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Bioorganic & Medicinal Chemistry Letters 16 (2006) 77–80
Bioorganic & Medicinal Chemistry Letters

Pyrazole CCK_1 receptor antagonists. Part 2: SAR studies by solid-phase library synthesis and determination of Free–Wilson additivity

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Received 1 August 2005; revised 9 September 2005; accepted 13 September 2005
Available online 19 October 2005

Abstract—High-throughput screening revealed compound **1** as a potent antagonist of the CCK_1 receptor. Here, we disclose the synthesis of combinatorial libraries by solid-phase synthesis on Kenner 'safety catch' resin. Additive QSAR models were used to determine a lack of consistent additive SAR within the matrix.

Cholecystokinin (CCK) is a 33 amino acid peptide hormone that is released in response to food intake and regulates gall bladder contraction, pancreatic enzyme secretion, gastric acid secretion, gastric emptying, and duodenal and colonic motility.[1] The biological actions of CCK are mediated through two G-protein coupled receptors, CCK_1 and CCK_2. CCK's actions on gallbladder contraction, pancreatic enzyme secretion, and duodenal motility, and gastric emptying rate appear to be mediated through agonism of the CCK_1 receptor. As a result, a number of CCK_1 antagonists have been evaluated in the clinic for pancreatic disorders, IBS, and bilary colic. Promising clinical results from a Phase II trial of constipation dependent IBS with the peptide derived CCK_1 antagonist dexloxiglumide encouraged our pursuit of a differentiated non-peptide derived antagonist of CCK_1.[2]

In the preceding paper, a novel series of pyrazole-based CCK_1 receptor antagonists was described.[3] As reported, compound **1** was identified through high-throughput screening as a potent antagonist of the CCK_1 receptor (see Fig. 1). In that work, a solution-phase library synthesis, which allowed for access to derivatives of **1** where the A- or B-ring was varied simultaneously with the C-ring, was described. To modify the A- and B-rings simultaneously while maintaining a constant C-ring, an alternative route in which the variable elements of the matrix are installed late in the synthesis was desirable. In this paper, we describe a solid-phase library strategy, which allows for this late stage simultaneous modification of the A- and B-rings within this series.

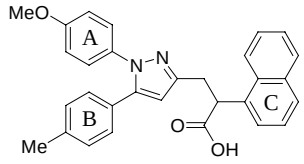

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Figure 1. HTS lead compound.

A solid-phase synthesis of diaryl-pyrazoles, similar to compound **1**, was previously described by Chapman and co-workers.[4] The 3-methylphenyl group at position C in place of the 1-naphthyl ring was chosen because of its high CCK_1 affinity (see, accompanying paper).[3] Synthesis of the solid-phase libraries began with the large-scale preparation of the keto-acid **4** (Scheme 1). Allylation of the phenylacetic acid ester **2**, followed by Wacker oxidation and hydrolysis, provided **4** in good yield on a 5–10 gram scale. Initially, **4** was coupled to Kenner 'safety-catch' resin. Treatment with excess base and various aryl esters provided diketones of type **6** on

Keywords: CCK1; Cholecystokinin; Combinatorial; Additivity; QSAR.
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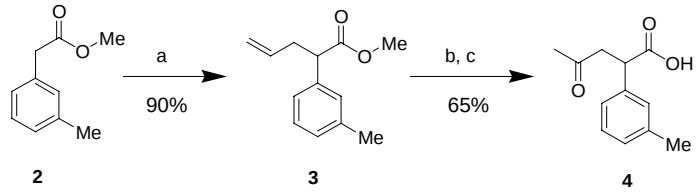
doi:10.1016/j.bmcl.2005.09.041



