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RESEARCH ARTICLE

Design, synthesis and biological evaluation of hydrazones of 2-phenyl imidazo[1,2-a]pyridines

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ABSTRACT

The phenyl hydrazones of 2-phenyl-imidazo[1,2-a]pyridines (**7a-l**) were prepared by the condensation of 2-phenyl-3-formyl-imidazo[1,2-a]pyridines **5** with phenyl hydrazines **6** in ethanol. The compounds were characterized by IR, ^{1}H NMR and Mass spectral analysis. All the synthesized compounds were subjected for anti-inflammatory screening using protein denaturation assay and antioxidant screening. Most of the compounds were found to be potent anti-inflammatory and antioxidant agents. Compounds **7k, 7j, 7h** and **7g** were found to possess significant anti-inflammatory and antioxidant potential.

KEYWORDS

Imidazo[1,2-a]pyridine, Hydrazone, Anti-inflammatory, Antioxidant

INTRODUCTION

Bridge nitrogen containing fused heterocycles represents significant building blocks in both natural and synthetic bioactive molecules which have been shown to possess diverse therapeutic activities.[1] Hence they are interesting targets in the field of medicinal chemistry. The aza-indolizine is one of the important bridged nitrogen containing fused heterocycle possessing important medicinal properties. The aza-indolizine comprises a phenyl ring fused to a imidazole ring is indicated in the structure, hence it is also known as imidazo[1,2-a]pyridine.[2] It is a common structural motif in pharmacologically important molecules, due to their wide spectrum of therapeutic importance.

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A large number of substituted imidazo[1,2-a]pyridine derivatives are synthesized and screened for varieties of biological activities such as, anti-inflammatory[3], anti-cancer[4], antiviral[5], antifungal[6], and antibacterial[7] agents.

Similarly the functional framework of hydrazone (-CO-NH-N=CH-) have extensive applications in building heterocyles8 with potential activities such as anti-inflammatory, antimalarial, anticonvulsant, anti-tubercular, antitumor, and antimicrobial.[9] Apart from bio-importance of hydrazone core, it has been studied and applied in supramolecular chemistry, metal and covalent organic framework, dynamic combinatorial chemistry and dyes pigment chemistry.[10]

Thus the important role shown by imidazo[1,2-a]pyridine and its derivatives for various therapeutic and biological activities prompted us to synthesize some hydrazones of 2-phenyl substituted imidazo[1,2-a]pyridines in order to achieve compounds having better therapeutic potential.

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MATERIAL AND METHOD

Generals

All chemicals used for the work are of Lab Grade like Merck, Sigma Aldrich, Spectrochem etc. Chemical reaction is monitored by Thin Layer Chromatography and also confirmed by direct mass and finally compound is confirmed by NMR 400 MHz, Mass and IR Spectra. NMR of synthesised compound is analysed at Instrumentation center Sholapur University Maharashtra. Crystallization and Column chromatography technique used for purification of Compounds.

Chemistry- Synthesis of Compounds

The synthesis of target molecules (7a-l) was synthesised by the reaction of 2-phenyl-3-formyl-imidazo[1,2-a]pyridine 5 with phenyl hydrazine 6 in ethanol under reflux condition. The intermediate 2-phenyl-3-formyl-imidazo[1,2-a]pyridine 5 was prepared by the formylation of 2-phenyl-imidazo[1,2-a]pyridine 4 by using dimethyl formamide (DMF) and phosphorus oxychloride (POCl3) as per the procedure reported in literature.11 Further the preparation of 2-phenyl-imidazo[1,2-a]pyridine 4 was carried out by refluxing in ethanol the mixture of 2-aminopyridine 3 and phenacyl bromide 2 which was prepared by the bromination of acetophenone 1 in acetic acid. The complete synthetic route is depicted in scheme 1.

Scheme 1. Synthesis of hydrazones of 2-phenyl substituted imidazo[1,2-a]pyridines. Reaction conditions: (a) Br_2, Acetic acid (b) Ethanol, Reflux (c) DMF, POCl3 (d) Ethanol, Reflux.

Preparation of phenacyl bromide (2)

A mixture of bromine (1.1 eq.) in glacial acetic acid was added drop wise to the solution of acetophenone (1 eq.) in glacial acetic acid at room temperature over the period of 45 minutes. After complete addition of bromine, reaction mixture was stirred at room temperature. After completion of reaction (TLC) diluted with ice cold water and separated solid was filtered off, washed with water and dried to obtain pure product.

