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Perspective

Dihydropyridines and atypical MDR: A novel perspective of designing general reversal agents for both typical and atypical MDR

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ABSTRACT

Multidrug resistance (MDR) is defined as resistance of tumor cells to the cytotoxic action of multiple structurally dissimilar and functionally divergent drugs commonly used in chemotherapy. 1,4-Dihydropyridines (DHP_s) are one of the major classes of Ca^{2+} channel blockers, and it has been shown that these agents are a new class of drug resistance reversers in cancer treatment. Analysis of various investigations on MDR reversing effects of DHPs shows that they can be a potential class for designing compounds simultaneously effective on both typical and atypical MDR. Also, it is possible to include some considerations on essential structural features for MDR reversing and further decreasing of Ca^{2+} channel blocking activity as an adverse effect.

1. Introduction

Multidrug resistance (MDR) is defined as resistance of tumor cells to the cytotoxic action of multiple structurally dissimilar and functionally divergent chemotherapeutic agents.[1,2] Such resistance is considered to be one of the major reasons of failure of chemotherapy for the majority of cancer patients.[3]

MDR includes two types: in the first type, resistance is present in cancer cells at the time of the first treatment, which is called intrinsic resistance. The second is the acquired type when the cancer cells become insensitive to treatment after relapse.[2,4] There are many molecular pathways by which cells become drug resistant. Table 1 shows some of these pathways and their brief descriptions.

The problem of MDR has brought about many efforts to clarify major mechanisms of this phenomenon. However, the mechanisms are numerous and complex, and despite more than four decades of attempts, it is still a matter of controversy as to how cancer cells become resistant against various types of chemotherapeutic agents. In this regard, better understanding of the molecular bases of MDR may lead to more efficient treatments.

2. Atypical MDR

Although the mechanisms of MDR appear to be complex, they can be grouped into several categories based upon their presumed mechanisms (Table 1).[5] However, there is no classification that has been accepted by everyone. One of the most common classifications is dividing MDR to classical MDR or ATP-Binding Cassette (ABC)-transporters-mediated MDR and atypical MDR that includes other mechanisms.[6] Among the ABC-mediated MDR, P-glycoprotein-mediated MDR is one of the main causes of limited effectiveness of chemotherapy.[7] Some other ABC transporters are also involved in less common types of ABC-mediated MDR (Table 1).[8,9]

Atypical MDR, which is usually referred to as non-ABC-mediated MDR, differs from classical MDR in several important ways. Resistance in these cells is not usually associated with a drug transport defect or over-expression. Additionally, these cells are usually sensitive to drugs associated to classical MDR.[5] However, due to the fact that most of MDR types occur multifactorially,[10] this rule has some exceptions.

Atypical MDR has some subcategories based on their mechanisms. Topoisomerases are nuclear enzymes critical for DNA replication, transcription, and recombination. Two major forms of topoisomerases have been shown to be present in all cells: the type I topoisomerase, a 100 kDa protein that makes single-stranded cuts in DNA, and the type II enzyme, which cuts and passes double-stranded DNA. Topoisomerase II is an important intracellular target for a number of cytotoxic drugs.[11] Topoisomerase II-related MDR is one of major types of atypical MDR that in some references is considered as the unique mechanism of atypical MDR.[12] This type of atypical MDR occurs following the alteration in Topoisomerase II.[5,12]

Other types of atypical MDR mainly include altered expression of some metabolizing enzymes such as glutathione S-transferases and Cytochrome P_{450}-dependent oxidases.[5] In this way, tumor cells

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; DHP, 1,4-dihydropyridine; MRP, multidrug resistance-associated protein; MDR, multidrug resistance; P-gp, permeability-glycoprotein.

