Synthesis and Biological Evaluation of Some New 4-{[2-Chloro-5-(4-substitutedphenyl)pyridin-3-yl]methylene}-1-substituted-2-phenyl-1*H*-Imidazol-5(4*H*)-one Derivatives

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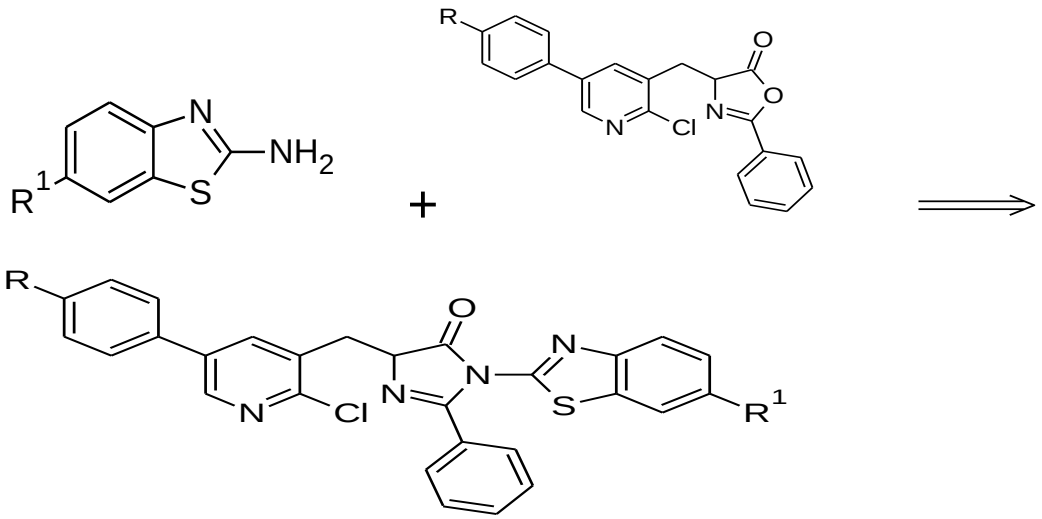
Abstract

A new series of 4-{[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl]methylene}-1-substituted-2-phenyl-1*H*-imidazol-5(4*H*)-one derivatives was synthesized by the reaction of 4-{[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl)]methylidene}-2-phenyl- 1,3-oxazol-5(4*H*)-one with various 2-amino-benzo-thiazole and pyridine. The structures of the synthesized compounds are established with the help of TLC, IR, ^{1}HNMR, MASS spectrometric and elemental analysis. The synthesized compounds were screened for *in Vitro* antibacterial activity against various bacterial strains and antifungal activity against various fungal strains.



Keywords: Antibacterial, Antifungal activity, Imidazole, Substituted phenyl.

Introduction

Imidazolones and their related derivatives are a class of important heterocyclic compounds which show a various biological and pharmaceutical properties such as anti-inflammatory (El-Araby et al 2012), antiparkinsonian (Naithani et al 1989), antimicrobial (Gomha et al 2011, Desai et al 2009, Revanasiddappa et al 2017), anticonvulsant (Chatrabhuji et al 2015, Mohamed et al 2015, Upadhyay et al 1991), anticancer (Solankee et al 2004). The therapeutic importance of the compounds inspired us to synthesize some potential imidazolinones (Desai et al 2000, Tripathy et al 2004, Hirapara et al 2004, RamaSharma et al 1993) and CNS depressant (Mukherji et al 1981, Write et al 1966). The imidazolinones are associated with a wide range of therapeutic activities (Duschinsky et al 1995, Luigi et al 1969, Godefroi et al 1972, Harfenist et al 1978, Meenakshi et al 1990) such as anticonvulsant, sedative and hypnotic potent, CNS depressant, antihistamine, antimalarial, bactericidal, fungicidal, anti-inflammatory, MAO inhibitory, antiparkinsonian, antihypertensive and anthelmintic. quinolone substituted imidazol-5(4*H*)-ones derivatives are also reported anti-inflammatory, anticancer agents cytotoxic activity(Aghara et al 2020, RaniShantaram Kankate et al 2023).