Preparation of 2-phenyl-imidazo[1,2-a]pyridine (4)

A mixture of phenacyl bromide (1 eq.) and 2-amino pyridine (1 eq.) in ethanol was taken in a round bottomed flask. The resulting mixture was refluxed for 10 h using reflux condenser. Formation of precipitate with the change in colour indicates completion of reaction. After completion of reaction (TLC) cooled the reaction mixture, filtered and dried to obtain pure product.

Preparation of 2-phenyl-3-formyl-imidazo[1,2-a]pyridine (5)

Freshly distilled DMF 2.88 ml (2.74 g, 37.4 mmole) was placed in a three-necked round bottom flask. Cooled the flask in an ice bath for about 30 min and phosphorus oxychloride 0.86 ml (1.44 g, 9.4 mmole) was slowly added to it with constant stirring. The pinkish colored complex formed. To this pink colored complex, a solution of 2-phenyl-imidazo[1,2-a]pyridine 4 (8.5 mmole) in 2 ml of dimethylformamide is added over a period of 1h, maintaining the temperature below 10°C. Once the solution well mixed, the temperature of the viscous solution brought to 35°C and stirred efficiently for 1 hour. At the end of the reaction period, 30 g of crushed ice was added to the paste with careful stirring, produced a clear, cherry-red aqueous solution. This resulting solution is neutralized with a solution of 3.75 g. of sodium hydroxide in 10 ml

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of water, after which it is placed in a refrigerator overnight. The precipitate is collected on a filter and suspended in 10 ml of water. Most of the inorganic material dissolves, and the product is then collected on a filter, washed with water and air-dried. It may be recrystallized from ethanol if desired.

Preparation of hydrazones of 2-phenyl-3-formyl-imidazo[1,2-a]pyridine (7a-l)

A mixture of 2-phenyl-3-formyl-imidazo[1,2-a]pyridine 5 (1 eq.) and phenyl hydrazine (1 eq.) in ethanol was taken in a round bottomed flask. The resulting mixture was refluxed for 3 h using reflux condenser. After completion of reaction (TLC), cooled the reaction mixture, filtered, dried recrystallized from ethanol to obtain pure product.

Spectral data of representative compounds

2-(4-bromophenyl)-3-((2-phenylhydrazono)methyl)imidazo[1,2-a]pyridine (7a)

IR (cm-1): 3505 (NH), 3054 (CH), 1632 (C=N);

1H NMR (200 MHz, CDCl3): δ=6.90-6.95 (m-1H,ArH), 7.05-7H (m,3H,ArH) 7.33-7.40(m,3H,ArH), 7.53-7.64 (m,4H,ArH) 7.71-7.73 (m,1-H ArH) 7.76-7.79 (m-1H,ArH), 8.12 (S-1H, N=CH) 9.55 (S,1H, NH); Mass (m/z): 392 [M+1]

2-(4-bromophenyl)-3-((2-(4-chlorophenyl)hydrazono)methyl)imidazo[1,2-a]pyridine(7b)

IR (cm-1): 3421 (NH), 3062, 2958 (CH), 1633 (C=N);

1H NMR (200 MHz, DMSO): δ = 7.00 (d, J = 8Hz, 2H, ArH), 7.17 (d, J = 8Hz, 2H, ArH), 7.55-7.70 (m, 2H, ArH), 7.48-7.78 (m, 4H, ArH), 9.55 (d, J = 6.82 Hz, 1H, ArH), 9.72 (d, J = 6.8 Hz, 1H, ArH), 9.96 (s, 1H, =CH), 10.78 (s, 1H, NH); Mass (m/z): 426 [M+1]

4-(2-((2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)methylene)hydrazinyl)benzonitrile (7c)

IR (cm-1): 3379 (NH), 3093, 2978 (CH), 2210 (CN), 1640 (C=N);

1H NMR (200 MHz, DMSO): δ = 7.11 (d, J = 8Hz, 2H, ArH), 7.52 (d, J = 8Hz, 2H, ArH), 7.68-7.70 (m, 4H, ArH), 7.81-7.92 (m, 4H, ArH), 8.40 (s, 1H, =CH), 11.13 (s, 1H, NH); Mass (m/z): 417 [M+1]

6-chloro-2-(4-chlorophenyl)-3-((2-phenylhydrazono)methyl)imidazo[1,2-a]pyridine (7d)

IR (cm-1): 3442 (NH), 3058, 2985 (CH), 1633 (C=N)

