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Synthesis, Characterization of Some Novel Schiff bases Derived from Imidazo [1, 2-a] pyridines for Anti-inflammatory and Antibacterial Activities

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ABSTRACT

Imidazo [1, 2-a] pyridine based Schiff bases have been synthesized by condensing different 3-aryl-5-methyl isoxazole hydrazides with 2-aryl imidazo [1, 2-a] pyridine carbaldehydes by following hybridization approach. The structures of newly synthesized Schiff bases have been characterized by spectral data and elemental analysis. In In vivo anti-inflammatory screening, compounds 4b & 4f showed significant activity and the results are comparable with the standard drug, diclofenac. None of the compounds exhibited significant activity in anti-bacterial study. The work might result in the emergence of new series of compounds with potent anti-inflammatory activity.

Keywords: Imidazo [1, 2-a] pyridines, isoxazole hydrazides, Schiff bases, anti-bacterial activity, anti-inflammatory activity

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INTRODUCTION

Imidazo[1,2-a]pyridines are bridge-head heterocycles and are considered to be an important scaffolds in medicinal chemistry because of their diverse biological activities like anxiolytic[1-3],analgesic and anti-inflammatory[4,5] , anti-convulsant[6,7],CDK1 & CDK2 inhibitor activity[8,9] , anti-ulcer[10,11] , anti-bacterial[12,13] , anti-microbial[14,15] and amoebicidal. Isoxazole is another important scaffold and derivatives of isoxazole are reported for analgesic and anti-inflammatory[16-19], anti-bacterial[20,21],anti fungal, anti-convulsant , anti-cholesteremic , anti-cancer, anti-viral, insecticidal, nematocidal and anti-microbial properties. Inspired by the biological importance of above two heterocycles,in the present study it was thought worthwhile synthesizing new series of Schiff bases by condensing different isoxazole hydrazides with imidazo [1, 2-a] pyridine carbaldehydes hoping that these new compounds would be potential biological agents for anti-microbial and anti-inflammatory activities.

MATERIALS AND METHOD

All the solvents and chemicals used were of synthetic grade from SD fine chemicals, E.Merck, NR chemicals and Aldrich chemicals. Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E- Merck 0.25 mm silica gel plates. Visualization was accomplished with UV light (256 nm) and iodine chamber. Purification of synthesized compounds was done by re-crystallization process. The purity of the compounds was checked by a single spot in TLC. Melting points were determined in open capillary tubes using ANALAB melting point apparatus and are uncorrected. All the ^{1}H NMR spectra were recorded on AVANCE 300 MHz spectrometer using $CDCl_3$ as solvent and tetra methyl silane (TMS) as an internal standard. Chemical shift values are listed in δ scale. The IR spectra were recorded on Shimadzu FTIR spectrophotometer by using 1% potassium bromide discs. Mass spectra of the compounds were recorded on Agilent 6430 mass spectrophotometer.

General procedure for synthesis of 2-(4-aryl) imidazo [1, 2-a] pyridine-3-carbaldehydes 3(a-c)

To Vilsmeier-Haack reagent (0.02 mol), 2-(4-aryl) imidazo [1,2-a] pyridine (0.01mol) was added slowly in 10ml of chloroform with stirring and then refluxed for 10-12 h at 60-70 ^{0}c.The reaction was monitored by TLC and after completion, the reaction mixture was concentrated to remove chloroform and poured into ice cold water. Neutralized with aq.sodium bicarbonate and followed by extraction with chloroform. The chloroform layer was dried over anhyd. sodium sulphate and

concentrated in rotary evaporator in order to give the crude product. The product was recrystallised from aq.ethanol.

General procedure for synthesis of 3-aryl-5-methyl isoxazole-4-carbohydrazides 3(A-C)

To 3-aryl-5-methyl isoxazole ester (0.01 mol) in 20 ml of ethanol, was added excess hydrazine hydrate (0.04 mol) and placed in 100 ml R.B flask and heated to reflux for 12-16 h.The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice drop by drop with constant stirring. The solid separated was filtered under vacuum and dried. The product obtained was recrystallised from aq. ethanol.

