Synthetic utility of 4-acetyl-3-arylsydnones: synthesis, spectral characterisation and antimicrobial activity of 3-aryl-4-[(2′,3′-dihydrospiro-1′,4′-benzodiazepine-5′,[3″-3″H]-2″-oxindol]-(1″H))-7′-yl] sydnones

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3-Aryl-4-[3′-hydroxy-2′oxo)-3′-indol]acetylsydnones **IIa–n** have been synthesised from 4-acetyl-3-arylsdnones **Ia–n** and isatin. These β-hydroxy derivatives were readily converted into the corresponding α, β-unsaturated ketones **IIIa–n** which were further condensed with 1,2-phenylenediamine to give the 3-aryl-4-[2′,3′-dihydrospiro-1′,4′-benzodiazepine-5′,3″-[3″H]-2″-oxindol-)1″H))-7′-yl]sydnones **IVa–n**. All the compounds have been evaluated for their *in vitro* growth inhibitory activity against few microbes.

Acetyl derivatives of 3-arylsydnones are useful precursors for the synthesis of many sydnone derivatives coupled with a variety of heterocycles [1–6]. In this paper, we report the further utilisation of 4-acetyl-3-arylsydnones **Ia–n** in the preparation of 3-arylsydnone-[β-2′-oxo-3′-indolo]-α, β-unsaturated ketones **IIIa–n**, which have been used as key intermediates for the title compounds **IVa–n** 3-aryl-4-[2′,3′-dihydrospiro-1′,4′-benzodiazepine-5′,3″-[3″H]-2″-oxindol]-(1″H))-7′yl]sydnones. The synthesis and antimicrobial activity of spiroheterocyclic and 1,5-benzodiazepine derivatives of 3-arylsydnones have been recently reported and significant enhanced *in vitro* inhibitory activity has been observed for the latter compounds [7,8]. These observations and the ease with which the spiroheterocycles could be synthesised from enones led us to the present work.

The 4-acetyl-3-arylsydnones **Ia–n [2]** when treated with isatin in presence of a base afforded the 3-aryl-4-[(3′-hydroxyl-2′oxo-3′-indolo)]-acetyl sydnones **IIa–n**. The IR spectra of all these compounds showed a band ~ 3369 cm^{-1} for ν_{OH} and ν_{NH}. The $\nu_{C=O}$ of the sydnone ring and the cyclic amide appeared at 1782 and 1671cm^{-1} respectively. A sharp band at 1720cm^{-1} for the acetyl $\nu_{C=O}$ and the absence of a broad band for ν_{OH} indicate that the two groups are not intramolecularly H-bonded. This is also evidenced by ^{1}H-NMR (300MHz) spectra which showed a signal at δ 4.8 (D_2O exchanged) for the unassociated OH proton. The diastereotopic (also anisochronous) methylene protons appeared as two doublets at δ 3.1 and 3.9 due to geminal coupling (*J*-15 Hz). The NH proton was observed at δ 8.0 (D_2O exchanged) and the multiplet at δ 6.65–7.2 integrated for the aromatic protons. Studies on the stereochemistry of these compounds is being carried out and yet to be finalised.

These β-hydroxy derivatives **IIa–n** readily underwent dehydration in presence of an acid to yield the α,β-unsaturated oxindol derivatives **IIIa–n**. The formation of the enones was characterised by the absence of ν_{OH} and the shift of the acetyl $\nu_{C=O}$ to a lower frequency to 1702 cm^{-1} in their IR spectra. The ^{1}H-NMR (300MHz) signals at δ3.1 and 3.9 and 4.8 (–CH_2 and OH of **IIa–n**) disappeared and the appearance of a singlet at δ 8.00 for the methine proton further comfirmed this conversion from **II** to **III**. Cyclocondensation of **IIIa–n** with 1,2-phenylenediamine resulted in the formation of the title compounds **IVa–n** in about 75%. The mechanism involves a chemoselective nucleophilic attack at the electron deficient enone carbonyl rather than the amide carbonyl, resulting in the formation of a seven membered heterocyclic compound **IVa–n**. The formation of the benzodiazepine derivatives **IVa–n** were evidenced by the absence of enone $\nu_{C=O}$ at 1702 cm^{-1}. The broad band ~ 3410 cm^{-1} was accounted for the two ν_{NH}. No significant changes were observed for the $\nu_{C=O}$ of sydnone ring and amide carbonyl (1748 and 1719 cm^{-1}). The typical ^{1}H-NMR (300MHz) of all these compounds showed obscured doublets at ~ δ 1.8 with very small chemical shifts for the diastereotopic CH_2 protons. The presence of two NH protons at δ 8.04 (amide NH) and δ 7.78 (both D_2O exchanged) confirmed the formation of the 1,4-benzodiazepine ring spiro to the oxindole ring. These compounds with a rare combination of three different heterocycles would help to evaluate several aspects of our program of diversity of structural variants for structure activity relationship (SAR) studies of sydnone derivatives.