1H NMR (200 MHz, CDCL3): δ = 6.94-9.98 (m, 1H, ArH,) 7.10 (d, J = 8Hz, 2H, ArH), 7.34-7.39 (m, 4H, ArH), 7.44-7.55 (m, 2H, ArH), 7.67-7.77 (m, 4H, ArH), 8.11 (s, 1H, =CH), 9.69 (s, 1H, NH); Mass (m/z): 382 [M+1]

6-chloro-2-(4-chlorophenyl)-3-((2-(4-chlorophenyl)hydrazono)methyl)imidazo[1,2-a]pyridine (7e)

IR (cm-1): 3415 (NH), 2898, 2830 (CH), 1644 (C=N);

1H NMR (200 MHz, CDCl3): δ = 7.40-7.44 (m, 2H, ArH), 7.50-7.54 (m, 3H, ArH), 7.58-7.60 (m, 2H, ArH), 7.63-7.67 (m, 4H, ArH), 9.58 (s, 1H, =CH), 9.95 (s, 1H, NH); Mass (m/z):416 [M+1].

4-(2-((6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)methylene)hydrazinyl)benzonitrile (7f)

IR (cm-1): 3385 (NH), 2972, 2885 (CH), 2218 (CN), 1643 (C=N);

1H NMR (200 MHz, DMSO): δ = 7.41-7.46 (m, 3H, ArH), 7.54-7.57 (m, 4H, ArH), 7.70-7.74 (m, 4H, ArH), 9.63 (s, 1H, =CH), 9.96 (s, 1H, NH); Mass (m/z):407 [M+1]

2-(4-methoxyphenyl)-3-((2-phenylhydrazono)methyl)imidazo[1,2-a]pyridine (7g)

IR (cm-1): 3410 (NH), 2890, 2840 (CH), 1645 (C=N);

1H NMR (200 MHz, CDCl3): δ = 3.87 (s, 3H, OCH3), 6.87-7.11 (m, 4H, ArH), 7.29-7.33 (m, 4H, ArH), 7.67-7.81 (m, 5H, ArH), 8.17 (s, 1H, N=CH) 9.56 (s, 1H, NH); Mass (m/z):343 [M+1]

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3-((2-(4-chlorophenyl)hydrazono)methyl)-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (7h)

IR (cm-1): 3411 (NH), 2889, 2834 (CH), 1648 (C=N);

1H NMR (200 MHz, CDCl3): δ = 3.89 (s, 3H) 7.02-7.10 (m, 5H,) 7.57-7.66 (m, 4H, ArH), 7.70-7.82 (m, 3H, ArH), 8.22 (s, 1H, =CH), 9.49 (s, 1H, NH); Mass (m/z): 377 [M+1]

4-(2-((2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)methylene)hydrazinyl)benzonitrile (7i)

IR (cm-1): 3398 (NH), 2982, 2875 (CH), 2228 (CN), 1646 (C=N);

1H NMR (200 MHz, CDCl3): δ = 3.89 (s, 3H, OCH3), 7.57-7.61 (m, 4H, ArH), 7.66-7.70 (m, 4H, ArH), 7.75-7.82 (m, 4H, ArH), 8.22 (s, 1H, =CH), 9.45 (s,1H, NH); Mass (m/z):368 [M+1].

6-chloro-2-(4-nitrophenyl)-3-((2-phenylhydrazono)methyl)imidazo[1,2-a]pyridine (7j): IR (cm-1): 3375 (NH), 3090, 2972 (CH), 1638 (C=N), 1516, 1330 (NO2);

1H NMR (200 MHz, CDCl3): δ = 7.39-7.48 (m, 2H, ArH) 7.60-7.65 (m, 3H, ArH), 7.75-7.78 (m, 2H), 7.82 (s, 1H, ArH), 8.01 (d, J = 8.4 Hz, 2H, ArH), 8.40 (d, J = 8.4 Hz, 2H, ArH), 9.77 (s,1H, CH), 10.11 (s-1H,NH); Mass (m/z):392 [M+1].

6-chloro-3-((2-(4-chlorophenyl)hydrazono)methyl)-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (7k)

IR (cm-1): 3380 (NH), 3091, 2973 (CH), 1640 (C=N), 1518, 1322 (NO2); 1H NMR (200 MHz, CDCL3): δ = 7.36-7.65 (m, 3H, ArH) 7.74-8.05 (m, 4H, ArH), 8.05-8.43 (m, 5H), 9.77 (s, 1H, =CH), 10.11 (s, 1H, NH); Mass (m/z):427 [M+1].

