Thalidomide Analogs

By: Robert B. Login rloginconsulting.com

Many people are facing multiple myeloma, a cancer of the blood("**Multiple myeloma** is a cancer that forms in a type of white blood cell called a plasma cell. Plasma cells help you fight infections by making antibodies that recognize and attack germs. **Multiple myeloma** causes cancer cells to accumulate in the bone marrow, where they crowd out healthy blood cells") . I looked at the organic chemistry of the current best drugs employed to counteract this cancer. Could I review their structures and suggest alternatives that might have been overlooked and could improve their performance. I found that a current treatment is Revlimid in combination with Dexamethasone which are the leading medicinals and have significantly improved survival rates. Hopefully further progress with new medications such as monoclonal antibodies and PROTACs(proteolysis-targeting chimeras) will emerge and possibly this cancer will someday be cured.

I am not a biochemist, molecular biologist or an expert in cellular biology. I'm an organic/polymer chemist with 158 patents and 50yrs of experience. What follows is my take on this chemistry. I hope you find this interesting!

Lenalidomide (trade name**Revlimid**) is a analog of thalidomide.

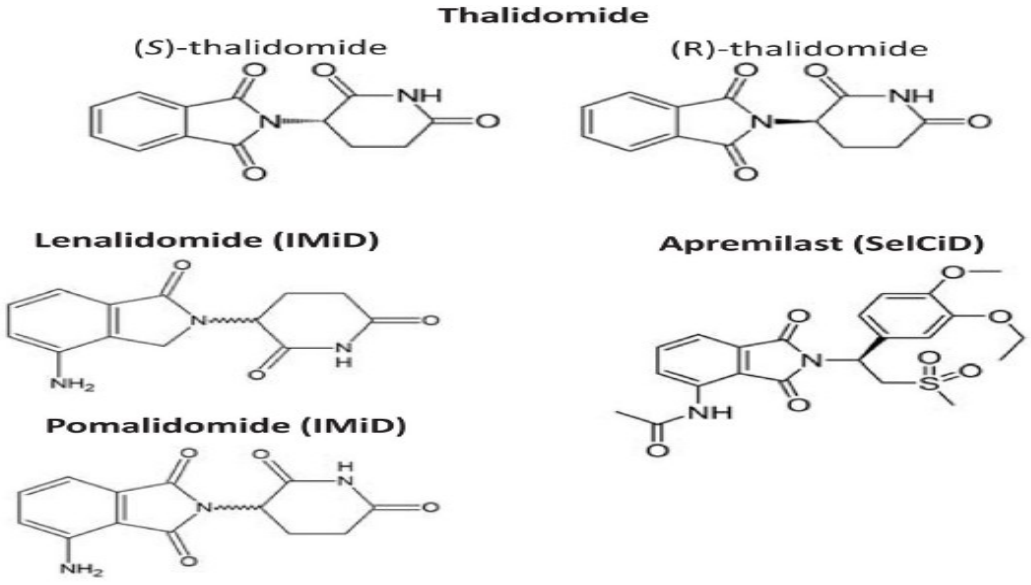
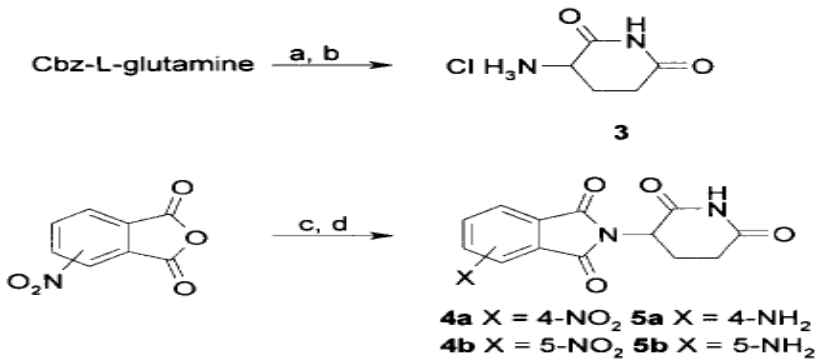


Fig. (1).
Structure of thalidomide and its analogs.

Lenalidomide is a rather simple compound that apparently does not have to be resolved into its isomers to be effective.

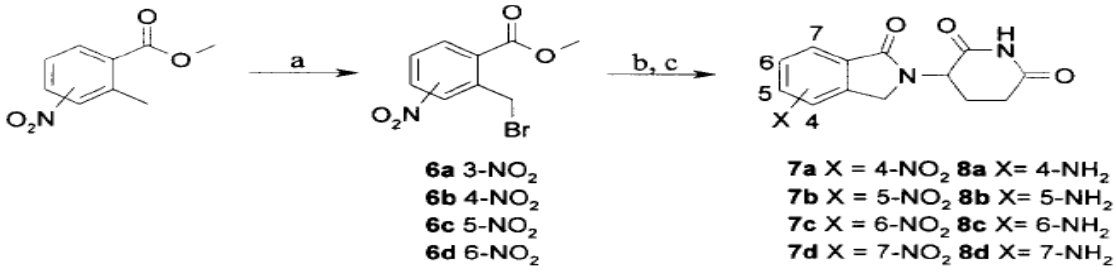
The following reference illustrates their synthesis.

Scheme 1



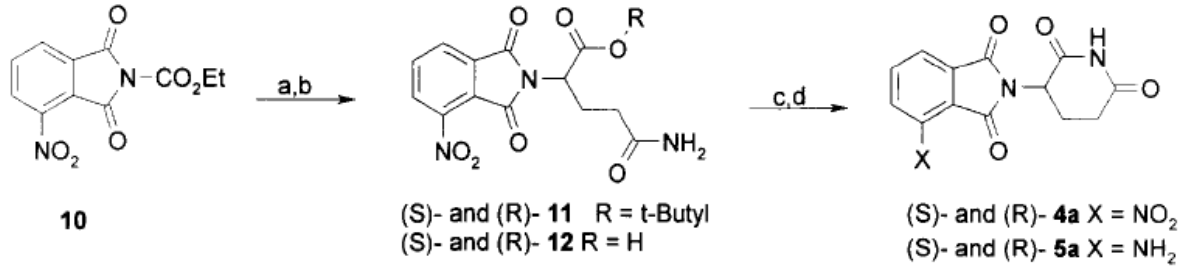
Reagents: (a) CDI, THF, reflux; (b) H_2, 10% Pd/C, EtOAc/4N HCl; (c) **3**, AcOH, reflux; (d) 10% Pd/C, acetone.

Scheme 2



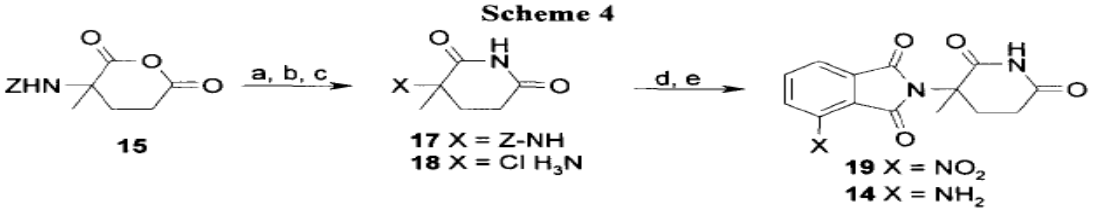
Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

Scheme 3



Reagents: (a) Et_3N, (*R*) or (*S*) *t*-butyl glutamine HCl; (b) HCl, CH_2Cl_2; (c) $SOCl_2$, pyr/Et_3N; (d) H_2, 10% Pd/C, acetone.

Scheme 4



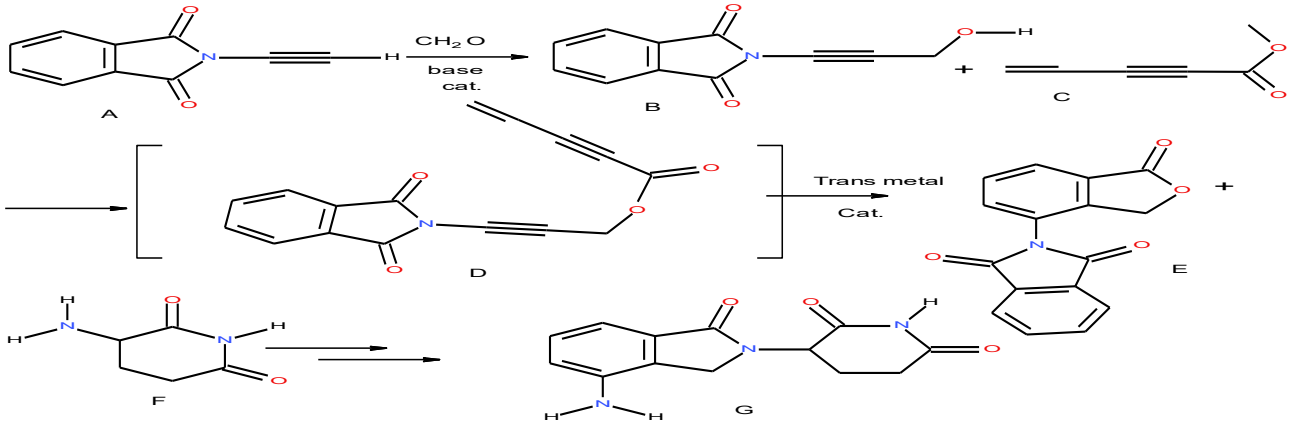
Reagents: (a) NH_3, CH_2Cl_2; (b) CDI, THF; (c) H_2, 10% Pd/C, EtOH/4N HCl; (d) 3-NO_2-phthalic anydride, AcOH, reflux; (e) H_2, Pd/C, acetone.

