# Synthesis and Biological Activities of some New Acid Hydrazides and their Derivatives†

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Hydrazides and their condensation products are known for various biological activities[1]. In view of the above, the new hydrazides have been synthesised and screened for their antitubercular, antifungal and antibacterial activities.

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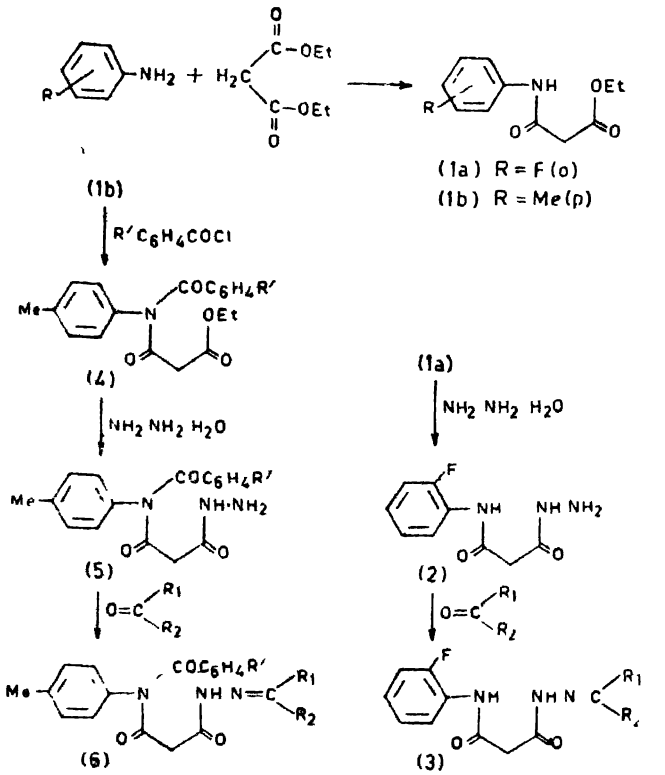
*o*-Fluoroaniline or *p*-toluidine on being refluxed with diethylmalonate gave ethyl 2-(*o*-fluoroanilido)-ethanoate (**1a**) and ethyl 2-(*p*-methylanilido)ethanoate (**1b**). **1b** on treatment with aroyl chlorides furnished the esters (**4a**−**c**), which when treated with hydrazine hydrate furnished 2-[(*N*-aroyl)-*p*-methylanilido]acetohydrazides (**5a**−**c**). 2-(*o*-Fluoro-

anilido)acetohydrazide (**2**) was obtained when **1a** was treated with hydrazine hydrate. Synthetic strategy has been outlined in Scheme 1.



**4,5** ; R′=H for **a**, *o*-Cl for **b**, *p*-Cl for **c**
**6** ; R′=H for **a**–**h**, *o*-Cl for **i**–**p**, *p*-Cl for **q**–**x**
**3a,6a i q** ; $R_1$=$R_2$=Me, **3b 6b j r** ; $R_1$/$R_2$=Me/Ph,
**3c,6c,k s** ; $R_1$/$R_2$=Me/ArOMe, **3d,6d l t** ; $R_1$/$R_2$=Me/ArOH,
**3e,6e,m,u** ; $R_1$/$R_2$=Me/ArCl.
**3f,6f n v** ; $R_1$/$R_2$=H/Ar(OH, OMe),
**3 q6g,o w** ; $R_1$/$R_2$=H/ArOH,
**3h 6h p x** ; $R_1$/$R_2$=H/Ph

Scheme 1

Compounds **2** and **5b** inhibited the growth of *M. tuberculosis* at 100 $\mu$g ml$^{-1}$ concentration only. Other compounds were found to be inactive. Comparative study of inhibition revealed that blocking of the $NH_2$ group of acid hydrazide by preparation of acid hydrazones augmented antimicrobial activity.

