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Research Paper

Synthesis and characterization of some 4-thiazolidinones derivatives based on PFP and their antibacterial activity

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Abstract- *4-Thiazolidinones have been prepared by the reaction of various substituted schiff bases with mercapto acetic acid. The structures of the compounds have been confirmed by elemental analysis and spectral analysis. The antibacterial activity of the compounds has also been screened against B. subtillis, S. aureus, E. coli and P. aeruginosa.*

Key words: Synthesis, Biological activity, Thiazolidinone, Mercapto acetic acid etc.

Introduction:

4-Thiazolidinones are an important group of heterocycles found in numerous natural products and pharmaceuticals[1]. The growing potent literature of recent years demonstrates that the thiazole derivatives exhibit better pharmacological properties such as antitubercular[2], anti-inflammatory[3], pesticides[4], anticonvulsant[5], antimicrobial[6] and many others. Further more significant biological properties are associated with thiazolidinone derivatives like anticonvulsant[7], antihelmintics[8], antidiabetic[9].

In present study we have used various schiff bases on heterocyclization reaction with mercapto acetic acid gave the desired products 4-thiazolidinones. Their structure have been characterized on the basis of their analytical and spectral data.

Experimental

Melting Points were determined on Gallen-Kamp melting point apparatus and are uncorrected. All the compounds were routinely checked for their homogeneity by TLC on silica gel-G plates, IR spectra were recorded in KBr on a Perkin-Elmer BX series FT-IR spectrophotometer, ^{1}H NMR spectra were recorded BRUKER Spectrometer on a 400 MH_z in $CDCl_3$ using TMS as internal standard and satisfactory C, H, N and S analysis were obtained for all the compounds. The mass spectra were recorded on (FAB mass), spectrometry used to confirm their structure.

Antibacterial activity (anti-microbial activity) was carried out by cup-plate agar diffusion method. The bacterial strains studied are identified strains and were obtained from National chemical laboratory (NCL) Pune, India

Experimental procedures for the synthesis of this series of compounds have been adopted according to reported methods[10, 11, 12, 13].

Synthesis of 2-[1-N-phenyl-3-phenyl-pyrrazole]-3-N-aryl-thiazolidine-4-ones (2a-h): The 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) and then after 2-[1-N-phenyl-3-phenyl-pyrrazole]-3-N-aryl-thiazolidine-4-ones was prepared followed by method reported in literature[14-17]. The procedure is as follows:

Synthesis of (1E)-1-(phenyl)-ethanone-(phenyl)-hydrazone: A mixture of phenyl hydrazine (I) (0.01 mole) and acetophenone (II) (0.01 mole) in absolute ethanol was refluxed in water bath for 2 hrs. in presence of 1 ml glacial acetic acid. The crude product was isolated and crystallized from absolute alcohol. Yield was about 94%.

Synthesis of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP): (1E)-1-(phenyl)-ethanone-(phenyl)-hydrazone (III) (0.01 mole) was added in mixture of Vilsmeir-Haack reagent (prepared by drop wise addition of 3 ml of $POCl_3$ in ice cooled 25 ml di-methylformamide [DMF] and refluxed for 5 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from ethanol. Yield was about 82%.

Synthesis of Arylidine-[1-N-phenyl-3-phenyl-pyrazole](1ah): A mixture of equimolar amount of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) (0.01 mole) (1) and various aromatic amines (0.01 mole) in 50 ml acetic acid was refluxed for about 10-12 hrs. on oil bath with TLC monitoring. The reaction mixture was cooled and it was poured into ice water and extracted with ethyl acetate and water and finally dried

over anhydrous sodium sulfate. The solvent was evaporated to give the solid product. It was crystallized from ethyl acetate-hexane using decolorizing charcoal to give various anils (i.e. Schiff bases) (1a-h).

Synthesis of 2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-aryl-thiazolidine-4-ones (2a-h): A mixture of schiff bases (1a-h) (0.01 mole) in THF (30ml) and mercapto acetic acid (thioglycolic acid) (0.01 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed for 12 hours. The solvent was removed to get a residue, which was dissolved in benzene and passed through column of silica gel using benzene: chloroform (8:2; v/v) mixture as eluent. The eluent was concentrated and the product crystallized from alcohol to give 4-thiazolidinones (2a-h), which were obtained in 55-70% yield.

The analytical and spectral data of compounds (2a-h) are described.