CDI=carbonyl diimidazole

Muller, G. W., Chen, R., Huang, S. Y., Corral, L. G., Wong, L. M., Patterson, R. T., ... & Stirling, D. I. (1999). Amino-substituted thalidomide analogs: potent inhibitors of TNF-α production. *Bioorganic & medicinal chemistry letters*,

9(11), 1625-1630.

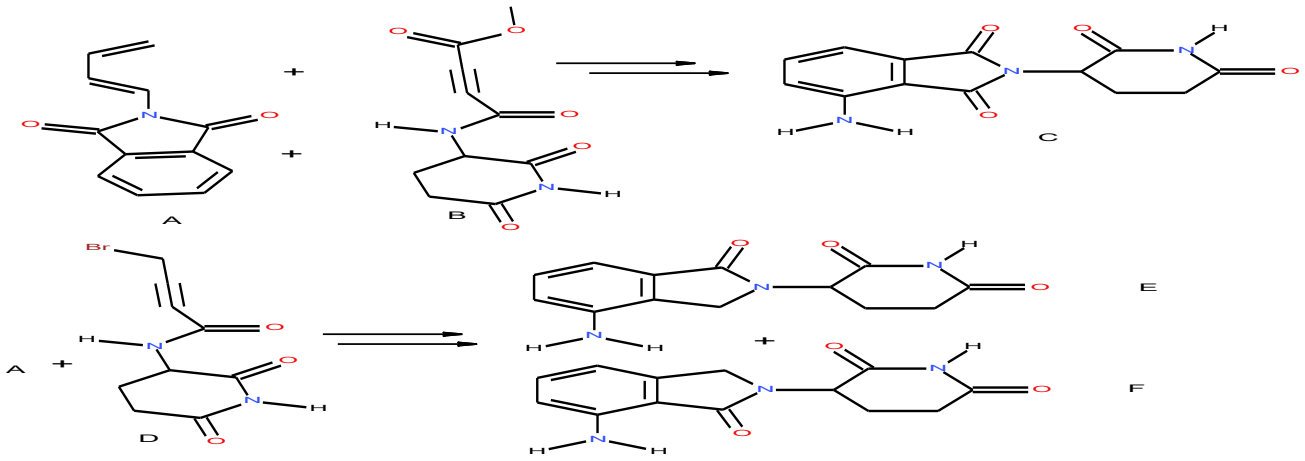
My ideas for the synthesis of Lenalidomide and Pomalidomide.



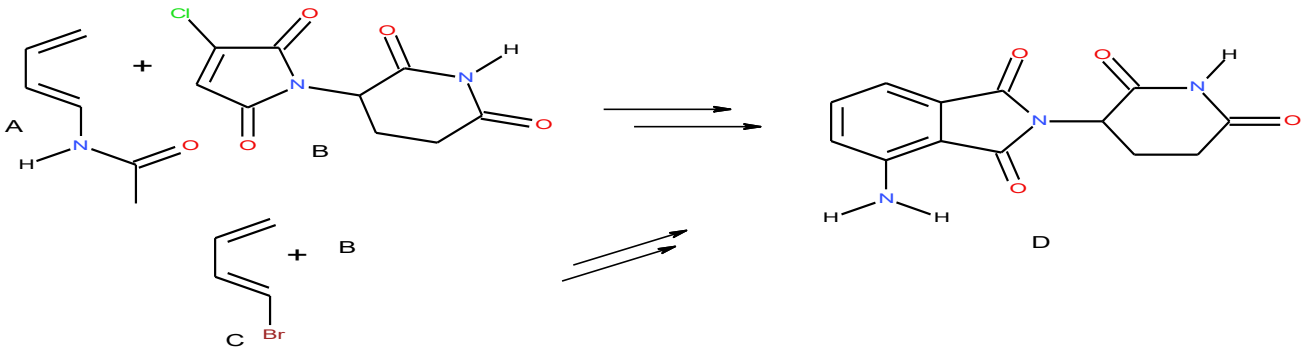
Scheme 1: All of the above RM's are known compounds that I think are readily available. The advantage of the above is that the lenalidomide nitration step is eliminated.

See Chap. 14 in “Transition Metal-Mediated Aromatic Ring Construction”
Ken Tanaka Ed., Wiley, 2013.

Sueda, T., Oshima, A., & Teno, N. (2011). N-Alkynyl Imides (Ynimides): Synthesis and Use as a Variant of Highly Labile Ethynamine.*Organic letters*, *13*(15), 3996-3999.



Scheme 2: I would expect that F would be minor because of steric hindrance. The DA reaction results in a cyclohexadiene that should be easily converted to benzene by mild oxidation.



Scheme 3: Chloromaleic anhydride is commercially available and should result in the hexadiene which can be easily oxidized to benzene.

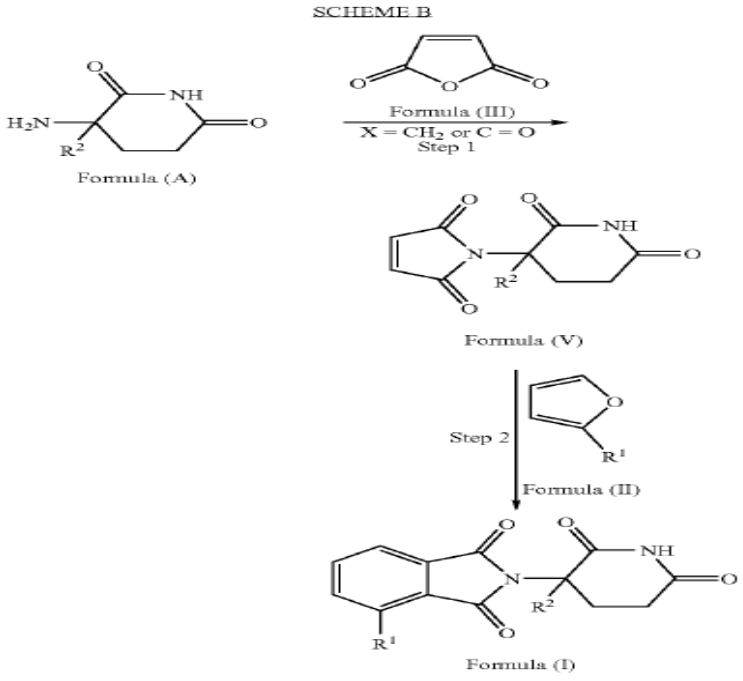
See:

Wolinsky, J., & Login, R. B. (1970). Diels-Alder reaction of acetoxy-1, 3-dienes with dimethyl acetylenedicarboxylate and chloromaleic anhydride. Synthesis of benzene derivatives. *The Journal of Organic Chemistry*, *35*(10), 3205-3207.

And Chap. 13 in the Tanaka book above.

"The Diels-Alder Reaction selected practical methods" by Fringuelli and Taticchi; Wiley, 2002.

Alternative similar patent example:



(19) **United States**
(12) **Patent Application Publication**
Muller et al.
(10) **Pub. No.: US 2008/0064876 A1**
(43) **Pub. Date: Mar. 13, 2008**

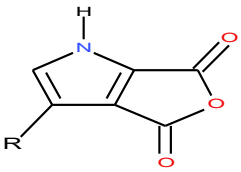
(54) **PROCESS FOR THE PREPARATION OF SUBSTITUTED 2-(2,6-DIOXOPIPERIDIN-3-YL) ISOINDOLE-1,3-DIONE**

Related U.S. Application Data

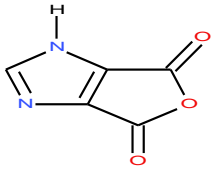
(60) Provisional application No. 60/800,708, filed on May 16, 2006.

This patent application shows how to prepare formula 5 above that should also be possible with chloromaleic anhydride as in scheme 3. This patent application suggests a very clever approach to thalidomide analogs(note my scheme 3 doesn't employ step 2).

