Two Novel Alkylating Structural Analogues of Chloramphenicol Suitable for Topical Treatment of Dermal Neoplasms

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Author's contribution

This whole work was carried out by the author RB.

Original Research Article

ABSTRACT

Aims: To evaluate the efficacy of two alkylating structural analogues of chloramphenicol that have potential for application for treatment of dermal sited neoplasms.
Study Design: Two compounds have been shown to alkylate guanosine-5'-diphosphate (GDP) at physiological conditions. These same compounds are evaluated for dermal penetration based on Kp and compared to other alkylating agents applied for treatment of skin cancer.
Place and Duration of Study: University of Nebraska, Omaha Nebraska from December 2013 to May 2014 and March to August of 2002.
Methodology: Two analogues of chloramphenicol were synthesized and shown to alkylate GDP at pH 7.4 and 37ºC. Various pharmacological properties of these two analogues, such as Log P, molecular weight, polar surface area, etc, were determined and compared. The dermal permeability coefficient Kp was determined for two analogues based on their molecular weight and partition coefficient Log P. The numerical values of Kp were used to prediction of the distance each analogue is expected to travel in penetration of a dermal barrier. Result was plotted and compared to the anticancer agent's carmustine, mustargen, and 5-fluorouracil. Evaluation of the analogues included findings of previous studies.
Results: Two analogues of chloramphenicol alkylate sites on GDP. The properties of

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compound 1 and compound 2 were determined and when compared to the parent structure chloramphenicol were found to have favorable drug likeness. Values of Log P and permeability coefficient Kp for compounds 1 and 2 are; 3.343, 3.312, 0.00244 cm/hour, 0.000768 cm/hour, respectively. Values of Kp for both compound 1 and 2 were greater than that of chloramphenicol at 0.000131 cm/hour. Plots of skin penetration showed compounds 1 and 2 to be superior to 5-fluorouracil.

Conclusion: Analogues 1 and 2 were shown to have alkylation activity and properties suitable for drug likeness. Both compounds have high penetration rates of dermal layers.

Keywords: Chloramphenicol; dermal neoplasm; skin cancer; nitrogen mustard.

ACRONYMS

Term: CAM, chloramphenicol; 5-FU, 5-fluorouracil; BCC, basal cell carcinoma; IUPAC, International Union of Pure and Applied Chemistry; (BCNU), carmustine; NMSC, non-melanoma skin cancer; MF, mycosis fungoides: DNA, deoxyribonucleic acid.

1. INTRODUCTION

Nomenclature identifying skin cancer (skin neoplasms) is based on the type of skin that is associated with the condition [1]. Generally, there are three major types of skin neoplasms, as follows [2]: 1) Basal cell carcinoma (BCC); 2) Squamous-cell carcinoma (SCC); 3) Malignant melanoma. Melanoma originates in the pigment generating cells referred to as melanocytes and lower stages do have a high rate of survival among these cancers [3]. BCC has as its origin the lowest layer of the epidermis and is the most common but least dangerous of skin neoplasms [1]. The less common SCC has its origins in the middle layer of the skin and, interestingly, is more likely to spread than BCC with fatal results if left untreated [1]. A less common neoplasm is the Merkel cell carcinoma; however, this form can and most often grows quite rapidly [4]. For SCC, the tumor form sheets of masses that destroy basement membrane and invade subjacent connective tissue (i.e. dermis) [5]. Fortunately, the use of sunscreen has been shown to be an effective preventive measure in the case of SCC [5] and melanoma [6]. In the case of higher stage malignant melanoma the survival rate drops sharply and ultimately is responsible for 75% of all skin cancer fatalities [6].

Treatment of skin neoplasms will depend on the location, type, whether it is primary or recurrent. For low-risk forms, then effective treatment includes radiation therapy, topical chemotherapy (5-fluorouracil is common), cryotherapy, photodynamic therapy, electrodessication or curettage, and ultimately, surgery. For selected cases of non-melanoma skin cancer (NMSC), the topical treatments are preferred over invasive approaches, particularly in consideration of surgical risk factors [7]. The use of 5-fluorouracil is a common instrument for treatment of NMSC [7].