2a: 2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(phenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1680 (-C=O of thiazolidinone); PMR Spectra ($CDCl_3$): δ (ppm) 6.12-7.8 (1H, m, aromatic + H of pyrazole), 3.1 (2H of CH_2 for thiazolidinone), 5.35 (2H of C_2H for thiazolidinone); CMR Spectra ($CDCl_3$): δ (ppm) 113-130 (benzene), 136-145 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH).

2b:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(4-methoxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1600, 1500 (-C-H, aromatic), 1690 (pyridine ring, -C=O of thiazolidinone), 1200 (Ar-O-CH_3); PMR Spectra ($CDCl_3$): δ (ppm) 6.12-7.8 (1H, m, aromatic + H of pyrazole), 3.2 (2H of CH_2 for thiazolidinone), 5.35 (H of C_2H for thiazolidinone), 3.35 (3H of CH_3 for thiazolidinone); CMR Spectra ($CDCl_3$): δ (ppm) 113-131 (benzene), 135-145 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH), 56 (CH_3).

2c:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(4-hydroxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1670 (-C=O of thiazolidinone), 3200-2600 (-OH), 2880, 2920, 1400 (CH_2); PMR Spectra ($CDCl_3$): δ (ppm) 6.12-7.8 (1H, m, aromatic + H of pyrazole), 3.2 (2H for CH_2 of C_5 thiazolidinone), 5.35 (H for C_2H of thiazolidinones), 3.9 (H of OH); CMR Spectra ($CDCl_3$): δ (ppm) 113-132 (benzene), 135-146 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH).

2d:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(2-hydroxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1690 (-C=O of thiazolidinone), 3200-2600 (-OH), 2880, 2920, 1400 (CH_2); PMR Spectra ($CDCl_3$): δ (ppm) 6.12-7.8 (1H, m, aromatic + H of pyrazole), 3.1 (2H for C_5H), 5.35 (H for C_2H), 3.9 (H of OH); CMR Spectra ($CDCl_3$): δ (ppm) 113-133 (benzene), 135-147 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH).

2e:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(4-methyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1690 (-C=O of thiazolidinone), 2950, 1370 (CH_3), 2880, 2920, 1400 (CH_2); PMR Spectra ($CDCl_3$): δ (ppm) 6.2-7.9 (1H, m, aromatic + H of pyrazole), 3.2 (2H for C_5H), 2.1 (3H for CH_3), 5.35 (H for C_2H); CMR Spectra ($CDCl_3$): δ (ppm) 113-134 (benzene), 135-148 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH), 25 (CH_3).

2f:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(3,4-methelenedioxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic, thiazole ring), 1690 (-C=O of thiazolidinone), 1200 (aryl-alkyl ether), 2880, 2920, 1400 (CH_2); PMR Spectra ($CDCl_3$): δ (ppm) 6.15-7.8 (1H, m, aromatic + H of pyrazole), 5.35 (H for C_2H), 5.35 (2H for CH_2 of –O-CH_2-O-), 3.2 (2H of C_5H); CMR Spectra ($CDCl_3$): δ (ppm) 114-130 (benzene), 135-149 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH), 95 (O-CH_2-O).

2g:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(4-hydroxy-3-methoxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1680 (-C=O of thiazolidinone), 3200-2600 (-OH), 1200 (aryl-alkyl ether), 2880, 2920, 1400 (CH_2); PMR Spectra ($CDCl_3$): δ (ppm) 6.12-7.9 (1H, m, aromatic + H of pyrazole), 3.2 (2H for C_5H), 5.35 (H for C_2H), 3.9 (H of OH), 3.35 (3H for OCH_3); CMR Spectra ($CDCl_3$): δ (ppm) 113-135 (benzene), 135-150 (pyrazole), 169 (C=O), 36 (CH_2), 46 (CH), 56 (CH_3).

2h:2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-(3,4-diethoxyphenyl)-thiazolidine-4-ones: IR (KBr, cm^{-1}): 3030, 1500, 1600 (-C-H, aromatic), 1670 (-C=O of thiazolidinone), 1200 (aryl-alkyl ether), 2880, 2920, 1400 (-CH_2-); PMR Spectra ($CDCl_3$): δ (ppm) 7.2-8.1 (1H, m, aromatic + H of pyrazole), 3.25 (2H for C_5H), 3.35 (H for C_2H), 2.1-2.5 (6H for 2 CH_3), 2.89-3.18 (4H for 2 CH_2); CMR Spectra ($CDCl_3$): δ (ppm) 113-136 (benzene), 135-151 (pyrazole), 169 (C=O), 36 (CH_2), 14 (CH_3), 58 (OCH_2).

