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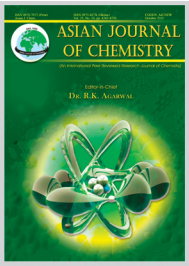

Synthesis of Biologically Active and Novel Antifungal Agents Like Substituted Hetero Aryl amines of Dihydro Imidazo[1,2-a]pyridine Derivatives

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Some substituted hetero aryl amines of dihydro imidazo[1,2-a]pyridine-3yl-methyl derivatives were synthesized and the final compounds elucidated by FTIR, ^{1}H NMR, MASS and micro analysis and were evaluated for antifungal activity by *Candida albcans*. The preliminary results showed that all of the tested compounds were protective against *Candida albcans* at 50-200 mcg/mL concentrations levels.

Key Words: Mannich reaction, Imidazo[1,2-a]pyridine aryl amines, Antifungal activity, *Candida albicans*, IR, ^{1}H NMR, Mass.

INTRODUCTION

Generally azoles antifungal agents may impair hepatic clearance of drugs metabolized by cytochrome P450-3A isoforms. The imidazopyridine hypnotic agent zolpidem is metabolized in humans in part by P450-3A, as well as by a number of other cytochromes. The current work was originated from zolpidem synthesis and several works were done in the same way, but different derivatives made by them. Hydrazide derivatives of imidazo[1,2-a]pyridine have been synthesized and evaluated for anticandidal activity[1]. The reaction of imidazo[1,2-a]pyridine-2-carboxylic acid hydrazides with various benzaldehydes gave *N*-(benzylidene)imidazo[1,2-a]pyridine-2-carboxylic acid hydrazide derivatives. Their anticandidal activities against *Candida albicans* and *Candida glabrata*. Analgesic and antipyretic activities of 2-(4-(2-imidazo[1,2-a]pyridylphenyl) propionic acid (Y-9213) were studied with various experimental models[2]. The analgesic activity of Y-9213 was found to be more potent than that of indometacin and morphine in the silver nitrate, Randall-Selitto and phenylquinone writhing tests. Y-9213 also showed analgesia in the tail pinch and electric stimulation test. On the warm water induced foot withdrawal reflex, Y-9213 was more effective in spinal-sectioned mice than in intact mice similarly to mephenesin and diazepam. Y-9213 was also proved to possess antipyretic activity as potent as indometacin and to be devoid of morphine-like property. Y-9213 exhibited little effect on the respiration and cardiovascular system in dogs. Y-9213 was found to be rapidly absorbed and eliminated from the blood with a half-life of about 2.5 h in rats. These findings indicate that Y-9213 may be an effective and well tolerated antipyretic and analgesic agent. New antimicrobial agents, imidazo[1,2-a]pyridine and imidazo[2,1-b][1,3]benzothiazole, have been synthesized[3]. Their antimicrobial activities were conducted against various Gram-positive, Gram-negative bacteria and fungi. Coadministration of zolpidem with ketoconazole impairs zolpidem clearance[4] and enhances its benzodiazepine-like against pharmacodynamic effects. Itraconazole and fluconazole had a small influence on zolpidem kinetics and dynamics. The findings are consistent with *in vitro* studies of differentially impaired zolpidem metabolism by azoles derivatives. Some publications available on[5,6] one pot synthesis of annulated imidazo [1, 2-a] pyridines and pyrazoles. Our present work is based on Mannich reaction, by using this method. We have taken different heterocyclic aryl amines for making Mannich derivatives such as [6-methyl-2-{4-methyl-1-methylene-hexa-2,4-dienyl-3H-imidazo[1,2-a]pyridine-3ylmethyl]-(5-methyl-pyridin-2-yl)amine (Sd). The structures of the compounds were elucidated by FTIR, ^{1}H NMR, MASS and micro analysis. They were evaluated for antifungal activity by *Candida albcans*. The preliminary results showed that all of the tested compounds were protective against *Candida albcans* at 50-200 mcg mL concentrations levels.

EXPERIMENTAL

Melting points were determined routinely in open capillary tube and are uncorrected. The completion of reaction was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. Elemental analyses of the newly synthesized compounds was carried out on Carlo

Reba 1108 analyzer and are found within the range of theoretical value. IR spectra were recorded on Shimadzu-8400 FT-IR spectrometer in Ker (cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ on a Bruckner DRX-300 at 300 MHz EI-MS spectra were recorded on Shimadzu GC-MS QP-2010 by electron impact method.