Topical chemotherapy for the more common form of cutaneous T-cell lymphoma known as mycosis fungoides (MF) is the alkylating compound mechlorethamine hydrochloride [8]. Use of this alkylating agent for this application is shown to be both effective and safe [8]. Another alkylating agent shown to be safe and effective for treatment of MF type of cutaneous T-cell lymphoma is carmustine (BCNU) [9,10,11]. Other studies have shown the effectiveness, safety, and ease of usage for both methlorethamine and BCNU as topical treatment for MF

[12,13]. Other studies have demonstrated the efficacy of simply twice per seven-day treatment for early stage MF using topical standalone methlorethamine with corticosteroids [14].

A topically applied mustine (alkylating cytostatic mechlorethamine hydrochloride) treatment for Langerhans cell histiocytosis (clonal proliferation of Langerhans cells) has been shown to be safe and effective for most children [15]. The treatment of severe alopecia areata (hair loss being total or localized) utilizing a topical the nitrogen mustard mechlorethamine has been shown to be effective [16,17]. Advanced studies have demonstrated that alkylating nitrogen mustard agents can be topically delivered in the forms of aqueous-based preparations, ointment-based preparation, or as propylene glycol gel preparations [18].

In that skin neoplasms are the most common types of cancer in the United States and with increasing incidence [19], the need for novel alkylating agents for topical application is certainly warranted. At this current rate in United States, then one in six Americans will develop skin neoplasm in his or her life-time [19]. Clearly, new drug designs will be needed to enhance clinical treatment regimens. This study presents two structural analogues to chloramphenicol that have previously been shown to be efficient alkylating agents, even to guanosine-5'-diphosphate, that in addition have properties suitable for topical application for targeting dermal neoplasms.

2. METHODOLOGY

2.1 Molecular Modeling and Physicochemical Properties

Molecular modeling enabled the conception and visualization of all compounds/drugs discussed in this study. Advanced software and algorithmic analysis was the sole resource that could be utilized for this level of application. Molecular modeling and molecular graphics (visualization, analysis of structure, determination of properties) were accomplished by use of Advanced Chemistry Development ACD/Labs ChemSketch released 12.00 version (© copyright 1994-2009, Advanced Chemistry Development, Inc. 110 Yonge Street 14th Floor Toronto, Ontario M5C 1T4, Canada). Pharmacological properties Log P, polar surface area, number of atoms, molecular weight, number of oxygen/nitrogen/hydroxyl groups/amine groups, rule of 5, rotatable bonds and molecular volume were determined by Molinspiration Cheminformatics Molecular Properties version 2014 (Molinspiration Cheminformatics Nova ulica SK-900 26 Slovensky Grob Slovak Republic). Additional validation of properties and drug-likeness was ascertained through Molsoft L.L.C. molecular properties and drug-likeness © copyright Molsoft 2014 (Molsoft L.L.C. 11199 Sorrento Valley Road, S209 San Diego CA 92121).

2.2 Statistical Analysis and Pattern Recognition

Preliminary numerical analysis was performed by use of EXCEL Windows 7, Microsoft Office Professional Plus 2013 (copyright © 2012 Microsoft Corporation). Additional statistical analysis Kolmogorov-Smirnov, Kruskal-Wallis test, Mann-Whitney, F and t-test for two samples, univariate statistics, Spearman's D, and Pearson r correlation was completed by PAST version 2.15 (copyright © Hammer and Harper 1999-2012, http://folk.uio.no/ohammer/past). Statistical outliers among numerical data was accomplished utilizing Grubb's test or extreme studentized deviate of GraphPad Software (GraphPad, 7825 Fay Avenue, Suite 230, La Jolla CA 92037).

