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Synthesis, Spectral Characterization and Anti-microbial Studies of New 3- and 4 - substituted in 7- Aza Indole Derivatives

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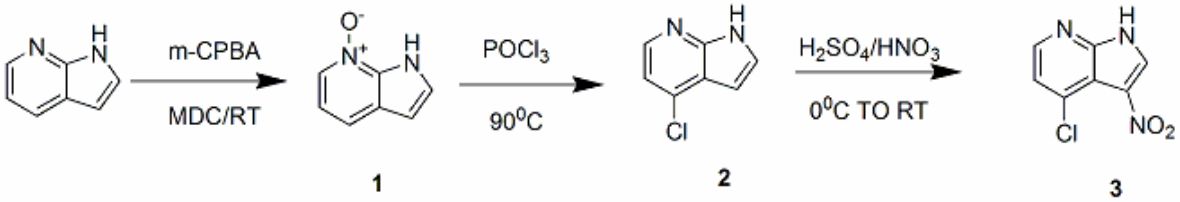
Abstract: In the present study, a number of new 3- and 4- substituted 7-azaindole derivatives have been prepared for the purposes of evaluating anti microbial activity studies. Comparing and vitro study of inhibitory effects of anti gram positive and gram negative bacteria, also in anti fungal studies by well dish method technique. Remarkable activity was observed and Chemical structures of all the novel compounds were characterized by LCMS, ^{1}H NMR, ^{13}C NMR Spectroscopy and Elemental analysis.
Keywords:1H-pyrrolo [2, 3-b] pyridine derivative, anti microbial study, Zone of inhibition concentration.

Introduction

The great interest in synthetic organic and medicinal chemistry - limited literature reference on the chemical reactivity of pyrrolo-(2, 3) pyridine[1-6]. The 3rd and 4th -position of pyrrolo-(2, 3) pyridine[7-15] is most susceptible to substitution reactions. The preparation of 3rd and 4th position of pyrrolo- (2, 3) pyridine containing thio urea derivatives, using simple aryl or alkyl substituted isothiocyanate couple with amine. Indole and 7-azindole heterocyclic are prevalent substructures in naturally occurring and synthetic molecules is playing biological activity[16-21]. Consequently, the development of efficient ways to prepare these compounds continues to be an active area of research. Aside from the vast array of more traditional methods, although this method has proven valuable, examination of the literature reveals considerable scope for refinement of the existing procedures.

Scheme-I



Experimental:

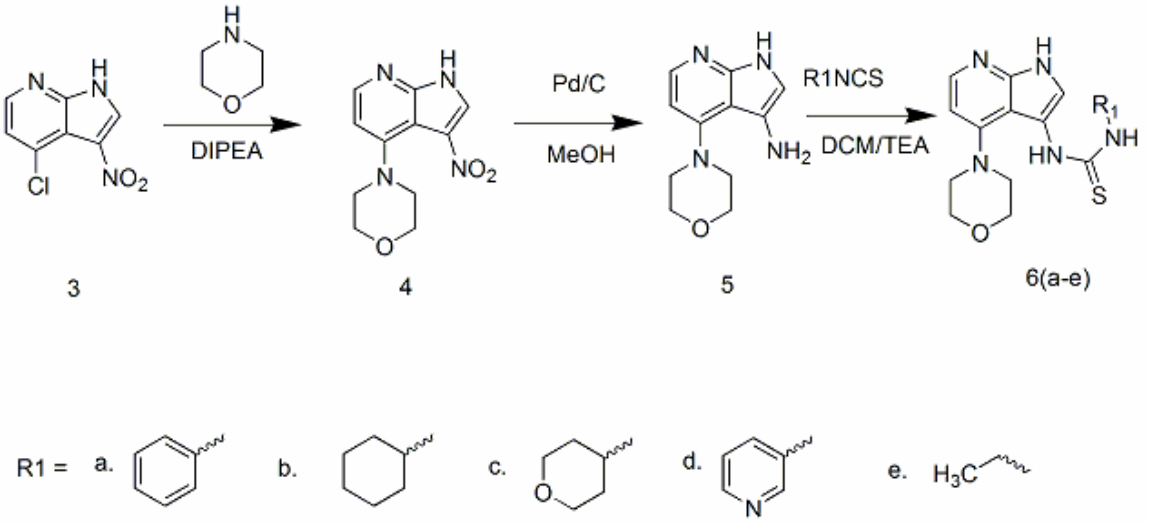
All starting materials were commercially available research grade chemicals and were used without further purification. Flash column chromatography was carried out in silica gel 230-400 mesh. The NMR spectra were obtained with 400MHz spectrometers using DMSO as solvent and TMS as an internal reference. LCMS spectra were obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Melting points were obtained on a Buchi 510 and are uncorrected.