General procedure for synthesis of Schiff bases 4(a-i)

Equimolar quantities of 2-aryl-imidazo [1,2-a] pyridine-3-carbaldehyde (0.01 mol) and 3-aryl-5-methyl isoxazole-4-carbohydrazide (0.01 mol) were taken in 15-20 ml DMF and heated at 100 ^{0}c for 3 to 4 h. The reaction mixture was cooled and added to ice cold water to obtain precipitate which was filtered and washed thoroughly with water. Without drying, the product was recrystallized from aq. ethanol.

Physical and Spectral Data of compounds 4(a-i)

3-(4-chloro phenyl)-*N*-((2-(4-chlorophenyl) imidazo [1,2-a] pyridine-3-yl) methylene)-5-methyl isoxazole-4-carbohydrazide [4a]

White powder; m.p. 193-195^{0}C; yield :73%;Elemental analysis: Calculated for $C_{25}H_{17}Cl_2N_5O_2$: C 61.09,H 3.69 , N 14.26;Found: C 61.12,H 3.72, N 14.34; FTIR (KBr,cm^{-1}) 3328(N-H), 2925(C-H of CH_3), 1649(C=O), 1598(C=N),761(C-Cl);^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1(s,1H, NH) , 8.8(s,1H,=CH), 7.0-8.0 (12H,Ar-H) , 2.9(s,3H,CH_3); EIMS(m/z) 490 $[M+1]^+$

***N*^{1}-((2-(4-chlorophenyl) imidazo [1, 2-a] pyridine-3-yl) methylene)-5-methyl-3-(4-nitro phenyl) isoxazole-4-carbohydrazide [4b]**

Yellowish powder; m.p. 258-260^{0}C;yield : 60% ;Elemental analysis: Calculated for $C_{25}H_{17}ClN_6O_4$: C 59.81,H 3.62 ,N 16.75;Found : C 59.86,H 3.68,N 16.87;FTIR (KBr,cm^{-1}) 3321(N-H), 2923(C-H of CH_3),1649(C=O), 1610(C=N),1514 & 1310 (NO_2) 761(C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.1(s,1H, NH),9.1 (s,1H,=CH),7.1-7.8(12H,Ar-H), 2.8 (s,3H,CH_3); EIMS(m/z) 500.90$[M]^+$

***N*^{1}-((2-(4-chlorophenyl) imidazo [1, 2-a] pyridine-3-yl) methylene)-3-(4-methoxyphenyl) isoxazole - 4-carbohydrazide [4c]**

White powder; m.p. 108-110^{0}C; yield:70%;Elemental analysis: Calculated for $C_{26}H_{20}ClN_5O_3$: C 64.15,H 4.35,N 14.39;Found: C 64.20,H 4.39,N 14.46; FTIR (KBr,cm^{-1}) 3330 (N-H), 2931(C-H of CH_3) , 1642(C=O), 1608(C=N), 756 (C-Cl);^{1}H NMR (300 MHz, $CDCl_3$): δ 10.3(s,1H, NH) , 8.6 (s,1H,=CH),7.1-7.8(12H,Ar-H), 3.81 (s,3H,OCH_3), 2.8 (s,3H,CH_3) ; EIMS(m/z) 486.10$[M+1]^+$

3-(4-chlorophenyl)-5-methyl-*N*^{1}-((2-(p-tolyl)imidazo[1,2-a]pyridine-3-yl)methylene)isoxazole-4-carbohydrazide [4d]

White powder; m.p. 276-278^{0}C;yield : 68%;Elemental analysis: Calculated for $C_{26}H_{20}ClN_5O_2$: C 66.30,H 4.50, N 14.88; Found: C 66.33, H 4.40,N 14.98;FTIR (KBr,cm^{-1}) 3326(N-H), 2921(C-H of CH_3) , 1644(C=O), 1602(C=N), 759 (C-Cl);^{1}H NMR (300 MHz, $CDCl_3$): δ 10.2(s,1H, NH),8.1 (s, 1H, =CH), 6.5-7.8 (12H, Ar-H), 2.8 (s, 6H, $2CH_3$); EIMS (m/z) 470.10[M+1]$^{+}$