2.3 Dermal Permeability Coefficient, Diffusion Time, Solubility in Water

Useful and vital determination of dermal permeability coefficient (Kp) and solubility in water was vital for the study. Determination of Kp property was achieved by use of DERWIN U.S. Environmental Protection Agency (copyright © 2000 US Environmental Protection Agency). Values of diffusion time was performed online Physiology Web (http://www.physiologyweb.com/calculators/diffusion_time_calculator.html). Solubility in water for all compounds was determined by WSKOWWIN version 1.40 U.S. Environmental Protection Agency (copyright © 2000 US Environmental Protection Agency).

2.4 Characterization and Formation of Structural Analogues

The synthesis and characterization of compound 1 and compound 2 was accomplished previously and is described in detail per study report published [20]. Full report available on June 4 2014: http://onlinelibrary.wiley.com/doi/10.1211/002235703765344568/pdf**.**

3. RESULTS AND DISCUSSION

The molecular structure of chloramphenicol has been modified in a previous work to incorporate a nitrogen mustard substituent ($-N(CH_2CH_2Cl)_2$) that did show significant inhibitory activitytoward a sarcoma line [20]. It is the nitrogen mustard substituent that gives that derivative of chloramphenicol the alkylation activit [20]. Chloramphenicol itself is an antibiotic with a wide spectrum of activity against Gram positive and Gram-negative cocci and bacilli (including anaerobes) [20]. The preparation of compound 1 and compound 2, the subject of this study for application against skin neoplasms, is fully described in a previous study [20]. Furthermore, the study to show rapid and efficient covalent alkylation of guanosine-5'-diphosphate (GDP), L-serine, L-glutamic acid, and p-chloroaniline by compound 1 and compound 2 is fully detailed at physiological conditions of pH 7.4 and 37ºC [20]. The objective of this study is to show that compound 1 and compound 2 has properties completely suitable for treatment of skin neoplasm.

The molecular scaffolding for chloramphenicol (the parent compound), compound 1 and compound 2 are presented in Fig. 1. In addition, presented are the IUPAC nomenclature, SMILES (Simplified Molecular-Input Line-Entry System) designation, and molecular formula.

For each of chloramphenicol, compound 1, and compound 2, there are a nitrobenzene substituent ($-C_6H_5NO_2$) and 2, 2-dichloroacetamide (-NHC(O)CHCl2) substituent. The compound 1 structure then replaces the two hydroxyl groups (-OH) on chloramphenicol with chlorine atoms for each creates two alkyl halides. Structure for compound 2 begins with the replacement of the two hydroxyl groups of chloramphenicol with ether groups ($-CH_n-O-CH_n-$). The next alteration can be described as the oxygen atoms of the ether groups covalently bonded to a chloroethane moiety ($-CH_2CH_2Cl$), forming an alkyl chloride. The replacement of hydroxyl groups with chlorine atoms in the case of compound 1 and covalent bonding of chloroethane substituents to oxygen atoms in the case of compound 2 (forming ether groups), will introduce the very strong leaving group chlorine atom (chlorine is a very weak base) that is necessary for an alkylation reaction. Alkyl halides are very reactive organic compounds [21]. The two chlorine atoms located within the dichloroacetamide ($-NHC(O)CHCl_2$) moiety, that is found on chloramphenicol, compound 1, and compound 2, are not good leaving groups in comparison, due to the close proximity of the double bond with a more electronegative oxygen having two lone pairs of electrons. The alkyl chlorine

atoms of compound 1 and compound 2 are the best leaving groups that in turn lead to alkylation of a suitable nucleophilic position of GDP or other target. The stronger the leaving group, the more efficient the alkylation outcome upon reaction with a nucleophilic site of a target molecule [21]. For DNA, the most reactive nucleophilic sites are the N-7 of guanine > N-3 of adenine > N-1 of adenine > N-1 of cytosine [21].