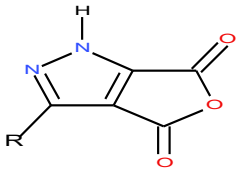
I want my following ideas to keep close to thalidomide's basic structure, an aromatic imide or lactam where the aromatic imide or lactam nitrogen is attached to a cyclic imide or lactam. For example:



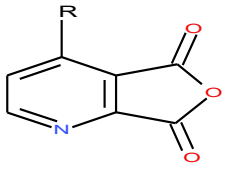
1H-furo[3,4-b]pyrrole-4,6-dione



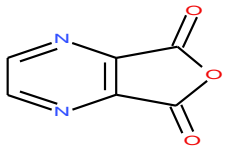
1H-furo[3,4-d]imidazole-4,6-dione



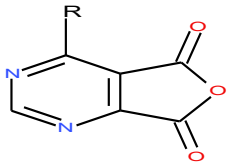
1H-furo[3,4-c]pyrazole-4,6-dione



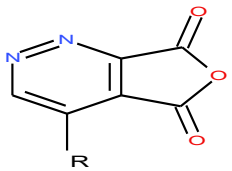
furo[3,4-b]pyridine-5,7-dione



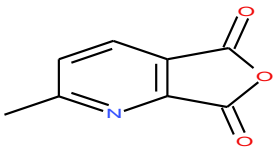
furo[3,4-b]pyrazine-5,7-dione



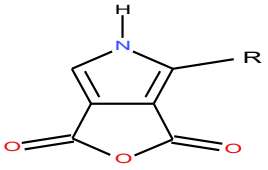
furo[3,4-d]pyrimidine-5,7-dione



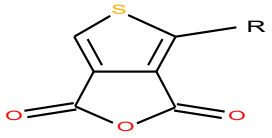
furo[3,4-c]pyridazine-5,7-dione



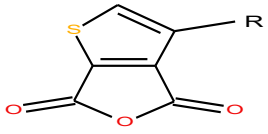
1-aminofuro[3,4-b]pyridine-5,7-dione

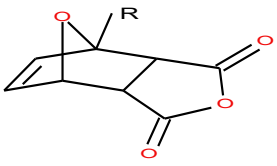


4-amino-5H-furo[3,4-c]pyrrole-1,3-dione



4-aminothieno[3,4-c]furan-1,3-dione



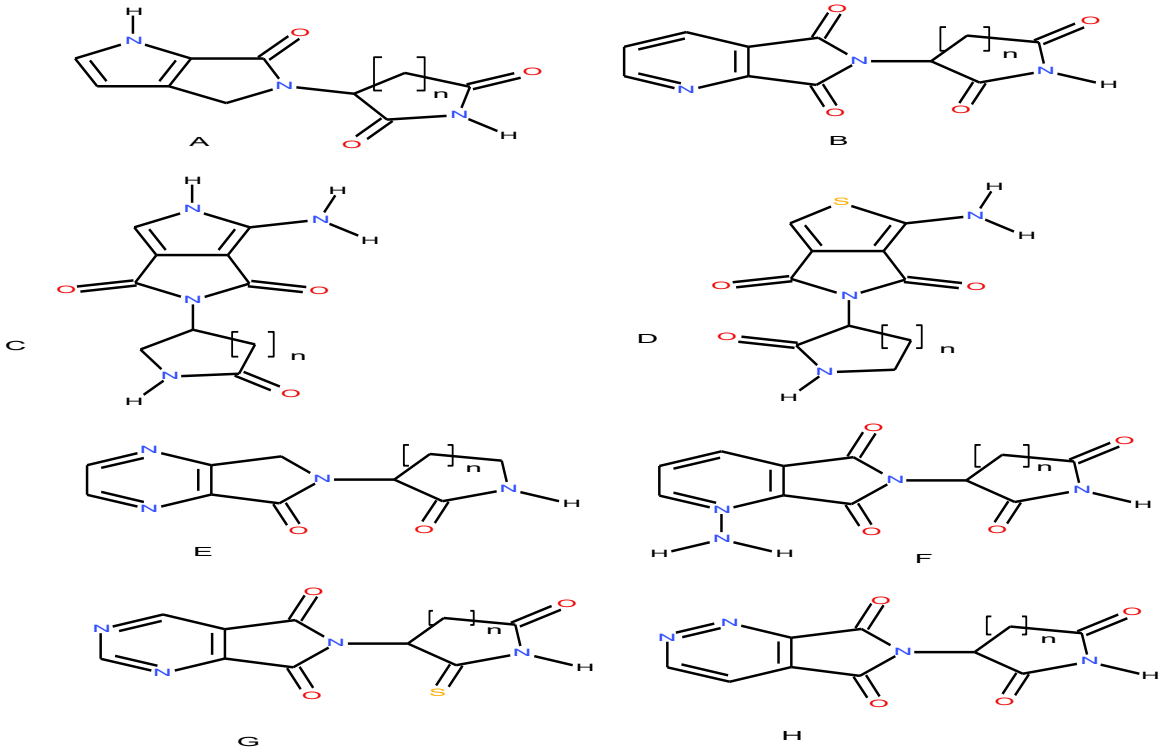


Scheme 4: Starting anhydride possibilities. Note that the R groups can be H or either

protected primary amines or their appropriate precursor moieties. Conversion to the Thalidomide analog is obvious.

I also searched SciFinder and found over 5000 derivatives of thalidomide. These retain the thalidomide or like core and have R groups attached everywhere. I decided to look at related structures and here at the 70% SciFinder level, I found 120 structures. Obviously there is great interest in this chemistry because of its important applications not to mention the billions of dollars in sales. My ideas however were not described.

What I hope is that my analog synthesis ideas might spark interest in new structures.



Scheme 5: "Thalidomide analogs". This is not an exhaustive list and many others could be included. I left out all the possible R groups for clarity. Note that A-E types where found on SciFinder. Also the indanone or the imide is illustrated randomly with the idea that either is worth considering.

The patent literature is very extensive and Celgene seems to have covered every possibility with patent examples. I have to confess that I could not bring myself to analyze their enormous patents. I looked mainly at the actual chemical examples and not the legal verbiage. So it is possible that some of these proposed structures are covered in the legalese? I direct you to look at the basic Celgene patent: https://patents.google.com/patent/US5635517A/en?oq=5%2c635%2c517

US5635517A

United States

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David I. Stirling

Roger S. -C. Chen

Current Assignee

Celgene Corp

Info

Patent citations (44)

Non-patent citations (8)

Cited by (213)

Legal events

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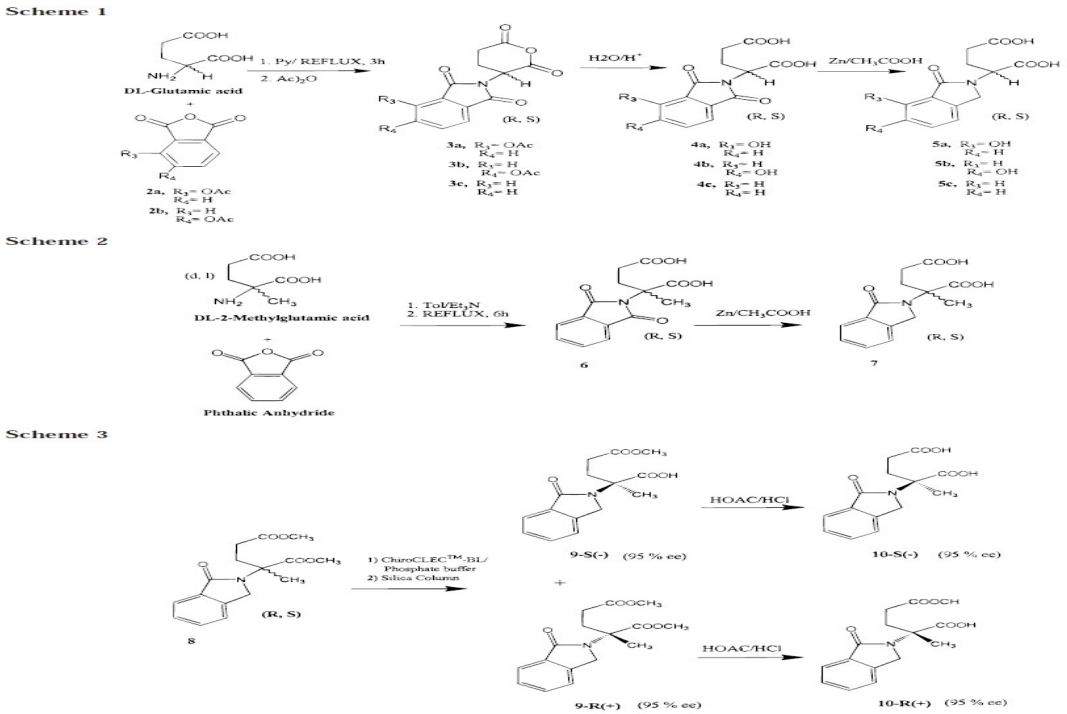
Notice that there are 213 patents that cited this patent.

Thalidomide, Lenalidomide and Pomalidomide apparently work by affixing themselves to cereblon(CRBN), a part of the ubiquin protosome damaged protein elimination system(UPS). Apparently, the aromatic ring sticks out and attracts MCL1 and other proteins that are responsible for cancer cell survival. (thalidomide and its derivatives were discovered to induce the degradation of IKZF1 and IKZF2 by binding to CRBN, thus resulting in the ubiquitination of targets.
Pei, H., Peng, Y., Zhao, Q., & Chen, Y. (2019). Small molecule PROTACs: an emerging technology for targeted therapy in drug discovery. *RSC Advances*, *9*(30), 16967-16976.)