Route of synthesis and procedures

Preparation of key intermediate 6-methyl-2-*para*-tolyl-3,8-dihydro imidazo[1,2-a]pyridine-3yl methyl]-(SKI): Charge 135 mL (3V) of methanol and maintain at 0-5 ºC. Add 45 g of 4-methylacetophenone slowly at 0-5 ºC with vigorous stirring. After complete addition of 4-methylacetophenone, add 2.24 g of $AlCl_3$ slowly to the RM at 0-5 ºC and maintain for 15 min. Add 19.3 mL of liquid bromine slowly drop wise at 0-5 ºC with vigorous stirring (when temperature is raised bromine addition is stopped) after complete addition of bromine, the reaction is maintained at 0-5 ºC until TLC is completed. Add 45 mL of demineralized water drop wise for 10-15 min at 0-5 ºC and then add 50 % Na_2CO_3 solution (45 g in 90 mL water) slowly. Then the reaction mixture is brought to room temperature, 38 g of 2-amino-5-methyl pyridine is dissolved in 90 mL water and added. Slowly to the reaction mixture (formation of foam is observed) and maintained until TLC completes. Then add 360 mL (8V) of demineralized water and maintain for 1 h, then the material is filtered and washed with 180 mL (4 V) water and dried at 60 ºC for 4 h. 54 g of dried material obtained was subjected for stage-2, after complete analysis. ^1H NMR ($CDCl_3$); 2.30 (3H, Ph-CH_3), 2.38 (3H, IMPy-CH_3), 6.9-7.8 (8H, ArH), MS; (M+), E/Z; 223.44. And HPLC purity: 99.95 %, (retention time: 7.32).

Preparation of [6-methyl-2-(4-methyl-1-methylene-hexa-2, 4-dienyl)-3H-imidazo[1,2-a]pyridin-3-yl methyl]-(4-methyl-pyrimidin-2-yl)amine (Sa): 10 g of SKI and 17 mL of acetic acid and stirred the mixture until it dissolves. Add 4.66 mL of *Para* formaldehyde drop wise. Maintain at room temperature for 0.5 h followed by slow addition of 11.45 g of 2-amino 4-methyl pyrimidine and the temp is rose to 65-75 ºC and maintained it for 8 h. After completion of the TLC (5 % MeoH in $CHCl_3$). Reaction mass cool to 10 ºC, is diluted with 90 mL of water and pH adjusted to 9.5-10.5. The obtained Crude solid was subjected to crystallization in acetone to get (yield: 65 %) pure compound (purity by HPLC: 98 %) as off white solid with melting point 153-156 ºC. Analysis: ^1H NMR; 2.28 (3H, Ph-CH_3), 2.32 (3H, IMPy-CH_3), 2.39 (3H, Py-CH_3), 5.6 (1H, -NH-), 5.03 (2H, -CH2-), 6.4-8.8 (9H, Ar-H).

Preparation of [6-methyl-2-(4-methyl-1-methylene-hexa-2, 4-dienyl)-3H-imidazo[1,2-a]pyridin-3-yl methyl]-(4-methyl-pyridin-2-yl)amine (Sb): 5 g of SKI, 8.5 mL of acetic acid, 5.66 g of 2-amino-4-methyl pyridine and 2.33 mL *Para* formaldehyde was taken and reaction has done as like as Sa procedure and the obtained crude material was purified in toluene to get an off white solid material having 98.9 % HPLC purity with melting point 214-217 ºC and obtained yield was reported as 80.2 %. Analysis: ^1H NMR; 2.2 (3H, Ph-CH_3), 2.28 (3H, IMPy-CH_3), 2.38 (3H, Py-CH_3), 4.5 (1H, -NH-), 4.9 (2H, -CH_2-), 6.2-8.2 (10H, Ar-H) FT-IR; 3462, 3237 (-N-H str), 1517, 1452 (N-H bend), 3029 (Ar, C-H str), 2864, 2949 (-CH_2 str), 1655 (C=C str); MS: scan $E^{+[1.04e8}$(M+) E/Z, 344.7.