Drug-likeness is a concept used in drug design for how drug-like a potential substance is in terms of bioavailability. Predictive methodologies that assist in the selection of orally bioavailable drug candidates are extremely helpful [22]. The concept of drug-likeness assists in optimizing pharmacokinetic and other desirable pharmaceutical properties, including solubility, chemical stability, and bioavailability [22]. Various descriptors have been shown to be highly useful in prediction of bioavailability, this includes the parameters proposed by the Rule of 5 [23]. The Rule of 5 states a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria [23]: 1) A molecular weight is less 500; 2) It has Log P less than 5; 3) The number of hydrogen bond donors (sum of -OH and $-NH_n$ groups) is less than 5; 4) The number of hydrogen bond acceptors (sum of oxygen and nitrogen atoms) is less than 10.

For comparison, the determined molecular properties of compound 1, compound 2, and parent structure chloramphenicol (CAM) are shown in Table 1. These include lipophilic partitioning descriptor Log P, in addition to polar surface area, molecular weight, molecular volume, etc. Notable is that all compounds show zero violations of the Rule of 5, which designates compound 1 and compound 2 having favorable membrane permeability and ease of absorption into the body (i.e. both analogues have good oral activity).

Furthermore, other studies have shown that polar surface area can be an accurate indication of drug absorption from the intestinal tract [22]. Numerical values of polar surface area for chloramphenicol, compound 1, and compound 2 are 115.4 A^2, 74.9 A^2, and 93.4 A^2, respectively. Considering solely the polar surface area, an estimate of percent of total drug orally administered absorbed from the intestinal tract would be 18%, 51%, and 35% for CAM, compound 1, and compound 2, respectively.

The Pearson r correlation of Log P to polar surface area is very strongly inversely related (r = -0.8945). The molecular weight is very strongly directly correlated to rotatable bonds and volume of agent (r = 0.9579 and 0.9826, respectively). Polar surface area is very strongly directly correlated to the number of oxygens & nitrogens and number of –OH & $-NH_n$ (r = 0.8400 and 0.8898, respectively).

Delivery of any drug through the dermal layers is a complex process, because the skin is an effective barrier [24]. A vital role is to prevent the ingress or egress of compounds across it and therefore, skin protects the body from environmental, biological, and chemical insults [24]. The skin has the outermost avascular epidermis and the dermis, which is vascular, and contains free nerve endings [25]. The superficial layer of epidermis is the stratum corneum which is almost impermeable and responsible for the barrier function of the skin [24]. However, the stratum corneum still plays a vital role in the absorption of drugs as it provides the rate-limiting step in the penetration process [24]. The stratum corneum is the major barrier to drug absorption. The stratum corneum contains merely 20% of water and is a highly lipophilic membrane which is 10 to 20 micrometers μm thick depending on its state of hydration [26]. The thickness of the epidermis varies from 0.06 mm on eyelids to 0.8 mm on the soles of the feet [26]. Hydrophilic compounds reach the dermis by pathways such as hair follicles, sweat glands, nerve endings, and blood and lymph vessels [26]. However, these

routes contribute very little to steady-state drug flux [26]. The dermis is the thickest layer of the skin and possesses hair follicles, sweat glands, nerve endings, and blood and lymph vessels, which act as the systemic absorption site for drugs [26].
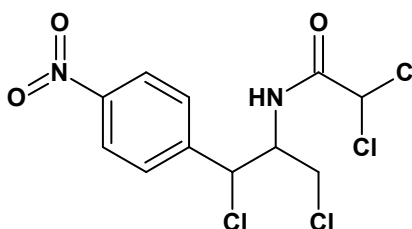
Chloramphenicol
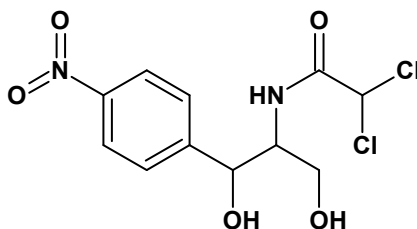
2,2-dichloro-*N*-[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide

