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Research Article

SYNTHESIS, CHARACTERIZATION AND IN-VITRO ANTIMICROBIAL EVALUATION OF SOME NOVEL HETROCYCLIC COMPOUNDS

Mahendrasinh M. Raj[1]*, Hemul V. Patel[2], Lata M. Raj[3] and Naynika K. Patel[4]

[1]Institute of Science and Technology for Advanced Studies and Research (ISTAR), Vallabh Vidyanagar-388120, Gujarat, India.
[2]Ashok and Rita Patel Institute of Integrated study and Research in Biotechnology and Allied Sciences (ARIBAS), New Vallabh Vidyanagar-388121, Gujarat, India.
[3] C.N.P.F Arts and D.N Science College, Dabhoi, Gujarat, India.
[4]Department of Biosciences, Sardar Patel Universty, Vallabh Vidyanagar -388120, Gujarat, India.

ABSTRACT

A series of various Novel heterocyclic derivatives were synthesized. The synthesized compounds were characterized by their melting point, solubility against organic solvents, thin layer chromatography, percentage of nitrogen by Kjeldahl's method. The structures of synthesized derivatives were established by means of Infrared and Nuclear Magnetic Resonance spectral studies. All compounds were evaluated for their Antimicrobial activity.

Keywords: Hetrocyclic, Chalcone, Synthesis, antimicrobial activity, IR, NMR.

INTRODUCTION

Heterocycles with multiple hydrogen bonding sites have gained attention recently for their utility in host-guest systems[1]. Many of these heterocyclic hosts were designed with a preorganized array of hydrogen bonding sites that is complementary to that of a guest molecule. Successful heterocyclic hosts were reported for nucleotide bases,[1] ureas,[2] and several other biologically relevant guest molecules[3]. Hydrogen bonding interactions between heterocycles has also found a place in the rapidly expanding area of self-assembling systems[4]. These systems incorporate hydrogen bonding sites to control the organization of small components into supramolecular structures, either insolution or the solid state. The most desirable hydrogen bonding partners recognize each other with high selectivity and form tight complexes. Such compounds are said to be well-programmed to self- organize. Among heterocycles, chalcone are a class of compounds with biological activity such as antimicrobial, antitumour, antipyretic, antitubercular, anticancer, antifungal, antineoplastic, anti-inflammatory, analgesic, antiplatelet, antiulceraative, antimalarial, antiviral, antileishmania, antioxidant, antihyperglycemic, immunomodulatory, inhibition of chemical modulator release, inhibition of leukotriene B4, inhibition of tyrosinase, inhibition of aldose reductase and prostaglandin binding properties. Many heterocyclic analogs of chalcones have been synthesized and subsequently demonstrated to possess biological and pharmacological activities, which may possibly result in chemotherapeutic agents. Because of great synthetic potentiality the heterocyclic analogs of chalcones are most useful synthons[5]. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The presence of a reactive unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent aromatic rings[6].

In recent years there has been a lot of work done in preparation of chalcones containing heterocyclic. This is due to some specific advantages of the reaction of chalcones synthesis which are as follows[7]

- Solvent free reaction
- Use of non-hazardous chemicals
- Quick reaction
- High yield
- Minimum energy requirement
- Room temperature reaction

Chalcones were prepared by condensation of acetophenone in presence of suitable condensing agent[8, 9]. They undergo a variety of chemical reactions that leads to many heterocyclic compounds[10-13]. Chalcones have been used as intermediates for the preparation of compounds having therapeutic value[14, 15]. Many reviews reveal that chalcone derivatives exhibit diverse pharmacological activities, such as potential cytotoxic agents, antimicrobial agents, antiviral, anti-inflammatory, anesthetic, and etc[16, 17]. The present work was designed to synthesize hetrocyclic compounds via chalcones route and were evaluated by different physical properties, Spectral analysis and antibacterial activity.