Results and Discussion

Synthesis of 5-(4-substitutedphenyl)-2-chloro-3-formyl pyridine [1]

Dimethylformamide (9.66 mL, 60 moles) and N-(2-arylethenyl) acetamide (5 moles) in a three-necked round-bottomed flask equipped with a thermometer pocket, reflux condenser, guard tube and mechanical stirrer. Reaction mixture cooled to 0^{o}C. To it phosphorous oxychloride (40 moles) was added drop wise with stirring over a period of 30-40 minutes at 0-5^{o}C. Stirred the reaction mixture for 1 hour at room temperature and then stirred at 90^{o}C for 4hours.

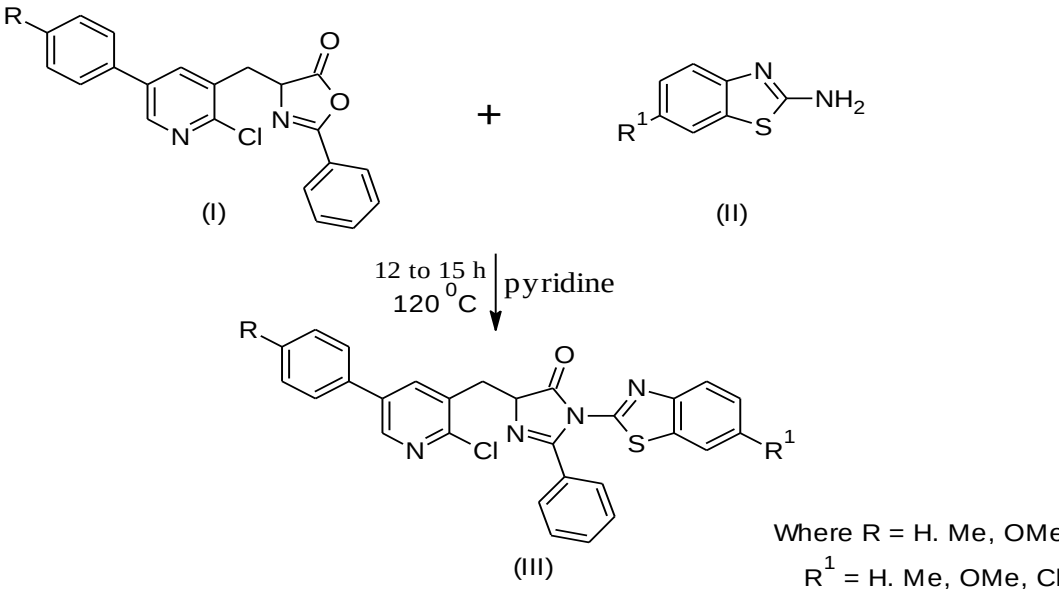
Synthesis of 4-{[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl)] methylidene} -2-phenyl-1, 3-oxazol-5(4*H*)-one. [II]

5-(4-substitutedphenyl)-2-chloro-3-formyl pyridine (0.03 mole), anhydrous sodium acetate (0.03 mole), acetic anhydride (0.08 mole) and Hippuric acid (0.03 mole) in a three-necked round-bottomed flask equipped with a

thermometer pocket, reflux condenser and mechanical stirrer on a heating mental. Heated the reaction mass up to 3 hrs till the mixture liquidified completely. The reaction mixture was cooled to room temperature and ethanol (30 mL) was added slowly to the contents of flask and the mixture was allowed to stand overnight.

Synthesis of 4-{[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl] methylene}-1-substituted-2-phenyl-1*H*-imidazol-5(4*H*)-one derivatives. [III] (C-1 to12)

4-{[2-chloro-5-(4-substitutedphenyl)pyridin-3-yl)]methylidene}-2-phenyl-1,3-oxazol-5(4*H*)-one (0.003 mol) and appropriate 2-amino-benzo-thiazole(0.003 mol) and pyridine (30mL) in a three-necked round-bottomed flask equipped with a thermometer pocket, reflux condenser and mechanical stirrer on a oil bath at 120 ^{0}C. The reaction mixture was refluxed for 12 to 15 h. The excess of pyridine was distilled off and the reaction mixture was cooled to room temperature. Pour the reaction mass into crushed ice and acidified with dilute HCl. The solid was precipitated out, filtere it and washed with hot water till neutral pH to obtain desired product.



