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Short Communication

Synthesis of Biheterocycles Containing Indole Nucleus and Their Antibacterial Activity

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Abstract

Indole-3-carboxaldehydes (1a-d) undergo condensation with ethyl cyanoacetate and malononitrile to give the acrylonitrile 2a-d and 3a-d which on reaction with hydrazine hydrate yield 3,5-diamino-5-hydroxy-4-(3-indolylmethylene)pyrazoles (4a-d) and 3-amino-5-hydroxy -4-(3-indolylmethylene)pyrazoles (5a-d), respectively. The new compounds were also screened for their antibacterial activity.

Keywords: Indole-3-carboxaldehydes ; Active methylene compounds; Base; Hydrazine hydrate; Pyrazoles.

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1. Introduction

Indole and its derivatives represent one of the most important class of compounds possessing a wide spectrum of biological activity [1-5]. The importance of indoles is well recognized by synthetic as well as biological chemists. The most ubiquitous of the known bioactive alkaloids are based on the indole moiety. Medicinal chemists repeatedly turn to indole based compounds as a target pharmacophore for the development of therapeutic agents [6]. Nitrogen heterocycles are ubiquitous systems in nature and are consequently considered as privileged structures in drug discovery. Derivatisation of these heterocyclic pharmacophores represents a convenient approach to generate chemical diversity during lead identification and optimization [7-9]. Many pyrazole derivatives are associated with antifungal [10], antidiabetic [11] and anti-inflammatory [12] properties. Hence, it was thought that a pyrazole ring, if coupled to an indole moiety, another pharmacophore, the resulting compound might have considerable

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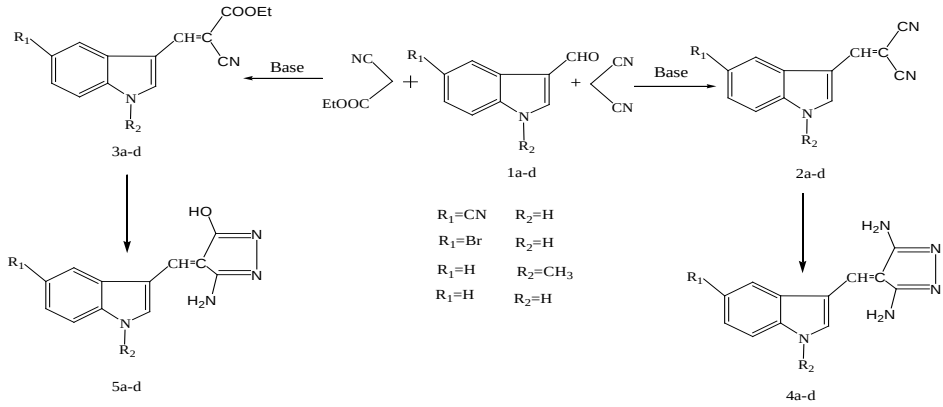
biological potency. We report herein the synthesis of a large number of indolylpyrazole derivatives.

Indole-3-carboxaldehyde (1a-d), obtained by the Vilsmeier-Haack formylation [13] of the respective indoles using $POCl_3$ and DMF, on condensation with active methylene compounds [14] such as ethyl cyanoacetate and malononitrile, in the presence of L-proline, yielded the intermediate acrylonitriles **2a-d** and **3a-d** (Table 1), respectively. Compound **3c** in its IR spectrum showed absorption peaks at 2210 and 1670 due to C≡N and CO functions, respectively. The PMR spectrum of **3c** exhibited a quartet and triplet at 4.2 and 1.3 accounting for ethoxy protons of ester groups. The methane and indole-N-methyl protons appeared at 8.5 and 3.9, respectively.

The acrylonitriles **2a-d** and **3a-d** when refluxed with hydrazine hydrate in ethanol furnished 3,5-diamino-5-hydroxy-4-(3-indolylmethylene)pyrazoles (4a-d) and 3-amino-5-hydroxy-4-(3-indolylmethylene)pyrazoles (5a-d) (Table 2), respectively (Scheme 1).



Scheme 1. Reflux of acrylonitriles with hydrazine hydrate.