5-methyl-3-(4-nitrophenyl)-*N*^{1}-((2-(p-tolyl)imidazo[1,2-a]pyridine-3-yl)methylene)isoxazole-4-carbohydrazide [4e]

Yellowish powder; m.p. 268-271^{0}C; yield :71%,Elemental analysis: Calculated for $C_{26}H_{20}N_6O_4$: C 66.93,H 4.79,N 18.02;Found : C 66.95, H 4.82,N 18.05;FTIR (KBr,cm^{-1}) 3311(N-H), 2921(C-H of CH_3),1647(C=O), 1610(C=N),1514 &1320 (NO_2); ^{1}H NMR(300 MHz,$CDCl_3$): δ 10.1 (s,1H,NH), 9.1(s,1H,=CH),6.5(12H,Ar-H), 2.8(s,6H,$2CH_3$);EIMS(m/z) 480.4[M]$^{+}$

3-(4-methoxyphenyl)-5-methyl-*N*^{1}-((2-(p-tolyl) imidazo [1, 2-a] pyridine-3-yl) methylene) isoxazole-4-carbohydrazide [4f]

White powder ; m.p. 107-108^{0}C;yield :69% ;Elemental analysis: Calculated for $C_{27}H_{23}N_5O_3$: C 69.65,H 4.98,N 15.05; Found: C 69.70, H 5.02,N 15.09;FTIR (KBr,cm^{-1}) 3329(N-H), 2923(C-H of CH_3) , 1670(C=O), 1610(C=N); ^{1}H NMR(300 MHz,$CDCl_3$): δ 10.1 (s,1H,NH) ,8.5 (s,1H,=CH) , 6.5 (12H,Ar-H), 3.8(s,3H,OCH_3), 2.8(s,3H,CH_3);EIMS(m/z) 466 [M+1]$^{+}$

3-(4-chlorophenyl)-5-methyl-*N*^{1}-((2-(napthylen-2-yl) imidazo [1, 2-a] pyridine-3-yl) methylene) isoxazole-4-carbohydrazide [4g]

White powder; m.p. 149-151^{0}C; yield : 72% ;Elemental analysis: Calculated for $C_{29}H_{20}ClN_5O_2$: C 68.55,H 4.37,N 13.79;Found: C 68.58, H 4.40,N 13.75;FTIR (KBr, cm^{-1}) 3318(N-H), 2925(C-H of CH_3), 1670(C=O), 1600(C=N), 759(C-Cl); ^{1}H NMR (300 MHz,$CDCl_3$): δ 10.1(s, 1H,NH),8.8 (s, 1H,=CH) ,7.2-7.8 (15H, Ar-H), 2.9(s,3H,CH_3); EIMS(m/z) 506[M+1]$^{+}$

5-methyl -(*N*^{1}-((2-(napthalen-2-yl) imidazo [1, 2-a] pyridine-3-yl) methylene)-3-(4-nitro phenyl) isoxazole-4-carbohydrazide [4h]

Yellowish powder; m.p. 275-278^{0}C; yield :66% ;Elemental analysis: Calculated for $C_{29}H_{20}N_6O_4$: C 69.16,H 4.61,N 16.70;Found: C 69.18, H 4.65, N 16.74; FTIR (KBr,cm^{-1}) 3319(N-H), 2925(C-H of CH_3),1666(C=O), 1660(C=N),1521 & 1407 (NO_2);^{1}H NMR (300 MHz,$CDCl_3$): δ 10.1 (s,1H,NH) , 9.1 (s,1H,=CH), 7.2-7.8 (15H,Ar-H), 2.9(s,3H,CH_3); EIMS(m/z) 517 [M+1]$^{+}$

3-(4-methoxyphenyl)-5-methyl-*N*^{1}-((2-(napthalen-2-yl)imidazo[1,2-a]pyridine-3-yl) methylene) isoxazole-4-carbohydrazide [4i]