EXPERIMENTAL

Melting points were determined on Stuart apparatus and were uncorrected. IR spectra were recorded on FTIR Perkin Elmer spectrophotometer using KBr disc method. 1H-NMR spectra were recorded on Bruker AMX-400 MHz spectrometer in d6-DMSO. Chemical shifts relative to TMS used as internal standard were obtained in ð unit. Physical and spectral data are shown in tables 1 and 2. The heterocyclic derivatives of chalcone were subjected to antimicrobial screening using nutrient agar medium by well diffusion method[18]. The antibacterial activity was tested against various types of bacteria and compared with standard drugs (Ampicillin and Vibromycin) and were carried out at the botany department, Garyounis university; the results are given in table 3. The chalcones then the heterocyclic derivatives were prepared as shown in the following scheme:

Synthesis of (2E)-)-3-(furan-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one

p-methoxyacetophenone (0.01 mol) and furfural (0.01 mol) were dissolved in ethanol (25 mL). Sodium hydroxide solution, 10% (25 mL) was added slowly and the mixture stirred for 4 hrs then it was poured into 400 mL of water with constant stirring and left overnight in refrigerator. The precipitate obtained was filtered, washed and recrystallized from ethanol.

Synthesis of 6-(furan-2-yl)-4-(4-methoxyphenyl)-2H-1, 3-oxazin-2-amine

(0.01 mol) product obtained from step-1and Urea (0.04M) were mixed with 5ml of ethanol and then heated under reflux for 8 hours. The contents were evaporated to dryness and the product so obtained was washed with water repeatedly and then recrystallized from ethanol. The yield obtained was 65% and melting point is 88^{o}C.

(0.01mol) product of step-2 was taken in 20 ml methanol was charged in to a three necked flask equipped with a stirrer and dropping funnel. The solution was stirred to dissolve it completely. To this methanolic solution, 0.01mol formaldehyde was added dropwise during over the period of fifteen minutes. The resultant mixture was stirred for about half an hour to complete reaction of formaldehyde and yield methylol derivative. To this reaction mixture, the methanolic solution of 0.01M benzimiazole was added dropwise with stirring over the period of half an hour at room temperature and then refluxed for one hour at 65-70^{o}C. after that the reaction was allowed to cool and poured in ice water. The solid obtained was filtered off, washed thoroughly with ice water and air-dried. The yield of the product is 77% and melting point is 74^{o}C. The reaction is described in scheme 2.4. The same method was utilized using benzotriazole, phthelamide,p-aminophenol.p-nitro aniline,morpholine andimidazole. The reaction scheme of all these are shown in figure-3.

The data of physical characteristics of synthesized compounds are shown in table-1. Percentage of nitrogen was estimated by Kjeldahl method. All the synthesized compounds were characterized by IR and 1 H NMR. The spectral data of synthesized compounds are shown in table-2.

Antibacterial activity

Antibacterial activity of the hetrocyclic derivative have been carried out against several types of bacteria such as *E.coli;S.aureus* and *P.aregenosa* using nutreant agar medium by well diffusion method. All compounds were suspended in aquous solution in different concentration ranged from 100mcg/mL. The results are expressed in MIC(Minimal Inhibitory Concentration). Solvent Blanks were run against each test organism in well assays and the experimental biological data is given in table-3.

RESULT AND DISCUSSION

All synthesized compounds as well as the reactions that carried out were characterized and monitored by TLC, melting point, nitrogen estimation, IR and ^{1}H NMR and they all gave satisfactory results as shown in table-2.

The compounds were evaluated for their antibacterial activity against various types of bacteria. The compounds A1-A7 have shown significant antibacterial activity in comparison against Norfloxacin and Ampicillin at 100mcg/mL. Compounds A5 and A6 showed higher activity compare to othercompounds. How ever all the synthesized compounds showed activity. The furfural was reacted with substituted acetophenones to obtain chalcones. Further various seven derivatives were obtained by the described procedure.All the synthesized compounds have shown promising antibacterial and antifungal activitys with suitable molecular modifications the compounds may show better activities.

Table 1: Characterization data of synthesized compounds (A1 – A7)

Compd	Molecular Formula	Mol.Wt gm/mol	M.P (^{o}C)	Yield (%)	Nitrogen (%)	
A1	$C_{23}H_{22}N_4O_3$	402.44	74	77	13.91	11.85
A2	$C_{22}H_{19}N_5O_3$	401.41	71	77	17.43	15.78
A3	$C_{24}H_{19}N_3O_5$	429.42	77	79	9.78	7.45
A4	$C_{22}H_{21}N_3O_4$	391.41	79	78	10.73	8.88
A5	$C_{22}H_{20}N_4O_5$	420.41	78	75	13.32	11.56
A6	$C_{20}H_{23}N_3O_4$	369.41	77	76	11.37	9.87
A7	$C_{19}H_{22}N_4O_3$	354.40	82	75	15.80	13.96

