Synthesis of 9-[1-Benzyl-5-(alkylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinediones

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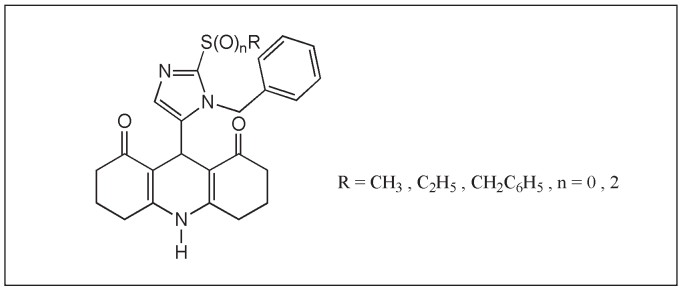

Tricyclic dihydropyridines like ZM244085 are potential K_{ATP} channel openers. In this study 3-cyanophenyl ring of ZM244085 was replaced with imidazolyl ring. So, 9-[1-benzyl-5-(alkylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinediones (**5d-f**) were synthesized from 2-alkylsulfonyl-1-benzyl-5-formylimidazole (**4d-f**) and cyclohexane-1,3-dione according to classical Hantzch synthesis as potential potassium channel modulators.

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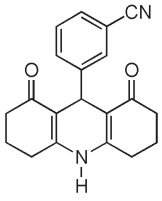
The dihydropyridine system is usually associated with calcium L-channel blockade and activation. This class of compounds have been the subject of many structure-activity relationship (SAR) studies [1-5] and recent developments in the chemistry of DHPs has been reviewed [6]. The potassium channel in particular has several general features analogous to the calcium channel [5], it has been found that some tricyclic dihydropyridines (*e.g*. 1,8-acridinedione) like ZM244085 or 9-(3- cyanophenyl)hexahydro-1,8-acridinedione serve as activators at the ATP-sensitive K^+ channel where glibenclamide and related agents serve as clinically useful antagonists [7]. K_{ATP} openers have been studied in clinical studies for overactive bladder, although it is expected that hypotensive effects may limit dosing [8]. The reported bladder selective actions of tricyclic dihydropyridine, ZM244085 make it an attractive lead from which to design novel K_{ATP} openers. A previous SAR study on ZM244085 has been focused on the modification of tricyclic dihyropyridine core structure [8].

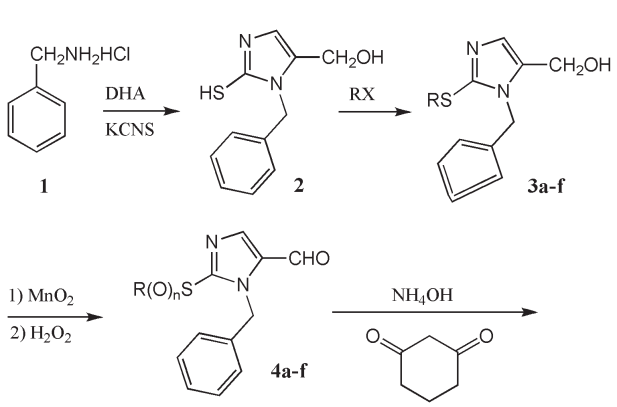
In the present report we studied aromatic ring, 3-cyanophenyl, substitution with imidazolyl heterocycle, which can mimic 3-cyanophenyl as an electron deficient ring. The synthesis of desired compounds as possible effective activators at the ATP-sensitive K^+ channel was accomplished according to Scheme 1.

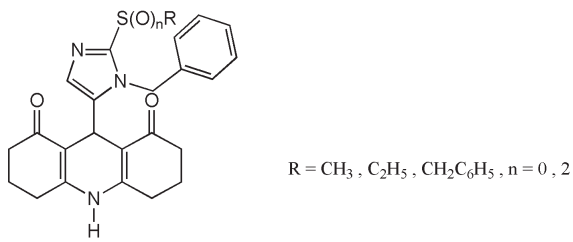
Benzylamine hydrochloride (**1**) was stirred with 1,3-dihydroxyacetone dimer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-benzylmidazole (**2**).