7- aza indole N-oxide (1)[22]: Meta- Chloro perbenzoic acid ("m-CPBA", 22gm, 0.1270mole) was added portionwise to 7-azaindole (10gm, 0.08470 mole) in dichloromethane(100ml) at 0^0C-10^0C. The reaction mass stirred for 4-5hrs. TLC complies. The reaction mass concentrated to residue stage and made slurry with pet-ether, filtered and washed with pet-ether. The precipitate was then dried to give 7-hydroxy-1H-pyrrolo [2,3-b]pyridin-7-ium Mol.Wt.135.14, ^{1}HNMR (400MHz,DMSO-d6) (δ ppm) 6.43 (q, 1H) , 7.03 (q,1H) , 7.46 (t,1H),7.95(q, 1H), 8.19(q, 1H); 11.62 (s,1H,-NH) , LCMS : M^++1 (135.0), MS/MS(m/z) : 119.3; Anal Calcd. For $C_7H_7N_2O$: C, 62.21%; H, 5.22%; N, 20.73%; O, 11.84%. Found: C, 63.14%; H, 5.12%; N, 20.52%.

4-Chloro 1H-pyrrolo [2, 3-b] pyridine (2)[23]: To 7-azaindole N-oxide (8gm, 0.05923mole) was added $POCl_3$ (40ml, 5Vol) at room temperature. The solution was heated to 90^0C for 24hrs. Then reaction media was cooled to room temperature, and $POCl_3$ was distilled off in vacuum. The residue was dissolved in acetonitrile and quenched with slow addition of ice water. The mixture was basified to basic using 10% NaOH solution. The slurry was allowed to cool to room temperature, and the precipitates were filtered. The wet crude dried to afford the (2), Mol. Wt.152.58, ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 6.50 (q, 1H) , 7.21 (d,1H) , 7.59 (t,1H),8.18 (d, 1H), 12.04 (s, 1H,-NH); LCMS : M^++1 (153.6), MS/MS(m/z) : 119.2; Anal Calcd. For $C_7H_5ClN_2$: C, 55.10%; H, 3.30%; Cl, 23.24%; N, 18.36%; Found: C, 55.14%; H, 3.42%; N, 18.35%.

4-chloro-3-nitro-1H-pyrrolo[2,3-b]pyridine (3): To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine (7gm, 0.0460 mol) in H_2SO_4 (cooled to 0^0C was added pre-cooled solution of HNO_3 (14ml, 2vol) in H_2SO_4 (7ml, 1vol). After 1hr, the solution was poured over ice and the precipitate was filtered and dried affording the title compound (3) as a yellow solid, Mol. Wt.197.58, ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 7.66 (d, 1H) , 8.23 (d,1H) , 8.90 (d,1H), 13.49 (s, 1H,-NH), LCMS : M^++1 (198.5), MS/MS(m/z) : 153.5; Anal Calcd. For $C_7H_4ClN_3O_2$: C, 42.55%; H, 2.04%; Cl,17.94%; N, 21.27%; O, 16.20%. Found: C, 42.62%; H, 2.12%; N, 21.52%.