## Experimental

All melting points are uncorrected. Ir spectra (KBr) were recorded on a Perkin-Elmer 577 spectrophotometer and pmr spectra on a Jeol-Ex-90 spectrophotometer. All compounds gave satisfactory results for elemental analysis.

Ethyl 2-(*o*-fluoroanilido)ethanoate[2] (**1a**) and ethyl 2-(*p*-methylanilido)ethanoate[3] (**1b**) were prepared by reported methods.

*2-(o-Fluoroanilido)acetohydrazide* (**2**) : A mixture of **1a** (4.50 g, 0.02 mol), ethanol (6 ml) and hydrazine hydrate (12 ml, 80%) was stirred for 10 min when a crystalline solid separated. It was filtered and recrystallised from ethanol as white crystals (50%), m.p. 100° (Found : N, 19.82, $C_9H_{10}FN_3O_2$ calcd. for : N, 19.20%) ; $\nu_{max}$ 3 150 (N–H), 1 665 (C=O) and 1 250 (C–F) cm$^{-1}$ ; $\delta$ (DMSO) 2.9 (2H, s, $CH_2$), 4.2 (1H, s, NH) and 7.1–7.3 (4H, m, ArH).

*Ethyl 2-[(N-benzoyl)-p-methylanilido]ethanoate* (**4a**) : A mixture of **1b** (13.26 g, 0.06 mol), dioxane (6 ml), benzoyl chloride (8.46 g, 0.06 mol), dioxane (6 ml), **1b** (13.26 g, 0.06 ml) and triethylamine (6.06 g, 0.06 mol) was refluxed for 2 h on a boiling water-bath. The contents were kept overnight and triethylamine hydrochloride formed was filtered out and the filtrate was poured on crushed ice. The solid obtained was recrystallised from 50% aqueous methanol as white crystals (68%), m.p. 72° (Found : C, 69.32 ; H, 5.40 ; N, 4.21. $C_{19}H_{19}NO_4$ calcd. for : C, 70.15 ; H, 5.84 ; N, 4.30%) ; $\nu_{max}$ 1 716 (C=O) ; $\delta$ ($Me_2CO$) 1.10–1.32 (3H, t, *J* 7 Hz, $CH_2CH_3$), 2.25 (2H, s, $CH_2$), 4.0–4.3 (2H, q, *J* 7 Hz, $CH_2$) and 6.95–7.2 (4H, m, ArH).

Compounds **4b** and **4c** were prepared similarly : **4b** (80%), m.p. 64° (Found : N, 4.00 ; Cl, 10.32. $C_{19}H_{18}ClNO_4$ calcd. for : N, 4 06 ; Cl, 10.46%) ; $\nu_{max}$ 1 720 (C=O) ; $\delta$ ($Me_2CO$) 1.10–1.32 (3H, t, *J* 7 Hz, $CH_2CH_3$), 2.25 (2H, s, $CH_2$), 4.01–4.3 (2H, q, *J* 7 Hz, $CH_2$) and 7.1–7.3 (4H, m, ArH) ; **4c** (71%), m.p. 59° (Found : N, 3.97 ; Cl, 10.42. $C_{19}H_{18}ClNO_4$ calcd. for : N, 4.06 ; Cl, 10.46%) ; $\nu_{max}$ 1 712 (C=O) ; $\delta$ ($Me_2CO$) 1.10–1.35 (3H, t, *J* 7 Hz, $CH_2CH_3$), 2.21 (2H, s, $CH_2$), 4.01–4.27 (2H, q, *J* 7 Hz, $CH_2$) and 7.0–7.27 (4H, m, ArH).

