Identification of *N*-acylhydrazones as potent TNF inhibitors

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N-acylhydrazones, phthalimides, TNF, hits identification.

INTRODUCTION

Modulation of the immune system is an emerging concept in the control of tumor growth. Among the anticancer and immunomodulatory drug candidates, that have entered into clinical trials, the majority are analogues of thalidomide (Thl), such as lenalidomide (Revlimid, CC-5013) and ACTIMID (CC-4047).[1]

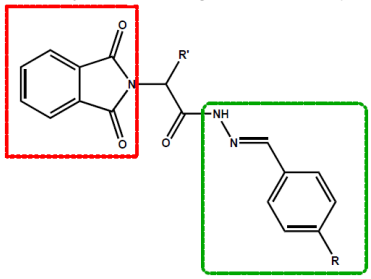
Given this promising outlook, the strategy of molecular hybridization using phthalimide as a pharmacophoric fragment has figured prominently in recent research and has given rise to many successful outcomes.[2]

Bearing in mind the pharmacophore groups previously described in literature and its structural requirements, we describe here the initial identification of *N*-acylhydrazone-based immunomodulatory agentes.

RESULTS AND DISCUSSION

Figure 1 summarizes the congener series (102-109), which was synthesized using a direct synthetic route, recently developed in our laboratory. These compounds were fully structurally characterized (NMR, IR, MS).

Figure 1. Summary of the congener series (102-109).

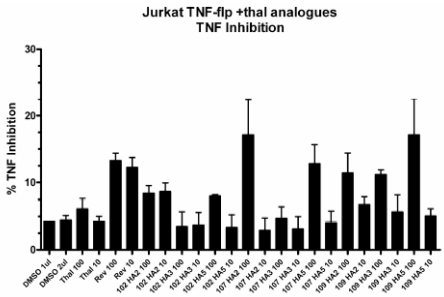


Compound screening was performed on a TNF transcriptional reporter cell line (FRT-Jurkat TNF),[3] using Thalidomide and Revlimid as reference drugs (Figure 2). After the identification of the most potent TNF expression inhibitors, IC_{50} values were determined (data not shown).

Figure 2 shows the initial screening of the chemical library (102-109). From this, more potent TNF expression inhibitors than Revlimid were identified, as exemplified by 107H02 and 109H05.

During this screening, novel data of Structure-Activity Relationships were gathered, including the importance of the substituents at *para*-position and the direct comparison between the spacer groups at phthalimide (pharmacophoric unit 1) and *N*-acylhydrazone (pharmacophoric unit 2). 109H05 was also able to induce apoptosis in Jurkat cells though caspase-3 assay (data not shown).

Figure 2. Compound screening on a TNF transcriptional reporter cell line (FRT-Jurkat TNF).



CONCLUSION

Identification of potent TNF expression inhibitors was achieved. As a result, important data of Structure-Activity Relationships were gathered during this screening. Details are presented at poster section.

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REFERENCES

1 S. M. Capitosti, T. P. Hansen, M. L. Brown, Bioorg. Med. Chem. 2004, 12, 327– 336; b) T. Noguchi, H. Fujimoto, H. Sano, H. Miyajima, Y. Hashimoto, Bioorg. Med. Chem. Lett. 2005, 15, 5509– 5513; c) H. Sano, T. Noguchi, A. Miyajima, Y. Hashimoto, H. Miyachi, Bioorg. Med. Chem. Lett. 2006, 16, 3068 –3072.
2 C. Pessoa, P. M. P. Ferreira, L. V. C. Lotufo, M. O. de Moraes, S. M. T. Cavalcanti, L. Cunha D. Coelho, M. Z. Hernandes, A. C. L. Leite, C. A. De Simone, Vlaudia M. A. Costa, V. M. O. Souza, ChemMedChem, 2010, 4, 523-528.
3 S. G. Stewart, D. Spagnolo, M. E. Polomska, M. Sin, M. Karimi, L. J. Abraham, Bioorg. Med. Chem. Lett. 2007, 17, 5819 –5824.