Reaction Scheme

Reaction Scheme 1: 4-{[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl]methylene} -1-substituted-2-phenyl-1H-imidazol-5(4*H*)-one derivatives

Experimental Section

General

Measured melting points are uncorrected on the basis of available melting apparatus and present in degree Celsius. The monitoring of reaction and purity of the synthesized compounds including intermediates were checked on TLC aluminum sheet silica gel F_{245} (E. Merck) using a mixture of Toluene:Ethylacetate (8:2) as mobile phase and visualize under U.V. light 254nm. Elemental analysis (% C, H, N) was carried out by a Perkin Elmer 2400 CHN analyzer. IR spectra of all the compounds have been recorded on a Shimadzu FT-IR 8401 spectrophotometer in KBr disks. The ^{1}H-NMR spectra have been recorded on a Bruker AC 400F (400MHz) instrument using TMS as an internal standard in DMSO-d_6 as a solvent, with chemical shifts in δ_H. Mass spectra, JEOL-JMS 600 spectrometer. The solvent was removed under reduced pressure using a Buchi rotary evaporator. Chemicals were purchased from AR grade and substituted anilines, malononitrile are commercial products and were used without further purification.

Spectroscopic analysis of 4-{[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl] methylene}-1-substituted-2-phenyl-1*H*-imidazol-5(4*H*)-one derivatives(C-1 to12)

C-1: M.P. 188-192^{0}C, Yield 60%, **IR cm^{-1}**1725 (s, C=O str.), 1630 & 1486 (m, C=C aromatic str), 720 (m, C-Cl str)**^{1}H NMR δ_H** 6.5 – 8.9 (17H.m, Ar-H). **Mol. For**. $C_{28}H_{17}ClN_4OS$, **Mol.Wt**. 492, **Anal. data**. (Cal/Found) C% 68.22/67.88, H% 3.48/3.24, N% 11.36/11.86. (where R, R_1 = -H, -H).

C-2: M.P. 198-202^{0}C, Yield 57%, **IR cm^{-1}**2830 (w, C-H str,O-CH_3), 1733(s,C=O str), 1630 & 1520 (m, C=C str), 1280 & 1025(s, C-O-C str), 730 (m, C-Clstr). **^{1}H NMR δ_H** 3.8 (3H, s, -OCH_3), 6.6 - 8.9 (16H. m, Ar-H). **Mol. For**. $C_{29}H_{19}ClN_4O_2S$**Mol. Wt**. 523, **Anal. data**. (Cal/Found) C% 66.60/65.97, H% 3.66/3.85, N% 10.71/10.32. (where R, R_1 = -H, -OCH_3).

C-3: M.P. 215-218^{0}C, Yield 66%, **IR cm^{-1}**1725 (s, C=O str.), 1635 & 1525 (m, C=C aromatic str), 2856 (m, C-H str), 1330 (m, C-H bending, Ar-CH_3), 760 (m, C-Clstr). **^{1}H NMR δ_H** 2.3 (3H, s, CH_3), 6.7 - 8.6 (16H. m, Ar-H).

Mol. For. $C_{29}H_{19}ClN_4OS$, **Mol. Wt**. 507, **Anal. data**. (Cal/Found) C% 68.70/67.65, H% 3.78/3.95, N% 11.05/10.27. (where R, R_1 = -H, -CH_3).

C-4: M.P. 222-225^{0}C, Yield 55%, **IR cm^{-1}**1725 (s, C=O str.), 1605 & 1540 (m, C=C str), 2860 (m, C-H str), 730 (m, C-Clstr). **^{1}H NMR δ_H** 6.8-9.4 (16H, m, Ar-H). **Mol. For**. $C_{28}H_{16}Cl_2N_4OS$, **Mol. Wt**. 527, **Anal. data**. (Cal/Found) C% 63.76/63.28, H% 3.06/2.81, N% 10.62/10.17. (where R, R_1 = -H, -Cl).