Antimicrobial activity

The amtimicrobial activity was done against two pathogenic bacteria *E. coli* and *C. bacillus* and *A. candida* and *R. bataticola* as the fungal strains. The reference drugs used were norfloxacin and griseofulvin respectively. Compounds **II** with halogen substitution showed bacterial growth inhibition equal to that of the reference drug only against *E.coli* while with halogens, methyl and methoxy derivatives the antifungal activity increased 2–3 times more than the reference compounds. Only some of the compounds **III** showed enhanced activity against *E. coli* but none against *C. bacillus*. It is worth mentioning that fungal growth inhibitory activity for most of these compounds increased by 2–3 times compared to the reference compounds, against both the fungal strains. The presence of an oxoindole ring in both types of the compounds could be responsible for the enhanced antimicrobial activity, as the sydnone ring alone does not contribute much. However, the presence of the benzodiazepine ring did not prove fruitful as in most of the compounds **IVa–n**, the growth inhibitory activity decreased to a considerable extent against all the strains.

Experimental

The IR were recorded on IR NICOLET-IMPACT-410 FTIR. ^{1}H-NMR were recorded on a Bruker AC-300 F-300 MHz spectrometer in $CDCl_3$ with TMS as an internal standard.

Synthesis of 3-aryl-4-[3′-hydroxyl-2′-oxo-indolo]acetyl sydnones **IIa–n**: A mixture of 4-acetyl-3-arylsydnone (0.01mol) and isatin (0.01mol) in absolute ethanol (100 ml) and piperidine (not more than two drops) was stirred for half an hour at room temperature. The reaction mixture was allowed to stand overnight at room temperature. The yellow needles formed were crystallised from ethanol.

Synthesis of 3-arylsydnone-4-[β-(2′-oxo-3-indol)]α,β-unsaturated ketones **IIIa–n**: These are prepared by two methods.

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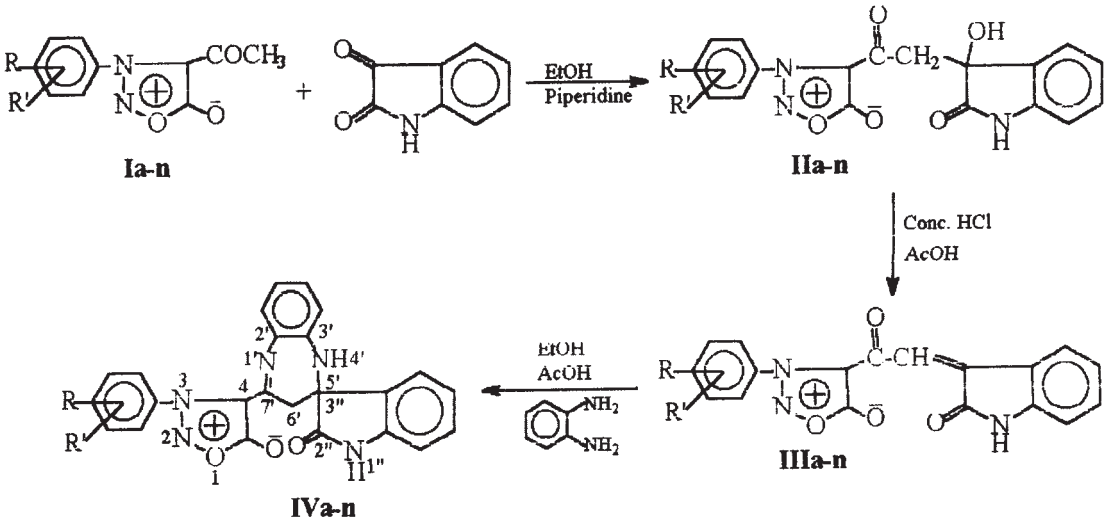

For II, III and IV

R= H,	R' = H
2, 4-CH_3,	H
2, 4-OCH_3,	H
4,3-Cl,	H
4-Br,	H
4-CO_2CH_3,	H
4-$CO_2C_2H_5$	H
3-CH_3	4-CH_3
2-CH_3	5-CH_3
3-Cl	4-CH_3
4-Cl	2-OCH_3

Scheme 1

Method A: 3-Aryl-4-[3′-hydroxyl-2′oxo-indol]acetylsydnones 5g were treated with conc. hydrochloric acid (0.5 ml), glacial acetic acid (20 ml) and warmed on the water bath for 10min. Orange needles of the title compounds separated were crystallised from ethanol.

Method B: To 3-Aryl-4-[3′-hydroxyl-2′-oxo-indol]acetylsydnones (5g), in ethanol (25ml) was added conc. hydrochloric acid (50 ml) and the reaction mixture was allowed to stand overnight. Fine orange needles were obtained.

Synthesis of 3-aryl-4-[(2′,3′-dihydrospiro [1′,4′-benzodiazepine-5′,3″-[3″H]-2″oxindol]-(1″H)-7′-yl]sydnones. **IVa–n**: To a solution of 3-arylsydnone-4-[β-(2′-oxo-3′-indol)]-α,β-unsaturated ketones (0.01mol) in ethanol (20ml) was added 1,2-phenylenediamine (1.08g, 0.01mol) and the reaction mixture was refluxed on a water bath for 5 hours. The crystalline brown compound separated on cooling was recrystallised from ethanol.

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