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NOTE

Michael Addition to Nalidixic Acid and its Antitubercular Activity

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α,β-Unsaturated site of nalidixic acid was subjected to Michael addition that afforded 14 new derivatives. All the compounds were characterized by spectral data and evaluated for its antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ by Alamar blue assay.

Key Words: Nalidexic acid, Michael addition, Antitubercular.

With reference to quinolones antimicrobial and antitubercular spectrum the present investigation was aimed on a known chemical structure of known biological activity to made attempts as modification in view to get new derivative with altered/potential antimicrobial spectrum[1,2].

Nalidixic acid is a quinolone antibacterial reserved for urinary tract infection that posses α,β-unsaturated carboxylic acid at 2, 3 positions of 1,8 naphthyridine moiety[3]. The nalidixic compound (**1**) was treated with amino and phenolic compounds in presence of pyridine/$NiCl_2$ (Michal addition)[2] afforded 2,3 dihydro 2-substituted nalidixic acid (**2a-g**) as intermediate that up on thermal cyclization in presence of concentrated H_2SO_4, gave tetracyclic derivatives (**3a-g**) (**Scheme-I**). The purity and authentication of the compound was confirmed on TLC plate using ethanol and ethylacetoacetate (1:1) as irrigant. The structures were assigned based on IR (KBr, ν_{max}, cm^{-1}) and ^1H NMR (δ ppm, TMS) data.

Synthesis of 2,3-dihydro-2-substituted nalidixic acid (2a-g): 0.01 mol of nalidixic acid (**1**) and appropriate phenolic amino compounds (0.01 mol), $NiCl_2 \cdot 6H_2O$ (2.3 g, 0.1 mol) were refluxed in mixture of 3:1 ratio of pyridine and ethanol for 2 h (Michael addition). Cooled mixture was acidified with concentrated HCl and the obtained precipitate was dissolved in sodium bicarbonate and reprecipitated with concentrated HCl. The product was dried and recrystallized with ethanol to afford compounds (**1a-g**) and single spot in TLC plate confirmed the purity of the compounds.

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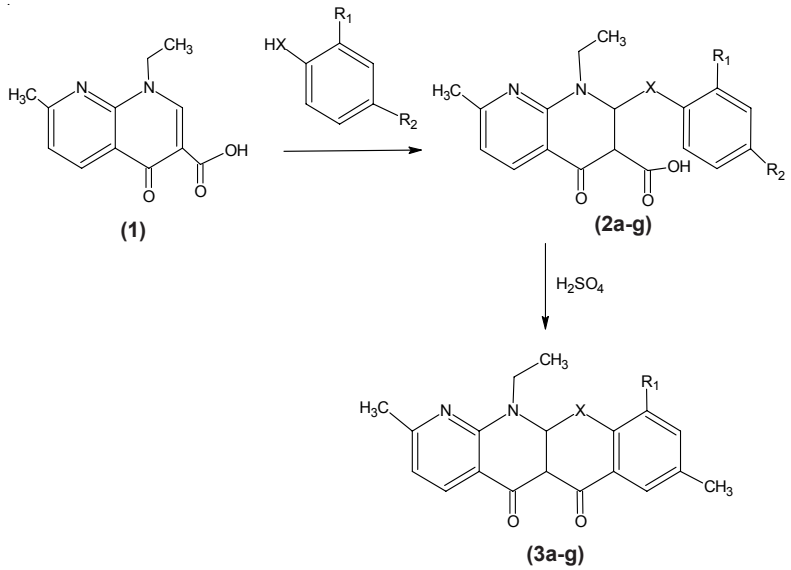

Scheme-I

2a: m.p. 227 ºC, yield 63 %, IR (KBr, ν_{max}, cm^{-1}) : 3412 (OH and NH coupled, *str.*), 3012, 3003 (Ar-H *str.*), 2970 (C-H *str.*), 1712 (C=O *str.*), 1623, 1587, 1510 (C=C and C=N *str.*), 1069 (C-N *str.*) and 752 (Ar-H def. out of plane); PMR: 3.43 (s, 3H, CH_3), 2.2 (t, 3H, CH_3), 2.9 (q, 2H, -CH_2-), 5.1-5.5 (dd, -CH-CH- of naphthyridine), 7.2-7.93 (m, 8H, Ar-H and -NH-), 10.3 (s, 1H, COOH).

Synthesis of 3a-g: A mixture of compounds **2a-g** (0.01 mol) and 5 mL of sulphuric acid were refluxed for 2 h at 110 ºC. The reaction mixture was cooled and poured into the crushed ice. The obtained product was filtered and washed until the filtrate was neutral to pH paper. The product was dried and recrystallized with ethanol to afford compounds **3a-g** and single spot on TLC plate confirmed the purity of the compound.

3e: m.p. 330 ºC, yield 72 %, IR (KBr, ν_{max}, cm^{-1}): 3011, 3005 (Ar-H *str.*), 2972 (C-H *str.*), 1719 (C=O *str.*), 1622, 1583, 1511 (C=C and C=N *str.*), 1065 (C-N *str.*), 1015 (C-O *str.*) and 749 (Ar-H def out of plane); PMR: 3.42 (s, 3H, CH_3), 2.21 (t, 3H, CH_3), 2.89 (q, 2H, -CH_2-), 5.2-5.6 (m, tautomer of -CH-CH- of naphthyridine), 7.2-7.7 (m, 7H, Ar-H).

Antitubercular activity: All the compounds were evaluated for its antitubercular activity against *Mycobacterium tuberculosis* $H_{37}R\nu$ by microplate alamar blue assay (MABA) method[4]. The screening results that the tetracyclic derivatives found to exhibit moderate anti tubercular activity with % exhibition in between 37-60 that reveals derivation of Micheal addition in to tetracyclic compounds potentiates the antitubercular activity of nalidixic acid.

TABLE-1
ANTITUBERCULAR ACTIVITY OF DERIVATIVES SYNTHESIZED

Compd.	X	R_1	R_2	Antitubercular activity (6.25 µg/mL)
2a	NH	H	H	0
2b	NH	H	COOH	4
2c	NH	COOH	H	15
2d	NH	Cl	H	9
2e	O	H	H	2
2f	O	COOH	H	13
2g	O	COOH	SO_3H	17
3a	NH	H	H	16
3b	NH	H	COOH	60
3c	NH	COOH	H	37
3d	NH	Cl	H	46
3e	O	H	H	54
3f	O	COOH	H	56
3g	O	COOH	SO_3H	48
Nalidixic acid	-	-	-	8

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