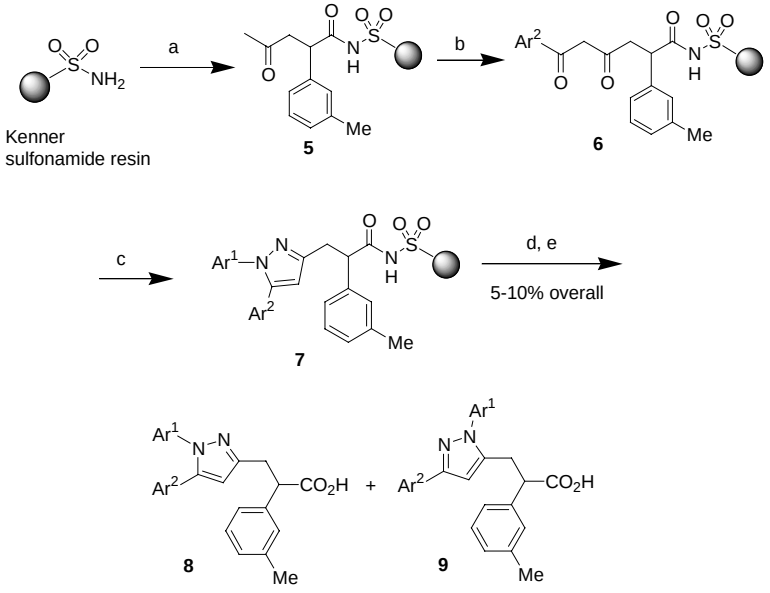
Scheme 1. Reagents and conditions: (a) NaH, allyl bromide, DMF, 0 °C, 1 h; (b) $PdCl_2$ (cat), CuCl, O_2, DMF/H_2O, 12 h; (c) LiOH, THF/MeOH/H_2O, 24 h.

solid support (Scheme 2). Addition of hydrazines and cleavage from resin provided the desired 1,5-pyrazoles along with the undesired 1,3-pyrazoles.

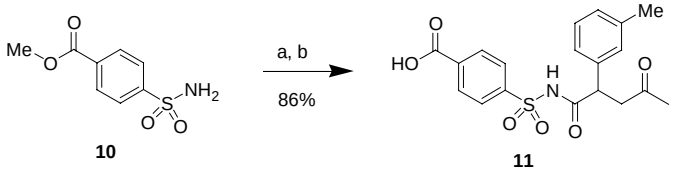
The regioselectivity of ring formation was variable and dependent upon the nature of the hydrazine and diketone coupling partners, but in all cases favored the 1,5-regioisomer. Fortunately the regioisomers were readily separated by chromatography. Problems with this initial procedure included incomplete loading of the keto-acid **4**, and some cleavage of the diketone from the Kenner linker upon treatment with hydrazines. For these reasons, and the regiochemical issues, low yields of the desired 1,5-pyrazoles were obtained by this route.

Alternatively the coupling of keto-acid **4** to sulfonamide **10** could be effectively accomplished in solution prior to attachment to solid support (Scheme 3). Coupling of the resulting acid **11** onto aminomethyl polystyrene afforded high loading levels of **12** as judged by sulfur elemental analysis. Procedures similar to those described above resulted in the desired 1,5-pyrazoles **13** in 20–35% overall yield (see Scheme 4). There were no differences in pyrazole regioselectivity using the two procedures. This recovery was sufficient to obtain material for biological testing (5–10 mg product from 200 mg resin).

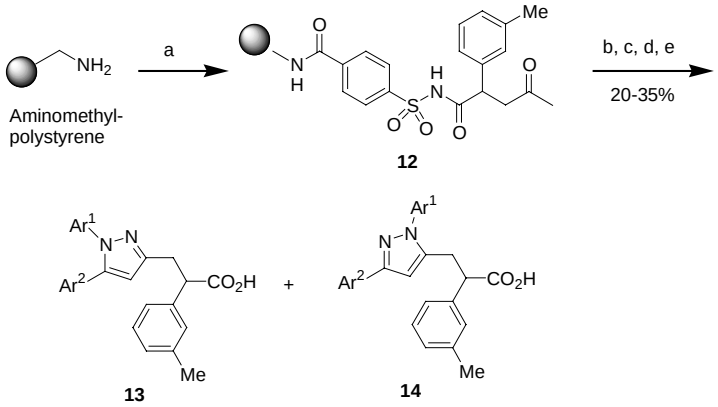
The first library was composed of the elements shown in Figure 2. The binding data (pK_I) are shown in graphical form in Figure 3. Analysis of the best fit additive data was performed as described in Eq. 1 of the accompanying paper.[3] These data were then plotted against the measured pK_I's and graphed (Fig. 4).



Scheme 2. Reagents and conditions: (a) **4**, DIC, DMAP (cat), DIPEA, THF/DCM, 12 h; (b) Ar^2CO_2Me, NaHMDS, DMA, 85 °C, 3 h; (c) $Ar^1NHNH_2 \cdot HCl$, DIPEA, 50 °C, 12 h; (d) $TMSCHN_2$, THF, 1 h; (e) Bu_4NOH, dioxane, 60 °C, 12 h.