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Table 1
General mechanisms related to multidrug resistance

No	Mechanism	Description	Reference
1	Alteration in pharmacokinetic of drug	This phenomenon usually occurs because of over-expression of metabolizing enzyme especially various subtypes of CYP450 and glutathione-*S*-transferase	5
2	Increased drug efflux	This mechanism is often due to over-expression of efflux pump (ABC transporters) on cell surface especially P-gp, MRP, and BCRP	6,8,9
3	Increased repair of DNA	In some cases, intrinsic repair systems are changed in order to influence drug sensitivity like alteration in DNA methyl transferase	2
4	Alteration in drug target	Qualitative or quantitative changes in some targets especially intracellular enzymes, which influence efficacy of cytotoxic drugs including dihydrofolate reductase and topoisomerase II	2,5
5	Decreased drug influx	This mechanism may result from some defects in carrier-mediated influx systems such as folate-transport system.	5
6	Defects in apoptosis	One of the often-efficient resistance methods is defects in apoptotic pathways (over- or under-expression of some related genes like p53 and Bcl-2)	2
7	Decreased drug activation	Some cytotoxic drugs are administered in the form of pro-drug, so they need activation in tumor tissue. In some cases, alteration in converting enzymes results in decreased drug activity	5

are sometimes sensitive in vitro while their resistance is restored in vivo.[13]

Although some efforts were made in order to find inhibitors of atypical MDR, most studies have been focused on classical MDR. Furthermore, some reports on the inhibition of atypical MDR were related to MDR associated to ABC transporters other than P-gp such as Multidrug Resistance-associated Protein (MRP) and Breast Cancer Resistance Protein (BCRP), which in some texts are referred to as a kind of atypical MDR. In such cases, different approaches including prevention of biosynthesis of transporters at the gene level such as antisense technologies,[14] RNA interferences (RNAi)[15,16] methods, and hammerhead ribozymes have been used.[17] In a different approach, some modifications in derivatives of anthracyclines caused significant decrease in both typical (P-gp-mediated) and atypical (topoisomerase II-mediated) MDR. Such process of retaining the cytotoxicity may be due to these facts that new anthracycline derivatives are not effective on topoisomerase-mediated DNA cleavage, and also they are not substrates for P-gp efflux.[18,19]

3. Dihydropyridines and MDR

The 1,4-dihydropyridines (DHPs) were initially introduced as a class of calcium channel blockers, and are widely used in cardiovascular diseases such as angina pectoris, some types of cardiac arrhythmias, and in the treatment of hypertension.[20,21] It is believed that they act directly on the voltage-gated calcium channels,[22] which are localized in cell membranes, controlling the influx of extracellular calcium to the cytoplasm.[23] Also, it has been discovered that DHPs have other beneficial biological effects such as anti-convulsant,[24] anti-diabetic,[25] and analgesic[26] and they have also been used as chemical drug delivery systems especially for brain delivery.[27] However, most of these effects have not found any clinical applications mostly due to the potential cardiovascular side effects of DHPs.

In the beginning of the 1980s, it was found that calcium channel blockers are inhibitors of MDR development.[28,29] In fact, Verapamil was the first compound to reach clinical trials for its ability to reverse MDR.[30] However, these clinical trials failed due to the high toxicity of verapamil or absence of improvement in the clinical outcome.[31]

In 1980, Tsuruo and his group showed that DHPs have reversing effects on MDR in cell lines.[32] These findings resulted in the entrance of Nifedipine to a clinical trial by Philip and coworkers. However, the clinical trial failed due to the reasons similar to previous failed trials; obtained outcome was very poor (6% response, 1 patient out of 15); and cardiovascular side effects of Nifedipine were dose limiting, which resulted in limited tolerable administered dosage.[33] These limitations encouraged the development of a new generation of dihydropyridines, which are categorized as the second generation of MDR reversals.[2] In the development of these new derivatives, it tried to achieve two goals; First, to increase the MDR reversing effect, and second, to decrease significantly the Ca^{2+} channel blocking activity. In this way, it was found that enantiomers of some dihydropyridines have different MDR reversing and Ca^{2+} channel blocking effects. For instance, R-enantiomers of Verapamil and Niguldipine (Dexniguldipine) have the same MDR reversing effect compared to their L-enantiomers, while their Ca^{2+} channel blocking effects are much weaker (Fig. 1).[34]