Table 2: Infra Red / 1H NHR spectral study of the synthesized compounds

Compound	Infra Red (cm^{-1})	1H – NMR (δ ppm)
A1	3411 (N-H str.), 2965 (C-H Ar str.), 2855 (C-H str.), 1670 (C=O Amide Str.), 1592 (C=N str.), 880 (C-H Ar. def.), 1254(C-O str.), 1443(-C=C- Ar. str.).	7.44-7.80 (m, 12H, Ar-H), 8.40 (3H, NH), 3.89 (s, 3H, OCH_3), 3.69 (s, 2H, CH_3)
A2	3430 (N-H str.), 2920 (C-H Ar str.), 1680 (C=O Amide Str.), 1612 (C=N str.), 910 (C-H Ar. def.), 1250(C-O str.), 1450(-C=C- Ar. str.).	7.38-7.88 (m, 12H, Ar-H), 8.50 (3H, NH), 3.98 (s, 3H, OCH_3), 3.59 (s, 2H, CH_3)
A3	3405 (N-H str.), 2965 (C-H Ar str.), 2855 (C-H str.), 1442 (C=O Amide Str.), 1592 (C=N str.), 780 (C-H Ar. def.), 1254(C-O str.), 1443(-C=C- Ar. str.).	7.30-7.70 (m, 12H, Ar-H), 8.40 (3H, NH), 3.89 (s, 3H, OCH_3), 3.99 (s, 2H, CH_3)
A4	3411 (N-H str.), 2965 (C-H Ar str.), 2855 (C-H str.), 1590 (C=O Amide Str.), 1550 (C=N str.), 755 (C-H Ar. def.), 1254(C-O str.), 1443(-C=C- Ar. str.).	7.40-7.85 (m, 12H, Ar-H), 8.49 (3H, NH), 3.49 (s, 3H, OCH_3), 3.78 (s, 2H, CH_3)
A5	3411 (N-H str.), 2965 (C-H Ar str.), 2855 (C-H str.), 1640 (C=O Amide Str.), 1480(C=N str.), 880 (C-H Ar. def.), 1254(C-O str.), 1470(-C=C- Ar. str.).	7.50-7.90 (m, 12H, Ar-H), 8.25 (3H, NH), 3.95 (s, 3H, OCH_3), 3.88 (s, 2H, CH_3)
A6	3411 (N-H str.), 2965 (C-H Ar str.), 2855 (C-H str.), 1670 (C=O Amide Str.), 1560 (C=N str.), 880 (C-H Ar. def.), 1254(C-O str.), 1443(-C=C- Ar. str.).	7.20-7.60 (m, 12H, Ar-H), 8.70 (3H, NH), 3.69 (s, 3H, OCH_3), 3.65 (s, 2H, CH_3)
A7	3390 (N-H str.), 2950 (C-H Ar str.), 2845 (C-H str.), 1640 (C=O Amide Str.), 1598 (C=N str.), 890 (C-H Ar. def.), 1254(C-O str.), 1455(-C=C- Ar. str.).	7.48-7.80 (m, 12H, Ar-H), 8.55 (3H, NH), 3.70 (s, 3H, OCH_3), 3.95 (s, 2H, CH_3)

Table 3: In-vitro antibacterial and antifungal activity of synthesized compounds

Compound	Zone of inhibition at 100 mcg/mL (in mm.)		
	E.coli	*S.aureus*	*P.aregenosa*
A1	17	18	16
A2	20	17	19
A3	21	19	17
A4	17	19	21
A5	21	20	18
A6	22	20	19
A7	16	18	17
Norfloxacin	24	21	22
Ampicillin	25	23	21