Scheme-II



4-morpholino-3-nitro-1H-pyrrolo[2,3-b]pyridine (4) : To the solution of 4-chloro-3-nitro-1H-pyrrolo[2,3-b]pyridine (10gm, 0.05037mol) in isopropyl alcohol (100ml) and Morpholine (0.06045mol) Diisopropylethyl amine (DIPEA, 0.005037mol) heated to 110^0c for 12-15hrs. The reaction was completed monitoring by TLC, then concentrated to residue stage under high vacuum, diluted with non polar solvent (pet ether, diethyl ether, etc.,) filtered and dried. Mol. Wt. 248.24, ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 2.49 (t, 4H), 3.78 (t, 4H), 6.80 (d, 1H), 8.18 (d, 1H), 8.63(s, 1H), 12.99 (s, 1H); LCMS: M^++1 (249.09), MS/MS (m/z): 198.0; Anal Calcd. For $C_{11}H_{12}N_4O_3$: C, 53.22%; H, 4.87%; N, 22.57%; O, 19.34%. Found: C, 53.44%; H, 4.92%; N, 23.27%;

4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-amine (5): The 10% of palladium-on-carbon was added to 4-morpholino-3-nitro-1H-pyrrolo [2, 3-b] pyridine (4) (10mmol) in dry Methanol (25ml), then kept under 1kg hydrogen pressure (bladder pressure) for 12-15hrs. The reaction was completed monitoring by TLC, and then filtered through celite pad. After the removal of the solvent, 4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-amine (5) was isolated as a brownish color solid. This will proceed to further next step without any purification.

General procedure for the thio urea derivatives of 4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-amine (6a-e): To a Solution of amine **(5)** (10mmol), TEA (Tri ethylamine) (2mmol) and Isothiocyanates (12mmol) in dry Dichloromethane (5ml) were added. The reaction media was stirred at room temperature for 3-4hrs. The progress of the reaction was monitored by TLC. After the completion of the reaction, it was quench with water and extracted with Dichloro methane and washed with water and brine solution , dried over Na_2SO_4 and finally purified by column chromatography (~30% of ethyl acetate in pet ether) to get the product in good yield.

Spectral data for derivatives

1-(4-morpholino-1H-pyrrolo [2,3-b] pyridine-3-yl)-3-phenylthiourea (6a)

Purified by column chromatography, brown color solid, 91% yield; Ms Calcd. For $C_{18}H_{19}N_5OS$: 353.13, Found: LCMS: M^++1 (354.8); m.pt. : 180-182^0C; ^{1}HNMR (400MHz,DMSO-d6) (δ ppm) 11.52 (s, 1H) , 9.02 (s, 1H) , 8.01 (d, 1H), 7.02 (t, 1H), 6.64 (d, 1H), 6.62 (d, 2H), 6.51 (d, 1H), 6.46 (d, 2H), 3.75(t, 4H); 3.02(t, 4H); ^{13}CNMR (DMSO-d6) :179.8, 149.3, 149.6, 143.3, 137.1, 129.1, 126.5, 126.1, 124.8, 100.4, 107.2, 101.6, 66.4, 46.7.

1-cyclohexyl-3-(4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl) thiourea (6b)

Purified by column chromatography, dark brown solid, 89% yield; Ms Calcd. For $C_{18}H_{25}N_5OS$: 359.18, Found: LCMS: M^++1 (360.0); m.pt. : 175-177^0C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.5 (s, 1H) , 9.03 (s, 1H) , 8.07 (d, 1H), 7.24 (d, 1H),7.03(d,1H), 6.52 (d, 1H), 3.77(t, 4H), 3.02 (t, 4H), 2.8 (m,1H), 1.78 (m, 4H), 1.49(m, 4H),1.32 (m, 2H); ^{13}CNMR (DMSO-d6) 177.9, 149.6, 143.3, 126.1,107.0, 101.2, 100.4, 66.4, 54.6, 46.7, 34.6, 34.0, 28.0, 23.5.

1-(tetrahydro-2H-pyran-4-yl)-3-(4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl) thiourea (6c)

Purified by column chromatography, Golden brown solid, 91% yield; Ms Calcd. For $C_{17}H_{23}N_5O_2S$: 361.16, Found: LCMS: M^++1 (362.2); m.pt. : 170-172^0C ; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) : 11.59 (s, 1H) , 9.03 (br, s, 1H) , 8.0 (d, 1H), 7.24 (d, 1H), 7.12(d, 1H), 6.52 (d, 1H), 3.77(t, 8H), 3.22 (m, 1H), 3.04 (t, 8H); ^{13}CNMR (DMSO-d6): 153.11, 144.67, 122.25, 109.00, 104.12, 66.77, 66.52, 52.61, 50.91, 40.65, 40.44, 40.23, 39.82, 39.61, 39.40, 32.5.