Therefore, there are many studies done in order to find new derivatives of dihydropyridines for reversal of MDR.[35] In this way, some lead compounds were introduced, which are currently in preclinical studies. For instance, Zhou and coworkers synthesized some derivatives of Niguldipine and also their pyridine counterparts.[36] Also, Kuwano and his group prepared many derivatives of DHPs as MDR reversing agents. Most of the reported compounds have pyridyl group on 3,5 positions of dihydropyridine nucleus.[37–39]

An important point in most studies is that they have included general considerations of the Ford rule. Ford and colleagues' studies in some drug categories revealed some structural features important to MDR reversal. They showed that in phenothiazines, compounds with tertiary amines were better anti-MDR agents

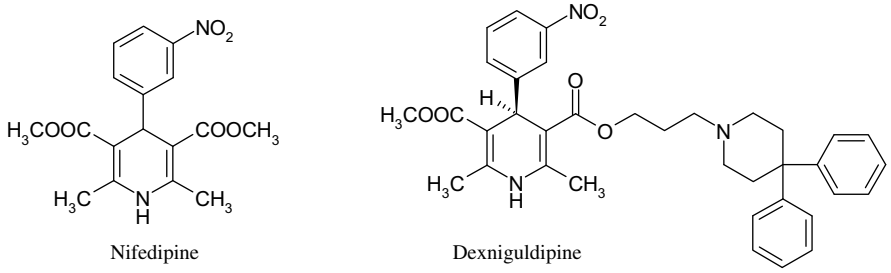


Figure 1. Chemical structures of Nifedipine and Dexniguldipine.

than those with secondary or primary amines. For instance, they observed that the presence of a piperazinyl amine rather than a non-cyclic amino group in the side chain resulted in better MDR reversal activity.[40] Also in thioxanthenes, cyclic amines such as piperazinyl or piperidinyl groups resulted in higher activity.[41] Therefore, they concluded that tertiary and cyclic amino groups have an important role in reversing MDR.[42]

3.1. Dihydropyridines and atypical MDR

A survey in the literature shows that there are limited studies about the potential effects of dihydropyridines on atypical MDR. A large part of the studies have focused on P-glycoprotein-mediated MDR, and even the reports about the effect of DHPs on other ABC transporters such as MRP and BCRP are very limited in