4-(2-((6-chloro-2-(4-nitrophenyl)imidazo[1,2-a]pyridin-3-yl)methylene)hydrazinyl)benzonitrile (7l)

IR (cm-1): 3385 (NH), 3094, 2970 (CH), 2216 (CN), 1644 (C=N), 1514, 1327 (NO2); 1H NMR (200 MHz, CDCl3): δ = 7.26 (s, 2H, ArH) 7.59-7.65 (m, 1H, ArH), 8.00-8.05 (m, 3H), 8.39-8.44 (m, 3H), 9.77 (s, 1H, CH), 10.11 (s, 1H, NH); Mass (m/z):417 [M+1].

RESULT AND DISCUSSION

In vitro Anti-inflammatory activity by Protein denaturation method

The reaction mixture (10 mL) consist of 0.4 mL of egg albumin (from fresh hen's egg), 5.6 mL of phosphate buffered saline (PBS, pH 6.4) and 4 mL of synthetic derivatives (1 mM).12 Similar volume of double-distilled water served as control. Then the mixtures were incubated at (37oC ±2) in an incubator for 15 min, and heated at 70oC for 5 min. After cooling, the absorbance measured at 660 nm using vehicle as blank. Diclofenac sodium at 1 mM was used as reference drug, and treated similarly for the determination of absorbance. The percentage inhibition of protein denaturation was calculated by using the following formula.

$$\% \text{ inhibition} = 100 \times (V_t / V_c - 1)$$

Where, Vt = absorbance of test sample,

Vc = absorbance of control.

Antioxidant Activity

DPPH Radical Scavenging Activity

The ability of compounds to scavenge DPPH radical was assessed using literature method14 with slight modification. Concisely, 1 mL of synthesized compounds as 1mM was mixed with 3.0 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 min. incubation at 37 °C. The percentage scavenging activity were derived using the following formula,

Percentage of inhibition (%) = [(A control – A sample) / A control] x 100

Where,

A control= absorbance of DPPH.

A sample= absorbance of reaction mixture (DPPH with Sample).

NO Radical Scavenging Activity

NO radical scavenging activity carried out as per the reported method.14 Nitric oxide radicals generated from sodium nitroprusside solution. 1 mL of 10 mM sodium nitroprusside mixed with 1 mL of 1mM synthesized compounds in

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phosphate buffer (0.2 M pH 7.4). The mixture incubated at 25 °C for 150 min. After incubation, the reaction mixture mixed with 1.0 mL of prepared Griess reagent (1% sulfanilamide, 0.1% napthylethylenediamine dichloride and 2% phosphoric acid). The absorbance was measured at 546 nm, and percentage of inhibition was calculated using the same formula as above. The decreasing absorbance indicates a high nitric oxide scavenging activity. Percentage of inhibition (%) = (A Control – A sample) /A control) X 100 where, A control=absorbance of Nitric oxide.

A sample= absorbance reaction mixture (Nitric oxide with Sample).

H_2O_2 Scavenging Activity

The hydrogen peroxide scavenging assay carried out by the reported method.15 A solution of hydrogen peroxide (40 mM) prepared in phosphate buffer (pH 7.4). The 1 mM concentration of various synthetic compounds added to a hydrogen peroxide solution (0.6 mL, 40 mM). Absorbance of hydrogen peroxide at 230 nm was determined after 10 min. against a blank solution containing phosphate buffer without drug. The percentage scavenging of hydrogen peroxide of synthetic compounds and standard compounds calculated by using the following formula: Percentage scavenged

$$(H2O2) = (A0 - A1) / A0 \times 100$$

Where,

A0 =the absorbance of control;

A1= the absorbance in presence of the sample of MO and standards.

SOR Scavenging Assay

The superoxide radical scavenging activity was performed by the reported method.16 The superoxide radicals generated in 3.0 mL of Tris–HCl buffer (16 mM, pH 8.0), containing 0.5 mL of nitroblue tetrazolium (NBT) (0.3 mM), 0.5 mL NADH (0.936 mM) solution, 1.0 mL of synthetic compound (1 mM) solution and 0.5 mL Tris–HCl buffer (16 mM, pH 8.0). The reaction initiated by adding 0.5 mL phenazinemethosulfate (PMS) solution (0.12 mM) to the mixture, incubated at 25 0C for 5 min and then the absorbance measured at 560 nm against a blank sample. Decreased absorbance of reaction mixture, indicate increased superoxide anion scavenging activity.