Scheme 3. Reagents and conditions: (a) **4**, PyBrop, DIPEA, DMAP (cat), DCM, 12 h; (b) LiOH, THF/MeOH/H_2O, 50 °C, 3 h.



Scheme 4. Reagents and conditions: (a) **11**, DIC, HOBt, THF, 12 h; (b) Ar^2CO_2Me, NaHMDS, DMA, 85 °C, 3 h; (c) $Ar^1NHNH_2 \cdot HCl$, DIPEA, 50 °C, 12 h; (d) $TMSCHN_2$, THF, 1 h; (e) Bu_4NOH, dioxane, 60 °C, 12 h.

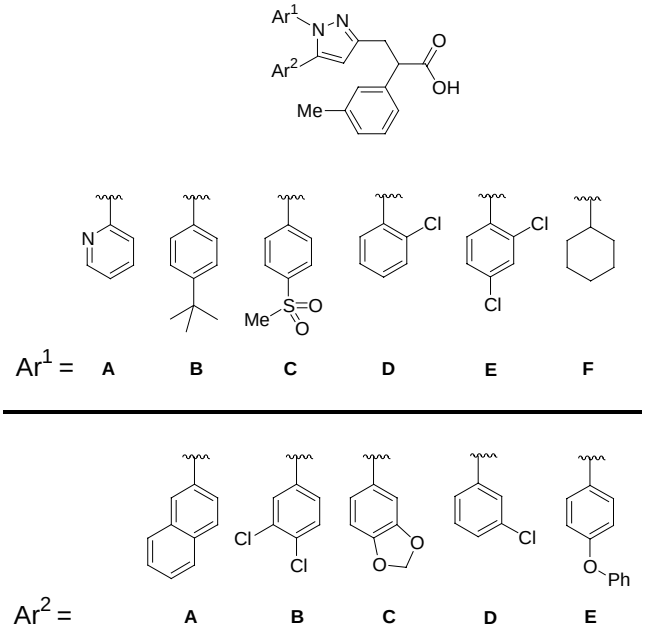


Figure 2. Input variables for library 1.

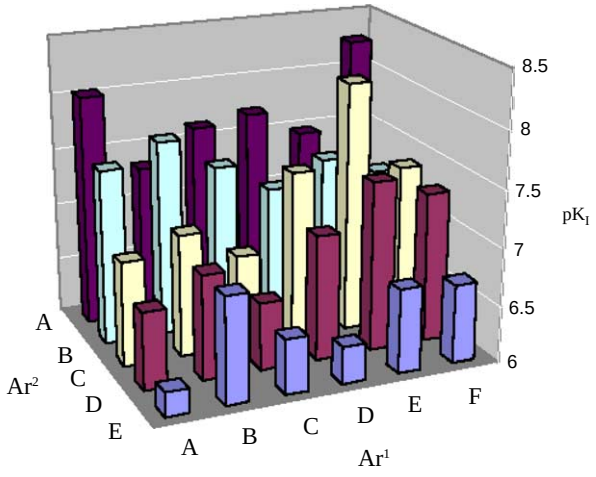


Figure 3. CCK_1 binding data for library 1.

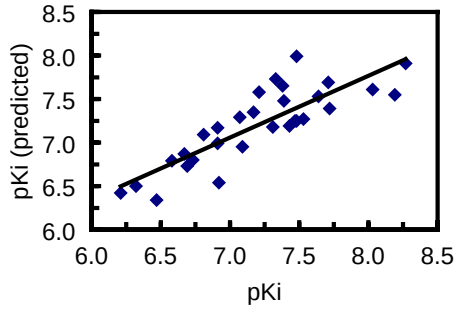


Figure 4. Correlation between actual pK_I and predicted pK_I for the best fit to additive model.

The correlation of best fit additive data to actual data was poor, r^2 value being 0.71 and the RMS error being 0.34. By comparison, the experimental variability had an average standard error of 0.17 log units in triplicate measurements. Thus, there is clearly non-additive SAR present in this library.

In the previous paper, one of the libraries we examined also showed non-additive effects. In that case, the non-additive behavior was limited to a single series, and removal of that series from the calculation afforded an additive result. In this case, the non-additive behavior is not systematic and is found distributed throughout the matrix. This can be seen more clearly when the actual activity is subtracted from the predicted activity showing the deviation from the additive model for each individual member of the matrix (Fig. 5).