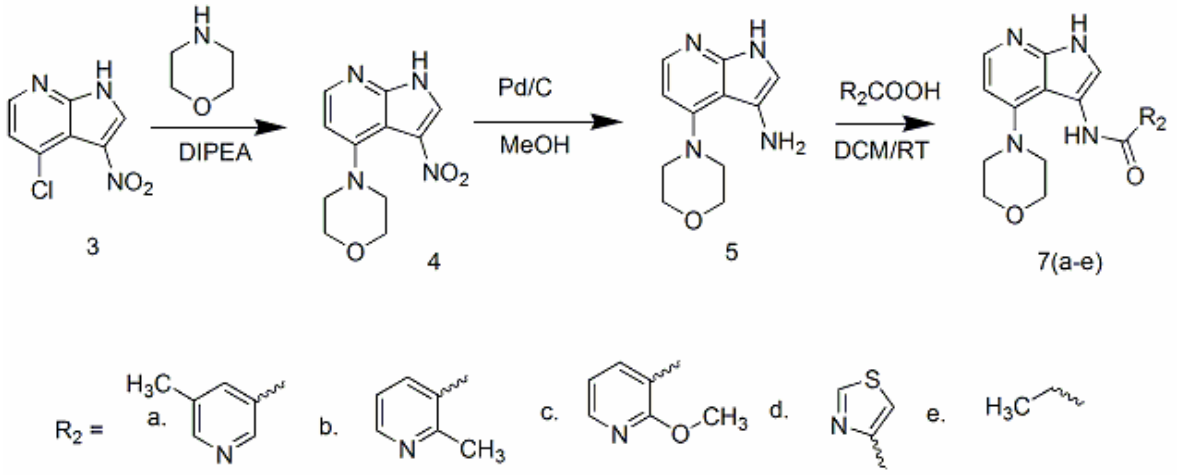
1-(4-morpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl)-3-(pyridine-4-yl) thiourea (6d)

Purified by column chromatography, pale brown color solid, 85% yield; Ms Calcd. For $C_{17}H_{18}N_6OS$: 354.13, Found: LCMS: M^++1 (355.2); m.pt. : 180-182^0C ; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) : 11.59 (s, 1H) , 9.03 (s, 1H) , 8.02 (s, 1H), 7.22 (d, 1H), 7.02 (d, 1H), 6.6 (d, 2H), 6.51 (d, 1H), 6.46 (d, 2H), 3.67(t, 4H), 3.04 (t, 4H); ^{13}CNMR (DMSO-d6): 153.21, 150.3, 149.6, 120.2, 108.00, 102.12, 66.37, 66.50, 45.7, 45.5.

1-methyl-3-(4-morpholino-1H-pyrrolo[2,3-b] pyridine-3-yl) thiourea (6e)

Crystallization and recrystallization using diethyl ether, brown color solid, 80% yield; Ms Calcd. For $C_{13}H_{17}N_5OS$: 291.12, Found: LCMS: M^++1 (292.2); m.pt. : 180-182^0C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.59 (s, 1H) , 9.03 (s, 1H), 8.02 (d, 1H), 7.23 (d, 1H), 7.02 (br, s, 1H), 6.51 (d, 1H), 3.77 (t, 4H), 3.04(t, 4H), 2.84 (d, 3H); ^{13}CNMR (DMSO-d6) : 182.20, 152.71, 148.41, 144.20, 121.47, 108.70, 103.78, 66.34, 52.08, 40.12, 39.91, 39.70, 39.49, 39.29, 39.08, 38.87, 31.58.