*2-[(N-Benzoyl)-p-methylanilido]acetohydrazide* (**5a**) : A mixture of **4a** (9.33 g, 0.03 mol), ethanol (8 ml) and hydrazine hydrate (15 ml ; 70%) was stirred for 25 min. The resulting white crystals were recrystallised from ethanol, (52%), m.p. 180° (Found : C, 64.32 ; H, 5.40 ; N, 13.21. $C_{17}H_{17}N_3O_3$ calcd. for : C, 65.59 ; H, 5.46 ; N, 13.50%) ; $\nu_{max}$ 3 160 (NH) and 1 660 cm$^{-1}$ (C=O) ; $\delta$ (DMSO) 2.25 (2H, s, $CH_2$), 3.15 (3H, s, $CH_3$), 4.2–4.31 (2H, s, NH) and 6.95–7.2 (4H, m, ArH) ; **5b** (66.4%), m.p. 174° (Found : N, 12.10 ; Cl, 10.26. $C_{17}H_{16}ClN_3O_3$ calcd. for : N, 12.13 ; Cl, 10.40%) ; $\nu_{max}$ 3 155 (NH), 1 665 (C=O) and 1 090 cm$^{-1}$ (C–Cl) ; $\delta$ (DMSO) 2.3 (2H, s, $CH_2$), 3.02 (3H, s, $CH_3$), 4.22 (1H, s, NH) and 6.91–7.2 (4H, m, ArH) ; **5c** (77%), m.p. 187° (Found : N, 12.09 ; Cl, 10.38. $C_{17}H_{16}ClN_3O_3$ calcd. for : N, 12.13 ; Cl, 10.40%) ; $\nu_{max}$ 3 160 (NH), 1 655 (C=O) and 1 080 (C–Cl) ; $\delta$ (DMSO) 2.22 (2H, s, $CH_2$), 3.08 (3H, s, $CH_3$), 4.2 (2H, s, NH) and 7.0–7.3 (4H, m, ArH).

*2(o-Fluroanilido)acetohydrazone of aldehydes and ketones* (**3** *and* **6**). *General method :* To a mixture of 2-(*o*-fluroanilido)acetohydrazide (0.211 g, 0 001 mol) and benzaldehyde (0.106 g, 0.001 mol) dissolved in ethanol was added a drop of concentrated $H_2SO_4$ and the mixture was stirred for 5 min. The resulting solid was crystallised from ethanol : **3a** (25%),

m.p. 198° ; **3b** (54%), 192° ; **3c** (95%), 222° ; **3d** (85%), 240° ; **3e** (95%), 208° ; **3f** (55%), 174° ; **3g** (67%), 194° ; **3h** (73%), 189° ; **6a** (54%), 220° ; **6b** (49%), 216° ; **6c** (95%), 231° ; **6d** (79%), 214° ; **6e** (95%), 245° ; **6f** (32%), 204°, **6g** (84%), 222° ; **6h** (75%), 206° ; **6i** (66%), 230° ; **6j** (89%) 219° ; **6k** (52%), 208° ; **6l** (65%), 232° ; **6m** (77%), 238° ; **6n** (73%) 214° ; **6o** (67%), 210° ; **6p** (58%), 204° ; **6q** (58%), 250° ; **6v** (98%), 213° ; **6s** (89%), 221° ; **6t** (56%), 218° ; **6u** (93%), 233° ; **6v** (31%), 226° ; **6w** (78%), 208° ; **6x** (67%), 198°.

*Antitubercular activity :* Compounds **2**, **3g**, **5a**–**c**, **6c** and **6j** were incorporated into Lowenstein-Jensen egg medium having concentrations of 10 and 100 $\mu$g ml$^{-1}$ and were inoculated with *Mycobacterium tuberculosis* $H_{37}R_v$ strains, incubated at 37° and observed weekly for the growth of organism for eight weeks.

*Antimicrobial activity :* Compounds **2**, **3b**, **d**, **h**, **5a**–**c**, **6f**, **g**, **l**, **o**, **p**, **r**, **s**, **u**, **v** were screened for antibacterial and antifungal activity by agar-plate diffusion technique[4]. The testing was carried out at a concentration of 50 $\mu$g ml$^{-1}$ using bacteria *S. aureas*, *S. albus*, *E. coli* and fungi *Aspergillus niger*, *Alternaria alternata* and *Candida albicans*.

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