Percentage of inhibition (%) = (A Control – A sample) /A control) X 100

Where,

A control= absorbance of control

A sample = absorbance reaction mixture (Superoxide with Sample).

Anti-inflammatory activity

The denaturation of proteins as one of the causes of inflammation is well documented in literature. Production of auto-antigens in certain rheumatic diseases may be due to denaturation of proteins in vivo. As the number of anti-inflammatory drugs are known to inhibit denaturation of proteins. All the synthesized compounds (7a-l) were evaluated for their anti-inflammatory potential using egg albumin protein denaturation method12 and results are summarized in table 1. The results presented in table 1 revealed that all the synthesized compounds possess significant anti-inflammatory potential by inhibiting the protein denaturation. Diclofenac sodium was used as a reference standard. Among the synthesized compounds compound 7k, 7j, 7h and 7g have shown excellent inhibition of protein denaturation as good as the standard drug Diclofenac sodium. All other compounds were moderate inhibitors of protein denaturation.

Antioxidant activity

The uncontrolled production of oxygen derived free radicals is involved in eliciting many diseases such as cancer, rheumatoid arthritis, cirrhosis and arteriosclerosis. Exogenous chemical and endogenous metabolic processes in the human body or in the digestive system might produce highly reactive free radicals, especially oxygen derived radicals, which are capable of

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Table 1. In vitro anti-inflammatory and anti-oxidant activities of hydrazones

SN	Compound	% Inhibition (1 mM)				
		Anti-inflammatory	Antioxidant activity			
		Egg albumin	DPPH	NO	H_2O_2	SOR
1.	**7a**	71.00	70.00	34.48	15.74	40.88
2.	**7b**	77.00	70.00	20.83	14.31	50.63
3.	**7c**	66.00	70.00	25.86	15.33	44.27
4.	**7d**	73.00	65.00	17.24	16.56	40.35
5.	**7e**	78.00	60.00	22.41	15.54	45.08

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6.	**7f**	69.00	70.00	20.68	19.42	47.82
7.	**7g**	80.00	70.00	31.03	22.49	53.44
8.	**7h**	88.00	65.00	27.58	17.99	48.96
9.	**7i**	76.00	70.00	44.82	23.10	52.67
10.	**7j**	89.00	25.00	15.51	22.69	54.05
11.	**7k**	90.00	35.00	36.20	15.33	68.12
12.	**7l**	75.00	20.00	44.82	10.02	55.45
13.	**DS**	90.21	--	--	--	--
14.	**AA**	--	44.18	42.63	43.51	74.05

DS = Diclofenac Sodium; AA = Ascorbic acid; DPPH= 1,1-Diphenyl-2-picryl-hydrazyl; NO = Nitric Oxide; H_2O_2 = Hydrogen Peroxide; SOR = Superoxide Radical

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oxidizing biomolecules, resulting in the death of cells and tissue damage.13 Thus all the synthesized compounds (7a-l) were also tested for their antioxidant capabilities using 1,1-Diphenyl-2-picryl-hydrazyl (DPPH), Nitric Oxide (NO), Hydrogen peroxide (H_2O_2) and superoxide radical (SOR) assays with reference to the standard drug ascorbic acid. The results of inhibition of these radicals are presented in table 1. The results in table 1 revealed that most of the compounds were found to be good antioxidant agents. In case of DPPH, most of the compounds were found to be the excellent inhibitors of DPPH radical (70-25%) compared to standard drug Ascorbic acid. Compounds 7i, 7l, 7k and 7a have shown significant inhibition of NO radical where as all other are moderate inhibitors. All the compounds were found to possess weak inhibition of H_2O_2 radical. These compounds have shown moderate to significant inhibition of SOR. Compound 7k, 7l, 7j, 7g, 7i and 7b showed significant inhibition of SOR compared to the standard drug whereas all other compounds showed moderate inhibition.

CONCLUSION

In conclusion, the hydrazones of 2-phenyl-imidazo[1,2-a]pyridine were synthesized in good to excellent yields. All the synthesized compounds were subjected for in vitro anti-inflammatory and antioxidant screening. The compounds were found to be potential anti-inflammatory and antioxidant agents. All the compounds were significantly inhibited the denaturation of proteins in egg albumin. Compounds 7i, 7l, 7k and 7a have shown significant inhibition of NO radical inhibition. Compounds 7k, 7l, 7j, 7g, 7i and 7b showed significant inhibition of superoxide radical whereas all the compounds have shown weak H_2O_2 inhibition.

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