3a**.

Similarly, the remaining compounds (3a-j) were prepared by this method. Their physical data are given in Table-1.

Compound (3a) IR (KBr,cm^{-1}) : 3201 (N-H bonded str.), 1637 & 1525 (N-H def plus C-N str.), 1396 (sulphonamide -S=O str.), 1292 (Ar-O-CH_3 ,ether, str.); ^{1}H NMR (DMSO – d_6, δ, ppm): 2.3 (3H, s, Ar-CH_3), 3.8 (3H, s, -OCH_3), 6.9-7.7 (8H, m, Ar-H), 7.9-8.0 (3H, s, Imidazo[1,2-a]pyrazine moiety), 8.6 (1H, s, Sec. Amine), 10.5 (1H, s, -$NHSO_2Ar$) ; Mass m/z = 410.9, 409.9, 308

RESULTS AND DISCUSSION

Antibacterial activity and Antifungal activity
Among imidazo[1,2-a]pyrazine derivatives tested compounds 3a, 3h, 3i and 3j showed greater degree of antibacterial activity against Bacillus subtilis. However, the compounds 3a, 3b, 3c, 3h and 3i were shown excellent growth inhibiter activity against *Staphylococcus aureus*. The compounds 3a, 3b, 3h and 3i showed excellent growth inhibition against *E.coli*. However, the compounds 3c, 3e, 3h and 3i exhibited greater degree of antibacterial activity against *Pseudomonas aeruginosa*.

The compounds 3c shows excellent antifungal activity against Aspergillus niger where as compounds 3a, 3h and 3i shows greater antifungal activity against Aspergillus flavus. The remaining imidazo[1,2-a]pyrazine derivatives possess good to moderate activity against all six bacterial species.

Table -1 Characterisation data of compound (3a-j).

Com. No.	R	Molecular Formula	M.P. (°C)	Nitrogen %	
				Calcd	Found
3a	4-$CH_3C_6H_4$	$C_{20}H_{19}N_5O_3S$	135°C	17.10	17.16
3b	4-CH_3CONH-C_6H_4	$C_{21}H_{20}N_6O_4S$	192°C	18.57	18.63
3c	4-$(CH_3)_3C$-C_6H_4	$C_{23}H_{25}N_5O_3S$	165°C	15.51	15.54
3d	2-CN-C_6H_4	$C_{20}H_{16}N_6O_3S$	130°C	19.99	20.03
3e	-$N(CH_3)_2$	$C_{15}H_{18}N_6O_3S$	155°C	23.19	23.26
3f	2-F-C_6H_4	$C_{19}H_{16}FN_5O_3S$	170°C	16.94	17.03
3g	2-Cl-C_6H_3COOH	$C_{20}H_{16}ClN_5O_5S$	185°C	14.78	14.67
3h	2-OH-C_6H_3COOH	$C_{20}H_{17}N_5O_6S$	190°C	15.38	15.46
3i	-$C(CH_3)_2$	$C_{16}H_{19}N_5O_3S$	172°C	19.38	19.30
3j	4-(-CH=CHCOOH)C_6H_4	$C_{22}H_{19}N_5O_5S$	200°C	15.05	15.15

Table 2 – Antibacterial and antifungal activity data of compounds 3(a-j).

Com. No.	**Antibacterial activity (zone of inhibition in mm)**				**Antifungal activity**	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Aspergillus flavus*
3a	1000	1000	1000	500	500	1000
3b	500	1000	1000	500	500	500
3c	250	1000	500	1000	1000	250
3d	250	500	1000	500	500	500
3e	250	250	1000	1000	250	250
3f	500	500	500	500	500	500
3g	250	250	250	250	250	250
3h	1000	1000	1000	1000	500	1000
3i	1000	1000	1000	1000	500	1000
3j	1000	500	500	500	500	500
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	10

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds which shows significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

Acknowledgment
The authors are thankful to authorities of M. D. Science College, Porbandar, Gujarat, India for providing research facilities and we are also thankful to Department of Chemistry Saurashtra University Rajkot for I.R., N.M.R., Mass spectral & elemental analysis and Department of Microbiology, Sree M & N Virani Science college, Rajkot for microbial screening. The authors are also thankful to Dr. Paresh Patoliya for his valuable guidance and also thankful to Mr. Vraj Pansuriya for his kind support.

REFERENCES

[1] Hemasrilatha S, Sruthi K, Manjula A, Harinadha Babu V, Vittal Rao *B. Indian J Chem* **2012**; 51B: 981-7.
[2] Rimoli M G, Avallone L, De Caprariis P, Luraschil E, Abignente E, Filippelli W. *Eur J Med Chem,* **1997**; 32: 195-203.
[3] Ozdemir A, Turan-Zitouni G, Kaplancikli ZA, Tunali Y. *J Enzym Inhib Med Chem* **2009**; 24: 825-31.
[4] Ozdemir A, Turan-Zitouni G, Asim Kaplancikli Z, Işcan G, Khan S, Demirci F. *Eur J Med Chem,* **2010**; 45: 2080-4.
[5] Basiuk V. A. Imidazo[1,2-a]pyrazines. *Russ Chem Rev.*, **1997**; 66; 187-204. [CrossRef]
[6] Sablayrolles C, Cros G. H, Milhavet J. C, Rechenq E, Chapat J. P, Boucard M et al.. *J Med Chem*., **1984**; 27: 206-12. [CrossRef]
[7] Laurent F, Michel A, Bonnet P A, Chapat JP, Boucard M. *Br J Pharmacol* **1993**; 108: 622-6. [CrossRef]
[8] De Wael F, Muccioli GG, Lambert DM, Sergent T, Schneider YJ, Rees JF, et al. *Eur J Med Chem,* **2010**; 45: 3564-74
[9] Barlin G. B, Davies L. P, Ireland S. J, Ngu M. M. L, Zhang J. K. *Aust J Chem* , **1992**; 45: 877-88. [CrossRef]
[10] Abignente E, De Caprariis P, Rimoli M. G, Capasso G, Autore F. *Farmaco* **1992**; 47: 919-30.
[11] Michael A, Laurent F, Chapat J. P, Boucard M, Bonnet P. A. *Arzneimittel-Forsch* **1995**; 45: 1288-93.
[12] A. L. Barry; The antimicrobial susceptibility test: Principle and practices, edited by llluslea & Febiger , (Philadelphia), USA, 180; Biol. Abstr., 1977, 64, 25183.

[13] Panda J. Srinivas S. V., Rao M. E.; *J. Indian Chem. Soc.*, 79(9), 770-1 (**2002**); Chem. Abstr., 138, 153499n (2003)