Antibacterial activity

The study has been conducted according to the method adopted by Cruickshank et. al.[18]. Nutrient agar broth was melted in a water bath and cooked to 45^0C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 ml of 24 hour old culture especially and mixed well by gentle shaking before pouring on the sterilized Petri dish (25 ml each). The poured material was allowed to set (1.5 hour) and there after the "cups" were made by punching into the agar surface with a sterile cork borer. Into this "cups" 0.1 ml of test solution (prepared by dissolving 10gm of sample in 10ml DMF) was added by sterile micropipette. The plates were noted. Ampicillin, Tetracycline, Gentamycin, and Chloramphenicol were used as standard drugs and a solvent control was also run to know the activity.

Activity of standards and inhibition due to DMF (solvent) are given in Table-II.

The compounds tested for antimicrobial activity are listed in Table-III show size of zone of inhibition of bacterial growth procedure by test compounds for broad range of antimicrobial activity inhibiting growth of gram-positive bacterial strains *B. subtillis* and *S. aureus*, and gram-negative bacterial strains *E. coli* and *P. aeruginosa*.

Comparison of antimicrobial activity of produced compounds with that of standard antimicrobial drugs reveals that the produce compounds (Schiff Bases, 2-Azetidinones, 4-Thiazolidinones, 2H-Pyrrole-2-ones and 2-Pyrrolidiones) shows moderate to good activity against all four bacterial strains.

Among 2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-aryl-thiazolidine-4-ones (2a-h) (Table-III) compound, 2b, 2c, 2d, 2f and 2h show good antimicrobial activity.

Results and Discussion

As we know that the azomethines are the crucial material for the preparation of heterocyclic compounds like 2-azetidinones, 4-thiazolidinones, etc.. These azomethines (1a-h) on cyclocondensation reaction with thioglycolic acid in the

presence of anhydrous $ZnCl_2$ affords the biologically active of 4-thiazolidinones derivatives (2a-h). Their structures were confirmed by analytical and spectral data. The C, H, N and S contents of the prepared compounds were consistent with their predicted structures as shown in Scheme-3. The infrared spectra show the band in the region 1680-1700cm^{-1} for carbonyl (>C=O) group of 4-thiazolidinone ring.

The proton magnetic resonance spectra of the prepared compounds (2a-h) shows signal at 5.35 δ for CH_2 proton at position-5 in the 4-thiazolidinone ring and a signal at 3.2 δ for -CH protons at position-2 in the ring. All other signals are at their respective positions in the PMR spectrum.

The CMR spectra of the compounds also show the signal at 163 for C=O and 36 δ ppm for CH_2 of 4-thiazolidinone. All other signals appeared at their respective positions.

Conclusion

Newly synthesized compounds of azomethines (2a to 2h) have been tested for their anti bacterial activity against gram positive bacteria *B. subtillis and S. aureus* gram negative bacteria *E. coli and P. aeruginosa* by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMF. Ampicillin, Tetracyclin, Gentamycin, Chloramphenicol were used as a reference compound. The compound 2b, 2c, 2d, 2f and 2h were shown significant activities and compound 2a, 2e and 2g have shown moderate activity against gram positive and gram negative bacteria.