O=N(=O)c1ccc(cc1)C(O)C(CO)NC(=O)C(Cl)Cl

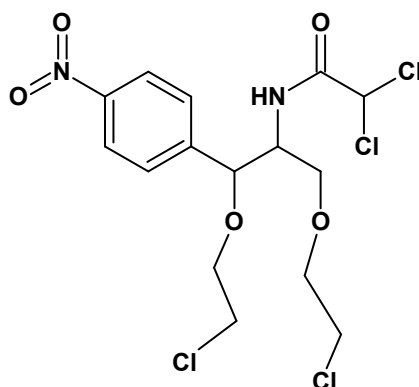Molecular Formula   = $C_{11}H_{12}Cl_2N_2O_5$

Compound 2

2,2-dichloro-*N*-[1,3-dichloro-1-(4-nitrophenyl)propan-2-yl]acetamide

O=N(=O)c1ccc(cc1)C(Cl)C(CCl)NC(=O)C(Cl)Cl

Molecular Formula   = $C_{11}H_{10}Cl_4N_2O_3$

Compound 3

N-[1,3-bis(2-chloroethoxy)-1-(4-nitrophenyl)propan-2-yl]-2,2-dichloroacetamide

O=N(=O)c1ccc(cc1)C(OCCCl)C(COCCCl)NC(=O)C(Cl)Cl

Molecular Formula   = $C_{15}H_{18}Cl_4N_2O_5$

Fig. 1. Molecular structures, IUPAC name, SMILES, and molecular formula of chloramphenicol, compound 1, and compound 2

Table 1. Physicochemical Properties of chloramphenicol, compound 1 and compound 2

Agent	Log P	Polar surface area (A^2)	Number of Atoms	Molecular weight	Number of Oxygens, Nitrogens	Number of –OH, -NH_n	Violations of rule of 5	Number of rotatable bonds	Volume of agent (A^3)
CAM	0.731	115.4	20	323.13	7	3	0	6	249.2
1	3.343	74.9	20	360.02	5	1	0	6	260.2
2	3.312	93.4	26	448.13	7	1	0	12	345.4

A^2 = angstroms^2; A^3 = angstroms^3; CAM = chloramphenicol.

The major route of diffusion through the skin is presented in Fig. 2, by intercellular, transcellular, and transappendageal [27]. Penetrating molecules can follow an intercellular or transcellular route through the stratum corneum, as shown in Fig. 2, depending on their relative solubility and partitioning in each phase [27]. An alternative to transport of a compound through transcellular or intercellular pathways in the stratum corneum, shown in Fig. 2, is penetration by skin appendages such as hair follicles, sebaceous glands, and sweat glands [27]. These appendages could thereby facilitate the skin absorption of topically applied drugs. However, since they occupy less than 1% of the skin surface overall for humans, their activity as transport channels for drugs from the external environment to the capillary bed is usually negligible [27]. Therefore, the primary pathway is by Intercellular migration [27]. The ultimate end of compounds applied to the skin can be placed into the three following categories [27]: 1) Evaporation from the surface of the skin; 2) Uptake into the stratum corneum, followed by reversible or irreversible binding; or 3) Penetration into the viable epidermis, followed by metabolism.
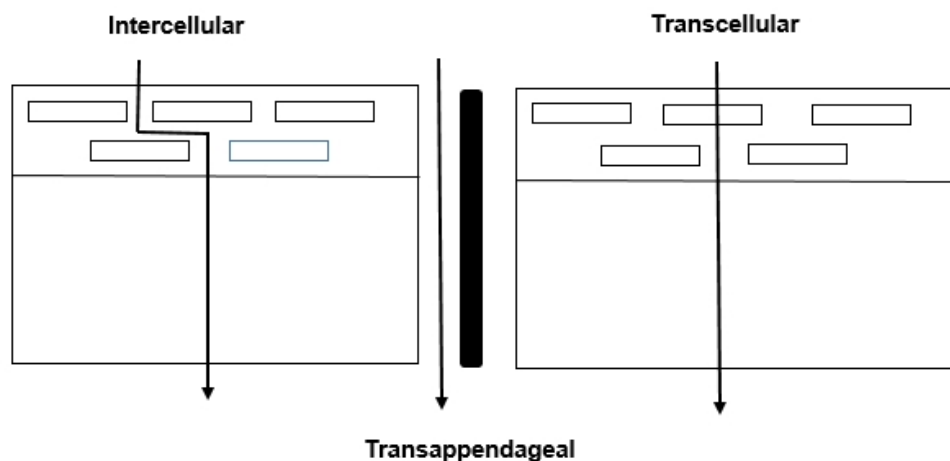
Fig. 2. Potential routes through skin by diffusion. Primary pathway is by Intercellular route [27]