Scheme-III



General procedure for the thio urea derivatives of 4-morpholino-1H-pyrrolo [2,3-b]pyridine-3-amine (7): To a Solution of amine(5) (10mmole) , TEA (Tri ethyl amine, 3mmol), acids (R_2, 11mmol) in dry Dichloromethane(4ml). Then added EDCI.HCl (2mmol) and HOBT (0.02mmol). The reaction media was stirred at room temperature for 5-6hrs. The progress of the reaction was monitored by TLC. After the completion of the reaction water was added and purified by column chromatography using pet ether: ethyl acetate mixture (~30% of ethyl acetate in pet ether product was isolated)

5-methyl-N-(4-thiomorpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl) pyridine-3-carboxamide (7a)
Purified by column chromatography, pale brown solid, 80% yield; Ms Calcd. For $C_{18}H_{19}N_5O_2$: 337.15, Found: LCMS: M^++1 (338.2); m.pt.: 190-192^{0}C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.52 (s, 1H) , 9.93 (s, 1H) , 9.00 (d, 1H), 8.61 (d, 1H), 8.17 (d, 1H), 8.07 (d, 1H), 7.45 (d, 1H), 6.62 (d, 1H), 3.55(t, 4H), 3.05 (t, 4H) 2.48(s, 3H); ^{13}CNMR (DMSO-d6) : 164.65, 153.27, 152.93, 148.46, 146.10, 144.77, 135.84, 133.45, 129.85, 119.86, 111.81, 108.78, 104.63, 66.55, 52.53, 40.65, 40.23, 39.81.

2-methyl-N-(4-thiomorpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl) pyridine-3-carboxamide (7b)
Purified by column chromatography, pale brown solid, 82% yield; Ms Calcd. For $C_{18}H_{19}N_5O_2$: 337.15, Found: LCMS: M^++1 (338.2); m.pt.: 192-194^{0}C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.58 (s, 1H) , 9.61 (s, 1H) , 8.56 (d, 1H), 8.06 (d, 1H), 7.92 (d, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 6.62 (d, 1H), 3.60(t, 4H), 3.05 (t, 4H), 2.48(s, 3H); 13CNMR (DMSO-d6) : 164.65, 153.27, 152.93, 148.46, 146.10, 144.77, 135.84, 133.45, 129.85, 119.86, 111.81, 108.78, 104.63, 66.55, 52.53, 40.65, 40.23, 39.81.

2-methoxy-N-(4-thiomorpholino-1H-pyrrolo [2, 3-b] pyridine-3-yl) pyridine-3-carboxamide (7c)
Purified by column chromatography, dark brown solid, 88% yield; Ms Calcd. For $C_{18}H_{19}N_5O_3$: 353.15, Found: LCMS: M^++1(354.2); m.pt. : 188-190^{0}C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.58 (s, 1H) , 9.61 (s, 1H) , 8.56 (d, 1H), 8.06 (d, 1H), 7.92 (d, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 6.62 (d, 1H), 3.72 (s, 3H), 3.60(t, 4H), 3.05 (t, 4H); 13CNMR (DMSO-d6): 163.65, 154.27, 153.93, 149.46, 147.10, 142.77, 134.84, 132.45, 130.85, 120.86, 112.81, 109.78, 106.63, 65.55, 51.53, 41.65, 40.33, 39.71.

N-(4-morpholino-1H-pyrrolo [2,3-b] pyridine-3-yl) thiazole-4-carboxamide (7d)
Purified by column chromatography, yellowish brown color solid, 88% yield; Ms Calcd. For $C_{15}H_{15}N_5O_2S$: 329.09, Found: LCMS: M^++1 (330.0); m.pt. : 240-242^{0}C ; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) : 11.52 (s, 1H) , 10.28 (s, 1H) , 9.34 (d, 1H), 8.48 (d, 1H), 8.16 (d, 1H), 7.89 (d, 1H), 6.84 (d, 1H), 3.95(t, 4H), 3.05 (t, 4H); ^{13}CNMR (DMSO-d6): 154.27, 153.93, 149.46, 134.84, 132.45, 112.81, 109.78, 106.63, 65.55, 53.21, 51.53, 45.7, 46.7, 41.65, 40.33.

N-(4-thiomorpholino-1H-pyrrolo [2,3-b] pyridine-3-yl) acetamide (7e)
Purified by column chromatography, brown color solid, 90% yield; Ms Calcd. For $C_{13}H_{16}N_4O_2$: 260.13, Found: LCMS: M^++1 (261.2); m.pt.: 150-152^{0}C; ^{1}HNMR (400MHz, DMSO-d6) (δ ppm) 11.52 (s, 1H) , 9.16 (s, 1H), 8.07 (q, 1H), 7.34 (d, 1H), 6.57

(d, 1H), 3.83 (t, 4H), 3.04 (t, 4H), 2.04 (s, 3H); ^{13}CNMR (DMSO-d6): 152.71, 149.41, 121.47, 108.70, 66.34, 52.08, 40.12, 39.91, 39.70, 39.29, 38.87, 31.58, 21.9.

