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Studies on synthesis and evaluation of quantitative structure–activity relationship of 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides

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Abstract—A new series of 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** has been synthesized and evaluated as antimicrobial agents. Structures of all the synthesized compounds were established on the basis of elemental analysis and spectroscopic data. Quantitative structure–activity relationship (QSAR) investigations were applied to find out the correlation between the experimentally evaluated activity with various parameters of the compounds studied. QSAR equations showed that the molecular refractivity correlates significantly with the antimicrobial activity.

Benzodiazepines (BDZs) and their derivatives are well known to the chemists mainly because of the broad-spectrum biological properties exhibited by this class of compounds.[1–5] Interest in the chemistry, synthesis and biology of this pharmacophore continues to be fuelled by their activity against a variety of CNS disorders as well as due to wide biological properties such as antianxiety, anticonvulsant, sedative/hypnotic, muscle relaxing and tranquilizing.[6–8] Many drugs incorporating BDZ core nucleus which extensively binds to plasma and tissue proteins have been developed over the past two decades and they became the most commonly prescribed group of psychotherapeutic drugs worldwide.[9,10] After the discovery of benzodiazepine receptors in the CNS and peripheral tissues[11,12] many attempts have also been made to correlate the molecular structure with the biological activity of these compounds.[13] In an attempt to prepare even more potent drugs, the ability of BDZ analogues to adjoin with another four- or five-membered ring has been investigated.[14–16] It has been reported that the introduction of an additional five-membered heterocyclic ring to seven-membered azepine nucleus tends to exert profound influence in conferring novel biological activities in these molecules.[17] The attachment of a five-membered ring often produces potent anti-HIV active compounds.[11–13] These compounds exert their biological activity by covalently binding to the N-2 of guanine in the minor groove of DNA through the imine or equivalent functionality at N10–C11 of the BDZ. The aminal linkage thus interferes with DNA function.[18] Furthermore, these molecules have been shown to interact with DNA in a sequence-selective manner as a result they may have the potential to inactivate particular genes.[19]

Hence, in view of the variegated importance associated with the five-membered phosphole ring system, we decided to link up this moiety with the benzodiazepine nucleus in order to frame the novel molecular architecture of annulated heterophospholobenzodiazepines. Keeping this in mind and in continuation of our enduring research on the synthesis of biologically significant compounds,[20–25] we have attempted the synthesis of hitherto unknown, 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** with fascinating structural features.

Keywords: 1,4-Benzodiazepine; Azaphohole; Intramolecular cyclocondensation; Antimicrobial activity; QSAR; Molecular refractive index (MR).
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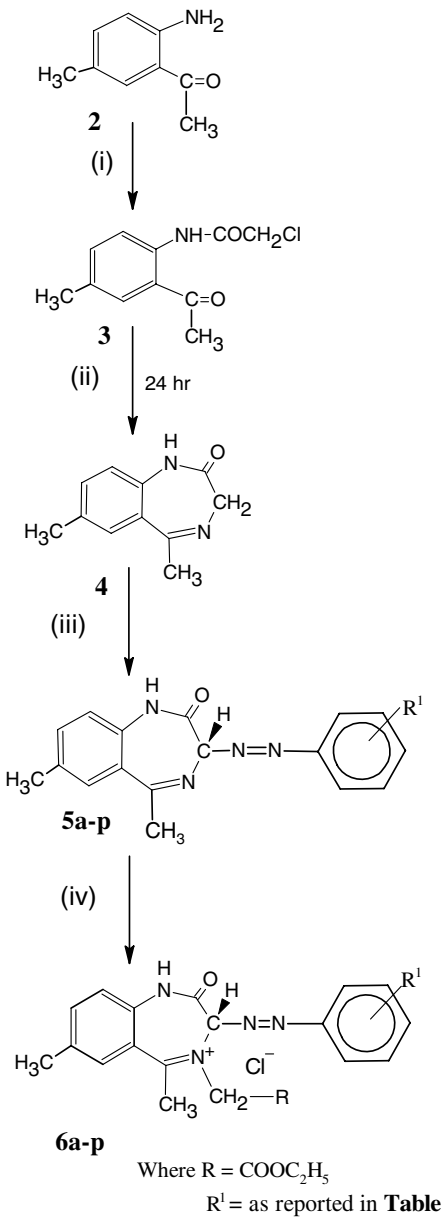
Moreover, to find a role of this nucleus against the problem of multidrug-resistant pathogens, the constructed molecules were screened for their antimicrobial activity.