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References

1. Verma A. and Saraf S. K., *Eur. J. Med. Chem*, **43,** 897 [PubMed:17870209] (**2008**).
2. Monian A. K., Khadse G. G. and Sengupta S. R., Indian Drugs, **30**(7), 324-326 (**1993**), *Chem. Abstr.*, **120**, 323 (**1994**)
3. Shinji T. and Yoshitaka M., Eur. Pat. Appl., EP 149: 884, *Chem. Abstr.*, **104**, 34071e (**1984**)
4. Gunether B., Wilhelm B., Stefan D. and Wilfried P., Ger. Offen., DE 3: 842, 790, *Chem. Abstr.*, **113**, 6330f (**1990**)
5. Bernard D., Pierce R. J., Patrick H. and Yyes L. J., Eur. Pat. Appl.; EP 322: 296, *Chem. Abstr.*, **111**, 232799 (**1990**)
6. Harode R., Jain V. K. and Harma T. C., *J. Indian Chem. Soc.*, **67**, 262 (**1990**) *Chem. Abstr.*, **113**, 132066f (**1990**)
7. Nagar S., Singh H. H., Sinha J. N. and Parmar S. S., *J. Med. Chem.*, **16**, 178 (**1973**)
8. Aries R., French Patent; 21, 85, 245 (**1974**) *Chem. Abstr.*, **81**, 140868 (**1974**)
9. Moustfa M. A., Bayomi S. M., El-man A. A. and Kerdwy M. M., *Sci. Pharma.*, **57**(2), 125 (**1989**) *Chem. Abstr.*, **112**, 98444b (**1990**)
10. Kidwai M., Kumar P., Goel Y. and Kumar K., *Ind. J. Chem.*, **36**(B), 175 (**1997**).
11. Patel V. K., Ph.D. Thesis, S P University, Vallabh Vidyanagar, Gujarat, India; (**2002**)
12. Desai N. C., Shukla H. K. and Thaker K. A., *J. Ind. Chem. Soc.*, **61**, 239 (**1984**)
13. Srivastava S. K., Pathak R. B. and Bhel S. C., *J. Ind. Chem. Soc.*, **68**, 113 (**1991**)
14. Sheehan and Izzo; *J. Am. Chem. Soc.*, **70**, 1985 (**1948**)
15. Clark H. T., Johnson J. R. and Robinson R., The Chemistry of Penicillins, Princton University Press, N.Y., (**1949**)
16. Abraham E. P., *Q. Rev.*, **21**, 231 (**1967**)
17. Barton D. H. R., *Pure Appl. Chem.*, **33**, 1 (**1973**) *Chem. Abstr.*, **78**, 743 (**1973**)
18. Cruickshank R., Dugid J. P., Marmion D. P. and Swain R. H. A., Medical microbiology, Churchil-Livingstone, Edinburgh, London, **2**, 12th edition (**1975**)

Table 1: Physical constants of synthesis of 2-[1-N-phenyl-3-phenyl-pyrazole]-3- N-aryl-thiazolidine-4-ones: (2a-h)

S. No	Ar	Molecular Formula	Molecular Weight	M.P. °C	Yield %	% of C, H, N & S Cal / Found			
						C	H	N	S
2a	$-C_6H_5$	$C_{24}H_{19}N_3OS$	397	142	56	72.5	4.7	10.5	8.0
						72.3	4.5	10.4	7.8
2b	4- $OCH_3C_6H_4$	$C_{25}H_{21}N_3O_2S$	427	156-158	60	70.2	4.9	9.8	7.4
						70.5	4.6	9.4	7.3
2c	4- OHC_6H_4	$C_{24}H_{19}N_3O_2S$	413	164-165	59	69.7	4.6	10.1	7.7
						69.3	4.5	9.9	7.6
2d	2- OHC_6H_4	$C_{24}H_{19}N_3O_2S$	413	168	72	69.7	4.6	10.1	7.7
						69.5	4.5	9.9	7.4
2e	4- $CH_3C_6H_4$	$C_{25}H_{21}N_3OS$	411	172	59	72.9	5.1	10.2	7.7
						72.7	5.0	10.0	7.4
2f	3,4- $O_2CH_2C_6H_3$	$C_{25}H_{19}N_3O_3S$	441	170	58	68.0	4.3	9.5	7.2
						67.8	4.2	9.0	7.0
2g	4-OH-3-$CH_3C_6H_3$	$C_{25}H_{21}N_3O_3S$	443	160	56	67.7	4.7	9.4	7.2
						67.6	4.7	9.3	7.2
2h	3,4-$(C_2H_5O)_2C_6H_3$	$C_{28}H_{27}N_3O_3S$	485	171	56	69.2	5.5	8.6	6.5
						68.8	5.3	8.5	6.4