White powder; m.p. 125-127^{0}C;yield :62%;Elemental analysis: Calculated for $C_{30}H_{23}N_5O_3$: C 71.69,H 4.82,N 13.94;Found : C 71.72, H 4.85, N 13.96;FTIR (KBr,cm^{-1}) 3316(N-H), 2927(C-H of CH_3), 1670(C=O), 1610(C=N);^{1}H NMR(300 MHz, $CDCl_3$): δ 10.1(s,1H,NH), 8.5 (s,1H,=CH) , 7.2-7.8(15H,Ar-H), 2.9(s,3H,CH_3); EIMS(m/z) 502 $[M+1]^+$

BIOLOGICAL EVALUATION

Anti-inflammatory activity

All the synthesized compounds were screened for *in vivo* anti-inflammatory activity by carrageenan induced paw edema method. Albino wistar rats of either sex (150- 200 g) were divided into 11 groups of six animals each. Animals were deprived of food for 12 h prior to the experiment and only water was given . First group was used as a control group and received 1 ml of 1% w/v sodium carboxymethyl cellulose in saline, the second group received the drug, diclofenac at a concentration of 10 mg/kg body weight orally, while the other groups received test compounds at a dose of 10 mg/kg body weight orally. One hour after the administration of the compounds, carrageenan suspension (0.1 ml of 1% w/v suspension in 0.9% saline solution) was injected into the sub planter region of left hind paw of animals. Immediately, the paw volume was measured using plethysmometer with one hour intervals. The difference between initial and final readings gave the change in oedema volume for the corresponding time. Oedema volume of control (V_c) and Oedema volume of treated (V_t) were used to calculate percentage (%) inhibition by using following formula.

% Inhibition = $(V_c-V_t)/V_c \times 100$

Anti-bacterial activity

The inhibition of growth of microorganisms against *staphylococcus aureus* & *Bacillus subtilis* (Gram +ve) and *Escherichia coli* & *Pseudomonas aeruginosa* (Gram –ve) was measured as the Zone of inhibition produced by test and as well as standard drugs using Cup-Plate method .The prepared liquefied agar medium (25 ml) was inoculated with 10^{-7} to 10^{-8} cfu/ml seeded broth. The suspension containing microorganisms was added at a temperature between 40-50 ^{0}C and vortexed to distribute the microorganisms evenly throughout the medium and poured immediately into petri dishes to give depth of 3-4 mm. The petri dishes were placed on a flat surface to ensure that the layers of the medium were of uniform thickness. Using a sterile bore, cylindrical cavities of 8 mm diameter were made on the medium. 5 bores were made on each petri dish. 50 µl of test and standard solutions were transferred into cylindrical cavities using a micropipette, aseptically. The petri dishes were allowed to stand for 1 h at room temperature, as a pre incubation diffusion, to minimize the effects of variation in time between the applications of different solutions. Later, the

plates were incubated for 24 h at 37 ^{0}C and the circular inhibition zone was measured. Amoxicillin was used as standard drug for comparison.

RESULTS AND DISCUSSION

Chemistry

The route for the synthesis of compounds is shown under Scheme-1.Different phenacyl bromides 1(a-c) were prepared from substituted acetophenones and condensed with 2-aminopyridine to give 2-aryl imidazo [1, 2-a] pyridines 2(a-c). Vilsmeier-Haack reaction of 2-aryl imidazo [1, 2-a] pyridines afforded 2-aryl imidazo [1, 2-a] pyridine 3-carbaldehydes 3(a-c) in good yields. In FTIR, the compounds showed absorption peaks around 1640 cm^{-1} for carbonyl absorption of CHO group. The compounds were further confirmed by mass spectral data. Subsequently isoxazole hydrazides were prepared from aryl oximes in three steps in the following manner. Aryl oximes were chlorinated with N-chlorosuccinamide in DMF to give *N*-benzene carboxymoyl chlorides which were then cyclised with ethyl acetoacetate in presence of sodium hydroxide in methnol to give 3-aryl-5-methyl isoxazole-4-carboxylates. Further, the esters were converted into hydrazides by heating with excess hydrazine hydrate under reflux for 12-15 h .The characterization of the structures of isoxazole hydrazides 3(A-C) was done on the basis of FTIR and mass spectral data. In FTIR, compounds have showed absorption peaks around 1640 cm^{-1} due to C=O absorption of hydrazide along with two absorption peaks around 3390 and 3280 cm^{-1} due to N-H stretchings of NH_2 .The molecular ion peaks of 100% intensity in mass spectra corresponding to their molecular weights further confirmed the structures. Lastly, the condensation of compounds 3(a-c) with three different isoxazole hydrazides 3(A-C) in DMF afforded 3-(4-aryl)-N^1-((2-(4-aryl)imidazo[1,2-a]pyridine-3-yl)methylene)-5-methyl isoxazole-4-carbohydrazides 4(a-i) and were characterized on the basis of FTIR, mass and ^{1}H NMR spectral data. The physical data of compounds is given in Table 1.