Once a drug molecule crosses the stratum corneum barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily [28]. In general, drug absorption into the skin occurs by passive diffusion and the rate of drug transport across the stratum corneum follows Fick's Law of Diffusion [28]. Fick's Law of Diffusionappears as follows, equation (1) [28]:

$$\frac{dM}{dt} = \frac{D(\Delta C)K}{h} \tag{1}$$

where dM/dt is the steady-state flux across the stratum corneum; D is the diffusion coefficient or diffusivity of drug molecules; ΔC is the drug concentration gradient across the stratum corneum; K is the partition coefficient of the drug between skin and formulation medium; and h is the thickness of the stratum corneum.

The permeability coefficient (Kp) is a key parameter in estimating dermal absorption [27, 28], and is characterized according to Fick's first law of diffusion [27]. That relationship can be represented as follows, equation (2) [27]:

$$\text{Log Kp} = -2.72 + 0.71\text{Log P} - 0.0061(\text{molecular weight}) \qquad (2)$$

The diffusion time (t) is inversely proportional to the diffusion coefficient (D) [28, 29]. The diffusion coefficient determines the time it takes a drug to diffuse a given distance in any medium [29]. The relationship of elapse time (t), mean distance traveled (x), and diffusion coefficient D can be estimated by use of equation (3) [29]:

$$t \sim (x^2)/2D \qquad (3)$$

Topical treatments of non-melanoma skin neoplasm are preferred over invasive procedures, especially when there are surgical risk factors or unsatisfactory cosmetic surgery outcomes [7]. A popular method of topical treatment is by use of 5-fluorouracil [7]. In the case of mycosis fungoids, it has been shown in multiple studies that effective topical treatments can be achieved by use of alkylating nitrogen mustard compounds such as mechlorethamine hydrochloride (also known as mustargen or mustine) [8,9,10,11,12,18] and carmustine, which are an alkylating nitrosourea agent (also known as BCNU) [9,10,11,12].

Values of the dermal permeability coefficients (Kp) were determined by use of equation (2), aqueous solubility, and diffusion coefficient by equation (3) for chloramphenicol, compound 1, compound 2, carmustine, mustargen, and 5-fluorouracil are presented in Table 2. In the determination of diffusion coefficient D (see equation (3)) the elapse time (t) is one hour and mean distance traveled in centimeters calculated from their respective value of the dermal permeability coefficients Kp. These properties are presented in Table 2 for comparison of compound 1 and compound 2 to chloramphenicol (CAM), and the common topical alkylating drugs carmustine, mustargen, and antimetabolite 5-fluorouracil.

Note that the values of Kp are larger for compound 1 (0.00244 cm/hour) and compound 2 (0.000768 cm/hour) than for the parent compound CAM (0.000131 cm/hour). This is due largely to the larger values of Log P for compounds 1 and 2 (see Table 1) and its contribution in the equation (2) which is greater than the contribution of the larger molecular weights. The aqueous solubility of compounds 1 and 2 are significantly less than that for chloramphenicol, an expected outcome for a significant increase of lipophilic partition coefficient Log P (larger Log P values indicate greater permeation across biological membranes). For the six agents in Table 2, a comparison of their Kp values to aqueous solubility indicated by Mann-Whitney test that the medians are not equal (P =.009) and Kruskal-Wallis not equal (P =.01). The Kp and solubility values are not from populations of equal distribution by Kolmogorov-Smirnov test (P =.002). The paired t-test indicates that values of Kp and aqueous solubility have equal means (P =.26). Furthermore, the Kp values and aqueous solubility values of the six agents have no outliers, based on Grubb's test. The Spearman's D value for Kp and aqueous solubility is 0.6547, which indicates a moderate positive correlated ranking of these two sets of values.