Biological Activity:

Anti microbial Activity

Antibacterial activity of all the synthesized derivatives was evaluated against pathogenic bacterial strains viz., staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, and Anti fungal activity of these derivatives are evaluated against fungal strains viz., Aspergillus niger, Candida kefir, Candida albicans using well diffusion methods. Ciprofloxacin was used as reference/standard antibacterial agent. The zones of inhibition of the compounds against above bacterial and fungal strains are summarized in Table I & Table II. Ciprofloxacin was used as reference antibacterial agent. Ketoconazole was used as reference antifungal agent. The results obtained showed that most of the compounds possess high to moderate activity.

From the above table I: The Synthesis compound shows moderate activity in the Pseudomonas aeruginosa and Klebsiella pneumonia. The comp (**6c**), comp (**7b**) possesses good activity when compared to other compounds in Pseudomonas aeruginosa.

Table I- Anti bacterial activity of 7-azaindole derivatives.

Comp. NO	Zone of inhibition (mm)*		
	Staphylococcus aureus	**Klebsiella pneumoniae**	***Pseudomonas aeruginosa***
DMSO	NZ	NZ	NZ
6a	NZ	**5**	**18**
6b	**7**	**7**	**18**
6c	NZ	**6**	**20**
6d	**4**	**7**	**18**
6e	NZ	**6**	**16**
7a	NZ	**7**	**17**
7b	NZ	**5**	**19**
7c	NZ	**7**	**12**
7d	**9**	**7**	**17**
7e	NZ	**6**	**16**
Ciprofloxacin	**22±1.2**	**20±1.2**	**22±1.2**

Table II – Antifungal activity of 7-azaindole derivatives

Comp. NO	Zone of inhibition (mm)*		
	Aspergillus niger	**Candida kefir**	***Candida albicans***
DMSO	NZ	NZ	NZ
6a	NZ	**5**	NZ
6b	**5**	**5**	NZ
6c	NZ	NZ	NZ
6d	NZ	NZ	NZ
6e	NZ	**7**	NZ
7a	NZ	**8**	NZ
7b	NZ	**6**	NZ
7c	NZ	NZ	NZ
7d	NZ	NZ	NZ
7e	NZ	NZ	NZ
Ketoconazole	**22±1.2**	**25±1.2**	**25±1.2**

*Values are mean of three determinations, the ranges of which are less than 5% of the mean in all cases.
*Compounds 5µg compound in 500 µL DMSO, used for experiments, NZ= No Zone.

From the above table II: The Synthesis compound shows poor activity in fungal activity studies (Candida kefir). The comp (**6a**), comp (**7a**) comps (**7b**) possess very less activity in Candida kefir when compared to other compounds and other two fungal strains.

Antimicrobial assay

Antimicrobial analysis was followed using standard agar well diffusion method to study the antimicrobial activity of compounds[25-28]. Each bacterial and fungal isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per ml. They were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30 µL (5µg compound in 500 µL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria and at room temperature for fungi. Antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. The tests were carried out in triplicates.

Conclusion

This method has several advantages over the existing methods such as sufficient synthetic route, high yields, mild reaction condition and nontedious experimental procedure. The synthesized noval derivatives showed good antibacterial activity against Pseudomonas aeruginosa. The spectral data and anti-microbial data shows that thiourea derivatives of 7-azaindoles are potential biologically actives in future discovery.