In the IR spectrum of **5c** , C═N absorption appeared at 1618. Further, the appearance of a broad band at 3435-3216 indicated the presence of OH group of pyrazole moiety. A singlet at 3.8 and 5.2 due to N-CH_3 and NH protons was observed on the PMR spectrum of **5c**. The methaine proton appeared as a sharp singlet at 8.8. The spectral data established the structure assigned to **5c**.

Table 1. Reaction time, yields and melting points of the products 2a-d and 3a-d

Products	Time (min)	Yield (%)	Mp (°C)
2a	36	96	216
2b	44	89	210
2c	39	94	214
2d	32	81	223
3a	47	91	161
3b	31	76	219
3c	40	87	225
3d	32	81	268

2. Experimental

2.1 *General Procedure*

IR spectra were recorded on a spectrum BX Series. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHZ spectrometer in DMSO-d_6 using TMS as internal standard. M.Ps. were taken on a Haake Bucher meting point apparatus and are uncorrected.

2.2 *General synthetic procedure*

To a solution of malononitrile or ethyl cyanoacetate (2.2 mmol) in ethanol and the catalyst (0.2 mmol) was added indolealdehyde **1a-d** (2 mmol) rapidly and all at once. The resulting reaction mixture was refluxed for appropriate time and the progress of the reaction was monitored by TLC. After complete conversion of the starting material as indicated by TLC, the reaction mixture was quenched with water and the solid produced was isolated by simple filtration and dried. The solid product **2a-d** and **3a-d** were identified by spectroscopic measurements (Table 1).

2.3 *Spectral data of some of the representative compounds are as follows*

2-((1H-indol-3-yl)methylene)malononitrile (2d) : yellow solid: M.P. 223°C; (Found): C, 74.60; H, 3.65; N, 21.75. $C_{12}H_7N_3$ requires C, 74.62; H, 3.67; N, 21.77; IR (KBr) 3270, 2915, 2843, 2215, 1566, 1495, 1336, 1225, 1139, 825, 789cm^{-1}; 1H-NMR (400 MHz, DMSO-d_6), 7.31(t, 1H, 7.65Hz), 7.36(t, 1H, 7.23), 7.54(d, 1H, 8Hz), 7.92(d, 1H, 8Hz), 8.52(s, 1H), 9.2(s, 1H), 11.2(s, 1H); ^{13}C-NMR (50MHz,): 73.45, 110.24, 112.45 (2CN),115.24, 118.70, 122.40, 123.45, 128.63, 135.6, 137.01, 150.48; MS: m/z 193 (M^+).

Ethyl 2-cyano-3-(1-methyl-3 indolyl)acrylate (3c) : yellow crystals: M.P.225°C; (Found): C, 70.81; H, 5.54; N, 11.00; O, 12.56. $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02; O, 12.58; IR (KBr) 3400-3200, 3100-2900, 2210, 1670, 1600, 1590,1240, 1100 cm^{-1} ; ^{1}H-NMR (400MHz, DMSO-d_6), 1.307(t, 3H, J=7.2Hz), 3.977 (s, 3H), 4.286(q, 2H, J= 7.2Hz), 7.317-7.375(dt, 2H, J= 7.2Hz), 7.637(d, 1H, J= 8Hz), 7.97(d, 1H, 8Hz), 8.522(s, 1H), 9.01(s, 1H); ^{13}C-NMR (50MHz,): 14.15(CH_3), 33.82(N-CH_3), 61.42(OCH_2), 73.04, 108.94, 111.41, 117.80, 118.65,122.55, 123.75, 127.43, 135.8, 136.96, 145.82, 163.30(CO); MS: m/z 254 (M^+).

2.4 *General synthetic procedure for 4a-d & 5a-d*

To a solution of **2a-d** (0.01 mol) in ethanol (10 ml), hydrazine hydrate (7 ml) was added and the solution was heated under reflux for 2-4 hr, cooled and poured into ice-cold water. The separated solid was filtered, dried and recrystallized from a suitable solvent to give

4a-d (Table 2). Similar reaction conditions were used for the preparation of compounds **5a-d**.