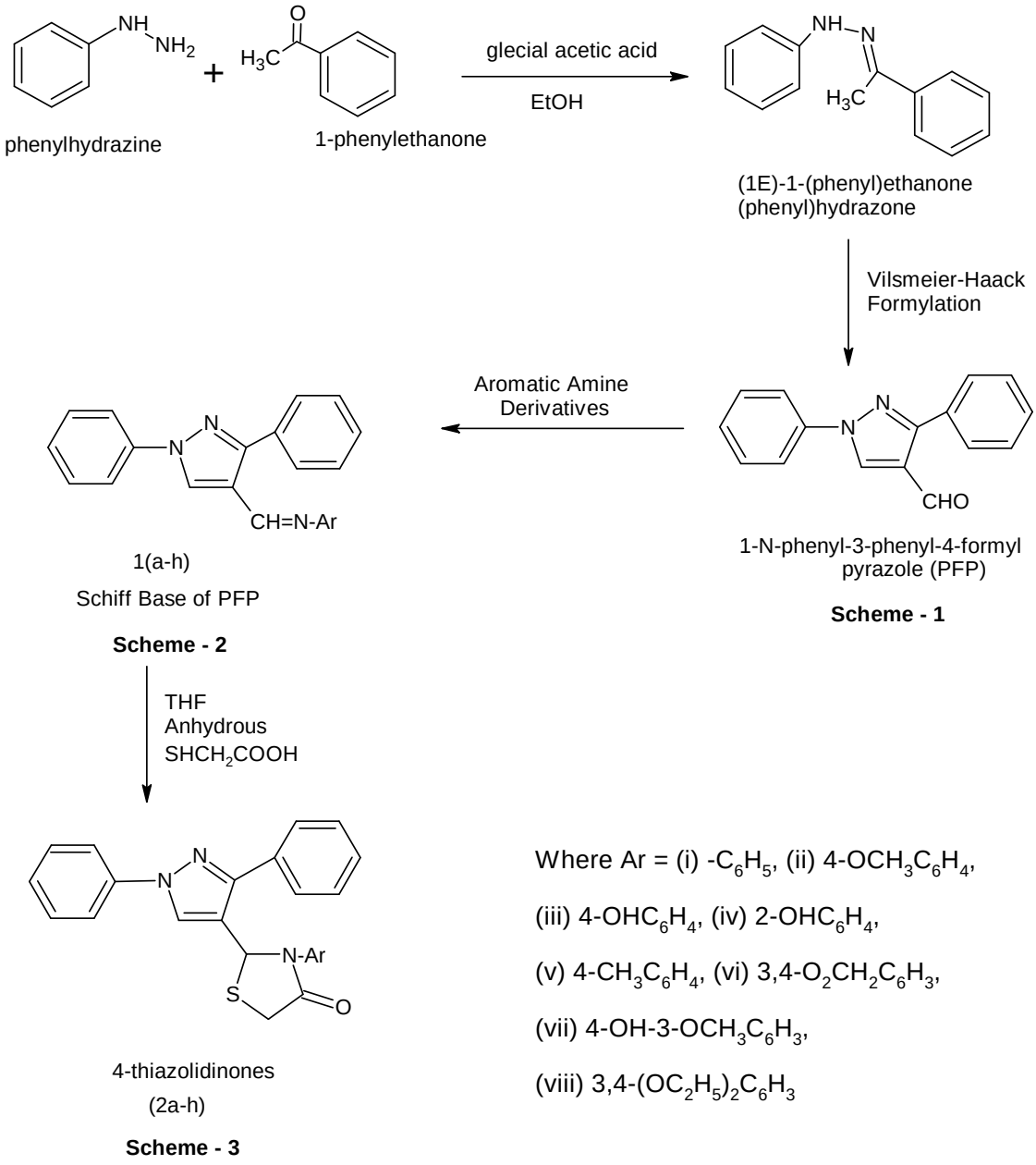
Table 2: Antibacterial activity of standards and solvent (DMF)

No.	Name of Compounds	Zone of inhibition (in mm)			
		Gram positive		Gram negative	
		B. subtillis	*S. aureus*	*E. coli*	*P. aeruginosa*
1	DMF	6	5	5	5
2	Ampicillin	18	15	20	20
3	Tetracyclin	21	22	15	19
4	Gentamycin	20	18	18	22
5	Chloramphenicol	20	23	18	23

Table 3: Antibacterial activity of 2-[1-N-phenyl-3-phenyl-pyrazole]-3-N-aryl-thiazolidine-4-ones: (2a-h)

Compound (designation)	Zone of Inhibition (in mm)			
	Gram positive		Gram negative	
	B. subtillis	*S. aureus*	*E. coli*	*P. aeruginosa*
2a	09	09	16	09
2b	10	10	14	10
2c	11	13	11	16
2d	15	17	18	14
2e	07	09	10	08
2f	12	12	15	13
2g	08	09	10	12
2h	16	15	12	13

Reaction Scheme



Scheme - 1

Scheme - 2

Scheme - 3

Where Ar = (i) $-C_6H_5$, (ii) $4\text{-}OCH_3C_6H_4$,

(iii) $4\text{-}OHC_6H_4$, (iv) $2\text{-}OHC_6H_4$,

(v) $4\text{-}CH_3C_6H_4$, (vi) $3,4\text{-}O_2CH_2C_6H_3$,

(vii) $4\text{-}OH\text{-}3\text{-}OCH_3C_6H_3$,

(viii) $3,4\text{-}(OC_2H_5)_2C_6H_3$