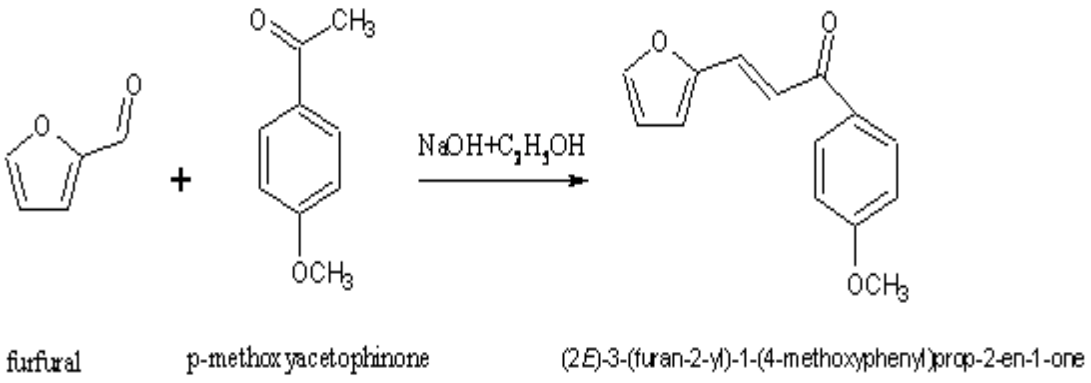


Fig. 1: Synthesis of Chalcone

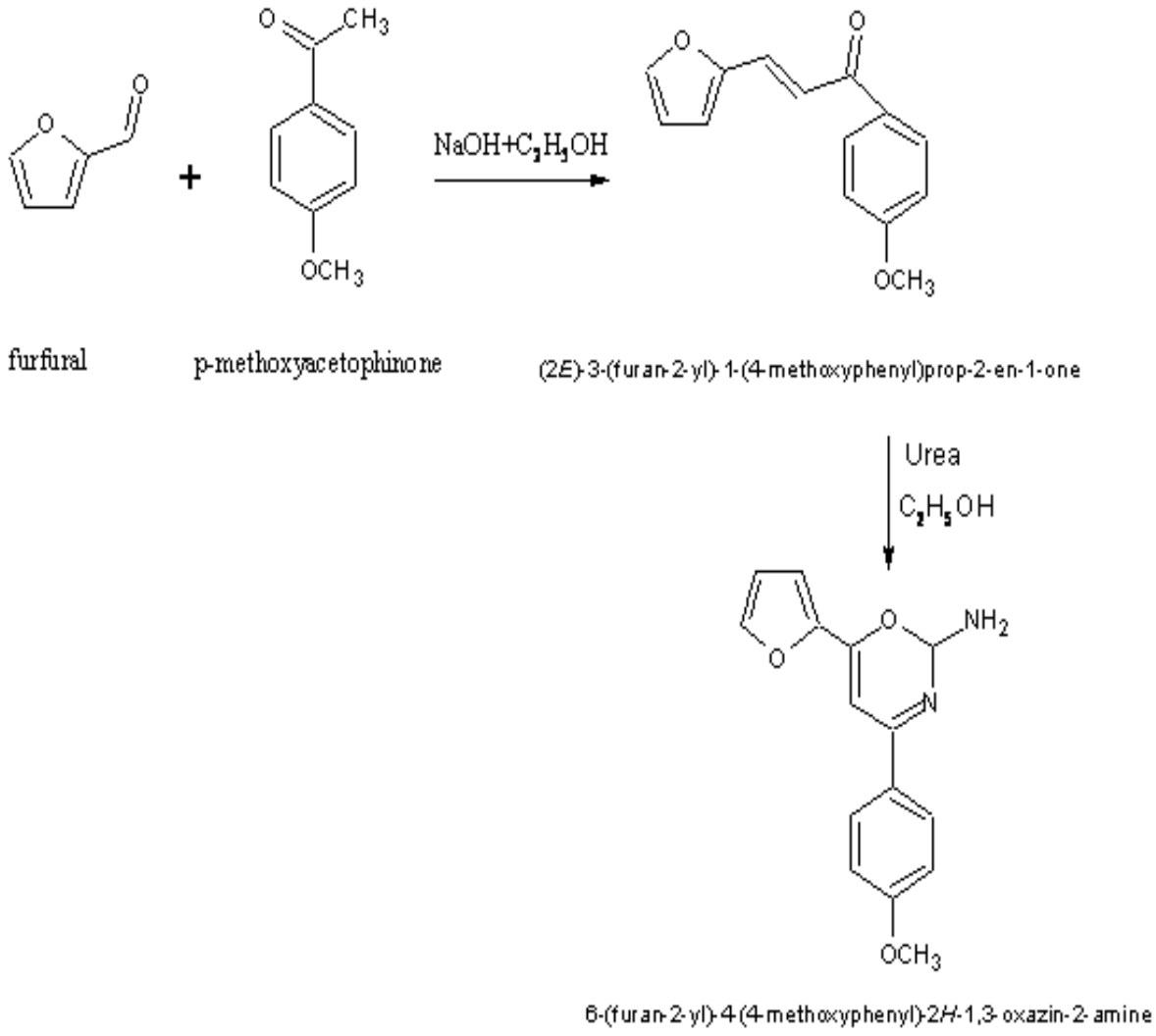
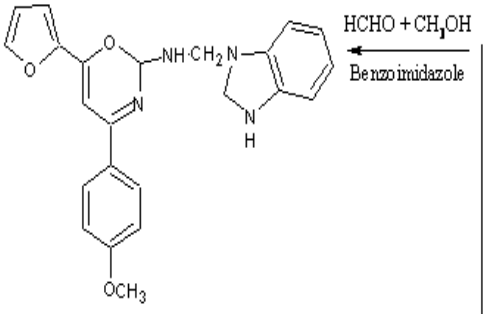
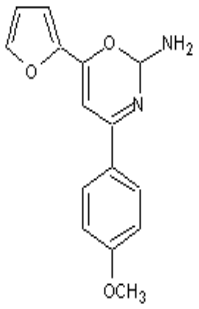
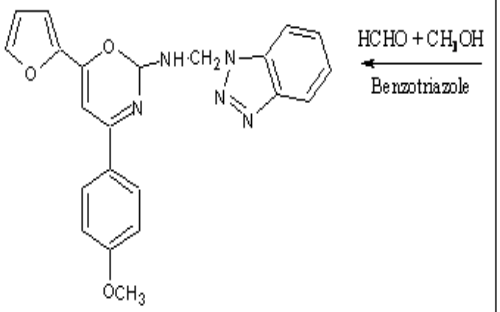