Table 2. Reaction time, yields and melting points of the product 4a-d and 5a-d.

Products	Time (hr)	Yield (%)	Mp (°C)
4a	4	96	320(d)
4b	4	89	314
4c	2	94	323
4d	4	81	340
5a	4	91	325
5b	3.5	76	321
5c	4	87	327
5d	3.5	81	344

2.5. *Spectral data of some of the representative compounds*

3,5-diamino-4-(3-indolylmethylene)pyrazole (4d) : Brown solid: M.P.340°C; (Found): C, 62.99; H, 4.89; N, 30.75.$C_{12}H_{11}N_5$ requires C, 63.99; H, 4.92; N, 31.09; ^{1}H-NMR (400MHz, DMSO-d_6), IR(KBr pellet): 3216, 3111,1647,1623,1581,1535,1444 cm^{-1}; ^{1}H-NMR(δppm): 5.202(s,4H,2NH_2), 7.905(s,1H,NH-CH=C), 7.198-8.341(m,4H,ArH), 8.901 (s, 1H,CH=C), 11.692(s,1H,NH); ^{13}C-NMR(δppm): 112.10-131.79(aromatic carbon), 120.52(Ar-C), 137.20(CH=C), 155.07(2C-NH_2); MS: m/z 225 (M^+).

3-amino-5-hydroxy-4-(N-methyl-3-indolylmethylene)pyrazole (5c) : Brown solid: M.P.327°C; (Found): C, 64.81; H, 4.99; N, 23.02; O, 6.08. $C_{13}H_{12}N_4O$ requires C, 64.99; H, 5.03; N, 23.32; O, 6.66; ^{1}H-NMR (400MHz, DMSO-d_6),IR(KBr pellet): 3435, 3216, 3111,1647, 1618,1584, 1531,1449 cm^{-1}; ^{1}H-NMR(δppm): 3.86(s,3H,N-CH_3), 5.208(s,2H,NH_2), 7.228-8.361(m,4H,ArH), 7.886(s,1H,N-CH=C), 8.871 (s,1H,CH=C); ^{13}C-NMR(δppm): 32.87(N-CH_3),111.09-135.28(Ar-C), 120.82(CH=C), 137.72 (CH= C), 154.60 (C-OH, C-NH_2) ; MS: m/z 240 (M^+).

2.6 *Antibacterial activity*

Biological activity of some of the representative compounds were studied by disc diffusion technique in which some of the compounds showing the interesting results are tabulated in the Table 3. Most bromo substituted and cyno substituted compounds showed the potent activity against the tested bacteria. This activity test was repeated for 3-5 times to get the statistical reliable values and finally concluded these are showing good biological activity.

Table 3. Antimicrobial screening results of synthesized indole compound.

Compds.	Fungi		Gram(+Ve) bacteria			Gram(-Ve) bacteria		
	A. niger	*P.notatum*	S.aureus	S.faecalis	B.Subtillis	E.coli	K.pneumoniae	S.typhi
2a	+++	++	+++	_	+++	+	+	+++
3b	+	-	++	_	_	+	+	_
4a	_	_	+	+	++	_	_	+
5c	_	_	+++	_	+++	+++	+++	+
5b	++	_	+	+++	++	_	+	+

+ = weakly active, ++ = moderately active ++++ = highly active.
Inhibition values beyond control are + = 6–10 mm, ++ = 11–15 mm, +++ = 16–20 mm, ++++ = 21–25 mm and – = not active (the values are including disc diameter); R = Terbinafin (antifungal agent) and Tetracycline (antibacterial agent). The standards are in the form of sterile Hi-Disc cartridges, each disc containing 10 µg of the drug

3. Conclusion

In summary, we have synthesized various pyrazole substituted indoles via Knoevenagel condensation between indole carboxaldehyde, malononitrile or ethylcyanoacetate and hydrazine hydrate. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic and heterocyclic aldehydes. The attractive feature of this procedure are the mild reaction conditions, high conversions, clear reaction profiles, operation simplicity and readily available catalyst, all of which make it a useful and attractive strategy for the preparation of indole substituted pyrazoles.

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