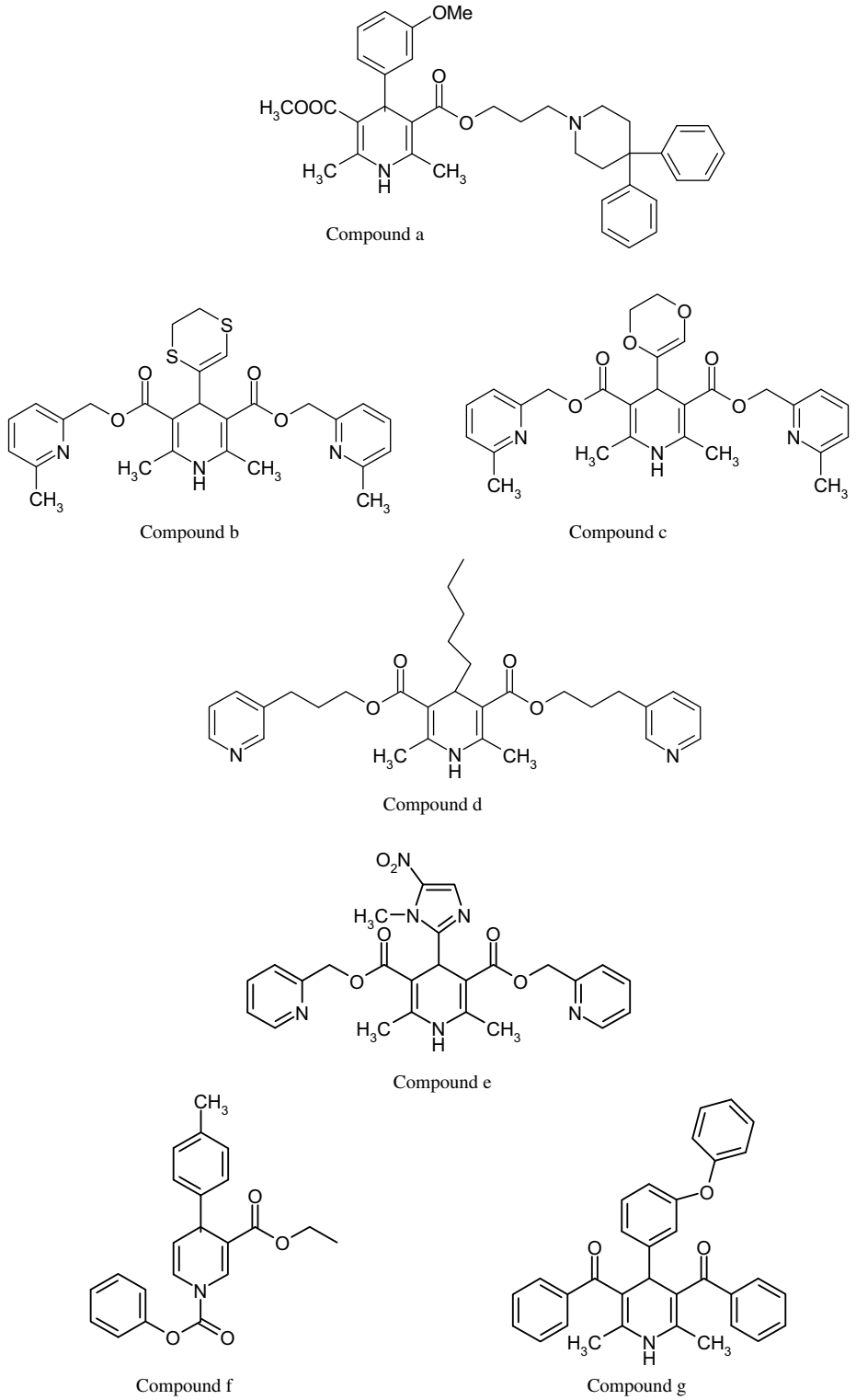


Figure 2. Structures of some synthesized DHP derivatives as MDR modulators.

comparison. Zhou and colleagues reported some DHP derivatives, which were effective on MRP and BCRP-mediated MDR.[43,44]

Very recently, our research group reported some newly synthesized derivatives with good effects on MDR reversal in HL60/MX1 cell line.[45] It was shown that this cell line shows MDR in the absence of P-glycoprotein. Its MDR mechanism is postulated to be mediated by altered Topoisomerase II activity or level.[46] Two compounds could reduce the IC_{50} of Mitoxantrone more than 10 times, which indicates their high potency against this type of MDR.[45] Furthermore, it has been previously reported that Dexniguldipine exerts its cytotoxic activity through inhibiting Topoisomerase I non-competitively.[47] These findings showed that DHPs might have the ability to reverse atypical MDR in addition to their capability to modulate ABC transport-mediated MDR (classical MDR). However, because of the nature of the biological assay that we used in our study (cytotoxicity assay), it is not possible to comment on the accurate mechanisms of reversing effect of DHPs in such a cell line. Therefore, it is necessary to perform a more precise evaluation especially at the molecular level.

3.2. Possibility of a dual effect

Comparison of various studies about the effect of DHP on MDR shows that it is possible to obtain a general pharmacophore effective on different types of MDR.

Zhou and coworkers synthesized some compounds that were effective on P-gp-mediated MDR, and also on MRP and BCRP-mediated MDR (Fig. 2, compound a).[36,43,44] These compounds were structurally similar to Dexniguldipine, which is a Topoisomerase I inhibitor as well as a P-gp-mediated MDR reversal agent.[47]

Also, there are some similarities between derivatives synthesized by Kuwano and colleagues (NIK and NK series; Fig. 2, compounds b, c, and d) and our group, both of them used pyridyl group on $C_{3,5}$ positions (Fig. 2, compound e).[37–39,45] NK and NIK series contained molecules with aliphatic and heterocyclic substituents containing S and O atoms in C_4 position, while in our study phenyl and a heterocyclic substituents containing N atom were used. These studies showed that replacement of phenyl group with other groups (aliphatics or heterocycles) results in significant decrease in Ca^{2+} channel blocking activity, which is in agreement with pervious findings showing the importance of the conformation at C_4 of dihydropyridine nucleus in Ca^{2+} channel blocking activity.[48–50] It seems that the main difference between derivatives effective on atypical MDR with other compounds is the presence of a heterocyclic substituent on C_4, which contains N atom and also bears a nitro group (nitroimidazolyl moiety) (Fig. 2, compound e).