C-5: M.P.180-184^{0}C, Yield 61%, **IR cm^{-1}**2866 (w, C-H str), 1320 (m, C-H bending, Ar-CH_3), 1722 (s, C=O str.),1615 & 1510 (m, C=C str), 715 (m, C-Clstr). **^{1}H NMR δ_H** 2.5 (3H, s, -CH_3), 7.0–9.5 (16H. m, Ar-H). **Mol. For**. $C_{29}H_{19}ClN_4OS$, **Mol. Wt**. 507, **Anal. data**. (Cal/Found) C% 68.70/67.43, H% 3.78/3.56, N% 11.05/10.65. (where R, R_1 = -CH_3, -H).

C-6: M.P. 172-176^{0}C, Yield 68%, **IR cm^{-1}**2823 (w, -OCH_3str),2865 (w, C-H str), 1325 (s, C-H bending, Ar-CH_3), 1718 (s, C=O str.),1599 & 1535 (m, C=C str), 1240 & 1035 (s, C-O-C), 750 (m, C-Clstr). **^{1}H NMR δ_H** 2.2 (3H, s, -CH_3), 3.9 (3H, s, -OCH_3), 7.1–8.9. (15H. m, Ar-H). **Mol. For**. $C_{30}H_{21}ClN_4O_2S$, **Mol. Wt**. 537, **Anal. data**. (Cal/Found) C% 67.09/66.81, H% 3.94/3.75, N% 10.43/10.96. (where R, R_1 = -CH_3, -OCH_3).

C-7: M.P. 224-227^{0}C, Yield 57%, **IR cm^{-1}**2855 (w, -OCH_3str), 2795 (w, C-H str), 1315 (s, C-H bending, Ar-CH_3), 1720 (s, C=O str.),1610 & 1510 (m, C=C str), 750 (m, C-Clstr). **^{1}H NMR δ_H** 2.5 (6H, s, -CH_3), 6.6-9.3 (15H, m, Ar-H). **Mol. For**. $C_{30}H_{21}ClN_4OS$, **Mol. Wt**. 521, **Anal. data**. (Cal/Found) C% 69.16/68.94, H% 4.06/4.37, N% 10.75/10.32. (where R, R_1 = -CH_3, -CH_3).

C-8: M.P. 210-213^{0}C, Yield 65%, **IR cm^{-1}**2860 (m, -OCH_3str), 2835 (w, C-H str), 1315 (s, C-H bending, Ar-CH_3), 1725 (s, C=O str.),1625 & 1510 (m, C=C str), 735 (m, C-Clstr). **^{1}H NMR δ_H** 2.5 (3H, s, -CH_3), 7.0-8.9 (15H, m, Ar-H). **Mol. For**. $C_{29}H_{18}Cl_2N_4OS$, **Mol. Wt**. 541, **Anal. data**. (Cal/Found) C% 64.33/64.92, H% 3.35/3.13, N% 10.35/9.77. (where R, R_1 = -CH_3, -Cl).

C-9: M.P. 231-217^{0}C, Yield 56%, **IR cm^{-1}**2820 (m, -OCH_3str), 2873 (w, C-H str), 1718 (v, C=O str),1280 & 1025 (s, C-O-C str),1605 & 1490 (m, C=C str), 810 (m, C-Clstr). **^{1}H NMR δ_H** 3.8 (3H, s, -OCH_3), 7.0-9.2 (16H, m, Ar-H). **Mol.**

For. $C_{29}H_{19}ClN_4O_2S$, **Mol. Wt**. 523, **Anal. data**. (Cal/Found) C% 66.60/66.25, H% 3.66/3.95, N% 10.71/10.27 (where R, R_1 = -OCH_3, -H).

C-10: M.P. 209-213^{0}C, Yield 70%, **IR cm^{-1}**2832 (m, -OCH_3str), 2862 (w, C-H str), 1720 (s, C=O str),1240 & 1036 (s, C-O-C str),1615 & 1495 (m, C=C str), 790 (m, C-Clstr). **^{1}H NMR δ_H** 3.9 (6H, s, -OCH_3), 6.7-9.2 (15H, m, Ar-H). **Mol. For**. $C_{30}H_{21}ClN_4O_3S$, **Mol. Wt**. 553, **Anal. data**. (Cal/Found) 65.15/64.82, H% 3.83/3.63, N% 10.13/9.63. (where R, R_1 = -OCH_3, OCH_3).