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Referrences

1) Xin Wang, Ben Zhi, et al., A practicle synthesis of 2-((1H-Pyrrolo[2,3-b]pyridine-4yl) methylamino)-5-fluoronicotinic Acid., J. Org. Chem. 2006,71, 4021-4023.
2) Terence A. Kelly, Novel Non-Nucleoside Inhibitors of Human Immunodeficiency virus Type 1 reverse Transcriptase. 6.2-indol-3-yl and 2-azaindol-3-yl dipyridodiazepinoones, J. Med. Chem. 1997, 40, 2430-2433.
3) US Patent: PCT/US2006/062453; WO 2007/ 076423.
4) John J. Caldwell, Kwai-Ming Cheung and Ian Collins., Synthesis of 4-(cyclic dialkylamino)-7-azaindoles by microwave heating of 4-halo-7-azaindoles and cyclic secondary amines, Tetrahedron Letters 48 (2007) 1527-1529.
5) ARRAY BIOPHARMA INC., Publ.; WO2009/140320 A1 (2009/11/19), Appl.; WO2009 -US43691 (2009/05/13).
6) Florence Popowycz, Sylvain Routier, Benoît Joseph, Jean-Yves Mérour, Synthesis and reactivity of 7-azaindole (1H-pyrrolo [2,3-b]pyridine, Review Tetrahedron, Volume 63, Issue 5, 29 January 2007, Pages 1031-1064.
7) Santiago Figueroa-Pérez, Samir Bennabi, Hartmut Schirok, Michael Thutewohl, Efficient synthesis of 4-O-and C-substituted-7-azaindoles , Tetrahedron Letters, Volume 47, Issue 13, 27 March 2006, Pages2069-2072.
8) Alexandre L'Heureux, Carl Thibault, Réjean Ruel , Synthesis of functionalized 7-azaindoles via directed ortho-metalations, Tetrahedron Letters, Volume 45, Issue 11, 8 March 2004, Pages 2317-2319.
9) G. Lavecchia, S. Berteina-Raboin, G. Guillaumet, Synthesis and functionalisation of 1H-pyrazolo[3,4-b]pyridines involving copper and palladium-promoted coupling reactions , Tetrahedron Letters, Volume 45, Issue 11, 8 March 2004, Pages 2389-2392.
10) Axel R. Stoit, Arnold P. den Hartog, Harry Mons, Sjoerd van Schaik, Nynke Barkhuijsen, Cees Stroomer, Hein K.A.C. Coolen, Jan Hendrik Reinders, Tiny J.P. Adolfs, Martina van der Neut, Hiskias Keizer, Chris G. Kruse, 7-Azaindole derivatives as potential partial nicotinic agonists, Bioorg. Med. Chem. Lett. 18, (2008) 188–193.
11) G. Lavecchia, S. Berteina-Raboin, G. Guillaumet, Synthesis and functionalisation of 1H-pyrazolo[3,4-b]pyridines involving copper and

palladium-promoted coupling reactions, Tetrahedron Letters, Volume 45, Issue 11, 8 March 2004, Pages 2389-2392.

12) Niels Krogsgaard-Larsen, Mikael Begtrup, Karla Frydenvang, Jan Kehler, Syntheses of aza-analogous iso-ergoline scaffolds using carbene mediated C–H insertion, Tetrahedron, Volume 66, Issue 47, 20 November 2010, Pages 9297-9303.

13) Jérome Guillard, Maÿlis Decrop, Nathalie Gallay, Claire Espanel, Elodie Boissier, Olivier Herault and Marie-Claude Viaud-Massuard, Synthesis and biological evaluation of 7-azaindole derivatives, synthetic cytokinin analogues , Bioorganic & Medicinal Chemistry Letters, Volume 17, Issue 7, 1 April 2007, Pages 1934-1937.

14) Santiago Figueroa-Pérez, Samir Bennabi, Hartmut Schirok, Michael Thutewohl, Efficient synthesis of 4-O- and C-substituted-7-azaindoles , Tetrahedron Letters, Volume 47, Issue 13, 27 March 2006, Pages 2069-2072.

15) Abderaouf Ahaidar, David Fernández, Olga Pérez, Gerardo Danelón, Carmen Cuevas, Ignacio Manzanares, Fernando Albericio, John A.Joule, Mercedes Álvarez, Synthesis of variolin B , Tetrahedron Letters, Volume 44, Issue 33, 11 August 2003, Pages 6191-6194.