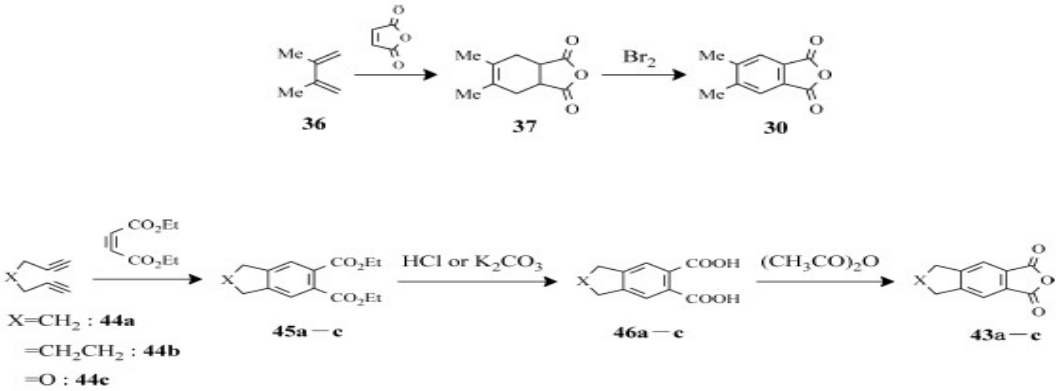
Getting too close to cereblon is a death sentence to MCL1and other proteins and then the cancer cell. Because Lenalidomide and Pomalidomide are electron richer than Thalidomide, I believe they are stickier towards MCL1 and other survival proteins. I would expect electron rich heterocycles of scheme 5 to possibly be superior.

What follows are references I found that illustrate some of this analog chemistry. Note this is not a review but examples of synthesis descriptions I was able to obtain that I

found interesting.



Shah, J. H., Swartz, G. M., Papathanassiu, A. E., Treston, A. M., Fogler, W. E., Madsen, J. W., & Green, S. J. (1999). Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis. *Journal of medicinal chemistry*, *42*(16), 3014-3017.



Kanamitsu, N., Osaki, T., Itsuji, Y., Yoshimura, M., Tsujimoto, H., & Soga, M. (2007). Novel water-soluble sedative-hypnotic agents: isoindolin-1-one derivatives. *Chemical and Pharmaceutical Bulletin*, *55*(12), 1682-1688.

The above reference shows amine benzene derivatives as anhydride co-reactants outside of my desire to stay close as possible to the thalidomide structure.

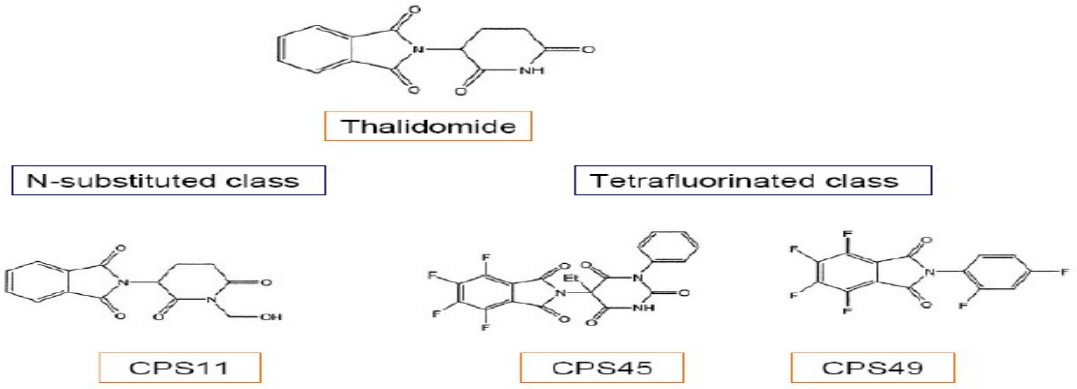
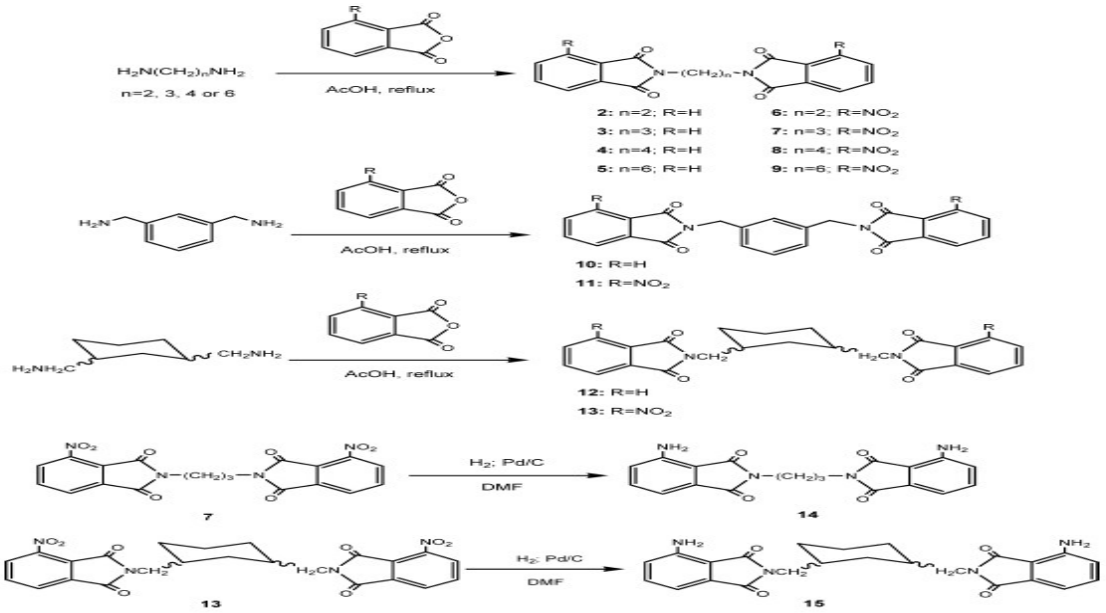


Fig. (3) . The analogues CPS11, CPS45 and CPS49

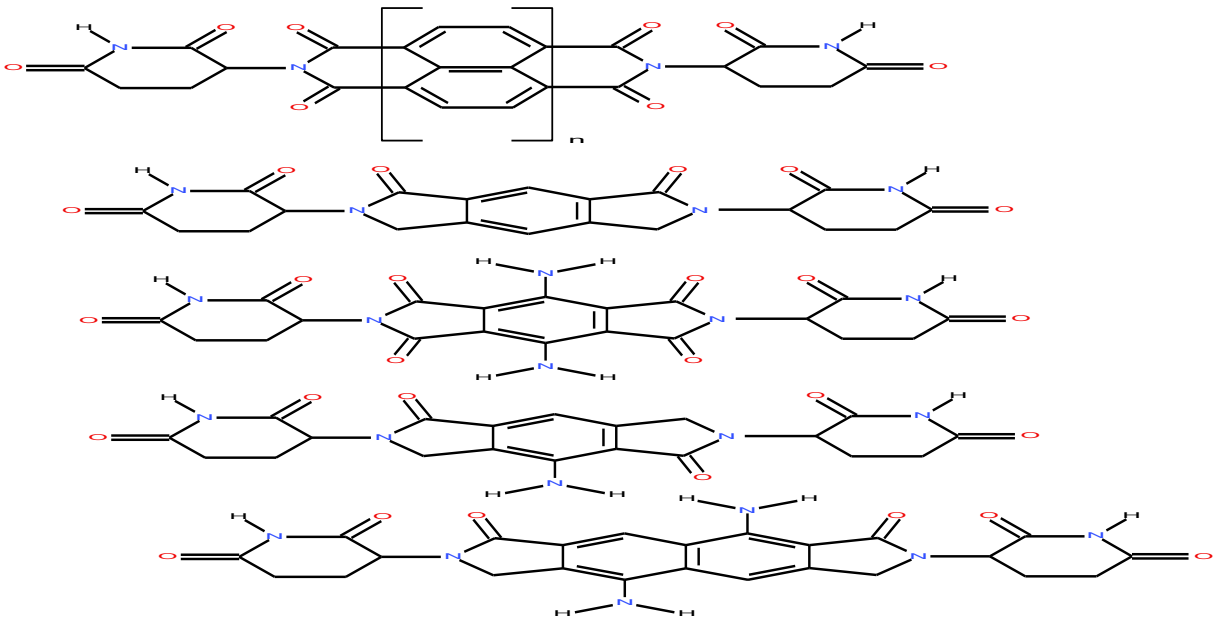
Aragon-Ching, J. B., Li, H., Gardner, E. R., & Figg, W. D. (2007). Thalidomide analogues as anticancer drugs. *Recent patents on anti-cancer drug discovery*, *2*(2), 167-174.

CPS49 is an analog outside of my thalidomide type examples but representative of many aromatic types.