C-11: M.P. 235-239^{0}C, Yield 72%, **IR cm^{-1}**2820 (m, C-H str,-OCH_3), 2851 (w, C-H str,), 1735 (s, C=O str), 1325 (s, C-H bending Ar-CH_3), 1240 & 1035 (s, C-O-C str),1640 & 1530 (m, C=C str), 771 (m, C-Clstr). **^{1}H NMR δ_H** 2.4 (3H, s, -CH_3), 3.9 (6H, s, -OCH_3), 6.9-9.2 (15H, m, Ar-H). **Mol. For**. $C_{30}H_{21}ClN_4O_2S$, **Mol. Wt**. 537, **Anal. data**. (Cal/Found) C% 67.09/65.81, H% 3.94/3.53, N% 10.43/10.67 (where R, R_1 = -OCH_3, -CH_3).

C-12: M.P. 187-191^{0}C, Yield 64%, **IR cm^{-1}**2830 (w, C-H str,), 1721 (s, C=O str), 1245 & 1035 (s, C-O-C str),1599 & 1490 (m, C=C str), 770 (m, C-Clstr). **^{1}H NMR δ_H** 2.4 (3H, s, -CH_3), 3.9 (6H, s, -OCH_3), 6.9-9.2 (15H, m, Ar-H). **Mol. For**. $C_{29}H_{18}Cl_2N_4O_2S$, **Mol. Wt**. 557, **Anal. data**. (Cal/Found) C% 62.48/61.02, H% 3.25/3.02, N% 10.05/9.54. (where R, R_1 = -OCH_3, -Cl).

Table 1: Antimicrobial activity of Synthesis 4-{[2-chloro-5-(4-substitutedphenyl) yridin-3-yl] methylene}-1-substituted-2-phenyl-1*H*-imidazol-5(4*H*)-one derivatives

Compound Name	Inhibition Zone (in mm)against			Growth diameter in mm (%inhibitation)	
	E. coli	***B.substilis***	***B.cereus***	***S.rolfsii***	***A.parasiticus***
C-1	9	10	19	19(56)	20(59)
C-2	10	14	15	23(68)	24(70)
C-3	19	19	20	29(76)	26(72)
C-4	17	17	18	27(72)	26(71)
C-5	18	16	19	28(74)	27(73)
C-6	10	12	13	22(64)	25(69)
C-7	9	10	10	14(49)	20(59)
C-8	10	14	15	20(69)	20(68)
C-9	12	16	16	21(65)	22(70)
C-10	11	12	12	20(66)	21(68)
C-11	16	15	17	28(74)	27(71)
C-12	15	13	16	24(68)	25(70)
Ciprofloxacine	37	36	40	-	-
Ampicilline	30	26	29	-	-
Griseofulvin	-	-	-	00(100)	00(100)

Anti microbial activity

All the synthesized compounds C-1 to C-12 were tested against microorganism species at 1000 ppm concentration. The observed results of antibacterial screening reported in above table indicate that compounds C-3, C-4, C-5 and C-11 shows good activity against the bacterial species used. The results indicate that compare to all three bacterial species, against, *B.Sereus* all

compounds shows good results compared to other two species used. Compounds C-1, C-7 and C-10 shows poor activity against the bacterial species used. From the anti fungal activity compounds show significant efficacy against the conventional fungicidal Griseofulvin.

Conclusion

In concluded a new series of derivatives C-1 to C-12 were synthesized. Examination of the IR-spectra of these compounds reveals the expected frequencies. Some of the important frequencies are indicated as 3150-3020cm^{-1} (Aromatic C-H stretching), 2240cm^{-1}, (C≡N stretching), 1610, 1498cm^{-1} (Aromatic C=C with C=N stretching). 1630-1590 cm-1 (Aromatic C=C stretching), 850-700 (C-Cl stretching). The characteristic IR band of these compounds appears at 850-700 cm-1 (C-Cl stretching) and at 1730-1700 cm-1 (C=O stretching) confirmed the structure. 1H-NMR spectra also showed the peak at 2.11 - 2.40 (4H, m CH_2), 5.51 (1H, s, CH), 0.91-1.07 (6H, s, CH_3) δ_H value and other protons of the compound were resonated at expected frequencies. The investigation of antimicrobial activities data revealed that some of the derivatives displayed excellent activity and some showed moderate activity against standard drugs.

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