16) John Liddle, Paul Bamborough, Michael D. Barker, Sebastien Campos, Rick P.C. Cousins, Geoffrey J. Cutler, Heather Hobbs, Duncan S. Holmes, Chris Ioannou, Geoff W. Mellor, Mary A. Morse, 4-Phenyl-7-azaindoles as potent and selective IKK2, inhibitors, Bioorganic & Medicinal Chemistry Letters, Volume 19, Issue 9, 1 May 2009, Pages 2504-2508.

17) Sylvain Routier, Nathalie Ayerbe, Jean-Yves Mérour, Gérard Coudert, Christian Bailly, Alain Pierré, Bruno Pfeiffer, Daniel-Henri Caignard, Pierre Renard, Synthesis and biological evaluation of 7-azaindolocarbazoles; Tetrahedron, Volume 58, Issue 33, 12 August 2002, Pages 6621-6630.

18) Gee-Hong Kuo, Catherine Prouty, Alan DeAngelis, Lan Shen, David J. O'Neill, Chandra Shah, Peter J. Connolly, William V. Murray, Bruce R. Conway, Peter Cheung, Lori Westover, Jun Z. Xu, Richard A. Look, Keith T. Demarest, Stuart Emanuel, Steven A. Middleton, Linda Jolliffe, Mary Pat Beavers, and Xin Chen., Synthesis and Discovery of Macrocyclic Polyoxygenated Bis-7-azaindolylmaleimides as a Novel Series of Potent and Highly Selective Glycogen Synthase Kinase-3β Inhibitors, J. Med. Chem., 2003, 46 (19), pp 4021–4031.

19) Antonella Ermoli, Alberto Bargiotti, Maria Gabriella Brasca, Antonella Ciavolella, Nicoletta Colombo, Gabriele Fachin, Antonella Isacchi, Maria Menichincheri, Antonio Molinari, Alessia Montagnoli, Antonio Pillan, Sonia Rainoldi, Federico Riccardi Sirtori, Francesco Sola, Sandrine Thieffine, Marcellino Tibolla, Barbara Valsasina, Daniele Volpi, Corrado Santocanale and Ermes Vanotti, Cell Division Cycle 7 Kinase Inhibitors: 1H-Pyrrolo[2,3-b]pyridines, Synthesis and Structure−Activity Relationships, J. Med. Chem., 2009,52 (14), pp 4380–4390.

20) Terrine K. Adler, Adrien Albert. The Biological and Physical Properties of the Azaindoles, J. Med. Chem., 1963, 6 (5), pp 480–483.

21) Tao Wang, Zhongxing Zhang, Owen B. Wallace, Milind Deshpande, Discovery of 4-Benzoyl-1-[(4-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)oxoacetyl] -2- (R)-methylpiperazine (BMS-378806): A Novel HIV-1 Attachment Inhibitor That Interferes with CD4-gp120 Interactions, J. Med. Chem., 2003, 46 (20), pp 4236–4239.

22) Merour, J. Y.; Joseph, B, Curr. Org. Chem. 2001, 5, 471 and reference cited therein.

23) Carl Thibault,, Alexandre L Heureux, Rajeev S. Bhide, and Rejean Ruel., Concise and Efficient Synthesis of 4-Fluoro-1H-pyrrolo[2,3-b]pyridine.

24) John J. Caldwell, Kwai-Ming Cheung and Ian Collins., Synthesis of 4-(cyclic dialkylamino) -7-azaindoles by microwave heaing of 4-halo-7-azaindoles and cyclic secondary amines. Tetrahedron Letters 48 (2007) 1527-1529.

25) Perez, C., Pauli, M., Bazerque, P. 1990. An antibiotic assay by the agar-well diffusion method. Acta Biol. Med. Exp., 15: 13- 115.

26) Bagamboula, C.F., Uyttendaele, M., Debevere, J. 2004. Inhibitory effect of thyme and basil essential oils, carvacrol, thymol, estragol, linalool and p-cymene towards Shigella sonnei and S. flexneri. Food Microbiol, 21: 33-42.

27) Erdemog˘lu, N., Ku¨ Peli, E., Yes, E., Ilada, R. 2003. Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. J. Ethnopharmacol., 89: 123-1.

28) Perez, C., Pauli, M., Bazerque, P. 1990. An antibiotic assay by the agar-well diffusion method. Acta Biol. Med. Exp., 15: 13- 115.

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