Procedure for preparation of [6-methyl-2-(4-methyl-1-methylene-hexa-2, 4-dienyl)-3H-imidazo[1,2-a]pyridin-3-ylmethyl]-(6-methyl-pyridin-2-yl)amine (Sc): 8 g of SKI, 13.6 mL of acetic acid, 9.082 g of 2-amino-6-methyl-pyridine and 3.728 mL *Para* formaldehyde was taken and reaction has done as like as Sa procedure and the obtained crude material was thru silica gel (100-200 mesh) column with 1 % MeOH/$CHCl_3$ to get a pale yellow coloured solid material having 97.1 % HPLC purity with melting point 168-172 ºC and obtained yield was reported as 90 %. Analysis: ^1H NMR; 2.3 (3H, Ph-CH_3), 2.32 (3H, IMPy-CH_3), 2.44 (3H, Py-CH_3), 5.99 (1H, -NH-), 4.9 (2H, -CH_2-), 6.2-8.10 (10H, Ar-H) FT-IR; 3398, 3254 (-N-H str), 1513 (N-H bend), 3080 (Ar, C-H str), 2857, 2918 (-CH_2 str), 1601 (C=C str); MS: scan $E^{+[1.04e8}$(M+), E/Z,344.8).

Preparation of [6-methyl-2-(4-methyl-1-methylene-hexa-2, 4-dienyl)-3H-imidazo[1,2-a]pyridin-3-ylmethyl]-(5-methyl-pyridin-2-yl)amine (Sd): 10 g of SKI, 17 mL of acetic acid 11.35 g of 2-amino-5-methylpyridine and 4.66 mL *Para* formaldehyde was taken and reaction has done as like as Sa procedure and the obtained crude material was aurified by crystallization in acetone to get a white coloured solid material having 98.4 % HPLC purity with melting point 215-220- ºC and obtained yield was reported as 71.2 %. Analysis: ^1H NMR; 2.2 (3H, Ph-CH_3), 2.28 (3H, IMPy-CH_3), 2.38 (3H, Py-CH_3), 4.4 (1H, -NH-), 4.9 (2H, -CH_2-), 6.4-7.98 (10H, Ar-H) FT-IR; 3295, 3146 (-N-H str), 1503 (N-H bend), 3060 (Ar, C-H str), 2853, 2913 (-CH_2 str), 1614 (C=C str); MS: scan $E^{+[1.04e8}$(M+), E/Z; 344.7).

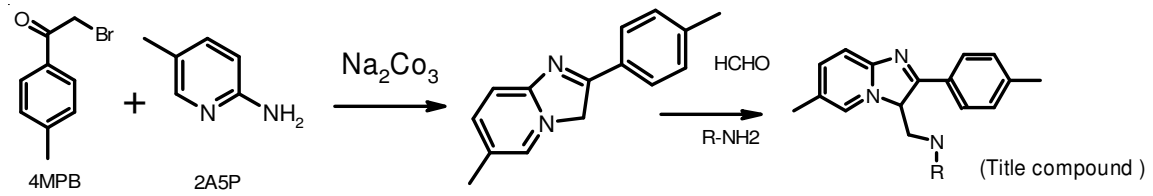
Procedure for preparation of 3-imidazol-1ylmethyl-6-methyl-2-(4-methyl-1-methylene-hexa-2,4-dienyl)-3H-imidazo[1,2-a]pyridine (Se): 6 g of SKI, 10.2 mL of acetic acid, 4.3 g of imidazole and 2.8 mL *para* formaldehyde was taken and reaction has done as like as Sa procedure and the obtained crude material was purified thru silica gel (100-200 mesh) column with 1 % EtOAc /$CHCl_3$ to get a pale yellow coloured solid Material having 97 % HPLC purity with melting point 145-149 ºC and obtained yield was reported as 60 %. Analysis: ^1H NMR; 2.3 (3H, Ph-CH_3), 2.4 (3H, IMPy-CH_3), 5.5 (2H (S)-CH_2-), 6.8-7.6 (10H, Ar-H) FT-IR; 2205 (-C=N str), 3072 (Ar, C-H str), 2957, 2921(-CH_2 str), 1648 (C=C str); MS: scan $E^{+[1.04e8]}$(M+), E/Z; 303.7).