ZM244085

Scheme 1





5a-f

Subsequent alkylation of compound **2** with alkyl halides afforded 2-alkylthio-1-benzyl-5-hydroxymethylimidazole (**3**). Oxidation of **3** with manganese dioxide in chloroform gave 2-alkylthio-1-benzyl-5-formylimidazole (**4**) [9]. Compound **4** was reacted in the dark with 1,3-cyclohexanedione and ammonium hydroxide in methanol according to Hanzsch synthesis to give the title 9-[1-benzyl-5-(alkylsulfanyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinediones (**5a,b,c**) [10]. 2-Alkylthio-1-benzyl-5-formylimidazole (**4a,b,c**) was also oxidized by hydrogen peroxide in acetic acid [11] to the corresponding 2-alkylsulfonyl-1-benzyl-5-formylimidazole (**4d,e,f**) which was reacted with 1,3-cyclohexandione in the same manner to give 9-[1-benzyl-5-(alkylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinediones (**5d,e,f**).

EXPERIMENTAL

Melting points were determined on an Electrothermal Capillary apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 1000. ^{1}H nmr were obtained on Bruker Ac-80 NMR spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Elemental analyses (C, H, N) were within ±0.4% of theoretical values. Title compounds (**5a-f**) are sensitive to light; all chemical procedures involving these were shielded from light whatever present. Compounds **2**, **3a-c**, **4a-c** were prepared as described previously [9].

2-Methylsulfonyl-1-benzyl-5-formylimidazole (**4d**).

To a stirring solution of **4a** (0.6 g, 2.6, mmoles) in acetic acid (5 ml) was added 30% hydrogen peroxide (4 drops) at room temperature. Two additional portions of 30% hydrogen peroxide (4 drops) were added after 2 and 4 hours. The reaction was continued overnight, the mixture diluted with water (10 ml) and neutralized with 10% aqueous solution of sodium hydroxide. The resulting aqueous mixture was extracted with chloroform (3 x 30 ml). The organic layer was dried (sodium sulfate) and concentrated under vacuum to give 0.6 g (85%) of **4d** mp 200 °C; ir: 1661cm^{-1} (C=O); ^{1}H nmr (deuteriomethanol): δ 9.63(s, 1H, CHO), 7.85 (s, 1H, H_4-imidazole), 7.63-7.13(m, 5H, arom), 5.26(s, 2H, CH_2N), 3.19ppm(s, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: H, 4.58; C, 54.53; N, 10.60; O, 18.16; S, 12.13. Found: H, 4.57; C, 54.33; N, 10.57; O, 18.20; S, 12.11.

2-Ethylsulfonyl-1-benzyl-5-formylimidazole (**4e**).

This compound was prepared from **4b** similar to **4d** as a brown oil (81%); ir: 1660cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.63 (s, 1H, CHO), 7.85 (s, 1H, H_4-imidazole), 7.63-7.13 (m, 5H, arom), 5.26 (s, 2H, CH_2N), 3.88 (q, 2H, CH_2S), 1.37 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: H, 5.07; C, 56.10; N,10.06; O, 17.25; S, 11.52. Found: H, 5.05; C, 55.87; N,10.10; O, 17.31; S, 11.46.

2-Benzylsulfonyl-1-benzyl-5-formylimidazole (**4f**).

This compound was prepared from **4c** similar to **4d** as a brown oil (70%); ir: 1661cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.63 (s, 1H, CHO), 7.85 (s, 1H, H_4-imidazole), 7.63-7.13 (m, 10H, arom), 5.25 (s, 2H, CH_2N), 4.96 (s, 2H, CH_2S).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: H, 4.74; C, 63.51; N, 8.23; O, 14.10; S, 9.42. Found: H, 4.75; C, 63.25; N, 8.26; O, 14.04; S, 9.38.

9-[1-Benzyl-5-(methylsulfanyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5a**).

A solution of ammonium hydroxide (25%, 0.4 ml) was added to a stirring solution of **4a** (0.3 g, 1.2 mmoles) and 1,3-cyclohexanedione (0.3 g, 2.5 mmoles) in methanol (5 ml). The mixture was protected from light and refluxed overnight. The methanol was evaporated at reduced pressure to give 0.4 g of **5a** as a brown oil (78%); ^{1}H nmr (deuterichloroform): δ 7.83-6.60 (m, 6H, arom, NH, H_4-imidazole), 5.6 (s, 2H, CH_2N), 5.34 (s, 1H, H_4-DHP), 2.6-1.5 (m, 15H, CH_2, CH_3S).