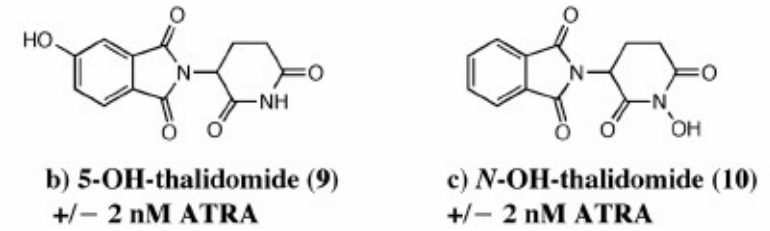
de Almeida, M. V., Teixeira, F. M., de SOUZA, M. V. N., Amarante, G. W., de Souza Alves, C. C., Cardoso, S. H., ... & Teixeira, H. C. (2007). Thalidomide analogs from diamines: Synthesis and evaluation as inhibitors of TNF-α production. *Chemical and pharmaceutical bulletin*, *55*(2), 223-226.

The above are not close to thalidomide's structure but interesting.



Scheme 6: Ideas for other dimers closer to thalidomide. Many other structures could be listed but these make the point. Some are known compounds...see below. Apparently, this dimer idea is already known and is claimed to be a way to UPS cereblon itself by bringing two of these together so that one is sent to the Proteasome.

Maniaci, C., Hughes, S. J., Testa, A., Chen, W., Lamont, D. J., Rocha, S., ... & Ciulli, A. (2017). Homo-PROTACs: bivalent small-molecule dimerizers of the VHL E3 ubiquitin ligase to induce self-degradation. *Nature communications*, *8*(1), 830.



Hashimoto, Y. (2008). Thalidomide as a multi-template for development of biologically active compounds. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, *341*(9), 536-547.

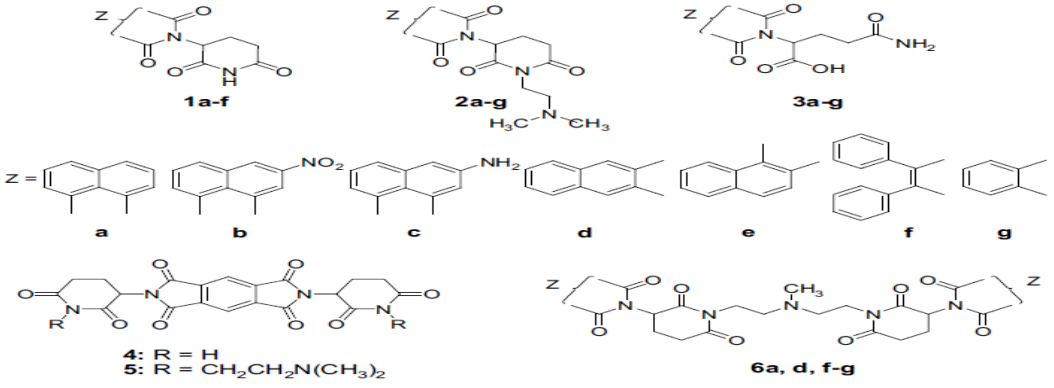
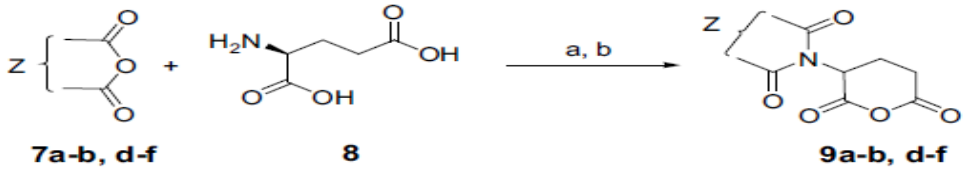
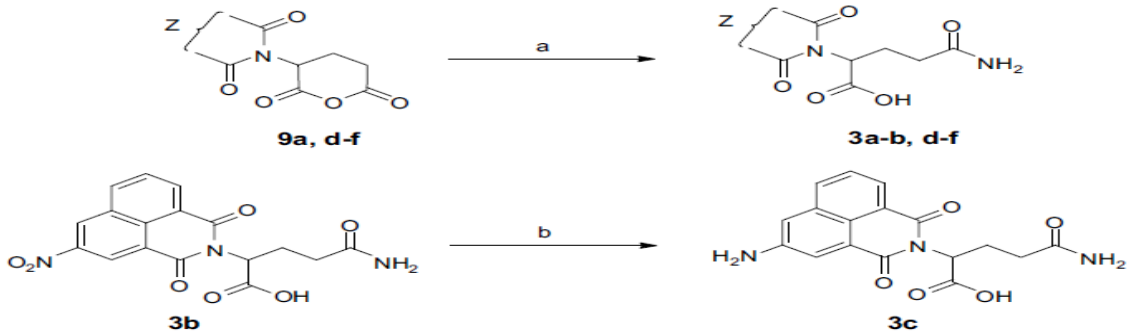


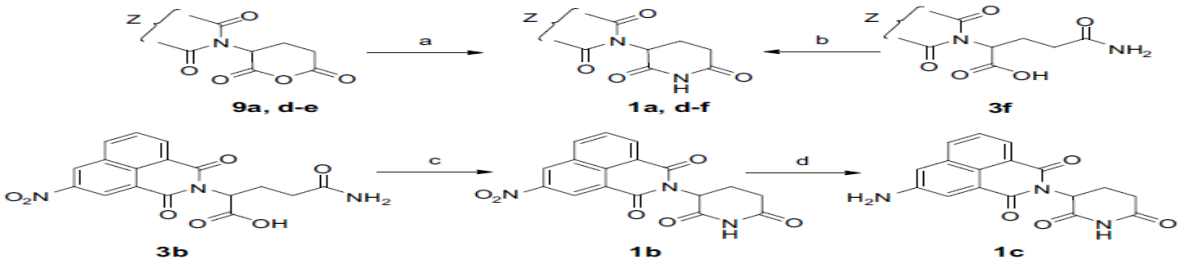
Fig. 2. Compounds 1a–f, 2a–g, 3a–g, 4, 5, 6a–g.



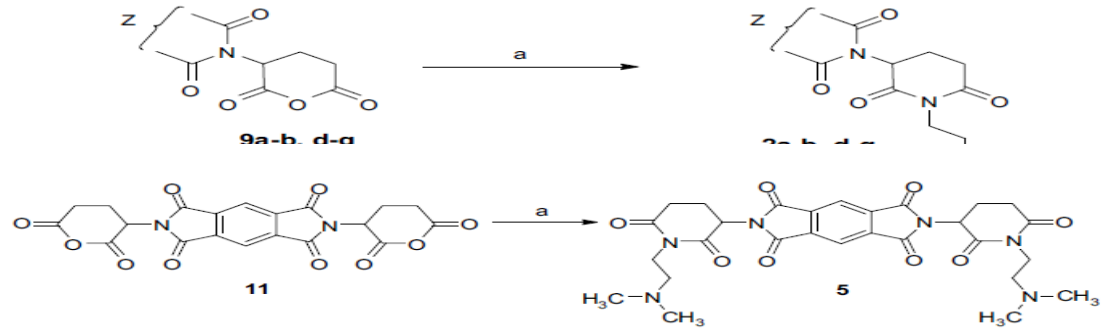
Scheme 1. Reagents: (a) pyridine, Δ; (b) Ac_2O, Δ.



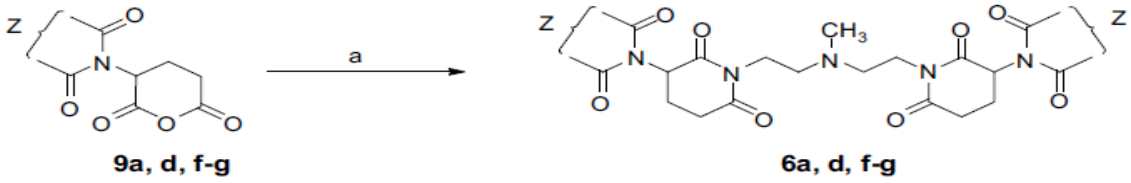
Scheme 2. Reagents: (a) (i) NH_3 (g), dioxane, RT; (ii) H_3O^+; (b) H_2, Pd/C 10%, DMF, 50 psi.



Scheme 3. Reagents: (a) $(NH_4)_2CO_3$, Δ; (b) Ac_2O, AcCl, Δ; (c) Δ, 250 °C; (ii) H_3O^+; (d) H_2, Pd/C 10%, DMF, 50 psi.

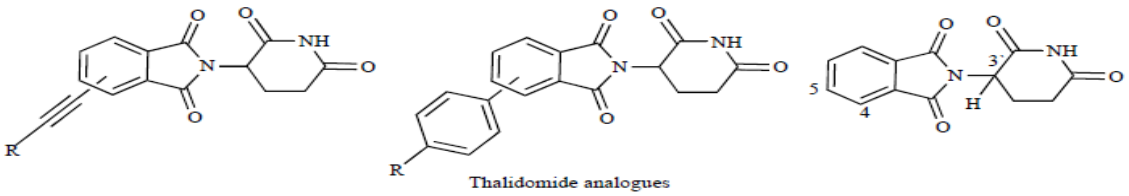


Scheme 6. Reagents: (a) (i) 0.5 $H_2NCH_2CH_2N(CH_3)_2$, DMF, RT; (ii) H_3O^+; (iii) Ac_2O, AcCl, Δ.