On the other hand, presence of Ca^{2+} channel blocking activity results in a major problem in designing appropriate MDR reversal agents and also failure in clinical trials. In Table 2, some related SARs are shown. It has been shown that MDR reversal activity of DHPs is independent of their calcium channel blocking activity;[38] enantiomers of some Ca^{2+} channel blockers such as verapamil and niguldipine with the same MDR reversal capacity showed different Ca^{2+} channel blocking activities.[34] Survey on the literature indicates that most effective SARs in order to decrease Ca^{2+} channel blocking activity are deletion of methyl groups from $C_{2,6}$ positions, addition of acyloxy group to N of DHP (Fig. 2, compound f),[51] conversion of ester groups of $C_{3,5}$ to acyl group (Fig. 2: compound g),[52,53] presence of hetero-aromatic groups on $C_{3,5}$ and C_4 positions, and also conversion of DHPs into the cage dimeric forms[54] (Table 2).

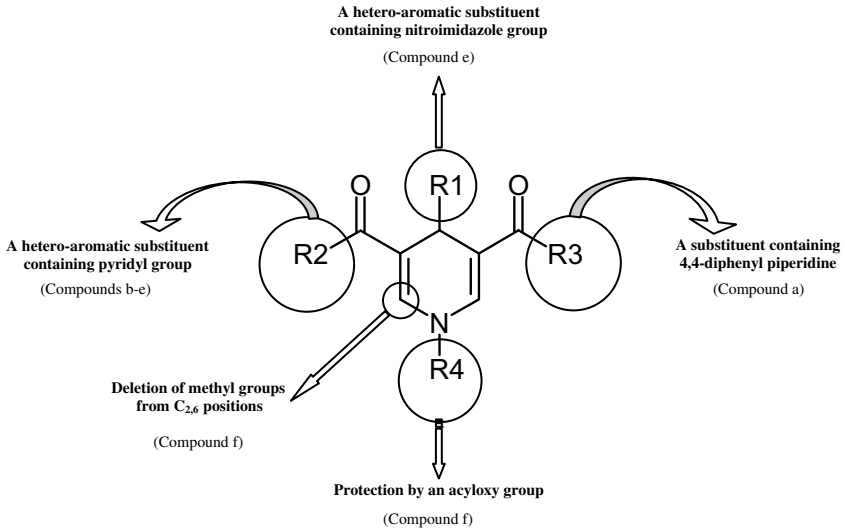
Therefore, it seems that a combination of these findings can be helpful to derive a pharmacophore. Scheme 1 shows a possible pharmacophore, which might be effective on all kinds of MDR. It should be noted that there are some other possible pharmacophores.

In this way, it is suggested to synthesize asymmetrical derivatives of DHP. Substituents on $C_{3,5}$ positions can be moieties containing pyridyl group on one side (Fig. 2, compounds b–e)[37–39,45] and 4,4-diphenyl piperidine group on the other side (Fig. 2, compound a);[43,44] since, it was proved that pyridyl group is helpful in reversal of P-gp-mediated MDR and also it was used in derivatives which can overcome atypical MDR. Moreover, 4,4-diphenyl piperidine group is very effective on ABC transporters such as P-gp, MRP, and BCRP.[43,44,55] Ester groups in these positions ($C_{3,5}$) are critical for Ca^{2+} channel blocking activity. Therefore, conversion of esters into acyl group can significantly reduce cardiovascular side effects (Fig. 2, compound g).[53] On C_4 position, replacement of phenyl group with heteroaromatic or aliphatic groups is effective both in increasing MDR reversing activity and in decreasing Ca^{2+} channel blocking activity (Fig. 2, compound b–e). However, the differentiating factor of DHP derivatives effective on atypical MDR is presence of nitroimidazole on C_4 position; so, the best choice for this position is presence of nitroimidazole (Fig. 2, compound e).[45] Methyl groups in $C_{2,6}$ positions are important for Ca^{2+} channel blocking activity. Replacement of one methyl group with an amino alkyl chain is tolerated without loss of anti-hypertensive activity.[50,56] However, their removal has positive effects on reducing Ca^{2+} channel blocking activity. Voigt and coworkers have recently shown that protection of N_{DHP} by transforming it into *N*-acyloxy caused better effects in reversing P-gp-mediated MDR. Therefore, addition of acyloxy group and removal of methyl group

