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One pot synthesis of substituted imidazoles containing indole and their antimicrobial activities

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ABSTRACT

Substituted indole aldehydes were condensed with 1, 2-diketones under reflux in acetic acid in presence of ammonium acetate to yield the title compounds. The structures of the synthesized compounds have been established by their analytical and spectral data. The compounds were screened for their antimicrobial activity.
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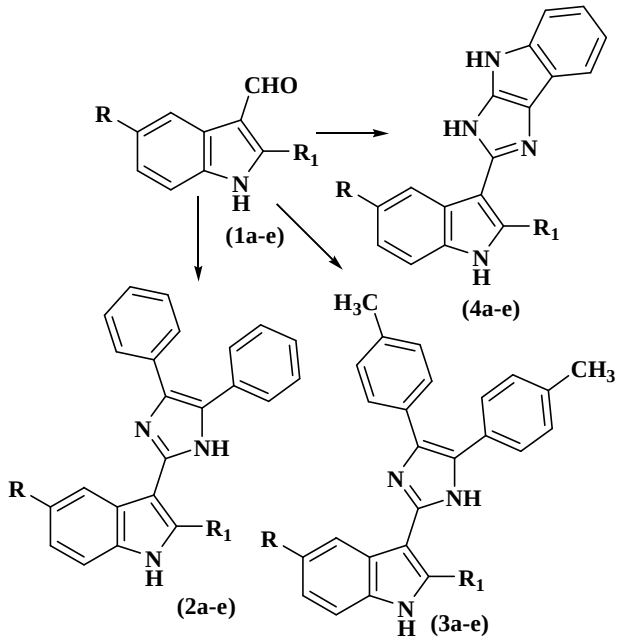
KEYWORDS

Indole aldehyde;
Imidazole;
Ammonium acetate;
Antimicrobial activity.

INTRODUCTION

Imidazole and indole residues are probably the most well-known heterocycles which are common in a variety of natural products and medicinal agents[1-4]. Indole and its derivatives have occupied a unique place in the nitrogen heterocyclic compounds because of their varied biodynamic properties[5-10]. Also, there are many compounds in the literature bearing imidazole residue and possessing antibacterial and antifungal activities[11-14]. The objective of the present study is to combine the two structures, i.e. indole and imidazole residues, in order to develop a hybrid molecule and test for antibacterial and antifungal activities of the newly synthesized compounds.

The substituted indole aldehydes **(1a-e)** were condensed with 1, 2-diketones (1, 2- dicarbonyl compounds) under reflux in acetic acid in presence of ammonium acetate to yield the title compounds in a single step (SCHEME 1). The compounds were character-



SCHEME 1

ized by their analytical and spectral data. The newly synthesized compounds were screened for antimicrobial activity.

RESULTS AND DISCUSSION

The IR spectral data of **(2a)** did not show characteristic absorption band in the region 1675 cm^{-1} (C=O) of aldehyde, but has showed peaks at 3212 cm^{-1} (NH) and 1599 cm^{-1} (C=N). These observations indicate that the reaction has taken place to give the final product. The ^{1}H NMR spectrum of compound **(2a)** showed a peak at δ12.2 (s, 1H, NH) a deshielded proton accounting for a single proton assigned to indole NH. Another less deshielded peak appeared at δ 11.3 (s, 1H, NH) accounting for imidazole NH. Multiplet in the region δ 7.1-8.4 (m, 15H, Ar-H) accounts for fifteen aromatic protons present in the molecule.

In the mass spectrum of compound **(2a)** showed molecular ion peak which is observed at m/z 336 (100 %) corresponding to the molecular weight (M^+, 335) of the compound. Also it is the base peak due to the most stable fragment. This has undergone into further fragmentation and showed peaks at m/z 181 (5 %), m/z 154(2%), m/z 130 (3%), and m/z 117 (2%). These spectral data supports the formation of compounds**(2a-e)**.