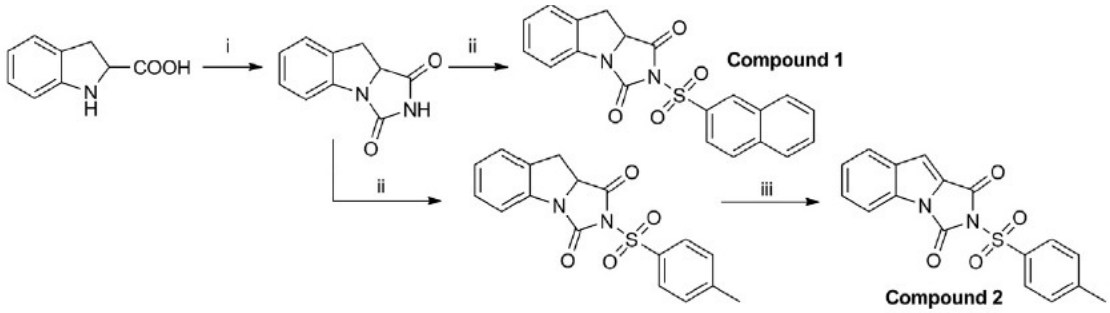
Scheme 7. Reagents: (a) (i) 0.5 $H_2NCH_2CH_2N(CH_3)CH_2CH_2NH_2$, DMF, RT; (ii) H_3O^+; (iii) Ac_2O, AcCl, Δ.

Braña, M. F., Acero, N., Anorbe, L., Mingarro, D. M., Llinares, F., & Domínguez, G. (2009). Discovering a new analogue of thalidomide which may be used as a potent modulator of TNF-α production. *European journal of medicinal chemistry*, *44*(9), 3533-3542.

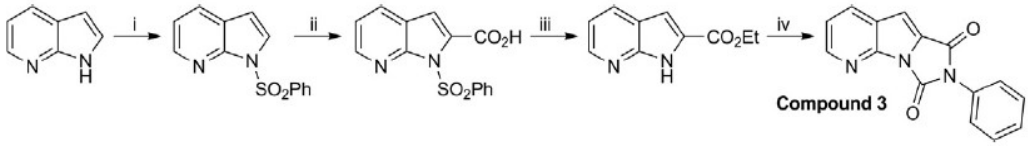


Thalidomide analogues

B De Sanctis, J., Mijares, M., Suárez, A., Compagnone, R., Garmendia, J., Moreno, D., & Salazar-Bookaman, M. (2010). Pharmacological properties of thalidomide and its analogues. *Recent patents on inflammation & allergy drug discovery*, *4*(2), 144-148.



Scheme 2. Reagents and conditions: (i) KNCO, HCl, H_2O, reflux, 3 h; 49%; (ii) arylsulfonyl-methylimidazolium triflate, Et_3N, THF, rt, 12 h; 63%; (iii) NBS, AIBN, CCl_4, reflux, 1 h; 85%.



Scheme 3. Reagents and conditions: (i) NaOH, Bu_4NBr, $ClSO_2Ph$, DCM, 0 °C to rt, 2 h; 90%; (ii) (a) LDA, THF, −35 °C, 30 min; (b) CO_2, −35 °C to rt, 12 h; 65%; (iii) H_2SO_4, EtOH, reflux, 12 h; 80%; (iv) PhNCO, $NaOCH_3$, toluene; 45%.

Chaulet, C., Croix, C., Alagille, D., Normand, S., Delwail, A., Favot, L., ... & Viaud-Massuard, M. C. (2011). Design, synthesis and biological evaluation of new thalidomide analogues as TNF-α and IL-6 production inhibitors. *Bioorganic & medicinal chemistry letters*, *21*(3), 1019-1022.

Above included because of use of heterocycles.

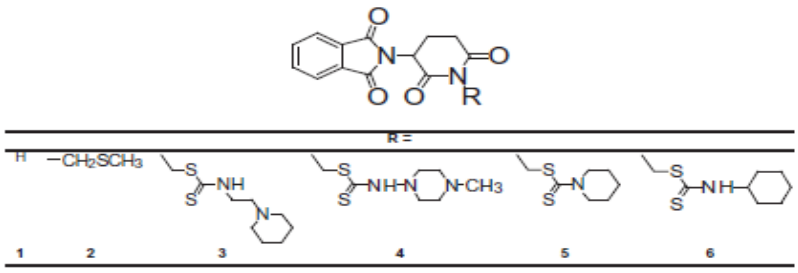
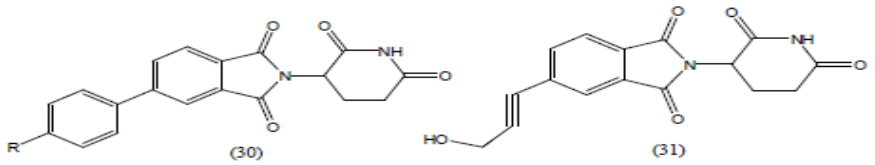


Figure 1 Thalidomide **1** and its sulfur analogs **2–6**.

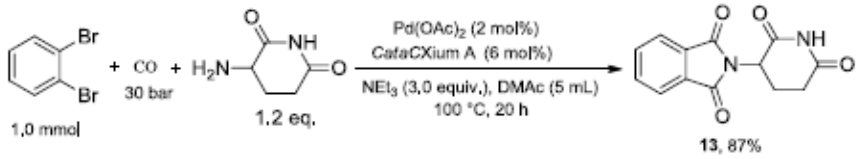
Zahran, M. A., Gamal-Eldeen, A. M., El-Hussieny, E. A., & Agwa, H. S. (2014). Thalidomide dithiocarbamate and dithioate derivatives induce apoptosis through inhibition of histone deacetylases and induction of caspases. *Journal of Genetic Engineering and Biotechnology*, *12*(1), 65-70.



(30) (31)

Sharma *et al.*, (2012) synthesized novel schiff bases of imide moiety (compound **32**) which exhibited anti-inflammatory and analgesic activity.

Kushwaha, N., & Kaushik, D. (2016). Recent advances and future prospects of phthalimide derivatives. *J. Appl. Pharm. Sci*, *6*, 159-171.



Scheme 1. Synthesis of thalidomide.

Chen, J., Natte, K., Spannenberg, A., Neumann, H., Beller, M., & Wu, X. F. (2014). Efficient palladium-catalyzed double carbonylation of o-dibromobenzenes: synthesis of thalidomide. *Organic & biomolecular chemistry*, *12*(30), 5578-5581.

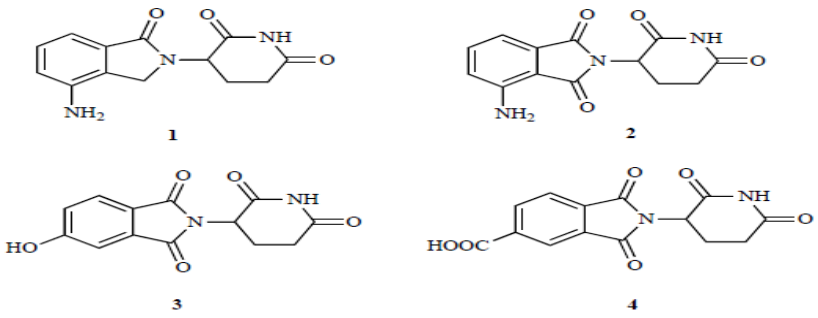
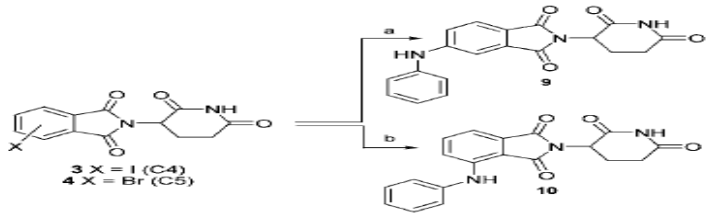


Fig. (1). Phthalimide analogs in literature.

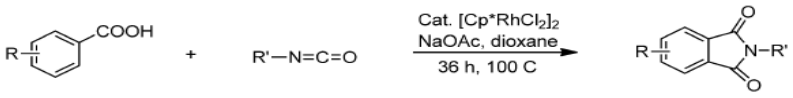
Gupta, A., Kamble, B., & MJ Nanjan, C. (2013). Synthesis of Biologically Potent Novel 5-(2-bromopyridin-3-yl-amino)-2-alkyl/aryl-isoindoline-1, 3-dione Analogs Via Buchwald-Hartwig CN Coupling Reaction. *Letters in Organic Chemistry*, *10*(2), 139-146.