The diffusion coefficient D implies that the mass of the substance diffuses through a unit surface in a unit time at a concentration gradient [28]. The higher the diffusivity, the faster they diffuse. Notably, the diffusion coefficient D of compound 1 is greater than that of CAM, carmustine, mustargen, and 5-fluorouracil. This favorable outcome shows that structural analogue 1 will be more efficient delivery through dermal layers. For compound 2, the value of D is greater than that of CAM and the anticancer agent 5-fluorouracil.

Table 2. Dermal permeability coefficient (Kp), aqueous solubility, and diffusion coefficient

Agent	Dermal permeability coefficient Kp (cm/hour)	Aqueous solubility (grams/liter)	†Diffusion coefficient (cm²/sec)
CAM	0.000131	0.389	2.38×10^{-12}
1	0.00244	0.00373	8.27×10^{-10}
2	0.000768	0.000958	8.19×10^{-11}
Carmustine	0.00115	1.83	1.84×10^{-10}
Mustargen	0.000942	121	1.23×10^{-10}
5-fluorouracil	0.0000716	25.9	7.12×10^{-13}

CAM = chloramphenicol. †Values based on one hour time period and Kp.

Applying the values of Kp for each agent in Table 2 over the time period of one hour to 24 hours, it is possible to plot the expected distance of penetration in centimeters for comparison of these agents. The results of distance traveled versus time (hours) is completed and shown in Fig. 3 and found to be highly linear for all agents (r >0.9900 for all agents).
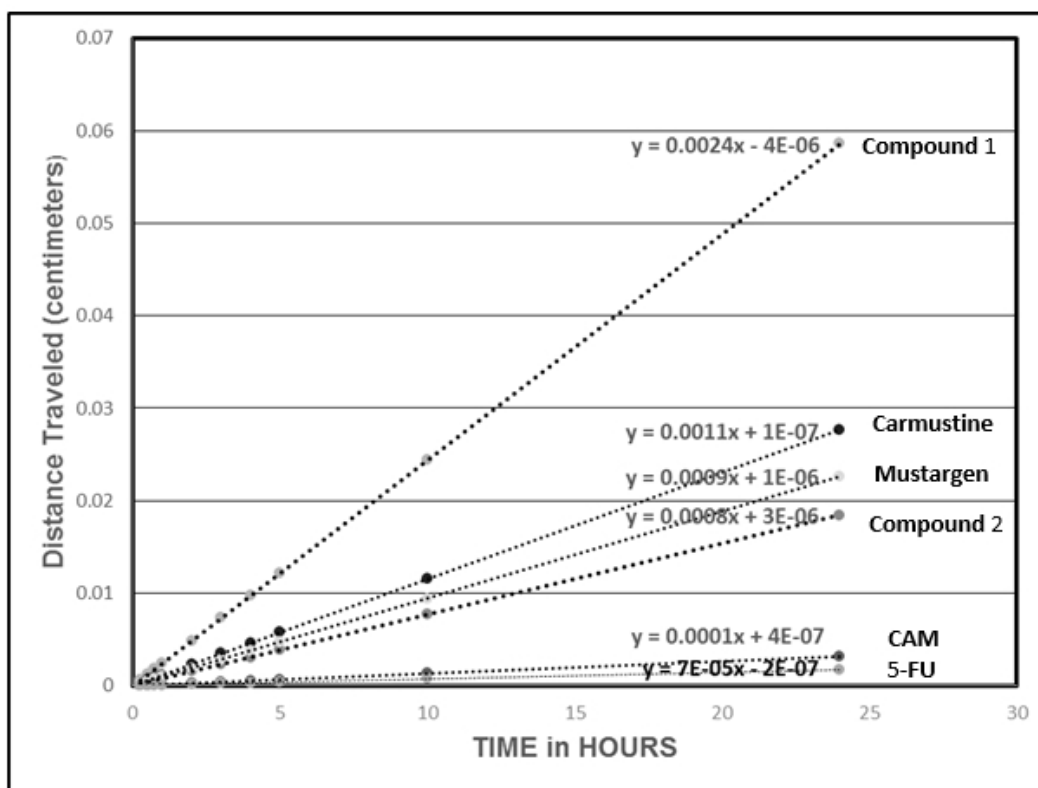
Fig. 3. Distance and extent of penetration into dermal layers, determined by comparsion and calculation utilizing Kp in cm/hours. Linear equations describing relationships of distance of penetration to time in hours are adjacent to plots (values of r for all lines are greater than 0.9900). Abbreviations CAM and 5-FU are chloramphenicol and 5-fluorouracil, respectively