Procedure for preparation of [6-methyl-2-(4-methyl-1-methylene-hexa-2,4-dienyl)-3H-imidazo[1,2-a]pyridine-3-ylmethyl]pyridin-2-yl-amine (Sf): 10 g of SKI, 15 mL of acetic acid, 9.87 g of 2-amino pyridine and 4.26 mL *para* formaldehyde was taken and reaction has done as like as Sa procedure and the obtained crude material was purified in toluene/DMF to get an off white solid material having 98.5 % HPLC purity with melting point 186-189 ºC and obtained yield was reported as 74.5 %. Analysis: ^1H NMR; 2.2 (3H, Ph-CH_3), 2.28 (3H, Ar-CH_3), 2.38 (3H, IMPy-CH_3), 4.4 (1H, -NH-), 4.9 (2H, -CH_2-), 6.5-8.1 (11H, Ar-H) FT-IR; 3263, 3170 (-N-H str), 1502 (N-H bend), 3020 (Ar, C-H str), 2855, 2913 (-CH_2 str), 1602 (C=C str); MS: scan $E^{+[1.04e8}$(M+), E/Z; 329.8). (**Scheme-I**) (Table-1).

Antifungal activity: The synthesized derivatives were finally evaluated for antifungal activity by *Candida albicans*. The preliminary results showed that all of the tested compounds were protective against *Candida albicans* at 50-200 mcg/mL.

TABLE-1
EXPERIMENTAL RESULT

S.No.	Derivative code	Rxn temp. (ºC)	Rxn time (h)	m.p. (ºC)	Colour	Yield (%)	Purity by HPLC
1	Sa	71	8.0	153-156	Off white	64.5	98.0
2	Sb	72	7.0	214-217	Off white	80.2	98.9
3	Sc	71	7.5	168-172	Pale yellow	90.0	97.1
4	Sd	66	6.5	215-220	Pure white	71.2	98.4
5	Se	72	6.0	145-149	Pale yellow	60.0	97.0
6	Sf	76	8.0	186-189	Off white	74.5	98.5



6-Methyl-2-P-tolyl-3,8a-Dihydro imidazo[1,2a]-pyridin-3ylmethyl)-Arylamine

Scheme-I

RESULTS AND DISCUSSION

The total synthesis involves mainly two stages, the phanacylbromide is reacted with aminomethylpyiridine first in presence of a weak base and then get cyclized as 6-methyl-2-*p*-tolyl-3H-imidazo[1,2a]pyridine in the first stage and in the second stage the active methylene group presented in 6-methyl-2-*p*-tolyl-3H-imidazo[1,2a]pyridine stage-1 material is subjected for mannich reaction using different amino heterocyclic derivatives in presence of *Para* formaldehyde and in glacial acetic acid to synthesis our desired products as mentioned in the route of synthesis. These imidazo [1,2a] pyridine derivatives were tested their biological activity test such as antifungal activity against *Candida albicans* (ATCC 90028) as shown as in Table-2.

TABLE-2
ANTIFUNGAL ACTIVITY AGAINST
Candida albicans (ATCC90028)

S.No.	Derivative code	Zonal Diameter (mm)		
		200 (µg/mL)	100 (µg/mL)	50 (µg/mL)
1	Sa	10.8	10.6	10.5
2	Sb	12.4	12.4	12.3
3	Sc	11.8	11.8	11.5
4	Sd	12.8	12.8	12.3
5	Se	14.6	14.6	14.1
6	Sf	11.9	11.9	11.8

REFERENCES

1. Z.A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir and G. Revial, *J. Enzyme Inhib. Med. Chem.*, **23**, 866 (2008).
2. Y. Maruyama, K. Anami and T. Katoh, *Arzneim.-Forsch.*, **28**, 2102 (1978).
3. T.H. Al-Tel, R.A. Al-Qawasmeh and R. Zaarour, *Cheminform*, **42**, 31 (2011).
4. D.J. Greenbelt, L.L. von Moltke, J.S. Harmatz, P. Mertzon's, J.A. Graf, A.L. Durol, M. Counihan, B. Roth-Schechter and R.I. Shader, *Clin. Pharmacol. Ther.*, **64**, 661 (1998).
5. A. Shaabani, E. Soliemani and A. Maleki, *Monatsh. Chem.*, **138**, 73 (2007).
6. R.S. Varma and D. Kumar, *Tetrahedron Lett.*, **40**, 7665 (1999).