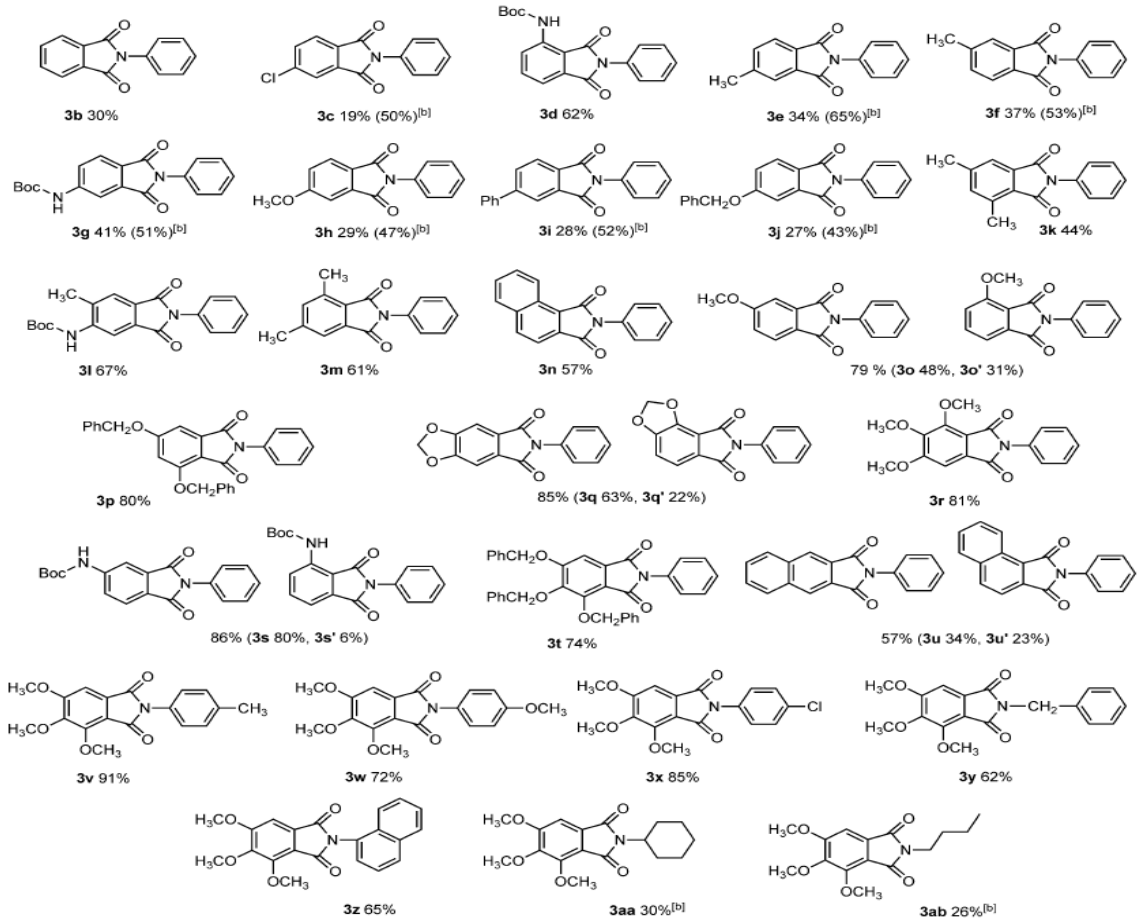


Scheme 2 Reagents and conditions: (a) $Pd_2(dba\text{-}4,4'\text{-}OMe)_3$, XPhos, K_3PO_4, toluene, 110 °C, 21 h, 48%; (b) $Pd_2(dba)_3$ (5 mol%), HP(*t*-Bu)$_3BF_4$ (14 mol%), Cy_2NMe, toluene, 110 °C, 16 h, 7%.

Yeung, S. Y., Kampmann, S., Stubbs, K. A., Skelton, B. W., Kaskow, B. J., Abraham, L. J., & Stewart, S. G. (2011). Novel thalidomide analogues with potent NFκB and TNF expression inhibition. *MedChemComm*, *2*(11), 1073-1078.

Table 2. Reaction scope.[a]





[a] *Reactions conditions:* acid (0.2 mmol), isocyanate (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), NaOAc (0.2 mmol), dioxane (0.5 mL), 100°C, 36 h, argon. Yield of purified product is reported.
[b] NaOAc (0.15 mmol) and AgOAc (0.05 mmol) were used. Yield of purified product is reported.

Shi, X. Y., Renzetti, A., Kundu, S., & Li, C. J. (2014). A Rhodium-Catalyzed Cascade Cyclization: Direct Synthesis of N-Substituted Phthalimides from Isocyanates and Benzoic Acids. *Advanced Synthesis & Catalysis*, *356*(4), 723-728. The above illustrate the potential for a phythera of aromatic derivatives.

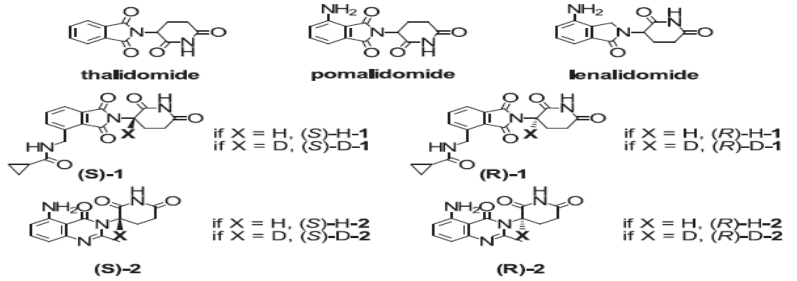
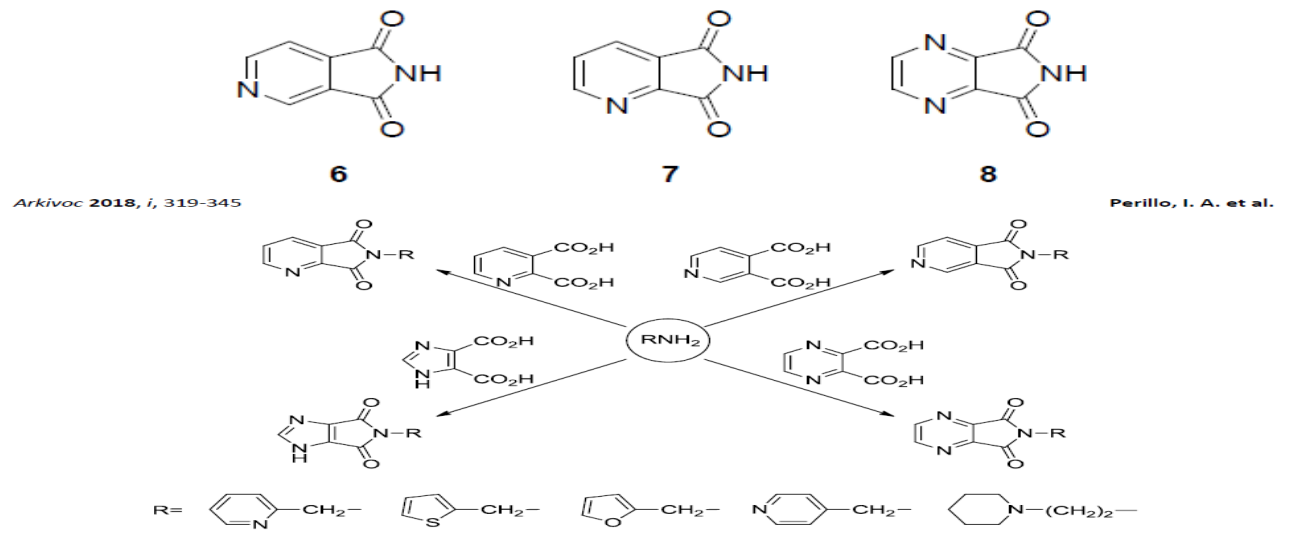