Fig. 2: synthesis of 6-(furan-2-yl)-4-(4-methoxyphenyl)-2H-1, 3-oxazin-2-amine



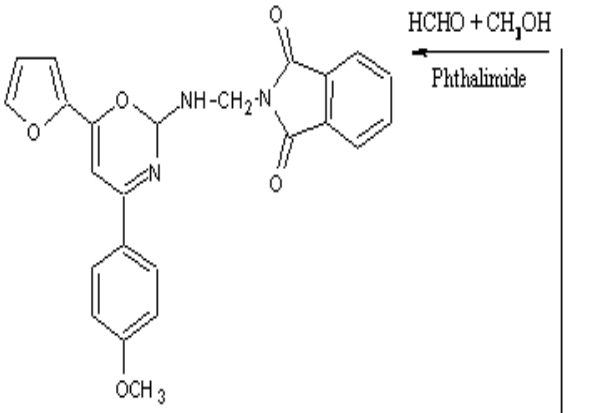
4-(4-methoxyphenyl)-*N*-(2,3-dihydro-1*H*-benzimidazol-1-ylmethyl)-6-(furan-2-yl)-2*H*-1,3-oxazin-2-amine



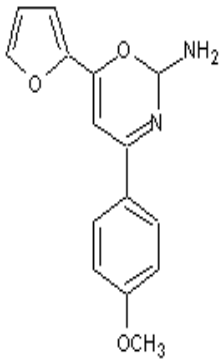


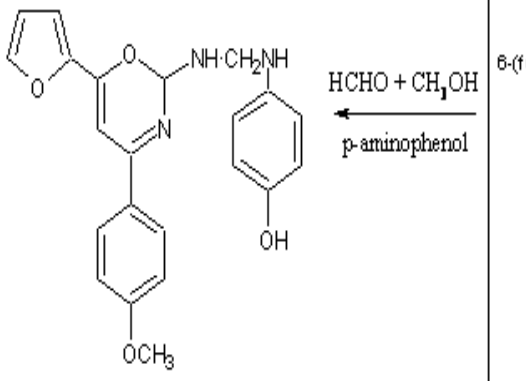
N-(1*H*-benzotriazol-1-ylmethyl)-4-(4-methoxyphenyl)-6-(furan-2-yl)-2*H*-1,3-oxazin-2-amine

6-(furan-2-yl)-4-(4-methoxyphenyl)-2*H*-1,3-oxazin-2-amine



2-({[4-(4-methoxyphenyl)-6-(furan-2-yl)-2*H*-1,3-oxazin-2-yl]amino}methyl)-1*H*-isoindole-1,3(2*H*)-dione





