Bioorganic & Medicinal Chemistry Letters, Vol.3, No.4, pp. 555-556, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

4-ALKYLAMINO-3-BROMO-*N*-ALKYL-1,8-NAPHTHALIMIDES: NEW PHOTOCHEMICALLY ACTIVATABLE ANTIVIRAL COMPOUNDS.

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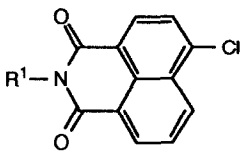
(*Received in USA* 30 *November* 1992)

Abstract: The synthesis of several 3-bromo-4-alkylamino-*N*-alkyl-1,8-naphthalimides is described. These compounds have been shown to be effective, non-oxygen based photochemical inactivators of enveloped viruses, including herpes simplex virus and HIV.

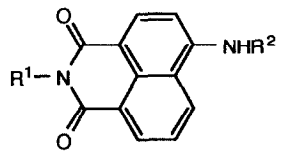
Enveloped viruses, which include such pathogens as herpes viruses, hepatitis B virus and human immunodeficiency virus, are characterized by the presence of a lipid bilayer envelope which renders them susceptible to membrane-based strategies for inactivation such as photodynamic therapy,[1] as well as the more traditional antiviral strategies, which are targeted at the pathogen-specific components of the viral infection cycle (the protein, carbohydrate or nucleic acid components of the virus). We have discovered that monomeric 3-halo-4-alkylamino-*N*-alkyl-1,8-naphthalimides (**3**) and their dimeric analogs (**5**) function as excellent photoinactivators of enveloped viruses and cells at dye concentrations of 0.1 μ*M* or less in the presence *or absence* of molecular oxygen. This distinguishes their mechanism of action from photodynamic therapy, which is due to oxidation of membrane components by singlet oxygen.[2] Typically, 5-6 $\log_{10}$ decreases in activity of cell-free HIV-1 are realized by photoinactivation in the presence of 1 μ*M* **5** and 300 n*M* **5** with cell-associated HIV-1; similar results are obtained with herpes simplex virus, type 1, at concentrations below 500 n*M*. These results are consistent with an inactivation efficiency (calculated as dye concentration/light dose) approximately three orders of magnitude better than that reported[3] for psoralens. The full virological details will be disclosed in a more appropriate forum;[4] herein we describe the synthesis of the more active members of this class of antiviral agents.

The basic photoactive moiety of these dyes is the 4-alkylamino-3-bromo-*N*-alkyl-1,8-naphthalimide nucleus.[5] This was prepared from 4-chloro-1,8-naphthalic anhydride by sequential conversion to the *N*-alkyl-4-chloro-1,8-naphthalimide (**1**) [R^1NH_2 (1.0 eq.)/PhMe/Δ/48 h; 80-95%],[6] the 4-alkylamino-*N*-alkyl-1,8-naphthalimide (**2**) [R^2NH_2/Δ/5 h or R^2NH_2 (4 eq.)/DME/Δ/24 h 50-60%],[7] and the 4-alkylamino-3-bromo-*N*-alkyl-1,8-naphthalimide (**3**) [Br_2 (4 eq.)/CH_2Cl_2/r.t./5 h; 60-85%]. Where both alkyl groups were identical, the synthesis of the 4-alkylamino-1,8-naphthalimide (**2**) could be effected in one step [RNH_2/Δ/18 h; 80-85%]. The rate of formation of the imide **2** is dramatically retarded when the amine alkyl group is secondary or β-branched. Bromination of these compounds has not been reported heretofore. It occurs regiospecifically to give only the 3-bromo compound (**3**) when the *N*-alkyl group is a straight-chain group; when the *N*-alkyl group is secondary or branched at the β position, *N*-dealkylation occurs during the bromination step. Extended bromination leads to a similar *N*-dealkylation of the 4-alkylamino group prior to disubstitution in the naphthalimide nucleus. All attempts to brominate imides **2d-2f** led to the formation of intractable black tars; we

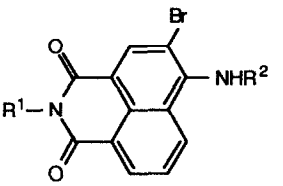
ascribe this to the interception of the arenonium ion intermediate formed by addition of bromine to the arene by the intramolecular nucleophile, and subsequent decomposition. All three simple 3-bromo-4-alkylamino-*N*-alkyl-1,8-naphthalimides (**3a-3c**) show *in vitro* activity against herpes simplex virus.[8] The synthesis of the dimeric naphthalimide is effected simply from the imide **2f** by condensation with adipoyl chloride [$ClCO(CH_2)_4COCl$ (0.45 eq.)/py (2 eq.)/CH_2Cl_2/r.t./18 h; 53%] to give the diamide (**4**) and subsequent bromination of (**4**) [Br_2 (4 eq.)/CH_2Cl_2/r.t./5 h; 77%] to give the active antiviral compound (**5**).



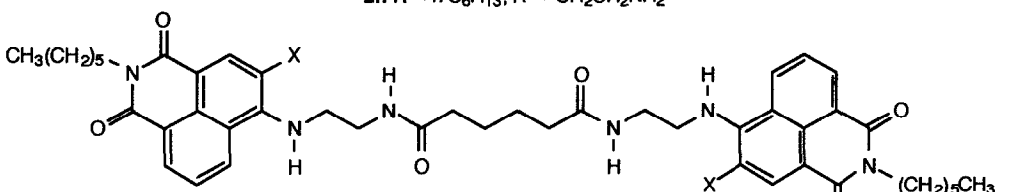
1a: $R^1 = n\text{-}C_4H_9$
1b: $R^1 = n\text{-}C_6H_{13}$
1c: $R^1 = n\text{-}C_8H_{17}$



2a: $R^1 = R^2 = n\text{-}C_4H_9$
2b: $R^1 = R^2 = n\text{-}C_6H_{13}$
2c: $R^1 = R^2 = n\text{-}C_8H_{17}$
2d: $R^1 = n\text{-}C_4H_9$; $R^2 = CH_2CH_2OH$
2e: $R^1 = n\text{-}C_4H_9$; $R^2 = CH_2CH_2NH_2$
2f: $R^1 = n\text{-}C_6H_{13}$; $R^2 = CH_2CH_2NH_2$



3a: $R^1 = R^2 = n\text{-}C_4H_9$
3b: $R^1 = R^2 = n\text{-}C_6H_{13}$
3c: $R^1 = R^2 = n\text{-}C_8H_{17}$



4: X = H
5: X = Br

Acknowledgement:
This work was supported by the South Dakota Governor's Office of Economic Development – CITE, MicroBioMed Corporation, the South Dakota State University Research Fund, the Office of Naval Research (Grant # SDIO 84-88-C-0031), and the National Institutes of Health (Grant # HL43421-01).

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6. For imide formation using acetic acid as solvent, see: Goto, N.; Nagai, Y. *Kogyo Kagaku Zasshi*, **1964**, *67*, 152-155; *Chem. Abstr.*, **1964**, *61*, 624a.
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