The IR spectral data of compound **(3a)** has shown peaks at 3252 cm^{-1} (NH) and 1580 cm^{-1} (C=N) indicating the formation of product. In ^{1}H NMR spectrum of 3a showed peak at δ12.1 (s, 1H, NH), a deshielded proton integrating for one proton of indole NH. Less deshielded peak at δ 10.9 (s, 1H, NH) accounting for imidazole NH. A multiplet appeared in the region δ 7.2-8.2 (m, 13H, Ar-H) accounting for thirteen aromatic protons. The sharp singlet at δ 2.3 (s, 6H, CH_3) accounts for six protons of two methyl groups. The mass spectrum of compound **(3a)** shown molecular ion peak at m/z 363, which is the molecular weight of the compound.

The IR spectral data of 4a has shown characteristic absorption peaks at 3241, 3230 cm^{-1} (NH) and 1590 cm^{-1} (C=N). The ^{1}H NMR spectrum of **(4a)** displayed peaks in the downfield at δ 11.9 (s, 1H, NH) accounts for the single proton of indole NH. Appearance of a singlet at δ11.4 (s, 1H, NH) integrating for one proton is due to imidazole NH. Another less deshielded singlet at δ 10.6 (s, 1H, NH) is attributed to NH of indole fused to imidazole ring. Multiplet in the region δ7-8.1 (m, 9H, Ar-H) accounts for the nine aromatic protons present in the molecule. The mass spectrum of compound **(4a)** displayed molecular ion peak at m/z 272, which supports the proposed structure.

TABLE 1: Physical data of synthesized compounds (2, 3 and 4a-e)

Compound no	Substitutents R	Substitutents R_1	M.P, (^{0}C)	Yield (%)
(2a)	H	H	158-60	76
(2b)	H	CH_3	174-75	65
(2c)	H	Ph	205-06	69
(2d)	CH_3	Ph	224-25	71
(2e)	Cl	Ph	242-43	80
(3a)	H	H	181-82	70
(3b)	H	CH_3	159-60	68
(3c)	H	Ph	221-23	62
(3d)	CH_3	Ph	217-18	76
(3e)	Cl	Ph	262-63	85
(4a)	H	H	219-20	72
(4b)	H	CH_3	179-80	62
(4c)	H	Ph	164-66	60
(4d)	CH_3	Ph	239-40	70
(4e)	Cl	Ph	230-31	82

All compounds gave satisfactory elemental analysis

TABLE 2: Antimicrobial activity results of synthesized compounds (2, 3 and 4a-e)

Compound no	Organisms used (zone of inhibition in mm) *E.coli*	*S.aureus*	*P.aeruginosa*	*B.subtilis*	*A.niger*	*A.flavous*
(2a)	14	15	10	12	10	09
(2b)	16	16	14	15	12	10
(2c)	15	13	11	14	08	10
(2d)	14	17	12	16	11	12
(2e)	19	20	17	22	14	17
(3a)	12	14	09	13	07	11
(3b)	15	14	12	15	13	12
(3c)	16	11	13	11	10	10
(3d)	17	15	15	18	12	14
(3e)	21	19	19	20	15	16
(4a)	16	12	14	14	09	12
(4b)	17	14	15	16	12	14
(4c)	11	14	10	15	10	12
(4d)	15	16	11	14	10	11
(4e)	20	18	18	17	12	16
Standard 1	22	20	18	21	--	--
Standard 2	--	--	--	--	16	18
Control	--	--	--	--	--	--

Standard 1 -Gentamycine; Standard 2 - Clotrimazole; Control-DMF

Antimicrobial activity

The newly synthesized compounds were screened for their in vitro antibacterial activity against *E.coli*, *S.aureus*, *P.aeruginosa* and *B.subtilis* and antifungal activity against *A.niger*, and *A.flavous* using DMF as