Anal. Calcd. for $C_{24}H_{25}N_3O_2S$: H, 6.01; C, 68.71; N, 10.02; O, 7.63; S, 7.64. Found: H, 6.03; C, 68.47; N, 9.98; O, 7.60; S, 7.61.

9-[1-Benzyl-5-(ethylsulfanyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5b**).

This compound was prepared from **4b** similar to **5a** as a brown oil (83%); ^{1}H nmr (deuteriochloroform): δ 7.8-6.6 (m, 7H, arom, NH, H_4-imidazole), 5.62 (s, 2H, CH_2N), 5.18 (s, 1H, H_4-DHP), 2.7-1.5 (m, 14H, CH_2), 1.1 (t, 3H, CH_3).

Anal. Calcd. for $C_{25}H_{27}N_3O_2S$: H, 6.28; C, 69.26; N, 9.69; O, 7.38; S, 7.39. Found: H, 6.28; C, 69.20; N, 9.66; O, 7.41; S, 7.42.

9-[1-Benzyl-5-(benzylsulfanyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5c**).

This compound was prepared from **4c** similar to **5a** as a brown oil (77%); ^{1}H nmr (deuteriochloroform): δ 7.2-6.7 (m, 12H, arom, NH, H_4-imidazole), 5.6 (s, 2H, CH_2N), 5.34 (s, 1H, H_4-DHP), 3.92 (s, 2H, CH_2S), 2.7-1.5 (m, 12H, CH_2).

Anal. Calcd. for $C_{30}H_{29}N_3O_2S$: H, 5.90; C, 72.70; N, 8.48; O, 6.46; S, 6.47. Found: H, 5.89; C, 72.45; N, 8.44; O, 6.43; S, 6.45.

9-[1-Benzyl-5-(methylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5d**).

This compound was prepared from **4d** similar to **5a** as a brown oil (85%); ^{1}H nmr (deuterichloroform): δ 7.83-6.60 (m, 7H, arom, NH, H_4-imidazole), 5.6 (s, 2H, CH_2N), 5.34 (s, 1H, H_4-DHP), 3.3 (s, 3H, CH_3), 2.6-1.5 (m, 12H, CH_2).

Anal. Calcd. $C_{24}H_{25}N_3O_4S$: H, 5.58; C, 63.84; N, 9.31; O, 14.17; S, 7.10. Found: H, 5.55; C, 64.09; N, 9.34; O, 14.11; S, 7.12.

9-[1-Benzyl-5-(ethylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5e**).

This compound was prepared from **4e** similar to **5a** as a brown oil (78%); ^{1}H nmr (deuteriochloroform): δ 7.8-6.6 (m, 7H, arom, NH, H_4-imidazole), 5.62 (s, 2H, CH_2N), 5.18 (s, 1H, H_4-DHP), 3.88 (q, 2H, CH_2S), 2.7-1.5 (m, 12H, CH_2), 1.37 (t, 3H, CH_3).

Anal. Calcd. for $C_{25}H_{27}N_3O_4S$: H, 5.85; C, 64.50; N, 9.03; O, 13.75; S, 6.89. Found: H, 5.85; C, 64.50; N, 9.03; O, 13.75; S, 6.89.

9-[1-Benzyl-5-(benzylsulfonyl)-1*H*-2-imidazolyl]perhydro-1,8-acridinedione (**5f**).

This compound was prepared from **4f** similar to **5a** as a brown oil (77%); ^{1}H nmr (deuteriochloroform): δ 7.83-6.60 (m, 12H,

arom, NH, H_4-imidazole), 5.6 (s, 2H, CH_2N), 5.34 (s, 1H, H_4-DHP), 4.96 (s, 2H, CH_2S), 2.6-1.5 (m, 12H, CH_2).

Anal. Calcd. for $C_{30}H_{29}N_3O_2S$: H, 5.90; C, 72.70; N, 8.48; O, 6.46; S, 6.47. Found: H, 5.89; C, 72.45; N, 8.44; O, 6.43; S, 6.45.

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