SCHEME-1

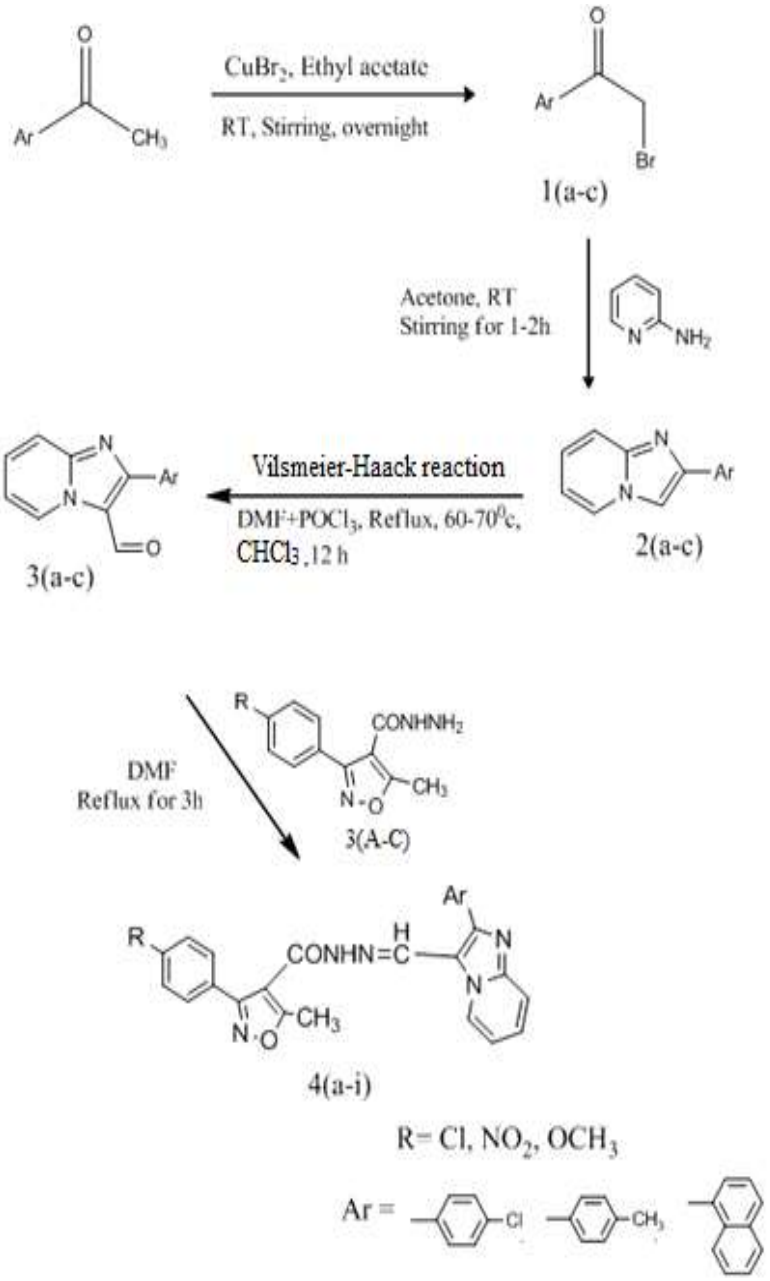

Table 1: Physical data of synthesized compounds (4a-4i)