TABLE 3: Spectral data of synthesized compounds 2, 3 and 4a-e

Compd. no	Substitutents R	Substitutents R_1	IR (cm^{-1})	^{1}H NMR (δ ppm)
2a	H	H	3212 (NH/NH), 1599 (C=N),	12.2 (s, 1H, indole NH), 11.3 (s, 1H, imidazole NH) and 7.1-8.4 (m, 15H, Ar-H).
2b	H	CH_3	3240/3210 (NH/NH), 1590 (C=N),	12 (s, 1H, indole NH), 11.4 (s, 1H, imidazole NH), 7-8.1 (m, 14H, Ar-H), and 2.1(s, 3H, CH_3).
2c	H	Ph	3250 (NH/NH), 1605 (C=N),	12.4 (s, 1H, indole NH), 11.3 (s, 1H, imidazole NH), and 7.2-8.2(m, 19H, Ar-H).
2d	CH_3	Ph	3221 (NH/NH), 1610 (C=N),	12.2 (s, 1H, indole NH), 11.6 (s, 1H, imidazole NH), 7-8.2 (m, 18H, Ar-H) and2.0 (s, 3H, CH_3).
2e	Cl	Ph	3280/3245 (NH/NH), 1600 (C=N),	12.3 (s, 1H, indole NH), 11.5 (s, 1H, imidazole NH), and 7.1-8 (m, 18H, Ar-H).
3a	H	H	3252 (NH/NH), 1580 (C=N),	12.1 (s, 1H, indole NH), 10.9 (s, 1H, imidazole NH), 7.2-8.2 (m, 13H, Ar-H) and 2.3 (s, 6H, CH_3).
3b	H	CH_3	3234/3220 (NH/NH), 1590 (C=N),	12.1 (s, 1H, indole NH), 11 (s, 1H, imidazole NH), 7.1-8.3 (m, 12H, Ar-H), 2.2 (s, 6H, CH_3) and 1.9 (s, 3H, CH_3).
3c	H	Ph	3260/3215 (NH/NH), 1601 (C=N),	12.5 (s, 1H, indole NH), 11.2 (s, 1H, imidazole NH) 7-8.2(m, 17H, Ar-H),and 2.4 (s, 6H, CH_3).
3d	CH_3	Ph	3241/3228 (NH/NH), 1595 (C=N),	12.3 (s, 1H, indole NH), 11.1 (s, 1H, imidazole NH), 7.2-8.3 (m, 16H, Ar-H), 2.3 (s, 6H, CH_3) and 2.1 (s, 3H, CH_3).
3e	Cl	Ph	3260/3220 (NH/NH), 1590 (C=N),	12.4 (s, 1H, indole NH), 11.2 (s, 1H,imidazole NH), 7.3-8.3 (m, 16H, Ar-H), and 2.2 (s, 6H, CH_3).
4a	H	H	3241/3230 (NH/NH), 1590 (C=N),	11.9 (s, 1H, indole NH), 11.4 (s, 1H, imidazole NH), 10.6 (s, 1H, NH) and7-8.1 (m, 9H, Ar-H).
4b	H	CH_3	3250/3226 (NH/NH), 1580 (C=N),	12 (s, 1H, indole NH), 11.3 (s, 1H, imidazole NH), 10.4 (s, 1H, NH), 7.2-8(m, 8H, Ar-H) and 2.1 (s, 3H, CH_3) .
4c	H	Ph	3270/3231 (NH/NH), 1604 (C=N),	12.4 (s, 1H, indole NH), 11.4 (s, 1H, imidazole NH), 10.7 (s, 1H, NH) and7.1-8.3(m, 13H, Ar-H).
4d	CH_3	Ph	3260/3215 (NH/NH), 1590 (C=N),	12.1 (s, 1H, indole NH), 11.3 (s, 1H,imidazole NH), 10.4 (s, 1H, NH), 7-8.2 (m, 12H, Ar-H) and 2.0 (s, 3H, CH_3).
4e	Cl	Ph	3250/3220 (NH/NH), 1600 (C=N),	12.2 (s, 1H, indole NH), 11.2 (s, 1H, imidazole NH), 10.5 (s, 1H, NH) and

solvent at 100µg/ml concentration by cup- plate diffusion method. After 24 hours of incubation at 37^{0}C, for antibacterial activity and after 48 hours for antifungal activity. The zone of inhibition was measured in mm and was compared with standard drug. The activity was compared with the available standard drugs, Gentamycine for antibacterial activity and Clotrimazole for the antifungal activity. The observed zones of inhibition are presented in TABLE 2.