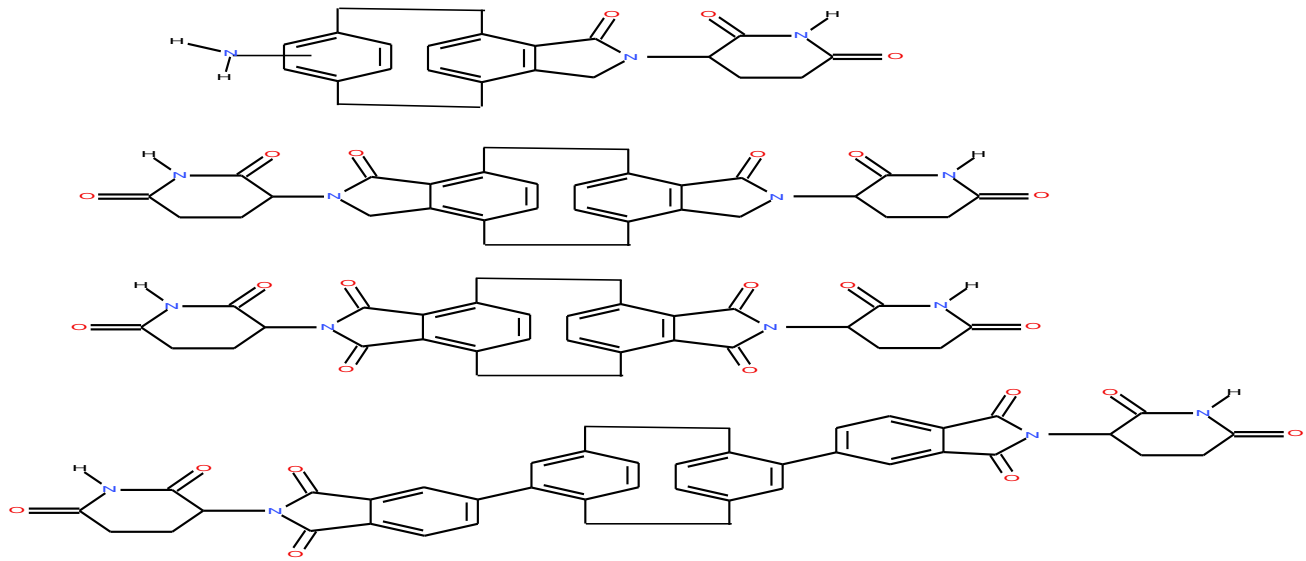
Fig. 1. Structures of thalidomide, pomalidomide, lenalidomide, and protonated and deuterated enantiomers of compound 1 [CC-11006; i.e., (*S*)-H-1, (*R*)-H-1, (*S*)-D-1, and (*R*)-D-1] as well as protonated and deuterated enantiomers of compound 2 [CC-122; (*S*)-H-2, (*R*)-H-2, (*S*)-D-2, and (*R*)-D-2 (absolute configuration was not established for compound 2; enantiomers are referred to by the sign of their optical rotation; i.e., (+) or (–); details in the text)].

Jacques, V., Czarnik, A. W., Judge, T. M., Van der Ploeg, L. H., & DeWitt, S. H. (2015). Differentiation of antiinflammatory and antitumorigenic properties of stabilized enantiomers of thalidomide analogs. *Proceedings of the National Academy of Sciences*, *112*(12), E1471-E1479.



Perillo, I. A., Shmidt, M. S., Prieto, S. C., & Blanco, M. M. (2018). Microwave-promoted synthesis of cyclic imides. *ARKIVOC: Online Journal of Organic Chemistry*, *2018*.

What follows is the possibility that [2,2]paracyclophanes might be another useful idea. Such cyclophanes are actually conjugated to some extent through the closeness of the benzene rings.



Scheme 7: Some examples of [2,2]paracyclophanes. The synthesis of the above can be readily inferred in Gleiter, R., & Hopf, H. (Eds.). (2006). *Modern cyclophane chemistry*. John Wiley & Sons.page 465. and Nakano, T. (2016)*pi-stacked polymers and molecules*. Springer Verlag, Japan, pages 185-200 .

I actually found patents that employed this moiety in a medicinal context. It is also possible but not illustrated to put a "thalidomide" on one aromatic of the [2,2]paracyclophane and something else, say a PROTAC warhead and coupler on the other. Or to use them as thalidomide analog dimers as described in the following

referance.

Maniaci, C., Hughes, S. J., Testa, A., Chen, W., Lamont, D. J., Rocha, S., ... & Ciulli, A. (2017). Homo-PROTACs: bivalent small-molecule dimerizers of the VHL E3 ubiquitin ligase to induce self-degradation. *Nature communications*, *8*(1), 830.

US005147882A

United States Patent [19]
Psiorz et al.

[11] **Patent Number: 5,147,882**
[45] **Date of Patent: Sep. 15, 1992**

[54] **CYCLOPHANES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS AND PROCESSES FOR PREPARING THEM**

Hagishita et al., "Synthesis and absolute . . . ", Chem. Pharm. Bull. 24 (8) 1724–1730 (1976).

Primary Examiner—Alan L. Rotman
Assistant Examiner—Celia Chang

(12) **United States Patent**
Wiles et al.

(10) **Patent No.: US 8,809,313 B2**
(45) **Date of Patent: Aug. 19, 2014**

(54) **SUBSTITUTED ALIPHANES, CYCLOPHANES, HETERAPHANES, HETEROPHANES, HETERO-HETERAPHANES AND METALLOCENES USEFUL FOR TREATING HCV INFECTIONS**

2010/0152103 A1 6/2010 Phadke et al.
2010/0158862 A1 6/2010 Kim et al.
2010/0216725 A1 8/2010 Phadke et al.
2010/0310512 A1 12/2010 Guo et al.

FOREIGN PATENT DOCUMENTS

(12) **United States Patent**
Wiles et al.

(10) **Patent No.: US 9,273,082 B2**
(45) **Date of Patent: Mar. 1, 2016**

(54) **SUBSTITUTED ALIPHANES, CYCLOPHANES, HETERAPHANES, HETEROPHANES, HETERO-HETERAPHANES AND METALLOCENES USEFUL FOR TREATING HCV INFECTIONS**

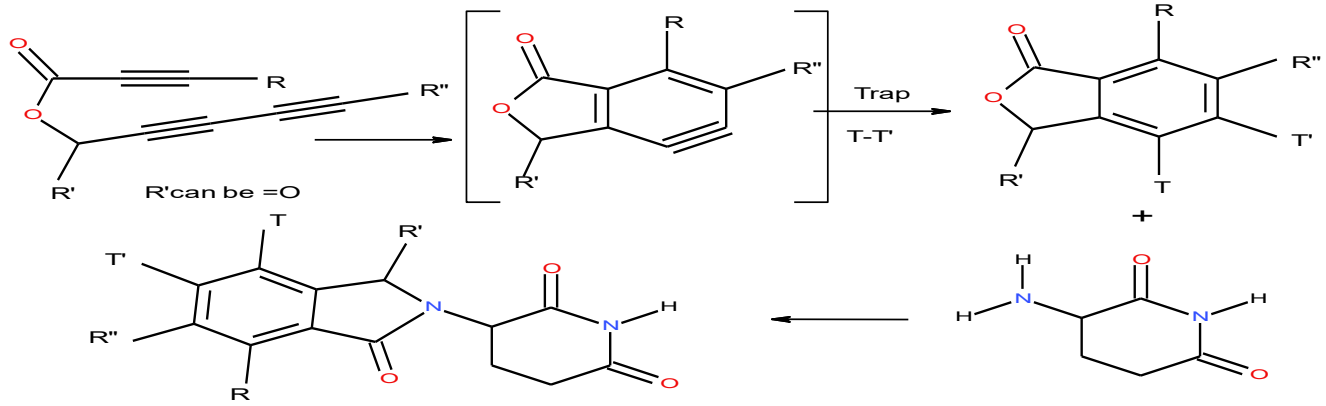
(56) **References Cited**

U.S. PATENT DOCUMENTS

5,147,882 A 9/1992 Psiorz et al.
6,448,392 B1 9/2002 Hostetler et al.

(Continued)

Another possibility is the following:



Scheme 8: I refer you to the extensive literature of Prof. Hoye's group. It is very impressive and interesting. This HHDA(Hexadehydro-Diels–Alder Benzynes) reaction has the potential to produce many analogs. Please look at the following patent to see what is meant by the trap compound.

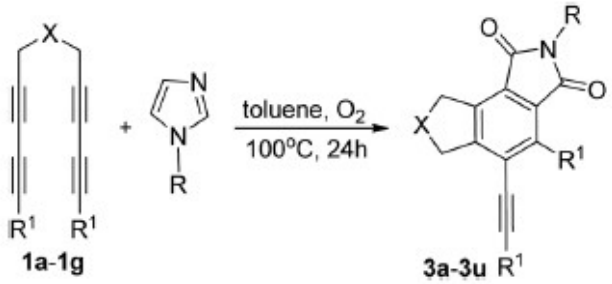
United States Patent Hoye et al. US 9,505,789 B2 Nov. 29, 2016
(A very complete explanation.)

Ross, S. P., & Hoye, T. R. (2017). Multiheterocyclic Motifs via Three-Component Reactions of Benzynes, Cyclic Amines, and Protic Nucleophiles. *Organic letters*, *20*(1), 100-103.

Ross, S. P., Baire, B., & Hoye, T. R. (2017). Mechanistic Duality in Tertiary Amine Additions to Thermally Generated Hexadehydro-Diels–Alder Benzynes. *Organic letters*, *19*(20), 5705-5708.

Ross, S. P., & Hoye, T. R. (2017). Reactions of hexadehydro-Diels–Alder benzynes with structurally complex multifunctional natural products. *Nature chemistry*, *9*(6), 523.

Another interesting reaction in this vein:



Hu, Q., Li, L., Yin, F., Zhang, H., Hu, Y., Liu, B., & Hu, Y. (2017). Fused multifunctionalized isoindole-1, 3-diones via the coupled oxidation of imidazoles and tetraynes. *RSC Advances*, *7*(78), 49810-49816.
This reference can be suggestive of numerous Thalidomide anolog possibilities.

Obviously I presented several possible synthesis routes to the currently employed Myeloma drugs with the idea that instead of the amine thalidomide analogs other derivatives might be visualized.

I would hope that the above proposals would spark some new ideas for thalidomide analogs with improved utility.
.
Thank you for reading my proposals.
Dr. Robert B. Login rloginconsulting.com (please visit my web page)