4-[({[6-(furan-2-yl)-4-(4-methoxyphenyl)-2*H*-1,3-oxazin-2-yl]amino}methyl)amino]phenol

6-(furan-2-yl)-4-(4-methoxyphenyl)-2*H*-1,3-oxazin-2-amine

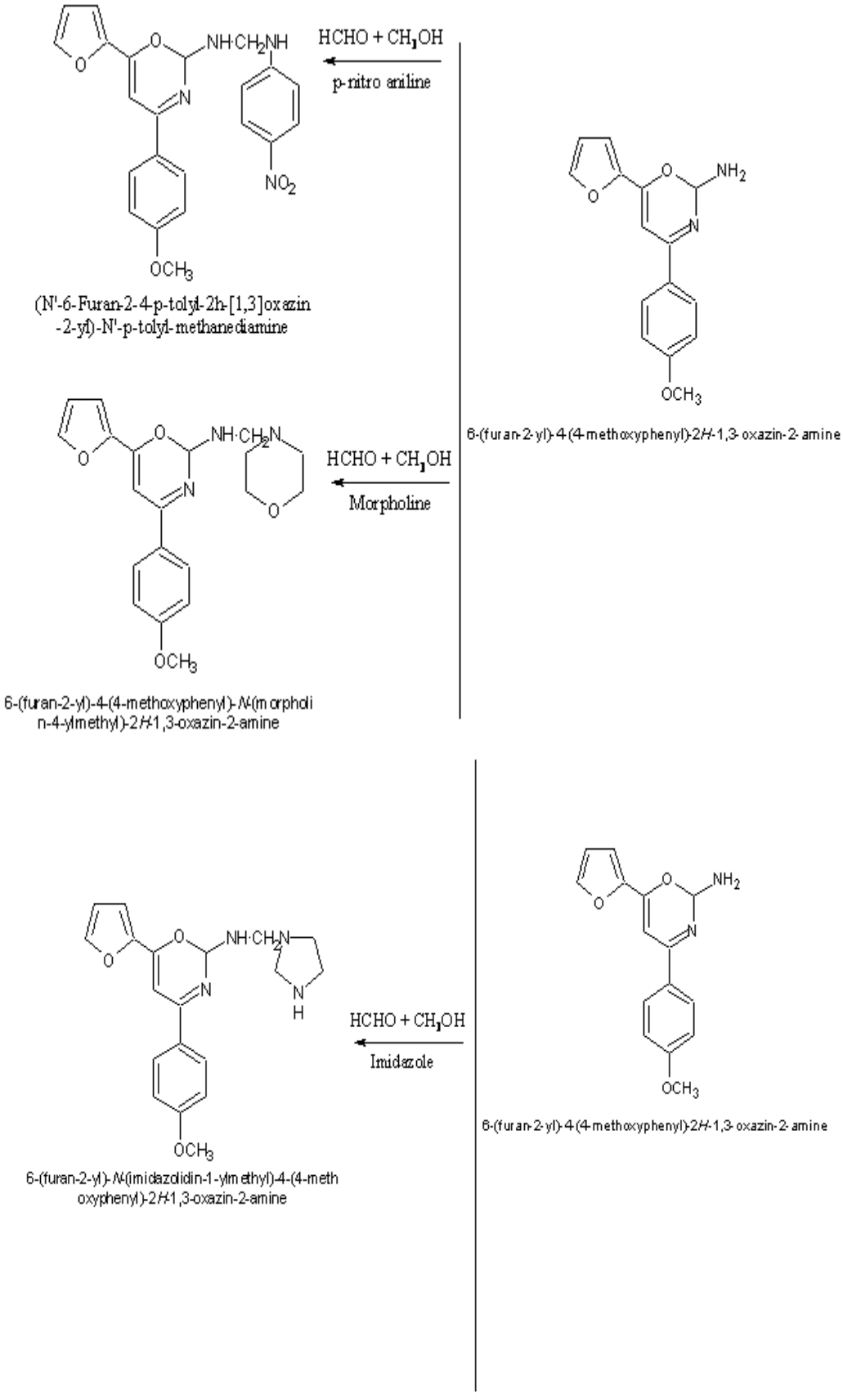


Fig. 3: Various derivatives of p-methoxy acetophenone

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