The compounds screened for the antimicrobial activities have shown varying degree of antimicrobial activity. Relatively higher activity of compound **(2e, 3e** and **4e)** against the antibacterial and antifungal organisms may be attributed to the chlorine present in the molecule. Compound **(2e)** showed comparable activity against *S.aureus* and higher activity against *A.flavous* compared with standard. Compound **(3e)** shown higher activity against *P.aeruginosa* compared with standard. Among the molecules containing methyl shown good activity when compared to the standard. Compounds **(2b, 2d, 3b, 3d, 4b and 4d)** showed good activity against most of the organisms as compared with standard. The remaining compounds shown moderate activity against all organisms.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC. IR spectra (cm^{-1}) were recorded using KBr disc on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 (chemical shift in δ ppm) using TMS as an internal standard. Mass spectra were recorded with an LCMS-2010A Data Report-Shimadzu.

The starting compounds **(1a-e)** were obtained by Simple and substituted indoles on Vilsmeier-Haack formylation gave indole-3-aldehydes, which are prepared according to the literature method[15].

General procedure for the preparation of substituted imidazoles

The substituted indole-3-aldehydes (2 mmoles) were refluxed with different 1, 2-diketones (2 mmoles) in acetic acid in presence of ammonium acetate (10 mmoles) for 4-5 hr. the progress of the reaction was

monitored by TLC. The reaction mixture was allowed to stand to attain room temperature, the mixture was poured in ice-water and neutralized with ammonium hydroxide. The solid separated was filtered and washed with water, dried and recrystallised from ethanol.

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REFERENCES

[1] W.J.Houlihan, J.A.Remers, B.K.Brown; Indoles: Part I, John Wiley and Sons, Inc., New York, **(1972)**.
[2] M.E.Wolff; 'Burger's Medicinal Chemistry and Drug Discovery', 5th ed., John wiley and Sons, New York, **2**, 637 **(1996)**.
[3] M.R.Grimmett, A.R.Katritzsky, A.J.Boulton; 'Advances in Imidazole Chemistry', Adv. Heterocyclic chem, Edited by, (Academic Press, New York), **12**, 103 **(1970)**.
[4] P.N.Preston; Benzimidazoles and Congeneric Tricyclic Compounds, John Wiley and Sons, New York, 1 **(1981)**.
[5] A.Baeyer; Chem.Ber., **13**, 2254 **(1980)**.
[6] E.Bansal, V.K.Srivastav, A.Kumar; Indian J.Chem., **39B**, 357 **(2000)**.
[7] L.Canoira, J.G.Rodriguez, J.B.Subirats, J.Escario, I.Jimenez, A.R.Martinez-fernandez; Eur.J.Med. Chem., **24**, 39 **(1989)**.
[8] M.F.Comber, C.J.Moody; Synthesis, 731 **(1992)**.
[9] A.Quyang, E.B.Skibo; J.Org.Chem., **63**, 1893 **(1998)**.
[10] J.S.Biradar, Doddappa Anekal; Indian J. Heteterocyclic.Chem., **16**, 375 **(2007)**.
[11] R.Di Santo, R.Costi, M.Artico, P.La Colla; Eur.J.Med.Chem., **32**, 143 **(1997)**.
[12] H.Ji, W.Zhang, Y.Zhou, M.Zhang, J.Zhu, Y.Song, J.Lu, J.Zhu; J.Med.Chem., **43**, 2493 **(2000)**.
[13] C.Enguehard, J.L.Renou, H.Allouchi, J.M.Leger, A. Gueiffier; Chem.Pharm.Bill., **48(7)**, 2000,935 **(2000)**.
[14] S.Demirayak, U.Abu Mohsen, K.Guven; Boll. Chim.Farmac., **141**, 443 **(2002)**.
[15] S.P.Hiremath, J.S.Biradar, M.G.Purohit; Indian J. Chem., **21B**, 249 **(1982)**.