Compounds	R	Ar	Mol. formula	Mol.wt	M.P (^{0}C)	Yield (%)
4a	Cl	C_6H_4Cl(p)	$C_{25}H_{17}N_5O_2Cl_2$	489	193-195	73
4b	NO_2	C_6H_4Cl(p)	$C_{25}H_{17}N_6O_4Cl$	500.5	258-260	60
4c	OCH_3	C_6H_4Cl(p)	$C_{26}H_{20}N_5O_3Cl$	485.5	108-110	70
4d	Cl	$C_6H_4CH_3$(p)	$C_{26}H_{20}N_5O_2Cl$	469.5	276-278	68
4e	NO_2	$C_6H_4CH_3$(p)	$C_{26}H_{20}N_6O_4$	480	268-271	71
4f	OCH_3	$C_6H_4CH_3$(p)	$C_{27}H_{23}N_5O_3$	465	107-108	69
4g	Cl	Napthyl	$C_{29}H_{20}N_5O_2Cl$	505.5	149-151	72
4h	NO_2	Napthyl	$C_{29}H_{20}N_6O_4$	516	275-278	66
4i	OCH_3	Napthyl	$C_{30}H_{23}N_5O_3$	501	125-127	62

Anti-inflammatory activity

All the synthesized compounds were screened for anti-inflammatory activity by carrageenan induced paw edema method. The anti-inflammatory data of synthesized compounds is shown in Table 2. Among the nine compounds **4b&4f** exhibited 65% and 64% protection against edema formation at 3rd hour and the values are comparable to standard drug,vdiclofenac. The remaining compounds exhibited moderate activity. From the data obtained, the mean edema volume and percentage reduction in edema was calculated.

Table 2: Anti-inflammatory activity of newly synthesized compounds.

Treatment	1h	% red	2h	% red	3h	% red
Control	1.25±0.04		0.95±0.04		1.40±0.04	
Diclofenac (standard)	1.50±0.03	36	1.50±0.03	45	1.35±0.07	68
4a	1.40±0.03	20	1.20±0.09	30	1.15±0.16	46
4b	1.15±0.20	29	1.10±0.13	39	1.60±0.18	**65**
4c	1.11±0.07	25	0.90±0.05	30	1.25±0.04	54
4d	1.34±0.06	14	1.44±0.09	12	1.30±0.28	22
4e	1.50±0.05	16	1.60±0.03	20	1.50±0.05	30
4f	1.05±0.07	26	0.90±0.05	36	1.60±0.18	**64**
4g	1.20±0.09	30	1.15±0.16	46	1.05±0.07	52
4h	1.25±0.04	36	1.05±0.07	25	0.90±0.05	30
4i	1.25±0.05	24	1.55±0.04	20	1.10±0.13	39

Values are in Mean±Standard Deviation. Statistically significant ($p<0.05$) difference in comparison to control. Each group contains six animals.

Anti-bacterial activity

All the synthesized compounds were screened at concentration of 500 µg/ml and 1000 µg/ml against two Gram positive bacteria (*staphylococcus aureus* & *Bacillus subtilis*) and two Gram negative bacteria (*Escherichia coli* & *pseudomonas aeruginosa*) using Cup-Plate method. None of the compounds exhibited any significant activity.

CONCLUSION

In present study nine new derivatives of imidazo[1,2-a]pyridine based Schiff bases were synthesized and screened for anti-inflammatory and anti-bacterial activities. In anti-inflammatory screening, among nine compounds, **4b & 4f** exhibited significant protection against the edema formation at the concentration of 10 mg/kg and the activity was comparable with standard drug, diclofenac. The remaining compounds exhibited moderate activity. The synthesized compounds have not exhibited any significant anti-bacterial activity against Gram positive bacteria and Gram negative bacteria even at 500 µg/ml & 1000 µg/ml concentrations. In conclusion the synthesized compounds might emerge as potent anti-inflammatory agents in further research.

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