Table 2
Different SARs of DHP and their relevance to various types of MDR, and also their effect on decrease in Ca^{2+} channel blocking activity

No.	SAR	Exp compound[a]	Observed effects				Reference
			P-gp-mediated MDR	Other transporters-mediated MDR[b]	Atypical MDR	Decrease in Ca^{2+} channel blocking activity	
1	Presence of pyridyl group on $C_{3,5}$ positions	Compounds b–e	+++	ND[c]	++	++	37–39,45
2	Presence of 4,4-diphenyl piperidine group on $C_{3,5}$ positions	Compound a	+++	+++	ND	++	36,43,44,54
3	addition of acyloxy group to N_{DHP}	Compound f	++	ND	ND	++	50
4	Deletion of methyl's from $C_{2,6}$	Compound f	++	ND	ND	+	50
5	Presence of dithiene group on C_4 positions	Compound b	++	ND	ND	–	39
6	Presence of dioxene group on C_4 positions	Compound c	++	ND	ND	+	39
7	Presence of nitroimidazolyl group on C_4 positions	Compound e	ND	ND	++	++	45
8	Conversion ester group on $C_{3,5}$ positions into acetyl group	Compound g	++	ND	ND	++	51,52
9	Alkyl chain at 4-position	Compound d	+	ND	ND	+	37,38

[a] Structures of these compounds are shown in Figure 2.
[b] Other ABC transporters like MRP and BCRP.
[c] Not determined.



Scheme 1. A possible pharmacophore for multi-target compounds with DHP structure used in MDR reversing.

might have better results (Fig. 2, compound f).[51] Therefore, the derived pharmacophore has most of the essential features in order to overcome ABC transporters (P-gp, MRP, and BCRP)-mediated MDR and atypical MDR (Topoisomerase-mediated MDR). Furthermore, most of these features reduce the Ca^{2+} channel blocking activity. Common structure of pharmacophore is shown in Scheme 1. A potential example of this pharmacophore is presented in Figure 3, which can potentially be a potent inhibitor of ABC transporters and atypical MDR reversal agent, while its Ca^{2+} channel blocking activity would probably be negligible.

4. Conclusion

Many efforts have been made to find effective MDR reversal agents in the past four decades, but they have not been fully successful yet. It has numerous reasons, which are mainly due to the challenging differences between the nature of the in vitro, in vivo, and clinical studies. However, some categories of compounds seem to be promising. Dihydropyridines are one of the classes that showed MDR reversing ability, but their advancement to clinical applications has been restricted due to some concerns about their cardiovascular side effects. Second generation of dihydropyridines has been developed to address these concerns by decreasing the Ca^{2+} channel blocking effect by and increasing the MDR reversing effect of these compounds. Furthermore, reviewing different studies shows that DHPs have the appropriate ability to modulate most types of MDR, which reveals their great potential in overcoming this important pharmaceutical challenge.

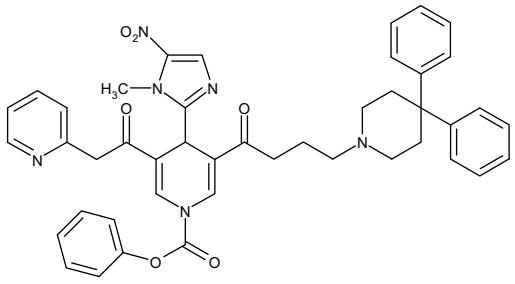


Figure 3. Structure of a possible derivative of derived pharmacophore.

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