The exact equation of the line plotted is indicated for all agents (see Fig. 3). It noted that the least distance traveled per 24 hours is the topical antimetabolite 5-Fluorouracil (5-FU). This is followed by the parent structure of the analogues, chloramphenicol antibiotic. Favorable for the analogues compound 1 and compound 2, is that they travel a greater distance per 24 hours than the anticancer agent 5-Fluorouracil. Although compound 2 is slower than the alkylating agents carmustine and Mustargen (used to treat MF), the analogue compound 1 is the fastest of the entire set. This favorable outcome for analogues 1 and 2 further supports the potential of these two alkylating agents for application as topical drugs in the treatment of mycosis fungoides and skin neoplasms.

It is known that skin cancer is the most common form of cancer in the United States. An overall total of more than 3.5 million skin cancers in over two million people is being diagnosed annually [30]. Furthermore, the treatment of non-melanoma skin cancers increased by nearly 77 percent between 1992 and 2006 [30]. Over the past three decades, more people have had skin cancer than all other cancers combined [31]. Thirteen million white non-Hispanics individuals living in the US at the beginning of 2007 had at least one non-melanoma skin cancer, typically diagnosed as basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) [31]. One in five Americans will develop skin cancer in the course of a lifetime [32]. Clearly, the study and characterization of novel drug designs and treatment methodologies is highly desired and valuable.

4. CONCLUSION

The pharmaceutical properties of two structural analogues of the antibiotic chloramphenicol were determined and analyzed for potential of topical administration. Compound 1 and compound 2 were both shown in previous studies to alkylate guanosine-5'-diphosphate, amino acids, and p-chloroaniline. Both analogues 1 and 2 possess alkyl chloride substituents in place of hydroxyl groups found on chloramphenicol. The Log P values of analogues 1 and 2 are substantially greater (more lipophilic) at 3.343 and 3.312, respectively, than for chloramphenicol. Analogues 1 and 2 show favorable drug-likeness and bioavailability due to zero violations of Rule of 5. Analogue 1 is expected to have 51% efficiency in intestinal absorption with 35% for analogue 2 based on the polar surface area. Dermal permeability coefficient Kp of analogue 1 (0.00244 cm/hour) is greater than Kp for carmustine, Mustargen, and 5-fluorouracil. Analogue 2 value of Kp (0.000768 cm/hour) is greater than Kp for anticancer drug 5-fluorouracil. The diffusion coefficient D for analogue 1 and 2 are competitive with those of carmustine, Mustargen, and 5-fluorouracil. Aqueous solubility of analogues 1 and 2 are considerably lower than for chloramphenicol, which is consistent with the much larger Log P values for 1 and 2. Plots of distance traveled, based on their values of Kp, showed that compound 1 moves further than carmustine, Mustargen, and 5-fluorouracil. Compound 2 still travels further than chloramphenicol and anticancer agent 5-fluorouracil. These results strongly support the potential of compound 1 and 2 as effective topical agents in treatment of skin neoplasms and mycosis fungoides.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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