Because the deviations are not systematic, there is little specific justification that can be offered for the non-additive behavior observed. However, it is likely that this outcome is a result of the close proximity of the two variables in the matrix. This makes it more likely that electronic and steric differences in one substituent will have an influence on the ground-state or conformational dynamics of the other substituent. Additional explanations may lie in alternative binding modes for the different compounds to the receptor.[5]

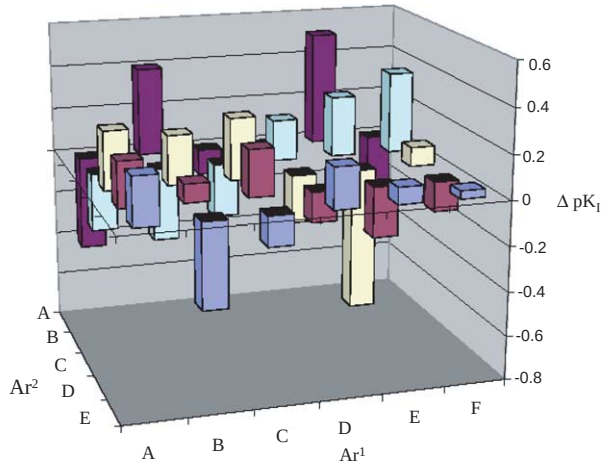


Figure 5. Difference between experimental pK_I and that predicted by the best least-squares fit to the additive model for each compound in the matrix.

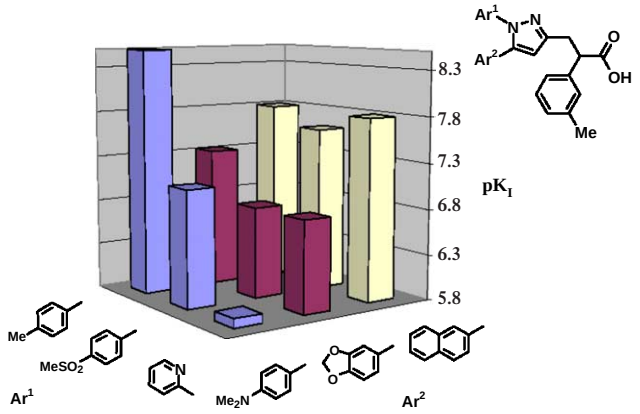


Figure 6. CCK_1 binding affinity for library 2.

An additional library was made which more clearly illustrates the extent of the non-additive relationships in this series of CCK_1 receptor antagonists (Fig. 6). In this case, when Ar^2 is naphthyl or methylenedioxyphenyl the SAR resulting from changes in Ar^1 is roughly flat. However, when Ar^2 is dimethylaminophenyl the SAR is quite pronounced, resulting in compounds having >300-fold differences in binding affinity. These results demonstrate the potential magnitude of non-additive SAR. It is clear from these results that non-additive effects can have a significant impact on medicinal chemistry programs that are managed with the expectation of additive behavior, and illustrates the usefulness of generating a combinatorial matrix of compounds to verify additive behavior before embarking on linear analoging.

This case also demonstrates the importance of exercising caution when using certain QSAR models to predict biological activity. For instance, fragment-based descriptors such as TPSA, C log *P*, MW, H-bond donors, and acceptors, etc., have become increasingly common as inputs for QSAR regression analysis. These descriptors offer the advantage of requiring less computational time to generate than whole molecule descriptors. However, Cammareta[6] has eloquently outlined the dangers of using such descriptors when a system is not additive. Thus, any linear regression analysis that uses exclusively fragment-based descriptors cannot by definition be any more than anecdotally relevant if the system in question is found to be non-additive. In fact, for libraries such as those we consider here, it can be shown that the additive model described in the previous paper represents an upper limit to the accuracy obtainable through fragment-based QSAR. To adequately describe non-additive effects in this case, for instance, descriptors that simultaneously treat both rings A and B are required.

Another advantage of determining the inherent additivity in a system is a more practical one. It is often necessary for the medicinal chemist to optimize multiple properties in a molecular series simultaneously (i.e., activity and bioavailability). In these instances, knowledge about a system's additivity would serve to provide confidence that when one portion of a series is altered to optimize a second property, the SAR trends for the primary target will not be altered. Conversely if a system has a low degree of additivity then it might be advantageous to adopt a strategy of combinatorial analoging to avoid missing key parts of the SAR.

Acknowledgments

We thank Dale Boger for helpful discussions on the synthesis of compound **4**, and Jiejun Wu and Heather McAllister for analytical support.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2005.09.041.

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