Additionally, the systematic quantitative structure–activity relationship (QSAR) studies have also been carried out to reach a thorough understanding of the effect of substituents on the observed activities of the synthesized compounds.

The synthetic route to the desired target molecule 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** includes the cyclization (**3** → **4**) (Scheme 1) to generate the imine moiety of the B-ring. The approach involves the initial preparation of precursor, viz., chloroacetamidoacetophenone[26] **3** as the representative of B-ring fragment. Subsequently, this was allowed to reflux in ammonia/methanol for 24 h, which leads to cyclization to give 5,7-dimethyl-1, 3-dihydro-2*H*-1, 4-benzodiazepin-2-one **4** in an excellent yield (80%). Moreover, stereochemical asymmetry at C11a of **5a**–**p** was accessible by introducing a diazonium fragment in an electrophilic substitution mode which resulted in the formation of compound (3*S*)-3-arylazo-5,7-dimethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **5a**–**p**.[27] This in turn was allowed to react with an equimolar quantity of a pertinent alkyl halide in THF and stirred for 36 h at room temperature to give the N-alkylated product **6a**–**p** in good yield.[28]



Scheme 1. Reagents and conditions: (i) 1,4-di-oxan, $ClCH_2COCl$, 3 N NaOH, CH_2Cl_2, 30 min; (ii) NH_3/CH_3OH; (iii) $RC_6H_4NH_2$, $NaNO_2$/HCl, 0–5 °C; (iv) $ClCH_2COOC_2H_5$,THF, 36 h.

Condensation of **6a**–**p** with phosphors trichloride (2 equiv) in the presence of triethylamine (3 equiv.) in toluene yielded intermediate synthesis of 5-bis(dichlorophosphino)-ylidene-(3*S*)-*N*-ethoxycarbonyl-7-methyl-3-arylazo-2-oxo-1,2,3,5-tetrahydro-5*H*-1,4-benzodiazepine **9a**–**p**.[29] The initially formed mono dichlorophosphino derivative **7a**–**p** is highly activated and undergoes instantaneous substitution by phosphorus trichloride to provide the bis(dichlorophosphino) derivative **9a**–**p**. Further, the absence of any ^1H NMR signal at δ 6.00 ppm, which is characteristic of a C-5 methine proton, also supports the formation of **9a**–**p**. This was cyclized to give **10a**–**p** on heating with an additional amount of triethylamine in acetonitrile (Scheme 2).

The polarity of the solvent influences the progress of the above reaction. In non-polar solvents such as toluene and xylene, the reaction stops at stage **9a**–**p**, whereas in polar solvents, viz., acetonitrile, ethylacetate the initially formed bis(dichlorophosphino) derivative **9a**–**p** undergoes intramolecular cyclocondensation to form species**10a**–**p** and finally 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p**.[30]

Structures of all the newly obtained compounds have been ascertained on the basis of their consistent IR, NMR and mass spectral assignments.[31–34]

The newly obtained derivatives were evaluated for in vitro antibacterial activity against *Escherichia coli* ATCC 6633, *Bacillus subtilis* ATCC 16404 and antifungal activity against *Aspergillus niger* ATCC 16404 and *Candida albicans* ATCC 10231. Nutrient agar and saboured dextrose agar were employed for bacterial and fungal growth, respectively. Minimum inhibitory concentrations (MIC) were determined by means of standard 2-fold serial dilution method using agar media.[35] Stock solutions of test compounds were prepared in DMSO at a concentration of 1 mg/mL. Suspension containing approximately 10^7 CFUs/mL of bacteria and 10^6 CFUs/mL of fungi was prepared from broth cultures. Bacterial and fungal plates were made in triplicate and incubated at 37 °C for 16–47 h for bacteria and 48–72 h for fungi. Ampicillin trihydrate and clotrimazole were also screened under similar conditions as